

Supporting Information 1

Supplementary material

This appendix was part of the submitted manuscript and has been peer reviewed. It is posted as supplied by the authors.

Appendix to: Mitra B, Jorgensen M, Reade MC, et al. Patient blood management guideline for adults with critical bleeding. *Med J Aust* 2024; doi: 10.5694/mja2.52212.

Supplementary Material

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

Literature search date: 29 September 2021

R1: In patients with critical bleeding, it is recommended that institutions use a major haemorrhage protocol that includes a multidisciplinary approach to haemorrhage control, correction of coagulopathy and normalisation of physiological derangement.

Evidence to decision

| Benefits and harms | Substantial net benefits of the recommended alternative | | | | | | | |
|--|--|--|--|--|--|--|--|--|
| In the meta-analysis of observational cohort studies that include trauma settings, a large effect on mortality (latest timepoint or a unknown due to a very low certainty of evidence. A low certaint | ll-cause) was demonstrated. The true benefits are | | | | | | | |
| | | | | | | | | |
| Certainty of the Evidence | Very low | | | | | | | |
| The overall certainty in effect estimates across outcomes was eith | er very low (benefits) or low (harms). | | | | | | | |
| | | | | | | | | |
| Values and preferences | No substantial variability expected | | | | | | | |
| There is no plausible reason to suspect that patients who are critically bleeding would not accept treatment via an MH as recommended. A subgroup of patients may decline blood components based on personal preference. | | | | | | | | |
| | | | | | | | | |
| | | | | | | | | |
| Resources | Important issues, or potential issues not investigated | | | | | | | |
| Resources In the absence of high certainty evidence, the resource implication | investigated | | | | | | | |
| | investigated | | | | | | | |
| | investigated | | | | | | | |
| In the absence of high certainty evidence, the resource implication | investigated ns of an MHP are uncertain. Important issues, or potential issues not investigated | | | | | | | |
| In the absence of high certainty evidence, the resource implication Equity It is acknowledged that there is jurisdictional, geographical and/or | investigated ns of an MHP are uncertain. Important issues, or potential issues not investigated | | | | | | | |
| In the absence of high certainty evidence, the resource implication Equity It is acknowledged that there is jurisdictional, geographical and/or | investigated ns of an MHP are uncertain. Important issues, or potential issues not investigated | | | | | | | |

Acceptability of an MHP was not investigated.

Feasibility

Important issues, or potential issues not investigated

The reference group acknowledged the logistical challenges associated with implementing an MHP to treat patients who are critically bleeding. Adaptation of this guidance at a local level is required upon consideration of the resources available.

Rationale

Practical benefits of an MHP include:

- allowing blood bank to anticipate needs and provide blood components and products quickly.
- optimising timing of delivery of blood components and products
- optimising administration of blood components and products

Figure S1: Forest plot of comparison: MHPs vs no MHPs, outcome: Mortality, latest timepoint

| | MHF | , | no Mł | ΗP | | Odds Ratio | Odds Ratio |
|--|-------------------------|-------|--------|-------|--------|--------------------|----------------------------|
| Study or Subgroup | Events | Total | Events | Total | Weight | M-H, Random, 95% C | I M-H, Random, 95% CI |
| .2.1 Trauma setting | | | | | | | |
| Brinck 2016 (Coh, truama) | 35 | 206 | 39 | 146 | 4.8% | 0.56 [0.34, 0.94] | |
| Campion 2013 (Coh, trauma) | 27 | 99 | 42 | 117 | 4.5% | 0.67 [0.37, 1.20] | |
| Cotton 2008 (Coh, trauma) | 77 | 117 | 48 | 94 | 4.6% | 1.84 [1.06, 3.22] | |
| Cotton 2009 (Coh, trauma) | 54 | 125 | 88 | 141 | 5.0% | 0.46 [0.28, 0.75] | |
| Pente 2009 (Coh, trauma) | 25 | 73 | 46 | 84 | 4.1% | 0.43 [0.23, 0.82] | |
| 0 Dirks 2010 (Coh, trauma) | 47 | 156 | 24 | 97 | 4.5% | 1.31 [0.74, 2.33] | - +- |
| Duchesne 2010 (Coh, trauma) | 19 | 72 | 56 | 124 | 4.2% | 0.44 [0.23, 0.82] | |
| lwang 2018 (Coh, trauma) | 43 | 126 | 35 | 64 | 4.3% | 0.43 [0.23, 0.79] | |
| ohansson 2009 (Coh, trauma) | 17 | 50 | 46 | 82 | 3.7% | 0.40 [0.19, 0.84] | |
| laciel 2015 (Coh, trauma) | 9 | 17 | 25 | 29 | 1.6% | 0.18 [0.04, 0.75] | |
| oorman 2016 (Coh, trauma) | 10 | 144 | 13 | 57 | 3.0% | 0.25 [0.10, 0.62] | |
| lunn 2017 (Coh, trauma) | 83 | 208 | 113 | 239 | 5.6% | 0.74 [0.51, 1.08] | |
| 'Keeffe 2008 (Coh, trauma) | 69 | 132 | 23 | 46 | 4.0% | 1.10 [0.56, 2.14] | _ _ |
| iskin 2009 (Coh, trauma) | 7 | 37 | 18 | 40 | 2.6% | 0.29 [0.10, 0.80] | |
| haz 2010 (Coh, trauma) | 63 | 132 | 42 | 84 | 4.7% | 0.91 [0.53, 1.58] | |
| immons 2010 (Coh, trauma) | 81 | 426 | 84 | 351 | 5.8% | 0.75 [0.53, 1.05] | |
| inha 2013 (Coh, trauma) | 24 | 83 | 16 | 69 | 3.7% | 1.35 [0.65, 2.81] | |
| isak 2012 (Coh, trauma) | 13 | 28 | 12 | 30 | 2.5% | 1.30 [0.46, 3.68] | |
| an der Meij 2019 (Coh, trauma) | 14 | 47 | 16 | 54 | 3.2% | 1.01 [0.43, 2.37] | |
| ubtotal (95% CI) | | 2278 | | 1948 | 76.7% | 0.67 [0.53, 0.85] | ◆ |
| otal events | 717 | | 786 | | | | |
| eterogeneity: Tau ² = 0.16; Chi ² = 48.19, df = 18 (P = 0.0 | 0001); l ² = | 63% | | | | | |
| est for overall effect: Z = 3.30 (P = 0.0010) | | | | | | | |
| 2.2 Mixed trauma and non-trauma setting | | | | | | | |
| alvers 2015 (RCoh, 9% trauma, 63% surgical) | 124 | 355 | 65 | 192 | | 1.05 [0.72, 1.52] | |
| ubtotal (95% CI) | | 355 | | 192 | 5.7% | 1.05 [0.72, 1.52] | • |
| otal events | 124 | | 65 | | | | |
| leterogeneity: Not applicable | | | | | | | |
| est for overall effect: $Z = 0.25$ (P = 0.80) | | | | | | | |
| 2.3 Non-trauma setting | | | | | | | |
| utta 2017 (RCoh, Obstetrics) | 0 | 23 | 0 | 39 | | Not estimable | |
| phansson 2007 (RCoh, ruptured AAA) | 17 | 50 | 46 | 82 | 3.7% | 0.40 [0.19, 0.84] | |
| artinez-Calle 2016 (RCoh, surgical & nonsurgical) (1) | 12 | 92 | 29 | 96 | 3.7% | 0.35 [0.16, 0.73] | — — |
| IcDaniel 2013 (RCoh, non-trauma) | 13 | 26 | 16 | 38 | 2.7% | 1.38 [0.50, 3.75] | |
| ubtotal (95% CI) | | 191 | | 255 | 10.1% | 0.54 [0.25, 1.15] | |
| otal events | 42 | | 91 | | | | |
| leterogeneity: Tau² = 0.27; Chi² = 5.17, df = 2 (P = 0.08) | ; l² = 61% | | | | | | |
| est for overall effect: Z = 1.60 (P = 0.11) | | | | | | | |
| 2.4 Paediatric setting | | | | | | | |
| hidester 2012 (Coh, paediatric trauma) | 15 | 33 | 10 | 22 | 2.4% | 1.00 [0.34, 2.95] | |
| lendrickson 2012 (Coh, paediatric trauma) | 20 | 53 | 11 | 49 | 3.1% | 2.09 [0.88, 5.00] | ├ |
| lwu 2016 (Coh, paediatric trauma) | 8 | 17 | 14 | 26 | 2.0% | 0.76 [0.22, 2.59] | |
| ubtotal (95% CI) | | 103 | | 97 | 7.6% | 1.31 [0.71, 2.42] | — |
| otal events leterogeneity: Tau ² = 0.01; Chi ² = 2.10, df = 2 (P = 0.35) est for overall effect: Z = 0.88 (P = 0.38) | 43 ; I² = 5% | | 35 | | | | |
| otal (95% CI) | | 2927 | | 2492 | 100.0% | 0.71 [0.57, 0.87] | ◆ |
| otal events | 926 | | 977 | | | | |
| eterogeneity: Tau ² = 0.16; Chi ² = 66.10, df = 25 (P < 0.0 est for overall effect: Z = 3.26 (P = 0.001) | 0001); l² = | 62% | | | | | 0.01 0.1 1 10 |
| |)5) 12 - 60 | 8% | | | | | Favours MHP Favours no MHP |
| Test for subgroup differences: $Chi^2 = 7.66$, $df = 3$ (P = 0.0 | J⊃), I² = 60 | .0% | | | | | |
| | | | | | | | |

Footnotes

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

MHP in Trauma: PICO

Population: People with critical bleeding (trauma setting) Intervention: Defined MHP Comparator: No defined MHP

| Table S1: M | /IHP vs no | MHP in | trauma | setting |
|-------------|------------|--------|--------|---------|
|-------------|------------|--------|--------|---------|

| | | - | | |
|---|---|--|---|---|
| Outcome Timeframe | Study results and measurements | Absolute effect estimates No defined MHP | Certainty of the Evidence (Quality of evidence) | Plain language summary |
| Mortality 24 hours | Odds ratio: 0.79 (Cl 95% 0.56 - 1.11) Based on data from 1030 participants in 6 studies | 296 249 per 1000 per 1000 Difference: 47 fewer per 1000 (CI 95% 105 fewer – 160 fewer) | Very low Due to serious risk of bias, Due to serious imprecision | There is little to no association between a defined MHP and lower 24-hour mortality in people with critical bleeding in the trauma setting, but the evidence is very uncertain. |
| Mortality, all cause latest reported timepoint | Odds ratio: 0.67 (CI 95% 0.53 - 0.85) Based on data from 4226 participants in 19 studies | 403 311 per 1000 per 1000 Difference: 92 fewer per 1000 (Cl 95% 140 fewer - 38 fewer) | Very low Due to serious risk of bias, Due to serious inconsistency | There is a large association between a defined MHP and lower mortality in people with critical bleeding in the trauma setting but the evidence is very uncertain. |
| Red blood cell transfusion volume | Measured by: Number of Units Lower better Based on data from 2493 participants in 10 studies | 12-25 11.8-24 Difference: SMD 0.13 fewer (CI 95% 0.33 fewer - 0.07 more) | Very low Due to serious risk of bias, Due to very serious inconsistency, Due to serious imprecision | A defined MHP may reduce volume of red blood cells transfused but the evidence is very uncertain and MHPs can be overactivated leading to wastage. |

MHP in non-trauma: PICO

Population: People with critical bleeding (non-trauma setting) Intervention: Defined MHP Comparator: No defined MHP

Table S2: MHP vs no MHP in non-trauma setting

| | Study results and measurements | Absolute effect estimates | | Certainty of the | | |
|-----------------------|--|--|---------------------------|--|--|--|
| | | No defined MHP | Defined MHP | Evidence (Quality of evidence) | Plain language summary | |
| | Odds ratio: 1.05 (CI 95% 0.35 - 3.12) pe | 99 per 1000 | 103 per 1000 | Very low Due to serious risk of bias. | There is little to no association between | |
| Mortality 24 hours | Based on data from 861 participants in 4 studies | Difference per 2 (CI 95% 6 156 r | L 000 2 fewer - | Due to serious imprecision, Due to serious inconsistency | a defined MHP and lower 24-hour mortality in the non-trauma setting, but the evidence is very uncertain. | |
| Mortality, all cause | Odds ratio: 0.67 (CI 95% 0.35 - 1.29) | 349 per 1000 | 264 per 1000 | Very low | There is little to no association between a defined MHP and lower mortality in | |

| latest reported timepoint | Based on data from 993 participants in 5 studies | Difference: 85 fewer per 1000 (Cl 95% 191 fewer - 60 more) | | fewer per 1000 L (Cl 95% 191 fewer - incol | | Due to serious risk of bias, Due to serious inconsistency, Due to serious imprecision | patients with critical bleeding in the non-trauma setting, but the evidence is very uncertain. |
|---|---|---|---|--|---|--|--|
| Red blood cell transfusion volume | Measured by: Number of Units Lower better Based on data from 462 participants in 4 studies | 0.04 (CI 95% 0. | 12.6 Units (Mean) ce: SMD more 46 fewer - more) | Very low Due to serious risk of bias, Due to serious imprecision, Due to serious inconsistency | An MHP has little or no effect on volume of red blood cels transfused in patients with critical bleeding in the non-trauma setting, but the evidence is very uncertain. | | |

MHP in critical bleeding (any setting: PICO)

Population: People with critical bleeding (any setting) Intervention: Defined MHP Comparator: No defined MHP

Table S3: MHP vs no MHP in any setting

| Outcome Timeframe | Study results and measurements | Absolute eff No defined MHP | ect estimates Defined MHP | Certainty of the Evidence (Quality of evidence) | Plain language summary |
|---|---|--|--|--|---|
| Mortality, all cause latest reported timepoint | Odds ratio: 0.71 (CI 95% 0.57 - 0.87) Based on data from 5419 participants in 27 studies | 10 | 314 per 1000 78 fewer per 000 wer - 33 fewer) | Very low Due to serious risk of bias, Due to serious inconsistency | There is a large association between a defined MHP and lower mortality in people with critical bleeding, but the evidence is very uncertain. |
| FFP transfusion volume | Measured by: Number of Units Lower better Based on data from 2459 participants in 9 studies | | 8-14 MD 0.09 fewer wer - 0.23 more) | Very low Due to serious risk of bias, Due to very serious inconsistency, Due to serious imprecision | A defined MHP may reduce volume of FFP transfused but the evidence is very uncertain and MHPs can be overactivated leading to wastage. |
| Platelet transfusion volume | Measured by: Number of Units Lower better Based on data from 3715 participants in 15 studies | | 1.1-31 MD 0.54 more wer - 1.33 more) | Very low Due to serious risk of bias, Due to very serious inconsistency, Due to serious imprecision | A defined MHP may increase the volume of platelets transfused but the evidence is very uncertain and MHPs can be overactivated leading to wastage. |

Research question: 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?

Literature search date: 29 September 2021

Strong recommendation

R2: In patients with critical bleeding requiring a major haemorrhage protocol, the following parameters should be measured early and frequently*:

- temperature
- acid–base status
- ionised calcium
- haemoglobin
- platelet count
- PT/INR
- APTT
- fibrinogen level

*in addition to standard continuous physiological monitoring.

Evidence to decision

Benefits and harms Identified cohort studies suggest there is an association between prognostic factors and higher risk of mortality. However, the overall certainty of the evidence was low. The true benefits are unknown due to a very low certainty of evidence. Certainty of the Evidence Very low

The overall certainty in the effect across outcomes was either very low (benefits) or low (harms).

Values and preferences

No substantial variability expected

There is no plausible reason to suspect that patients who are critically bleeding would not accept assessment of prognostic factors as recommended.

Resources No important issues with the recommended alternative

Resource implications associated with measuring prognostic factors are likely to be limited given standard laboratory testing is available, with the exception of fibrinogen which may not be considered standard.

| Equity | No important issues with the recommended alternative |
|--|---|
| Equity is unlikely to be impacted as standard laboratory testing is a not be considered standard. | available, with the exception of fibrinogen which may |
| | |
| Acceptability | No important issues with the recommended alternative |
| Acceptability is unlikely to be impacted as standard laboratory test which may not be considered standard. | ting is available, with the exception of fibrinogen |
| | |
| Feasibility | No important issues with the recommended |

Feasibility is unlikely to be impacted as standard laboratory testing is available, with the exception of fibrinogen which may not be considered standard.

alternative

Rationale

The early identification and management of derangement in the above parameters may prevent the development or worsening of the lethal triad (hypothermia, coagulopathy, acidosis).

