Technical report

Volume 1 – Findings of the review

Prepared for

National Blood Authority

Project

Patient Blood Management Guideline for people with Critical Bleeding

The Commonwealth of Australia

as represented by the National Blood Authority

prepared by

Health Technology Analysts Pty Ltd

September 2022

Contents

Contents 2
Report information 5
List of Tables 8
List of Figures 13
Abbreviations 17
1 Background 19
1.1 Description of condition and setting 20
1.2 Description of intervention and how it might work 20
2 Rationale and objectives 22
3 Methods 23
3.1 Criteria for selecting studies for this review 23
3.1.1 Types of participants 23
3.1.2 Types of interventions 25
3.1.3 Types of outcome measures 25
3.1.4 Types of studies 26
3.2 Search methods for identification of studies 30
3.2.1 Search terms 30
3.2.2 Databases 31
3.2.3 Other sources 31
3.3 Screening of studies 31
3.3.1 Title/abstract screening 31
3.3.2 Full text screening 32
3.3.3 Screening process 32
3.4 Critical appraisal, data collection and evidence synthesis 35
3.4.1 Critical appraisal process 35
3.4.2 Critical appraisal tools 35
3.4.3 Data collection 38
3.4.4 Data synthesis 39
3.5 Summary of findings and draft recommendations 39
3.5.1 GRADE evidence profiles 39
3.5.2 Evidence to decisions 43
3.6 Consensus process 48

3.6.1 Consensus guiding principles and values 48
3.6.2 Consensus ground rules 50

4 Findings of the systematic review 51

4.1 Literature search results 51
4.1.1 Flow of studies 51
4.1.2 Studies awaiting classification or not included 51
4.1.3 Included studies 51
4.2 Prognostic factors (Question 1) 56
4.2.1 Methods 56
4.2.2 Summary of evidence 57
4.2.3 Results 63
4.3 Defined major haemorrhage protocol (Question 2) 75
4.3.1 Methods 75
4.3.2 Summary of evidence 76
4.3.3 Results 83
4.4 Dose, timing and ratio (algorithm) of RBCs to blood component therapy (Question 3) 101
4.4.1 Methods 101
4.4.2 Summary of evidence 102
4.4.3 Results 112
4.5 Volume of RBCs transfused (Question 4) 125
4.5.1 Methods 125
4.5.2 Summary of evidence 126
4.5.3 Results 131
4.6 Recombinant factor VIIa (Question 5) 136
4.6.1 Methods 136
4.6.2 Summary of evidence 137
4.6.3 Results 145
4.7 Blood components (Question 6) 171
4.7.1 Methods 171
4.7.2 Summary of evidence 172
4.7.3 Results 185
4.8 Antifibrinolytics (Question 7) 238
4.8.1 Methods 238
4.8.2 Summary of evidence 239
4.8.3 Results 247

4.9 Viscoelastic haemostatic assays (Question 8) 273
4.9.1 Methods 273
4.9.2 Summary of evidence 274
4.9.3 Results 285
4.10 Cell salvage (Question 9) 314
4.10.1 Methods 314
4.10.2 Summary of evidence 315
4.10.3 Results 320
5 References 336
Appendix A – Literature search results 351
Appendix B – Literature screening results 351
Appendix C – List of excluded studies 351
Appendix D – Critical appraisal 351
Appendix E – Data extraction forms 351

Report information

This evidence evaluation report has been developed by **HT**Analysts in conjunction with the National Blood Authority (NBA) and a Clinical/Consumer Reference Group (CRG). It describes the main body of evidence related to a systematic review of the evidence for the management of people with critical bleeding with regards to blood components and blood conservation strategies. Supplementary data (Appendices A to E) are provided in the Technical Reports (volume 1, volume 2 and volume 3).

History

The *2011 Patient Blood Management (PBM) Guidelines Module 1: Critical Bleeding/ Massive Transfusion* were developed by the NBA (in collaboration with a CRG) to improve patient outcomes; by ensuring that the focus of a patients' medical and surgical management was on improving and conserving the patient's own blood (1). Approval of the *2011 PBM Guidelines: Module 1* was granted by The National Health and Medical Research Council (NHMRC) in 2011 after undergoing public consultation, peer review and an independent AGREE II assessment.

To ensure the *2011 PBM Guidelines: Module 1* reflect the best available evidence, and remain current and relevant for the Australian context, **HT**Analysts were engaged in April 2018 to update the evidence-based recommendations and practice points made in the *2011 PBM Guidelines: Module 1* as informed by a systematic review of the evidence.

NHMRC approval has not been sought for this update, however, all associated materials have been developed in a robust and transparent manner (including public consultation and an independent AGREE II assessment) in accordance with relevant best practice standards (2-5).

Dates

The 2022 *PBM Guideline for people with Critical Bleeding* were approved by the NBA and CRG on DD MMM 2022.

The draft guidelines were made available for public consultation on DD MMM 2022, with all feedback and responses to comments recorded.

The evidence review informing the 2022 *PBM Guideline for people with Critical Bleeding* includes studies published up until 29 September 2021. The technical report (and associated appendices) outlining the best available evidence were presented to the NBA and CRG over several meetings held between December 2021 and August 2022.

The research protocol outlining the methodology to be used to systematically review the evidence to support an update of the *2011 PBM Guidelines: Module 1* received approval from the CRG and NBA on 03 July 2018.

Funding

The review was funded by the Commonwealth of Australia, as represented by the National Blood Authority.

Authors

[1] **HT**Analysts, Level 8, 46 Kippax Street, Surry Hills New South Wales 2010 Australia

The Research Protocol and the Evidence Evaluation and Technical Reports were written and developed by **HT**Analysts in conjunction with the NBA. Expert advice was provided by the CRG, particularly in relation to development of the research questions, eligibility criteria of identified studies, interpretation of the evidence in relation to clinical important effects and the development of recommendations.

The following named authors (and specific contributions) are outlined in the table below:

Name	Contribution
Dr Margaret Jorgensen	Project Lead and methodological oversight. Draft protocol, development of search strategy with contributions from other authors. Oversight of study selection/eligibility, data extraction and data synthesis Meeting attendance to facilitate GRADE summary of findings, evidence to decisions and development of recommendations.
Stephanie Allerdice	Senior Project Manager 2018-2019 Draft methods and development of literature search strategy. Selection of studies (screening), data extraction and critical appraisal. Data synthesis and meeting attendance to facilitate GRADE summary of findings.
Alison Miles	Senior Project Manager 2021-2022 Selection of studies (screening), data extraction and critical appraisal. Data synthesis and meeting attendance to facilitate GRADE summary of findings.
Jessica Shi	2021-2022 Selection of studies (screening), data extraction and critical appraisal. Data synthesis and meeting attendance to facilitate evidence to decisions and development of recommendations. Documentation of public consultation feedback.
Jack Hide	2021-2022 Preliminary data extraction and critical appraisal of selected studies. Record of meetings, documentation of public consultation feedback.

Acknowledgments

Dr Santwona Baidya, Wendy van Zuijlen, Adrian Peacock, and Kevin Phan are not listed as authors but contributed to the 2018-2019 evidence review (including conduct of the literature search, screening for eligible studies and preliminary data extraction and critical appraisal).

Declarations of interest

All named authors declare they have no financial, personal or professional interests that could be construed to have influenced the conduct or results of the systematic review. Funding, Secretariat and Project Management was provided by the National Blood Authority. The development of the final recommendations was not influenced by the views or interests of the funding body.

In line with NBA processes, CRG members completed a conflict of interests register before commencement of guideline development as outlined in the NBA conflicts of interest policy. Any additional conflicts of interest were declared at the start of each meetings and appropriately recorded. If a member declared a conflict in relation to a

specific intervention (with the exception of conducting research), the member did not participate in the discussion or decision-making for the intervention.

Funding, Secretariat and Project Management was provided by the National Blood Authority. The development of the final recommendations was not influenced by the views or interests of the funding body.

List of Tables

Table 3.1 Types of participants eligible for inclusion 24

Table 3.2 List of eligible interventions 25

Table 3.3 Characteristics of the ideal evidence base for each question 27

Table 3.4 AMSTAR-2: Domain classification 36

Table 3.5 Evidence to decision framework 44

Table 4.1 Overview of studies identified for each question 52

Table 4.2 Characteristics and quality of included systematic reviews 57

Table 4.3 Characteristics and quality of additional primary studies included in the review 62

Table 4.4 Results for physiologic, biochemical and metabolic (including temperature) parameters indicative of critical physiologic derangement: Patients with critical bleeding – Mortality 65

Table 4.5 Results for physiologic, biochemical and metabolic (including temperature) parameters indicative of critical physiologic derangement: Patients with critical bleeding – Transfusion volume 72

Table 4.6 Characteristics and quality of systematic reviews by clinical setting: defined MHPs versus no defined MHPs 76

Table 4.7 Overlap table primary studies included in the identified systematic reviews: defined MHPs versus no defined MHPs 78

Table 4.8 Characteristics and quality of observational and cohort studies by clinical setting: defined MHPs versus no defined MHPs 79

Table 4.9 Results for defined MHP versus no defined MHP: Patients *with* critical bleeding – Mortality 86

Table 4.10 Results for defined MHP versus no defined MHP: Patients *with* critical bleeding – Transfusion volume, red blood cells 90

Table 4.11 Results for defined MHP versus no defined MHP: Patients *with* critical bleeding – Transfusion volume, fresh frozen plasma 93

Table 4.12 Results for defined MHP versus no defined MHP: Patients *with* critical bleeding – Transfusion volume, platelets 96

Table 4.13 Results for defined MHP versus no defined MHP: Patients with critical bleeding – Wastage of blood components 99

Table 4.14 Results for defined MHP versus no defined MHP: Patients with critical bleeding – Time to delivery of blood components 100

Table 4.15 Characteristics and quality of systematic review evidence: ratio of RBCs to blood component therapy 103

Table 4.16 Overlap table of RCTs identified by included systematic reviews: RBC:FFP and RBC:PLT ratios 105

Table 4.17 Characteristics and quality of RCT evidence: ratio of RBCs to blood component therapy 106

Table 4.18 Overlap table of observational and cohort primary studies identified by included systematic reviews that meet the 1:1:1 ratio inclusion criterion: RBC:FFP and RBC:PLT ratios 107

Table 4.19 Overlap table of observational and cohort primary studies identified by included systematic reviews that do not meet the 1:1:1 ratio inclusion criterion: RBC:FFP and RBC:PLT ratios 108

Table 4.20 Characteristics and quality of observational and cohort evidence: RBC:FFP, RBC:PLT or RBC:CRYO ratio 109

Table 4.21 Results for high ratio of blood components versus low ratio of blood components: Patients *with* critical bleeding – Mortality 114

Table 4.22 Results for high ratio of blood components versus low ratio of blood components: Patients *with* critical bleeding – Morbidity, thromboembolic events 118

Table 4.23 Results for high ratio of blood components versus low ratio of blood components: Patients *with* critical bleeding – Morbidity, critical complications 119

Table 4.24 Results for high ratio of blood components versus low ratio of blood components: Patients *with* critical bleeding – Transfusion volumes, red blood cells 123

Table 4.25 Results for high ratio of blood components versus low ratio of blood components: Patients *with* critical bleeding – Transfusion volumes, other blood components 124

Table 4.26 Characteristics and quality of systematic review evidence: increased RBCs transfusion 126

Table 4.27 Overlap table showing included systematic reviews and identified cohort studies: increased RBCs transfusion 127

Table 4.28 Characteristics and quality of prospective cohort evidence: increased RBCs transfusion 128

Table 4.29 Characteristics and quality of retrospective cohort evidence: increased RBCs transfusion 130

Table 4.30 Results for increased volume of RBC transfused versus decreased volume of RBC transfused: Patients *at risk of* critical bleeding – Mortality 132

Table 4.31 Results for increased volume of RBC transfused versus decreased volume of RBC transfused: Patients *at risk of* critical bleeding – Morbidity 134

Table 4.32 Characteristics and quality of systematic review evidence: rFVIIa 138

Table 4.33 Overlap table of RCTs identified by included systematic reviews: rFVIIa 139

Table 4.34 Overlap table of nonrandomised cohort studies identified by included systematic reviews: rFVIIa 140
Table 4.35 Characteristics and quality of RCT evidence: rFVIIa 141
Table 4.36 Results for rFVIIa versus no rFVIIa: Patients *with* critical bleeding – Mortality 147
Table 4.37 Results for rFVIIa versus no rFVIIa: Patients *with* critical bleeding – Morbidity: thromboembolic events 152
Table 4.38 Results for rFVIIa versus no rFVIIa: Patients *with* critical bleeding – Morbidity: other adverse events 157
Table 4.39 Results for rFVIIa versus no rFVIIa: Patients *with* critical bleeding – Morbidity: other second-line interventions (obstetrics and maternity only) 162
Table 4.40 Results for rFVIIa versus no rFVIIa: Patients *with* critical bleeding – RBC transfusion volume 165
Table 4.41 Results for rFVIIa versus no rFVIIa: Patients *with* critical bleeding – transfusion volume, other blood components 169
Table 4.42 Characteristics and quality of systematic reviews by clinical setting: blood components 173
Table 4.43 Overlap table of RCTs identified by included systematic reviews: blood components 174
Table 4.44 Overlap table of cohort studies identified by included systematic reviews: blood components 175
Table 4.45 Characteristics and quality of RCTs by clinical setting: blood components 177
Table 4.46 Characteristics and quality of observational and cohort studies by clinical setting: the effect of blood component therapy on patient outcomes 181
Table 4.47 Results for FFP versus no FFP: Patients with critical bleeding – Mortality 187
Table 4.48 Results for FFP versus no FFP: Patients with critical bleeding – Morbidity: any adverse outcome 190
Table 4.49 Results for FFP versus no FFP: Patients with critical bleeding – Transfusion volumes 192
Table 4.50 Results for FFP versus no FFP: Patients with critical bleeding – Length of stay 194
Table 4.51 Results for CRYO versus no CRYO: Patients with critical bleeding – Mortality 196
Table 4.52 Results for CRYO versus no CRYO: Patients with critical bleeding – Morbidity 199
Table 4.53 Results for CRYO versus no CRYO: Patients with critical bleeding – RBC transfusion volume 201
Table 4.54 Results for CRYO versus no CRYO: Patients with critical bleeding – Transfusion volume, other blood components 202

Table 4.55 Results for CRYO versus no CRYO: Patients with critical bleeding – Length of stay 204
Table 4.56 Results for FC versus no FC: Patients with critical bleeding – Mortality 207
Table 4.57 Results for FC versus no FC: Patients with critical bleeding – Morbidity: critical complications 213
Table 4.58 Results for FC versus no FC: Patients with critical bleeding – Morbidity: ARDS 216
Table 4.59 Results for FC versus no FC: Patients with critical bleeding – RBC transfusion volume 219
Table 4.60 Results for FC versus no FC: Patients with critical bleeding – Transfusion volume, other blood components 223
Table 4.61 Results for FC versus no FC: Patients with critical bleeding – Hospital LOS .. 228
Table 4.62 Results of FC versus no FC: Patients with critical bleeding – ICU LOS 229
Table 4.63 Results for PCC versus no PCC: Patients with critical bleeding – Mortality, latest timepoint 232
Table 4.64 Results for PCC versus no PCC: Patients with critical bleeding – Morbidity: critical complications 234
Table 4.65 Results for PCC versus no PCC: Patients with critical bleeding – RBC transfusion volume 236
Table 4.66 Characteristics and quality of systematic review evidence: Antifibrinolytics versus no antifibrinolytics 240
Table 4.67 Overlap table of studies identified by included systematic reviews: Antifibrinolytics 242
Table 4.68 Characteristics and quality of RCT evidence: Antifibrinolytics versus no antifibrinolytics 243
Table 4.69 Characteristics and quality of cohort evidence: Antifibrinolytics versus no antifibrinolytics 244
Table 4.70 Results for TXA versus no TXA: Patients with critical bleeding – Mortality 250
Table 4.71 Results for TXA versus no TXA: Patients with critical bleeding – Morbidity 259
Table 4.72 Results for TXA versus no TXA: Patients with critical bleeding – Blood loss .. 269
Table 4.73 Results for TXA versus no TXA: Patients with critical bleeding – Transfusion volume 271
Table 4.74 Characteristics and quality of systematic review evidence: TEG or ROTEM versus usual care 275
Table 4.75 Overlap table of RCTs identified by included systematic reviews: TEG or ROTEM versus usual care 277
Table 4.76 Overlap table of nonrandomised cohort studies identified by included systematic reviews: TEG or ROTEM versus usual care 278

Table 4.77 Characteristics and quality of RCT evidence: TEG or ROTEM versus usual care 280
Table 4.78 Characteristics and quality of Observational and cohort studies evidence: TEG or ROTEM versus usual care 282
Table 4.79 Results for TEG or ROTEM to guide BCT versus no TEG or ROTEM to guide BCT: Patients *with* critical bleeding – Mortality 288
Table 4.80 Results for TEG or ROTEM to guide BCT versus no TEG or ROTEM to guide BCT: Patients *with* critical bleeding – Morbidity (thromboembolic events) 294
Table 4.81 Results for TEG or ROTEM to guide BCT versus no TEG or ROTEM to guide BCT: Patients *with* critical bleeding – Major morbidities 296
Table 4.82 Results for TEG or ROTEM to guide BCT versus no TEG or ROTEM to guide BCT: Patients *with* critical bleeding – RBC transfusion volume 301
Table 4.83 Results for TEG or ROTEM to guide BCT versus no TEG or ROTEM to guide BCT: Patients *with* critical bleeding – FFP transfusion volume 306
Table 4.84 Results for TEG or ROTEM to guide BCT versus no TEG or ROTEM to guide BCT: Patients *with* critical bleeding – PLT, CRYO, PCC transfusion volume, Units 311
Table 4.85 Characteristics and quality of SR and MA evidence: cell salvage versus no cell salvage 316
Table 4.86 Overlap table showing systematic reviews and included primary studies: cell salvage versus no cell salvage 316
Table 4.87 Characteristics and quality of RCT evidence: cell salvage versus no cell salvage 317
Table 4.88 Characteristics and quality of observation and cohort studies: cell salvage versus no cell salvage 318
Table 4.89 Results for cell salvage versus no cell salvage: Patients with critical bleeding – Mortality 322
Table 4.90 Results for cell salvage versus no cell salvage: Patients with critical bleeding – Morbidity: post-operative complications 326
Table 4.91 Results for cell salvage versus no cell salvage: Patients with critical bleeding – Transfusion volume 332
Table 4.92 Results for cell salvage versus no cell salvage: Patients with critical bleeding – Cost 335

List of Figures

Figure 3.1 Schematic representation of literature review hierarchy 33

Figure 3.2 Consensus Process Flow chart 49

Figure 4.1 Summary of the process used to identify and select studies for the assessment of Question 1 (prognostic factors) 53

Figure 4.2 Summary of the process used to identify and select studies for the assessment of Question 2 (major haemorrhage protocols), Question 3 (ratios of blood components), Question 4 (RBC transfusion volume), and Question 6 (individual blood components) 54

Figure 4.3 Summary of the process used to identify and select studies for the assessment of Question 5 (rFVIIa), Question 7 (TXA), Question 8 (viscoelastic haemostatic assays) and Question 9 (cell salvage) 55

Figure 4.4 PPO criteria: Question 1 – physiologic, biochemical and metabolic parameters 56

Figure 4.5 PICO criteria: Question 2 – defined MHPs 75

Figure 4.6 Forest plot of comparison: MHPs vs no MHPs, outcome: Mortality, 24 hours .84

Figure 4.7 Forest plot of comparison: MHPs vs no MHPs, outcome: Mortality, latest timepoint 85

Figure 4.8 Forest plot of comparison: MHPs vs no MHPs, outcome: Transfusion volume, red blood cells 89

Figure 4.9 Forest plot of comparison: MHPs vs no MHPs, outcome: Transfusion volume, FFP 92

Figure 4.10 Forest plot of comparison: MHPs vs no MHPs, outcome: Transfusion volume, platelets 95

Figure 4.11 PICO criteria: Question 3 – dose, timing and ratio of different ratios of red blood cells 101

Figure 4.12 Forest plot of comparison: high ratio vs low ratio blood components, outcome: Mortality, latest timepoint 113

Figure 4.13 Forest plot of comparison: high ratio vs low ratio blood components, outcome: Morbidity, thromboembolic events 116

Figure 4.14 Forest plot of comparison: high ratio vs low ratio blood components, outcome: Morbidity, multiple organ failure 117

Figure 4.15 Forest plot of comparison: high ratio vs low ratio blood components, outcome: Transfusion volume, red blood cells 121

Figure 4.16 Forest plot of comparison: high ratio vs low ratio blood components, outcome: Transfusion volume, FFP 122

Figure 4.17 PPO criteria: Question 4 – effect of transfusion of increased volumes of RBCs 125

Figure 4.18 PICO criteria: Question 5 – recombinant factor VIIa 136
Figure 4.19 Forest plot of comparison: rFVIIa vs placebo, outcome: Mortality, latest timepoint 146
Figure 4.20 Forest plot of comparison: rFVIIa vs placebo, outcome: total thromboembolic events 151
Figure 4.21 Forest plot of comparison: rFVIIa vs placebo, outcome: Other adverse events (trauma setting) 156
Figure 4.22 Forest plot of comparison: rFVIIa vs placebo, outcome: Morbidity – need for second-line intervention (obstetrics and maternity) 160
Figure 4.23 Forest plot of comparison: rFVIIa vs placebo, outcome: Morbidity - other second-line interventions (obstetrics and maternity) 161
Figure 4.24 Forest plot of comparison: rFVIIa vs placebo, outcome: RBC transfusion volume, Units 164
Figure 4.25 Forest plot of comparison: rFVIIa vs placebo, outcome: transfusion volume (other blood components), Units 168
Figure 4.26 PICO criteria: Question 6 – effect of blood component therapy on patient outcomes 171
Figure 4.27 Forest plot of comparison: FFP vs no FFP (or varying administration of), outcome: Mortality, all-cause (at 24 hours) 186
Figure 4.28 Forest plot of comparison: FFP vs no FFP (or varying administration of), outcome: Mortality, all-cause (latest reported timepoint) 186
Figure 4.29 Forest plot of comparison: FFP vs no FFP (or varying administration of), outcome: Morbidity 189
Figure 4.30 Forest plot of comparison: CRYO vs no CRYO (or varying administration of...), outcome: Mortality, latest timepoint. 195
Figure 4.31 Forest plot of comparison: CRYO vs no CRYO (or varying administration of...), outcome: Morbidity, thromboembolic events. 198
Figure 4.32 Forest plot of comparison: CRYO vs no CRYO (or varying administration of...), outcome: Morbidity, other. 198
Figure 4.33 Forest plot of comparison: FC vs no FC (or varying concentration of), outcome: Mortality, all-cause (latest timepoint) 206
Figure 4.34 Forest plot of comparison: FC vs no FC (or varying administration of), outcome: Morbidity, thromboembolic events 211
Figure 4.35 Forest plot of comparison: FC vs no FC (or varying administration of), outcome: Morbidity, multiple organ failure 212
Figure 4.36 Forest plot of comparison: FC vs no FC (or varying administration of), outcome: RBC transfusion volume, units 218
Figure 4.37 Forest plot of comparison: FC vs no FC (or varying administration of), outcome: Transfusion volume, other blood components, FFP (trauma) 222

Figure 4.38 Forest plot of comparison: FC vs no FC (or varying administration of), outcome: Transfusion volume, other blood components, FFP (surgical) 222

Figure 4.39 Forest plot of comparison: FC vs no FC (or varying administration of), outcome: Length of stay, hospital (days) 227

Figure 4.40 Forest plot of comparison: FC vs no FC (or varying administration of), outcome: Length of stay, ICU (days) 227

Figure 4.41 Forest plot of comparison: PCC vs no PCC (or varying administration of), outcome: Mortality (trauma setting) 231

Figure 4.42 Forest plot of comparison: PCC vs no PCC (or varying administration of), outcome: Morbidity, thromboembolic events (trauma setting) 233

Figure 4.43 Forest plot of comparison: PCC vs no PCC (or varying administration of), outcome: RBC transfusion volume, Units (trauma setting) 235

Figure 4.44 PICO criteria: Question 7 – antifibrinolytics 238

Figure 4.45 Forest plot of comparison: TXA vs no TXA, outcome: Mortality, latest timepoint 248

Figure 4.46 Forest plot of comparison: TXA vs no TXA, outcome: Mortality, latest timepoint (trauma only) 249

Figure 4.47 Forest plot of comparison: TXA vs no TXA, outcome: Morbidity, vascular events (any) 257

Figure 4.48 Forest plot of comparison: TXA vs no TXA, outcome: Morbidity, other 258

Figure 4.49 Forest plot of comparison: TXA vs no TXA, outcome: RBC transfusion volume 270

Figure 4.50 PICO criteria: Question 8 – viscoelastic haemostatic assays 273

Figure 4.51 Forest plot of comparison: TEG or ROTEM vs MHP or standard laboratory tests, outcome: Mortality, latest timepoint 286

Figure 4.52 Forest plot of comparison: TEG or ROTEM vs MHP or standard laboratory tests, outcome: Mortality, by setting 287

Figure 4.53 Forest plot of comparison: TEG or ROTEM vs MHP or standard laboratory tests, outcome: thromboembolic events 293

Figure 4.54 Forest plot of comparison: TEG or ROTEM vs MHP or standard laboratory tests, outcome: morbidity (multiorgan failure, need for hysterectomy) 293

Figure 4.55 Forest plot of comparison: TEG or ROTEM vs MHP or standard laboratory tests, outcome: RBC transfusion volume (units), by study design. 299

Figure 4.56 Forest plot of comparison: TEG or ROTEM vs MHP or standard laboratory tests, outcome: RBC transfusion volume (units), by setting. 300

Figure 4.57 Forest plot of comparison: TEG or ROTEM vs MHP or standard laboratory tests, outcome: FFP transfusion volume (units), by study design. 304

Figure 4.58 Forest plot of comparison: TEG or ROTEM vs MHP or standard laboratory tests, outcome: FFP transfusion volume (units), by setting. 305

Figure 4.59 Forest plot of comparison: TEG or ROTEM vs MHP or standard laboratory tests, outcome: PLT transfusion volume (units), by study design. 309

Figure 4.60 Forest plot of comparison: TEG or ROTEM vs MHP or standard laboratory tests, outcome: PLT transfusion volume (units), by setting. 310

Figure 4.61 PICO criteria: Question 9 – cell salvage 314

Figure 4.62 Forest plot of comparison: cell salvage vs no cell salvage, outcome: Mortality, any timepoint up to 30 days 321

Figure 4.63 Forest plot of comparison: cell salvage vs no cell salvage, outcome: Morbidity - post-operative complications 324

Figure 4.64 Forest plot of comparison: cell salvage vs no cell salvage, outcome: Morbidity - post-operative complications (urgent AAA repair) 325

Figure 4.65 Forest plot of comparison: cell salvage vs no cell salvage, outcome: Transfusion volume (RBCs) 329

Figure 4.66 Forest plot of comparison: cell salvage vs no cell salvage, outcome: Transfusion volume (FFP) 330

Figure 4.67 Forest plot of comparison: cell salvage vs no cell salvage, outcome: Transfusion volume (PLTs) 331

Abbreviations

AAA	Abdominal aortic aneurysm
AGREE	Appraisal of Guidelines for Research and Evaluation
ALI	Acute lung injury
AMSTAR	A MeaSurement Tool to Assess systematic Reviews
AOD	Aortoiliac occlusive disease
ARDS	Acute respiratory distress syndrome
APTT	activated partial thromboplastin time
AUC	Area under the curve
C.A.T.S	Continuous AutoTransfusion System
CRG	Clinical/Consumer Reference Group
CRYO	Cryoprecipitate
BCT	Cloodd component therapy
DVT	Deep vein thrombosis
ED	Emergency department
EtD	Evidence to Decision
FC	Fibrinogen concentrate
FFP	Fresh frozen plasma
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HSCT	Haematopoietic stem cell transplant
HTA	Health technology assessment
ICU	Intensive care unit
INR	International normalised ratio
IQR	Interquartile range
LOS	Length of stay
MD	Mean difference
MHP	Major haemorrhage protocol
MODS	Multiorgan dysfunction syndrome
MOF	Multiple organ failure
MTP	Massive transfusion protocol
NBA	National Blood Authority
NHMRC	National Health and Medical Research Council
NRSI	Nonrandomised study of intervention
OR	Odds ratio
PBM	Patient blood management
PCC	Prothrombin complex concentrate
pCoh	Prospective cohort study
PE	Pulmonary embolus
PICO	Population, Intervention, Comparator, Outcome

PPH	Primary postpartum haemorrhage
PPO	Population, Prognostic factor, Comparator, Outcomes
PT	Prothrombin time
PLTs	Platelets
PT	Prothrombin time
RBCs	Red blood cells
rCoh	Retrospective cohort study
RCT	Randomised controlled trial
ROC	Receiver operating characteristic curve
rFVIIa	Recombinant activated factor VII
RR	Risk ratio/Relative risk
ROTEM	Rotational thromboelastometry
SBP	Systolic blood pressure
SC	Single centre
SEM	Standard error of the mean
SoC	Standard of care
SMD	Standardised mean difference
SR	Systematic review
RoB	Risk of bias
TBI	Traumatic brain injury
TEG	Thromboelastography
TXA	Tranexamic acid
UGIB	Upper gastrointestinal bleeding
VHAs	viscoelastic haemostatic assays

1 Background

The National Blood Authority (NBA), in collaboration with a Clinical/Consumer Reference Group (CRG), is updating the *2011 Patient Blood Management (PBM) Guidelines Module 1: Critical Bleeding/ Massive Transfusion (Module 1)* to ensure it reflects the best available evidence, is current and relevant for the Australian context. Module 1 is part of a series of PBM Guidelines that aims to improve patient outcomes by ensuring that the focus of the patient's medical and surgical management is on improving and conserving the patient's own blood (1).

Based on the best available evidence and knowledge at the time, the *2011 PBM Guidelines: Module 1* made two recommendations:

1. Institutions should develop a standardised massive transfusion protocol (MTP) that includes the dose, timing, and ratio of blood component therapy for use in trauma patients with, or at risk of, critical bleeding requiring massive transfusion.
2. The routine use of rFVIIa in trauma patients with critical bleeding requiring massive transfusion is not recommended, because of its lack of effect of mortality and variable effect on morbidity.

However, no recommendations could be made on:

- the dose, timing, ratio of blood components or use of individual blood components
- the effect of variation of physiologic, biochemical and metabolic parameters on morbidity, mortality and transfusion rate
- the effect of rFVIIa on morbidity, mortality and transfusion rate in patients with critical bleeding.

A review of Module 1 commenced in late 2015 with the establishment of a multidisciplinary CRG. **HT**ANALYSTS were contracted in 2018 to conduct the systematic review of the scientific literature to update or inform new sections of the *2011 PBM Guidelines: Module 1*.

A Research Protocol was then developed to describe the methodology intended to be used to: (i) source the clinical evidence by performing a systematic literature search of the literature, (ii) selecting the best available evidence; (iii) critically appraising and presenting the evidence, and (iv) determining the quality of the evidence base for each question, using a structured assessment of the body of evidence in accordance GRADE[1] methodology.

[1] Grading of Recommendations Assessment, Development and Evaluation. Available at http://gdt.guidelinedevelopment.org/app/handbook/handbook.html

1.1 Description of condition and setting

Critical bleeding is a term used to describe a range of clinical scenarios where bleeding may result in significant patient morbidity or mortality (1). Critical bleeding results in decreased circulating volume, loss of oxygen-carrying capacity, and coagulopathy (impaired clot formation).

Broadly, critical bleeding falls into one of two categories (which may overlap):

1. major haemorrhage that is life-threatening and is likely to result in the need for massive transfusion, or
2. haemorrhage of a smaller volume in a critical area or organ (e.g. intracranial, intraspinal or intraocular), resulting in patient morbidity or mortality.

For the purpose of this document, critical bleeding refers only to the first category.

1.2 Description of intervention and how it might work

Different transfusion interventions have been used to restore the circulating blood volume and achieve haemostasis[2] – two key elements of critical bleeding management (1). These interventions include massive transfusion with different combinations or ratios of blood components – such as red blood cells (RBCs), fresh frozen plasma (FFP), platelets, cryoprecipitate, fibrinogen concentrate, prothrombin complex concentrate (PCC), whole blood, lyophilised platelets, lyophilised plasma or liquid plasma. Blood component therapy involves the separation of whole blood into specific cellular and plasma components (RBC, FFP, etc.), which are then then transfused separately according to patients' perceived need.

Major haemorrhage is defined based on the volume of blood loss or on the volume transfused. The most widely used definition proposes the loss or transfusion of one blood volume (about 7% of body weight in adults) over 24 hours, or approximately 10 units of RBCs. Alternatively, 'real-time' definitions include replacement of half a blood volume within four hours, or blood loss of more than 150 mL per minute (1).

Traditionally, it has been assumed that massive transfusion benefits all patients with critical bleeding. While in certain circumstances such therapy can save lives, a benefit of massive transfusion has not been demonstrable in many clinical scenarios (1). In addition, massive transfusion of blood components is not without risk. Blood transfusion in trauma, surgery and critical care is an independent predictor of multiple organ failure, systemic inflammatory response syndrome, increased infection, and increased mortality (10). It is increasingly clear that the decision to transfuse must be made with great care, and the evidence for the risks and benefits need to be regularly reviewed.

Controversy over the benefits of interventions that aim to improve haemostasis (e.g. FFP, cryoprecipitate, fibrinogen concentrate and PCC) in both surgical and nonsurgical settings also exist. The use of these interventions may be associated with infection,

[2] a function of balance between procoagulant systems (platelets, coagulation cascade) and anticoagulant systems (APC/protein S, fibrinolysis, serpins).

allergic reactions, haemolysis, transfusion-related circulatory overload and transfusion-related acute lung injury. Monitoring dynamic changes in haemostasis in patients with critical bleeding may help guide transfusion of blood component therapy. Whole blood coagulation analysers are viscoelastic haemostatic assays that may help clinicians assess the cause of bleeding and improve the care of patients with critical bleeding.

Other interventions that may play a role in the management of critical bleeding are tranexamic acid (TXA), recombinant activated factor VII (rFVIIa), and cell salvage. TXA is a synthetic derivative of the amino acid lysine, which competitively inhibits the activation of plasminogen to plasmin, thus reducing fibrin degradation. rFVIIa is a synthetic form of blood factor VIIa, which activates the formation of prothrombinase complex. The synthetic form has a local mode of action, acting directly on activated platelets at the injury site, which bypasses conventional steps in the coagulation cascade and leads to the generation of a fully stabilised fibrin clot at the wound site.

Cell salvage is the process that allows blood lost from surgical procedures to be collected, filtered, and washed for re-transfusion to the patient to minimise or prevent allogeneic red cell transfusion.

2 Rationale and objectives

The rationale for conducting this review was to update and enhance the evidence and guidance used to inform the *2011 PBM Guidelines: Module 1* (i.e. to identify whether any new high-quality studies had been published and to address the evidence gaps noted). This was to ensure recommendations relating to the appropriate use of blood components and strategies that aim to minimise blood loss in patients who are critically bleeding remain relevant and up-to-date.

In brief, the objectives of the review were to systematically examine the evidence relating to optimisation of blood volume and red blood cell mass, minimisation of blood loss, use of viscoelastic haemostatic assays to assess coagulation function, antifibrinolytics or rFVIIa in patients who are critically bleeding.

The specific questions to be investigated were reviewed and/or developed by the CRG at meetings held in September 2016 and June 2018 and are outline in Box 1 below.

Box 1 Research questions for the update of the 2011 PBM Guidelines: Critical Bleeding

Q1 – In patients with critical bleeding, which physiologic, biochemical and metabolic (including temperature) parameters should be measured early and frequently, and what values of these parameters are indicative of critical physiologic derangement?

Q2 – In patients with critical bleeding, what is the effectiveness of major haemorrhage protocols.

Q3 – In patients with critical bleeding, what is the optimal dose, timing and ratio (algorithm) to RBCs, of blood component therapy to reduce morbidity, mortality and transfusion?

Q4 – In patients at risk of critical bleeding, is the transfusion of increased volumes of RBCs associated with an increased risk of mortality or adverse effects?

Q5 – In patients with critical bleeding, what is the effect of rFVIIa treatment on morbidity, mortality and transfusion rate?

Q6 – In patients with critical bleeding, what is the effect of FFP, cryoprecipitate, fibrinogen concentrate, PCC and/or platelet transfusion on RBC transfusion and patient outcomes?

Q7 – In patients with critical bleeding, what is the effect of antifibrinolytics on blood loss, RBC transfusion and patient outcomes?

Q8 – In patient with critical bleeding, does the use of viscoelastic haemostatic assays change patient outcomes?

Q9 – In patients with critical bleeding, what is the effect of cell salvage on patient outcomes?

3 Methods

Methods reported here were based on those described in the Cochrane Handbook for Systematic Reviews of Interventions (11, 12) and relevant sections in the JBI Manual for Evidence Synthesis (13, 14). Covidence, a web-based platform for producing systematic reviews, was used for screening citations and recording decisions made. RevMan 5.4 was used for the main analyses and GRADEPro was used to derive an overall GRADE relating to the certainty of evidence (high, moderate, low, or very low) for each outcome (guided by the GRADE handbook). MAGICApp was then used to record evidence to decisions regarding the development of recommendations.

To identify the evidence for the nine clinical questions detailed in Box 1, a systematic search of published medical literature was conducted. All potentially relevant studies were identified after applying prespecified inclusion and exclusion criteria as outlined in the research protocol. For eligible studies, the risk of bias was assessed, appropriate data was extracted into data extraction tables, and the results summarised into appropriate categories according to each question. Details on the methods and approach used to conduct the evidence evaluation are provided below.

3.1 Criteria for selecting studies for this review

3.1.1 Types of participants

The types of participants specific to each question are outlined in Table 3.1.

In all questions, the specified population was *people who are critically bleeding*, defined as: *people who have decreased circulating volume, loss of oxygen-carrying capacity, and coagulopathy due to major haemorrhage that is life-threatening and is likely to result in the need for massive transfusion*[3].

In question 3, the specific population of interest was people *who received* a massive transfusion.

In question 4, the population included people who were *at risk of* critical bleeding. The broader definition was included to account for patients with penetration injuries who *may* not develop critical bleeding, but if over-transfused before haemorrhage control may go on to do so.

In question 5, the focus was *people who fail to reach adequate haemostasis* and did not include patients with hereditary bleeding disorders such as haemophilia[4] or those after cardiopulmonary bypass.

In question 9, the focus was on *people in the emergency setting*, and did not include patients in the elective setting.

[3] Because the definition of massive transfusion varies across centres, this was to be defined by the literature.

[4] An X-linked congenital bleeding disorder caused by a deficiency of coagulation factor VIII (FVIII) (in haemophilia A) or factor IX (FIX) (in haemophilia B). The deficiency is the result of mutations of the respective clotting factor genes. See https://www.blood.gov.au/haemophilia-guidelines

Table 3.1 Types of participants eligible for inclusion

Question	Types of participants
Q1, Q2 and Q6	People with critical bleeding
Q3	People with critical bleeding *Focus: patients who received a massive transfusion*
Q4	People *at risk* of critical bleeding
Q5	People with critical bleeding, *Focus: patients who fail to achieve adequate haemostasis despite surgical management and appropriate blood component therapy* [a]
Q7	People with critical bleeding *Subgroup: patients who have received a massive transfusion*
Q8	People with critical bleeding. *Subgroups: trauma, obstetrics, perioperative [surgical bleeding, cardiothoracic, liver transplantation], other settings*
Q9	People with critical bleeding *Focus: patients* in the emergency setting (not elective)

a. Adequate haemostasis is a function of balance between procoagulant systems (platelets, coagulation cascade) and anticoagulant systems (APC/protein S, fibrinolysis, serpins). If haemostasis is out of balance due to a defect in one of these systems, then either thrombosis (too much clotting) or bleeding (not enough clotting) may be the result (15).

Settings: Studies were stratified according to the following patient settings:

- *Trauma* (meaning physical trauma involving a serious injury to the body).
  The two main types of physical trauma were: (i) blunt force trauma—when an object or force strikes the body, often causing concussions, deep cuts, or broken bones, and (ii) penetrating trauma—when an object pierces the skin or body, usually creating an open wound.[5]
- *Surgical* (or perioperative – meaning around the time of surgery).
  This usually lasts from the time the patient goes into the hospital or doctor's office for surgery until the time the patient goes home[6]. Here, studies were usually in (but were not limited) cardiothoracic or major abdominal surgery, with patients often considered life-threatening, emergency[7], or urgent[8].
- *Obstetrics & maternity*: referring to medical care of women during pregnancy and childbirth and in the diagnosis and treatment of diseases of the female reproductive organs[9].
- *Paediatrics*: referring to medical care of infants (1–23 months of age), children (2–12 years of age), and adolescent (13–18 years of age).

Restrictions: There were no limits to age, race or nationality.

Geographical restrictions: There were no geographical restrictions.

[5] https://www.nigms.nih.gov/education/pages/Factsheet_Trauma.aspx
[6] https://www.cancer.gov/publications/dictionaries/cancer-terms/def/perioperative
[7] Patient require immediate attention
[8] Patient requires urgent attention but is not a life-threatening situation
[9] https://www.cancer.gov/publications/dictionaries/cancer-terms/def/obstetrics-and-gynecology

3.1.2 Types of interventions

Question 1 and Q4 were prognostic questions:

For question 1, studies examining the following parameters as predictors of mortality were eligible for inclusion: temperature, acid-base status, ionised calcium, haemoglobin, platelet count, PT/INR, APTT or fibrinogen level.

For question 4, studies examining the volume of RBCs transfused as a predictor for mortality or adverse effects were eligible for inclusion.

Questions 2, 3, 5, 6, 7, 8 and 9 were interventional questions, with eligible studies being those that evaluated the effects of the interventions outlined in Table 3.2. Restrictions on the product type, mode of administration, number of doses or dosage are noted in the table.

Table 3.2 List of eligible interventions

Question	Intervention
Q2	A defined major haemorrhage protocol
Q3	MHP, RBC:FFP ratio, RBC:PLT ratio, RBC:CRYO ratio
Q5	rFVIIa (as treatment)
Q6	FFP, CRYO, PLTs, fibrinogen concentrate, PCC [a]
Q7	Antifibrinolytics (TXA or aprotinin)[b]
Q8	Use of viscoelastic haemostatic assays to guide transfusion of blood component therapy [c]
Q9	Cell salvage

CRYO, cryoprecipitate; FFP, fresh frozen plasma; MHP, major haemorrhage protocol; PCC, prothrombin complex concentrate; PLT, platelets; RBC, red blood cell; rFVIIa, recombinant activated factor seven; ROTEM, thromboelastometry; TEG, thromboelastography; TXA, tranexamic acid

a. Three-factor and four-factor preparations were eligible for inclusion; noting the three-factor preparation is used in Australia/ New Zealand.

b. Limited to IV only (not oral).

c. Limited to TEG or ROTEM (not Sonoclot).

3.1.3 Types of outcome measures

The critical outcome measure to inform decisions on benefits was all-cause mortality reported at 30-days or at the latest measured timepoint. Other measures related to mortality (e.g. death due to bleeding) were also recorded.

The critical outcome measures to inform decisions on harms were related to morbidity. Specifically, any prespecified adverse event relevant to the included population and typically associated with the intervention, such as:

- thromboembolic events[10] (TEs),
- acute respiratory distress syndrome (ARDS),
- time on mechanical ventilator,
- transfusion-related acute lung injury (TRALI),

[10] Inclusive of myocardial infarction, pulmonary embolism and stroke

- transfusion-associated circulatory overload, and
- multiorgan system failure.

Important or critical outcome measures related to resource use included:

- volume of blood component or blood product transfused (RBC, FFP, PLT, CRYO, fibrinogen concentrate, PCC),
- wastage of blood components,
- time to delivery of blood components, and
- length of hospital or ICU stay.

3.1.4 Types of studies

Eligible studies were those designed to measure a prognostic (Q1 and Q4) or intervention effect (Q2, Q3, Q5, Q6, Q7, Q8, Q9) (16). A summary of the types of studies eligible for each question is provided in Table 3.3.

For prognostic questions, studies with the following design labels were eligible for inclusion[11]:

- A systematic review of prospective cohort studies (Level I)
- A prospective cohort study (Level II)
- 'All or none' (Level III-1)
- Analysis of prognostic factors among persons in a single arm of an RCT (Level III-2)
- A retrospective cohort study (Level III-3)

For interventional question, studies with the following design labels were eligible for inclusion[11]:

- A systematic review of RCTs (Level I)
- An RCT (Level II)
- A pseudo (or quasi) RCT (Level III-1)
- A comparative study with concurrent controls – including non-randomised, experimental trials, cohort studies, case-control studies and interrupted time series with a control group (Level III-2)
- A comparative study without concurrent controls – including historical control studies, two or more single arm studies, interrupted time series without a parallel control group (Level III-3).

Level IV evidence[12] was not eligible for any research question, irrespective of whether insufficient higher-level evidence was found to address all critical and important outcomes for that question. This is because results from these studies were likely to lead to misinformed judgements about the effect estimate.

[11] https://www.nhmrc.gov.au/_files_nhmrc/file/guidelines/developers/nhmrc_levels_grades_evidence_120423.pdf

[12] For prognostic questions Level IV = i.e. case series; for interventional questions Level IV = single arm studies with either post-test, or pre-test and post-test outcomes

Table 3.3 Characteristics of the ideal evidence base for each question

Question	What type of question is this?	What type of evidence is appropriate?	What size of study is acceptable?	How should the impact of time be considered?	What publication time frame is appropriate?
1	Prognostic	Narrative or systematic review A prospective cohort study Analysis of prognostic factors among persons in a single arm of an RCT A retrospective cohort study Cohort studies of persons with different degrees of bleeding	Any. No restrictions to be applied. *Preference to be given to observational studies with at least 500 subjects*	Reported as per included studies No restrictions to be applied	January 2009 to current (previous search conducted in June 2009)
2	Interventional	Comparative study with concurrent or historical controls: RCTs Quasi- or pseudo-RCT Cohort study Case-control study Interrupted time series (with or without parallel control group) *Include all studies that compare outcomes from the one institution before and after the implementation of a major haemorrhage protocol*	Any. Small studies (N≥20 subjects) are acceptable. *If observational studies are included, preference is to be given to studies with at least 500 subjects*	Reported as per included studies *Sensible timeframe for outcomes related to blood component use is 24 h and 48 h; and out to the latest reported measure of mortality*	From January 2013 to current (search span for the SR by Mitra 2013 was January 1990 – June 2013)
3	Interventional	SR of RCTs Individual RCTs *If little is found, then SR of observational studies can be assessed.*	Any. No restrictions to be applied	Reported as per included studies No restrictions to be applied	From June 2015 to current (search span for SR by Monash was May 2009.[14] to December 2015)

[14] last date of search for current PBM guideline Module 1.

Question	What type of question is this?	What type of evidence is appropriate?	What size of study is acceptable?	How should the impact of time be considered?	What publication time frame is appropriate?
		Individual observational studies will be excluded.[13]			
4	Prognostic	A meta-analysis of interventional and/or observational studies A prospective cohort study Analysis of RBC transfusion volume among persons in a single arm of an RCT A retrospective cohort study Case series, or cohort study of persons with different RBC transfusion volumes *Preference to be given to SRs and meta-analyses published by others (i.e. Patel, 2014).* *Only individual studies published since the Patel 2014 search date to be included.*	Any. No restrictions to be applied. *If individual observational studies are to be included, preference will be given to studies with at least 500 subjects and/or studies that undertook a multivariate analysis and present adjusted finding.*	Reported as per included studies No restrictions to be applied	From January 2012 to current (search span for SR by Patel, 2014 was 1947 – 2012)
5	Interventional	SR of RCTs (with or without meta-analysis) Individual RCT *Preference to be given to published SRs and meta-analyses (in broad populations and in specific subpopulations). Inclusion of individual studies only as required.*	Any. No restrictions to be applied. *For the interpretation of harms, preference will be given to larger studies.*	Reported as per included studies No restrictions to be applied	From January 2009 to current (Previous NBA search span was 1990 – June 2009; also provides overlap with relevant Cochrane review (Simpson 2012), and other SRs published in 2011) Note: rFVIIa has been available since the early 2000s

[13] CRG noted that evaluating all the available observational studies would not add significantly to the RCT data available however, evidence to support the use of ratios is likely to come from observational studies and that this may be best included by way of the most recent fulsome SR of observational studies (Johannson 2012).

Question	What type of question is this?	What type of evidence is appropriate?	What size of study is acceptable?	How should the impact of time be considered?	What publication time frame is appropriate?
		Non-RCTs and observational studies (with concurrent or noncurrent controls) will be excluded.			
6	Interventional	Individual RCTs Prospective observational studies Retrospective observational studies and interrupted time series will be excluded.	Any size RCT. Observational studies with at least 500 participants in total (this is the same restriction applied in the previous SR for this question)	Reported as per included studies Latest reported mortality	For PCC: from 1990 to current For all other interventions: from 2009 to current (Previous NBA search span was 1990 – June 2009, but it did not include PCC)
7	Interventional	SR of RCTs RCTs Observational studies *Regarding observational studies, preference to be given to prospective studies.*	Any size RCT. Observational studies with at least 500 participants	Reported as per included studies Latest reported mortality	From 2000 to current (Cochrane Targeted Update conducted for the NBA in August 2015 relied on a search conducted in January 2015)
8	Interventional	SR of RCTs RCTs Comparative observational studies	Any. No restrictions to be applied. *Limited results will be available on this topic.* *Consider exclusions after the search.*	Reported as per included studies Latest reported mortality	From 2000 to current Relevant Cochrane Review (Wikkelsø, 2016) search date January 2016
9	Interventional	SR of RCTs RCTs Cohort studies (prospective or retrospective) Interrupted time series	Any. No restrictions to be applied. *For observational studies preference will be given to larger studies*	Reported as per included studies Latest reported mortality	From 1990 to current (New question for Module 1)

PCC, prothrombin complex concentrate; RCT, randomised controlled trial; SR, systematic review

3.2 Search methods for identification of studies

3.2.1 Search terms

The search strategy was developed in Ovid (for Embase and MEDLINE) based on key elements of the research questions (i.e. PICO/PPO criteria). The search strategy was then adapted to suit the Cochrane Library (database of systematic reviews, other reviews, clinical trials, technology assessments, economic evaluations) and PubMed (limited to in-process citations and citations not indexed in MEDLINE).

Search terms and results for each question are provided in **Appendix A** (see technical report, volume 1).

In developing the search strategy, we appraised and adapted the search strategies provided in the technical report, other health technology assessment reports (including Module 5 and Module 6 of the PBM Guidelines) and those suggested in the scoping report; with terms or concepts proven not suitable removed and other terms added. The overall approach was based on the search methods described in the Technical Report of the *2011 PBM Guidelines*: *Module 1* (17).

The searches were not limited by outcome, but rather by population, intervention (or prognostic factor), and then study type (applied using the stepped approach outlined above). Methodological filters for identifying different levels of evidence (Level I, Level II, and Level III) developed previously for the *PBM Guidelines* were applied (these filters are based on those developed by NHMRC.[15] and SIGN.[16]) with exclusions for publication types added. The search syntax from embase.com was converted to the Ovid platform.

To facilitate the search and screening of studies, and to minimise duplication of effort, the literature searches were grouped and run under three categories:

- Question 1 (prognostic) [screened independently]
- Questions 2, 3, 4, & 6 (blood components or blood products) [screened simultaneously]
- Questions 5, 7, 8, & 9 (blood conservation strategies) [screened simultaneously]

No date, language or geographic limitations were applied when conducting the search:

- Literature search start dates defined by the CRG for each question are provided in Table 3.3. These date limits were applied once citations were imported into the bibliographic management database (EndNote).
- Non-English databases were not searched, however, publications in languages other than English were considered if an English language abstract was available. English language abstracts that appeared to meet the inclusion criteria were supplied to the CRG to confirm if translation in English of the full article was required.
- All studies were considered by the CRG regardless of enrolment country, with a judgement on the applicability of the evidence to the Australian health care

[15] National Health and Medical Research Council
[16] Scottish Intercollegiate Guidelines Network

context (participant and health system resources) made when assessing the indirectness of the evidence (see Section 3.5).

3.2.2 Databases

In addition to the primary databases listed above (Embase, MedLine, the Cochrane Library and PubMed), searches of additional secondary databases were conducted. This included:

- OpenGrey
- Clinical trial registries (ClinicalTrials.gov and WHO ICTRP[17])
- Health technology assessment/government websites (NICE[18], CADTH[19], and AHRQ[20])
- Guideline databases (Guidelines International Network, National Guidelines Clearing House)

3.2.3 Other sources

The review considered both peer reviewed literature, as well as unpublished and grey literature. Studies recommended by CRG members, and potentially relevant studies/systematic reviews identified in the scoping report were also included if they satisfied eligibility criteria and were published within the specified search period of the systematic review.

To maintain the rigour of the systematic review process, studies published after the literature search date of the systematic review were not eligible for inclusion in the technical report. However, pivotal new evidence could be discussed in the guidelines and could be used to inform consensus-based recommendations.

3.3 Screening of studies

3.3.1 Title/abstract screening

Citations (title/abstracts) retrieved by the literature searches for each category were imported into EndNote and duplicates across the databases removed. Citations were then imported into Covidence and screened for inclusion against the eligibility criteria for each question.

At title/abstract stage, one systematic reviewer independently screened each citation who discarded ineligible studies (marked as irrelevant and tagged with a reason for exclusion) and retained potentially eligible ones (marked as relevant or maybe). Where there was uncertainty regarding relevance, a decision was made through discussion with the lead reviewer (MJ), who decided to either mark the citation as irrelevant or take it through for full text review. A second reviewer then checked the screening process to ensure any citation marked as irrelevant did not meet the eligibility criteria. Any differences were resolved by discussion.

[17] World Health Organization International Clinical Trials Registry Platform
[18] National Institute for Health and Care and Excellence
[19] Canadian Agency for Drugs and Technologies in Health
[20] Agency for Healthcare Research and Quality

3.3.2 Full text screening

Full text articles identified for possible inclusion in the evidence synthesis were retrieved then assessed for inclusion independently by two reviewers. Where there was uncertainty regarding inclusion, a decision was made through discussion with the lead reviewer (MJ), or advice was sought from the CRG to confirm eligibility based on PICO/PPO criteria.

A prespecified, hierarchical approach was used to annotate reasons for exclusion, with the results of the study selection process illustrated in a PRISMA flow diagram.

Studies were excluded based on hierarchical, prespecified exclusion criteria as follows:

- Study published prior to search date specified in the protocol
- Duplicate citation
- Non-human study
- PICO out of scope
- Publication type out of scope (e.g. nonsystematic review, editorial, commentary, conference abstract)
- Study type out of scope (e.g. not a comparative clinical study), or
- Other (e.g. study superseded, withdrawn)

Additional prespecified criteria for excluding studies included the following:

- No usable data (systematic review (SR) does not provide data relating to the primary studies)
- Primary study (RCT and/or nonrandomised study) already assessed and included in a systematic review
- Sample size (as specified in the protocol for each question)
- Insufficient or no adjustment for confounders (observational studies only)

Trial registration numbers, author names and study titles, locations and dates were used to identify multiple citations arising from the same study. Ongoing trials and studies published as abstracts were also identified and are listed under “Studies awaiting classification”.

3.3.3 Screening process

To minimises the potential for bias, a hierarchical approach to the screening for each question was conducted as illustrated in Figure 3.1.

Using a stepped process, the highest ‘level’ of evidence was assessed before studies with other design labels were considered. This meant that a systematic review of Level II studies was considered the highest level of evidence (Level I) for all question types (see section 3.1.4 for study design labels).

If high-quality (see Section 3.4.2) systematic review evidence was available to address the specified outcomes of interest, assessment of studies with other design labels (Level II or Level III) was not conducted[21].

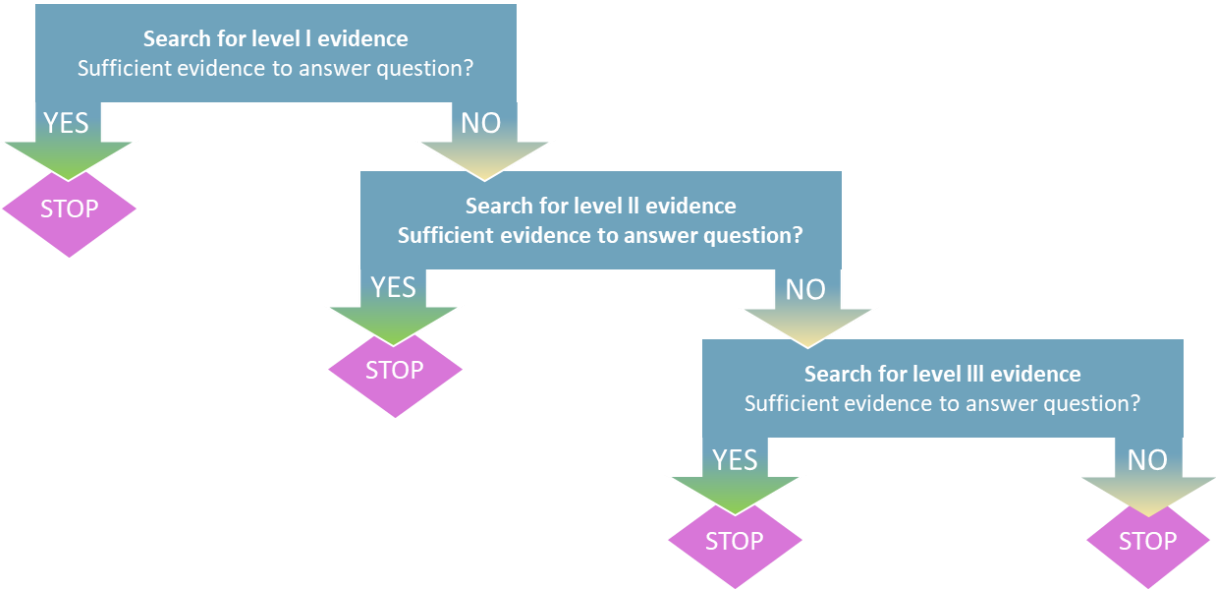
[21] Noting that eligible RCTs (or Level II studies) published since the search date of the key systematic review were identified and incorporated into the review.

If there were no relevant systematic reviews available for a specific research question, the citations retrieved from the Level II[22] search were screened, and if no Level II studies were identified the process was repeated for Level III studies (to the level specified in the PICO/PPO criteria).

For critical and important outcomes not addressed in higher-level evidence, the screening of lower-level evidence was targeted to that outcome only.

Where there was insufficient or no evidence available to answer a research question, a 'consensus recommendation' or 'good practice statement' was made.

Figure 3.1 Schematic representation of literature review hierarchy



In 2018, for each group of questions, all citations identified in the search for systematic reviews (meta-analyses, guidelines etc.) were screened according to the date limits indicated in Table 3.3. Date limits specific to each question were applied within EndNote.

Systematic reviews and meta-analyses identified for potential inclusion were scrutinised and assessed for eligible primary studies (RCTs and/or nonrandomised studies) for each question. Any systematic review that provided duplicate information (duplicate data) or did not provide enough information about the primary studies (no usable data) was excluded, with the most comprehensive and most recent systematic review retained. Reviews that did not include any eligible primary studies were excluded.

Based on the literature search dates of the most recent systematic review, a date limit was then applied to Level II and PubMed searches, which was then screened for additional studies not already identified.

At this point), a list of potentially relevant studies, and the existing clinical questions to which they applied, was supplied to the NBA and CRG with an understanding of the

[22] For prognostic questions Level II = prospective cohort studies; for interventional questions = RCTs

scope of new evidence to undergo full critical appraisal and data extraction reached before proceeding to the next stage of this review (either continue screening for RCTs and observational searches or move on the critical appraisal, data collection and evidence synthesis).

Here, the CRG was consulted to advise whether the identified evidence would likely answer and address each research question, and whether the inclusion of additional lower-level evidence would likely substantially change the overall results.

Specifically, each question custodian was asked to respond to the following three questions:

- What is missing from the list of identified primary studies?
- Are there any 'landmark' studies that are not included in the proposed included studies?
- If there are no 'landmark' studies that would capture the missing data or they are insufficient to answer the question or the missing data is unknown, should any of the following options be considered?
    - Search the Level II and/or Level III evidence bases for studies published after publication of the most recent systematic review literature.
    - Conduct a targeted review focusing only on components not included in the systematic review evidence. What are these components?
    - Other?

An agreement to stop screening was reached in December 2018 after all relevant systematic reviews had been identified (and the included primary studies) and any pivotal new studies had been included. While some CRG members noted the paucity of systematic review evidence, they acknowledged the considerable work required to investigate primary studies may not be justified.

The searches were re-run in 2019 and again in 2021, with the stepped process again used when screening the body of evidence. This occurred after the application of date limits that incorporated a minimum 6 months prior to the previous search date (see Appendix A, technical report, volume 2).

In 2019, citations retrieved in the search for systematic reviews and published between January 2018 to August 2019 were screened; however due to a pause in the project in 2020, screening of citations retrieved in the lower-level searches did not proceed.

In 2021, citations retrieved in the Level I search (systematic reviews) and published between January 2019 to September 2021 were screened, followed by the application of date limits according to the most recent and comprehensive systematic review identified for each question. A new date limit was then applied to remaining searches (Level II, Level III, PubMed), which were screened for additional studies published after the systematic review search date.

3.4 Critical appraisal, data collection and evidence synthesis

3.4.1 Critical appraisal process

The methodological quality of included systematic reviews and the of risk of bias of primary studies was assessed using a variety of assessment tools according to the type of study. Here, the clarity and completeness or reporting, strengths and weaknesses of methods and processes used, as well as the underlying assumptions and limitations of a study was assessed. For each systematic review or primary study, supporting information and a rationale for each judgement is provided in **Appendix D** (see technical report, volume 1).

Critical appraisal of each included systematic review or primary study was assessed by one reviewer. A second reviewer then checked and confirmed each assessment made. Disagreements were resolved through discussion, with advice sought from a third reviewer if needed.

3.4.2 Critical appraisal tools

3.4.2.1 Systematic reviews and meta-analyses

Systematic reviews and meta-analysis of RCTs and/or observational studies were assessed using the AMSTAR-2 quality assessment checklist (18). The AMSTAR-2 consists of 16 domain questions (classified as critical flaws or weaknesses as outlined in Table 3.4) that are answered as 'yes', 'no', 'partial yes'. A 'yes' answer denotes a positive result.

The overall quality of the systematic review was summarised based on the criteria outlined in Box 2.

Prior to 2019, systematic reviews and meta-analyses of RCTs were assessed using the AMSTAR[23] quality assessment checklist (19), which consists of 11 signalling questions that are answered as 'yes', 'no', 'can't answer', or 'not applicable'. A 'yes' answer denotes a positive result.

The overall quality of systematic reviews assessed with the original AMSTAR checklist was summarised based on the following criteria: (i) high quality, scoring 'yes' on 9 or more questions, (ii) moderate quality, scoring 'yes' on between 6 and 8 questions, and (iii) low quality, scoring 'yes' on 5 or less questions.

It is noted that AMSTAR and AMSTAR-2 lead to a judgement of methodological quality (or limitations) of a systematic review, not a judgement about risk of bias of the body of evidence included within the systematic review. The risk of bias of primary studies included within the systematic review (if reported) were noted during data collection (see **Appendix E** [technical report, volume 3]).

[23] A MeaSurement Tool to Assess systematic Reviews

Table 3.4 AMSTAR-2: Domain classification

Critical weakness	Critical flaw
Domain 1: Inclusion of PICO in research questions and inclusion criteria Domain 2: Registration of protocol before commencement of the review Domain 3: Discussion of selection of study designs for inclusion Domain 5: Duplicate study selection Domain 6: Duplicate data extraction Domain 7: Justification for excluding individual studies Domain 10: Review of sources of funding for included studies Domain 12: Discussion of impact of risk of bias of included studies on meta-analysis results Domain 14: Discussion of heterogeneity Domain 15: Assessment of presence and likely impact of publication bias Domain 16: Reporting of potential sources of conflict of interest including any funding received	Domain 4: Adequacy of the literature search Domain 8: Detailed description of included studies Domain 9: Risk of bias from individual studies being included in the review Domain 11: Appropriateness of meta-analytical methods Domain 13: Consideration of risk of bias when interpreting the results of the review

Source: (18)

Box 2 Overall quality of included systematic reviews

Overall quality of included systematic reviews

High quality (*no or one noncritical weakness)* – the systematic review provides an accurate and comprehensive summary of the results of the available studies that address the question of interest.

Moderate quality (more than one noncritical weakness) – the systematic review has more than one weakness but no critical flaws. It may provide an accurate summary of the results of the available studies that were included in the review.

Low quality (one critical flaw with or without noncritical weaknesses) – the review has a critical flaw and may not provide an accurate and comprehensive summary of the available studies that address the question of interest.

Critically low quality (more than one critical flaw with or without noncritical weaknesses) – the review has more than one critical flaw and should not be relied on to provide an accurate and comprehensive summary of the available studies.

3.4.2.2 Randomised controlled trials

The risk of bias of included RCTs was assessed using the Cochrane Collaboration's Risk of Bias tool (20). This tool is made up of six bias domains assessing seven sources of bias including: selection bias (random sequence generation and allocation concealment), performance bias (blinding of researchers and patients), detection bias (blinding of outcome assessment), attrition bias (incomplete outcome data), reporting bias (selective reporting) and other bias.

For each domain, concerns of bias were raised (recorded as 'high', 'low', or 'unclear') when it was considered plausible (i.e. likely, probable, possible or conceivable) that bias was present. Supporting information and a rationale for each judgement is provided in **Appendix D** (see technical report, volume 1).

The overall risk of bias for an RCT was determined based on the criteria outlined in Box 3.

Box 3 Overall risk of bias within identified RCTs

Overall risk of bias within identified RCTs

Overall low risk – low risk of bias for ALL key domains

Overall unclear risk – low or unclear risk of bias for ALL key domains

Overall high risk – high risk of bias for one or more key domains

3.4.2.3 Observational (nonrandomised) cohort studies

The risk of bias of observational cohort studies was guided by GRADE[24], with the focus being on bias relating to the following four domains: selection of participants, measurement of exposure/outcomes, confounding and follow-up.

It is noted that formal risk of bias assessment of cohort studies using the Cochrane Collaboration's ROBINS-I (or another appropriate tool) was not conducted.

For each domain, concerns of bias were raised (recorded as 'low', 'moderate', 'serious', 'critical', or 'no information provided') when it was considered plausible (i.e. likely, probable, possible or conceivable) that bias was present. Supporting information and a rationale for each judgement is provided in **Appendix D** (see technical report, volume 1).

The overall risk of bias for observational studies was determined based on the guide outlined in Box 4.

[24] Table 5.5 in GRADE handbook
http://gdt.guidelinedevelopment.org/app/handbook/handbook.html#h.m9385o5z3li7

Box 4 Overall risk of bias within identified observational (cohort) studies

Overall risk of bias within identified observational (cohort) studies

Overall low risk of bias – the study is comparable to a well-performed RCT and is judged to be a low risk of bias for ALL domains

Overall moderate risk of bias – the study appears to provide sound evidence for a nonrandomised study but cannot be considered comparable to a well-performed randomised trial. The study is judged to be a low or moderate risk of bias for ALL domains

Overall serious risk of bias – the study has some important problems and is judged to be at serious risk of bias *in* at least ONE domain, but not a critical risk of bias in any domain

Overall critical risk of bias – the study is too problematic with regards to this domain to provide any useful evidence on the safety of the intervention. The study is judged to be at critical risk of bias in at least ONE domain

No information – there is no information on which to base a judgement about overall risk of bias. There is no clear indication that the study is at serious or critical risk of bias AND there is a lack of information in one or more key domains of bias.

3.4.3 Data collection

The characteristics and results of each included systematic review or primary study were extracted by a single evidence reviewer using standardised data collection forms (see **Appendix E** [technical report, volume 3]). Data extraction forms were then checked by a second reviewer, with any disagreements resolved through discussion.

The following characteristics of included studies was extracted:

- study design
- year conducted
- funding sources and funder involvement in study
- setting and location (such as prehospital, trauma setting, military zone)
- participant characteristics (including enrolment number and any notable demographics or comorbidities)
- intervention and comparator characteristics (including product, timing, dose and administration technique)
- outcomes measure and results (including measurement method, timing or severity)

Only data from systematic reviews judged to be of high or moderate quality were used to inform the evidence base. Here, data was extracted from the systematic review or meta-analyses and a return to the source documents (primary studies) to verify data was not done. A return to source documents occurred if their where concerns about the completeness of data reported in the systematic review.

3.4.4 Data synthesis

After data collection, the available effect estimates (including 95% confidence intervals, *p*-values) for critical and important outcomes and those relating to resource use were presented in evidence summary tables, alongside the population and intervention characteristics. The evidence summary tables were structured by question, comparisons, study design and outcome measure (see results tables in Section 4). All available information was reported, including if the results were incompletely reported (e.g. no effect estimate, but the direction of effect with a *p*-value was reported). Implications of the missing outcome data were considered when interpreting the evidence (see Section 3.5).

Where possible, data synthesis of results within each comparison was performed[25] according to methods described in Chapter 6 of the Cochrane Handbook (21). Using RevMan 5.4, effect estimates were combined across studies for each outcome using a random effects model, with data from RCTs and observational studies presented separately. Forest plots were used to visually depict the results. If the reported information allowed for direct calculation of effect estimates or imputation of missing statistics (e.g. standard deviations), calculations were performed within the computer program[26] (21).

Heterogeneity was assessed by visually by inspecting the overlap of confidence intervals on the forest plots, formally test for heterogeneity using the Chi^2 test (using a significance level of $\alpha = 0.1$), and quantify heterogeneity using the I^2 statistic (22).

Indirect treatment comparisons were not conducted.

3.5 Summary of findings and draft recommendations

For each comparison, setting and outcome, the available evidence was assessed using the GRADE approach (23), which provides a framework for rating the certainty of the evidence for each outcome (see Box 5) and grading recommendations in health care (see Box 6).

3.5.1 GRADE evidence profiles

For each question, evidence profiles were initially developed by the lead reviewer (MJ), using the GRADEpro GDT software (www.gradepro.org), with the CRG then considering each profile and relevance to the Australian context. In the absence of data, a narrative summary was provided. All critical and important outcomes were reported, regardless of whether the findings demonstrate a clinically meaningful change.

[25] i.e. the PICO criteria and study design features were considered sufficiently homogenous or suitable to be combined.

[26] Usually transformed from published confidence intervals or standard errors of the mean

Box 5 GRADE certainty of evidence (per outcome)

GRADE certainty of evidence

High (⊕⊕⊕⊕): further research is very unlikely to change the confidence in the estimate of effect

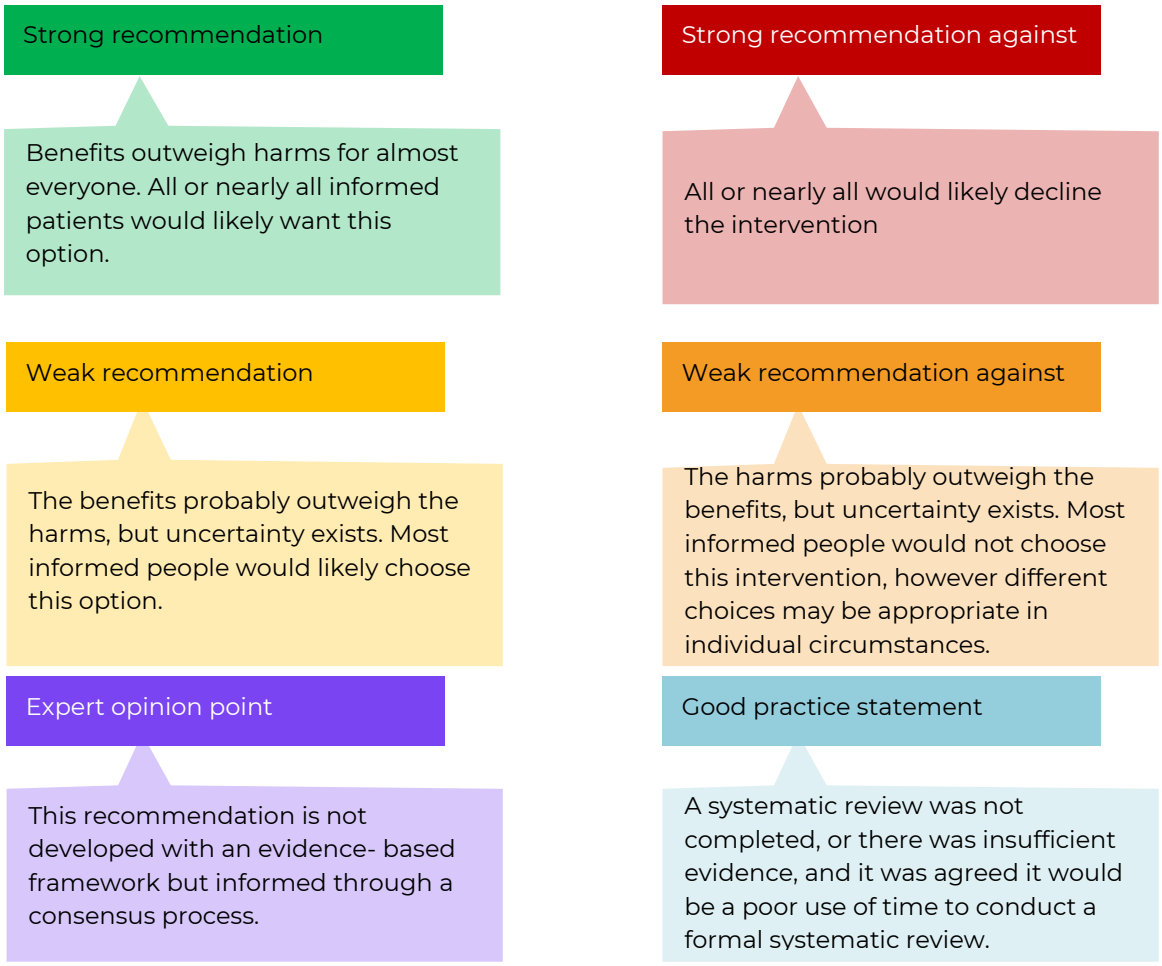
Moderate (⊕⊕⊕⊖): further research is likely to have an important impact in the confidence in the estimate of effect

Low (⊕⊕⊖⊖): further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate

Very low (⊕⊖⊖⊖): any estimate of effect is very uncertain

Box 6 GRADE Recommendations

GRADE Recommendations



Beginning with the study design (RCTs or observational studies), five factors were considered that can reduce the certainty of evidence and three factors were considered that can increase the certainty of evidence (see Box 7). Here, scoring of the certainty of the evidence begins as 'high' for RCTs (score=4), and 'low' for observational studies (score=2).

For each outcome, a judgement was recorded against each factor that could reduce the certainty of evidence (no concerns, serious or very serious). Each factor was downgraded by –1 for serious concerns or –2 for very serious concerns. Footnotes were used to record judgements made about downgrading or upgrading the evidence. Factors that can increase the certainty of evidence were considered only where relevant.

Box 7 GRADE factors that can reduce or increase the certainty of the evidence

Factors that can reduce the certainty of the evidence

Risk of bias. Based on the summary risk of bias assessment across studies for each outcome reported for a comparison (24).

Inconsistency. Based on heterogeneity in the observed effects across studies that suggests important differences in the effect of the intervention and whether this can be explained (25).

Imprecision. Based on interpretation of the upper and lower confidence limits of the pooled result and whether the intervention has a clinically important effect (26).

Indirectness. Based on important differences between the review questions and the characteristics of included studies that may lead to important differences in the intervention effects (27).

Publication bias. Based on the extent to which the evidence is available and the likley non-reporting of results (28).

Factors that can increase the certainty of the evidence

Large magnitude of effect

All plausible confounding would reduce the demonstrated effect or increase the effect if no effect was observed

Dose-response gradient

Risk of bias

For GRADE assessments it was necessary to first draw conclusions about the overall risk of bias for each outcome within a study, and then summarise risk of bias assessments across studies for each outcome. These summary assessments of risk of bias were used in determining the overall certainty of evidence, and the basis for each was reported as footnotes to the GRADE summary of findings tables.

Serious concerns were raised if the outcome result was influenced by the inclusion of studies judged to be at high risk of bias (i.e. removing these studies changed the size of the effect). Serious concerns were also raised if it was considered plausible (i.e. likely, probable or conceivable) that missing outcome data made a difference to the estimated effect (considering the weight of studies that had substantial missing data).

Inconsistency

For GRADE assessments we considered measures of statistical heterogeneity (e.g. I^2 statistic) as well as any non-overlap of confidence intervals that could not be explained, suggesting important difference in the observed effect.

Inconsistency was not downgraded when there was only one study.

Imprecision

For GRADE assessments we considered the upper and lower confidence limits of the pooled result in relation to a minimal clinically important threshold (i.e. the confidence interval includes both appreciable benefit and harm); and whether the optimal information size has been reached (i.e. the total number of patients meets the required sample size for a sufficiently powered individual study).

In determining the clinical importance, a rough threshold guide was used: for dichotomous outcomes a 25% relative risk reduction (or increase); for continuous outcomes we used Cohen's guidance (29) for interpreting the magnitude of the SMD: 0.2 represents a small difference, 0.5 is moderate, and 0.8 is a large difference.

Indirectness

Studies were downgraded for indirectness if a large proportion of participants included in the study did not meet the definition for critical bleeding or when clinical decisions relating to transfusion of blood components or blood conservation strategies differed to that typically used in Australian practice.

Publication bias.

Judgements regarding missing results across the identified studies were made based an assessment of 'known-unknowns' (i.e. selective non-reporting or non-inclusion of results from identified studies). This included checking for missing outcome results in published studies, checking the ongoing studies and studies awaiting classification and making a judgement on whether the studies were not complete, failed to report an outcome, were not published (or translated) due to the nature of their results (e.g. results were in favour of the comparator, or no observed effect) and if the missing result for the outcome would materially influence the meta-analysis results. Given most of the outcome results came from small studies, any missing results due to non-reporting was considered likely to impact the results.

A judgement about 'unknown-unknowns' was made based on the likelihood that missing data from studies not identified was likely to have included that outcome. Publication bias was suspected when the evidence for an outcome was limited to a small number of small trials. all reporting a positive effect. No additional statistical analysis for testing for small-study effects (e.g. contour enhanced funnel plots) was conducted.

3.5.2 Evidence to decisions

GRADE evidence profiles were transitioned into MAGICApp and summary of findings tables reporting estimates of treatment effects for each outcome as absolute and relative risks were presented and discussed with the CRG. Here, an evidence statement pertaining to each outcome was included. The evidence statement was guided by the format prescribed in MAGICApp (30).

The evidence to decisions framework provided within MAGICApp was used to inform translation of the evidence into recommendations for use in the clinical guidance chapter.

Recommendations were made after considering the following key concepts (see Table 3.5):

- Benefits and harms
- Certainty of evidence
- Values and preferences
- Resources
- Equity
- Acceptability
- Feasibility

As noted by GRADE (31):

> *"In the context of a systematic review, the ratings of the quality of evidence reflect the extent of our confidence that the estimates of the effect are correct. In the context of making recommendations, the quality ratings reflect the extent of our confidence that the estimates of an effect are adequate to support a particular decision or recommendation."*

As such, the certainty of the evidence was used to inform the strength of any evidence-based recommendations that are made, with higher certainty evidence resulting in a strong recommendation for or against a particular action, and lower certainty resulting in a weak or conditional recommendation for or against a particular action.

A consensus process (see Section 3.6) was used to ensure the clinical guidance is consistent with the evidence presented. Any dissenting opinions regarding the wording or grading of recommendations was documented.

Table 3.5 Evidence to decision framework

Decision domain	Questions to consider	Ratings (from MAGICapp)	Summary of judgement (from MAGICapp)
Benefits and harms *A narrative summary of the most important benefits and harms* Tips: If possible, state absolute numbers of the most important outcomes and differences in benefit and harms. Large absolute benefits are more likely to lead to a strong recommendation, than small absolute effects. Consider the baseline risk which can influence the balance of desirable and undesirable effects.	How substantial are the benefits? How substantial are the harms? Are you confident that the benefits outweigh the harms or burden for most patients? Is the baseline risk similar across different patients? Should there be separate recommendations for different patients?	Not set Trivial/no benefits Small benefits Moderate benefits Large benefits Varies Don't know n/a	Not set Small net benefit, or little difference between alternatives Substantial net benefit of the recommended alternative Important harms
Certainty of evidence *Overall certainty in effect estimates across outcomes* Note: This step has been completed by the Subgroup as part of the critical appraisal and is already entered into MAGICApp.	What is the certainty of the evidence?	Not set Very low Low Moderate High n/a	Not set Very low Low Moderate High
Values and preferences *Typical patient preferences and values? Common issues or expected variability?* Tips: Clinicians may like to consider additional resources applicable to the values and preferences (e.g. panels experience, consumer	Considering values and preference of patients and their carer's, are you confident the benefits outweigh the harms and burdens for most patients?		Not set Substantial variability is expected or uncertain No substantial variability expected We expect few to want the intervention

Decision domain	Questions to consider	Ratings (from MAGICapp)	Summary of judgement (from MAGICapp)
representative, studies of values and preferences). Highlight the instances where you may expect some patients to choose an alternative to the recommended/ suggested strategy.			
Resources *Issues with costs or resource use? For whom? Cost benefit analysis? Implementation or other issues?* Tips: Consider information about expected resource use, including for the patient and for the institution responsible for the costs that incur. Resources are not only direct money paid, but personnel or time -resources spent. Include logic or evidence that was considered to make the judgement.	Do the resources used (including cost, personnel time, etc.) favour the intervention or the comparator?	Not set Large savings Moderate savings Negligible cost or savings Moderate cost Large cost Varies Don't know n/a	Not set Factor not considered Important issues or potential issues not investigated No important issues with the recommended alternative Important negative issues
Equity *How do the different alternatives affect equity?*	Are there reasons for anticipating differences in the effectiveness of the intervention for any disadvantaged patients or settings (e.g. place of residence, ethnicity, education, socioeconomic status)? Is the recommendation likely to reduce existing inequity? Are there different baseline conditions across patients or settings, that would change the absolute effectiveness of the intervention, or is the issue more/less important, for any disadvantaged patients or settings?	Not set Increased equity Probably increased equity Probably no impact Probably reduced equity Reduced equity Varies Don't know n/a	Not set Factor not considered Important issues or potential issues not investigated No important issues with the recommended alternative Intervention likely increases inequity

Decision domain	Questions to consider	Ratings (from MAGICapp)	Summary of judgement (from MAGICapp)
	Are there important considerations that should be made when implementing the option to ensure inequities are not increased?		
Acceptability *Is the option acceptable to key stakeholders?*	Are there key stakeholders (e.g. private and public hospitals, consumers and carer's, health professions, Hospitals and Health Services, state health departments) that would not accept the distribution of the benefits, harms and costs? Are there key stakeholders that would not accept the costs or undesirable effects in the short term for desirable effects (benefits) in the future? Are there stakeholders that would put more value (relative importance) on the undesirable consequences than the desirable consequences or costs? Are there key stakeholders that would disapprove of the intervention morally, i.e. in relationship to ethical principles such as autonomy, nonmaleficence, beneficence or justice?	Not set Acceptable Probably acceptable Probably not acceptable Not acceptable Varies Don't know n/a	Not set Factor not considered Important issues or potential issues not investigated No important issues with the recommended alternative Intervention is likely poorly accepted
Feasibility *How feasible will it be to implement the different alternatives? Any issues?* Tips: Consider the sustainability of the intervention and any potential barriers (such as, individual health professional factors, patient factors, professional interactions, incentives and	Is there lots of variability in the resource requirements across settings? Is the intervention feasible to implement for either patients and their carer's or for health professionals?	Not set Feasible Probably feasible Probably not feasible Not feasible Varies Don't know n/a	Not set Factor not considered Important issues or potential issues not investigated No important issues with the recommended alternative Intervention is likely difficult to implement

Decision domain	Questions to consider	Ratings (from MAGICapp)	Summary of judgement (from MAGICapp)
resources, capacity for organisational change, political factors). For any identified barriers, consider if they are they likely to limit the feasibility of implementing the intervention or require consideration.			

Source: (32, 33)

3.6 Consensus process

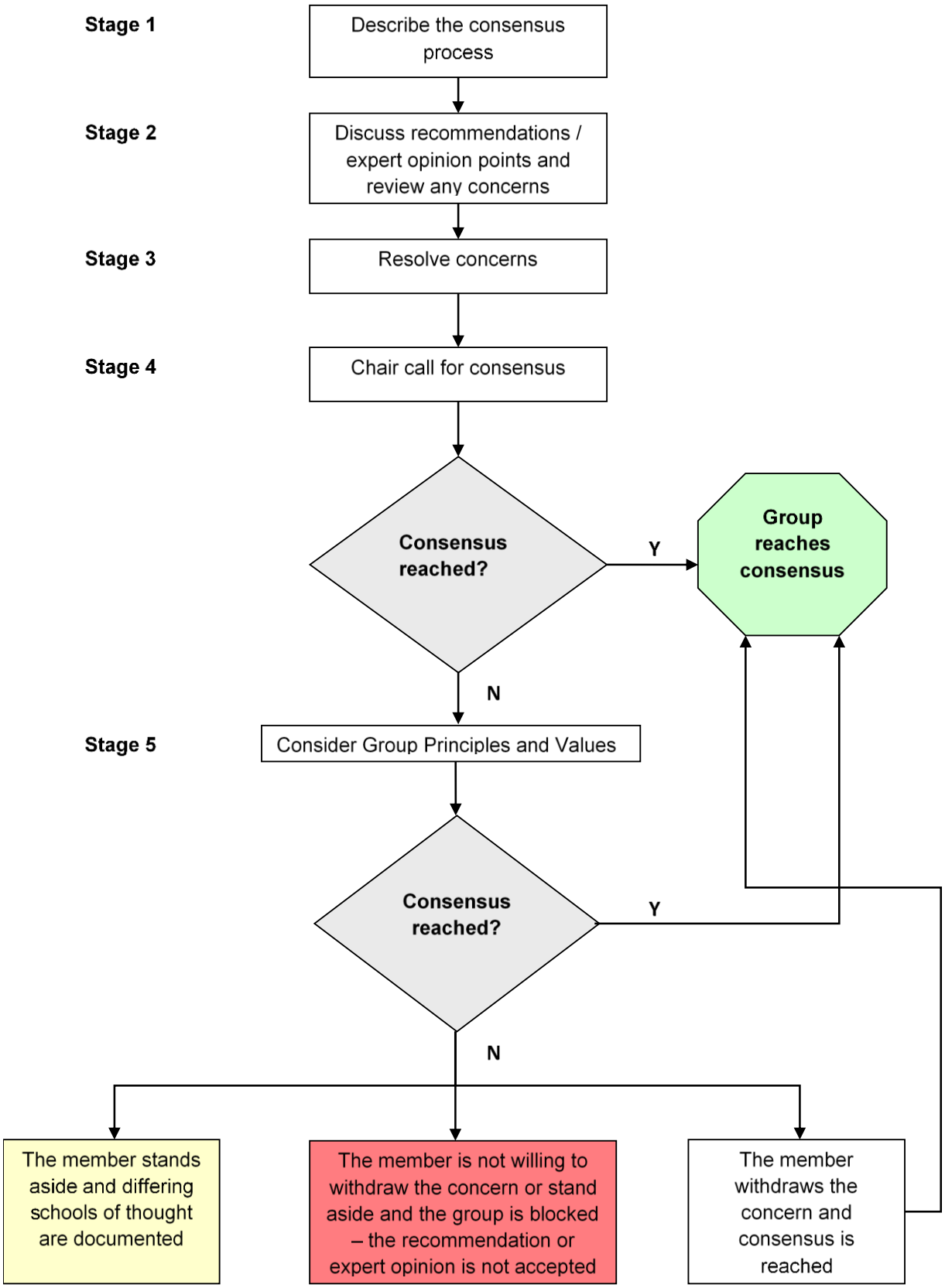
The consensus process for developing evidence-based recommendation and expert opinion points is illustrated in Figure 3.2:

- *Stage 1 – Introduction.* The Chair describes the consensus process, participants' roles and responsibilities, ground rules and the guiding principles.
- *Stage 2 – Open discussion.* The Chair opens the floor to a general discussion and suggestions for recommendation / expert opinion wording, noting that recommendations will be based on the GRADE framework. The Chair provides an opportunity for concerns or issues to be raised.
- *Stage 3 – Resolve concerns.* The Chair has the first option to resolve concerns by clarifying or changing the wording, or seeing whether those with concerns will stand aside. Where concerns are not resolved and the time is short, the discussion will be carried over to a later meeting.
- *Stage 4 – First call for consensus.* The Chair calls for consensus.
- *Stage 5 – Second call for consensus.* If consensus is not reached, the CRG will consider the consensus process guiding principles and values, and:
    - the member stands aside and the differing schools of thought are documented
    - the member is not willing to withdraw the concern or stand aside, and the CRG declares itself blocked – the recommendation or expert opinion is not accepted
    - the member withdraws their concern and consensus is reached

3.6.1 Consensus guiding principles and values

- Consensus is reached where all members agree with the recommendation / expert opinion point. Consensus is not achieved on the basis of a 'majority'.
- The opinions of all members of the group are equally valid/important, notwithstanding that some members may have discipline-specific expert opinion.
- Where consensus is not reached, the dissenting members may present their case. This may be done immediately in the current meeting, or be carried over to the subsequent meeting to allow the members to succinctly formulate their concerns or provide other documentation/ research.
- Issues of semantics, language or content, while recognised as important, should preferably not absorb discussion time within the meetings.
- Members are respectfully asked to reflect upon their own values and conflicts of interests, and be mindful of the extent to which these may influence their opinions.

Figure 3.2 Consensus Process Flow chart



3.6.2 Consensus ground rules

- Members agree to take turns speaking and not interrupt each other.
- Members agree to stay away from establishing hard positions or express themselves in terms of personal needs and interests and the outcomes that they wish to realise.
- Members recognise that, even if they do not agree with it, each of them is entitled to their own perspective.
- Members will not dwell on things that did not work in the past, but instead will focus on the future they would like to create.
- Members agree to make a conscious, sincere effort to refrain from unproductive arguing, venting, or narration, and agree to use their time to work towards what they perceive to be their fairest and most constructive agreement possible.
- Members will speak up if something is not working for them during the consensus process.
- Members will request a break when they need to.
- Members will point out if they feel the Chair is not being impartial.

4 Findings of the systematic review

4.1 Literature search results

4.1.1 Flow of studies

The medical literature was searched on 11 August 2018 to identify relevant systematic reviews and primary studies published from database inception to the literature search date. The searches were repeated on 09 August 2019 and again on 29 September 2021[27] to ensure the most recent and relevant evidence had been identified to inform clinical guidance.

Searches were conducted using the databases and sources described in Section 3.2, with citations returned by the literature searches screened based on information in the publication title and abstract using a stepped process as described in Section 3.3.

Search terms and search results are described in **Appendix A** (see technical report, volume 2). Details on the application of the study selection criteria are provided in **Appendix B** (see technical report, volume 2).

A PRISMA flow summarising the number of studies at each stage of the search and screening process for Question 1 is shown in Figure 4.1.

A PRISMA flow summarising the number of studies at each stage of the search and screening process for Questions 2, 3, 4, and 6 is shown in Figure 4.2.

A PRISMA flow summarising the number of studies at each stage of the search and screening process for Questions 5, 7, 8, and 9 is shown in Figure 4.3.

4.1.2 Studies awaiting classification or not included

No language limits were applied to the search strategy, however eligible studies published in a language other than English were not included. These studies, and other studies that could not be retrieved or those that met the inclusion criteria but contained insufficient or inadequate data for inclusion are listed in **Appendix C** (see technical report, volume 2).

4.1.3 Included studies

Overall, the systematic review and handsearching process identified 73 systematic reviews (that had assessed 156 eligible primary studies) and 23 additional primary studies covering the nine research questions.

An overview of the number studies that informed the evidence is provided in Table 4.1. Details are provided within the summary of evidence section relating to each intervention.

[27] Due to unforeseen challenges and delays (including COVID).

DRAFT

Table 4.1 Overview of studies identified for each question

Intervention	SRs (k)	Additional RCTs	Additional NRSIs	Total evidence base	Section
Physiological parameters	13 (k=50) [a]	1	2 pCoh 3 rCoh[b]	56 primary studies	4.2.2
Major haemorrhage protocol	8 (k=5 pCoh, 24 rCoh)	0	0	5 pCoh 24 rCoh	4.3.2
RBC ratios, timing and dose	16 (k=12 RCTs, 2 pCoh, 20 rCoh)	0	0	12 RCTs 2 pCoh 20 rCoh	4.4.2
RBC transfusion volume	2 (k=9 pCoh, 12 rCoh)	0	1 pCoh 1 rCoh	10 pCoh 13 rCoh	4.5.2
Recombinant activated factor VII	8 (k= 9 RCTs)	2	Not eligible	11 RCTs	4.6.2
Blood components and/or products	11 (k=15 RCTs, 3 pCoh, 13 rCoh)	0	1 rCoh	15 RCTs 3 pCoh 14 rCoh	4.7.2
Antifibrinolytics	13 (k=5 RCTs, 4 pCoh, 12 rCoh)	0	0	5 RCTs 4 pCoh 12 rCoh	4.8.2
Viscoelastic haemostatic assays	12 (k=6 RCTs, 1 pCoh, 13 rCoh)	1	1 rCoh	7 RCTs 1 pCoh 14 rCoh	4.9.2
Cell salvage	3 (k=1 RCT, 2 pCoh, 3 rCoh)	0	1 pCoh	1 RCT 3 pCoh 3 rCoh	4.10.2

Coh, observational or cohort study; pCoh, prospective cohort; rCoh, retrospective cohort; NRSI, nonrandomised study of an intervention; RCT, randomised controlled trial; SRs, systematic reviews

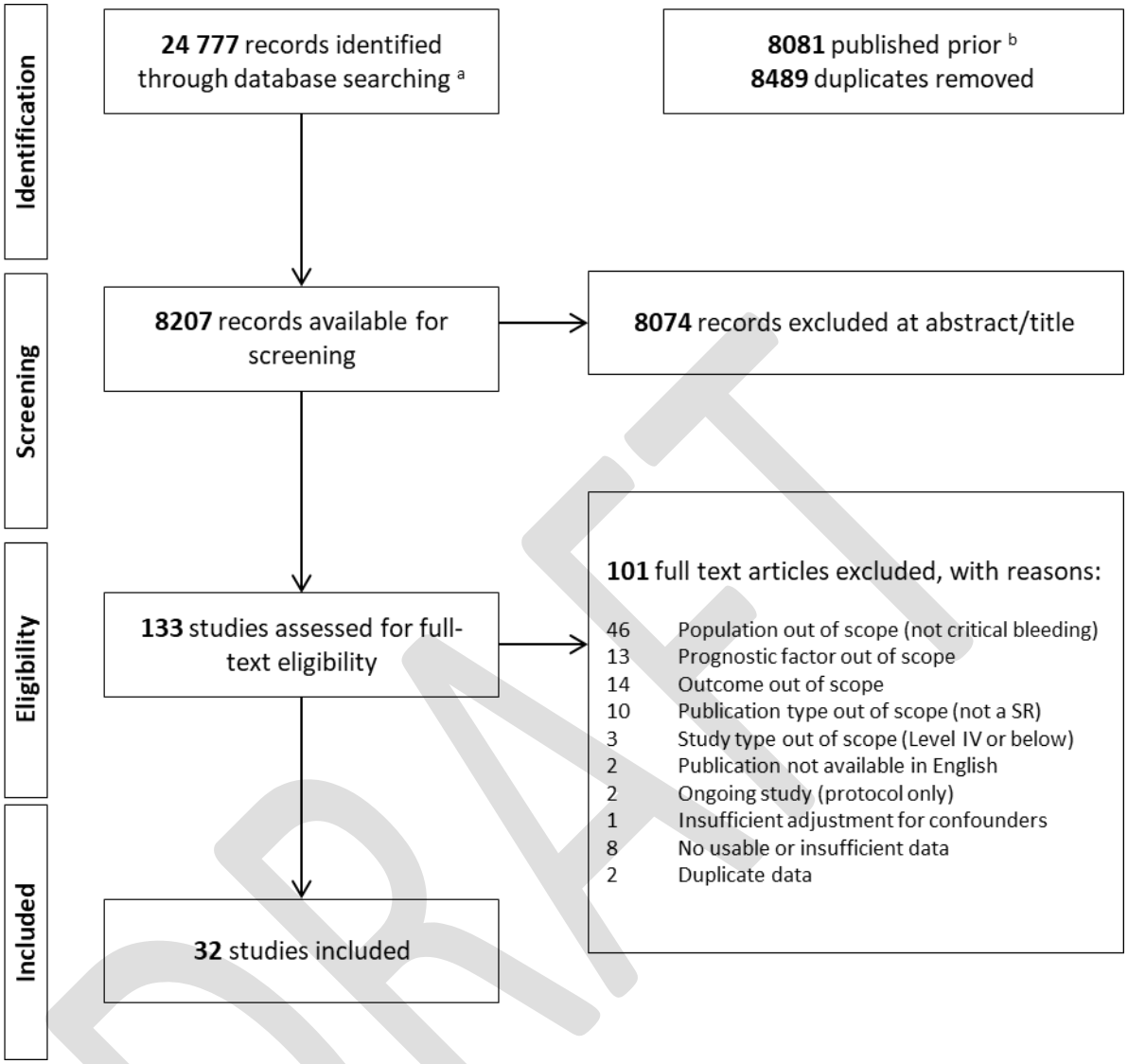
k = number of eligible primary studies included within the SRs

a. Study design features of primary studies included within the SRs were not always specified. Includes prospective cohort studies, retrospective analyses with before and after design, and single-arm analysis of RCTs.

b. Retrospective cohort studies are inclusive of before and after studies that include an historical control.

DRAFT

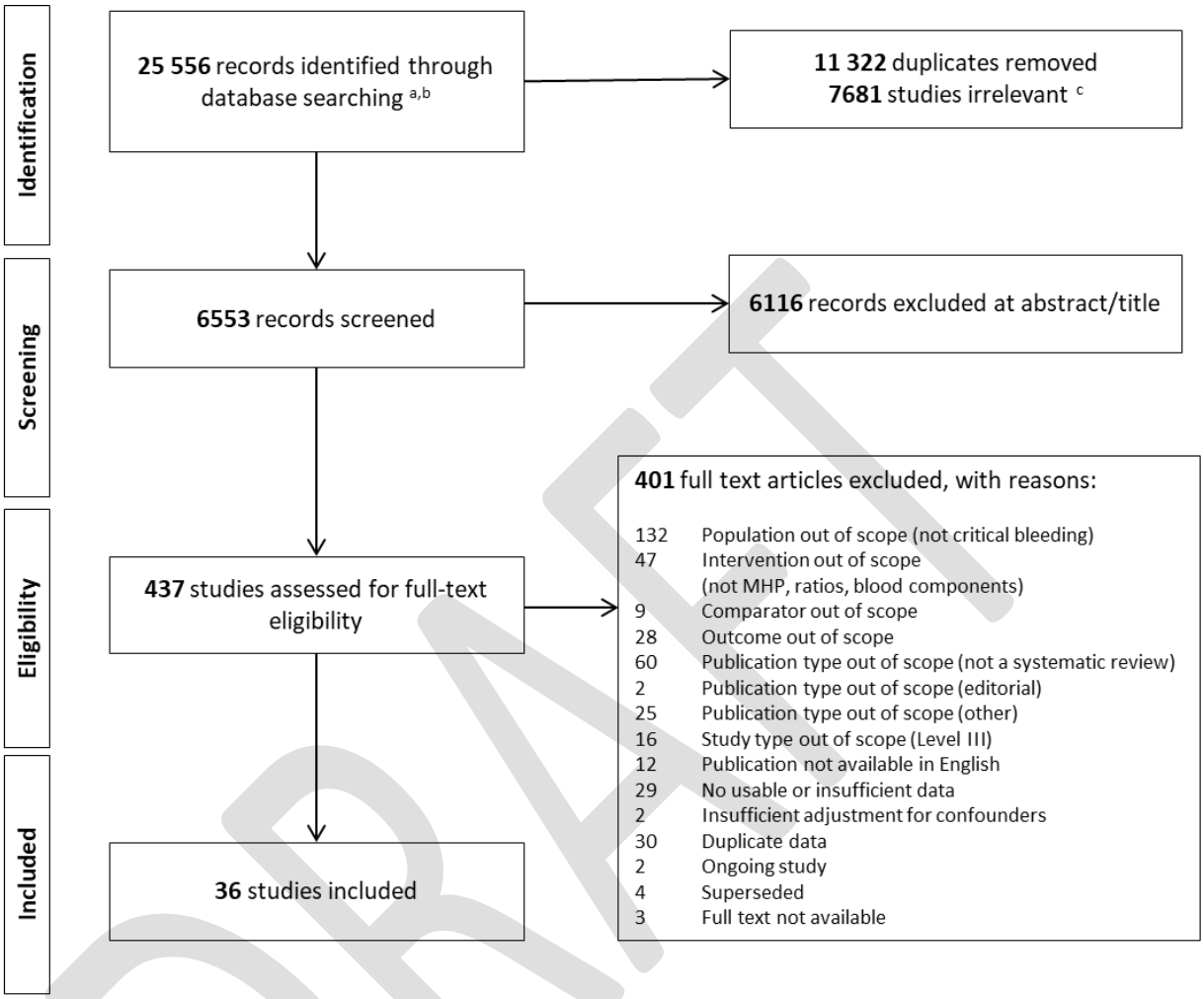
Figure 4.1 Summary of the process used to identify and select studies for the assessment of Question 1 (prognostic factors)



a. Search for SRs, RCTs, and cohort studies conducted via Ovid (Embase, MEDLINE, EBM Reviews) and PubMed (in-process and citations not indexed in MEDLINE).
b. Protocol date limits as follows: Q1 SRs – studies published prior to 2009; Q1 RCTs, cohort, PubMed – studies published prior to 2016 (initial search); Q1 (updated search) – studies published prior to 2019.

DRAFT

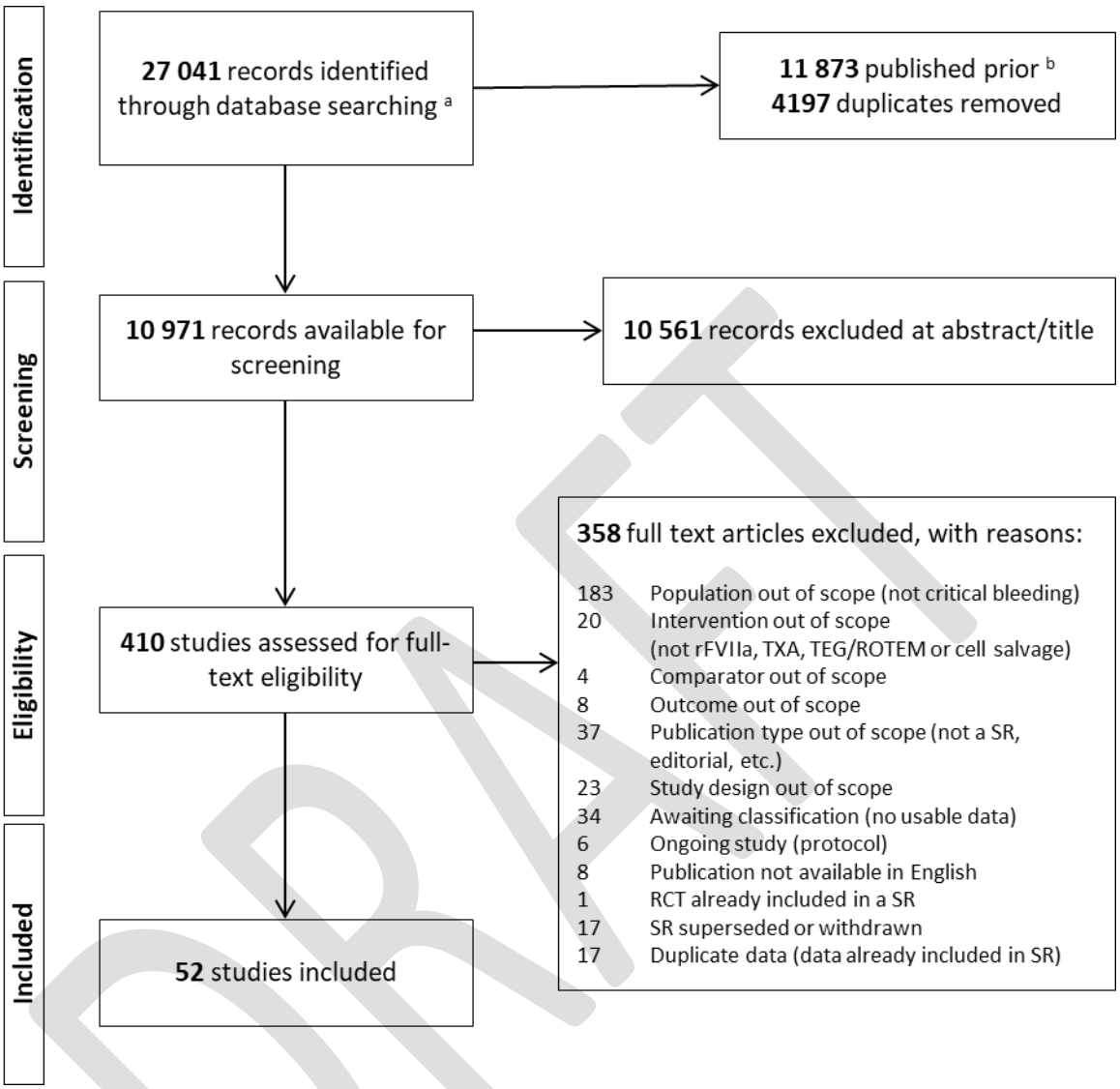
Figure 4.2 Summary of the process used to identify and select studies for the assessment of Question 2 (major haemorrhage protocols), Question 3 (ratios of blood components), Question 4 (RBC transfusion volume), and Question 6 (individual blood components)



a. Search for Level I studies conducted via Ovid (Embase, Medline, EBM Reviews) and PubMed (in-process and citations not indexed in Medline), where possible date limits from 2019 (not applied to PubMed), restricted to Q2, Q3, Q4 and Q6.
b. Search for Level II studies conducted via Ovid (Embase, Medline, EBM Reviews) and PubMed (in-process and citations not indexed in Medline), where possible date limits from 2019 (not applied to PubMed), restricted to Q2, Q3, Q4 and Q6.
c. Studies outside data limits and/or were not tagged as either level I or level II study design.

DRAFT

Figure 4.3 Summary of the process used to identify and select studies for the assessment of Question 5 (rFVIIa), Question 7 (TXA), Question 8 (viscoelastic haemostatic assays) and Question 9 (cell salvage)



a. Search for SRs, RCTs, cohort studies conducted via Ovid (Embase, MEDLINE, EBM Reviews) and PubMed (in-process and citations not indexed in MEDLINE).
b. Protocol date limits as follows: Q5 – studies published prior to 2009; Q7 – studies published prior to 2000; Q8 – studies published prior to 2000; Q9 – studies published prior to 1990. In PubMed, studies published prior to 2015 were not screened (initial search); Updated search, studies published prior to 2019.

DRAFT

4.2 Prognostic factors (Question 1)

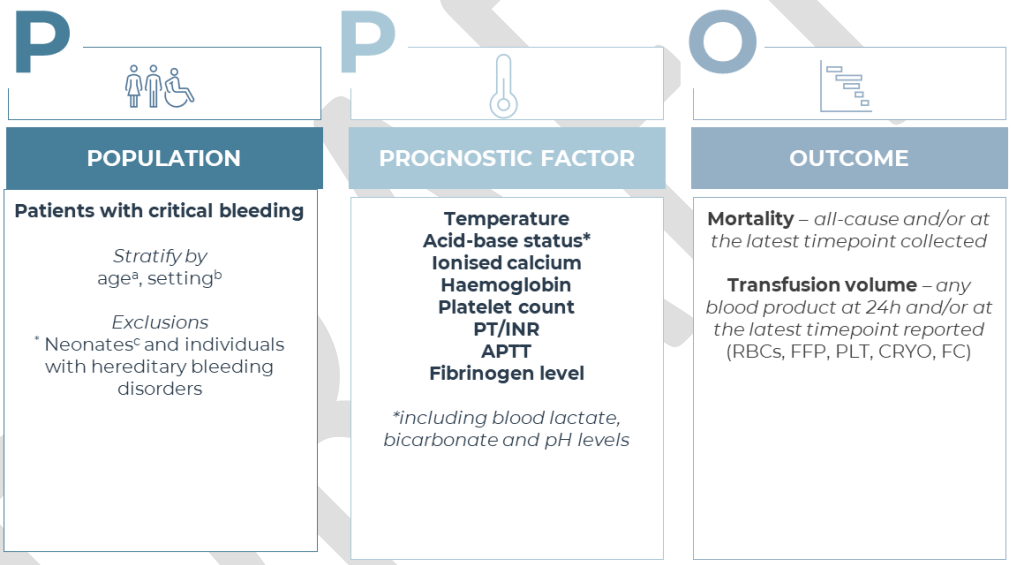
Question 1 – (Prognostic)

In patients with critical bleeding, which physiologic, biochemical and metabolic (including temperature) parameters should be measured early and frequently, and what values of these parameters are indicative of critical physiologic derangement?

4.2.1 Methods

This review sought to identify eight potential prognostic factors associated with increased mortality and transfusion volume requirements in patients who are critically bleeding (i.e. major haemorrhage that is life-threatening and is likely to result in the need for massive transfusion), regardless of age or clinical setting, as outlined in Figure 4.4 below.

Figure 4.4 PPO criteria: Question 1 – physiologic, biochemical and metabolic parameters



APTT, activated partial thromboplastin time; CRYO, cryoprecipitate; FC, fibrinogen concentrate; FFP, fresh frozen plasma; INR, international normalised ratio; PLTs, platelets; PT, prothrombin time; RBCs, red blood cells

Notes:

a. Adult (aged over 18 years), child (aged 2 to 12 years), adolescent (aged 13 to 18 years), infants (aged 1 to 23 months).

b. e.g. trauma, obstetric, perioperative (cardiothoracic, general surgery, gastrointestinal, liver transplant), paediatric, other.

c. Newborns up to 28 days following birth.

The selection of studies was conducted according to the screening criteria described in Section 3.3.

The initial 2018 search was limited to studies published after 2009, noting primary studies published prior to 2009 that had been included in a systematic review were also eligible for inclusion. There were no restrictions applied to study sample size. Assuming all relevant primary studies had been identified in the included systematic review; screening for lower-level evidence was not conducted.

The literature search was updated in August 2019[28] and again in September 2021 to identify any new systematic review studies meeting the eligibility criteria. In 2021, a systematic screen for prospective cohort studies was carried out and limited to studies published from 2019. This is because the most recent studies identified in the updated review did not cover all prognostic factors. No further limits were applied.

4.2.2 Summary of evidence

4.2.2.1 Systematic reviews

Thirteen systematic reviews (34-46) were found that searched for, and assessed, at least one of the eight prognostic factors of interest in this review. The characteristics of each review and the relevant prognotic factor/s and outcomes assessed are shown in Table 4.2.

One systematic review (Kamyszek 2019) searched for evidence relating to transfusion triggers in paediatric patients but found no data about the prognostic factors and their association with the outcomes of interest for this review. One systematic review (Razzaghi 2012) also did not identify any data in patients with thrombocytopenia in the setting of nonvariceal upper gastrointestinal bleeding. These reviews are not discussed further in this report.

Table 4.2 Characteristics and quality of included systematic reviews

Review ID ***Review quality***	**Study design (No. of studies)**	**Population**	**Prognostic factor/s**	**Outcomes**
Vasudeva 2021 (34) *Critically low*	SR of RCTs and observational studies (3 studies)	Adult trauma patients with an admission ionised calcium measurement	Ionised calcium	Mortality Transfusion volume
Moore 2020 (35) *High*	MA of RCTs (2 studies)	Adults with traumatic haemorrhagic shock	Ionised calcium	Mortality
Kamyszek 2019 (36) *Critically low*	SR of observational studies (29 studies)	Paediatric population requiring massive blood transfusion	PT/INR, temperature	No relevant outcomes identified
Shih 2019 (37) *Critically low*	SR of observational studies (45 studies)	Trauma patients	Any scores or predictors of massive transfusion	Transfusion volume
Lilitsis 2018 (38) *Critically low*	Narrative SR (NR studies)	Severely injured patients	Any predictive factors that describe patient's status including coagulation	Mortality
Tran 2018 (39) *Critically low*	SR / MA (84 studies)	Adult patients with traumatic torso injuries	Any clinical, laboratory or imaging predictors available during the initial hour of resuscitation	Transfusion volumes
Levy 2017 (40) *Critically low*	Narrative review (8 studies)	Bleeding patients in the perioperative setting	Platelet transfusion in relation to triggers, dose and assessment of haemostatic efficacy	Transfusion volumes

[28] One additional systematic review was found (Kamyszek 2019).

Review ID *Review quality*	Study design (No. of studies)	Population	Prognostic factor/s	Outcomes
Baxter 2016 (42) *Critically low*	SR / MA of RCTs and observational studies (28 studies)	Adult trauma patients presenting to the ED	Blood lactate	Mortality Transfusion volumes
Poole 2016 (41) *Critically low*	SR / MA of RCTs and observational studies (5 studies)	Adult trauma patients in non-military setting (excluding TBI)	Measures of coagulopathy (fibrinogen, APTT, platelet count, INR)	Mortality
Haas 2015 (43) *Critically low*	SR of RCTs and observational studies (64 studies)	Patients in the perioperative setting or with massive bleeding	PT/INR or APTT	Mortality Transfusion volumes
Abdul-Kadir 2014 (44) *Critically low*	Narrative SR (NR studies)	Women with PPH	Fibrinogen levels	Transfusion volume
Pacagnella 2013 (45) *Critically low*	SR of observational studies (11 studies)	Obstetrics patients with haemorrhage	Shock index, heart rate, systolic blood pressure	Mortality Blood loss
Razzaghi 2012 (46) *Critically low*	SR of RCTs and cohort studies (18 studies)	Patients with thrombocytopenia in the setting of nonvariceal upper GI bleeding.	Platelets	No studies identified specifically assessing patients with active GI haemorrhage

APTT, activated partial thromboplastin time; ED, emergency department; GI, gastrointestinal; INR, international normalised ratio; MA, meta-analysis; NR, not reported; PPH, postpartum haemorrhage; PT, prothrombin time; RCT, randomised controlled trial; SR, systematic review; TBI, traumatic brain injury

Overall, there were 50 primary studies reported in the included systematic reviews, which were often judged by the review authors to have high or moderate concerns of bias related to study design features and likely reporting bias.

(Martin 2005, Balvers 2016, Aslar 2004, Callaway 2009, Duane 2008, Lavery 2000, Mizushima 2011, Neville 2011, Odom 2012, Regnier 2012, Vandromme 2010, Gale 2016, Odom 2013, Heinonen 2014, Cherry 2006, Vasudeva 2020, Hagemo 2014, Mitra 2010, MacLeod 2003, Hess 2009, Mitra 2007, Rourke 2012, Sambavisan 2011, Ciavarella 1987, Callcut 2011, Vandromme 2011, Baron 2004, Ipekci 2013, Paulus 2014, Calcutt 2013, Leemann 2010, Schöchl 2011, Schreiber 2007, Arnold 2006, Fayed 2013, McGrath 2008, Premaratne 2001, Tanaka 2014, Wu 2014, van Hout 2017, Mannucci 1982, Murray 1998, Charbit 2007, Cortet 2012, Peyvandi 2012, Rouse 2006, Nakamura 2017, Magnotti 2011, Sperry 2018 [PAMPer], Moore 2018 [COMBAT]).

