Supplemental electronic material 1: Evidence summaries

Title: Transfusion strategies in non-bleeding critically ill adults: a clinical practice guideline from the European Society of Intensive Care Medicine.

Writing committee:
Alexander Vlaar*, Simon Oczkowski*, Sanne de Bruin, Marije Wijnberge, Massimo Antonelli, Cecile Aubron, Philippe Aries, Jacques Duranteau, Nicole P. Juffermans, Jens Meier, Gavin J. Murphy, Riccardo Abbasciano, Marcella Muller, Akshay Shah, Anders Perner, Sofie Rygaard, Timothy S. Walsh, Gordon Guyatt, Joanna Dionne*, Maurizio Cecconi*

*Contributed equally

Correspondence:
A.P.J. Vlaar, MD, PhD, MBA
Department of Intensive Care Medicine
Room, C3-430
Meibergdreef 9
1105 AZ Amsterdam, the Netherlands
Telephone: 00-31-20-5669111
Fax: 00-31-20-5669568
E-mail: a.p.vlaar@amc.uva.nl

Evidence summaries:

1. Restrictive vs. liberal red blood cell transfusion
2. Alternative transfusion triggers
3. Transfusion prevention
4. Platelet transfusion
5. Plasma transfusion
Question: Restrictive transfusion strategy compared to liberal transfusion strategy in a general adult ICU population

| Certainty assessment | № of patients | Effect | Certainty | Importance |
|-----------------------|---------------|--------|-----------|------------|
|                        | № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Restrictive strategy | Liberal strategy | Relative (95% CI) | Absolute (95% CI) | |
| Mortality (60 days to 1 year) | 4 | RCTs | not serious | not serious | not serious | serious a | none | 395/1003 (39.4%) | 420/1001 (42.0%) | RR 0.92 (0.79 to 1.07) | 34 fewer per 1,000 (from 88 fewer to 29 more) | ⬤️ ⬤️ ⬤️ CRITICAL |
| Mortality (28 to 60 days) | 5 | RCTs | not serious | not serious | not serious | serious a | none | 325/1026 (31.7%) | 359/1025 (35.0%) | RR 0.91 (0.81 to 1.03) | 32 fewer per 1,000 (from 67 fewer to 11 more) | ⬤️ ⬤️ ⬤️ CRITICAL |
| Quality of life | 2 | RCTs | serious b | not serious | not serious b | serious a | none | 142 | 140 | - | MD 0.02 SD lower (0.25 lower to 0.21 higher) | ⬤️ ⬤️ ⬤️ LOW CRITICAL |
| Functional recovery | 1 | RCTs | serious b | not serious | serious d | serious a | none | 51 | 49 | - | MD 3 points higher (0.82 higher to 5.18 higher) | ⬤️ ⬤️ ⬤️ VERY LOW CRITICAL |
| Stroke | 3 | RCTs | serious e | not serious | not serious | serious a | none | 29/957 (3.0%) | 44/958 (4.6%) | RR 0.67 (0.42 to 1.05) | 15 fewer per 1,000 (from 27 fewer to 2 more) | ⬤️ ⬤️ ⬤️ LOW IMPORTANT |
| Myocardial infarction | 3 | RCTs | not serious f | serious g | not serious | serious a | none | 18/957 (1.9%) | 20/958 (2.1%) | RR 0.90 (0.48 to 1.69) | 2 fewer per 1,000 (from 11 fewer to 14 more) | ⬤️ ⬤️ ⬤️ VERY LOW IMPORTANT |
| ARDS |
Explanations

a. 95% confidence interval which does not exclude a significant benefit or harm of likely importance to patients.
b. High loss to follow-up in both included studies.
c. Trials used a reliable instruments for measuring quality of life (SF-12 and SF-36) both tested for validity in the intensive care unit.
d. Single study used Rivermeade Mobility Index, a scale designed for stroke and not validated for use in the ICU population.
e. Given the lack of blinding, and lack of standardized screening procedures, there is a risk of detection bias contributing to the demonstrated effect.
f. Although the lack of standardized screening procedures and blinding of clinicians could have resulted in detection bias, we did not observe a differences in event rates between the two groups making it unlikely this resulted in a biased estimate of effect.
g. High value for I² (>50%) not easily explained by trial characteristics or study populations.
h. The included study reported a composite of multiple infections, which may vary significantly in their severity and importance to patients.