Temperature and critical bleeding in any setting: PICO

Population: People with critical bleeding (any setting) Intervention: Temperature Comparator: N/A

Table S4: Temperature and outcomes

| Outcome | Study results and | d Absolute effect estimates | | Certainty of the Evidence | Plain language |
|---|---|---|--|--|---|
| Timeframe | measurements N/A | | Temperature | (Quality of evidence) | summary |
| Mortality, all cause latest reported timepoint | Based on data from 707803 participants in 4 studies | between hy increased risk hours (OR ran at 30-days | und an association pothermia and an of mortality at 24- ge 2.7 to 2.72) and (OR range 1.8 to 2.82). | Very low Due to serious risk of bias | Hypothermia (< 35°C) is associated with higher mortality. |

| Transfusion Based on dat volume participants | | Very low Due to serious risk of bias, Due to serious imprecision, Due to serious publication bias | Hypothermia (<35°C) is associated with higher volume of red blood cells transfused. |
|---|--|--|---|
|---|--|--|---|

Acid-base status and critical bleeding in any setting: PICO

Population: People with critical bleeding (any setting) Intervention: Acid-base status Comparator: N/A

Table S5: Acid-base status and outcomes

| Outcome Timeframe | Study results and measurements | Absolute ef N/A | fect estimates Acid-base status | Certainty of the Evidence (Quality of evidence) | Plain language summary |
|---|---|---|--|--|--|
| Mortality, all cause latest reported timepoint | Based on data from 41328 participants in 14 studies | Studies report an association between high lactate levels and increased risk of mortality. The OR varied across studies depending on lactate levels. At lactate levels > 4 mmol/L the OR ranged between 3.8 and 10.58 | | Very low Due to serious risk of bias ¹ | Higher lactate levels are associated with higher mortality. |
| Transfusion volume | Based on data from 1193 participants in 6 studies | Studies found an association between increased lactate levels and increased volume of red | | Very low Due to serious risk of bias, Due to serious imprecision, Due to serious publication bias | Higher lactate levels are associated with higher volume of red blood cells transfused. |

Calcium levels and critical bleeding in any setting: PICO

Population: People with critical bleeding (any setting) Intervention: Ionised calcium Comparator: N/A

Table S6: Calcium and outcomes

| Outcome | Outcome Study results and | | fect estimates | Certainty of the Evidence | Plain language |
|---|---|---|--------------------|---|--|
| Timeframe | measurements | N/A | lonised calcium | (Quality of evidence) | summary |
| Mortality, all cause latest reported timepoint | Based on data from 1373 participants in 4 studies | A significant association between low ionised calcium levels and mortality observed (OR 1.87; 95% CI 1.27, 2.75; P = 0.001; random effects, 12= 0%) | | Very low Due to serious risk of bias, Due to serious imprecision | Hypocalcaemia (<1mmol/L ionised calcium) is associated with higher mortality. |
| Red blood cell transfusion volume | Based on data from 977 participants in 3 studies | Data from one study suggested a significant association between low ionised calcium levels and increased volume of red blood cells transfused within 24 hours | | Very low Due to serious risk of bias, Due to serious imprecision | Hypocalcaemia (<1 mmol/L ionised calcium) is associated with higher volume of red blood cells transfused. |

| | | 5 or >10 units of red blood cells transfused). | | |
|--|--|---|---|--|
| Transfusion volume, other blood products | Based on data from 160 participants in 1 studies | Data from one study suggested a significant association between low ionised calcium levels reported and increased volume of plasma (P = 0.007) and cryoprecipitate (P = 0.0003) transfused within 24 hours. | Very low Due to serious risk of bias, Due to serious imprecision | Hypocalcaemia (<1mmol/L ionised calcium) is associated with higher volume of blood products (red blood cells, plasma and cryoprecipitate) transfused. |

Haemoglobin levels and critical bleeding in any setting: PICO

Population: People with critical bleeding (any setting) Intervention: Haemoglobin Comparator: N/A

Table S7: Haemoglobin levels and outcomes

| Outcome | Study results and | Absolute effect estimates | | Certainty of the Evidence | Plain language | |
|---|---|--|---|--|--|--|
| Timeframe | measurements | N/A | Haemoglobin | (Quality of evidence) | summary | |
| Mortality, all cause latest reported timepoint | | the assoc haemoglob | o studies assessing iation between vin and mortality n the literature. | | No studies were found that looked at all-cause mortality. | |
| Transfusion volume | Based on data from 2349 participants in 5 studies | Studies reported a significant association between lower haemoglobin levels (< 11 g/L) and an increased risk of massive | | Very low Due to serious risk of bias, Due to serious indirectness, Due to serious imprecision | Lower haemoglobin levels are associated with increased volume of red blood cells transfused. | |

Platelet counts and critical bleeding in any setting: PICO

Population: People with critical bleeding (any setting) Intervention: Platelet count Comparator: N/A

Table S8: Platelet count and outcomes

| Outcome Study results and | | Absolute effect estimates | | Certainty of the Evidence | Plain language |
|---|---|--|--|--|---|
| Timeframe measurements | N/A | Platelet count | (Quality of evidence) | summary | |
| Mortality, all cause latest reported timepoint | Based on data from 6762 participants in 5 studies | count and mo Three studie significant asso OR range betw P > 0.5). One st association (adjusted OR 0 suggested incr | between platelet rtality is unclear. es reported no ociation (adjusted een 0.99 and 1.0; sudy suggested an o with survival .5) and one study eased prediction usted OR 1.097) | Very low Due to serious risk of bias, Due to serious imprecision, Due to serious inconsistency | The association between platelet count and mortality is uncertain. |

| Transfusion volume | Based on data from 30735 participants in 7 studies | Included studies used different measurements to trigger transfusion. Different platelet doses per transfusion were administered in all studies, ranging from 1 to 6-12 units. Heterogeneity between studies was so substantial that quantitative synthesis was not possible. | Very low Due to serious risk of bias, Due to serious imprecision | Lower platelet counts are associated with higher volume of red blood cells transfused. | |
|-----------------------|--|---|---|--|--|
|-----------------------|--|---|---|--|--|

INR/PT and critical bleeding in any setting: PICO

Population: People with critical bleeding (any setting) Intervention: PT/INR Comparator: N/A

Table S9: INR/PT and outcomes

| Outcome | Study results and | Absolute effect estimates | | Certainty of the Evidence | Plain language |
|---|--|---|--|---|--|
| Timeframe | measurements | | | (Quality of evidence) | summary |
| Mortality, all cause latest reported timepoint | Based on data from 50466 participants in 7 studies | Seven studies reported an association between high PT/INR levels and mortality in the trauma setting (adjusted OR ranged between 1.35 to 3.23). | | Very low Due to serious risk of bias, Due to serious imprecision | Abnormal PT/INR (INR >1.2) is associated with higher mortality. |
| Transfusion volume | Based on data from participants in 3 studies | Studies found an association between high PT/INR levels and | | Very low Due to serious risk of bias, Due to serious indirectness | Abnormal PT/INR (>1.2) is associated with higher volume of red blood cells transfused. |

APTT and critical bleeding in any setting: PICO

Population: People with critical bleeding (any setting) Intervention: APTT Comparator: N/A

Table S10: aPTT and outcomes

| Outcome | Outcome Study results and | | ect estimates | Certainty of the Evidence | Plain language | |
|---|---|--|---------------|---|---|--|
| Timeframe | measurements | N/A APTT | | (Quality of evidence) | summary | |
| Mortality, all cause latest reported timepoint | Based on data from 9516 participants in 6 studies | Five studies reported an association between high APTT levels and mortality (4 studies reported OR range 1.01 and 4.26, one study reported no risk data). | | Very low Due to serious risk of bias, Due to serious imprecision | Higher APTT levels are associated with higher mortality. | |
| Transfusion volume | Based on data from participants in 2 studies | Studies reported an association between high APTT levels and the need for increased transfusion volume. No risk data reported. | | Very low Due to serious risk of bias, Due to serious imprecision | Higher APTT levels are associated with higher volume of red blood cells transfused. | |

Fibrinogen count and critical bleeding in any setting: PICO

Population: People with critical bleeding (any setting) Intervention: Fibrinogen levels Comparator: N/A

Table S11: Fibrinogen count and outcomes

| Outcome Study results and | | Absolute ef | fect estimates | Certainty of the Evidence | Plain language |
|---|---|--|----------------------|--|--|
| Timeframe | measurements | N/A | Fibrinogen levels | (Quality of evidence) | summary |
| Mortality, all cause latest reported timepoint | Based on data from 9714 participants in 6 studies | Five studies reported an association between low fibrinogen levels and survival (adjusted OR range 0.08 to 0.22) or mortality (adjusted OR range 1.29 and 12.5). One study suggested a correlation with mortality but did not provide any data | | Very low Due to serious risk of bias, Due to serious imprecision | Lower fibrinogen levels are associated with higher mortality. |
| Transfusion volume | Based on data from 625 participants in 5 studies | Four studies reported an association between low fibrinogen levels and transfusion volume (one study reported OR | | Very low Due to serious risk of bias, Due to serious imprecision, Due to serious publication bias | Lower fibrinogen levels are associated with higher volume of red blood cells transfused. |

A ratio of 2:1:1 of RBC:FFP:PLT is lower than a ratio of 1:1:1, as the number of units of red blood cells increases without a proportionate increase in FFP or platelets.

Research questions: In patients with critical bleeding, what is the optimal dose, timing and ratio (algorithm) to red blood cells, of blood component therapy to reduce morbidity, mortality and transfusion?

Literature search date: 29 September 2021

| Weak recommendation | |
|---|---|
| | reding, the implementation of a major haemorrhage protocol with a high ratio of al, although there is insufficient evidence to support a 1:1:1 ratio over a 2:1:1 ratio^. |
| *1 adult unit of apheresis or p donor units. | ooled platelets in Australia is equivalent to platelets derived from 4 single whole blood |
| ^A ratio of 2:1:1 of RBC:FFP:Pl a proportionate increase in FF | T is lower than a ratio of 1:1:1, as the number of units of red blood cells increases without P or platelets. |

Evidence to decision

| Benefits and harms | Small net benefit, or little difference between alternatives |
|---|--|
| In the meta-analysis of RCTs comparing 1:1:1 versus 2:1:1 ratios, no meta-analysis of observational cohort studies a large effect on mort the evidence was very low. Based on the available evidence the true In the meta-analysis of RCTs, thromboembolic events and MOF rate higher ratios of blood components or products compared to those v evidence the harms are not known. | tality was demonstrated, however, the certainty of e benefit is unknown. es did not differ among populations that received |
| Certainty of the Evidence | Very low |
| The overall certainty in effect estimates across outcomes was eithe | r very low (benefits) or low (harms). |
| Values and preferences | No substantial variability expected |
| There is no plausible reason to suspect that patients who are critica components as recommended. A subgroup of patients may decline | |
| Resources | Important issues, or potential issues not investigated |
| In the absence of high certainty evidence, the resource implications | s of 1:1:1 ratio of blood components are uncertain. |
| Equity | Important issues, or potential issues not investigated |
| The reference group acknowledged that there is jurisdictional, geog availability of blood components. | graphical and/or institutional variability in the |
| Acceptability | No important issues with the recommended |
| | alternative |
| The acceptability of a ratio at least 2:1:1 of RBC:FFP:PLT was not inv | restigated. |

Feasibility

The reference group acknowledged the logistical challenges associated with providing ratios of blood components to treat patients who are critically bleeding. Adaptation of this guidance at a local level is required upon consideration of the resources available.

Rationale

The evidence supports a ratio of 2:1:1.

Figure S2: Forest plot of comparison: high ratio vs low ratio blood components on mortality at latest timepoint