Temperature

Two reviews (Lilitis 2018, Shih 2019) reported evidence from three observational studies relating to temperature in critically bleeding patients. Two studies (Martin 2005, Balvers 2016) examined the association between temperature with mortality and one study (Callcut 2011) assessed the association between temperature and transfusion requirements. The studies were carried out in trauma centres in the US (two studies) or The Netherlands (one study).

Two studies (Martin 2005, Balvers 2016) were judged by Lilitis 2018 to be at high risk of bias, and one study (Callcut 2011) was judged by Shih 2019 to have overall low concerns of bias.

Acid-base status

Three reviews (Baxter 2016, Lilitis 2018, Tran 2018) reported evidence from 17 observational studies relating to acid-base status in critically bleeding patients. Twelve studies (Aslar 2004, Callaway 2009, Duane 2008, Lavery 2000, Mizushima 2011, Neville 2011, Odom 2012, Regnier 2012, Vandromme 2010, Gale 2016, Heinonen 2014, Odom 2013) assessed the association between lactate levels and mortality and five studies (Vandromme 2010, Vandromme 2011, Regnier 2012, Baron 2004, Ipecki 2013) assessed the association between lactate levels and transfusion volume.

The studies were carried out in various trauma centres in the US, France, Switzerland and South Africa. The overall risk of bias was judged to be moderate or high due to attrition, confounding and reporting biases.

Ionised calcium

Three reviews (Vasudeva 2021, Moore 2020, Shih 2019) reported evidence from nine studies relating to ionised calcium in critically bleeding patients. Three observational studies (Cherry 2006, Magnotti 2011, Vasudeva 2020) and two single arm analyses of RCTs (COMBAT, PAMPer) assessed the association between ionised calcium and mortality. Four studies (Magnotti 2011, Vasudeva 2020, COMBAT, PAMPer) reported on transfusion volume. The studies were carried out in trauma centres in the US and Australia.

Moore 2020 aimed to evaluate the association between prehospital plasma and hypocalcaemia, which in turn is associated with lower survival. To investigate this, Moore 2020 used data collected from two RCTs, COMBAT (Moore 2018) which included injured adults ≥18 years with acute blood loss and PAMPer (Sperry 2018) which included injured adults at risk of haemorrhagic shock. Moore 2020 did not assess the risk of bias of the two included RCTs. However, review authors noted limitations of the studies for the purposes of the meta-analysis acknowledging that these biases can potentially limit the generalisability of the results. These include biases due to outcome data (lack of ionised calcium measurements for all enrolled patients), pre-existing disease severity and survivor bias.

Vasudeva 2021 assessed the quality of included studies to be moderate, noting that none of the included studies were blinded nor explicitly stated the utilisation of different reviewers for data collection and cross checking. Shih 2019 did not assess risk of bias of included studies. Overall, risk of bias for included observational studies was judged to be moderate due to limited by sample size and confounding.

Haemoglobin

Two reviews (Tran 2018, Shih 2019) identified seven observational studies (Callcut 2013, Paulus 2014, Vandromme 2011, Callcut 2011, Leemann 2010, Schöchl 2011, Schreiber 2007) that assessed the association between haemoglobin and transfusion volume or transfusion requirements in trauma patients with critical bleeding. The studies were carried out in trauma centres in the US, Switzerland, Austria and Iraq. No studies were found that assessed the association between haemoglobin and mortality.

Tran 2018 found the quality of included studies was poor noting the frequent lack of justification, inadequate reporting and suboptimal handling of missing data. Overall, risk of bias for the included observational studies was judged to be moderate to high due to study design and confounding.

Platelet count

Two reviews (Poole 2016, Levy 2017) included data from nine observational studies in trauma or perioperative surgical patients with critical bleeding that examined the association between platelet count and mortality (two studies) (Hagemo 2014, Mitra 2010) or transfusion volume (seven studies) (Arnold 2006, Fayed 2013, McGrath 2008, Premaratne 2001, Tanaka 2014, Wu 2014, van Hout 2017). Three studies were carried out in trauma or emergency centres in the US, UK, Norway and Australia. Eight studies were carried out in surgical settings in the US, Canada, Netherlands and Egypt.

Poole 2016 noted the included studies provided very low certainty of evidence, with issues arising due to variables utilised in prediction models and generalisability or results. Overall, the included observational studies were judged to have high risk of bias related to patient selection and confounding.

PT/INR

Five reviews (Lilitis 2018, Poole 2016, Haas 2015, Tran 2018, Shih 2019) included data from eight observational studies that assessed the association between PT/INR levels with mortality (five studies; Macleod 2003, Hess 2009, Mitra 2007, Hagemo 2014, Mitra 2010) or transfusion volume (three studies; Callcut 2013, Vandromme 2011, Schreiber 2007) in trauma patients with critical bleeding.

All studies were conducted in trauma centres in the US, UK, Norway, Australia and Iraq. Overall, risk of bias for included observational studies was judged to be high for inadequate control for confounding, study design and reporting.

APTT

Three reviews (Poole 2016, Lilitis 2018, Hass 2015) identified seven observational studies that assessed the association between APTT levels with mortality (five studies; Rourke 2012, Macleod 2003, Sambavisan 2011, Ciavarella 2987, Mitra 2007) or transfusion volume (two studies; Mannucci 1982, Murray 1998) in trauma patients with critical bleeding.

All studies were conducted in trauma centres in the US, UK, Norway, Italy and Australia. Overall, risk of bias for included observational studies was judged to be unclear to high due to study design, reporting and control for confounding.

Fibrinogen levels

Three reviews (Poole 2016, Abdul-Kadir 2014, Shih 2019) identified two observational studies that assessed the association between fibrinogen levels and mortality (Hagemo 2014, Rourke 2012) in critically bleeding trauma patients. The review also included five studies that assessed the association between fibrinogen levels and transfusion volumes in trauma and obstetric patients with critical bleeding (Charbit 2007, Cortet 2012, Peyvandi 2012, Rouse 2006, Nakamura 2017).

Four studies were conducted in obstetric settings in the US, France and Italy and three studies were carried out in trauma centres in the US, UK, Norway and Japan. Overall,

included studies was judged to be high risk of bias due to study design, confounding and reporting biases.

4.2.2.2 Primary studies

There were two additional prospective cohort studies (Gaessler 2021, Javali 2017), three additional retrospective cohort studies (Kawatani 2016, Noorbhai 2016, Sawamura 2009) and one single arm analysis of an RCT (Lester 2019) identified through the systematic review and handsearching process that evaluated one or more of the eight prognostic factors of interest in this review.

A summary of the characteristics and risk of bias of the additional studies and relevant outcomes assessed are shown in Table 4.3.

Three other retrospective cohort studies (Figueiredo 2018, Verma 2017, Wang 2016) were identified in the literature search but were later excluded as they did not report any data on the prognostic factors of interest and were not considered further.

Prospective cohort studies

Gaessler 2021 was a single centre prospective observational study conducted in Germany which aimed to assess the impact of coagulopathy in 148 injured patients who were medical treated by the Helicopter Emergency Medical Service and transported to Level 1 trauma centres. The study was found to be at serious risk of bias due related to lack of blinding or outcome assessors.

Javali 2017 was a prospective observational study in 100 trauma patients at risk of haemodynamic compromise in a tertiary care centre emergency department in India. This study was found to be at serious risk of bias due to inadequate control of confounding factors and patient selection bias. The study included 92 patients in the analysis of base deficit and did not provide justification for patients lost to follow-up.

Retrospective cohort studies

Kawatani 2016 was a retrospective study of the medical records of 25 patients who underwent endovascular aortic repair for ruptured abdominal aortic aneurysms (rAAA) at Chiba-Nishi General Hospital in Japan between October 2013 and December 2015. Major coagulopathy was defined using INR or activated partial thromboplastin time (APTT) ratio of at least 1.5, or platelet count less than 50 × 10/L. The study was judged to be at serious risk of bias due to lack of control for confounding factors and lack of blinding.

Noorbhai 2016 was a retrospective cohort study that aimed to assess the correlation between coagulopathy (INR) and mortality in 1000 patients admitted to a level 1 trauma unit in South Africa. Overall, INRs were not recorded in 61 patients and were therefore excluded from the analysis to a total of 939 remaining patients. This study was found to have critical risk of bias due to inadequate reporting of follow-up and lack of control for confounding factors.

Sawamura 2009 was a retrospective cohort study conducted in Japan which aimed to assess the impact of disseminated intravascular coagulation on patient outcomes. Data obtained at four time points (within 24 hours of arrival to the emergency department) was collected from 314 consecutive severe trauma patients which was further subdivided into 259 survivors and 55 nonsurvivors. This study was found to have critical risk of bias due to lack of blinding and inadequate reporting of follow-up.

Single arm analysis of RCT

Lester 2019 provided a secondary analysis of data from an RCT to evaluate the association between hypothermia and patient outcomes using the dataset collected during the PROPPR RCT (Holcomb 2015). Hypothermia was defined as a temperature less than 36°C and normothermia was considered to be between ≥36°C and 38.5°C. The study had several limitations relating to measurement of the outcome (no standardised method and variability in devices used), reporting of the outcome (pooling of data across 12 sites) and differences in protocols. Overall, Lester 2019 was judged to be at serious risk of bias due to study design, confounding and reporting.

Table 4.3 Characteristics and quality of additional primary studies included in the review

Review ID ***Risk of bias***	**Study design**	**Population** **N**	**Prognostic factor**	**Outcomes**
Prospective cohort studies				
Gaessler 2021 (47) *Serious*	Prospective cohort, SC	Adult trauma patients medically treated by HEMS enroute to a Level 1 trauma centre N=148	Coagulopathy	Mortality Transfusion volume
Javali 2017 (48) *Critical*	Prospective cohort, SC	Trauma patients at risk of hemodynamic compromise N=100	Acid-base status	Mortality Transfusion volumes
Retrospective cohort studies				
Kawatani 2016 (49) *Critical*	Retrospective cohort	Patients who undergo endovascular aortic repair for rAAA N=25	Measures of coagulopathy	Mortality
Noorbhai 2016 (50) *Critical*	Retrospective cohort	Patients admitted to the level 1 trauma unit N=1000	INR	Mortality
Sawamura 2009 (51) *Critical*	Retrospective cohort	Severe trauma patients with ISS ≥ 9 N=314	Coagulation and fibrinolytic markers (fibrinogen, PT, lactate, platelet count)	Mortality Transfusion volumes
Single arm analysis of RCT				
Lester 2019 (52) PROPPR trial *Serious*	Single arm of RCT (secondary analysis)	Severely injured patients ≥ 15 years N=586	Hypothermia [a]	Mortality

HEMS, Helicopter Emergency Medical Service; INR, international normalised ratios; INR, international normalised ratio; ISS, injury severity score; MC, multicentre; PT, prothrombin time; rAAA, ruptured abdominal aortic aneurysm; SC, single centre

a: Data sets from RCTs were used to evaluate prognostic markers

4.2.3 Results

4.2.3.1 Mortality

A summary of the evidence relating to mortality in patients with critical bleeding is presented in Table 4.4. Due to the limited evidence and significant heterogeneity among included studies, no meta-analysis was performed.

Temperature

Identified literature suggests an increased risk of mortality associated with hypothermia among patients with critical bleeding. Three studies in trauma settings contributed mortality data and reported an odds ratio (OR) of around 2.7 to 2.72 observed at 24 hours and an OR of 1.8 to 2.8 observed at 30 days. Hypothermia was generally reported by study authors to be below 35.5°C.

Acid-base status

Identified literature suggests risk of mortality is significantly increased with increasing lactate levels among patients with critical bleeding.

Fourteen observational studies in trauma settings contributed mortality data. At high lactate levels (> 4 mmol/L), authors reported OR ranges between 4.2 and 10.58.

Ionised calcium

Identified literature suggests an increased risk of mortality associated with hypocalcaemia. Four observational studies in trauma settings contributed data. One study reported an OR of 1.92 observed with statistical difference. Hypocalcaemia was considered < 1.1 mmol/L.

Haemoglobin

No identified literature reported on the effect of haemoglobin levels and mortality.

Platelet count

Identified literature suggests an increased risk of mortality associated with lower platelet count in patients with critical bleeding. Four studies in trauma and surgical settings contributed data reporting no statistical difference in mortality and platelet count.

PT/INR

Identified literature suggests an increased risk of mortality associated with abnormal PT/INR levels among patients with critical bleeding. Included studies contributing data were in trauma and surgical settings, reporting an OR of around 1.35 to 1.65 and an adjusted risk ratio (aRR) of 3.68 observed for elevated PT/INR levels compared to normal levels.

APTT

Identified literature suggests an increased risk of mortality associated with abnormal APTT levels among patients with critical bleeding. Six studies in trauma and surgical settings contributed data reporting OR ranges between 1.01 and 4.26 observed for elevated APTT levels compared to normal APTT levels.

DRAFT

Fibrinogen

Identified literature suggests the risk of mortality significantly increased with low fibrinogen levels among patients with critical bleeding. Three studies in trauma settings contributed data reporting OR ranges between 0.08 and 0.989 observed for low compared to high fibrinogen levels. Definitions of low fibrinogen levels varied across the studies but were generally considered to be levels < 1.5 g/L.

DRAFT

Table 4.4 Results for physiologic, biochemical and metabolic (including temperature) parameters indicative of critical physiologic derangement: Patients with critical bleeding – Mortality

Study ID Study design[a]	Sample size (no. of trials) included in analysis	Patient population	Setting (Location)	Predictor	Results			
					Predictor n/N (%)	No predictor n/N (%)	Risk estimate (95% CI)	*Statistical significance* *p*-value Heterogeneity[b]
Temperature								
Lilitis 2018 SR *Critically low quality*	N = 702 444 (2 Coh)	Trauma patients	Trauma (US, Netherlands)	Hypothermia	Authors suggest hypothermia is associated with significant increased mortality risk.			*Favours normothermia*
	Martin 2005				Hypothermia 25.5% increased risk	Normothermia 3% risk	NR	*Significant association* *p* = NR
	Balvers 2016			24-hr mortality 30-day mortality	NR NR	NR NR	OR 2.72 OR 2.82	*Significant association* *p* = NR *p* = NR
Lester 2019 Single arm analysis of RCT *Serious risk of bias*	N = 586 (1 Coh)	Trauma patients	Level 1 trauma centres (US)	Hypothermia 24-hr mortality 30-day mortality	NR/399	NR/187	 OR 2.7 (1.7, 4.5) OR 1.8 (1.3, 2.4)	*Significant association* p < 0.00 p < 0.00
Acid-base status								
Baxter 2016 SR *Critically low quality*	N = 34 120 (9 Coh) Aslar 2004 Callaway 2009 Duane 2008 Lavery 2000 Mizushima 2011 Neville 2011 Odom 2012 Regnier 2012 Vandromme 2010	Trauma patients	Trauma/ Emergency (US, France, Switzerland)	Lactate levels	Authors report higher odds of mortality as lactate levels increase.			*Favours lactate < 2 mmol/L*
				≥2 mmol/L	NR	NR	OR range 1.067 to 1.79	*p* = NR
				≥4 mmol/L	NR	NR	OR range 4.2 to 10.58	*Significant association* *p* < 0.001
Lilitis 2018 SR *Critically low quality*	N = 6794 (3 Coh)	Trauma patients	Trauma (US, South Africa)	Acid-base status				*Favours lower lactate levels*
	Gale 2016			Lactate levels Base deficit	A one mmol/l increase in lactate levels is associated with a 17% increased mortality risk A one mq/l increase in base deficit is associated with approximately 4% increased mortality risk			*Significant association* *p* = NR
	Heinonen 2014			Lactate levels	High lactate* associated with 54% mortality rate	< 2.5 mmol/L associated with 22% mortality rate	NR	*Favours lower lactate levels* *Significant association*

Study ID Study design[a]	Sample size (no. of trials) included in analysis	Patient population	Setting (Location)	Predictor	Results			
					Predictor n/N (%)	**No predictor n/N (%)**	**Risk estimate (95% CI)**	***Statistical significance* *p*-value Heterogeneity[b]**
					*not normalised within 24 hrs			*p* = NR
	Odom 2013			Lactate levels < 2.5 mmol/L 2.5–3.9 mmol/L > 4 mmol/L	NR	NR	OR 1 (NR) OR 1.5 (NR) OR 3.8 (NR)	*Favours lactate < 2 .5 mmol/L* *Significant association* *p* = NR
Javali 2017 Prospective cohort *Critical risk of bias*	N = 100 (1 Coh)	Trauma patients at risk of haemodynamic compromise	Tertiary care centre ED (India)	Arterial lactate 24-hour mortality	≥ 4 mmol/L NR (38.1%)	<4 mmol/L NR (0%)	NR	*Favours lactate < 2 mmol/L Significant association* *p* < 0.001
				Base deficit 24-hour mortality	≥ 12 mEq/L 30.4% increased risk	< 12 mEq/L NR (1.3%)	NR	*Favours base deficit < 12 mEq/L* *Significant association* *p* = NR
Sawamura 2009 Retrospective cohort *Criticalv risk of bias*	N = 314 (1 Coh)	Severe trauma patients with an ISS of ≥ 9	ED (Japan)	Lactate (mmol/L)	NR	NR	OR 1.236 (1.016, 1.502)	*Favours lower lactate levels* *Significant association* *p* = 0.034
Ionised calcium								
Vasudeva 2021 SR *Critically low quality*	N = 1213 (3 Coh) Cherry 2006 Magnotti 2011 Vasudeva 2020	Trauma patients not receiving blood transfusion	Trauma centres (US, Australia)	Hypocalcaemia (< 1.11 mmol/L) prior to transfusion	NR 24/91 (26.4) NR/332 (15.5) 29/113 (25.6)	NR 48/305 (15.7) NR/259 (8.7) 17/113 (15.0)	NR OR 1.92 (NR) NR NR	*NR* *p* < 0.05 *p* = 0.036 *p* = 0.047
Moore 2020 SR *High quality*	N = 160 (2 RCTs) COMBAT trial PAMPer trial	Patients with traumatic haemorrhagic shock from blunt or penetrating injuries	Trauma centres (US)	Hypocalcaemia (i-Ca < 1.0 mmol/L) vs normocalcaemia (i-Ca > 1.0 mmol/L)	13/70 (18.6)	11/90 (12.2)	NR	No significant association *p* = 0.26
Haemoglobin – no studies identified								
Platelet count								
Poole 2016 SR	N = 1650 (2 Coh) Hagemo 2014 Mitra 2010	Patients with non-TBI trauma	Trauma (MC [US, UK, Norway] and Australia)	Platelet count	99/1133 (8.7)		OR 1 (1.0-1.0)	No significant association *p* = NR

DRAFT

Study ID Study design[a]	Sample size (no. of trials) included in analysis	Patient population	Setting (Location)	Predictor	Results			
					Predictor n/N (%)	**No predictor n/N (%)**	**Risk estimate (95% CI)**	***Statistical significance* *p*-value Heterogeneity[b]**
Critically low quality					99/331 (29.9)		OR 0.99 (0.99-0.99)	
Sawamura 2009 Retrospective cohort *Critical risk of bias*	N = 314	Severe trauma patients with an ISS of ≥ 9	ED (Japan)	Platelet count	Survivors (n=259) 159 ±79	Non-survivors (n=55) 147 ±82	OR 1.097 (1.003, 1.116)	No significant association *p* = 0.182
					Stepwise logistic regression for prediction of death.			*p* = 0.003
Kawatani 2016 Retrospective cohort *Critical risk of bias*	N= 25	Perioperative patients	Surgical (Japan)	Preoperative platelet count (10^4/uL) 24-hour 30-day	Survival N = 22/25 16.1 +/- 5.4 N = 20/25 16.2 +/- 5.54	Mortality N = 3/25 17.3 +/- 3.0 N = 5/25 16.8 +/- 2.7	NR	NR *p* = 0.616 *p* = 0.767
				Post-operative platelet count (10^4/uL) 24-hour 30-day	Survival N = 22/25 10.2 +/- 5.0 N = 20/25 10.4 +/- 5.0	Mortality N = 3/25 7.7 +/- 1.9 N = 5/25 7.2 +/- 1.9	NR	NR *p* = 0.558 *p* = 0.299
PT/INR								
Lilitis 2018 SR *Critically low quality*	N = 7638 (1 Coh) MacLeod 2003	Trauma patients	Trauma (US)	PT	Abnormal PT 35% greater risk			
Poole 2016 SR *Critically low quality*				PT	NR	NR	OR 1.35 (1.11–1.68)	NR
Haas 2015 SR *Critically low quality*	N= 35 441 (2 Coh) Hess 2009	Patients with critical bleeding	Trauma (US, Australia)	INR	Hess 2009 reported an increase in INR demonstrated stepwise relationship with in-hospital mortality (no OR data reported).			
	Mitra 2007				Mitra 2007 reported an association between high INR and mortality		OR 1.62 (1.18, 2.24)	*p* <0.01
Poole 2016 SR *Critically low quality*	N = 1650 (2 Coh) Hagemo 2014 Mitra 2010	Patients with non-TBI trauma	Trauma (MC [UK, US, Norway], Australia)	INR	99/1133 (8.7) 99/331 (29.9)		OR 1.65 (0.65-4.18) OR 1.43 (1.02-2.01)	NR

Study ID Study design[a]	Sample size (no. of trials) included in analysis	Patient population	Setting (Location)	Predictor	Results			
					Predictor n/N (%)	No predictor n/N (%)	Risk estimate (95% CI)	*Statistical significance* *p*-value Heterogeneity[b]
Noorbhai 2016 Retrospective cohort *Critical risk of bias*	N = 939	Trauma patients	Level I trauma centre (South Africa)	INR All patients External admissions Interhospital transfers	High (>1.20) 74/482 (15.4) 15/121 (12.4) 59/361 (16.3)	low (<1.20) 132/457 (28.9) 44/107 (41.1) 88/350 (28.9)	 aRR 1.92 (1.49, 2.48) aRR 3.68 (2.11, 6.44) aRR 1.54 (1.15, 2.05)	 *p* < 0.001 p < 0.001 p = 0.004
Kawatani 2016 Retrospective cohort *Critical risk of bias*	N = 25	Perioperative patients	Surgical (Japan)	PT-INR, preoperative 24-hour 30-days	Survival N = 22/25 1.2 +/- 0.16 N = 20/25 1.2 +/- 0.16	Mortality N = 3/25 1.2 +/- 0.2 N = 5/25 1.23 +/- 0.19	NR	NR *p* = 0.802 *p* = 0.0767
				PT-INR, post-operative 24-hour 30-day	Survival N = 22/25 1.3 +/- 0.2 N = 20/25 1.4 +/- 0.2	Mortality N = 3/25 1.5 +/- 0.28 N = 5/25 1.5 +/- 0.2	NR	NR *p* = 0.295 *p* = 0.148
APTT								
Poole 2016 SR *Critically low quality*	N = 9336 (3 Coh) Rourke 2012 MacLeod 2003 Sambavisan 2011	Trauma patients	Trauma (UK, US, Norway)	APTT	 62/517 (12.0) NR 173/1181 (14.6)	NR	 OR 1.05 (1.01–1.09) OR 4.26 (3.23–5.62) OR 1.015 (1.01–1.02)	NR
Lilitis 2018 SR *Critically low quality*	N = 7638 (1 Coh) MacLeod 2003	Trauma patients	Trauma (US)	APTT	Elevated APTT 326% greater risk			
Haas 2015 SR *Critically low quality*	N = 155 (2 Coh) Ciavarella 1987 Mitra 2007	Patients with critical bleeding	Trauma (US, Australia)	APTT	Ciavarella 1987 reported microvascular bleeding was associated with severe abnormalities of coagulation factor levels, 20% (PT and aPTT values 1.8 times control). Mitra 2007 reported higher APTT associated with higher mortality (OR 1.01 [95% CI 1.01, 1.02; *p* <0.01]).			
Kawatani 2016 Retrospective cohort *Critical risk of bias*	N = 25	Perioperative patients	Surgical (Japan)	APTT, seconds (preopoerative) 24-hour 30-days	Survival N = 22/25 27.0 +/- 4.3 N = 20/25 26.8 +/- 4.3	Mortality N = 3/25 33.6 +/- 8.4 N = 5/25 32 +/- 7.0	NR	NR *p* = 0.21 *p* = 0.119
				APTT, seconds (post-operative)	Survival	Mortality	NR	NR

Study ID Study design[a]	Sample size (no. of trials) included in analysis	Patient population	Setting (Location)	Predictor	Results			
					Predictor n/N (%)	**No predictor n/N (%)**	**Risk estimate (95% CI)**	***Statistical significance p*-value Heterogeneity[b]**
				24-hour 30-day	N = 22/25 38.9 +/-8.7 N = 20/25 38.1 +/- 7.9	N = 3/25 108.7 +/- 63.4 N = 5/25 95.7 +/- 57.9		*p* = 0.006 *p* = 0.002
Fibrinogen level								
Poole 2016 SR *Critically low quality*	N = 1650 (2 Coh)	Patients with non-TBI trauma	Trauma (UK, US, Norway)	Fibrinogen Hagemo 2014 Low level High level Rourke 2012	99/1133 (8.7) 62/517 (12.0)		OR 0.08 (0.03, 0.20) OR 1.77 (0.94, 3.32) OR 0.22 (0.10, 0.47)	p <0.001 p = 0.076 p <0.001
Gaessler 2021 Prospective cohort *Serious risk of bias*	N = 148	Trauma patients	Level 1 trauma centres (Germany)	Fibrinogen	The study found that TIC and TIC with hyperfibrinolysis resulted in worse prognosis for mortality compared to those without coagulopathy. However, no data reported on prognostic factors and their association with outcomes of mortality or transfusion requirements. A correlation between prognostic indicators and mortality could not be determined.			
Sawamura 2009 Retrospective cohort *Critical risk of bias*	N = 314	Severe trauma patients with an ISS of ≥9	ED (Japan)	Fibrinogen (g/L)	Survivors N = 259/314	Mortality N=55/314	OR 0.989 (0.979, 0.998)	p = 0.015

APTT, activated partial thromboplastin time; aRR, adjusted relative risk; CI, confidence interval; Coh, cohort study; ED, emergency department; i-Ca; ionised calcium; INR, international normalised ratio; ISS, injury severity score; MC, multicentre; NR, not reported; OR, odds ratio; PT; prothrombin time; RCT, randomised controlled trial; SR, systematic review; TBI, traumatic brain injury; TIC, trauma-induced coagulopathy; UK, United Kingdom; US, United States

a. The risk of bias of the included primary studies is based on the quality assessment reported by the systematic review authors.

b. Only applicable to Systematic reviews with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if Phet >0.1 and I2 <25%; (ii) mild heterogeneity if I2 <25%; moderate heterogeneity if I^2 between 25–50%; substantial heterogeneity I^2 >50%.

DRAFT

4.2.3.2 Transfusion volume

A summary of the evidence reported in the identified literature relating to mortality in patients with critical bleeding is presented in Table 4.5. Due to the limited evidence and significant heterogeneity, no meta-analysis was performed.

Temperature

Only limited conclusions can be drawn from the available evidence. Included studies were in trauma settings and reported an increased risk of transfusion requirements associated with hypothermia in patients with critical bleeding.

Acid-base status

Identified literature suggests only limited conclusions can be drawn from the available evidence. Included studies were in trauma settings and reported an increased risk of transfusion requirements associated with increased lactate levels in patients with critical bleeding. High lactate levels were reported above 2.9 mmol/L.

Ionised calcium

Identified literature suggests only limited conclusions can be drawn from the available evidence, with observational studies in trauma settings reporting a significant association between hypocalcaemia and increased transfusion requirements in critically bleeding patients.

Haemoglobin

Identified literature suggests only limited conclusions can be drawn from the available evidence. Seven observational studies in trauma settings contributed data, reporting an association between low haemoglobin levels and increased risk of transfusion requirements.

Platelet count

Identified literature suggests only limited conclusions can be drawn from the available evidence. Included studies were in surgical settings and reported an association between platelet count and increased transfusion requirements. Studies included varying measurements of platelet count to trigger transfusion requirements, making it difficult to draw conclusions.

PT/INR

Identified literature suggests only limited conclusions can be drawn from the available evidence. Included studies were in trauma settings, reporting increased PT/INR levels were associated with increased transfusion requirements in patients with critical bleeding (OR ranges between 2.1 and 5.9 observed).

APTT

Identified literature suggests only limited conclusions can be drawn from the available evidence, with studies in trauma and surgical settings reporting an association between increased APTT levels and transfusion requirements in patients with critical bleeding.

DRAFT

Fibrinogen

Identified literature suggests only limited conclusions can be drawn from the available evidence. Five observational studies in trauma settings contributed data, with three studies reporting a positive association between low fibrinogen levels and increased transfusion requirements in patients with critical bleeding. Definitions of low fibrinogen levels were commonly considered less than 2 g/L.

DRAFT

Table 4.5 Results for physiologic, biochemical and metabolic (including temperature) parameters indicative of critical physiologic derangement: Patients with critical bleeding – Transfusion volume

Study ID Study design[a]	Sample size (no. of trials) included in analysis	Patient population	Setting (Location)	Predictor	Results			
					Predictor n/N (%)	No predictor n/N (%)	Risk estimate (95% CI)	*Statistical significance* *p*-value Heterogeneity[b]
Temperature								
Lester 2019 Single arm analysis of RCT *Serious risk of bias*	N = 586	Trauma patients	Level 1 trauma centre (US)	Hypothermia (< 35.5˚C) RBC units required	N = 399 9.9 (11.4)	N = 187 6.3 (7.9)	RR 0.90 (0.89, 0.92)	No significant difference *p* = 0.00
Shih 2019 SR *Critically low quality*	N = 170 (1 Coh) Callcut 2011	Trauma patients	Trauma (US)	Hypothermia (< 35.5˚C) ≥10 units RBCs / 6hrs	NR	NR	OR 4.0 (1.6, 10.1)	NR
Acid-base status								
Tran 2018 SR *Critically low quality*	N = NR (2 Coh) Vandromme 2010 Vandromme 2011	Adult patients with traumatic torso injuries (civilian and military)	Trauma (US)	Lactate risk of massive transfusion	NR	NR	OR 4.10 (2.50, 6.74) OR 5.20 (3.51, 7.71) OR 3.13 (1.96, 5.00)	*Favours severe lactic acidosis* *p* < 0.0001 Substantial heterogeneity I^2 = 62% (*p* < 0.10)
Baxter 2016 SR *Critically low quality*	N = 1093 (3 Coh) Regnier 2012 Baron 2004 Ipekci 2013	Trauma patients	Trauma/ED (US, France)	Lactate (mmol/L)	In all trauma patients, increased lactate and lactate clearance were found to predict major haemorrhage, defined as blood transfusion of more than six red cell units within 24 hours and/or death from haemorrhagic shock. Increased lactate was also found to be associated with increased blood loss in penetrating torso trauma patients. Two studies found that raised lactate was associated with blood component requirements, but this was not significant in a study that only looked at patients with isolated extremity injuries.			
Javali 2017 Prospective cohort *Critical risk of bias*	N = 100	Trauma patients at risk of haemodynamic compromise	Tertiary care centre emergency department (India)	Arterial lactate (mmol/L) Transfusion requirement	lactate < 2.9 mmol/L 24.6%	lactate ≥2.9 mmol/L 85.7%		*p* < 0.001
				Base deficit (mEq/L)	< 12 mEq/L 36.4%	≥ 12 mEq/L 78.3%		*P* = NR
Ionised calcium								
Moore 2020 SR *High quality*	N = 160 (2 RCTs) COMBAT trial PAMPer trial	Patients with traumatic haemorrhagic shock from blunt or penetrating injuries	2 trauma centres (US)	Hypocalcaemia (< 1.0 mmol/L) RBC Plasma Platelet CRYO	N = 70 5 (2-10) 2 (1-7) 0 (1-1) 0 (0-1)	N = 90 1 (0-5) 2 (0-4) 0 (0-0) 0 (0-0)	NR	 *p* = 0.0002 *p* = 0.007 *p* = 0.30 *p* = 0.0003

Study ID Study design[a]	Sample size (no. of trials) included in analysis	Patient population	Setting (Location)	Predictor	Results			
					Predictor n/N (%)	No predictor n/N (%)	Risk estimate (95% CI)	*Statistical significance* *p*-value Heterogeneity[b]
Vasudeva 2021 SR *Critically low quality*	N = 817 (2 Coh)	Trauma patients	Trauma centres (US, Australia)	Hypocalcaemia (< 1.11 mmol/L) Magnotti 2011 ≥5 U ≥10 U Vasudeva 2020	NR NR/332 (17.1) NR/332 (8.2) 75/113 (62.5)	NR NR/259 (7.1) NR/259 (2.2) 45/113 (37.5)	NR NR NR NR	NR *p* = 0.005 *p* = 0.017 *p* < 0.001
Shih 2019 SR *Critically low quality*	N = 591 (1 Coh) Magnotti 2011	Civilian trauma patients	Regional trauma centre (US)	Hypocalcaemia (i-Ca < 1.0 mmol/L) Multiple transfusions Massive transfusion	 NR/332 (17.1) NR/332 (8.2)	 NR/259 (7.1) NR/259 (2.2)	 OR 2.294 (1.053, 4.996) NR	 *p* = 0.005 [c] *p* = 0.017 [c]
Haemoglobin								
Tran 2018 SR *Critically low quality*	N = NR (3 Coh) Callcut 2013 Paulus 2014 Vandromme 2011	Adult patients with traumatic torso injuries (civilian and military)	Trauma (US)	Haemoglobin (< 110 to 115 g/L) (MT risk)	NR	NR	OR 3.78 (1.97, 7.26) OR 2.40 (1.82, 3.16) OR 2.56 (2.02, 3.25) OR 10.12 (6.01, 17.05)	Favours low haemoglobin *p* < 0.0001 Substantial heterogeneity I^2 = 92% (*p* < 0.00001)
Shih 2019 SR *Critically low quality*	N = 2349 (5 Coh) Callcut 2011 Callcut 2013 Leemann 2010 Schöchl 2011 Schreiber 2007	Trauma patients	Trauma (US, Iraq, Switzerland, Austria)	Haemoglobin (< 11 g/dL) (MT risk)	NR	NR	NR OR 3.1 (1.2, 8.4) OR 1.8 (1.3, 2.5) OR 18.18 (2.73, 125.00) ROC AUC 0.87 (0.83, 0.91) OR 7.7 (5.0, 11.9)	NR
Platelet count								
Levy 2017 SR *Critically low quality*	N = 30 735 (7 Coh) Arnold 2006 Fayed 2013 McGrath 2008 Premaratne 2001 Tanaka 2014 Wu 2014 van Hout 2017	Adult perioperative surgical patients receiving platelet transfusion (cardiac, acute aortic dissection, liver transplant)	Surgical (US, Canada, Egypt, Netherlands)	Platelet count	Included studies used different measurements to trigger platelet transfusion, including platelet count, bleeding (visual measure), and viscoelastic measures. The platelet counts used as triggers varied between the two publications, ranging from a median of 51 (IQR 26–68) $\times 10^9$ /l for interventional treatment in a study evaluating patients in a mixed medical/surgical intensive care unit (Arnold 2006) to a trigger of <100 $\times 10^9$ /l accompanied by bleeding in cardiac surgery patients (van Hout 2017). Different platelet doses per transfusion were administered in all studies, ranging from one to 6 to 12 units (van Hout 2017, Tanaka 214, Fayed 2013). Wu 2014 and McGrath 2008 did not report a measurement for triggering transfusion or dose of transfusion administered. Premaratne 2001 observed a change in bleeding time (NR) between cardiopulmonary bypass patients who received less than 10 units or 10 or more units of platelet transfusions.			Heterogeneity between studies was so substantial that quantitative synthesis was not possible.

Study ID Study design[a]	Sample size (no. of trials) included in analysis	Patient population	Setting (Location)	Predictor	Results			
					Predictor n/N (%)	No predictor n/N (%)	Risk estimate (95% CI)	*Statistical significance* *p*-value Heterogeneity[b]
PT/INR								
Tran 2018 SR *Critically low quality*	N = NR (2 Coh) Callcut 2013 Vandromme 2011	Adult patients with traumatic torso injuries (civilian and military)	Trauma (US)	INR and risk of MT	NR	NR	OR 4.16 (2.57, 6.73) OR 3.40 (2.48, 4.66) OR 5.61 (2.57, 6.73)	Favours coagulopathy $p < 0.00001$ Substantial heterogeneity $I^2 = 60\%$ ($p < 0.11$)
Shih 2019 SR *Critically low quality*	N = 1803 (2 Coh) Callcut 2013 Schreiber 2007	Trauma patients	Trauma (US, Iraq)	INR (> 1.5) ≥ 10 units RBCs / 24 hr	NR	NR	OR 2.1 (1.4, 3.1) OR 5.9 (3.5, 10.2)	NR
APTT								
Hass 2015 SR *Critically low quality*	N = NR (2 Coh) Mannucci 1982 Murray 1998	Patients with critical bleeding	Trauma (US, Italy)	APTT	Mannucci 1982 reported PT > 1.2 times normal or APTT>1.25 times normal were found in 93% of patients who underwent major surgery and received massive transfusion. Murray 1998 recommended FFP transfusion if PT or aPTT is >1.5 times prolonged during massive transfusion.			
Fibrinogen level								
Abdul-Kadir 2014 SR *Critically low quality*	N = NR (4 Coh) Charbit 2007 Cortet 2012 Peyvandi 2012 Rouse 2006	Obstetrics	Obstetrics (US, France, Italy)	Hyperfibrinogen (> 2g/L)	Three studies assessed the association between PPH requiring transfusion and fibrinogen levels. Two studies (Charbit 2007, Cortet 2012) reported a lower (≤2g/L) mean plasma fibrinogen level in women who developed more severe PPH. Peyvandi 2012 however was unable to determine if decreased fibrinogen is an independent and measurable predictor of severe PPH or simply a measure of blood loss. Rouse 2006 notes that low fibrinogen may require transfusion of fibrinogen concentrate, which has been used in obstetrics for the management of PPH since 1948.			
Shih 2019 SR *Critically low quality*	N = 625 (1 Coh) Nakamura 2017	Trauma patients	Trauma (Japan)	Fibrinogen (≤ 190 mg/dL)	NR	NR	OR 0.931 (0.898, 0.963)	NR

APTT, activated partial thromboplastin time; AUC, area under the curve; CI, confidence interval; Coh, cohort; ED, emergency department; FFP, fresh frozen plasma; hrs, hours; INR, international normalised ratio; IQR, interquartile range; MT, massive transfusion; N, number; NR, not reported; OR, odds ratio; PPH, postpartum haemorrhage; PT, prothrombin time; RBC, red blood cells; RCT, randomised controlled trial; ROC, receiver operating characteristic; RR, relative risk; SR, systematic review; US, United States

a. Where only one RCT is identified in a systematic review, the evidence has been considered as RCT evidence. Where the systematic review assesses observational and cohort studies, the evidence has been considered as according to the study design features. The risk of bias of the included primary studies is based on the quality assessment reported by the systematic review authors.

b. Only applicable to Systematic reviews with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if Phet >0.1 and I^2 <25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25–50%; substantial heterogeneity I^2 >50%.

c. Data extracted from primary study.

4.3 Defined major haemorrhage protocol (Question 2)

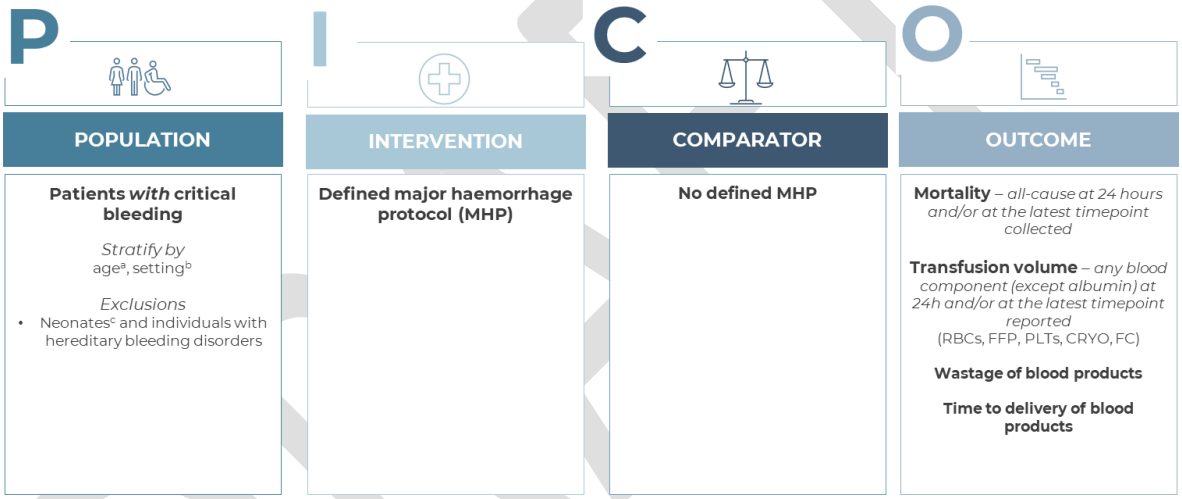
Question 2 – (Interventional)

In patients with critical bleeding, what is the effectiveness of major haemorrhage protocols?

4.3.1 Methods

This review examined the effects of defined major haemorrhage protocols (MHPs) versus no defined MHPs in patients with critical bleeding (i.e. major haemorrhage that is life-threatening and is likely to result in the need for massive transfusion) as outlined in Figure 4.5 below.

Figure 4.5 PICO criteria: Question 2 – defined MHPs



CRYO, cryoprecipitate; FC, fibrinogen concentrate; FFP, fresh frozen plasma; MHP, major haemorrhage protocol; PLTs, platelets; RBCs, red blood cells

Notes:

a. Adult (aged over 18 years), child (aged 2 to 12 years), adolescent (aged 13 to 18 years), infants (aged 1 to 23 months).

b. e.g. trauma, obstetric, perioperative (cardiothoracic, general surgery, gastrointestinal, liver transplant), paediatric, other.

c. Newborns up to 28 days following birth.

The selection of studies was conducted according to the screening criteria described in Section 3.3.

The initial 2018 search was limited to studies published after 2013, noting primary studies published prior to 2013 that had been included in a systematic review were also eligible for inclusion. There were no restrictions applied to study sample size. Screening of RCTs and nonrandomised studies (with concurrent or noncurrent controls) and observational cohort studies was performed.

Studies of lower-level evidence were only screened for primary outcomes insufficiently addressed in systematic reviews. Assuming all relevant primary studies had been identified in the included systematic review; screening for lower-level evidence was not conducted.

An updated literature search was conducted in August 2019 and again in September 2021 to identify any new systematic reviews meeting the eligibility criteria.

Assuming all relevant primary studies have been identified in the included systematic review studies; the systematic screen for RCTs was limited to studies published from September 2019. This is based on the literature search date of the most recent identified systematic review (Consunji 2020), which was assumed to have identified all relevant RCTs in the trauma and non-trauma setting.

4.3.2 Summary of evidence

4.3.2.1 Systematic reviews

There were eight systematic reviews (36, 53-59) identified in the systematic review and handsearching process that assessed the effects of a defined MHP versus no defined MHP in patients with critical bleeding. Two other systematic reviews (Hallet 2013, Johansson 2012) were identified in the search, but these did not provide any additional data to that provided by the included reviews, thus are not discussed further in this report (see Appendix B for a complete list of excluded studies that met the PICO criteria for this question).

Four reviews (Cannon 2017, Mitra 2013, Vogt 2012, Consunji 2020) we focused on critical bleeding in the trauma setting, three reviews (Maw 2018, Kamyszek 2019, Kinslow 2020) included paediatric trauma patients and one review (Sommer 2019) included both trauma and non-trauma patients.

The main characteristics and quality of these reviews and relevant outcomes assessed are summarised in Table 4.6. A matrix illustrating the overlap of studies included in each review is provided in Table 4.7.

Table 4.6 Characteristics and quality of systematic reviews by clinical setting: defined MHPs versus no defined MHPs

Review ID ***Review quality***	**Study design**	**Population**	**Intervention**	**Comparator**	**Outcomes**
Trauma setting					
Consunji 2020 (53) *High*	SR / MA of cohort and observational studies (17 studies)	Trauma patients receiving or anticipated to receive a massive blood transfusion	MTP	No MTP	Mortality
Cannon 2017 (57) *Moderate*	SR / MA of RCTs and cohort studies (11 studies)	Severely injured adult patients requiring blood transfusion and/or ISS >25	MT/DCR protocol	no MT/DCR protocol	Mortality Transfusion volumes
Mitra 2013 (58) *Moderate*	SR / MA of clinical trials, clinical studies, guidelines and meta-analyses (10 studies)	Adult trauma patients in the initial trauma resuscitation phase	After implementation of a predefined MHP	Before implementation of a predefined MHP	Mortality

Review ID *Review quality*	Study design	Population	Intervention	Comparator	Outcomes
Vogt 2012 (59) *Moderate*	SR / MA of comparative observational studies (7 studies)	Adult civilian trauma patients expected to require MT	Formal TTP	no formal TTP	Mortality Transfusion volumes
Non-trauma setting					
Sommer 2019 (55) *Critically low*	SR / MA of RCTs, observational studies and retrospective studies (12 studies)	Adult non-trauma (perioperative, obstetric, gastrointestinal bleeding and vascular emergencies) patients with massive bleeding	MHP	No MHP	Mortality Transfusion volume Wastage of blood components
Paediatric setting					
Kinslow 2020 (54) *Critically low*	SR of observational studies (3 studies)	Paediatric trauma patients	MTP	No MTP	Mortality
Kamyszek 2019 (36) *Critically low*	SR / MA of clinical trials, clinical studies, guidelines and meta-analyses (3 studies)	Paediatric patients receiving an MT	Formal MHP implementation	Before MTP implementation	Mortality Transfusion volume
Maw 2018 (56) *Critically low*	SR / MA of RCTs, observational studies and retrospective studies (5 studies)	Paediatric patients, younger than 18 years, with traumatic injury requiring blood transfusion	Predetermined ratios of blood component therapy, including MHP	Transfusion at physician discretion	Mortality

DCR, damage control resuscitation; FFP, fresh frozen plasma; ICU, intensive care unit; ISS, injury severity score; LOS, length of stay; MA, meta-analysis; MHP, major haemorrhage protocol; MT, massive transfusion; MTP, massive transfusion protocol; PLT, platelet; RBCs, red blood cells; RCTs, randomised controlled trials; SR, systematic review; TTP, trauma transfusion pathway

Table 4.7 Overlap table primary studies included in the identified systematic reviews: defined MHPs versus no defined MHPs

		Trauma																												
	Study ID	Campion 2014	Cinat 1999	Cotton 2009	Cotton 2011	Duchesne 2010	Fox 2008	Kahn 2008	Nascimento 2013	O'Keefe 2008	Riskin 2009	Shaz 2010	Cotton 2008	Dirks 2010	Johannson 2008	Simmons 2010	Sinha 2013	Sisak 2012	Dente 2009	Johansson 2009	Vogt 2009	Ball 2013	Brinck 2016	Hwang 2018	Maciel 2015	Noorman 2016	Nunn 2017	Soderlund 2017	van der Meij 2019	Zaydfudim 2009
Review ID	Consunji 2020			✓						✓	✓	✓		✓		✓	✓	✓				X	✓	✓	✓	✓	✓	X	✓	X
	Cannon 2017	✓	X	✓	X	✓	✓	X	X	✓	✓	✓																		
	Mitra 2013			✓						✓	✓	✓	X	✓	X	✓	✓	✓												
	Vogt 2012			✓						✓	✓		✓						✓	✓	✓									

		Mixed trauma and non-trauma												Paediatrics				
	Study ID	Bauman Kreuziger 2014	Balvers 2015	Chay 2016	Dutta 2017	Goodnough 2011	Gutierrez 2012	Johansson 2007	Martinez-Calle 2016	McDaniel 2013	Morse 2012	Sinha 2013	Wijaya 2016	Chidester 2012	Edwards 2015	Hendrickson 2012	Hwu 2016	Nosanov 2013
Review ID	Kinslow 2020													✓		✓	✓	
	Sommer 2019	X	✓	X	✓	X	X	✓	✓	✓	X	X	X					
	Kamyszek 2019													✓		✓	✓	
	Maw 2018													✓	X	✓		X

✓ = study included in this review; X = study did not meet the inclusion criteria for this review; -- = study identified by the systematic review authors but not included (no usable data)

4.3.2.2 Randomised controlled trials

No RCTs were found in the systematic review and handsearching process that examined the effects of defined MHPs versus no defined MHPs in patients with critical bleeding.

4.3.2.3 Observational and cohort studies

There were 29 nonrandomised studies identified in the included systematic reviews that examined the effects of defined MHPs versus no defined MHPs on mortality and transfusion volumes in patients with critical bleeding and were considered relevant to this review. The main characteristics and quality of included cohort studies and relevant outcomes assessed are summarised in Table 4.8.

Table 4.8 Characteristics and quality of observational and cohort studies by clinical setting: defined MHPs versus no defined MHPs

Review ID *Risk of bias*	Study design	Population N	Intervention	Comparator	Outcomes
Mixed trauma and non-trauma setting					
Balvers 2015 *Moderate*	Retrospective cohort	Adult trauma and non-trauma patients with massive bleeding N=547	MTP	No MTP	Mortality Transfusion volume
Trauma setting					
van der Meij 2019 *Moderate*	Retrospective study (prospective cohort), SC	Civilian trauma patients with haemorrhage requiring MT N=101	MHP	No MHP	Mortality MOF Ventilator days LOS Transfusion volume
Hwang 2018 *Moderate*	Retrospective cohort	Civilian trauma patients with haemorrhage requiring MT N=190	MHP	No MHP	Mortality Transfusion volume
Nunn 2017 *Moderate*	Retrospective cohort	Civilian trauma patients with haemorrhage requiring MT N=447	MHP	No MHP	Mortality Ventilator days LOS
Brink 2016 *Moderate*	Retrospective cohort	Trauma patients ≥16 years with ISS >15 requiring MT N=352	MHP	No MHP	Mortality Transfusion volume
Noorman 2016 *Moderate*	Retrospective cohort, SC	Trauma patients requiring MT N=201	MHP	No MHP	Mortality Transfusion volume LOS
Maciel 2015 *Moderate*	Retrospective cohort, SC	Patients with abdominal aorta injuries N=46	MHP	No MHP	Mortality Duration on mechanical ventilator LOS Complications
Campion 2013 *High*	Retrospective cohort, SC	Adult patients requiring surgery within 24 hours of admission to Level I trauma centre	DCR	Pre-DCR	Mortality Transfusion volume

		N=216			
Sinah 2013 *Moderate*	Prospective cohort	Civilian trauma patients with haemorrhage requiring MT N=152	MHP	No MHP	Mortality Transfusion volume
Sisak 2012 *Moderate*	Retrospective cohort	Civilian trauma patients with haemorrhage requiring MT N=58	MHP	No MHP	Mortality
Dirks 2010 *Moderate*	Before-after with historical control	Civilian trauma patients with haemorrhage requiring MT N=66	MHP	No MHP	Mortality Transfusion volume
Duchesne 2010 *High*	Retrospective cohort, SC	Trauma patients requiring transfusion during surgery N=196	DCR	Pre-DCR	Mortality
Shaz 2010 *Moderate*	Prospective cohort	Civilian trauma patients with haemorrhage requiring MT N=224	MHP	No MHP	Mortality Transfusion volume
Simmons 2010 *Moderate*	Retrospective cohort	Military trauma patients with haemorrhage requiring MT N=777	MHP	No MHP	Mortality Transfusion volume
Riskin 2009 *Moderate*	Retrospective cohort	Civilian trauma patients with haemorrhage requiring MT N=77	MHP	No MHP	Mortality Transfusion volume
Cotton 2008 *Moderate*	Prospective cohort	Civilian trauma patients with haemorrhage requiring MT N=211	MHP	No MHP	Mortality Transfusion volume
Cotton 2009 *Moderate*	Prospective cohort	Civilian trauma patients with haemorrhage requiring MT N=264	MHP	No MHP	Mortality Transfusion volume
O'Keefe 2008 *Moderate*	Retrospective before-after study	Civilian trauma patients with haemorrhage requiring MT N=178	MHP	No MHP	Mortality Transfusion volume
Dente 2009 *High*	Prospective cohort, SC	Trauma patients requiring MT N=157	MHP	No MHP	Mortality Transfusion volume
Vogt 2009 *High*	Retrospective cohort	Trauma patients requiring MT N=46	MHP	No MHP	Mortality Transfusion volume
Johansson 2009 *High*	Before-after with historical control	Trauma patients requiring MT N=832	MHP	No MHP	Mortality Transfusion volume
Fox 2008 *High*	Retrospective two cohort case-control study	Military patients with life-threatening haemorrhage N=40	DCR	Pre-DCR	Transfusion volume

Non-trauma setting					
Dutta 2017 *Moderate*	Retrospective cohort	Obstetric patients with massive bleeding N=62	MTP	No MTP	Mortality Transfusion volume
Martinez-Calle 2016 *Moderate*	Retrospective cohort	Adult non-trauma (perioperative, obstetric, gastrointestinal bleeding and vascular emergencies) patients with massive bleeding N=304	MTP	No MTP	Mortality Transfusion volume
McDaniel 2013 *Moderate*	Retrospective cohort	Adult non-trauma (perioperative, obstetric, gastrointestinal bleeding and vascular emergencies) patients with massive bleeding N=64	MTP	No MTP	Mortality Transfusion volume Wastage of blood components
Johansson 2007 *Moderate*	Retrospective cohort	Adult patients with ruptured abdominal aortic aneurysm N=132	MTP	No MTP	Mortality Transfusion volume
Paediatric setting					
Hwu 2016 *High*	Retrospective cohort, SC	Paediatric trauma patients receiving MT N=43	MHP	Pre-MHP	Mortality Transfusion LOS
Chidester 2012 *High*	Prospective cohort, SC	Paediatric trauma patients receiving MT N=55	MHP	Pre-MHP	Mortality Morbidity
Henrickson 2012 *High*	Retrospective cohort, SC	Paediatric trauma patients receiving MT N=102	MHP	Pre-MHP	Mortality LOS

DCR, damage control resuscitation; LOS, length of stay; MHP, major haemorrhage protocol; MOF, multiple organ failure; MT, massive transfusion; MTP, massive transfusion protocol; SC, single centre

Trauma setting

The four systematic reviews (Consunji 2020, Cannon 2017, Mitra 2013, Vogt 2012) identified a total of 21 observational studies in adult trauma patients relevant to this review question.

Consunji (2020) identified 14 relevant studies (Brink 2016, Cotton 2009, Dirks 2010, Shaz 2010, Hwang 2018, Maciel 2015, Noorman 2016, Riskin 2009, O'Keefe 2008, Nunn 2017, Simmons 2010, Sinah 2013, Sisak 2012, van der Meij 2019). Cannon 2017 identified three additional studies (Champion 2013, Duchesne 2010, Fox 2008) not identified elsewhere. Mitra (2013) identified eight studies, all of which were also identified in Consunji (2020). Vogt 2012 identified four additional studies (Cotton 2008, Dente 2009, Johansson 2009, Vogt 2009) not identified elsewhere.

Most studies were carried out in single and multicentre trauma centres in the US, Canada, Denmark and Australia. Overall, the systematic reviews judged included observational studies to be moderate to high risk of bias due to study design, data collection and adjustments for confounding.

The 14 studies identified in Consunji 2020 and Mitra 2013 evaluated the effect of implementing defined MHPs in adult trauma patients, assessing patient outcomes before

and after implementation. The three studies identified in Cannon 2017 evaluated the implementation of an MHP with or without a formal damage control resuscitation protocol in adult trauma patients. The four studies identified in Vogt 2012 only included studies in adult civilian trauma patients. Identified systematic reviews did not define MHPs and most acknowledged differences between included observational studies in the definitions and triggers of MHPs.

All systematic reviews aimed to evaluate the association between MHPs and mortality as a patient outcome, pooling analysis of included studies. Cannon 2017 and Vogt 2012 reported pooled volume of red blood cells (RBCs) transfused as a surrogate endpoint for the total blood components transfused. Cannon 2017, Mitra 2013 and Vogt 2012 reported volume of other blood components transfused.

Mixed trauma and non-trauma setting

One systematic review (Sommer 2019) assessing the effects of MHPs in both trauma and non-trauma settings was identified in the literature. Sommer 2019 reported outcome data of one observational study (Balvers 2015) including a mixture of trauma (8.8%) and non-trauma patients requiring massive transfusion (defined as the administration of five of more units of RBCs within 12-hours).

Balvers 2015 was carried out in an academic medical centre in the Netherlands and was judged by review authors to have high risk of bias due to study design, data collection and adjustments for confounding.

Sommer 2019 also identified 12 observational studies in the non-trauma settings. Of these, only four were included in the quantitative analysis. Studies were in the non-trauma setting and included patients with bleeding due to obstetric complications (Dutta 2017), ruptured abdominal aortic aneurysm (Johansson 2007) or perioperative surgery (McDaniel 2013, Martinez-Calle 2016).

Studies included patients with major bleeding who required transfusion, which was defined as four or more units of RBCs (Dutta 2017), 10 or more units of RBCs (McDaniel 2013, Johansson 2007) or the replacement of whole blood volume in 24-hours, 50% of volume in 3-hours or blood loss of more than 1500 mL in 10 minutes (Martinez-Calle 2016).

The four included observational studies (Dutta 2017, McDaniel 2013, Martinez-Calle 2016, Johansson 2007) were carried out in single centre settings in the US, Denmark and Spain. Overall, included observational studies were judged by review authors to be high risk of bias due to study design and confounding.

Paediatric setting

Three reviews (Kinslow 2020, Kamyszek 2019, Maw 2018) assessing MHPs in paediatric patients were identified in the literature. All reviews identified several observational studies, however, only three met our inclusion criteria. Two systematic reviews (Kinslow 2020 and Kamyszek 2019) identified all three studies. One review (Maw 2018) only identified two of the three studies as one was published after the search date.

All three included observational studies (Chidester 2013, Hendrickson 2012, Hwu 2016) were carried out in single centre paediatric trauma centres in the US, Afghanistan and Iraq. Overall, risk of bias for included studies was judged by review authors to be high risk due to study design and selection bias.

4.3.3 Results

4.3.3.1 MHP compared to no MHP

Mortality

A summary of the evidence relating to in-hospital mortality in patients with critical bleeding treated with an MHP is presented in Table 4.9.

All identified systematic reviews reported a weak association between defined MHPs and mortality (latest timepoint) in trauma patients (Consunji 2020, Cannon 2017, Mitra 2013, Vogt 2012, Sommer 2019). For all other subgroups, the identified systematic reviews reported no association between a defined MHPs and mortality (Kamyszek 2019, Kinslow 2020, Maw 2018, Sommer 2019).

A meta-analysis of data from observational studies included in this review (Figure 4.7) showed the mortality rate (latest timepoint) in patients with critical bleeding was better among those who received a MHP (926/2927, 13.6%) compared with those who did not (977/2492, 39.2%) with the odds ratio (OR) of 0.71 observed (95% CI 0.57, 0.87; $p = 0.001$; random effect, $I^2 = 62\%$).

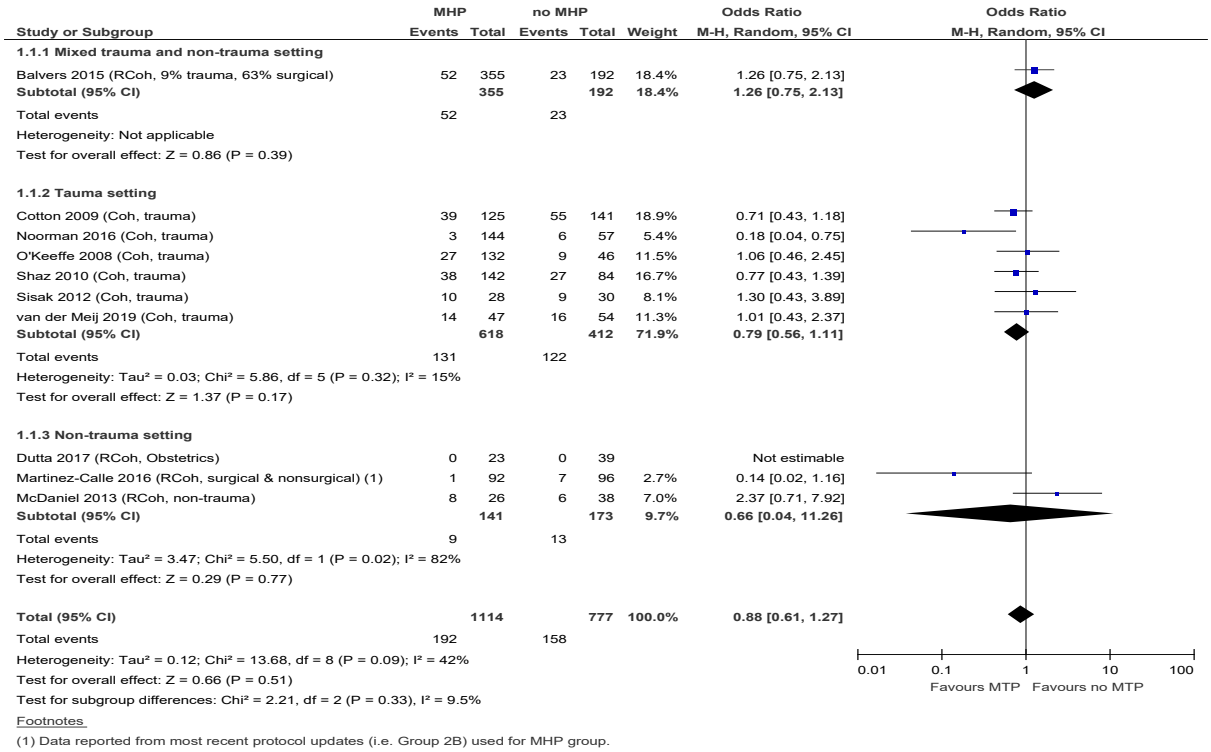
Among patients with blunt and penetrating trauma, a meta-analysis of data from observational studies included in this review (Figure 4.6) showed no significant difference in mortality rate (24 hours) among those who received a MHP (131/618, 21.2%) compared with those who did not (122/412, 29.6%) with the odds ratio (OR) of 0.79 observed (95% CI 0.56, 1.11; $p = 0.17$; random effect, $I^2 = 15\%$). However, the mortality rate (latest timepoint) in patients with critical bleeding was better among those who received a MHP (717/2278, 31.5%) than among those who did not (786/1948, 40.3%) with the OR of 0.67 observed (95% CI 0.53, 0.85; $p = 0.001$; random effect, $I^2 = 63\%$).

Among paediatric trauma patients who received MHPs, the mortality rate of 41.7% (43/103) was not significantly different from the mortality rate of 36.1% (35/97) observed among those who did not receive MHPs. This corresponded to an OR of 1.31 (95% CI 0.71, 2.42; $p = 0.38$; random effect, $I^2 = 5\%$).

Among non-trauma patients who received MHPs, the mortality rate 22% (42/191) was not significantly different from the mortality rate of 35.7% (91/255) observed among those who did not receive MHPs. This corresponded to an OR of 0.54 (95% CI 0.25, 1.15; $p = 0.11$; random effects, $I^2 = 61\%$).

DRAFT

Figure 4.6 Forest plot of comparison: MHPs vs no MHPs, outcome: Mortality, 24 hours



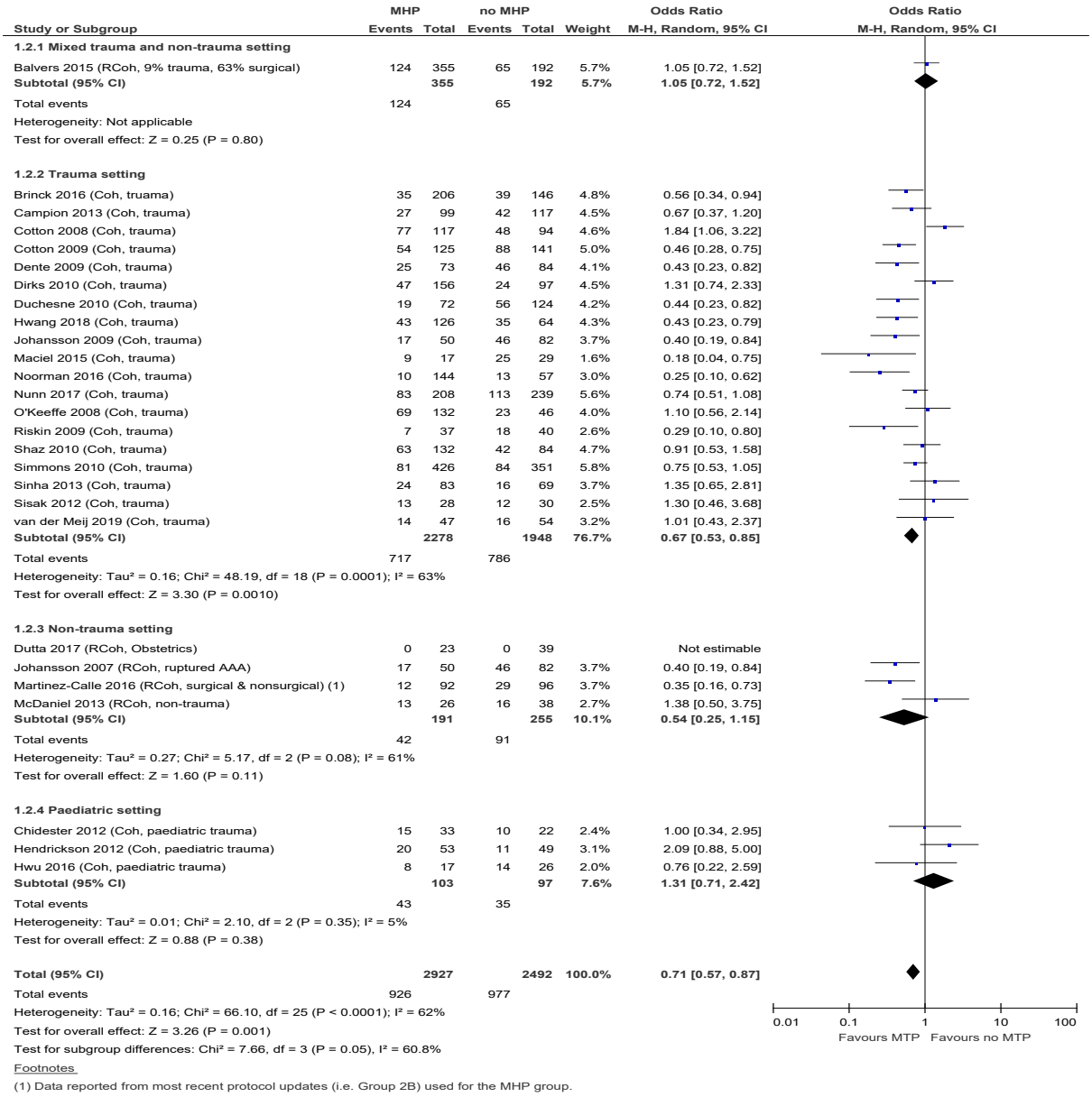
Study or Subgroup	MHP Events	MHP Total	no MHP Events	no MHP Total	Weight	Odds Ratio M-H, Random, 95% CI
1.1.1 Mixed trauma and non-trauma setting						
Balvers 2015 (RCoh, 9% trauma, 63% surgical)	52	355	23	192	18.4%	1.26 [0.75, 2.13]
Subtotal (95% CI)		**355**		**192**	**18.4%**	**1.26 [0.75, 2.13]**
Total events	52		23			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.86 (P = 0.39)						
1.1.2 Tauma setting						
Cotton 2009 (Coh, trauma)	39	125	55	141	18.9%	0.71 [0.43, 1.18]
Noorman 2016 (Coh, trauma)	3	144	6	57	5.4%	0.18 [0.04, 0.75]
O'Keeffe 2008 (Coh, trauma)	27	132	9	46	11.5%	1.06 [0.46, 2.45]
Shaz 2010 (Coh, trauma)	38	142	27	84	16.7%	0.77 [0.43, 1.39]
Sisak 2012 (Coh, trauma)	10	28	9	30	8.1%	1.30 [0.43, 3.89]
van der Meij 2019 (Coh, trauma)	14	47	16	54	11.3%	1.01 [0.43, 2.37]
Subtotal (95% CI)		**618**		**412**	**71.9%**	**0.79 [0.56, 1.11]**
Total events	131		122			
Heterogeneity: Tau² = 0.03; Chi² = 5.86, df = 5 (P = 0.32); I² = 15%						
Test for overall effect: Z = 1.37 (P = 0.17)						
1.1.3 Non-trauma setting						
Dutta 2017 (RCoh, Obstetrics)	0	23	0	39		Not estimable
Martinez-Calle 2016 (RCoh, surgical & nonsurgical) (1)	1	92	7	96	2.7%	0.14 [0.02, 1.16]
McDaniel 2013 (RCoh, non-trauma)	8	26	6	38	7.0%	2.37 [0.71, 7.92]
Subtotal (95% CI)		**141**		**173**	**9.7%**	**0.66 [0.04, 11.26]**
Total events	9		13			
Heterogeneity: Tau² = 3.47; Chi² = 5.50, df = 1 (P = 0.02); I² = 82%						
Test for overall effect: Z = 0.29 (P = 0.77)						
Total (95% CI)		**1114**		**777**	**100.0%**	**0.88 [0.61, 1.27]**
Total events	192		158			
Heterogeneity: Tau² = 0.12; Chi² = 13.68, df = 8 (P = 0.09); I² = 42%						
Test for overall effect: Z = 0.66 (P = 0.51)						
Test for subgroup differences: Chi² = 2.21, df = 2 (P = 0.33), I² = 9.5%						

Footnotes

(1) Data reported from most recent protocol updates (i.e. Group 2B) used for MHP group.

DRAFT

Figure 4.7 Forest plot of comparison: MHPs vs no MHPs, outcome: Mortality, latest timepoint



Footnotes

(1) Data reported from most recent protocol updates (i.e. Group 2B) used for the MHP group.

Table 4.9 Results for defined MHP versus no defined MHP: Patients *with* critical bleeding – Mortality

Study ID Study design[a]	Sample size (no. of trials) included in analysis	Patient population	Setting (Location)	Comparison	Outcome	Results			
						MHP n/N (%)	No MHP n/N (%)	Risk estimate (95% CI)	*Statistical significance* *p*-value Heterogeneity[b]
Mixed trauma and non-trauma settings									
Sommer 2019 SR *Critically low quality*	N = 547 (1 Coh) Balvers 2015	Adult patients with major bleeding	Trauma and non-trauma (surgical, general medicine). SC (Netherlands)	MHP vs pre-MHP	Mortality, 24-hour	52/355 (15)	23/192 (12)	OR 1.26 (0.75, 2.13)[c]	*p* = 0.39[c]
					Mortality, 30-days	124/355 (35)	62/192 (34)	OR 1.05 (0.72, 1.52)[c]	*p* = 0.80[c]
Trauma setting									
Consunji 2020 SR *High quality*	N = 1030 (6 Coh)	Various patients with haemorrhage requiring transfusion	Trauma, MC and SC (US, Australia)	MHP vs no MHP	Mortality, 24-hour	131/618 (21.2)	122/412 (29.6)	OR 0.79 (0.56, 1.11)[c]	*No significant difference* *p* = 0.17[c] *Mild heterogeneity* I^2 = 15%
					Noorman 2016	3/144 (2)	6/57 (11)	OR 0.18 (0.04, 0.75)	*Favours MHP, p = 0.004*
					Cotton 2009	39/125 (31)	55/141 (39)	OR 0.71 (0.43, 1.18)	*p = 0.185*
					O'Keeffe 2008	27/132 (20.5)	9/46 (19.6)	OR 1.06 (0.46, 2045)	*p > 0.05*
					Shaz 2010	38/142 (29)	27/84 (32)	OR 0.85 (0.47, 1.54)	*p = 0.28*
					Sisak 2012	10/28 (35.7)	9/30 (30)	OR 1.30 (0.43, 3.89)	*p = 1.00*
					van der Meij 2019	14/47 (29.8)	16/54 (29.6)	OR 1.01 (0.43, 2.37)	*p = 0.99*
	N = 3314 (14 Coh)	Various patients with haemorrhage requiring transfusion	Trauma, MC and SC (US, Denmark, Australia)	MHP vs no MHP	Mortality, 30-days or latest timepoint	552/1867 (29.6)	548/1447 (37.9)	OR 0.69 (0.53, 0.89)[c]	*Favours MHP* *p* = 0.004[c] *Substantial heterogeneity* I^2 = 57%[c]
					Brinck 2016	35/206 (16.9)	39/146 (26.5)	OR 0.56 (0.34, 0.94)	*Favours MHP, p = 0.032*
					Cotton 2009	54/125 (43.2)	88/141 (62.4)	OR 0.46 (0.28,0.75)	*Favours MHP, p = 0.001*
					Dirks 2010	47/156 (30.1)	24/97 (24.7)	OR 1.31 (0.74, 2.33)	*p = 0.382*
					Shaz 2010	63/132 (48)	42/84 (50)	OR 0.91 (0.53, 1.58)	*p = 0.47*
					Hwang 2018	43/126 (34.1)	35/64 (54.7)	OR 0.48 (0.26, 0.88)	*Favours MHP, p = 0.007*
					Maciel 2015	9/17 (53)	25/29 (86)	OR 0.23 (0.06, 0.91)	*Favours MHP, p = 0.03*
					Noorman 2016	10/144 (7)	13/57 (23)	OR 0.25 (0.10, 0.62)	*Favours MHP, p = 0.002*
					Riskin 2009	7/37 (19)	18/40 (45)	OR 0.29 (0.00, 0.80)	*Favours MHP, p = 0.02*
					O'Keeffe 2008	69/132 (52.3)	23/46 (50.0)	OR 1.10 (0.56, 2.14)	*p = NR*
					Nunn 2017	83/208 (40.1)	113/239 (47.2)	OR 0.77 (0.53, 1.12)	*p = 0.1732*
					Simmons 2010	81/426 (19.0)	84/351 (23.9)	OR 0.75 (0.53, 1.05)	*p = 0.115*
					Sinha 2013	24/83 (29)	16/69 (23)	OR 0.77 (0.16, 3.75)	*p = 0.43*
					Sisak 2012	13/28 (46)	12/30 (40)	OR 1.30 (0.46, 3.68)	*p = 0.791*
					van der Meij 2019	14/47 (29.8)	16/54 (29.6)	OR 1.16 (0.53, 2.58)	*p = 0.99*

DRAFT

Study ID Study design[a]	Sample size (no. of trials) included in analysis	Patient population	Setting (Location)	Comparison	Outcome	Results			
						MHP n/N (%)	No MHP n/N (%)	Risk estimate (95% CI)	*Statistical significance* *p*-value Heterogeneity[b]
Cannon 2017 SR *Moderate quality*	N = 412 (2 Coh) Campion 2013 Duchesne 2010	Adult patients with severe trauma at risk of death from haemorrhage (civilian and military)	SC (US)	MHP vs pre-MHP	Mortality, 30-days or in hopsital	46/171 (26.9) 27/99 (27.3) 19/72 (26.4)	98/241 (40.7) 42/117 (35.9) 56/124 (45.2)	OR 0.55 (0.36, 0.84)[c] 0.67 (0.37, 1.20) 0.44 (0.23, 0.82)	*Favours MHP* *p* = 0.006 No heterogeneity I^2 = 0% (*p* = 0.33)
Vogt 2012 SR *Moderate quality*	N = NR (4 Coh)	Adult trauma patients (civilian) requiring massive transfusion	Trauma (Canada, Denmark, US)	MHP vs no MHP	Mortality, 30-day or in-hospital Cotton 2008[e] Dente 2009 Johansson 2009 Vogt 2009	 48/94 (51.1) 25/73 (34.2)[f] 17/50 (34)[f] NR	 77/117 (65.8) 46/84 (55)[f] 46/82 (56)[f] NR	Adjusted RR estimate 0.51 (0.29, 0.90) Unadjusted RR estimates 0.69 (0.52, 0.91)[f] 0.65 (0.51, 0.82)[f] 0.64 (0.32, 1.27)	NR
Non-trauma setting									
Sommer 2019 SR *Critically low quality*	N = 314 (3 Coh)	Adult patients with major bleeding	Non-trauma (surgical, obstetric). SC (Denmark, Spain, US)	MHP vs pre-MHP	Mortality, 24-hour McDaniel 2013 Martinez -Calle 2016[d] Dutta 2017	9/141 (6.4)[c] 8/26 (30.8) 1/92 (0.5) 0/23 (0)	13/173 (7.5)[c] 6/38 (15.8) 7/96 (7.3) 0/39 (0)	OR 0.66 (0.04, 11.26)[c] 2.37 (0.71, 7.92)[c] 0.14 (0.02, 1.16)[c] NE	*No significant difference* *p* = 0.77[c] Substantial heterogeneity I^2 = 82% (*p* = 0.02)[c]
	N = 446 (4 Coh)				Mortality, 30-days Johansson 2007 McDaniel 2013 Martinez-Calle 2016[d] Dutta 2017	42/191[c] 17/50 (34) 13/26 (50.0) 12/92 (13) 0/23 (0)	91/255[c] 46/82 (56) 16/38 (42.1) 29/96 (30.2) 0/39 (0)	OR 0.54 (0.25, 1.15)[c] 0.40 (0.19, 0.84)[c] 1.38 (0.50, 3.75)[c] 0.35 (0.16, 0.73)[c] NE	*No significant difference* *p* = 0.11[c] Substantial heterogeneity I^2 = 61% (*p* = 0.08)[c]
Paediatrics, trauma setting									
Kinslow 2020 SR *Critically low quality*	N = 328 (3 Coh) Hwu 2016 Chidester 2012 Hendrickson 2012	Paediatric trauma patients with various ISS.	Paediatric trauma (US, Iraq, Afghanistan)	MHP vs no MHP	Mortality, in-hospital	43/103 (41.7)[c] 8/17 (47.1) 15/33 (45) 20/53 (38)	35/97 (36.1)[c] 14/26 (53.8) 10/22 (45) 11/49 (23)	OR 1.31 (0.71, 2.42)[c] 0.76 (0.22, 5.29)[c] 1.00 (0.34, 2.95)[c] 2.09 (0.88, 5.00)[c]	*p = 0.38*[c] I^2 = 5% (*p* = 0.35)[c]

CI, confidence interval; Coh, cohort study; ISS, injury severity score; MC, multicentre; MHP, major haemorrhage protocol; MT, massive transfusion; NR, not reported; OR, odds ratio; RR, relative risk; SC single centre; SR, systematic review; US, United States

a. Where only one RCT is identified in a systematic review, the evidence has been considered as RCT evidence. Where the systematic review assesses observational and cohort studies, the evidence has been considered as according to the study design features. The risk of bias of the included primary studies is based on the quality assessment reported by the systematic review authors.

b. Only applicable to Systematic reviews with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if P_{het} >0.1 and I^2 <25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25–50%; substantial heterogeneity I^2 >50%.
c. Calculated post-hoc using RevMan 5.4.
d. Martinez–Calle 2016 report MHP mortality for group A and B based on protocol updates in different years. For this review, data reported from the most recent protocol updates (i.e. Group 2B) are used and compared to pre-MHP. Where necessary, data from primary study was sourced.
e. Cotton 2008 reported estimate adjusted for age, gender, mechanism of injury, TRISS, and 24–hour transfusion requirements.
f. Data sourced from primary study.

DRAFT

Transfusion volume

Red blood cells

A summary of the evidence reported in the identified systematic reviews relating to transfusion volume of other blood components in patients with critical bleeding is presented in Table 4.10.

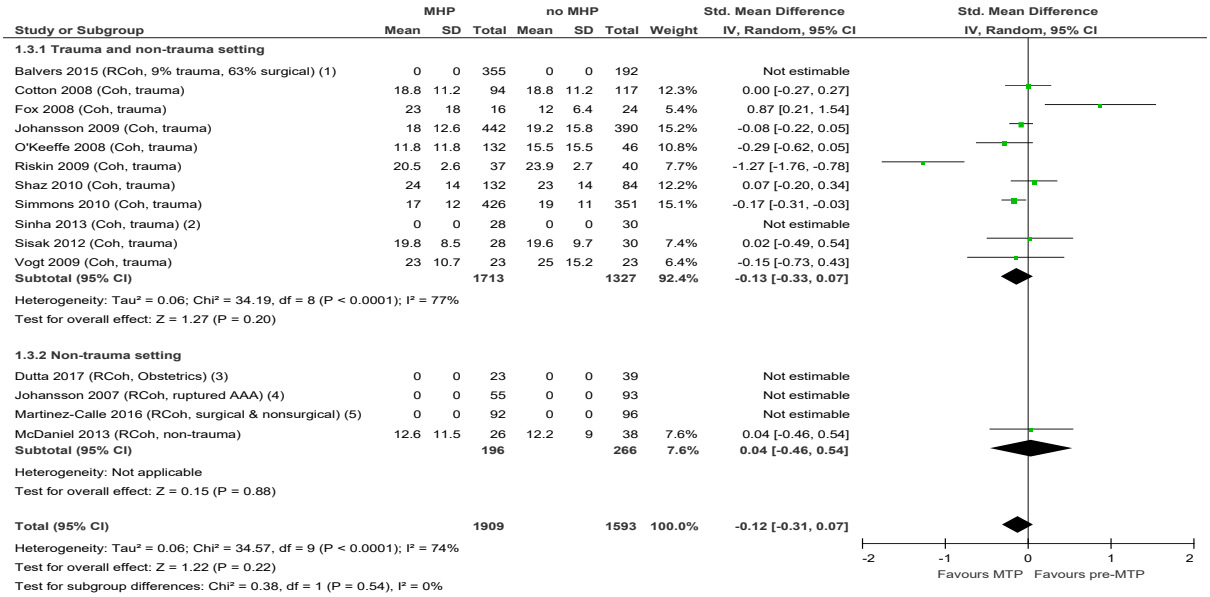
The systematic reviews (Sommer 2019, Cannon 2017, Mitra 2013, Vogt 2012) suggest only limited conclusions can be drawn from the available evidence, with a nonsignificant reduction in the volume of RBCs transfused (less than one red cell unit saved).

A meta-analysis of data from observational studies included in this review (see Figure 4.8) revealed a nonsignificant reduction in the volume of RBC transfusion in patients with critical bleeding who received MHPs (n=1356) compared with those who did not (n=1143), with an overall standardised mean difference (SMD) of –0.12 units observed (95% CI –0.31, 0.07; $p = 0.22$; random effect, $I^2 = 74\%$).

Among patients with blunt and penetrating trauma, no significant difference in the volume of RBC transfusion was observed among those who received MHPs compared with those who did not, with an overall SMD of –0.13 units observed (95% CI –0.33, 0.07; $p = 0.20$; random effect, $I^2 = 77\%$).

Among non-trauma patients, no significant difference in the volume of RBC transfusion was observed among those who received MHPs compared with those who did not, with an overall SMD of 0.04 units observed (95% CI –0.46, 0.54; $p = 0.88$).

Figure 4.8 Forest plot of comparison: MHPs vs no MHPs, outcome: Transfusion volume, red blood cells



Footnotes

(1) Median RBCs transfused: MHP 8 (7-13) vs pre-/no MHP 8 (6-12)
(2) Median RBCs transfused: MHP 14 (11-21) vs pre-/no MHP 16 (12-20)
(3) Median RBCs transfused: MHP 7 (5-9) vs pre-/no MHP 6 (5-8)
(4) Median RBCs transfused for ICU patients: MHP 2 (0-30) vs pre-/no MHP 6 (0-54)
(5) Median RBCs transfused: MHP 10 (18-12) vs pre-no/MHP 9 (8-14)

Table 4.10 Results for defined MHP versus no defined MHP: Patients *with* critical bleeding – Transfusion volume, red blood cells

Study ID Study design[a]	Sample size (no. of trials) included in analysis	Patient population	Setting (Location)	Comparison	Outcome	Results			
						MHP Mean ± SD (n)	No MHP Mean ± SD (n)	Risk estimate (95% CI)	*Statistical significance* *p*-value Heterogeneity[b]
Mixed trauma and non-trauma settings									
Sommer 2019 SR *Critically low quality*	N = 1261 (6 Coh)	Adult patients (aged 18 years or older) with major bleeding in trauma and non-trauma setting	Trauma and non-trauma (surgical, obstetrics, general). Single centres (Australia, The Netherlands, US)	MHP vs pre-MHP	RBC transfusion volume, units McDaniel 2013 Balvers 2015 Sinha 2013 Dutta 2017 Martinez-Calle 2016[d] Johansson 2007 (operating room) (intensive care unit)	Mean ± SD (n 12.6 ± 11.5 (26) Median (IQR) 8 (7–13) (n355) 14 (11–21) (n83) 7 (5–9) (n23) 10 (8–12) (n92) NR 2 (0–30)(n50)	Mean ± SD (n 12.2 ± 9.0 (38) Median (IQR) 8 (6–12) (n192) 16 (12–20) (n69) 6 (5–8) (n39) 9 (8–14) (n96) NR 6 (0–54)(n82)	MD 0.40 (–4.87, 5.67) [c]	*No significant difference* *p* = 0.864 *p* = 0.279 p = NR *p* = 0.85 *p* = NR *p* = NR Favours MHP, *p* < 0.05
Trauma setting									
Cannon 2017 SR *Moderate quality*	N = 551 (4 Coh)	Adult patients with severe trauma at risk of death from haemorrhage (civilian and military)	SC (Iraq, US)	MHP vs pre-MHP	RBC transfusion volume, units, 24 hours Fox 2008 O'Keeffe 2008 Riskin 2009 Shaz 2010	n=217 23 ± 18 (16) 11.8 ± 11.8 (132) 20.5 ± 2.6 (37) 24 ± 14 (132)	n=194 12 ± 6.4 (24) 15.5 ± 15.5 (46) 23.9 ± 2.7 (40) 23 ± 14 (84)	MD 0.36 (–4.54,3.83) 11.00 (1.82, 20.18) –3.70 (–8.61, 1.21) –3.40 (–4.58, –2.22) 1.00 (–4.54, 3.83)	*No significant difference* *p* = 0.87 Substantial heterogeneity I^2 = 78% (*p* = 0.004)
Mitra 2013 SR *Moderate quality*	N = 835 (2 Coh)	Adult trauma patients (civilian and military) in the initial trauma resuscitation phase	SC (US, Australia)	MHP vs pre-MHP	RBC transfusion volume Simmons 2010 Sisak 2012	NR 17 ± 12 (426) 19.8 ± 8.5 (28)	NR 19 ± 11 (351) 19.6 ± 9.7 (30)	NR	NR
Vogt 2012 SR *Moderate quality*	N = 1267 (4 Coh) Cotton 2008 Johansson 2009 Vogt 2009	Adult patients requiring massive transfusion due to civilian trauma	SC, trauma (Canada, US, Denmark)	MHP vs no MHP	RBC transfusion volume, units at 24 hours	NR 18.8 ± 11.2 (94) 18 ± 12.6 (442) 23 ± 10.7 (23)	NR 18.8 ± 11.2 (117) 19.2 ± 15.8 (390) 25 ± 15.2 (23)	MD -0.90 (–2.51, 0.71)[c] MD 0.00 (–3.04, 3.04) MD –1.20 (–3.16, 0.76) –2.00 (–9.60, 5.60)	*No significant difference* *p* = 0.27[c] *No heterogeneity* I^2 = 0% (*p* = 0.78)[c]
Non-trauma setting – no identified studies reported on outcome of interest									
Paediatrics, trauma setting – no identified studies reported on outcome of interest									

CI, confidence interval; Coh, cohort; MD, mean difference; MHP, major haemorrhage protocol; NR, not reported; RBC, red blood cell; SC, single centre; SD, standard deviation; SR, systematic review; US, United States

a. Where only one RCT is identified in a systematic review, the evidence has been considered as RCT evidence. Where the systematic review assesses observational and cohort studies, the evidence has been considered as according to the study design features. The risk of bias of the included primary studies is based on the quality assessment reported by the systematic review authors.
b. Only applicable to Systematic reviews with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if P_{het} >0.1 and I^2 <25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25–50%; substantial heterogeneity I^2 >50%.
c. Calculated post-hoc using RevMan 5.4.
d. Martinez-Calle 2016 report MHP mortality for group A and B based on protocol updates in different years. For this review, data reported from the most recent protocol updates (i.e. Group 2B) are used and compared to pre-MHP. Where necessary, data from primary study was sourced.

DRAFT

Fresh frozen plasma

A summary of the evidence reported in the identified systematic reviews relating to transfusion volume of FFP in patients with critical bleeding is presented in Table 4.11.

Included systematic reviews (Sommer 2019, Mitra 2013, Vogt 2012) suggest only limited conclusions can be drawn from the available evidence, reporting slight nonsignificant reduction in the volume of FFP transfused (less than one FFP unit saved).

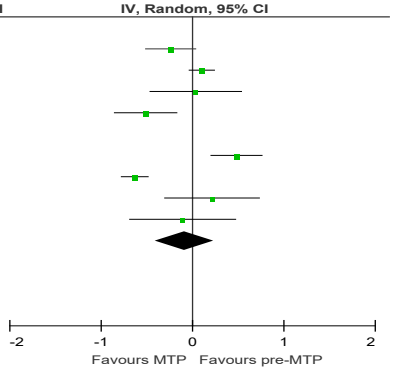
A meta-analysis of data from observational studies included in this review (see Figure 4.9) revealed a nonsignificant reduction in the volume of FFP transfusion in patients with critical bleeding who received MHPs (n=1340) compared with those who did not (n=1119), with an overall standardised mean difference (SMD) of –0.09 units observed (95% CI –0.41, 0.23; p = 0.57; random effect, I^2 = 92%). Heterogeneity was substantial with effect estimate largely influenced by three observational studies (O'Keefe 2008, Shaz 2010 and Simmons 2010). Furthermore, differences in triggers activating MHPs varied between studies.

Figure 4.9 Forest plot of comparison: MHPs vs no MHPs, outcome: Transfusion volume, FFP

	MHP			no MHP				Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
1.4.1 Mixed trauma and non-trauma settings									
Cotton 2008 (Coh, trauma)	9.9	7	94	12.4	12.5	117	13.4%	-0.24 [-0.51, 0.03]	
Johansson 2009 (Coh, trauma)	13.5	12.3	442	12.1	15.2	390	14.5%	0.10 [-0.03, 0.24]	
McDaniel 2013 (RCoh, non-trauma)	9.2	8	26	8.9	8.7	38	10.9%	0.04 [-0.46, 0.53]	
O'Keeffe 2008 (Coh, trauma)	5.7	5.4	132	8.7	6.9	46	12.7%	-0.51 [-0.85, -0.17]	
Riskin 2009 (Coh, trauma) (1)	10.7	0	37	12.3	0	40		Not estimable	
Shaz 2010 (Coh, trauma)	13	12	132	8	7	84	13.4%	0.48 [0.20, 0.76]	
Simmons 2010 (Coh, trauma)	8	8	426	14	11	351	14.4%	-0.63 [-0.78, -0.49]	
Sisak 2012 (Coh, trauma)	9.4	5.8	28	8.1	6.2	30	10.7%	0.21 [-0.30, 0.73]	
Vogt 2009 (Coh, trauma)	14	8	23	15	10.1	23	10.0%	-0.11 [-0.69, 0.47]	
Subtotal (95% CI)			**1340**			**1119**	**100.0%**	**-0.09 [-0.41, 0.23]**	

Heterogeneity: Tau² = 0.18; Chi² = 82.70, df = 7 (P < 0.00001); I² = 92%

Test for overall effect: Z = 0.57 (P = 0.57)



Test for subgroup differences: Not applicable

Footnotes

(1) Standard deviation and patient numbers not reported

Table 4.11 Results for defined MHP versus no defined MHP: Patients *with* critical bleeding – Transfusion volume, fresh frozen plasma

Study ID Study design[a]	Sample size (no. of trials) included in analysis	Patient population	Setting (Location)	Comparison	Outcome	Results			
						MHP Mean ± SD (n)	No MHP Mean ± SD (n)	Risk estimate (95% CI)	*Statistical significance* *p*-value Heterogeneity [b]
Mixed trauma and non-trauma settings									
Sommer 2019 SR *Critically low quality*	N = 1261 (6 Coh)	Adult patients (≥18 years) with major bleeding in trauma and non-trauma setting	SC (Australia, The Netherlands, US)	MHP vs pre-MHP	FFP transfusion volume, units McDaniel 2013 Median (IQR) Balvers 2015 Sinha 2013 Dutta 2017 Martinez-Calle 2016[d] Johansson 2007 (operating room) (intensive care unit)	 9.2 ± 8.0 (26) Median (IQR) 6 (4–11)(n355) 10 (7–17)(n83) 2 (0–4) (n23) 5 (3–9)(n92) 4 (2–16)(n50) 0 (0–4)	 8.9 ± 8.7 (38) Median (IQR) 6 (3–9) (n192) 6 (5–10)(n69) 4 (1–5) (n39) 5 (3–9) (n96) 0 (0–3)(n82) 1 (0–6)	 MD 0.30 (–3.84, 4.44)[c]	 *No significant difference* *p* = 0.631 *p* = 0.224 *p* = NR *p* = 0.28 *p* = 0.376 Favours MHP, *p* < 0.05 Favours MHP, *p* < 0.05
Trauma setting									
Mitra 2013 SR *Moderate quality*	N = 1532 (7 Coh)	Adult trauma patients (civilian) in the initial trauma resuscitation phase	SC (US, Australia, Denmark)	MHP vs pre-MHP	FFP transfusion volume Riskin 2009 Sisak 2012 O'Keeffe 2008 Simmons 2010 Shaz 2010 Dirks 2010 Sinha 2013	NR 10.7 ± NR 9.4 ± 5.8 (28) 5.7 ± 5.4 (132) 8 ± 8 (426) 13 ± 12 (132) NR NR	NR 12.3 ± NR 8.1 ± 6.2 (30) 8.7 ± 6.9 (46) 14 ± 11 (351) 8 ± 7 (84) NR NR	NR	 *No significant difference* *p* = NR Favours MHP, *p* = NR Favours no MHP, *p* = NR Favours no MHP, *p* = NR *p* = NR *p* = NR
Vogt 2012 SR *Moderate quality*	N = 1089 (3 Coh)	Adult trauma patients (civilian) requiring massive transfusion	SC, trauma (Canada, US, Denmark)	MHP vs no MHP	FFP transfusion volume, unit at 24 hours Cotton 2008 Johansson 2009 Vogt 2009	NR 9.9 ± 7 (94) 13.5 ± 12.3 (442) 14 ± 8 (23)	NR 12.4 ± 12.5 (117) 12.1 ± 15.2 (390) 15 ± 10.1 (23)	MD –0.50 (–3.37, 2.37) –2.50 (–5.17, 0.17) 1.40 (–0.49, 3.29) –1.00 (–6.27, 4.27)	*No significant difference* *p* = 0.22[c,e] *Substantial heterogeneity* I^2 = 0% (*p* = 0.06)[c,e]
Non-trauma setting – no identified studies reported on outcome of interest									
Paediatrics, trauma setting – no identified studies reported on outcome of interest									

CI, confidence interval; Coh, cohort; FFP, fresh frozen plasma; IQR, interquartile range; MD, mean difference; MHP, major haemorrhage protocol; NR, not reported; SC, single centre; SD, standard deviation; SR, systematic review; US, United States

a. Where only one RCT is identified in a systematic review, the evidence has been considered as RCT evidence. Where the systematic review assesses observational and cohort studies, the evidence has been considered as according to the study design features. The risk of bias of the included primary studies is based on the quality assessment reported by the systematic review authors.

b. Only applicable to Systematic reviews with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if P_{het} >0.1 and I^2 <25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25–50%; substantial heterogeneity I^2 >50%.

c. Calculated post-hoc using RevMan 5.4

d. Martinez-Calle 2016 report MHP mortality for group A and B based on protocol updates in different years. For this review, data reported from the most recent protocol updates (i.e. Group 2B) are used and compared to pre-MHP. Where necessary, data from primary study was sourced.
e. Data from Cotton 2008 not included in the meta-analysis due to substantial heterogeneity (I^2=64%, p = 0.06)

DRAFT

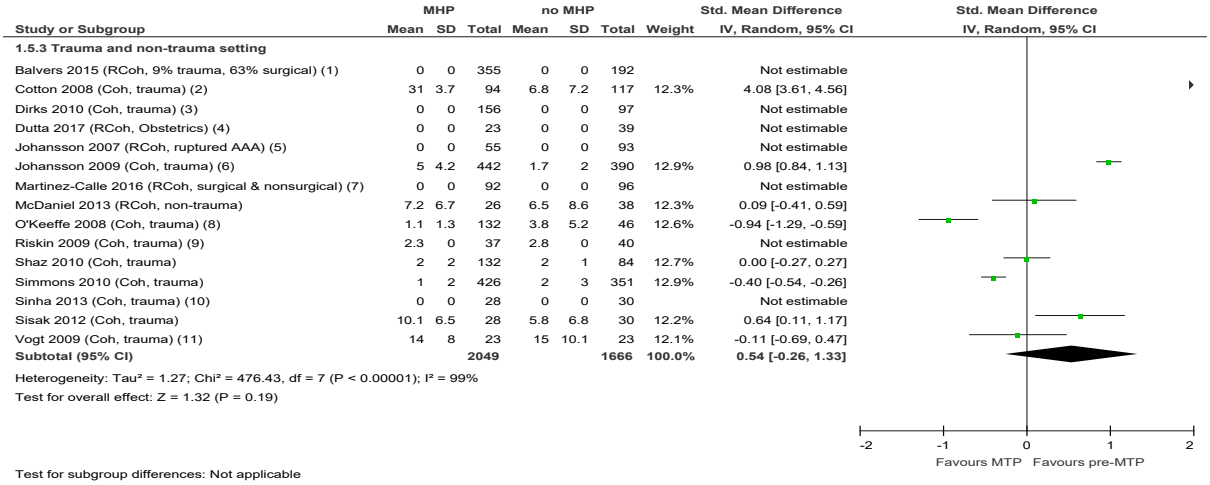
Platelets

A summary of the evidence reported in the identified systematic reviews relating to transfusion volume of platelets in patients with critical bleeding is presented in Table 4.12.

The systematic reviews (Sommer 2019, Mitra 2013, Vogt 2012) suggest only limited conclusions can be drawn from the available evidence, with a nonsignificant increase in the volume of platelets transfused (more than one plasma unit wasted).

A meta-analysis of data from observational studies included in this review (see Figure 4.10) revealed a nonsignificant increase in the volume of platelet transfusion in patients with critical bleeding who received MHPs (n=2049) compared with those who did not (n=1666), with an overall standardised mean difference (SMD) of 0.54 units observed (95% CI –0.26, 1.33; p = 0.19; random effect, I^2 = 99%). Heterogeneity was substantial with effect estimate likely to be largely influenced by differences between studies for MHP activation.

Figure 4.10 Forest plot of comparison: MHPs vs no MHPs, outcome: Transfusion volume, platelets



Test for subgroup differences: Not applicable

Footnotes

(1) Median (IQR): MHP 2 (0-4) vs pre-/no MHP 2 (1-3)
(2) Missing SD data
(3) Median (IQR): MHP 0 (0-0) vs pre-no MHP 1 (0-4)
(4) Median (IQR): MHP 0 (0-0.6) vs pre-/no MHP 0 (0-0.6)
(5) Median (IQR) in operating room: MHP 11 (2-42) vs pre-/no MHP 7 (0-46): and in ICU: MHP 2 (0-12) vs pre-/no MHP 4 (0-32)
(6) SD data missing
(7) Median (IQR): MHP 1 (0-2) vs pre-/no MHP 1 (0-2)
(8) SD data missing
(9) Standard devation and patient numbers not reported
(10) Median (IQR): MHP 3 (2-4) vs pre-/no MHP 2 (1-3)
(11) SD data missing

Table 4.12 Results for defined MHP versus no defined MHP: Patients *with* critical bleeding – Transfusion volume, platelets

Study ID Study design[a]	Sample size (no. of trials) included in analysis	Patient population	Setting (Location)	Comparison	Outcome	Results			
						MHP Mean ± SD (n)	No MHP Mean ± SD (n)	Risk estimate (95% CI)	*Statistical significance* *p*-value Heterogeneity[b]
Mixed trauma and non-trauma settings									
Sommer 2019 SR *Critically low quality*	N = 863 (6 Coh)	Adult patients with major bleeding in trauma and non-trauma setting	SC (Australia, The Netherlands, US)	MHP vs pre-MHP	PLT transfusion volume, units McDaniel 2013 Balvers 2015 Sinha 2013 Dutta 2017 Martinez-Calle 2016c Johansson 2007 (operating room) (intensive care unit)	 7.2 ± 6.7 (26) Median (IQR) 2 (0–4) (n355) 3 (2–4) (n83) 0 (0–0.6) (n23) 1 (0–2) (n) 11 (2–42) 2 (0–12)	 6.5 ± 8.6 (38) Median (IQR) 2 (1–3) (n192) 2 (1–3) (n69) 0 (0–0.6) (n39) 1 (0–2) 7 (0–46) 4 (0–32)	NR	NR
Trauma setting									
Mitra 2013 SR *Moderate quality*	N = 1532 (7 Coh) Riskiin 2009 Shaz 2010 O'Keefe 2008 Sisak 2012 Simmons 2010 Dirks 2010 (total) Sinha 2013 (24 hours)	Adult trauma patients (civilian) in the initial trauma resuscitation phase	SC (US, Australia, Denmark)	MHP vs pre-MHP	PLT transfusion volume	 2.3 ± NR 2 ± 2 (132) 1.1 ± 1.3[f] (132) 10.1 ± 6.5 (28) 1 ± 2 (426) Median (IQR) 0 (0-0)[f] 3 (2-4)[f]	 2.8 ± NR 2 ± 1 (84) 3.8 ± 5.2[f] (46) 5.8 ± 6.8 (30) 2 ± 3 (351) Median (IQR) 1 (0-4)[f] 2 (1-3)[f]	NR	NR[d]
Vogt 2012 SR *Moderate quality*	N = 435 (3 Coh) Cotton 2008 Johansson 2009 Vogt 2009	Adult trauma patients (civilian) requiring massive transfusion	SC, trauma (Canada, Denmark, US)	MHP vs no MHP	PLT transfusion volume, units at 24 hours	 31 ± 3.7[f] (94) 5.0 ± 4.2[f] (442) 3 ± NR (23)	 6.8 ± 7.2[f] (117) 1.7 ± 2.0[f] (390) 2 ± NR (23)	NR	NR [d]
Non-trauma setting – no identified studies reported on outcome of interest									
Paediatrics, trauma setting – no identified studies reported on outcome of interest									

CI, confidence interval; Coh, cohort; IQR, interquartile range; MD, mean difference; MHP, major haemorrhage protocol; NR, not reported; PLT, platelets; SC single centre; SR, systematic review; US, United States

a. Where only one RCT is identified in a systematic review, the evidence has been considered as RCT evidence. Where the systematic review assesses observational and cohort studies, the evidence has been considered as according to the study design features. The risk of bias of the included primary studies is based on the quality assessment reported by the systematic review authors.

b. Only applicable to Systematic reviews with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if P_{het} >0.1 and I^2 <25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25–50%; substantial heterogeneity I^2 >50%.

c. Calculated post-hoc using RevMan 5.4

d. Meta-analysis not conducted due to substantial heterogeneity (I^2=89%–100%)
e. The MHP implemented in Martinez-Calle 2016 was updated during the study period (MHP 1: 2007–2009 and MHP 2: 2010–2012). The p-value is pre-MHP vs MHP 1 vs MHP2
f. Sourced from primary study

DRAFT

Wastage of blood components

A summary of the evidence reported in the identified systematic reviews relating to wastage of blood components in patients with critical bleeding is presented in Table 4.13.

Systematic review suggests only limited conclusions can be drawn from the available evidence, reporting significant wastage of platelets following MHP implementation. As noted by Sommer 2018, MHP termination may influence wastage of blood components. Furthermore, overactivation of MHPs can also lead to wastage of blood components. Due to the limited data, no meta-analysis was performed.

Time to delivery of blood components

A summary of the evidence reported in the identified systematic reviews relating to time to delivery of blood components in patients with critical bleeding is presented in Table 4.14.

Systematic review suggests only limited conclusions can be drawn from the available evidence, reporting significant reduction in the time to first FFP administration following MHP implementation. Due to the limited data, no meta-analysis was performed.

DRAFT

Table 4.13 Results for defined MHP versus no defined MHP: Patients with critical bleeding – Wastage of blood components

Study ID Study design[a]	Sample size (no. of trials) included in analysis	Patient population	Setting (Location)	Comparison	Outcome	Results			
						MHP units/total issued (%)	No MHP units/total issued (%)	Risk estimate (95% CI)	*Statistical significance* *p*-value Heterogeneity[b]
Mixed trauma and non-trauma settings – not identified studies reported on outcome of interest									
Trauma setting – no identified studies reported usable data									
Non-trauma setting									
Sommer 2019 SR *Critically low quality*	N = 164 (1 Coh) McDaniel 2013	Adult patients with major bleeding due to non-trauma	Non-trauma (surgical, general medicine) SC (US)	MHP vs pre-MHP	Wastage of RBCs	3/613 (0.5)	3/848 (0.35)	OR 1.39 (0.28, 6.89)[c]	*No significant difference* *p* = 0.69[c]
					Wastage of FFP	1/406 (0.25)	4/553 (0.72)	OR 0.34 (0.04, 3.04)[c]	*No significant difference* *p* = 0.33[c]
					Wastage of PLTs	39/304 (12.8)	29/358 (8.1)	OR 1.67 (1.01, 2.77)[c]	*Favours no MHP* *p* = 0.05[c]
Paediatrics, trauma setting – not identified studies reported on outcome of interest									

CI, confidence interval; Coh, cohort; FFP, fresh frozen plasma; MHP, major haemorrhage protocol; OR, odds ratio; PLT, platelet; RBC, red blood cell; SC, single centre; SR, systematic review; US, United States

a. Where only one RCT is identified in a systematic review, the evidence has been considered as RCT evidence. Where the systematic review assesses observational and cohort studies, the evidence has been considered as according to the study design features. The risk of bias of the included primary studies is based on the quality assessment reported by the systematic review authors.

b. Only applicable to Systematic reviews with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if P_{het} >0.1 and I^2 <25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25–50%; substantial heterogeneity I^2 >50%.

c. Calculated post-hoc using RevMan 5.4.

DRAFT

Table 4.14 Results for defined MHP versus no defined MHP: Patients with critical bleeding – Time to delivery of blood components

Study ID Study design[a]	Sample size (no. of trials) included in analysis	Patient population	Setting (Location)	Comparison	Outcome	Results			
						MHP Mean ± SD (n)	No MHP Mean ± SD (n)	Risk estimate (95% CI)	*Statistical significance* *p*-value Heterogeneity[b]
Mixed trauma and non-trauma settings – no identified studies reported on outcome of interest									
Trauma settings – no identified studies reported on outcome of interest									
Non-trauma settings – no identified studies reported on outcome of interest									
Paediatrics, trauma setting									
Kamyszek 2019 SR *Critically low quality*	N = 43 (1 Coh) Hwu 2016	Paediatric trauma patients receiving MT	MC (US, Iraq, Afghanistan)	MHP vs pre-MHP	Hours to first blood component	0.9 ± NR (17)	0.8 ± NR (26)	NR	*No significant difference* *p* = 0.688
					Hours to first RBC	1.4 ± NR (17)	0.8 ± NR (26)	NR	*No significant difference* *p* = 0.180
					Hours to first PLT	4.4 ± NR (17)	6 ± NR (26)	NR	*No significant difference* *p* = 0.421
	N = NR (2 Coh) Hwu 2016 Henderickson 2012				Hours to first FFP	1.0 ± NR 0.8 ± NR	2.7 ± NR 3.3 ± NR	NR	*Favours MHP* *p* = 0.005 *p* <0.001

CI, confidence interval; Coh, cohort; FFP, fresh frozen plasma; MHP, major haemorrhage protocol; MC, multicentre; MT, massive transfusion; NR, not reported; PLT, platelet; RBC, red blood cell; SD, standard deviation; SR, systematic review; US, United States

a. Where only one RCT is identified in a systematic review, the evidence has been considered as RCT evidence. Where the systematic review assesses observational and cohort studies, the evidence has been considered as according to the study design features. The risk of bias of the included primary studies is based on the quality assessment reported by the systematic review authors.

b. Only applicable to Systematic reviews with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if Phet >0.1 and I2 <25%; (ii) mild heterogeneity if I2 <25%; moderate heterogeneity if I2 between 25–50%; substantial heterogeneity I2 >50%.

DRAFT

4.4 Dose, timing and ratio (algorithm) of RBCs to blood component therapy (Question 3)

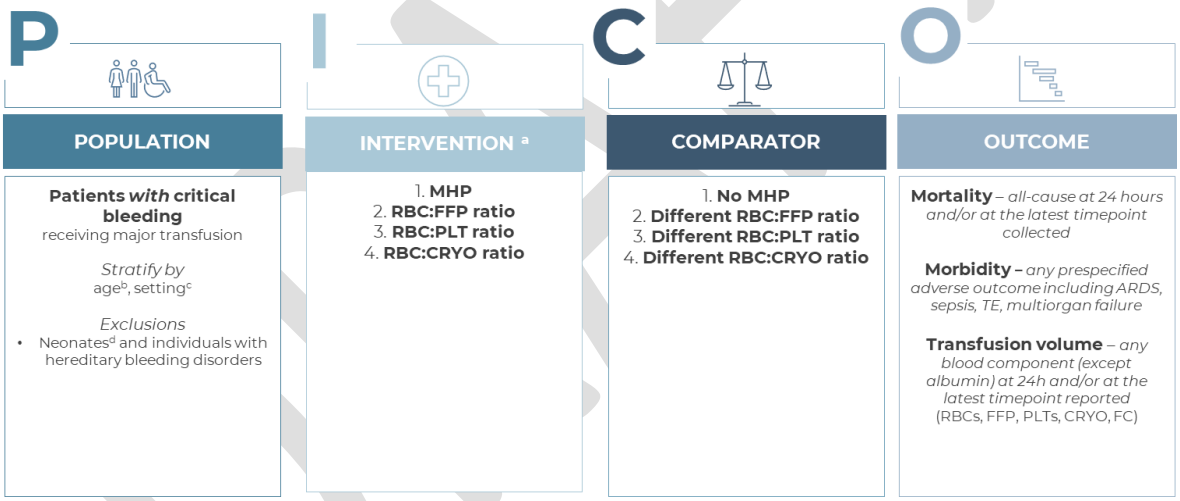
Question 3 – (Interventional)

In patients with critical bleeding, what is the optimal dose, timing and ratio (algorithm) of RBCs to blood component therapy (FFP, platelets, cryoprecipitate or fibrinogen concentrate) to reduce morbidity, mortality and transfusion?

4.4.1 Methods

This question investigated the optimal dose, timing and ratio of different ratios of red blood cells (RBCs) to blood component therapy including fresh frozen plasma (FFP), platelets (PLT) and cryoprecipitate (CRYO) in patients with critical bleeding, outlined in Figure 4.11 below.

Figure 4.11 PICO criteria: Question 3 – dose, timing and ratio of different ratios of red blood cells



ARDS, acute respiratory distress syndrome; CRYO, cryoprecipitate; FC, fibrinogen concentrate; FFP, fresh frozen plasma; MHP, major haemorrhage protocol; PLTs, platelets; RBCs, red blood cells; TE, thromboembolic event

Notes:

a. 1 vs 1; 2 vs 2; etc.

b. Adult (aged over 18 years), child (aged 2 to 12 years), adolescent (aged 13 to 18 years), infants (aged 1 to 23 months).

c. e.g. trauma, obstetric, perioperative (cardiothoracic, general surgery, gastrointestinal, liver transplant), paediatric, other.

d. Newborns up to 28 days following birth.

The selection of studies was conducted according to the screening criteria described in Section 3.3.

This question was included in the previous version of the guidelines, which investigated literature published up to 2009. Further, a comprehensive systematic review conducted by Monash included a search of the literature published between 2009 and 2015. However, this comprehensive review only included RCTs. Hence, for this question, evidence published after June 2015 was considered but any articles published prior to 2015 that had been identified in a systematic review were also included.

An updated literature search was conducted in September 2021 to identify any new systematic reviews meeting the eligibility criteria. Assuming all relevant primary studies have been identified in the included systematic review studies; the systematic screen for RCTs was limited to studies published from January 2021. This is based on the literature search dates of the most recent identified systematic review (Rijnhout 2021), which was assumed to have identified all relevant RCTs in the trauma and non-trauma setting.

Overall, the systematic review and handsearching process identified 16 systematic reviews that included three RCTs and 22 nonrandomised cohort studies that met the criteria and were relevant to the research question. The systematic review process also identified one additional nonrandomised cohort study relevant to this research question that was not included in the systematic reviews.

4.4.2 Summary of evidence

4.4.2.1 Systematic reviews evidence

Sixteen systematic reviews (41, 54, 56, 57, 60-71) were included that assessed the effect of different ratios of RBCs to blood component therapy including FFP, PLT and CRYO in patients with critical bleeding. The main characteristics and quality of these systematic reviews and relevant outcomes assessed are summarised in Table 4.15.

McQuilten 2018, Kleinveld 2021 and Richie 2020 restricted their search to RCTs only. All other systematic reviews included RCTs and observational studies as part of their search criteria. Most reviews (da Luz 2019, Rahouma 2017, Cannon 2017, Jones 2016, Poole 2016, Tapia 2013, Kinslow 2020, Maw 2018, Meneses 2020, Rijnhout 2021, Ritchie 2020, Rodriguez 2020, Wirtz 2020) included trauma patients. One review (Rahouma 2017) included trauma and perioperative patients and one review (Phillips 2021) included patients with diagnosed ruptured abdominal aortic aneurysms.

Identified systematic reviews investigated various ratios of blood components. For the purpose of this review, a high ratio was defined as 1:1:1 and was compared to lower ratios of blood components. Overall, 12 systematic reviews (Kleinveld 2021, Rijnhout 2021, Meneses 2020, Richie 2020, Rodriguez 2020, Wirtz 2020, da Luz 2019, McQuilten 2018, Cannon 2017, Rahouma 2017, Poole 2016, Tapia 2013) identified three RCTs (Holcomb 2015, Nascimento 2013, Galganski 2016) relevant to this research question (see 'RCT evidence'). A matrix illustrating the overlap of RCTs included in the reviews is provided in Table 4.16.

Twelve systematic reviews (da Luz 2019, Rahouma 2017, Rijnhout 2021, Rodriguez 2020, Meneses 2020, Cannon 2017, Rahouma 2017, Poole 2016, Jones 2016, Tapia 2013, Phillips 2021, Kinslow 2020, Maw 2018) identified 22 nonrandomised cohort studies that met inclusion criteria for this question (see 'Observational and cohort studies'). A matrix illustrating the overlap of cohort studies included in the reviews is provided in Table 4.18.

Eight other systematic reviews (McQuilten 2015, Bhangu 2013, Hallet 2013, Johansson 2012, Rajasekhar 2011, Murad 2010, Phan 2010, Zehtabchi 2009, Kozek-Langeneck 2011) were identified in the literature but these reviews did not conduct pooled analyses or provide any additional evidence relevant to this question and are therefore not discussed further in this report. A complete list of excluded studies that met the PICO criteria for this question but were later excluded is provided in Appendix B (technical report, volume 2).