Summary statements:
1. Restrictive transfusion strategy probably does not increase long-term mortality (60 days to 1 year), although our certainty is limited by imprecision.
2. Restrictive transfusion strategy probably does not increase short-term mortality, though our certainty is limited by imprecision.
3. Restrictive transfusion strategy may result in little to no difference in quality of life, though our certainty is limited by risk of bias and imprecision.
4. We are uncertain about the effects of restrictive transfusion strategy upon function outcomes, due to risk of bias, indirectness, and imprecision.
5. Restrictive transfusion strategy may reduce stroke though our certainty is limited by the possibility of detection bias and imprecision.
6. Restrictive transfusion strategy may result in little to no difference in myocardial infarction, though our certainty is limited by inconsistency and imprecision.
7. Restrictive transfusion strategy may reduce ARDS though our certainty is limited by risk of detection bias and imprecision.
8. Restrictive transfusion strategy probably results in little to no difference in need for renal replacement therapy, though our certainty is limited by imprecision.
9. Restrictive transfusion strategy may result in little to no difference in infections, though our certainty is limited by indirectness and imprecision.
1. Mortality (long term: 60 days to 1 year)

| Study or Subgroup | Restrictive | Total | Liberal | Total | Weight | Risk Ratio M–H, Random, 95% CI | Year |
|-------------------|-------------|-------|---------|-------|--------|-------------------------------|------|
| Hebert 1995       | 13          | 33    | 11      | 36    | 5.2%   | 1.29 [0.67, 2.47]            | 1995 |
| Hebert 1999       | 95          | 418   | 111     | 420   | 27.5%  | 0.86 [0.68, 1.09]            | 1999 |
| Walsh 2013        | 19          | 51    | 27      | 49    | 10.7%  | 0.68 [0.44, 1.05]            | 2013 |
| Holst 2014        | 268         | 501   | 271     | 496   | 56.6%  | 0.98 [0.87, 1.10]            | 2014 |

Total (95% CI) 1003 1001 100.0% 0.92 [0.79, 1.07]

Total events 395 420
Heterogeneity: Tau² = 0.01; Chi² = 4.15, df = 3 (P = 0.25); I² = 28%
Test for overall effect: Z = 1.05 (P = 0.29)

2. Mortality (short term: 28-60 days)

| Study or Subgroup | Restrictive | Total | Liberal | Total | Weight | Risk Ratio M–H, Random, 95% CI | Year |
|-------------------|-------------|-------|---------|-------|--------|-------------------------------|------|
| Hebert 1995       | 8           | 33    | 9       | 36    | 2.0%   | 0.97 [0.42, 2.22]            | 1995 |
| Hebert 1999       | 78          | 418   | 98      | 420   | 19.7%  | 0.80 [0.61, 1.04]            | 1999 |
| Walsh 2013        | 12          | 51    | 16      | 49    | 3.4%   | 0.72 [0.38, 1.36]            | 2013 |
| Holst 2014        | 216         | 502   | 223     | 496   | 70.4%  | 0.96 [0.83, 1.10]            | 2014 |
| Mazza 2015        | 11          | 22    | 13      | 24    | 4.5%   | 0.92 [0.53, 1.61]            | 2015 |

Total (95% CI) 1026 1025 100.0% 0.91 [0.81, 1.03]

Total events 325 359
Heterogeneity: Tau² = 0.00; Chi² = 1.99, df = 4 (P = 0.74); I² = 0%
Test for overall effect: Z = 1.51 (P = 0.13)

3. Quality of life (180 days to 1 year; measured with SF-12, SF-36)

| Study or Subgroup | Restrictive Mean | SD | Total | Liberal Mean | SD | Total | Weight | Std. Mean Difference IV, Fixed, 95% CI | Year |
|-------------------|------------------|----|-------|--------------|----|-------|--------|----------------------------------------|------|
| Walsh 2013        | 30               | 11.9 | 51    | 31            | 11.1 | 49    | 35.4%  | -0.09 [-0.48, 0.31]                    | 2013 |
| Holst 2014        | 7.6              | 27.8 | 91    | 7.2          | 29.2 | 91    | 64.6%  | 0.01 [-0.28, 0.30]                     | 2014 |

Total (95% CI) 142 140 100.0% -0.02 [-0.25, 0.21]

Heterogeneity: Chi² = 0.16, df = 1 (P = 0.69); I² = 0%
Test for overall effect: Z = 0.18 (P = 0.86)
4. Functional recovery (assessed with Rivermeade mobility index)

| Study or Subgroup | Restrictive Mean | SD | Total | Liberal Mean | SD | Total | Weight | Mean Difference IV, Fixed, 95% CI | Year |
|-------------------|------------------|----|-------|--------------|----|-------|--------|----------------------------------|------|
| Walsh 2013        | -13              | 5.9| 51    | -10          | 5.2| 49    | 100.0% | -3.00 [-5.18, -0.82]             | 2013 |
| Total (95% CI)    | 51               |    |       | 49           |    |       | 100.0% | -3.00 [-5.18, -0.82]             |      |