| | High ratio (| | Low ratio (| | | Risk Ratio | Risk Ratio |
|--|---|--|--|--|---------------------------------------|--|---------------------|
| Study or Subgroup | Events | Total | Events | Total | Weight | M-H, Random, 95% Cl | M-H, Random, 95% Cl |
| .1.1 Trauma (RCTs) | | | | | | | |
| Holcomb 2015 (RCT) | 75 | 338 | 89 | 342 | 5.9% | 0.85 [0.65, 1.11] | - |
| Nascimento 2013 (RCT) | 13 | 40 | 5 | 35 | 2.9% | 2.27 [0.90, 5.74] | |
| Subtotal (95% CI) | | 378 | | 377 | 8.8% | 1.26 [0.49, 3.22] | |
| otal events | 88 | | 94 | | | | |
| Heterogeneity: Tau ² = 0.30 | | | P = 0.05); I ² = | = 75% | | | |
| Test for overall effect: Z = | 0.47 (P = 0.64 | 4) | | | | | |
| 1.1.2 Trauma (observatio | onal) | | | | | | |
| Duchesne 2008 | 18 | 71 | 56 | 64 | 5.2% | 0.29 [0.19, 0.44] | |
| Duchesne 2009 | 13 | 46 | 22 | 43 | 4.5% | 0.55 [0.32, 0.95] | _ . |
| laltmeier 2017 | 53 | 156 | 46 | 86 | 5.8% | 0.64 [0.47, 0.85] | |
| lolcomb 2011 | 65 | 216 | 101 | 211 | 6.0% | 0.63 [0.49, 0.81] | - |
| laegele 2008 | 28 | 115 | 220 | 484 | 5.6% | 0.54 [0.38, 0.75] | |
| Perkins 2009 | 15 | 96 | 86 | 150 | 4.8% | 0.27 [0.17, 0.44] | |
| Sambasivan 2011 | 47 | 202 | 126 | 979 | 4.8% 5.8% | 1.81 [1.34, 2.44] | |
| /ulliamy 2017 | 25 | 107 | 120 | 54 | 5.8% 4.5% | 0.84 [0.49, 1.46] | _ _ |
| | | 210 | | | | | |
| Vafaisade 2011 | 31 | | 194 | 760 | 5.5% | 0.58 [0.41, 0.82] | |
| Zink 2009 Subtotal (95% CI) | 13 | 51 1270 | 56 | 102 2933 | 4.8% 52.6% | 0.46 [0.28, 0.77] 0.58 [0.41, 0.82] | |
| | | 1270 | | 2933 | 52.0% | 0.56 [0.41, 0.62] | • |
| otal events | 308 | | 922 | | | | |
| Heterogeneity: Tau ² = 0.26 Fest for overall effect: Z = | | | (P < 0.00001 |); I ² = 88 | % | | |
| 1.1.3 Surgical (observati Hall 2013 | ional) 21 | 68 | 6 | 21 | 3.5% | 1.08 [0.50, 2.32] | |
| Henriksson 2012 | 21 | 100 | 23 | 74 | 3.5% 4.7% | 0.64 [0.38, 1.08] | |
| Johansson 2007 | 17 | 50 | 46 | 82 | 4.7 % 5.1% | 0.61 [0.39, 0.93] | |
| Johansson2008 | 16 | 50 64 | 46 | 82 | 5.1% 4.9% | 0.45 [0.28, 0.71] | |
| Mell 2010 | | 87 | | | | | |
| | 13 | 87 | 16 6 | 41 8 | 4.1% | 0.38 [0.20, 0.72] | |
| adlock 2010 | 1 | | | | 1.2% | 0.33 [0.06, 1.91] | ▲ |
| | | | 0 | | 22 E9/ | 0 56 10 42 0 721 | ▲ |
| | | 373 | | 308 | 23.5% | 0.56 [0.43, 0.72] | • |
| Total events | 88 | 373 | 143 | 308 | 23.5% | 0.56 [0.43, 0.72] | • |
| Fotal events Heterogeneity: Tau² = 0.02 | 88 2; Chi² = 5.91, | 373 , df = 5 (P | 143 | 308 | 23.5% | 0.56 [0.43, 0.72] | • |
| Fotal events Heterogeneity: Tau² = 0.02 | 88 2; Chi² = 5.91, | 373 , df = 5 (P | 143 | 308 | 23.5% | 0.56 [0.43, 0.72] | • |
| Total events Heterogeneity: Tau² = 0.0 Test for overall effect: Z = | 88 2; Chi² = 5.91, 4.37 (P < 0.00 | 373 , df = 5 (P | 143 | 308 | 23.5% | 0.56 [0.43, 0.72] | • |
| Fotal events Heterogeneity: Tau ² = 0.02 Fest for overall effect: Z = 1.1.4 Paediatrics (observ | 88 2; Chi² = 5.91, 4.37 (P < 0.00 | 373 , df = 5 (P | 143 | 308 | 23.5% 5.9% | 0.56 [0.43, 0.72] 0.75 [0.57, 0.99] | ◆ |
| Fotal events Heterogeneity: Tau ² = 0.02 Fest for overall effect: Z = 1.1.4 Paediatrics (observ Butler 2019 | 88 2; Chi² = 5.91, 4.37 (P < 0.00 vational) | 373 , df = 5 (F 001) | 143 P = 0.32); I ² = | 308 = 15% | | | • |
| Fotal events Heterogeneity: Tau ² = 0.02 Fest for overall effect: Z = 1.1.4 Paediatrics (observ Butler 2019 Cunningham 2019 | 88 2; Chi² = 5.91, 4.37 (P < 0.00 vational) 46 | 373 , df = 5 (F 001) 136 | 143 P = 0.32); I ² = 104 | 308 = 15% 232 | 5.9% | 0.75 [0.57, 0.99] | |
| Total events Heterogeneity: Tau ² = 0.02 Test for overall effect: Z = 1.1.4 Paediatrics (observation) Suttler 2019 Cunningham 2019 Voland 2018 | 88 2; Chi ² = 5.91, 4.37 (P < 0.00 vational) 46 15 | 373 , df = 5 (F 001) 136 126 | 143 P = 0.32); I ² = 104 38 | 308 = 15% 232 163 | 5.9% 4.5% | 0.75 [0.57, 0.99] 0.51 [0.29, 0.89] | |
| otal events leterogeneity: Tau ² = 0.02 rest for overall effect: Z = .1.4 Paediatrics (observa- Butter 2019 Sunningham 2019 Joland 2018 Josanov 2013 | 88 2; Chi ² = 5.91, 4.37 (P < 0.00 vational) 46 15 6 | 373 , df = 5 (F 001) 136 126 39 | 143 P = 0.32); I ² = 104 38 10 | 308 = 15% 232 163 35 | 5.9% 4.5% 3.0% | 0.75 [0.57, 0.99] 0.51 [0.29, 0.89] 0.54 [0.22, 1.33] | |
| otal events leterogeneity: Tau ² = 0.02 rest for overall effect: Z = .1.4 Paediatrics (observ Butler 2019 Cunningham 2019 Joland 2018 Josanov 2013 Subtotal (95% CI) | 88 2; Chi ² = 5.91, 4.37 (P < 0.00 vational) 46 15 6 | 373 , df = 5 (F 001) 136 126 39 34 | 143 P = 0.32); I ² = 104 38 10 | 308 = 15% 232 163 35 15 | 5.9% 4.5% 3.0% 1.7% | 0.75 [0.57, 0.99] 0.51 [0.29, 0.89] 0.54 [0.22, 1.33] 2.43 [0.61, 9.63] | |
| Total events Heterogeneity: Tau ² = 0.02 Test for overall effect: Z = .1.4 Paediatrics (observ Butler 2019 Cunningham 2019 Voland 2018 Nosanov 2013 Subtotal (95% CI) Total events | 88 2; Chi ² = 5.91, 4.37 (P < 0.00 vational) 46 15 6 11 78 | 373 , df = 5 (F 001) 136 126 39 34 335 | 143 P = 0.32); l ² = 104 38 10 2 154 | 308 = 15% 232 163 35 15 445 | 5.9% 4.5% 3.0% 1.7% | 0.75 [0.57, 0.99] 0.51 [0.29, 0.89] 0.54 [0.22, 1.33] 2.43 [0.61, 9.63] | |
| Fotal events Heterogeneity: Tau ² = 0.02 Fest for overall effect: Z = 1.1.4 Paediatrics (observ Butler 2019 Cunningham 2019 Noland 2018 Nosanov 2013 Subtotal (95% CI) Fotal events Heterogeneity: Tau ² = 0.00 | 88 2; Chi ² = 5.91, 4.37 (P < 0.00 vational) 46 15 6 11 78 6; Chi ² = 4.98, | 373 df = 5 (F 001) 136 126 39 34 335 df = 3 (F | 143 P = 0.32); l ² = 104 38 10 2 154 | 308 = 15% 232 163 35 15 445 | 5.9% 4.5% 3.0% 1.7% | 0.75 [0.57, 0.99] 0.51 [0.29, 0.89] 0.54 [0.22, 1.33] 2.43 [0.61, 9.63] | |
| Fotal events Heterogeneity: Tau ² = 0.02 Fest for overall effect: Z = 1.1.4 Paediatrics (observ Butler 2019 Cunningham 2019 Noland 2018 Nosanov 2013 Subtotal (95% CI) Fotal events Heterogeneity: Tau ² = 0.00 Fest for overall effect: Z = | 88 2; Chi ² = 5.91, 4.37 (P < 0.00 vational) 46 15 6 11 78 6; Chi ² = 4.98, | 373 df = 5 (F 001) 136 126 39 34 335 df = 3 (F | 143 P = 0.32); l ² = 104 38 10 2 154 | 308 = 15% 232 163 35 15 445 = 40% | 5.9% 4.5% 3.0% 1.7% | 0.75 [0.57, 0.99] 0.51 [0.29, 0.89] 0.54 [0.22, 1.33] 2.43 [0.61, 9.63] 0.70 [0.47, 1.04] | |
| Total events Heterogeneity: Tau ² = 0.02 Fest for overall effect: Z = 1.1.4 Paediatrics (observ Butler 2019 Cunningham 2019 Noland 2018 Nosanov 2013 Subtotal (95% CI) Fotal events Heterogeneity: Tau ² = 0.00 Fest for overall effect: Z = Fotal (95% CI) | 88 2; Chi ² = 5.91, 4.37 (P < 0.00 vational) 46 15 6 11 78 6; Chi ² = 4.98, 1.77 (P = 0.08 | 373 , df = 5 (F 001) 136 126 39 34 335 , df = 3 (F 8) | 143 P = 0.32); I ² = 104 38 10 2 154 P = 0.17); I ² = | 308 = 15% 232 163 35 15 445 = 40% | 5.9% 4.5% 3.0% 1.7% 15.1% | 0.75 [0.57, 0.99] 0.51 [0.29, 0.89] 0.54 [0.22, 1.33] 2.43 [0.61, 9.63] | |
| otal events leterogeneity: Tau ² = 0.0: est for overall effect: Z = .1.4 Paediatrics (observ- tutier 2019 cunningham 2019 loland 2018 losanov 2013 ubtotal (95% CI) otal events leterogeneity: Tau ² = 0.00 est for overall effect: Z = otal (95% CI) otal events | 88 2; Chi ² = 5.91, 4.37 (P < 0.00 vational) 46 15 6 11 78 6; Chi ² = 4.98, 1.77 (P = 0.08 | 373 df = 5 (F 001) 136 126 39 34 335 df = 3 (F 8) 2356 | 143 P = 0.32); I ² = 104 38 10 2 154 P = 0.17); I ² = 1313 | 308 = 15% 232 163 35 15 445 = 40% 4063 | 5.9% 4.5% 3.0% 1.7% 15.1% | 0.75 [0.57, 0.99] 0.51 [0.29, 0.89] 0.54 [0.22, 1.33] 2.43 [0.61, 9.63] 0.70 [0.47, 1.04] | |
| Subtotal (95% CI) Total events Heterogeneity: Tau ² = 0.0; Test for overall effect: Z = 1.1.4 Paediatrics (observ Butler 2019 Cunningham 2019 Noland 2018 Nosanov 2013 Subtotal (95% CI) Total events Heterogeneity: Tau ² = 0.0; Total (95% CI) Total events Heterogeneity: Tau ² = 0.1; Total events Heterogeneity: Tau ² = 0.1; Total events Heterogeneity: Tau ² = 0.1; Total events | 88 2; Chi ² = 5.91, 4.37 (P < 0.00 vational) 46 15 6 11 78 6; Chi ² = 4.98, 1.77 (P = 0.05 562 7; Chi ² = 101.1 | 373 df = 5 (F 001) 136 126 39 34 335 df = 3 (F 8) 2356 13, df = 2 | 143 P = 0.32); I ² = 104 38 10 2 154 P = 0.17); I ² = 1313 | 308 = 15% 232 163 35 15 445 = 40% 4063 | 5.9% 4.5% 3.0% 1.7% 15.1% | 0.75 [0.57, 0.99] 0.51 [0.29, 0.89] 0.54 [0.22, 1.33] 2.43 [0.61, 9.63] 0.70 [0.47, 1.04] | |

Ratio of blood components in trauma: PICO

Population: People with critical bleeding (trauma setting) Intervention: High ratio (1:1:1) of blood components Comparator: Lower ratios of blood components

Table S12: Ratio of blood components and outcomes in trauma setting

| | | Absolute effect estimates | | |
|--|---|--|--|--|
| Outcome Timeframe | Study results and measurements | Lower ratios of blood components components | Certainty of the Evidence (Quality of evidence) | Plain language summary |
| Mortality, all cause (RCTs) latest reported timepoint | Relative risk: 1.26 (CI 95% 0.49 - 3.22) Based on data from 755 participants in 2 studies | 249 314 per 1000 per 1000 Difference: 65 more per 1000 (Cl 95% 127 fewer - 553 more) | Very low Due to very serious inconsistency, Due to very serious imprecision | High (1:1:1) RBC:FFP:PLT ratio may result in little or no difference in mortality in trauma patients with critical bleeding but we are very uncertain about the evidence. |
| Mortality, all cause (Coh) latest reported timepoint | Odds ratio: 0.38 (CI 95% 0.22 - 0.69) Based on data from 4203 participants in 10 studies | 314 148 per 1000 per 1000 Difference: 166 fewer per 1000 (CI 95% 223 fewer - 74 fewer) | Very low Due to serious risk of bias, Due to very serious inconsistency | High (1:1:1) RBC:FFP:PLT ratio may reduce mortality in trauma patients with critical bleeding but we are very uncertain about the evidence. |
| Morbidity, thromboembolic events | Relative risk: 1.07 (CI 95% 0.7 - 1.63) Based on data from 680 participants in 1 studies | 108 116 per 1000 per 1000 Difference: 8 more per 1000 (Cl 95% 32 fewer - 68 more) | Low Due to very serious imprecision | High (1:1:1) RBC:FFP:PLT ratio may have little or no difference on thromboembolic events in trauma patients with critical bleeding. |
| Morbidity, MOF | Relative risk: 1.39 (CI 95% 0.74 - 2.64) Based on data from 749 participants in 2 studies | 40 56 per 1000 per 1000 Difference: 16 more per 1000 (Cl 95% 10 fewer - 66 more) | Low Due to very serious imprecision | High (1:1:1) RBC:FFP:PLT ratio may have little or no difference on MOF in trauma patients with critical bleeding. |
| Red blood cell transfusion volume | Measured by: Number of Units Lower better Based on data from 749 participants in 2 studies | 9-10.3 7.7-9.7 Difference: SMD 0.1 lower (CI 95% 0.24 lower - 0.05 higher) | Low Due to serious imprecision | High (1:1:1) RBC:FFP:PLT ratio may slightly reduce red blood cell transfusion volume i trauma patients with critical bleeding. |
| Transfusion volume, other blood products | Measured by: Number of Units of FFP transfused Lower better Based on data from 749 participants in 2 studies | 5-5.7 6-7.7 Difference: SMD 0.3 higher (Cl 95% 0.15 higher - 0.44 higher) | Low Due to serious imprecision | High (1:1:1) RBC:FFP:PLT ratio may slightly increase the volume of FFP transfused in trauma patients with critica bleeding. The effect on other blood products is unclear. |

Ratio of blood components in surgical setting: PICO

Population: People with critical bleeding (surgical setting) Intervention: High ratio (1:1:1) of blood components Comparator: Lower ratios of blood components

Table S13: Ratio of blood components and outcomes in surgical setting

| | | Absolute effe | ect estimates | | |
|-------------------------------|--|--|---|--|---|
| Outcome Timeframe | Study results and measurements | Lower ratios of blood components | High ratio (1:1:1) of blood components | Certainty of the Evidence (Quality of evidence) | Plain language summary |
| Mortality, all cause (Coh) | Odds ratio: 0.41 (CI 95% 0.26 - 0.63) | 464 per 1000 | 262 per 1000 | Very low | High (1:1:1) RBC:FFP:PLT ratio may reduce mortality |
| latest reported timepoint | Based on data from 681 participants in 6 studies | Difference: 2 10 (Cl 95% 280 few | • | Due to serious risk of bias | in the surgical setting but the evidence is very uncertain. |

Red cell transfusion volumes and outcomes: PICO

Population: People at risk of critical bleeding (any setting) Intervention: Increased red blood cell transfusion volumes Comparator: Normal red blood cell transfusion volumes

Table S14: Blood volumes and outcomes

| | | Absolute effect estimates | | |
|---|---|--|---|--|
| Outcome Timeframe | Study results and measurements | Normal RBC transfusion volumes Increased RBC transfusion volumes | Certainty of the Evidence (Quality of evidence) | Plain language summary |
| Mortality, all cause (Coh) latest reported timepoint | Based on data from 18009 participants in 9 studies ¹ | The odds of mortality increases with each additional red blood cell unit transfused OR 1.07 (95% Cl 1.04, 1.10) | Very low Due to serious risk of bias, Due to serious inconsistency, Due to serious imprecision | Each additional red blood cell unit transfused is associated with higher mortality. |
| Morbidity, MOF (Coh) Any timepoint | Based on data from 3050 participants in 3 studies | The odds of MOF increases with each additional red blood cell unit transfused OR 1.08 (95% CI 1.02, 1.14). | Very low Due to serious risk of bias, Due to serious inconsistency, Due to serious imprecision | Each additional red blood cell unit transfused is associated with higher risk of MOF. |
| Morbidity, ARDS (Coh) Any timepoint | Based on data from 14136 participants in 2 studies | The odds of ARDS or acute lung injury increases with each additional red blood cell unit transfused OR 1.06 (95% Cl 1.03, 1.10). | Very low Due to serious risk of bias, Due to serious imprecision | Each additional red blood cell unit transfused is associated with higher risk of ARDS or acute lung injury. |

Research question: In patients with critical bleeding, what is the effect of FFP, cryoprecipitate, fibrinogen concentrate, prothrombin complex and/or platelet transfusion on red blood cell transfusion and patient outcomes?

Literature search date: 29 September 2021

Weak recommendation

R4: In patients with critical bleeding, the following initial doses of FFP and platelets are suggested:

- FFP: a minimum 1 unit for every 2 units of red blood cells
 - Platelets * *: a minimum of 1 adult unit for 8 units of red blood cells

*1 adult unit of apheresis or pooled platelets in Australia is equivalent to platelets derived from 4 single whole blood donor units.

Evidence to decision

Benefits and harms

Small net benefit, or little difference between alternatives

The clinical heterogeneity in the trials and studies precludes a strong recommendation on the dose and/or timing of FFP, platelets, prothrombin complex, cryoprecipitate or fibrinogen concentrate. The effect of blood components or blood products is uncertain and therefore makes it difficult to make recommendations with regard to timing and/or dose of fibrinogen concentrate, cryoprecipitate or prothrombin complex for patients who are critically bleeding.

| Certainty of the Evidence | Very low | | | | | | |
|---|---------------------------------------|--|--|--|--|--|--|
| The overall certainty in effect estimates across outcomes was eithe | r very low (benefits) or low (harms). | | | | | | |
| | | | | | | | |
| Values and preferences | No substantial variability expected | | | | | | |
| There is no plausible reason to suspect that patients who are critically bleeding would not accept blood components as recommended. A subgroup of patients may decline blood components based on personal preference. | | | | | | | |

| Resources | Important issues, or potential issues not |
|-----------|---|
| | investigated |

In the absence of high certainty evidence, the effect of blood components on resources (transfusion volume, hospital LOS) is not clear.

| Equity | Important issues, or potential issues not investigated |
|--|---|
| The reference group acknowledged that there is jurisdictional, geopavailability of blood components. | graphical and/or institutional variability in the |
| | |
| Acceptability | Important issues, or potential issues no |

| Feasibility | Important issues, or potential issues not investigated |
|---|---|
| The reference group acknowledged the logistical challenges associate patients who are critically bleeding Adaptation of this guidance at resources available. | |

Rationale

Red blood cell units contain negligible amounts of coagulation factors or platelets.

Figure S3: Forest plot of comparison: FFP vs no FFP on mortality at latest reported timepoint

| | FFF | | No FFP (or vary | /ing) | | Risk Ratio | | Risk Ratio |
|--|--------------|----------|----------------------------|-------|--------|--------------------|------|---|
| Study or Subgroup | Events | Total | Events | Total | Weight | M-H, Random, 95% C | 1 | M-H, Random, 95% CI |
| 1.2.1 RCTs | | | | | | | | |
| Moore 2018 (RCT, trauma) | 10 | 65 | 6 | 60 | 5.0% | 1.54 [0.60, 3.98] | | |
| Sperry 2018 (RCT, trauma) | 68 | 230 | 98 | 271 | 69.2% | 0.82 [0.63, 1.05] | | |
| Subtotal (95% CI) | | 295 | | 331 | 74.2% | 0.95 [0.56, 1.59] | | • |
| Total events | 78 | | 104 | | | | | |
| Heterogeneity: Tau ² = 0.08; Chi ² = | = 1.60, df = | 1 (P = | 0.21); l² = 38% | | | | | |
| Test for overall effect: Z = 0.21 (P | = 0.83) | | | | | | | |
| 1.2.2 Observational | | | | | | | | |
| Holcomb 2017 (Coh, trauma) | 8 | 43 | 14 | 66 | 7.4% | 0.88 [0.40, 1.91] | | |
| Innerhofer 2013 (Coh, trauma) | 6 | 78 | 5 | 66 | 3.4% | 1.02 [0.32, 3.18] | | |
| O'Reilly 2014 (Coh, trauma) | 8 | 79 | 19 | 97 | 7.6% | 0.52 [0.24, 1.12] | | |
| Shackelford 2017 (Coh, trauma) | 6 | 54 | 76 | 332 | 7.4% | 0.49 [0.22, 1.06] | | |
| Subtotal (95% CI) | | 254 | | 561 | 25.8% | 0.65 [0.43, 0.98] | | \bullet |
| Total events | 28 | | 114 | | | | | |
| Heterogeneity: Tau ² = 0.00; Chi ² = | = 2.05, df = | 3 (P = | 0.56); l ² = 0% | | | | | |
| Test for overall effect: Z = 2.05 (P | = 0.04) | | | | | | | |
| Total (95% CI) | | 549 | | 892 | 100.0% | 0.79 [0.64, 0.98] | | ◆ |
| Total events | 106 | | 218 | | | | | |
| Heterogeneity: Tau ² = 0.00; Chi ² = | = 4.91, df = | 5 (P = | 0.43); l ² = 0% | | | | | |
| Test for overall effect: Z = 2.13 (P | = 0.03) | | | | | | 0.01 | 0.1 1 10 10 Favours FFP Favours no FFP |
| Test for subgroup differences: Chi | 2 - 1.24 d | f _ 1 /P | - 0 27) 12 - 10 1 | 07 | | | | Tavouistir Tavouis no FFP |