Table 4.15 Characteristics and quality of systematic review evidence: ratio of RBCs to blood component therapy

Review ID *Review quality*	Study design (No. of studies)	Population	Intervention	Comparator	Outcomes
Trauma setting					
Kleinveld 2021 *Moderate*	SR / MA of RCTs (5 studies)	Trauma patients	High PLT:RBC ratio	Low PLT:RBC ratio	Mortality MOF TE
Rijnhout 2021 *Moderate*	SR / MA of RCTs and observational studies (12 studies)	Military and civilian adult trauma patients	High PLT:RBC ratio	Low PLT:RBC ratio	Mortality Transfusion volumes
Meneses 2020 *Critically low*	SR of observational studies (11 studies)	Adult trauma patients	High ratio of blood components	Low ratio of blood components	Mortality
Ritchie 2020 *Low*	SR of RCTs (7 studies)	Trauma patients	Higher ratio of blood components	Lower ratio of blood components	Mortality TE Transfusion volumes
Rodriguez 2020 *Moderate*	SR / MA of observational studies (33 studies)	Adult trauma patients	High FFP:RBC ratio	Low FFP:RBC ratio	Mortality
Wirtz 2020 *Moderate*	SR of RCTs and observational studies (40 studies)	Patients ≥16 years with severe trauma (ISS ≥16) resulting in haemorrhage	High FFP:RBC ratio PLT:RBC ratio	High FFP:RBC ratio PLT:RBC ratio	TE
da Luz 2019 *Moderate*	SR / MA of RCTs and observational studies (54 studies)	Civilian and military trauma patients	High FFP:PLT:RBC ratio	Low FFP:PLT:RBC ratio	Mortality
McQuilten 2018 *Moderate*	SR / MA of RCTs (16 studies)	Trauma patients	Higher ratio of RRP, PLTs, CRYO or FC to RBCs	Lower ratio of RRP, PLTs, CRYO or FC to RBCs	Mortality MOF TE Transfusion volumes
Cannon 2017 *Moderate*	SR / MA of RCTs and observational studies (19 studies)[a]	Severely injured adult patients requiring transfusion and/or ISS >25	High FFP:RBC ratio PLT:RBC ratio	Low FFP:RBC ratio PLT:RBC ratio	Mortality Transfusion volume
Rahouma 2017 *Critically low*	SR / MA of RCTs and observational studies (36 studies)	Trauma and surgical patients requiring transfusion	High FFP:RBC ratio	Low FFP:RBC ratio	Mortality
Jones 2016 *Critically low*	SR of observational studies (25 studies)[b]	Civilian or military trauma patients	High FFP:RBC ratio PLT:RBC ratio	Different FFP:RBC ratio PLT:RBC ratio	Mortality MOF

Poole 2016 *Critically Low*	SR of RCTs and observational studies (10 studies)	Adult trauma patients (excluding TBI) in non-military setting	High ratio FFP:RBC FFP:PLT:RBC	Lower ratio FFP:RBC FFP:PLT:RBC	Mortality
Tapia 2013 *Critically low*	SR / MA of RCTs, Coh & IV studies (20 studies)	Military and civilian trauma patients with at least 30% penetrating injury receiving MT	High FFP:RBC ratio PLT:RBC ratio	Low FFP:RBC ratio PLT:RBC ratio	Mortality
Paediatric, trauma setting					
Kinslow 2020 *Critically low*	SR of observational studies (33 studies)	Paediatric trauma patients	Higher ratio of RBC to blood components (PLTs or FFP)	Lower ratio of RBC to blood components (PLTs or FFP)	Mortality Adverse outcomes
Maw 2018 *Critically low*	SR of observational studies (4 studies)	Paediatric patients (<18 years) with traumatic injury requiring blood transfusion	MHP High ratios: FFP:RBC Plasma/PLT:RBC	MHP Low ratios: FFP:RBC Plasma/PLT:RBC	Mortality ICU LOS Unnecessary transfusion
Surgical setting					
Phillips 2021 *Low*	SR of observational studies (7 studies)	Surgical patients diagnosed with AAA	High FFP:RBC ratio	Low FFP:RBC ratio	Mortality

AAA, abdominal aortic aneurism; CRYO, cryoprecipitate; FC, fibrinogen concentrate; FFP, fresh frozen plasma; ICU, intensive care unit; ISS, injury severity score; LOS, length of stay; MHP, major haemorrhage protocol; MOF, multiple organ failure; MT, massive transfusion; PLT, platelets; RBC, red blood cells; RCT, randomised controlled trial; SR, systematic review; TBI, traumatic brain injury; TE, thromboembolic event

a. 15 studies (N=5292) assessed RBC:FFP and four studies (N=1607) assessed RBC:PLTs.

b. 17 studies (N=6801) assessed RBC:FFP and eight studies (N=3960) assessed RBC:PLTs.

4.4.2.2 Randomised controlled trials

A matrix illustrating the RCTs identified in the included systematic reviews is provided in Table 4.16. Among the 12 RCTs identified by the included systematic reviews, three were considered relevant to this review because they examine the effect of high (1:1:1) ratios in patients with critical bleeding.

One review (Kleinveld 2021) identified three RCTs that did not meet inclusion criteria for this research question and are not included. One study (Sperry 2018) assessed prehospital plasma resuscitation compared to standard care resuscitation and did not meet any PICO criteria for this review. Two studies (Baksaas-Aasen 2020, Gonzalez 2016) investigated the addition of viscoelastic haemostatic assays to MHPs on patient outcomes and are considered in Section 4.9 (question 8).

One other review (McQuilten 2018) identified 13 RCTs, of which 10 were ongoing trials and did not have any data available for inclusion in the analysis. Three RCTs did not meet the inclusion criteria for this question. One RCT (Cotton 2013) compared treatment with whole blood to treatment with blood components in adult trauma patients, the other two studies (Curry 2015, Nascimento 2016) compared the use of CRYO or fibrinogen concentrate (FC) versus no CYRO or FC in trauma patients. Both Curry 2015 and Nascimento 2016 are considered in Section 4.7 (question 6).

Table 4.16 Overlap table of RCTs identified by included systematic reviews: RBC:FFP and RBC:PLT ratios

	Trauma											
	Study ID	Holcomb 2015	Nascimento 2013	Galganski 2016	Gonzalez 2016	Sperry 2018	Baksaas-Aasen 2020	Curry 2015	Cotton 2013	Nascimento 2016	Rahbar 2015	Curry 2018	Akbari 2018
Review ID	Kleinveld 2021	✓	✓		X	X	X						
	Rijnhout 2021	✓	✓										
	Meneses 2020	✓											
	Richie 2020	✓	✓					X	X		X	X	X
	Rodriguez 2020	✓	✓										
	Wirtz 2020	✓											
	da Luz 2019	✓	✓										
	McQuilten 2018	✓	✓	✓				X	X	X			
	Cannon 2017	✓											
	Rahouma 2017	✓	✓										
	Poole 2016	✓											
	Tapia 2013	✓											

FFP, fresh frozen plasma; PLT, platelet; RBC, red blood cell; RCT, randomised controlled trial
✓ = study included in this review; X = study did not meet the inclusion criteria for this review; -- = study identified by the systematic review authors but not included (no usable data)

No additional RCTs were identified in the systematic review and handsearching process. The main characteristics and quality of eligible RCTs and the relevant outcomes assessed are detailed in Table 4.17.

Two RCTs (Holcomb 2015, Nascimento 2013) compared the effect of high (1:1:1) RBC:FFP transfusion ratios to lower ratios on the 28-day mortality in trauma patients (≥15 years) requiring massive transfusion. One RCT (Galganski 2016) compared the effect of a high (1:1) RBC:FFP ratio versus low (1:4) ratio in 45 children (aged younger than 18 years) who had a third degree burn injury of greater than 20% of the total body surface area. The study reported no deaths at hospital discharge and is not included in the meta-analysis for this research question. Transfusion requirements reported did not meet criteria for this question and are not reported further.

All three included RCTs were carried out in the US; two in trauma centres and one in a children's hospital. Overall, systematic review authors judged included RCTs to be high risk of bias with blinding being the main sources of bias. Holcomb 2015 was the only RCT that attempted to minimise bias from lack of blinding by having each death adjudicated by a clinician blinded to group assignment (McQuilten 2018).

Table 4.17 Characteristics and quality of RCT evidence: ratio of RBCs to blood component therapy

Study ID *Risk of bias*	Study design	Population N	Intervention	Comparator	Outcomes
Trauma setting					
Holcomb 2015 (PROPPR trial) *Moderate*	RCT, multicentre	Severely injured patients predicted to require MT N=680	FFP:PLT:RBC 1:1:1	FFP:PLT:RBC 1:1:2	Mortality Morbidity
Nascimento 2013 *High*	RCT, SC, unblinded	Patients with hypotension and bleeding expected to need MT N=78	Fixed FFP:PLT:RBC ratio 1:1:1	Transfusion guided by the institution's usual MT protocol	Mortality Transfusion volume
Paediatric, trauma setting					
Galganski 2016 *High*	RCT, SC	Paediatric patients (<18 years) admitted to ICU *with a third degree burn injury of ≥ 20% TBSA N=45	FFP:RBC 1:1	FFP:RBC 1:4	Mortality Transfusion volume

FFP, fresh frozen plasma; ICU, intensive care unit; MC, multicentre; MT, massive transfusion; PLT, platelet; RBC, red blood cells; RCT, randomised controlled trial; SC, single centre; TBSA, total body surface area

4.4.2.3 Observational and cohort studies

Twenty-two observational studies identified by the included systematic reviews met the inclusion criteria and were considered relevant to this question. A matrix illustrating the overlap of nonrandomised cohort studies identified in the included systematic reviews that met our inclusion criterion is provided in Table 4.18. The main characteristics of these studies is provided in Table 4.20.

Ten reviews (da Luz 2019, Rahouma 2017, Rijnhout 2021, Rodriguez 2020, Meneses 2020, Wirtz 2020, Cannon 2017, Poole 2016, Jones 2016, Tapia 2013) identified 47 cohort studies reporting outcome data for mortality, morbidity and transfusion volume but the studies assessed ratios of blood components that did not meet the high ratio criteria of 1:1:1 and were therefore not included in this review. An overlap table listing the observational and cohort studies that did not meet the high ratio criterion for this question is provided in Table 4.19.

One other review (Tanaka 2017) searched for evidence regarding the ratio of RBC to FFP used in patients with major obstetric bleeding. The authors identified five retrospective non-controlled observational studies that reported RBC:FFP ratios use in the obstetric setting. As these were noncomparative case series, they were not eligible for inclusion and were not considered further.

One additional cohort study (Peralta 2016) (72) was identified in the literature search that investigated the effect of high PLT:RBC ratio defined as 1:1.5 or more within four hours post-injury and their impact on the outcomes of trauma patient receiving MHP. As this ratio does not meet the set criteria of 1:1:1 for this question, this study was not considered further.

Table 4.18 Overlap table of observational and cohort primary studies identified by included systematic reviews that meet the 1:1:1 ratio inclusion criterion: RBC:FFP and RBC:PLT ratios

	Trauma													Surgical							Paediatrics, trauma				
	Study ID	Balvers 2017	Duchesne 2008	Duchesne 2009	Haltmeier 2017	Holcomb 2011	Maegele 2008	Perkins 2009	Sambasivan 2011	Vulliamy 2017	Wafaisade 2011	Zink 2009	Holcomb 2013	Mell 2010	Mazzeffi 2016	Johansson 2007	Johansson 2008	Henricksson 2012	Hall 2013	Tadlock 2010	Butler 2019	Cunningham 2019	Edwards xxx	Noland 2018	Nosanov 2013
Review ID	da Luz 2019	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓													
	Rijnhout 2021	✓				✓																			
	Rodriguez 2020		✓				✓				✓	✓													
	Meneses 2020		✓																						
	Cannon 2017			✓				✓																	
	Rahouma 2017		✓	✓			✓				✓	✓		✓	✓										
	Poole 2016					✓			✓		✓		✓												
	Jones 2016			✓		✓	✓	✓				✓													
	Tapia 2013		✓						✓			✓													
	Phillips 2021													✓	✓	✓	✓	✓	✓	✓					
	Kinslow 2020																				✓	✓		✓	✓
	Maw 2018																						--		--

FFP, fresh frozen plasma; PLT, platelet; RBC, red blood cell

✓ = study included in this review; X = study did not meet the inclusion criteria for this review; -- = study identified by the systematic review authors but not included (no usable data)

Table 4.19 Overlap table of observational and cohort primary studies identified by included systematic reviews that do not meet the 1:1:1 ratio inclusion criterion: RBC:FFP and RBC:PLT ratios

		Trauma																																													
	Study ID	Borgman 2007	Borgman 201	Brown 2011	Brown 2012	Bui 2016	Cap 2012	Cotton 2008	de Biasi 2011	Dente 2009	Duchesne 2010	Duchesne 2013	Endo 2018	Guidry 2013	Gunter 2008	Halmin 2013	Hardin 2014	Holcomb 2008 [a]	Holcomb 2012 [b]	Inaba 2010	Kashuk 2008	Kim 2014	Kudo 2014	Kutcher 2014	Lustenberger 2011	Magnotti 2011	Mitra 2010	Nardi 2015	Peinger 2011	Peralta 2015	Perkins 2011	Pidcoke 2012	Rowell 2011	Scalea 2008	Sharpe 2012	Shaz 2010	Simms 2014	Simmons 2011	Sperry 2008	Spinella 2011	Spoerke 2011	Stanworth 2016	Synder 2009	Teixeira 2009	Undurraga 2015	Van 2010	Yang 2015	Zielinski 2013
Review ID	da Luz 2019	X	X			X											X	X				X	X		X	X	X	X				X		X				X			X	X	X				
	Rahouma 2017	X	X	X	X				X	X					X			X			X	X			X	X	X		X				X		X	X			X	X	X	X	X	X	X	X	
	Rijnhout 2021				X		X													X					X						X			X			X	X									
	Rodriguez 2020		X		X				X	X		X	X	X	X			X			X	X	X		X	X	X		X	X			X		X	X	X		X	X	X	X	X	X			
	Meneses 2020	X								X								X			X												X		X				X					X				
	Wirtz 2020													X																																			X
	Cannon 2017	X														X		X				X		X		X	X		X							X			X				X	X				
	Poole 2016		X																	X							X							X										X			
	Jones 2016	X			X		X											X					X				X		X									X				X			X		
	Tapia 2013	X		X			X	X	X	X	X				X			X	X	X												X	X		X	X		X									

FFP, fresh frozen plasma; PLT, platelet; RBC, red blood cell

✓ = study included in this review; X = study did not meet the inclusion criteria for this review; -- = study identified by the systematic review authors but not included (no usable data)

[a] Superseded by Holcomb 2009

[b] Superseded by Holcomb 2013

Table 4.20 Characteristics and quality of observational and cohort evidence: RBC:FFP, RBC:PLT or RBC:CRYO ratio

Review ID ***Risk of bias***	Study design	Population N	Intervention	Comparator	Outcomes
Trauma setting					
Balvers 2017 *High*	Prospective, MC	Trauma patients receiving ≥4 units of RBCs in 24 hours N=385	High ≥1:1 ratio Plasma:RBC	High <1:1 ratio Plasma:RBC	Transfusion volume Waste of blood components
Maegele 2008 *High*	Retrospective	Trauma patients with an ISS >16 and who received ≥10 RBC N=713	High 1:1 ratio FFP:RBC	Low <1:1 ratio FFP:RBC	Mortality Morbidity Transfusion volume
Perkins 2009 *High*	Retrospective	Trauma patients receiving MT (≥10 units of blood within 24 hours) N=310	High PLT:RBC	Low PLT:RBC	Mortality
Vulliamy 2017 *High*	Prospective	Patients who received at least four units RBC N=161	High ratio FFP:RBC	Low ratio FFP:RBC	Mortality
Wafaisade 2011 *High*	Retrospective	Trauma patients ≥16 years with an ISS ≥16 who had received multiple transfusion but not MT N=970	High >1:1 ratio FFP:RBC	Low <1:1 ratio FFP:RBC	Mortality Morbidity Transfusion volume
Duchesne 2008 *High*	Retrospective	Adult trauma patients (blunt and penetrating) requiring surgical intervention and >10 units of RBC transfusion N=135	High 1:1 ratio FFP:RBC	Low 1:4 ratio FFP:RBC	Mortality
Duchesne 2009 *High*	Retrospective	Trauma patients with initial ED diagnosis of TIC who required transfusion during initial surgical intervention N=89	High 1:1 ratio FFP:RBC	Low 1:4 ratio FFP:RBC	Mortality
Haltmeier 2017 *High*	Retrospective	Patients with isolated severe blunt TBI N=242	High ratio Plasma/PLT:RBC	Low ratio Plasma/PLT:RBC	Mortality
Holcomb 2011 *High*	Retrospective, MC	Adult trauma patients who had received at least one unit of RBC in the ED N=427	High 1:1 ratio PLT:RBC	Low >1:20 ratio PLT:RBC	Mortality Transfusion volume
Sambasivan 2011 *High*	Retrospective, MC	Trauma patients N=1181	High 1:1 ratio FFP/PLT:RBC	Low <1:1 ratio FFP/PLT:RBC	Mortality

Review ID ***Risk of bias***	Study design	Population N	Intervention	Comparator	Outcomes
Zink 2009 *Moderate*	Retrospective	Trauma patients requiring massive transfusion N=153	High ≥1:1: ratio FFP:RBC	Low <1:4: ratio FFP:RBC	Mortality Transfusion volume
Paediatric, trauma setting					
Noland 2018 *High*	Retrospective	Paediatric trauma patients (≤18 years) requiring MT N=110	High ratio FFP:RBC	Low ratio FFP:RBC	Mortality
Cunningham 2019 *High*	Retrospective	Paediatric trauma patients (≤18 years) requiring MT N=465	High ratio Plasma:RBC	Low ratio Plasma:RBC	Mortality Transfusion volume
Butler 2019 *High*	Retrospective	Paediatric trauma patients (≤14 years) receiving MT N=583	High ratio FFP/PLT:RBC	Low ratio FFP/PLT:RBC	Mortality
Nosanov 2013 *High*	Retrospective	Paediatric trauma patients (≤18 years) requiring MT (transfusion of ≥50% total blood volume) N=105	High ratio Plasma/PLT:RBC	Low ratio Plasma/PLT:RBC	Mortality
Surgical setting					
Mell 2010 *Serious*	Retrospective observational	Patients with diagnosed rAAA N=128	High ratio FFP:RBC	Low ratio FFP:RBC	Mortality
Johansson 2007 *Serious*	Pre-post observational	Patients with diagnosed rAAA N=132	High ratio FFP:RBC	Low ratio FFP:RBC	Mortality
Johansson 2008 *Serious*	Pre-post observational	Patients with diagnosed rAAA N=146	High ratio FFP:RBC	Low ratio FFP:RBC	Mortality
Henriksson 2012 *Serious*	Retrospective observational	Patients with diagnosed rAAA N=174	High ratio FFP:RBC	Low ratio FFP:RBC	Mortality
Hall 2013 *Serious*	Pre-post observational	Patients with diagnosed rAAA N=89	High ratio FFP:RBC	Low ratio FFP:RBC	Mortality
Tadlock 2010 *Serious*	Retrospective observational	Patients with diagnosed rAAA N=12	High ratio FFP:RBC	Low ratio FFP:RBC	Mortality
Kauvar 2011 *Serious*	Retrospective observational	Patients with diagnosed rAAA N=87	High ratio FFP:RBC	Low ratio FFP:RBC	Mortality

ED, emergency department; FFP, fresh frozen plasma; ISS, injury severity score; MC, multicentre; MT, massive transfusion; PLT, platelet; rAAA, ruptured abdominal aortic aneurysm; RBC, red blood cells; TBI, traumatic brain injury; TIC, trauma-induced coagulopathy

Trauma setting

There were 11 observational studies identified by nine systematic reviews (41, 57, 62, 63, 65, 67, 69-71) conducted in adult trauma patients that met the PICO criteria for this question (inclusive of a high 1:1:1 ratio).

Five studies (Vulliamy 2017, Wafaisade 2011, Duchesne 2009, Maegele 2008, Duchesne 2008) assessed RBC:FFP ratios, two studies (Holcomb 2011, Perkins 2009) assessed RBC:PLT ratios and four studies (Hatimeier 2017, Balvers 2017, Sambasivan 2011, Zink 2009) assessed both RBC:FFP and RBC:PLT ratios.

The cohort studies were carried out in trauma centres in Denmark, Germany, Iraq, the Netherlands, UK or the US. Overall, risk of bias of included studies was judged to be moderate with concerns arising due to confounding.

Surgical setting

One review (Phillips 2021), evaluating whether a higher FFP:RBC ratio improves patient outcomes in the surgical setting, identified seven cohort studies (Hall 2013, Henriksson 2012, Johansson 2007, Johansson 2008, Kauvar 2011, Mell 2010, Tadlock 2010) that included patients with diagnosed ruptured abdominal aortic aneurysms.

Five studies (Hall 2013, Henriksson 2012, Johansson 2007, Johansson 2008, Tadlock 2010) defined a 1:1 ratio of FFP:RBC as high and two studies (Kauvar 2011, Mell 2010) did not define a high ratio.

All seven studies were carried out in single-centre surgical settings in North America or Denmark. Overall, review authors judged included studies as serious risk of bias, with a significant amount of bias arising from confounding and patient selection.

Paediatric setting

One review (Kinslow 2020), assessing blood component ratios in paediatric patients undergoing massive transfusion, identified six cohort studies (total 1025 patients) that met their inclusion criteria. Four studies (Butler 2019, Cunningham 2019, Noland 2018, Nosanov 2013) reported data relevant to our review.

All four studies compared a high ratio of 1:1 to lower ratios and included paediatric trauma patients with predominantly blunt injuries. Three studies (Butler 2019, Noland 2018, Nosanov 2013) assessed FFP:RBC and one study (Cunningham 2019) assessed RBC:Plasma.

Included cohort studies were carried out in paediatric trauma centres in the US. Review authors did not conduct a risk of bias assessment of included studies but noted there was significant heterogeneity throughout due to adherence to ratio targets and differences in activation of major haemorrhage protocols. For these reasons, authors were unable to conduct a formal meta-analysis.

DRAFT

4.4.3 Results

4.4.3.1 High (1:1:1) ratio vs lower ratio

4.4.3.2 Mortality

A summary of the evidence reported in the identified systematic reviews relating to mortality in patients with critical bleeding is presented in Table 4.21.

All identified systematic reviews reported significant difference in mortality between patients who received high ratios of blood components compared with those who received lower ratios, regardless of clinical setting. There was also significant effect on mortality shown in three of the subgroup analyses.

A meta-analysis of data from RCTs included in this review (see Figure 4.12) showed the mortality rate (latest timepoint) in the trauma setting to be comparable among those who received high ratios of blood components compared to those who received lower ratios with the relative risk (RR) of 1.26 observed (95% CI 0.49, 3.22; $p = 0.64$; random effect, $I^2 = 75\%$). Neither of the included RCTs were powered to detect differences in mortality.

In contrast, a meta-analysis of data from nonrandomised cohort studies included in this review showed a significant difference in mortality rate of 24% (474/1978) observed among patients who received a high ratio of blood components compared to 33.1% (1219/3686) among patients who did not (RR 0.60; 95% CI 0.48, 0.74; $p < 0.00001$, random effect, $I^2 = 79\%$).

Among patients with blunt and penetrating trauma, a total of 308 patients received a high 1:1:1 ratio of blood components compared with 922 patients who received lower ratios. A significant difference in mortality was observed between groups (24.3% vs 31.4%, RR 0.58; 95% CI 0.41, 0.82; $p = 0.002$, random effect, $I^2 = 88\%$).

Among patients with ruptured abdominal aortic aneurysms, the observed mortality rate of 23.6% (88/373) among patients receiving a high ratio was significantly different to the mortality rate of 46.4% (143/308) among patients receiving lower ratios (RR of 0.56; 95% CI 0.43, 0.72; $p < 0.0001$; random effect, $I^2 = 15\%$).

Among paediatric trauma patients, a total of 78 patients received a high ratio of blood components compared to 154 patients who received lower ratios, with no significant difference in mortality observed (23.3% vs 34.6%, RR 0.70; 95% CI 0.47, 1.04; random effect, $I^2 = 40\%$).

DRAFT

Figure 4.12 Forest plot of comparison: high ratio vs low ratio blood components, outcome: Mortality, latest timepoint

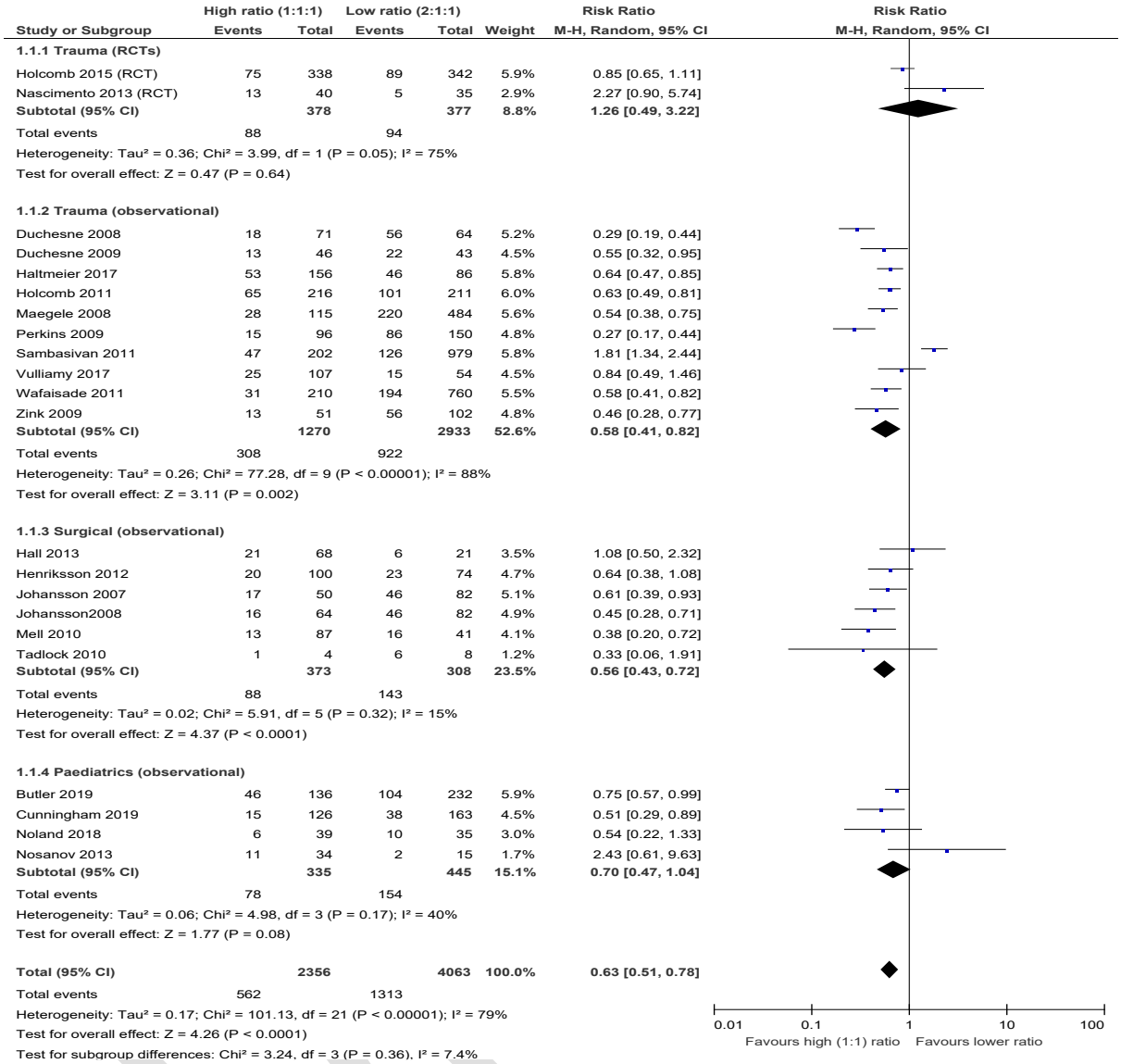


Table 4.21 Results for high ratio of blood components versus low ratio of blood components: Patients *with* critical bleeding – Mortality

Study ID Study design[a]	Sample size (no. of trials) included in analysis	Patient population	Setting (Location)	Comparison	Outcome	Results			
						High ratio n/N (%)	Low ratio n/N (%)	Risk estimate (95% CI)	*Statistical significance* *p*-value Heterogeneity [b]
Trauma setting									
da Luz 2019 SR *Moderate quality*	N = 2414 (5 Coh)	Adult trauma patients	Trauma centres (UK, Denmark, Netherlands, Germany, Iraq)	FFP:RBC High ratio (1:1) vs lower ratio (<1:1)	Mortality, 24 hours Balvers 2017 Maegele 2008 Perkins 2009 Vulliamy 2017 Wafaisade 2011	126/738 (17.1) 89/210 (42.4) 13/115 (11.3) 5/96 (5.2) 8/107 (7.5) 11/210 (5.2)	420/1676 (25.1) 65/169 (38.5) 158/484 (32.6) 75/209 (35.9) 9/54 (16.7) 113/760 (14.9)	OR 0.34 (0.14, 0.82) 1.18 (0.78, 1.78) 0.26 (0.14, 0.48) 0.10 (0.04, 0.25) 0.40 (0.15, 1.12) 0.32 (0.17, 0.60)	*Favours high ratio* $p = 0.02$ Substantial heterogeneity $I^2 = 88\%$ ($p < 0.00001$)
	N = 749 (2 RCTs)	Adult trauma patients	Trauma centres (US, Canada)	FFP:PLT:RBC High (1:1:1) vs lower ratio (1:1:2)	Mortality, 28-30 days Holcomb 2015 Nascimento 2013	88/378 (23.3) 75/338 (22.2) 13/40 (32.5)	94/377 (25) 89/342 (26) 5/35 (14.3)	OR 1.35 (0.40, 4.59) 0.81 (0.57, 1.15) 2.89 (0.91, 9.17)	*No significant difference* $p = 0.63$ Substantial heterogeneity $I^2 = 76\%$ ($p = 0.04$)
	N = 4203 (10 Coh)	Adult trauma patients	Trauma centres (UK, Germany, US, Iraq)	FFP:RBC High ratio (1:1) vs lower ratio (<1:1)	Mortality, 30 days Duchesne 2008 Duchesne 2009 Haltmeier 2017 Holcomb 2011 Maegele 2008 Perkins 2009 Sambasivan 2011 Vulliamy 2017 Wafaisade 2011 Zink 2009	308/1270 (24.3) 18/71 (23.4) 13/46 (28.3) 53/156 (34) 65/216 (30.1) 28/115 (24.3) 15/96 (15.6) 47/202 (23.3) 25/107 (23.4) 31/210 (14.8) 13/51 (25.5)	922/2933 (31.4) 56/64 (87.5) 22/43 (51.2) 46/86 (53.5) 101/211 (47.9) 220/484 (45.5) 86/150 (57.3) 126/979 (12.9) 15/54 (27.8) 194/760 (25.5) 56/102 (54.9)	OR 0.38 (0.22, 0.68) 0.05 (0.02, 0.12) 0.38 (0.16, 0.90) 0.45 (0.26, 0.77) 0.47 (0.32, 0.70) 0.39 (0.24, 0.61) 0.14 (0.07, 0.26) 2.05 (1.41, 2.99) 0.79 (0.38, 1.67) 0.51 (0.33, 0.76) 0.28 (0.13, 0.59)	*Favours high ratio* $p = 0.001$ Substantial heterogeneity $I^2 = 91\%$ ($p < 0.0001$)
Kleinveld 2021 SR *Moderate quality*	N = 1757 (2 RCTs)	Trauma patients (≥16 years)	Trauma centres (US, Canada)	PLT:RBC High ratio vs lower ratio	Mortality, 24-hours Nascimento 2013 Holcomb 2015	 8/37 (21.6) 43/338 (12.7)	 3/32 (9.4) 58/342 (17.0)	 OR 2.67 (0.64, 11.07) OR 0.71 (0.47, 1.09)	NR
Cannon 2017 SR *Moderate quality*	N = 927 (3 Coh)	Adult trauma patients	Trauma centres (UK, Denmark, Netherlands, Germany, Iraq)	PLT:RBC High ratio (1:1) vs lower ratio (<1:1)	Mortality, overall Holcomb 2008 Perkins 2008 Shaz 2010	163/505 (32.3) 67/234 (28.6) 49/145 (33.8) 47/126 (37.3)	239/764 (31.3) 94/184 (51.1) 86/150 (57.3) 59/88 (67)	OR 0.36 (0.27, 0.47) 0.38 (0.26, 0.58) 0.38 (0.24, 0.61) 0.29 (0.16, 0.52)	*Favours high ratio* $p < 0.00001$ No heterogeneity $I^2 = 0\%$ (p =72%)

Study ID Study design[a]	Sample size (no. of trials) included in analysis	Patient population	Setting (Location)	Comparison	Outcome	Results			
						High ratio n/N (%)	Low ratio n/N (%)	Risk estimate (95% CI)	*Statistical significance* *p*-value Heterogeneity [b]
Paediatrics, trauma setting									
Kinslow 2020 SR *Critically low quality*	N = 804 (4 Coh)	Paediatric trauma patients with various ISS	Paediatric trauma (US, Iraq, Afghanistan)	FFP:RBC or PLT:RBC High vs lower ratios	Mortality, overall [d] Noland 2018 Cunningham 2019 Butler 2019 Nosanov 2013	NR 6/39 (15) 15/126 (12) 46/136 (33.8) 11/34 (32.6)	NR 10/35 (29) 38/163 (23) 104/232 (44.8) 2/15 (13.3)	NR	NR
Surgical setting									
Phillips 2021 SR *Low quality*	N = 681 (6 Coh)	Adults with a diagnosis of AAA	Surgical, SC (North America, Denmark)	FFP:RBC High vs lower ratios	Mortality, 30 days or latest timepoint Mell 2010 Johansson 2007 Johansson 2008 Henriksson 2012 Hall 2013 Tadlock 2010	NR 13/87 (15) 17/50 (34) 16/64 (25) 20/100 (20) 21/68 (31) 1/4 (25)	NR 16/41 (39) 46/82 (56) 46/82 (56) 23/74 (31) 6/21 (28) 6/8 (75)	NR NR NR NR NR NR NR	NR *p* <0.03 *p* = 0.02 *p* <0.01 *p* = 0.111 *p* > 0.05 *p* = 0.222
	N = 87 (1 Coh) Kauvar 2011				Mortality, in-hospital	19/39 (49)	19/48 (40)	NR	*p* = 0.39

AAA, abdominal aortic aneurysm; CI, confidence interval; Coh, cohort; FFP, fresh frozen plasma; ISS, injury severity score; NR, not reported; OR, odds ratio; PLT, platelet; RBC, red blood cell; RCT, randomised controlled trial; SC, single centre; SR, systematic review; UK, United Kingdom; US, United States

a. Where only one RCT is identified in a systematic review, the evidence has been considered as RCT evidence. Where the systematic review assesses observational and cohort studies, the evidence has been considered as according to the study design features. The risk of bias of the included primary studies is based on the quality assessment reported by the systematic review authors.

b. Only applicable to Systematic reviews with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if P_{het} >0.1 and I^2 <25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25–50%; substantial heterogeneity I^2 >50%.

c. Calculated post-hoc using RevMan 5.4

d. Mortality data for identified by Kinslow 2020 sourced from primary study. No meta-analysis conducted by Kinslow 2020.

4.4.3.3 Morbidity

A summary of the evidence reported in the identified systematic reviews relating to morbidity (e.g. thromboembolic events, multiple organ failure [MOF], acute respiratory distress syndrome [ARDS]) in patients with critical bleeding is presented in Table 4.22 and Table 4.23.

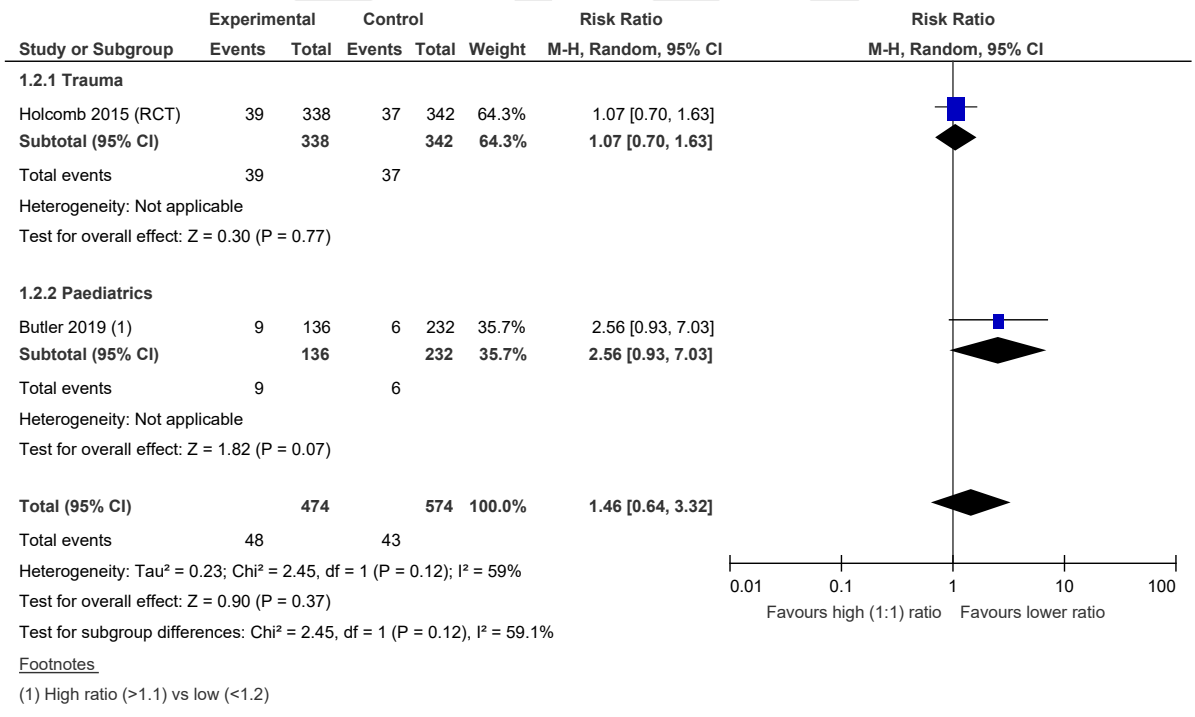
Thromboembolic events

One RCT (Holcomb 2015) in the trauma setting and one cohort study (Butler 2019) in the paediatric setting reported on the outcome of thromboembolic events. Combined data (see Figure 4.13) suggest no important difference between groups (RR 1.46; 95% CI 0.64, 3.32; p = 0.37; random effect; I^2=59%).

Holcomb 2015 suggested no significant difference in thromboembolic events (deep vein thrombosis, pulmonary embolus) between patients who received high ratio of blood components (39/338, 11.5%) compared with those who did not (37/342, 10.8%) (RR 1.07; 95% CI 0.64, 3.32; p = 0.37; random effect; I^2=59%).

Butler 2019 suggested a nonsignificant increased risk in thromboembolic events (deep vein thrombosis) between paediatric patients who received a high ratio of blood components (9/136, 6.6%) compared to paediatric patients who received a low ratio (6/323, 2.6%) (RR 2.56; 95% CI 0.93, 7.03; p = 0.07).

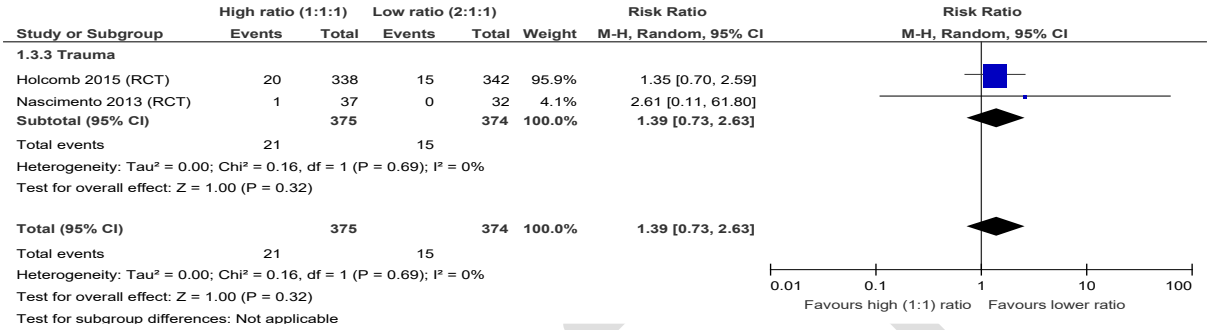
Figure 4.13 Forest plot of comparison: high ratio vs low ratio blood components, outcome: Morbidity, thromboembolic events



Multiple organ failure

Two RCTs reported on the outcome of MOF in the trauma setting. A meta-analysis of the two RCTs (Figure 4.14) found no significant difference in MOF between patients who received a high ratio of blood components (21/375, 5.6%) compared with patients who received a low ratio (15/374, 4%) (RR 1.39, 95% CI 0.73, 2.63; p = 0.32; random effects; I^2 = 0%).

Figure 4.14 Forest plot of comparison: high ratio vs low ratio blood components, outcome: Morbidity, multiple organ failure



Other adverse events

Two RCTs and six cohort studies were found in the trauma setting that reported on the outcome of other adverse events.

For the outcome of ARDS, one RCT (Holcomb 2015) reported no significant difference between patients who received high ratio of blood components (46/338, 13.6%) compared with those who did not (48/342, 14%). Another RCT (Nascimento 2013) reported a difference between patients who received high ratio of blood components (17/37, 46%) compared with patients who received a low ratio (7/32, 21.9%), however, sample sizes were small and not powered to inform the outcome of ARDS.

One systematic review (Rahouma 2017) using data from six cohort studies reported no significant difference on the outcome of ARDS between patients who received a high ratio of blood components (133/833, 16%) and patients who received a low ratio (199/1165, 17.1%).

One RCT (Holcomb 2015) reported no significant difference in acute kidney injury between patients who received high ratio of blood components (74/338, 21.9%) compared with those who did not (85/342, 24.9%). Similarly, one cohort study (Kim 2014) reported no difference in acute lung injury between patients who received a high ratio of blood components (1/68, 1.5%) compared to patients who received a low ratio (0/32, 0%).

One RCT (Holcomb 2015) reported no significant difference in sepsis between patients who received a high ratio of blood components (99/338, 28.9%) compared with patients who received a low ratio (91/342, 26.6%).

One RCT (Holcomb 2015) reported no significant difference in myocardial infarction between patients who received a high ratio of blood components (0/338, 0%) compared with those who did not (2/342, 0.6%).

Table 4.22 Results for high ratio of blood components versus low ratio of blood components: Patients *with* critical bleeding – Morbidity, thromboembolic events

Study ID Study design[a]	Sample size (no. of trials) included in analysis	Patient population	Setting (Location)	Comparison	Outcome	Results			
						High ratio n/N (%)	Low ratio n/N (%)	Risk estimate (95% CI)	*Statistical significance* *p*-value Heterogeneity[b]
Trauma setting									
Kleinveld 2021 SR *Moderate quality*	N = 1187 (1 RCT) Holcomb 2015	Trauma patients (≥16 years)	Trauma centres (US, Canada)	PLT:RBC High (1:1:1) vs lower ratios	TE (DVT & symptomatic pulmonary embolus)	39/338 (11.5)	37/342 (10.8)	OR 1.08 (0.67, 1.73)	*p* = 0.77[c]
McQuilten 2018 SR *Moderate quality*	N = 680 (1 RCT) Holcomb 2015	Trauma patients	Trauma centres (US, Canada)	Transfusion ratio 1:1:1 versus 1:1:2	DVT	25/338 (7.4)	24/342 (7.0)	RR 1.05 (0.61,1.81)	*p* = 0.85[c]
					Pulmonary embolus, symptomatic	14/338 (4.1)	13/342 (3.8)	RR 1.09 (0.52,2.28)	*p* = 0.82[c]
					Stroke	8/338 (2.4)	11/342 (3.2)	RR 0.74 (0.30,1.81)	*p* = 0.50[c]
Paediatrics, trauma setting									
Kinslow 2020 SR *Critically low quality*	N = 583[d] (1 Coh) Butler 2019	Paediatric trauma patients with various injury severity scores	Paediatric trauma database (US)	FFP:RBC or PLT:RBC High vs lower ratios	DVT	9/136 (6.6)	6/232 (2.6)	NR	*p* = 0.07[c]
						2:1 FFP:RBC associated with 6.9x increased risk for development of DVT compared to lower ratios			
Surgical setting – not identified studies reported on outcome of interest									

CI, confidence interval; Coh, cohort; DVT, deep vein thrombosis; FFP, fresh frozen plasma; NR, not reported; OR, odds ratio; PLT, platelets; RBC, red blood cells; RCT, randomised controlled trial; RR, relative risk; SR, systematic review; TE, thromboembolic event; US, United States

a. Where only one RCT is identified in a systematic review, the evidence has been considered as RCT evidence. Where the systematic review assesses observational and cohort studies, the evidence has been considered as according to the study design features. The risk of bias of the included primary studies is based on the quality assessment reported by the systematic review authors.

b. Only applicable to Systematic reviews with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if P_{het} >0.1 and I^2 <25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25–50%; substantial heterogeneity I^2 >50%.

c. Calculated post-hoc using RevMan 5.4

d. Information sourced from primary study

Table 4.23 Results for high ratio of blood components versus low ratio of blood components: Patients *with* critical bleeding – Morbidity, critical complications

Study ID Study design[a]	Sample size (no. of trials) included in analysis	Patient population	Setting (Location)	Comparison	Outcome	Results			
						High ratio n/N (%)	Low ratio n/N (%)	Risk estimate (95% CI)	*Statistical significance* *p*-value Heterogeneity[b]
Trauma setting									
Kleinveld 2021 SR *Moderate quality*	N = 749 (2 RCTs) Nascimento 2013 Holcomb 2015	Trauma patients (paediatric and adult)	Trauma centres (US, Canada)	High PLT:RBC ratio v low PLT:RBC ratio	MOF	1/37 (2.7) 20/338 (5.9)	0/32 (0) 15/342 (4.4)	OR 2.67 (0.11, 67.89) OR 1.37 (0.69, 2.73)	*p* = 0.32[c]
McQuilten 2018 SR *Moderate quality*	N = 680 (1 RCT) Holcomb 2015	Trauma patients (paediatric and adult)	Trauma centres (US, Canada)	High (1:1:1) vs lower (1:1:2) ratios	ARDS	46/338 (13.6)	48/342 (14)	RR 0.97 (0.67,1.41)	*p* = NR
					acute kidney injury	74/338 (21.9)	85/342 (24.9)	RR 0.88 (0.67,1.16)	*p* = NR
					Sepsis	99/338 (28.9)	91/342 (26.6)	RR 1.10 (0.86,1.40)	*p* = NR
					myocardial infarction	0/338 (0)	2/342 (0.6)	RR 0.20 (0.01,4.20)	*p* = NR
Rahouma 2017 SR *Critically low quality*	N = 1998 (1 RCT, 6 Coh)	Trauma patients	Trauma centres (US, Canada)	High vs lower ratio	ARDS Nascimento 2013 (RCT) Brown 2012 Kim 2014 Lustenberger 2011 Sperry 2008 Undurraga 2015 Van 2010	133/833 (16.0) 17/37 (46) 47/116 (40.5) 4/68 (5.9) 10/177 (5.6) 24/102 (23.5) 22/174 (12.6) 9/159 (5.7)	199/1165 (17.1) 7/32 (21.9) 133/476 (27.9) 1/32 (3.1) 1/52 (1.9) 24/313 (7.7) 19/172 (11) 14/88 (15.9)	NR OR 0.33 (0.11, 0.95) OR 0.57 (0.37, 0.87) OR 0.52 (0.06, 4.81) OR 0.33 (0.04, 2.62) OR 0.27 (0.15, 0.50) OR 0.86 (0.45, 1.65) OR 3.15 (1.30, 7.62)	NR
	N = 100 (1 Coh) Kim 2014	Trauma patients	Trauma centres (US, Canada)		acute lung injury	1/68 (1.5)	0/32 (0)	NR	NR
Paediatrics, trauma setting									
Kinslow 2020 SR *Critically low quality*	N = 583[d] (1 Coh) Butler 2019	Paediatric trauma patients with various ISS	Paediatric trauma database (US)	FFP:RBC or PLT:RBC High vs lower ratios	Pneumonia	NR	NR	NR	NR
						Authors conclude >2:1 PLT:RBC associated with 23.6x increased risk for development of pneumonia compared to lower ratios			
Surgical setting – no identified studies reported on outcome of interest									

ARDS, acute respiratory distress syndrome; CI, confidence interval; Coh, cohort; DVT, deep vein thrombosis; FFP, fresh frozen plasma; ICU, intensive care unit; ISS, injury severity score; MI, myocardial infarction; MOF, multiple organ failure; NR, not reported; OR, odds ratio; PLT, platelets; RBC, red blood cells; RCT, randomised controlled trial; RR, relative risk; SR, systematic review; TE, thromboembolic event; US, United States

a. Where only one RCT is identified in a systematic review, the evidence has been considered as RCT evidence. Where the systematic review assesses observational and cohort studies, the evidence has been considered as according to the study design features. The risk of bias of the included primary studies is based on the quality assessment reported by the systematic review authors.

b. Only applicable to Systematic reviews with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if P_{het} >0.1 and I^2 <25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25–50%; substantial heterogeneity I^2 >50%.
c. Calculated post-hoc using RevMan 5.4
d. Information sourced from primary study.

DRAFT

4.4.3.4 Transfusion volumes

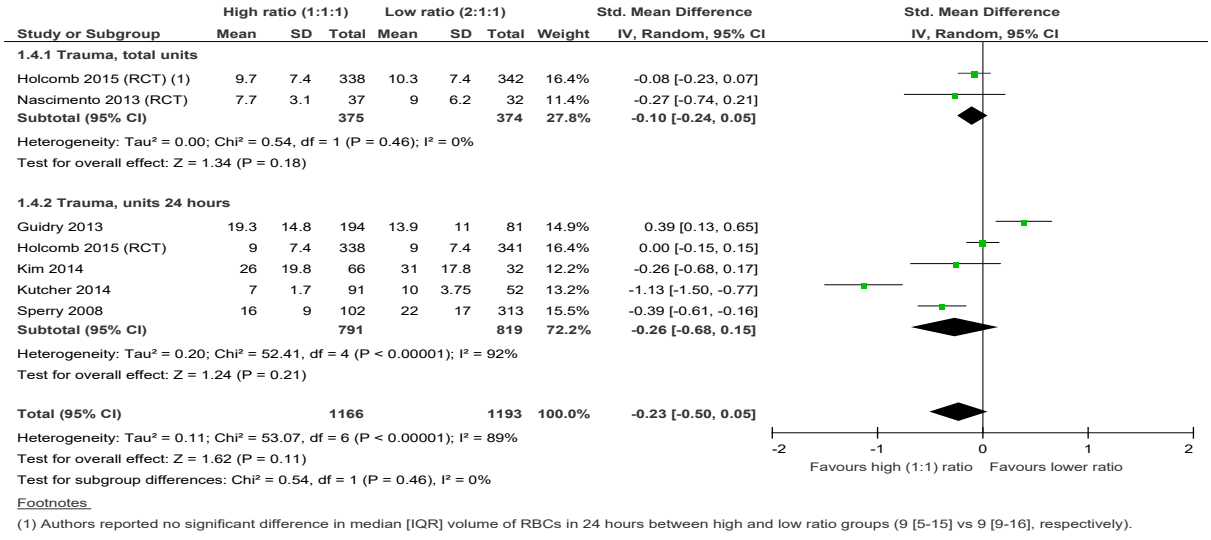
A summary of the evidence reported in the identified systematic reviews relating to transfusion of red blood cells and other blood components in patients with critical bleeding is presented in Table 4.24 and Table 4.25.

Red blood cells

A meta-analysis of data from two RCTs in the trauma setting (see Figure 4.15) showed no significant difference in median volume of RBCs transfused in the first 24-hours between patients receiving a high ratio of blood components compared to patients receiving a low ratio (SMD –0.1; 95% CI –0.24, 0.05; $p = 0.18$, random effect, $I^2 = 0\%$).

Similarly, a meta-analysis of data from nonrandomised cohort studies in the trauma setting showed showed no significant difference in median volume of RBCs transfused in the first 24-hours between patients receiving a high ratio of blood components compared to patients receiving a low ratio (SMD –0.26; 95% CI –0.68, 0.15; $p = 0.21$, random effect, $I^2 = 92\%$).

Figure 4.15 Forest plot of comparison: high ratio vs low ratio blood components, outcome: Transfusion volume, red blood cells



Footnotes

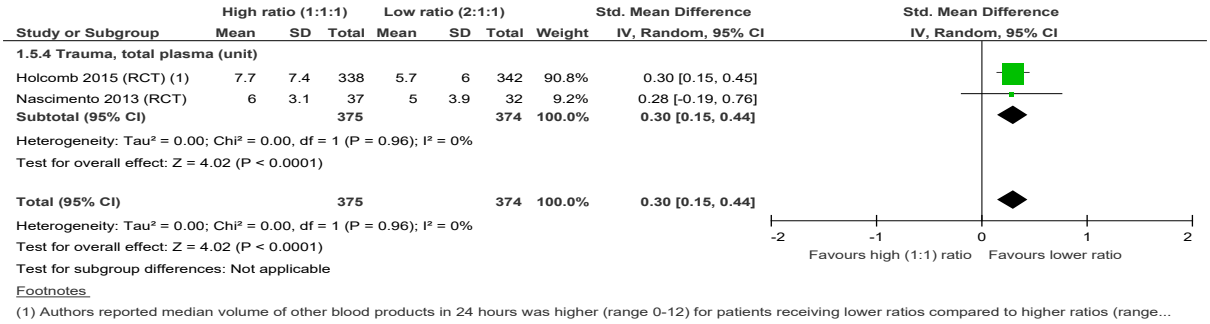
(1) Authors reported no significant difference in median [IQR] volume of RBCs in 24 hours between high and low ratio groups (9 [5-15] vs 9 [9-16], respectively).

Other blood components

A meta-analysis of data from two RCTs in the trauma setting (see Figure 4.16) showed a significant difference in median volume of FFP transfused in the first 24-hours between patients receiving a high ratio of blood components compared to patients receiving a low ratio (SMD 0.3; 95% CI 0.15, 0.44; $p < 0.0001$, random effect, $I^2 = 0\%$).

Holcomb (2015) reported a significant reduction in volume of PLT and CRYO transfused among patients who received high ratio of blood components compared with those who did not.

Figure 4.16 Forest plot of comparison: high ratio vs low ratio blood components, outcome: Transfusion volume, FFP



Footnotes

(1) Authors reported median volume of other blood products in 24 hours was higher (range 0-12) for patients receiving lower ratios compared to higher ratios (range...

DRAFT

Table 4.24 Results for high ratio of blood components versus low ratio of blood components: Patients *with* critical bleeding – Transfusion volumes, red blood cells

Study ID Study design[a]	Sample size (no. of trials) included in analysis	Patient population	Setting (Location)	Comparison	Outcome	Results			
						High ratio Median (SD)	Low ratio Median (SD)	Risk estimate (95% CI)	*Statistical significance* *p*-value Heterogeneity[b]
Trauma setting									
Rijnhout 2021 SR *Moderate quality*	N = 749 (2 RCTs) Holcomb 2015 Nascimento 2013	Trauma patients with an ISS ranging between 26 and 37	Trauma, military and civilian (North America, UK, Iran)	PLT:RBC ≥1 vs PLT:RBC 0.6 or <1	RBC transfusion	NR 9.7 (7.4) (n=338) 7.7 (3.1) (n=37)	NR 10.3 (7.4) (n=342) 9 (6.2) (n=32)	MD –0.73 (–1.73, 0.28) MD –0.60 (–1.71, 0.51) MD –1.30 (–3.67, 1.07)	*No significant difference* *p* = 0.16 No significant heterogeneity I^2 = 0% (*p* = 0.60)
Cannon 2017 SR *Moderate quality*	N = 1610 (1 RCT, 4 Coh studies) Holcomb 2015 Kutcher 2014 Sperry2008 Guidry 2013 Kim 2014	Adult patients with severe trauma	Various locations (North America, South Korea, Iran)	High vs low ratios (plasma:RBC)	RBC in 24 hours, units	NR 9 (7.4) (n=338) 7 (1.7) (n=91) 16 (9) (n=102) 19.3 (14.8) (n=194) 26 (19.8) (n=66)	NR 9 (7.4) (n=341) 10 (3.75) (n=52) 22 (17) (n=313) 13.9 (11) (n=81) 31 (17.8) (n=32)	MD –1.42 (–4.39, 1.54) MD 0.00 (–1.11, 1.11) MD –3.0 (–4.08, –1.92) MD 6.00 (–8.57, –3.43) MD 5.40 (2.23, 8.57) MD –5.00 (–12.80, 2.80)	*No significant difference* *p* = 0.35 Substantial heterogeneity I^2=91% (*p* < 0.0001)
Paediatrics, trauma setting – no identified studies reported on outcome of interest									
Surgical setting – no identified studies reported on outcome of interest									

CI, confidence interval; Coh, cohort; IQR, interquartile range; ISS, injury severity score; MD, mean difference; NR, not reported; PLT, platelets; RBC, red blood cells; RCT, randomised controlled trial; SD, standard deviation; SR, systematic review; UK, United Kingdom

a. Where only one RCT is identified in a systematic review, the evidence has been considered as RCT evidence. Where the systematic review assesses observational and cohort studies, the evidence has been considered as according to the study design features. The risk of bias of the included primary studies is based on the quality assessment reported by the systematic review authors.

b. Only applicable to Systematic reviews with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if P_{het} >0.1 and I^2 <25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25–50%; substantial heterogeneity I^2 >50%.

c. Calculated post-hoc using RevMan 5.4

Table 4.25 Results for high ratio of blood components versus low ratio of blood components: Patients *with* critical bleeding – Transfusion volumes, other blood components

Study ID Study design[a]	Sample size (no. of trials) included in analysis	Patient population	Setting (Location)	Comparison	Outcome	Results			
						High ratio Mean (SD)	Low ratio Mean (SD)	Risk estimate (95% CI)	*Statistical significance* *p*-value Heterogeneity[b]
Trauma setting									
McQuilten 2018 SR *Moderate quality*	N = 680 (1 RCT) Holcomb 2015	Trauma patients (paediatric and/or adult)	Trauma centres (US, Canada)	High (1:1:1) vs lower (1:1:2) ratios	PLT[c] in 24 hours Median (IQR) values reported	12 (6-18) n=338	6 (0-12) n=342	NE	*p* < 0.001
					CRYO in 24 hours Median (IQR) values reported	0 (0-0) n=338	0 (0-9) n=342	NE	*p* = 0.01
					Total blood products transfused to 24 hrs, median Median (IQR) values reported	25.5 (n=338)	19 (n=342)	NE	p = NR
Rijnhout 2021 SR *Moderate quality*	N = 749 (RCTs) Holcomb 2015 Nascimento 2013	Trauma patients with an ISS ranging between 26 and 37	Trauma, military and civilian (North America)	PLT:RBC ≥1 versus PLT:RBC 0.6 or <1	FFP transfusion	NR 7.7 (7.4) (n=338) 6 (3.1) (n=37)	NR 5.7 (6) (n=342) 5 (3.9) (n=32)	MD 1.73 (0.87, 2.60) MD 2.00 (0.99, 3.01) MD 1.00 (-0.68, 2.68)	*Favours high ratio* *p* < 0.0001 No significant heterogeneity I^2 = 0% (*p* = 0.32)
Paediatrics, trauma setting – no identified studies reported on outcome of interest									
Surgical setting – no identified studies reported on outcome of interest									

CI, confidence interval; CRYO, cryoprecipitate; FFP, fresh frozen plasma; IQR, interquartile range; ISS, injury severity score; NE, not estimable; NR, not reported; PLT, platelets; RBC, red blood cells; RCT, randomised controlled trial; SD, standard deviation; SR, systematic review; US, United States

a. Where only one RCT is identified in a systematic review, the evidence has been considered as RCT evidence. Where the systematic review assesses observational and cohort studies, the evidence has been considered as according to the study design features. The risk of bias of the included primary studies is based on the quality assessment reported by the systematic review authors.

b. Only applicable to Systematic reviews with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if P_{het} >0.1 and I^2 <25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25–50%; substantial heterogeneity I^2 >50%.

c. Five- or six-unit pools of whole blood-derived platelets were considered equivalent to a unit of apheresis platelets (e.g. an adult dose of platelets).

4.5 Volume of RBCs transfused (Question 4)

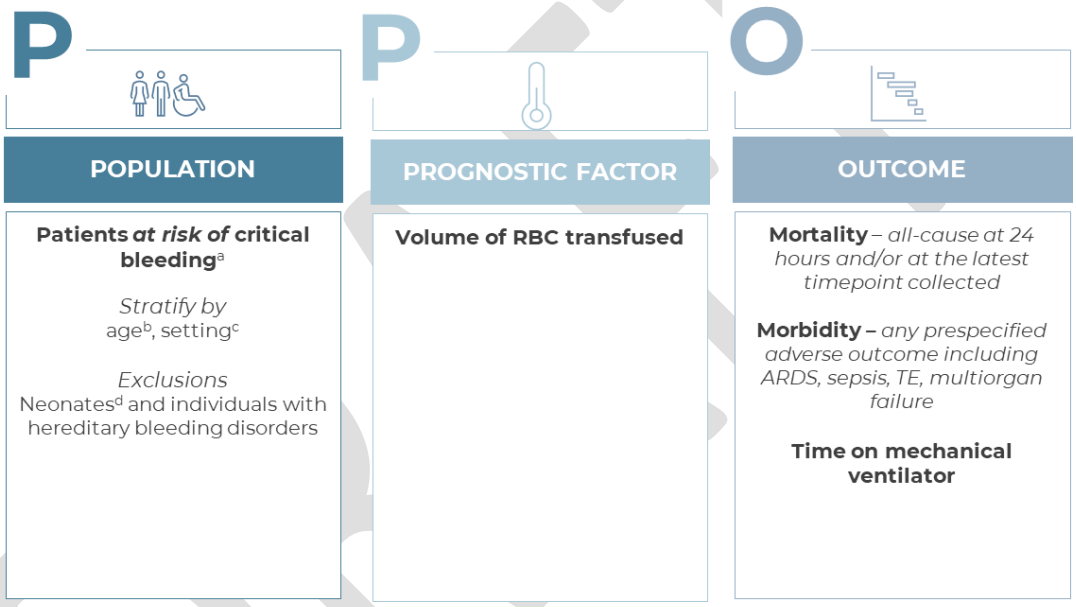
Question 4 – (Prognostic)

In patients at risk of critical bleeding, is the transfusion of increased volumes of RBCs associated with an increased risk of mortality or adverse effects?

4.5.1 Methods

This review examined the effect of transfusion of increased volumes of RBCs in patients at risk of critical bleeding (see Figure 4.17 for PICO criteria).

Figure 4.17 PPO criteria: Question 4 – effect of transfusion of increased volumes of RBCs



ARDS, acute respiratory distress syndrome; RBCs, red blood cells; TE, thromboembolism
Notes:
a. Patients at risk of critical bleeding includes patients with penetration injuries who may not otherwise develop critical bleeding but if over-transfused before haemorrhage control may go on to do so.
b. Adult (aged over 18 years), child (aged 2 to 12 years), adolescent (aged 13 to 18 years), infants (aged 1 to 23 months).
c. e.g. trauma, obstetric, perioperative (cardiothoracic, general surgery, gastrointestinal, liver transplant), paediatric, other.
d. Newborns up to 28 days following birth.

The selection of studies was conducted according to the screening criteria described in Section 3.3.

This systematic review only considered studies published after 2009. Articles published prior to 2009 that had been included within a systematic review were also eligible for inclusion. As outlined in the protocol, this review only considered individual studies published after 2012.

An updated literature search was conducted in August 2019 and again in September 2021 to identify any new SRs or RCTs meeting the eligibility criteria.

4.5.2 Summary of evidence

4.5.2.1 Systematic Reviews

Two systematic reviews (73, 74) were included that examined the impact of transfusion of increased volumes of RBCs in patients at risk of clinical bleeding. The main characteristics and quality of these systematic reviews and relevant outcomes assessed are summarised in A matrix illustrating the overlap of prospective and retrospective cohort studies identified in the included systematic reviews is provided in Table 4.27

Table 4.26.

One systematic review (Balvers 2015) identified 50 prospective and retrospective cohort studies but did not report any usable data and is therefore not reported further in this review. The authors searched for, but did not find any studies that assessed the association between transfusion of increased volumes of RBCs in patients *at risk of* critical bleeding in another setting (i.e. perioperative, obstetric, paediatric).

One systematic review (Patel 2014) was carried out in the trauma setting with no limits to trauma severity, mechanism of injury or pattern of injury. The review authors identified 40 prospective and retrospective cohort studies that assessed the association between RBC transfusion and mortality and morbidity in trauma patients. Of these, 21 studies were considered relevant to this review and were included in the meta-analysis.

A matrix illustrating the overlap of prospective and retrospective cohort studies identified in the included systematic reviews is provided in Table 4.27

Table 4.26 Characteristics and quality of systematic review evidence: increased RBCs transfusion

Review ID ***Review quality***	**Study design**	**Population**	**Prognostic factor**	**Outcomes**
Trauma setting				
Balvers 2015 (73) *Critically low*	SR / MA of RCTs, prospective and retrospective cohort studies (50 studies)	Patients aged ≥16 years with blunt or penetrating trauma injuries *mean ISS ≥ 16	Volume of RBCs transfused	Morbidity
Patel 2014 (74) *Low*	SR / MA of prospective and retrospective cohort studies (40 studies)	Trauma patients without restrictions on trauma severity, mechanism of injury or pattern of injury	Volume of RBCs transfused	Mortality Morbidity

ALI; acute lung injury; ARDS, acute respiratory distress syndrome; ICU, intensive care unit; ISS, injury severity score; MOF, multiple organ failure; RBCs, red blood cells; RCTs, randomised controlled trials

Table 4.27 Overlap table showing included systematic reviews and identified cohort studies: increased RBCs transfusion

		Trauma: prospective cohort studies														Trauma: retrospective cohort studies																
	Study ID	Bochicchio 2008	Ciesla 2005	Dunne 2004	Edens 2010	Johnson 2010	Malone 2003	Moore 1997	Sauaia 1994	Silverboard 2005	Brakenridge 2011	Brattstrom 2010	Brown 2012	Cryer 1999	Sperry 2008	Zallen 1999	Barbosa 2011	Charles 2007	Chaiwat 2009	Cotton 2009	Croce 2005	George 2008	Mahambrey	Mostafa 2004	Murrell 2005	Phelan 2010	Plurad 2007	Robinson 2005	Spinella 2008	Texeira 2008	Weinberg 2008	Dewar 2009	Lehmann 1995
Review ID	Patel 2014	✓	✓	✓	✓	✓	✓	✓	✓	✓				X			✓	X	✓	✓	✓	X	✓	X	✓	✓	✓	✓	✓	✓	✓		
	Balvers 2015		--					--	--		--	--	--	--	--	--							--									--	--

✓ = study included in this review; X = study did not meet the inclusion criteria for this review; -- = study identified by the systematic review authors but not included (no usable data)

DRAFT

4.5.2.2 Prospective cohort studies

Patel 2014 included data from nine prospective cohort studies that investigated the association between the transfusion of increased volumes of RBCs and patient outcomes in patients at risk of critical bleeding. One additional prospective cohort study (Liu 2018) was identified in this systematic review that met our inclusion criteria.

The main characteristics and quality of the prospective cohort studies included in this review is provided in Table 4.28.

Table 4.28 Characteristics and quality of prospective cohort evidence: increased RBCs transfusion

Review ID *Risk of bias*	Study design	Population	Prognostic factor	Outcomes
Trauma setting				
Liu 2018 (75) *Serious*	Prospective cohort, SC	Adult trauma patients who received between 0 and 87 units of RBCs within 24 hours N=131	Volume of RBCs transfused	Mortality Hospital LOS
Edens 2010 *Moderate*	Prospective cohort	Military trauma patients N=66	Volume of RBCs transfused	Morbidity (ALI)
Johnson 2010 *High*	Prospective cohort	Trauma patients with ISS >16 N=1440	Volume of RBCs transfused	Morbidity (MOF)
Bochicchio 2008 *Moderate*	Prospective cohort	Trauma patients admitted to the ICU N=1172	Volume of RBCs transfused	Mortality
Ciesla 2005 *Low*	Prospective cohort	Trauma patients with ISS >15 N=1344	Volume of RBCs transfused	Morbidity (MOF)
Silverboard 2005 *Low*	Prospective cohort	Trauma patients with ISS >16 and intubation N=102	Volume of RBCs transfused	Mortality
Dunne 2004 *Moderate*	Prospective cohort	Trauma patients N=9539	Volume of RBCs transfused	Mortality
Malone 2003 *Low*	Prospective cohort	Any trauma patients over 18 years N=15 534	Volume of RBCs transfused	Mortality
Moore 1997 *Low*	Prospective cohort	Adult trauma patients with ISS >15 N=513	Volume of RBCs transfused	Morbidity (MOF)
Sauaia 1994 *Moderate*	Observational cohort (first year: retrospective; last 2 years: prospective).	Trauma patients with ISS >15 N=394	Volume of RBCs transfused	Morbidity (MOF)

ALI; acute lung injury; ICU, intensive care unit; ISS, injury severity score; LOS, length of stay; MOF, multiple organ failure; RBCs, red blood cells; SC, single centre

Trauma setting

Among the nine prospective cohort studies identified by Patel 2014, there were four studies (Bochicchio 2008, Silverboard 2005, Dunne 2004, Malone 2003) that assessed the effect of RBC on mortality, four studies (Ciesla 2005, Johnson 2010, Moore 1997, Sauaia 1994) that assessed the effect of RBC on MOF and one study (Edens 2010) that assessed the effect of RBC on acute lung injury. Meta-analyses were conducted to determine the effect of increased volume of RBCs transfusions on each of the outcome measures.

The studies were conducted in the trauma settings and commonly queried trauma databases or registries, resulting in most studies having good representativeness. Overall, Patel 2014 considered there to be no serious concerns of bias among the included prospective cohort studies.

Liu 2018 was a single centre prospective cohort study conducted in the US that investigated the association between RBC transfusion and mortality and hospital LOS in the trauma setting. Included trauma patients (predominantly due to assault and motor vehicle accidents) were over 18 years and had received between 0 and 87 units of RBCs within 24 hours of injury. The study was had serious concerns of bias raised, relating to inadequate adjustment for confounders, and lack of details regarding study design.

4.5.2.3 Retrospective cohort studies

Patel 2014 included data from 12 retrospective cohort studies that investigated the association between the transfusion of increased volumes of RBCs and patient outcomes in patients at risk of clinical bleeding. One additional retrospective cohort study (Hassainien 2015) (76) was identified in this systematic review that met our inclusion criteria.

The main characteristics and quality of the retrospective cohort studies included in this review is provided in Table 4.29.

Trauma setting

Among the 12 retrospective cohort studies identified by Patel 2014, there were 10 studies (Barbosa 2011, Chaiwat 2009, Mahambrey 2009, Murrell 2005, Phelan 2010, Robinson 2005, Spinella 2008, Croce 2005, Teixeira 2008, Weinberg 2008) that assessed the effect of RBC on mortality, one study (Cotton 2009) that assessed the effect of RBC on MOF and three studies (Plurad 2007, Weinberg 2008, Croce 2005) that assessed the effect of RBC on acute respiratory distress syndrome (ARDS). Meta-analyses were conducted to determine the effect of increased volume of RBC transfusions on each of the outcome measures.

The studies were conducted in the trauma settings and commonly queried trauma databases or registries, resulting in most studies having good representativeness. Overall, Patel 2014 considered there to be no serious risk of bias of included studies but noted that the study design is prone to confounding bias (particularly in relation to adjusting for the injury severity scores). Review authors attempted to mitigate confounding by only including studies that attempted to adjust for injury severity in the pooled analysis.

Medical setting

Hassanein 2015 was a retrospective hospital-based study conducted in Egypt. The study included 70 patients with liver cirrhosis and hepatocellular carcinoma presenting with

acute upper gastrointestinal bleeding. Patients must meet criteria of either hematemesis or melena with a diagnostic esophagogastroduodenoscopy, or both. The study was considered to be at moderate risk of bias due to a lack of details regarding blinding and study design.

Table 4.29 Characteristics and quality of retrospective cohort evidence: increased RBCs transfusion

Review ID ***Risk of bias***	Study design	Population N	Prognostic factor	Outcomes
Trauma setting				
Barbosa 2011 *Low*	Retrospective l cohort	Massively transfused patients N=704	Volume of RBCs transfused	Mortality
Phelan 2010 *Low*	Retrospective cohort	Adult trauma patients N=399	Volume of RBCs transfused	Mortality
Chaiwat 2009 *Moderate*	Retrospective cohort	Adults with at least one injury >AIS 3 N=14 070	Volume of RBCs transfused	Mortality
Cotton 2009 *Moderate*	Retrospective cohort	Surgical patients requiring massive transfusion N=266	Volume of RBCs transfused	Morbidity (MOF)
Mahambrey 2009 *Low*	Retrospective cohort	Trauma patients requiring massive transfusion N=260	Volume of RBCs transfused	Mortality
Spinella 2008 *Serious*	Retrospective cohort	Military trauma patients N=708	Volume of RBCs transfused	Mortality
Texeira 2008 *Serious*	Retrospective cohort	Trauma patients N=25 599	Volume of RBCs transfused	Mortality
Weinburg 2008 *Moderate*	Retrospective cohort	Patients with blunt trauma and ISS <25 N=1624	Volume of RBCs transfused	Mortality Morbidity (ARDS)
Plurad 2007 *Moderate*	Retrospective cohort	ICU trauma patients with intubation N=2346	Volume of RBCs transfused	Morbidity (ARDS)
Croce 2005 *Low*	Retrospective cohort	Patients with blunt trauma requiring ICU admission N=5260	Volume of RBCs transfused	Mortality Morbidity (ARDS)
Murrell 2005 *Low*	Retrospective cohort	Trauma patients transfused with at least one unit N=275	Volume of RBCs transfused	Mortality
Robinson 2005 *Low*	Retrospective cohort	Patients with blunt hepatic/splenic injury N=319	Volume of RBCs transfused	Mortality
Medical setting				
Hassanien 2015 (76) *Moderate*	Retrospective cohort, SC	Adult patients with liver cirrhosis and HCC presenting with acute upper gastrointestinal bleeding N=70	Volume of RBCs transfused	Mortality

AIS, abbreviated injury scale; ARDS, acute respiratory distress syndrome; HCC, hepatocellular carcinoma; ICU, intensive care unit; ISS, injury severity score; MOF, multiple organ failure; RBCs, red blood cells; SC, single centre

4.5.3 Results

4.5.3.1 Mortality

A summary of the evidence reported in the identified literature relating to mortality in patients at risk of critical bleeding is presented in Table 4.30.

The identified literature suggests transfusion of increased RBCs is associated with an increased risk of mortality among patients at risk of critical bleeding in the trauma setting.

Nine studies identified by Patel 2014 assessed RBC transfusion as a continuous variable. Pooled analysis showed an increased in the odds of mortality with each additional RBC unit transfused (OR 1.07; 95% CI 1.04, 1.10; $p < 0.001$; random effects; $I^2 = 82.9\%$).

Similarly, Liu 2018 showed increasing odds of mortality with increasing units of RBCs transfused.

Due to the limited evidence and significant heterogeneity, no additional meta-analysis was performed.

DRAFT

Table 4.30 Results for increased volume of RBC transfused versus decreased volume of RBC transfused: Patients *at risk of* critical bleeding – Mortality

Study ID Study design[a]	Sample size (no. of trials) included in analysis	Patient population	Setting (Location)	Comparison	Outcome	Results			
						High volume RBC n/N (%)	Low volume RBC n/N (%)	Risk estimate (95% CI)	*Statistical significance* *p*-value Heterogeneity[b]
Trauma setting									
Patel 2014 SR *Low quality*	N = 18 009 (9 Coh) Barbosa 2011 Bochicchio 2008 Chaiwat 2009 Mahambrey 2009 Murrell 2005 Phelan 2010 Robinson 2005 Spinella 2008 Silverboard 2005	Trauma patients, not limited by trauma severity, mechanism or pattern of injury	Trauma and non-trauma centres, (US, Canada)	RBC transfusion as continuous variable vs no RBC transfusion	Mortality	NR	NR	OR 1.07 (1.04-1.10) 1.05 (1.03, 1.07) 1.05 (1.03, 1.07) 1.05 (1.00, 1.10) 1.01 (0.97, 1.05) 0.83 (0.69, 0.99) 1.13 (1.10, 1.16) 1.16 (1.01, 1.24) 1.16 (1.09, 1.25) 1.08 (1.04, 1.15)	*Favours no RBC transfusion* *p* < 0.001 Substantial heterogeneity I^2 = 82.9%; *p* < 0.0001
						The odds of mortality increased with each additional unit transfused			
	N = 57 875 (6 Coh) Croce 2005 Dunne 2004 Malone 2003 Robinson 2005 Texeira 2008 Weinberg 2008			RBC transfusion as dichotomous variable vs no RBC transfusion	Mortality	NR	NR	OR 3.15 (1.82–5.46) 2.46 (2.00, 3.20) 4.23 (3.07, 5.84) 2.83 (1.82, 4.40) 4.75 (1.37, 16.40) 6.70 (6.10, 7.50) 0.96 (0.48, 1.94)	*Favours no RBC transfusion* *p* < 0.001 Substantial heterogeneity I^2 = 94.6%; *p* < 0.0001
Liu 2018 Prospective *Serious risk of bias*	N = 131	Adult trauma patients	Trauma, single centre (US)	High vs low units of RBCs	Mortality 0-9 units (n=95) 10-19 units (n=19) 20-29 units (n=8) 30-39 units (n=4) 40+ units (n=5)	 4/19 (21) 3/8 (38) 2/2 (50) 4/5 (80)	23/95 (24)	 OR 0.83 (0.25, 2.77) OR 1.88 (0.42, 8.47) OR 3.13 (0.41, 23.49) OR 12.52 (1.33, 117.7)	OR for 40+ units was 12.52 and did not contain the null, indicating a statistically significant difference from control (0-9 units)
Medical setting									
Hassanien 2015 Retrospective *Moderate risk of bias*	N = 70	Patients with liver cirrhosis and HCC presenting with AUGI bleeding	Single medical centre (Egypt)	Survivor vs non-survivor	Units of RBC transferred	Survivor (n=32) 1.9 ± 0.23	Non-survivor (n=38) 2.6 ± 0.74	NR	*p* < 0.01

AUGI; acute upper gastrointestinal; CI, confidence interval; Coh, cohort; HCC, hepatocellular carcinoma; NR, not reported; OR, odds ratio; RBC, red blood cells; SR, systematic review; US, United States

a. Where only one RCT is identified in a systematic review, the evidence has been considered as RCT evidence. Where the systematic review assesses observational and cohort studies, the evidence has been considered as according to the study design features. The risk of bias of the included primary studies is based on the quality assessment reported by the systematic review authors.

b. Only applicable to Systematic reviews with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if P_{het} >0.1 and I^2 <25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25–50%; substantial heterogeneity I^2 >50%.

4.5.3.2 Morbidity

A summary of the evidence reported in the identified literature relating to mortality in patients at risk of critical bleeding is presented in Table 4.31.

Identified literature suggests transfusion of increased RBCs is associated with an increased risk of morbidity among patients at risk of critical bleeding in the trauma setting.

Multiple organ failure

Three studies identified by Patel 2014 assessed RBC transfusion as a continuous variable. Pooled analysis showed a significant increase in the odds of MOF with each additional RBC unit transfused (OR 1.08; 95% CI 1.02, 1.14; $p = 0.012$; random effects; $I^2 = 95.9\%$).

Due to the limited evidence and significant heterogeneity, no additional meta-analysis was performed.

Acute respiratory distress syndrome / acute lung injury

Two studies identified by Patel 2014 assessed RBC transfusion as a continuous variable. Pooled analysis showed a significant increase in the odds of ARDS or ALI with each additional RBC unit transfused (OR 1.06; 95% CI 1.03, 1.10; $p < 0.001$; random effects; $I^2 = 0\%$).

Due to the limited evidence and significant heterogeneity, no additional meta-analysis was performed.

Length of stay

One cohort study by Liu (2018) found no association between the transfusion of increased RBCs and length of stay in trauma patients.

DRAFT

Table 4.31 Results for increased volume of RBC transfused versus decreased volume of RBC transfused: Patients *at risk of* critical bleeding – Morbidity

Study ID Study design[a]	Sample size (no. of trials) included in analysis	Patient population	Setting (Location)	Comparison	Outcome	Results			
						High volume RBC mean ± SD	Low volume RBC mean ± SD	Risk estimate (95% CI)	Statistical significance *p*-value Heterogeneity[b]
Trauma setting									
Patel 2014 SR *Low quality*	N = 3050 (3 Coh) Ciesla 2005 Cotton 2009 Johnson 2010	Trauma patients, not limited by trauma severity, mechanism or pattern of injury	Trauma (US)	RBC transfusion as continuous variable vs no RBC transfusion	MOF	NR	NR	OR 1.08 (1.02, 1.14) 3.40 (2.53, 4.58) 2.90 (1.20, 6.70) 8.60 (4.20, 17.70)	*Favours no RBC transfusion* *p* = 0.012 Substantial heterogeneity I^2 = 95.9%; p < 0.0001
	N = 2251 (3 Coh) Ciesla 2005 Moore 1997 Sauaia 1994			RBC transfusion of > 6 units as a dichotomous variable vs no transfusion		NR	NR	OR 4.30 (2.36, 7.85) 3.40 (2.53, 4.58) 2.90 (1.20, 6.70) 8.60 (4.20, 17.70)	*Favours RBC transfusion ≤ 6 units* *p* <0.0001 Moderate heterogeneity I^2 = 65.9%; *p* = 0.053
	N = 14 136 (2 Coh) Chaiwat 2009 Edens 2010			RBC transfusion as continuous variable vs no RBC transfusion	ARDS/ALI	NR	NR	OR 1.06 (1.03–1.10) 1.06 (1.03, 1.10) 1.09 (0.74, 1.58)	*Favours no RBC transfusion* *p* < 0.001 No heterogeneity I^2 = 0.0%, p = 0.886
	N = 9230 (3 Coh) Plurad 2007 Weinburg 2008 Croce 2005			RBC transfusion as a dichotomous variable vs no transfusion		NR	NR	OR 2.04 (1.47, 2.83) 1.98 (1.38, 2.83) 1.96 (0.73, 5.26) 3.42 (2.02, 34.20)	*Favours no RBC transfusion* *p* < 0.001 No heterogeneity I^2 = 0.0%, p = 0.761
Liu 2018 Prospective *Serious risk of bias*	N = 131	Adult trauma patients	Trauma, single centre (US)	High vs low units of RBCs	LOS, mean ±SD 0-9 units (n=95) 10-19 units (n=19) 20-29 units (n=8) 30-39 units (n=4) 40+ units (n=5)	 9.3 ± 5.5 9.0 ± 8.0 6.8 ± 6.0 4.6 ± 6.2	10.1 ± 12.1	NR	No significant difference p = 0.793 p = 0.806 p = 0.588 p = 0.321
Medical setting – no identified studies reported outcome of interest									

ALI, acute lung injury; ARDS, acute respiratory distress syndrome; CI, confidence interval; Coh, cohort; LOS, length of stay; MOF, multiorgan failure; NR, not reported; OR, odds ratio; RBC, red blood cells; SD, standard deviation; SR, systematic review; US, United States

a. Where only one RCT is identified in a systematic review, the evidence has been considered as RCT evidence. Where the systematic review assesses observational and cohort studies, the evidence has been considered as according to the study design features. The risk of bias of the included primary studies is based on the quality assessment reported by the systematic review authors.

b. Only applicable to Systematic reviews with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if P_{het} >0.1 and I^2 <25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25–50%; substantial heterogeneity I^2 >50%.

c. Calculated post-hoc using RevMan 5.4

4.5.3.3 Time on mechanical ventilator

No studies identified.

DRAFT

4.6 Recombinant factor VIIa (Question 5)

Question 5 – (interventional)

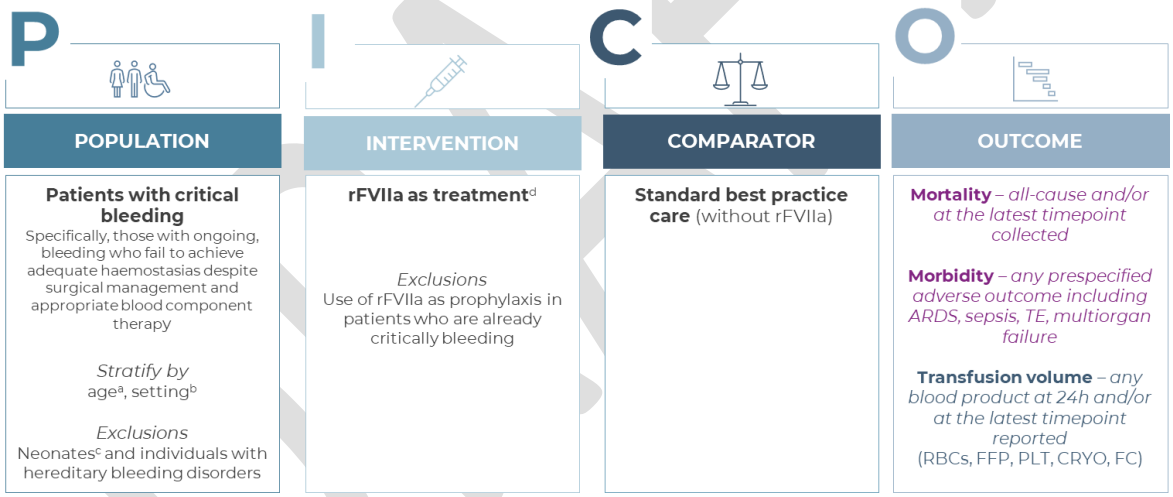
In patients *with* critical bleeding, what is the effect of rFVIIa treatment on morbidity, mortality and transfusion rate?

4.6.1 Methods

This review examined the effect of rFVIIa treatment on outcomes in patients with critical bleeding (i.e. major haemorrhage that is life-threatening and is likely to result in the need for massive transfusion) as outlined in Figure 4.18.

For this question there was particular focus on *patients who failed to achieve adequate haemostasis despite surgical management and appropriate blood component therapy*. Studies in patients with haemophilia and studies that examined the prophylactic use of rFVIIa were not eligible for inclusion.

Figure 4.18 PICO criteria: Question 5 – recombinant factor VIIa



Abbreviations: ARDS, acute respiratory distress syndrome; CRYO, cryoprecipitate; FC, fibrinogen concentrate; FFP, fresh frozen plasma; PLTs, platelets; RBCs, red blood cells; rFVIIa, recombinant activated factor seven; TE, thromboembolic event
a. Adult (aged over 18 years), child (aged 2 to 12 years), adolescent (aged 13 to 18 years), infants (aged 1 to 23 months).
b. e.g. trauma, obstetric, perioperative (cardiothoracic, general surgery, gastrointestinal, liver transplant), paediatric, other.
c. Newborns up to 28 days following birth.
d. rFVIIa is approved in Australia and NZ for the control of bleeding and prophylaxis for surgery in patients with specific clotting disorders. Use outside these indications (including critical bleeding following trauma) is considered 'off-label'.

The selection of studies was conducted according to the screening criteria described in Section 3.3.

The initial 2018 search was limited to studies published after 2009, noting primary studies published prior to 2009 that had been included in a systematic review were also eligible for inclusion. Nonrandomised studies (with concurrent or noncurrent controls) and observational cohort studies were excluded. There were no restrictions applied to study sample size.

Assuming all relevant primary studies had been identified in the included systematic review studies; the systematic screen for RCTs was limited to studies published from January 2015. This was based on the literature search date of the most recent identified systematic review (Canon 2017), which was assumed to have identified all relevant RCTs in the trauma and non-trauma setting. A targeted search.[29] for studies that focused on critical bleeding in the obstetrics and surgical setting and had been published between 2010 and 2015 was also conducted.

The literature search was updated in August 2019 with no new systematic review found.

In March 2021 it was agreed that this question would be retired, as research in this field is not evolving and updates to the literature search would likely find no new evidence (i.e. the citations in the September 2021 literature search update relating to rFVIIa were not screened).

4.6.2 Summary of evidence

4.6.2.1 Systematic reviews

Eight systematic reviews (57, 77-83) were included that evaluated the effects of rFVIIa treatment in patients with critical bleeding. The main characteristics and quality of these reviews and relevant outcomes assessed are summarised in Table 4.32.

Five systematic reviews were focused on critical bleeding in the trauma and non-trauma setting (Cannon 2017, Curry 2011, McQuilten 2015, Simpson 2012; Yank 2011), one in paediatric surgical trauma (Okanta 2012), and two in the obstetric setting (Franchini 2010, Magon 2012).

A matrix illustrating the overlap of studies included in each review is provided in Table 4.33 and Table 4.34. Among the 48 publications identified by the included systematic reviews, there were three RCTs and 34 nonrandomised cohort studies that were not included in the evidence evaluation as they did not meet the review criteria for this question (see Section 3.1.4).

4.6.2.2 Randomised controlled trials

There were 11 citations related to nine RCTs (84-94) that were considered relevant to this review. The primary studies varied in the clinical setting, and included trauma (blunt or penetrating), surgical (cardiac), medical emergency and obstetrics. All identified studies were supported by the manufacturer.

Two additional RCTs were identified through the handsearching process. One RCT sponsored by the manufacturer (Novo Nordisk A/S; NCT00323570) was withdrawn (and merged with the RCT reported by Hauser 2010). The other evaluated the safety and effectiveness of rFVIIa in women with severe primary postpartum haemorrhage (95).

A summary of the characteristics and quality of all identified RCTs is provided in Table 4.35.

[29] Keyword search for “obstetrics” and “maternity” or “cardiac” in identified studies.

Table 4.32 Characteristics and quality of systematic review evidence: rFVIIa

Review ID *Review quality*	Study design	Population	Intervention	Comparator	Outcomes
Trauma and non-trauma setting					
Cannon 2017 (57) *Moderate*	SR of RCTs and cohort studies	Patients at risk of death from haemorrhage *defined as patients requiring blood transfusions and/or injury severity score greater than 25	rFVIIa	No rFVIIa	Mortality Morbidity (TEs) Blood components used Massive transfusion
McQuilten 2015 (77) *Moderate*	SR review of SRs and RCTs	Patients with critical bleeding who had received or were anticipated to receive a massive transfusion in any clinical setting	rFVIIa	No rFVIIa	Mortality Morbidity (hospital LOS, serious AEs, transfusion-related AEs) Transfusion volume
Simpson 2012 *High* (80)	SR of RCTs	Patients who had received treatment to manage bleeding (medical, surgical, or obstetric)	rFVIIa	Placebo or different dose	Mortality Morbidity (TE) Transfusion volume
Curry 2011 (81) *Moderate*	SR of RCTs	Trauma patients with haemorrhagic shock within the first 24 hours of injury	rFVIIa	No rFVIIa	Mortality Morbidity (MOF, ARDS) Transfusion volume
Yank 2011[a] (82, 96) *High*	SR of RCTs, cohort studies, case series and case reports	Hospitalised patients with off-label use in cardiac surgery, body trauma, ICH, TBI, liver transplantation and prostatectomy [b]	rFVIIa	Placebo, alternative therapies or usual care	Mortality Morbidity (ARDS, TE) Transfusion volume
Surgical setting					
Okanta 2012 (79) *Critically low*	SR of best available evidence	Paediatric patients with excessive bleeding after cardiac surgery	rFVIIa	Placebo or other dose	Mortality Morbidity (TE) Transfusion volume
Obstetrics and maternity setting					
Magon 2012 (78) *Critically low*	SR of best available evidence	Women with major postpartum haemorrhage	rFVIIa	Not specified	Mortality Transfusion volume
Franchini 2010 (83) *Critically low*	SR of best available evidence	Women with major postpartum haemorrhage	rFVIIa	Not specified	Mortality Transfusion volume

Abbreviations: AE, adverse event; ARDS, acute respiratory distress syndrome; ICH, intracranial haemorrhage; LOS, length of stay; MOF, multiorgan failure; RCT, randomised controlled trial; SR, systematic review; TBI, traumatic brain injury, TE, thromboembolic events

a. An updated 2016 report (96) of the published systematic review by Yank 2011 also reviewed.

b. Data for ICH, TBI, liver transplantation and prostatectomy not relevant for this review (not critical bleeding or prophylactic use).

Table 4.33 Overlap table of RCTs identified by included systematic reviews: rFVIIa

		Trauma						Medical emergency					Surgical (cardiac)		
	Study IsD	Dutton 2011[a]	Hauser 2010	Boffard 2005a&b	McMullin 2010[b]	Boffard 2009[b]	Rizoli 2006(a)[b]	Narayan 2008[c]	Bosch 2008	Chuansumrit 2005	Pihusch 2005	Bosch 2004	Gill 2009	Ma 2006	Diprose 2005
Review ID	Cannon 2017		✓	✓											
	McQuilten 2015	✓	✓	✓											
	Simpson 2012		✓			✓		X	✓	✓	✓	✓			
	Okonta 2012[d]														
	Magon 2012[d]														
	Curry 2011		✓	✓	✓	✓	✓								
	Yank 2011		✓	✓									✓	X	X
	Franchini 2010[d]														

✓ = study included in this review X = study did not meet the inclusion criteria for this review.
a. Dutton 2011 and Hauser 2010 report data from the same randomised trial (CONTROL)
b. Post-hoc analysis of Boffard 2005a&b.
c. Population out of scope. Adult patients with traumatic intracranial haemorrhage with contusion.
d. Authors did not identify any RCTs in the population of interest.

DRAFT

Table 4.34 Overlap table of nonrandomised cohort studies identified by included systematic reviews: rFVIIa

		Trauma						Surgical (cardiac, adult)						Surgical (cardiac, paediatric)												Obstetric and maternity								
	Study ID	Wade 2010	Woodruff 2010	Fox 2009	Spinella 2008	Rizoli 2006(b)	Harrison 2005	Mitra 2010	Gelsomino 2008	Trowbridge 2008	Tritapepe 2007	Karkouti 2005	Von Heymann 2005	Ekert 2006 [a]	Warren 2009 (SR)	Singh 2012	Karsies 2010	Guzzetta 2009	Niles 2008	Agarwal 2007	Veldman 2007	Kylasam 2006	Razon 2005	Egan 2004	Pynchynka-Pokorska	Tobias 2004	Isbister 2008	Bouma 2008	Ahonen 2007	Alfirevic 2007	Barillari 2007	Hossain 2007	Ahonen 2005	Sobieszczyk 2006	Segal 2004
Review ID	Cannon 2017				X	X	X																											
	McQuilten 2015 [b]																																	
	Magon 2012																									No studies identified								
	Okonta 2012													X	X	X	X	X	X	X	X	X	X	X	X	X								
	Simpson 2012 [b]																																	
	Curry 2011 [b]																																	
	Yank 2011	X	X	X	X	X		X	X	X	X	X	X																					
	Franchini 2010																									X	X	X	X	X	X	X	X	X

✓ = study included in this review X = study did not meet the inclusion criteria for this review (nonrandomised studies not eligible for this question).
a. Intervention out of scope. Prophylactic use.
b. Authors did not search for nonrandomised studies.

DRAFT

Table 4.35 Characteristics and quality of RCT evidence: rFVIIa

Study ID *Risk of bias*	Study design	Population	Intervention	Comparator	Outcomes
Trauma setting					
Boffard 2005a *High*	RCT	Adult patients with haemorrhage from a severe blunt traumatic injury requiring ≥ 6 units of RBCs within 4 hours of hospitalisation	rFVIIa at 0, 1, 3 hrs (total 400 µg/kg)	Placebo	Mortality Morbidity (MOF, ARDS) Number of RBCs transfused
Boffard 2005b (86, 87, 90, 91) *High*	RCT	Adult patients with haemorrhage from a severe penetrating traumatic injury requiring ≥ 6 units of RBCs within 4 hours of hospitalisation	rFVIIa at 0, 1, 3 hrs (total 400 µg/kg)	Placebo	Mortality Morbidity (MOF, ARDS) Number of RBCs transfused
Hauser 2010 (CONTROL) (85) *Unclear*	RCT	Adult patients (aged 18 to 70 years) with major haemorrhage from blunt or penetrating trauma who received 4 to 8 units of RBCs within 12 hours of injury	rFVIIa at 0, 1, 3 hrs (total 400 µg/kg)	Placebo	Mortality Morbidity (MOF, SOF, ARDS, TEs, DIC, SAEs) Blood component use
Medical					
Bosch 2004 (94) *Unclear*	RCT	Adult patients with cirrhosis and upper gastrointestinal haemorrhage	rFVIIa at 0, 2, 4, 6, 12, 18, 24 & 30 hrs (total 800 µg/kg)	Placebo	Mortality Morbidity (AEs) RBC transfusion volume
Bosch 2008 (94) *Unclear*	RCT	Adult patients with cirrhosis and upper gastrointestinal haemorrhage	rFVIIa at 0, 2, 8, 14 & 20 hrs (total 1000 µg/kg)	Placebo	Mortality Morbidity (AEs) RBC transfusion volume
Haematology/oncology					
Pihusch 2005 (93) *High*	RCT	Patients (aged >12 yrs.) with bleeding occurring 2 to 180 days after HSCT	rFVIIa 40, 80 or 160 µg/kg every 6 hrs for 36 hrs	Placebo	Morbidity (AEs) Transfusion volume (RBC, PLTs, FFP)
Chuansumrit 2005 (92) *High*	RCT	Children with dengue haemorrhagic fever	rFVIIa 100 µg/kg additional dose allowed after 30 minutes	Placebo	Transfusion volume (RBC, PLTs, FFP)
Surgical setting					
Gill 2009 (88) *Unclear*	RCT	Patients with bleeding after cardiac surgery [a]	rFVIIa 40, 80 or 160 µg/kg	Placebo	Morbidity (SAEs) Transfusion volume (RBC, PLTs, FFP)
Obstetrics and maternity					
Lavigne-Lissalde 2015 (95) *High*	RCT	Women with severe PPH [b] after vaginal or caesarean birth that persisted after sulprostone treatment	rFVIIa 60 µg/kg	SoC [c]	Mortality Morbidity (TEs, reduction in need for specific second-line therapies)

Abbreviations: AEs, adverse events; ARDS, acute respiratory distress syndrome; DIC, disseminated intravascular coagulation; FFP, fresh frozen plasma; HSCT, haematopoietic stem cell transplant; MOF, multiorgan failure;; RCT, randomised controlled trial; rFVIIa, recombinant activated factor seven; PLT, platelets; PPH, primary postpartum haemorrhage; SAEs, serious adverse events; SoC, standard of care; SOF, single organ failure; TE, thromboembolic events

a. defined as post-operative bleeding for a minimum of 30 minutes following completion of a stabilisation period, and meeting at least one of the following criteria: ≥ 200 ml/hr in any one hour or part thereof; or ≥ 2 ml/kg/hr for two consecutive hours.

b. defined as the loss of more than 1500 mL of blood within 24 hours.
c. compassionate rFVIIa given late to avoid emergency peripartum hysterectomy.

Trauma

Three RCTs (Boffard 2005a & b, Hauser 2010) were identified that examined the effect of rFVIIa in patients with critical bleeding after blunt or penetrating trauma (85, 91). All three RCTs were judged to be of an overall unclear to high risk of bias (80), with high threats to validity due to lack of details provided by Boffard 2005a and 2005b (selective reporting) or unclear blinding of outcome assessment in Hauser 2010, which may have favoured the intervention.

Two parallel, double-blind RCTs were run simultaneously and published in the one article (91). The studies enrolled patients with haemorrhage from a blunt (Boffard 2005a) or penetrating (Boffard 2005b) traumatic injury requiring a least six unit of RBCs within four hours of hospitalisation. The studies were sponsored by the manufacturer and enrolled 301 patients (143 blunt and 134 penetrating) from 32 centres across eight countries (including Australia, Canada, France, Germany, Israel, Singapore, South Africa and the UK). Both RCTs censored deaths that occurred within 48 hours (comprising nearly 20% of patients) as the primary outcomes were RBC transfusion needs during the 48-hour observation period, which indicates that some end-stage use of rFVIIa may have occurred. Mortality and morbidity (ARDS, TEs) were also reported, noting the studies were not powered to detect a difference in these outcomes. Post-hoc analyses on the effect of rFVIIa on coagulopathic patients (90), on trauma patients who survived the first 48 hours after randomisation (87), and exploring the association between poorer outcomes and baseline haematologic and coagulation parameters (86) were also identified.

The double-blind RCT published by Hauser 2010 (CONTROL) enrolled patients with blunt or penetrating trauma who, despite strict damage control resuscitation and operative management had continued bleeding after receiving four units of RBC within 12 hours of injury. The study was sponsored by the manufacturer and enrolled 573 patients (481 blunt and 92 penetrating) from 150 hospitals in 26 countries. Subgroup analyses on patients with blunt (Hauser 2010a) and penetrating (Hauser 2010b) trauma were also conducted. The aim of the study was to detect a 16.7% mortality reduction with rFVIIa, assuming a 30% mortality in placebo patients, however, the study was terminated early due to unexpectedly low mortality in the placebo group detected during planned interim futility analysis. Extended safety data on patients enrolled in CONTROL are also available (84).

The three RCTs evaluated a total dose of 400 μg/kg intravenous rFVIIa administered in three doses (200 μg/kg at 0 hour, 100 μg/kg at one and three hours); which is higher than that reported among trauma patients in the Australian and New Zealand Haemostasis Registry, with 76% of patients (352/461) receiving only a single dose (median first dose of 95 μg/kg; IQR 80 to 108) (97). Patients enrolled in Hauser 2010 received the first dose earlier during the resuscitation period (after the fourth unit of RBCs) and required participating hospitals to use a prespecified resuscitation protocol.

Medical emergency

Two RCTs (Bosch 2004, Bosch 2008) were identified in the medical emergency setting that evaluated the therapeutic use of rFVIIa in patients with cirrhosis presenting with upper gastrointestinal haemorrhage (89, 94). Both RCTs were assessed to be at low to

unclear risk of bias, predominantly due to lack of clear detail and poor reporting in the published reports (80).

The RCT reported by Bosch 2004 was conducted in 245 cirrhotic patients with upper gastrointestinal bleeding (UGIB) enrolled from 26 centres in Europe. Subject were administered 100 μg/kg rFVIIa eight times *before* first endoscopy (t0), then at 2, 4, 6, 12, 18, 24, and 30 hours *after* endoscopy (total dose: 800 μg/kg total), with follow-up of patients occurring through to 42 days.

In the second RCT reported by Bosch 2008, 256 patients with advanced cirrhosis and active variceal bleeding were enrolled from 31 hospitals across Europe and Asia. Patients were randomised to receive 200 μg/kg rFVIIa initially as soon as possible *after* endoscopy, then either 4 x 100 μg/kg (total dose: 600 μg/kg) or a single 100 μg/kg (total dose: 300 μg/kg), or placebo; with the subsequent doses given at 2, 8, 14 and 20 hours after the first dose.

In both trials, the total dose of rFVIIa is again notably higher than that reported among patients with UGIB in the Australian and New Zealand Haemostasis Registry, with 74% of patients (140/189) receiving only a single dose (median first dose of 89 μg/kg; IQR 67 to 104) (97). The primary outcome measures in both trials were a composite of failure to control UGIB within 24 hours after first dose, failure to prevent rebleeding between 24 hours and day five, or death within five days. Outcomes of relevance for this review were transfusion requirements within five days (at discharge), and mortality and thromboembolic events recorded at latest follow-up.

Haematology/oncology setting

One multicentre RCT (Pihusch 2005) was identified that evaluated the use of rFVIIa in 100 patients with moderate or severe bleeding complications following haematopoietic stem cell transplantation (+2 to +180 weeks post-transplant) (93). Patients with bleeding (52 gastrointestinal; 26 haemorrhagic cystitis; seven pulmonary; one cerebral; 14 other) were randomised to receive seven doses of rFVIIa at 40, 80 or 160 μg/kg (total dose: 280, 560, or 1120 μg/kg) or placebo every six hours. The primary efficacy endpoint was the change in bleeding score between the first administration and 38 hours. The study was at high risk of bias due to baseline difference observed between treatment groups, suggesting randomisation or allocation concealment was compromised (80).

One RCT (Chuansumrit 2005) conducted in 25 paediatric patients with active bleeding due to dengue fever was identified in the literature (92). Patients were administered 100 μg/kg rFVIIa with repeat dose at 30 minutes if ongoing bleeding was observed. The study was small and not powered to detect differences in any outcomes and was therefore considered to be at high risk of bias for all outcomes (80).

Surgical setting

One Phase II dose-escalation study (Gill 2009) conducted in 13 countries in Africa, Asia, Europe, South America and US was identified that evaluated the therapeutic use of rFVIIa in patients with intractable bleeding after cardiac surgery (88). Patients were randomised to receive either 40 or 80 μg/kg rFVIIa (n= 35 and n=69, respectively) or placebo (n=68) after cardiopulmonary bypass (CPB) as treatment for excessive post-operative bleeding in the ICU.

The trial was terminated in November 2007 without proceeding to the highest dosing cohort (160 µg/kg) as it was determined to no longer reflect common clinical practice. The primary outcome was the incidence of critical serious adverse events at 30 days. The RCT was had overall unclear risk of bias (80).

Obstetrics and maternity

One multicentre RCT (Lavigne-Lissalde 2015) was identified that assessed the safety and effectiveness of rFVIIa given to women with severe primary postpartum haemorrhage (PPH), defined as loss of more than 1500 mL of blood within 24 hours after birth, after sulprostone failure (95). The women were aged over 18 years and had delivered after the end of 27 weeks of gestation by either vaginal or Caesarean section.

Subjects were randomly assigned to receive a single dose of 60 µg/kg rFVIIa or not, with the primary outcome being a reduction in the need for specific second-line therapies (inclusive of arterial embolisation, hysterectomy). Safety outcomes were also recorded up to five days post infusion.

The study was assessed to be at high risk of bias due to non-blinding that seriously weakens confidence in the results. The study allowed for compassionate use of rFVIIa in the comparator arm (8 out of 42 women in the standard care group received late rFVIIa) so it is possible that this introduced bias into the subsequent management of patients.

DRAFT

4.6.3 Results

4.6.3.1 Mortality

A summary of the evidence relating to in-hospital mortality in patients with critical bleeding treated with rFVIIa is presented in Table 4.36.

For most bleeding patients there does not seem to be clear significant survival benefits associated with rFVIIa (GRADE: low or very low).

A meta-analysis of data from RCTs included in this review (see Figure 4.19) showed the mortality rate (latest timepoint) in patients with critical bleeding to be comparable among those who received rFVIIa (157/934, 16.8%) and those who did not (120/776, 15.5%) with a relative risk (RR) of 0.99 observed (95% CI 0.80, 1.23; $p = 0.84$; fixed effect, $I^2 = 0\%$). For most bleeding patients, there is little or no difference in mortality compared with placebo or no rFVIIa.

Among patients with blunt and penetrating trauma, a total of 409 patients received rFVIIa compared with 428 patients who did not, with no difference in mortality observed (16.6% vs 17.1%, RR 0.96; 95% CI 0.71, 1.29; $p = 0.71$; fixed effect, $I^2 = 0\%$) *(GRADE: low)*.

Among patients with UGIB who received rFVIIa, the mortality rate of 19.2% (55/286) was not significantly different from the mortality rate of 17.5% (36/206) observed among those who did not receive rFVIIa. This corresponded to a RR of 1.02 (95% CI 0.55, 1.90; $p = 0.95$; random effects, $I^2 = 56\%$) *(GRADE: very low)*.

Among patients with uncontrolled bleeding due to other medical conditions (after HSCT, Dengue fever), the mortality rate was 25.8% (24/93) among those who received rFVIIa, compared with 21.9% (7/32) in those who did not, corresponding to a RR of 1.02 (95% CI 0.51, 2.07; $p = 0.95$; fixed effects, I^2 = not applicable [one study]) *(GRADE: very low)*.

Among patients with intractable bleeding after cardiac surgery, the mortality rate among those who received rFVIIa (9.6%)[30] was higher than that observed among those who did not receive rFVIIa (5.9%); however, this difference was not significant (RR 1.63; 95% CI 0.53, 5.00; $p = 0.95$; fixed effects, I^2 = not applicable [one study]) *(GRADE: very low)*.

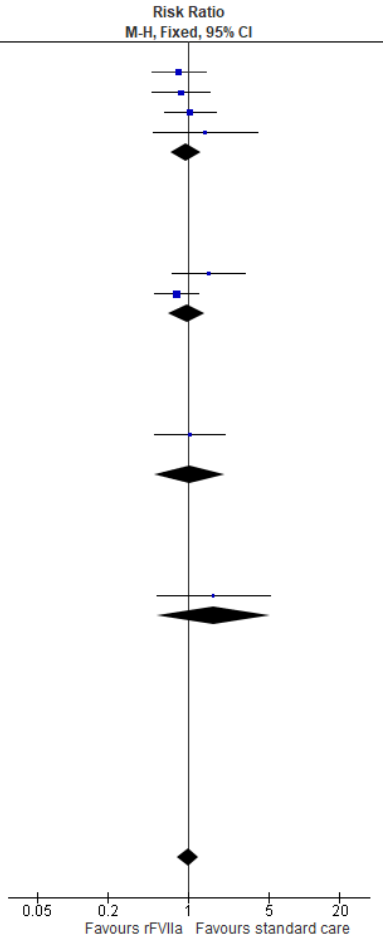
No deaths were observed in the RCT that assessed the effects of rFVIIa among women with severe PPH with persistent bleeding after sulprostone treatment and the included RCT was not large enough to detect differences in mortality *(GRADE: very low)*.

In agreeance with our findings, all identified systematic reviews reported no significant difference in mortality between patients who received in rFVIIa compared with those who did not, regardless of clinical setting (57, 77-83). There was also no significant effect on mortality shown in any of the subgroup analyses.

[30] noting the mortality rate among patients administered 40 and 80 µg/kg rFVIIa was 11.4% (4/35) and 8.7% (6/69), respectively.

Figure 4.19 Forest plot of comparison: rFVIIa vs placebo, outcome: Mortality, latest timepoint

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
1.1.1 Trauma (RCTs)							
Boffard 2005a (blunt)	17	69	22	74	16.1%	0.83 [0.48, 1.42]	2005
Boffard 2005b (penetrating)	17	70	18	64	14.3%	0.86 [0.49, 1.53]	2005
Hauser 2010a (blunt)	26	224	28	250	20.1%	1.04 [0.63, 1.71]	2010
Hauser 2010b (penetrating)	8	46	5	40	4.1%	1.39 [0.49, 3.91]	2010
Subtotal (95% CI)		**409**		**428**	**54.6%**	**0.96 [0.71, 1.29]**	
Total events	68		73				
Heterogeneity: Chi² = 1.00, df = 3 (P = 0.80); I² = 0%							
Test for overall effect: Z = 0.30 (P = 0.77)							
1.1.3 Medical emergency							
Bosch 2004 (GI haemorrhage in cirrhosis)	16	116	11	120	8.2%	1.50 [0.73, 3.10]	2004
Bosch 2008 (GI haemorrhage in cirrhosis) (1)	39	170	25	86	25.3%	0.79 [0.51, 1.21]	2008
Subtotal (95% CI)		**286**		**206**	**33.5%**	**0.96 [0.67, 1.39]**	
Total events	55		36				
Heterogeneity: Chi² = 2.29, df = 1 (P = 0.13); I² = 56%							
Test for overall effect: Z = 0.19 (P = 0.85)							
1.1.4 Haemotology/Oncology							
Pihusch 2005 (haemorrhage after HSCT)	24	77	7	23	8.2%	1.02 [0.51, 2.07]	2005
Chuansumrit 2005 (dengue)	0	16	0	9		Not estimable	2005
Subtotal (95% CI)		**93**		**32**	**8.2%**	**1.02 [0.51, 2.07]**	
Total events	24		7				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.07 (P = 0.95)							
1.1.5 Cardiac, adult							
Gill 2009 (treatment)	10	104	4	68	3.7%	1.63 [0.53, 5.00]	2009
Subtotal (95% CI)		**104**		**68**	**3.7%**	**1.63 [0.53, 5.00]**	
Total events	10		4				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.86 (P = 0.39)							
1.1.6 Obstetrics							
Lavigne-Lissalde 2015 (PPH)	0	42	0	42		Not estimable	
Subtotal (95% CI)		**42**		**42**		**Not estimable**	
Total events	0		0				
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
Total (95% CI)		**934**		**776**	**100.0%**	**0.99 [0.80, 1.23]**	
Total events	157		120				
Heterogeneity: Chi² = 4.22, df = 7 (P = 0.75); I² = 0%							
Test for overall effect: Z = 0.09 (P = 0.92)							
Test for subgroup differences: Chi² = 0.85, df = 3 (P = 0.84), I² = 0%							



Footnotes

(1) Data for 600 and 300 ug/kg rFIIVa groups combined.