Heterogeneity: Not applicable
Test for overall effect: $Z = 2.70$ ($P = 0.007$)

5. Stroke

| Study or Subgroup | Restrictive Events | Total | Liberal Events | Total | Weight | Risk Ratio M–H, Fixed, 95% CI | Year |
|-------------------|--------------------|-------|----------------|-------|--------|-------------------------------|------|
| Hebert 1999       | 25                 | 418   | 33             | 420   | 74.1%  | 0.76 [0.46, 1.26]             | 1999 |
| Walsh 2013        | 0                  | 51    | 1              | 49    | 3.4%   | 0.32 [0.01, 7.68]             | 2013 |
| Holst 2014        | 4                  | 488   | 10             | 489   | 22.5%  | 0.40 [0.13, 1.27]             | 2014 |
| Total (95% CI)    | 957                | 958   | 100.0%         |       |        | 0.67 [0.42, 1.05]             |      |

Total events: 29, 44
Heterogeneity: Chi² = 1.22, df = 2 ($P = 0.54$); I² = 0%
Test for overall effect: $Z = 1.77$ ($P = 0.08$)

6. Myocardial infarction

| Study or Subgroup | Restrictive Events | Total | Liberal Events | Total | Weight | Risk Ratio M–H, Fixed, 95% CI | Year |
|-------------------|--------------------|-------|----------------|-------|--------|-------------------------------|------|
| Hebert 1999       | 3                  | 418   | 12             | 420   | 59.8%  | 0.25 [0.07, 0.88]             | 1999 |
| Walsh 2013        | 2                  | 51    | 2              | 49    | 10.2%  | 0.96 [0.14, 6.56]             | 2013 |
| Holst 2014        | 13                 | 488   | 6              | 489   | 30.0%  | 2.17 [0.83, 5.67]             | 2014 |
| Total (95% CI)    | 957                | 958   | 100.0%         |       |        | 0.90 [0.48, 1.69]             |      |

Total events: 18, 20
Heterogeneity: Chi² = 7.20, df = 2 ($P = 0.03$); I² = 72%
Test for overall effect: $Z = 0.33$ ($P = 0.74$)
7. ARDS

| Study or Subgroup | Restrictive Events | Total | Liberal Events | Total | Weight | Risk Ratio M-H, Fixed, 95% CI | Year |
|-------------------|--------------------|-------|----------------|-------|--------|-------------------------------|------|
| Hebert 1999       | 32                 | 418   | 48             | 420   | 100.0% | 0.67 [0.44, 1.03]               | 1999 |

Total (95% CI) | 418 | 420 | 100.0% | 0.67 [0.44, 1.03]

Test for overall effect: Z = 1.84 (P = 0.07)

8. Renal failure requiring renal replacement therapy

| Study or Subgroup | Restrictive Events | Total | Liberal Events | Total | Weight | Risk Ratio M-H, Fixed, 95% CI | Year |
|-------------------|--------------------|-------|----------------|-------|--------|-------------------------------|------|
| Holst 2014        | 24                 | 488   | 28             | 489   | 100.0% | 0.86 [0.51, 1.46]               | 2014 |

Total (95% CI) | 488 | 489 | 100.0% | 0.86 [0.51, 1.46]

Test for overall effect: Z = 0.56 (P = 0.57)

9. Infections

| Study or Subgroup | Restrictive Events | Total | Liberal Events | Total | Weight | Risk Ratio M-H, Random, 95% CI | Year |
|-------------------|--------------------|-------|----------------|-------|--------|-------------------------------|------|
| Hebert 1995       | 50                 | 420   | 42             | 418   | 100.0% | 1.18 [0.80, 1.75]               | 1995 |

Total (95% CI) | 420 | 418 | 100.0% | 1.18 [0.80, 1.75]

Test for overall effect: Z = 0.86 (P = 0.39)
**Question:** Restrictive transfusion strategy compared to liberal transfusion strategy in adult ICU patients with acute coronary syndromes