Test for subgroup differences: $Chi^2 = 1.24$, df = 1 (P = 0.27), $I^2 = 19.1\%$

Figure S4: Forest plot of comparison: Fibrinogen concentrate vs no fibrinogen concentrate (or varying administration of) on mortality at latest reported timepoint)

| Study or Subgroup | FC | Total | No FC (or vary Events | | Woish | Risk Ratio | | Ratio |
|---|-------------|------------|----------------------------|------------|----------------|--|----------------------------------|-----------------------------------|
| Study or Subgroup 5.1.1 Trauma setting (RCTs) | Events | rotal | Events | rotal | weight | M-H, Random, 95% CI | M-H, Rand | lom, 95% Cl |
| | | | | | | | | |
| Nascimento 2016 (RCT, trauma) | 3 | 24 | 2 | 25 | 3.2% | 1.56 [0.29, 8.55] | | |
| Innerhofer 2017 (RCT, trauma) | 5 | 50 | 2 | 44 | 3.5% | 2.20 [0.45, 10.78] | | |
| Lucena 2020 (RCT, trauma) | 5 | 16 | 3 | 16 | 5.2% | 1.67 [0.48, 5.83] | | · · |
| Akbari 2018 (RCT, trauma) | 3 | 30 | 11 | 30 | 5.8% | 0.27 [0.08, 0.88] | | |
| Curry 2018 (RCT, trauma) Subtotal (95% CI) | 10 | 24 144 | 7 | 24 139 | 9.8% 27.5% | 1.43 [0.65, 3.13] 1.12 [0.53, 2.35] | | |
| Total events | 26 | | 25 | | | | | |
| Heterogeneity: Tau ² = 0.32; Chi ² = 7.2 Test for overall effect: $Z = 0.29$ (P = 0. | | (P = 0.1 | 2); l ² = 45% | | | | | |
| 3.1.2 Trauma setting (Coh) | | | | | | | | |
| Nienaber 2011 (Coh, trauma) | 3 | 18 | 2 | 18 | 3.3% | 1.50 [0.28, 7.93] | | · · · · · · |
| Inokuchi 2017 (Coh, trauma) | 17 | 115 | 6 | 109 | 8.4% | 2.69 [1.10, 6.56] | | |
| Schochl 2011 (Coh, trauma) | 6 | 80 | 60 | 601 | 9.5% | 0.75 [0.34, 1.68] | | <u> </u> |
| Almskog 2020 (Coh, trauma) | 23 | 108 | 11 | 108 | 11.6% | 2.09 [1.07, 4.07] | | |
| Wafaisade 2013 (Coh, trauma) | 82 | 294 | 73 | 294 | 19.6% | 1.12 [0.86, 1.47] | | - |
| Subtotal (95% CI) | 02 | 294 615 | /3 | 1130 | 52.3% | 1.39 [0.91, 2.13] | | ◆ |
| Total events | 131 | | 152 | | | | | 1 |
| Heterogeneity: Tau ² = 0.10; Chi ² = 7.3 | 1, df = 4 | (P = 0.1 | 2); l ² = 45% | | | | | 1 |
| Test for overall effect: Z = 1.53 (P = 0. | .13) | | | | | | | |
| 3.1.3 Surgical setting (RCTs) | | | | | | | | |
| Tanaka 2014 (RCT, surgical) (1) | 0 | 10 | 0 | 10 | | Not estimable | | |
| Bilecen 2017 (RCT, surgical) | 2 | 60 | 0 | 60 | 1.1% | 5.00 [0.25, 102.00] | | |
| Rahe-Meyer 2013 (RCT, surgical) | 1 | 29 | 4 | 32 | 2.1% | 0.28 [0.03, 2.33] | | <u> </u> |
| Rahe-Meyer 2016 (RCT, surgical) | 1 | 78 | 5 | 74 | 2.1% | 0.19 [0.02, 1.59] | | <u> </u> |
| Subtotal (95% CI) | | 177 | | 176 | 5.4% | 0.48 [0.08, 2.83] | | |
| Total events | 4 | | 9 | | | | | |
| Heterogeneity: $Tau^2 = 0.97$; $Chi^2 = 3.3$ Test for overall effect: $Z = 0.80$ (P = 0. | | (P = 0.1 | 9); l² = 40% | | | | | |
| 3.1.4 Surgical setting (Coh) | | | | | | | | |
| Rahe-Meyer 2009a (Coh, surgical) | 0 | 10 | 0 | 5 | | Not estimable | | |
| Rahe-Meyer 2009b (Coh, surgical) | 0 | 6 | 2 | 12 | 1.2% | 0.37 [0.02, 6.71] | | |
| Bilicen 2013 (Coh, surgical) Subtotal (95% CI) | 18 | 264 280 | 33 | 881 898 | 13.6% 14.8% | 1.82 [1.04, 3.18] 1.58 [0.65, 3.85] | - | |
| Total events | 18 | | 35 | | | | | |
| Heterogeneity: $Tau^2 = 0.14$; $Chi^2 = 1.1$ Test for overall effect: $Z = 1.01$ (P = 0. | | (P = 0.2 | 29); l ² = 11% | | | | | |
| 3.1.5 Obstetrics and maternity (RCT | īs) | | | | | | | |
| Collins 2017 (RCT, obstetrics) | 0 | 28 | 0 | 27 | | Not estimable | | 1 |
| Wikkelso 2015 (RCT, obstetrics) | 0 | 123 | 0 | 121 | | Not estimable | | |
| Subtotal (95% CI) | | 151 | | 148 | | Not estimable | | |
| Total events | 0 | | 0 | | | | | |
| Heterogeneity: Not applicable Test for overall effect: Not applicable | | | | | | | | |
| 3.1.6 Pediatrics (RCTs) | | | | | | | | |
| Galas 2014 (RCT, paediatrics) (2) Subtotal (95% CI) | 0 | 30 30 | 0 | 33 33 | | Not estimable Not estimable | | |
| Total events | 0 | | 0 | | | | | |
| Heterogeneity: Not applicable | 0 | | - | | | | | 1 |
| Test for overall effect: Not applicable | | | | | | | | |
| Total (95% CI) | | 1397 | | 2524 | 100.0% | 1.26 [0.91, 1.75] | | • |
| Total events | 179 | | 221 | | | | | 1 |
| Heterogeneity: Tau ² = 0.12; Chi ² = 22. | .85, df = 1 | 14 (P = | | | | | 0.005 0.1 | 1 10 20 |
| Test for overall effect: $Z = 1.39$ (P = 0. | | | | | | | | Favours no fibrinogen concentrate |
| Test for subgroup differences: Chi ² = 7 | 1.65, df = | 3 (P = | 0.65), l ² = 0% | | | | . avoure instituegen concentrate | no instituingen concentrate |
| | | | | | | | | |
| Footnotes | | | | | | | | |
| (1) FC vs Platelets | | | | | | | | |

FFP and outcomes: PICO

Population: People with critical bleeding (trauma setting) Intervention: FFP Comparator: No FFP (or varying administration of)

Table S15: FFP and outcomes

| | | Absolute effe | ect estimates | | | |
|----------------------|-----------------------------------|--|---|--|---------------------------|--|
| Outcome Timeframe | Study results and measurements | No FFP (or varying administration of) | FFP (or varying administration of) | Certainty of the Evidence (Quality of evidence) | Plain language summary | |

| Mortality, all cause (RCTs) latest reported timepoint | Relative risk: 0.95 (CI 95% 0.56 - 1.59) Based on data from 626 participants in 2 studies | 314 298 per 1000 per 1000 Difference: 16 fewer per 1000 (Cl 95% 138 fewer - 185 more) | Low Due to serious inconsistency, Due to serious imprecision | The evidence suggests FFP may have little or no effect on 30-day mortality in trauma patients with critical bleeding. |
|--|---|--|--|---|
| Mortality, all cause (Coh) latest reported timepoint | Relative risk: 0.65 (CI 95% 0.43 - 0.98) Based on data from 815 participants in 4 studies | 203 132 per 1000 per 1000 Difference: 71 fewer per 1000 (CI 95% 116 fewer - 4 fewer) | Very low Due to serious risk of bias, Due to serious indirectness, Due to serious imprecision | FFP appears to reduce 30-day mortality in trauma patients with critical bleeding, but the evidence is very uncertain. |
| Morbidity, thromboembolic events | Relative risk: 0.85 (CI 95% 0.29 - 2.5) Based on data from 144 participants in 1 studies | 91 77 per 1000 per 1000 Difference: 14 fewer per 1000 (Cl 95% 65 fewer - 137 more) | Very low Due to serious risk of bias, Due to very serious imprecision | The evidence is very uncertain about the effect of FFP on thromboembolic events in trauma patients with critical bleeding. |
| Morbidity, MOF | Relative risk: 1.76 (CI 95% 0.4 - 7.68) Based on data from 626 participants in 2 studies | 476 838 per 1000 per 1000 Difference: 362 more per 1000 (Cl 95% 286 fewer - 3180 more) | Low Due to serious inconsistency, Due to serious imprecision | FFP may have little to no effect on MOF in trauma patients with critical bleeding, but the evidence is very uncertain. |
| Red blood cell transfusion volume | Based on data from 144 participants in 1 studies | The median (IQR) volume of red blood cells transfused (units to 24 hours) among patients who received FFP was 7 (4, 11) compared with a median volume of 2 (0, 6) among those who did not receive FFP (P = 0.001). | Very low Due to serious risk of bias, Due to serious imprecision | The evidence is very uncertain about the effect of FFP on the volume of red blood cells transfused in trauma patients with critical bleeding. |
| Transfusion volume, other blood products | Based on data from 144 participants in 1 studies | The median (IQR) volume of platelets transfused (units to 24 hours) was higher among patients who received FFP compared with those who did not receive FFP (P = 0.003). There was no significant difference between treatment groups for the volume of fibrinogen concentrate or prothrombin complex transfused (units to 24 hours). | Very low Due to serious risk of bias, Due to very serious imprecision | The evidence is very uncertain about the effect of FFP on the volume of platelets, fibrinogen concentrate or prothrombin complex transfused in trauma patients with critical bleeding. |
| LOS, hospital or ICU Days | Based on data from 144 participants in 1 studies | No significant difference in the median hospital or ICU LOS among patients who received FFP compared to patients who did not. | Very low Due to serious risk of bias, Due to very serious imprecision | The evidence is very uncertain about the effect of FFP on hospital or ICU LOS in trauma patients with critical bleeding. |

Cryoprecipitate and outcomes: PICO

Population: People with critical bleeding (trauma setting) Intervention: Cryoprecipitate Comparator: No cryoprecipitate (or varying administration of)

Figure S5: Forest plot of comparison: CRYO vs no CRYO on mortality at latest timepoint.

| | CRY | 0 | no CRYO (or v | arying) | | Risk Ratio | | | Risk Ratio | • | |
|------------------------------------|-------------|-------|---------------|---------|--------|---------------------|------|------------------|------------|-------------------|-----------|
| Study or Subgroup | Events | Total | Events | Total | Weight | M-H, Random, 95% Cl | | М-Н, | Random, 9 | 95% CI | |
| Curry 2015 (RCT, trauma)) | 2 | 20 | 6 | 21 | 100.0% | 0.35 [0.08, 1.54] | | | | | |
| Total (95% CI) | | 20 | | 21 | 100.0% | 0.35 [0.08, 1.54] | | | | | |
| Total events | 2 | | 6 | | | | | | | | |
| Heterogeneity: Not applicable | Э | | | | | | | | | | 400 |
| Test for overall effect: $Z = 1.3$ | 39 (P = 0.1 | 16) | | | | | 0.01 | 0.1 Favours C | RYO Favo | 10 ours no CRN | 100 70 |

Table S16: Cryoprecipitate and outcomes

| | | Absolute effect estimates | | |
|--|---|--|---|--|
| Outcome Timeframe | Study results and measurements | No cryoprecipitate (or varying Cryoprecipitate administration of) | Certainty of the Evidence (Quality of evidence) | Plain language summary |
| Mortality, all cause (RCTs) latest reported timepoint | Relative risk: 0.35 (CI 95% 0.08 - 1.54) Based on data from 41 participants in 1 studies | 286 100 per 1000 per 1000 Difference: 186 fewer per 1000 (Cl 95% 263 fewer - 154 more) | Very low Due to serious risk of bias, Due to very serious imprecision | Cryoprecipitate may have little or no effect on mortality in trauma patients with critical bleeding, but the evidence is very uncertain. |
| Morbidity, thromboembolic events | Relative risk: 0.35 (CI 95% 0.02 - 8.1) Based on data from 41 participants in 1 studies | 95 33 per 1000 per 1000 Difference: 62 fewer per 1000 (Cl 95% 93 fewer - 675 more) | Very low Due to serious risk of bias, Due to very serious imprecision | There were too few who experienced the outcome to determine whether cryoprecipitate made a difference on thromboembolic events (including DVT, myocardial infarction, PE, stroke) in trauma patients with critical bleeding. |
| Morbidity, MOF | Relative risk: 3.14 (CI 95% 0.14 - 72.92) Based on data from 41 participants in 1 studies | 0 0 per 1000 per 1000 Difference: 0 fewer per 1000 (Cl 95% 0 fewer - 0 fewer) | Very low Due to serious risk of bias, Due to very serious imprecision | There were too few who experienced the outcome to determine whether cryoprecipitate made a difference on MOF (or other adverse events including sepsis and ARDS) in trauma patients with critical bleeding. |
| Red blood cell transfusion volume | Based on data from 41 participants in 1 studies | No significant difference in the median volume of red blood cells transfused (to 24 hours or 28 days) among patients who received cryoprecipitate compared to patients who did not. | Very low Due to serious risk of bias, Due to very serious imprecision | We are very uncertain about the effect of cryoprecipitate on the volume of red blood cells transfused in trauma patients with critical bleeding. |

| Transfusion volume, other blood products | Based on data from 41 participants in 1 studies | No significant difference in the median volume of FFP, cryoprecipitate, or platelets transfused (to 24 hours or 28 days) among patients who received cryoprecipitate compared to patients who did not. | Very low Due to serious risk of bias, Due to very serious imprecision | We are very uncertain about the effect of cryoprecipitate on the volume of FFP, platelets or cryoprecipitate transfused in trauma patients with critical bleeding. |
|--|---|--|---|---|
| LOS, hospital or ICU | Based on data from 41 participants in 1 studies | No significant difference in the median hospital or ICU LOS among patients who received cryoprecipitate compared to patients who did not. | Very low Due to serious risk of bias, Due to very serious imprecision | We are very uncertain about the effect of cryoprecipitate on hospital or ICU LOS in trauma patients with critical bleeding. |

Fibrinogen concentrate and outcomes in trauma setting: PICO

Population: People with critical bleeding (trauma setting)

Intervention: Fibrinogen concentrate

Comparator: No Fibrinogen concentrate (or varying administration of)

| | - | | | - | |
|--|--|---|--|---|---|
| Outcome Timeframe | Study results and measurements | Absolute effect No fibrinogen concentrate (or varying administration of) | t estimates Fibrinogen concentrate | Certainty of the Evidence (Quality of evidence) | Plain language summary |
| Mortality, all cause (RCTs) latest reported timepoint | Relative risk: 1.12 (Cl 95% 0.53 - 2.35) Based on data from 283 participants in 5 studies | 180 per 1000 Difference: 22 m (CI 95% 85 fewer | • | Very low Due to serious indirectness, Due to very serious imprecision | The evidence is very uncertain about the effect of fibrinogen concentrate on mortality in trauma patients with critical bleeding. |
| Mortality, all cause (Coh) latest reported timepoint | Relative risk: 1.39 (Cl 95% 0.91 - 2.13) Based on data from 1745 participants in 5 studies | 135 per 1000 Difference: 53 m (CI 95% 12 fewer | | Very low Due to serious risk of bias, Due to serious indirectness, Due to very serious imprecision | The evidence is very uncertain about the effect of fibrinogen concentrate on mortality in trauma patients with critical bleeding. |
| Morbidity, thromboembolic events (RCTs) | Relative risk: 0.9 (CI 95% 0.42 - 1.91) Based on data from 210 participants in 4 studies | 117 per 1000 Difference: 12 1000 (CI 95% 68 fewer | 0 | Low Due to very serious imprecision | The evidence suggests that fibrinogen concentrate may have little or no difference on thromboembolic events in trauma patients with critical bleeding. |
| Morbidity, MOF (RCTs) | Relative risk: 0.74 (Cl 95% 0.53 - 1.03) Based on data from 195 participants in 3 studies | 388 per 1000 Difference: 10 2 100 0 | | Low Due to very serious imprecision | The evidence suggests that fibrinogen concentrate may have little or no |

| | | (CI 95% 182 fewer - 12 more) | | difference on MOF in trauma patients with critical bleeding. |
|---|---|---|---|---|
| Red blood cell transfusion volume Units | Based on data from 1574 participants in 5 studies | No significant difference observed for volume of red blood cells transfused among patients who received fibrinogen concentrate compared with those who did not. Reported median values ranged from 3 to 12.8 units (fibrinogen concentrate) and 3 to 12.5 units (no fibrinogen concentrate). | Very low Due to serious risk of bias, Due to serious imprecision | The evidence is very uncertain about the association of fibrinogen concentrate on the volume of red blood cells transfused in trauma patients with critical bleeding. |
| Transfusion volume, other blood products Units | Based on data from 1574 participants in 5 studies | No significant difference observed for volume of FFP transfused among patients who received fibrinogen concentrate compared with those who did not. Reported median values ranged from 0 to 10.6 units (fibrinogen concentrate) and 1.75 to 10 units (fibrinogen concentrate). | Very low Due to serious risk of bias, Due to serious inconsistency, Due to serious imprecision, Due to serious publication bias | The evidence is very uncertain about the association of fibrinogen concentrate on the volume of FFP transfused in trauma patients with critical bleeding. |
| LOS, hospital Days | Based on data from 1491 participants in 7 studies | No significant difference observed for hospital LOS among patients who received fibrinogen concentrate compared with those who did not. | Very low Due to serious risk of bias, Due to serious imprecision, Due to serious inconsistency | Fibrinogen concentrate may have little or no difference on hospital LOS in the trauma setting but the evidence is very uncertain. |
| LOS, ICU Days | Based on data from 1647 participants in 6 studies | Five out of 6 studies reported no significant difference in ICU LOS among patients who received fibrinogen concentrate compared with those who did not. | Very low Due to serious risk of bias, Due to serious imprecision | Fibrinogen concentrate may have little or no difference on ICU LOS in the trauma setting but the evidence is very uncertain. |