Table 4.36 Results for rFVIIa versus no rFVIIa: Patients *with* critical bleeding – Mortality

Study ID Study design [a]	Sample size (no. of trials) included in analysis	Patient population	Setting (Location)	Comparison	Outcome	Results			
						rFVIIa n/N (%)	No rFVIIa n/N (%)	Risk estimate (95% CI)	*Statistical significance* *p*-value Heterogeneity [b]
Any setting									
Simpson 2012 SR *High quality*	N = 2856 (13 RCTs)	Patients with critical bleeding due to trauma, or who had received treatment to manage bleeding	trauma, medical, oncology (multicentre, multicountry)	rFVIIa (therapeutic) vs placebo	Mortality, in-hospital, 28 or 30 day (including patients with spontaneous ICH)	332/1777 (18.7)	202/1079 (18.7)	RR 0.91 (0.78, 1.06)	*No significant difference* *p* = 0.2 No significant heterogeneity I^2 = 0% (*p* = 0.66)
	N = 1569 (8 RCTs) Boffard 2005a Boffard 2005b Hauser 2010 Hauser 2010 Bosch 2004 Bosch 2008 Pihusch 2005 Chuansumrit 2005 Narayan 2008[d]				Mortality, in-hospital, 28 or 30 day (excluding patients with spontaneous ICH)	154/849 (18.1) 17/69 17/70 26/224 8/46 16/116 39/170 24/77 0/16 7/61	120/720 (16.7) 22/74 18/64 28/250 5/40 11/120 25/86 7/23 0/9 4/36	RR 0.95 (0.77, 1.18) RR 0.83 (0.48, 1.42) RR 0.86 (0.49, 1.53) RR 1.04 (0.63, 1.71) RR 1.39 (0.49, 3.91) RR 1.50 (0.73, 3.10) RR 0.79 (0.51, 1.21) RR 1.02 (0.51, 2.07) Not estimable RR 1.03 (0.32, 3.29)	*No significant difference* *p* = 0.65 [c] No significant heterogeneity I^2 = 0% (*p* = 0.85)
Trauma setting									
Cannon 2017 SR *Moderate quality*	N = 1292 (3 RCTs, 3 NRSIs) [e]	Patients with severe trauma at risk of death from haemorrhage	Trauma	rFVIIa vs no rFVIIa	Mortality, in-hospital, 28 or 30 day	112/517 (21.7)	237/775 (30.6)	OR 0.88 (0.64, 1.20)	*No significant difference* *p* = 0.42 No significant heterogeneity I^2 = 15% (*p* = 0.32)
	N = 825 (3 RCTs) Boffard 2005a&b Hauser 2010					66/401 (16.5) 34/139 (24.5) 32/262 (12.2)	71/424 (16.7) 40/144 (27.8) 31/280 (11.1)	OR 0.97 (0.67, 1.41) OR 0.84 (0.49, 1.43) OR 1.12 (0.66, 1.89)	*No significant difference* *p* = 0.88 No heterogeneity I^2 = 0% (*p* = 0.46)
Simpson 2012 SR *High quality*	N = 934 (4 RCTs) Boffard 2005a Boffard 2005b Hauser 2010 Hauser 2010 Narayan 2008 [d]	Adult patients with severe bleeding due blunt or penetrating trauma, or traumatic ICH	Trauma (multicentre, multicountry)	rFVIIa (therapeutic) vs placebo	Mortality blunt penetrating blunt penetrating ICH	75/470 (16.0) 17/69 17/70 26/224 8/46 7/61	77/464 (16.6) 22/74 18/64 28/250 5/40 4/36	RR 0.95 (0.71, 1.27) RR 0.83 (0.48, 1.42) RR 0.86 (0.49, 1.53) RR 1.04 (0.63, 1.71) RR 1.39 (0.49, 3.91) RR 1.03 (0.32, 3.29)	*No significant difference* *p* = 0.73 [c] No significant heterogeneity I^2 = 0% (*p* = 0.91)
Curry 2011 SR *Moderate quality*	N = 850 (3 RCTs) Boffard 2005a Boffard 2005b Hauser 2010 Hauser 2010	Adult patients with severe bleeding due blunt or penetrating trauma	Trauma (multicentre, multicountry)	rFVIIa (therapeutic) vs placebo	Mortality blunt penetrating blunt penetrating	NR/412 NR/69 NR/70 NR/226 NR/47	NR/438 NR/74 NR/64 NR/255 NR/45	Not calculated	*No significant difference* *p* = 0.58 *p* = 0.69 *p* = NR *p* = NR

Study ID Study design [a]	Sample size (no. of trials) included in analysis	Patient population	Setting (Location)	Comparison	Outcome	Results			
						rFVIIa n/N (%)	No rFVIIa n/N (%)	Risk estimate (95% CI)	*Statistical significance* *p*-value Heterogeneity [b]
Medical emergency									
Simpson 2012 SR *High quality*	N = 934 (3 RCTs) Bosch 2004 Bosch 2008 Chuansumrit 2005	Adult patients with cirrhosis and GI haemorrhage or children with dengue haemorrhagic fever	Trauma (multicentre, multicountry)	rFVIIa (therapeutic) vs placebo	Mortality, not specified	55/302 16/116 39/170 0/16	36/215 11/120 25/86 0/9	RR 1.02 (0.55, 1.90) RR 1.50 (0.73, 3.10) RR 0.79 (0.51, 1.21) Not estimable	*No significant difference* *p* = 0.95 [c] Substantial heterogeneity I^2 = 56% (*p* = 0.13)
McQuilten 2015 SR *Moderate quality*	N = 510 (1 SR, κ=2 RCTs) Marti-Caravajal 2012	Adult patients with cirrhosis and GI haemorrhage	Medical (multicentre, multicountry)	rFVIIa (therapeutic) vs placebo	Mortality, 5 days	NR	NR	RR 0.95 (0.36, 2.50)	*No significant difference* *p* = 0.16
					Mortality, 42 days	NR	NR	RR 1.01 (0.55, 1.87)	*No significant difference* *p* = 0.14
Oncology setting									
Simpson 2012 RCT *High risk of bias*	N = 934 (1 RCT) Pihusch 2005	Patients with moderate to severe bleeding after HSCT	Oncology (multicentre, multicountry)	rFVIIa (therapeutic) vs placebo	Mortality	24/77	7/23	1.02 (0.51, 2.07)	*No significant difference* *p* = 0.95 [c] Heterogeneity NA
Surgical setting									
Yank 2011 RCT *Unclear risk of bias*	N = 172 (1 RCT) Gill 2009	Adult patients who had undergone cardiac surgery and were bleeding	Cardiology (multicentre, multicountry)	rFVIIa (therapeutic) vs placebo	Mortality 40 ug/kg rFVIIa 80ug/kg rFVIIa	10/104 4/35 (11.4) 6/69 (8.7)	4/68 (5.8)	RD 0.04 (–0.04, 0.12)	*No significant difference* Heterogeneity NA *p* = NR
Obstetrics and maternity setting									
Lavigne-Lissalde 2015 RCT *High risk of bias*	N = 84	Women (aged 18 years or older) with severe persistent primary PPH [f] after sulprostone treatment	Obstetrics (multicentre, France, Switzerland)	rFVIIa (therapeutic) vs standard care	Mortality	0/42 (0)	0/42 (0)	Not estimable	Not estimable
Franchini 2010 SR (case series)	N = 272 (9 case series)	Women with severe PPH (≥ 500 mL after vaginal delivery and ≥ 1000 mL after caesarean delivery)	Obstetrics and gynaecology (multicountry including Europe and Australia)	rFVIIa	Mortality	The authors identified no RCTs, case-control or interventional cohort studies, therefore attempted to extract useful information from published case reports (N>10) to provide recommendations for the management of severe PPH. Two retrospective Coh studies (Kalina 2011, Hossain 2007) identified and discussed in PBM Module 5 (technical report vol. 1 Section 3.4.4).		*One study reported an association favouring rFVIIa after adjustment for confounders.*

Study ID Study design [a]	Sample size (no. of trials) included in analysis	Patient population	Setting (Location)	Comparison	Outcome	Results			
						rFVIIa n/N (%)	No rFVIIa n/N (%)	Risk estimate (95% CI)	*Statistical significance* *p*-value Heterogeneity [b]
Paediatrics - no comparative evidence found									

Abbreviations: CI, confidence interval; GI, gastrointestinal; HSCT, haemopoietic stem cell transplant; ICH, intracerebral haemorrhage; NA, not applicable; NR, not reported; NRSIs, non-randomised study of intervention; OR, odds ratio; PPH, postpartum haemorrhage; RCTs, randomised controlled, trials; rFVIIa, recombinant activated factor seven; RR, relative risk; UK, United Kingdom; US, United States

a. Where only one RCT is identified in a systematic review, the evidence has been considered as RCT evidence. Where the systematic review assesses observational or cohort studies, the evidence has been considered as According to the study design features. The risk of bias of the included primary studies is based on the quality assessment reported by the systematic review authors.

b. Only applicable to Systematic reviews with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if P_{het} >0.1 and I^2 <25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25–50%; substantial heterogeneity I^2 >50%.

c. Calculated post-hoc using RevMan 5.4. M-H, random effects.

d. Narayan 2008 does not meet the PICO criteria for this review as it in a population with ICH (not critical bleeding with haemodynamic compromise).

e. NRSIs not included in the review for this question.

f. Defined as the loss of more than 1500 mL of blood within 24 hr after vaginal or caesarean delivery.

DRAFT

4.6.3.2 Morbidity

Thromboembolic events

A summary of the evidence relating to thromboembolic events in patients with critical bleeding treated with rFVIIa is presented in Table 4.37.

Overall, the evidence for harms (thromboembolic events) is limited. The studies were not large enough to detect important differences with variance for methods for detection of thromboembolic events also noted *(GRADE: very low)*.

In a meta-analysis of data from included RCTs (Figure 4.20), there was slight increased risk of total thromboembolic events among patients administered rFVIIa (77/945; 8.1%) compared with placebo or no rFVIIa (58/780; 7.4%), however the difference was not statistically significant (RR 1.17, 95%CI 0.85, 1.63, $p = 0.52$, fixed effect, $I^2 = 0\%$).

Among patients with blunt and penetrating trauma who received rFVIIa, 10.8% (44/409) had a thromboembolic event compared with 10.0% (43/428) in the placebo group, corresponding to a nonsignificant difference between treatment groups (RR 1.10; 95% CI 0.74, 1.63; $p = 0.63$, fixed effect, $I^2 = 0\%$).

Among patients with UGIB, the rate of thromboembolic events in patients who received rFVIIa was also not significantly different from those who did not receive rFVIIa (5.4% vs 6.6%, RR 0.80; 95% CI 0.40, 1.60, $p = 0.54$, fixed effect, $I^2 = 0\%$).

Among patients with uncontrolled bleeding after HSCT, the risk of thromboembolic events was higher in the group who received rFVIIa (8/93, 10.4%) compared with those who did not (0/23, 0%) (RR 5.23; 95% CI 0.31, 87.34; $p = 0.25$).

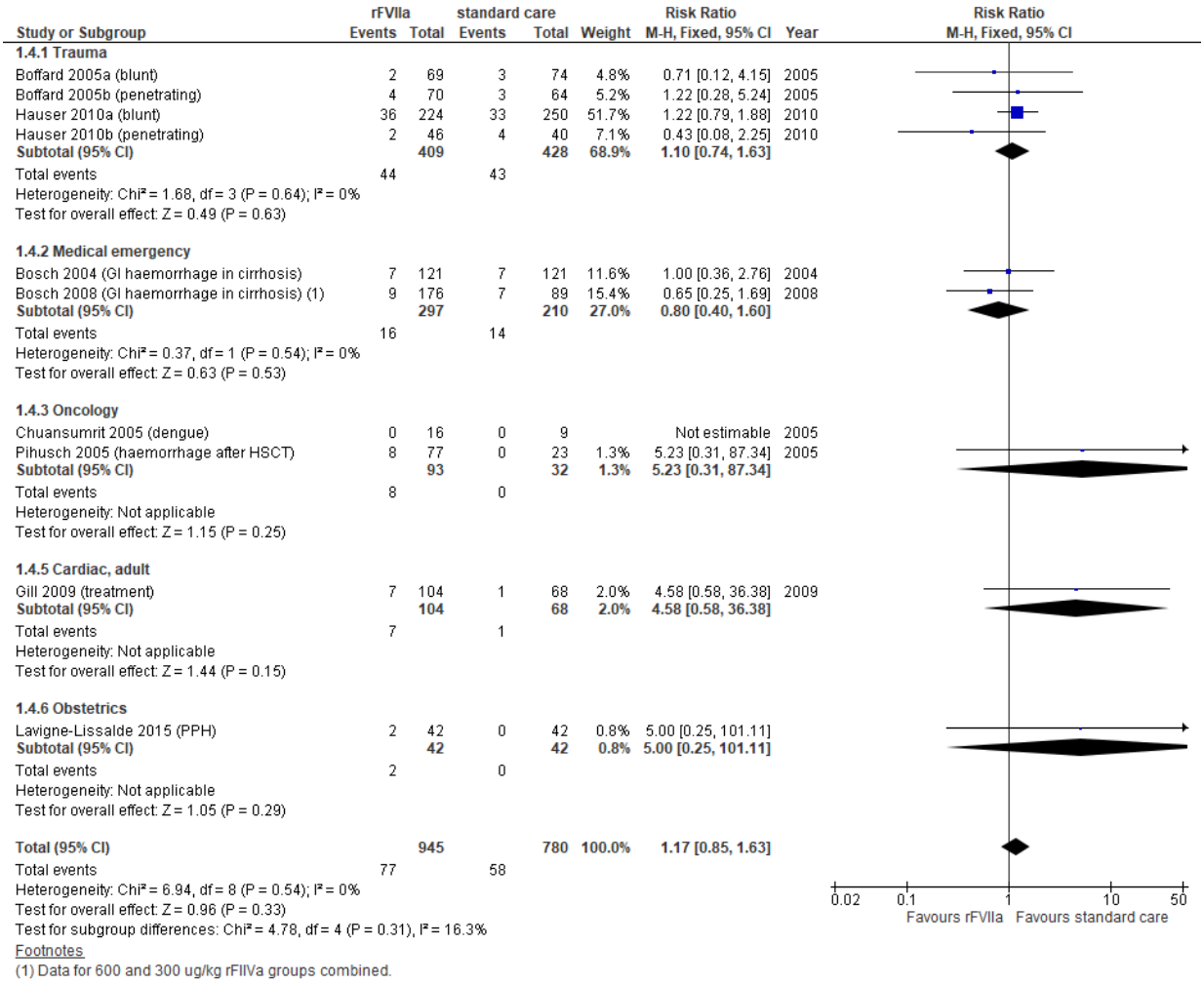
Among patients with uncontrolled bleeding due after cardiac surgery, the risk of thromboembolic events was higher in the group who received rFVIIa (7/104, 6.7%) compared with those who did not (1/68, 1.5%) (RR 4.58; 95% CI 0.58, 36.38; $p = 0.15$).

Among patients with PPH, the risk of thromboembolic events was higher in the group who received rFVIIa (2/42, 4.8%) compared with those who did not (0/42, 0%) (RR 5.00; 95% CI 0.25, 101.11.00; $p = 0.29$).

All identified systematic review suggested no increased risk of thromboembolic events among patients treated with rFVIIa, except one (Yank 2011), who suggested an increased (borderline) risk among patients with intractable bleeding after cardiac surgery. This is consistent with the review by Simpson 2012 and McQuilten 2015, who noted an increased risk of arterial thromboembolic events when both prophylactic and therapeutic studies were considered.

DRAFT

Figure 4.20 Forest plot of comparison: rFVIIa vs placebo, outcome: total thromboembolic events



Footnotes

(1) Data for 600 and 300 ug/kg rFIIVa groups combined.

Table 4.37 Results for rFVIIa versus no rFVIIa: Patients *with* critical bleeding – Morbidity: thromboembolic events

Study ID Study design [a]	Sample size (no. of trials) included in analysis	Patient population	Setting (Location)	Comparison	Outcome	Results			
						rFVIIa n/N (%) mean ± SD (n)	No rFVIIa n/N (%) mean ± SD (n)	Risk estimate (95% CI)	*Statistical significance* *p*-value Heterogeneity [b]
Any setting									
Simpson 2012 SR *High quality*	N = 2873 (13 RCTs)	Patients with critical bleeding due to trauma, or who had received treatment to manage bleeding	Trauma, medical, oncology (multicentre, multicountry)	rFVIIa (therapeutic) vs placebo	Total thromboembolic events (including patients with spontaneous ICH)	169/1789	89/1084	RR 1.14 (0.89, 1.47)	*No significant difference* *p* = 0.30 No significant heterogeneity I^2 = 0% (*p* = 0.67)
	N = 1566 (9 RCTs) Boffard 2005a Boffard 2005b Hauser 2010a Hauser 2010b Bosch 2004 Bosch 2008 Pihusch 2005 Chuansumrit 2005 Narayan 2008[d]				Total thromboembolic events (excluding patients with spontaneous ICH) 2/69 4/70 36/224 2/46 7/121 9/176 8/77 0/16 13/61	81/860 3/74 3/64 33/250 4/40 7/121 7/89 0/23 0/9 5/36	62/706 0.71 (0.12, 4.15) 1.22 (0.28, 5.24) 1.22 (0.79, 1.88) 0.43 (0.08, 2.25) 1.00 (0.36, 2.76) 0.65 (0.25, 1.69) 5.23 (0.31, 87.34) Not estimable 1.53 (0.60, 3.95)	RR 1.10 (0.80, 1.52) *No significant difference* *p* = 0.56 [c] No significant heterogeneity I^2 = 0% (*p* = 0.72)
McQuilten 2015 SR *Moderate quality*	N = 4119 (1 SR, κ=35 studies) Levi 2010	Off-label use in bleeding patients and healthy volunteers	Any	rFVIIa versus placebo	Total thromboembolic events Venous Cerebrovascular Arterial Coronary	NR	NR	OR 1.17 (0.94, 1.47) OR 0.93 (0.70, 1.23) OR 1.27 (0.74, 2.17) OR 1.68 (1.2, 2.36) OR 2.39 (1.39, 4.09)	*No significant difference* *p* = 0.16 *p* = 0.61 *Not significant* *p* = 0.39 *Not significant* *p* = 0.003 *Favours rFVIIa* *p* = 0.002 *Favours rFVIIa*
Trauma setting									
Cannon 2017 SR *High quality*	N = 1061 (2 RCTs, 2 Coh)[e]	Patients with severe trauma at risk of death from haemorrhage	Trauma	rFVIIa vs no rFVIIa	Venous thromboembolic events	48/487 (9.9%)	57/574 (9.9%)	OR 0.97 (0.49, 1.92)	*No significant difference* *p* = 0.94 Mild heterogeneity I^2 = 29% (*p* = 0.24)
	N = 837 (2 RCTs) Boffard 2005 Hauser 2010					44/409 (10.8%) 6/139 (4.3%) 38/270 (14.1%)	43/428 (10.0%) 6/138 (4.3%) 37/290 (12.8%)	OR 1.10 (0.70, 1.72) OR 0.99 (0.31, 3.16) OR 1.12 (0.69, 1.82)	*No significant difference* *p* = 0.68 No heterogeneity I^2 = 0% (*p* = 0.85)

DRAFT

Study ID Study design [a]	Sample size (no. of trials) included in analysis	Patient population	Setting (Location)	Comparison	Outcome	Results			
						rFVIIa n/N (%) mean ± SD (n)	No rFVIIa n/N (%) mean ± SD (n)	Risk estimate (95% CI)	*Statistical significance* *p*-value Heterogeneity [b]
McQuilten 2015 SR *Moderate*	N = 560 (1 RCT) Dutton 2011	Adult patients with blunt and/or penetrating trauma with continuing bleeding after receiving 4 units RBC despite standard haemostatic interventions	Trauma (multicentre, multicountry)	rFVIIa (therapeutic) vs placebo	Thromboembolic events Venous Arterial	 25/270 (9) 16/270 (6)	 26/287 (9) 12/290 (4)	 NR NR	*No significant difference* *p* = 0.90 *p* = 0.33
Simpson 2012 SR *High quality*	N = 934 (4 RCTs) Boffard 2005a Boffard 2005b Hauser 2010 Hauser 2010 ~~Narayan 2008~~ [d]	Adult patients with severe bleeding due blunt or penetrating trauma, or traumatic ICH	Trauma (multicentre, multicountry)	rFVIIa (therapeutic) vs placebo	Total thromboembolic events	57/470 2/69 4/70 36/224 2/46 13/61	46/464 3/74 3/64 33/250 4/40 5/36	RR 1.17 (0.81, 1.69) RR 0.71 (0.12, 4.15) RR 1.22 (0.28, 5.24) RR 1.22 (0.79, 1.88) RR 0.43 (0.08, 2.25) RR 1.53 (0.60, 3.95)	*No significant difference* *p* = 0.40 [c] No significant heterogeneity I^2 = 0% (*p* = 0.73)
Medical emergency									
McQuilten 2015 SR *Moderate*	N = 510 (1 SR, κ=2 RCTs) Marti-Caravajal 2012	Adult patients with cirrhosis and GI haemorrhage	Medical (multicentre, multicountry)	rFVIIa (therapeutic) vs placebo	Total thromboembolic events	NR	NR	RR 0.80 (0.40, 1.60)	*No significant difference* *p* = 0.20
Simpson 2012 SR *High quality*	N = 532 (3 RCTs) Bosch 2004 Bosch 2008 Chuansumrit 2005	Adult patients with cirrhosis and GI haemorrhage or children with dengue haemorrhagic fever	Medical (multicentre, multicountry)	rFVIIa (therapeutic) vs placebo	Total thromboembolic events	16/313 7/121 9/176 0/16	14/219 7/121 7/89 0/9	RR 0.80 (0.40, 1.60) RR 1.00 (0.36, 2.76) RR 0.65 (0.25, 1.69) Not estimable	*No significant difference* *p* = 0.52 [c] No significant heterogeneity I^2 = 0% (*p* = 0.54)
Oncology setting									
Simpson 2012 RCT *High risk of bias*	N = 100 (1 RCT) Pihusch 2005	Patients with moderate to severe bleeding after HSCT	Oncology trauma (multicentre, multicountry)	rFVIIa (therapeutic) vs placebo	Total thromboembolic events	8/77	0/23	RR 5.23 (0.31, 87.34)	*No significant difference* *p* = 0.25 Heterogeneity NA
Surgical setting									
Yank 2011 RCT *High risk of bias*	N = 172 (1 RCT) Gill 2009	Adult patients who had undergone cardiac surgery and were bleeding	Surgical (multicentre, multicountry)	rFVIIa (therapeutic) vs placebo	Total thromboembolic events 40 ug/kg rFVIIa 80ug/kg rFVIIa	7/104 (6.7) 3/35 (8.6) 4/69 (5.8)	1/68 (1.5)	RD 0.05 (0.00, 0.11)	*Favours rFVIIa* *p* = NR *(borderline)*

Study ID Study design [a]	Sample size (no. of trials) included in analysis	Patient population	Setting (Location)	Comparison	Outcome	Results			
						rFVIIa n/N (%) mean ± SD (n)	No rFVIIa n/N (%) mean ± SD (n)	Risk estimate (95% CI)	*Statistical significance* *p*-value Heterogeneity [b]
Obstetrics and maternity setting									
Lavigne-Lissalde 2015 RCT *High risk of bias*	N = 84	Women (aged 18 years or older) with severe persistent primary PPH [f] after sulprostone treatment	Obstetrics (multicentre, France, Switzerland)	rFVIIa (therapeutic) vs standard care	Thromboembolic events	2/42 (5)	0/42 (0)	NR	*No significant difference* *p* = 0.25
Franchini 2010 SR (case series) *High risk of bias*	N = 272 (9 case series)	Women with severe PPH (≥ 500 mL after vaginal delivery and ≥ 1000 mL after caesarean delivery)	Obstetrics and gynaecology (various countries including Europe and Australia)	rFVIIa vs no rFVIIa	Thromboembolic events	The authors identified no RCTs, case-control or interventional cohort studies, therefore attempted to extract useful information from published case reports (total N>10) to provide recommendations for the management of severe PPH. Three retrospective cohort studies (Kalina 2011, Ahonen 2007, Hossain 2007) identified and discussed in PBM Module 5 (TR vol. 1 Section 3.4.4). One TE event reported.			*No significant association between treatment with rFVIIa and TE observed.*
Paediatrics - no comparative evidence found									

Abbreviations: CI, confidence interval; GI, gastrointestinal; HSCT, haemopoietic stem cell transplant; NR, not reported; OR, odds ratio; PPH, postpartum haemorrhage; RCTs, randomised controlled, trials; rFVIIa, recombinant activated factor seven; RR, relative risk; UK, United Kingdom; US, United States

a. Where only one RCT is identified in a systematic review, the evidence has been considered as RCT evidence. Where the systematic review assesses observational or cohort studies, the evidence has been considered according to the study design features. The risk of bias of the included primary studies is based on the quality assessment reported by the systematic review authors.

b. Only applicable to Systematic reviews with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if P_{het} >0.1 and I^2 <25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25–50%; substantial heterogeneity I^2 >50%.

c. Calculated post-hoc using RevMan 5.4. M-H random effects.

d. Narayan 2008 does not meet the PICO criteria for this review as it in a population with ICH (not critical bleeding with haemodynamic compromise).

e. NRSIs not included in the review for this question.

f. Defined as the loss of more than 1500 mL of blood within 24 hr after vaginal or caesarean delivery.

DRAFT

Other adverse events

A summary of the evidence relating to other adverse events in patients with critical bleeding treated with rFVIIa is presented in Table 4.38.

The available evidence suggested a slight increased benefit associated with a reduced incidence of acute respiratory distress syndrome (ARDS) and multiorgan failure (MOF) among patients with blunt or penetrating trauma, however it is noted that the evidence is weak and limited to post-hoc analyses *(GRADE: low)*.

In a meta-analysis of data from RCTs included in this review (Figure 4.21), fewer patients with blunt and penetrating trauma who received rFVIIa were reported to have ARDS compared with those who received placebo (3.4% vs 8.9%); an effect that was statistically significant (RR 0.39, 95%CI 0.22, 0.71, $p = 0.002$, fixed effect, $I^2 = 0\%$). Similarly, significantly fewer patients who received rFVIIa were reported to have MOF compared with the placebo group (4.4% vs 7.9%; RR 0.56; 95% CI 0.32, 0.97; $p = 0.04$, fixed effect, $I^2 = 0\%$).

Evidence for ARDS or MOF was not reported in the RCTs evaluating the effects of rFVIIa in patients with UGIB or those with uncontrolled bleeding due to other medical conditions (after HSCT, dengue haemorrhagic fever, cardiac surgery, primary PPH).

One RCT (Hauser 2010) examining the effects of rFVIIa among patients with blunt or penetrating trauma also reported on the incidence of sepsis and disseminated intravascular coagulation among treated patients. For both outcomes, a non-significant difference between the treatment groups was observed (RR 0.86; 95% CI 0.58, 1.28; $p = 0.47$, fixed effect, $I^2 = 0\%$ and RR 0.69; 95% Ci 0.27, 1.76; $p = 0.44$, fixed effect, $I^2 = 0\%$, respectively).

Evidence from the included systematic reviews suggested a slight increased benefit among patients treated with rFVIIa associated with a reduced incidence of acute respiratory distress syndrome (ARDS) and multiorgan failure (MOF) among patients with blunt or penetrating trauma, however it was noted that the evidence is weak and limited to post-hoc analyses.

DRAFT

Figure 4.21 Forest plot of comparison: rFVIIa vs placebo, outcome: Other adverse events (trauma setting)

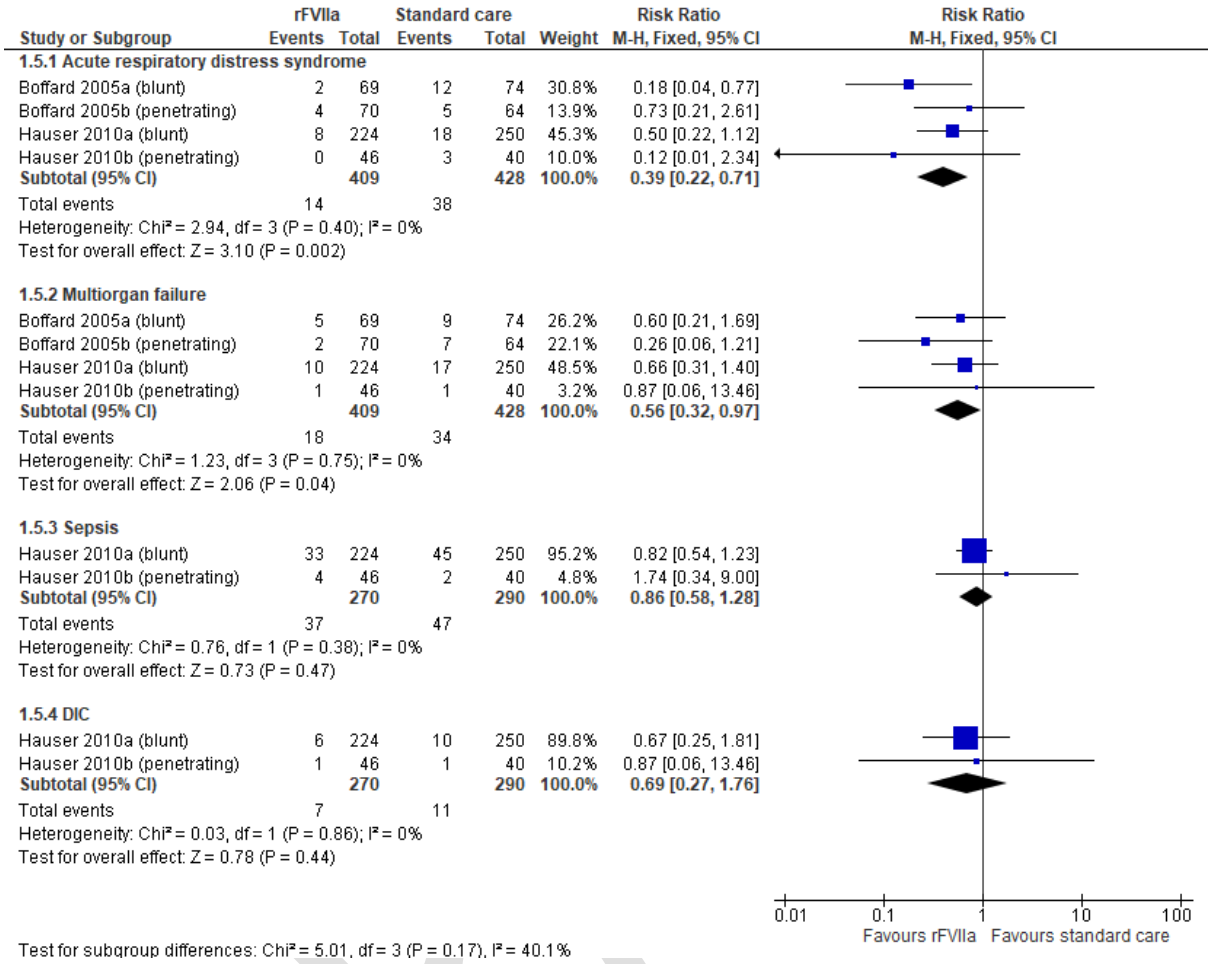


Table 4.38 Results for rFVIIa versus no rFVIIa: Patients *with* critical bleeding – Morbidity: other adverse events

Study ID Study design [a]	Sample size (no. of trials) included in analysis	Patient population	Setting (Location)	Comparison	Outcome	Results rFVIIa n/N (%)	No rFVIIa n/N (%)	Risk estimate (95% CI)	*Statistical significance* *p*-value Heterogeneity [b]
Trauma setting									
Updated in this review *data retrieved from primary studies	N = 961 (3 RCTs) Boffard 2005a Boffard 2005b Hauser 2010	Adult patients with blunt and/or penetrating trauma with critical bleeding	Trauma (multicentre, multicountry)	rFVIIa (therapeutic) vs placebo	ARDS, 30 or 90 days blunt penetrating blunt penetrating	14/409 (3.4) 3/69 (4) 4/70 (5) 8/224 (3.6) 0/46 (0.0)	38/428 (8.9) 12/74 (16) 5/64 (8) 18/250 (7.2) 3/40 (7.5)	RR 0.39 (0.22, 0.71) 0.18 (0.04, 0.77) 0.73 (0.21, 2.61) 0.5 (0.22, 1.12) 0.12 (0.01, 2.34)	*Favours rFVIIa* *p* = 0.002 [c] No significant heterogeneity I^2 = 0% (*p* = 0.4)
					MOF, 30 or 90 days blunt penetrating blunt penetrating	18/409 (4.4) 5/69 (7) 2/70 (3) 10/224 (4.5) 1/46 (2.2)	34/428 (7.9) 9/74 (12) 7/64 (11) 17/250 (6.8) 1/40 (2.5)	RR 0.56 (0.32, 0.97) RR 0.6 (0.21, 1.69) 0.26 0.06, 1.21) 0.66 (0.31, 1.40) 0.87 (0.06, 13.46)	*No significant difference* *p* = 0.04 [c] No significant heterogeneity I^2 = 0% (*p* = 0.75)
	N = 560 (1 RCT) Hauser 2010				Sepsis, 90 days blunt penetrating	37/270 33/224 (14.7) 4/46 (8.7)	47/290 45/250 (18) 2/40 (5.0)	RR 0.86 (0.57, 1.28) RR 0.82 (0.54, 1.23) RR 1.74 (0.34, 9.00)	*No significant difference* *p* = 0.44 [c] No significant subgroup heterogeneity I^2 = 0% (*p* = 0.38)
					DIC, 90 days blunt penetrating	7/270 6/224 (2.7) 1/46 (2.2)	11/290 10/250 (4.0) 1/40 (2.5)	RR 0.69 (0.27, 1.76) RR 0.67 (0.25, 1.81) RR 0.87 (0.06, 13.46)	*No significant difference* *p* = 0.44 [c] No significant subgroup heterogeneity I^2 = 0% (*p* = 0.86)
	N = 220 (2 RCTs) Boffard 2009	Patients who did not survive the first 48 hours excluded	Trauma (multicentre, multicountry)	rFVIIa (therapeutic) vs placebo	ARDS, 30 days blunt trauma penetrating trauma	11/NR (5) NR	3/NR (18) NR	NR NR	*Favours rFVIIa* *p* = 0.05 (blunt) *p* = NR
						Logistic regression analysis (See Boffard 2009) adjusted for demographic and baseline variables known to predict ARDS confirmed reduced risk favouring rFVIIa (OR 0.16; 95% CI 0.02, 0.73; *p* = 0.0163) in patients with blunt trauma. Data on patients with penetrating trauma NR.			
					MOF, 30 day blunt trauma penetrating trauma	7/NR (11) NR	3/NR (5) NR	NR NR	*No significant difference* *p* = 0.30 (blunt) *p* = NR
						Logistic regression analysis adjusted for demographic and baseline variables known to predict MODS suggested a significant			

Study ID Study design [a]	Sample size (no. of trials) included in analysis	Patient population	Setting (Location)	Comparison	Outcome	Results			
						rFVIIa n/N (%)	No rFVIIa n/N (%)	Risk estimate (95% CI)	*Statistical significance* *p*-value Heterogeneity [b]
						difference in favour of rFVIIa (OR 0.05: 95% CI 0.00, 0.89; *p* = 0.0406). (See Boffard 2009) Data on patients with penetrating trauma NR.			
McQuilten 2015 SR *Moderate quality*	N = 560 (1 RCT) Dutton 2011	Adult patients with blunt and/or penetrating trauma with continued bleeding after receipt of 4U RBC despite standard haemostatic interventions	Trauma (multicentre, multicountry)	rFVIIa (therapeutic) vs placebo	ARDS, 30 days	8/270 (3)	21/290 (7.2)	NR	*Favours rFVIIa* *p* = 0.02
	N = 573 (1 RCT) Hauser 2010				MOF, 30 day blunt and penetrating blunt	NR/267 (23) NR/221 (45)	NR/287 (24) NR/247 (53)	NR NR	*No significant difference* *p* = 0.09 *p* = 0.06
Curry 2011 SR *Moderate quality*	N = 850 (3 RCTs) Boffard 2005a Boffard 2005b Hauser 2010	Adults patients with blunt or penetrating injury	Trauma (multicentre, multicountry)	rFVIIa (therapeutic) vs placebo	ARDS, not specified blunt penetrating blunt & penetrating	NR/411 NR/69 NR/70 NR/272	NR/438 NR/74 NR/64 NR/300	NR NR NR NR	*p* = NR *Favours rFVIIa* *p* = NR *no difference* *p* = NR *trend towards (blunt only)*
						Post-hoc analyses of Boffard 2005 a&b			
					Rizoli 2006 (coagulopathic patients)	NR/60	NR/76	NR	*Favours rFVIIa* *p* = NR
					Boffard 2009 (patients surviving 48 hours or more)	NR/139	NR/138	OR 0.16 (0.02, 0.73)	*Favours rFVIIa* *p* = NR
					MOF, not specified blunt penetrating blunt & penetrating	NR/411 NR/69 NR/70 NR/272	NR/438 NR/74 NR/64 NR/300	NR	*p* = NR *no difference* *p* = NR t*rend towards* *p* = NR *trend towards* (blunt only)
						Post-hoc analyses of Boffard 2005 a&b			
					Rizoli 2006 (coagulopathic patients)	NR/60	NR/76	NR	p = NR *trend towards*
					Boffard 2009 (patients surviving 48 hours or more)	NR/69 (blunt) NR/70 (penetrating)	NR/74 NR/64	OR 0.05 (0.0, 0.89) NR	*Favours rFVIIa (blunt injury)* *p* = NR
					MOF and ARDS Boffard 2009 (patients surviving 48 hours or more)	NR/139	NR/138	OR 0.16 (0.02, 0.81)	*Favours rFVIIa (blunt injury)* *p* = NR
Yank 2011	N = 277 (2 RCTs)				ARDS				

DRAFT

Study ID Study design [a]	Sample size (no. of trials) included in analysis	Patient population	Setting (Location)	Comparison	Outcome	Results			
						rFVIIa n/N (%)	No rFVIIa n/N (%)	Risk estimate (95% CI)	*Statistical significance* *p*-value Heterogeneity [b]
SR *High quality*	Boffard 2005a Boffard 2005b				blunt penetrating	NR/69 (4.3) NR/70 (5.7)	NR/74 (16.2) NR/64 (7.8)	NR NR	*p* = 0.03 *Favours rFVIIa* *p* = 0.74 *no difference*
Obstetrics and maternity setting - no comparative evidence found									
Paediatrics - no comparative evidence found									

Abbreviations: CI, confidence interval; DIC, disseminated intravascular coagulation; GI, gastrointestinal; HSCT, haemopoietic stem cell transplant; MODS, multiorgan dysfunction syndrome; NR, not reported; OR, odds ratio; RCTs, randomised controlled, trials; rFVIIa, recombinant activated factor seven; RR, relative risk; UK, United Kingdom; US, United States

a. Where only one RCT is identified in a systematic review, the evidence has been considered as RCT evidence. Where the systematic review assesses observational and cohort studies, the evidence has been considered as according to the study design features. The risk of bias of the included primary studies is based on the quality assessment reported by the systematic review authors.

b. Only applicable to Systematic reviews with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if P_{het} >0.1 and I^2 <25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25–50%; substantial heterogeneity I^2 >50%.

c. Calculated post-hoc using RevMan 5.4. M-H, random effects.

DRAFT

Need for second-line therapies

A summary of the evidence relating to other second-line therapies in the obstetrics and maternity setting in patients with critical bleeding treated with rFVIIa is presented in Table 4.37. This outcome was recognised as a critical patient relevant outcome of interest in this setting only.

Among women with severe PPH with persistent bleeding after sulprostone treatment, the use of rFVIIa was reported to reduce the incidence of second-line therapies compared with standard care (RR 0.56; 95 CI 0.42, 0.76; $p = 0.0002$); however, the data is limited by low patient numbers. *(GRADE: very low)*

Specifically, there was a reduced need for arterial embolisation (see Figure 4.23).

Figure 4.22 Forest plot of comparison: rFVIIa vs placebo, outcome: Morbidity – need for second-line intervention (obstetrics and maternity)

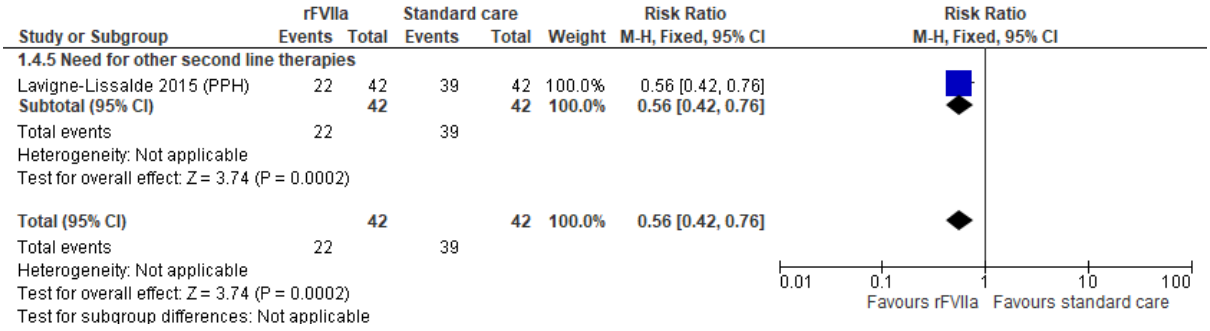


Figure 4.23 Forest plot of comparison: rFVIIa vs placebo, outcome: Morbidity - other second-line interventions (obstetrics and maternity)

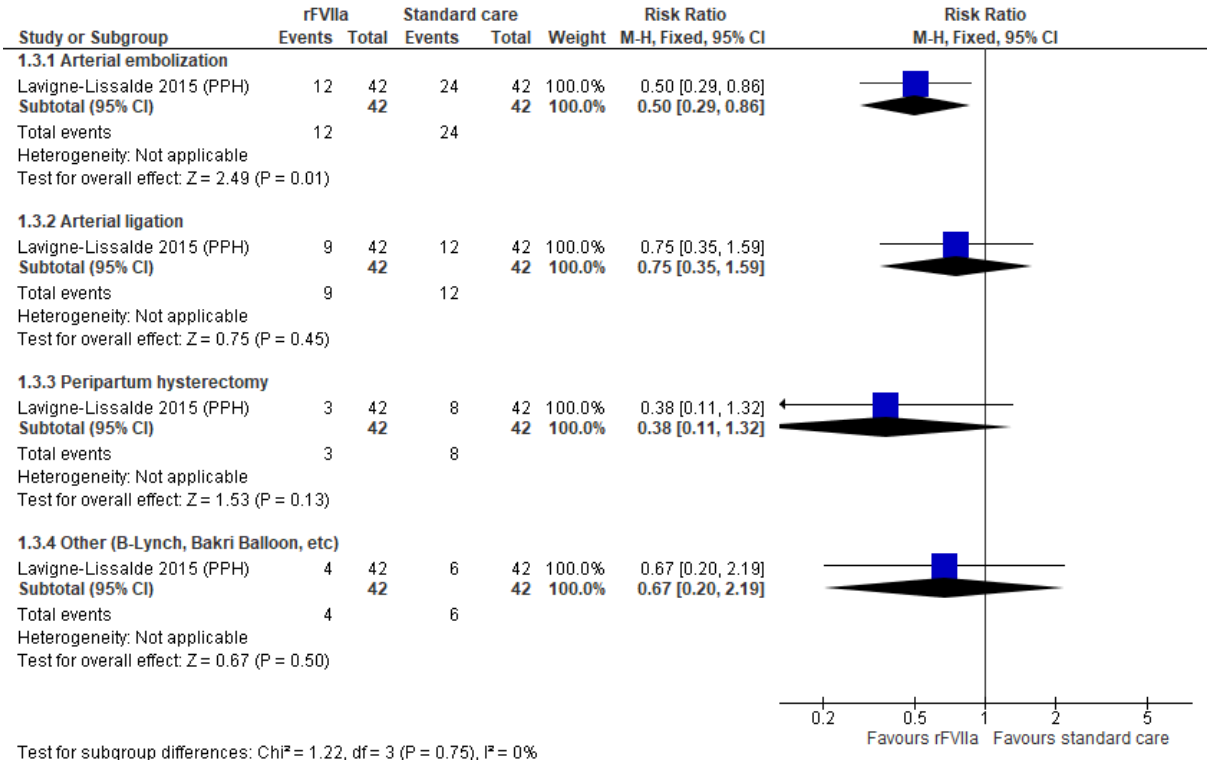


Table 4.39 Results for rFVIIa versus no rFVIIa: Patients *with* critical bleeding – Morbidity: other second-line interventions (obstetrics and maternity only)

Study ID Study design [a]	Sample size (no. of trials) included in analysis	Patient population	Setting (Location)	Comparison	Outcome	Results			
						rFVIIa n/N (%) mean ± SD (n)	No rFVIIa n/N (%) mean ± SD (n)	Risk estimate (95% CI)	*Statistical significance* *p*-value Heterogeneity [b]
Obstetrics and maternity setting									
Lavigne-Lissalde 2015 RCT *High risk of bias*	N = 84	Women (aged 18 yrs or older) with severe persistent primary PPH [c] after sulprostone treatment	Obstetrics (multicentre, France, Switzerland)	rFVIIa (therapeutic) vs standard care	Reduction in the need for specific second-line therapies (composite)	22/42	39/42 (93)	RR 0.56 (0.42, 0.76)	*Favours rFVIIa* *p* < 0.0001
					Arterial embolisation	12/42 (29)	24/42 (57)	RR 0.50 (0.29, 0.86)	*p = 0.0082*
					Arterial ligation	9/42 (21)	12/42 (29)	RR 0.75 (0.35, 1.59)	*p = 0.45*
					Peripartum hysterectomy	3/42 (7)	8/42 (19)	RR 0.38 (0.11, 1.32)	*p = 0.11*
					Other (B-lynch, Bakri Balloon etc.)	4/42 (10)	6/42 (14)	RR 0.67 (0.20, 2.19)	*p = 0.50*

Abbreviations: CI, confidence interval; GI, gastrointestinal; HSCT, haemopoietic stem cell transplant; NR, not reported; OR, odds ratio; PPH, postpartum haemorrhage; RCTs, randomised controlled, trials; rFVIIa, recombinant activated factor seven; RR, relative risk; UK, United Kingdom; US, United States

a. Where only one RCT is identified in a systematic review, the evidence has been considered as RCT evidence. Where the systematic review assesses observational and cohort studies, the evidence has been considered as According to the study design features. The risk of bias of the included primary studies is based on the quality assessment reported by the systematic review authors.

b. Only applicable to Systematic reviews with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if P_{het} >0.1 and I^2 <25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25–50%; substantial heterogeneity I^2 >50%.

c. Defined as the loss of more than 1500 mL of blood within 24 hr after vaginal or caesarean delivery.

4.6.3.3 Transfusion volumes

Red blood cells

A summary of the evidence relating to RBC transfusion volumes in patients with critical bleeding treated with rFVIIa is presented in Table 4.40.

Only limited conclusions can be drawn from the available evidence, with an overall modest reduction in the volume of RBCs transfused (less than one red cell unit saved). The Cochrane review by Simpson 2012 noted that these favourable findings were likely overestimated because data were not available from larger negative studies for inclusion in the meta-analysis.

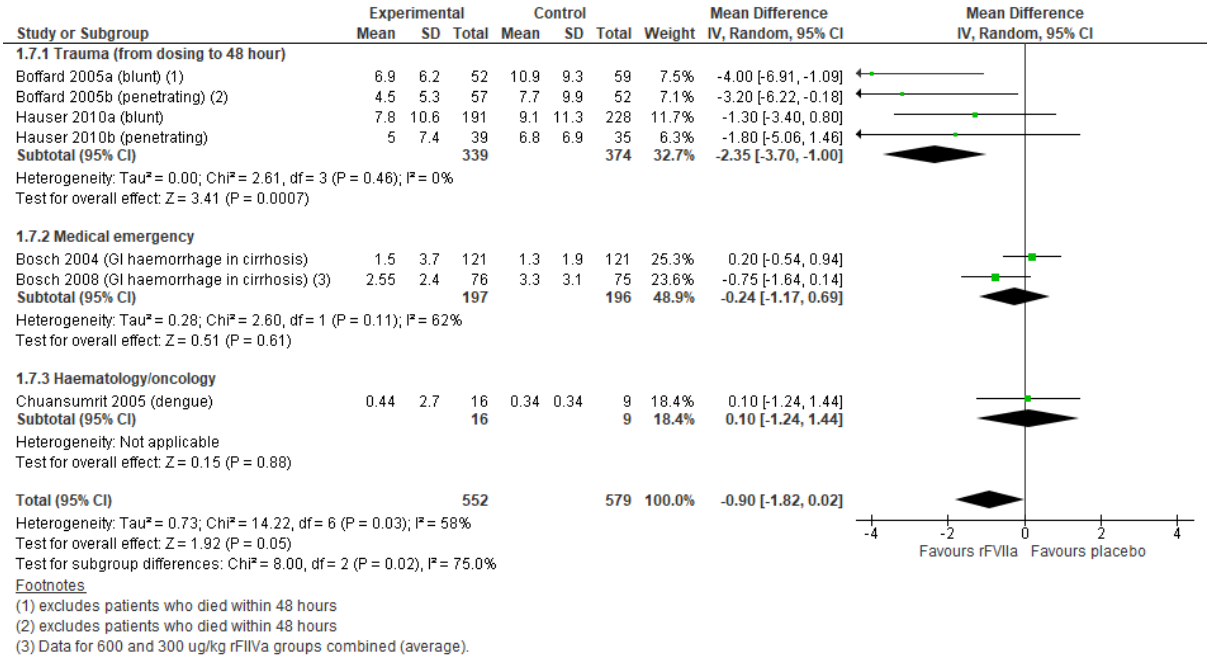
A meta-analysis of data from RCTs included in this review (see Figure 4.24) revealed a reduction in the volume of RBC transfusion in patients with critical bleeding who received rFVIIa (n=552) compared with those who did not (n=579), with an overall mean difference (MD) of –0.90 units observed (95% CI –1.82, 0.02; $p = 0.05$; random effect, $I^2 = 58\%$).

There was a large difference among the subgroups, with the RCTs conducted in bleeding patients with blunt or penetrating trauma suggesting a reduction in the volume of RBC transfusion to be closer two units saved (MD –2.35; 95% CI –3.70, –1.00; $p = 0.0007$) *(GRADE: very low)*. It was noted that these data are confounded by the exclusion of trauma patients who died within 48 hours of admission to hospital.

Among patients with UGIB who received rFVIIa there was no difference in RBC transfusion volumes between treatment groups (MD –0.24, 95% CI –1.17, 0.69; $p = 0.61$, $I^2 = 62\%$) *(GRADE: very low)*. A similar result was observed in paediatric patients with dengue haemorrhagic fever (MD 0.10, 95% CI –1.24, 1.44; $p = 0.88$) *(GRADE: very low)*.

The volume of RBC transfused was not reported in the RCTs conducted in patients with intractable bleeding after cardiac surgery or in women with severe PPH with persistent bleeding after sulprostone treatment.

Figure 4.24 Forest plot of comparison: rFVIIa vs placebo, outcome: RBC transfusion volume, Units



Footnotes

(1) excludes patients who died within 48 hours

(2) excludes patients who died within 48 hours

(3) Data for 600 and 300 ug/kg rFIIVa groups combined (average).

Table 4.40 Results for rFVIIa versus no rFVIIa: Patients *with* critical bleeding – RBC transfusion volume

Study ID Study design [a]	Sample size (no. of trials) included in analysis	Patient population	Setting (Location)	Comparison	Outcome	Results			
						rFVIIa mean ± SD (n)	No rFVIIa mean ± SD (n)	Mean Difference (95% CI)	*Statistical significance* *p*-value Heterogeneity [b]
Any setting									
Simpson 2012 SR *High quality*	N = 911 (4 RCTs) Hauser 2010 Bosch 2004 Bosch 2008 Chuansumrit 2005	Patients with critical bleeding due to trauma, or who had received treatment to manage bleeding	Trauma, medical, oncology (multicentre, multicountry)	rFVIIa (therapeutic) vs placebo	RBC transfusion volume, mL blunt penetrating GI haemorrhage GI haemorrhage dengue	(n = 443) 2340 ± 3180 (191) 1500 ± 2220 (39) 450 ± 1110 (121) 764 ± 719 (76) 131 ± 812 (16)	(n = 468) 2730 ± 3390 (228) 2040 ± 2070 (35) 390 ± 570 (121) 990 ± 930 (75) 103 ± 102 (9)	MD –88.60 (–263.88, 86.68) –390.00 (–1020.09, 240.09) –540.00 (–1517.62, 437.62) 60.00 (–162.33, 282.33) –226.00 (–491.39, 39.39) 28.00 (–375.41, 431.41)	*No significant difference* *p* = 0.32 Mild heterogeneity I^2 = 16% (*p* = 0.32)
Trauma setting									
Cannon 2017 SR *High quality*	N = 933 (3 RCTs, 2 NRSIs)[c]	Patients with severe trauma at risk of death from haemorrhage	Trauma	rFVIIa vs placebo or no rFVIIa	RBC transfusion volume, units to 24 hours	(n = 424)	(n = 509)	MD –0 .92 (–2.31, 0.47)	*No significant difference* *p* = 0.19 No significant heterogeneity I^2 = 17% (*p* = 0.30)
	N = 742 (3 RCTs) Boffard 2005a Boffard 2005b Hauser 2010 Hauser 2010				 blunt penetrating blunt penetrating	(n = 354) 7.8 ± 12 (64) 4 ± 9.25 (69) 6.9 ± 10.4 (184) 4.5 ± 7.3 (37)	(n = 388) 7.2 ± 8.75 (72) 4.8 ± 10.25 (61) 8.1 ± 10.9 (222) 6.2 ± 6.5 (33)	MD –0.94 (–2.36, 0.48) MD 0.60 (–2.97, 4.17) MD –0.80 (–4.17, 2.57) MD –1.20 (–3.28, 0.88) MD –1.70 (–4.93, 1.53)	*No significant difference* *p* = 0.20 No heterogeneity I^2 = 0% (*p* = 0.80)
McQuilten 2015 SR *Moderate quality* *additional data sought from primary studies	N = 554 (1 RCT) Hauser 2010	Adult patients with severe bleeding due blunt or penetrating trauma	Trauma (multicentre, multicountry)	rFVIIa (therapeutic) vs placebo	RBC transfusion, units to 24 hrs blunt penetrating	(n = 221) 6.9 ± 10.4 (184) 4.5 ± 7.3 (37)	(n = 255) 8.1 ± 10.9 (222) 6.2 ± 6.5 (33)	MD –1.35 (–3.09, 0.40) NR NR	*No significant difference* *p* = 0.13 [d] *p* = 0.04 *Favours rFVIIa* *p* = 0.11 *No difference*
	N = 277 (2 RCTs) Boffard 2005a Boffard 2005b				RBC transfusion, units to 48 hrs blunt penetrating	NR (69) NR (70)	NR (74) NR (64)	Est. 2.0 (0.0, 4.6) Est. 0.2 (–0.9, 2.4)	*No significant difference* *p* = 0.07 *p* = 0.24
						Estimated reduction. Hodges-Lehmann point estimate of the shift in transfusion amount from placebo to active group, including 90% CI. Patients who died within 48 hours were assigned the highest rank (see Boffard 2009).[d]			
Simpson 2012 SR *High quality*	N = 493 (1 RCT) Hauser 2010	Adult patients with severe bleeding due blunt or penetrating trauma	Trauma (multicentre, multicountry)	rFVIIa (therapeutic) vs placebo	RBC transfusion volume, mL blunt penetrating	(n = 230) 2340 ± 3180 (191) 1500 ± 2220 (39)	(n = 263) 2730 ± 3390 (228) 2040 ± 2070 (35)	MD –434.02 (–963.64, 95.59) –390.00 (–1020.09, 240.09) –540.00 (–1517.62, 437.62)	*No significant difference* *p* = 0.11 [d] No significant heterogeneity I^2 = 0% (*p* = 0.80)

Study ID Study design [a]	Sample size (no. of trials) included in analysis	Patient population	Setting (Location)	Comparison	Outcome	Results			
						rFVIIa mean ± SD (n)	No rFVIIa mean ± SD (n)	Mean Difference (95% CI)	*Statistical significance* *p*-value Heterogeneity [b]
Yank 2011 SR *High quality*	N = 220 (2 RCTs) Boffard 2005a Boffard 2005b	Adult patients with severe bleeding due blunt or penetrating trauma	Trauma (multicentre, multicountry)	rFVIIa (therapeutic) vs placebo	RBC transfusion, units up to 48 hrs blunt penetrating (excludes patients who died within 48 hours)	(n = 109) 6.9 ± 6.2 4.5 ± 5.3 (57)	(n = 111) 10.9 ± 9.3 (59) 7.7 ± 9.9	 NR NR	 p = 0.02 Favours rFVIIa *p* = 0.10 No difference
Curry 2011 SR *Moderate quality*	N = 850 (3 RCTs) Boffard 2005a Boffard 2005b Hauser 2010 Hauser 2010	Adult patients with severe bleeding due blunt or penetrating trauma	Trauma (multicentre, multicountry)	rFVIIa (therapeutic) vs placebo	RBC transfusion volume blunt penetrating blunt penetrating	(n = 412) NR (69) NR (70) NR (226) NR (46)	(n = 438) NR (74) NR (64) NR (255) NR (45)	NR	*Favours rFVIIa (blunt)* trend towards (penetrating)
						Post-hoc analyses of Boffard 2005a&b			
					Rizoli 2006 coagulopathic patients	(n = 60) NR	(n = 76) NR	NR	*Favours rFVIIa* *p* = 0.02
Medical emergency									
Simpson 2012 SR *High quality*	N = 418 (3 RCTs) Bosch 2004 Bosch 2008 Chuansumrit 2005	Adult patients with cirrhosis and GI haemorrhage or children with dengue haemorrhagic fever	Medical trauma (multicentre, multicountry)	rFVIIa (therapeutic) vs placebo	RBC transfusion volume, mL	(n = 213) 450 ± 1110 (121) 764 ± 719 (76) 131 ± 812 (16)	(n = 205) 390 ± 570 (121) 990 ± 930 (75) 103 ± 102 (9)	MD –48.74 (–239.88, 142.40) 60.00 (–162.33, 282.33) –226.00 (–491.39, 39.39) 28.00 (–375.41, 431.41)	*No significant difference* *p* = 0.62 [d] Moderate heterogeneity I^2 = 28% (*p* = 0.62)
Surgical setting - no comparative evidence found									
Obstetrics and maternity setting									
Lavigne-Lissalde 2015 RCT *High risk of bias*	N = 84	Women (aged 18 years or older) with severe persistent primary PPH [e] after sulprostone treatment	Obstetrics (multicentre, France, Switzerland)	rFVIIa (therapeutic) vs standard care	RBC transfusion volume, units	(n = 42) median (IQR) 2 (0, 3)	(n = 42) median (IQR) 2 (0, 4)	0 (NR)	*No significant difference* *p* = NR
Franchini 2010 SR (case series) *High risk of bias*	N = 272 (9 case series)	Women with severe PPH (≥ 500 mL after vaginal delivery and ≥ 1000 mL after caesarean delivery)	Obstetrics and gynaecology (multicountry, including Europe and Australia)	rFVIIa (therapeutic) vs placebo or no rFVIIa	Transfusion volume	The authors identified no RCTs, case-control or interventional cohort studies, therefore attempted to extract useful information from published case reports (N >10) to provide recommendations for the management of severe PPH. Three retrospective cohort studies (Ahonen 2007, Hossain 2007, Kalina 2011) identified and discussed in PBM Module 5 (TR vol. 1 Section 3.4.4).			*Women who received rFVIIa were given more RBC than the comparator groups, but those women had more severe haemorrhaging.*

Study ID Study design [a]	Sample size (no. of trials) included in analysis	Patient population	Setting (Location)	Comparison	Outcome	Results			
						rFVIIa mean ± SD (n)	No rFVIIa mean ± SD (n)	Mean Difference (95% CI)	*Statistical significance* *p*-value Heterogeneity [b]
Paediatrics - no comparative evidence found									

Abbreviations: CI, confidence interval; hrs, hours; IU, international units; M-H, Mantzel-Hentzel; NR, not reported; OR, odds ratio; PPH, postpartum haemorrhage; RR, relative risk; UK, United Kingdom; US, United States

a. Where only one RCT is identified in a systematic review, the evidence has been considered as RCT evidence. Where the systematic review assesses observational and cohort studies, the evidence has been considered as according to the study design features. The risk of bias of the included primary studies is based on the quality assessment reported by the systematic review authors.

b. Only applicable to Systematic reviews with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if P_{het} >0.1 and I^2 <25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25–50%; substantial heterogeneity I^2 >50%.

c. NRSIs not included in the review for this question.

d. Calculated post-hoc using RevMan 5.4. M-H random effects.

d. Exclusion of patients who died within 48 hours shows a significant reduction in total RBC transfusions in 48 hours among patients with blunt trauma (estimated reduction 2.6 units; 90% CI 0.7, 4.6; $p = 0.02$) but not patients with penetrating trauma (1.0 unit; 90% CI 0.0, 2.6; $p = 0.10$). (see Boffard 2009)

e. Defined as the loss of more than 1500 mL of blood within 24 hr after vaginal or caesarean delivery

Other blood components

A summary of the evidence relating to transfusion volumes of other blood components in patients with critical bleeding treated with rFVIIa is presented in Table 4.41.

A meta-analysis of usable data from RCTs included in this review (see Figure 4.25) revealed a significant (borderline) reduction in the transfusion of allogenic blood components at 24 hours in trauma patients with critical bleeding who received rFVIIa (n=237) compared with those who did not (n=263), with an overall MD of –4.17 units observed (95% CI –8.40, 0.07; $p = 0.05$; fixed effect, $I^2 = 0\%$). This effect was significant for FFP (MD –2.14; 95% CI –3.54, –0.73; $p = 0.003$) but not platelets, fibrinogen concentrate or cryoprecipitate.

Data for patients with UGIB, paediatric patients with dengue haemorrhagic fever, patients with intractable bleeding after cardiac surgery or in women with severe PPH with persistent bleeding after sulprostone treatment were not able to be assessed.

Figure 4.25 Forest plot of comparison: rFVIIa vs placebo, outcome: transfusion volume (other blood components), Units

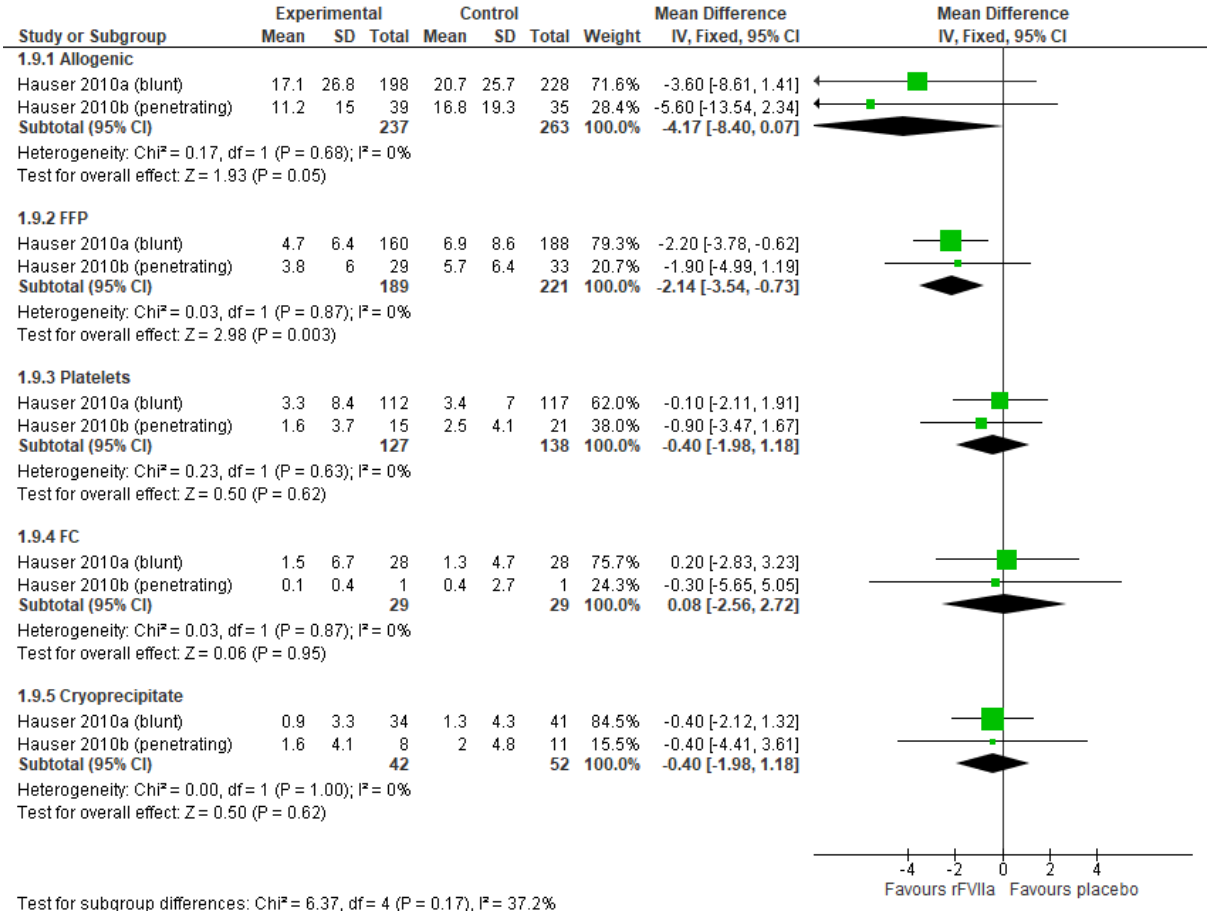


Table 4.41 Results for rFVIIa versus no rFVIIa: Patients *with* critical bleeding – transfusion volume, other blood components

Study ID Study design [a]	Sample size (no. of trials) included in analysis	Patient population	Setting (Location)	Comparison	Outcome	Results			
						rFVIIa mean ± SD (n)	No rFVIIa mean ± SD (n)	Mean Difference (95% CI)	*Statistical significance* *p*-value Heterogeneity [b]
Trauma setting									
Updated in this review *additional data from primary studies retrieved	N = 573 (1 RCT) Hauser 2010	Adult patients with blunt or penetrating trauma who are critically bleeding	Trauma (multicentre, multicountry)	rFVIIa (therapeutic) vs placebo	Allogenic transfusions, units to 24 hrs blunt penetrating	 17.1 ± 26.8 (198) 11.2 ± 15 (39)	 20.7 ± 25.7 (228) 16.8 ± 19.3 (35)	 NR NR	 *p* = 0.09 No difference *p* = 0.03 *Favours rFVIIa*
					FFP, units to 24 hours blunt penetrating	 4.7 ± 6.4 (160) 3.8 ± 6.0 (29)	 6.9 ± 8.6 (188) 5.7 ± 6.4 (33)	 NR NR	 *p* < 0.001 *Favours rFVIIa* *p* = 0.04 *Favours rFVIIa*
					Platelets, units to 24 hours blunt penetrating	 3.3 ± 8.4 (112) 1.6 ± 3.7 (15)	 3.4 ± 7.0 (117) 2.5 ± 4.1 (21)	 NR NR	 *p* = 0.84 No difference *p* = 0.08 No difference
					FC, units to 24 hours blunt penetrating	 1.5 ± 6.7 (28) 0.1 ± 0.4 (1)	 1.3 ± 4.7 (28) 0.4 ± 2.7 (1)	 NR NR	 *p* = 0.68 No difference *p* = 0.92 No difference
					Cryoprecipitate, units to 24 hours blunt penetrating	 0.9 ± 3.3 (34) 1.6 ± 4.1 (8)	 1.3 ± 4.3 (41) 2.0 ± 4.8 (11)	 NR NR	 *p* = 0.66 No difference *p* = 0.33 No difference
	N = 277 (2 RCTs) Boffard 2005a&b	Adult patients with severe bleeding due blunt or penetrating trauma	Trauma (multicentre, multicountry)	rFVIIa (therapeutic) vs placebo	Transfusion volume, mL to 48 hours, FFP, platelets or cryoprecipitate	NR	NR	NR	No significant difference
						Among patients surviving 48 hours, a significant difference favouring rFVIIa reported for FFP (*p* = 0.023), and platelets (*p* = 0.023) and a trend towards for cryoprecipitate (*p* = 0.053). (See Boffard 2009, figure 2)			
Curry 2011 SR *Moderate quality*	N = 277 (2 RCTs) Boffard 2005a&b	Adult patients with severe bleeding due blunt or penetrating trauma (coagulopathic patients)	Trauma (multicentre, multicountry)	rFVIIa (therapeutic) vs placebo	Transfusion volume, mL to 48 hours	*Post-hoc analyses of Boffard 2005a&b by Rizoli 2006*			
					FFP	(n = 60) NR	(n = 76) NR	NR	*Favours rFVIIa* *p* = 0.04
					platelets	(n = 60) NR	(n = 76) NR	NR	No significant difference *p* = 0.09

Study ID Study design [a]	Sample size (no. of trials) included in analysis	Patient population	Setting (Location)	Comparison	Outcome	Results			
						rFVIIa mean ± SD (n)	No rFVIIa mean ± SD (n)	Mean Difference (95% CI)	*Statistical significance* *p*-value Heterogeneity [b]
Medical emergency - no comparative evidence found									
Surgical setting									
Yank 2011 SR *High quality*	N = 172 (1 RCT) Gill 2009	Adult patients who had undergone cardiac surgery and were bleeding.	Surgical (multicentre, multicountry)	rFVIIa (therapeutic) vs placebo	Total transfusion volume*, mL 40 ug/kg rFVIIa 80ug/kg rFVIIa *inclusive of all products	(n = 104) median (IQR) 640 (0, 1920) 500 (0, 1750)	(n = 68) median (IQR) 825 (326.5, 1893)	--	*Favours rFVIIa* *p* = 0.047 *p* = 0.042
Obstetrics and maternity setting									
Lavigne-Lissalde 2015 RCT *High risk of bias*	N = 84	Women (aged 18 years or older) with severe persistent primary PPH [d] after sulprostone treatment	Obstetrics (multicentre, France, Switzerland)	rFVIIa (therapeutic) vs standard care	Transfusion volume, number of units FFP PC	(n = 42) median (IQR) 0 (0, 3) NR	(n = 42) median (IQR) 0 (0, 4) NR	 NR NR	*No significant difference* *p* = NR *p* = NR
Franchini 2010 SR (case series) *High risk of bias*	N = 272 (9 case series)	Women with severe PPH (≥ 500 mL after vaginal delivery and ≥ 1000 mL after caesarean delivery)	Obstetrics and gynaecology (various countries including Europe and Australia)	rFVIIa (therapeutic) vs placebo or no rFVIIa		The authors identified no RCTs, case-control or interventional cohort studies, therefore attempted to extract useful information from published case reports (N>10) to provide recommendations for the management of severe PPH. Three retrospective cohort studies (Kalina 2011, Ahonen 2007, Hossain 2007) identified and discussed in PBM Module 5 (TR vol. 1 Section 3.4.4).			*Women who received rFVIIa were given more fibrinogen and platelets than the comparator groups, but those women had more severe haemorrhaging.*
Paediatrics - no comparative evidence found									

Abbreviations: CI, confidence interval; hrs, hours; FC, fibrinogen concentrate; M-H, Mantzel-Hentzel; NR, not reported; OR, odds ratio; PPH, postpartum haemorrhage; RR, relative risk; UK, United Kingdom; US, United States

a. Where only one RCT is identified in a systematic review, the evidence has been considered as RCT evidence. Where the systematic review assesses observational and cohort studies, the evidence has been considered as according to the study design features. The risk of bias of the included primary studies is based on the quality assessment reported by the systematic review authors.

b. Only applicable to Systematic reviews with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if P_{het} >0.1 and I^2 <25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25–50%; substantial heterogeneity I^2 >50%.

c. Calculated post-hoc using RevMan 5.4. M-H random effects.

d. Defined as the loss of more than 1500 mL of blood within 24 hr after vaginal or caesarean delivery.

4.7 Blood components (Question 6)

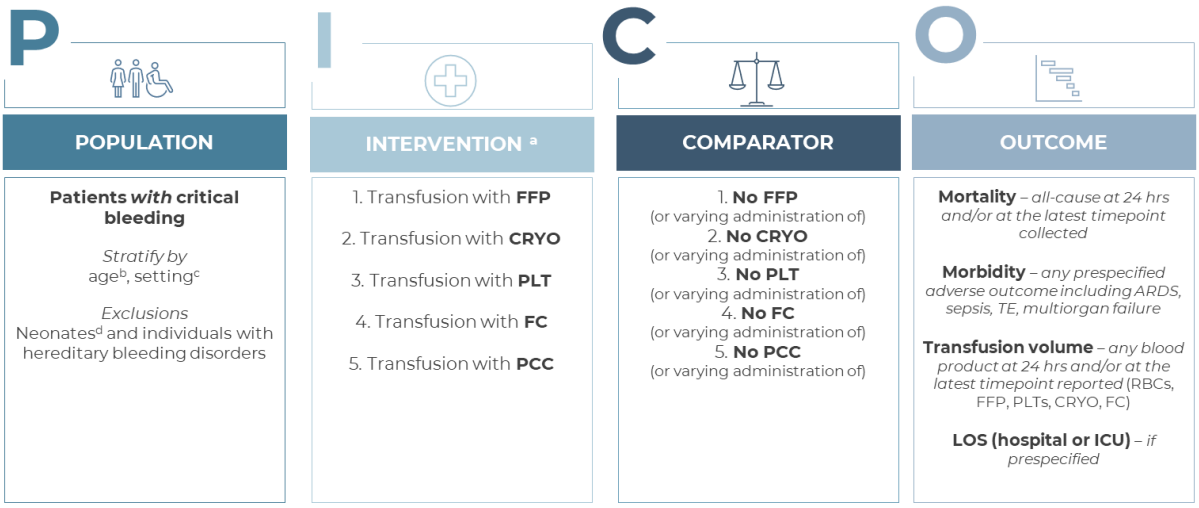
Question 6 – (Interventional)

In patients with critical bleeding, what is the effect of fresh frozen plasma, cryoprecipitate, fibrinogen concentrate, prothrombin complex concentrate and/or platelet transfusion on RBC transfusion and patient outcomes?

4.7.1 Methods

This review assessed the evidence of fresh frozen plasma (FFP), cryoprecipitate (CRYO), fibrinogen concentrate (FC), platelet (PLT) and prothrombin complex concentrate (PCC) on red blood cell (RBC) transfusion and patient outcomes in patients with critical bleeding as outlined in Figure 4.26.

Figure 4.26 PICO criteria: Question 6 – effect of blood component therapy on patient outcomes



ARDS, acute respiratory distress syndrome; CRYO, cryoprecipitate; FC, fibrinogen concentrate; FFP, fresh frozen plasma; ICU, intensive care unit; LOS, length of stay; PCC, prothrombin complex concentrate; PLTs, platelets; RBCs, red blood cells, TE, thromboembolism

a. 1 vs 1; 2 vs 2; etc.
b. Adult (aged over 18 years), child (aged 2 to 12 years), adolescent (aged 13 to 18 years), infants (aged 1 to 23 months).
c. e.g. trauma, obstetric, perioperative (cardiothoracic, general surgery, gastrointestinal, liver transplant), paediatric, other.
d. Newborns up to 28 days following birth.

The selection of studies was conducted according to the screening criteria described in Section 3.3.

The initial 2018 search was limited to studies published after 2009 for evidence of FFP, CRYO, FC and PLT and limited to studies published after 1990 for evidence of PCC. However, primary studies published prior to the date limits that had been identified in a systematic review were included. There were no restrictions applied in relation to study size for RCTs. The protocol outlined restrictions for observational studies (at least 500 participants in total), however, due to the evidence identified, this was not applied.

Assuming all relevant primary studies had been identified in the included systematic reviews; the systematic screen of RCTs was limited to studies published after 2015. This is based on the most recent identified systematic review (Cannon 2017), which was assumed to have identified all relevant RCTs in the trauma and non-trauma setting.

An updated literature search was conducted in August 2019 and again in September 2021 to identify any new studies meeting the eligibility criteria. In these updated searches, the focus was the identification of systematic reviews, with date limitations based on the most recent systematic reviews used to identify any new RCTs.

Assuming all relevant primary studies have been identified in the included systematic review studies; the systematic screen for RCTs was limited to studies published after the search date outlined in the systematic review.

- For FC, the date limit for RCTs was 2019 based on the most recent identified systematic review (Stabler 2020), which was assumed to have identified all relevant RCTs in the trauma and non-trauma setting.
- For PCC, the date limit for screening RCTs was 2020 based on the most recent identified systematic review (van den Brink 2020), which was assumed to have identified all relevant RCTs in the trauma and non-trauma setting.
- For all other blood component therapy, the date limit for screening RCTs was 2019.

4.7.2 Summary of evidence

4.7.2.1 Systematic reviews evidence

Eleven systematic reviews (68, 98-107) were identified in the literature search that were relevant to the research question. The main characteristics and quality of these systematic reviews and relevant outcomes assessed are summarised in Table 4.42.

Four systematic reviews (van den Brink 2020, Fabes 2018, Lunde 2014, Warmuth 2012) assessed the effect of blood component therapy on patient outcomes in mixed clinical settings (including trauma, surgical and obstetrics); three systematic reviews assessed FC and one systematic review assessed PCC. One systematic review (Zaidi 2020) assessed the effect of FC on patient outcomes in the obstetric and maternity setting.

Six systematic reviews (Stabler 2020, Coccolini 2019, Rijnhout 2019, McQuilten 2018, Mengoli 2017, Aubron 2014) assessed the effect of blood component therapy on patient outcomes in the trauma setting; three systematic reviews assessed FC, two systematic reviews assessed FFP, one systematic review assessed FC and CRYO, and one systematic review assessed any blood component.

The reviews included 15 RCTs and 17 observational cohort studies that examined the effect of blood components in patients who were critically bleeding.

A matrix illustrating the overlap of RCTs identified in the included systematic reviews is provided in Table 4.43.

A matrix illustrating the overlap of cohort studies identified in the included systematic reviews is provided in Table 4.44.

Table 4.42 Characteristics and quality of systematic reviews by clinical setting: blood components

Review ID ***Review Quality***	Study design	Population	Intervention	Comparison	Outcomes
Mixed trauma and non-trauma setting					
van den Brink 2020 (100) *Low*	SR of RCTs and observational studies (17 studies)	Patients with critical bleeding	PCC	No PCC	Mortality Morbidity
Fabes 2018 *High*	SR of RCTs (31 studies)	Adults and children at risk of or with critical bleeding	FC	No FC or other blood components	Mortality Morbidity Transfusion volumes
Lunde 2014 *Critically low*	SR of RCTs and nonrandomised trials (30 studies)	Patients with critical bleeding	FC	No FC	Mortality Transfusion volume
Warmuth 2012 *Low*	SR of RCTs and nonrandomised trials (4 studies)	Adults/children with major haemorrhage	FC	No FC	Transfusion volume
Trauma setting					
Stabler 2020 *Moderate*	SR of RCTs and observational studies (26 studies)	Patients older than 16 years of age with trauma-related bleeding	FC	No FC	Mortality Morbidity LOS
Coccolini 2019 *Moderate*	SR of RCTs (2 studies)	Severely injured adult trauma patients	FFP	Standard resuscitation protocol	Mortality Morbidity
Rijnhout 2019 *Low*	SR of RCTs and observational studies (9 studies)	Civilian blunt trauma patients	FFP	No FFP	Mortality
McQuilten 2018 *Moderate*	SR of RCTs (16 studies)	Paediatric and adult trauma patients who had or were expecting to receive a massive transfusion	FC CRYO + MTP	No FC (n=45) MTP (n=41)	Mortality Morbidity LOS Transfusion volumes
Mengoli 2017 *Low*	SR of RCTs and observational studies (7 studies)	Trauma patients with critical bleeding	FC	No FC or other blood components	Mortality Morbidity Transfusion volume
Aubron 2014 *Critically low*	SR of observational studies (8 studies)	Trauma patients with critical bleeding	FC	No FC or other blood components	Mortality Morbidity Transfusion volume
Obstetrics and maternity setting					
Zaidi 2020 *Low*	SR of RCTs (5 studies)	Women with PPH	FC	No FC	Mortality Morbidity LOS Transfusion volume

CYRO, cryoprecipitate; FC, fibrinogen concentrate; FFP, fresh frozen plasma; LOS, length of stay; MTP, massive transfusion protocol; MOF, multiple organ failure; PCC, prothrombin complex concentrate; PPH, primary postpartum haemorrhage; RBCs, red blood cells; RCTs, randomised controlled trials; SR, systematic review

Table 4.43 Overlap table of RCTs identified by included systematic reviews: blood components

		Trauma									Obs		Surgical						
	Study ID	Ziegler 2019	Curry 2015	Moore 2018	Sperry 2018	Curry 2018	Nascimento 2016	Akbari 2018	Innerhofer 2017	Lucena 2020	Collins 2017	Wikkelsø 2015	Bilicen 2017	Rahe-Meyer 2013	Rahe-Meyer 2016	Galas 2014	Tanaka 2014	Jeppsson 2016	Lance 2012
Review ID	Fabes 2018					✓	✓		✓		✓	✓	✓	✓	✓	✓	✓	X	X
	McQuilten 2018		✓				✓												
	Coccolini 2019			✓	✓														
	Rijnhout 2019			✓	✓														
	Stabler 2020	✓				✓	✓	✓		✓									
	Zaidi 2020										✓	✓							

Obs, obstetrics; RCT, randomised controlled trial
✓ = study included in this review; X = study did not meet the inclusion criteria for this review.

Table 4.44 Overlap table of cohort studies identified by included systematic reviews: blood components

		Trauma																									Surgical			Obs
	Study ID	Innerhofer 2013	Nienaber 2011	Wafaisade 2013	Schöchl 2011	Joseph 2016	Joseph 2014	O'Reilly 2014	Holcomb 2017	Shackelford 2017	Inokuchi 2017	Schlimp 2016	Almskog 2020	Zeeshan 2019	Jehan 2018	Yamamoto 2016	Bocci 2019	David 2016	Gonzalez-Guerrero 2017	Grassetto 2012	Hilbert 2013	Itagaki 2020	Javier 2019	Schöchl 2010	Schöchl 2014	Schlimp 2013	Schlimp 2016	Seebold 2019	Rahe-Meyer 2009a	Rahe-Meyer 2009b	Bilicen 2013	Ahmed 2012
Review ID	Stabler 2020		✓	✓	✓						✓	X	✓			X	X	X	X	X	X	X	X	--	X	--	X				
	van den Brink 2020					✓	✓							✓	✓																	
	Rijnhout 2019							✓	✓	✓																						
	Mengoli 2017	✓	✓	✓	✓																											
	Aubron 2014	✓	✓	✓	✓																											
	Lunde 2014	✓	✓	✓																									✓	✓	✓	✓
	Warmuth 2012																												✓	✓		

Obs, obstetrics

✓ = study included in this review; -- = no usable data; X = study did not meet the inclusion criteria for this review for reasons including comparator or intervention out of scope.

Fresh frozen plasma versus no FFP (or varying administration of)

Two systematic reviews (Coccolini 2019, Rjinhout 2019) identified two RCTs (Moore 2018, Sperry 2018) conducted in adult trauma patients relevant to this review question (see Section 4.7.2.2). There were discrepancies found across the two systematic reviews for the outcome of mortality. In one review (Rijnhout 2019), authors reported the outcome data for one RCT (Sperry 2018) as FFP combined with RBCs and plasma. As this does not meet criteria for this question, data from Rijnhout 2019 was not used. Outcome data reported by Coccolini 2019 was used in the meta-analysis.

Four systematic reviews (Aubron 2014, Mengoli 2017, Lunde 2014, Rjinhout 2019) identified four cohort studies (Holcomb 2017, Shackelford 2017, O'Reilly 2014, Innerhofer 2013) in the trauma setting relevant to the review question (see Section 4.7.2.3).

The search did not find any additional SRs that examined the effect of FFP compared to no FFP (or varying administration of) in patients with critical bleeding in another setting (i.e. perioperative, obstetric, paediatric).

Cryoprecipitate versus no CRYO (or varying administration of)

One systematic review (McQuilten 2018) identified one RCT (Curry 2015) relevant to the review question (see Section 4.7.2.2).

Platelets

The search did not identify any SRs that assessed the use of PLTs compared to no PLTs (or varying administration of) in patients with critical bleeding on patient outcomes.

Fibrinogen concentrate versus no FC (or varying administration of)

Six systematic reviews (Fabes 2018, McQuilten 2018, Coccolini 2019, Rijnhout 2019, Stabler 2020, Zaidi 2020) identified 12 RCTs that were relevant to the review question (see Section 4.7.2.2). There were slight differences in reporting of outcome data across systematic reviews. Authors of two reviews (McQuilten 2018, Stabler 2020) reported per protocol mortality outcome data for one RCT (Nascimento 2016) and another review (Fabes 2018) reported intent-to-treat data. To reduce potential bias, mortality data reported by Fabes 2018 was used in the meta-analysis.

Authors of one review (Fabes 2018) reported lower patient numbers for the morbidity outcome of thrombosis for one RCT (Collins 2017) compared to another review (Zaidi 2020) which reported intent-to-treat numbers. Intent-to-treat morbidity (thrombosis) data reported by Zaidi 2020 was used in the meta-analysis.

Five systematic reviews (Stabler 2020, Aubron 2014, Mengoli 2017, Lunde 2014, Warmuth 2012) identified nine cohort studies that were relevant to the review question. There were slight differences in reporting of outcome data across two systematic reviews. Authors of one review (Stabler 2020) reported organ failure outcome data for one cohort study (Wafaisade 2013) and another review (Aubron 2014) reported multiple organ failure outcome data. Morbidity data for multiple organ failure reported by Aubron 2014 was used in the meta-analysis to align with the key outcome of interest in this review.

Prothrombin complex concentrate versus no PCC (or varying administration of)

One systematic review (van den Brink 2020) identified four cohort studies (Johan 2018, Zeeshan 2019, Joseph 2014, Joseph 2016) that assessed the use of PCC and FFP versus FFP alone in the trauma setting (see Section 4.7.2.3).

4.7.2.2 Randomised controlled trials

The included systematic reviews identified 15 RCTs that were relevant to this review (Curry 2015, Moore 2018, Sperry 2018, Curry 2018, Nascimento 2016, Akbari 2018, Innerhofer 2017, Lucena 2020, Collins 2017, Wikkelsø 2015, Bilicen 2017, Rahe-Meyer 2013, Rahe-Meyer 2016, Galas 2014, Tanaka 2014).

No additional RCTs were identified in the systematic review and handsearching process.

The main characteristics and quality of the included RCT and the relevant outcomes assessed are detailed in Table 4.45.

Table 4.45 Characteristics and quality of RCTs by clinical setting: blood components

Review ID ***Risk of bias***	**Study design**	**Population** **N**	**Intervention**	**Comparison**	**Outcomes**
Trauma setting					
Lucena 2020 (108) *Low*	RCT Unblinded	Patients (18-80 years) admitted to ED with severe trauma (ISS ≥15) N=32	FC *early administration (50 mg/kg)	No FC	Transfusion volume Morbidity LOS
Akbari 2018 (109) *High*	quasi-RCT	Patients with severe blunt trauma N=90	FC	FFP	Mortality LOS Transfusion volume Morbidity
Curry 2018 (E-FIT 1) (110) *Low*	RCT MC, double-blinded	Adult trauma patients who triggered MHP N=48	FC *within 45 minutes of hospital admission, maintaining fibrinogen levels ≥ 2 g/L during active haemorrhage	No FC	Transfusion volume Mortality Morbidity
Moore 2018 (COMBAT) (111) *Low*	RCT, SC	Trauma patients in haemorrhagic shock* N=125 * SBP ≤ 70 mmHg or 71-90 mmHg plus HR ≥ 108 bpm	FFP (prehospital)	Saline	Mortality Transfusion volume
Sperry 2018 (PAMPer) (112) *Low*	RCT, MC	Injured patients at risk of haemorrhagic shock N=501	FFP (prehospital)	No FFP (Standard care)	Mortality Morbidity Transfusion volumes
Innerhofer 2017 (RETIC) (113) *Low*	RCT SC, unblinded	Adult trauma patients (18-80 years) with ISS >15 and clinical signs or risk of haemorrhage N=100	FC	FFP	Morbidity LOS Transfusion volume

Nascimento 2016 (FiiRST) (114) *Low*	RCT SC, double-blinded	Adult patients aged 18 years or older with blunt or penetrating trauma at risk for significant haemorrhage N=45	FC	No FC	Mortality Morbidity Transfusion volume
Curry 2015 (CRYOSTAT) (115) *Low*	RCT Unblinded	Adult patients aged 16 years or older with active bleeding and requiring activation of the MTP N=41	CRYO	No CRYO	Mortality Morbidity Transfusion volume
Surgical setting					
Bilicen 2017 *High*	RCT	Patients >18 years with intraoperative bleeding following high-risk cardiac surgery N=120	FC	No FC	Transfusion volume Mortality Morbidity
Rahe-Meyer 2016 (REPLACE) *High*	RCT MC	Adult patients with intraoperative bleeding following cardiac surgery N=152	FC	No FC	Transfusion volume Mortality
Tanaka 2014 *High*	RCT SC, prospective	Patients with moderate or severe bleeding following cardiac surgery N=20	FC	PLT	Morbidity Mortality
Rahe-Meyer 2013 *High*	RCT SC, prospective, double-blind	Patients ≥18 years undergoing elective aortic replacement surgery with CPB N=61	FC	No FC	Transfusion volume
Surgical setting, paediatrics					
Galas 2014 *High*	RCT	Patients <7 years with diffuse bleeding following elective cardiac surgery N=60	FC	CYRO	Transfusion volume Morbidity LOS Mortality
Obstetric and maternal setting					
Collins 2017 *High*	RCT MC	Women aged >18 years and >24weeks gestation who had ongoing major PPH (1000–1500 mL blood loss) N=57	FC	TEG	Mortality, Morbidity Transfusion volume LOS
Wikkelsø 2015 *High*	RCT MC, double-blinded	Women with early postpartum haemorrhage N=244	FC	Saline	Mortality Morbidity Transfusion volume (RBC)

BPM, beats per minute; CPB, cardiopulmonary bypass; CRYO, cryoprecipitate; ED, emergency department; FC, fibrinogen concentrate; FFP, fresh frozen plasma; HR, heart rate; ISS, injury severity score; LOS, length of stay; MC, multicentre; MHP, major haemorrhage protocol; MT, massive transfusion; PLT, platelet; PPH, postpartum haemorrhage; RBC, red blood cell; RCT, randomised controlled trial; SBP, systolic blood pressure, SC, single centre; TEG, thromboelastography

a. as evidenced by a) SBP < 100mmHg and b) requiring uncrossmatched RBC transfusion at any time from injury until 30 minutes after hospital arrival

Fresh frozen plasma

Two RCTs (Moore 2018, Sperry 2018) were included in this review. Both RCTs were conducted in US trauma centres and enrolled severely injured adults (aged 18 – 90 years) with systolic blood pressure 70 mmHg or lower or 71–90 mmHg and heart rate 108 beats per min. thought to be due to acute blood loss, either before the arrival of air medical transport or before arrival at the trauma centre. The RCTs assessed the use of two units of FFP compared with the standard resuscitation protocol according to local rules. Moore (2018) included a total of 125 patients in the analysis and Sperry (2018) included 501 patients. Both RCTs reported on the outcomes of mortality and morbidity (including acute lung injury and multiple organ failure) and were judged by the systematic review authors to be at low risk of bias.

Cryoprecipitate

One RCT (Curry 2015) evaluated the effect of CRYO on mortality, morbidity and transfusion volume in trauma patients with major haemorrhage requiring activation of the major haemorrhage protocol. The study included a total of 44 patients and was carried out in two civilian UK trauma centres. Risk of bias was judged by review authors as unclear due to small sample size and lack of blinding of participants, clinical staff and research staff.

Platelets

The search did not identify any RCTs that assessed the use of PLTs compared to no PLTs (or varying administration of) in patients with critical bleeding on patient outcomes.

Fibrinogen concentrate

Five RCTs were conducted in critically bleeding trauma patients (Lucena 2020, Curry 2018, Akbari 2017, Innerhofer 2017, Nascimento 2016), two RCTs were in the obstetrics setting (Collins 2017, Wikkelsø 2015), and five RCTs were in the surgical setting (Bilicen 2017, Rahe-Meyer 2016, Galas 2014, Tanaka 2014, Rahe-Meyer 2013).

Trauma setting

Five RCTs conducted in the trauma setting were conducted in Austria, UK, Canada, Iran and Brazil and all assessed the use of FC in adult patients with severe trauma. Three RCTs (Curry 2018, Nascimento 2016, Lucena 2020) compared the use of FC with saline or no FC, one RCT (Akbari 2017) compared FC to an active (FFP) and an inactive (no coagulation factor) comparator, and one RCT (Innerhofer 2017) compared FC to an active comparator (FFP) only.

For the purpose of this review, only the inactive comparator in Akbari (2017) was considered. Also, as both FC and FFP were considered in this review, the results from Innerhofer 2017 have been presented with FC as the intervention as reported by the Cochrane review conducted by Fabes 2018.

The studies were assessed to be at overall moderate risk of bias due to lack of allocation concealment, blinding of study personnel and outcome assessors, incomplete outcome data and selective reporting.

Surgical setting

Four RCTs were conducted in the Netherlands, Germany and US and evaluated the therapeutic use of FC in the setting of cardiac surgery. Three RCTs (Bilicen 2017, Rahe-Meyer 2013, Rahe-Meyer 2016) compared the use of FC with saline while one RCT (Tanaka 2014) compared the use of FC with one unit of PLTs. All four RCTs were assessed by the systematic review authors to have overall no serious concerns of bias, however domains assessed to have some risk of bias included allocation concealment, blinding, incomplete outcome data and selective reporting.

One RCT (Galas 2014) evaluated the safety and efficacy of FC compared with CRYO in paediatric patients (aged less than 15 years) undergoing cardiopulmonary bypass surgery. The RCT was conducted in 63 children in Brazil, of which 30 patients were randomised to receive 60mg/kg FC and 33 patients were randomised to receive 10 mL/kg cryoprecipitate if they had diffuse bleeding requiring haemostatic therapy and plasma fibrinogen concentration less than 1 g/L. The primary outcome for this study was post-operative blood loss during 48 hours of surgery. The RCT was assessed by the systematic review to be at low risk of bias.

Obstetric and maternity setting

Two RCTs (Collins 2017, Wikkelsø 2015) were conducted in Denmark and the UK and evaluated the use of FC in the obstetrics setting. In both RCTs, adult women with postpartum haemorrhage were randomised to receive FC or saline and reported on the outcomes of mortality and morbidity. The RCTs were assessed by the review authors to be at overall low risk of bias for these outcomes.

Prothrombin complex concentrate

The search did not identify any RCTs that examined the effect of PCC compared to no PCC (or varying administration of) in patients with critical bleeding on patient outcomes.

4.7.2.3 Observational and cohort studies

The included systematic reviews identified 16 cohort studies that were relevant to this review (Almskog 2020, Zeeshan 2019, Jehan 2018, Holcomb 2017, Shackelford 2017, Joseph 2016, Joseph 2014, O'Reilly 2014,Innerhofer 2013, Wafaisade 2013, Nienaber 2011, Schöchl 2011, Rahe-Meyer 2009a, Rahe-Meyer 2009b, Bilicen 2013, Ahmed 2012).

The main characteristics and quality of these studies and the relevant outcomes assessed are detailed in Table 4.46.

The systematic review process identified two cohort studies (Inokuchi 2017, Yamamoto 2016) relevant to this review. Both studies were identified in the included systematic reviews, however one study (Yamamoto 2016) did not present analysis for comparator of interest (i.e. FC compared to no FC) and is not reported further.

Among the identified cohort studies, 12 were retrospective cohorts. As outlined in Section 3.1.4, retrospective cohort studies were to be excluded. However, given the lack of available evidence for blood component therapy, these studies were included in the review.

Table 4.46 Characteristics and quality of observational and cohort studies by clinical setting: the effect of blood component therapy on patient outcomes

Review ID ***Risk of bias***	Study design	Population	Intervention	Comparison	Outcomes
Trauma setting					
Almskog 2020 *High*	Retrospective (matched) cohort	Adult patients with blunt trauma N=216	FC	No FC	Mortality Morbidity LOS
Zeeshan 2019 *Moderate*	Retrospective cohort	Severely injured trauma patients N=468	4-factor PCC (+FFP)	FFP	Mortality Transfusion volumes LOS Morbidity
Jehan 2018 *Moderate*	Retrospective cohort	Adult trauma patients N=120	4-factor PCC (+FFP)	FFP	Transfusion volumes Mortality LOS Morbidity
Holcomb 2017 *High*	Retrospective (matched) cohort	Adult civilian trauma patients N=109	FFP	Standard care	Mortality
Inokuchi 2017 *Serious*	Retrospective (before and after) cohort SC	Patients with pelvic fractures stemming from blunt injury N=224	FC (+FFP)	FFP	Transfusion volume Mortality
Shackelford 2017 *High*	Retrospective (matched) cohort	Military trauma patients N=386	FFP	Standard care	Mortality
Joseph 2016 *Moderate*	Retrospective cohort	Trauma patients N=81	3-factor PCC (+FFP)	FFP	Mortality Morbidity Transfusion volume LOS
Joseph 2014 *Moderate*	Retrospective cohort	Trauma patients N=252	3-factor PCC (+FFP)	FFP	Mortality Transfusion volumes Morbidity
O'Reilly 2014 *High*	Retrospective (matched) cohort	Military trauma patients N=194	FFP	Standard care	Mortality
Innerhofer 2013 *High*	Retrospective cohort study	Adult trauma patients (≥18 years) with an ISS ≥15 N=144	FFP (+FC)	FC	Morbidity Transfusion volume
Wafaisade 2013 *High*	Retrospective (matched) cohort	Severely injured trauma patients N=588	FC	No FC	Mortality Morbidity LOS Transfusion volume
Nienaber 2011 *High*	Retrospective (matched) cohort	Adult trauma patients (≥18 to ≤70 years) with ISS ≥16. N=36	FC and/or PCC	FFP	Mortality Morbidity LOS Transfusion volume

Schöchl 2011 *High*	Prospective (unmatched) cohort	Trauma patients who received ≥ 5 units of RBC concentrate within 24 hours. N=36	FC	FFP	Mortality Transfusion volumes
Surgical setting					
Bilicen 2013 *High*	Prospective cohort SC	Patients who underwent complex cardiac surgery N=120	FC	No FC	Transfusion volume
Rahe-Meyer 2009a *High*	Comparative prospective	Patients with TAAA N=18	FC	Standard transfusion algorithm	Mortality Transfusion volume
Rahe-Meyer 2009b *High*	Comparative study with historical control	Patients undergoing AV-AA N=15 (Group B and C)	FC	Standard transfusion algorithm	Mortality Transfusion volume
Obstetric and maternal setting					
Ahmed 2012 *High*	Retrospective cohort	Patients with major obstetric haemorrhage N=34	FC	CRYO	LOS Transfusion volume

AV-AA, aortic valve operation and ascending aorta replacement; CRYO, cryoprecipitate; FC, fibrinogen concentrate; FFP, fresh frozen plasma; ISS, injury severity score; LOS, length of stay; PCC, prothrombin complex concentrate; RBC, red blood cell; SC, single centre; TAAA, thoracoabdominal aortic aneurysm

Fresh frozen plasma

Innerhofer 2013 was a single centre, prospective cohort study conducted in Austria that assessed the effect of FFP in 144 patients with blunt major trauma. All patients in the study received FC and PCC; 78 patients additionally received FFP transfusions and constitute the interventional arm in this analysis. Review authors judged the study to have high risk of bias due to small sample sizes, inadequate follow-up and lacked rigorous analyses.

Holcomb 2017 was a multicentre, prospective cohort study conducted in the US that assessed the effect of prehospital transfusion of FFP, RBC or FFP in addition to RBC compared with standard of care in 109 patients with penetrating trauma. A total of 26 patients received FFP only, eight patients received RBC only and 75 patients received both FFP and RBC and constitute the interventional arm in this analysis. The study was found to be at high risk of bias due to imbalances in baseline characteristics which limited matching.

Two retrospective cohort studies (O'Reilly 2014, Shackelford 2017) investigated the effect of prehospital transfusion of FFP compared to standard of care in military trauma patients in Afghanistan with gunshot wounds or explosive trauma. O'Reilly 2014 assessed prehospital blood transfusion in 194 patients. A total of 97 patients received a median of one unit RBC and two units of FFP and 97 patients received standard of care. Shackelford 2017 was a study of 386 US military combat casualties who received prehospital blood transfusion between 2012 to 2015. A total of 54 patients received RBC and FFP; 332 patients received standard of care.

Review authors judged the studies to be at high risk of bias due to retrospective analyses and a lack of uniform guidelines for initiating prehospital blood transfusion which makes it difficult to determine the effect of individual blood components.

Cryoprecipitate

The search did not identify any cohort studies that assessed the use of CRYO compared to no CRYO (or varying administration of) in patients with critical bleeding on patient outcomes.

Platelets

The search did not identify any cohort studies that assessed the use of PLTs compared to no PLTs (or varying administration of) in patients with critical bleeding on patient outcomes.

Fibrinogen concentrate

Five cohort studies (Almskog 2020, Wafaisade 2013, Inokuchi 2017, Schöchl 2011, Nienaber 2011) were conducted in the trauma setting, three studies (Bilicen 2013, Rahe-Meyer 2009a, Rahe-Meyer 2009b) were in the surgical setting, and one study (Ahmed 2012) was in the obstetrics setting.

Trauma setting

Five cohort studies were conducted in Europe and Japan and examined the effect of FC in trauma patients with critical bleeding. Two studies reported the comparator to be no FC (Wafaisade 2013, Almskog 2020), while the remaining three cohort studies reported the comparator to be FFP (Schöchl 2011, Nienaber 2011, Inokuchi 2017). For the purposes of this review, the patients who received FC were considered as the interventional arm for this analysis.

The cohort studies were judged by systematic reviews to be at high risk of bias due to missing data, absence of a clear objective criterion for the activation of MTP and lack of control for potential confounders.

Surgical setting

Three cohort studies were identified in the surgical setting that evaluated the use of FC in patients with major haemorrhage (Bilicen 2013, Rahe-Meyer 2009a, Rahe-Meyer 2009b). All three cohort studies were assessed to be at high risk of bias, predominately due to failure to in blinding, lack of information on the allocation of groups and insufficient information about comparability of groups at baseline and at the analysis stage.

Bilicen 2013 was a single centre prospective cohort study that assessed 1075 patients who underwent complex cardiac surgery in the Netherlands. A total of 264 patients received a median dose of 2g FC; the 811 patients that did not receive FC represent the control group. The authors note that due to the nonrandomised design of the study, the association between the infusion of FC and each of the outcomes were likely biased by potential confounders.

Rahe-Meyer 2009a was a pilot study that prospectively enrolled 15 patients undergoing aortic valve operation and ascending aorta replacement surgery in Germany. Five patients received transfusion according to the predefined blood components transfusion algorithm while the remaining 10 patients received FC before being transfused according

to the algorithm. Rahe-Meyer 2009b was a retrospective group analysis of 18 patients who underwent elective thoracoabdominal aortic aneurysm surgery. All patients in the study were treated with allogenic blood components according to a predetermined algorithm; six patients also received a mean (SD) dose of 7.8 g (2.7) FC as a first step therapy. The small sample size prevents any meaningful analysis of the results.

Obstetric and maternity setting

One cohort study (Ahmed 2012) was found that evaluated the use of FC in women with major obstetric haemorrhage. Among 77 patients with major obstetric haemorrhage, 20 received a mean dose of 4 ± 0.8 g FC and 34 received a mean dose of 2.21 ± 0.35 pooled units of CRYO. Due to the nature of the active comparator, both treatment arms represent eligible interventions. For the purpose of this review, FC has been chosen as the interventional arm for this analysis.

Ahmed 2012 was assessed by review authors to be at serious risk of bias due to small sample size and inadequate follow-up.

Prothrombin complex concentrate

The search did not find any additional studies that examined the effect of PCC compared to no PCC (or varying administration of) in patients with critical bleeding in another setting (i.e. perioperative, obstetric, paediatric).

The four cohort studies were conducted in trauma patients presenting to the emergency department (total sample size 924). Two studies (Jehan 2018, Zeeshan 2019) investigated the effect of 4-factor PCC plus FFP compared to FFP only and two studies (Joseph 2014, Joseph 2016) investigated the effect of 3-factor PCC plus FFP compared to FFP only. Dose of PCC administered was 25 IU/kg for three studies and indication for administration was by clinical judgement for all four studies.

Review authors judged the studies as moderate risk of bias due to the retrospective study design, in which PCC was administered based on clinical judgement and may have resulted in confounding and bias. The authors also noted considerable variety in the type and dose for PCC that could lead to under or overrepresentation of the actual effects of PCC on the outcomes.

4.7.3 Results

4.7.3.1 Fresh frozen plasma

Mortality

A summary of the evidence relating to the effect of fresh frozen plasma (FFP) on mortality in patients with critical bleeding is presented in Table 4.47.

A meta-analysis of data from studies included in this review showed no significant difference in mortality at 24 hours (Figure 4.27) or latest reported timepoint (Figure 4.28) between patients who received FFP compared to those who did not.

24 hours

One RCT (Moore 2018) and two cohort studies (Holcomb 2017, Shackelford 2017) were identified that reported on the effect of FFP on the outcome of 24-hour mortality among patients with trauma. Combined data from all three studies (see Figure 4.27) showed the 24-hour mortality rate in patients who received FFP (16/162, 9.9%) to be lower than that observed among patients who did not receive FFP (83/458, 18.1%). The difference was not statistically significant (RR 0.66; 95% CI 0.28, 1.57; p = 0.35; random effects; I2 = 53%).

Latest timepoint

Two RCTs (Moore 2018, Sperry 2018) and four cohort studies (Holcomb 2017, Shackelford 2017, Innerhofer 2013, O'Reilly 2014) reported on the effect of FFP on the outcome of mortality, latest timepoint. All six studies were conducted in the trauma setting. Combined data from the two RCTs (see Figure 4.28) showed the mortality rate to be 26.4% (78/295) among those who received FFP compared to 31.4% (104/331) among those who did not. The difference was not statistically significant (RR 0.95; 95% CI 0.56, 1.59; p = 0.83; random effects, I^2 = 38%), with moderate statistical heterogeneity observed.

Combined data from the four cohort studies (see Figure 4.28) suggested a significant association between FFP and mortality among trauma patients with critical bleeding (RR 0.65, 95%CI 0.43, 0.98; p = 0.04; random effects, I^2 = 0%) with the rate of mortality observed among those who received FFP (19.3%, 106/549) being lower than the mortality rate of those who did not receive FFP (24.4%, 218/892).

Figure 4.27 Forest plot of comparison: FFP vs no FFP (or varying administration of), outcome: Mortality, all-cause (at 24 hours)

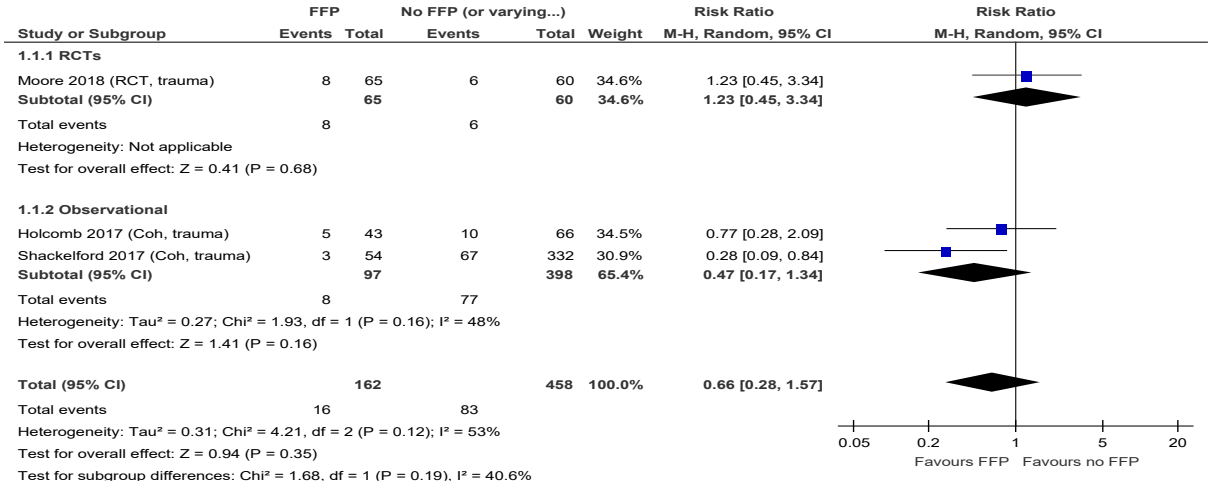


Figure 4.28 Forest plot of comparison: FFP vs no FFP (or varying administration of), outcome: Mortality, all-cause (latest reported timepoint)

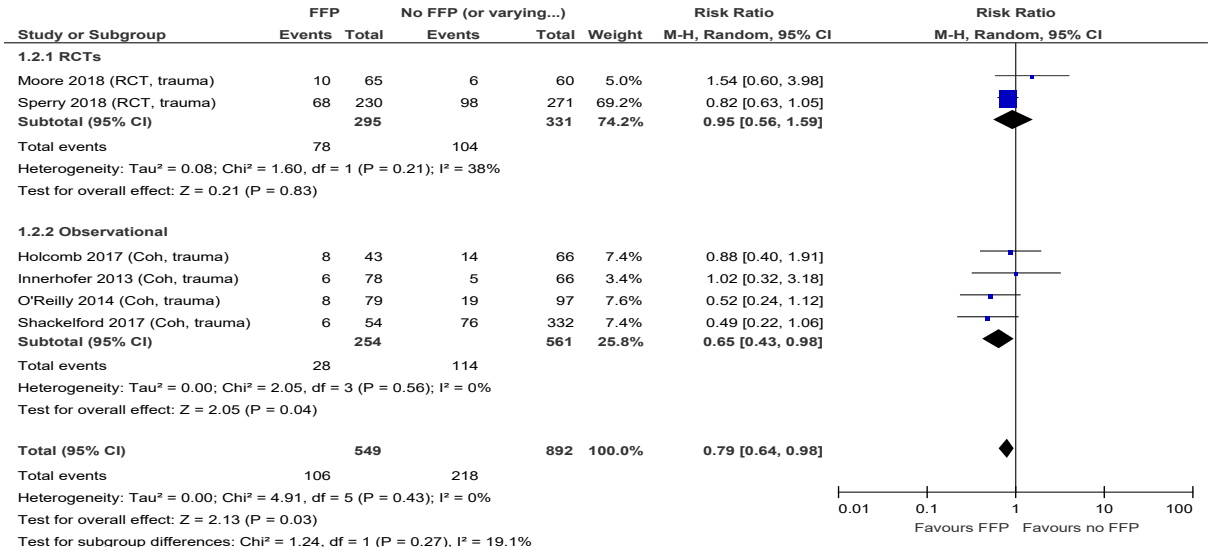


Table 4.47 Results for FFP versus no FFP: Patients with critical bleeding – Mortality

Study ID Study design[a]	Sample size (no. of trials) included in analysis	Patient population	Setting (Location)	Comparison	Outcome	Results			
						FFP n/N (%)	No FFP n/N (%)	Risk estimate (95% CI)	*Statistical significance* *p*-value Heterogeneity [b]
Trauma setting									
Coccolini 2019 SR *Moderate quality*	N = 626 (2 RCTs) Moore 2018 Sperry 2018	Severely injured adults with acute blood loss	Trauma centre, civilian (US)	FFP vs standard resuscitation protocol	Mortality, 1 month	78/295 (26.4) 10/65 (15.4) 68/230 (29.6)	104/331 (31.4) 6/60 (10) 98/271 (36.3)	RR 0.86 (0.68, 1.11) 1.54 (0.60, 3.98) 0.82 (0.63, 1.05)	No significant difference $p = 0.24$ Minimal heterogeneity $I^2 = 38\%$ ($p = 0.21$)
Mengoli 2017 SR *Low quality*	N = 144 (1 Coh) Innerhofer 2013	Patients with severe trauma-related bleeding	Trauma centre (SC, Austria)	FFP vs no FFP (± FC and/or PCC in both groups)	Mortality, 30 days	6/78 (7.7)	5/66 (7.6)	NR	No significant difference $p = 0.979$
Rjinhout 2019 SR *Low quality*	N = 495 (2 Coh) Shackelford 2017 Holcomb 2017	Civilian and military trauma patients	Trauma (US, Afghanistan)	FFP vs standard care	Mortality, 24 hours	8/97 (8.2) 3/54 (5.6) 5/43 (11.6)	77/398 (19.3) 67/332 (20.2) 10/66 (15.2)	RR 0.47 (0.17, 1.34) 0.28 (0.09, 0.84) 0.77 (0.28, 2.09)	No significant difference $p = 0.16$ Moderate heterogeneity $I^2 = 48\%$ ($p = 0.16$)
	N = 689 (3 Coh) O'Reilly 2014 Shackelford 2017 Holcomb 2017				Mortality, long-term	22/194 (11.3) 8/97(8.2) 6/54 (11.1) 8/43 (18.6)	109/495 (22) 19/97 (19.6) 76/332 (22.9) 14/66 (21.2)	OR 0.54 (0.32, 0.91) [c] 0.37 (0.15, 0.89) 0.42 (0.17, 1.02) 0.85 (0.32, 2.24)	*Favours FFP* $p = 0.02$ [c] No significant heterogeneity $I^2 = 0\%$ ($p = 0.53$)[c]

CI, confidence interval; Coh, cohort study; FC, fibrinogen concentrate; FFP, fresh frozen plasma; NR, not reported; OR, odds ratio; PCC, prothrombin complex concentrate; RCT, randomised controlled trial; RR, relative risk; SC, single centre; SR, systematic review; US, United States

a. Where only one RCT is identified in a systematic review, the evidence has been considered as RCT evidence. Where the systematic review assesses observational and cohort studies, the evidence has been considered as according to the study design features. The risk of bias of the included primary studies is based on the quality assessment reported by the systematic review authors.

b. Only applicable to Systematic reviews with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if $P_{het} > 0.1$ and $I^2 < 25\%$; (ii) mild heterogeneity if $I^2 < 25\%$; moderate heterogeneity if I^2 between 25–50%; substantial heterogeneity $I^2 > 50\%$.

c. Calculated post-hoc using RevMan 5.4.

Morbidity

A summary of the evidence reported in the identified systematic reviews relating to morbidity in patients with critical bleeding is presented in Table 4.48.

Three studies identified in the systematic reviews reported on the outcome of morbidity; two RCTs (Moore 2018, Sperry 2018) reported on multiple organ failure and acute lung injury and one cohort study (Innerhofer 2013) reported on multiple organ failure and thromboembolic events (Figure 4.29). The studies were not sufficiently powered to detect important differences in event rates, therefore evidence for morbidity outcomes should be considered with caution.

Thromboembolic events

One cohort study (Innerhofer 2013) reported a lower rate of thromboembolic events among patients who received FFP (7.7%, 6/78) compared with those who did not (9.0%, 6/66), but the difference between groups was not significant (RR 0.85, 95% CI 0.29, 2.50; $p = 0.76$).

Multiple organ failure

A meta-analysis of data from the included studies showed an increased risk of multiple organ failure among patients who received FFP (179/373, 48.0%) compared with those who did not (169/397, 42.6%). The difference between groups was not significant (RR 1.56, 95% CI 0.2, 2.96; $p = 0.17$; random effects; $I^2 = 68\%$); noting statistical heterogeneity is substantial. The results were not substantially different when only RCT evidence was considered (RR 1.76, 95% CI 0.40, 7.68); $p = 0.45$; random effects; $I^2 = 58\%$).

Acute lung injury

A meta-analysis of data from the RCTs showed no difference in the risk of acute lung injury between treatment groups. The rate of acute lung injury was 25.7% (76/295) among those who received FFP compared with 24.2% (80/331) among those who did not, corresponding to a RR of 0.99 (95% CI 0.76, 1.30; $p = 0.97$; random effects; $I^2 = 9\%$).

Figure 4.29 Forest plot of comparison: FFP vs no FFP (or varying administration of), outcome: Morbidity

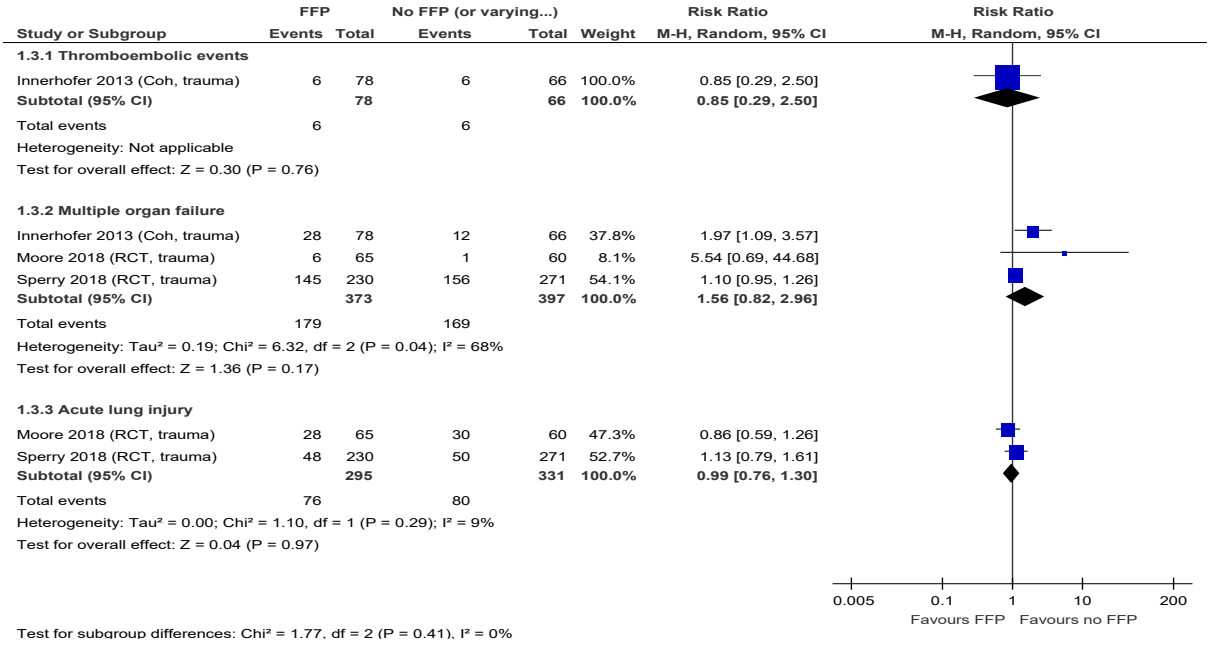


Table 4.48 Results for FFP versus no FFP: Patients with critical bleeding – Morbidity: any adverse outcome

Study ID Study design[a]	Sample size (no. of trials) included in analysis	Patient population	Setting (Location)	Comparison	Outcome	Results			
						FFP n/N (%)	No FFP n/N (%)	Risk estimate (95% CI)	*Statistical significance* *p*-value Heterogeneity[b]
Trauma setting									
Coccolini 2019 SR *Moderate quality*	N = 626 (2 RCTs) Moore 2018 Sperry 2018	Severely injured adults with acute blood loss	Trauma centre, civilian (US)	FFP vs standard resuscitation protocol	Acute lung injury	76/295 (25.8) 28/65 (43.1) 48/230 (20.9)	80/331 (24.2) 30/60 (50) 50/271 (18.5)	OR 1.03 (0.71, 1.50) OR 1.17 (0.75, 1.81)	No significant difference *p* = 0.87 Minimal heterogeneity I^2 = 3% (*p* = 0.31)
				FFP vs standard resuscitation protocol	MOF	149/295 (50.5) 4/65 (6.2) 145/230 (63.0)	157/331 (47.4) 1/60 (1.7) 156/271 (57.6)	OR 1.30 (0.92, 1.86) OR 3.87 (0.42, 35.63) OR 1.26 (0.88, 1.80)	No significant difference *p* = 0.14 No significant heterogeneity I^2 = 0% (p = 0.33)
Mengoli 2017 SR *Low quality*	N = 144 (1 Coh) Innerhofer 2013	Patients with severe trauma-related bleeding	Trauma centre (SC, Austria)	FFP ± FC ± PCC vs FC ± PCC	Thromboembolism [c]	6/78 (7.7)	6/66 (10)	NR	No significant difference *p* = 0.772
					Sepsis [c]	28/78 (35.9)	11/66 (16.7)	NR	No significant difference *p* = 0.014
					MOF [c]	29/78 (37.2)	12/66 (18.2)	NR	No significant difference *p* = 0.015

CI, confidence interval; Coh, cohort; FC, fibrinogen concentrate; FFP, fresh frozen plasma; ISS, injury severity score; MOF, multiorgan failure; NR, not reported; OR, odds ratio; PCC, prothrombin complex concentrate; RCT, randomised controlled trial; SC, single centre; SR, systematic review; US, United States

a. Where only one RCT is identified in a systematic review, the evidence has been considered as RCT evidence. Where the systematic review assesses Observational and cohort studies, the evidence has been considered as according to the study design features. The risk of bias of the included primary studies is based on the quality assessment reported by the systematic review authors.

b. Only applicable to Systematic reviews with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if P_{het} >0.1 and I^2 <25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25–50%; substantial heterogeneity I^2 >50%.

c. Data extracted from primary study

Transfusion volumes

A summary of the evidence reported in the identified systematic reviews relating to transfusion volumes in patients with critical bleeding is presented in Table 4.49.