| Certainty assessment | No of patients | Effect | Certainty | Importance |
|----------------------|----------------|--------|-----------|------------|
| **Mortality (short term) (30 to 60 days)** | | | | |
| 5 RCTs | serious a | not serious | not serious b | serious c | none | 74/282 (26.2%) | 60/303 (19.8%) | RR 1.31 (0.98 to 1.75) | 61 more per 1,000 (from 4 fewer to 149 more) | ☮️ ☮️ ☮️ LOW CRITICAL |
| **Stroke** | | | | | |
| 1 RCTs | serious a,d | not serious | serious c | serious c | none | 0/55 (0.0%) | 1/55 (1.8%) | RR 0.33 (0.01 to 8.01) | 12 fewer per 1,000 (from 18 fewer to 127 more) | ☮️ ☮️ ☮️ ☮️ VERY LOW IMPORTANT |
| **Myocardial infarction** | | | | | |
| 5 RCTs | serious a | not serious | not serious b | serious c | none | 28/331 (8.5%) | 43/354 (12.1%) | RR 0.74 (0.47 to 1.16) | 32 fewer per 1,000 (from 64 fewer to 19 more) | ☮️ ☮️ ☮️ LOW IMPORTANT |
| **Infections** | | | | | |
| 1 RCTs | not serious d | not serious | serious f | very serious g | none | 2/55 (3.6%) | 0/55 (0.0%) | RR 5.00 (0.25 to 101.81) | 0 fewer per 1,000 (from 0 fewer to 0 fewer) | ☮️ ☮️ ☮️ ☮️ VERY LOW IMPORTANT |

CI: Confidence interval; RR: Risk ratio

**Explanations**

a. Clinicians were not blinded in any study, leading to the possibility of performance bias. This is particularly relevant in patients with ACS as many co-interventions known to affect mortality in ACS and stroke can cause bleeding and worsen anemia. Given the absence of monitoring of cointervention, and the fact that outcome assessors were only blinded in one ACS study (Carson 2013), we chose to rate down for risk of bias.
b. Though the two studies with the primary objective of evaluating transfusion thresholds in patients with acute coronary syndromes were not specifically ICU studies, the effects of transfusion upon ICU patients with acute coronary syndromes are likely similar. This judgement is further supported as the effects seen in these studies are consistent with post-hoc analyses of patients with vascular disease included in ICU transfusion trials.

c. 95% confidence interval does not exclude significant harm or benefit, with absolute risk numbers of likely importance to patients.

d. Outcome assessors were blinded in the single study (Carson 2013).

e. Unclear how stroke was diagnosed (eg. imaging, clinical exam) or if it included minor events such as TIAs. Though the single study (Carson 2013) was not conducted in ICU patients with ACS, it is likely that the effects would be similar in ICU patients.

f. Unclear how infections were defined (pneumonia, blood stream infection) or their severity and impact upon patients. Though the single study (Carson 2013) was not conducted in ICU patients with ACS, it is likely that the effects would be similar in ICU patients.

g. Very small number of events (2) with wide 95% confidence interval, resulting in very serious imprecision.

Summary statements

1. Restrictive transfusion strategy may increase mortality (short term) slightly, though our certainty is limited by imprecision, and risk of bias from co-intervention from non-blinding.

2. We are uncertain about the effect of restrictive transfusion strategy on stroke, due to indirectness, imprecision, and risk of bias due to co-intervention from non-blinding.

3. Restrictive transfusion strategy may result in a small, possibly unimportant, reduction in myocardial infarction, though our certainty is limited by imprecision, and risk of bias from co-intervention from non-blinding.

4. We are uncertain about the effect of restrictive transfusion strategy on infections, due to indirectness and very serious imprecision.
1. Mortality (short term) (30 to 60 days)

| Study or Subgroup | Restrictive Events | Total Events | Liberal Events | Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|-------------------|-------------------|--------------|----------------|-------|--------|-------------------------------|
| Carson 2013       | 7                 | 55           | 1              | 55    | 1.7%   | 7.00 [0.89, 55.01]           |
| Cooper 2011       | 2                 | 24           | 1              | 21    | 1.9%   | 1.75 [0.17, 17.95]           |
| **Subtotal (95% CI)** | **79**         | **76**       |                |       | **3.6%** | **4.29 [0.97, 18.99]**        |
| Total events      | 9                 |              | 2              |       |        |                               |
| Heterogeneity: Chi² = 0.79, df = 1 (P = 0.38); I² = 0% |
| Test for overall effect: Z = 1.92 (P = 0.05) |