Fibrinogen concentrate and outcomes in surgical setting: PICO

Population: People with critical bleeding (surgical setting)

Intervention: Fibrinogen concentrate

Comparator: Fibrinogen concentrate (or varying administration of)

Table S18: Fibrinogen concentrate and outcomes in surgical setting

| | - | | | | | | | |
|--|--|--|---|---|--|--|--|--|
| Outcome Timeframe | Study results and measurements | Absolute effer No Fibrinogen concentrate (or varying administration of) | ct estimates Fibrinogen concentrate | Certainty of the Evidence (Quality of evidence) | Plain language summary | | | |
| Mortality, all cause (RCTs) latest reported timepoint | Relative risk: 0.48 (Cl 95% 0.08 - 2.83) Based on data from 353 participants in 4 studies | 51 per 1000 Difference: 2 ' 100 (CI 95% 47 few | 00 | Low Due to very serious imprecision | There were too few who experienced the outcome to determine whether fibrinogen concentrate made a difference on mortality in patients with critical bleeding in the surgical setting. | | | |

| Mortality, all cause (Coh) latest reported timepoint | Relative risk: 1.58 (CI 95% 0.65 - 3.85) Based on data from 1178 participants in 3 studies | 39 62 per 1000 per 1000 Difference: 23 more per 1000 (CI 95% 14 fewer - 111 more) | Very low Due to serious risk of bias, Due to very serious imprecision | The evidence is very uncertain about the effect of fibrinogen concentrate on mortality in patients with critical bleeding in the surgical setting. |
|---|--|---|--|---|
| Morbidity, thromboembolic events (RCTs) | Relative risk: 2.03 (CI 95% 0.63 - 6.58) Based on data from 201 participants in 3 studies | 39 79 per 1000 per 1000 Difference: 40 more per 1000 (Cl 95% 14 fewer - 218 more) | Low Due to very serious imprecision | There were too few who experienced the outcome to determine whether fibrinogen concentrate made a difference on thromboembolic events in patients with critical bleeding in the surgical setting. |
| Transfusion volume, other blood products Units | Based on data from 33 participants in 2 studies | Two studies found a significant reduction in the volume of FFP transfused among patients who received fibrinogen concentrate compared with those who did not. One study reported SMD - 4.78. | Very low Due to serious risk of bias, Due to very serious imprecision | There were too few who experienced the outcome to determine whether fibrinogen concentrate made a difference on the volume of FFP transfused in patients with critical bleeding in the surgical setting. |
| Red blood cell transfusion volume Units | Based on data from 33 participants in 2 studies | Two studies found a significant reduction in the volume of red blood cells transfused among patients who received fibrinogen concentrate compared with those who did not. One study reported SMD -1.69. | Low Due to very serious imprecision | There were too few who experienced the outcome to determine whether fibrinogen concentrate made a difference on the volume of red blood cells transfused in patients with critical bleeding in the surgical setting. |
| LOS, ICU | Based on data from 18 participants in 1 studies | One small cohort study suggested fibrinogen concentrate is associated with a reduction in the LOS in the ICU (MD –3.27, 95% Cl –4.82, –1.71; P < 0.0001); however, the sample size is small and survivorship bias may have influenced the results. | Very low Due to serious risk of bias, Due to very serious imprecision | There were too few who experienced the outcome to determine whether fibrinogen concentrate made a difference on ICU LOS in patients with critical bleeding in the surgical setting. |

Prothrombin complex concentrates and outcomes in trauma: PICO

Population: People with critical bleeding (trauma setting) Intervention: Prothrombin complex Comparator: No Prothrombin complex (or varying administration of)

Figure S6: Forest plot of comparison: PCC vs no PCC on mortality (trauma setting)

| | PCC | ; | no PCC (or va | rying) | | Odds Ratio | | Odds Ratio | | |
|--|------------|--------|----------------|--------|--------|--------------------|------|-----------------------------|----------------|-----|
| Study or Subgroup | Events | Total | Events | Total | Weight | M-H, Random, 95% C | 1 | M-H, Random, 95% | 6 CI | |
| 4.1.1 trauma setting | | | | | | | | | | |
| Jehan 2018 (Coh, trauma) (1) | 10 | 40 | 26 | 80 | 14.2% | 0.69 [0.29, 1.63] | | | | |
| Joseph 2014 (Coh, trauma) (2) | 15 | 63 | 53 | 189 | 23.8% | 0.80 [0.41, 1.55] | | | | |
| Joseph 2016 (Coh, trauma) (3) | 6 | 27 | 15 | 54 | 8.8% | 0.74 [0.25, 2.20] | | | | |
| Zeeshan 2019 (Coh, trauma) (4) | 41 | 234 | 65 | 234 | 53.2% | 0.55 [0.35, 0.86] | | | | |
| Subtotal (95% CI) | | 364 | | 557 | 100.0% | 0.64 [0.46, 0.88] | | • | | |
| Total events | 72 | | 159 | | | | | | | |
| Heterogeneity: Tau ² = 0.00; Chi ² = | 0.98, df = | 3 (P = | 0.81); l² = 0% | | | | | | | |
| Test for overall effect: Z = 2.72 (P | = 0.007) | | | | | | | | | |
| Total (95% CI) | | 364 | | 557 | 100.0% | 0.64 [0.46, 0.88] | | • | | |
| Total events | 72 | | 159 | | | | | | | |
| Heterogeneity: Tau ² = 0.00; Chi ² = | 0.98, df = | 3 (P = | 0.81); l² = 0% | | | | | + + | -+ | |
| Test for overall effect: Z = 2.72 (P | = 0.007) | | | | | | 0.01 | 0.1 1 Favours PCC Favour | 10 s no PCC | 100 |
| Test for subgroup differences: Not | applicable | • | | | | | | Tavouis FCC Tavoui | 5110 FCC | |
| Footnotes | | | | | | | | | | |
| (1) Study carried out in any setting | 1 | | | | | | | | | |
| (2) Study carried out in any setting | 1 | | | | | | | | | |

Study carried out in any setting

(3) Study carried out in any setting

(4) Study carried out in any setting

Table S19: Fibrinogen concentrate and outcomes in trauma setting

| Outcome Timeframe | Study results and measurements | prothromhin | estimates othrombin complex | Certainty of the Evidence (Quality of evidence) | Plain language summary |
|---|--|--|-----------------------------------|--|--|
| Mortality, all cause latest reported timepoint | Odds ratio: 0.64 (CI 95% 0.46 - 0.88) Based on data from 921 participants in 4 studies | 285 per 1000 Difference: 82 fe 1000 (CI 95% 130 fewer - | • | Very low Due to serious risk of bias | The use of prothrombin complex in trauma patients with critical bleeding may reduce mortality, but the evidence is very uncertain. |
| Morbidity, thromboembolic events | Odds ratio: 0.9 (CI 95% 0.49 - 1.67) Based on data from 921 participants in 4 studies | 48 per 1000 Difference: 5 fewe (CI 95% 24 fewer - | • | Very low Due to serious risk of bias, Due to serious imprecision | The evidence is very uncertain about the effect of prothrombin complex on thromboembolic events in trauma patients with critical bleeding. |
| Red blood cell transfusion volume | Measured by: Number of Units Lower better Based on data from 921 participants in 4 studies | 5.4-10 Difference: SMD 0 (Cl 95% 0.98 lower - | | Very low Due to serious risk of bias, Due to serious inconsistency, Due to serious imprecision | The use of prothrombin complex in trauma patients with critical bleeding may reduce the volume of red blood cells transfused but the evidence is very uncertain. |

Research question: In patients with critical bleeding, what is the effect of recombinant activated factor VII treatment on morbidity, mortality and transfusion rate?

Literature search date: 12 August 2019.

This question was retired in March 2021 as research in this area is not expected to substantially evolve.

Weak recommendation against

R5: The reference group suggest against the routine use of recombinant activated factor VII in patients with critical bleeding*.

* Recombinant activated factor VII is approved in Australia and New Zealand for the control of bleeding and prophylaxis for surgery in patients with specific bleeding disorders. Use of recombinant activated factor VII outside these indications (including critical bleeding after trauma) is considered 'off-label' and is associated with harm.

Use of **recombinant activated factor VII** should only be considered in exceptional circumstance where all other available measures to control bleeding have been exhausted.

Evidence to decision

Benefits and harms

There was no significant survival benefit observed in patients with critical bleeding who received recombinant activated factor VII and evidence for harms (thromboembolic events) was limited. In a large and comprehensive meta-analysis of placebo-controlled trials of recombinant activated factor VII, treatment with high doses of recombinant activated factor VII on an off-label basis significantly increased the risk of arterial but not venous thromboembolic events [108].

Certainty of the Evidence

The overall certainty in effect estimates across outcomes was either very low (benefits) or low (harms).

Values and preferences

Resources

Equity

The use of recombinant activated factor VII in patients with critical bleeding has been declining, and the urgency to address the 'off-label' use of this product has waned.

Important issues, or potential issues not investigated

The intervention is considered costly.

Important issues, or potential issues not investigated

We expect few to want the intervention

Important Harms

Very low

While the intervention is considered costly, equity is unlikely to be impacted as there is no recommended change to current practice.

Acceptability

No important issues with the recommended alternative

While the intervention is considered costly, acceptability is unlikely to be impacted as there is no recommended change to current practice.

Feasibility

No important issues with the recommended alternative

While the intervention is considered costly, feasibility is unlikely to be impacted as there is no recommended change to current practice.

Rationale

The use of recombinant activated factor VII in patients with critical bleeding requiring an MHP is not recommended because of its lack of effect on mortality and variable effect on morbidity. The 'off-label' use of recombinant activated factor VII in patients with critical bleeding has declined.

Figure S7: Forest plot of comparison: rFVIIa vs placebo, outcome: Mortality, latest timepoint

| | Experim | | Cont | | | Risk Ratio | | Risk Ratio |
|---|------------|-----------------------|--------|------------------|-----------------------|---|------|---|
| Study or Subgroup | Events | Total | Events | Total | Weight | M-H, Fixed, 95% Cl | Year | M-H, Fixed, 95% Cl |
| 1.1.1 Trauma (RCTs) | | | | | | | | |
| Boffard 2005a (blunt) | 17 | 69 | 22 | 74 | 16.1% | 0.83 [0.48, 1.42] | | |
| Boffard 2005b (penetrating) | 17 | 70 | 18 | 64 | 14.3% | 0.86 [0.49, 1.53] | | |
| Hauser 2010a (blunt) | 26 | 224 | 28 | 250 | 20.1% | 1.04 [0.63, 1.71] | | _ |
| Hauser 2010b (penetrating) Subtotal (95% CI) | 8 | 46 409 | 5 | 40 428 | 4.1% 54.6% | 1.39 [0.49, 3.91] 0.96 [0.71, 1.29] | 2010 | • |
| Total events | 68 | | 73 | | | | | |
| Heterogeneity: Chi² = 1.00, df = 3 (P = 0.80); l² = 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) Subtotal (95% CI) | 39 | 170 286 | 25 | 86 206 | 25.3% 33.5% | 0.79 [0.51, 1.21] 0.96 [0.67, 1.39] | 2008 | + ◆ |
| Total events Heterogeneity: Chi² = 2.29, df = 1 (P = 0.13); l² = 5 Test for overall effect: Z = 0.19 (P = 0.85) | 55 6% | | 36 | | | | | |
| 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) Subtotal (95% CI) | 0 | 16 <mark>93</mark> | 0 | 9 32 | 8.2% | Not estimable 1.02 [0.51, 2.07] | 2005 | • |
| 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) Subtotal (95% CI) | 0 | 42 42 | 0 | 42 42 | | Not estimable 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 | | | | | Ţ |
| Heterogeneity: Chi² = 4.22, df = 7 (P = 0.75); l² = 0 Test for overall effect: Z = 0.09 (P = 0.92) | % | | | | | | | 0.05 0.2 1 5 20 Favours rFVIIa Favours standard care |
| Fest for subgroup differences: Chi² = 0.85, df = 3 Footnotes | (P = 0.84) |), I ≃ = 09 | 6 | | | | | |
| 1) Data for 600 and 300 ug/kg rEIIVa groups com | bined | | | | | | | |

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

Recombinant activated factor VII and outcomes in trauma: PICO

Population: People with critical bleeding, specifically those with ongoing bleeding who fail to achieve adequate haemostasis despite surgical management and appropriate blood component therapy (trauma setting)

Intervention: recombinant activated factor VII Comparator: standard best practice without recombinant activated factor VII

Table S20: Activated factor VIIa and outcomes in trauma setting

| | | Absolute effe | ect estimates | | | |
|---|--|--|--|--|---|--|
| Outcome Timeframe | Study results and measurements | standard best practice without recombinant activated factor VII | recombinant activated factor VII | Certainty of the Evidence (Quality of evidence) | Plain language summary | |
| Mortality, all cause latest reported timepoint | Relative risk: 0.96 (CI 95% 0.71 - 1.29) Based on data from 837 participants in 3 studies | 171 per 1000 Difference: 7 fe (Cl 95% 50 few | • | Low Due to serious risk of bias, Due to serious imprecision | The evidence suggests that the use of recombinant activated factor VII in patients with critical bleeding due to blunt | |

| | | | | or penetrating trauma may have little or no difference in mortality compared with placebo or no recombinant activated factor VII |
|---|--|--|--|--|
| Morbidity, thromboembolic events | Relative risk: 1.1 (CI 95% 0.74 - 1.63) Based on data from 837 participants in 3 studies | 100 110 per 1000 per 1000 Difference: 10 more per 1000 (CI 95% 26 fewer - 63 more) | Very low Due to serious risk of bias, Due to serious indirectness, Due to serious imprecision | The use of recombinant activated factor VII in patients with critical bleeding due to blunt or penetrating trauma may have little or no difference on thromboembolic events compared with placebo but we are very uncertain about the evidence. |
| Morbidity, ARDS | Relative risk: 0.39 (CI 95% 0.22 - 0.71) Based on data from 837 participants in 3 studies | 89 35 per 1000 per 1000 Difference: 54 fewer per 1000 (CI 95% 69 fewer - 26 fewer) | Low Due to serious risk of bias, Due to serious imprecision | The evidence suggests recombinant activated factor VII may result in a slight reduction in ARDS in patients with critical bleeding due to blunt or penetrating trauma. |
| Morbidity, MOF | Relative risk: 0.56 (Cl 95% 0.32 - 0.97) Based on data from 837 participants in 3 studies | 79 44 per 1000 per 1000 Difference: 35 fewer per 1000 (CI 95% 54 fewer - 2 fewer) | Low Due to serious risk of bias, Due to serious imprecision | The evidence suggests recombinant activated factor VII may result in a slight reduction in MOF in patients with critical bleeding due to blunt or penetrating trauma. |
| Red blood cell transfusion, units up to 48 hours | Measured by: Number of Units Lower better Based on data from 713 participants in 3 studies | 6.8-10.9 4.5-7.8 Difference: MD 2.35 fewer (CI 95% 3.70 fewer - 1.0 fewer) | Very low Due to very serious risk of bias, Due to serious imprecision | Recombinant activated factor VII may slightly reduce the volume of red blood cells transfused in patients with critical bleeding due to blunt or penetrating trauma, but we are very uncertain about the evidence. |
| Transfusion volume, other blood products | Based on data from 410 participants in 1 studies | Fewer units of FFP were used in patients in the recombinant activated factor VII group compared with placebo (MD – 2.14; 95% CI –3.54, –0.73), while no reduction in platelets, fibrinogen concentrate or cryoprecipitate was observed. | Low Due to serious risk of bias, Due to serious imprecision | Recombinant activated factor VII may slightly reduce the volume of FFP transfused, but not platelets, fibrinogen concentrate or cryoprecipitate, in patients with critical bleeding due to blunt or penetrating trauma, but we are very uncertain about the evidence. |

Recombinant activated factor VII and outcomes in medical emergencies: PICO

Population: People with critical bleeding, specifically those with ongoing bleeding who fail to achieve adequate haemostasis despite surgical management and appropriate blood component therapy (medical emergency)