There was one cohort study (Innerhofer 2013) identified by three systematic reviews (Mengoli 2017, Aubron 2014, Lunde 2014) that was considered relevant to this review.

Red blood cells

One small cohort study (Innerhofer 2013) reported that the median (IQR) volume of RBCs transfused (units to 24 hours) among the 78 patients who received FFP was 7 (4, 11) units, which was significantly higher than the median 2 (0, 6) units of RBCs transfused among the 66 patients who did not receive FFP ($p = 0.001$).

Other blood components

One small cohort study (Innerhofer 2013) reported that the median (IQR) volume of PLTs transfused (units to 24 hours) among the 78 patients who received FFP was 0 (0, 1) units, which was significantly higher than the median 0 (0, 0) units of PLTs transfused among the 66 patients who did not receive FFP ($p = 0.003$).

There was no significant difference between treatment groups reported for the outcome of FC transfusion volumes (units to 24 hours) and PCC transfusion volumes (units to 24 hours).

Table 4.49 Results for FFP versus no FFP: Patients with critical bleeding – Transfusion volumes

Study ID Study design[a]	Sample size (no. of trials) included in analysis	Patient population	Setting (Location)	Comparison	Outcome	Results			
						FFP median (IQR)	No FFP median (IQR)	Risk estimate (95% CI)	*Statistical significance* *p*-value Heterogeneity[b]
Trauma setting									
Mengoli 2017 SR *Low*	N = 144 (1 Coh) Innerhofer 2013	Patients with severe trauma-related bleeding	Trauma centre (SC, Austria)	FFP vs no FFP (± FC ± PCC in both groups)	RBC transfusion volume, units to 24 hours	(n = 78) 7 (4, 11)	(n = 66) 2 (0, 6)	NR	*Favours FFP* *p* = 0.001 [c]
					PLT transfusion volume, units to 24 hours [c]	(n = 78) 0 (0, 1)	(n = 66) 0 (0, 0)	NR	*Favours FFP* *p* = 0.003
Lunde 2014 SR *Critically low*	N = 144 (1 Coh) Innerhofer 2013	Patients with severe trauma-related bleeding requiring FC	Trauma centre (SC, Austria)	FFP vs no FFP (± FC and/or PCC in both groups)	FFP transfusion volume, units to 24 hours	(n = 78) 8 (5, 10)	(n = 66) 0 (0, 0)	NR	Not tested
					FC transfusion volume, units to 24 hours	(n = 78) 4 (2, 6)	(n = 66) 4 (2, 4)	NR	No significant difference *p* = 0.550
					PCC transfusion volume, units to 24 hours [c]	(n = 78) 0 (0, 1200)	(n = 66) 0 (0, 1200)	NR	No significant difference *p* = 0.943

CI, confidence interval; Coh, cohort; FC, fibrinogen concentrate; FFP, fresh frozen plasma; IQR, interquartile range; NR, not reported; OR, odds ratio; PCC, prothrombin complex concentrate; PLT, platelets; RBC, red blood cells; SC, single centre; SR, systematic review

a. Where only one RCT is identified in a systematic review, the evidence has been considered as RCT evidence. Where the systematic review assesses Observational and cohort studies studies, the evidence has been considered as according to the study design features. The risk of bias of the included primary studies is based on the quality assessment reported by the systematic review authors.

b. Only applicable to Systematic reviews with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if P_{het} >0.1 and I^2 <25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25–50%; substantial heterogeneity I^2 >50%.

c. Data extracted from primary study.

Length of stay

A summary of the evidence reported in the identified systematic reviews relating to length of stay (hospital and ICU) in patients with critical bleeding is presented in Table 4.50.

There was one cohort study (Innerhofer 2013) identified by three systematic reviews (Mengoli 2017, Aubron 2014, Lunde 2014) that was considered relevant to this review.

Hospital

One small cohort study (Innerhofer 2013) reported the median duration of hospital stay to be 29 days (IQR 16, 50) among 78 patients who received FFP which was longer than the median 24 days (IQR 12, 35) reported for the 66 patients who did not receive FFP. The difference was not statistically significant ($p = 0.074$).

Intensive care unit

One small cohort study (Innerhofer 2013) reported the median duration of ICU stay to be 14 days (IQR 7, 30) among 78 patients who received FFP which was longer than the median 12 days (IQR 6, 24) reported for the 66 patients who did not receive FFP. The difference was not statistically significant ($p = 0.217$).

Table 4.50 Results for FFP versus no FFP: Patients with critical bleeding – Length of stay

Study ID Study design[a]	Sample size (no. of trials) included in analysis	Patient population	Setting (Location)	Comparison	Outcome	Results			
						FFP median (IQR)	No FFP median (IQR)	Risk estimate (95% CI)	*Statistical significance* *p*-value Heterogeneity [b]
Trauma setting									
Mengoli 2017 SR *Low*	N = 144 (1 Coh) Innerhofer 2013	Patients with severe trauma-related bleeding	Trauma centre (SC, Austria)	FFP vs no FFP (± FC ± PCC in both groups)	LOS, In-patient days [c]	(n = 78) 29 (16-50)	(n = 66) 24 (12-35)	NR	No significant difference *p* = 0.074
					LOS, ICU days [c]	(n = 78) 14 (7-30)	(n = 66) 12 (6-24)	NR	No significant difference *p* = 0.217

CI, confidence interval; Coh, cohort; FC, fibrinogen concentrate; FFP, fresh frozen plasma; ICU, intensive care unit; IQR, interquartile range; LOS, length of stay; NR, not reported; PCC, prothrombin complex concentrate; SC, single centre; SR, systematic review

a. Where only one RCT is identified in a systematic review, the evidence has been considered as RCT evidence. Where the systematic review assesses Observational and cohort studies studies, the evidence has been considered as according to the study design features. The risk of bias of the included primary studies is based on the quality assessment reported by the systematic review authors.

b. Only applicable to Systematic reviews with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if P_{het} >0.1 and I^2 <25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25–50%; substantial heterogeneity I^2 >50%.

c. Data extracted from primary study.

4.7.3.2 Cryoprecipitate

Mortality

A summary of the evidence reported in the identified systematic reviews relating to the effect of CRYO on mortality in patients with critical bleeding is presented in Table 4.51.

One systematic review (McQuilten 2018) reported the results of one RCT (Curry 2015) that contributed data relevant to critically bleeding patients in a trauma setting.

The RCT reported a lower rate of mortality among patients who received CRYO (2/20, 10.0%) compared with those who did not (6/21, 28.6%). The difference between treatment groups was not statistically significant (RR 0.35, 95% CI 0.08, 1.54; $p = 0.14$).

Figure 4.30 Forest plot of comparison: CRYO vs no CRYO (or varying administration of...), outcome: Mortality, latest timepoint.

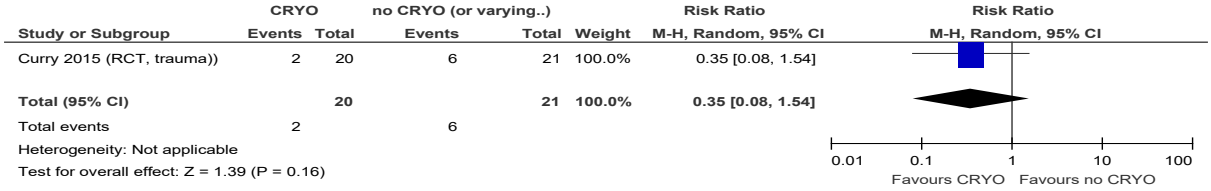


Table 4.51 Results for CRYO versus no CRYO: Patients with critical bleeding – Mortality

Study ID Study design[a]	Sample size (no. of trials) included in analysis	Patient population	Setting (Location)	Comparison	Outcome	Results			
						CRYO n/N (%)	No CRYO n/N (%)	Risk estimate (95% CI)	*Statistical significance* *p*-value Heterogeneity[b]
Trauma setting									
McQuilten 2018 SR *Moderate quality*	N = 41 (1 RCT) Curry 2015	Patients ≥ 16 years actively bleeding and required activation of major haemorrhage protocol	Multi trauma centres (UK)	CRYO vs standard therapy (6 units RBC vs 4 FFP)	Mortality, 28 days	2/20 (10)	6/21 (28.6)	RR 0.35 (0.08, 1.54)	No significant difference *p* = 0.14

CI, confidence interval; CRYO, cryoprecipitate; FFP, fresh frozen plasma; RBC, red blood cell; RCT, randomised controlled trial; RR, relative risk; SR, systematic review; UK, United Kingdom

a. Where only one RCT is identified in a systematic review, the evidence has been considered as RCT evidence. Where the systematic review assesses Observational and cohort studies, the evidence has been considered as according to the study design features. The risk of bias of the included primary studies is based on the quality assessment reported by the systematic review authors.

b. Only applicable to Systematic reviews with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if P_{het} >0.1 and I^2 <25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25–50%; substantial heterogeneity I^2 >50%.

Morbidity

A summary of the evidence reported in the identified systematic reviews relating to morbidity in patients with critical bleeding is presented in Table 4.52.

One systematic review (McQuilten 2018) reported the results of one RCT (Curry 2015) that contributed data relevant to this outcome in critically bleeding patients in a trauma setting. The study was not sufficiently powered to detect important differences in event rates, therefore evidence for morbidity outcomes should be considered with caution

Thromboembolic events

One RCT (Curry 2015) reported no thromboembolic events among critically bleeding trauma patients who received CRYO compared with a total of three events in the placebo group.

Specifically, a lower rate of deep vein thrombosis (DVT) was observed among patients who received CRYO (0/20, 0%) compared with those who did not (1/21, 4.8%) and a lower rate of pulmonary embolus (PE) was reported among patients who received CRYO (0/20, 0%) compared with those who did not (2/21, 9.5%). The event rates for both outcomes were not significantly different (DVT: RR 0.35, 95% CI 0.02, 8.10; $p = 0.51$) and (PE: RR 0.21, 95% CI 0.01, 4.11; $p = 0.30$).

There were no events of myocardial infarction or stroke reported in the RCT.

Multiple organ failure

One RCT (Curry 2015) reported a higher rate of multiple organ failure among critically bleeding trauma patients who received CRYO (1/20, 5%) compared with those who did not (0/21, 0%), corresponding to a RR of 3.14 (95% CI 0.14, 72.92; $p = 0.48$).

Other adverse outcomes

One RCT (Curry 2015) reported a lower rate of ARDS among critically bleeding trauma patients who received CRYO (0/20, 0%) compared with those who did not (1/21, 4.8%); corresponding to a RR of 0.35 (95% CI 0.02, 8.10; $p = 0.51$). A higher rate of sepsis among patients who received CRYO (3/20, 15%) compared with those who did not (0/21, 0%) was also observed (RR 7.33, 95%CI 0.40, 133.57; $p = 0.18$).

Figure 4.31 Forest plot of comparison: CRYO vs no CRYO (or varying administration of...), outcome: Morbidity, thromboembolic events.

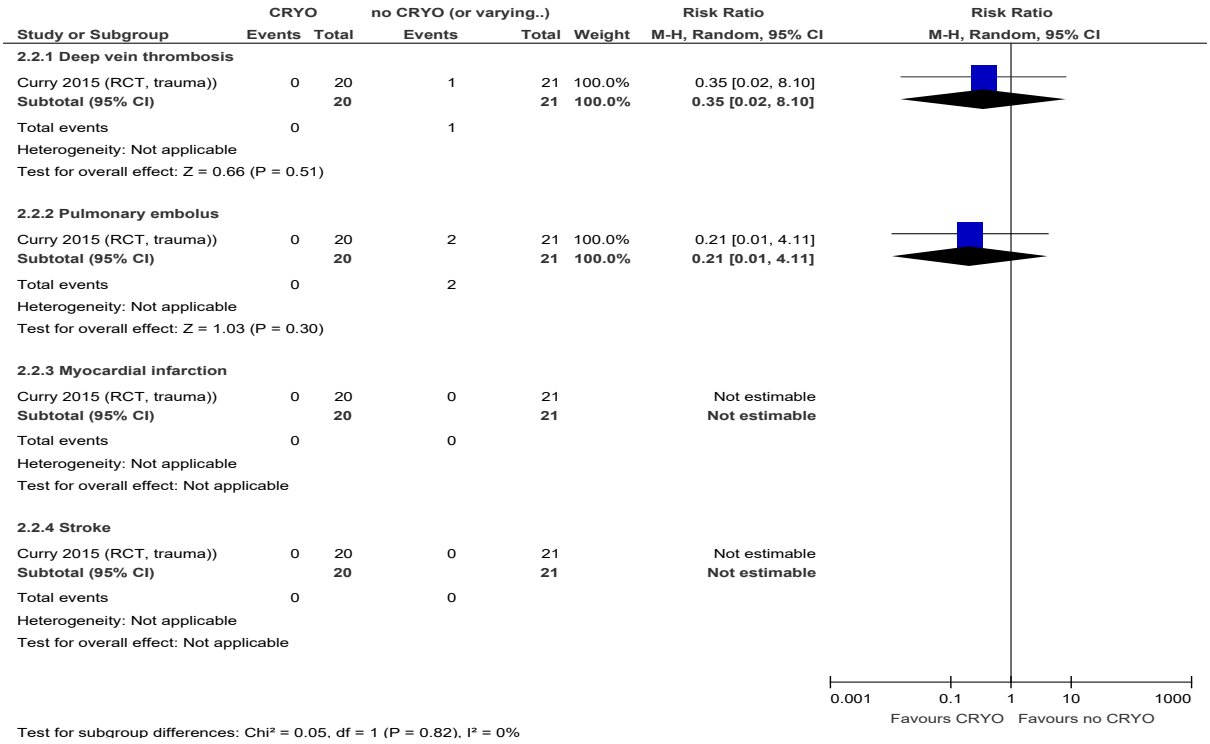


Figure 4.32 Forest plot of comparison: CRYO vs no CRYO (or varying administration of...), outcome: Morbidity, other.

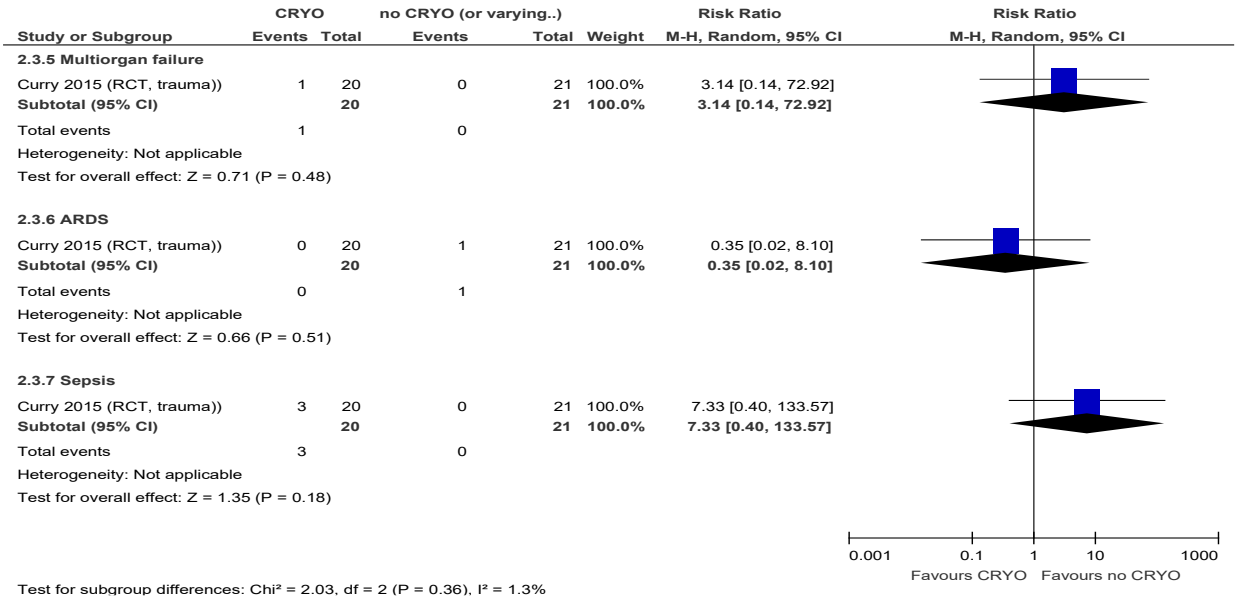


Table 4.52 Results for CRYO versus no CRYO: Patients with critical bleeding – Morbidity

Study ID Study design[a]	Sample size (no. of trials) included in analysis	Patient population	Setting (Location)	Comparison	Outcome	Results			
						CRYO n/N (%)	No CRYO n/N (%)	Risk estimate (95% CI)	*Statistical significance* *p*-value Heterogeneity[b]
Trauma setting									
McQuilten 2018 SR *Moderate quality*	n = 41 (1 RCT) Curry 2015	Patients ≥16 years actively bleeding and required activation of major haemorrhage protocol	Multiple trauma centres (UK)	CRYO vs standard therapy (6 U RBC vs 4 FFP)	Deep vein thrombosis	0/20 (0)	1/21 (4.8)	RR 0.35 (0.02, 8.10)	NR
					Pulmonary embolus	0/20 (0)	2/21 (9.5)	RR 0.21 (0.01, 4.11)	NR
					Myocardial infarction	0/20 (0)	0/21 (0)	Not estimable	Not estimable
					Stroke	0/20 (0)	0/21 (0)	Not estimable	Not estimable
					MOF	1/20 (5)	0/21 (0)	RR 3.14 (0.14, 72.92)	NR
					ARDS	0/20 (0)	1/21 (4.8)	RR 0.35 (0.02, 8.10)	NR
					Sepsis	3/20 (15)	0/21 (0)	RR 7.33 (0.40, 133.57)	NR

ARDS, acute respiratory distress syndrome; CI, confidence interval; CRYO, cryoprecipitate; FFP, fresh frozen plasma; MOF, multiorgan failure; NR, not reported; RBC, red blood cell; RCT, randomised controlled trial; RR, relative risk; UK, United Kingdom

a. Where only one RCT is identified in a systematic review, the evidence has been considered as RCT evidence. Where the systematic review assesses Observational and cohort studies, the evidence has been considered as according to the study design features. The risk of bias of the included primary studies is based on the quality assessment reported by the systematic review authors.

b. Only applicable to Systematic reviews with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if P_{het} >0.1 and I^2 <25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25–50%; substantial heterogeneity I^2 >50%.

Transfusion volumes

A summary of the evidence reported in the identified systematic reviews relating to transfusion volumes in patients with critical bleeding is presented in Table 4.53 (RBCs) and Table 4.54 (other blood component).

One systematic review (McQuilten 2018) reported the results of one RCT (Curry 2015) that contributed data relevant to this outcome in critically bleeding patients in a trauma setting.

Red blood cells

One small RCT (Curry 2015) reported no significant difference in the volume of RBCs transfused up to six hours, 24 hours or 28 days among patients who received CRYO compared to those who did not. At 24-hours, participants in the control group had received a median (IQR) of 7 (6, 9) units of RBCs compared to 8 (5,11) units given to those randomised to the CRYO group.

Other blood components

One small RCT (Curry 2015) reported no significant difference in the volume of FFP, PLTs, or CRYO transfused up to six hours, 24 hours or 28 days among patients who received CRYO compared to those who did not.

At 24-hours, participants in the control group had received a median (IQR) of 6 (3, 8) units of FFP compared to 7 (4, 8) units given to those randomised to the CRYO group.

At 24-hours, participants in the control group had received a median (IQR) of 1 (1, 2) unit of PLTs compared to 1 (0, 2) unit given to those randomised to the CRYO group.

At 24-hours, participants in the control group had received a median (IQR) of 2 (0, 2) unit of CRYO compared to 2 (2, 4) units given to those randomised to the CRYO group.

Table 4.53 Results for CRYO versus no CRYO: Patients with critical bleeding – RBC transfusion volume

Study ID Study design[a]	Sample size (no. of trials) included in analysis	Patient population	Setting (Location)	Comparison	Outcome	Results			
						CRYO median (IQR)	No CRYO median (IQR)	Risk estimate (95% CI)	*Statistical significance* *p*-value Heterogeneity [b]
Trauma setting									
McQuilten 2018 SR *Moderate*	n = 41 (1 RCT) Curry 2015	Patients ≥16 years actively bleeding and required activation of major haemorrhage protocol	Multiple trauma centres (UK)	CRYO vs standard therapy (6 U RBC vs 4 FFP)	RBC transfusion volume, units to 6 hours	(n = 20) 7 (4, 10)	(n = 21) 7 (4, 8)	Not estimable	No significant difference *p* = 0.49
					RBC transfusion volume, units to 24 hours [c]	(n = 20) 8 (5, 11)	(n = 21) 7 (6, 9)	Not estimable	No significant difference *p* = 0.83
					RBC transfusion volume, units to 28 days [c]	(n = 20) 9 (7, 15)	(n = 21) 8 (7, 11)	Not estimable	No significant difference *p* = 0.10

CI, confidence interval; CRYO, cryoprecipitate; FFP, fresh frozen plasma; IQR, interquartile range; RBC, red blood cells; RCT, randomised controlled trial; SR, systematic review; UK, United Kingdom

a. Where only one RCT is identified in a systematic review, the evidence has been considered as RCT evidence. Where the systematic review assesses Observational and cohort studies, the evidence has been considered as according to the study design features. The risk of bias of the included primary studies is based on the quality assessment reported by the systematic review authors.

b. Only applicable to Systematic reviews with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if P_{het} >0.1 and I^2 <25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25–50%; substantial heterogeneity I^2 >50%.

c. Data extracted from primary study.

Table 4.54 Results for CRYO versus no CRYO: Patients with critical bleeding – Transfusion volume, other blood components

Study ID Study design[a]	Sample size (no. of trials) included in analysis	Patient population	Setting (Location)	Comparison	Outcome	Results			
						CRYO median (IQR)	No CRYO median (IQR)	Risk estimate (95% CI)	*Statistical significance* *p*-value Heterogeneity [b]
Trauma setting									
McQuilten 2018 SR *Moderate quality*	n = 41 (1 RCT) Curry 2015	Patients ≥16 years actively bleeding and required activation of major haemorrhage protocol	Multiple trauma centres (UK)	CRYO vs standard therapy (6 U RBC vs 4 FFP)	FFP transfusion volume, units to 6 hours	(n = 20) 7 (4, 8)	(n = 21) 5 (3, 8)	Not estimable	No significant difference *p* = 0.31
					FFP transfusion volume, units to 24 hours [c]	(n = 20) 7 (4, 8)	(n = 21) 6 (3, 8)	Not estimable	No significant difference *p* = 0.36
					FFP transfusion volume, units to 28 days [c]	(n = 20) 8 (4, 12)	(n = 21) 5 (3, 8)	Not estimable	No significant difference *p* = 0.06
					PLT transfusion volume, units to 6 hours	(n = 20) 1 (0, 1)	(n =21) 1 (0, 1)	Not estimable	No significant difference *p* = 0.89
					PLT transfusion volume, units to 24 hours [c]	(n = 20) 1 (0, 2)	(n = 21) 1 (1, 2)	Not estimable	No significant difference *p* = 0.56
					PLT transfusion volume, units to 28 days [c]	(n = 20) 1 (0, 2)	(n = 21) 1 (1, 2)	Not estimable	No significant difference *p* = 0.82
					CRYO transfusion volume, units to 6 hours	(n = 20) 2 (2, 4)	(n = 21) 2 (0, 2)	Not estimable	*Favoured intervention* *p* = 0.03
					CRYO transfusion volume, units to 24 hours[c]	(n = 20) 2 (2, 4)	(n = 21) 2 (0, 2)	Not estimable	No significant difference *p* = 0.23
					CRYO transfusion volume, units to 28 days [c]	(n = 20) 2 (2, 4)	(n = 21) 2 (0, 2)	Not estimable	No significant difference *p* = 0.06

CI, confidence interval; CRYO, cryoprecipitate; FFP, fresh frozen plasma; IQR, interquartile range; PLT, platelets; RBC, red blood cells; RCT, randomised controlled trial; SR, systematic review; UK, United Kingdom

a. Where only one RCT is identified in a systematic review, the evidence has been considered as RCT evidence. Where the systematic review assesses Observational and cohort studies, the evidence has been considered as according to the study design features. The risk of bias of the included primary studies is based on the quality assessment reported by the systematic review authors.

b. Only applicable to Systematic reviews with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if P_{het} >0.1 and I^2 <25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25–50%; substantial heterogeneity I^2 >50%.

c. Data extracted from primary study.

Length of stay

A summary of the evidence reported in the identified systematic reviews relating to LOS (hospital and ICU) in patients with critical bleeding is presented in Table 4.55.

One systematic review (McQuilten 2018) reported the results of one RCT (Curry 2015) that contributed data relevant to this outcome in critically bleeding patients in a trauma setting.

Hospital

One RCT (Curry 2015) reported the median (IQR) duration of hospital LOS to be 31 days (29, 33) among 20 patients who received CRYO compared to 30 days (22, 38) among the 21 patients who did not receive CRYO. The difference was not statistically significant ($p = 0.66$).

Intensive care unit

One RCT (Curry 2015) reported the median (IQR) duration of ICU LOS to be 11 days (5, 17) among 20 patients who received CRYO compared to 18 days (16, 20) among the 21 patients who did not receive CRYO. The difference was not statistically significant ($p = 0.56$).

Table 4.55 Results for CRYO versus no CRYO: Patients with critical bleeding – Length of stay

Study ID Study design[a]	Sample size (no. of trials) included in analysis	Patient population	Setting (Location)	Comparison	Outcome	Results			
						CRYO Median (IQR)	No CRYO Median (IQR)	Risk estimate (95% CI)	*Statistical significance* *p*-value Heterogeneity[b]
Trauma setting									
McQuilten 2018 SR *Moderate quality*	n = 41 (1 RCT) Curry 2015	Patients ≥16 years actively bleeding and required activation of major haemorrhage protocol	Multiple trauma centres (UK)	CRYO vs standard therapy (6 U RBC vs 4 FFP)	In-patient LOS, days	31 (29, 33)	30 (22, 38)	Not estimable	No significant difference *p* = 0.66
					ICU LOS, days	11 (5, 17)	18 (16, 20)	Not estimable	No significant difference *p* = 0.56

CI, confidence interval; CRYO, cryoprecipitate; FFP, fresh frozen plasma; ICU, intensive care unit; IQR, interquartile range; LOS, length of stay; RBC, red blood cells; RCT, randomised controlled trial; SR, systematic review; UK, United Kingdom

a. Where only one RCT is identified in a systematic review, the evidence has been considered as RCT evidence. Where the systematic review assesses Observational and cohort studies, the evidence has been considered as according to the study design features. The risk of bias of the included primary studies is based on the quality assessment reported by the systematic review authors.

b. Only applicable to Systematic reviews with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if P_{het} >0.1 and I^2 <25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25–50%; substantial heterogeneity I^2 >50%.

4.7.3.3 Platelets

No studies identified.

4.7.3.4 Fibrinogen concentrate

Mortality

A summary of the evidence reported in the identified systematic reviews relating to mortality (latest timepoint) in patients with critical bleeding is presented in Table 4.56.

There does not seem to be clear significant survival benefits for critically bleeding patients administered FC, but none of the RCTs and several nonrandomised cohort studies were sufficiently powered to detect differences in mortality.

Among critically bleeding trauma patients, a meta-analysis of data from the included RCTs (see Figure 4.33) showed the mortality rate (latest timepoint) among those who received FC (26/144, 18.1%) to be comparable to those who did not (25/139, 18.0%) with a RR of 1.12 observed (95% CI 0.53, 2.35; $p = 0.77$; random effects; $I^2 = 45\%$). Statistical heterogeneity was moderate.

Data from the included cohort studies (see Figure 4.33) suggests a non-significant association with higher mortality among trauma patients who received FC (131/615, 21.3%) compared with those who did not (152/1130, 13.5%) with the RR of 1.39 observed (95% CI 0.91, 2.13; $p = 0.13$; random effects; $I^2 = 45\%$).

Among critically bleeding patients in the surgical setting, a meta-analysis of data from the included RCTs (see Figure 4.33) showed no significant difference in the rate of mortality (latest timepoint) between patients who received FC (4/177, 2.3%) compared to patients who did not (9/176, 5.1%) with a RR of 0.48 observed (95%CI 0.08, 2.83; $p = 0.42$; random effects; $I^2 = 40\%$), noting the event rate was low across both treatment groups and statistical heterogeneity was moderate.

Data from the included cohort studies (see Figure 4.33) also suggested a non-significant association with higher mortality in patients who received FC (18/280, 6.4%) compared with those who did not (35/898, 3.9%), with a RR of 1.58 observed (95% CI 0.65, 3.85; $p = 0.31$; random effects; $I^2 = 11\%$).

There were no deaths (up to 30 days) reported in the RCTs that examined the effect of FC on mortality in women with major postpartum haemorrhage (Collins 2017, Wikkelsø 2015).

Similarly, there were no deaths (up to seven days) reported in the RCT that assessed the effect of FC on mortality in paediatric patients with diffuse bleeding after CPB.

Figure 4.33 Forest plot of comparison: FC vs no FC (or varying concentration of), outcome: Mortality, all-cause (latest timepoint)

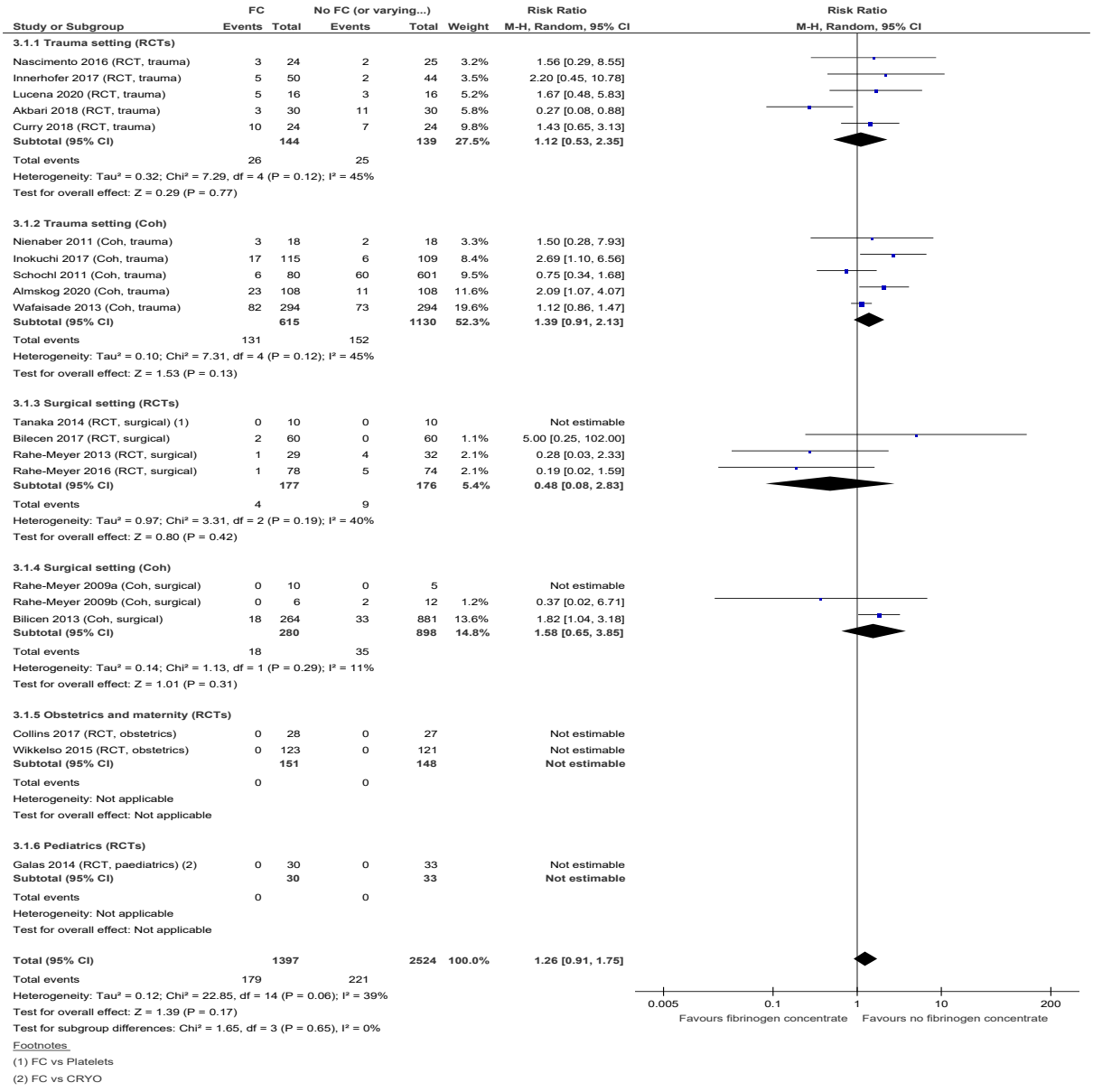


Table 4.56 Results for FC versus no FC: Patients with critical bleeding – Mortality

Study ID Study design[a]	Sample size (no. of trials) included in analysis	Patient population	Setting (Location)	Comparison	Outcome	Results			
						FC n/N (%)	No FC n/N (%)	Risk estimate (95% CI)	*Statistical significance* *p*-value Heterogeneity[b]
Trauma setting									
Fabes 2018 SR *High quality*	N = 97 (2 RCTs) Curry 2018 Nascimento 2016	Adult trauma patients (≥16 years, blunt or penetrating) with active bleeding and in/at risk of haemorrhagic shock.	Trauma, MC (UK, Canada)	FC vs placebo (normal saline)	Mortality, 28 days	13/48 (27) 10/24 (42) 3/24 (12.5)	9/49 (18) 7/24 (29) 2/25 (8)	RR 1.46 (0.71, 2.99) RR 1.43 (0.65, 3.13) RR 1.56 (0.29, 8.55)	No significant difference *p* = 0.30 No significant heterogeneity I^2 = 0%
	N = 94 (1 RCT) Innerhofer 2017	Adults with ISS > 15 and clinical signs or risk of substantial haemorrhage	Trauma (Austria)	FC vs FFP	Mortality, 30 days	5/50 (10)	2/44 (4.5)	OR 2.20 (0.45, 10.78)	NR
Stabler 2020 SR *Moderate quality*	N = 216 (1 Coh) Almskog 2020	Adult patients with major blunt trauma	Trauma (Sweden)	FC vs no FC	Mortality, 24 hours	7/108	1/108	NR	*p* = 0.494
	N = 896 (2 RCTs, 2 Coh) RCTs Akbari 2018 Lucena 2020 Observational Wafaisade 2013 Almskog 2020	Adult patients with major blunt trauma	Trauma (Iran, Brazil, Germany, Sweden)	FC vs no FC	Mortality, latest timepoint	NR 3/30 (10) 5/16 (31.2) 82/294 (27.9) 23/108 (21.3)	NR 11/30 (10) 3/16 (31.2) 73/294 (24.8) 11/108 (10.2)	NR NR NR NR NR	NR *p* = 0.029 *p* = 0.456 *p* = 0.40 *p* = 0.859
	N = 224 (1 Coh) Inokuchi 2017	Patients with pelvic fractures from blunt trauma requiring activation of MTP	Trauma (Japan)	FC + FFP vs FFP	Mortality, 28 days	17/115 (15)	6/109 (6)	NR	*Favours no FC* *p* <0.05
	N = 717 (2 Coh) Schöchl 2011 Nienaber 2011	Adult trauma patients	Trauma centre (Germany, Austria)	FC vs FFP	Mortality, overall in-hospital	6/80 (7.5) 3/18 (16.7)	60/601 (10) 2/18 (11.1)	NR	No significant difference p = 0.69 p = 0.50
Aubron 2014 SR *Critically low quality*	N = 588 (1 Coh) Wafaisade 2013	Trauma patients ≥ 16 years of age with ISS ≥ 16 + at least 1 RBC + TASH score ≥ 9	Trauma (MC, multicountry)	FC vs No FC	Mortality, 24 hours	41/294 (13.9) [c]	54/294 (18.4)[c]	RR 1.12 (0.86, 1.46)	No significant difference *p* = 0.15 [c]

Study ID Study design[a]	Sample size (no. of trials) included in analysis	Patient population	Setting (Location)	Comparison	Outcome	Results			
						FC n/N (%)	No FC n/N (%)	Risk estimate (95% CI)	*Statistical significance* *p*-value Heterogeneity[b]
Surgical setting									
Fabes 2018 SR *High*	N = 120 (1 RCT) Bilicen 2017	Adults >18 years undergoing elective high-risk cardiac surgery	Surgery (SC, Netherlands)	FC vs placebo (albumin in normal saline)	Mortality, 30 days	2/60 (3.3)	0/60	RR 5.00 (0.25, 102.00)	No significant difference *p* = 0.30
	N = 213 (2 RCTs) Rahe-Meyer 2013 Rahe-Meyer 2016	Aged ≥18 with elective aortic valve replacement surgery	Surgery (Germany)	FC vs 0.9% saline	Mortality, 46 days	2/107 (1.9) 1/29 (3.4) 1/78 (1.3)	9/106 (8.5) 4/32 (12.5) 5/74 (6.8)	RR 0.23 (0.05,1.01) 0.28 (0.03, 2.33) 0.19 (0.02, 1.59)	No significant difference *p* = 0.052 No significant heterogeneity I^2 = 0.0%
	N = 20 (1 RCT) Tanaka 2014	Patients undergoing elective CPB procedures	Surgery (US)	FC vs PLT	Mortality, 28 days	0/10	0/10	NR	NR
Lunde 2014 SR *Critically low*	N = 1075 (1 Coh) Bilicen 2013	Patients undergoing surgery	Surgery (Netherlands)	FC vs No FC	Mortality, 30 days[c]	18/264 (7)	33/811 (4)	RR 0.96 (0.48- 1.92)	No significant difference *p* = 0.07
Warmuth 2012 SR *Low*	N = 33 (2 Coh) Rahe-Meyer 2009a Rahe-Meyer 2009b	Adult patients undergoing surgery with major haemorrhage	Surgery (Germany)	FC vs standard infusion (FFP + PLT)	Mortality, 30 day	0/16 0/10 0/6	2/17 (11.8) 0/5 2/12 (17)	NR	NR
Paediatrics, surgical setting									
Fabes 2018 SR *High*	N = 63 (1 RCT) Galas 2014	Patients <15 years undergoing CPB, intraoperative bleeding and hypofibrinogenemia	Paediatric surgery (Brazil)	FC vs CRYO	Mortality, 7 days	0/30	0/33	NR	NR
Obstetrics and maternity setting									
Zaidi 2020 SR *Low*	N = 299 (2 RCTs) Collins 2017 Wikkelsø 2015	Women with major PPH	Obstetrics (Denmark and UK)	FC vs saline	Mortality, 30 days	0/151 0/28 0/123	0/148 0/27 0/121	NR	NR

CI, confidence interval; Coh, cohort; CPB, cardiopulmonary bypass; CRYO, cryoprecipitate; FC, fibrinogen concentrate; FFP, fresh frozen plasma; ISS, injury severity score; MC, multicentre; NR, not reported; OR, odds ratio; PLT, platelets; PPH, postpartum haemorrhage; RCT, randomised controlled trial; RR, relative risk; SC, single centre; SR, systematic review; TASH, trauma associated severe haemorrhage; UK, United Kingdom; US, United States

a. Where only one RCT is identified in a systematic review, the evidence has been considered as RCT evidence. Where the systematic review assesses Observational and cohort studies, the evidence has been considered as according to the study design features. The risk of bias of the included primary studies is based on the quality assessment reported by the systematic review authors.

b. Only applicable to Systematic reviews with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if P_{het} >0.1 and I^2 <25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25–50%; substantial heterogeneity I^2 >50%.
c. Data extracted from primary study

Morbidity

A summary of the evidence reported in the identified systematic reviews relating to morbidity (thromboembolic events, multiple organ failure, ARDs) in patients with critical bleeding is presented in Table 4.57 and Table 4.58.

Thromboembolic events

Among patients with critical bleeding in the trauma setting, a meta-analysis of data from four RCTs (see Figure 4.34) showed that the rate of thromboembolic events was comparable between patients who received FC (12/107, 11.2%) and those who did not (12/103, 11.7%). This corresponds to a RR of 0.90 (95% CI 0.42, 1.91; $p = 0.78$; random effects; $I^2 = 0\%$).

Data from the cohort studies (see Figure 4.34) also suggested no significant association with thromboembolic events among patients who received FC (53/511, 10.4%) compared with those who did not (49/517, 9.5%). This corresponds to a RR of 1.26 (95% CI 0.64, 2.49; $p = 0.51$; random effects; $I^2 = 58\%$), noting there was substantial statistical heterogeneity.

Among patients with critical bleeding in the surgical setting (see Figure 4.34) the rate of thromboembolic events was higher in patients who received FC (8/99, 8.0%) compared with those who did not (4/102, 3.9%) but the difference was not statistically significant (RR 2.03; 95% CI 0.63, 6.58; $p = 0.24$; random effects; $I^2 = 0\%$). It is noted that the evidence for thromboembolic events was limited by small patient numbers, with the included studies not sufficiently powered to detect important differences in event rates.

Among women with major postpartum haemorrhage (see Figure 4.34), the rate of thromboembolic events was comparable between patients who received FC (1/151, 0.7%) and those who did not (1/148, 0.7%); corresponding to a RR of 0.96 (95% CI 0.06, 14.65; $p = 0.98$; random effects; I^2 = not applicable). The RCTs were small and not sufficiently powered to detect this outcome with one study (Wikkelsø 2015) reporting no thromboembolic events.

In paediatric patients with diffuse bleeding after CPB, a lower rate of thromboembolic events was reported among those who received FC (2/30, 6.7%) compared with those who did not (5/33, 12.2%) but the difference was not statistically significant (RR 0.44; 95% CI 0.09, 2.10; $p = 0.3$; random effects; I^2 = not applicable).

Multiple organ failure

Three RCTs and three cohort studies were identified in the included systematic reviews that reported on the outcome of multiple organ failure (MOF) in the trauma setting.

A meta-analysis of data from the RCTs (see Figure 4.35) showed that the rate of MOF was lower among patients who received FC (29/97, 30%) compared with those who did not (38/98, 38.8%), but the difference did not reach statistical significance (RR 0.74; 95% CI 0.53, 1.03; $p = 0.07$; random effects; $I^2 = 0\%$).

Data from the cohort studies showed no significant difference in MOF among patients who received FC (184/420, 43.8%) compared with those who did not (156/420, 37.1%), corresponding to a RR of 0.70 (95%CI 0.21, 2.36; $p = 0.57$; random effects; $I^2 = 73\%$), noting the heterogeneity was substantial.

Acute respiratory distress syndrome

One RCT (Nascimento 2016) reported a lower event rate of ARDS among patients who received FC (0/21, 0%) compared with patients who did not receive FC (2/24, 8.3%), but the the sample size was small and therefore no further analysis was performed.

Figure 4.34 Forest plot of comparison: FC vs no FC (or varying administration of), outcome: Morbidity, thromboembolic events

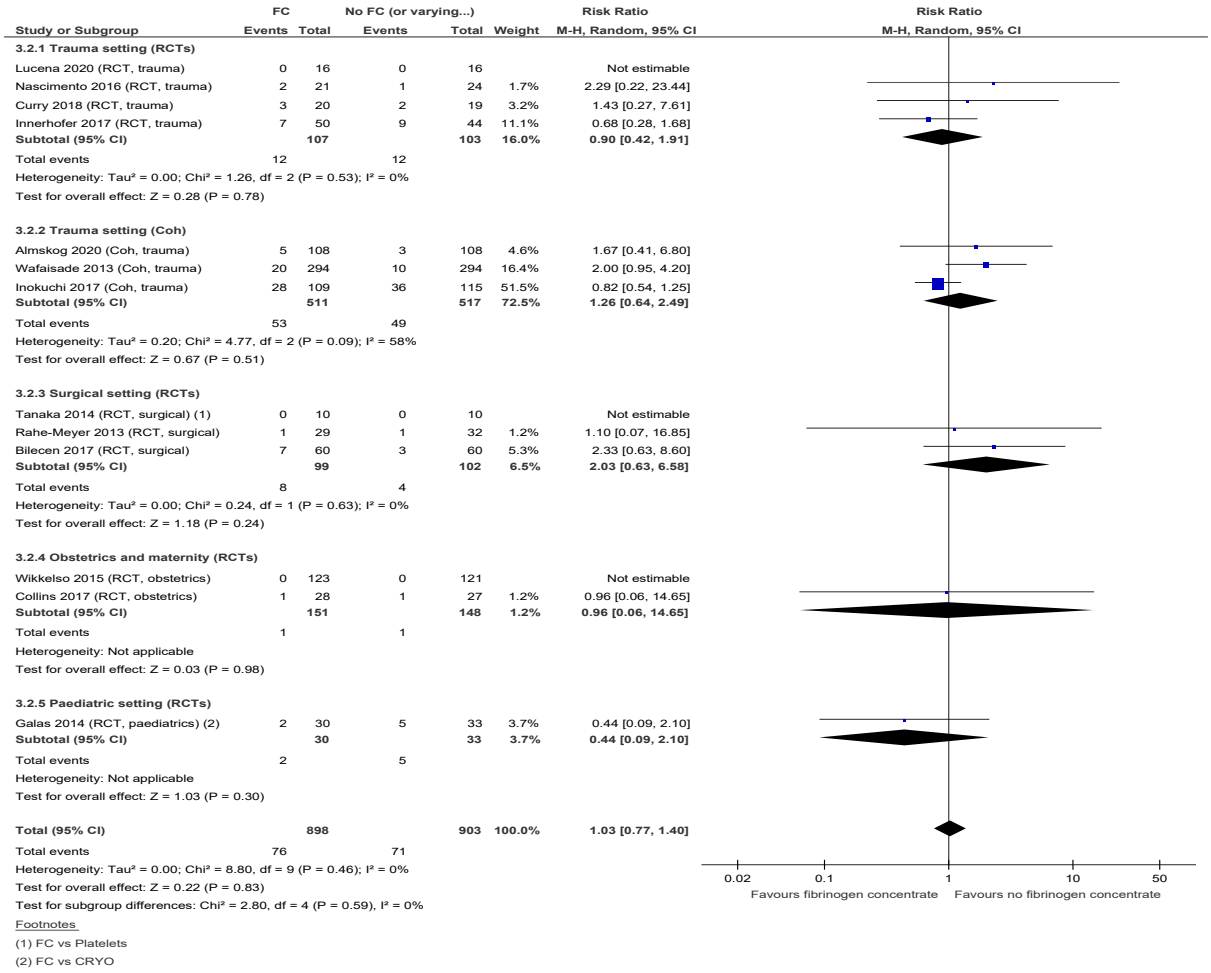


Figure 4.35 Forest plot of comparison: FC vs no FC (or varying administration of), outcome: Morbidity, multiple organ failure

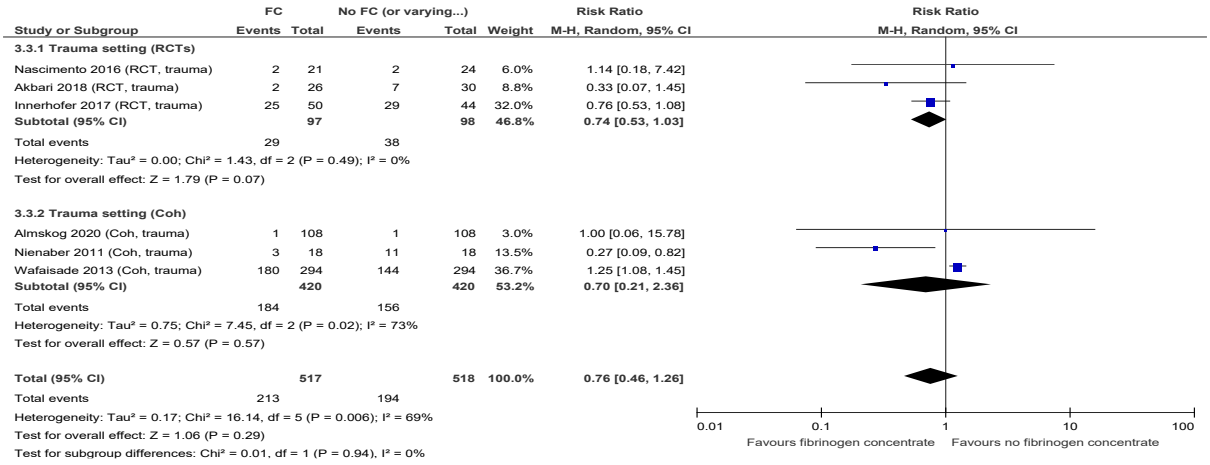


Table 4.57 Results for FC versus no FC: Patients with critical bleeding – Morbidity: critical complications

Study ID Study design[a]	Sample size (no. of trials) included in analysis	Patient population	Setting (Location)	Comparison	Outcome	Results			
						FC n/N (%)	No FC n/N (%)	Risk estimate (95% CI)	*Statistical significance* *p*-value Heterogeneity[b]
Trauma setting									
Fabes 2018 SR *High quality*	N = 39 (1 RCT) Curry 2018	Adults ≥16 years with active bleeding	Trauma centre (UK)	FC vs saline	TEs (arterial or venous)	3/20 (15)	2/19 (10.5)	NR	NR
	N = 94 (1 RCT) Innerhofer 2017	Adults with ISS >15 and clinical signs or risk of substantial haemorrhage	Trauma centre (Austria)	FC vs FFP		7/50 (14)	9/44 (20.5)	RR 0.63 (0.21, 1.87)	NR
McQuilten 2018 SR *Moderate quality*	N = 45 (1 RCT) Nascimento 2016	Patients at risk for significant haemorrhage	Trauma (Canada)	FC vs placebo (normal saline)	Pulmonary embolus	2/21 (9.5)	1/24 (4.2)	RR 2.3 (0.2, 23.4)	NR
					Symptomatic DVT	0	0	Not estimable	NR
					DVT on leg doppler	2/15 (13.3)	3/14 (21.4)	RR 0.62 (–0.1, 3.2)	NR
					Myocardial Infarction	0	0	Not estimable	NR
					Stroke	0	0	Not estimable	NR
					Acute kidney injury	3/21 (14.3)	2/24 (8.3)	RR 1.7 (–0.3, 9.3)	NR
					MOF	2/21 (9.5)	2/24 (8.3)	RR 1.1 (–0.2, 7.4)	NR
					Infection	5/21 (23.8)	8/24 (33.3)	RR 0.7 (–0.3, 1.8)	NR
Stabler 2020 SR *Moderate quality*	N = 836 (1 RCT, 2 Coh)	Adult patients with major blunt trauma	Trauma (Germany, Sweden)	FC vs no FC	TEs RCTs Lucena 2020 Observational Wafaisade 2013 Almskog 2020	 0/16 (0) 20/294 (6.8) 5/108 (4.6)	 0/16 (0) 10/294 (3.4) 3/108 (2.8)	 NR NR NR	 *p* = NR Favours no FC *p* = 0.06 *p* = 0.47
	N = 366 (2 RCT, 1 Coh)	Adult patients with major blunt trauma	Trauma centre (Iran, Sweden)	FC vs no FC	MOF RCTs Akbari 2018 Innerhofer 2017 Observational Almskog 2020	 2/26 (7.6) 25/50 (50) 1/108 (0.9)	 7/30 (23.3) 29/44 (66) 1/108 (0.9)	 NR NR NR	 p = 0.106 p = 0.15 *p* = 1.00

Study ID Study design[a]	Sample size (no. of trials) included in analysis	Patient population	Setting (Location)	Comparison	Outcome	Results			
						FC n/N (%)	No FC n/N (%)	Risk estimate (95% CI)	*Statistical significance* *p*-value Heterogeneity[b]
Aubron 2014 SR *Critically low quality*	N = 588 (1 Coh) Wafaisade 2013	Adult trauma patients with ISS >16 + at least 1 RBC + TASH score >9	Trauma (Germany)	FC vs No FC	MOF	180/294 (61.2)	144/294 (49)	NR	*Favours FC* *p* = 0.003
	N = 36 (1 Coh) Nienaber 2011	Adult trauma patients	Trauma (Germany, Austria)	FC vs FFP		3/18 (16.7)	11/18 (61)	NR	*Favours FC* *p* = 0.015
Mengoli 2017 SR *Low quality*	N = 36 (1 Coh) Nienaber 2011	Patients with severe trauma-related bleeding	Trauma (Germany, Austria)	FC vs FFP	Sepsis [c]	3/18 (16.7)	6/18 (33.3)	NR	No significant difference *p* = 0.443
Inokuchi 2017 Coh *Serious risk of bias*	N = 224 (1 Coh)	Patients with pelvic fractures from blunt trauma requiring activation of MTP	Trauma (SC, Japan)	FC (after revision of MTP) vs MTP (before revision)	Transarterial embolisation	28/109 (26)	36/115 (31)	NR	No significant difference *p* = 0.764
					Patients requiring external fixation	14/109 (13)	13/115 (11)	NR	No significant difference *p* = 0.838
					Patients requiring internal fixation	43/109 (39)	42/115 (36)	NR	No significant difference p = 0.681
					Patients requiring pelvic packing	2/109 (2)	3/115 (3)	NR	No significant difference p = 1.000
Surgical setting									
Fabes 2018 SR *High quality*	N = 120 (1 RCT) Bilecen 2017	Adults >18 undergoing elective high-risk cardiac surgery	Surgery (Netherlands)	FC vs placebo	TEs (arterial or venous)	7/60 (11.7)	3/60 (5)	RR 2.33 (0.63, 8.60)	NR
					Allergic AEs up to 30 days	0/60	0/60	RD 0.0 (-0.03, 0.03)	NR
	N = 61 (1 RCT) Rahe-Meyer 2013	Adults >18 with elective aortic valve replacement surgery	Surgery (Germany)	FC vs saline	TEs (arterial or venous)	1/29 (3.4)	2/32 (3.1)	NR	NR
					Allergic AEs up to 10 days	0/29	0/32	RD 0.0 (-0.06, 0.06)	NR

Study ID Study design[a]	Sample size (no. of trials) included in analysis	Patient population	Setting (Location)	Comparison	Outcome	Results			
						FC n/N (%)	No FC n/N (%)	Risk estimate (95% CI)	*Statistical significance* *p*-value Heterogeneity[b]
	N = 20 (1 RCT) Tanaka 2014	Patients undergoing elective cardiopulmonary bypass procedures	Surgery (US)	FC vs PLT	TEs (arterial or venous)	0/10	1/10 (10)	RR 0.33 (0.02, 7.32)	NR
					Post-operative atrial fibrillation [c]	0/6	1/12 (8%)	NR	NR
					Renal failure [c]	0/6	2/12 (17%)	NR	NR
					Major neurologic events [c]	0/6	2/12 (17%)	NR	NR
Paediatric, surgical setting									
Fabes 2018 SR *High*	N = 63 (1 RCT) Galas 2014	Patients <15 years undergoing CPB, intraoperative bleeding and hypofibrinogenemia	Paediatric surgery (Brazil)	FC vs CRYO	TEs (arterial or venous)	2/30 (6.7)	5/33 (12.2)	RR 0.44 (0.09, 2.10)	NR
Obstetrics and maternity setting									
Zaidi 2020 SR *Low*	N = 299 (2 RCTs) Collins 2017 Wikkelsø 2015	Women with major PPH	Obstetrics (Denmark, UK)	FC vs saline	Thrombosis up to 6 weeks	1/28 (3.6) 0/123	1/27 (3.7) 0/121	NR	NR

AEs, adverse events; CI, confidence interval; Coh, cohort; CPB, cardiopulmonary bypass; CRYO, cryoprecipitate; DVT, deep vein thrombosis; FC, fibrinogen concentrate; FFP, fresh frozen plasma; ISS, injury severity score; MOF, multiorgan failure; NR, not reported; PLT, platelets; PPH, postpartum haemorrhage; RBC, red blood cell; RCT, randomised controlled trial; RD, risk difference; RR, relative risk; SC, single centre; SR, systematic review; TASH, trauma associated severe haemorrhage; TEs, thromboembolic events; UK, United Kingdom; US, United States

a. Where only one RCT is identified in a systematic review, the evidence has been considered as RCT evidence. Where the systematic review assesses Observational and cohort studies, the evidence has been considered as according to the study design features. The risk of bias of the included primary studies is based on the quality assessment reported by the systematic review authors.

b. Only applicable to Systematic reviews with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if P_{het} >0.1 and I^2 <25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25–50%; substantial heterogeneity I^2 >50%.

c. Data extracted from primary study

d. Calculated post-hoc using RevMan 5.4

Table 4.58 Results for FC versus no FC: Patients with critical bleeding – Morbidity: ARDS

Study ID Study design[a]	Sample size (no. of trials) included in analysis	Patient population	Setting (Location)	Comparison	Outcome	Results			
						FC n/N (%)	No FC n/N (%)	Risk estimate (95% CI)	*Statistical significance* *p*-value Heterogeneity[b]
Trauma setting									
McQuilten 2018 SR *Moderate quality*	N = 45 (1 RCT) Nascimento 2016	Patients at risk for significant haemorrhage	Trauma, SC (Canada)	FC vs placebo (normal saline)	ARDS	0/21 (0)	2/24 (8.3)	NA	NR
Surgical setting – no identified studies reported on outcome of interest									
Paediatrics, surgical setting – no identified studies reported on outcome of interest									
Obstetrics and maternity setting – no identified studies reported on outcome of interest									

ARDS, acute respiratory distress syndrome; CI, confidence interval; FC, fibrinogen concentrate; NA, not applicable; NR, not reported; RCT, randomised controlled trial; SC, single centre; SR, systematic review

a. (16)Where only one RCT is identified in a systematic review, the evidence has been considered as RCT evidence. Where the systematic review assesses Observational and cohort studies, the evidence has been considered as according to the study design features. The risk of bias of the included primary studies is based on the quality assessment reported by the systematic review authors.

b. Only applicable to Systematic reviews with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if P_{het} >0.1 and I^2 <25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25–50%; substantial heterogeneity I^2 >50%.

Transfusion volumes

Red blood cells

A summary of the evidence reported in the identified systematic reviews relating to RBC transfusion volumes in patients with critical bleeding is presented in Table 4.59.

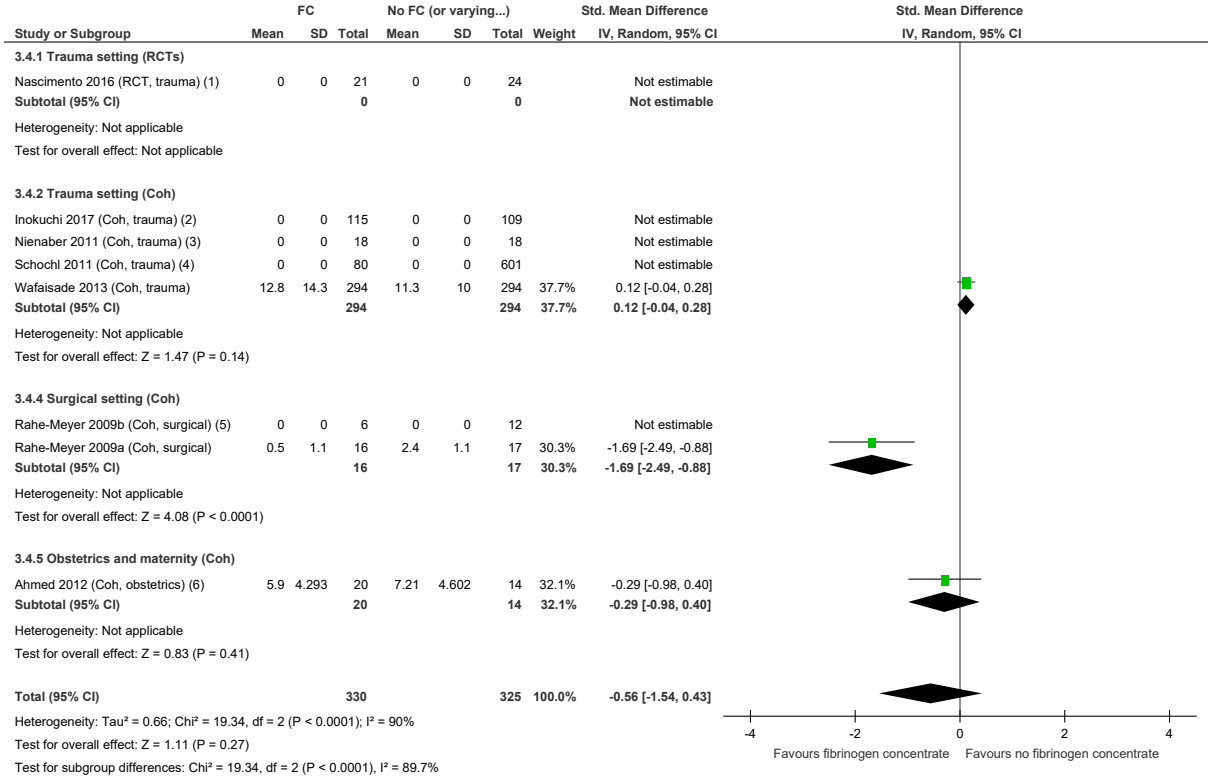
One RCT and four cohort studies reported the effect of FC on RBC transfusion volume in trauma patients with critical bleeding (see Figure 4.36). Data from Wafaisade 2013 suggested a higher volume of RBCs was required for patients who received FC (n=294) compared with those who did not (n=294), but the difference was not significant (SMD 0.12; 95% CI –0.04, 0.28; $p = 0.14$). The other four studies (one RCT, three cohort studies) reporting median [IQR] values suggested there was no significant difference in the volume of RBCs transfused (comparing patients who received FC compared with those who did not). Reported median values ranged from three to 12.8 units (FC) and three to 12.5 units (no FC).

Two cohort studies reported the effect of FC on RBC transfusion volume in the surgical setting (see Figure 4.36). Data from Rahe-Meyer 2009a suggested that patients who received FC had a lower volume of RBCs transfused compared with patients who did not receive FC (SMD –1.69, 95% CI –2.49, –0.88; $p < 0.0001$). The other study (Rahe-Meyer 2009b) reported that there were significantly fewer ($p < 0.05$) median units of RBCs transfused to 24 hours in patients who received FC compared with those who did not.

One cohort study (Ahmed 2012) reported the effect of FC on RBC transfusion volume among women with major postpartum haemorrhage. The study reported a lower volume of RBCs transfused among women who received FC compared with those who did not (SMD –0.29; 95% CI –0.98, 0.40; $p = 0.41$) but the difference was not significant.

There were no studies that reported on the outcome of RBC transfusion volume in the paediatric setting.

Figure 4.36 Forest plot of comparison: FC vs no FC (or varying administration of), outcome: RBC transfusion volume, units



Footnotes

(1) No significant difference for RBC transfusion volume (median [IQR]) to 24 hours between FC (3 [2, 5]) and no FC (3 [2, 4]).

(2) No significant difference for RBC transfusion volume (median [IQR]) up to 7 days between FC (10 [6, 20]) and no FC (10 [4, 22]).

(3) No significant difference for RBC transfusion volume (median [IQR]) to 24 hours between FC (3 [0, 5]) and no FC (12.5 [8, 20]).

(4) No difference for RBC transfusion volume (median [IQR]) between FC (5.5 [0, 9.5]) and no FC (6 [4, 11]). Timepoint and p-values not reported.

(5) Significantly fewer (p<0.05) median units of RBCs transfused to 24 hours in patients who recieved FC (1.0) compared with those who did not (4.1). IQR values not reported.

(6) SD calculated from SEM.

Table 4.59 Results for FC versus no FC: Patients with critical bleeding – RBC transfusion volume

Study ID Study design[a]	Sample size (no. of trials) included in analysis	Patient population	Setting (Location)	Comparison	Outcome	Results			
						FC Mean ± SD	No FC Mean ± SD	Risk estimate (95% CI)	*Statistical significance* *p*-value Heterogeneity[b]
Trauma setting									
McQuilten 2018 SR *Moderate quality*	N = 45 (1 RCT) Nascimento 2016	Patients at risk for significant haemorrhage	Trauma (SC, Canada)	FC vs placebo (normal saline)	RBC transfusion volume, units to 24 hours	Median (IQR) 3 (2, 5) (n = 21)	Median (IQR) 3 (2, 4) (n = 24)	Not estimable	No significant difference *p* = 0.41
Mengoli 2017 SR *Low quality*	N = 588 (1 Coh) Wafaisade 2013	Patients with severe trauma-related bleeding	Trauma (MC, multicountry)	FC vs No FC	RBC transfusion volume, units [c]	12.8 ± 14.3 (n = 294)	11.3 ± 10.0 (n = 294)	NR	No significant difference *p* = 0.20
Aubron 2014 SR *Critically low quality*	N = 717 (2 Coh) Schöchl 2011 Nienaber 2011	Adult trauma patients	Trauma (MC, Germany and Austria)	FC vs FFP Schöchl 2011	RBC transfusion volume, units [c]	Median (IQR) 5.5 (0, 9.5) (n = 80)	Median (IQR) 6 (4, 11) (n = 601)	NR	NR
				FC vs FFP Nienaber 2011	RBC transfusion volume, units to 24 hours [c]	Median (IQR) 3 (0, 5) (n = 18)	Median (IQR) 12.5 (8, 20) (n = 18)	NR	*p* < 0.005
Inokuchi 2017 Coh *Serious risk of bias*	N = 224 (1 Coh)	Patients with pelvic fractures from blunt trauma requiring activation of MTP	Trauma (SC, Japan)	FC (after revision of MTP) vs MTP (before revision)	RBC transfusion volume, units to 7 days	Median (IQR) 10 (6, 20) (n = 109)	Median (IQR) 10 (4, 22) (n = 115)	NR	No significant difference *p* = 0.958
Surgical setting									
Lunde 2014 SR *Critically low quality*	N = 18 (1 Coh) Rahe-Meyer 2009b	Patients undergoing cardiac surgery with bleeding requiring FC	Surgery (SC, Germany)	FC vs standard infusion (FFP + PLT)	RBC transfusion volume, units to 24 hours	1.0 (n = 6)	4.1 (n = 12)	NR	*Favoured FC* *p* < 0.05
					RBC transfusion volume, mL to 24 hours	449.2 (n = 6)	1092.5 (n = 12)	NR	*Favoured FC* *p* < 0.05
Warmuth 2012 SR *Low quality*	N = 33 (2 Coh)	Adult patients undergoing surgery with major haemorrhage	Surgery (Germany)	FC vs standard infusion (FFP + PLT)	RBC transfusion volume, units Rahe-Meyer 2009a Rahe-Meyer 2009b	(n = 16) 0.5 ± 1.1 1.0	(n = 17) 2.4 ± 1.1 4.1	NR	*Favoured FC* *p* < 0.05

Study ID Study design[a]	Sample size (no. of trials) included in analysis	Patient population	Setting (Location)	Comparison	Outcome	Results			
						FC Mean ± SD	No FC Mean ± SD	Risk estimate (95% CI)	*Statistical significance* *p*-value Heterogeneity[b]
Paediatrics, surgical setting – no identified studies reported on outcome of interest									
Obstetrics and maternity setting									
Lunde 2014 SR *Critically low*	N = 34 (1 Coh) Ahmed 2012	Women with PPH requiring FC	Obstetrics (Ireland)	FC vs CRYO	RBC transfusion volume, units [c]	(n = 20) 5.90 (SEM 0.96)	(n = 14) 7.21 (SEM 1.23)	NR	No significant difference *p* = 0.40

CI, confidence interval; Coh; cohort; CRYO, cryoprecipitate; FC, fibrinogen concentrate; FFP, fresh frozen plasma; IQR, interquartile range; MC, multicentre; MTP, massive transfusion protocol; NR, not reported; PLT, platelets; PPH, postpartum haemorrhage; RBC, red blood cells; RCT, randomised controlled trial; SC, singe centre; SD, standard deviation; SEM, standard error of mean; SR, systematic review

a. Where only one RCT is identified in a systematic review, the evidence has been considered as RCT evidence. Where the systematic review assesses observational and cohort studies, the evidence has been considered as according to the study design features. The risk of bias of the included primary studies is based on the quality assessment reported by the systematic review authors.

b. Only applicable to Systematic reviews with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if P_{het} >0.1 and I^2 <25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25–50%; substantial heterogeneity I^2 >50%.

c. Data extracted from primary study

d. Calculated post-hoc using RevMan 5.4

Other blood components

A summary of the evidence reported in the identified systematic reviews relating to transfusion volumes (other blood components) in patients with critical bleeding is presented in Table 4.60.

One RCT and four cohort studies reported on the effect of FC on the volume of FFP transfused in the trauma setting (see Figure 4.37).

Data from Wafaisade 2013 showed a statistically significant increase in the volume of FFP transfused among patients who received FC (n=294) compared with those who did not (n=294) (SMD 0.19, 95% CI 0.03, 0.35; $p = 0.02$).

Among the other four studies (one RCT, three cohort studies), two studies reporting median [IQR] values suggested there was no significant difference in the volume of FFP transfused between patients who received FC compared with those who did not (Inokuchi 2017, Nascimento 2016). One study found a decrease in the volume of FFP transfused among patients who received FC compared with those who did not (Nienaber 2011), and one study did not report comparative data for this outcome.

One RCT and three cohort studies reported on the effect of FC on the volume of PLT transfused in the trauma setting. Among the three studies that reported comparative data, two studies suggested there was no significant difference in the volume of PLT transfused between patients who received FC compared with those who did not (Nascimento 2016, Inokuchi 2017). One cohort study (Nienaber 2011) reported a significant reduction ($p < 0.005$) in platelet transfusion among patients who received FC compared with those who did not, but no further data was provided.

One RCT reported on the effect of FC on the volume of CRYO transfused in the trauma setting and found no significant difference between treatment groups ($p = 0.18$).

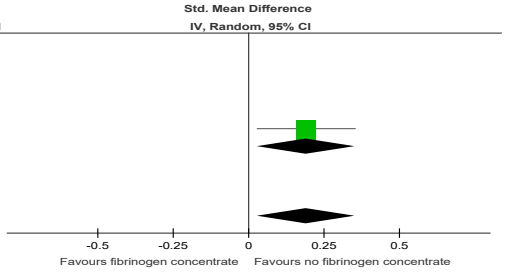
Among critically bleeding patients in the surgical setting, there was a significant reduction in the volume of FFP transfused among patients who received FC compared to those who did not (SMD -4.78, 95%CI -7.04, -2.51; $p < 0.0001$). Two cohort studies also found a statistically significant reduction in the volume of PLT and PCC transfused among patients who received FC compared to those who did not ($p < 0.05$) (see Figure 4.38).

Among women with major postpartum haemorrhage, no significant difference in the volume of FFP or PLT transfused between treatment groups was observed.

One systematic review (Zaidi 2020) reported the effect of FC on transfusion volume among women with major postpartum haemorrhage. The systematic review authors identified one RCT (Collins 2017) that they used to determine the total volume of blood transfused per patient at seven days (inclusive of RBCs, FFP, CRYO, FC, PLTS, PC) between women who received TEG guided early administration of FC compared with those who did not. An adjusted rate ratio 0.72 (95% CI 0.30, 1.70) was reported ($p = 0.45$).

Figure 4.37 Forest plot of comparison: FC vs no FC (or varying administration of), outcome: Transfusion volume, other blood components, FFP (trauma)

Study or Subgroup	FC Mean	FC SD	FC Total	No FC (or varying...) Mean	No FC (or varying...) SD	No FC (or varying...) Total	Weight	Std. Mean Difference IV, Random, 95% CI
3.5.1 FFP, units								
Inokuchi 2017 (Coh, trauma) (1)	0	0	115	0	0	109		Not estimable
Nascimento 2016 (RCT, trauma) (2)	0	0	21	0	0	24		Not estimable
Nienaber 2011 (Coh, trauma) (3)	0	0	18	0	0	18		Not estimable
Schochl 2011 (Coh, trauma) (4)	0	0	80	0	0	601		Not estimable
Wafaisade 2013 (Coh, trauma)	10.6	11.4	294	8.7	8.2	294	100.0%	0.19 [0.03, 0.35]
Subtotal (95% CI)			**528**			**1046**	**100.0%**	**0.19 [0.03, 0.35]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.31 (P = 0.02)								
Total (95% CI)			**528**			**1046**	**100.0%**	**0.19 [0.03, 0.35]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.31 (P = 0.02)								
Test for subgroup differences: Not applicable								



Footnotes

(1) No significant difference (median [IQR]) for FFP transfusion volume up to 7 days comparing FC (8 [6, 20]) with no FC (10 [6, 20]).

(2) No significant difference (p=0.72) in median [IQR] FFP transfusion volume up to 24 hours among patients who received FC (2.73 [2.4, 3.6]) compared with no FC 1.75 [1.4, 2.0]).

(3) FFP transfusion volume (units) up to 24 hours reported to be lower in patients who received FC (0) compared with no FC (10). IQR and p-value not reported.

(4) No data reported for the outcome of transfusion volume, other blood products.

Figure 4.38 Forest plot of comparison: FC vs no FC (or varying administration of), outcome: Transfusion volume, other blood components, FFP (surgical)

Study or Subgroup	FC Mean	FC SD	FC Total	No FC (or varying...) Mean	No FC (or varying...) SD	No FC (or varying...) Total	Weight	Std. Mean Difference IV, Random, 95% CI
3.6.3 FFP, units (Coh)								
Rahe-Meyer 2009a (Coh, surgical)	0.2	0.6	10	4.2	1.1	5	100.0%	-4.78 [-7.04, -2.51]
Rahe-Meyer 2009b (Coh, surgical)	1	0	6	9.1	0	12		Not estimable
Subtotal (95% CI)			**16**			**17**	**100.0%**	**-4.78 [-7.04, -2.51]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 4.14 (P < 0.0001)								
Total (95% CI)			**16**			**17**	**100.0%**	**-4.78 [-7.04, -2.51]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 4.14 (P < 0.0001)								
Test for subgroup differences: Not applicable								

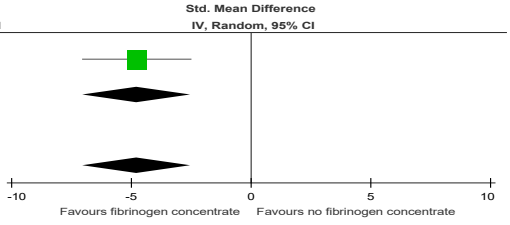


Table 4.60 Results for FC versus no FC: Patients with critical bleeding – Transfusion volume, other blood components

Study ID Study design[a]	Sample size (no. of trials) included in analysis	Patient population	Setting (Location)	Comparison	Outcome	Results			
						FC Mean ± SD	No FC Mean ± SD	Risk estimate (95% CI)	*Statistical significance* *p*-value Heterogeneity[b]
Trauma setting									
McQuilten 2018 SR *Moderate quality*	N = 45 (1 RCT) Nascimento 2016	Patients at risk for significant haemorrhage	Trauma (SC, Canada)	FC vs placebo (normal saline)	Plasma transfusion volume, units to 24 hours Median (IQR)	(n = 21) 2.73 (2.4, 3.6)	(n = 24) 1.75 (1.4, 2.0)	Not estimable	No significant difference *p* = 0.72
					PLT transfusion volume, units to 24 hours Median (IQR)	(n = 21) 2.81 (2.5, 3.6)	(n = 24) 2.32 (1.9, 2.7)	Not estimable	No significant difference *p* = 0.53
					CRYO transfusion volume, units to 24 hours Median (IQR)	(n = 21) 4.0 (3.1, 4.6)	(n = 24) 3.5 (2.9, 4.0)	Not estimable	No significant difference *p* = 0.18
Aubron 2014 SR *Critically low quality*	N = 717 (2 Coh) Schöchl 2011 Nienaber 2011	Adult trauma patients	Trauma (MC, Germany and Austria)	FC vs FFP Schöchl 2011	FFP transfusion volume, units[c]	(n = 80) NA	(n = 601) 3	NR	NR
					PLT transfusion volume, units[c]	(n = 80) 1 or 2	(n = 601) NR	NR	NR
					PCC transfusion volume, units[c]	(n = 80) 1200	(n = 601) NR	NR	NR
					FC transfusion volume, grams[c]	(n = 80) 6	(n = 601) NA	NR	NR
				FC vs FFP Nienaber 2011	FFP transfusion volume, units to 6 hours [c]	(n = 18) 0	(n = 18) 6	NR	NA
					FFP transfusion volume, units to 24 hours [c]	(n = 18) 0	(n = 18) 10	NR	NA
					PLT transfusion volume, units to 24 hours [c]	(n = 18) 0	(n = 18) 2	NR	p < 0.005
					FC transfusion volume, units to 6 hours [c]	(n = 18) 4	(n = 18) 0	NR	NA

Study ID Study design[a]	Sample size (no. of trials) included in analysis	Patient population	Setting (Location)	Comparison	Outcome	Results			
						FC Mean ± SD	No FC Mean ± SD	Risk estimate (95% CI)	*Statistical significance* *p*-value Heterogeneity[b]
					FC transfusion volume, units to 24 hours [c]	(n = 18) 4	(n = 18) 0	NR	NA
					PCC transfusion volume, units to 6 hours [c]	(n = 18) 1200	(n = 18) 0	NR	NA
					PCC transfusion volume, units to 24 hours [c]	(n = 18) 1200	(n = 18) 0	NR	NA
Mengoli 2017 SR *Low*	N = 588 (1 Coh) Wafaisade 2013	Adult trauma patients	Trauma (MC, multicountry)	FC vs No FC	FFP transfusion volume, units[c]	(n = 294) 10.6 ± 11.4	(n = 294) 8.7 ± 8.2	NR	No significant difference *p* = 0.07
Inokuchi 2017 Coh *Serious risk of bias*	N = 224 (1 Coh)	Patients with pelvic fractures from blunt trauma requiring activation of MTP	Trauma (SC, Japan)	FC (after revision of MTP) vs MTP (before revision)	FFP transfusion volume, units to 7 days	Median (IQR) (n = 109) 8 (6, 20)	(n = 115) 10 (6,20)	NR	No significant difference *p* = 0.685
					PLT transfusion volume, units to 7 days	Median (IQR) (n = 109) 20 (20, 20)	(n = 115) 20 (20, 37.5)	NR	No significant difference *p* = 0.251
Surgical setting									
Lunde 2014 SR *Critically low*	N = 18 (1 Coh) Rahe-Meyer 2009b	Patients undergoing cardiac surgery with bleeding requiring FC	Surgery (SC, Germany)	FC vs standard infusion (FFP + PLT)	FFP transfusion volume, units to 24 hours [c]	(n = 6) 1.0	(n = 12) 9.1	NR	Favoured FC *p* < 0.05
					PLT transfusion volume, units to 24 hours [c]	(n = 6) 0.5	(n = 12) 3.2	NR	Favoured FC *p* < 0.05
Warmuth 2012 SR *Low*	N = 33 (2 Coh)	Adult patients undergoing surgery with major haemorrhage	Surgery (Germany)	FC vs standard infusion (FFP + PLT)	FFP transfusion volume, units to 24 hours Rahe-Meyer 2009a	(n = 16) 0.2 ± 0.6	(n = 17) 4.2 ± 1.1	NR	*Favoured FC* *p* < 0.05
					PCC transfusion volume, units to 24 hours Rahe-Meyer 2009a Rahe-Meyer 2009b	(n = 16) 0.0 0.5	(n = 17) 1.6 ± 0.9 3.2	NR	*Favoured FC* *p* < 0.05

Study ID Study design[a]	Sample size (no. of trials) included in analysis	Patient population	Setting (Location)	Comparison	Outcome	Results			
						FC Mean ± SD	No FC Mean ± SD	Risk estimate (95% CI)	*Statistical significance* *p*-value Heterogeneity[b]
Paediatrics, surgical setting									
Obstetrics and maternity setting									
Zaidi 2020 SR *Low*	N = 299 (2 RCTs) Collins 2017	Women with major PPH	Obstetrics (UK)	FC vs saline	Total volume of blood transfused (inclusive of RBCs, FFP, CRYO, FC, PLTs, PCC)	(n=28) NR	(n=27) NR	NR	No significant difference *p* = 0.45
Lunde 2014 SR *Critically low*	N = 34 (1 Coh) Ahmed 2012	Patients with PPH requiring FC	Obstetrics (Ireland)	FC vs CRYO	FFP transfusion volume, units [c]	(n = 20) 3.15 (SEM 0.65)	(n =14) 4.07 (SEM 0.74)	NR	No significant difference *p* = 0.36
					PLT transfusion volume, pools [c]	(n = 20) 1.00 (SEM 0.30)	(n =14) 1.00 (SEM 0.36)	NR	No significant difference *p* = 0.99
					FC transfusion volume, units post treatment [c]	(n = 20) 3.34 SEM (0.22)	(n =14) 3.05 (SEM 0.19)	NR	No significant difference *p* = 0.35

CI, confidence interval; Coh, cohort; CRYO, cryoprecipitate; FC, fibrinogen concentrate; FFP, fresh frozen plasma; IQR, interquartile range; MC, multicentre; MTP, massive transfusion protocol; NR, not reported; PLT, platelets; PPH, postpartum haemorrhage; RCT, randomised controlled trial; SC, single centre; SD, standard deviation; SEM, standard error of mean; SR, systematic review; UK, United Kingdom

a. (16)Where only one RCT is identified in a systematic review, the evidence has been considered as RCT evidence. Where the systematic review assesses Observational and cohort studies, the evidence has been considered as according to the study design features. The risk of bias of the included primary studies is based on the quality assessment reported by the systematic review authors.

b. Only applicable to Systematic reviews with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if P_{het} >0.1 and I^2 <25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25–50%; substantial heterogeneity I^2 >50%.

c. Data extracted from primary study

d. Calculated post-hoc using RevMan 5.4

Length of stay

Hospital

A summary of the evidence reported in the identified systematic reviews relating to hospital LOS in patients with critical bleeding is presented in Table 4.61.

Four RCTs and three cohort studies reported the effect of FC on hospital LOS in the trauma setting (see Figure 4.39). Data were available for two studies (reported as mean [SD]), that showed FC has no significant impact on the duration of hospital stay comparing patients who received FC with those who did not (RR –1.30; 95% CI –6.76, 4.16; p = 0.64; random effects; I^2 = 69%), noting the heterogeneity was substantial. The remaining studies reported data as median (IQR) that also suggested there is no significant difference in-hospital LOS between patients who received FC and those who did not.

Among critically bleeding patients with postpartum haemorrhage, no significant difference was reported for hospital LOS between treatment groups.

Intensive care unit (ICU)

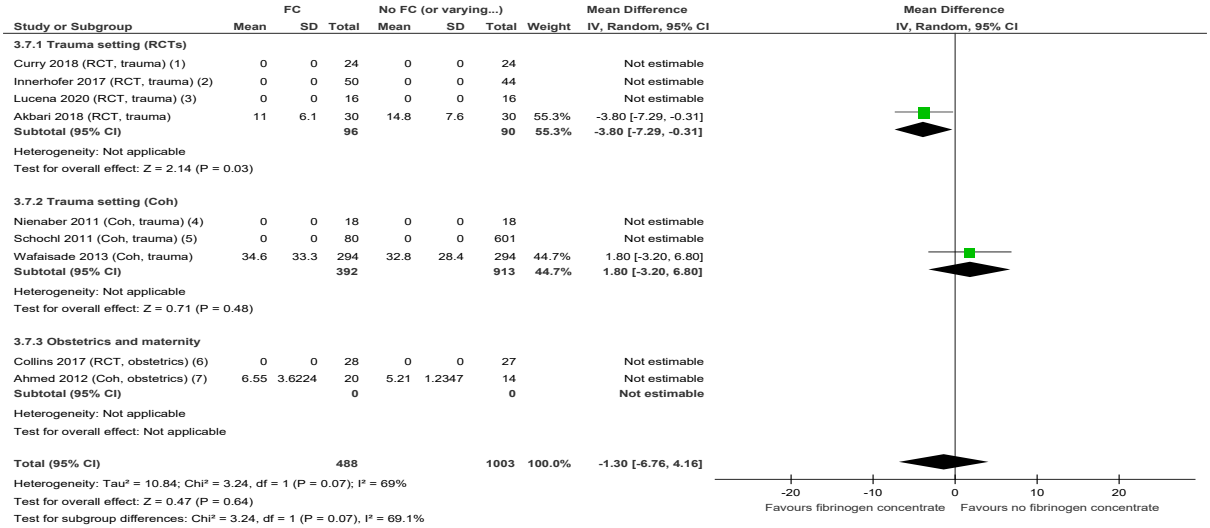
A summary of the evidence reported in the identified systematic reviews relating to ICU LOS in patients with critical bleeding is presented in Table 4.62.

Two RCTs and four cohort studies reported the effect of FC on ICU LOS (days) in the trauma setting (see Figure 4.40). Complete data were not available, but five of the six studies suggested that there is no significant difference in the duration of ICU stay for patients who received FC compared to those who did not. One RCT (Lucena 2020) suggested that the length of ICU stay among patients who received FC was lower (p = 0.021) than the length of ICU stay among patients who did not.

There was one cohort study in the surgical setting (Rahe-Meyer 2009b) that reported on ICU LOS (hours) which suggested FC is associated with a reduction in the length of ICU stay among patients who received FC compared with those who did not (MD – 3.27, 95% CI –4.82, –1.71; p < 0.0001; [hours converted to days]); however, the sample size is small and survivorship bias may have influenced the results.

Among women with major postpartum haemorrhage, one cohort study (Ahmed 2012) reported that there was no significant difference in the length of ICU stay between patients who received FC compared with those who did not (p = 0.95).

Figure 4.39 Forest plot of comparison: FC vs no FC (or varying administration of), outcome: Length of stay, hospital (days)



Footnotes

(1) No data reported for hospital LOS

(2) No difference (p=0.61) in median [IQR] reported for hospital LOS for patients who received FC (28 [18, 28]) compared with those who did not (27 [16, 28]).

(3) No difference (p=NR) in median [IQR] reported for hospital LOS for patients who received FC (28 [18, 28]) compared to those who did not (27 [16, 28]).

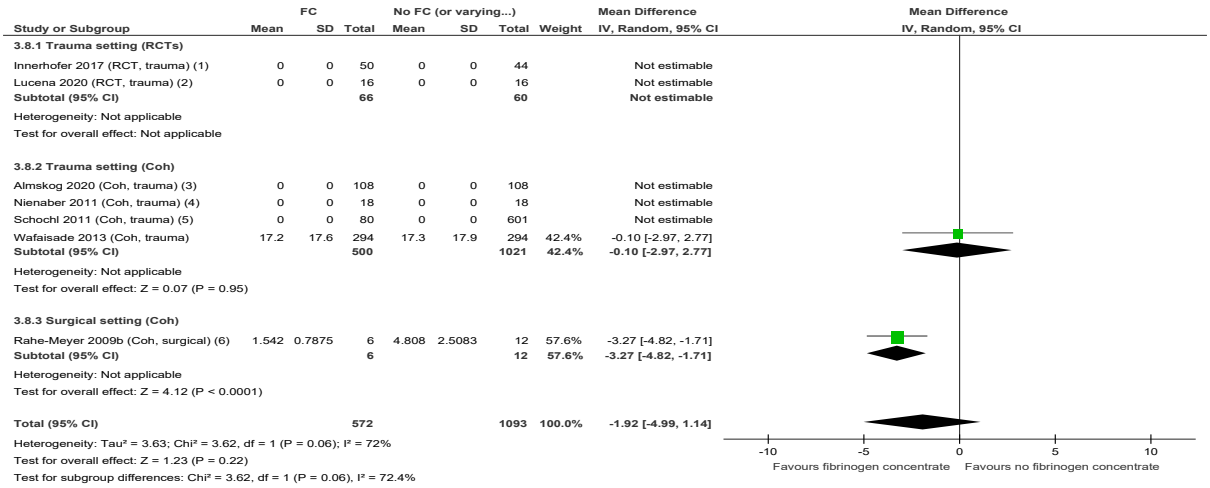
(4) No difference (p=0.48) in median [IQR]) reported for hospital LOS for patients who received FC (26 [19, 50]) compared with those who did not (38 [21, 48]).

(5) Hospital LOS (median [IQR]) was significantly lower (p=0.005) for patients who received FC (23 [14.5, 40.5]) compared with those who did not (32 [20, 49]).

(6) No difference (p=0.19) in median [IQR]) reported for hospital LOS for patients who received FC (3 [2, 5]) compared with those who did not (3 [2, 4]).

(7) SD calculated from SEM.

Figure 4.40 Forest plot of comparison: FC vs no FC (or varying administration of), outcome: Length of stay, ICU (days)



Footnotes

(1) No difference (p=0.65) in median [IQR] ICU LOS for patients who received FC (9 [4, 22]) compared with those who did not (10 [4.8, 23.3]).

(2) Median [IQR] ICU LOS was significant lower (p=0.021) for patients who received FC (8 [5.75, 10]) compared to those who did not (11 [8.5, 16]).

(3) No difference (p=0.97) in median [IQR] ICU LOS for patients who received FC (7 [1, 20]) compared to those who did not (5 [1, 16]).

(4) No difference (p=0.628) in median [IQR] ICU LOS for patients who received FC (19 [9, 33]) compared to those who did not (16 [13, 25]).

(5) No difference (p=0.95) in median [IQR] ICU LOS for patients who received FC (14.5 [8.5, 21]) compared to those who did not (14 [6, 23]).

(6) Data converted from hours to days

Table 4.61 Results for FC versus no FC: Patients with critical bleeding – Hospital LOS

Study ID Study design[a]	Sample size (no. of trials) included in analysis	Patient population	Setting (Location)	Comparison	Outcome	Results			
						FC Mean ± SD	No FC Mean ± SD	Risk estimate (95% CI)	*Statistical significance* *p*-value Heterogeneity[b]
Trauma setting									
Stabler 2020 SR *Moderate*	N = 822 (4 RCTs, 1 Coh)	Adult patients with major blunt trauma	Trauma (MC, multi-country)	FC vs no FC	Hospital LOS, days Curry 2018 Akbari 2018 Wafaisade 2013 (Coh) Lucena 2020 Innerhofer 2017	 NR 11 (6.1) 34.6 (33.3) Median (IQR) 12 (10-22) 28 (18-28)	 NR 14.8 (7.6) 32.8 (28.4) Median (IQR) 18.5 (17-21) 7 (16-28)	NR	 p = NR p = 0.045 p = NR p = 0.61 p = 0.96
Mengoli 2017 SR *Low*	N = 717 (2 Coh)	Patients with severe trauma-related bleeding	Trauma (MC, multi-country)	FC vs FFP	In-patient, days [c] Schöchl 2011 Nienaber 2011	Median (IQR) (n = 80) 23 (14.5-40.5) (n = 18) 26 (19-50)	Median (IQR) (n = 601) 32 (20-49) (n = 18) 38 (21-48)	NR	 p = 0.005 No significant difference p = 0.481
	N = 588 (1 Coh) Wafaisade 2013	Patients with severe trauma-related bleeding	Trauma (MC, multi-country)	FC vs No FC	In-patient, days [c]	(n = 294) 34.6 ± 33.3	(n = 294) 32.8 ± 28.4	NR	No significant difference *p* = 0.96
Surgical setting – no identified studies reported on outcome of interest									
Paediatrics, surgical setting – no identified studies reported on outcome of interest									
Obstetrics and maternity setting									
Zaidi 2020 SR *Low*	N = 55 (1 RCT) Collins 2017	Women with major PPH	Obstetrics (UK)	FC vs saline	Hospital LOS, days	Median (IQR) 3 (2, 5)	Median (IQR) 3 (2, 4)	NR	No significant difference *p* = 0.13
Lunde 2014 SR *Critically low*	N = 34 (1 Coh) Ahmed 2012	Patients with PPH requiring FC	Obstetrics (UK)	FC vs CRYO	In-patient, days [c]	(n = 20) 6.55 (SEM 0.81)	(n =14) 5.21 (SEM 0.33)	NR	No significant difference *p* = 0.19

CI, confidence interval; Coh, cohort; CRYO, cryoprecipitate; FC, fibrinogen concentrate; FFP, fresh frozen plasma; IQR, interquartile range; LOS, length of stay; MC, multicentre; NR, not reported; PPH, postpartum haemorrhage; RCT, randomised controlled trial; SEM, standard error of the mean; SD, standard deviation; SR, systematic review; UK, United Kingdom

a. Where only one RCT is identified in a systematic review, the evidence has been considered as RCT evidence. Where the systematic review assesses Observational and cohort studies, the evidence has been considered as according to the study design features. The risk of bias of the included primary studies is based on the quality assessment reported by the systematic review authors.

b. Only applicable to Systematic reviews with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if P_{het} >0.1 and I^2 <25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25–50%; substantial heterogeneity I^2 >50%.

c. Data extracted from primary study

Table 4.62 Results of FC versus no FC: Patients with critical bleeding – ICU LOS

Study ID Study design[a]	Sample size (no. of trials) included in analysis	Patient population	Setting (Location)	Comparison	Outcome	Results			
						FC Mean ± SD	No FC Mean ± SD	Risk estimate (95% CI)	*Statistical significance* *p*-value Heterogeneity[b]
Trauma setting									
Stabler 2020 SR *Moderate quality*	N = 930 (2 RCTs, 2 Coh)	Adult patients with major blunt trauma	Trauma (MC, multi-country)	FC vs no FC	ICU LOS, days Wafaisade 2013 (Coh) Lucena 2020 Innerhofer 2017 Almskog 2020 (Coh)	Mean (SD) 17.2 (17.6) Median (IQR) 8 (5.75-10) 9 (4-22) 7 (1-20)	Mean (SD) 17.3 (17.9) Median (IQR) 11 (8.5-16) 10 (4.8-23.3) 5 (1-16)	NR	 p = 0.68 p = 0.021 p = 0.65 p = 0.97
Mengoli 2017 SR *Low quality*	N = 717 (2 Coh) Schöchl 2011 Nienaber 2011	Patients with severe trauma-related bleeding	Trauma (MC, multi-country)	FC vs FFP	ICU LOS, days [c] Schöchl 2011 Nienaber 2011	Median (IQR) 14.5 (8.5-21) (n = 80) 19 (9-33) (n = 18)	14 (6-23) (n = 601) 16 (13-25) (n = 18)	NR	No significant difference p = 0.95 p = 0.628
	N = 588 (1 Coh) Wafaisade 2013	Patients with severe trauma-related bleeding	Trauma (MC, multi-country)	FC vs No FC No FC	ICU LOS, days [c]	(n = 294) 17.2 ± 17.6	(n = 294) 17.3 ± 17.9	NR	No significant difference p = 0.68
Surgical setting									
Lunde 2014 SR *Critically low quality*	N = 18 (1 Coh) Rahe-Meyer 2009b	Patients undergoing cardiac surgery with bleeding requiring FC	Surgery (SC, Germany)	FC vs standard infusion (FFP + PLT)	ICU LOS, hours [c]	(n = 6) 37 ± 18.9	(n =12) 115.4 ± 60.2	NR	p < 0.05
Paediatrics, surgical setting – no identified studies reported on outcome of interest									
Obstetrics and maternity setting									
Lunde 2014 SR *Critically low quality*	N = 34 (1 Coh) Ahmed 2012	Patients with PPH requiring FC	Obstetrics	FC vs CRYO	High dependency unit, hours [c]	(n =20) 33.6 (SEM 5.44)	(n = 14) 34.1 (SEM 4.32)	NR	No significant difference p = 0.95
Zaidi 2020 SR *Low quality*	N = 55 (1 RCT) Collins 2017	Women with major PPH	Obstetrics (MC, UK)	FC vs saline	Length of ICU stay, median days (IQR)	16 (12-25)	20.5 (10.5-28.5)	Difference 0.90	NR

CI, confidence interval; Coh, cohort; CRYO, cryoprecipitate; FC, fibrinogen concentrate; FFP, fresh frozen plasma; ICU, intensive care unit; IQR, interquartile range; LOS, length of stay; MC, multicentre; NR, not reported; PLT, platelets; PPH, postpartum haemorrhage; RCT, randomised controlled trial; SC, single centre; SD, standard deviation; SEM, standard error of mean; SR, systematic review; UK, United Kingdom

a. Where only one RCT is identified in a systematic review, the evidence has been considered as RCT evidence. Where the systematic review assesses Observational and cohort studies, the evidence has been considered as according to the study design features. The risk of bias of the included primary studies is based on the quality assessment reported by the systematic review authors.
b. Only applicable to Systematic reviews with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if P_{het} >0.1 and I^2 <25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25–50%; substantial heterogeneity I^2 >50%.
c. Data extracted from primary study

4.7.3.5 Prothrombin complex concentrate

Mortality

A summary of the evidence reported in the identified systematic reviews relating to mortality in patients with critical bleeding is presented in Table 4.63.

A meta-analysis of data from the four retrospective cohort studies identified in the systematic review by van den Brink 2020 (see Figure 4.41) revealed a significant reduction in mortality among patients who received PCC (72/364, 19.8%) compared with those who did not (159/557, 28.5%), representing an odds ratio (OR) of 0.64 (95%CI 0.46, 0.88; p = 0.007; random effects; I^2 = 0%).

Figure 4.41 Forest plot of comparison: PCC vs no PCC (or varying administration of), outcome: Mortality (trauma setting)

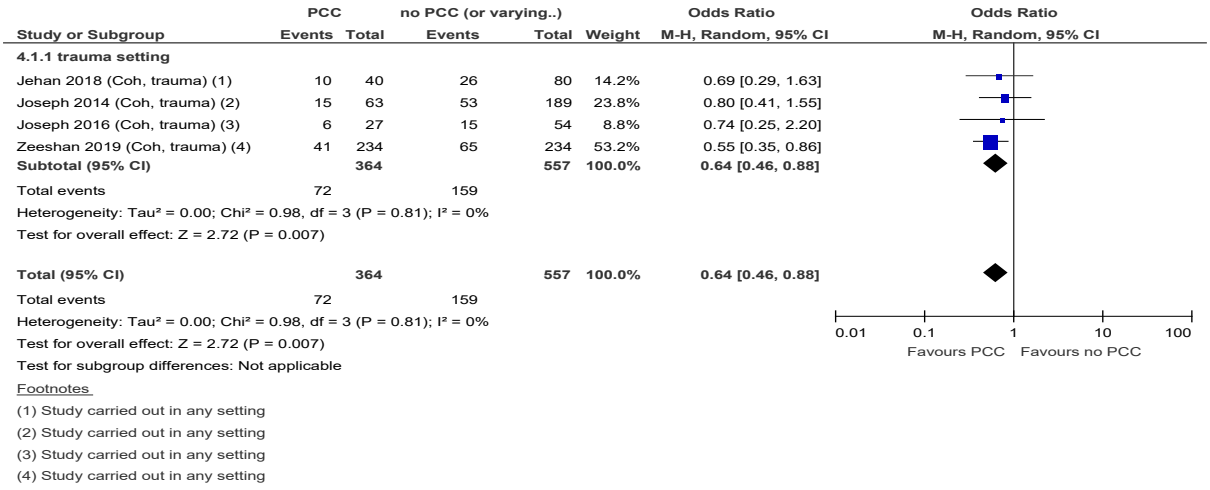


Table 4.63 Results for PCC versus no PCC: Patients with critical bleeding – Mortality, latest timepoint

Study ID Study design[a]	Sample size (no. of trials) included in analysis	Patient population	Setting (Location)	Comparison	Outcome	Results			
						PCC n/N (%)	No PCC n/N (%)	Risk estimate (95% CI)	*Statistical significance* *p*-value Heterogeneity[b]
Trauma setting									
van den Brink 2020 SR *Low quality*	N = 921 (4 Coh)	Patients ≥18 years with active bleeding	Trauma (US)	4 factor PCC + FFP vs FFP	Mortality, overall	72/364 (19.8)	159/557 (28.5)	OR 0.64 (0.46, 0.88)	*Favours PCC* *p* = 0.007 No heterogeneity I^2 = 0% (*p* = 0.81)
					Jehan 2018	10/40 (25)	26/80 (32.5)	0.69 (0.29, 1.63)	
					Zeeshan 2019	41/234 (17.5)	65/234 (27.8)	0.55 (0.35, 0.86)	
				3 factor PCC + FFP vs FFP	Joseph 2014	15/63 (23.8)	53/189 (28.0)	0.80 (0.41, 1.55)	
					Joseph 2016	6/27 (22.2)	15/54 (27.8)	0.74 (0.25, 2.20)	

CI, confidence interval; Coh, cohort; FFP, fresh frozen plasma; OR, odds ratio; PCC, prothrombin complex concentrate; SR, systematic review; US, United States

a. Where only one RCT is identified in a systematic review, the evidence has been considered as RCT evidence. Where the systematic review assesses Observational and cohort studies, the evidence has been considered as according to the study design features. The risk of bias of the included primary studies is based on the quality assessment reported by the systematic review authors.

b. Only applicable to Systematic reviews with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if P_{het} >0.1 and I^2 <25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25–50%; substantial heterogeneity I^2 >50%.

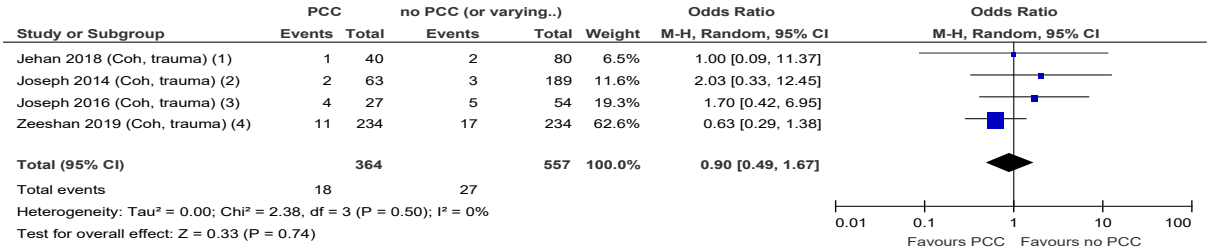
Morbidity

Thromboembolic events

A summary of the evidence reported in the identified systematic reviews relating to morbidity (critical complications) in patients with critical bleeding is presented in Table 4.64.

A meta-analysis of data from the four retrospective cohort studies identified in the systematic review by van den Brink 2020 (see Figure 4.42) showed no significant difference in thromboembolic events between treatment groups (OR 0.90, 95%CI 0.49, 1.67; $p = 0.74$; random effects; $I^2 = 0\%$).

Figure 4.42 Forest plot of comparison: PCC vs no PCC (or varying administration of), outcome: Morbidity, thromboembolic events (trauma setting)



Footnotes
(1) Study carried out in any setting
(2) Study carried out in any setting
(3) Study carried out in any setting
(4) Study carried out in any setting

Acute respiratory distress or other adverse outcomes

No comparative evidence for PCC versus no PCC was reported in the systematic review by van den Brink 2020 for the outcome of ARDS or other adverse outcomes.

The four retrospective cohort studies may have measured and reported these outcomes, but because retrospective studies were considered to be inappropriate for inclusion (see Section 3.1.4), we did not retrieve for inspection.

Table 4.64 Results for PCC versus no PCC: Patients with critical bleeding – Morbidity: critical complications

Study ID Study design[a]	Sample size (no. of trials) included in analysis	Patient population	Setting (Location)	Comparison	Outcome	Results			
						PCC n/N (%)	No PCC n/N (%)	Risk estimate (95% CI)	*Statistical significance* *p*-value Heterogeneity[b]
Trauma setting									
van den Brink 2020 SR *Low quality*	N = 921 (4 Coh)	Patients ≥ 18 years of age with active bleeding	Trauma (US)	4 factor PCC + FFP vs FFP	TEs Jehan 2018 Zeeshan 2019	18/364 (4.9) 1/40 (2.5) 2/63 (3.2)	27/557 (4.8) 2/80 (2.5) 3/189 (1.6)	OR 0.90 (0.49, 1.67) 1.00 (0.09, 11.37) 2.03 (0.33, 12.45)	No significant difference *p* = 0.74 No heterogeneity I^2 = 0% (p<0.50)
				3 factor PCC + FFP vs FFP	Joseph 2014 Joseph 2016	4/27 (14.8) 11/234 (4.7)	5/54 (9.3) 17/234 (7.3)	1.70 (0.42, 6.95) 0.63 (0.29, 1.38)	

CI, confidence interval; Coh, cohort study; FFP, fresh frozen plasma; PCC, prothrombin complex concentrate; OR, odds ratio; SR, systematic review; TEs, thromboembolic events; US, United States

a. Where only one RCT is identified in a systematic review, the evidence has been considered as RCT evidence. Where the systematic review assesses Observational and cohort studies, the evidence has been considered as according to the study design features. The risk of bias of the included primary studies is based on the quality assessment reported by the systematic review authors.

b. Only applicable to Systematic reviews with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if P_{het} >0.1 and I^2 <25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25–50%; substantial heterogeneity I^2 >50%.

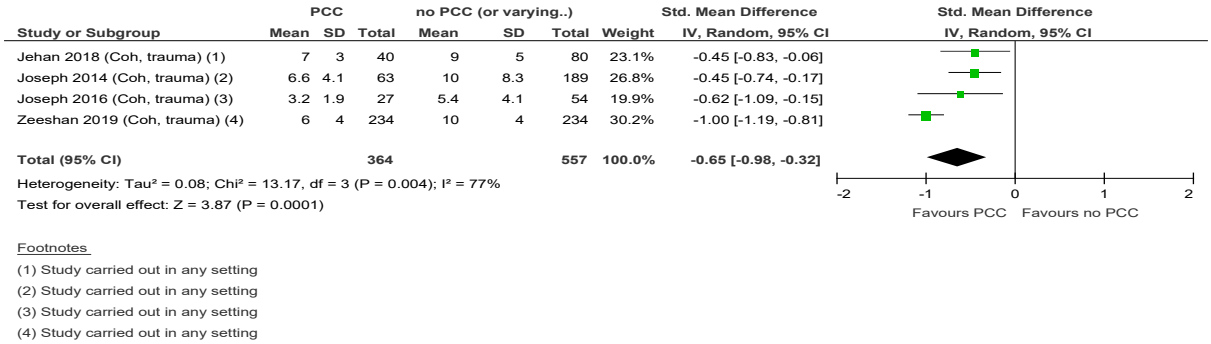
Transfusion volumes

Red blood cells

A summary of the evidence reported in the identified systematic reviews relating to RBC transfusion volumes in patients with critical bleeding is presented in Table 4.65.

A meta-analysis of data from the four retrospective cohort studies identified in the systematic review by van den Brink 2020 (see Figure 4.43) showed a significant reduction in the volume of RBCs transfused among patients that received PCC compared with those who did not (standardised MD –0.65; 95%CI –0.98, –0.32; p = 0.0001; random effects; I^2 = 77%), noting the heterogeneity was substantial.

Figure 4.43 Forest plot of comparison: PCC vs no PCC (or varying administration of), outcome: RBC transfusion volume, Units (trauma setting)



Footnotes
(1) Study carried out in any setting
(2) Study carried out in any setting
(3) Study carried out in any setting
(4) Study carried out in any setting

Other blood components

No comparative evidence for PCC versus no PCC was reported in the SR by van den Brink 2020 for the outcome of transfusion volume (other blood components).

The four retrospective cohort studies may have measured and reported these outcomes, but because retrospective studies were considered to be inappropriate for inclusion (see Section 3.1.4), we did not retrieve for inspection.

Table 4.65 Results for PCC versus no PCC: Patients with critical bleeding – RBC transfusion volume

Study ID Study design[a]	Sample size (no. of trials) included in analysis	Patient population	Setting (Location)	Comparison	Outcome	Results			
						PCC Mean ± SD	No PCC Mean ± SD	Risk estimate (95% CI)	*Statistical significance* *p*-value Heterogeneity[b]
Trauma setting									
van den Brink 2020 SR *Low quality*	N = 921 (4 Coh)	Patients ≥ 18 years of age with active bleeding	Trauma (US)	4 factor PCC + FFP vs FFP	RBC utilisation, units	N = 364	N = 557	MD –2.99 (–4.06, –1.91)	*Favours PCC* *p* <0.00001 Significant heterogeneity I^2 = 68% (p<0.0001)
					Jehan 2018	7±3 (n=40)	9±5 (n=80)	–2.00 (–2.44, –0.56)	
					Zeeshan 2019	6±4 (n=234)	10±4 (n=234)	–4.00 (–4.72, –3.28)	
				3 factor PCC + FFP vs FFP	Joseph 2014	6.6±4.1 (n=63)	10±8.3 (n=189)	–3.40 (–4.96, –1.84)	
					Joseph 2016	3.2±1.9 (n=27)	5.4±4.1 (n=54)	–2.20 (–3.51, –0.89)	

CI, confidence interval; Coh, cohort study; FFP, fresh frozen plasma; MD, mean difference; PCC, prothrombin complex concentrate; RBC, red blood cell; SD, standard deviation; SR, systematic review; US, United States

a. Where only one RCT is identified in a systematic review, the evidence has been considered as RCT evidence. Where the systematic review assesses Observational and cohort studies, the evidence has been considered as according to the study design features. The risk of bias of the included primary studies is based on the quality assessment reported by the systematic review authors.

b. Only applicable to systematic reviews with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if P_{het} >0.1 and I^2 <25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25–50%; substantial heterogeneity I^2 >50%.

Length of stay

No comparative evidence for PCC versus no PCC was reported in the systematic review by van den Brink 2020 regarding length of stay (hospital or ICU).

The four retrospective cohort studies may have measured and reported this outcome, but because retrospective studies were considered to be inappropriate for inclusion (see Section 3.1.4), we did not retrieve for inspection.

4.8 Antifibrinolytics (Question 7)

Question 7 – (interventional)

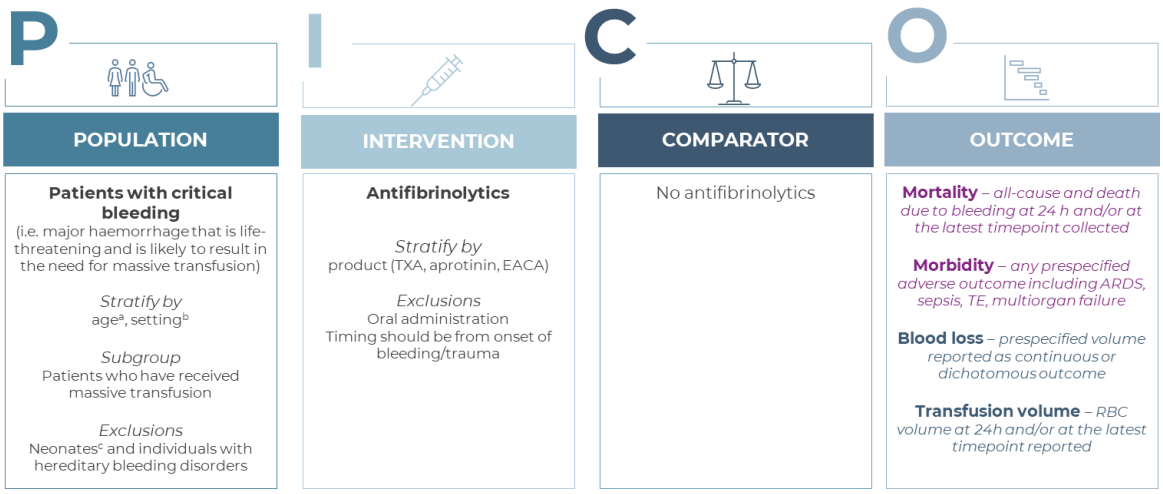
In patients with critical bleeding, what is the effect of antifibrinolytics on blood loss, RBC transfusion and patient outcomes?

4.8.1 Methods

Question 7 examined the effect of antifibrinolytics (TXA, aprotinin, or EACA) on patient outcomes compared to no antifibrinolytics in patients with critical bleeding (i.e. major haemorrhage that is life-threatening and is likely to result in the need for massive transfusion) as outlined in Figure 4.44.

This question focuses on intravenous delivery of TXA.[31] with the timing of delivery being at onset of bleeding (i.e. therapeutic use). Patients admitted in any setting were eligible for inclusion including trauma, obstetrics, and perioperative (e.g. cardiothoracic, liver transplant), with a subgroup analysis of evidence in patients who received a massive transfusion to be conducted where possible. Studies where bleeding status was not assessed at the time of enrolment were excluded (such as those that randomised patients prior to elective cardiac surgery). No age limits were applied, however studies in neonates (newborns up to 28 days) and studies in individuals with hereditary bleeding disorders were not eligible for inclusion.

Figure 4.44 PICO criteria: Question 7 – antifibrinolytics



ARDS, acute respiratory distress syndrome; EACA, epsilon-aminocaproic acid; RBC, red blood cell; TE, thromboembolic event; TXA, tranexamic acid

a. Adult (aged over 18 years), child (aged 2 to 12 years), adolescent (aged 13 to 18 years), infants (aged 1 to 23 months).

b. e.g. trauma, obstetric, perioperative (cardiothoracic, general surgery, gastrointestinal, liver transplant), paediatric, other.

c. Newborns up to 28 days following birth.

[31] EACA is not available or licensed for use in Australia and aprotinin, although on the Australian Register of Therapeutic Goods, is not being supplied or marketed by the Australian sponsor.

The selection of studies was conducted according to the screening criteria described in Section 3.3.

The initial 2018 search was limited to studies published after 2000, noting primary studies published prior to 2000 and identified within a systematic review were also eligible for inclusion. All RCTs were eligible for inclusion regardless of sample size, however, nonrandomised or observational cohort studies were required to enrol at least 500 participants.

Assuming all relevant primary studies had been identified in the included systematic reviews[32]; the screening of primary studies for this question was not conducted. This is because the latest literature search date of the most comprehensive identified systematic reviews was 2018 (El-Menyar 2018, Gayet-Ageron 2018, Shakur 2018).