6.1.2 Post-hoc RCT analyses

| Study or Subgroup | Restrictive Events | Total Events | Liberal Events | Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|-------------------|-------------------|--------------|----------------|-------|--------|-------------------------------|
| Hebert 1999       | 29                | 111          | 31             | 146   | 46.5%  | 1.23 [0.79, 1.91]           |
| Holst 2014        | 33                | 75           | 23             | 66    | 42.5%  | 1.26 [0.83, 1.92]           |
| Walsh 2013        | 3                 | 17           | 4              | 15    | 7.4%   | 0.66 [0.18, 2.49]           |
| **Subtotal (95% CI)** | **203**          | **227**      |                |       | **96.4%** | **1.20 [0.89, 1.62]**        |
| Total events      | 65                |              | 58             |       |        |                               |
| Heterogeneity: Chi² = 0.84, df = 2 (P = 0.66); I² = 0% |
| Test for overall effect: Z = 1.21 (P = 0.23) |

| Total (95% CI) | 282 | 303 | 100.0% | 1.31 [0.98, 1.75] |
|----------------|-----|-----|--------|-------------------|
| Total events   | 74  | 60  |        |                   |
| Heterogeneity: Chi² = 3.73, df = 4 (P = 0.44); I² = 0% |
| Test for overall effect: Z = 1.84 (P = 0.07) |
| Test for subgroup differences: Chi² = 2.71, df = 1 (P = 0.10), I² = 63.1% |

2. Stroke

| Study or Subgroup | Restrictive Events | Total Events | Liberal Events | Total | Weight | Risk Ratio M-H, Random, 95% CI |
|-------------------|-------------------|--------------|----------------|-------|--------|-------------------------------|
| Carson 2013       | 0                 | 55           | 1              | 55    | 100.0% | 0.33 [0.01, 8.01]            |

| **Total (95% CI)** | 55 | 55 | 100.0% | 0.33 [0.01, 8.01] |
|-------------------|----|----|--------|-------------------|
| Total events      | 0  | 1  |        |                   |
| Heterogeneity: Not applicable |
| Test for overall effect: Z = 0.68 (P = 0.50) |
3. Myocardial infarction

| Study or Subgroup | Restrictive Events | Total | Liberal Events | Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|-------------------|-------------------|-------|----------------|-------|--------|-----------------------------|
| Carson 2013       | 7                 | 55    | 5              | 55    | 12.3%  | 1.40 [0.47, 4.14]           |
| Cooper 2011       | 0                 | 24    | 1              | 21    | 3.9%   | 0.29 [0.01, 6.84]           |
| **Subtotal (95% CI)** | **79**           | **55** | **76**         | **16.2%** | **1.13 [0.42, 3.06]** |

Total events 76
Heterogeneity: Chi² = 0.85, df = 1 (P = 0.36); I² = 0%
Test for overall effect: Z = 0.25 (P = 0.81)

6.3.2 Post-hoc RCT analysis

| Study or Subgroup | Restrictive Events | Total | Liberal Events | Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|-------------------|-------------------|-------|----------------|-------|--------|-----------------------------|
| Hebert 1999       | 14                | 160   | 35             | 197   | 77.2%  | 0.49 [0.27, 0.88]           |
| Holst 2014        | 6                 | 75    | 2              | 66    | 5.2%   | 2.64 [0.55, 12.64]          |
| Walsh 2013        | 1                 | 17    | 0              | 15    | 1.3%   | 2.67 [0.12, 60.93]          |
| **Subtotal (95% CI)** | **252**          | **278** | **83.8%**      | **0.66 [0.40, 1.10]** |

Total events 21
Heterogeneity: Chi² = 4.74, df = 2 (P = 0.09); I² = 58%
Test for overall effect: Z = 1.58 (P = 0.11)

**Total (95% CI)** 331 354 100.0% 0.74 [0.47, 1.16]

Total events 28
Heterogeneity: Chi² = 6.70, df = 4 (P = 0.15); I² = 40%
Test for overall effect: Z = 1.32 (P = 0.19)
Test for subgroup differences: Chi² = 0.89, df = 1 (P = 0.34). I² = 0%

4. Infections

| Study or Subgroup | Restrictive Events | Total | Liberal Events | Total | Weight | Risk Ratio M-H, Random, 95% CI | Year |
|-------------------|-------------------|-------|----------------|-------|--------|-------------------------------|------|
| Carson 2013       | 2                 | 55    | 0              | 55    | 100.0% | 5.00 [0.25, 101.81]          | 2013 |

**Total (95% CI)** 55 55 100.0% 5.00 [0.25, 101.81]

Total events 2
Heterogeneity: Not applicable
Test for overall effect: Z = 1.05 (P = 0.30)
**Question:** Restrictive transfusion strategy compared to liberal transfusion strategy in adult ICU patients with sepsis and septic shock