Intervention: recombinant activated factor VII

Comparator: standard best practice without recombinant activated factor VII

| | | Absolute effect estimates | | |
|---|--|---|---|--|
| Outcome Timeframe | Study results and measurements | standard best practice without recombinant activated factor VII | Certainty of the Evidence (Quality of evidence) | Plain language summary |
| Mortality, all cause latest reported timepoint | Relative risk: 1.02 (CI 95% 0.55 - 1.9) Based on data from 492 participants in 2 studies | 175 179 per 1000 per 1000 Difference: 4 more per 1000 (CI 95% 79 fewer - 158 more) | Very low Due to serious inconsistency, Due to serious indirectness, Due to serious imprecision | Recombinant activated factor VII may have little or no effect on mortality in patients with severe gastrointestinal bleeding, but we are very uncertain about the evidence. |
| Morbidity, thromboembolic events | Relative risk: 0.8 (CI 95% 0.4 - 1.6) Based on data from 507 participants in 2 studies | 67 54 per 1000 per 1000 Difference: 13 fewer per 1000 (Cl 95% 40 fewer - 40 more) | Low Due to serious indirectness, Due to serious imprecision | The evidence suggests that the us of recombinant activated factor VII may have little or no difference on thromboembolic events in patients with severe gastrointestinal bleeding. |
| Red blood cell transfusion volume | Measured by: Number of Units Lower better Based on data from 393 participants in 2 studies | 1.3-3.3 1.5-2.55 Difference: MD 0.24 fewer (Cl 95% 1.17 fewer - 0.69 more) | Very low Due to serious inconsistency, Due to serious indirectness, Due to serious imprecision | Recombinant activated factor VII may have little to n effect on the volum of red blood cells transfused in patien with severe gastrointestinal bleeding, but we ar very uncertain abou the evidence. |

Table S21: Activated factor VIIa and outcomes in medical emergency setting

Recombinant activated factor VII and outcomes in haematology oncology emergencies: PICO

Population: People with critical bleeding, specifically those with ongoing bleeding who fail to achieve adequate haemostasis despite surgical management and appropriate blood component therapy (haematology/oncology setting)

Intervention: recombinant activated factor VII

Comparator: standard best practice without recombinant activated factor VII

Table S22: Activated factor VIIa and outcomes in haematology/oncology setting

| Outcome Timeframe | Study results and measurements | Absolute effect estimates standard best practice without recombinant activated factor VII | Certainty of the Evidence (Quality of evidence) | Plain language summary |
|---|---|---|---|---|
| Mortality, all cause latest reported timepoint | Relative risk: 1.02 (Cl 95% 0.51 - 2.07) Based on data from 125 participants in 2 studies | 219 223 per 1000 per 1000 Difference: 4 more per 1000 (CI 95% 107 fewer - 234 more) | Very low Due to serious risk of bias, Due to serious imprecision, Due to serious indirectness | The use of recombinant activated factor VII in patients with critical bleeding after HSCT may result in little or no difference in mortality but we are very uncertain about the evidence. |
| Morbidity, thromboembolic events | Relative risk: 5.23 (CI 95% 0.31 - 87.34) Based on data from 125 participants in 2 studies | 0 0 per 1000 per 1000 Difference: 0 fewer per 1000 (CI 95% 0 fewer - 0 fewer) | Very low Due to serious risk of bias, Due to serious indirectness, Due to very serious imprecision | Recombinant activated factor VII may result in a slight increase in thromboembolic events in patient witl critical bleeding after HSCT, but we are ver uncertain about the evidence. |
| Red blood cell transfusion volume | | No studies reported this outcome | | The effect of recombinant activated factor VII or red blood cell transfusion volume in patients with critical bleeding after HSCT i unknown. |

Recombinant activated factor VII and outcomes in cardiac emergencies: PICO

Population: People with critical bleeding, specifically those with ongoing bleeding who fail to achieve adequate haemostasis despite surgical management and appropriate blood component therapy (cardiac setting)

Intervention: recombinant activated factor VII

Comparator: standard best practice without recombinant activated factor VII

Table S23: Activated factor VIIa and outcomes in cardiac surgery setting

| Outcome Timeframe | Study results and measurements | Absolute effe standard best practice without recombinant activated factor VII | ect estimates recombinant activated factor VII | Certainty of the Evidence (Quality of evidence) | Plain language summary |
|-----------------------------|--|---|---|---|------------------------------------|
| Mortality, all cause | Relative risk: 1.63 (Cl 95% 0.53 - 5.0) | 59 per 1000 | 96 per 1000 | Low Due to very serious imprecision | The evidence suggests that the use |

| latest reported timepoint | Based on data from 172 participants in 1 studies | Difference: 37 more per 1000 (CI 95% 28 fewer - 236 more) | | of recombinant activated factor VII in patients with critical bleeding after cardiac surgery results in little to no difference in mortality compared with no recombinant activated factor VII |
|---|---|--|---|--|
| Morbidity, thromboembolic events | Relative risk: 4.58 (CI 95% 0.58 - 36.38) Based on data from 172 participants in 1 studies | 15 69 per 1000 per 1000 Difference: 54 more per 1000 (Cl 95% 6 fewer - 531 more) | Low Due to very serious imprecision | The evidence suggests recombinant activated factor VII results in a slight increase in thromboembolic events in patient with critical bleeding after cardiac surgery. |
| Red blood cell transfusion volume | | No studies reported this outcome | | The effect of recombinant activated factor VII on red blood cell transfusion volume in patients admitted to intensive care with intractable bleeding after cardiac surgery is unknown. |

Research question: In patients with critical bleeding, what is the effect of antifibrinolytics on blood loss, red blood cell transfusion and patient outcomes?

Latest search date: 29 September 2021

*Aprotinin is on the Australian Register of Therapeutic Goods but is not being supplied or marketed by an Australian sponsor.

^6-aminocaproic acid is not available or registered for use in Australia.

Weak recommendation

R6: In trauma patients with critical bleeding, the reference group suggest the early use (within 3 hours of injury) of tranexamic acid as part of a major haemorrhage protocol.

Evidence to decision

| Benefits and harms | Small net benefit, or little difference between | |
|--------------------|---|--|
| | alternatives | |

The evidence suggests tranexamic acid may provide a small benefit. The effects on harms are uncertain.

| Certainty of the Evidence | Very low |
|---|--|
| The overall certainty in effect estimates across outcomes was eithe | er very low (benefits) or low (harms). |
| | |
| Values and preferences | No substantial variability expected |
| There is no plausible reason to suspect that patients who are critica recommended. | ally bleeding would not accept tranexamic acid as |
| | |
| Resources | No important issues with the recommended alternative |
| While tranexamic acid is not funded under the national blood arran recommended use to have a significant impact on resources. | ngements, the reference group did not expect its |
| | |
| Equity | No important issues with the recommended alternative |
| Equity of implementation was not investigated but was not conside | ered to be an issue. |
| | |
| Acceptability | No important issues with the recommended alternative |
| The acceptability of implementation was not investigated but was | not considered to be an issue. |
| | |
| Feasibility | No important issues with the recommended alternative |
| Feasibility of implementation was not investigated but was not cor | isidered to be an issue. |
| | |

<u>Rationale</u>

The CRASH-2 trial supported the use of tranexamic acid in trauma patients, however the evidence is not directly generalisable to the Australian and New Zealand settings where there are advanced trauma centres. The results of the PATCH-Trauma Study were not included in the evidence base as it was completed after the literature search cut-off date.

| tudy or Subgroup 1.1 Trauma (RCTs) akaei 2017 (Civilian) uyette 2020 (STAAMP) (Civilian) RASH-2 2010 (Civilian) (1) ubtotal (95% Cl) otal events eterogeneity: Tau ² = 0.00; Chi ² = 0.10 | Events 3 37 1463 1503 | Total 30 447 10060 | Events 4 43 | Total 30 | Weight | M-H, Random, 95% Cl | M-H, Random, 95% Cl |
|--|-----------------------------------|-----------------------------|-------------------|-------------|--------|---------------------|---------------------|
| akaei 2017 (Civilian) uyette 2020 (STAAMP) (Civilian) RASH-2 2010 (Civilian) (1) ubtotal (95% CI) otal events | 37 1463 | 447 | | 30 | 0.001 | | |
| uyette 2020 (STAAMP) (Civilian) RASH-2 2010 (Civilian) (1) ubtotal (95% CI) otal events | 37 1463 | 447 | | 30 | | | |
| RASH-2 2010 (Civilian) (1) ubtotal (95% CI) otal events | 1463 | | 43 | | 0.2% | 0.75 [0.18, 3.07] | |
| ubtotal (95% CI) otal events | | 10060 | | 453 | 2.3% | 0.87 [0.57, 1.33] | |
| otal events | 1503 | | 1613 | 10067 | 97.4% | 0.91 [0.85, 0.97] | |
| | 1503 | 10537 | | 10550 | 100.0% | 0.91 [0.85, 0.97] | • |
| eterogeneity: Tau ² = 0.00; Chi ² = 0.10 | | | 1660 | | | | |
| | |).95); l ² = | 0% | | | | |
| est for overall effect: Z = 2.99 (P = 0.0 | 03) | | | | | | |
| .1.2 Trauma (Coh) | | | | | | | |
| arvin 2014 (adult trauma) (2) | 39 | 98 | 157 | 924 | | Not estimable | |
| ole 2015 (Civilian, ISS 15) (3) | 30 | 160 | 36 | 225 | | Not estimable | |
| ckert 2014 (paediatric trauma) (4) | 10 | 66 | 56 | 700 | | Not estimable | |
| ipsky 2014 (Coh, trauma) | 6 | 28 | 0 | 12 | 0.8% | 5.83 [0.35, 95.93] | |
| eeki 2017 (prehospital) | 8 | 128 | 13 | 125 | 5.1% | 0.60 [0.26, 1.40] | |
| wendsen 2013 (adult trauma) | 9 | 52 | 17 | 74 | 6.0% | 0.75 [0.36, 1.56] | |
| eeki 2018 (Civilian) | 13 | 362 | 30 | 362 | 6.9% | 0.43 [0.23, 0.82] | |
| alle 2014 (adult trauma) | 25 | 109 | 14 | 105 | 7.2% | 1.72 [0.95, 3.12] | |
| I-Menyar 2020 (Civilian) | 25 | 102 | 30 | 102 | 8.7% | 0.83 [0.53, 1.31] | |
| /afaisade 2016 (prehospital, civilian) | 38 | 258 | 42 | 258 | 9.3% | 0.90 [0.60, 1.35] | |
| lorrison 2013 (MATTERS II) (5) | 57 | 406 | 179 | 758 | 10.6% | 0.59 [0.45, 0.78] | _ _ |
| ivas 2021 (Civilian) | 106 | 654 | 91 | 254 | 10.9% | 0.45 [0.36, 0.57] | |
| oward 2017 (Coh, combat) | 82 | 849 | 271 | 2924 | 11.0% | 1.04 [0.82, 1.32] | |
| lorrison 2012 (MATTERS) (6) | 148 | 293 | 218 | 603 | 11.6% | 1.40 [1.20, 1.63] | |
| lyers 2019 (Civilian) | 136 | 189 | 161 | 189 | 11.9% | 0.84 [0.76, 0.94] | + |
| ubtotal (95% CI) | | 3430 | | 5766 | 100.0% | 0.83 [0.64, 1.06] | \bullet |
| otal events | 653 | | 1066 | | | | |
| eterogeneity: Tau ² = 0.14; Chi ² = 86.7 | '8, df = 11 (P | < 0.0000 | 1); l² = 87 | % | | | |
| est for overall effect: Z = 1.50 (P = 0.1 | 3) | | | | | | |
| 1.3 Medical emergency (RCT) | | | | | | | |
| oberts 2020 (HALT-IT) | 564 | 5956 | 548 | 5981 | 100.0% | 1.03 [0.92, 1.16] | |
| ubtotal (95% CI) | | 5956 | | 5981 | 100.0% | 1.03 [0.92, 1.16] | • |
| otal events | 564 | | 548 | | | | |
| eterogeneity: Not applicable | | | | | | | |
| est for overall effect: Z = 0.58 (P = 0.5 | i6) | | | | | | |
| .1.4 Obstetrics and maternity (RCTs | 5) | | | | | | |
| ucloy-Bouthers 2011 | 0 | 77 | 0 | 74 | | Not estimable | |
| /OMAN 2017 (PPH) | 227 | 10034 | 255 | | 100.0% | 0.89 [0.74, 1.06] | |
| ubtotal (95% CI) | | 10111 | _50 | 10051 | | 0.89 [0.74, 1.06] | |
| otal events | 227 | | 255 | | | | |
| eterogeneity: Not applicable | | | | | | | |
| est for overall effect: Z = 1.35 (P = 0.1 | 8) | | | | | | |
| | | | | | | | |
| | | | | | | _ | |

Figure S8: Forest plot of comparison: TXA vs no TXA, outcome: Mortality, latest timepoint

Test for subgroup differences: $Chi^2 = 5.18$, df = 3 (P = 0.16), l² = 42.0%

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) Effect favouring TXA observed after adjusting for confounders (OR 0.27; 95% CI 0.85, 0.89; p=0.03)

(5) within 48 hours of injury

(6) within 48 hours of injury

Antifibrinolytics and outcomes in trauma setting: PICO

Population: People with critical bleeding (trauma setting) Intervention: Antifibrinolytics Comparator: Placebo or no antifibrinolytics

Table S24: Antifibrinolytics in trauma setting

| Outcome Timeframe | Study results and measurements | Absolute effect estimates Placebo or no antifibrinolytics | Certainty of the Evidence (Quality of evidence) | Plain language summary |
|--|--|---|---|---|
| Mortality, all cause (RCTs) latest reported timepoint | Relative risk: 0.91 (CI 95% 0.85 - 0.97) Based on data from 21087 participants in 3 studies | 157 143 per 1000 per 1000 Difference: 14 fewer per 1000 (Cl 95% 24 fewer - 5 fewer) | Low Due to very serious indirectness | The evidence suggests antifibrinolytics may slightly reduce mortality in trauma patients with critical bleeding. |
| Mortality, all cause (Coh) latest reported timepoint | Relative risk: 0.97 (CI 95% 0.75 - 1.25) Based on data from 11369 participants in 15 studies | 144 140 per 1000 per 1000 Difference: 4 fewer per 1000 (Cl 95% 36 fewer - 36 more) | Very low Due to very serious risk of bias, Due to serious inconsistency, Due to serious indirectness, Due to serious imprecision | We are very uncertain about the association of antifibrinolytics on all-cause mortality in trauma patients with critical bleeding. |
| Morbidity, thromboembolic event (RCTs) | Relative risk: 0.84 (CI 95% 0.68 - 1.02) Based on data from 20127 participants in 1 studies ⁷ | 20 17 per 1000 per 1000 Difference: 3 fewer per 1000 (CI 95% 6 fewer - 0 fewer) | Very low Due to very serious indirectness, Due to serious imprecision | Antifibrinolytics appear to have little to no effect on vascular thromboembolic events, but we are very uncertain about the evidence. |
| Morbidity, thromboembolic events (Coh) | Relative risk: 1.63 (CI 95% 1.17 - 2.29) Based on data from 4958 participants in 10 studies | 39 64 per 1000 per 1000 Difference: 25 more per 1000 (Cl 95% 7 more - 50 more) | Very low Due to serious risk of bias, Due to serious indirectness, Due to very serious imprecision, Due to serious inconsistency | We are very uncertain about the association of antifibrinolytics on thromboembolic events in trauma patients with critical bleeding. |
| Red blood cell transfusion volume (RCTs) | Measured by: Number of Units Lower better Based on data from 10227 participants in 1 studies | 6.29 6.06 Units (Mean) Units (Mean) Difference: SMD 0.02 fewer (CI 95% 0.06 fewer - 0.02 more) | Low Due to very serious indirectness | The evidence suggests that antifibrinolytics may have little or no difference on the volume of red blood cells transfused in trauma patients with critical bleeding. |
| Red blood cell transfusion volume (Coh) | Measured by: Number of Units Lower better Based on data from 2095 participants in 4 studies | 2-20.1 4.43 - 22 Difference: SMD 0.53 more (Cl 95% 0.22 more - 0.85 more) | Very low Due to serious risk of bias, Due to serious inconsistency, Due to serious indirectness, Due to serious imprecision | We are very uncertain about the association of antifibrinolytics with the volume of red blood cells transfused in trauma patients with critical bleeding. |

Antifibrinolytics and outcomes in medical emergency settings: PICO

Population: People with critical bleeding (medical emergency)

Intervention: Antifibrinolytics

Comparator: Placebo or no antifibrinolytics

Table S25: Antifibrinolytics in medical emergency

| Outcome | Study results and | Absolute effect estimates | Certainty of the Evidence | Plain language | |
|---|--|--|---|---|--|
| Timeframe | measurements | Placebo or no antifibrinolytics Antifibrinolytics | (Quality of evidence) | summary | |
| Mortality, all cause latest reported timepoint | Relative risk: 1.03 (CI 95% 0.92 - 1.16) Based on data from 11937 participants in 1 studies Follow up discharge up to 28-days | 92 95 per 1000 per 1000 Difference: 3 more per 1000 (CI 95% 7 fewer - 15 more) | Low Due to very serious indirectness | The evidence suggests that antifibrinolytics may have no difference on all-cause mortality in patients with severe gastrointestinal bleeding. | |
| Morbidity, thromboembolic events (venous) | Relative risk: 1.85 (CI 95% 1.15 - 2.98) Based on data from 11929 participants in 1 studies Follow up discharge up to 28-days | 4 7 per 1000 per 1000 Difference: 3 more per 1000 (CI 95% 1 more - 8 more) | Low Due to very serious indirectness | Antifibrinolytics may increase the risk of thromboembolic events (vascular) in patients with severe gastrointestinal bleeding. | |
| Morbidity, thromboembolic events (arterial) | Relative risk: 0.92 (CI 95% 0.6 - 1.39) Based on data from 11929 participants in 1 studies Follow up discharge up to 28-days | 8 7 per 1000 per 1000 Difference: 1 fewer per 1000 (CI 95% 3 fewer - 3 more) | Low Due to very serious indirectness | Antifibrinolytics may have little to no difference on the risk of thromboembolic events (arterial) in patients with severe gastrointestinal bleeding. | |
| Red blood cell transfusion volume | Measured by: Number of units Lower better Based on data from 8205 participants in 1 studies Follow up discharge up to 28-days | 2.9 2.8 Units (Mean) Units (Mean) Difference: MD 0.06 fewer (CI 95% 0.05 more - 0.18 fewer) | Low Due to very serious indirectness | Antifibrinolytics may have little or no difference on the volume of red blood cells transfused in patients with severe gastrointestinal bleeding. | |
| FFP transfusion volume | Measured by: Number of units Lower better Based on data from 8205 participants in 1 studies Follow up discharge up to 28-days | 1.0 0.9 Units (Mean) Units (Mean) Difference: MD 0.05 fewer (CI 95% 0.01 fewer - 0.23 fewer) | Low Due to very serious indirectness | Antifibrinolytics may have little or no difference on the volume of FFP transfused in patients with severe gastrointestinal bleeding. | |

Weak recommendation

R7: In obstetric patients with critical bleeding, the early use (within 3 hours of the onset of haemorrhage) of tranexamic acid may be considered as part of a major haemorrhage protocol.