The literature search was updated in August 2019[33] and again in September 2021[34] to identify any new studies meeting the eligibility criteria. In these updated searches the focus was the identification of systematic reviews (of RCTs or cohort studies). Based on the latest literature search date of the most comprehensive identified systematic reviews, the screening for additional primary studies was not conducted.

It was noted that there is an ongoing international multicentre, randomised, double-blind, placebo-controlled trial of prehospital treatment with TXA for severely injured patients at risk of acute traumatic coagulopathy. The study aims to determine the effects of early administration of TXA on survival and recovery of severely injured patients treated within advanced trauma systems.

4.8.2 Summary of evidence

4.8.2.1 Systematic reviews

Thirteen systematic reviews (57, 116-127) were included that assessed the effects of antifibrinolytics compared to no antifibrinolytics in patients with critical bleeding. The main characteristics and quality of these reviews and relevant outcomes assessed are summarised in Table 4.66. A matrix illustrating the overlap of studies included in each review is provided in Table 4.67.

Six systematic reviews were identified for inclusion (128-133), but were later excluded. One review (Bennett 2014) was in adults undergoing emergency or urgent surgery for upper gastrointestinal bleeding, but oral TXA was administered (in combination with IV TXA) and the studies were not reflective of current standard of care. Five reviews (Baskaran 2018, Gausden 2017, Wang 2017, Zhang 2017, Perel 2013) patients were undergoing orthopaedic trauma surgery but the patients within the included studies with not critically bleeding at study entry. A list of studies that met the PICO criteria for this question but are excluded or awaiting classification is provided in Appendix B (technical report, volume 2).

[32] Nine SRs identified (El-Menyar 2018, Gayet-Ageron 2018, Shakur 2018, Cannon 2017, Huebner 2017, Nishida 2017, Ausset 2015, Ker 2015, Bennett 2014)

[33] One additional SR (Chornenki 2019) and two observational studies identified (Marsden 2019, Myers 2019)

[34] Four additional SRs identified (Al-Jeabory 2021, Almuwallad 2021, Ageron 2020, Della Corte 2020,)

Table 4.66 Characteristics and quality of systematic review evidence: Antifibrinolytics versus no antifibrinolytics

Review ID *Review quality*	Study design *Risk of bias*	Population	Intervention	Comparator	Outcomes
Any setting					
Ageron 2020 (134) *Moderate*	MA of individual patient-level data from RCTs involving over 1000 patients (2 studies)	Patients with acute severe haemorrhage (trauma, PPH) N=28 333	Antifibrinolytics (TXA, aprotinin, EACA)	Placebo or SoC	Mortality* (due to bleeding) Morbidity* (TE) *By baseline risk of death
Chornenki 2019 (119) *High*	SR / MA of RCTs (22 studies) [a]	Patients with haemorrhage, TBI or non-specific trauma injury N= 49 538	TXA	Placebo or no TXA	Mortality Morbidity (TE)[b]
Gayet-Ageron 2018 (122) *High*	MA of individual patient-level data from RCTs involving over 1000 patients (2 studies) [c]	Patients with acute severe haemorrhage (traumatic, PPH, emergency) N=40 138	Antifibrinolytics (TXA, aprotinin, EACA)	Placebo or SoC	Mortality (due to bleeding) Morbidity (TE)
Trauma setting					
Al-Jeabory 2021 (116) *High*	SR / MA of RCTs and cohort studies (17 studies)	Adult patients following acute traumatic injury	TXA	Placebo or no TXA	Mortality Morbidity (TE, MOF) Transfusion volume
Almuwallad 2021 (117) *High*	SR / MA of RCTs and cohort studies (17 studies)	Adult patients following acute traumatic injury	TXA (prehospital administration)	Placebo or no TXA	Mortality Morbidity (TE)
El-Menyar 2018 (121) *Moderate*	SR / MA of RCTs (2 studies)	Traumatic injury patients presenting to the ED requiring blood transfusions N=769	TXA (prehospital administration)	Placebo or no TXA	Mortality Morbidity (TE)
Nishida 2017 (125) *Moderate*	SR of RCTs and observational studies (8 studies) [d]	Adult patients with trauma-induced coagulopathy N=23 117	TXA	Placebo or no TXA	Morbidity (TE)
Huebner 2017 (124) *Critically low*	Narrative review of RCTs and cohort studies (8 studies)	Haemorrhaging paediatric and adult trauma patients	TXA (early and prehospital administration)	Placebo	Mortality
Cannon 2017 (57) *Moderate*	SR of RCTs and cohort studies (4 studies)	Adult patients with severe traumatic haemorrhage	TXA	Placebo or no TXA	Mortality Transfusion rates Morbidity (TE)
Ker 2015 (127) *High*	SR of RCTs (3 studies) [d, e]	People of any age following acute traumatic injury N=20 528	Antifibrinolytics (aprotinin, TXA, EACA or AMBA)	Placebo or no TXA	Mortality Morbidity (TE) Transfusion volume

Review ID ***Review quality***	**Study design** ***Risk of bias***	**Population**	**Intervention**	**Comparator**	**Outcomes**
					Transfusion rate
Ausset 2015 (126) *Critically low*	Narrative review	Trauma management in the prehospital setting	TXA	Placebo or no TXA	Mortality Morbidity (TE)
Obstetrics and maternity					
Della-Corte 2020 (118) *Moderate*	SR / MA of RCTs	Women with PPH after vaginal birth N=20 212 (2 studies)	Antifibrinolytics (TXA, aprotinin, EACA)	Placebo or SoC	Mortality (all-cause, due to bleeding) Morbidity (MOF, hysterectomy, TE, shock) Transfusion volume
Shakur 2018 (123) *High*	SR / MA of RCTs (3 studies) [e]	Women with PPH after birth (vaginal or caesarean section) following a pregnancy of at least 24 weeks' gestation N=20 212	Antifibrinolytics (TXA, aprotinin, EACA)	Placebo or SoC	Mortality Morbidity (MOF, hysterectomy, TE, shock) Transfusion volume

AMBA, aminomethylbenzoic acid; EACA, epsilon-aminocaproic acid; ED, emergency department; MA, meta-analysis; RCT, randomised controlled trial; SoC, standard of care; SR, systematic review; TBI, traumatic brain injury; TE, thromboembolic events; TXA, tranexamic acid

a. 20 studies did not meet eligibility criteria for this review as they were in adults with non-surgical indications (including TBI) where TXA was used for prevention of bleeding as part of a planned protocol.

b. TE includes vascular occlusive events, myocardial infarct, deep vein thrombosis, pulmonary embolism, stroke, etc.

c. The authors conducted logistic regression models assessing overall treatment effect and effect of treatment delay. All models were controlled for systolic blood pressure (5 mm Hg interval) and age (10-yr intervals), which are strong risk factors for death due to bleeding.

d. One RCT (Yutthakasemsunt 2013) was in patients with traumatic brain injury and is not relevant to this review.

e. One RCT (McMichan 1982) examined the effect of aprotinin in patients with a combination of hypovolaemic shock and major fractures of the lower limb and or pelvis and diddd not provided any data relevant to this review..

f. One RCT (Sahaf 2014) did not contribute data for outcomes relevant to this review (only estimated blood loss) and is not further discussed.

Three reviews assessed patients in both the trauma and non-trauma setting (Ageron 2020, Chornenki 2019, Gayet-Ageron 2018). Two of these reviews (Ageron 2020, Gayet-Ageron 2018) were secondary analyses of individual patient data from two large RCTs conducted in trauma (CRASH-2) and obstetrics (WOMAN) patients. One review (Chornenki 2019) included studies that administered TXA for the prevention of bleeding as part of a planned surgical protocol or as planned medical management (including brain injury) therefore the reported analysis was not relevant for this review.

Eight reviews focused on patients in the trauma setting (Al-Jeabory 2021, Almuwallad 2021, El-Menyar 2018, Nishida 2017, Huebner 2017, Cannon 2017, Ker 2015, Ausset 2015). The most recent and comprehensive review was that by Al-Jeabory 2021, which included and reported data from three RCTs and 14 prospective or retrospective cohort studies. Two reviews (Almuwallad 2021, El-Menyar 2018) focused on the impact of prehospital TXA administered to bleeding trauma patients during air and/or ground medical transport, or upon arrival to designated trauma centres. One review (Heubner 2017) included paediatric patients (one cohort study found) and the remaining four reviews (Nishida

2017, Cannon 2017, Ker 2015, Ausset 2015) reported additional that was not covered in the reviews by Al-Jeabory 2021.

There were two systematic reviews (Della-Corte 2020, Shakur 2018) that focused on women in the obstetric setting, both of which reported data from two RCTs conducted in women after birth (vaginal or caesarean section) with postpartum haemorrhage.

Table 4.67 Overlap table of studies identified by included systematic reviews: Antifibrinolytics

		Trauma: RCTs			Trauma: Observational cohort studies																		Obstetric: RCTs	
	Study ID	Guyette 2020 (STAAMP)	Kakaei 2017	Shakur 2010 (CRASH-2) a	Rivas 2021	Adair 2020	Cole 2020	El-Menyar 2020	Myers 2019	Ng 2019	Neeki 2018	Howard 2017	Neeki 2017	Wafaisade 2016	Cole 2015	Harvin 2015	Eckert 2014	Lipsky 2014	Haren 2014	Morrison 2013 (MATTERs II)	Swendsen 2013	Valle 2014	Morrison 2012 (MATTERs I)	Arulkumaran 2017 (WOMAN)	Ducloy-Bouthers 2011
Review ID	Ageron 2020			✓																				✓	
	Chornenki 2019			✓																				✓	
	Gayet-Ageron 2018			✓																				✓	
	Al-Jeabory 2021	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓				✓			✓	✓	✓		
	Almuwallad 2021	✓						✓			✓			✓											
	El-Menyar 2018												✓	✓											
	Nishida 2017			✓										✓	✓	✓			✓		✓		✓		
	Huebner 2017			✓										✓	✓	✓	✓				✓	✓	✓		
	Cannon 2017			✓											✓					✓			✓		
	Ker 2015			✓																					
	Ausset 2015			✓											✓					✓		✓	✓		
	Della-Corte 2020																							✓	✓
	Shakur 2018																							✓	✓

4.8.2.2 Randomised controlled trials

There were five RCTs identified through the included systematic reviews that met the inclusion criteria and were considered relevant to this review.

The main characteristics and quality of these studies and the relevant outcomes assessed are summarised in Table 4.68

Table 4.68 Characteristics and quality of RCT evidence: Antifibrinolytics versus no antifibrinolytics

Study ID *Risk of bias*	Study design	Population	Intervention	Comparator	Outcomes
Trauma setting					
Guyette 2020 (STAAMP)	RCT, multicentre	Civilian trauma patients (US)	TXA 1 g TXA loading dose prehospital	No TXA	Mortality
Kakaei 2017	RCT, SC	Civilian trauma patients (Iran) *with potentially life-threatening injuries or evidence of critical illness, which could include respiratory and cardiac arrest.	TXA 1 g TXA loading dose over 10 minutes followed by infusion of 1g over 8 hours	No TXA	Mortality
Shakur 2010 (CRASH-2)[a]	RCT	Civilian trauma patients with wide range of injury severity scores *68% with blunt mechanism of injury, 18% with Glasgow Coma Score of ≤ 8.	TXA 1 g TXA loading dose over 10 minutes followed by infusion of 1g over 8 hours	No TXA	Mortality Morbidity (VE) Transfusion volume
Obstetric and maternity					
Ducloy-Bouthors 2011	RCT	Women with clinically diagnosed PPH after vaginal delivery of a baby or caesarean section.	TXA 4g TXA in 1 hour (loading dose) then 1g TXA per hour over 6 hours	No TXA	Mortality
Arulkumaran 2017 (WOMAN)	RCT	Women with clinically diagnosed PPH (estimated blood loss after vaginal birth > 500 mL, or > 1000 mL after caesarean section or estimated blood loss enough to compromise the haemodynamic status of the woman)	TXA 1 g TXA as soon as possible [b]	Placebo [c]	Mortality Morbidity (vascular events, MOF)

PPH, primary postpartum haemorrhage; RCT, randomised controlled trial; TE, thromboembolic events; TXA, tranexamic acid; VE, vascular events

a. The previous guidelines referred to the CRASH-2 study (published after the literature search date), and guidance regarding the use of TXA was provided (not a Recommendation or a PP). The CRASH-2 study population does not fully align with the population of interest for the Guidelines.

b. a second dose could be given if bleeding continued after 30 minutes or if bleeding stopped and restarted within 24 hours after first dose.

c. other interventions allowed included: oxytocin, ergometrine, misoprostol, prostaglandin, uterine massage, bladder catheter, manual removal of retained placenta (if necessary), intrauterine tamponade.

Trauma

Three RCTs (Guyette 2020, Kakaei 2017, CRASH-2) examined the effect of TXA in civilian trauma patients with critical bleeding. Participants were typically administered a loading dose of 1 g TXA as soon possible, followed by a maintenance dose of 1 g TXA over eight hours. Patients included in the largest study (CRASH-2, ~20 000 participants) were classified as being at risk of significant bleeding, in addition to being diagnosed with

major haemorrhage. Around 50% of enrolled patients did not receive a blood product. Participants had a wide range of injury severities, with most enrolled from over 40 low-income countries. The severity of diagnosis and life-threatening nature of haemorrhage for these patients was not specified and there was no systematic adverse event reporting, making it difficult to interpret results relating to thrombotic risk, and blood loss.

Obstetrics and maternity

Two RCTs (Ducloy-Bouthors 2011, WOMAN) assessed the safety and effectiveness of TXA given to women with primary postpartum haemorrhage (PPH). Participants were typically administered a loading dose of 1 g TXA as soon possible after randomisation, and if bleeding continued after 30 minutes, or stopped and restarted within 24 hours after first dose, a second dose could be given.

The largest study (WOMAN, ~20 000 participants) enrolled women aged 16 years or older with clinically diagnosed PPH (estimated blood loss after vaginal birth more than 500 mL, or more than 1000 mL after caesarean section or estimated blood loss enough to compromise the haemodynamic status of the woman). Approximately 50% of participants had an estimated volume of blood loss less than 1000 mL and 41% had no clinical signs of haemodynamic instability. Around 54% of women received a blood product. There was no systematic adverse event reporting, making it difficult to interpret results relating to thrombotic risk and blood loss.

4.8.2.3 Observational and cohort studies

There were 16 cohort studies identified through the included systematic reviews that met the inclusion criteria and were considered relevant to this review. The main characteristics and quality of these reviews and relevant outcomes assessed are summarised in Table 4.70.

No additional retrospective cohort studies were identified in the systematic review and handsearching process.

The included cohort studies examined the effect of TXA in patients with critical bleeding after trauma (mixed combat and civilian trauma, including one paediatric trauma). All had concerns of bias relating to confounding (related to the co-administration of other products) and patient selection bias. There was also concerns for reporting bias with a lack of detail regarding injury severity, and protocols for adverse event reporting.

Table 4.69 Characteristics and quality of cohort evidence: Antifibrinolytics versus no antifibrinolytics

Study ID	Study design	Population	Intervention	Comparator	Outcomes
Trauma setting					
Rivas 2021	Retrospective cohort	Civilian trauma patients	TXA	No TXA	Mortality
El-Menyar 2020	Retrospective cohort	Civilian trauma patients	TXA	No TXA	Mortality Morbidity (VE)
Myers 2019	Retrospective cohort	Civilian trauma patients	TXA	No TXA	Mortality Morbidity (VE) RBC transfusion volume

Study ID	Study design	Population	Intervention	Comparator	Outcomes
Neeki 2018	Prospective cohort, MC	Civilian trauma patients	TXA	No TXA *retrospective control group	Mortality
Howard 2017	Retrospective cohort	Combat trauma	TXA	No TXA	Mortality
Neeki 2017	Prospective cohort, MC	Civilian trauma patients, with blunt or penetrating trauma* *resulting in signs and symptoms of haemorrhagic shock	TXA, prehospital	No TXA *retrospective control group	Mortality Morbidity (VE)
Wafaisade 2016	Retrospective cohort	Trauma registry (German) Patients with potentially life-threatening injuries or evidence of critical illness, which could include respiratory and cardiac arrest	TXA, prehospital	No TXA *matched control	Mortality Morbidity (VE)
Cole 2014	Prospective cohort	Civilian trauma patients, (UK) ISS > 15 SBP < 90 mm Hg, poor response to fluids, suspected active haemorrhage)	TXA in trauma protocol	No TXA in trauma protocol	Mortality Morbidity (VE) RBC transfusion volume
Eckert 2014	Retrospective cohort	Paediatric trauma (Afghanistan) with predominantly penetrating injury (mean age 11 yrs)	TXA	No TXA	Mortality
Haren 2014	Retrospective cohort	Civilian trauma patients with hypercoagulable state defined as Greenfield's risk assessment profile ≥ 10	TXA	No TXA	Morbidity (VE)
Harvin 2014	Retrospective cohort	Civilian trauma patients with hyperfibrinolysis determined by rapid thromboelastography	TXA	No TXA	Mortality Morbidity (VE)
Lipsky 2014	Retrospective cohort	Civilian trauma patients	TXA	No TXA	Mortality
Valla 2014	Prospective cohort	Civilian trauma patients	TXA	No TXA	Mortality
Morrison 2013 (MATTERS II	Retrospective cohort	Combat trauma patients receiving ≥ 1 Unit RBCs	TXA, administered within 48hrs of injury	No TXA	Mortality RBC transfusion volume
Swendson 2013	Retrospective cohort	Civilian trauma patients within 3 hours of injury with an SBP < 90 mm Hg, activation of MTP at ED or taken directly to operating theatre matched to historical controls	TXA	No TXA	Mortality Morbidity (VE)

Study ID	Study design	Population	Intervention	Comparator	Outcomes
Morrison 2012 (MATTERS)	Retrospective cohort	Combat trauma patients receiving ≥ 1 unit RBC 30% injured by gunshot wound, 70% injured by explosion, 29% with Glasgow Coma Score of ≤ 8	TXA, administered within 48 hrs of injury	No TXA	Mortality Morbidity (VE) RBC transfusion volume

Abbreviations: hrs, hours; TXA, tranexamic acid; RBC, red blood cells, VE, vascular events

4.8.3 Results

4.8.3.1 Mortality

A summary of the evidence relating to mortality (all-cause) in patients with critical bleeding treated with TXA is presented in Table 4.70.

A meta-analysis of data from studies included in this review (see Figure 4.45), the RCT evidence showed a slight decrease in the risk of mortality (latest timepoint) among trauma patients who received TXA (1503/10 537, 14.26%) compared with those who did not 1660/10 550, 15.73%) (RR 0.91; 95% CI 0.85, 0.97; $p = 0.003$; random effect, $I^2 = 0\%$) *(GRADE: Low).*

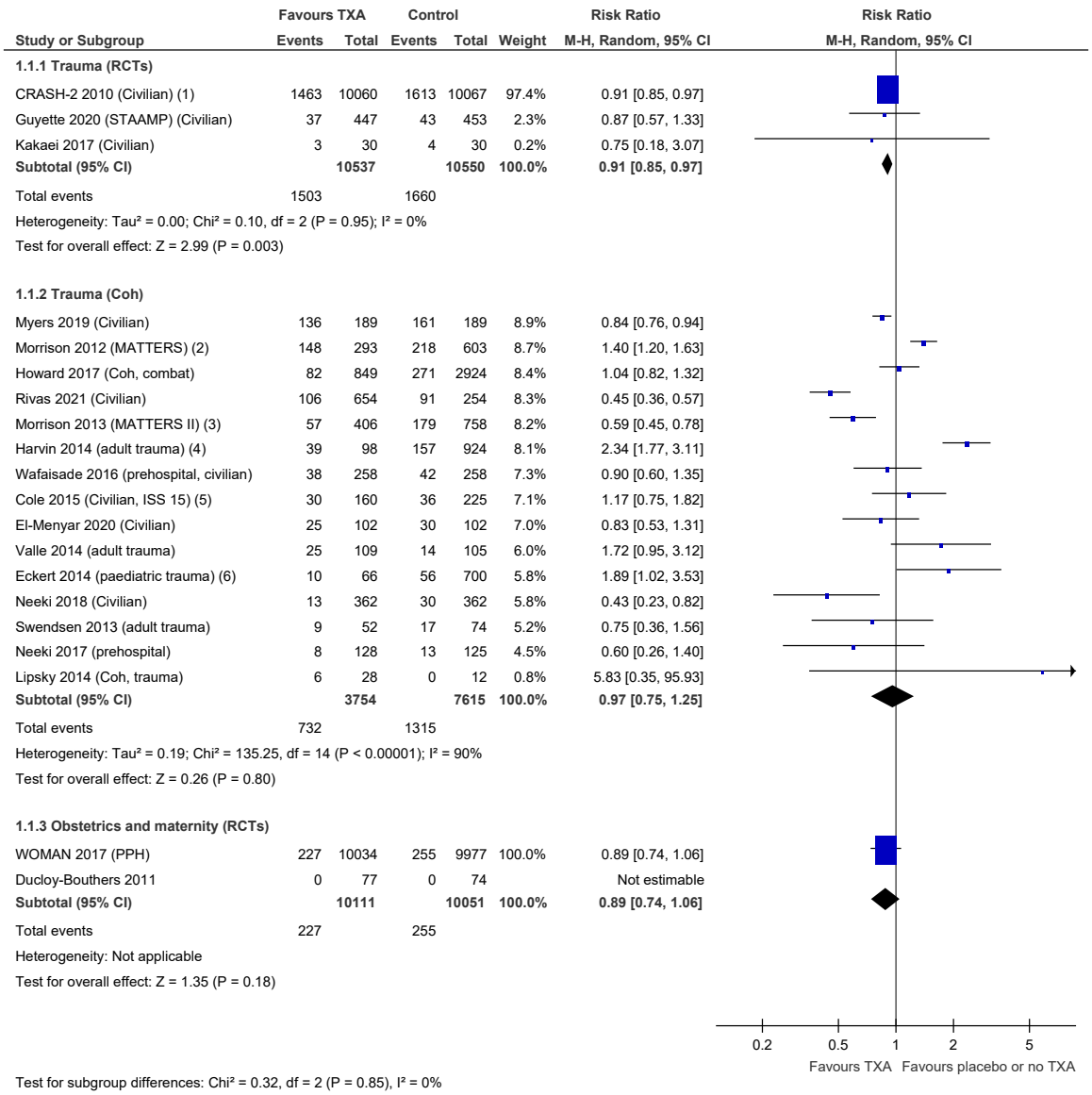
Among the cohort studies conducted in critically bleeding trauma patients, the risk of mortality was not different between groups (19.4% vs 17.26%, RR 0.97; 95%CI 0.75, 1.25; $p = 0.80$, $I^2 = 90\%$) *(GRADE: Very low).* Noting there was substantial heterogeneity with a wide variety of injury severity and bleeding risk in the included studies, with the results likely to differ after adjustments for confounders across all studies (e.g. patients who received TXA had higher incidence of shock, blood loss or transfusion requirements).

In a sensitivity analysis, the risk estimate for mortality moved towards favouring TXA (RR 0.83, 95% CI 0.64, 1.06; $p = 0.13$, $I^2 = 87\%$) when the three studies that reported adjustment for confounders (Harvin 2014, Eckert 2014, Cole 2015) were removed from the analysis.

In a subgroup analysis examining the effect of TXA among civilian trauma patients (see Figure 4.46), a total of 12 649 patients received TXA compared with 13 168 patients who did not; with the combined RCT and cohort evidence suggesting no difference between the group (15.2% vs 17.1%, RR 0.90; 95% CI 0.73, 1.11; $p = 0.32$, random effect, $I^2 = 87\%$). In a sensitivity analysis, the risk estimate for mortality suggested a slight decrease in the risk of mortality favouring TXA (RR 0.78, 95% CI 0.65, 0.93; $p = 0.006$, $I^2 = 76\%$) when the two studies that reported adjustment for confounders (Harvin 2014, Cole 2015) were removed from the analysis.

In the obstetric setting, the RCT evidence (see Figure 4.45) suggested the mortality rate among women who received TXA (227/10 111, 2.2%) was comparable to the mortality rate among women who did not receive TXA (255/10 051, 2.5%). This corresponded to a RR of 0.89 (95% CI 0.74, 1.06; $p = 0.18$; random effect, I^2 = not applicable) *(GRADE: Low).*

Figure 4.45 Forest plot of comparison: TXA vs no TXA, outcome: Mortality, latest timepoint



Test for subgroup differences: Chi² = 0.32, df = 2 (P = 0.85), I² = 0%

Footnotes

(1) within 4 weeks of injury

(2) within 48 hours of injury

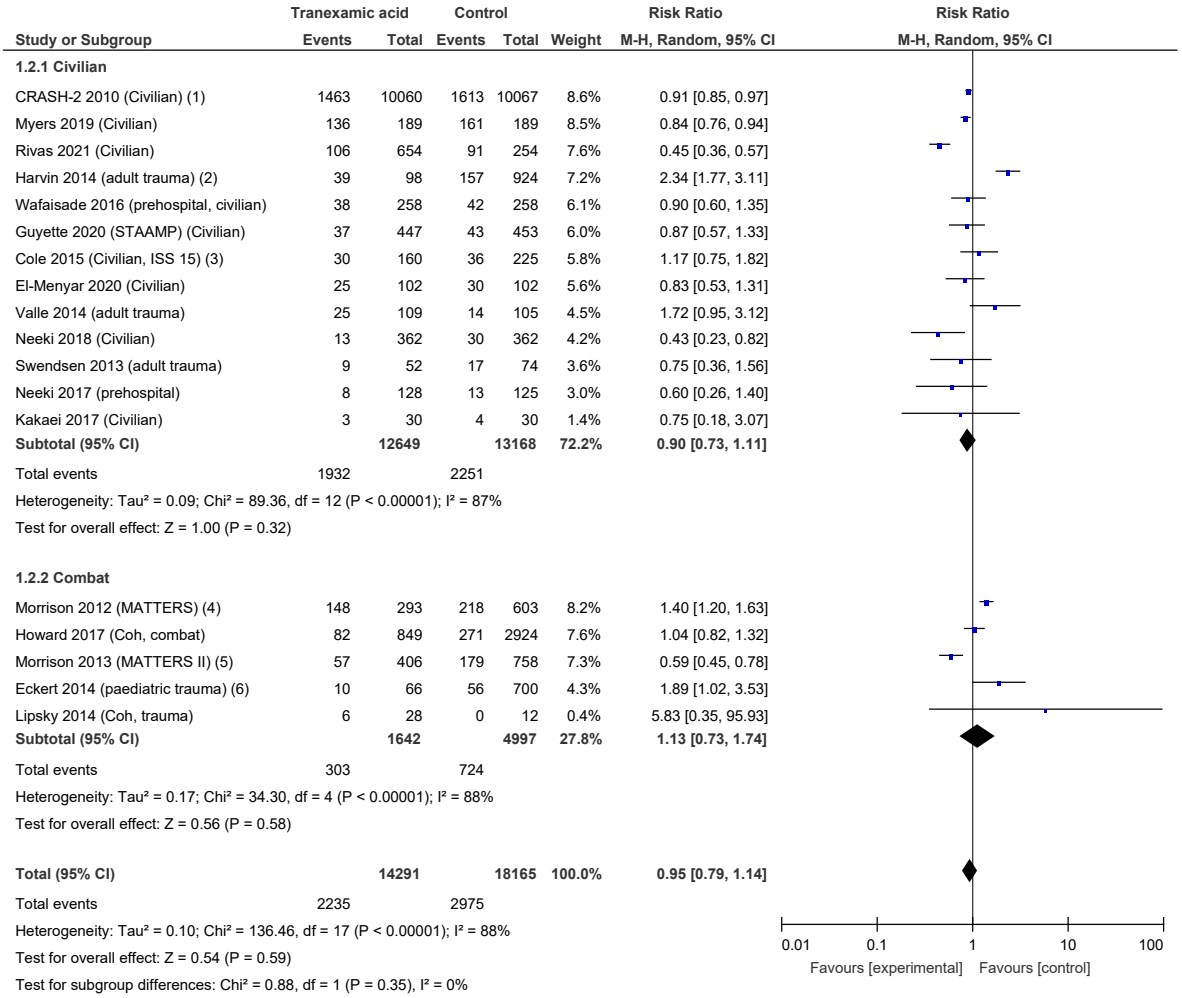
(3) within 48 hours of injury

(4) in-hospital; non significant effect after adjustment for confounders (OR 0.74, 95% CI 0.380, 1.403; p=0.801).

(5) not adjusted for confounders

(6) Effect favouring TXA observed after adjusting for confounders (OR 0.27; 95% CI 0.85, 0.89; p=0.03)

Figure 4.46 Forest plot of comparison: TXA vs no TXA, outcome: Mortality, latest timepoint (trauma only)



Footnotes

(1) within 4 weeks of injury

(2) in-hospital; non significant effect after adjustment for confounders (OR 0.74, 95% CI 0.380, 1.403; p=0.801).

(3) not adjusted for confounders

(4) within 48 hours of injury

(5) within 48 hours of injury

(6) Combat zone (Afghanistan).Effect favouring TXA observed after adjusting for confounders (OR 0.27; 95% CI 0.85, 0.89; p=0.03)

Table 4.70 Results for TXA versus no TXA: Patients with critical bleeding – Mortality

Study ID Study design[a]	Sample size (no. of trials) included in analysis	Patient population	Setting (Location)	Comparison	Outcome	Results			
						TXA n/N (%)	No TXA n/N (%)	Risk estimate (95% CI)	*Statistical significance* *p*-value Heterogeneity[b]
Any setting									
Ageron 2020 SR *Moderate quality*	N = 28 333 (2 RCTs) CRASH-2 WOMAN	CRASH-2 are trauma patients, the WOMAN trials are women with a postpartum haemorrhage	Trauma, Obstetrics (MC, over 40 countries)	TXA vs placebo	Mortality, all-cause	434/14270 (3) NR NR	597/14063 (4.3) NR NR	RR 0.72 (0.63, 0.81) NR NR	No significant difference *p* = 0.98
	N = 28 333 (2 RCTs) CRASH-2 WOMAN				Mortality, occlusive event	27/14270 (0.00) NR NR	40/14063 (0.00) NR NR	NR NR NR	No significant difference *p* = 0.058
Chornenki 2019 SR *High quality*	N = 44 077 (10 RCTs) ~~Chowdhary 1986~~ ~~Tsementzis 1990~~ ~~Roos 2000~~ ~~Hillman 2002~~ Shakur 2010 ~~Yutthakasemsunt 2013~~ ~~Sprigg 2014~~ Arulkumaran 2017 ~~Sprigg 2018~~ ~~Fakharian 2018~~	Patients requiring treatment or prevention of postpartum haemorrhage, intracranial haemorrhage, subarachnoid haemorrhage, traumatic brain injury or non-specific trauma injury	Trauma, Obstetrics and Medical (MC, over 40 countries)	TXA vs placebo or no TXA	Mortality, all-cause	2087/22014 (9.5) 5/65 (7.7) 22/50 (44.0) 76/229 (33.2) 27/254 (10.6) 1463/10060 (14.5) 12/120 (10.0) 3/16 (18.8) 227/9985 (2.3) 250/1161 (21.5) 2/74 (2.7)	2269/22063 (10.3) 8/64 (12.5) 14/50 (28.0) 75/233 (32.2) 32/251 (12.7) 1613/10067 (16.0) 17/118 (14.4) 2/8 (25.0) 256/10033 (2.6) 249/1164 (21.4) 3/75 (4)	 RR 0.62 (0.21, 1.78) RR 1.57 (0.91, 2.71) RR 1.03 (0.79, 1.34) RR 0.83 (0.52, 1.35) RR 0.91 (0.85, 0.97) RR 0.69 (0.35, 1.39) RR 0.75 (0.16, 3.62) RR 0.89 (0.75, 1.06) RR 1.01 (0.86, 1.18) RR 0.68 (0.12, 3.93)	*p = NR*
Gayet-Ageron 2018 SR *High quality*	N = 40 138 (2 RCTs) CRASH-2 2010 WOMAN 2017	Patients with acute severe bleeding	Trauma, Obstetrics (MC, over 40 countries)	TXA vs placebo	Mortality, all-cause	1690/20094 (8.4) 1463/10060 (14.5) 227/10034 (2.3)	1868/20044 (9.3) 1613/10067 (16.0) 255/9977 (2.6)	RR 0.90 (0.85, 0.96) [c] RR 0.91 (0.85, 0.97) RR 0.89 (0.74, 1.06)	*Favours TXA* *p* = 0.001 [c] No significant heterogeneity I^2 = 0% (*p* = 0.79)
	N = 40 138 (2 RCTs) CRASH-2 2010 WOMAN 2017				Mortality, due to bleeding	644/20094 (3.2) 489/10060 (4.9) 155/10034 (1.5)	764/20044 (3.8) 574/10067 (5.7) 190/9977 (1.9)	RR 0.84 (0.76, 0.93) [c] RR 0.85 (0.76, 0.96) RR 0.81 (0.66, 1.00)	*Favours TXA* *p* = 0.001 [c] No significant heterogeneity I^2 = 0% (*p* = 0.69)

Study ID Study design[a]	Sample size (no. of trials) included in analysis	Patient population	Setting (Location)	Comparison	Outcome	Results			
						TXA **n/N (%)**	**No TXA** **n/N (%)**	**Risk estimate (95% CI)**	***Statistical significance*** ***p*-value** **Heterogeneity[b]**
						Based on a logistic regression simulation model, the authors found improved survival (absence of death from bleeding) favouring immediate administration of TXA (OR 1.72, 95 CI 1.42, 2.10; $p < 0.0001$). Thereafter, survival benefits decreased until 150 to 200 minutes treatment delay (95 CI lower and estimates), at which point the models estimated no benefit (OR 1.00).			Nonlinear association with increasing delay [d] $p = 0.0109$
	N = 40 138 (2 RCTs) CRASH-2 2010 WOMAN 2017				Mortality, not due to bleeding	1046/20094 (5.2) 974/10060 (9.7) 72/10034 (0.7)	1104/20044 (5.5) 1039/10067 (10.3) 65/9977 (0.7)	RR 0.95 (0.87, 1.03) [c] RR 0.94 (0.86, 1.02) RR 1.10 (0.79, 1.54)	No significant difference $p = 0.18$ [c] No significant heterogeneity $I^2 = 0\%$ ($p = 0.36$)
	N = 40 138 (2 RCTs) CRASH-2 2010 WOMAN 2017				Mortality due to vascular occlusive event	43/20094 (0.2) 33/10060 (0.3) 10/10034 (0.1)	59/20044 (0.3) 48/10067 (0.5) 11/9977 (0.1)	OR 0·73 (0·49, 1·09) OR 0·69 (0·44, 1·08) OR 0·90 (0·38, 2·12)	No significant difference $p = 0.1204$ No significant heterogeneity I^2 = NR ($p = 0.5956$)
Trauma setting									
Al-Jeabory 2021 SR *High quality*	N = 29 115 (3 RCTs and 11 Coh) CRASH-2 2010 (RCT) Guyette 2020 (RCT) Kakaei 2017 (RCT) El-Menyar 2020 Howard 2017 Lipsky 2014 Morrison 2012 Myers 2019 Neeki 2017 Neeki 2018 Rivas 2021 Swendsen 2013 Valle 2014 Wafaisade 2016	Mix of combat and civil trauma patients Civil Civil Civil Civil Combat Combat Combat Civil Civil Civil Civil Civil Civil Civil	Multiple countries Multi-country USA Iran Qatar USA Israel Afghanistan USA USA USA USA USA USA Germany	TXA vs no TXA	In-hospital mortality	2099/13559 (15.5) 1463/10060 (14.5) 37/447 (8.3) 3/30 (10) 25/102 (24.5) 82/849 (9.7) 6/26 (23.1) 148/293 (50.5) 136/189 (72.0) 8/128 (6.3) 13/362 (3.6) 106/654 (16.2) 9/52 (17.3) 25/109 (22.9) 38/258 (14.7)	2547/15556 (16.4) 1613/10067 (16.0) 43/453 (9.5) 4/30 (13.3) 30/102 (29.4) 271/2924 (9.3) 0/10 218/603 (36.2) 161/189 (85.2) 13/125 (10.4) 30/362 (8.3) 91/254 (35.8) 17/74 (23.0) 14/105 (13.3) 42/258 (16.3)	OR 0.81 (0.62, 1.06) OR 0.89 (0.83, 0.96) OR 0.86 (0.54, 1.36) OR 0.72 (0.15, 3.54) OR 0.78 (0.42, 1.45) OR 1.05 (0.81, 1.36) OR 6.66 (0.34, 129.92) OR 1.80 (1.36, 2.39) OR 0.45 (0.27, 0.74) OR 0.57 (0.23, 1.44) OR 0.41 (0.21, 0.80) OR 0.35 (0.25, 0.48) OR 0.70 (0.29, 1.73) OR 1.93 (0.94, 3.97) OR 0.89 (0.55, 1.43)	No significant difference $p = 0.12$ Significant heterogeneity $I^2 = 83\%$ ($p < 0.00001$)
Almuwallad 2021 SR *High quality*	N = 2140 (1 RCT and 2 Coh) Guyette 2020 (RCT) Wafaisade 2016 Neeki 2018	Civilian trauma patients	Trauma, MC USA Germany USA	TXA vs no TXA	Mortality, 24 hour	38/1067 (3.6) 16/447 (3.6) 15/258 (5.8) 7/362 (1.9)	62/1073 (5.8) 17/453 (3.8) 32/258 (12.4) 13/362 (3.6)	OR 0.60 (0.37, 0.99) OR 0.95 (0.47, 1.91) OR 0.44 (0.23, 0.83) OR 0.53 (0.21, 1.34)	No significant difference $p = 0.05$ Minimal heterogeneity $I^2 = 27\%$ ($p = 0.26$)

Study ID Study design[a]	Sample size (no. of trials) included in analysis	Patient population	Setting (Location)	Comparison	Outcome	Results			
						TXA n/N (%)	No TXA n/N (%)	Risk estimate (95% CI)	*Statistical significance* *p*-value Heterogeneity[b]
	N = 2143 (1 RCT and 2 Coh) Guyette 2020 (RCT) Wafaisade 2016 Neeki 2018		Multiple countries USA Germany USA		Mortality, 28 to 30 days	85/1062 (8.0) 36/442 (8.1) 36/258 (14.0) 13/362 (4.0)	117/1072 (10.9) 45/452 (10) 42/258 (16.3) 30/362 (8.3)	OR 0.69 (0.47, 1.02) OR 0.80 (0.51, 1.27) OR 0.83 (0.51, 1.35) OR 0.41 (0.21, 0.80)	No significant difference *p* = 0.06 Minimal heterogeneity I^2 = 38% (*p* = 0.20)
El-Menyar 2018 SR *Moderate quality*	N = 769 (2 Coh) Wafaisade 2016 Neeki 2017	Adult patients with traumatic injury presenting to the emergency department requiring blood transfusion	Prehospital (air rescue)	TXA vs placebo	Mortality, 24 hour	20/386 (5.2)	41/383 (10.7)	OR 0.49 (0.27, 0.84) OR 0.47 (0.25, 0.89) OR 0.54 (0.18, 1.66)	*Favours TXA* *p* = NR No significant heterogeneity I^2 = 0% (*p* = 0.82)
	N = 769 (2 Coh) Wafaisade 2016 Neeki 2017				Mortality, 30-day	44/386 (11.4)	55/383 (14.4)	OR 0.86 (0.56, 1.32) OR 0.86 (0.53, 1.38) OR 0.87 (0.32, 2.32)	*No significant difference* *p* = NR No significant heterogeneity I^2 = 0% (*p* = 0.98)
Cannon 2017 SR *Moderate quality*	N = 21 666 (1 RCT, 2 Coh) CRASH-2 2010 (RCT) Cole 2015 Morrison 2013	Patients with severe trauma at risk of death from haemorrhage* *patients requiring blood transfusion and/or with an injury score greater than 25	Civilian and military trauma	TXA vs no TXA	Mortality, timing not specified	1550/10616 (14.6) 1463/10050 (14.6) 30/160 (18.8) 57/406 (14.0)	1828/11050 (16.5) 1613/10067 (16.0) 36/225 (16) 179/758 (23.6)	RR 0.70 (0.54, 1.20) OR 0.81 (0.54, 1.20) OR 0.89 (0.83, 0.96) OR 1.21 (0.71, 2.07) OR 0.53 (0.38, 0.73)	*No significant difference* *p* = 0.29 Substantial heterogeneity I^2 = 82% (*p* < 0.04) *p* = 0.004 *p* = 0.48 *p* = 0.0001
Myers 2019 Retrospective Coh *Serious risk of bias*	N = 378	Patients presenting to a level 1 trauma centre	Level 1 trauma centre (NR)	TXA within three hours of presentation vs No TXA	Survival	136/189 (72)	161/189 (85)	aOR 0.86 (0.23, 3.25)	*No significant difference* *p = 0.83*
Huebner 2017 SR *Critically low quality*	N = 6797 (2 Coh) Wafaisade 2016 Harvin 2015	Patients with trauma at risk of death from haemorrhage	Trauma Air Rescue (German) SC (US)	TXA vs placebo or no TXA	Mortality, all-cause within 24 hours	NR/NR (5.8) NR/98 (34)	NR/NR (12.8) NR/924 (10)	NR aOR 1.92 (1.05, 3.25)	*Favours TXA, p* = 0.01 *Favours placebo, p* = 0.035
	N = 896 (1 Coh) MATTERs 2012		Military trauma (US)		Mortality, within 48 hours	NR/NR (NR)	NR/NR (NR)	RD 6.6 (NR)	*Favours TXA, p* = 0.004
	N = 7693 (3 Coh)		Trauma		Mortality, In-hospital *MT subgroup*				

Study ID Study design[a]	Sample size (no. of trials) included in analysis	Patient population	Setting (Location)	Comparison	Outcome	Results			
						TXA n/N (%)	No TXA n/N (%)	Risk estimate (95% CI)	*Statistical significance* *p*-value Heterogeneity[b]
	MATTERs 2012 Wafaisade 2016 Harvin 2015		Military (US) Air Rescue (German) SC (US)			NR/NR (NR) NR/NR (14.4) NR/NR (14.7) NR/98 (40)	NR/NR (NR) NR/NR (28.1) NR/NR (16.3) NR/924 (17)	RD 6.5 (NR) RD 13.7 (NR) RR 0.49 (NR) NR aOR 0.74 (0.38, 1.40)	*Favours TXA*, *p* = 0.03 *Favours TXA*, *p* = 0.04 *Favours TXA*, *p* = NR *Favours TXA*, *p* = NR
	N = NR (4 Coh) Eckart 2014 Valle 2014 Swendsen 2013 Cole 2015 *(patients in shock)*		Trauma (Afghanistan) (UK) (US) (US)		Mortality, timing not specified Swendsen 2013 re-analysis (N = NR)	 NR/NR (15) NR/NR (27) NR/NR (5.8) NR/NR (4.3) NR/NR (NR)	 NR/NR (9) NR/NR (17) NR/NR (17.6) NR/NR (19.1) NR/NR (NR)	 aOR 0.27 (0.85, 0.89) NR NR NR OR 0.16 (0.03, 0.86)	 *Favours TXA*, *p* = 0.03 *Favours placebo*, *p* = 0.024[f] *Favours TXA*, *p* = 0.05 *Favours TXA*, *p* = 0.03 *Favours TXA*, *p* 0.03[g]
	N = 20 211 (1 RCT) CRASH-2 2010		Adult trauma MC (over 40 countries)		Mortality, within 4 weeks of injury	 NR/NR (14.5)	 NR/NR (16.0)	 RR 0.91 (0.85, 0.97)	 *Favours TXA*, *p* = 0.0035
	N = 20 211 (1 RCT) CRASH-2 2010				Mortality due to bleeding TXA within 1 hour 1 to 3 hours after 3 hours	 NR/NR (5.3) NR/NR (4.8) NR/NR (4.4)	 NR/NR (7.7) NR/NR (6.1) NR/NR (3.1)	 RR 0.68 (0.57, 0.82) RR 0.79 (0.64, 0.97) RR 1.44 (1.12, 1.84)	 *Favours TXA*, *p* < 0.0001 *Favours TXA*, *p* = 0.03 *Favours placebo*, *p* = NR
Ker 2015 SR *High quality*	N = 20 367 (2 RCTs) CRASH-2 2010 ~~Yutthakasemsunt 2013~~	Adult trauma patients with, or at risk of, significant bleeding, including patients with moderate to severe TBI	MC (over 40 countries, Thailand)	IV TXA vs standard care	Mortality, all-cause *All trauma*	1475/10180 (14.5) 1463/10060 (14.5) 12/120 (10)	1631/10187 (16.0) 1613/10067 (16.0) 18/120 (15)	RR 0.90 (0.85, 0.97) RR 0.91 (0.85, 0.97) RR 0.67 (0.34, 1.32)	*Favours TXA* *p* = 0.003 No significant heterogeneity I^2 = 0 (*p* = 0.38)
Ausset 2015 SR *Critically low quality*	N = 20 896 (1 RCT, 2 Coh) CRASH-2 2010 Valle 2014 Cole 2014	Adult trauma patients with wide range of injury severities	Civilian trauma MC (over 40 countries, US)	TXA vs no TXA	Mortality, overall	NR NR (14.5) NR/150 NR/160 (8)	NR NR (16) NR/150 NR/225 (8)	NR aRR 0.015 NR NR	Meta-anlaysis not conducted *p* = NR, *Favours TXA*[e] *p* = NR, Not significant[f] *p* = NR, Not significant[g]
						Cole 2014 noted a multivariate analysis in the subgroup of patients with shock that revealed an effect favouring TXA OR 0.16 (0.31, 0.86)			
	N = 2228 (2 Coh) Morrison 2012 Morrison 2013		Combat trauma, SC (Afghanistan)		Mortality, overall	 NR/293 (17.4) NR	 NR/603 (23.9) NR	 OR 0.61 (0.42, 0.89 NR	 *Favours TXA*[h] *p* = NR, Not significant[i]
						Morrison 2012 noted an effect favouring TXA in a subgroup of patients requiring a massive transfusion			
						NR (14.4)	NR (28.1)	OR 7.2 (3.0, 17.3)	*p* = NR, *Favours TXA*

Study ID Study design[a]	Sample size (no. of trials) included in analysis	Patient population	Setting (Location)	Comparison	Outcome	Results			
						TXA n/N (%)	No TXA n/N (%)	Risk estimate (95% CI)	*Statistical significance* *p*-value Heterogeneity[b]
Medical setting									
~~Bennett 2014~~ ~~SR~~ ~~*Low*~~	~~N = 301 (3 RCTs)~~[f] ~~Bagnenko 2011~~ ~~Bergqvist 1980~~ ~~Engqvist 1979~~	~~Adult patients with severe or massive upper gastrointestinal bleeding~~	~~SC (Russia, Sweden, Stockholm)~~	~~IV and oral TXA vs placebo or no TXA~~	~~Mortality, all-cause~~	~~15/149 (10.1)~~ ~~1/22 (4.5)~~ ~~3/25 (12)~~ ~~11/102 (10.8)~~	~~20/152 (13.2)~~ ~~3/25 (12)~~ ~~5/25 (20)~~ ~~12/102 (11.8)~~	~~RR 0.77 (0.41, 1.46)~~[e] ~~RR 0.38 (0.04, 3.38)~~ ~~RR 0.60 (0.16, 2.25)~~ ~~RR 0.92 (0.42, 1.98)~~	~~*No significant difference*~~ ~~*p* = 0.42~~[e] ~~No significant heterogeneity~~ ~~I^2 = 0 (*p* = 0.69)~~
Obstetrics and maternity setting									
Della-Corte 2020 SR *Moderate quality*	N = 14 335 (2 RCTs) Ducloy-Bouthors 2011 WOMAN 2017	Patients with postpartum haemorrhage	Obstetrics France Multiple countries	TXA vs placebo or not treatment	Mortality (maternal) due to bleeding	110/7155 (1.5) 0/72 110/7083 (1.6)	135/7180 (1.9) 0/72 135/7108 (1.9)	RR 0.82 (0.64, 1.05)	NR
	N = 14 335 (2 RCTs) Ducloy-Bouthors 2011 WOMAN 2017		Obstetrics France Multiple countries		Mortality (maternal), all-cause	148/7155 (2.1) 0/72 148/7083 (2.1)	172/7180 (2.4) 0/72 172/7108 (2.4)	RR 0.86 (0.69, 1.07)	NR
Shakur 2018 SR *High quality*	N = 20 172 (2 RCTs) WOMAN 2017 Ducloy-Bouthers 2011	Women after birth following a pregnancy of at least 24 weeks' gestation with PPH, regardless of mode of birth or other aspects of third stage management *Estimated blood loss after vaginal birth > 500 mL, or > 1000 mL after caesarean section or estimated blood loss enough to compromise the haemodynamic status of the woman	Obstetrics (France, UK, Nigeria, Pakistan, Uganda, Kenya, Cameroon, Sudan, Tanzania, Nepal, Zambia, Albania, Democratic Republic of Congo, Bangladesh, Ethiopia, Burkina Faso, Jamaica, Ghana, Papua New Guinea, Egypt, Colombia and Cote d'Ivoire)	IV TXA vs placebo or standard care	Mortality (maternal), all-cause	227/10036 (2.3)	256/9985 (2.6)	RR 0.88 (0.74, 1.05)	*No significant difference* *p* = 0.16 Heterogeneity NA
						All estimable data are from one study (WOMAN 2017). There were zero events in either group in Ducloy-Bouthers 2011 (N = 151)			
	N = 20 011 (1 RCT) WOMAN 2017				*Timing from birth* Less than 1 hr 1 to 3 hrs More than 3 hrs	80/4846 (1.7) 57/2674 (2.1) 90/2514 (3.6)	80/4726 (1.7) 83/2682 (3.1) 92/2569 (3.6)	RR 0.98 (0.72, 1.33) RR 0.69 (0.49, 0.96) RR 1.00 (0.75, 1.33)	*p* = 0.87 No difference *p* = 0.028 *Favours TXA* *p* = 1.0 No difference
	N = 20 172 (2 RCTs) WOMAN 2017 Ducloy-Bouthers 2011				Mortality (maternal), due to bleeding	155/10036 (1.5)	191/9985 (1.9)	RR 0.81 (0.65, 1.00)	*Favours TXA* *p* = 0.046 Heterogeneity NA
						All estimable data are from one study (WOMAN 2017). There were zero events in either group in Ducloy-Bouthers 2011 (N = 151)			
	N = 20 011 (1 RCT) WOMAN 2017				*Timing from birth* Less than 1 hr 1 to 3 hrs More than 3 hrs	49/4846 (1.0) 40/2674 (1.5) 66/2514 (2.6)	60/4726 (1.3) 67/2682 (2.5) 63/2569 (2.5)	RR 0.80 (0.55, 1.16) RR 0.60 (0.41, 0.88) RR 1.07 (0.76, 1.51)	*p* = 0.23 No difference *p* = 0.096 *Favours TXA* *p* = 0.70 No difference

Study ID Study design[a]	Sample size (no. of trials) included in analysis	Patient population	Setting (Location)	Comparison	Outcome	Results			
						TXA n/N (%)	No TXA n/N (%)	Risk estimate (95% CI)	*Statistical significance* *p*-value Heterogeneity[b]
Paediatrics									
Huebner 2017 SR *Critically low quality*	N = 766 (1 Coh) Eckart 2014, adjusted for confounders	Patients with trauma at risk of death from haemorrhage Patients were predominantly male, mean age 11 years with penetrating trauma	Paediatric trauma (Afghanistan)	TXA vs no TXA	Mortality, timing not specified	NR/NR (15)	NR/NR (9)	OR 0.27 (0.85, 0.89)	*Favours TXA, p* = 0.03

Studies with ~~strikethrough~~ do not meet the PICO criteria for this question.

aOR, adjusted odds ratio; aRR, adjusted risk ratio; CI, confidence interval; Coh, cohort study; hrs, hours; IU, international units; IV, intravenous; MC, multicentre; M-H, Mantzel-Hentzel; NR, not reported; OR, odds ratio; RCT, randomised controlled trial; RD, risk difference; RR, relative risk; SC, single centre; TXA, tranexamic acid; UK, United Kingdom; US, United States

a. Where only one RCT is identified in a systematic review, the evidence has been considered as RCT evidence. Where the systematic review assesses observational and cohort studies, the evidence has been considered as according to the study design features. The risk of bias of the included primary studies is based on the quality assessment reported by the systematic review authors.

b. Only applicable to systematic review studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if P_{het} >0.1 and I^2 <25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25–50%; substantial heterogeneity I^2 >50%.

c. Calculated post-hoc using RevMan 5.4

d. Due to missing data, the analysis excludes four patients in the intervention group and four patients in the placebo group in CRASH-2; a further 109 patients in the WOMAN trial were excluded (50 in the intervention group and 59 in the placebo group) as time to treatment was greater than 24 hours. All models were controlled for systolic blood pressure (5 mm Hg interval) and age (10-yr intervals), which are strong risk factors for death due to bleeding.

e. Ausset 2015 noted a post-hoc analysis of CRASH-2 had revealed when TXA was administered within 1 hour after trauma, mortality was reduced by one-third. Between hours 1–3, mortality was reduced by one-fifth. When given after the third hour, mortality due to bleeding appeared to increase.

f. The study by Valle (2014) is confounded. Ausset 2015 noted that mortality was higher in the TXA group, but that the propensity score failed to account for important variables, resulting in the TXA group being more severely injured than the control group. No multivariate analysis was performed to account for these differences.

g. The survival benefit of TXA in Cole 2014 is confounded. Patients who received TXA had higher ISS, incidence of shock (base deficit > 6 mEq/L) and transfusion requirements. A multivariate analysis in the subgroup of patients with shock revealed an effect favouring TXA OR 0.16 (0.31, 0.86).

h. Ausset 2015 noted that the survival benefit of TXA in Morrison 2012 is confounded by the retrospective study design, with cryoprecipitate used more often in the TXA massive transfusion group. Factors significantly associated with death in the entire cohort included: Glasgow Coma Score of eight or less, hypotension and coagulopathy.

i. Propensity score adjusted for predictors of mortality, including RBCs, FFP and plasma. After adjustment for platelet administration the OR was 0.62 (95 CI 0.43, 0.90). Ausset 2015 noted that the survival benefit of TXA in Morrison 2013 remained confounded by the heterogeneous use of rFVIIa.

j. Bennett (2014) meta-analysed eight RCTs involving patients with upper gastrointestinal bleeding. Only three RCTs were in patients with critical bleeding and are included here.

4.8.3.2 Morbidity

A summary of the evidence relating to morbidity (e.g. vascular events, multiple organ failure, acute respiratory distress syndrome) associated with TXA in patients with critical bleeding is presented in Table 4.71.

Vascular events (any)

In a meta-analysis of data from studies included in this review (see Figure 4.47), the RCT evidence in critically bleeding trauma patients (CRASH-2) suggested there was little to no difference on the incidence of vascular events in trauma patients who received TXA (168/10 060, 1.67%) compared with those who did not receive TXA (201/ 10 067, 1.99%) (RR 0.84, 95% CI 0.68, 1.02; *p* = 0.08; random effect) (*GRADE: very low*).

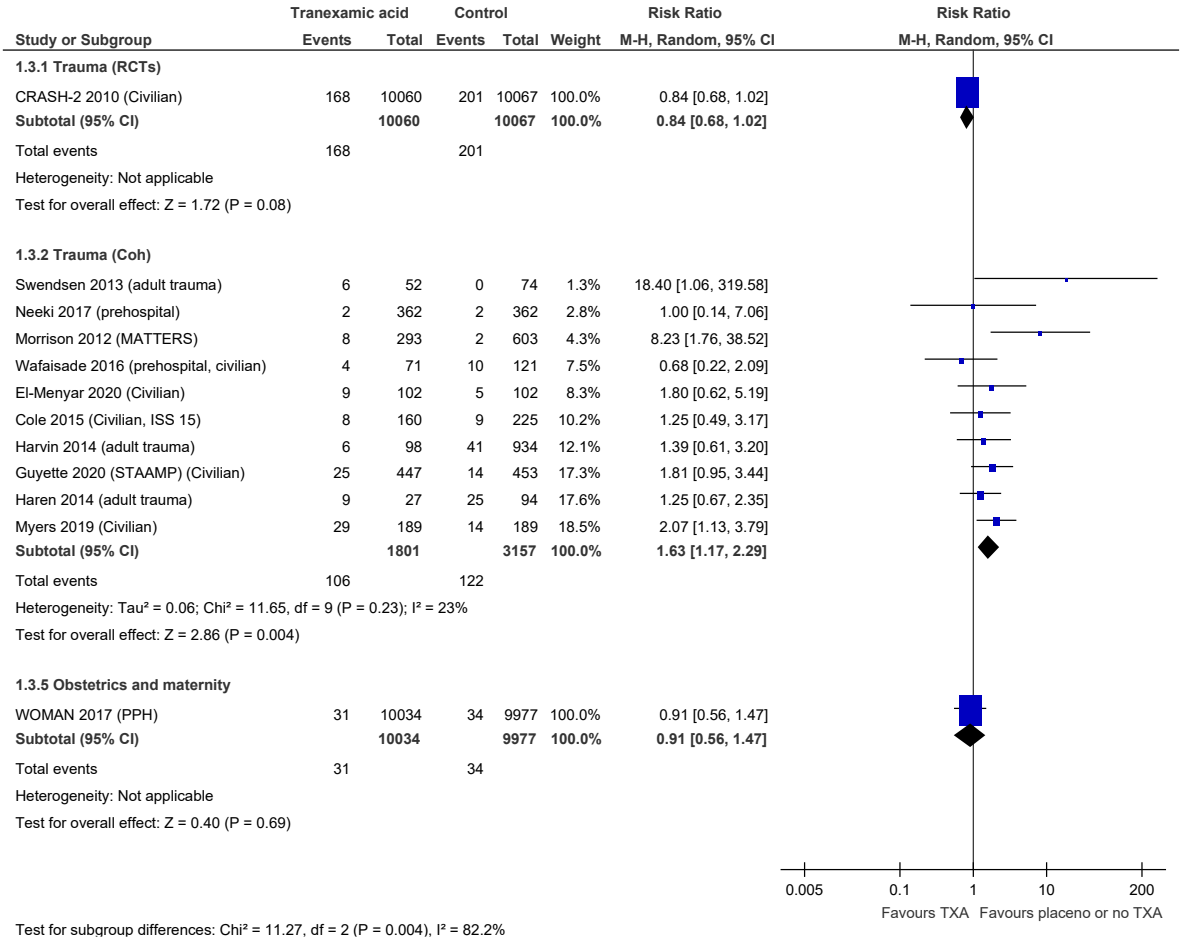
Among the cohort studies conducted in critically bleeding trauma patients, the risk of vascular events was higher among those who received TXA (106/1801, 5.89%) compared with those who did not receive TXA (122/ 3157, 3.86%) (RR 1.63; 95%CI 1.17, 2.29; *p* = 0.23, I^2 = 23%) *(GRADE: Very low).* Noting there was a wide variety of injury severity and bleeding risk in the included studies, with the likelihood a missing data relating to inconsistencies in the measurement of the outcome.

In the obstetric setting, the RCT evidence (WOMAN) suggested there was little to no difference on the incidence of vascular events in women with major obstetric haemorrhage who received TXA (31/10 034, 0.31%) compared with those who did not receive TXA (34/ 9977, 0.34%) (RR 0.91, 95% CI 0.56, 1.47; *p* = 0.69; random effect) (*GRADE: very low*).

Organ failure

One RCT (WOMAN 2017) in the obstetric setting reported on other morbidity outcomes that were considered in this review. The data (see Figure 4.48) suggested this is no differences between women with major obstetric haemorrhage who received TXA compared with those who did not for the outcomes of multiple organ failure (RR 0.94, 95% CI 0.71, 1.23; *p* = 0.65; random effect), respiratory failure (RR 0.87, 95% CI 0.67, 1.12; *p* = 0.27; random effect), or renal failure (RR 1.09; 95% CI 0.85, 1.39; *p* = 0.51; random effect) (*GRADE: very low*).

Figure 4.47 Forest plot of comparison: TXA vs no TXA, outcome: Morbidity, vascular events (any)



Test for subgroup differences: Chi² = 11.27, df = 2 (P = 0.004), I² = 82.2%

Figure 4.48 Forest plot of comparison: TXA vs no TXA, outcome: Morbidity, other

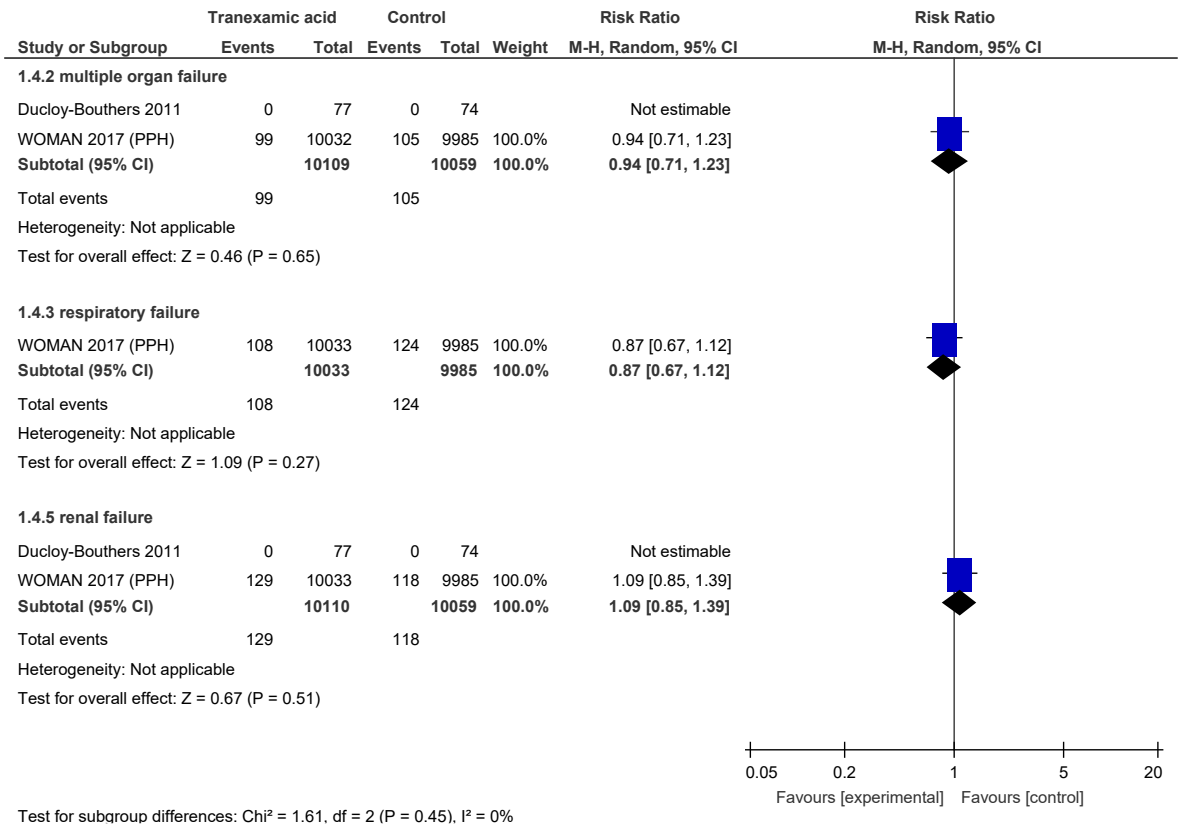


Table 4.71 Results for TXA versus no TXA: Patients with critical bleeding – Morbidity

Study ID Study design[a]	Sample size (no. of trials) included in analysis	Patient population	Setting (Location)	Comparison	Outcome	Results			
						TXA n/N (%)	No TXA n/N (%)	Risk estimate (95% CI)	*Statistical significance* *p*-value Heterogeneity[b]
Any setting									
Ageron 2020 SR *Moderate quality*	N = 28 333 (2 RCTs) CRASH-2 WOMAN	CRASH-2 are trauma patients, the WOMAN trials are women with a postpartum haemorrhage	Trauma and Obstetrics	TXA vs placebo	Any vascular occlusive events	118/14270 (0.01) NR NR	152/14063 (0.01) NR NR	NR NR NR	No significant difference *p* = 0.255
						The authors stratified individual patient data by baseline risk of death due bleeding and found no increased risk of vascular occlusive events with TXA and it did not vary by baseline risk categories (*p* = 0.25)			
	N = 28 333 (2 RCTs) CRASH-2 WOMAN				Myocardial infarction	24/14270 (0.00) NR NR	46/14063 (0.00) NR NR	NR NR NR	No significant difference *p* = 0.909
	N = 28 333 (2 RCTs) CRASH-2 WOMAN				Stroke	32/14270 (0.00) NR NR	42/14063 (0.00) NR NR	NR NR NR	No significant difference *p* = 0.152
	N = 28 333 (2 RCTs) CRASH-2 WOMAN				Pulmonary embolism	54/14270 (0.00) NR NR	56/14063 (0.00) NR NR	NR NR NR	No significant difference *p* = 0.739
	N = 28 333 (2 RCTs) CRASH-2 WOMAN				Deep vein thrombosis	28/14270 (0.00) NR NR	30/14063 (0.00) NR NR	NR NR NR	No significant difference *p = 0.214*
Chornenki 2019 SR *High quality*	N = 42 808 (5 RCTs)		Trauma, Obstetrics and Medical (No countries listed)	TXA vs placebo or no TXA	Stroke	85/21424 (0.4) 6/50 (12.0) 55/10060 (0.5) 0/120 (0) 8/10033 (0.1) 16/1161 (1.4)	88/21384 (0.4) 2/50 (4.0) 66/10067 (0.7) 3/118 (2.5) 6/9985 (0.1) 11/1164 (0.9)	RR 1.10 (0.68, 1.78) RR 3.00 (0.64, 14.16) RR 0.83 (0.58, 1.19) RR 0.14 (0.01, 2.69) RR 1.33 (0.46, 3.82) RR 1.46 (0.68, 3.13)	No significant difference *p* = 0.71 Mild heterogeneity I^2 = 31% (*p* = 0.21)

Study ID Study design[a]	Sample size (no. of trials) included in analysis	Patient population	Setting (Location)	Comparison	Outcome	Results			
						TXA n/N (%)	No TXA n/N (%)	Risk estimate (95% CI)	*Statistical significance* *p*-value Heterogeneity[b]
	~~Tsementzis 1990~~ CRASH-2 2010 ~~Yutthakasemsunt 2013~~ Arulkumaran 2017 ~~Sprigg 2018~~	Patients requiring treatment or prevention of postpartum haemorrhage, intracranial haemorrhage, subarachnoid haemorrhage, traumatic brain injury or non-specific trauma injury							
	N = 42 470 (3 RCTs) CRASH-2 2010 Arulkumaran 2017 ~~Sprigg 2018~~				Myocardial infarction	48/21254 (0.2) 35/10060 (0.3) 2/10033 (0.0) 11/1161 (0.9)	64/21216 (0.3) 55/10067 (0.5) 3/9985 (0.0) 6/1164 (0.5)	RR 0.88 (0.43, 1.84) RR 0.64 (0.42, 0.97) RR 0.66 (0.11, 3.97) RR 1.84 (0.68, 4.95)	No significant difference *p = 0.74* Moderate heterogeneity I^2 = 46% (*p* = 0.15)
	N = 43 161 (6 RCTs) ~~Chowdhary 1986~~ ~~Tsementzis 1990~~ ~~Roos 2000~~ CRASH-2 2010 Arulkumaran 2017 ~~Sprigg 2018~~				Pulmonary embolism	113/21598 (0.5) 1/65 (1.5) 2/50 (4.0) 1/229 (0.4) 72/10060 (0.7) 17/10033 (0.2) 20/1161 (1.7)	116/21563 (0.5) 1/64 (1.6) 1/50 (2.0) 0/233 (0) 71/10067 (0.7) 20/9985 (0.2) 23/1164 (2.0)	OR 0.97 (0.75, 1.26) OR 0.98 (0.06, 16.08) OR 2.04 (0.18, 23.27) OR 3.07 (0.12, 75.65) OR 1.01 (0.73, 1.41) OR 0.85 (0.44, 1.62) OR 0.87 (0.47, 1.59)	No significant difference *p* = 0.83 No significant heterogeneity I^2 = 0 (*p* = 0.94)
	N = 46 287 (6 RCTs) ~~Tsementzis 1990~~ ~~Shakur 2010~~ ~~Sprigg 2014~~ Arulkumaran 2017 ~~Sprigg 2018~~ ~~Sentilhes 2018~~				Deep vein thrombosis	63/23164 (0.3) 0/50 (0) 40/10060 (0.4) 1/16 (6.25) 3/10033 (0.0) 19/1161 (1.6) 0/1844 (0)	66/23123 (0.3) 3/50 (6.0) 41/10067 (0.4) 0/8 (0) 7/9985 (0.1) 14/1164 (1.2) 1/1849 (0.1)	 RR 0.14 (0.01, 2.70) RR 0.98 (0.63, 1.51) RR 1.59 (0.07, 35.15) RR 0.43 (0.11, 1.65) RR 1.36 (0.69, 2.70) RR 0.33 (0.01 (8.20)	*p* = NR
Gayet-Ageron 2018 SR *High quality*	N = 40 138 (2 RCTs) CRASH-2 2010 WOMAN 2017	Patients with acute severe bleeding	Trauma (MC, over 40 countries)	TXA vs placebo	Myocardial infarction (fatal and non-fatal)	37/20094 (0.2) 35/10060 (0.3) 2/10034 (0.0)	58/20044 (0.3) 55/10067 (0.5) 3/9977 (0.0)	OR 0·64 (0·43, 0·97) OR 0·64 (0·42, 0·98) OR 0·66 (0·11, 3·95)	*Favours TXA* *p* = 0.0371 No significant heterogeneity I^2 = NR (*p* = 0.9788)
	N = 40 138 (2 RCTs) CRASH-2 2010 WOMAN 2017	Patients with acute severe bleeding	Obstetrics and maternity (MC, 21 countries)	TXA vs placebo	Deep vein thrombosis (fatal and non-fatal)	43/20094 (0.2) 40/10060 (0.4) 3/10034 (0.0)	48/20044 (0.2) 41/10067 (0.4) 7/9977 (0.1)	OR 0·90 (0·60, 1·36) OR 0·98 (0·63, 1·52) OR 0·42 (0·11, 1·64)	*No significant difference* *p* = NR No significant heterogeneity I^2 = NR (*p* = 0.2483)
					Pulmonary embolism	89/20094 (0.4)	91/20044 (0.5)	OR 0·98 (0·73, 1·32)	*No significant difference* *p* = NR

Study ID Study design[a]	Sample size (no. of trials) included in analysis	Patient population	Setting (Location)	Comparison	Outcome	Results			
						TXA n/N (%)	No TXA n/N (%)	Risk estimate (95% CI)	*Statistical significance* *p*-value Heterogeneity[b]
					(fatal and non-fatal)	72/10060 (0.7) 17/10034 (0.2)	71/10067 (0.7) 20/9977 (0.2)	OR 1·02 (0·74, 1·42) OR 0·84 (0·44, 1·61)	No significant heterogeneity I^2 = NR (p = 0.6025)
					Stroke (fatal and non-fatal)	65/20094 (0.3) 57/10060 (0.6) 8/10034 (0.1)	72/20044 (0.4) 66/10067 (0.7) 6/9977 (0.1)	OR 0·91 (0·65, 1·27) OR 0·87 (0·61, 1·24) OR 1·32 (0·46, 3·81)	*No significant difference* p = NR No significant heterogeneity I^2 = NR (p = 0.4647)
Trauma setting									
Al-Jeabory 2021 SR *High quality*	N = 22 270 (5 studies)	Mix of combat and civilian trauma patients	Trauma (multiple countries)	TXA vs no TXA	Myocardial infarction	45/11288 (0.4)	64/10982 (0.6)	OR 0.66 (0.45, 0.97)	*Favours TXA* p = 0.03 No significant heterogeneity I^2 = 0%
	N = 22 270 (5 studies)				Stroke	73/11288 (0.6)	76/10982 (0.7)	OR 0.90 (0.65, 1.24)	No significant difference p = 0.50 Moderate heterogeneity I^2 = 40%
	N = 2271 (6 studies)				Thromboembolic events	67/1308 (5.1)	62/963 (6.4)	OR 0.89 (0.37, 2.11)	No significant difference p = 0.79 Moderate heterogeneity I^2 = 60%
	N = 25 912 (5 studies)				Pulmonary embolism	137/1211 (1.1)	117/1380 (0.8)	OR 1.57 (0.79, 3.13)	No significant difference *p = 0.20* Significant heterogeneity I^2 = 80%
	N = 26 165 (6 studies)				Deep vein thrombosis	105/12240 (0.9)	105/13925 (0.8)	OR 1.13 (0.51, 2.51)	No significant difference *p = 0.77* Significant heterogeneity I^2 = *83%*
	N = 385 (1 study)				Coagulation failure	5/160 (3.1)	5/225 (2.2)	OR 1.42 (0.40, 4.99)	No significant difference p = 0.58 Heterogeneity NA
	N = 1480 (3 studies)				Multiple organ failure	106/681 (15.6)	156/799 (19.5)	OR 0.87 (0.66, 1.16)	No significant difference p = 0.35

Study ID Study design[a]	Sample size (no. of trials) included in analysis	Patient population	Setting (Location)	Comparison	Outcome	Results			
						TXA n/N (%)	No TXA n/N (%)	Risk estimate (95% CI)	*Statistical significance* *p*-value Heterogeneity[b]
									Moderate heterogeneity I^2 = *39%*
	N = 1011 (2 studies)				Acute kidney failure	22/212 (10.4)	17/799 (2.1)	OR 1.97 (1.01, 3.86)	No significant difference *p* = 0.05 No significant heterogeneity I^2 = 0%
	N = 385 (1 study)				Hepatic failure	5/160 (3.1)	2/225 (0.9)	OR 1.21 (0.81, 1.82)	No significant difference *p* = 0.35 Heterogeneity NA
	N = 186 (1 study)				Sepsis	4/67 (6.0)	8/119 (6.7)	OR 0.88 (0.26, 3.04)	No significant difference *p* = 0.84 Heterogeneity NA
	N = 385 (1 study)				Infection	89/160 (55.6)	113/225 (50.2)	OR 1.24 (0.83, 1.87)	No significant difference *p* = 0.30 Heterogeneity NA
Almuwallad 2021 SR *High quality*	N = 2020 (1 RCT, 3 Coh)	Civilian trauma patients	Trauma, MC Germany USA Qatar USA	TXA vs no TXA	Thromboembolic events (Venous) Wafaisade 2016 Neeki 2018 El-menyar 2019 Guyette 2020 (RCT)	40/982 (4.0) 4/71 (5.6) 2/362 (0.6) 9/102 (8.8) 25/447 (5.6)	31/1038 (3.0) 10/121 (8.3) 2/362 0.6) 5/102 (4.9) 14/453 (3.1)	OR 1.49 (0.90, 2.46) OR 0.66 (0.20, 2.20) OR 1.00 (0.14, 7.14) OR 1.88 (0.61, 5.81) OR 1.86 (0.95, 3.62)	No significant difference *p* = 0.12 No significant heterogeneity I^2 = 0% (*p* = 0.48)
El-Menyar 2018 SR *Moderate quality*	N = 769 (2 Coh)	Adult patients with traumatic injury presenting to the emergency department requiring blood transfusion	Prehospital (air rescue)	TXA vs placebo	Thromboembolic events (Venous) Wafaisade 2016 Neeki 2017	6/386 (1.55)	12/383 (3.1)	OR 0.74 (0.27, 2.07) OR 0.67 (0.20, 2.22) OR 0.98 (0.14, 7.04)	*No significant difference* *p* = NR No significant heterogeneity I^2 = 0% (*p* = 0.75)
Nishidia 2017 SR *Critically low quality*	N = 23 117 (2 RCTs, 6 Coh)	Patients with trauma-induced coagulopathy	MC (~40 countries)	TXA vs standard care	Thromboembolic events (Venous)	209/10881(1.9)	288/12236 (2.4)	RR 1.32 (0.80, 2.16)	*No significant difference* *p* = 0.28 Substantial heterogeneity I^2 = 61% (*p* = 0.02)
					N = 20 365 (2 RCTs)	168/10180 (1.7) 168/10060 (1.7) 0/120	201/10185 (2.0) 201/10067 (2.0) 0/118	RR 0.84 (0.68, 1.02) RR 0.84 (0.68, 1.02) Not estimable	*No significant difference* *p* = 0.08 Heterogeneity NA

Study ID Study design[a]	Sample size (no. of trials) included in analysis	Patient population	Setting (Location)	Comparison	Outcome	Results			
						TXA n/N (%)	No TXA n/N (%)	Risk estimate (95% CI)	*Statistical significance* *p*-value Heterogeneity[b]
					Shakur 2010 ~~Yutthakasemsunt 2013~~)				
					N = 2752 (6 Coh) Morrison 2012 Swendsen 2013 Haren 2014 Harvin 2014 Cole 2015 Wafaisade 2015	41/701 (5.8) 8/293 (2.7) 6/52 (11.5) 9/27 (3.3) 6/98 (6.1) 8/160 (5) 4/71 (5.6)	87/2051 (4.2) 2/603 (0.3) 0/74 25/94 (26.6) 41/934 (4.4) 9/225 (4) 10/121 (8.2)	RR 1.61 (0.86, 3.01) RR 8.23 (1.76, 38.52) RR 18.40 (1.06, 319.58) RR 1.25 (0.67, 2.35) RR 1.39 (0.61, 3.20) RR 1.25 (0.49, 3.17) RR 0.68 (0.22, 2.09)	*No significant difference* *p* = 0.14 Substantial heterogeneity I^2 = 52% (*p* = 0.06)
Cannon 2017 SR *Moderate quality*	N = 21 408 (1 RCT, 2 Coh)	Patients with severe trauma at risk of death from haemorrhage* *patients requiring blood transfusion and/or with an injury score greater than 25	Civilian and military trauma	TXA vs no TXA	Thromboembolic events (Venous) CRASH-2 2010 Cole 2015 Morrison 2012	191/10513 (1.8) 168/10060 (1.7) 8/160 (5) 15/293 (5.1)	213/10895 (1.95) 201/10067 (2) 3/603 (0.5) 9/225 (4)	OR 2.00 (0.53, 7.50) RD 0.019 OR 0.83 (0.68, 1.03) OR 1.26 (0.48, 3.35) OR 10.79 (3.10, 37.58)	*No significant difference* *p* = 0.30 Substantial heterogeneity I^2 = 88% (*p* = 0.0003)
Myers 2019 Retrospective cohort *Serious risk of bias*	N = 378	Patients presenting to a level 1 trauma centre	Level 1 trauma centre (NR)	TXA within three hours of presentation vs No TXA	Thromboembolic events (Venous)	29/189 (15.3)	14/189 (7.4)	OR 3.26 (1.3, -9.1)	*Favours intervention* *p= 0.02*
Huebner 2017 SR *Critically low quality*	N = 20 211 (1 RCT) CRASH-2	Patients with trauma at risk of death from haemorrhage	Civilian trauma	TXA vs placebo or no TXA	Vasco occlusive events	NR/NR (1.7)	NR/NR (2.0)	NR	No significant difference *p* = NR Heterogeneity NA
	N = NR (1 Coh) Cole 2015				Thromboembolic events	NR/NR (8)	NR/NR (2)	NR	*Favours placebo* *p* = 0.01 Heterogeneity NA
	N = 126 (1 Coh) Swendsen 2013				DVT/PE Subgroup analysis	NR/NR (11.5) NR/NR (12)	NR/NR (0) NR/NR (0)	NR NR	*Favours placebo*, *p* = 0.004 *p* = 0.012 Heterogeneity NA
Ker 2015 SR *High quality*	N = 20 367 (2 RCTs)	Adult trauma patients with, or at risk of, significant bleeding,	MC, 40 countries, Thailand	IV TXA vs standard care	Myocardial infarction	351/10180 (3.4) 35/10060 (0.3) 0/120	58/10187 (0.6) 55/10067 (0.5) 3/120 (2.5)	RR 0.61 (0.40, 0.92) RR 0.64 (0.42, 0.97) RR 0.14 (0.01, 2.74)	*No significant difference* *p* = 0.019 No significant heterogeneity I^2 = 0 (*p* = 0.32)

Study ID Study design[a]	Sample size (no. of trials) included in analysis	Patient population	Setting (Location)	Comparison	Outcome	Results			
						TXA n/N (%)	No TXA n/N (%)	Risk estimate (95% CI)	*Statistical significance* *p*-value Heterogeneity[b]
	CRASH-2 2010 ~~Yutthakasemsunt 2013~~	including patients with moderate to severe TBI with wide range of injury severities							
	N = 20 367 (2 RCTs) CRASH-2 2010 ~~Yutthakasemsunt 2013~~				Deep vein thrombosis	40/10180 (0.4) 40/10060 (0.4) 0/120	42/10187 (0.4) 41/10067 (0.4) 1/120 (0.8)	RR 0.95 (0.62, 1.47) RR 0.98 (0.63, 1.51) RR 0.33 (0.01, 8.10)	*No significant difference* *p* = 0.83 No significant heterogeneity $I^2 = 0$ (*p* = 0.51)
	N = 20 367 (2 RCTs) CRASH-2 2010 ~~Yutthakasemsunt 2013~~				Pulmonary embolism	72/10180 (0.7) 72/10060 (0.7) 0/120	71/10187 (0.7) 71/10067 (0.7) 0/120	RR 1.01 (0.73, 1.41) RR 1.01 (0.73, 1.41) Not estimable	*No significant difference* *p* = 0.93 Heterogeneity NA
	N = 510 (2 RCTs) CRASH-2 2010 ~~Yutthakasemsunt 2013~~				Stroke	0/253 0/133 0/120	1/257 (0.4) 1/137 (0.7) 0/120	RR 0.34 (0.01, 8.35) RR 0.34 (0.01, 8.35) Not estimable	*No significant difference* *p* = 0.51 Heterogeneity NA
	N = 510 (2 RCTs) CRASH-2 2010 ~~Yutthakasemsunt~~ 2013				Deep vein thrombosis	0/253 0/133 0/120	3/257 (1.2) 2/137 (1.5) 1/120 (0.8)	RR 0.25 (0.03, 2.26) RR 0.21 (0.01, 4.25) RR 0.33 (0.01, 8.10)	*No significant difference* p = 0.22 No significant heterogeneity $I^2 = 0$ (*p* = 0.83)
Ausset 2015 SR *Critically low quality*	N = 20 211 (1 RCT) CRASH-2 2010		Civilian trauma MC (over 40 countries, US)	TXA vs no TXA	Vaso-occlusive events, overall	NR (1.7)	NR (2.0)	NR	*No significant difference* *p* = NR Heterogeneity NA
					Thromboembolic events (Venous)	NR	NR	NR	*No significant difference* *p* = NR Heterogeneity NA
					Pulmonary embolism	NR	NR	NR	*No significant difference* *p* = NR Heterogeneity NA
					Stroke	NR	NR	NR	*No significant difference* *p* = NR Heterogeneity NA
					Myocardial infarction	NR	NR	NR	*Favours TXA* *p* = NR

Study ID Study design[a]	Sample size (no. of trials) included in analysis	Patient population	Setting (Location)	Comparison	Outcome	Results			
						TXA n/N (%)	No TXA n/N (%)	Risk estimate (95% CI)	*Statistical significance* *p*-value Heterogeneity[b]
									Heterogeneity NA
	N = 385 (1 Coh) Cole 2014				Multiorgan failure	NR/160 (30)	NR/225 (37)	NR	*No significant difference* *p* = NR Heterogeneity NA
					Patients with shock	NR	NR	OR 0.27 (0.1 , 0.73)	*Favours TXA* [d]
	N = 896 (1 Coh) Morrison 2012		Combat trauma, SC (Afghanistan)	TXA vs no TXA	Thromboembolic events (Venous)	NR/293	NR/603	NR	*No significant difference* *p* = NR Heterogeneity NA
	N = 9127 (1 RCT) CRASH-3 2019				Haemorrhagic complications	16/4613 (0.3)	22/4514 (0.5)	RR 0.71 (0.37, 1.35)	*No significant difference* *p = 0.30*
Medical setting									
Bennett 2014 SR *High quality*	N = 251 (2 RCT) [e] ~~Bagnenko 2011~~ ~~Engqvist 1979~~	Adult patients admitted with severe or major upper gastrointestinal bleeding	SC (Russia, Stockholm)	IV and oral TXA vs placebo or no TXA	Any thromboembolic event	5/124 (4.0) 0/22 5/102 (4.9)	2/127 (1.6) 0/25 2/102 (2.0)	RR 2.50 (0.50, 12.59) Not estimable RR 2.50 (0.50, 12.59)	*No significant difference* *p* = 0.27 [c] Heterogeneity NA
	N = 204 (1 RCT) [e] ~~Engqvist 1979~~				Deep vein thrombosis	4/102 (3.9)	2/102 (2.0)	RR 2.00 (0.37, 10.68)	*No significant difference* *p* = 0.42 [c] Heterogeneity NA
	N = 204 (1 RCT) [e] ~~Engqvist~~ 1979				Myocardial infarction, pulmonary embolism and cerebral infarction	4/102 (3.9)	2/102 (2.0)	RR 2.00 (0.37, 10.68)	*No significant difference* *p* = 0.42 [c] Heterogeneity NA
Obstetric setting									
Della-Corte 2021 SR *Moderate quality*	N = 144 (1 RCT) Ducloy-Bouthors 2011	Patients with postpartum haemorrhage	Obstetrics France	TXA vs placebo or no treatment	Deep vein thrombosis	0/72	0/72	Not estimable	NR
					Pulmonary embolism	0/72	0/72	Not estimable	NR
					Myocardial infarction	0/72	0/72	Not estimable	NR
	N = 144 (1 RCT) Ducloy-Bouthors 2011	Patients with postpartum haemorrhage	Obstetrics France	TXA vs placebo or no treatment	Stroke	0/72	0/72	Not estimable	NR
	N = 14 332 (2 RCTs) Ducloy-Bouthors 2011 WOMAN 2017		Obstetrics France Multiple countries		Surgical intervention	1379/7152 (19.3) 4/72 (5.6) 1375/7080 (19.4)	1453/7180 (20.2) 5/72 (6.9) 1448/7108 (20.4)	RR 0.95 (0.89, 1.02) NR NR	*p* = NR No significant heterogeneity I^2 = 0%

Study ID Study design[a]	Sample size (no. of trials) included in analysis	Patient population	Setting (Location)	Comparison	Outcome	Results			
						TXA n/N (%)	No TXA n/N (%)	Risk estimate (95% CI)	*Statistical significance* *p*-value Heterogeneity[b]
	N = 144 (1 RCT) Ducloy-Bouthors 2011		Obstetrics France		Organ failure	0/72	0/72	Not estimable	*NR*
Shakur 2018 SR *High quality*	N = 20 015 (1 RCT) WOMAN 2017	Women after birth following a pregnancy of at least 24 weeks' gestation with PPH, regardless of mode of birth or other aspects of third stage management *Estimated blood loss after vaginal birth > 500 mL, or > 1000 mL after caesarean section or estimated blood loss enough to compromise the haemodynamic status of the woman	(France, UK, Nigeria, Pakistan, Uganda, Kenya, Cameroon, Sudan, Tanzania, Nepal, Zambia, Albania, Democratic Republic of Congo, Bangladesh, Ethiopia, Burkina Faso, Jamaica, Ghana, Papua New Guinea, Egypt, Colombia and Cote d'Ivoire)	IV TXA vs placebo or standard care	Serious maternal morbidity (any)	223/10030 (2.2)	224/9985 (2.2)	RR 0.99 (0.83, 1.19)	No significant difference *p* = 0.92 Heterogeneity NA
	N = 20 168 (2 RCTs) WOMAN 2017 Ducloy-Bouthers 2011				Serious maternal morbidity, multiple organ failure	99/10109 (1.0) 99/10032 (1.0) 0/77	105/10059 (1/0) 105/9985 (1.1) 0/74	RR 0.94 (0.71, 1.23) RR 0.94 (0.71, 1.23) Not estimable	No significant difference *p* = 0.65 Heterogeneity NA
	N = 20 169 (2 RCTs) WOMAN 2017 Ducloy-Bouthers 2011				Serious maternal morbidity, renal failure	129/10220 (1.3) 129/10033 (1.3) 0/77	118/10059 (1.2) 118/9985 (1.2) 0/74	RR 1.09 (0.85, 1.39) RR 1.09 (0.85, 1.39) Not estimable	No significant difference *p* = 0.51 Heterogeneity NA
	N = 20 169 (2 RCTs) WOMAN 2017 Ducloy-Bouthers 2011				Serious maternal morbidity, maternal seizure	33/10110 (0.3) 33/10033 (0.3) 0/77	43/10059 (0.4) 43/9985 (0.4) 0/74	RR 0.76 (0.49, 1.20) RR 0.76 (0.49, 1.20) Not estimable	No significant difference *p* = 0.24 Heterogeneity NA [d]
	N = 20 018 (1 RCT) WOMAN 2017				Serious maternal morbidity, respiratory failure	108/10033 (1.1)	124/9985 (1.2)	RR 0.87 (0.67, 1.12)	No significant difference *p* = 0.27 Heterogeneity NA
	N = 20 018 (1 RCT) WOMAN 2017				Serious maternal morbidity, cardiac arrest	110/10033 (1.1)	115/9985 (1.2)	RR 0.95 (0.73, 1.23)	No significant difference *p* = 0.71 Heterogeneity NA
	N = 20 169 (1 RCT) WOMAN 2017				Serious maternal morbidity, hepatic failure	29/10033 (0.3)	30/9985 (0.3)	RR 0.96 (0.58, 1.60)	No significant difference *p* = 0.88 Heterogeneity NA

Studies with ~~strikethrough~~ do not meet the PICO criteria for this question.

aOR, adjusted odds ratio; CI, confidence interval; Coh, cohort study; DVT, deep vein thrombosis; hrs, hours; IU, international units; IV, intravenous; MC, multicentre; M-H, Mantzel-Hentzel; NA, not applicable; NR, not reported; OR, odds ratio; PE, pulmonary embolism; PPH, postpartum haemorrhage; RCT, randomised controlled trials, RR, relative risk; SC, single centre; SD, standard deviation; TXA, tranexamic acid; UK, United Kingdom; US, United States

a. Where only one RCT is identified in a systematic review, the evidence has been considered as RCT evidence. Where the systematic review assesses observational and cohort studies, the evidence has been considered as according to the study design features. The risk of bias of the included primary studies is based on the quality assessment reported by the systematic review authors.

b. Only applicable to systematic review studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if P_{het} >0.1 and I^2 <25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25–50%; substantial heterogeneity I^2 >50%.

c. Calculated post-hoc using RevMan 5.4

d. The benefit of TXA in Cole 2014 is confounded. Patients who received TXA had higher ISS, incidence of shock (base deficit > 6 mEq/L) and transfusion requirements. A multivariate analysis in the subgroup of patients with shock revealed an effect favouring TXA OR 0.27 (0.1, 0.7).

4.8.3.3 Blood loss

A summary of the evidence relating to blood loss associated with TXA in patients with critical bleeding is presented in Table 4.72.

None of the included RCTs or cohort studies were found to report reliable data relating to blood loss. The available evidence was therefore not further considered.

Table 4.72 Results for TXA versus no TXA: Patients with critical bleeding – Blood loss

Study ID Study design[a]	Sample size (no. of trials) included in analysis	Patient population	Setting (Location)	Comparison	Outcome	Results			
						TXA Mean ± SD (n)	No TXA Mean ± SD (n)	Risk estimate (95% CI)	*Statistical significance* *p*-value Heterogeneity[b]
Obstetrics and maternity setting									
Shakur 2018 SR *High quality*	N = 151 (1 RCT) Ducloy-Bouthors 2011	Women after vaginal birth following a pregnancy of at least 24 weeks' gestation with PPH Estimated blood loss after vaginal birth > 800 mL	MC (France)	IV TXA vs placebo or standard care	Blood loss, 500 mL or more after randomisation	12/77 (15.6)	23/74 (31.1)	RR 0.50 (0.27, 0.93)	*Favours TXA* *p* = 0.029 Heterogeneity NA
	N = 151 (1 RCT) Ducloy-Bouthors 2011				Blood loss, 1000 mL or more after randomisation	4/77 (5.2)	8/74 (10.8)	RR 0.48 (0.15, 1.53)	*No significant difference* *p* = 0.21 Heterogeneity NA
	N = 151 (1 RCT) Ducloy-Bouthors 2011				Mean blood loss, mL	280 ± 320 (n = 77)	387 ± 409 (n = 74)	MD –107.00 (–224.44, 10.44)	*No significant difference* *p* = 0.074 Heterogeneity NA

CI, confidence interval; hrs, hours; IU, international units; MC, multicentre; MD, mean difference; M-H, Mantzel-Hentzel; NR, not reported; OR, odds ratio; RCT, randomised controlled trial; RR, relative risk; SD, standard deviation; TXA, tranexamic acid; UK, United Kingdom; US, United States; WMD, weighted mean difference

a. Where only one RCT is identified in a systematic review, the evidence has been considered as RCT evidence. Where the systematic review assesses observational and cohort studies, the evidence has been considered as according to the study design features. The risk of bias of the included primary studies is based on the quality assessment reported by the systematic review authors.

b. Only applicable to systematic review studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if P_{het} >0.1 and I^2 <25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25–50%; substantial heterogeneity I^2 >50%.

c. Calculated post-hoc using RevMan 5.4

4.8.3.4 Transfusion volume

A summary of the evidence relating to transfusion volumes associated with TXA in patients with critical bleeding is presented in Table 4.73

In a meta-analysis of data from studies included in this review (see Figure 4.49), the RCT evidence in critically bleeding trauma patients (CRASH-2) suggested there was little to no difference on the volume of RBCs transfused in patients who received TXA (mean 6.06 units) compared with those who did not receive TXA (mean 6.29 units) (SMD –0.02, 95%CI –0.02, 0.02; p = 0.25; random effect) (*GRADE: low*).

Among the cohort studies that reported data, the volume of RBCs transfused was higher among patients who received TXA (range 4.42 units to 22 units) compared with those who did not receive TXA (range 2 to 16 units) (SMD 0.53; 95%CI 0.22, 0.85; p = 0.001, I^2 = 90%) *(GRADE: Very low).* Noting there was substantial heterogeneity with a wide variety of injury severity and bleeding risk in the included studies, with the results likely to differ after adjustments for confounders across all studies (e.g. patients who received TXA had higher incidence of shock, blood loss and transfusion needs).

None of the included RCTs or cohort studies reported sufficient data relating to transfusion volumes of other blood components. The available evidence was therefore not further considered.

Figure 4.49 Forest plot of comparison: TXA vs no TXA, outcome: RBC transfusion volume

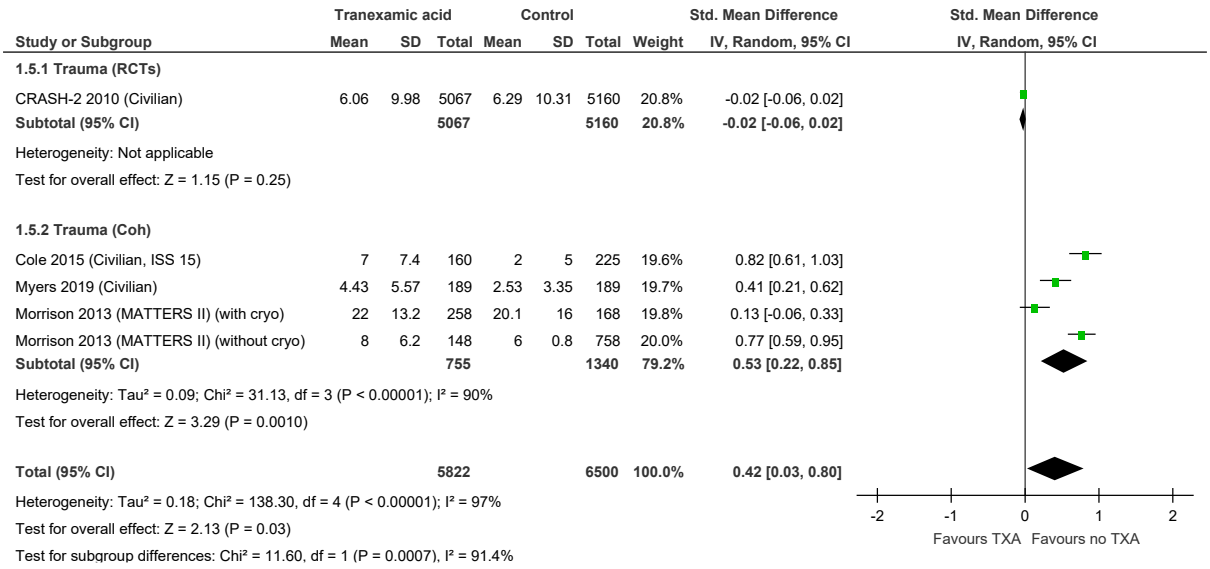


Table 4.73 Results for TXA versus no TXA: Patients with critical bleeding – Transfusion volume

Study ID Study design[a]	Sample size (no. of trials) included in analysis	Patient population	Setting (Location)	Comparison	Outcome	Results			
						TXA Mean ± SD (n)	No TXA Mean ± SD (n)	Risk estimate (95 CI)	*Statistical significance* *p*-value Heterogeneity[b]
Trauma setting									
Cannon 2017 SR *Moderate quality*	N = 11 944 (1 RCT, 2 Coh) CRASH-2 2010 Cole 2015 Morrison 2013 CRYO+ Morrison 2013 CRYO- Morrison 2013 total	Patients with severe trauma at risk of death from haemorrhage* *patients requiring blood transfusion and/or with an injury score greater than 25	Civilian and military trauma	TXA vs no TXA	RBC transfusion volume, units	NR (5633) 6.06 ± 9.98 (5067) 7 ± 7.4 (160) 22 ± 13.2 (258) 8 ± 6.2 (148)	NR (6311) 6.29 ± 10.31 (5160) 2 ± 5 (225) 20.1 ± 16 (168) 6 ± 0.8 (758)	MD 2.14 (–0.36, 4.63) MD –0.23 (–0.62, 0.16) MD 5.00 (3.68, 6.32) MD 1.90 (–1.01, 4.81) MD 2.00 (1.00, 3.00) MD 1.99 (1.04, 2.94)	*No significant difference* *p* = 0.09 Substantial heterogeneity I^2 = 96 (*p* < 0.00001)
Huebner 2017 SR *Critically low quality*	N = 300 (1 Coh) Valle 2014	Patients with trauma at risk of death from haemorrhage	Civilian trauma SC (US)	TXA vs no TXA	Total volume of RBC required in operating room, mL	2250	1500	NR	*Favours placebo* *p* = 0.002
					Total volume fluid received in ED, mL	2675	2250	NR	*Favours placebo* *p* = 0.025
					Total volume FFP in operating room, mL	1750	1125	NR	*Favours placebo* *p* = 0.009
Ker 2015 SR *High quality*	N = 20 127 (1 RCT) CRASH-2 2010	Adult trauma patients with, or at risk of, significant bleeding, including patients with moderate to severe TBI	MC, 40 countries, Thailand	IV TXA vs standard care	Volume of blood transfused, mean *All trauma*	3.05 ± 7.7 (10 060)	3.22 ± 8.02 (10 067)	MD –0.17 (–0.39, 0.05)	*No significant difference* *p* = 0.13 Heterogeneity NA
Myers 2019 Retrospective cohort *Serious risk of bias*	N = 378	Patients presenting to a level 1 trauma centre	Level 1 trauma centre (NR)	TXA within three hours of presentation vs No TXA	Transfusion of platelets, units	1.18 ± 2.17 (NR)	0.43 ± 1.43 (NR)	NR	*Favours intervention* *P < 0.001*
					Transfusion of RBCs, units	4.43 ± 5.57 (NR)	2.53 ± 3.35 (NR)	NR	*Favours intervention* *p < 0.001*
					Transfusion of FFP, units	2.77 ± 5.14	1.44 ± 3.37 (NR)	NR	*Favours intervention* *p < 0.001*

CI, confidence interval; Coh, cohort study; ED, emergency department; FFP, fresh frozen plasma; hrs, hours; IQR, interquartile range; IU, international units; IV, intravenous; MD, mean difference; M-H, Mantzel-Hentzel; NA, not applicable; NR, not reported; OR, odds ratio; RBC, red blood cells; RCT, randomised controlled trial; RR, relative risk; SC, single centre; SD, standard deviation; TXA, tranexamic acid; UK, United Kingdom; US, United States

a. Where only one RCT is identified in a systematic review, the evidence has been considered as RCT evidence. Where the systematic review assesses observational and cohort studies, the evidence has been considered as according to the study design features. The risk of bias of the included primary studies is based on the quality assessment reported by the systematic review authors.
b. Only applicable to systematic review studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if P_{het} >0.1 and I^2 <25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25–50%; substantial heterogeneity I^2 >50%.
c. Calculated post-hoc using RevMan 5.4

4.9 Viscoelastic haemostatic assays (Question 8)

Question 8 – (interventional)

In patients *with* critical bleeding, does the use of viscoelastic haemostatic assays change patient outcomes?

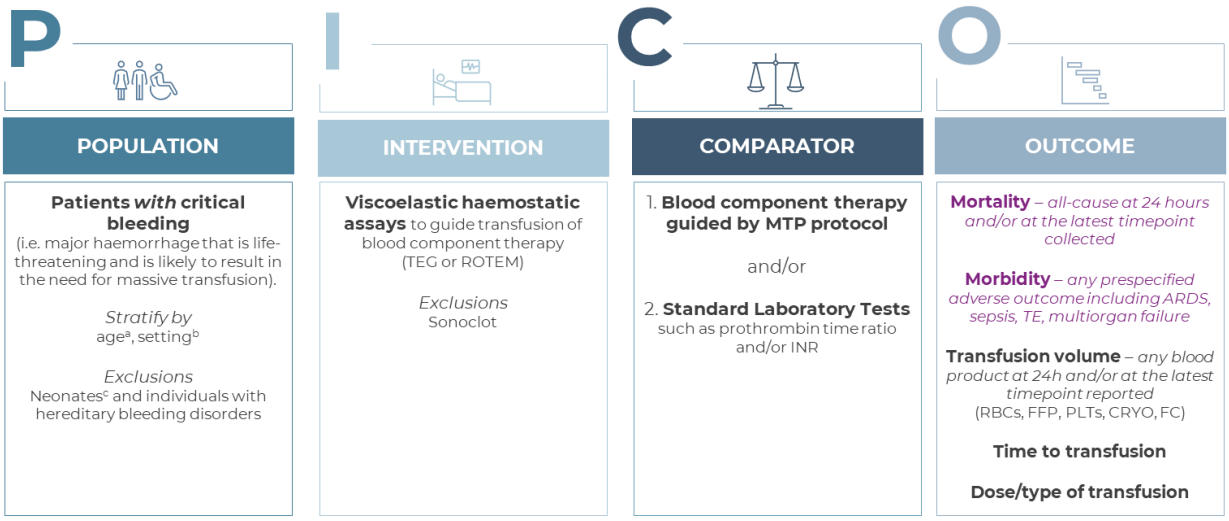
4.9.1 Methods

This question examined the effects of viscoelastic haemostatic assays (TEG and ROTEM) compared to the use of an MHP and/or standard laboratory tests in guiding the transfusion of blood components in patients with critical bleeding (i.e. major haemorrhage that is life-threatening and is likely to result in the need for massive transfusion) as outlined in Figure 4.50.

Studies were eligible for inclusion from any setting (including trauma, obstetrics, and perioperative) if, at the time of study inclusion, patients had major bleeding that was likely to result in the need for transfusion. Studies where bleeding status was not assessed at the time of inclusion were excluded (such as those that randomised patients prior to elective cardiac surgery). Studies in neonates (newborns up to 28 days) and studies in individuals with hereditary bleeding disorders were also not eligible for inclusion.

Viscoelastic haemostatic assays other than TEG or ROTEM (i.e. Sonoclot) were not eligible for inclusion.

Figure 4.50 PICO criteria: Question 8 – viscoelastic haemostatic assays



Abbreviations: ARDS, acute respiratory distress syndrome; CRYO, cryoprecipitate; FC, fibrinogen concentrate; FFP, fresh frozen plasma; INR, international normalised ratio; MTP, massive transfusion protocol; PLTs, platelets; RBCs, red blood cells; ROTEM, rotational thromboelastometry; TE, thromboembolic event; TEG, thromboelastography

a. Adult (aged over 18 years), child (aged 2 to 12 years), adolescent (aged 13 to 18 years), infants (aged 1 to 23 months).
b. e.g. trauma, obstetric, perioperative (cardiothoracic, general surgery, gastrointestinal, liver transplant), paediatric, other.
c. Newborns up to 28 days following birth.

The selection of studies was conducted according to the screening criteria described in Section 3.3.

The initial 2018 search was limited to studies published after 2000, noting studies published prior to 2000 and identified within a systematic review were also eligible for inclusion. No restrictions were applied to study design (or size), meaning nonrandomised studies (with concurrent or noncurrent controls) and observational cohort studies were eligible for inclusion.

Assuming all relevant primary studies had been identified in the included systematic reviews[35] (135-145); the screening of primary studies was limited to studies published from January 2015. This was based off the latest literature search date of the most comprehensive identified systematic review (Wikkelsø 2017).

An updated literature search was conducted in August 2019[36] and again in September 2021[37] to identify any new studies meeting the eligibility criteria. In these updated searches the focus was the identification of systematic reviews (of RCTs or cohort studies). With the latest search date of the best available systematic review used as a starting point for screening for additional RCTs.

4.9.2 Summary of evidence

4.9.2.1 Systematic reviews

Twelve systematic reviews (135-145) were included that that assessed the effects of TEG or ROTEM to guide blood component therapy in patients with critical bleeding.

Four reviews were focused on patients with acute need for transfusion due to bleeding in any clinical setting (Roullet 2018, Wikkelsø 2017, Fahrendorrf 2017, Hass 2014), two focused on adult trauma patients (Da Luz 2014, Bugaev 2020), one was in bleeding management in patients with end-stage liver disease (Saner 2016), four on patients with coagulopathic bleeding in cardiac surgery (Li 2019, Serriano 2017, Deppe 2016, Corredor 2015), and one in management of major obstetric haemorrhage (Amgalan 2020).

The main characteristics and quality of these reviews and relevant outcomes assessed are summarised in Table 4.74.

A matrix illustrating the overlap of RCTs identified in each review is provided in Table 4.75.

Among the 24 RCTs identified by the included systematic reviews, there were 16 RCTs that were not included in the evidence evaluation because they were conducted in patients who did not have major bleeding at study inclusion (146-161). Twelve of these RCTs were in the cardiac setting (Karkouti 2016, Agarwal 2015, Nakayama 2015, Cui 2010, Girdauskas 2010, Ak 2009, Westbrook 2009, Rauter 2007, Kultufan Turan 2006, Avidan 2004, Royston 2001, Shore-Lesserson 1999), one in liver transplant (Wang 2010), one in hepatic surgery (De Pietri 2016), one in surgical excision of burn wounds (Schaden 2012), and one in scoliosis surgery (Cao 2016).

[35] 10 systematic reviews found (Li 2019, Roullet 2018, Fahrendorrf 2017, Serriano 2017, Wikkelsø 2017, Deppe 2016, Saner 2016, Corredor 2015, Da Luz 2014, Hass 2014).

[36] One systematic review found (Drumheller 2019) did not provide any additional data than that already included, therefore was not considered further (duplicate data).

[37] Two systematic reviews found (Amgalan 2020, Bugaev 2020) and included in the review.

A further two RCTs (162, 163) were not included because the studies were not appropriately designed to answer our research question. The RCT by Rahe-Meyer 2013 was confounded by different transfusion protocols as it assessed the administration of fibrinogen concentrate guided by TEG compared with standard care (FFP and platelet therapy) in bleeding patients undergoing elective thoracic or thoracoabdominal aortic replacement surgery involving CPB. The RCT by Collins 2017 evaluated the effects of early fibrinogen replacement (with fibrinogen concentrate) compared with placebo in women with ongoing postpartum haemorrhage (1000 to 1500 mLs). Participants in both groups received ROTEM guided care.

A matrix illustrating the overlap of nonrandomised cohort studies identified in each reviews is provided in Table 4.76.

Among the 38 nonrandomised cohort studies identified by the included systematic reviews, 24 (164-186){Gorlinger, 2012 #95} were not included in the evidence evaluation because they did not include a comparator group (Rourke 2012, Johannsen 2013), involved patients who were not critically bleeding (Spiess 1995, Anderson 2006, Spalding 2007, Rahe-Meyer 2009a; Rahe-Meyer 2009b, Görlinger 2010, Noval-Padillo 2010, Trzebicki 2010, Görlinger 2011, Romlin 2011, Görlinger 2012, Hvas 2012, Wang 2012, Xu 2014, Leon-Justel 2015, Roullet 2015, Bedreli 2016, De Pietri 2016, St-Onge 2018, Kuiper 2019) or were confounded by inclusion of the intervention in both treatment groups (Mallaiah 2015, Collins 2017).

Table 4.74 Characteristics and quality of systematic review evidence: TEG or ROTEM versus usual care

Review ID ***Review quality***	Study design	Population	Intervention	Comparator	Outcomes
Any clinical setting					
Roullet 2018 (136) *Critically low*	Narrative review (Position paper)	Adult and paediatric patients with trauma, cardiac surgery and liver transplant, women with PPH	TEG or ROTEM guided algorithm	Standard care	Mortality Transfusion volume
Fahrendorrf 2017 (137) *Low*	SR / MA of RCTs	Patients in acute need for blood transfusions due to bleeding	TEG or ROTEM guided algorithm	Standard care (clinician's discretion and/or conventional coagulation tests)	Mortality Transfusion volume
Wikkelsø 2017 (139, 140) *High*	SR / MA of RCTs	Adults and children with bleeding	TEG or ROTEM guided algorithm	Standard care (clinical judgement, usual care and standard laboratory tests)	Mortality Transfusion volume
Hass 2014 (145) *Critically low*	Narrative review	Trauma patients, cardiac and aortic surgical patients, liver transplantation	TEG or ROTEM guided algorithm	Standard care	Mortality Transfusion needs

Review ID *Review quality*	Study design	Population	Intervention	Comparator	Outcomes
Trauma					
Da Luz 2014 (144) *Moderate*	SR of RCTs and observational studies	Adult trauma patients	TEG or ROTEM guided algorithm	Standard care	Mortality Transfusion needs
Bugaev 2020 (187) *Moderate*	SR / MA of RCTs and observational studies	Adult trauma patients a	TEG or ROTEM guided algorithm	Standard care	Mortality Transfusion needs
Surgical (liver transplant)					
Saner 2016 (141) *Critically low*	Narrative review (primary studies retrieved)	Bleeding management in patients with end-stage liver disease	TEG or ROTEM guided transfusion	Standard care	Mortality Transfusion needs
Surgical (cardiac)					
Li 2019 (135) *Moderate*	SR / MA of RCTs and observational studies	Patients with coagulopathic bleeding in cardiac surgery	TEG or ROTEM guided algorithm	Standard care	Mortality Morbidity Transfusion needs
Serriano 2017 (138) *High*	SR / MA of RCTs	Patients with coagulopathic bleeding in cardiac surgery	TEG or ROTEM guided algorithm	Standard care	Mortality Morbidity Transfusion needs
Deppe 2016 (142) *Moderate*	SR / MA of RCTs and observational studies	Patients undergoing cardiac surgery	TEG or ROTEM guided algorithm	Standard care	Mortality Major morbidity Transfusion needs
Corredor 2015 (142) *Moderate*	SR / MA of RCTs and observational studies	Patients undergoing cardiac surgery b	TEG or ROTEM guided algorithm	Standard care	Mortality Morbidity Transfusion needs
Obstetrics and maternity					
Amgalan 2020 (188) *Critically low*	SR of RCTs and observational studies	Pregnant women at risk of thrombosis or haemorrhage during pregnancy or peripartum	TEG or ROTEM guided transfusion	Standard care	Morbidity Transfusion needs

Abbreviations: MA, meta-analysis; RCT, randomised controlled trial; ROTEM, rotational thromboelastometry; SR, systematic review; TEG, thromboelastography

a. Bugaev 2020 examined the effects of TEG or ROTEM to guide blood component therapy in three populations: trauma, surgical and critically ill. Only the trauma population has been considered in this review.

b. Corredor 2015 also provided a narrative summary of 30 observational studies predicting post-operative bleeding loss. As this outcome was not considered in this review, these studies were not included here.

Table 4.75 Overlap table of RCTs identified by included systematic reviews: TEG or ROTEM versus usual care

		Trauma	Surgical (cardiac)																	Surgical (liver)	Surgical (other)			Obstetrics
	Study ID	Gonzalez 2016	Karkouti 2016 [a]	Agarwal 2015 [a]	Nakayama 2015 [a]	Rahe-Meyer 2013 [b]	Weber 2012	Kempfert 2011	Paniagua 2011	Cui 2010 [a]	Girdauskas 2010 [a]	Ak 2009 [a]	Westbrook 2009 [a]	Rauter 2007 [a]	Kultufan Turan 2006 [a]	Avidan 2004 [a]	NCT00772239	Nuttal 2001	Royston 2001 [a]	Shore-Lesserson 1999	Wang 2010 [a]	Schaden 2012 [a]	Cao 2016 [a]	De Pietri 2016 [a]	Collins 2017b [b]
Review ID	Amgalan 2020 [e]																							--
	Bugaev 2020	✓																			X			
	Li 2019 [d]		X				✓	✓	✓		X	X	X	X	X	X		✓	X	X					
	Roullet 2018	✓	X		X																No studies found			--
	Fahrendorrf 2017	✓					✓	✓	✓		X	X	X			X		✓	X	X	X	X	X	X	
	Wikkelsø 2017				X		✓	✓	✓	X	X	X	X	X	X	X	--	✓	X	X	X	X			
	Serraino 2017 [c]		X		X		✓		✓	X	X	X	X			X		✓	X	X					
	Deppe 2016 [c]						✓				X	X	X		X	X		✓	X	X					
	Saner 2016 [d]																				X			X	
	Corredor 2015 [c]			X			✓				X	X	X			X		✓	X	X					
	Da Luz 2014 [f]																								
	Haas 2014					X	✓				X											X			

✓ = study included in this review; X = study did not meet the inclusion criteria for this review; -- = study identified by the systematic review authors but not contribute any data
a. Population out of scope. Subjects not critically bleeding.
b. Study is confounded (all patients are assessed using a viscoelastic haemostatic assay) and does not provide usable data.
c. The systematic reviews by Li 2019, Serriano 2017, Deppe 2016 and Corredor 2015 were focused on patients in the cardiac setting.
d. The systematic review by Saner 2016 was focused on patients with end-stage liver disease.
e. The systematic review by Amgalan 2020 was focused on obstetrics patients
f. The systematic review by Da Luz 2014 was focused on patients admitted with trauma.