| Certainty assessment | № of patients | Effect | Certainty | Importance |
|----------------------|---------------|--------|------------|------------|
|                       | № of patients | Effect |            |            |
|                       | Restricted strategy | Liberal strategy | Relative (95% CI) | Absolute (95% CI) |
|                       | Mortality (long term) (follow up: 1 year) | 268/501 (53.5%) | 271/496 (54.6%) | RR 0.98 (0.87 to 1.10) | 11 fewer per 1,000 (from 71 fewer to 55 more) | MODERATE | CRITICAL |
|                       | Mortality (short term) (follow up: range 30 days to 90 days) | 333/675 (49.3%) | 324/669 (48.4%) | RR 1.02 (0.91 to 1.13) | 10 more per 1,000 (from 44 fewer to 63 more) | LOW | CRITICAL |
|                       | Quality of life (follow up: 12 months; assessed with: SF-36 Questionnaire) | 91 | 91 | MD 0.4 higher (7.88 lower to 8.68 higher) | LOW | CRITICAL |
|                       | Stroke | 7/639 (1.1%) | 12/638 (1.9%) | RR 0.58 (0.23 to 1.47) | 8 fewer per 1,000 (from 14 fewer to 9 more) | IMPORTANT |
|                       | Myocardial infarction | 17/639 (2.7%) | 10/638 (1.6%) | RR 1.70 (0.78 to 3.67) | 11 more per 1,000 (from 3 fewer to 42 more) | IMPORTANT |
|                       | Renal failure requiring renal replacement therapy | 42/639 (6.6%) | 41/638 (6.4%) | RR 1.02 (0.67 to 1.55) | 1 more per 1,000 (from 21 fewer to 35 more) | MODERATE | IMPORTANT |

CI: Confidence interval; RR: Risk ratio; MD: Mean difference
Explanations

a. Though clinicians were not blinded in any study, leading to a potential risk of performance bias, outcome assessors were blinded in the two largest studies, and our judgement is that the overall study results are at low risk of bias.

b. Even with a fixed-effect meta-analysis, the 95% confidence interval does not rule out a small but clinically significant effect of likely importance to patients.

c. Significant loss to follow-up and missing data.

d. Small sample size with very wide confidence intervals resulting in serious imprecision.

e. No standard protocol for screening for these events; as clinicians were unblinded there is a significant risk of detection bias.

Summary statements.
1. Restrictive transfusion strategy probably results in little to no difference in long-term mortality, though our certainty is limited by imprecision.
2. Restrictive transfusion strategy may result in little to no difference in 30 to 90 day mortality, though our certainty is limited by imprecision and inconsistency.
3. Restrictive transfusion strategy may result in little to no difference in quality of life, though our certainty is limited by imprecision and risk of bias.
4. Restrictive transfusion strategy may result in little to no difference in stroke, though our certainty is limited by the possibility of detection bias and imprecision.
5. Restrictive transfusion strategy may result in little to no difference in myocardial infarction slightly, though our results are limited by the possibility of detection bias and imprecision.
6. Restrictive transfusion strategy probably does not reduce renal failure requiring renal replacement therapy, though our certainty is limited by imprecision.
1. Mortality (long-term: 90 days to 1 year)

| Study or Subgroup | Restrictive Events | Total | Liberal Events | Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|-------------------|-------------------|-------|----------------|-------|--------|-----------------------------|
| Holst 2014        | 268               | 501   | 271            | 496   | 100.0% | 0.98 [0.87, 1.10]           |
| Total (95% CI)    |                   | 501   | 496            |       |        | 0.98 [0.87, 1.10]           |

Total events: 268, 271
Heterogeneity: Not applicable
Test for overall effect: Z = 0.36 (P = 0.72)

2. Mortality (short-term: 30 to 90 days)

| Study or Subgroup | Restrictive Events | Total | Liberal Events | Total | Weight | Risk Ratio M-H, Fixed, 95% CI | Year |
|-------------------|-------------------|-------|----------------|-------|--------|-----------------------------|------|
| Holst 2014        | 216               | 502   | 223            | 496   | 69.0%  | 0.96 [0.83, 1.10]           | 2014 |
| Mazza 2015        | 11                | 22    | 13             | 24    | 3.8%   | 0.92 [0.53, 1.61]           | 2015 |
| Bergamin 2017     | 106               | 151   | 88             | 149   | 27.2%  | 1.19 [1.00, 1.41]           | 2017 |
| Total (95% CI)    |                   | 675   | 669            |       | 100.0% | 1.02 [0.91, 1.13]           |      |

Total events: 333, 324
Heterogeneity: Chi² = 4.07, df = 2 (P = 0.13); I² = 51%
Test for overall effect: Z = 0.34 (P = 0.74)

3. Quality of life (12 months, assessed with SF-36)

| Study or Subgroup | Restrictive Mean | SD | Total | Liberal Mean | SD | Total | Weight | Mean Difference IV, Random, 95% CI |
|-------------------|------------------|----|-------|--------------|----|-------|--------|----------------------------------|
| Holst 2014        | 7.6              | 27.8 | 91     | 7.2          | 29.2 | 91     | 100.0% | 0.40 [-7.88, 8.68]               |
| Total (95% CI)    | 91               |     |       | 91           |     |       | 100.0% | 0.40 [-7.88, 8.68]               |