Evidence to decision

| Benefits and harms | Small net benefit, or little difference between alternatives |
|--|--|
| An assessment of harms is difficult due to the underlying low numbe 2018, there were 15 maternal deaths in Australia. Only one was attri | |
| | |
| Certainty of the Evidence | Very low |
| The overall certainty in effect estimates across outcomes was either | very low (benefits) or low (harms). |
| Values and preferences | No substantial variability expected |
| There is no plausible reason to suspect that maternity patients who a acid as recommended. | are critically bleeding would not accept tranexamic |
| | |
| Resources | No important issues with the recommended alternative |
| | |
| Equity | No important issues with the recommended alternative |
| Equity of implementation was not investigated but was not consider | ed to be an issue. |
| | |
| Acceptability | No important issues with the recommended alternative |
| The acceptability of implementation was not investigated but was no | ot considered to be an issue. |
| | |
| Feasibility | No important issues with the recommended alternative |
| Feasibility of implementation was not investigated but was not consi | dered to be an issue. |

| Rationale |) |
|-----------|---|
|-----------|---|

The WOMAN trial supported the use of tranexamic acid in critically bleeding obstetric patients, but no difference was observed for the primary outcome of hospital mortality [158].

Antifibrinolytics and outcomes in obstetric emergencies: PICO

Population: People with critical bleeding (obstetrics and maternity) Intervention: Antifibrinolytics Comparator: Placebo or no antifibrinolytics

| Outcome | Study results and | Absolute effect estimates | Certainty of the Evidence | Plain language |
|---|---|--|--|--|
| Timeframe | measurements | Placebo or no antifibrinolytics | (Quality of evidence) | summary |
| Mortality, all cause latest reported timepoint | Relative risk: 0.89 (CI 95% 0.74 - 1.06) Based on data from 20011 participants in 2 studies | 25 22 per 1000 per 1000 Difference: 3 fewer per 1000 (Cl 95% 6 fewer - 2 more) | Low Due to very serious indirectness | The evidence suggests that antifibrinolytics may have no difference on all-cause mortality in women with major obstetrio haemorrhage |
| Morbidity, thromboembolic events | Relative risk: 0.91 (CI 95% 0.56 - 1.47) Based on data from 20011 participants in 1 study | 3 3 per 1000 per 1000 Difference: 0 fewer per 1000 (Cl 95% 1 fewer - 1 more) | Very low Due to very serious indirectness, Due to serious imprecision | Antifibrinolytics may have little or no effect on thromboembolic events in women with major obstetric haemorrhage, but the evidence is very uncertain. |
| Morbidity, MOF | Relative risk: 0.94 (CI 95% 0.71 - 1.23) Based on data from 20168 participants in 2 studies | 10 9 per 1000 per 1000 Difference: 1 fewer per 1000 (CI 95% 3 fewer - 2 more) | Very low Due to very serious indirectness, Due to serious imprecision | Antifibrinolytics may have little or no effect on MOF in women with major obstetric haemorrhage, but the evidence is very uncertain. |
| Morbidity, respiratory failure | Relative risk: 0.87 (CI 95% 0.67 - 1.12) Based on data from 20018 participants in 1 study | 12 10 per 1000 per 1000 Difference: 2 fewer per 1000 (Cl 95% 4 fewer - 1 more) | Very low Due to very serious indirectness, Due to serious imprecision | Antifibrinolytics may have little or no effect on respiratory failure in women with major obstetric haemorrhage, but the evidence is very uncertain. |
| Morbidity, renal failure | Relative risk: 1.09 (CI 95% 0.85 - 1.39) Based on data from 20169 participants in 2 studies | 12 13 per 1000 per 1000 Difference: 1 more per 1000 (Cl 95% 2 fewer - 5 more) | Very low Due to very serious indirectness, Due to serious imprecision | Antifibrinolytics may have little or no effect on renal failure in women with major obstetric haemorrhage, but the evidence is very uncertain. |
| Red blood cell transfusion volume | Based on data from 20060 participants in 1 study | The mean number of blood units transfused did not differ significantly between patients in the tranexamic and placebo groups, but data were | Very low Due to very serious indirectness, Due to serious imprecision | Antifibrinolytics may have little or no effect on the volume of RBCs transfused in women with |

not provided.

imprecision

major obstetric haemorrhage, but

Table S26: Antifibrinolytics obstetric emergency

| | the evidence is very uncertain. |
|--|---------------------------------|
|--|---------------------------------|

Research question: In patients with critical bleeding, does the use of VHAs change patient outcomes?

Latest search date: 29 September 2021

GPS10: The reference group agreed that the use of viscoelastic haemostatic assays * may be beneficial in patients with critical bleeding. There is insufficient evidence to provide a recommendation.

If viscoelastic haemostatic assays are used in the assessment of patients with critical bleeding, they must be used in conjunction with a major haemorrhage protocol.

*Interpretation of results requires specific expertise and training.

Evidence to decision

Benefits and harms

Substantial net benefits of the recommended alternative

In the meta-analysis of RCTs and observational cohort studies a reduction in mortality was demonstrated. However, the certainty of the evidence for the trials was very low. Based on the available evidence the true benefit is unknown.

Certainty of the Evidence

The overall certainty in effect estimates across outcomes was either very low (benefits) or low (harms).

Values and preferences

No substantial variability expected

Very low

There is no plausible reason to suspect that patients who are critically bleeding would not accept VHAs as part of an MHP as recommended in this guideline.

Resources

Important negative issues

The reference group acknowledged there are significant additional resources associated with the implementation and use of VHAs as part of an MHP.

| Equity | Important issues, or potential issues not investigated |
|---|---|
| The reference group acknowledged that there is jurisdictional, geo availability of VHAs as part of an MHP. | ographical and/or institutional variability in the |
| | |
| Acceptability | Important issues, or potential issues not investigated |
| The reference group acknowledged that there may be jurisdictiona acceptability of VHAs as part of an MHP. | al, geographical and/or institutional variability in |

| Feasibility | Important issues, or potential issues not investigated |
|---|---|
| The reference group acknowledged that there may be jurisdictiona implementing VHAs as part of an MHP. | I, geographical and/or institutional variability in |

Rationale

VHAs may be used as part of an MHP in patients who are critically bleeding. However, there is insufficient evidence to support a recommendation. In addition to the certainty of evidence, the reference group considered the onset costs, logistical challenges, and jurisdictional, geographic and institutional variability associated with providing VHAs with an MHP. The reference group anticipates minimal variation in patient preferences for this intervention.

Implementation

Expertise is required to undertake and interpret the test.

Research needs

Further well designed RCTs are required to confirm potential benefits associated with VHAs.

Figure S9: Forest plot of comparison: TEG or ROTEM vs MHP or standard laboratory testson mortality at latest timepoint

| | TEG or R | OTEM | Contr | ol | | Risk Ratio | Risk Ratio |
|---|---------------|-----------|---------------------|-------|--------|---------------------|---|
| Study or Subgroup | Events | Total | Events | Total | Weight | M-H, Random, 95% Cl | M-H, Random, 95% Cl |
| 1.1.2 RCTs: coagulopathy or severe | bleeding at | inclusio | n | | | | |
| Weber 2012 (Cardiac) | 2 | 50 | 10 | 50 | 1.2% | 0.20 [0.05, 0.87] | · · · · · · · · · · · · · · · · · · · |
| Paniagua 2011 (Cardiac) | 3 | 26 | 4 | 18 | 1.4% | 0.52 [0.13, 2.05] | |
| Gonzalez 2016 (Trauma) | 11 | 56 | 20 | 55 | 6.4% | 0.54 [0.29, 1.02] | |
| Baksaas-Aasen 2020 (Trauma) | 50 | 201 | 55 | 194 | 23.8% | 0.88 [0.63, 1.22] | |
| Subtotal (95% CI) | | 333 | | 317 | 32.7% | 0.61 [0.37, 1.02] | \bullet |
| Total events | 66 | | 89 | | | | |
| Heterogeneity: Tau ² = 0.11; Chi ² = 5.38 | , df = 3 (P = | 0.15); l² | = 44% | | | | |
| Test for overall effect: Z = 1.88 (P = 0.0 | 6) | | | | | | |
| 1.1.3 NRSIs: patients with critical ble | eding | | | | | | |
| Snegovskikh 2018 (Coh, obstetrics) | 0 | 28 | 0 | 58 | | Not estimable | |
| Barinov 2015 (Coh, PPH) | 0 | 90 | 0 | 29 | | Not estimable | |
| McNamara 2019 (Coh, obstetrics) (1) | 0 | 203 | 0 | 52 | | Not estimable | |
| Prat 2017 (Coh, trauma) | 4 | 85 | 7 | 134 | 1.8% | 0.90 [0.27, 2.99] | |
| Schochl 2011 (Coh, trauma) | 6 | 80 | 60 | 601 | 3.9% | 0.75 [0.34, 1.68] | |
| Wang 2017 (Coh, trauma) | 12 | 86 | 19 | 80 | 6.0% | 0.59 [0.31, 1.13] | |
| Nardi 2015 (Coh, trauma) | 13 | 96 | 26 | 130 | 6.9% | 0.68 [0.37, 1.25] | |
| Kashuk 2012 (Coh, trauma) | 10 | 34 | 20 | 34 | 7.3% | 0.50 [0.28, 0.90] | |
| Unruh 2019 (Coh, trauma) | 15 | 47 | 11 | 20 | 7.7% | 0.58 [0.33, 1.03] | |
| Guth 2019 (Coh, trauma) | 33 | 102 | 34 | 102 | 16.6% | 0.97 [0.66, 1.44] | |
| Tapia 2013 (Coh, trauma) | 41 | 165 | 35 | 124 | 17.2% | 0.88 [0.60, 1.30] | |
| Subtotal (95% CI) | | 1016 | | 1364 | 67.3% | 0.75 [0.62, 0.92] | \bullet |
| Total events | 134 | | 212 | | | | |
| Heterogeneity: Tau ² = 0.00; Chi ² = 5.62 | , df = 7 (P = | 0.59); l² | = 0% | | | | |
| Test for overall effect: Z = 2.85 (P = 0.0 | 04) | | | | | | |
| Total (95% CI) | | 1349 | | 1681 | 100.0% | 0.75 [0.64, 0.88] | ◆ |
| Total events | 200 | | 301 | | | | |
| Heterogeneity: Tau ² = 0.00; Chi ² = 10.9 | 4, df = 11 (P | = 0.45); | l ² = 0% | | | | |
| Test for overall effect: Z = 3.54 (P = 0.0 | 004) | | | | | | 0.05 0.2 1 5 20 Favours TEG or ROTEM Favours Control |
| Test for subgroup differences: Chi ² = 0. | 54, df = 1 (P | = 0.46), | l ² = 0% | | | | |
| Footnotes | | | | | | | |

(1) women with major obstetric haemorrhage (estimated blood loss > 1500 mL) and coagulopathy

VHA and outcomes in any setting: PICO

Population: People with critical bleeding (any setting)

Intervention: VHA

Comparator: Standard best practice care (blood component therapy guided by MHP protocol or standard laboratory tests)

| Outcome | Study results and | Absolute effec | t estimates: | Certainty of the Evidence | Plain language |
|--|--|---|--------------|---|---|
| Timeframe | measurements | standard best practice care | VHA | (Quality of evidence) | summary |
| Mortality, all cause (RCTs) ¹ latest reported | Relative risk: 0.61 (CI 95% 0.37 - 1.02) Based on data from 650 participants in 4 studies | 281 171 per 1000 per 1000 Difference: 110 fewer per | | Very low Due to serious risk of bias, Due to serious inconsistency, Due | The use of TEG or ROTEM to guide blood component therapy may reduce mortality in patients with critical bleeding |
| timepoint | | 100 (Cl 95% 177 few | - | to serious imprecision | (any setting) but the evidence is very uncertain. |

| Mortality, all cause (Coh) latest reported timepoint | Relative risk: 0.75 (Cl 95% 0.62 - 0.92) Based on data from 2175 participants in 9 studies | 166 125 per 1000 per 1000 Difference: 41 fewer per 1000 (Cl 95% 63 fewer - 13 fewer) | Very low Due to serious risk of bias, Due to serious inconsistency, Due to serious imprecision | The use of TEG or ROTEM to guide blood component therapy may be associated with reduced mortality in patients with critical bleeding (any setting) but the evidence is very uncertain. |
|---|--|--|---|--|
| Morbidity, thromboembolic events | Relative risk: 0.83 (CI 95% 0.41 - 1.66) Based on data from 651 participants in 4 studies | 91 76 per 1000 per 1000 Difference: 15 fewer per 1000 (CI 95% 54 fewer - 60 more) | Very low Due to serious risk of bias, Due to serious imprecision, Due to serious publication bias | The use of TEG or ROTEM to guide blood component therapy may have no difference on thromboembolic events in patients with critical bleeding (any setting) but the evidence is very uncertain. |
| Red blood cell transfusion volume (RCTs) | Measured by: Number of Units Lower better Based on data from 153 participants in 2 studies | 6.42-15.65 7.1-13.96 Difference: SMD 0.06 fewer (CI 95% 0.38 fewer - 0.26 more) | Very low Due to serious risk of bias, Due to serious imprecision, Due to serious publication bias | The evidence suggests use of TEG or ROTEM to guide blood component therapy in patients with critical bleeding (any setting) may have little or no difference in the volume of red blood cells transfused. |
| Red blood cells transfusion volume (Coh) | Measured by: Number of Units Lower better Based on data from 1605 participants in 7 studies | 2-11 2-6.5 Difference: SMD 0.46 fewer (Cl 95% 0.72 fewer - 0.20 fewer) | Very low Due to serious risk of bias, Due to serious inconsistency | The use of TEG or ROTEM to guide blood component therapy in patients with critical bleeding (any setting) may be associated with a slight reduction in the volume of red blood cells transfused but the evidence is very uncertain. |
| Transfusion volume, other blood components | | The use of TEG or ROTEM did not demonstrate a statistically significant reduction the volume of FFP or platelets transfused across patients in trauma, cardiothoracic or obstetrics settings. There was little evidence reported relating to fibrinogen replacement therapy. | Very low Due to serious risk of bias, Due to serious imprecision, Due to serious inconsistency | The use of TEG or ROTEM to guide blood component therapy in patients with critical bleeding (any setting) may be associated with little or no difference in the volume of FFP or platelets transfused but the evidence is very uncertain. |