Table 4.76 Overlap table of nonrandomised cohort studies identified by included systematic reviews: TEG or ROTEM versus usual care

Review ID	Trauma												Surgical (cardiac)													Surgical (liver transplant)								Obstetrics and maternity				
Study ID	Johansson 2013 [a]	Tapia 2013	Görlinger 2012a	Kashuk 2012	Rourke 2012 [a]	Nienaber 2011	Schöchl 2011	Schöchl 2010 [a]	Unruh 2019	Guth 2019	Prat 2017	Nardi 2015	Kuiper 2019 [b]	St-Onge 2018 [b]	Sun 2014 [b]	Fassl 2013	Hanke 2012	Hvas 2012 [b]	Romlin 2011 [b]	Görlinger 2011 [b]	Rahe-Meyer 2009a [b]	Rahe-Meyer 2009b [b]	Spalding 2007 [b]	Anderson 2006 [b]	Spiess 1995 [b]	Bedreli 2016 [b]	Leon-Justel 2015 [b]	Roullet 2015 [b]	Görlinger 2012b [b]	Wang 2012 [b]	Görlinger 2010 [b]	Noval-Padillo 2010 [b]	Trzebicki 2010 [b]	Snegovskikh 2018	Collins 2017b [c]	Mallaiah 2015 [c]	Barinov 2015	McNamara 2019
Amgalan 2020																																		--	--	--		✓
Bugaev 2020							✓		✓	✓	✓	✓																										
Li 2019 [d]													X	X		✓	✓			X				X	X													
Roullet 2018	--			--				--					No studies found															X		X				✓	--	X		
Fahrendorrf 2017 [e]																																					✓	
Wikkelsø 2017 [e]																																						
Serriano 2017 [e]																																						
Deppe 2016 [d]															X	✓	✓			X	X		X	X	X													
Saner 2016 [f]																										X	X											
Corredor 2015 [d]																																						
Da Luz 2014 [g]		✓		✓			✓	X																														
Haas 2014			✓		X	✓	✓	X								✓	✓	X	X	X	X	X	X	X					X		X	X	X	No studies found				

✓ = study included in this review; X = study did not meet the inclusion criteria for this review; -- study identified by the systematic review authors but not included (no usable data)

a. Study design out of scope, not a comparative study.

b. Population out of scope. Not all participants are critically bleeding.

c. Study is confounded (all patients are assessed using a viscoelastic haemostatic assay).

d. The systematic reviews by Li 2019, Deppe 2016 and Corredor 2015 were focused on patients in the cardiac setting.

e. The systematic reviews by Fahrendorrf 2017, Serriano 2017 and Wikkelsø 2017 did not include nonrandomised studies.

f. The systematic review by Saner 2016 was focused on patients with end-stage liver disease.

g. The systematic review by Da Luz 2014 was focused on patients admitted with trauma.

4.9.2.2 Randomised controlled trials

The main characteristics and quality of the included RCTs and relevant outcomes assessed are summarised in Table 4.77.

There were six RCTs (189-194) identified by the included systematic reviews that were considered relevant to this review because they examined the effect of TEG or ROTEM in patients *with* critical bleeding. Two of the included studies used a TEG guided transfusion algorithm (Gonzalez 2016, Nuttall 2001) and the other four studies (Weber 2012, Kempfert 2011, Paniagua 2011, NCT00772239) used a ROTEM guided transfusion algorithm.

One additional RCT (Baksaas-Aasen 2020) was identified in the systematic review and handsearching process examined the effect of VHAs in adult trauma patients *with* critical bleeding (195, 196).

Baksaas-Aasen 2020 (iTACTIC) was a multicentre RCT conducted in Trauma centres located in Denmark, The Netherlands, Norway, Germany and the UK. The study focused on trauma-induced coagulopathy comparing outcomes in 396 patients in whom a local MHP had been initiated, with RBC transfusion guided by VHAs or conventional coagulation tests. The MHPs included empiric delivery of tranexamic acid, blood components delivered in a 1:1:1 ratio of RBCs, plasma and platelet transfusions and limited infusion of crystalloid fluids.

Gonzalez 2016 was a single centre RCT conducted in the US that enrolled adults patients (aged over 18 years) with blunt or penetrating trauma sustained less than six hours before admission. Patients had to have an injury severity score greater than 15 and were likely to require transfusion of RBC within six hours from admission as indicated by clinical assessment. Patients were predominantly male (70.3%0 with a median (IQR) age of 30 (24 to 43). The number of patients with blunt / penetrating trauma was not reported.

Five RCTs (Weber 2012, Paniagua 2011, Kempfert 2011, NCT00772239, Nuttall 2001) were conducted at single centres and involved adult patients scheduled for cardiothoracic surgery, with various definitions for enrolment relating to diffuse and/or abnormal bleeding from capillary beds and/or excessive blood loss after surgery. Three studies were stopped early. Paniagua 2011 was terminated early due to slow recruitment and included eight of 52 patients that did not meet the inclusion criteria. Weber 2012 was stopped early at an interim analysis due to clear benefits, and another study (NCT00772239) was stopped early due to futility (no data available).

The overall risk of bias for included RCTs was judged to be high (137, 138, 140). Most concerns were related to little or no allocation concealment or blinding of clinical personnel, which contributed to the high procedural bias favouring the intervention. Reporting bias was also considered high for blood loss, FFP transfusion and PLT transfusion due to incomplete reporting of outcome data, with no explanations given for missing data.

Table 4.77 Characteristics and quality of RCT evidence: TEG or ROTEM versus usual care

Study ID *Risk of bias*	Study design	Population	Intervention	Comparator	Outcomes
Trauma					
Baksaas-Aasen 2020 (iTACTIC) (195, 196) *High*	RCT, MC	Adult trauma patients with clinical signs of bleeding Activation of local MHP and if RBC transfusion had been initiated, randomised within 3 hours of injury and maximum of 1 hour after admission into the emergency department.	MHP guided by VHAs (n=201)	Conventional coagulation test (n=195)	Mortality Morbidity Transfusion needs
Gonzalez 2016 (189) *High*	RCT, SC	Adult patients with blunt or penetrating trauma Injury sustained < 6 hours before admission, with ISS >15 and likely to require transfusion of RBC within 6 hours as indicated by clinical assessment	MTP guided by TEG (n=56)	MTP guided by conventional coagulation tests (aPTT, INR, fibrinogen level, D-dimer) (n=55)	Mortality Morbidity Transfusion needs
Cardiothoracic surgery					
Weber 2012 (194) *High*	RCT, SC *study stopped at interim analysis	Adult patients scheduled for complex cardiothoracic surgery with CPB enrolled after heparin reversal if: (1) diffuse bleeding from capillary beds and/or (2) intraoperative or post-operative blood loss exceeding 250 mL/hour or 50 mL/10 min.	Peri- and post-operative management guided by ROTEM (n=50)	Algorithm based on standard laboratory tests (ACT, INR, aPTT, platelet count and fibrinogen level) (n=50)	Mortality, 6-mth Morbidity Transfusion needs
Paniagua 2011 (193) *High*	RCT, SC *study stopped due to slow enrolment	Adult patients undergoing cardiac surgery randomised if: (1) diffuse bleeding after protamine and/or (2) excessive bleeding after surgery (≥ 300 mL in the first hour; ≥ 250 mL in the second hour; ≥ 150 mL thereafter)	MTP guided by ROTEM (n=24)	Routine transfusion therapy based on standard laboratory coagulation tests (n=28)	Mortality Transfusion needs
Kempfert 2011 (190) *High*	RCT, SC	Adult patients with significant post-operative bleeding* following standard elective isolated or combined cardiac surgical procedures *(> 200 mL/hour)	MTP guided by ROTEM (n=52)	Transfusion protocol based on standard coagulation testing (n=52)	Transfusion needs
NCT00772239 (191) *High*	RCT, SC *study stopped due to futility	Adult patients with abnormal bleeding after cardiac surgery or heart transplantation	Therapeutic algorithm guided by ROTEM (n=50)	Coagulation management based on standard laboratory tests (n=50)	No usable data
Nuttall 2001 (192) *High*	RCT, SC	Adult patients with abnormal microvascular bleeding after CPB	Transfusion algorithm guided by TEG (n=41)	Algorithm based on clinical judgement with or without laboratory tests (n=51)	Transfusion needs

Abbreviations: aPTT, activated partial thromboplastin time; CPB, cardiopulmonary bypass; INR, international normalised ratio; ISS, injury severity score; MC, multicentre; MHP, major haemorrhage protocol; MTP, massive transfusion protocol, PPH, postpartum haemorrhage; RCT, randomised controlled trial; SC, single centre; TEG, thromboelastography; VHA, viscoelastic haemostatic assay

4.9.2.3 Observational and cohort studies

The main characteristics and quality of the included nonrandomised studies and relevant outcomes assessed are summarised in Table 4.78.

There were 14 nonrandomised cohort studies identified by the included systematic reviews that examined the effects of TEG or ROTEM in guiding blood component therapy in patients *with* critical bleeding and were considered relevant to this review (197-210). One additional nonrandomised cohort study (Wang 2017) (211) was identified in the literature search that examined the effects of TEG in patients who sustained traumatic liver and/or spleen injuries receiving emergent blood component therapy.

Six of the included studies used a TEG guided transfusion algorithm (Guth 2019, Unruh 2019, Wang 2017, Barinov 2015, Tapia 2013, Kashuk 2012), and nine studies (McNamara 2019, Snegovskikh 2018, Prat 2017, Nardi 2015, Fassl 2013, Görlinger 2012, Hanke 2012, Nienaber 2011, Schöchl 2011) used a ROTEM guided transfusion algorithm.

Overall, 10 studies were conducted in the trauma setting (Guth 2019, Unruh 2019, Prat 2017, Wang 2017, Nardi 2015, Tapia 2013, Görlinger 2012, Kashuk 2012, Nienaber 2011, Schöchl 2011), two in the cardiac setting (Fassl 2013, Hanke 2012), and three in the obstetrics setting (McNamara 2019, Snegovskikh 2018, Barinov 2017).

In the trauma setting, five studies (Guth 2019, Wang 2017, Tapia 2013, Görlinger 2012, Kashuk 2012) were conducted at single centres and involved adult trauma patients (blunt and/or penetrating) with various definitions for injury severity and the timing or need for blood components (i.e. within six or 24 hours of admission). Five studies (Unruh 2019, Prat 2017, Nardi 2015, Nienaber 2011, Schöchl 2011) involved the collection of data from trauma registries (civilian and/or combat), with patients being selected based on injury severity (e.g. ISS ≥ 16, base deficit ≥ 2.0 mmol/L) or the need for blood components (e.g. receiving at least three units of RBCs within the first 24 hours).

In the surgical setting, both studies were conducted at singles centres and included adult patients undergoing elective and urgent proximal aortic surgery with hypothermic circulatory arrest with major bleeding (Fassl 2013) or adult patients with acute type A aortic dissection and aortic valve replacement (Hanke 2012). The studies with conducted in Switzerland and Germany.

In the obstetric setting, all three studies evaluated the effect of a viscoelastic haemostatic assay guided algorithm for treatment of coagulopathy to improve outcomes for women with major obstetric haemorrhage. Two studies included women with severe PPH (defined as an estimated blood volume loss of ≥ 1500 mLs) who had received care either before or after the introduction of a MHP that included a point-of-care viscoelastic assay. The studies were conducted at single centres in either the US (Snegovskikh 2018) or the UK (McNamara 2019) and reported data covering a 4- to 4.5-year period.

One study (Barinov 2016) was conducted in Russia and prospectively included women with PPH managed using a combined strategy involving TEG assessment of coagulation, early surgical haemostasis (estimated blood volume loss of ≥ 1000 mLs) and mechanical compression of the uterine wall combined with uterine cavity draining, via intrauterine balloon tamponade. The comparator group received uterine massage, manual examination of the uterus, and transfusion of FFP, RBCs, PLTs and protease inhibitors,

with late surgical haemostasis (blood loss volume ≥ 2000 mL). In the cases of severe obstetric bleeding, autologous red blood cell reinfusion was carried out (cell salvage).

Many of the included observational cohort studies were at serious risk of bias. This is because they were often conducted before and after the introduction of the intervention into clinical practice, introducing concerns with procedural bias that would favour the intervention. The use of historical controls introduced issues with changes in clinical practices that occur over time. The studies also had issues with incomplete report of outcome data, short follow-up and small sample size.

Table 4.78 Characteristics and quality of Observational and cohort studies evidence: TEG or ROTEM versus usual care

Study ID *Risk of bias*	Study design	Population	Intervention	Comparator	Outcomes
Trauma					
Guth 2019 (208) *Serious*	Before/after analysis, SC *historical controls	Adult trauma patients (ISS > 8) *who received at least one blood component (RBC, FFP, PLT) or coagulation factor concentrates (fibrinogen or PCC) during the first 24 hours after admission N=380	TEG guided management including FFP, PCC and platelets * Patients admitted from 1 January 2005 to 31 December 2008	CCT-guided transfusion protocol * Patients admitted from 1 January 2012 to 31 December 2015	Mortality Transfusion volume
Unruh 2019 (210) *Serious*	Retrospective analysis, trauma registry [a] *historical controls	Adult trauma patients who underwent MTP activation N=67	MTP guided by TEG * patients who underwent MTP activation from 1 July 2015 to 30 June 2016	Non-TEG guided MTP *patients who underwent MTP activation from 1 January 2014 to 31 December 2014	Mortality Blood component utilisation
Prat 2017 (206) *Serious*	Retrospective analysis, trauma registry [b] *historical controls	Civilian and combat trauma patients N=219	ROTEM guided transfusion * after ROTEM deployment to Bagram Airfield.	Non-ROTEM guided transfusion * before ROTEM deployment to Bagram Airfield	Mortality Transfusion volume Transfusion ratios
Wang 2017 (211) *Critical*	Retrospective cohort, SC	Adult trauma patients with sustained liver and/or spleen injuries receiving emergent BCT N=166	Blood component therapy guided by TEG	Non-TEG guided blood component therapy	Mortality Transfusion volume
Nardi 2015 (204) *Serious*	Before/after analysis, MC [c] *historical controls	Severely injured trauma patients (ISS > 15) *receiving at least three units of RBCs within the first 24 hours) N=226	ECS protocol guided by ROTEM *post-ECS adoption period (1 January 2013 to 31 December 2013)	Non-ROTEM guided transfusion protocol *pre-ECS adoption period (1 January 2011 to 31 December 2011)	Mortality Transfusion volume
Tapia 2013 (203) *Moderate*	Before/after cohort, SC	Adult trauma patients (blunt or penetrating) *receiving ≥ 6 units of RBCs in the first 24 hours N=289	MTP guided by TEG	Non-TEG guided MTP	Mortality Transfusion volume
Görlinger 2012 (199) *High*	Retrospective analysis, 3 x SC [d] *historical controls	Patients admitted in different perioperative settings	ROTEM guided management with FC and PCC	Non-ROTEM guided transfusion protocol	Transfusion volume

Study ID *Risk of bias*	Study design	Population	Intervention	Comparator	Outcomes
		(trauma, visceral and transplant, cardiovascular and general and surgical intensive care) N=5590			
Kashuk 2012 (201) *Moderate*	Before/after analysis, SC	Adult trauma patients *receiving ≥ 6 units of RBCs in the first 6 hours N=64	MTP guided by TEG	Non-TEG guided MTP	Mortality Transfusion volume
Nienaber 2011 (197) *High*	Retrospective analysis, 2 trauma registries [e]	Adult trauma patients with severe blunt trauma (ISS ≥ 16, base excess ≤ –2.0 mmol/L) N=36	ROTEM guided management including factor concentrates	Non-ROTEM guided transfusion protocol including FFP (no factor concentrates)	Mortality Morbidity Transfusion volume
Schöchl 2011 (198) *High*	Retrospective analysis, 2 trauma registries [f]	Adult trauma patients with severe trauma (ISS ≥ 16, base deficit ≥ 2.0 mmol/L) N=36	ROTEM guided management including FC and PCC	Non-ROTEM guided transfusion protocol including FFP (no FC and PCC)	Mortality Morbidity Transfusion volume
Surgical setting					
Fassl 2013 (202) *High*	Retrospective case-control, SC	Adult patients undergoing elective and urgent proximal aortic surgery with hypothermic circulatory arrest with major bleeding[g] N=194	Haemostatic management guided by ROTEM including FFP, PLT, FC, PCC and rFVIIa	Conventional haemostatic management *matched controls	Mortality Morbidity Transfusion volume
Hanke 2012 (200) *High*	Case-control (pilot), SC	Adult patients with acute type A aortic dissection and aortic valve replacement N=10	Haemostatic management guided by ROTEM	Conventional haemostatic management *matched controls	Mortality Transfusion volume
Obstetrics and maternity					
McNamara 2019 (209) *Serious*	Retrospective analysis, SC *matched historical controls	Women with major obstetric haemorrhage N=255 **estimated >1500 mL	MHP guided by ROTEM	Non-ROTEM guided MHP	Mortality Morbidity Transfusion volume
Snegovskikh 2018 (207) *High*	Retrospective analysis, SC *historical controls	Women with severe PPH* N=86 *estimated >1500 mL	MHP guided by ROTEM	Non-ROTEM guided MHP	Morbidity
Barinov 2016 (205) *High*	Open, prospective controlled trial, SC	Women with PPH (gestational age 28 to 42 weeks) N=119 *estimated >1000 mL	Combined strategy [h] of haemorrhage management including TEG	Conventional management	Transfusion volume

Abbreviations: BCT, blood component therapy; CCT, conventional coagulation tests; ECS, early coagulation support; FC, fibrinogen concentrate; FFP, fresh frozen plasma; ICU, intensive care unit; ISS, injury severity score; MTP, massive transfusion protocol; RBC, red blood cells; PCC, prothrombin complex concentrate; PLT, platelets; RBC, red blood cell; ROTEM, rotational thromboelastometry; rFVIIa, recombinant activated factor VII; SC, single centre; TEG, thromboelastography

a. Trauma registry of the American College of Surgeons verified Level I trauma centre.

b. Data collected from the Department of Defence Trauma Registry.

c. Data collected from two hospitals: S Camillo Hospital in Rome and Bufalini Hospital in Cesena, Italy.

d. Each hospital reported separately: (a) Trauma Centre Salzburg (b). Intensive care, University Hospital Essen (c) General/Surgical Critical Care, Medical University Innsbruck. Data from (a) and (b)reported here.

e. Comparison between Innsbruck Trauma databank (intervention) and Trauma-Registry-DGU, Germany (control).

f. Comparison between Salzburg Trauma Centre and the Trauma-Registry-DGU, Germany (control).
g. Major bleeding defined as need for thoracic re-exploration or drainage volumes exceeding 1000 mL in the first 24 hours.
h. Combined strategy included *early* surgical haemostasis if blood volume loss exceeded 1000 mL, mechanical pressure and intrauterine balloon tamponade; the comparator included uterine massage, transfusion of blood components, and *late* surgical haemostasis (blood volume loss exceeded 2000 mL).

4.9.3 Results

4.9.3.1 Mortality

A summary of the evidence relating to the outcome of mortality in patients with critical bleeding in whom the blood component therapy was guided by TEG or ROTEM is presented in Table 4.79.

A meta-analysis of data including evidence from both RCTs and cohort studies (see Figure 4.51) showed the mortality rate (latest timepoint) among patients who are critically bleeding to be lower when blood component therapy was guided by TEG or ROTEM compared with haemostatic management guided by an MHP or standard laboratory tests (14.8% vs 17.9%; RR 0.75; 95% CI 0.64, 0.88; $p = 0.004$; random effect, $I^2 = 0\%$).

Data from the included RCTs suggested the mortality rate to be lower in the TEG or ROTEM groups (19.8%) when compared with haemostatic management that was not guided by a VHA (28.1%) (RR 0.61; 95% CI 0.37, 1.02; $p = 0.06$; random effect, $I^2 = 44\%$). The difference did not reach statistical significance but was considered clinically important. *(GRADE: very low)*.

Data from the included cohort studies, suggested that TEG or ROTEM guided protocols were associated with reduced mortality compared with haemostatic management not guided by TEG or ROTEM (RR 0.75; 95% CI 0.62, 0.94; $p = 0.004$; $I^2 = 0\%$) *(GRADE: very low)*.

All identified systematic reviews suggested that the use of viscoelastic haemostatic assays to guide blood component therapy provides no significant survival benefit in patients with critical bleeding, regardless of clinical setting.

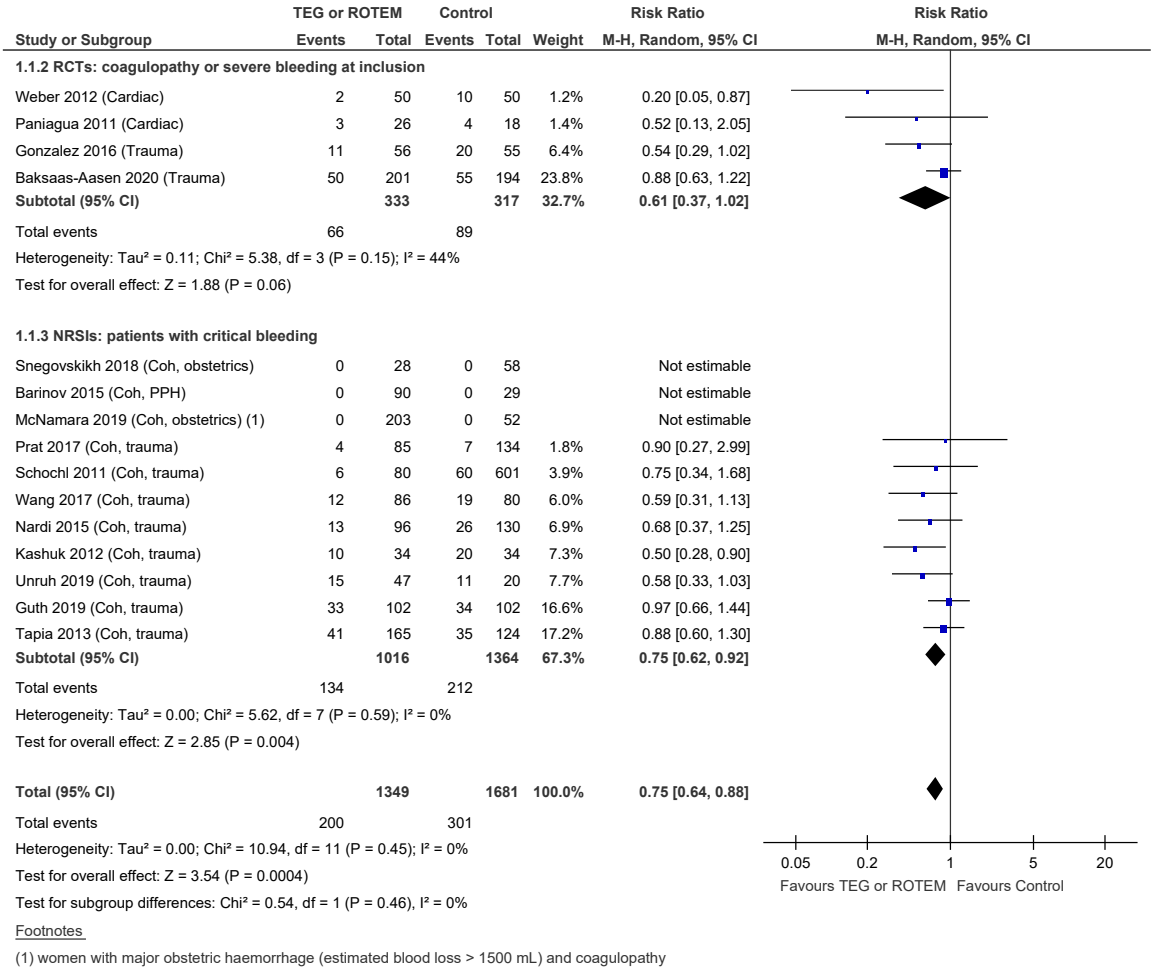
In trauma patients (see Figure 4.52), a total of 952 patients received blood component therapy guided by TEG or ROTEM, compared with 1474 patients who received blood component therapy guided by an MHP or standard laboratory tests. Among patients enrolled in an RCT, the mortality rate (latest timepoint) was lower when blood component therapy was guided by TEG or ROTEM (23.7%) than when haemostatic management was guided by an MHP or standard laboratory tests (30.1%). The difference was not statistically significant but was considered to be clinically important (RR 0.75; 95% CI 0.48, 1.17; $p = 0.20$; I^2=44%) (*GRADE: very low*).

In trauma patients, evidence in the cohort studies suggests that blood component therapy guided by TEG or ROTEM is associated with a significantly lower mortality rate than treatment guided by an MHP or standard laboratory tests (19.3% vs 17.3%; RR 0.75; 95% CI 0.62, 0.92; $p = 0.004$; $I^2 = 0\%$) (*GRADE: very low*).

In patients with diffuse and/or abnormal bleeding from capillary beds and/or excessive blood loss after surgery (see Figure 4.52), those who received blood component therapy guided by TEG or ROTEM had a mortality rate of 6.6% (5/76), which was lower than the mortality rate of 20.6% (14/68) observed among those whose management was not guided by TEG or ROTEM (RR 0.33; 95% CI 0.12, 0.91; $p = 0.03$; I^2= 0%) (*GRADE: very low*).

No deaths were observed in the observational studies that assessed the effects of blood component therapy guided by TEG or ROTEM among women with severe obstetric haemorrhage.

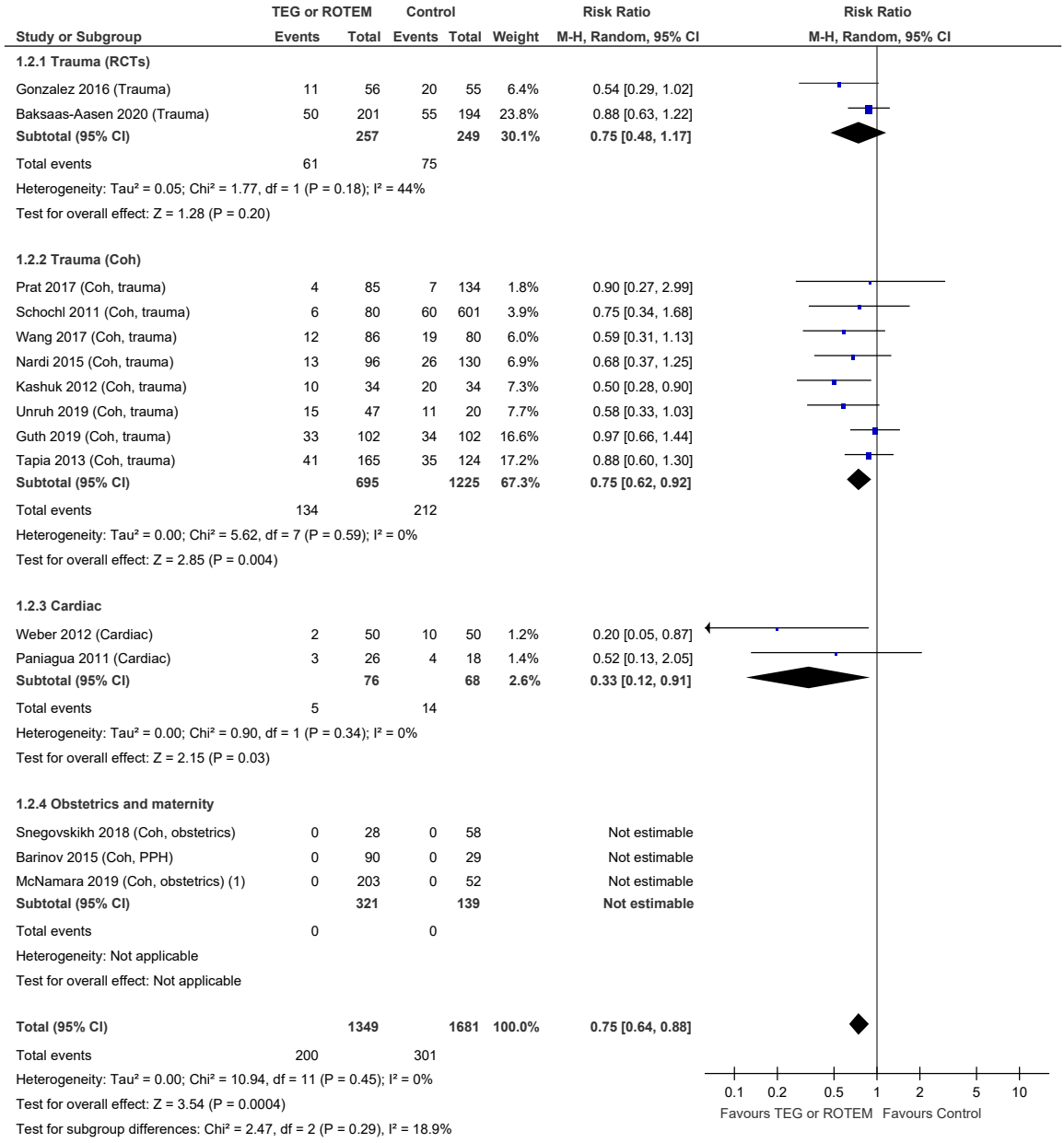
Figure 4.51 Forest plot of comparison: TEG or ROTEM vs MHP or standard laboratory tests, outcome: Mortality, latest timepoint



Footnotes

(1) women with major obstetric haemorrhage (estimated blood loss > 1500 mL) and coagulopathy

Figure 4.52 Forest plot of comparison: TEG or ROTEM vs MHP or standard laboratory tests, outcome: Mortality, by setting



Footnotes

(1) women with major obstetric haemorrhage (estimated blood loss > 1500 mL) and coagulopathy

Table 4.79 Results for TEG or ROTEM to guide BCT versus no TEG or ROTEM to guide BCT: Patients *with* critical bleeding – Mortality

Study ID Study design[a]	Sample size (no. of trials) included in analysis	Patient population	Setting (Location)	Comparison	Outcome	Results			
						TEG/ROTEM n/N (%)	No TEG/ROTEM n/N (%)	Risk estimate (95% CI)	*Statistical significance* *p*-value Heterogeneity [b]
Various settings									
Fahrendorff 2017 SR *High risk of bias*	N = 579 (6 RCTs) Ak 2009 Wang 2010 Girdauskas 2010 Weber 2012 Gonzalez 2016 De Pietri 2016	Patients with an acute need for blood components due to bleeding (includes trauma, liver transplant and cardiac surgery)	SC, Various	TEG or ROTEM guided algorithm vs the clinician's discretion and/or based on conventional coagulation tests	Mortality, all-cause	30/291 (10.3) 3/114 (2.6) 2/14 (14.3) 4/27 (14.8) 2/50 (4) 11/56 (19.6) 8/30 (26.7)	47/288 (16.3) 2/110 (1.8) 3/14 (21.4) 5/29 (17.2) 10/50 (20) 20/55 (36.3) 7/30 (23.3)	OR 0.60 (0.34, 1.07) OR 1.46 (0.24,8.91) OR 0.61 (0.09, 4.37) OR 0.83 (0-.20, 3.50) OR 0.17 (0.03, 0.81) OR 0.43 (0.18, 1.01) OR 1.19 (0.3.85)	*No significant difference* *p* = 0.08 Mild heterogeneity I^2 = 11% (*p* = 0.35)
Trauma setting									
Bugaev 2020 SR *High risk of bias*	N = 1488 (1 RCT, 5 Coh) Schöchl 2011 Nardi 2015 Gonzalez 2016 Prat 2017 Unruh 2019 Guth 2019	Severely injured trauma patients	Trauma (Germany, US, NR)	ROTEM or TEG guided algorithm vs no ROTEM or TEG	Mortality, all-cause	82/466 (17.6) 6/80 (7.5) 13/96 (13.5) 11/56 (19.6) 4/85 (4.7) 15/47 (32.0) 33/102 (32.4)	158/1042 (15.2) 60/601 (10) 26/130 (20) 20/55 (36.4) 7/134 (5.2) 11/20 (55) 34/102 (33.3)	RR 0.75 (0.59, 0.95) RR 0.75 (0.34, 1.68) RR 0.68 (0.37, 1.25) RR 0.54 (0.29, 1.02) RR 0.90 (0.27, 2.99) RR 0.58 (0.33, 1.03) RR 0.87 (0.66, 1.44)	*Favours TEG/ROTEM* *p = 0.02* No significant heterogeneity I^2 = 0 (*p* = 0.60)
Baksaas-Aasen 2020 RCT *High risk of bias*	N = 396	Adult trauma patients with clinical signs of bleeding and activation of local MHP.	MC, Various (Denmark, Netherlands, Norway, Germany, UK)	TEG or ROTEM guided algorithm vs conventional coagulation test	Mortality, all-cause 6 hours 24 hours 28 days 90 days	22/201 (11) 29/201 (14) 50/201 (25) 53/179 (29)	22/195 (11) 33/195 (17) 55/194 (28) 56/177 (31)	OR 0.97 (0.52,1.80) OR 0.83 (0.48, 1.42) OR 0.84 (0.54, 1.31) OR 0.91 (0.58, 1.42)	*No significant difference* *p = 0.915* *p = 0.495* *p = 0.435* *p = 0.678*
Roullet 2018 RCT *High risk of bias*	N = NR (1 RCT) Gonzalez 2016	Patients with severe trauma who are likely to require transfusion therapy	SC (US)	TEG or ROTEM guided algorithm vs the clinician's discretion and/or based on conventional coagulation tests	Mortality, 28 days < 6 hours 6-24 hours	11/56 (19.6) 4/56 (7.1) 7/56 (12.5)	20/55 (35.7) 12/55 (21.8) 8/55 (14.5)	RR 0.54 (0.29, 1.02)[c] RR 0.33 (0.11, 0.95) RR 0.86 (0.33, 2.21)	*Favours TEG* *p* = 0.049
Wang 2017 Coh *High risk of bias*	N = 166 (1 Coh)	Patients with traumatic liver and/or spleen injury	SC (US)	TEG guided algorithm vs clinical judgement or usual treatment	Mortality, in-hospital (total) N = 166	12/86 (14)	19/80 (15)	RR 0.59 (0.31, 1.13) [c]	*No association* *p* = 0.11

Study ID Study design[a]	Sample size (no. of trials) included in analysis	Patient population	Setting (Location)	Comparison	Outcome	Results			
						TEG/ROTEM n/N (%)	No TEG/ROTEM n/N (%)	Risk estimate (95% CI)	*Statistical significance* *p*-value Heterogeneity [b]
Da Luz 2014 Coh *Serious risk of bias*	N = 289 (1 Coh) Tapia 2013	Adult patients with severe trauma	SC (NR)	TEG or ROTEM guided algorithm vs standard of care	Mortality, 30 days patients receiving ≥ 6 U RBCs Blunt Penetrating	41/165 (25) 14/47 (30) 27/118 (23)	35/124 (28) 13/52 (25) 22/72 (31)	RR 0.88 (0.60, 1.30) [c] NR NR	*No association* *p* = 0.52 No association observed in multivariate analysis (blunt or penetrating trauma)
					Subgroup: patients with penetrating trauma receiving ≥ 10 U RBCs				*Favours TEG*
					Penetrating	22/66	20/37	NR	*p* = 0.04
	N = 68 (1 Coh) Kashuk 2012				Mortality *not adjusted for confounders	10/34 (29)	20/34 (59)	RR 0.50 (0.28, 0.90) [c]	Favours *TEG* *p* = 0.02
	N = 681 (1 Coh) Schöchl 2011			FC & PCC-guided vs FFP [d]	Mortality	6/80 (7.5)	60/601 (10)	RR 0.75 (0.34, 1.68) [c]	*No association* *p* = 0.69
	N = 131 (1 Coh) Schöchl 2010			FP, PLT, PCC- guided	Mortality vs TRISS predicted vs RISC predicted	NR (24.4)	 NR (33.7) NR (28.7)	 NR NR	*No association* *p* = 0.032 *p* > 0.05
					vs TRISS predicted vs RISC predicted	*Subgroup: excluding patients with TBI*			*Favours ROTEM*
						NR (14)	 NR (27.8) NR (24.3)	 NR NR	 *p* = NR *p* = NR
Haas 2014 Coh *Serious risk of bias*	N = 681 (1 Coh) Schöchl 2011	Adult patients with severe trauma	SC (Austria, Germany)	ROTEM guided algorithm vs standard of care [d, e]	Mortality	6/80 (7.5)	60/601 (10)	RR 0.75 (0.34, 1.68) [c]	*No association* *p* = NR
	N = 36 (1 Coh) Nienaber 2011					5/18 (13.9)	2/18 (11.1)	RR 2.50 (0.56, 11.25) [c]	*No association* *p* = 0.500
	N = 131 (1 Coh) Schöchl 2010				vs TRISS predicted	NR (24.4)	NR (33.7)	NR	*Favours ROTEM* *p* = 0.032
						Subgroup: excluding 17 patients with TBI			*Favours ROTEM*
						NR (14)	NR (27.8)	NR	*p* = 0.0018
Surgical setting									
Wikkelsø 2016 SR *High risk of bias*	N = 717 (8 RCTs)		SC		Mortality, latest follow-up * *7 out of 8 RCTs were at hospital discharge	14/364 (3.9)	26/353 (7.4)	M-H Random effects RR 0.57 (0.30, 1.07) Adj. 0.59 (0.23, 1.54) [f]	*No significant difference* *p* = 0.08 No heterogeneity I^2 = 0 (p = 0.54)

Study ID Study design[a]	Sample size (no. of trials) included in analysis	Patient population	Setting (Location)	Comparison	Outcome	Results			
						TEG/ROTEM n/N (%)	No TEG/ROTEM n/N (%)	Risk estimate (95% CI)	*Statistical significance* *p*-value Heterogeneity [b]
	Ak 2009 Girdauskas 2010 Royston 2001 Shore-Lesserson 1999 Nakayama 2015 Paniagua 2011 Wang 2010 Weber 2012	Adults with diffuse or excessive bleeding after cardiac surgery or orthotopic liver transplant	(Australia, Austria, China, France, Germany, Japan, Spain, Taiwan, Turkey, UK, US)	TEG or ROTEM guided transfusion vs clinical judgement or usual treatment with or without predefined algorithm to guide SLTs		14/364 (3.9)	26/353 (7.4)	M-H Fixed effect RR 0.52 (0.28, 0.95) Adj. 0.51 (0.21, 1.26) [f]	*Favours TEG/ROTEM* *p* = 0.033 No heterogeneity I^2 = 0 (*p* = 0.54)
					TEG (4 RCTs) ROTEM (4 RCTs)	5/211 (2.4) 9/153 (5.9)	7/206 (3.4) 19/147 (12.9)	RR 0.72 (0.25, 2.07) RR 0.44 (0.21, 0.93)	
						Subgroup analyses: By comparator			
					vs clinical judgement or usual treatment (4 RCTs)	7/224 (3.1)	9/221 (4.1)	RR 0.81 (0.32, 2.01)	*No significant difference* *p* = 0.65 No heterogeneity I^2 = 0 (p = 0.53)
					vs SLT-guided transfusion (4 RCTs)	7/140 (5)	9/132 (6.8)	RR 0.36 (0.16, 0.84)	*Favours TEG or ROTEM* *p* = 0.018 No heterogeneity I^2 = 0 (*p* = 0.49)
Li 2019 SR *High risk of bias*	N = NR (5 RCTs, 3 Coh) Ak 2009 Shore-Lesserson 1999 Girdauskas 2010 Paniagua 2011 Weber 2012 Görlinger 2011 Kuiper 2019 St-Onge 2018	Adult patients undergoing cardiac surgery with CPB	(Austria, Canada, Germany, Spain, The Netherlands Turkey, UK, US)	TEG or ROTEM guided transfusion vs standard of care	Mortality, latest follow-up	132/2680 (5)	124/2293 (5.4)	RR 0.83 (0.53, 1.30)	*No significant difference* *p* = 0.4 Moderate heterogeneity I^2 = 25 (*p* = NR)
					RCTs only	12/270 (4.4)	23/259 (8.9)	RR 0.5 (0.26, 0.96)	
Serraino 2017 SR *High risk of bias*	N = 689 (7 RCTs) Ak 2009 Girdauskas 2010 Nakayama 2015 Paniagua 2011 Royston 2001 Shore-Lesserson 1999 Weber 2012	Adult and paediatric patients undergoing cardiac surgery with bleeding	SC, cardiac (NR)	TEG or ROTEM guided transfusion (with or without other point-of-care platelet function tests) vs standard of care	Mortality, latest follow-up	12/350 (3.4)	23/339 (6.8)	RR 0.55 (0.28, 1.10)	*No significant difference* *p* = 0.09 No significant heterogeneity I^2 = 1 (*p* = 0.40)
Deppe 2016 SR *High risk of bias*	N = 5899 (6 RCTs, 5 Coh)	Patients with excessive bleeding after cardiac surgery	SC, cardiac (NR)	TEG or ROTEM guided transfusion vs standard of care	Mortality, all-cause	163/NR (5.4)	156/NR (5.7)	OR 0.92 (0.74, 1.16)	*No significant difference* *p* = 0.5193 Mild heterogeneity I^2 = 14 (*p* = 0.4520)

Study ID Study design[a]	Sample size (no. of trials) included in analysis	Patient population	Setting (Location)	Comparison	Outcome	Results			
						TEG/ROTEM n/N (%)	No TEG/ROTEM n/N (%)	Risk estimate (95% CI)	*Statistical significance* *p*-value Heterogeneity [b]
Corredor 2015 SR *High risk of bias*	N = 749 (6 RCTs) Shore-Lesserson 1999 Ak 2009 Girdauskas 2010 Royston 2001 Weber 2012 Agarwal 2015	Patients undergoing cardiac surgery	Cardiac surgery (NR)	TEG or ROTEM guided transfusion (with or without other point-of-care platelet function tests) vs standard of care	Mortality, latest follow-up	NR	NR	RR 0.66 (0.31, 1.39)	*No significant difference* *p* = 0.27 Heterogeneity NR
Haas 2014 RCT *High risk of bias*	N = 100 (1 RCT) Weber 2012	Adult patients undergoing cardiac or aortic surgery	SC (NR)	ROTEM guided algorithm vs standard of care	Mortality, 6 months	NR/NR (4)	NR/NR (20)	NR	*Favours ROTEM* *p* = 0.013
Obstetrics and maternity									
Amgalan 2020 Coh *High risk of bias*	N = 100 (1 Coh) McNamara 2019	Women with MOH associated with coagulopathy (estimated blood loss >1500mL)	SC (NR)	ROTEM guided algorithm vs standard of care	Mortality, latest follow-up	0/203	0/203	Not estimable	*No significant difference*

Studies with ~~strikethrough~~ do not meet the PICO criteria for this question.

Abbreviations: CI, confidence interval; Coh, cohort study; CPB, cardiopulmonary bypass; FC, fibrinogen concentrate; FFP, fresh frozen plasma; M-H, Mantzel-Hentzel; MHP, major haemorrhage protocol; MOH, major obstetric haemorrhage; NR, not reported; OR, odds ratio; PCC, prothrombin complex concentrate; PLT, platelets; RBC, red blood cells; RCT, randomised controlled trial; ROTEM, rotational thromboelastometry; RR, relative risk; SC, single centre; SLTs, standard laboratory tests; TEG, thromboelastography; UK, United Kingdom; US, United States; vs, versus

a. Where only one RCT is identified in a systematic review, the evidence has been considered as RCT evidence. Where the systematic review assesses Observational and cohort studies studies, the evidence has been considered as according to the study design features. The risk of bias of the included primary studies is based on the quality assessment reported by the systematic review authors.

b. Only applicable to Systematic reviews with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if P_{het} >0.1 and I^2 <25; (ii) mild heterogeneity if I^2 <25; moderate heterogeneity if I^2 between 25–50; substantial heterogeneity I^2 >50.

c. Calculated post-hoc using RevMan 5.4. M-H random effects.

d. Schöchl 2011 compared ROTEM guided administration of FC and PCC vs standard care guided transfusion (receiving >2 units FFP [no FC or PCC]). Patients in intervention group received median 6 g FC (range 0—15) and 1200 IU PCC (range 0—6600) and those in the comparator group received median 6 Units FFP (range 2—51)

e. Nienaber 2011 compared ROTEM guided administration of FC and PCC with standard care guided transfusion of 1:1 FFP:RBC ratio.

f. Trial sequential analysis showed only 54 of required information size (717/1325) had been reached. Not statistically significant with control event proportion of 7.4.

4.9.3.2 Morbidity

A summary of the evidence relating to the incidence of thromboembolic events in patients with critical bleeding in whom blood component therapy was guided by TEG or ROTEM is presented in Table 4.80.

A summary of the evidence relating to major morbidities (multiple organ failure, renal failure, or need for postpartum hysterectomy) in patients with critical bleeding in whom blood component therapy was guided by TEG or ROTEM is presented in Table 4.81.

Thromboembolic events

In a meta-analysis of data from the included RCTs (see Figure 4.53), the rate of thromboembolic events in patients with critical bleeding who received blood component therapy guided by TEG or ROTEM was 7.2% (24/333) compared with 9.4% (30/318) among those whose treatment was guided by an MHP or standard laboratory tests. This corresponds to a nonsignificant difference between treatment groups (RR 0.83; 95% CI 0.41, 1.66; p = 0.60, I^2= 26%) (*GRADE: very low*).

Among trauma patients, the rate of thromboembolic events reported in those who received blood component therapy guided by TEG or ROTEM was 9.3% (24/257) compared with 11.2% (28/250) in the comparator group. The difference was not statistically significant (RR 0.90; 95% CI 0.42, 1.95; p = 0.80, I^2= 46%) (*GRADE: very low*).

In patients with diffuse and/or abnormal bleeding from capillary beds and/or excessive blood loss after surgery, the rate of thromboembolic events among those who received blood component therapy guided by TEG or ROTEM was 0% (0/76) compared with 2.9% (2/68) in the comparator group. Only one study contributed data. The difference was not statistically significant (RR 0.20; 95% CI 0.01, 4.06; p = 0.29) (*GRADE: very low*).

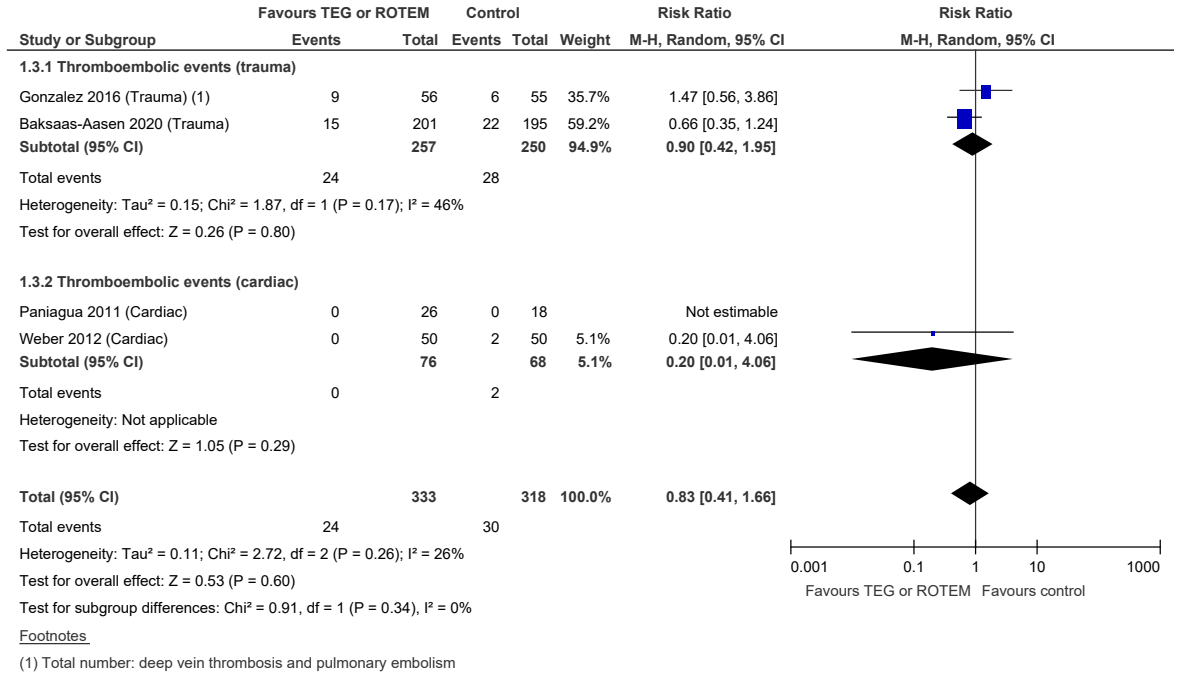
Multiple organ failure

Pooled data from the included RCTs (see Figure 4.54) suggested no difference in the incidence of multiple organ failure (4.3%, 11/257) among trauma patients who received blood component therapy guided by TEG or ROTEM compared with those whose treatment was guided by an MHP or standard laboratory tests (3.2%, 8/250) (RR 1.33; 95% CI 0.53, 3.34; p = 0.54, I^2=0%) (*GRADE: very low*).

Postpartum hysterectomy

Pooled data from the included cohort studies (see Figure 4.54) among women with severe PPH, suggested that the use of TEG or ROTEM is associated with a lower incidence of postpartum hysterectomy (8.4%) compared with treatment guided by standard care (33.8%) (RR 0.37; 95% CI 0.18, 0.77; p = 0.008; I^2=54% (*GRADE: very low*).

Figure 4.53 Forest plot of comparison: TEG or ROTEM vs MHP or standard laboratory tests, outcome: thromboembolic events



Footnotes

(1) Total number: deep vein thrombosis and pulmonary embolism

Figure 4.54 Forest plot of comparison: TEG or ROTEM vs MHP or standard laboratory tests, outcome: morbidity (multiorgan failure, need for hysterectomy)

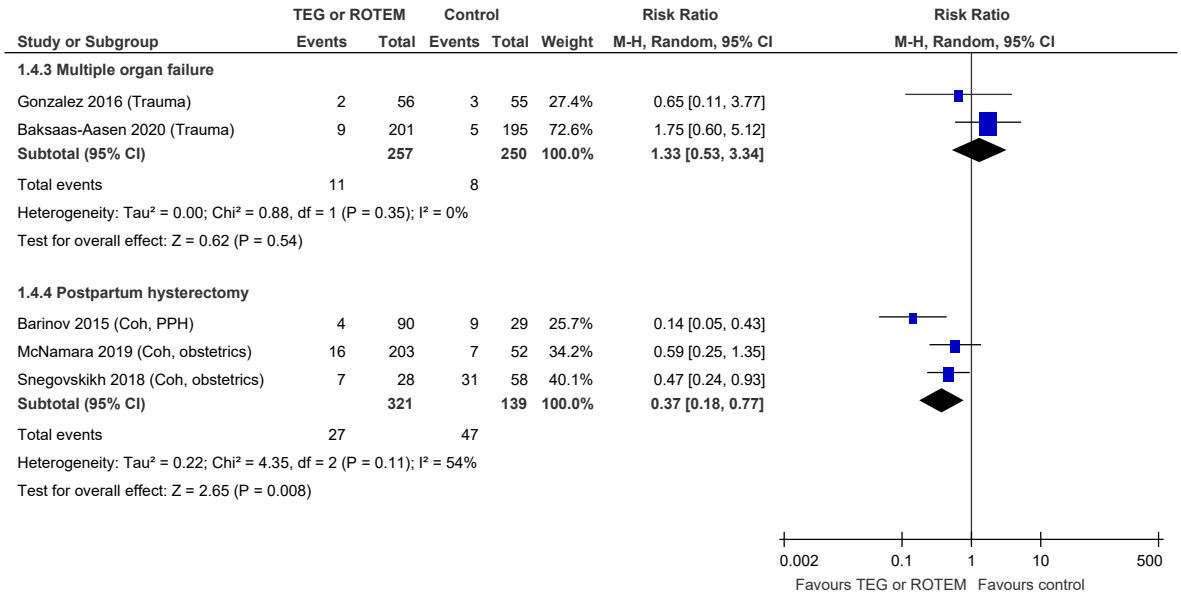


Table 4.80 Results for TEG or ROTEM to guide BCT versus no TEG or ROTEM to guide BCT: Patients *with* critical bleeding – Morbidity (thromboembolic events)

Study ID Study design[a]	Sample size (no. of trials) included in analysis	Patient population	Setting (Location)	Comparison	Outcome	Results			
						TEG/ROTEM n/N (%)	No TEG/ROTEM n/N (%)	Risk estimate (95% CI)	*Statistical significance* *p*-value Heterogeneity [b]
Trauma setting									
Baksaas-Aasen 2020 RCT *High risk of bias*	N = 396	Adult trauma patients with clinical signs of bleeding activating the local MHP * within 3 hours of injury and maximum of 1 hour after admission into the emergency department	MC, Various (Denmark, Netherlands, Norway, Germany, UK)	Viscoelastic haemostatic assays vs conventional coagulation test	Thromboembolic events *Inclusive of myocardial infarction and embolic stroke	15/201 (7.5)	22/195 (11.3)	NR	NR
Gonzalez 2016 RCT *High risk of bias*	N = 111	Patients with severe trauma who are likely to require transfusion therapy	SC (US)	TEG or ROTEM guided algorithm vs the clinician's discretion and/or based on conventional coagulation tests	Deep vein thrombosis	8/56 (14.3)	6/55 (10.9)	NR	No significant difference $p = 0.599$
					Pulmonary embolism	1/56 (1.8)	0/55 (0)	NR	No significant difference $p = 1.01$
Surgical setting									
Wikkelsø 2016 SR *High quality*	N = 305 (4 RCTs) Girdauskas 2010 Paniagua 2011 Shore-Lesserson 1999 Weber 2012	Adults with diffuse or excessive bleeding after cardiac surgery	SC (Germany, Spain, USA)	TEG or ROTEM guided transfusion vs clinical judgement or usual treatment with or without predefined algorithm to guide SLTs	Thromboembolic events	5/156 (3.2)	5/149 (3.4)	RR 1.04 (0.35, 3.07)	No significant difference $p = 0.94$ No heterogeneity $I^2 = 0$ ($p = 0.41$)
Serraino 2017 SR *High quality*	N = 163 (2 RCTs) Girdauskas 2010 Shore-Lesserson 1999	Adult patients undergoing cardiac surgery with bleeding	Cardiac surgery (NR)	TEG or ROTEM guided transfusion (with or without other point-of-care platelet function tests) vs standard of care	Cerebrovascular accident (stroke)	5/80 (6.3)	3/81 (3.7)	RR 1.73 (0.41, 7.23)	No significant difference $p = 0.45$ No heterogeneity $I^2 = 0$ ($p = 0.68$)
Deppe 2016 SR	N = 3975 (2 RCTs, 3 Coh)		SC, cardiac (NR)	TEG or ROTEM guided transfusion vs standard of care	Thromboembolic events	28/NR (1.3)	51/NR (2.9)	OR 0.44 (0.28, 0.70)	*Favours ROTEM* $p = 0.0006$ No heterogeneity

Study ID Study design[a]	Sample size (no. of trials) included in analysis	Patient population	Setting (Location)	Comparison	Outcome	Results			
						TEG/ROTEM n/N (%)	No TEG/ROTEM n/N (%)	Risk estimate (95% CI)	*Statistical significance* *p*-value Heterogeneity [b]
Moderate quality		Patients with excessive bleeding after cardiac surgery							I^2 = 0 (p = 0.0005)
	N = 4054 (2 RCTs, 3 Coh)				Cerebrovascular accident (stroke)	12/NR (0.5)	18/NR (1.0)	OR 0.64 (0.31, 1.30)	No significant difference p = 0.2841 No heterogeneity I^2 = 0 (p = 0.1345)
Haas 2014 Coh *High risk of bias*	N = 3865 (1 Coh) Görlinger 2011	Adult patients undergoing cardiac or aortic surgery	SC (NR)	TEG or ROTEM guided transfusion vs standard of care	Composite thromboembolic events	NR/2147 (1.77)	NR/1718 (3.19)	NR	*Favours ROTEM* p = 0.011
Obstetrics and maternity setting - no studies reported this outcome									
Paediatrics - no studies found									

Studies with ~~strikethrough~~ do not meet the PICO criteria for this question.

Abbreviations: CI, confidence interval; Coh, cohort study; MC, multicentre; MHP, major haemorrhage protocol; NR, not reported; OR, odds ratio; RBC, red blood cells; RCT, randomised controlled trial; ROTEM, rotational thromboelastometry; RR, relative risk; SC, single centre; TE, thromboembolic event; TEG, thromboelastography; UK, United Kingdom; USA, United States of America

a. Where only one RCT is identified in a systematic review, the evidence has been considered as RCT evidence. Where the systematic review assesses observational and cohort studies, the evidence has been considered as according to the study design features. The risk of bias of the included primary studies is based on the quality assessment reported by the systematic review authors.

b. Only applicable to Systematic reviews with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if P_{het} >0.1 and I^2 <25; (ii) mild heterogeneity if I^2 <25; moderate heterogeneity if I^2 between 25–50; substantial heterogeneity I^2 >50.

c. Calculated post-hoc using RevMan 5.4. M-H random effects

Table 4.81 Results for TEG or ROTEM to guide BCT versus no TEG or ROTEM to guide BCT: Patients *with* critical bleeding – Major morbidities

Study ID Study design[a] *Risk of bias*	Sample size (no. of trials) included in analysis	Patient population	Setting (Location)	Comparison	Outcome	Results			
						TEG/ROTEM n/N (%)	No TEG/ROTEM n/N (%)	Risk estimate (95% CI)	*Statistical significance* *p*-value Heterogeneity[b]
Trauma setting									
Baksaas-Aasen 2021 RCT *High risk of bias*	N = 396	Adult trauma patients with clinical signs of bleeding activating the local MHP *randomised within 3 hours of injury and maximum of 1 hour after admission into the emergency department	MC, Various (Denmark, Netherlands, Norway, Germany, UK)	TEG or ROTEM guided transfusion vs conventional coagulation test	Multiple organ dysfunction syndrome* *Sequential Organ Failure Assessment score of six or more	141/164 (86)	134/159 (84)	OR 1.14 (0.62, 2.10)	*No significant difference* *p = 0.668*
					Organ failure	9/201 (4.5)	5/195 (2.6)	RR 1.75 (0.60, 5.12) [c]	*NR*
					Acute kidney injury	6/201 (3.0)	6/195 (3.1)	RR 0.97 (0.32, 2.96) [c]	*NR*
Haas 2014 Coh *Serious risk of bias*	N = 36 (1 Coh) Nienaber 2011	Adult patients with severe trauma	Trauma registry (German, Austria)	ROTEM guided administration of FC and PCC vs standard care guided transfusion of 1:1 FFP:RBC ratio	Multiple organ failure	3/18 (16.7)	11/18 (61.1)	RR 0.27 (0.09, 0.82) [c]	*Favours ROTEM* *p* = 0.015
Surgical setting (cardiac)									
Serraino 2017 SR *High risk of bias*	N = 424 (4 RCTs) Ak 2009 Girdauskas 2010 Paniagua 2011 Weber 2012	Adult patients undergoing cardiac surgery with bleeding	Cardiac surgery (NR)	TEG or ROTEM guided transfusion (with or without other point-of-care platelet function tests) vs standard of care	Acute kidney injury	23/217 (10.6)	39/207 (18.8)	RR 0.42 (0.20, 0.86)	*Favours TEG/ROTEM* *p* = 0.02 Mild heterogeneity I^2 = 26 (*p* = 0.25)
Wikkelsø 2016 SR *High risk of bias*	N = 200 (3 RCTs) Girdauskas 2010 Paniagua 2011 Weber 2012	Adults with diffuse or excessive bleeding after cardiac surgery	SC (Germany, Spain)	TEG or ROTEM guided transfusion vs clinical judgement or usual treatment with or without predefined algorithm to guide standard laboratory tests	Dialysis dependent renal failure	16/103 (15.5)	30/97 (30.9)	RR 0.46 (0.28, 0.76)	*Favours TEG/ROTEM* *p* = 0.0028 No heterogeneity I^2 = 0 (*p* = 0.48)
Deppe 2016 SR *High risk of bias*	N = 4263 (3 RCTs, 2 Coh) NR	Patients with excessive bleeding after cardiac surgery	SC, cardiac (NR)	TEG or ROTEM guided transfusion vs standard of care	Acute kidney injury	142/NR (6.0)	150/NR (7.8)	OR 0.77 (0.61, 0.98)	*Favours TEG/ROTEM* *p* = 0.0403 No heterogeneity I^2 = 0 (*p* = 0.0278)

Study ID Study design[a] *Risk of bias*	Sample size (no. of trials) included in analysis	Patient population	Setting (Location)	Comparison	Outcome	Results			
						TEG/ROTEM n/N (%)	No TEG/ROTEM n/N (%)	Risk estimate (95% CI)	*Statistical significance* *p*-value Heterogeneity[b]
					RCTs only	NR	NR	OR 0.54 (0.27, 1.06)	*No significant difference* $p = 0.1001$ Heterogeneity NR
Haas 2014 RCT *High risk of bias*	N = 100 (1 RCT) Weber 2012	Adult patients undergoing cardiac or aortic surgery	SC (NR)	TEG or ROTEM guided transfusion vs standard of care	Composite AEs (Acute renal failure, sepsis, TE, allergic reaction)	NR/NR (8)	NR/NR (38)	RR 0.30 (0.09, 1.03) [c]	*Favours ROTEM* $p < 0.001$
Surgical setting (Liver)									
Saner 2016 Coh *Serious risk of bias*	N = 200 (1 Coh) ~~Leon-Justel 2015~~	Patients with end-stage liver disease undergoing invasive procedure	SC (Spain)	TEG or ROTEM guided transfusion vs standard of care	Acute kidney injury	2/100 (2)	17/100 (17)	RR 0.12 (0.03, 0.50) [c]	*Favours ROTEM* $p = 0.001$
Obstetrics and maternity									
Roullet 2018 Coh *Serious risk of bias*	N = 179 (2 Coh) Mallaiah 2015 Snegovskikh 2018	Patients with severe PPH	SC (UK, US)	ROTEM guided algorithm vs standard of care	Postpartum hysterectomy	10/79 (12.7)	37/100 (37)	RR 0.45 (0.25, 0.83) [c]	*Favours ROTEM* $p = 0.048$ No heterogeneity $I^2 = 0\%$ ($p = 0.55$)
Amgalan 2020 Coh *Serious risk of bias*	N = 100 (1 Coh) McNamara 2019	Women with MOH (estimated blood loss >1500mL) associated with coagulopathy	SC (UK)	ROTEM guided algorithm vs standard of care	Postpartum hysterectomy	16/203	7/52	RR 0.59 (0.25, 1.35) [c]	*No significant difference* $p = 0.21$

Studies with ~~strikethrough~~ do not meet the PICO criteria for this question.

Abbreviations: AE, adverse event; CI, confidence interval; Coh, cohort study; FC fibrinogen concentrate; FFP, fresh frozen plasma; MC, multicentre; MHP, major haemorrhage protocol; NR, not reported; OR, odds ratio; PCC, prothrombin complex concentrate; PPH, postpartum haemorrhage; RBC, red blood cells; ROTEM, rotational thromboelastometry; RR, relative risk; SC, single centre; TE, thromboembolic event; TEG thromboelastography; UK, United Kingdom; US, United States

a. Where only one RCT is identified in a systematic review, the evidence has been considered as RCT evidence. Where the systematic review assesses Observational and cohort studies studies, the evidence has been considered as according to the study design features. The risk of bias of the included primary studies is based on the quality assessment reported by the systematic review authors.

b. Only applicable to Systematic reviews with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if $P_{het} > 0.1$ and $I^2 < 25\%$; (ii) mild heterogeneity if $I^2 < 25\%$; moderate heterogeneity if I^2 between 25–50%; substantial heterogeneity $I^2 > 50\%$.

c. Calculated post-hoc using RevMan 5.4. M-H random effects.

4.9.3.3 Transfusion volume

A summary of the evidence relating to the volume of blood components transfused in patients with critical bleeding in whom the blood component therapy was guided by TEG or ROTEM is presented in Table 4.82.

Red blood cells

A meta-analysis of data from the RCT and cohort studies included in this review (see Figure 4.55) showed a significant reduction in the volume of RBCs transfused in patients with critical bleeding (any setting) who received blood component therapy guided by TEG or ROTEM (n=669) compared with those who received treatment guided by an MHP or standard laboratory tests (n=1089). The difference corresponded to around two units of RBCs saved (SMD –0.38; 95% CI –0.61, –0.15; p = 0.001, I^2= 75%).

Available data from the RCTs suggested that the volume of RBCs transfused was not different between groups (SMD –0.06; 95% CI –0.38, 0.26; p = 0.73, I^2= 0%), but data were not reported in three studies and two studies suggested an effect favouring TEG or ROTEM but did not provide suitable data for analysis.

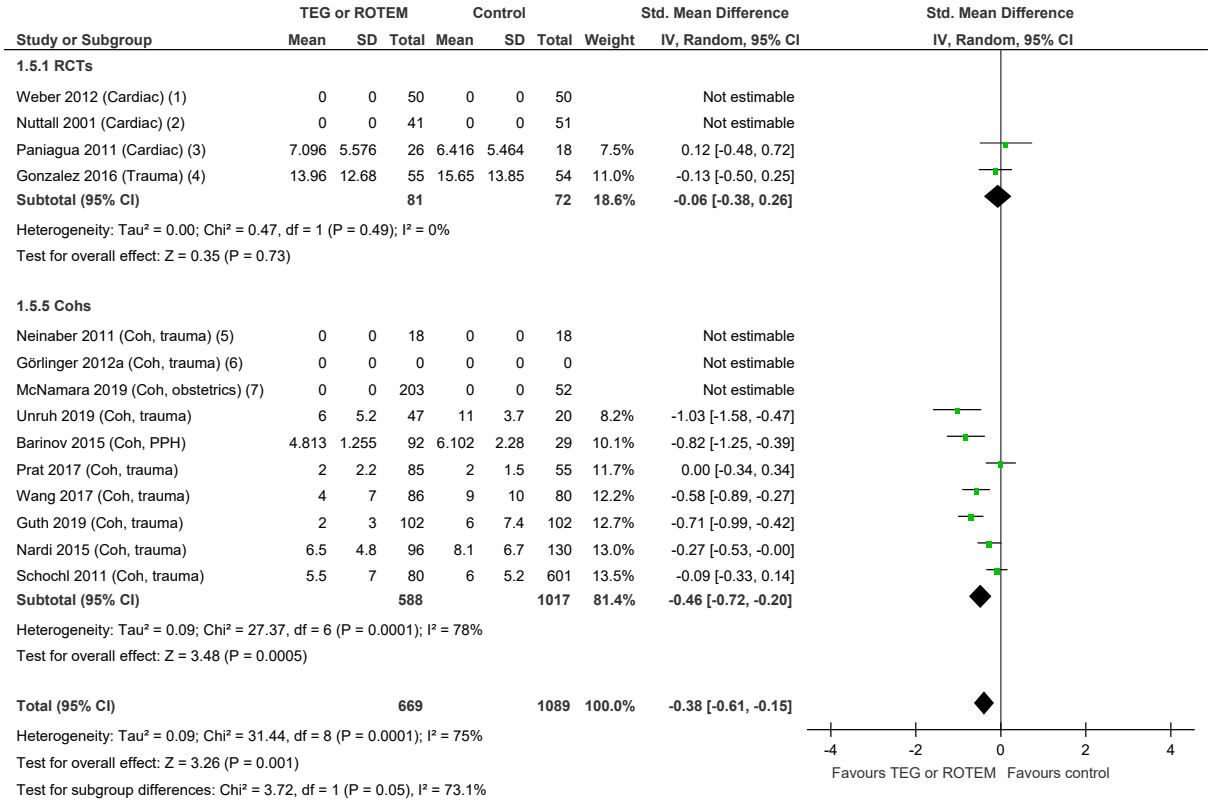
Among the included observational cohort studies, a statistically significant reduction in the volume of RBC transfused was observed between patients who received blood component therapy guided by TEG or ROTEM (n=588) compared with those who received treatment guided by an MHP or standard laboratory tests (n=1017) (SMD –0.46; 95% CI –0.92, –0.28; p = 0.0005; I^2= 78%).

In the trauma setting (see Figure 4.56), data from one RCT suggested that the use of TEG or ROTEM to guide blood component therapy did not reduce the volume of RBCs transfused when compared treatment not guided by TEG or ROTEM (SMD –0.13; 95% CI –0.50, 0.25; p = 0.51). Among the cohort studies a significant association was observed (SMD –0.41; 95% CI –0.68, –0.14; p = 0.03; I^2 = 78%).

In patients with diffuse and/or abnormal bleeding from capillary beds and/or excessive blood loss after surgery (see Figure 4.56), data from one small RCT suggested that there was no difference in volume of RBCs transfused comparing blood component therapy guided by TEG or ROTEM with routine transfusion therapy based on standard laboratory tests (SMD 0.12; 95% CI –0.48, 0.72; p = 0.69). Data were not reported in two studies and two studies suggested an effect favouring TEG or ROTEM but did not provide suitable data for analysis.

Among women with severe PPH (see Figure 4.56), data from one observational study suggested that the use of TEG or ROTEM is associated with a statistically significant reduction in the volume of RBCs transfused (around one unit saved) (SMD of –0.82; 95% CI –1.25, –0.39; p = 0.0002). One study suggested there was no reduction the median volume of RBCs transfused. One study did not report this outcome.

Figure 4.55 Forest plot of comparison: TEG or ROTEM vs MHP or standard laboratory tests, outcome: RBC transfusion volume (units), by study design.



Footnotes

(1) Favours TEG or ROTEM (p<0.001). Data reported as median (IQR): 3 (2, 6) vs 5 (4, 9)

(2) Favours TEG or ROTEM (p=0.039). Data reported as median (range): 2 (0, 9) vs 3 (0, 70)

(3) converted from mLs (250mL/U)

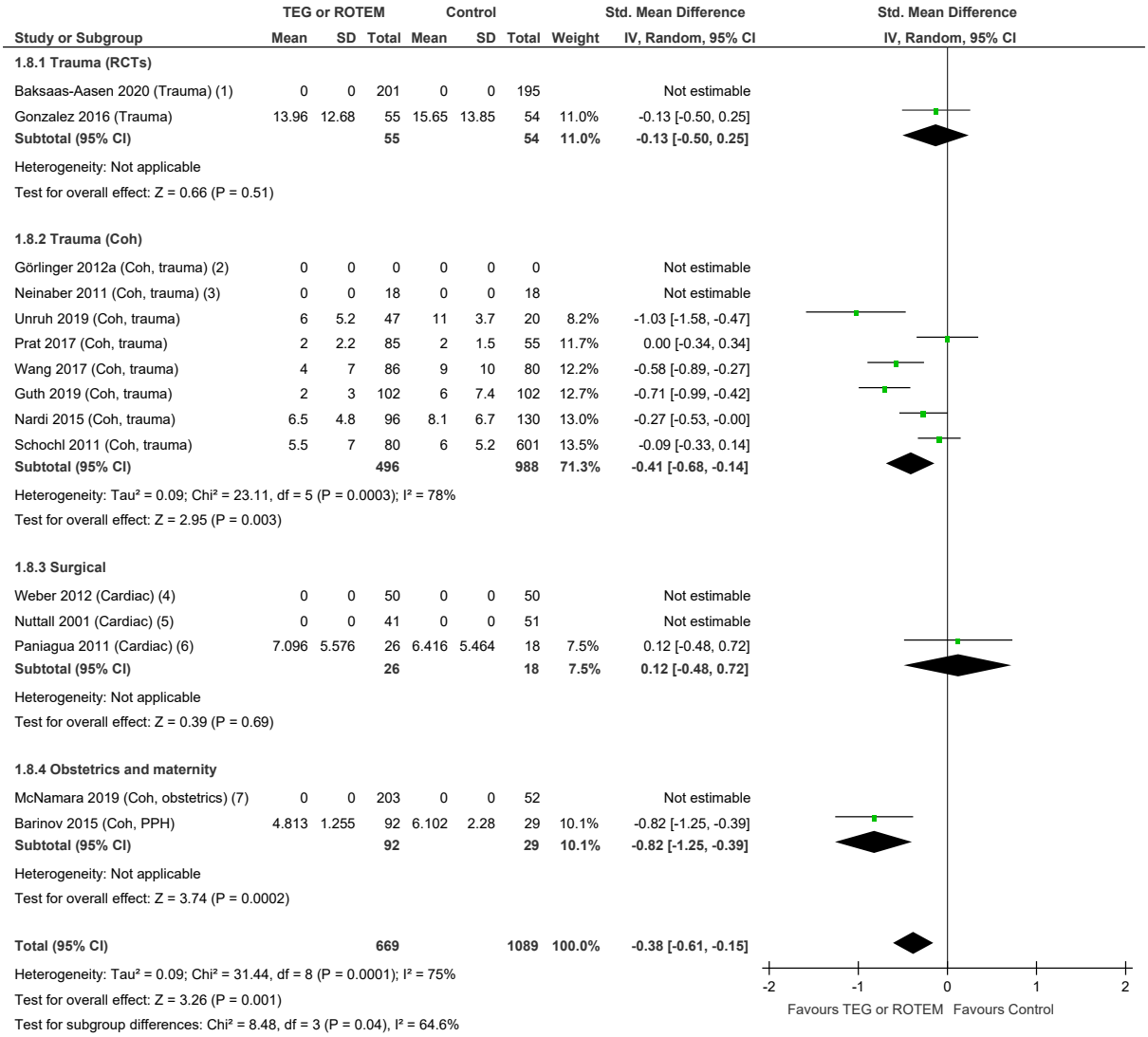
(4) As reported by Fahrendorff 2017 (total cumulative RBC transfusion needs)

(5) Favours TEG or ROTEM (p<0.005). Data presented as median (IQR): 3 (0, 5) vs 12.5 (8, 20).

(6) An estimated a 42% and 33% reduction in the total volume of RBCs transfused per year after the implementation of goal-directed therapy

(7) No difference between groups (p=0.158). Data reported as median (IQR) 3 (2, 5) vs 3 (2, 4).

Figure 4.56 Forest plot of comparison: TEG or ROTEM vs MHP or standard laboratory tests, outcome: RBC transfusion volume (units), by setting.



Footnotes

(1) Study did not report this outcome.

(2) An estimated 42% and 33% reduction in the total volume of RBCs transfused per year after the implementation of goal-directed therapy.

(3) Favours TEG or ROTEM (p<0.005). Data presented as median (IQR): 3 (0, 5) vs 12.5 (8, 20).

(4) Favours TEG or ROTEM (p<0.001). Data reported as median (IQR): 3 (2, 6) vs 5 (4, 9)

(5) Favours TEG or ROTEM (p=0.039). Data reported as median (range): 2 (0, 9) vs 3 (0, 70)

(6) Data converted from mLs (250mL/U)

(7) No difference between groups (p=0.158). Data reported as median (IQR) 3 (2, 5) vs 3 (2, 4).

Table 4.82 Results for TEG or ROTEM to guide BCT versus no TEG or ROTEM to guide BCT: Patients *with* critical bleeding – RBC transfusion volume

Study ID Study design[a] *Risk of bias*	Sample size (no. of trials) included in analysis	Patient population	Setting (Location)	Comparison	Outcome	Results			
						TEG/ROTEM Mean ± SD (n)	No TEG/ROTEM Mean ± SD (n)	Risk estimate (95% CI)	*Statistical significance* *p*-value Heterogeneity [b]
Various settings									
Fahrendorff 2017 SR *High risk of bias*	N = 453 (6 studies) Shore-Lesserson 1999 Wang 2010 Schaden 2012 Barinov 2015 Gonzalez 2016 Cao 2016	Patients with an acute need for blood components due to bleeding (includes trauma, burns excision, liver transplant, PPH and cardiac surgery)	Various	TEG or ROTEM guided algorithm vs the clinician's discretion and/or based on conventional coagulation tests	RBC transfusion volume, Units	Mean ± SD (260) 1.416 ± 1.948 (53) 14.2 ± 7.1 (14) 3.1 ± 2.1 (14) 4.813 ± 1.255 (92) 13.96 ± 12.68 (55) 4.5 ± 1.5 (32)	Mean ± SD (193) 1.9 ± 2.372 16.7 ± 12.8 (14) 4.8 ± 3 (16) 6.102 ± 2.28 (29) 15.65 ± 13.85 (54) 7.1 ± 1.2 (28)	SMD –0.64 (–1.12, –0.15) –0.22 (–0.61, 0.16) –0.23 (–0.98, 0.51) –0.63 (–1.37, 0.11) –0.82 (–1.25, –0.39) –0.13 (–0.59, 0.25) –1.88 (–2.49, –1.26)	*Favours TEG/ROTEM* *p* = 0.01 Substantial heterogeneity I^2 = 82 (*p* = 0.001)
Trauma setting									
Bugaev 2020 SR *Serious risk of bias*	N = 1459 (1 RCT, 6 Coh) Schaden 2012 Unruh 2019 Gonzalez 2016 Prat 2017 Guth 2019 Nardi 2015 Schöchl 2011	Severely injured trauma patients	SC (not reported)	ROTEM or TEG vs no ROTEM or TEG	RBC transfusion volume, Units	N=480 3.1±1.6 (14) 6±5.2 (47) 9.5±8.1 (56) 2±2.2 (85) 2±3 (102) 6.5±4.8 (96) 5.5±7 (80)	N=979 4.3±2.2 (16) 11±3.7 (20) 11±8.1 (55) 2±1.5 (55) 6±7.4 (102) 8.1±6.7 (130) 6±5.2 (601)	SMD –0.38 (–0.64, –0.12) SMD –0.85 (–1.60, –0.10) SMD –1.03 (–1.58, –0.47) SMD –0.18 (–0.56, 0.19) SMD 0.00 (–0.34, 0.34) SMD –0.71 (–0.99, –0.42) SMD –0.27 (–0.53, -0.00) SMD –0.09 (–0.33, 0.14)	*Favours TEG/ROTEM* *p = 0.004* Significant heterogeneity I^2 = 74% *(p = 0.0008)*
Wang 2017 Coh *Serious risk of bias*	N = 166 (1 Coh)	Patients with traumatic liver and/or spleen injury	SC (US)	TEG guided algorithm vs clinical judgement or usual treatment	RBC transfusion volume, Units	4 ± 7 (86)	9 ±10 (80)	NR	*Favours TEG* *p* < 0.01
Haas 2014 SR *High risk of bias*	N = 5590 (1 Coh) Görlinger 2012a Görlinger 2012b	Adult patients with severe trauma	SC (Germany, Austria)	ROTEM guided algorithm vs standard of care	RBC transfusion volume, Units	Total per year 1282 888	Total per year 2215 1332	42% reduction 33% reduction	*Favours ROTEM* *p* = NR
	N = 36 (1 Coh) Nienaber 2011			Algorithm with FC and PCC vs 1:1 FFP:RBC ratio	hrs after admission 0–6 hrs >24 hrs	Median (IQR) 1 (0, 3) 3 (0, 5)	Median (IQR) 7.5 (4, 12) 12.5 (8, 20)	NR NR	*p* < 0.005 *p* < 0.005
Surgical setting									
Wikkelsø 2016 SR *High risk of bias*	N = NR (2 RCTs) Weber 2012 Nuttal 2001		SC (Germany, Spain, US)		RBC transfusion volume, Units	Median (IQR) 3 (2, 6)	Median (IQR) 5 (4, 9)		*Favours TEG/ROTEM* *p* < 0.001
						Median (range) 2 (0, 9)	Median (range) 3 (0, 70)		*p* = 0.039

Study ID **Study design**[a] ***Risk of bias***	**Sample size (no. of trials) included in analysis**	**Patient population**	**Setting (Location)**	**Comparison**	**Outcome**	**Results**			
						TEG/ROTEM Mean ± SD (n)	**No TEG/ROTEM Mean ± SD (n)**	**Risk estimate (95% CI)**	***Statistical significance*** ***p*-value** **Heterogeneity** [b]
	N = 44 (1 RCT) Paniagua 2011	Adults or children with diffuse or excessive bleeding after cardiac surgery, orthotopic liver transplant or burns excision		TEG or ROTEM guided transfusion vs clinical judgement or usual treatment with or without predefined algorithm to guide SLTs	RBC transfusion volume, mL	Mean ± SD (n) 1774 ± 1394 (26)	Mean ± SD (n) 1604 ± 1366 (18)	SMD [c] 0.12 (–0.48, 0.72)	No significant difference *p* = NR
Haas 2014 SR *Serious risk of bias*	N = 5338 (1 Coh) Görlinger 2012b	Adult patients undergoing visceral surgery or liver transplant	SC (Germany, Austria)	ROTEM guided algorithm vs standard of care	RBC transfusion volume, Units	Units per year 1319	Units per year 3454	62% reduction	*Favours ROTEM* *p* = NR
	N = 100 (1 RCT) Weber 2012	Adult patients undergoing cardiac or aortic surgery	SC (Germany)	ROTEM guided algorithm vs standard of care	RBC transfusion volume, Units	Median (IQR) 3 (2, 6)	Median (IQR) 5 (4, 9)	NR	*Favours ROTEM* *p* < 0.001
Obstetrics setting									
Amgalan 2020 Coh *Serious risk of bias*	N = 100 (1 Coh) McNamara 2019	Women with MOH (estimated blood loss >1500mL) associated with coagulopathy	SC (UK)	ROTEM guided algorithm vs standard of care	RBC transfusion volume, Units	Median (IQR) 3 (2, 5) (n=203)	Median (IQR) 3 (2, 4) (n=52)	NR	*No significant difference* *p* = 0.158

Studies with ~~strikethrough~~ do not meet the PICO criteria for this question.

Abbreviations: CI, confidence interval; Coh, cohort study; CRYO, cryoprecipitate; FC, fibrinogen concentrate; FFP, fresh frozen plasma; hrs, hours; IQR, interquartile range; MC, multicentre; MD, mean difference; n, number; NR, not reported; PCC, prothrombin complex concentrate; PLT, platelets; PPH, postpartum haemorrhage; RBCs, red blood cells; RCT, randomised controlled trial; ROTEM, rotational thromboelastometry; SC, single centre; SD, standard deviation; SMD, standard mean difference; SoC, standard of care; TEG, thromboelastography; UK, United Kingdom; US, United States

a. Where only one RCT is identified in a systematic review, the evidence has been considered as RCT evidence. Where the systematic review assesses observational and cohort studies, the evidence has been considered as according to the study design features. The risk of bias of the included primary studies is based on the quality assessment reported by the systematic review authors.

b. Only applicable to Systematic reviews with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if P_{het} >0.1 and I^2 <25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25–50%; substantial heterogeneity I^2 >50%.

c. Calculated post-hoc using RevMan 5.4. M-H random effects.

Fresh frozen plasma

A summary of the evidence relating to the volume of FFP transfused in patients with critical bleeding is presented in Table 4.83

A meta-analysis of available data from the RCT and cohort studies included in this review (see Figure 4.57) showed a significant reduction in the volume of FFP transfused in patients with critical bleeding (any setting) who received blood component therapy guided by TEG or ROTEM (n=594) compared with those who received treatment guided by an MHP or standard laboratory tests (n=572). The difference corresponded to around 2.4 units of FFP saved (SMD –0.62; 95% CI –1.19, –0.05; p = 0.03, I^2= 95%).

Available data from the RCTs suggested that the volume of FFP transfused was not different between groups (SMD 0.02; 95% CI –0.30, 0.33; p = 0.93; I^2= 0%) but data were not able to be included for two studies that suggested an effect favouring TEG or ROTEM. Among the included observational cohort studies, a statistically significant reduction in the volume of FFP transfused was observed between patients who received blood component therapy guided by TEG or ROTEM (n=513) compared with those who received treatment guided by an MHP or standard laboratory tests (n=500) (SMD –0.82; 95% CI –1.51, –0.12; p = 0.02; I^2= 96%).

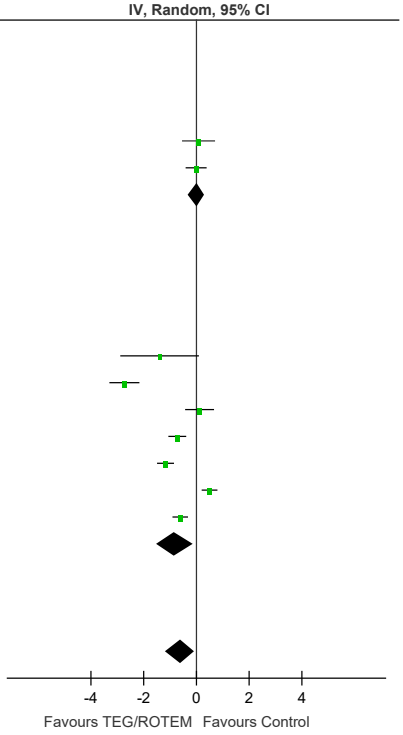
In the trauma setting (see Figure 4.58), data from one RCT suggested that the use of TEG or ROTEM to guide blood component therapy did not reduce the volume of FFP transfused when compared treatment not guided by TEG or ROTEM (SMD –0.01; 95% CI –0.39, 0.37; p = 0.96). Among the cohort studies no significant association was observed (SMD –0.39; 95% CI –1.01, 0.23; p = 0.22; I^2 = 95%), noting FFP transfusion volumes were not reported for all studies, possibly due to the direction of effect being unfavourable for the intervention. Taken together the pooled data from the RCT and cohort studies suggests that the use of TEG or ROTEM to guide blood component therapy does not reduce the volume of FFP transfused when compared treatment not guided by TEG or ROTEM (SMD –0.32; 95% CI –0.86, 0.21; p = 0.23; I^2 = 94%).

In patients with diffuse and/or abnormal bleeding from capillary beds and/or excessive blood loss after surgery (see Figure 4.58), data from one small RCT and one small cohort study suggested that there was no difference in volume of FFP transfused comparing blood component therapy guided by TEG or ROTEM with routine transfusion therapy based on standard laboratory tests (SMD –0.50; 95% CI –1.91, 0.91; p = 0.49; I^2 = 70%). Data were not reported in two studies and two studies suggested an effect favouring TEG or ROTEM but did not provide suitable data for analysis.

Among women with severe PPH (see Figure 4.58), data from one observational study suggested that blood component therapy guided by TEG or ROTEM is associated with a large reduction in the volume of FFP transfused (around 4.4 units saved) (SMD of –2.73; 95% CI –3.28, –2.19; p < 0.0001). The other two studies did not report this outcome.

Figure 4.57 Forest plot of comparison: TEG or ROTEM vs MHP or standard laboratory tests, outcome: FFP transfusion volume (units), by study design.

Study or Subgroup	TEG or ROTEM Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.9.1 RCTs								
Nuttall 2001 (Cardiac) (1)	0	0	41	0	0	51		Not estimable
Weber 2012 (Cardiac) (2)	0	0	50	0	0	50		Not estimable
Baksaas-Aasen 2020 (Trauma) (3)	0	0	201	0	0	195		Not estimable
Paniagua 2011 (Cardiac) (4)	3.196	4.752	26	2.828	3.988	18	10.9%	0.08 [-0.52, 0.68]
Gonzalez 2016 (Trauma)	7.49	7.37	55	7.57	7.86	54	11.8%	-0.01 [-0.39, 0.37]
Subtotal (95% CI)			**81**			**72**	**22.7%**	**0.02 [-0.30, 0.33]**
Heterogeneity: Tau² = 0.00; Chi² = 0.06, df = 1 (P = 0.80); I² = 0%								
Test for overall effect: Z = 0.09 (P = 0.93)								
1.9.2 Cohs								
Görlinger 2012a (Coh, trauma) (5)	0	0	0	0	0	0		Not estimable
Hanke 2012 (Coh, Cardiac)	1.6	2.2	5	9.2	6.6	5	6.8%	-1.40 [-2.86, 0.07]
Barinov 2015 (Coh, PPH)	4.8	1.537	92	9.25	1.862	29	11.2%	-2.73 [-3.28, -2.19]
Unruh 2019 (Coh, trauma)	4.5	4.1	47	4	4.1	20	11.2%	0.12 [-0.40, 0.64]
Wang 2017 (Coh, trauma)	1	5	86	5	6	80	12.0%	-0.72 [-1.04, -0.41]
Guth 2019 (Coh, trauma)	0.5	1.5	102	5	5.2	102	12.0%	-1.17 [-1.47, -0.87]
Prat 2017 (Coh, trauma)	2	2.6	85	1	1.5	134	12.1%	0.50 [0.22, 0.77]
Nardi 2015 (Coh, trauma)	4.2	4.6	96	9	9.5	130	12.1%	-0.61 [-0.88, -0.34]
Subtotal (95% CI)			**513**			**500**	**77.3%**	**-0.82 [-1.51, -0.12]**
Heterogeneity: Tau² = 0.80; Chi² = 142.73, df = 6 (P < 0.00001); I² = 96%								
Test for overall effect: Z = 2.30 (P = 0.02)								
Total (95% CI)			**594**			**572**	**100.0%**	**-0.62 [-1.19, -0.05]**
Heterogeneity: Tau² = 0.69; Chi² = 153.85, df = 8 (P < 0.00001); I² = 95%								
Test for overall effect: Z = 2.12 (P = 0.03)								
Test for subgroup differences: Chi² = 4.53, df = 1 (P = 0.03), I² = 77.9%								



Footnotes

(1) Favours TEG or ROTEM (p=0.005). Data reported as median (range): 2 (0, 10) vs 4 (0, 75).

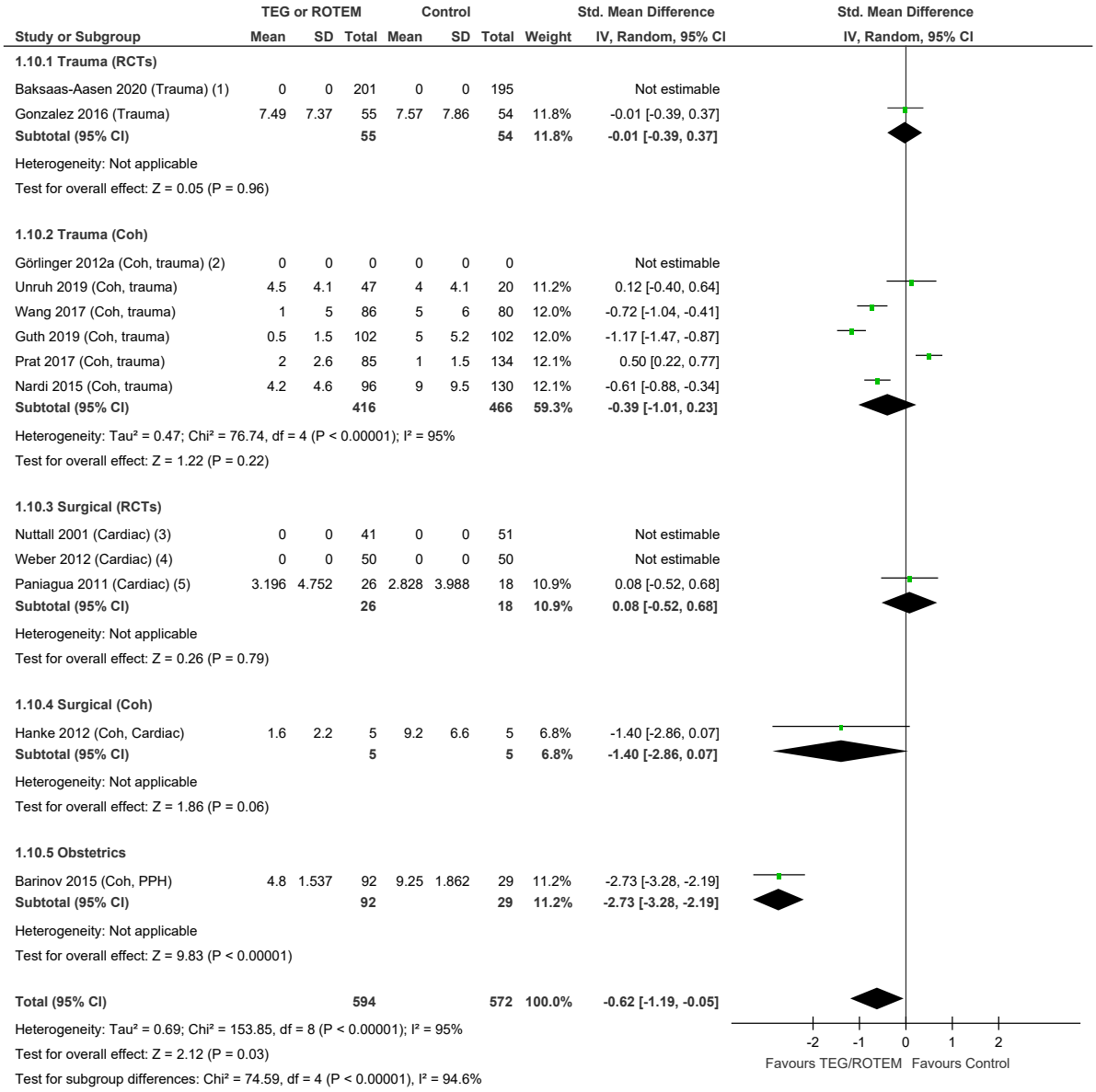
(2) Favours TEG or ROTEM (p<0.001). Data reported as median (IQR): 0 (0, 3) vs 5 (3, 8).

(3) Study did not report this outcome.

(4) Converted from mLs (250 mL/U)

(5) An estimated 79% and 94% reduction in the total volume of FFP transfused per year after the implementation of goal-directed therapy (two trauma centres).

Figure 4.58 Forest plot of comparison: TEG or ROTEM vs MHP or standard laboratory tests, outcome: FFP transfusion volume (units), by setting.



Footnotes

(1) Study did not report this outcome.

(2) An estimated 79% and 94% reduction in the total volume of FFP transfused per year after the implementation of goal-directed therapy (two trauma centres).

(3) Favours TEG or ROTEM (p=0.005). Data reported as median (range): 2 (0, 10) vs 4 (0, 75)

(4) Favours TEG or ROTEM (p<0.001). Data reported as median (IQR): 0 (0, 3) vs 5 (3, 8).

(5) converted from mLs (250 mL/U)

Table 4.83 Results for TEG or ROTEM to guide BCT versus no TEG or ROTEM to guide BCT: Patients *with* critical bleeding – FFP transfusion volume

Study ID Study design [a]	Sample size (no. of trials) included in analysis	Patient population	Setting (Location)	Comparison	Outcome	Results			
						TEG/ROTEM Mean ± SD (n)	No TEG/ROTEM Mean ± SD (n)	Risk estimate (95% CI)	*Statistical significance* *p*-value Heterogeneity[b]
Various settings									
Fahrendorff 2017 SR *High risk of bias*	N = 423 (5 studies) Shore-Lesserson 1999 Wang 2010 Barinov 2015 Gonzalez 2016 Cao 2016	Patients with an acute need for blood components due to bleeding (includes trauma, burns excision, liver transplant, PPH and cardiac surgery)	Various	TEG or ROTEM guided algorithm vs the clinician's discretion and/or based on conventional coagulation tests	FFP transfusion volume, Units	Mean ± SD (246) 0.133 ± 0.526 (53) 12.8 ± 7 (14) 4.8 ± 1.537 (92) 7.49 ± 7.37 (55) 0.867 ± 0.17 (32)	Mean ± SD (177) 0.804 ± 1.715 21.5 ± 12.7 (14) 9.25 ± 1.862 (29) 7.57 ± 7.86 (54) 1.904 ± 0.152 (28)	SMD –1.98 (–3.41, –0.54) –0.53 (–0.92, –0.14) –0.82 (–1.60, –0.05) –2.73 (–3.28, –2.19) –0.01 (–0.39, 0.37) –6.32 (–7.60, –5.05)	*Favours TEG/ROTEM* *p* = 0.007 Substantial heterogeneity I^2 = 97 (*p* = 0.00001)
Trauma setting									
Bugaev 2020 SR *High risk of bias*	N = 827 (5 studies) Unruh 2019 Gonzalez 2016 Guth 2019 Prat 2017 Nardi 2015	Severely injured trauma patients	Trauma (NR)	ROTEM or TEG vs no ROTEM or TEG	FFP transfusion volume, Units	N=386 4.5±4.1 (n=47) 5±4.4 (n=56) 0.5±1.5 (n=102) 2±2.6 (n=85) 4.2±4.6 (n=96)	N=441 4±4.1 (n=20) 6±3.7 (n=55) 5±5.2 (n=102) 1±1.5 (n=134) 9±9.5 (n=130)	SMD –0.29 (–0.91, 0.34) SMD 0.12 (-0.40, 0.64) SMD –0.24 (–0.62, 0.13) SMD –1.17 (–1.47, -0.87) SMD 0.50 (0.22, 0.77) SMD –0.61 (–0.88, –0.34)	*No significant difference* *p = 0.36* Significant heterogeneity I^2= 94% (*p* < 0.00001)
Roullet 2018 RCT *High risk of bias*	N = NR (1 RCT) Gonzalez 2016	Patients with severe trauma	Trauma (NR)	TEG or ROTEM guided algorithm vs the clinician's discretion and/or based on conventional coagulation tests	FFP transfusion volume, Units	Authors note that the group receiving the routine tests received more FFP early compared to the TEG group. *See Fahrendorff 2017 for values			*No significant difference* *p* = NR
Wang 2017 Coh *Serious risk of bias*	N = 166 (1 Coh)	Patients with traumatic liver and/or spleen injury	SC (US)	TEG guided algorithm vs clinical judgement or usual treatment	FFP transfusion volume, Units	1 ± 5 (86)	5 ± 6 (80)	NR	*Favours TEG* *p* < 0.01
Haas 2014 Coh *Serious risk of bias*	N = 5590 (1 Coh) Görlinger 2012a Görlinger 2012a	Adult patients with severe trauma	SC (Austria, Germany)	ROTEM guided algorithm vs standard of care	FFP transfusion volume, Units	Total per year (n) 48 (4) 261 (NR)	Total per year (n) 756 (63) 1221 (NR)	94% reduction 79% reduction	*p* = NR
Surgical setting									
Wikkelsø 2016	N = NR (2 RCTs)					Median (IQR)	Median (IQR)		*Favours TEG/ROTEM*

Study ID Study design [a]	Sample size (no. of trials) included in analysis	Patient population	Setting (Location)	Comparison	Outcome	Results			
						TEG/ROTEM Mean ± SD (n)	No TEG/ROTEM Mean ± SD (n)	Risk estimate (95% CI)	*Statistical significance* *p*-value Heterogeneity[b]
SR *High risk of bias*	Weber 2012 Nuttal 2001	Adults or children with diffuse or excessive bleeding after cardiac surgery, orthotopic liver transplant or burns excision	SC (Germany, Spain, US)	TEG or ROTEM guided transfusion vs clinical judgement or usual treatment with or without predefined algorithm to guide SLTs	FFP transfusion volume, Units	0 (0, 3) Median (range) 2 (0, 10)	5 (3, 8) Median (range) 4 (0, 75)		*p* < 0.001 *p* = 0.005
	N = 44 (1 RCT) Paniangua 2011				FFP transfusion volume, mL	Mean ± SD (n) 799 ± 1188 (26)	Mean ± SD (n) 707 ± 997 (18)	0.08 (–0.52, 0.68)	*No significant difference* *p* = NR
Haas 2014 Coh Serious risk of bias	N = 5338 (1 Coh) Görlinger 2012b	Adult patients undergoing visceral surgery or liver transplant	SC (Germany)	ROTEM guided algorithm vs standard of care	FFP transfusion volume, Units	Units per year 223	Units per year 4465	95% reduction	*Favours ROTEM* *p* = NR
	N = 10 (1 Coh) Hanke 2012	Adult patients undergoing cardiac or aortic surgery	SC (NR)	ROTEM guided algorithm vs standard of care	FFP transfusion volume, Units	Mean ± SD (n) 1.6 ± 2.2 (5)	Mean ± SD (n) 9.2 ± 6.6 (5)	MD –7.60 (–13.7, –1.5)[c]	*Favours ROTEM* *p* = 0.038
	N = 100 (1 RCT) Weber 2012					Median (IQR) 0 (0, 3)	Median (IQR) 5 (3, 8)	NR	*p* < 0.001
Obstetrics setting – no studies reporting data									

Studies with ~~strikethrough~~ do not meet the PICO criteria for this question.

Abbreviations: CI, confidence interval; Coh, cohort study; CRYO, cryoprecipitate; FC, fibrinogen concentrate; FFP, fresh frozen plasma; hrs, hours; IQR, interquartile range; MC, multicentre; MD, mean difference; n, number; NR, not reported; PCC, prothrombin complex concentrate; PLT, platelets; PPH, postpartum haemorrhage; RBCs, red blood cells; RCT, randomised controlled trial; ROTEM, rotational thromboelastometry; SC, single centre; SD, standard deviation; SMD, standard mean difference; SoC, standard of care; SLTs, standard laboratory tests; TEG, thromboelastography; UK, United Kingdom; US, United States

a. Where only one RCT is identified in a systematic review, the evidence has been considered as RCT evidence. Where the systematic review assesses Observational and cohort studies studies, the evidence has been considered as according to the study design features. The risk of bias of the included primary studies is based on the quality assessment reported by the systematic review authors.

b. Only applicable to Systematic reviews with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if P_{het} >0.1 and I^2 <25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25–50%; substantial heterogeneity I^2 >50%.

c. Calculated post-hoc using RevMan 5.4. M-H random effects.

Platelets

A summary of the evidence relating to the volume of platelets (PLTs) and other blood components transfused in patients with critical bleeding is presented in Table 4.84.

A meta-analysis of available data from the RCT and cohort studies included in this review (see Figure 4.59) showed no significant reduction in the volume of PLTs transfused in patients with critical bleeding (any setting) who received blood component therapy guided by TEG or ROTEM (n=402) compared with those who received treatment guided by an MHP or standard laboratory tests (n=331) (SMD –0.21; 95% CI –0.51, 0.09; $p = 0.17$, $I^2 = 72\%$).

Available data from the RCTs suggested that the volume of PLTs transfused was not different between groups (SMD 0.02; 95% CI –0.59, 0.64; $p = 0.94$; $I^2 = 65\%$) but data were not able to be included for two studies that suggested an effect favouring TEG or ROTEM. Among the observational cohort studies, the available data suggested there a non-significant reduction in the volume of PLTs transfused (around one unit saved) among patients who received blood component therapy guided by TEG or ROTEM (n=284) compared with those who received treatment guided by an MHP or standard laboratory tests (n=284) (SMD –0.31; 95% CI –0.64, 0.03; $p = 0.07$; $I^2 = 96\%$).

In the trauma setting (see Figure 4.60), data from one RCT suggested that the use of TEG or ROTEM to guide blood component therapy did not reduce the volume of PLTs transfused when compared treatment not guided by TEG or ROTEM (SMD 0.30; 95% CI –0.12, 0.72; $p = 0.16$). Among the cohort studies a significant association was observed (SMD –0.43; 95% CI –0.78, –0.08; $p = 0.02$; $I^2 = 67\%$), noting PLT transfusion volumes were not reported for all studies, possibly due to the p-value or direction of effect being unfavourable to the intervention. Taken together the pooled data from the RCT and cohort studies suggests that the use of TEG or ROTEM to guide blood component therapy does not reduce the volume of FFP transfused when compared treatment not guided by TEG or ROTEM (SMD –0.25; 95% CI –0.66, 0.15; $p = 0.22$; $I^2 = 80\%$).

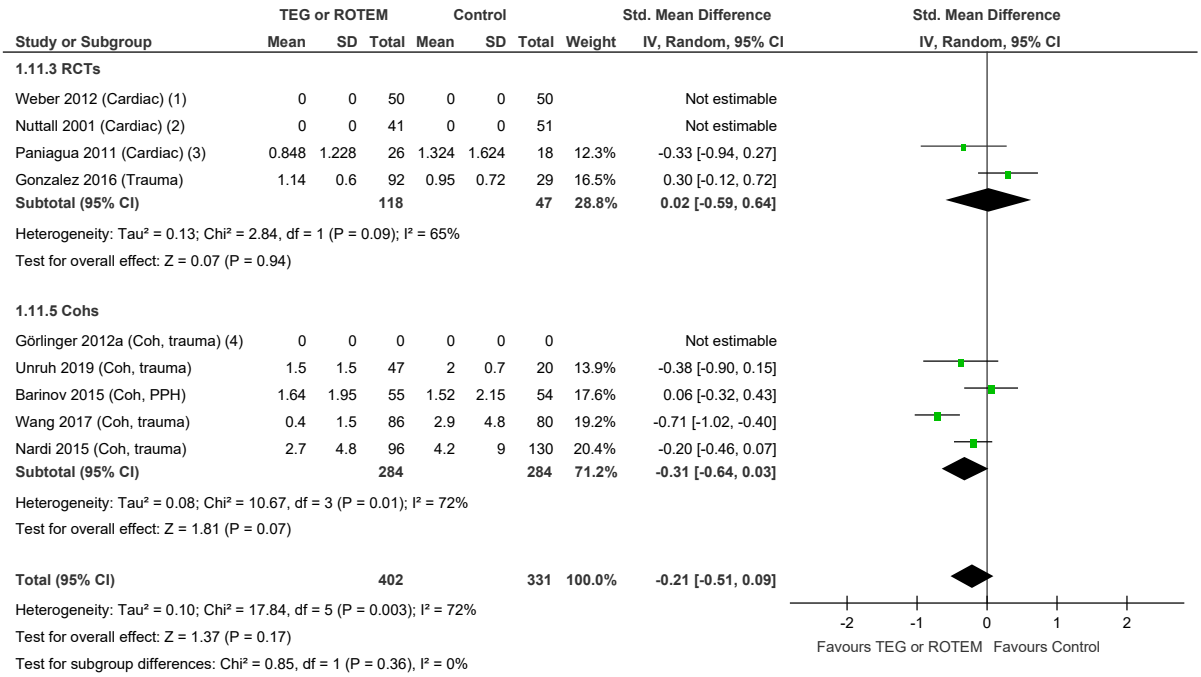
In patients with diffuse and/or abnormal bleeding from capillary beds and/or excessive blood loss after surgery (see Figure 4.60), data from one small RCT suggested that there was no difference in volume of PLTs transfused comparing blood component therapy guided by TEG or ROTEM with routine transfusion therapy based on standard laboratory tests (SMD –0.33; 95% CI –0.94, 0.27; $p = 0.28$). Data were not reported in two studies and two studies suggested an effect favouring TEG or ROTEM but did not provide suitable data for analysis.

Among women with severe PPH (see Figure 4.60), data from one observational study suggested that blood component therapy guided by TEG or ROTEM is not associated with any reduction in the volume of PLTs transfused (SMD of 0.06; 95% CI –0.32, 0.43; $p < 0.76$). The other two studies did not report this outcome.

Fibrinogen replacement

There was little evidence reported relating to fibrinogen replacement therapy in patients with critical bleeding in whom the blood component therapy was guided by TEG or ROTEM (see Table 4.84). The evidence was therefore not considered further.

Figure 4.59 Forest plot of comparison: TEG or ROTEM vs MHP or standard laboratory tests, outcome: PLT transfusion volume (units), by study design.



Footnotes

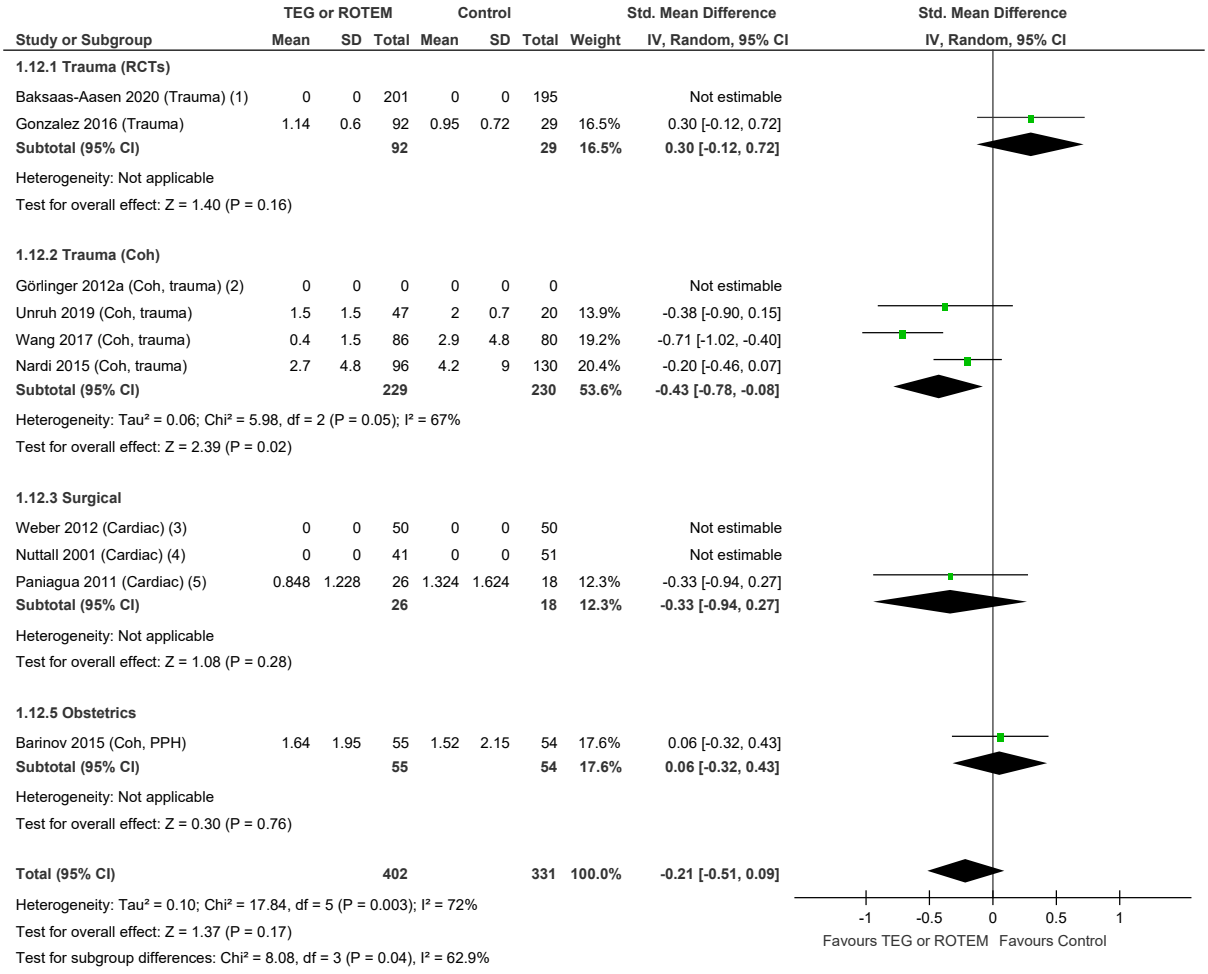
(1) Favours TEG or ROTEM (p=0.01). Data reported as median (IQR): 2 (0, 2) vs 2 (0, 5).

(2) Favours TEG or ROTEM (p=0.0001). Data reported as median (range): 6 (0, 18) vs 6 (0, 144).

(3) converted from mLs (250 mL/U)

(4) An estimated 72% and 65% reduction in the total volume of PLTs transfused per year after the implementation of goal-directed therapy (two trauma centres).

Figure 4.60 Forest plot of comparison: TEG or ROTEM vs MHP or standard laboratory tests, outcome: PLT transfusion volume (units), by setting.



Footnotes

(1) Study did not report this outcome.

(2) An estimated 72% and 65% reduction in the total volume of PLTs transfused per year after the implementation of goal-directed therapy (two trauma centres).

(3) Favours TEG or ROTEM (p=0.01). Data reported as median (IQR): 2 (0, 2) vs 2 (0, 5).

(4) Favours TEG or ROTEM (p=0.0001). Data reported as median (range): 6 (0, 18) vs 6 (0, 144).

(5) converted from mLs (250 mL/U)

Table 4.84 Results for TEG or ROTEM to guide BCT versus no TEG or ROTEM to guide BCT: Patients *with* critical bleeding – PLT, CRYO, PCC transfusion volume, Units

Study ID Study design [a] *Risk of bias*	Sample size (no. of trials) included in analysis	Patient population	Setting (Location)	Comparison	Outcome	Results			
						TEG/ROTEM Mean ± SD (n)	No TEG/ROTEM Mean ± SD (n)	Risk estimate (95% CI)	*Statistical significance* *p*-value Heterogeneity[b]
Various settings									
Fahrendorff 2017 SR *High risk of bias*	N = 423 (5 studies) Shore-Lesserson 1999 Wang 2010 Barinov 2015 Gonzalez 2016 Cao 2016	Patients with an acute need for blood components due to bleeding (includes trauma, burns excision, liver transplant, PPH and cardiac surgery)	Various	TEG or ROTEM guided algorithm vs the clinician's discretion and/or based on conventional coagulation tests	PLT transfusion volume, Units	Mean ± SD (246) 0.1 ± 0.276 (53) 27.3 ± 13.9 (14) 1.64 ± 1.95 (55) 1.14 ± 0.6 (92) 2.5 ± 1.3 (32)	Mean ± SD (177) 0.244 ± 0.471 30.1 ± 18.5 (14) 1.52 ± 2.15 (54) 0.95 ± 0.72 (29) 4.2 ± 0.6 (28)	SMD –0.34 (–0.92, 0.24) –0.37 (–0.76, 0.01) –0.17 (–0.91, 0.58) 0.06 (–0.32, 0.43) 0.30 (–0.12, 0.72) –1.62 (–2.21, –1.03)	*No significant difference* *p* = 0.25 Substantial heterogeneity I^2 = 87 (*p* = 0.00001)
Trauma setting									
Bugaev 2020 Coh *Serious risk of bias*	N = 404 (3 studies) Nardi 2015 Gonzalez 2016 Unruh 2019	Severely injured trauma patients	Trauma (NR)	ROTEM or TEG vs no ROTEM or TEG	PLT transfusion volume, Units	N=199 2.7±4.8 (n=96) 1±1.5 (n=56) 1.5±1.5 (n=47)	N=205 4.2±5.9 (n=130) 1±1.5 (n=55) 2±0.7 (n=20)	MD –0.44 (–1.05, 0.17) MD –1.50 (–2.90, -0.10) MD 0.00 (–0.56, 0.56) MD –0.50 (–1.03, 0.03)	*No significant difference* *p = 0.16* Moderate heterogeneity I^2 = 55% (*p* = 0.11)
Roullet 2018 RCT *High risk of bias*	N = NR (1 RCT) Gonzalez 2016	Patients with severe trauma	Trauma (NR)	TEG or ROTEM guided algorithm vs the clinician's discretion and/or based on conventional coagulation tests	PLT transfusion volume, Units	Authors note that the group receiving the routine tests received more platelets early compared to the TEG group. *See Fahrendorff 2017 for values			*No significant difference* *p* = NR
					Fibrinogen	At 24 hrs, only the amount of fibrinogen administered was different, being higher in the group managed with routine tests.			*No significant difference* *p* = NR
Wang 2017 Coh *Serious risk of bias*	N = 166 (1 Coh)	Patients with traumatic liver and/or spleen injury	SC (US)	TEG guided algorithm vs clinical judgement or usual treatment	PLTs transfusion volume, Units	0.4 ± 1.5 (86)	2.9 ± 4.8 (80)	NR	*Favours TEG* *p* < 0.01
					CRYO transfusion volume, Units	0.1 ± 0.5 (86)	0.3 ± 1.2 (80)	NR	*No significant difference* *p* = NR
Haas 2014 *Serious risk of bias*	N = 5590 (1 Coh) Görlinger 2012a Görlinger 2012a	Adult patients with severe trauma	SC (Austria, Germany)	ROTEM guided algorithm vs standard of care	PLT transfusion volume, Units	Total per year 25 29	Total per year 90 82	 72% reduction 65% reduction	*Favours ROTEM* *p* = NR
Surgical setting									
Wikkelsø 2016 SR	N = NR (2 RCTs) Weber 2012		SC (Germany, Spain, US)		PLT transfusion volume, Units	Median (IQR) 2 (0, 2)	Median (IQR) 2 (0, 5)		*Favours TEG or ROTEM* *p* = 0.010
						Median (range)	Median (range)		

Study ID Study design [a] *Risk of bias*	Sample size (no. of trials) included in analysis	Patient population	Setting (Location)	Comparison	Outcome	Results			
						TEG/ROTEM Mean ± SD (n)	No TEG/ROTEM Mean ± SD (n)	Risk estimate (95% CI)	*Statistical significance* *p*-value Heterogeneity[b]
High risk of bias	Nuttal 2001	Adults or children with diffuse or excessive bleeding after cardiac surgery, orthotopic liver transplant or burns excision		TEG or ROTEM guided transfusion vs clinical judgement or usual treatment with or without predefined algorithm to guide SLTs		6 (0, 18)	6 (0, 144)		$p = 0.0001$
	N = NR 1 RCTs) Paniangua 2011				PLT transfusion volume, mL	Mean ± SD 212 ± 307 (26)	Mean ± SD 331 ± 406 (18)	SMD [c] –0.33 (–0.94, 0.27)	p = NR
Haas 2014 RCT *High risk of bias*	N = 100 (1 RCT) Weber 2012	Adult patients undergoing cardiac or aortic surgery	SC (NR)	ROTEM guided algorithm vs standard of care	PLT transfusion volume, units	Median (IQR) 2 (0, 2)	Median (IQR) 2 (0, 5)	NR	*Favours ROTEM* $p = 0.01$
	N = 5338 (1 Coh) Görlinger 2012b	Adult patients undergoing visceral surgery or liver transplant	SC (Germany)	ROTEM guided algorithm vs standard of care	PLT transfusion volume, mL	Total per year 149	Total per year 433	66% reduction	p = NR
					FC required, g	per year 745	per year 68	9.9-fold increase	*Favours SoC* p = NR
					PCC required, IU	per year 238 500	per year 65 500	2.6-fold increase	*Favours SoC* p = NR

Studies with ~~strikethrough~~ do not meet the PICO criteria for this question.