Heterogeneity: Not applicable
Test for overall effect: Z = 0.09 (P = 0.92)
4. Stroke

| Study or Subgroup | Restrictive Events | Total | Liberal Events | Total | Weight | Risk Ratio M–H, Fixed, 95% CI |
|-------------------|--------------------|-------|----------------|-------|--------|-----------------------------|
| Bergamin 2017     | 3 151              |       | 2 149         | 16.8% | 1.48   [0.25, 8.73]          |
| Holst 2014        | 4 488              |       | 10 489        | 83.2% | 0.40   [0.13, 1.27]          |
| Total (95% CI)    | 639                | 100.0%| 638            |       | 0.58   [0.23, 1.47]          |
| Total events      | 7 12               |       | 12            |       |                     |
| Heterogeneity:    | $\chi^2 = 1.46$, df = 1 ($P = 0.23$); $I^2 = 32\%$ |       |               |       |                     |
| Test for overall effect: $Z = 1.14$ ($P = 0.25$) |                                |       |               |       |                     |

5. Myocardial infarction

| Study or Subgroup | Restrictive Events | Total | Liberal Events | Total | Weight | Risk Ratio M–H, Fixed, 95% CI |
|-------------------|--------------------|-------|----------------|-------|--------|-----------------------------|
| Bergamin 2017     | 4 151              |       | 4 149         | 40.2% | 0.99   [0.25, 3.87]          |
| Holst 2014        | 13 488             |       | 6 489         | 59.8% | 2.17   [0.83, 5.67]          |
| Total (95% CI)    | 639                | 100.0%| 638            |       | 1.70   [0.78, 3.67]          |
| Total events      | 17 10              |       | 10            |       |                     |
| Heterogeneity:    | $\chi^2 = 0.86$, df = 1 ($P = 0.35$); $I^2 = 0\%$ |       |               |       |                     |
| Test for overall effect: $Z = 1.34$ ($P = 0.18$) |                                |       |               |       |                     |

6. Renal failure requiring renal replacement therapy

| Study or Subgroup | Restrictive Events | Total | Liberal Events | Total | Weight | Risk Ratio M–H, Fixed, 95% CI |
|-------------------|--------------------|-------|----------------|-------|--------|-----------------------------|
| Bergamin 2017     | 18 151             |       | 13 149        | 31.9% | 1.37   [0.69, 2.69]          |
| Holst 2014        | 24 488             |       | 28 489        | 68.1% | 0.86   [0.51, 1.46]          |
| Total (95% CI)    | 639                | 100.0%| 638            |       | 1.02   [0.67, 1.55]          |
| Total events      | 42 41              |       | 41            |       |                     |
| Heterogeneity:    | $\chi^2 = 1.12$, df = 1 ($P = 0.29$); $I^2 = 11\%$ |       |               |       |                     |
| Test for overall effect: $Z = 0.10$ ($P = 0.92$) |                                |       |               |       |                     |
**Question:** Restrictive transfusion strategy compared to liberal transfusion strategy in patients with prolonged weaning from mechanical ventilation

| Certainty assessment | No of patients | Effect | Certainty | Importance |
|----------------------|----------------|--------|------------|------------|
|                       | No of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Restrictive strategy | Liberal strategy | Relative (95% CI) | Absolute (95% CI) | |
| **Mortality (long term)** | 2 | RCTs | not serious | not serious | not serious | serious a | none | 111/408 (27.2%) | 132/405 (32.6%) | RR 0.83 (0.68 to 1.03) | 55 fewer per 1,000 (from 104 fewer to 10 more) | ☞ ☞ ☞ ☞ MODERATE CRITICAL |
| **Mortality (short term)** | 2 | RCTs | not serious | not serious | not serious | serious a | none | 88/408 (21.6%) | 110/405 (27.2%) | RR 0.79 (0.62 to 1.01) | 57 fewer per 1,000 (from 103 fewer to 3 more) | ☞ ☞ ☞ ☞ MODERATE CRITICAL |
| **Quality of life** | 1 | RCTs | serious b | not serious | not serious | not serious | serious a | none | 51 | 49 | - | MD 1 lower (5.51 lower to 3.51 higher) | ☞ ☞ ☞ ☞ LOW CRITICAL |
| **Functional recovery** | 1 | RCTs | serious b | not serious | not serious | not serious | serious a | none | 51 | 49 | - | MD 3 points higher (0.82 higher to 5.18 higher) | ☞ ☞ ☞ ☞ LOW CRITICAL |
| **Stroke** | 2 | RCTs | not serious c | not serious | not serious | not serious | serious a | none | 24/408 (5.9%) | 33/405 (8.1%) | RR 0.73 (0.44 to 1.20) | 22 fewer per 1,000 (from 46 fewer to 16 more) | ☞ ☞ ☞ ☞ MODERATE IMPORTANT |
| **Myocardial infarction** | | | | | | | | | | | | |
Explanations