VHA and outcomes in trauma setting: PICO

Population: People with critical bleeding (trauma setting) Intervention: VHA

Comparator: Standard best practice care (blood component therapy guided by MHP protocol or standard laboratory tests)

| Outcome Timeframe | Study results and measurements | Absolute effect estimates standard best practice care VHA | Certainty of the Evidence (Quality of evidence) | Plain language summary |
|--|--|---|---|--|
| Mortality, all cause (RCTs) latest reported timepoint | Relative risk: 0.75 (CI 95% 0.48 - 1.17) Based on data from 506 participants in 2 studies | 301 226 per 1000 per 1000 Difference: 75 fewer per 1000 (CI 95% 157 fewer - 51 more) | Very low Due to serious risk of bias, Due to serious inconsistency, Due to serious imprecision | The use of TEG or ROTEM to guide blood component therapy in patients with critical bleeding in the trauma setting may reduce mortality but the evidence is very uncertain. |
| Mortality, all cause (Coh) latest reported timepoint | Relative risk: 0.75 (CI 95% 0.62 - 0.92) Based on data from 1920 participants in 8 studies | 173 130 per 1000 per 1000 Difference: 43 fewer per 1000 (Cl 95% 66 fewer - 14 fewer) | Very low Due to serious risk of bias, Due to serious imprecision | The use of TEG or ROTEM to guide blood component therapy in patients with critical bleeding in the trauma setting may be associated with reduced mortality but the evidence is very uncertain. |
| Morbidity, thromboembolic events | Relative risk: 0.9 (Cl 95% 0.42 - 1.95) Based on data from 507 participants in 2 studies | 113 102 per 1000 per 1000 Difference: 11 fewer per 1000 (Cl 95% 66 fewer - 107 more) | Very low Due to serious risk of bias, Due to serious inconsistency, Due to serious imprecision, Due to serious publication bias | The use of TEG or ROTEM to guide blood component therapy may have little or no difference on thromboembolic events in patients with critical bleeding in the trauma setting but the evidence is very uncertain. |
| Morbidity, MOF | Relative risk: 1.75 (CI 95% 0.6 - 5.12) Based on data from 396 participants in 1 studies | 26 46 per 1000 per 1000 Difference: 20 more per 1000 (Cl 95% 10 fewer - 107 more) | Very low Due to serious risk of bias, Due to very serious imprecision | The use of TEG or ROTEM to guide blood component therapy may have no difference on MOF in patients with critical bleeding in the trauma setting but the evidence is very uncertain. |
| Red blood cell transfusion volume (RCTs) | Measured by: Number of Units Lower better Based on data from 109 participants in 1 studies | 15.65 13.96 Units (Mean) Units (Mean) Difference: SMD 0.13 fewer (CI 95% 0.50 fewer - 0.25 more) 0.25 more) | Low Due to serious risk of bias, Due to serious imprecision | The evidence suggests the use of TEG or ROTEM to guide blood component therapy in patients with critical bleeding (any setting) may have little to no difference in the volume of red blood cells transfused. |
| Red blood cell transfusion volume (Coh) | Measured by: Number of Units Lower better Based on data from 1484 participants in 7 studies | 2-11 2-6.5 Difference: SMD 0.41 fewer (CI 95% 0.68 fewer - 0.14 fewer) | Very low Due to serious risk of bias, Due to serious imprecision, Due to serious inconsistency | The use of TEG or ROTEM to guide blood component therapy in patients with critical bleeding in the trauma setting may be associated |

Table S28: VHA guided resuscitation and outcomes in trauma setting

| | | | | with a slight reduction in the volume of red blood cells transfused but the evidence is very uncertain. |
|-----------------------------------|--|--|--|--|
| FFP transfusion volume | Measured by: Number of Units Lower better Based on data from 765 participants in 6 studies | 1-7.57 1-7.49 Difference: SMD 0.32 fewer (CI 95% 0.86 fewer - 0.21 more) | Very low Due to serious risk of bias, Due to very serious inconsistency, Due to serious imprecision | The use of TEG or ROTEM to guide blood component therapy in patient with critical bleeding in the trauma setting may be associated with little or no difference on the volume of FFP transfused but the evidence is very uncertain. |
| Platelet transfusion volume | Measured by: Number of Units Lower better Based on data from 580 participants in 4 studies | 0.95-4.2 0.4-2.7 Difference: SMD 0.91 fewer (Cl 95% 1.83 fewer - 0.11 more) | Very low Due to serious risk of bias, Due to serious inconsistency, Due to serious imprecision | The use of TEG or ROTEM to guide blood component therapy in patients with critical bleeding in the trauma setting may be associated with little or no difference in the volume of platelets transfused but the evidence is very uncertain. |

VHA and outcomes in surgical setting: PICO

Population: People with critical bleeding (surgical setting)

Intervention: VHA

Comparator: Standard best practice care (blood component therapy guided by MHP protocol or standard laboratory tests)

Table S29: VHA guided resuscitation and outcomes in surgical setting

| Outcome Timeframe | Study results and measurements | Absolute effect estimates standard best practice care VHA | Certainty of the Evidence (Quality of evidence) | Plain language summary |
|--|--|---|---|---|
| Mortality, all cause (RCTs) latest reported timepoint | Relative risk: 0.33 (CI 95% 0.12 - 0.91) Based on data from 144 participants in 2 studies | 206 68 per 1000 per 1000 Difference: 138 fewer per 1000 (CI 95% 181 fewer - 19 fewer) | Low Due to serious risk of bias, Due to serious imprecision | The evidence suggests the use of TEG or ROTEM to guide blood component therapy in patients with critical bleeding in the surgical setting (cardiothoracic) may reduce mortality. |
| Morbidity, thromboembolic events | Relative risk: 0.2 (CI 95% 0.01 - 4.06) Based on data from 144 participants in 2 studies | 29 6 per 1000 per 1000 Difference: 23 fewer per 1000 (Cl 95% 29 fewer - 89 more) | Very low Due to serious risk of bias, Due to very serious imprecision | The use of TEG or ROTEM to guide blood component therapy in patients with critical bleeding in the surgical setting (cardiothoracic) may be associated with |

| | | | | little or no difference on the incidence of thromboembolic events but the evidence is very uncertain. |
|--|---|--|---|---|
| Red blood cell transfusion volume (RCTs) | Measured by: Number of Units Lower better Based on data from 44 participants in 1 studies | 6.42 7.1 Units (Mean) Units (Mean) Difference: SMD 0.12 more (CI 95% 0.48 fewer - 0.72 more) | Very low Due to serious risk of bias, Due to serious imprecision, Due to serious publication bias | The use of TEG or ROTEM to guide blood component therapy in patients with critical bleeding in the surgical setting (cardiothoracic) may have little or no difference on the volume of red blood cells transfused but the evidence is very uncertain. |
| FFP transfusion volume | Measured by: Number of Units Lower better Based on data from 54 participants in 2 studies | 2.8-9.2 1.6-3.2 Difference: SMD 0.50 fewer (CI 95% 1.91 fewer - 0.91 more) | Very low Due to serious risk of bias, Due to serious inconsistency, Due to serious imprecision, Due to very serious publication bias | The use of TEG or ROTEM to guide blood component therapy in patients with critical bleeding in the surgical setting (cardiothoracic) may have little or no difference on the volume of FFP transfused but the evidence is very uncertain. |
| Platelet transfusion volume | Measured by: Number of Units Lower better Based on data from 44 participants in 1 studies | 1.34 0.85 Units (Mean) Units (Mean) Difference: SMD 0.33 fewer (CI 95% 0.94 fewer - 0.27 more) | Very low Due to serious risk of bias, Due to serious imprecision, Due to serious publication bias | The use of TEG or ROTEM to guide blood component therapy in patients with critical bleeding in the surgical setting (cardiothoracic) may have little or no difference on the volume of platelets transfused but the evidence is very uncertain. |

Research question: In patients with critical bleeding, what is the effect of cell salvage on patient outcomes?

Latest search date: 29 September 2021

GPS11: The reference group agreed that the use of cell salvage* in patients with critical bleeding may be considered as part of a major haemorrhage protocol. There is insufficient evidence to provide a recommendation.

*The use of cell salvage requires specific expertise and training.

Evidence to decision

| Benefits and harms | Small net benefit, or little difference between alternatives |
|--|--|
| In a meta-analysis of observational cohort studies little to no effect harms were uncertain. | t on mortality was demonstrated and evidence for |
| | |
| Certainty of the Evidence | Very low |
| For most bleeding patients there is no substantial survival benefit a salvage. The overall certainty in effect estimates across outcomes | |
| | |
| Values and preferences | No substantial variability expected |
| There is no plausible reason to suspect that patients who are critic an MHP as recommended. A subgroup of patients may decline cell | |
| | |
| Resources | Important negative issues |
| There are costs associated with the implementation and use of cel economic analysis was not conducted as part of this review. | l salvage as part of an MHP. However, a formal health |
| | |
| Equity | Important issues, or potential issues not investigated |
| The reference group acknowledged that there is jurisdictional, geo availability of cell salvage as part of an MHP. | graphical and/or institutional variability in the |
| | |
| Acceptability | Important issues, or potential issues not |

investigated

Feasibility

Important issues, or potential issues not investigated

The reference group acknowledged the logistical challenges associated with providing cell salvage as part of an MHP in patients who are critically bleeding. Adaptation of this guidance at a local level is required upon consideration of the resources available.

Rationale

Direct evidence about the benefits of cell salvage in patients who are critically bleeding is weak. The reference group agrees cell salvage may be considered as part of an MHP. The reference group considered the onset costs, logistical challenges and institutional variability associated with providing cell salvage. The reference group anticipates minimal variation in patient preferences for this intervention.

Figure S10: Forest plot of comparison: cell salvage vs no cell salvage on mortality at any timepoint up to 30 days

| | Experim | ental | Contr | ol | | Risk Ratio | Risk Ratio |
|---|-------------|------------|--------|-------|--------|---------------------|--|
| Study or Subgroup | Events | Total | Events | Total | Weight | M-H, Random, 95% Cl | M-H, Random, 95% Cl |
| 1.1.1 Trauma | | | | | | | |
| Bhangu 2012 (coh, combat trauma) (1) | 1 | 18 | 0 | 11 | 0.6% | 1.89 [0.08, 42.82] | · · · · · · · · · · · · · · · · · · · |
| Bowley 2006 (RCT, penetrating trauma) (2) | 14 | 21 | 15 | 23 | 33.1% | 1.02 [0.67, 1.56] | _ |
| Subtotal (95% CI) | | 39 | | 34 | 33.7% | 1.03 [0.68, 1.57] | \bullet |
| Total events | 15 | | 15 | | | | |
| Heterogeneity: Tau ² = 0.00; Chi ² = 0.16, df = 1 | (P = 0.69); | l² = 0% | | | | | |
| Test for overall effect: Z = 0.15 (P = 0.88) | | | | | | | |
| 1.1.2 Urgent abdominal aortic aneurysm rep | air | | | | | | |
| Shuhaiber 2003 (Coh, urgent AAA) (3) | 0 | 4 | 0 | 21 | | Not estimable | |
| Tawfick 2008 (Coh, urgent AAA) (4) | 6 | 27 | 9 | 28 | 7.6% | 0.69 [0.28, 1.68] | |
| Posacioglu 2002 (Coh, urgent AAA) (5) | 16 | 40 | 8 | 16 | 15.6% | 0.80 [0.43, 1.49] | |
| Markovic 2009 (Coh, ruptured AAA) (6) | 12 | 30 | 14 | 30 | 17.7% | 0.86 [0.48, 1.53] | |
| Serracino-Inglott 2005 (Coh, urgent AAA) (7) | 13 | 40 | 56 | 114 | 25.5% | 0.66 [0.41, 1.07] | |
| Subtotal (95% CI) | | 141 | | 209 | 66.3% | 0.74 [0.55, 1.01] | \bullet |
| Total events | 47 | | 87 | | | | |
| Heterogeneity: Tau ² = 0.00; Chi ² = 0.54, df = 3 | (P = 0.91); | l² = 0% | | | | | |
| Test for overall effect: Z = 1.92 (P = 0.05) | | | | | | | |
| Total (95% CI) | | 180 | | 243 | 100.0% | 0.83 [0.65, 1.06] | • |
| Total events | 62 | | 102 | | | | |
| Heterogeneity: Tau ² = 0.00; Chi ² = 2.35, df = 5 | (P = 0.80); | l² = 0% | | | | | |
| Test for overall effect: Z = 1.48 (P = 0.14) | | | | | | | |
| Test for subgroup differences: Chi ² = 1.54, df = | 1 (P = 0.2 | 1), l² = 3 | 5.2% | | | | Favours cell salvage Favours no cell salvage |

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.

Cell Salvage and outcomes in trauma setting: PICO

Population: People with critical bleeding (trauma setting) Intervention: Cell salvage Comparator: No cell salvage

Table S30: Cell salvage in trauma setting

| | | _ | | |
|--|---|--|--|--|
| Outcome Timeframe | Study results and measurements | Absolute effect estimates No cell salvage Cell salvage | Certainty of the Evidence (Quality of evidence) | Plain language summary |
| Mortality, all cause (RCTs) latest reported timepoint | Relative risk: 1.02 (Cl 95% 0.67 - 1.56) Based on data from 44 participants in 1 studies | 652 665 per 1000 per 1000 Difference: 13 more per 1000 (Cl 95% 215 fewer - 365 more) | Very low Due to serious indirectness, Due to very serious imprecision | Cell salvage may have little or no difference on mortality in trauma patients with critical bleeding, but the evidence is very uncertain. |
| Morbidity, post- operative complications sepsis | Relative risk: 0.78 (CI 95% 0.29 - 2.09) Based on data from 44 participants in 1 studies | 304 237 per 1000 per 1000 Difference: 67 fewer per 1000 (Cl 95% 216 fewer - 331 more) | Very low Due to serious indirectness, Due to very serious imprecision | Cell salvage may have little or no difference in morbidity (sepsis) in trauma patients with critical bleeding, but the evidence is very uncertain. |
| Red blood cell transfusion volume | Measured by: Number of Units Lower better Based on data from 44 participants in 1 studies | 11.17 6.47 Units (Mean) Units (Mean) Difference: SMD 0.82 fewer (CI 95% 1.44 fewer - 0.20 fewer) | Very low Due to serious indirectness, Due to very serious imprecision | Cell salvage may reduce the volume of allogenic red blood cell transfused slightly in trauma patients with critical bleeding, but the evidence is very uncertain. |
| FFP transfusion volume | Measured by: Number of Units Lower better Based on data from 44 participants in 1 studies | 4.04 4.76 Units (Mean) Units (Mean) Difference: SMD 0.16 more (CI 95% 0.44 fewer - 0.75 more) | Very low Due to serious indirectness, Due to very serious imprecision | Cell salvage may have no difference on the volume of FFP transfused in trauma patients with critical bleeding, but evidence is very uncertain. |
| Platelet transfusion volume | Measured by: Number of Units Lower better Based on data from 44 participants in 1 studies | 0.56 1 Units (Mean) Units (Mean) Difference: SMD 0.26 more (CI 95% 0.33 fewer - 0.85 more) | Very low Due to very serious indirectness, Due to serious imprecision | Cell salvage may have no difference on the volume of platelets transfused in trauma patients with critical bleeding, but the evidence is very uncertain. |

Cell Salvage and outcomes in medical emergencies: PICO

Population: People with critical bleeding (medical emergency) Intervention: Cell salvage Comparator: No cell salvage

Table S31: Cell salvage in medical emergency setting

| Outcom | Outcome Stud | Study results and | Absolute ef | fect estimates | Certainty of the Evidence | Plain language |
|----------|--------------|-------------------|--------------------|----------------|---------------------------|----------------|
| Timefrar | ne | measurements | No cell salvage | Cell salvage | (Quality of evidence) | summary |

| Mortality, all cause latest reported timepoint | Relative risk: 0.74 (CI 95% 0.55 - 1.01) Based on data from 350 participants in 5 studies | 416 308 per 1000 per 1000 Difference: 108 fewer per 1000 (CI 95% 187 fewer - 4 more) | Very low Due to serious risk of bias, Due to serious inconsistency, Due to serious imprecision | Cell salvage may be associated with little or no difference in mortality in patients undergoing urgent AAA repair, but the evidence is very uncertain. |
|---|--|---|---|--|
| Morbidity, respiratory complications | Relative risk: 3.2 (CI 95% 0.83 - 12.35) Based on data from 235 participants in 3 studies | 13 42 per 1000 per 1000 Difference: 29 more per 1000 (CI 95% 2 fewer - 148 more) | Very low Due to serious risk of bias, Due to serious imprecision | The evidence is very uncertain about the association of cell salvage with post- operative respiratory complications in patients undergoing urgent AAA repair. |
| Morbidity, renal complications | Relative risk: 2.0 (Cl 95% 0.49 - 8.14) Based on data from 235 participants in 3 studies | 13 26 per 1000 per 1000 Difference: 13 more per 1000 (Cl 95% 7 fewer - 93 more) | Very low Due to serious risk of bias, Due to serious imprecision, Due to serious risk of bias | The evidence is very uncertain about the association of cell salvage with post- operative renal complications in patients undergoing urgent AAA repair. |
| Morbidity, gastrointestinal complications | Relative risk: 1.6 (CI 95% 0.19 - 13.24) Based on data from 235 participants in 3 studies | 6 10 per 1000 per 1000 Difference: 4 more per 1000 (CI 95% 5 fewer - 73 more) | Very low Due to serious risk of bias, Due to serious imprecision | The evidence is very uncertain about the association of cell salvage with post- operative gastrointestinal complications in patients undergoing urgent AAA repair. |
| Red blood cell transfusion volume | Measured by: Number of Units Lower better Based on data from 350 participants in 5 studies | 3.63-12.6 4-11.2 Difference: SMD 0.36 fewer (CI 95% 0.87 fewer - 0.14 more) | Very low Due to serious risk of bias, Due to serious inconsistency, Due to serious imprecision | Cell salvage may be associated with little or no difference on the volume of allogenic red blood cells transfused in patients undergoing urgent AAA repair, but the evidence is very uncertain. |