Abbreviations: CI, confidence interval; Coh, cohort study; CRYO, cryoprecipitate; FC, fibrinogen concentrate; FFP, fresh frozen plasma; hrs, hours; IQR, interquartile range; MC, multicentre; MD, mean difference; n, number; NR, not reported; PCC, prothrombin complex concentrate; PLT, platelets; PPH, postpartum haemorrhage; RBCs, red blood cells; RCT, randomised controlled trial; ROTEM, rotational thromboelastometry; SC, single centre; SD, standard deviation; SMD, standard mean difference; SoC, standard of care; TEG, thromboelastography; UK, United Kingdom; US, United States

a. Where only one RCT is identified in a systematic review, the evidence has been considered as RCT evidence. Where the systematic review assesses observational and cohort studies, the evidence has been considered as according to the study design features. The risk of bias of the included primary studies is based on the quality assessment reported by the systematic review authors.

b. Only applicable to Systematic reviews with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if P_{het} >0.1 and I^2 <25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25–50%; substantial heterogeneity I^2 >50%.

c. Calculated post-hoc using RevMan 5.4. M-H random effects.

4.9.3.4 Time to transfusion

No evidence found.

4.9.3.5 Dose/type of transfusion

There was little evidence reported relating to the dose or type of transfusion (e.g. more than five units transfused) in patients with critical bleeding in whom the blood component therapy was guided by TEG or ROTEM. The evidence was therefore not considered further. The available data is provided in volume 3 of the Technical report.

4.10 Cell salvage (Question 9)

Question 9 – (interventional)

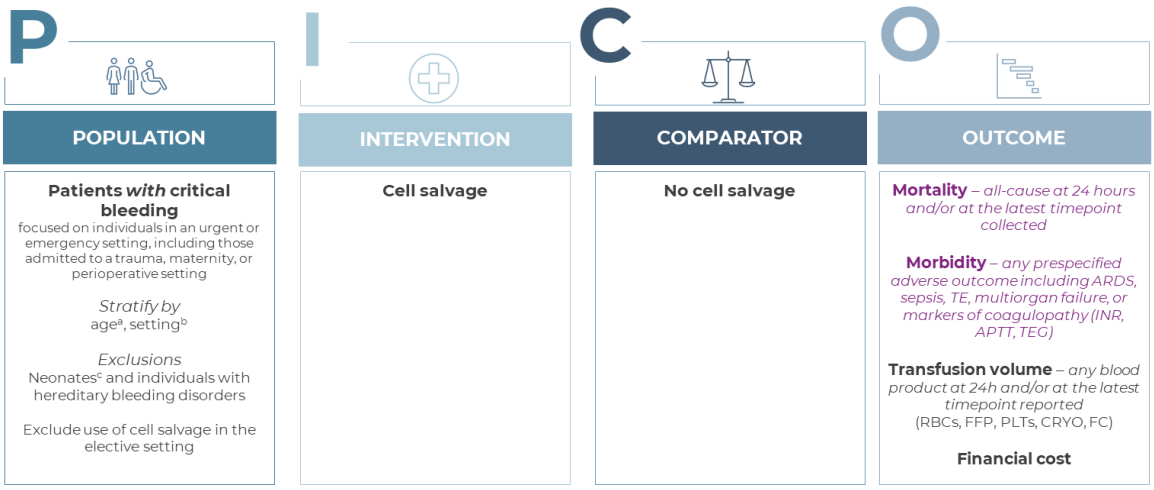
In patients *with* critical bleeding what is the effect of cell salvage on patient outcomes?

4.10.1 Methods

This question examined the effect and cost of cell salvage compared with no cell salvage in patients *with* critical bleeding (i.e. major haemorrhage that is life-threatening and is likely to result in the need for massive transfusion) as outlined in Figure 4.61.

The question focused on individuals in an urgent or emergency setting, including those admitted to a trauma, maternity or perioperative setting. No age limits were applied, however studies in neonates (newborns up to 28 days) and studies in individuals with hereditary bleeding disorders were not eligible for inclusion.

Figure 4.61 PICO criteria: Question 9 – cell salvage



Abbreviations: ARDS, acute respiratory distress syndrome; CRYO, cryoprecipitate; FC, fibrinogen concentrate; FFP, fresh frozen plasma; INR, international normalised ratio; PLTs, platelets; RBCs, red blood cells; ROTEM, thromboelastometry; TE, thromboembolic event; TEG, thromboelastography

a. Adult (aged over 18 years), child (aged 2 to 12 years), adolescent (aged 13 to 18 years), infants (aged 1 to 23 months).

b. e.g. trauma, obstetric, perioperative (cardiothoracic, general surgery, gastrointestinal, liver transplant), paediatric, other.

c. Newborns up to 28 days following birth.

Selection of studies was conducted according to the screening criteria described in Section 3.3.

The initial 2018 search was limited to studies published after 1990, noting primary studies published prior to 1990 that had been included within a systematic review were also eligible for inclusion. There were no restrictions applied to sample size.

Assuming relevant primary studies had been identified in the included systematic review and meta-analyses, the systematic screening of RCTs and nonrandomised studies was limited to studies published after 2015, based on the literature search date of the most recent and comprehensive identified systematic review (Meybohm 2016).

The literature search was updated in August 2019 and again in September 2021 to identify any new studies meeting the eligibility criteria. In this updated search, systematic reviews were first screened, then RCTs were screened. No new systematic reviews or RCTs were found.

Studies conducted in patients receiving intraoperative cell salvage in the elective setting, such as those scheduled for radical prostatectomy or other cancer-related surgery, total hip or knee arthroplasty, scoliosis surgery, minimally invasive cardiothoracic surgery, infrarenal abdominal aortic aneurysm surgery, craniosynostosis and caesarean section, were excluded. These studies were deemed more appropriate for assessment in the perioperative module.

4.10.2 Summary of evidence

4.10.2.1 Systematic reviews

Three systematic reviews (212-214) were identified that assessed the effects of cell salvage compared with no cell salvage in patients with critical bleeding (Nayar 2017, Meybohm 2016, Shatikumar 2011). The main characteristics and quality of these reviews and relevant outcomes assessed are summarised in Table 4.85. An overlap table listing the potentially relevant primary studies included in the reviews is provided in Table 4.86.

One other systematic review (Li 2015) (215) was identified in the literature search that did not provide any additional data than that of the Meybohm 2016, thus was not considered further in this review (duplicate data). A list of studies that met the PICO criteria for this question but were later excluded is provided in **Appendix B, Volume 2**.

Nayar 2017 was a narrative review that assessed blood conservation strategies in the setting of acute orthopaedic trauma. The review authors noted seven primary studies in their discussion of cell salvage that were retrieved for further assessment; but later deemed more appropriate for assessment in the perioperative module as patients were not critically bleeding.

Meybohn 2016 was a systematic review and meta-analysis of RCTs involving patients scheduled for all types of surgery randomised to washed cell salvage or no cell salvage. The primary outcome of interest was the number of patients exposed to RBC transfusion, with the volume of blood transfused, mortality and rates of infection also assessed. The authors identified 47 studies that met their inclusion criteria, one of which involved patients undergoing surgery for multiple trauma (penetrating abdominal trauma) and was considered relevant to this review (Bowley 2006).

Shatikumar 2011 was a systematic review of all available evidence relating to the use of cell salvage in abdominal aortic aneurysm (AAA) repair. Where possible, a meta-analysis of relevant data was performed, with a focus on the proportion of patients transfused, the volume of blood component used, complications and length of ICU and hospital stay. The author identified 23 studies that met their inclusion criteria, with five non-randomised studies involving ruptured AAA repair considered relevant to this review (Markovic 2009, Tawfick 2008, Serricino-Inglott 2005, Shuhaiber 2003, Poscaioglu 2002).

Table 4.85 Characteristics and quality of SR and MA evidence: cell salvage versus no cell salvage

Review ID ***Review quality***	Study design	Population	Intervention	Comparator	Outcomes
Surgical setting					
Nayar 2017 *Critically low*	Narrative review	Acute orthopaedic trauma (61 studies)[a]	Cell salvage	Any	Transfusion volume Cost
Meybohm 2016 *High*	SR / MA of RCTs	Patients scheduled for any type of surgery (47 studies)[b]	Washed cell salvage	No cell salvage	Mortality Morbidity Transfusion volume Costs
Shantikumar 2011 (213) *Critically low*	SR of RCTs and cohort studies	Abdominal aortic aneurysm surgery (23 studies)[c]	Washed cell salvage	No cell salvage	Mortality Morbidity Transfusion volume

Abbreviations: MA, meta-analysis; RCT, randomised controlled trial; SR, systematic review

a. The authors found no studies considered relevant to this review. There were six studies in orthopaedic trauma; but none were in patients *with* critical bleeding.

b. The authors included one study in multiple trauma surgery (Bowley 2006) considered relevant to this review. A further 15 studies in orthopaedic surgery, 21 in cardiac surgery, six in vascular surgery, two in cancer surgery and two in paediatric surgery were not relevant to this review.

c. The authors included five studies in urgent rupture repair considered relevant to this review. A further 18 studies (9 uncontrolled studies, 5 non-randomised trials and 4 RCTs) involved elective surgery and therefore did not meet the PICO criteria for this review.

Table 4.86 Overlap table showing systematic reviews and included primary studies: cell salvage versus no cell salvage

Review ID		Nayar 2017	Meybohm 2016	Shantikumar 2011
Trauma				
Study ID	Banghu 2013 [a]			
	Bowley 2006		✓	
Orthopaedic trauma				
Study ID	Firoozobadi 2015	X		
	Bigsby 2013	X		
	Canan 2013	X		
	Odak 2013	X		
	Scannell 2009	X		
	Cavallieru 1994	X		
	Schmidt 1998	X		
Ruptured aneurysm repair				
Study ID	Markovic 2009			✓
	Tawfick 2008			✓
	Serricino-Inglott 2005			✓
	Shuhaiber 2003			✓
	Poscaioglu 2002			✓

a. Study identified and excluded by Li 2015 (not randomised).

X = study does not meet PICO criteria (participants not critically bleeding).

✓= study meets PICO criteria (participants with major haemorrhage that is life-threatening and is likely to result in the need for massive transfusion).

4.10.2.2 Randomised controlled trials

One small RCT (Bowley 2006) examining the effect of cell salvage in patients with critical bleeding was identified in the included systematic reviews. No additional RCTs were identified through the systematic review and handsearching process. A summary of the characteristics and quality of the identified RCT is provided in Table 4.87.

Bowley 2006 enrolled adult patients (aged over 18 years) presenting to emergency with penetrating torso injury requiring laparotomy and had exhibited hypotension (< 90 mm Hg) either prehospital or on arrival and in whom there was significant blood loss. The study was conducted in South Africa (within the Johannesburg Hospital Trauma Unit), and patients were predominantly male (40/44, 91%).

Table 4.87 Characteristics and quality of RCT evidence: cell salvage versus no cell salvage

Study ID ***Risk of bias***	Study design	Population	Intervention	Comparator	Outcomes
Trauma					
Bowley 2006 (216) *High*	RCT	Adults with penetrating abdominal trauma N = 44	Cell salvage (n=21)	No cell salvage [a] (n=21)	Mortality Transfusion volume

Abbreviations: RCT, randomised controlled trial
a. Donor blood transfusion at the discretion of the attending medical staff

4.10.2.3 Observational and cohort studies

Five nonrandomised studies (Markovic 2009, Tawfick 2008, Serricino-Inglott 2005, Shuhaiber 2003, Poscaioglu 2002) involving urgent AAA repair were identified in the included systematic review and were considered relevant to this review. One additional cohort study (Banghu 2013) was identified through the systematic review and handsearching process that examined the effect of cell salvage in patients with critical bleeding. A summary of the characteristics and quality of the identified nonrandomised studies is provided in Table 4.88.

Trauma

Banghu 2013 was a prospective cohort study conduct in Afghanistan among patients admitted to a combat support hospital with battle-related injury. Out of 130 patients (76% blast-injury, 22% gunshot, 2% road), 29 patients were judged by the attending military surgeon to likely require at least 10 units of RBCs in the first 12 hours after injury. Eighteen cases were selected for intraoperative blood salvage, which was successfully completed in 17 patients (one died on operating table before cell salvage could occur). The control group included 11 patients who were admitted at the same time and received at least 10 units of RBCs in the first 12 hours after injury but did not undergo cell salvage.

The study had important problems relating to insufficient information about potential confounders. It was also noted that blast injuries (predominantly from improvised explosive devices) drive environmental material deep into patients' wounds, leading to gross contamination. The study was therefore judged not applicable to the Australian context and was not included in the GRADE evidence summary tables or when developing recommendations.

Surgical setting

Markovic 2009 retrospectively reviewed clinical and financial outcomes relating to abdominal aortic surgery among 90 patients who received intraoperative cell salvage compared with 90 patients who did not receive intraoperative cell salvage at a single institution in Serbia. The patients were subdivided according to the type of operation, being aortoiliac occlusive disease (AOD), elective AAA repair or ruptured AAA repair. Only the ruptured AAA repair was relevant to this review.

Tawfick 2008 retrospectively reviewed ruptured AAA over a 9-year period (between June 1997 and June 2006) at a single hospital in Ireland. The study included both emergency open AAA repair and scheduled or elective AAA repair[38]. The mean age for all patients who received cell salvage was 72 years, which was significantly higher (p = 0.01) than that of the control group (69 years). All other factors (preoperative cardiac, pulmonary and renal status, smoking, diabetes, mean preoperative haemoglobin) were comparable between groups.

Serracino-Inglott 2005 was a prospective cohort study that examined 154 ruptured AAA repairs reported to a regional vascular audit database in the UK over a 4-year period (January 2000 to June 2004). The two groups were matched for age, cardiac and respiratory symptoms, cardiac medication, incidence of myocardial infarction and diabetes.

Shuhaiber 2003 was a small retrospective cohort study conducted at a single centre in the UK among 128 patients who underwent AAA repair between 1992 and 1999 by a single vascular surgeon. Only 25 patients had emergency AAA repair (Group B), with the other 93 patients receiving elective AAA repair (Group A)[38]. Among patients in Group B, the mean age was 74.3 years (range 58 to 84), all but two patients were male (23/25; 92%).

Posacioglu 2002 retrospectively reviewed mortality, post-operative morbidity and blood loss in 56 patients with suprarenal and infrarenal ruptured AAA repairs by a single surgeon in Turkey. There were no differences in baseline characteristics (98% [55/56] were male), with the mean age being 68 ± 8 years.

None of the above studies were randomised, due to the unpredictability and urgency of admissions and difficulties with ethical approval. All studies had important problems relating to patient selection bias, and outcome assessment and reporting bias.

Table 4.88 Characteristics and quality of observation and cohort studies: cell salvage versus no cell salvage

Study ID ***Risk of bias***	Study design	Population	Intervention	Comparator	Outcomes
Trauma					
Bhangu 2012 (217) *Serious*	Prospective cohort	Patients with sustained combat-related injury requiring massive transfusion [a]	Cell salvage (n=18)	No cell salvage (n=11)	Mortality Transfusion volume

[38] Not relevant to this review.

Study ID *Risk of bias*	Study design	Population	Intervention	Comparator	Outcomes
Surgical setting					
Markovic 2009 (218) *Serious*	Prospective cohort with historical controls	Ruptured AAA repair	Cell salvage (n=15)	No cell salvage (n=15)	Mortality Morbidity Transfusion volume
Tawfick 2008 (219) *Serious*	Retrospective cohort	Emergency open AAA repair and scheduled or elective AAA repair	Cell salvage (n=27)	No cell salvage (n=28)	Mortality Morbidity Transfusion volume
Serrancino-Inglott 2005 (220) *Serious*	Prospective cohort (regional audit database)	Ruptured AAA repairs over a 4-year period (January 2000 to June 2004)	Cell salvage (n=40)	No cell salvage (n=114)	Mortality Morbidity Transfusion volume
Shuhaiber 2003 (221) *Serious*	Retrospective cohort	AAA surgery by a single surgeon	Cell salvage (n=4)	No cell salvage (n=21)	Mortality Morbidity Transfusion volume
Posacioglu 2002 (222) *Serious*	Retrospective cohort	Suprarenal and infrarenal ruptured AAA repairs by a single surgeon	Cell salvage (n=40)	No cell salvage (n=16)	Mortality Morbidity Transfusion volume

Abbreviations: AAA, abdominal aortic aneurysm
a. Requiring at least 10 units of RBCs in the first 12 hours after injury.

4.10.3 Results

4.10.3.1 Mortality

A summary of the evidence relating to mortality (at any timepoint up to 30 days) in patients with critical bleeding receiving intraoperative autologous transfusions (obtained by cell salvage) is presented in Table 4.89. None of the individual studies were powered to detect differences in mortality.

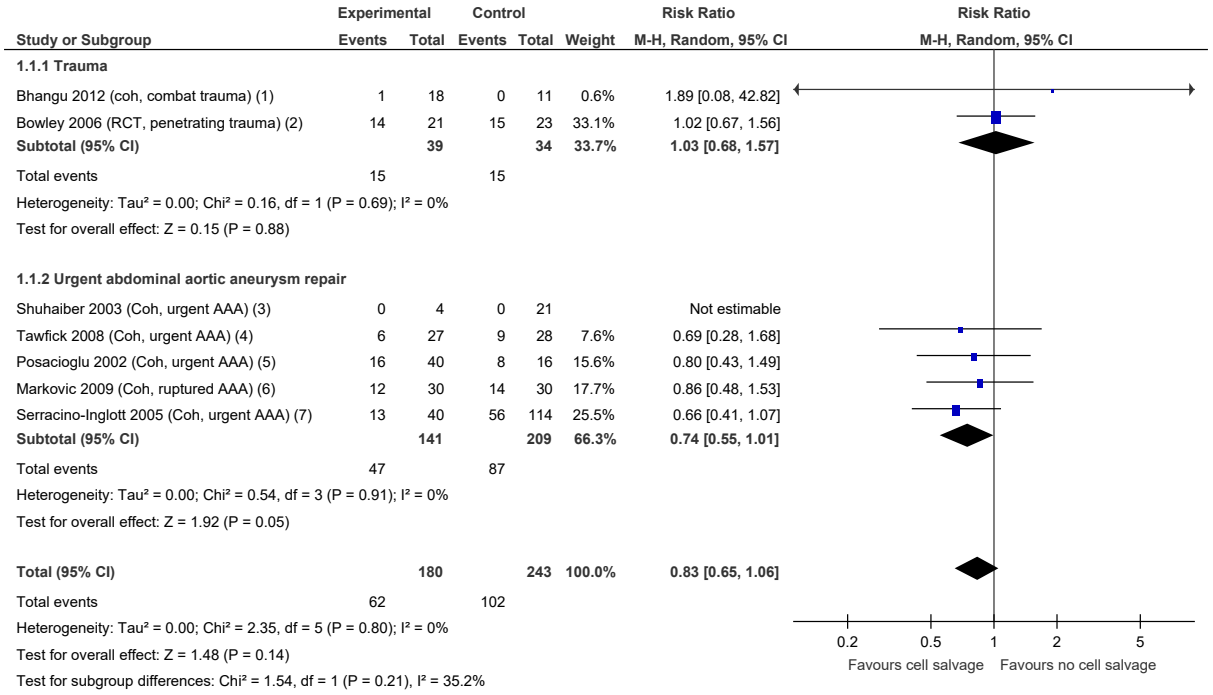
Overall, no difference in mortality comparing patients who received cell salvage with those who did not (regardless of clinical setting) was observed but the evidence is very uncertain. For most bleeding patients there is no substantial survival benefit associated with cell salvage.

Pooled data from the identified RCT and nonrandomised trials (see Figure 4.62) showed the mortality rate in patients with critical bleeding to be lower among those who received cell salvage (62/180, 34%) compared with those who did not (102/243, 42%). The difference was not significant (RR 0.83; 95% CI 0.65, 1.06; $p = 0.14$, $I^2 = 0\%$).

In trauma patients, there were 15 deaths among the 39 patients (38.5%) who received cell salvage compared with 15 deaths among the 34 (44%) patients who received standard care. The results suggest no difference between groups for the outcome of mortality (RR 1.03; 95% CI 0.68, 1.57; $p = 0.88$; $I^2 = 0\%$). In considering the RCT evidence alone, the mortality rate was higher (66.7% vs 65.2%), with no difference between groups observed (RR 1.02; 95% CI 0.67, 1.56; $p = 0.92$) *(GRADE: very low)*.

Among patients requiring urgent abdominal aortic aneurysm repair, there were fewer deaths among those who received cell salvage (47/141, 33%) compared with those who did not (87/209, 42%). An effect favouring cell salvage is suggested (RR 0.74; 95% CI 0.55, 1.01; $p = 0.05$; $I^2 = 0\%$) *(GRADE: very low)*. There were concerns of nonreporting bias for this outcome with some studies excluding patients who died in the theatre and other reporting combined mortality data (across treatment groups).

Figure 4.62 Forest plot of comparison: cell salvage vs no cell salvage, outcome: Mortality, any timepoint up to 30 days



Footnotes

(1) One patient in the intervention group died before cell salvage could occur.

(2) Cause of death: I = exsanguination (8/14) or MOF related to sepsis (6/14). C = exsanguination (10/15) and MOF related to sepsis (5/15).

(3) Ten out of 25 (40%) patients in the total study cohort died (intra- and post-operative). A further 5 patients in the control group died up to 30-days.

(4) Data retrieved from primary study. 30-day mortality

(5) Date retrieved from primary study. Includes post-opererative deaths only.

(6) Data retrieved from primary study. Includes intro-operative and post-operative deaths among patients with ruptured AAA.

(7) Data retrieved from primary study. Includes intro-operative and post-operative deaths.

Table 4.89 Results for cell salvage versus no cell salvage: Patients with critical bleeding – Mortality

Study ID Study design [a]	Sample size (no. of trials) included in analysis	Patient population	Setting (Location)	Comparison	Outcome	Results			
						Cell salvage n/N (%)	No cell salvage n/N (%)	Risk estimate (95% CI)	*Statistical significance* *p*-value Heterogeneity [b]
Trauma setting									
Meybohm 2016 RCT *High risk of bias*	N = 44 (1 RCT) Bowley 2006	Patients *with* penetrating torso injury requiring laparotomy and hypotension < 90 mm Hg	SC, trauma (South Africa)	Cell salvage vs no cell salvage	Mortality, timing not specified [c]	14/21 (66.7)	15/23 (65.2)	RR 1.02 (0.67, 1.56)	*No significant difference* *p* = 0.92 Heterogeneity NA
Bhangu 2012 Coh *High risk of bias*	N= 130 (1 Coh) Banghu 2012	Patients with sustained combat-related injury requiring massive transfusion [d]	SC, combat (Afghanistan)	Cell salvage vs no cell salvage	Mortality, timing not specified [e]	1/18	0/11	Not estimable	Not estimable
Surgical setting									
Shantikumar 2011 Coh *Serious risk of bias*	N= 360 (5 Coh) Markovic 2009 Posacioglu 2002 Tawfick 2008 Serrancino-Inglott 2005[f] Shuhaiber 2003[g]	Patients undergoing emergency AAA repair	SC, vascular surgery (Ireland, Serbia, Turkey, UK)	Cell salvage vs no cell salvage	Mortality, any timepoint up to 30 days	47/137 (34.3) 12/30 (40) 16/40 (40) 6/27 (22) NR/40 (32) NR/4	87/188 (46.28) 14/30 (46.6) 8/16 (50) 9/28 (32) NR/114 (49) NR/21	RR 0.74 (0.55, 1.01) [h]	*No significant difference* *p* = 0.05 Moderate heterogeneity I^2 = 0% (*p* = 0.91)

Abbreviations: AAA, abdominal aortic aneurysm; Coh, cohort study; CI, confidence interval; NR, not reported; RCT, randomised controlled trial; RR, relative risk; UK, United Kingdom

a. Where only one RCT is identified in a systematic review, the evidence has been considered as RCT evidence. Where the systematic review assesses observational and cohort studies, the evidence has been considered as according to the study design features. The risk of bias of the included primary studies is based on the quality assessment reported by the systematic review authors.

b. Only applicable to Systematic reviews with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if P_{het} >0.1 and I^2 <25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25–50%; substantial heterogeneity I^2 >50%.

c. Cause of death was exsanguination (10/15) and MOF related to sepsis (5/15) in the control group and exsanguination (8/14) and MOF related to sepsis (6/14) in the intervention group.

d. Requiring at least 10 units of RBCs in the first 12 hours after injury.

e. One patient in the intervention group died on operating table before cell salvage could occur.

f. Serracino-Inglott 2005 excluded patients who died in the theatre from the analysis and reported an effect favouring cell salvage (21% vs 44%; *p* = 0.01).

g. There were only four patients in the intervention group, therefore no meaningful difference in mortality between groups could be observed. Overall, 10/25 (40%) patients in the study cohort died (intraoperative and post-operative. A further five patients in the control group died within 30-days.

h. Calculated post-hoc using RevMan 5.4. M-H Random effects.

4.10.3.2 Morbidity

A summary of the evidence relating to morbidity in patients with critical bleeding receiving intraoperative autologous transfusions (obtained by cell salvage) is presented in Table 4.90.

Post-operative complications

The identified systematic reviews reported no significant difference in any post-operative complications between patients who received cell salvage compared with those who did not, regardless of clinical setting. For most bleeding patients there are no clear substantial harms associated with cell salvage, but the evidence is very uncertain (GRADE: very low).

Data from the identified RCT (see Figure 4.63), suggested that in patients with penetrating trauma, the risk of sepsis was comparable between those who received cell salvage and those who did not (RR 0.78; 95% CI 0.29, 2.09; $p = 0.62$).

In the surgical setting, patients requiring elective and urgent abdominal aortic aneurysm repair who had cell salvage were also no more likely to have respiratory complications, renal or gastrointestinal complications, than those who received standard care.

Not including the studies that reporting combined data for elective and urgent abdominal aortic aneurysm repair (see Figure 4.64), the risk of post-operative respiratory complications was higher among patients who received cell salvage (16/84, 19%) compared with those who did not (2/151, 1.3%); but the difference did not reach statistical significance (RR 3.20, 95% CI 0.83, 12.35; $p = 0.09$) *(GRADE: very low)*.

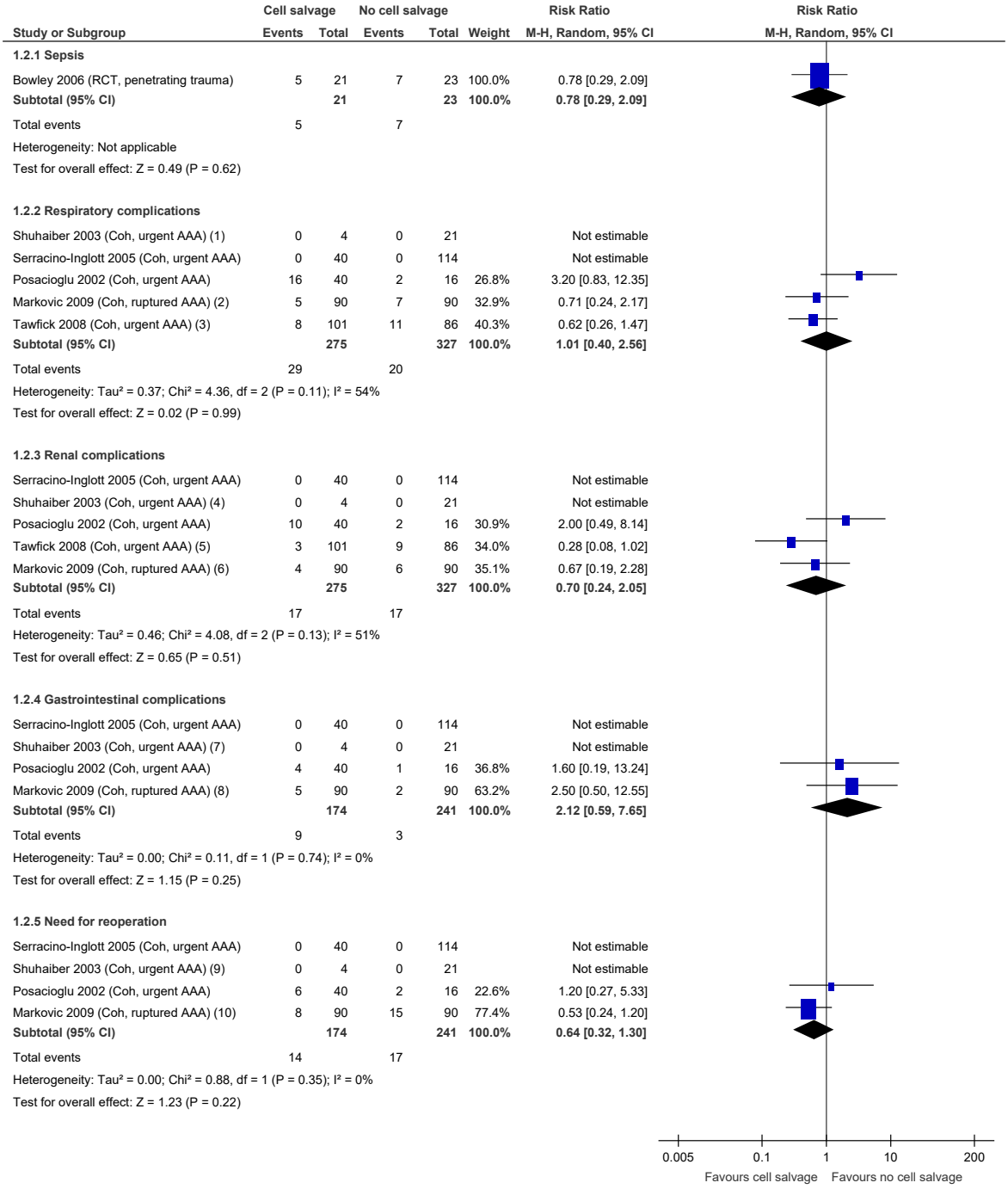
Similar data were observed for post-operative renal complications (12% vs 1.3%; RR 2.00, 95% CI 00.49, 8.14; $p = 0.33$) *(GRADE: very low)* and post-operative gastrointestinal complications (4.8% vs 0.7%; RR 1.60, 95% CI 0.19, 13.24; $p = 0.66$) *(GRADE: very low)*.

Need for re-operation

Among patients requiring elective and urgent abdominal aortic aneurysm repair, re-operation was needed in 8% (14/174) of patients who received cell salvage compared with 7% (17/241) in those who did not (RR 0.64, 95% CI 0.32, 1.30; $p = 0.35$; $I^2=0\%$).

Not including the studies that reporting combined data for elective and urgent abdominal aortic aneurysm repair (see Figure 4.64), the risk for re-operation was higher among patients who received cell salvage (6/84, 7%) compared with those who did not (2/151, 1.3%), but the difference was not significant (RR 1.20, 95% CI 0.27, 5.33; $p = 0.81$) *(GRADE: very low)*.

Figure 4.63 Forest plot of comparison: cell salvage vs no cell salvage, outcome: Morbidity - post-operative complications



Footnotes

(1) Small intervention group prevents meaningful comparison between groups. Overall, 14/25 (56%) patients had major complications.

(2) Data includes urgent and elective AAA and AOD. Separate data for ruptured AAA not available.

(3) Data includes elective and emergent AAA repair. Seperate data for emergency AAA not available.

(4) Small intervention group prevents meaningful comparison between groups. Overall, 14/25 (56%) patients had major complications.

(5) Need for dialysis. Data includes elective and emergent AAA repair. Seperate data for emergency AAA not available.

(6) Data includes urgent and elective AAA and AOD. Separate data for ruptured AAA not available.

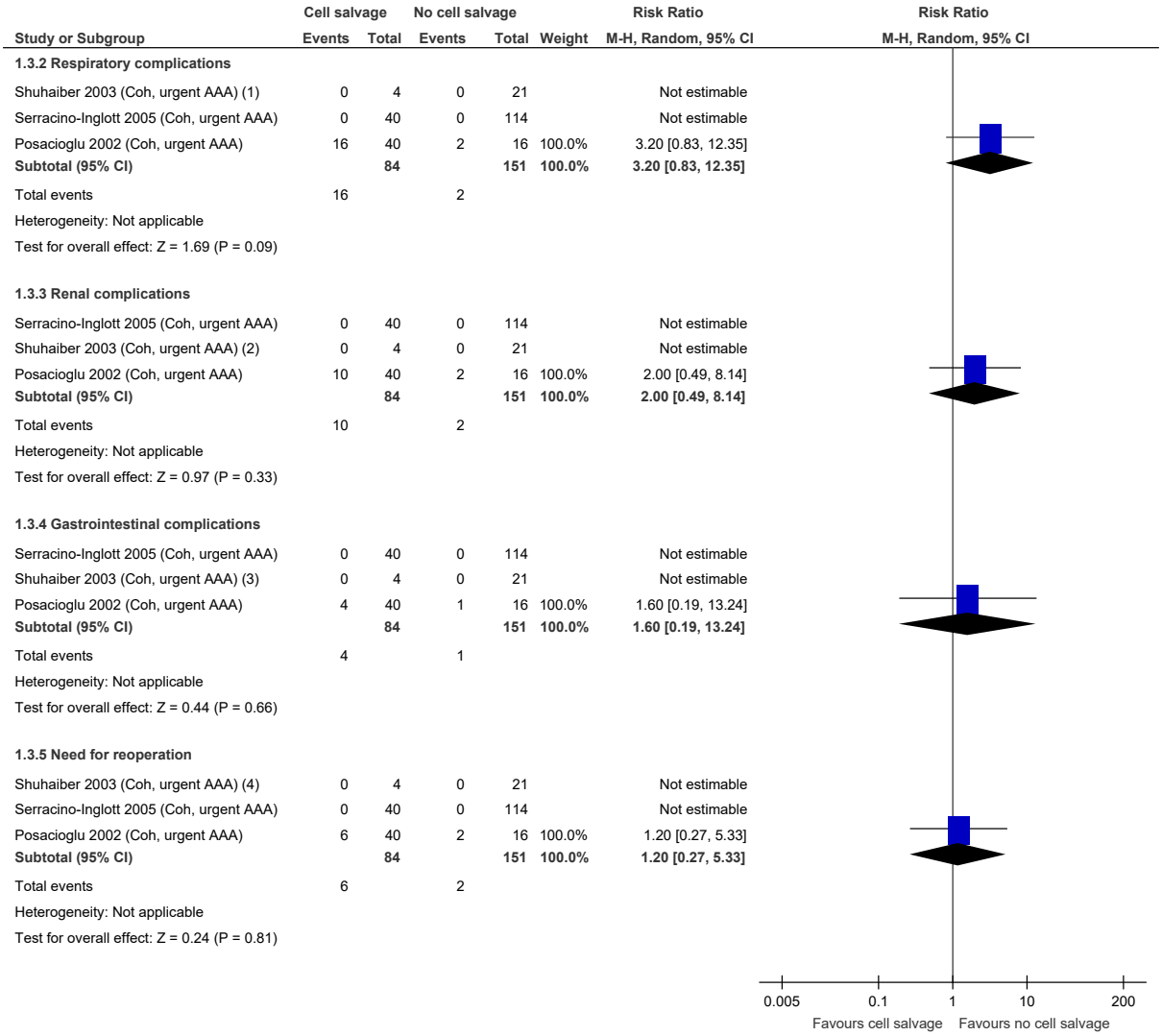
(7) Small intervention group prevents meaningful comparison between groups. Overall, 14/25 (56%) patients had major complications.

(8) Data includes urgent and elective AAA and AOD. Separate data for ruptured AAA not available.

(9) Small intervention group prevents meaningful comparison between groups. Overall, 14/25 (56%) patients had major complications.

(10) Data includes urgent and elective AAA and AOD. Separate data for ruptured AAA not available.

Figure 4.64 Forest plot of comparison: cell salvage vs no cell salvage, outcome: Morbidity - post-operative complications (urgent AAA repair)



Footnotes

(1) Small intervention group prevents meaningful comparison between groups. Overall, 14/25 (56%) patients had major complications.

(2) Small intervention group prevents meaningful comparison between groups. Overall, 14/25 (56%) patients had major complications.

(3) Small intervention group prevents meaningful comparison between groups. Overall, 14/25 (56%) patients had major complications.

(4) Small intervention group prevents meaningful comparison between groups. Overall, 14/25 (56%) patients had major complications.

Table 4.90 Results for cell salvage versus no cell salvage: Patients with critical bleeding – Morbidity: post-operative complications

Study ID Study design [a]	Sample size (no. of trials) included in analysis	Patient population	Setting (Location)	Comparison	Outcome	Results			
						Cell salvage n/N (%)	No cell salvage n/N (%)	Risk estimate (95% CI)	*Statistical significance* *p*-value Heterogeneity [b]
Trauma setting									
Meybohm 2016 RCT *High risk of bias*	N = 44 (1 trial) Bowley 2006	Patients with penetrating torso injury requiring laparotomy and hypotension < 90 mm Hg	SC, emergency (South Africa)	Cell salvage vs no cell salvage	Infection (sepsis)	5/21 (23.8)	7/23 (30.4)	RR 0.78 (0.29, 2.09)	No significant difference *p* = 0.62
Surgical setting									
Shantikumar 2011 Coh *Serious risk of bias*	N = 360 (5 Coh) Markovic 2009 Posacioglu 2002 Tawfick 2008 Serrancino-Inglott 2005 Shuhaiber 2003		SC, vascular surgery (Ireland, Serbia, Turkey, UK)	Cell salvage vs no cell salvage	Respiratory Posacioglu 2002	16/40 (40)	2/16 (12.5)	RR 3.20 (0.83, 12.35) [c]	No significant difference *p* = 0.09 [d]
					Renal Posacioglu 2002	10/40 (25)	2/16 (12.5)	RR 2.00 (0.49, 8.14) [c]	*No significant difference* *p* = 0.475
					Gastrointestinal Posacioglu 2002	4/40 (10)	1/16 (6.25)	RR 1.60 (0.19, 13.24) [c]	No significant difference *p* = 1.00
					Need for re-operation Posacioglu 2002	6/40 (15)	2/16 (12.5)	RR 1.20 (0.27, 5.33) [c]	No significant difference *p* = 0.588
					Any post-operative complication Serracino-Inglott 2005	The authors noted no significant difference between study groups for post-operative complications, but no further data provided.			No significant difference
					Shuhaiber 2003	No meaningful difference in complications could be observed (only four patients in the intervention group). Overall, 14/25 (56%) patients had major complications including: - haemorrhage and anastomotic leak, - infection, - non-graft thrombosis, embolism, myocardial infarction, - arrythmia, cardiac failure, impaired renal function and respiratory failure.			No significant difference
					Marcovic 2009	Data were presented for entire cohort that includes elective AAA and AOD and are therefore not presented here. The authors noted no significant difference between study groups for: - Transfusion-related complications - Multiorgan failure, Colon ischaemia, Respiratory failure, Renal failure - Stroke, Myocardial infarction - Wound infection, Bleeding or Re-operation			No significant difference

Study ID Study design [a]	Sample size (no. of trials) included in analysis	Patient population	Setting (Location)	Comparison	Outcome	Results			
						Cell salvage n/N (%)	No cell salvage n/N (%)	Risk estimate (95% CI)	*Statistical significance* *p*-value Heterogeneity [b]
					Tawfick 2008	Data were presented for entire study cohort that includes elective and emergency AAA and are therefore not presented here. The authors noted no significant difference between study groups for: - Respiratory complications (ARDS, pneumonia, atelectasis) - Cardiac complications (arrythmias, ischaemic cardiac event) A significant effect favouring no cell salvage observed for: - Need for renal dialysis ($p = 0.037$).			
Obstetrics and maternity setting – no comparative evidence found									
Paediatric setting – no comparative evidence found									

Abbreviations: AAA, abdominal aortic aneurysm; CI, confidence interval; M-H, Mantzel-Hentzel; NR, not reported; RR, relative risk; UK, United Kingdom

a. Where only one RCT is identified in a systematic review, the evidence has been considered as RCT evidence. Where the systematic review assesses Observational and cohort studies, the evidence has been considered as according to the study design features. The risk of bias of the included primary studies is based on the quality assessment reported by the systematic review authors.

b. Only applicable to Systematic reviews with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if P_{het} >0.1 and I^2 <25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25–50%; substantial heterogeneity I^2 >50%.

c. Calculated post-hoc using RevMan 5.4. M-H. Random effects.

d. Posacioglu 2002 reported a statistically significant effect favouring no cell salvage $p = 0.047$

4.10.3.3 Transfusion volume

A summary of the evidence relating to transfusion volumes in patients with critical bleeding receiving intraoperative autologous transfusions (obtained by cell salvage) is presented in Table 4.91 .

Overall, only limited conclusions can be drawn from the available evidence. For most bleeding patients there is a modest reduction in the volume of RBCs transfused (between two and five red cell units saved), but the evidence is very uncertain *(GRADE: very low)*.

Red blood cells

A meta-analysis of data from RCTs and cohort studies included in this review revealed a significant reduction in the volume of RBC transfused in patients with critical bleeding who received cell salvage (n=162) compared with those who did not (n=232), with an overall standardised mean difference (SMD) of –0.45 units (95% CI –0.87, –0.01; $p = 0.05$; random effects, $I^2 = 71\%$).

In patients with penetrating trauma, evidence from the small RCT suggests a significant reduction in the volume of RBC transfused (around 4.7 red cell units saved) favouring cell salvage (SMD –0.82; 95% CI –1.44, –0.20; $p = 0.009$) *(GRADE: very low)*.

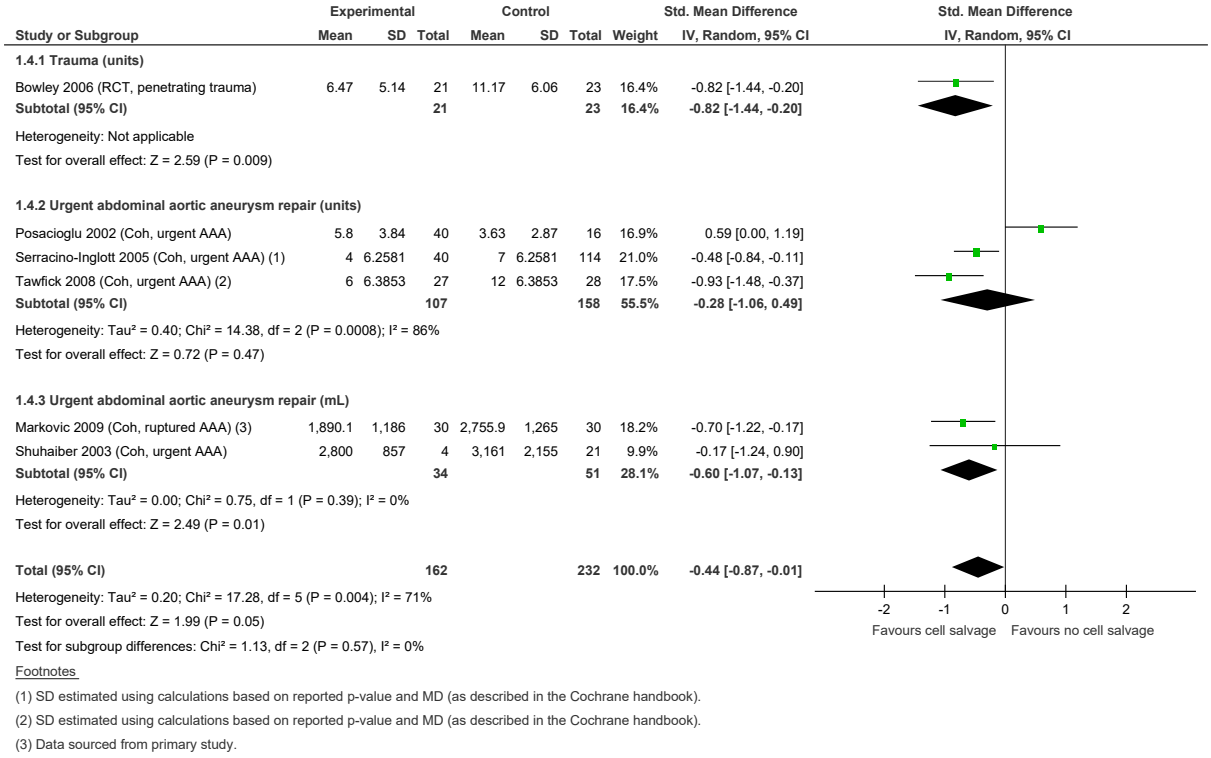
Among patients requiring urgent AAA repair, the volume of RBCs transfused was not significantly different between groups (SMD –0.36; 95% CI –0.87, –0.14; $p = 0.16$) *(GRADE: very low)*.

Other blood components

In patients with penetrating trauma, evidence from the small RCT comparing cell salvage with standard care suggests no difference in the the volume of FFP (SMD 0.16; 95% CI –0.44, 0.75; $p = 0.61$) or PLTs transfused (SMD 0.26; 95% CI –0.33, 0.85; $p = 0.39$) *(GRADE: very low)*.

Among patients requiring urgent AAA repair, there was no difference between groups in the the volume of FFP transfused (SMD 0.21; 95% CI –0.97, 1.40; $p = 0.72$) *(GRADE: very low)*. There was no data relating to the volume of PLTs transfused (if any).

Figure 4.65 Forest plot of comparison: cell salvage vs no cell salvage, outcome: Transfusion volume (RBCs)



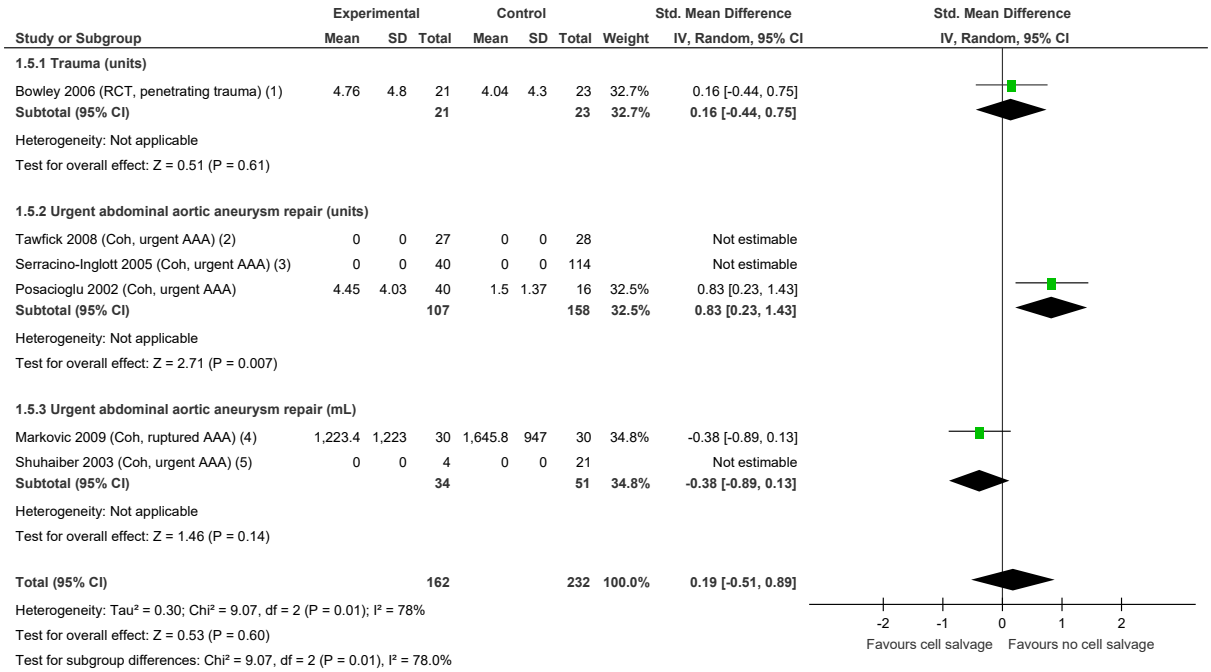
Footnotes

(1) SD estimated using calculations based on reported p-value and MD (as described in the Cochrane handbook).

(2) SD estimated using calculations based on reported p-value and MD (as described in the Cochrane handbook).

(3) Data sourced from primary study.

Figure 4.66 Forest plot of comparison: cell salvage vs no cell salvage, outcome: Transfusion volume (FFP)



Footnotes

(1) Data sourced from primary study.

(2) Authors do not report separate data for emergency AAA repair.

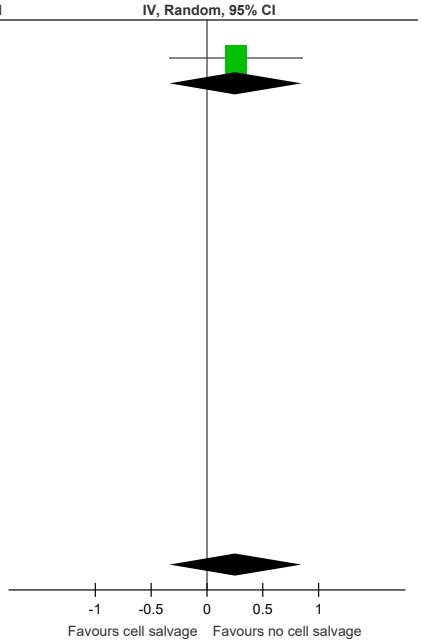
(3) not reported.

(4) Data retrieved from primary study.

(5) not reported.

Figure 4.67 Forest plot of comparison: cell salvage vs no cell salvage, outcome: Transfusion volume (PLTs)

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.6.1 Trauma (units)								
Bowley 2006 (RCT, penetrating trauma) (1)	1	2.2	21	0.56	0.94	23	100.0%	0.26 [-0.33, 0.85]
Subtotal (95% CI)			**21**			**23**	**100.0%**	**0.26 [-0.33, 0.85]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.86 (P = 0.39)								
1.6.2 Urgent abdominal aortic aneurysm repair (units)								
Tawfick 2008 (Coh, urgent AAA) (2)	0	0	27	0	0	28		Not estimable
Serracino-Inglott 2005 (Coh, urgent AAA) (3)	0	0	40	0	0	114		Not estimable
Posacioglu 2002 (Coh, urgent AAA) (4)	0	0	40	0	0	16		Not estimable
Subtotal (95% CI)			**0**			**0**		**Not estimable**
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								
1.6.3 Urgent abdominal aortic aneurysm repair (mL)								
Shuhaiber 2003 (Coh, urgent AAA) (5)	0	0	4	0	0	21		Not estimable
Markovic 2009 (Coh, ruptured AAA) (6)	0	0	30	0	0	30		Not estimable
Subtotal (95% CI)			**34**			**51**		**Not estimable**
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								
Total (95% CI)			**55**			**74**	**100.0%**	**0.26 [-0.33, 0.85]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.86 (P = 0.39)								
Test for subgroup differences: Not applicable								



Footnotes

(1) Data sourced from primary study.

(2) Authors do not report separate data for emergency AAA repair.

(3) not reported.

(4) not reported.

(5) not reported.

(6) not reported.

Table 4.91 Results for cell salvage versus no cell salvage: Patients with critical bleeding – Transfusion volume

Study ID Study design [a]	Sample size (no. of trials) included in analysis	Patient population	Setting (Location)	Comparison	Outcome	Results			
						Cell salvage Mean ± SD (n)	No cell salvage Mean ± SD (n)	Risk estimate (95% CI)	*Statistical significance* *p*-value Heterogeneity [b]
Trauma setting									
Meybohm 2016 RCT *High risk of bias*	N = 44 (1 RCT) Bowley 2006	Patients with penetrating torso injury requiring laparotomy and hypotension < 90 mm Hg	SC, emergency (South Africa)	Cell salvage vs no cell salvage	RBC transfusion volume, units (allogenic, first 24 hours)	6.47 ± 5.14 (21)	11.17 ± 6.06 (23)	MD –4.70 (–8.01, –1.39)	*Favours cell salvage* *p* = 0.005 Heterogeneity NA
					FFP transfusion volume, units (allogenic, first 24 hours)	4.76 ± 4.8 (21)	4.04 ± 4.3 (23)	MD 0.72 (–1.98, 3.42) [c]	No significant difference *p* = 0.6 Heterogeneity NA
					PLT transfusion volume, units	1.0 ± 2.2 (21)	0.56 ± 0.94 (23)	MD 0.44 (–0.58, 1.46) [c]	No significant difference *p* = 0.40 Heterogeneity NA
Bhangu 2012 Coh *Serious risk of bias*	N = 130	Patients with combat-related injury (blast-injury, gunshot, road)	SC, combat support (Afghanistan)	Cell salvage vs no cell salvage	RBC transfusion volume, units	Total Units (n) 463 (130) Median (IQR) 14 (9.5–18.5) range 2–27	The authors estimated approximate 7.6% total reduction when compared to allogeneic transfusions in the overall 130 patient cohort; and a potential median reduction per patient of 9.8%.		NR
					FFP transfusion volume, units Mechanism of injury (n) GSW (n=4) Blast (n=13) Body area (n) Cavity (n=8) Extremity (n=9)	Median (IQR) 11.5 (4.25–16.5) 17 (10–22) 10 (4–13.5) 21 (15.5–24)	NR		Test for subgroup difference *p* = 0.192 *p* = 0.004
					PLT transfusion volume, units Mechanism of injury (n) GSW (4) Blast (13) Body area (n) Cavity (8) Extremity (9)	Median (IQR) 2 (0.5–4.25) 3 (2–5) 2 (0.25–4.25) 3 (2.5–5.5)	NR	NR	Test for subgroup difference *p* = 0.327 *p* = 0.050

Study ID Study design [a]	Sample size (no. of trials) included in analysis	Patient population	Setting (Location)	Comparison	Outcome	Results			
						Cell salvage Mean ± SD (n)	**No cell salvage Mean ± SD (n)**	**Risk estimate (95% CI)**	***Statistical significance p*-value Heterogeneity [b]**
					CRYO transfusion volume, units Mechanism of injury (n) GSW (4) Blast (13) Body area (n) Cavity (8) Extremity (9)	Median (IQR) 1 (0.25–1.75) 2 (1–2) 1 (0–1.75) 2 (1–2)	NR	NR	Test for subgroup difference $p = 0.335$ $p = 0.046$
Surgical setting									
Shantikumar 2011 Coh *Serious risk of bias*	N= 265 (3 Coh) Posacioglu 2002 Tawfick 2008 Serrancino-Inglott 2005	Patients undergoing emergency AAA repair	SC, vascular surgery (Ireland, Serbia, Turkey, UK)	Cell salvage vs no cell salvage	RBC transfusion volume, units (allogenic)	5.8 ± 3.84 (40) 6 (range 0–34) (27) 4 (range 0–24) (40)	3.63 ± 2.87 (16) 12 (range 3–38) (28) 7 (range 0–29) (114)	NR $p = 0.026$ NR NR $p < 0.01$	*Favours no cell salvage* p = NR *Favours cell salvage*
	N= 85 (2 Coh) Markovic 2009 Shuhaiber 2003				RBC transfusion volume, mL (allogenic)	1890.1 ± 1186 (30) 2800 ± 857 (4)	2755.9 ± 1265 (30) 3161 ± 2155 (21)	NR $p = 0.0089$ NR p = NR	*Favours cell salvage* No significant difference
	N = 56 (1 Coh) Posacioglu 2002				FFP transfusion volume, units (allogenic)	4.45 ± 4.03 (40)	1.5 ± 1.37 (16)	MD 2.95 (1.53, 4.37)	*Favours no cell salvage* $p < 0.0001$ Heterogeneity NA
	N= 60 (1 Coh) Markovic 2009				FFP transfusion volume, mL (allogenic)	1223.4 ± 1223 (30)	1645.8 ± 947 (30)	MD –422.40 [c] (–975.90, 131.10)	*No significant difference* $p = 0.13$ Heterogeneity NA
	N = 56 (1 Coh) Tawfick 2008				PLT transfusion volume, units	NR (27)	NR (28)	NR	*No significant difference* p = NR Heterogeneity NA

Abbreviations: AAA, abdominal aortic aneurysm; CI, confidence interval; MD; mean difference; NR, not reported; UK, United Kingdom

a. Where only one RCT is identified in a systematic review, the evidence has been considered as RCT evidence. Where the systematic review assesses observational and cohort studies, the evidence has been considered as according to the study design features. The risk of bias of the included primary studies is based on the quality assessment reported by the systematic review authors.

b. Only applicable to Systematic reviews with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if $P_{het} > 0.1$ and $I^2 < 25\%$; (ii) mild heterogeneity if $I^2 < 25\%$; moderate heterogeneity if I^2 between 25–50%; substantial heterogeneity $I^2 > 50\%$.

c. Calculated post-hoc using RevMan 5.4. M-H. Random effects.

4.10.3.4 Financial cost

A summary of the evidence relating to transfusion volumes in patients with critical bleeding receiving intraoperative autologous transfusions (obtained by cell salvage) is presented in Table 4.92.

Overall, only limited conclusions can be drawn from the available evidence. Data appropriate to the Australian population and health care setting is needed.

In patients with penetrating trauma, there were no difference between study groups with regards to overall costs (MD –178.17, 95% CI –453.20 to 96.86) (2002 British Pound Sterling).

None of the included studies reported costs associated with cell salvage or allogenic transfusions specific to the emergency AAA patient population.

Table 4.92 Results for cell salvage versus no cell salvage: Patients with critical bleeding – Cost

Study ID Study design [a] *Risk of bias*	Sample size (no. of trials) included in analysis	Patient population	Setting (Location)	Comparison	Outcome	Results			
						Cell salvage Mean ± SD (n)	No cell salvage Mean ± SD (n)	Risk estimate (95% CI)	*Statistical significance* *p*-value Heterogeneity [b]
Trauma setting									
Meybohm 2016 RCT *High risk of bias*	N = 44 (1 RCT) Bowley 2006	Patients with penetrating torso injury requiring laparotomy and hypotension < 90 mm Hg	SC, emergency (South Africa)	Cell salvage vs no cell salvage	Financial cost, £ [c]	812.23 ± 451.23 (range 169.92, 1747.5)	990.4 ± 479.48 (range 19.9, 1753.3)	MD –178.17 (–453.20, 96.86) [d]	*No significant difference* *p* = 0.2
Surgical setting									
Shantikumar 2011 Coh *Serious risk of bias*	N= 350 (5 Coh) Markovic 2009 Posacioglu 2002 Tawfick 2008 Shuhaiber 2003 Serrancino-Inglott 2005	Patients undergoing emergency AAA repair	SC, vascular surgery (Germany, Serbia, Turkey, UK)	Cell salvage vs no cell salvage	Financial cost	None of the included studies reported costs associated with cell salvage or allogenic transfusions specific to the emergency AAA patient population.			

Abbreviations: AAA, abdominal aortic aneurysm; CI, confidence interval; MD; mean difference; NR, not reported; UK, United Kingdom

a. Where only one RCT is identified in a systematic review, the evidence has been considered as RCT evidence. Where the systematic review assesses observational and cohort studies, the evidence has been considered as according to the study design features. The risk of bias of the included primary studies is based on the quality assessment reported by the systematic review authors.

b. Only applicable to systematic reviews with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if P_{het} >0.1 and I^2 <25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25–50%; substantial heterogeneity I^2 >50%.

c. Data were in 2002 British Pound Sterling.

d. Calculated post-hoc using RevMan 5.4. M-H. Random effects.

5 References

1. NBA. Patient Blood Management Guidelines: Module 1 - Critical Bleeding/Massive Transfusion. https://www.blood.gov.au/pbm-module-1: National Blood Authority, Canberra; 2011. Available from: https://www.blood.gov.au/pbm-module-1.
2. Higgins JPT, Lasserson T, Chandler J, Tovey D, Thomas J, Flemyng E, et al. Methodological Expectations of Cochrane Intervention Reviews. London: Cochrane; 2019. Available from: https://community.cochrane.org/mecir-manual.
3. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 2009;6(7):e1000097.
4. Churchill R, Lasserson T, Chandler J, Tovey D, Thomas J, Flemyng E, et al. Standards for the reporting of new Cochrane Intervention Reviews. 2019 [cited 4 June 2020]. In: Methodological Expectations of Cochrane Intervention Reviews [Internet]. London: Cochrane, [cited 4 June 2020]. Available from: https://community.cochrane.org/mecir-manual/standards-reporting-new-cochrane-intervention-reviews-r1-r109.
5. Schünemann H, Brożek J, Guyatt G, Oxman A. GRADE Handbook. Handbook for grading the quality of evidence and the strength of recommendations using the GRADE approach [Internet]. 2013; (Updated October 2013). Available from: https://gdt.gradepro.org/app/handbook/handbook.html.
6. GBD 2013 Mortality and Causes of Death Collaborators. Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet (London, England). 2015;385(9963):117-71.
7. AIHW. Australian Instititute of Health and Welfare.; 2018 [Available from: https://www.aihw.gov.au/reports-statistics/health-conditions-disability-deaths/injury/overview.
8. Kauvar DS, Lefering R, Wade CE. Impact of hemorrhage on trauma outcome: an overview of epidemiology, clinical presentations, and therapeutic considerations. The Journal of trauma. 2006;60(6 Suppl):S3-11.
9. Allard S, Green L, Hunt BJ. How we manage the haematological aspects of major obstetric haemorrhage. British journal of haematology. 2014;164(2):177-88.
10. Sihler KC, Napolitano LM. Complications of massive transfusion. Chest. 2010;137(1):209-20.
11. Cochrane Handbook for Systematic Reviews of Interventions version 6.0 (updated July 2019): Cochrane; 2019. Available from: www.training.cochrane.org/handbook.
12. Higgins J, Lasserson T, Chandler J, Tovey D, Thomas J, Flemyng E, et al. Methodological Expectations of Cochrane Intervention Reviews. London: Cochrane; 2019. Available from: https://community.cochrane.org/mecir-manual.
13. Aromataris E, Munn Z, editors. JBI Manual for Evidence Synthesis. https://jbi-global-wiki.refined.site/space/MANUAL/4687404/About+this+Manual: Joanna Briggs Institute; 2020.
14. Tufanaru C, Munn Z, Aromataris E, Campbell J, Hopp L. Chapter 3: Systematic reviews of effectiveness. In: Aromataris E, Munn Z, editors. Joanna Briggs Institute Reviewer's Manual: The Joanna Briggs Institute; 2017.
15. Gale AJ. Continuing education course #2: current understanding of hemostasis. Toxicol Pathol. 2011;39(1):273-80.
16. Merlin T, Weston A, Tooher R. Extending an evidence hierarchy to include topics other than treatment: revising the Australian 'levels of evidence'. BMC medical research methodology. 2009;9:34.

17. NBA. Patient Blood Management Guidelines: Module 1 - Critical Bleeding/Massive Transfusion: Technical report volume 1 and volume 2 https://www.blood.gov.au/system/files/documents/pbm-module1-tech-vol1_0.pdf and https://www.blood.gov.au/system/files/documents/pbm-module1-tech-vol2.pdf: National Blood Authority, Canberra; 2011. Available from: https://www.blood.gov.au/system/files/documents/pbm-module1-tech-vol1_0.pdf https://www.blood.gov.au/system/files/documents/pbm-module1-tech-vol2.pdf.
18. Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ. 2017;358:j4008.
19. Shea BJ, Grimshaw JM, Wells GA, Boers M, Andersson N, Hamel C, et al. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. BMC medical research methodology. 2007;7:10.
20. Higgins JP, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ. 2011;343:d5928.
21. Higgins JPT, Li T, Deeks JJ. Chapter 6: Choosing effect measures and computing estimates of effect. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al., editors. Cochrane Handbook for Systematic Reviews of Interventions version 6,0 (updated July 2019).
22. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med. 2002;21(11):1539-58.
23. Schünemann Holger BJ, Guyatt Gordon, and Oxman Andrew Handbook for grading the quality of evidence and the strength of recommendations using the GRADE approach. Updated October 2013. Available at http://gdtguidelinedevelopmentorg/app/handbook/handbookhtml#hhnedbo8gqjqk. 2013.
24. Guyatt GH, Oxman AD, Vist G, Kunz R, Brozek J, Alonso-Coello P, et al. GRADE guidelines: 4. Rating the quality of evidence--study limitations (risk of bias). J Clin Epidemiol. 2011;64(4):407-15.
25. Guyatt GH, Oxman AD, Kunz R, Woodcock J, Brozek J, Helfand M, et al. GRADE guidelines: 7. Rating the quality of evidence--inconsistency. J Clin Epidemiol. 2011;64(12):1294-302.
26. Guyatt GH, Oxman AD, Kunz R, Brozek J, Alonso-Coello P, Rind D, et al. GRADE guidelines 6. Rating the quality of evidence--imprecision. J Clin Epidemiol. 2011;64(12):1283-93.
27. Guyatt GH, Oxman AD, Kunz R, Woodcock J, Brozek J, Helfand M, et al. GRADE guidelines: 8. Rating the quality of evidence--indirectness. J Clin Epidemiol. 2011;64(12):1303-10.
28. Guyatt GH, Oxman AD, Montori V, Vist G, Kunz R, Brozek J, et al. GRADE guidelines: 5. Rating the quality of evidence--publication bias. J Clin Epidemiol. 2011;64(12):1277-82.
29. Faraone SV. Interpreting estimates of treatment effects: implications for managed care. P T. 2008;33(12):700-11.
30. Santesso N, Glenton C, Dahm P, Garner P, Akl EA, Alper B, et al. GRADE guidelines 26: informative statements to communicate the findings of systematic reviews of interventions. J Clin Epidemiol. 2020;119:126-35.
31. Hultcrantz M, Rind D, Akl EA, Treweek S, Mustafa RA, Iorio A, et al. The GRADE Working Group clarifies the construct of certainty of evidence. J Clin Epidemiol. 2017;87:4-13.

32. Moberg J, Oxman AD, Rosenbaum S, Schunemann HJ, Guyatt G, Flottorp S, et al. The GRADE Evidence to Decision (EtD) framework for health system and public health decisions. Health Res Policy Syst. 2018;16(1):45.
33. Moberg J A-CP, Oxman AD. . GRADE Evidence to Decision (EtD) Frameworks Guidance. Version 1.1 2015. Available from: https://ietd.epistemonikos.org/#/help/guidance.
34. Vasudeva M, Mathew JK, Groombridge C, Tee JW, Johnny CS, Maini A, et al. Hypocalcemia in trauma patients: A systematic review. The Journal of Trauma and Acute Care Surgery. 2021;90(2):396-402.
35. Moore HB, Tessmer MT, Moore EE, Sperry JL, Cohen MJ, Chapman MP, et al. Forgot calcium? Admission ionized-calcium in two civilian randomized controlled trials of prehospital plasma for traumatic hemorrhagic shock. The journal of trauma and acute care surgery. 2020;88(5):588-96.
36. Kamyszek RW, Leraas HJ, Reed C, Ray CM, Nag UP, Poisson JL, et al. Massive transfusion in the pediatric population: A systematic review and summary of best-evidence practice strategies. Journal of Trauma and Acute Care Surgery. 2019;86(4):744-54.
37. Shih AW, Al Khan S, Wang AYH, Dawe P, Young PY, Greene A, et al. Systematic reviews of scores and predictors to trigger activation of massive transfusion protocols. Journal of Trauma and Acute Care Surgery. 2019;87(3):717-29.
38. Lilitsis E, Xenaki S, Athanasakis E, Papadakis E, Syrogianni P, Chalkiadakis G, et al. Guiding Management in Severe Trauma: Reviewing Factors Predicting Outcome in Vastly Injured Patients. J Emerg Trauma Shock. 2018;11(2):80-7.
39. Tran A, Matar M, Lampron J, Steyerberg E, Taljaard M, Vaillancourt C. Early identification of patients requiring massive transfusion, embolization or hemostatic surgery for traumatic hemorrhage: A systematic review and meta-analysis. J Trauma Acute Care Surg. 2018;84(3):505-16.
40. Levy JH, Rossaint R, Zacharowski K, Spahn DR. What is the evidence for platelet transfusion in perioperative settings? Vox Sang. 2017;112(8):704-12.
41. Poole D, Cortegiani A, Chieregato A, Russo E, Pellegrini C, De Blasio E, et al. Blood Component Therapy and Coagulopathy in Trauma: A Systematic Review of the Literature from the Trauma Update Group. PLoS One. 2016;11(10):e0164090.
42. Baxter J, Cranfield KR, Clark G, Harris T, Bloom B, Gray AJ. Do lactate levels in the emergency department predict outcome in adult trauma patients? A systematic review. J Trauma Acute Care Surg. 2016;81(3):555-66.
43. Haas T, Fries D, Tanaka KA, Asmis L, Curry NS, Schöchl H. Usefulness of standard plasma coagulation tests in the management of perioperative coagulopathic bleeding: is there any evidence? Br J Anaesth. 2015;114(2):217-24.
44. Abdul-Kadir R, McLintock C, Ducloy AS, El-Refaey H, England A, Federici AB, et al. Evaluation and management of postpartum hemorrhage: consensus from an international expert panel. Transfusion. 2014;54(7):1756-68.
45. Pacagnella RC, Souza JP, Durocher J, Perel P, Blum J, Winikoff B, et al. A systematic review of the relationship between blood loss and clinical signs. PloS one. 2013;8(3):e57594-e.
46. Razzaghi A, Barkun AN. Platelet transfusion threshold in patients with upper gastrointestinal bleeding: a systematic review. J Clin Gastroenterol. 2012;46(6):482-6.
47. Gaessler H, Helm M, Kulla M, Hossfeld B, Schmid U, Kerschowski J, et al. Prehospital evaluation and detection of induced coagulopathy in trauma: The PREDICT study. The Journal of Trauma and Acute Care Surgery. 2021;91(2):344-51.

48. Javali RH, Ravindra P, Patil A, Srinivasarangan M, Mundada H, Adarsh SB, et al. A Clinical Study on the Initial Assessment of Arterial Lactate and Base Deficit as Predictors of Outcome in Trauma Patients. Indian J Crit Care Med. 2017;21(11):719-25.
49. Kawatani Y, Nakamura Y, Kurobe H, Suda Y, Hori T. Correlations of perioperative coagulopathy, fluid infusion and blood transfusions with survival prognosis in endovascular aortic repair for ruptured abdominal aortic aneurysm. World J Emerg Surg. 2016;11:29.
50. Noorbhai MA, Cassimjee HM, Sartorius B, Muckart DJ. Elevated international normalised ratios correlate with severity of injury and outcome. S Afr Med J. 2016;106(11):1141-5.
51. Sawamura A, Hayakawa M, Gando S, Kubota N, Sugano M, Wada T, et al. Disseminated intravascular coagulation with a fibrinolytic phenotype at an early phase of trauma predicts mortality. Thromb Res. 2009;124(5):608-13.
52. Lester ELW, Fox EE, Holcomb JB, Brasel KJ, Bulger EM, Cohen MJ, et al. The impact of hypothermia on outcomes in massively transfused patients. J Trauma Acute Care Surg. 2019;86(3):458-63.
53. Consunji R, Elseed A, El-Menyar A, Sathian B, Rizoli S, Al-Thani H, et al. The effect of massive transfusion protocol implementation on the survival of trauma patients: A systematic review and meta-analysis. Blood Transfusion. 2020;18(6):434-45.
54. Kinslow K, McKenney M, Boneva D, Elkbuli A. Massive transfusion protocols in paediatric trauma population: A systematic review. Transfusion Medicine. 2020;30(5):333-42.
55. Sommer N, Schnüriger B, Candinas D, Haltmeier T. Massive transfusion protocols in nontrauma patients: A systematic review and meta-analysis. J Trauma Acute Care Surg. 2019;86(3):493-504.
56. Maw G, Furyk C. Pediatric Massive Transfusion: A Systematic Review. Pediatr Emerg Care. 2018;34(8):594-8.
57. Cannon JW, Khan MA, Raja AS, Cohen MJ, Como JJ, Cotton BA, et al. Damage control resuscitation in patients with severe traumatic hemorrhage: A practice management guideline from the Eastern Association for the Surgery of Trauma. Journal of Trauma and Acute Care Surgery. 2017;82(3):605-17.
58. Mitra B, O'Reilly G, Cameron PA, Zatta A, Gruen RL. Effectiveness of massive transfusion protocols on mortality in trauma: a systematic review and meta-analysis. ANZ J Surg. 2013;83(12):918-23.
59. Vogt KN, Van Koughnett JA, Dubois L, Gray DK, Parry NG. The use of trauma transfusion pathways for blood component transfusion in the civilian population: a systematic review and meta-analysis. Transfus Med. 2012;22(3):156-66.
60. Kleinveld DJB, van Amstel RBE, Wirtz MR, Geeraedts LMG, Goslings JC, Hollmann MW, et al. Platelet-to-red blood cell ratio and mortality in bleeding trauma patients: A systematic review and meta-analysis. Transfusion. 2021;61(S1):S243-S51.
61. Phillips AR, Tran L, Foust JE, Liang NL. Systematic review of plasma/packed red blood cell ratio on survival in ruptured abdominal aortic aneurysms. Journal of Vascular Surgery. 2021;73(4):1438-44.
62. Rijnhout TWH, Duijst J, Noorman F, Zoodsma M, van Waes O, Verhofstad MHJ, et al. Platelet to erythrocyte transfusion ratio and mortality in massively transfused trauma patients. A systematic review and meta-analysis. The journal of trauma and acute care surgery. 2021;02.
63. Meneses E, Boneva D, McKenney M, Elkbuli A. Massive transfusion protocol in adult trauma population. American Journal of Emergency Medicine. 2020;38(12):2661-6.
64. Ritchie DT, Philbrook FGA, Leadbitter S, Kokwe KN, Meehan E, McGeady M, et al. Empirical transfusion strategies for major hemorrhage in trauma patients: A systematic review. Journal of Trauma and Acute Care Surgery. 2020;88(6):855-65.

65. Rodriguez HO, Rios F, Rubio C, Arsanios DM, Herazo AF, Beltran LM, et al. Mortality in civilian trauma patients and massive blood transfusion treated with high vs low plasma: Red blood cell ratio. Systematic review and meta-analysis. Colombian Journal of Anesthesiology. 2020;48(3):126-37.
66. Wirtz MR, Schalkers DV, Goslings JC, Juffermans NP. The impact of blood product ratio and procoagulant therapy on the development of thromboembolic events in severely injured hemorrhaging trauma patients. Transfusion. 2020;60(8):1873-82.
67. da Luz LT, Shah PS, Strauss R, Mohammed AA, D'Empaire PP, Tien H, et al. Does the evidence support the importance of high transfusion ratios of plasma and platelets to red blood cells in improving outcomes in severely injured patients: a systematic review and meta-analyses. Transfusion. 2019;59(11):3337-49.
68. McQuilten ZK, Crighton G, Brunskill S, Morison JK, Richter TH, Waters N, et al. Optimal Dose, Timing and Ratio of Blood Products in Massive Transfusion: Results from a Systematic Review. Transfus Med Rev. 2018;32(1):6-15.
69. Rahouma M, Kamel M, Jodeh D, Kelley T, Ohmes LB, de Biasi AR, et al. Does a balanced transfusion ratio of plasma to packed red blood cells improve outcomes in both trauma and surgical patients? A meta-analysis of randomized controlled trials and observational studies. Am J Surg. 2018;216(2):342-50.
70. Jones AR, Frazier SK. Association of Blood Component Ratio With Clinical Outcomes in Patients After Trauma and Massive Transfusion: A Systematic Review. Adv Emerg Nurs J. 2016;38(2):157-68.
71. Tapia NM, Suliburk J, Mattox KL. The initial trauma center fluid management of penetrating injury: a systematic review. Clin Orthop Relat Res. 2013;471(12):3961-73.
72. Peralta R, Vijay A, El-Menyar A, Consunji R, Afifi I, Mahmood I, et al. Early high ratio platelet transfusion in trauma resuscitation and its outcomes. Int J Crit Illn Inj Sci. 2016;6(4):188-93.
73. Balvers K, Wirtz MR, van Dieren S, Goslings JC, Juffermans NP. Risk factors for trauma-induced coagulopathy- and transfusion-associated multiple organ failure in severely injured trauma patients. Front Med (Lausanne). 2015;2:24.
74. Patel SV, Kidane B, Klingel M, Parry N. Risks associated with red blood cell transfusion in the trauma population, a meta-analysis. Injury. 2014;45(10):1522-33.
75. Liu S, Fujii Q, Serio F, McCague A. Massive Blood Transfusions and Outcomes in Trauma Patients; An Intention to Treat Analysis. Bull Emerg Trauma. 2018;6(3):217-20.
76. Hassanien M, El-Talkawy MD, El-Ghannam M, El Ray A, Ali AA, Taleb HA. Predictors of In-Hospital Mortality in patients with hepatocellular carcinoma and Acute Variceal bleeding. Electron Physician. 2015;7(6):1336-43.
77. McQuilten ZK, Crighton G, Engelbrecht S, Gotmaker R, Brunskill SJ, Murphy MF, et al. Transfusion interventions in critical bleeding requiring massive transfusion: A systematic review. Transfusion Medicine Reviews. 2015;29(2):127-37.
78. Magon N, Babu K. Recombinant Factor VIIa in Post-partum Hemorrhage: A New Weapon in Obstetrician's Armamentarium. N Am J Med Sci. 2012;4(4):157-62.
79. Okonta KE, Edwin F, Falase B. Is recombinant activated factor VII effective in the treatment of excessive bleeding after paediatric cardiac surgery? Interactive Cardiovascular and Thoracic Surgery. 2012;15(4):690-5.
80. Simpson E, Lin Y, Stanworth S, Birchall J, Doree C, Hyde C. Recombinant factor VIIa for the prevention and treatment of bleeding in patients without haemophilia. Cochrane database of systematic reviews (Online). 2012;3:CD005011.
81. Curry N, Hopewell S, Doree C, Hyde C, Brohi K, Stanworth S. The acute management of trauma hemorrhage: A systematic review of randomized controlled trials. Critical Care. 2011;15 (2) (no pagination)(R92).

82. Yank V, Tuohy CV, Logan AC, Bravata DM, Staudenmayer K, Eisenhut R, et al. Systematic review: benefits and harms of in-hospital use of recombinant factor VIIa for off-label indications. Annals of Internal Medicine. 2011;154(8):529-40.
83. Franchini M, Franchi M, Bergamini V, Montagnana M, Salvagno GL, Targher G, et al. The use of recombinant activated FVII in postpartum hemorrhage. Clinical Obstetrics and Gynecology. 2010;53(1):219-27.
84. Dutton RP, Parr M, Tortella BJ, Champion HR, Bernard GR, Boffard K, et al. Recombinant activated factor VII safety in trauma patients: results from the CONTROL trial. The Journal of trauma. 2011;71(1):12-9.
85. Hauser CJ, Boffard K, Dutton R, Bernard GR, Croce MA, Holcomb JB, et al. Results of the CONTROL trial: efficacy and safety of recombinant activated Factor VII in the management of refractory traumatic hemorrhage. The Journal of trauma. 2010;69(3):489-500.
86. McMullin NR, Wade CE, Holcomb JB, Nielsen TG, Rossaint R, Riou B, et al. Prolonged prothrombin time after recombinant activated factor VII therapy in critically bleeding trauma patients is associated with adverse outcomes. The Journal of trauma. 2010;69(1):60-9.
87. Boffard KD, Choong PI, Kluger Y, Riou B, Rizoli SB, Rossaint R, et al. The treatment of bleeding is to stop the bleeding! Treatment of trauma-related hemorrhage. Transfusion. 2009;49 Suppl 5:240S-7S.
88. Gill R, Herbertson M, Vuylsteke A, Olsen PS, von Heymann C, Mythen M, et al. Safety and efficacy of recombinant activated factor VII: a randomized placebo-controlled trial in the setting of bleeding after cardiac surgery. Circulation. 2009;120(1):21-7.
89. Bosch J, Thabut D, Albillos A, Carbonell N, Spicak J, Massard J, et al. Recombinant factor VIIa for variceal bleeding in patients with advanced cirrhosis: A randomized, controlled trial. Hepatology. 2008;47(5):1604-14.
90. Rizoli SB, Boffard KD, Riou B, Warren B, Iau P, Kluger Y, et al. Recombinant activated factor VII as an adjunctive therapy for bleeding control in severe trauma patients with coagulopathy: subgroup analysis from two randomized trials. Crit Care. 2006;10(6):R178.
91. Boffard KD, Riou B, Warren B, Choong PI, Rizoli S, Rossaint R, et al. Recombinant factor VIIa as adjunctive therapy for bleeding control in severely injured trauma patients: two parallel randomized, placebo-controlled, double-blind clinical trials. The Journal of trauma. 2005;59(1):8-15; discussion -8.
92. Chuansumrit A, Wangruangsatid S, Lektrakul Y, Chua MN, Zeta Capeding MR, Bech OM, et al. Control of bleeding in children with Dengue hemorrhagic fever using recombinant activated factor VII: a randomized, double-blind, placebo-controlled study. Blood Coagul Fibrinolysis. 2005;16(8):549-55.
93. Pihusch M, Bacigalupo A, Szer J, von Depka Prondzinski M, Gaspar-Blaudschun B, Hyveled L, et al. Recombinant activated factor VII in treatment of bleeding complications following hematopoietic stem cell transplantation. J Thromb Haemost. 2005;3(9):1935-44.
94. Bosch J, Thabut D, Bendtsen F, D'Amico G, Albillos A, Gonzalez Abraldes J, et al. Recombinant factor VIIa for upper gastrointestinal bleeding in patients with cirrhosis: a randomized, double-blind trial. Gastroenterology. 2004;127(4):1123-30.
95. Lavigne-Lissalde G, Aya AG, Mercier FJ, Roger-Christoph S, Chauleur C, Morau E, et al. Recombinant human FVIIa for reducing the need for invasive second-line therapies in severe refractory postpartum hemorrhage: a multicenter, randomized, open controlled trial. J Thromb Haemost. 2015;13(4):520-9.
96. Veazie S, Kondo K, Winchell K. Comparative Effectiveness of In-Hospital Use of Recombinant Factor VIIa for Off-Label Indications vs Usual Care. Agency for Healthcare Research and Quality Systematic Review Surveillance Program. 2016.

97. Zatta A, McQuilten Z, Kandane-Rathnayake R, Isbister J, Dunkley S, McNeil J, et al. The Australian and New Zealand Haemostasis Registry: ten years of data on off-licence use of recombinant activated factor VII. Blood Transfus. 2015;13(1):86-99.
98. Rijnhout TWH, Duijst J, Noorman F, Zoodsma M, van Waes OJF, Verhofstad MHJ, et al. Platelet to erythrocyte transfusion ratio and mortality in massively transfused trauma patients. A systematic review and meta-analysis. J Trauma Acute Care Surg. 2021;91(4):759-71.
99. Stabler SN, Li SS, Karpov A, Vu EN. Use of fibrinogen concentrate for trauma-related bleeding: A systematic-review and meta-analysis. Journal of Trauma and Acute Care Surgery. 2020;89(6):1212-24.
100. van den Brink DP, Wirtz MR, Neto AS, Schochl H, Viersen V, Binnekade J, et al. Effectiveness of prothrombin complex concentrate for the treatment of bleeding: A systematic review and meta-analysis. Journal of Thrombosis and Haemostasis. 2020;18(10):2457-67.
101. Zaidi A, Kohli R, Daru J, Estcourt L, Khan KS, Thangaratinam S, et al. Early Use of Fibrinogen Replacement Therapy in Postpartum Hemorrhage-A Systematic Review. Transfusion Medicine Reviews. 2020;34(2):101-7.
102. Coccolini F, Pizzilli G, Corbella D, Sartelli M, Agnoletti V, Agostini V, et al. Pre-hospital plasma in haemorrhagic shock management: current opinion and meta-analysis of randomized trials. World journal of emergency surgery : WJES. 2019;14:6.
103. Fabes J, Brunskill SJ, Curry N, Doree C, Stanworth SJ. Pro-coagulant haemostatic factors for the prevention and treatment of bleeding in people without haemophilia. Cochrane Database of Systematic Reviews. 2018;12:CD010649.
104. Mengoli C, Franchini M, Marano G, Pupella S, Vaglio S, Marietta M, et al. The use of fibrinogen concentrate for the management of trauma-related bleeding: A systematic review and meta-analysis. 2017;15(4):318-24.
105. Aubron C, Reade MC, Fraser JF, Cooper DJ. Efficacy and safety of fibrinogen concentrate in trauma patients-a systematic review. 2014;29(3):471.e11-.e17.
106. Lunde J, Stensballe J, Wikkelso A, Johansen M, Afshari A. Fibrinogen concentrate for bleeding - A systematic review. 2014;58(9):1061-74.
107. Warmuth M, Mad P, Wild C. Systematic review of the efficacy and safety of fibrinogen concentrate substitution in adults. 2012;56(5):539-48.
108. Lucena LSd, Rodrigues RdR, Carmona MJC, Noronha FJD, Oliveira HP, Lima NM, et al. Early administration of fibrinogen concentrate in patients with polytrauma with thromboelastometry suggestive of hypofibrinogenemia: A randomized feasibility trial. Clinics. 2021;76:-.
109. Akbari E, Safari S, Hatamabadi H. The effect of fibrinogen concentrate and fresh frozen plasma on the outcome of patients with acute traumatic coagulopathy: A quasi-experimental study. Am J Emerg Med. 2018;36(11):1947-50.
110. Curry N, Foley C, Wong H, Mora A, Curnow E, Zarankaite A, et al. Early fibrinogen concentrate therapy for major haemorrhage in trauma (E-FIT 1): results from a UK multi-centre, randomised, double blind, placebo-controlled pilot trial. Crit Care. 2018;22(1):164.
111. Moore HB, Moore EE, Chapman MP, McVaney K, Bryskiewicz G, Blechar R, et al. Plasma-first resuscitation to treat haemorrhagic shock during emergency ground transportation in an urban area: a randomised trial. Lancet. 2018;392(10144):283-91.
112. Sperry JL, Guyette FX, Brown JB, Yazer MH, Triulzi DJ, Early-Young BJ, et al. Prehospital Plasma during Air Medical Transport in Trauma Patients at Risk for Hemorrhagic Shock. New England Journal of Medicine. 2018;379(4):315-26.
113. Innerhofer P, Fries D, Mittermayr M, Innerhofer N, von Langen D, Hell T, et al. Reversal of trauma-induced coagulopathy using first-line coagulation factor

concentrates or fresh frozen plasma (RETIC): a single-centre, parallel-group, open-label, randomised trial. Lancet Haematol. 2017;4(6):e258-e71.

114. Nascimento B, Callum J, Tien H, Peng H, Rizoli S, Karanicolas P, et al. Fibrinogen in the initial resuscitation of severe trauma (FiiRST): a randomized feasibility trial. Br J Anaesth. 2016;117(6):775-82.

115. Curry N, Rourke C, Davenport R, Beer S, Pankhurst L, Deary A, et al. Early cryoprecipitate for major haemorrhage in trauma: a randomised controlled feasibility trial. BJA: British Journal of Anaesthesia. 2015;115(1):76-83.

116. Al-Jeabory M, Szarpak L, Attila K, Simpson M, Smereka A, Gasecka A, et al. Efficacy and Safety of Tranexamic Acid in Emergency Trauma: A Systematic Review and Meta-Analysis. J Clin Med. 2021;10(5).

117. Almuwallad A, Cole E, Ross J, Perkins Z, Davenport R. The impact of prehospital TXA on mortality among bleeding trauma patients: A systematic review and meta-analysis. J Trauma Acute Care Surg. 2021;90(5):901-7.

118. Della Corte L, Saccone G, Locci M, Carbone L, Raffone A, Giampaolino P, et al. Tranexamic acid for treatment of primary postpartum hemorrhage after vaginal delivery: a systematic review and meta-analysis of randomized controlled trials. J Matern Fetal Neonatal Med. 2020;33(5):869-74.

119. Chornenki NLJ, Um KJ, Mendoza PA, Samienezhad A, Swarup V, Chai-Adisaksopha C, et al. Risk of venous and arterial thrombosis in non-surgical patients receiving systemic tranexamic acid: A systematic review and meta-analysis. Thrombosis Research. 2019;179(pp 81-86).

120. Marsden MER, Rossetto A, Duffield CAB, Woolley TGD, Buxton WP, Steynberg S, et al. Prehospital tranexamic acid shortens the interval to administration by half in Major Trauma Networks: A service evaluation. Emergency Medicine Journal. 2019.

121. El-Menyar A, Sathian B, Asim M, Latifi R, Al-Thani H. Efficacy of prehospital administration of tranexamic acid in trauma patients: A meta-analysis of the randomized controlled trials. American Journal of Emergency Medicine. 2018;36(6):1079-87.

122. Gayet-Ageron A, Prieto-Merino D, Ker K, Shakur H, Ageron F-X, Roberts I, et al. Effect of treatment delay on the effectiveness and safety of antifibrinolytics in acute severe haemorrhage: a meta-analysis of individual patient-level data from 40 138 bleeding patients. Lancet. 2018;391(10116):125-32.

123. Shakur H, Beaumont D, Pavord S, Gayet-Ageron A, Ker K, Mousa HA. Antifibrinolytic drugs for treating primary postpartum haemorrhage. Cochrane Database of Systematic Reviews. 2018;2018 (2) (no pagination)(CD012964).

124. Huebner BR, Dorlac WC, Cribari C. Tranexamic Acid Use in Prehospital Uncontrolled Hemorrhage. Wilderness & environmental medicine. 2017;S. 28(2):S50-S60.

125. Nishida T, Kinoshita T, Yamakawa K. Tranexamic acid and trauma-induced coagulopathy. Journal of Intensive Care. 2017;5 (1) (no pagination)(5).

126. Ausset S, Glassberg E, Nadler R, Sunde G, Cap AP, Hoffmann C, et al. Tranexamic acid as part of remote damage-control resuscitation in the prehospital setting: A critical appraisal of the medical literature and available alternatives. The Journal of Trauma and Acute Care Surgery. 2015;78(6 Suppl 1):S70-5.

127. Ker K, Roberts I, Shakur H, Coats TJ. Antifibrinolytic drugs for acute traumatic injury. Cochrane Database of Systematic Reviews. 2015(5):CD004896.

128. Baskaran D, Rahman S, Salmasi Y, Froghi S, Berber O, George M. Effect of tranexamic acid use on blood loss and thromboembolic risk in hip fracture surgery: systematic review and meta-analysis. HIP International. 2018;28(1):3-10.

129. Gausden EB, Qudsi R, Boone MD, O'Gara B, Ruzbarsky JJ, Lorich DG. Tranexamic Acid in Orthopaedic Trauma Surgery: A Meta-Analysis. Journal of Orthopaedic Trauma. 2017;31(10):513-9.
130. Wang W, Yu J. Tranexamic acid reduces blood loss in intertrochanteric fractures: A meta-analysis from randomized controlled trials. Medicine. 2017;96(52):e9396.
131. Zhang P, He J, Fang Y, Chen P, Liang Y, Wang J. Efficacy and safety of intravenous tranexamic acid administration in patients undergoing hip fracture surgery for hemostasis. Medicine (United States). 2017;96 (21) (no pagination)(e6940).
132. Bennett C, Klingenberg LS, Langholz E, Gluud LL. Tranexamic acid for upper gastrointestinal bleeding. Cochrane Database of Systematic Reviews. 2014(11).
133. Perel P, Ker K, Morales Uribe CH, Roberts I. Tranexamic acid for reducing mortality in emergency and urgent surgery. Cochrane database of systematic reviews (Online). 2013;1:CD010245.
134. Ageron FX, Gayet-Ageron A, Ker K, Coats TJ, Shakur-Still H, Roberts I, et al. Effect of tranexamic acid by baseline risk of death in acute bleeding patients: a meta-analysis of individual patient-level data from 28 333 patients. Br J Anaesth. 2020;124(6):676-83.
135. Li C, Zhao Q, Yang K, Jiang L, Yu J. Thromboelastography or rotational thromboelastometry for bleeding management in adults undergoing cardiac surgery: a systematic review with meta-analysis and trial sequential analysis. J Thorac Dis. 2019;11(4):1170-81.
136. Roullet S, de Maistre E, Ickx B, Blais N, Susen S, Faraoni D, et al. Position of the French Working Group on Perioperative Haemostasis (GIHP) on viscoelastic tests: What role for which indication in bleeding situations? Anaesthesia Critical Care and Pain Medicine. 2018.
137. Fahrendorff M, Oliveri RS, Johansson PI. The use of viscoelastic haemostatic assays in goal-directing treatment with allogeneic blood products - A systematic review and meta-analysis. Scandinavian journal of trauma, resuscitation and emergency medicine. 2017;25(1):39.
138. Serraino GF, Murphy GJ. Routine use of viscoelastic blood tests for diagnosis and treatment of coagulopathic bleeding in cardiac surgery: Updated systematic review and meta-analysis. British Journal of Anaesthesia. 2017;118(6):823-33.
139. Wikkelso A, Wetterslev J, Moller MA, Afshari A. Thromboelastography (TEG) or thromboelastometry (ROTEM) to monitor haemostatic treatment versus usual care in adults or children with bleeding. Cochrane Database of Systematic Reviews. 2017(1).
140. Wikkelso A, Wetterslev J, Moller AM, Afshari A. Thromboelastography (TEG) or rotational thromboelastometry (ROTEM) to monitor haemostatic treatment in bleeding patients: a systematic review with meta-analysis and trial sequential analysis. Anaesthesia. 2017;72(4):519-31.
141. Saner FH, Kirchner C. Monitoring and Treatment of Coagulation Disorders in End-Stage Liver Disease. Visc Med. 2016;32(4):241-8.
142. Deppe AC, Weber C, Zimmermann J, Kuhn EW, Slottosch I, Liakopoulos OJ, et al. Point-of-care thromboelastography/thromboelastometry-based coagulation management in cardiac surgery: A meta-analysis of 8332 patients. Journal of Surgical Research. 2016;203(2):424-33.
143. Corredor C, Wasowicz M, Karkouti K, Sharma V. The role of point-of-care platelet function testing in predicting postoperative bleeding following cardiac surgery: A systematic review and meta-analysis. Anaesthesia. 2015;70(6):715-31.
144. Da Luz LT, Nascimento B, Shankarakutty AK, Rizoli S, Adhikari NK. Effect of thromboelastography (TEG) and rotational thromboelastometry (ROTEM) on

diagnosis of coagulopathy, transfusion guidance and mortality in trauma: descriptive systematic review. Critical Care (London, England). 2014;18(5):518.

145. Haas T, Gorlinger K, Grassetto A, Agostini V, Simioni P, Nardi G, et al. Thromboelastometry for guiding bleeding management of the critically ill patient: a systematic review of the literature. Minerva Anestesiologica. 2014;80(12):1320-35.

146. Agarwal S, Johnson RI, Shaw M. Preoperative point-of-care platelet function testing in cardiac surgery. J Cardiothorac Vasc Anesth. 2015;29(2):333-41.

147. Ak K, Isbir CS, Tetik S, Atalan N, Tekeli A, Aljodi M, et al. Thromboelastography-based transfusion algorithm reduces blood product use after elective CABG: a prospective randomized study. J Card Surg. 2009;24(4):404-10.

148. Avidan MS, Alcock EL, Da Fonseca J, Ponte J, Desai JB, Despotis GJ, et al. Comparison of structured use of routine laboratory tests or near-patient assessment with clinical judgement in the management of bleeding after cardiac surgery. Br J Anaesth. 2004;92(2):178-86.

149. Cui Y, Hei F, Long C, Feng Z, Zhao J, Yan F, et al. Perioperative monitoring of thromboelastograph on blood protection and recovery for severely cyanotic patients undergoing complex cardiac surgery. Artif Organs. 2010;34(11):955-60.

150. De Pietri L, Bianchini M, Montalti R, De Maria N, Di Maira T, Begliomini B, et al. Thrombelastography-guided blood product use before invasive procedures in cirrhosis with severe coagulopathy: A randomized, controlled trial. Hepatology. 2016;63(2):566-73.

151. Girdauskas E, Kempfert J, Kuntze T, Borger MA, Enders J, Fassl J, et al. Thromboelastometrically guided transfusion protocol during aortic surgery with circulatory arrest: a prospective, randomized trial. J Thorac Cardiovasc Surg. 2010;140(5):1117-24 e2.

152. Karkouti K, Callum J, Wijeysundera DN, Rao V, Crowther M, Grocott HP, et al. Point-of-Care Hemostatic Testing in Cardiac Surgery: A Stepped-Wedge Clustered Randomized Controlled Trial. Circulation. 2016;134(16):1152-62.

153. Kultufan Turan S AB, Ayik H, Yaar S, Kazanci D, Karadenz Ü, et al. The role of rotational thromboelastgraphy on decision of blood transfusion in open heart surgery [Açik Kalp Cerrahisinde TromboelastografininTransfüzyon Karari Üzerine Etkisi]. Göğüs-Kalp-Damar Anestezi ve Yoğun Bakım Derneği Dergisi. 2006;12(4):154-9.

154. Nakayama Y, Nakajima Y, Tanaka KA, Sessler DI, Maeda S, Iida J, et al. Thromboelastometry-guided intraoperative haemostatic management reduces bleeding and red cell transfusion after paediatric cardiac surgery. Br J Anaesth. 2015;114(1):91-102.

155. Rauter M KT, Schwarz S, Fitzgerald R. Reduced number of red blood cell transfusions in cardiac surgery due to perioperative coagulation testing by thromboelastometry. Acta Anaesthesiologica Scandinavica. 2007;51 (Suppl 118):40.

156. Royston D, von Kier S. Reduced haemostatic factor transfusion using heparinase-modified thrombelastography during cardiopulmonary bypass. Br J Anaesth. 2001;86(4):575-8.

157. Shore-Lesserson L, Manspeizer HE, DePerio M, Francis S, Vela-Cantos F, Ergin MA. Thromboelastography-guided transfusion algorithm reduces transfusions in complex cardiac surgery. Anesth Analg. 1999;88(2):312-9.

158. Wang SC, Shieh JF, Chang KY, Chu YC, Liu CS, Loong CC, et al. Thromboelastography-guided transfusion decreases intraoperative blood transfusion during orthotopic liver transplantation: randomized clinical trial. Transplant Proc. 2010;42(7):2590-3.

159. Westbrook AJ, Olsen J, Bailey M, Bates J, Scully M, Salamonsen RF. Protocol based on thromboelastograph (TEG) out-performs physician preference using laboratory

coagulation tests to guide blood replacement during and after cardiac surgery: a pilot study. Heart Lung Circ. 2009;18(4):277-88.

160. Schaden E, Kimberger O, Kraincuk P, Baron DM, Metnitz PG, Kozek-Langenecker S. Perioperative treatment algorithm for bleeding burn patients reduces allogeneic blood product requirements. Br J Anaesth. 2012;109(3):376-81.

161. Cao X, Zhang X, Li Q. [Efficacy of thromboelastography to monitor the clinical massive transfusion in scoliosis: a randomized controlled trial]. Zhonghua Wai Ke Za Zhi. 2016;54(2):137-41.

162. Rahe-Meyer N, Hanke A, Schmidt DS, Hagl C, Pichlmaier M. Fibrinogen concentrate reduces intraoperative bleeding when used as first-line hemostatic therapy during major aortic replacement surgery: results from a randomized, placebo-controlled trial. J Thorac Cardiovasc Surg. 2013;145(3 Suppl):S178-85.

163. Collins PW, Cannings-John R, Bruynseels D, Mallaiah S, Dick J, Elton C, et al. Viscoelastometric-guided early fibrinogen concentrate replacement during postpartum haemorrhage: OBS2, a double-blind randomized controlled trial. Br J Anaesth. 2017;119(3):411-21.

164. Rourke C, Curry N, Khan S, Taylor R, Raza I, Davenport R, et al. Fibrinogen levels during trauma hemorrhage, response to replacement therapy, and association with patient outcomes. J Thromb Haemost. 2012;10(7):1342-51.

165. Johansson PI, Sorensen AM, Larsen CF, Windelov NA, Stensballe J, Perner A, et al. Low hemorrhage-related mortality in trauma patients in a Level I trauma center employing transfusion packages and early thromboelastography-directed hemostatic resuscitation with plasma and platelets. Transfusion. 2013;53(12):3088-99.

166. Spiess BD, Gillies BS, Chandler W, Verrier E. Changes in transfusion therapy and reexploration rate after institution of a blood management program in cardiac surgical patients. J Cardiothorac Vasc Anesth. 1995;9(2):168-73.

167. Anderson L, Quasim I, Soutar R, Steven M, Macfie A, Korte W. An audit of red cell and blood product use after the institution of thromboelastometry in a cardiac intensive care unit. Transfus Med. 2006;16(1):31-9.

168. Spalding GJ, Hartrumpf M, Sierig T, Oesberg N, Kirschke CG, Albes JM. Cost reduction of perioperative coagulation management in cardiac surgery: value of "bedside" thrombelastography (ROTEM). Eur J Cardiothorac Surg. 2007;31(6):1052-7.

169. Rahe-Meyer N, Pichlmaier M, Haverich A, Solomon C, Winterhalter M, Piepenbrock S, et al. Bleeding management with fibrinogen concentrate targeting a high-normal plasma fibrinogen level: a pilot study. Br J Anaesth. 2009;102(6):785-92.

170. Rahe-Meyer N, Winterhalter M, Boden A, Froemke C, Piepenbrock S, Calatzis A, et al. Platelet concentrates transfusion in cardiac surgery and platelet function assessment by multiple electrode aggregometry. Acta Anaesthesiol Scand. 2009;53(2):168-75.

171. Görlinger K, Dirkmann D, Mueller-Beissenhirtz H, Paul A, Hartmann M, Saner F. Thromboelastometry-Based Perioperative Coagulation Management in Visceral Surgery and Liver Transplantation: Experience of 10 Years and 1105 LTX2010. S86-S p.

172. Noval-Padillo JA, Leon-Justel A, Mellado-Miras P, Porras-Lopez F, Villegas-Duque D, Gomez-Bravo MA, et al. Introduction of fibrinogen in the treatment of hemostatic disorders during orthotopic liver transplantation: implications in the use of allogenic blood. Transplant Proc. 2010;42(8):2973-4.

173. Trzebicki J, Flakiewicz E, Kosieradzki M, Blaszczyk B, Kolacz M, Jureczko L, et al. The use of thromboelastometry in the assessment of hemostasis during orthotopic liver transplantation reduces the demand for blood products. Ann Transplant. 2010;15(3):19-24.

174. Gorlinger K, Dirkmann D, Hanke AA, Kamler M, Kottenberg E, Thielmann M, et al. First-line therapy with coagulation factor concentrates combined with point-of-care coagulation testing is associated with decreased allogeneic blood transfusion in cardiovascular surgery: a retrospective, single-center cohort study. Anesthesiology. 2011;115(6):1179-91.

175. Romlin BS, Wahlander H, Berggren H, Synnergren M, Baghaei F, Nilsson K, et al. Intraoperative thromboelastometry is associated with reduced transfusion prevalence in pediatric cardiac surgery. Anesth Analg. 2011;112(1):30-6.

176. Hvas AM, Boas TW, Jensen M, Lindskov C, Folkersen L, Ravn HB. Change in hemostatic intervention after implementation of thromboelastometry. J Cardiothorac Vasc Anesth. 2012;26(2):227-31.

177. Wang SC, Lin HT, Chang KY, Mandell MS, Ting CK, Chu YC, et al. Use of higher thromboelastogram transfusion values is not associated with greater blood loss in liver transplant surgery. Liver Transpl. 2012;18(10):1254-8.

178. Xu L, Wang L, Yang X, Li K, Sun H, Zhang D, et al. Platelet function monitoring guided antiplatelet therapy in patients receiving high-risk coronary interventions. Chinese medical journal. 2014;127(19):3364-70.

179. Leon-Justel A, Noval-Padillo JA, Alvarez-Rios AI, Mellado P, Gomez-Bravo MA, Alamo JM, et al. Point-of-care haemostasis monitoring during liver transplantation reduces transfusion requirements and improves patient outcome. Clin Chim Acta. 2015;446:277-83.

180. Roullet S, Freyburger G, Cruc M, Quinart A, Stecken L, Audy M, et al. Management of bleeding and transfusion during liver transplantation before and after the introduction of a rotational thromboelastometry-based algorithm. Liver Transpl. 2015;21(2):169-79.

181. Bedreli S, Sowa JP, Gerken G, Saner FH, Canbay A. Management of acute-on-chronic liver failure: rotational thromboelastometry may reduce substitution of coagulation factors in liver cirrhosis. Gut. 2016;65(2):357-8.

182. De Pietri L, Ragusa F, Deleuterio A, Begliomini B, Serra V. Reduced Transfusion During OLT by POC Coagulation Management and TEG Functional Fibrinogen: A Retrospective Observational Study. Transplantation direct. 2016;2(1):e49.

183. St-Onge S, Lemoine E, Bouhout I, Rochon A, El-Hamamsy I, Lamarche Y, et al. Evaluation of the real-world impact of rotational thromboelastometry-guided transfusion protocol in patients undergoing proximal aortic surgery. J Thorac Cardiovasc Surg. 2018.

184. Kuiper G, van Egmond LT, Henskens YMC, Roekaerts PM, Maessen JG, Ten Cate H, et al. Shifts of Transfusion Demand in Cardiac Surgery After Implementation of Rotational Thromboelastometry-Guided Transfusion Protocols: Analysis of the HEROES-CS (HEmostasis Registry of patiEntS in Cardiac Surgery) Observational, Prospective Open Cohort Database. J Cardiothorac Vasc Anesth. 2019;33(2):307-17.

185. Mallaiah S, Barclay P, Harrod I, Chevannes C, Bhalla A. Introduction of an algorithm for ROTEM-guided fibrinogen concentrate administration in major obstetric haemorrhage. Anaesthesia. 2015;70(2):166-75.

186. Collins PW, Cannings-John R, Bruynseels D, Mallaiah S, Dick J, Elton C, et al. Viscoelastometry guided fresh frozen plasma infusion for postpartum haemorrhage: OBS2, an observational study. Br J Anaesth. 2017;119(3):422-34.

187. Bugaev N, Como JJ, Golani G, Freeman JJ, Sawhney JS, Vatsaas CJ, et al. Thromboelastography and rotational thromboelastometry in bleeding patients with coagulopathy: Practice management guideline from the Eastern Association for the Surgery of Trauma. J Trauma Acute Care Surg. 2020;89(6):999-1017.

188. Amgalan A, Allen T, Othman M, Ahmadzia HK. Systematic review of viscoelastic testing (TEG/ROTEM) in obstetrics and recommendations from the women's SSC of the ISTH. J Thromb Haemost. 2020;18(8):1813-38.

189. Gonzalez E, Moore EE, Moore HB, Chapman MP, Chin TL, Ghasabyan A, et al. Goal-directed Hemostatic Resuscitation of Trauma-induced Coagulopathy: A Pragmatic Randomized Clinical Trial Comparing a Viscoelastic Assay to Conventional Coagulation Assays. Annals of surgery. 2016;263(6):1051-9.
190. Kempfert. J. Thromboelastography-guided blood component therapy after cardiac surgery: A randomised study. Interactive Cardiovascular and Thoracic Surgery. 2011;13:S106–7.
191. NCT00772239. Perioperative coagulation management in cardiac surgery (ROTEM)(first recieved 13 October 2008) 26 November 2019. Available from: clinicaltrials.gov/ct2/show/NCT00772239.
192. Nuttall GA, Oliver WC, Santrach PJ, Bryant S, Dearani JA, Schaff HV, et al. Efficacy of a simple intraoperative transfusion algorithm for nonerythrocyte component utilization after cardiopulmonary bypass. Anesthesiology. 2001;94(5):773-81; discussion 5A-6A.
193. Paniagua P, Koller T, Requena T, Gil J, Campos J, Galan J. Randomized controlled trial to evaluate postoperative coagulation management with bed-side trombelastometry (Rotem) compared with a transfusion protocol based on laboratory measurements in bleeding patients after cardiac surgery: Preliminary data. European Journal of Anaesthesiology. 2011;28:94.
194. Weber CF, Gorlinger K, Meininger D, Herrmann E, Bingold T, Moritz A, et al. Point-of-care testing: a prospective, randomized clinical trial of efficacy in coagulopathic cardiac surgery patients. Anesthesiology. 2012;117(3):531-47.
195. Baksaas-Aasen K, Gall L, Eaglestone S, Rourke C, Juffermans NP, Goslings JC, et al. iTACTIC - implementing Treatment Algorithms for the Correction of Trauma-Induced Coagulopathy: study protocol for a multicentre, randomised controlled trial. Trials. 2017;18(1):486.
196. Baksaas-Aasen K, Gall LS, Stensballe J, Juffermans NP, Curry N, Maegele M, et al. Viscoelastic haemostatic assay augmented protocols for major trauma haemorrhage (ITACTIC): a randomized, controlled trial. Intensive Care Med. 2021;47(1):49-59.
197. Nienaber U, Innerhofer P, Westermann I, Schochl H, Attal R, Breitkopf R, et al. The impact of fresh frozen plasma vs coagulation factor concentrates on morbidity and mortality in trauma-associated haemorrhage and massive transfusion. Injury. 2011;42(7):697-701.
198. Schochl H, Nienaber U, Maegele M, Hochleitner G, Primavesi F, Steitz B, et al. Transfusion in trauma: thromboelastometry-guided coagulation factor concentrate-based therapy versus standard fresh frozen plasma-based therapy. Crit Care. 2011;15(2):R83.
199. Gorlinger K, Fries D, Dirkmann D, Weber CF, Hanke AA, Schochl H. Reduction of Fresh Frozen Plasma Requirements by Perioperative Point-of-Care Coagulation Management with Early Calculated Goal-Directed Therapy. Transfus Med Hemother. 2012;39(2):104-13.
200. Hanke AA, Herold U, Dirkmann D, Tsagakis K, Jakob H, Gorlinger K. Thromboelastometry Based Early Goal-Directed Coagulation Management Reduces Blood Transfusion Requirements, Adverse Events, and Costs in Acute Type A Aortic Dissection: A Pilot Study. Transfus Med Hemother. 2012;39(2):121-8.
201. Kashuk JL, Moore EE, Wohlauer M, Johnson JL, Pezold M, Lawrence J, et al. Initial experiences with point-of-care rapid thrombelastography for management of life-threatening postinjury coagulopathy. Transfusion. 2012;52(1):23-33.
202. Fassl J, Matt P, Eckstein F, Filipovic M, Gregor M, Zenklusen U, et al. Transfusion of allogeneic blood products in proximal aortic surgery with hypothermic circulatory arrest: effect of thromboelastometry-guided transfusion management. J Cardiothorac Vasc Anesth. 2013;27(6):1181-8.

203. Tapia NM, Chang A, Norman M, Welsh F, Scott B, Wall MJ, Jr., et al. TEG-guided resuscitation is superior to standardized MTP resuscitation in massively transfused penetrating trauma patients. J Trauma Acute Care Surg. 2013;74(2):378-85; discussion 85-6.
204. Nardi G, Agostini V, Rondinelli B, Russo E, Bastianini B, Bini G, et al. Trauma-induced coagulopathy: impact of the early coagulation support protocol on blood product consumption, mortality and costs. Crit Care. 2015;19(1):83.
205. Barinov SV, Zhukovsky YG, Dolgikh VT, Medyannikova IV. Novel combined strategy of obstetric haemorrhage management during caesarean section using intrauterine balloon tamponade. J Matern Fetal Neonatal Med. 2017;30(1):29-33.
206. Prat NJ, Meyer AD, Ingalls NK, Trichereau J, DuBose JJ, Cap AP. Rotational thromboelastometry significantly optimizes transfusion practices for damage control resuscitation in combat casualties. J Trauma Acute Care Surg. 2017;83(3):373-80.
207. Snegovskikh D, Souza D, Walton Z, Dai F, Rachler R, Garay A, et al. Point-of-care viscoelastic testing improves the outcome of pregnancies complicated by severe postpartum hemorrhage. J Clin Anesth. 2018;44:50-6.
208. Guth C, Vassal O, Friggeri A, Wey PF, Inaba K, Decullier E, et al. Effects of modification of trauma bleeding management: A before and after study. Anaesth Crit Care Pain Med. 2019;38(5):469-76.
209. McNamara H, Kenyon C, Smith R, Mallaiah S, Barclay P. Four years' experience of a ROTEM((R)) -guided algorithm for treatment of coagulopathy in obstetric haemorrhage. Anaesthesia. 2019;74(8):984-91.
210. Unruh M, Reyes J, Helmer SD, Haan JM. An evaluation of blood product utilization rates with massive transfusion protocol: Before and after thromboelastography (TEG) use in trauma. Am J Surg. 2019;218(6):1175-80.
211. Wang H, Robinson RD, Phillips JL, Ryon A, Simpson S, Ford JR, et al. Traumatic Abdominal Solid Organ Injury Patients Might Benefit From Thromboelastography-Guided Blood Component Therapy. J Clin Med Res. 2017;9(5):433-8.
212. Nayar SK, Shafiq B. Blood Conservation in Orthopedic Trauma. Techniques in Orthopaedics. 2017;32(1):45-50.
213. Shantikumar S, Patel S, Handa A. The role of cell salvage autotransfusion in abdominal aortic aneurysm surgery. European Journal of Vascular & Endovascular Surgery. 2011;42(5):577-84.
214. Meybohm P, Choorapoikayil S, Wessels A, Herrmann E, Zacharowski K, Spahn DR. Washed cell salvage in surgical patients: A review and meta-analysis of prospective randomized trials under PRISMA. Medicine. 2016;95(31):e4490.
215. Li J, Sun LS, Tian HJ, Yang K, Liu R, Li J. Cell salvage in emergency trauma surgery. Cochrane Database of Systematic Reviews. 2015(1).
216. Bowley DM, Barker P, Boffard KD. Intraoperative blood salvage in penetrating abdominal trauma: a randomised, controlled trial. World J Surg. 2006;30(6):1074-80.
217. Bhangu A, Nepogodiev D, Doughty H, Bowley DM. Intraoperative cell salvage in a combat support hospital: a prospective proof of concept study. Transfusion. 2013;53(4):805-10.
218. Markovic M, Davidovic L, Savic N, Sindjelic R, Ille T, Dragas M. Intraoperative cell salvage versus allogeneic transfusion during abdominal aortic surgery: clinical and financial outcomes. Vascular. 2009;17(2):83-92.
219. Tawfick WA, O'Connor M, Hynes N, Sultan S. Implementation of the Continuous AutoTransfusion System (C.A.T.S) in open abdominal aortic aneurysm repair: an observational comparative cohort study. Vasc Endovascular Surg. 2008;42(1):32-9.

220. Serracino-Inglott F, Awad S, Barclay A, Nasim A. The use of a cell saver during repair of ruptured abdominal aortic aneurysms increases early survival. Ann R Coll Surg Engl. 2005;87(6):475.
221. Shuhaiber JH, Whitehead SM. The impact of introducing an autologous intraoperative transfusion device to a community hospital. Ann Vasc Surg. 2003;17(4):424-9.
222. Posacioglu H, Apaydin AZ, Islamoglu F, Calkavur T, Yagdi T, Atay Y, et al. Adverse effects of cell saver in patients undergoing ruptured abdominal aortic aneurysm repair. Ann Vasc Surg. 2002;16(4):450-5.

Appendix A – Literature search results

See Volume 2 of the Technical Report

Appendix B – Literature screening results

See Volume 2 of the Technical Report

Appendix C – List of excluded studies

See Volume 2 of the Technical Report

Appendix D – Critical appraisal

See Volume 2 of the Technical Report

Appendix E – Data extraction forms

See Volume 3 of the Technical Report