a. Wide 95% confidence intervals which do not exclude harm or benefit of likely significance to patients.
b. Significant loss to follow-up at 180 days which may have biased results.
c. Lack of blinding of clinicians may have led to detection bias, although it would be anticipated that if this had influenced results, more events would have been seen in the restrictive arm than the liberal arm.
d. Optimal information size not met; imprecision is likely significant despite confidence interval

Summary statements.
1. A restrictive transfusion strategy probably does not increase longer-term mortality, though our certainty is limited by imprecision.
2. A restrictive transfusion strategy probably does not increase short-term mortality though our certainty is limited by imprecision.
3. A restrictive transfusion strategy may result in a small possibly unimportant effect in quality of life, though our certainty is limited by risk of bias (loss to follow-up) and imprecision.
4. A restrictive transfusion strategy may result in a small possibly unimportant effect in functional recovery, though our certainty is limited by risk of bias (loss to follow-up) and imprecision.
5. A restrictive transfusion strategy probably results in no increase stroke, though our certainty is limited by imprecision.
6. A restrictive transfusion strategy probably reduces myocardial infarction slightly, though our certainty is limited by imprecision.
7. A restrictive transfusion strategy may reduce ARDS slightly though our certainty is limited by risk of bias (detection bias) and imprecision.
1. Mortality (long-term: 90 to 180 days)

| Study or Subgroup | Restrictive Events | Total | Liberal Events | Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|-------------------|--------------------|-------|----------------|-------|--------|-------------------------------|
| Hebert 1999       | 92                 | 357   | 105            | 356   | 79.2%  | 0.87 [0.69, 1.11]             |
| Walsh 2013        | 19                 | 51    | 27             | 49    | 20.8%  | 0.68 [0.44, 1.05]             |

Total (95% CI) 408 405 100.0% 0.83 [0.68, 1.03]

Total events 111 132
Heterogeneity: Chi² = 1.03, df = 1 (P = 0.31); I² = 3%
Test for overall effect: Z = 1.71 (P = 0.09)

2. Mortality (short-term: 30 days)

| Study or Subgroup | Restrictive Events | Total | Liberal Events | Total | Weight | Risk Ratio M-H, Fixed, 95% CI | Year |
|-------------------|--------------------|-------|----------------|-------|--------|-------------------------------|------|
| Hebert 1999       | 76                 | 357   | 94             | 356   | 85.2%  | 0.81 [0.62, 1.05]             | 1999 |
| Walsh 2013        | 12                 | 51    | 16             | 49    | 14.8%  | 0.72 [0.38, 1.36]             | 2013 |

Total (95% CI) 408 405 100.0% 0.79 [0.62, 1.01]

Total events 88 110
Heterogeneity: Chi² = 0.10, df = 1 (P = 0.75); I² = 0%
Test for overall effect: Z = 1.86 (P = 0.06)

3. Quality of life (Measured with SF-12, 180 days)

| Study or Subgroup | Restrictive Mean | SD | Total | Liberal Mean | SD | Total | Weight | Mean Difference IV, Random, 95% CI | Year |
|-------------------|------------------|----|-------|--------------|----|-------|--------|-----------------------------------|------|
| Walsh 2013        | -30              | 11.9 | 51    | -31          | 11.1 | 49    | 100.0% | 1.00 [-3.51, 5.51]                | 2013 |

Total (95% CI) 51 49 100.0% 1.00 [-3.51, 5.51]

Heterogeneity: Not applicable
Test for overall effect: Z = 0.43 (P = 0.66)
4. Functional outcome (Measured with Rivermeade Mobility Index, 180 days)

| Study or Subgroup | Restrictive Mean | SD | Total | Liberal Mean | SD | Total | Weight | Mean Difference | Year |
|-------------------|-----------------|----|-------|--------------|----|-------|--------|-----------------|------|
| Walsh 2013        | 10              | 5.2 | 51    | 12           | 5.9| 49    | 100.0% | -2.00 [-4.18, 0.18] | 2013 |

Total (95% CI) 51 49 100.0% -2.00 [-4.18, 0.18]

Heterogeneity: Not applicable
Test for overall effect: Z = 1.80 (P = 0.07)

---

4. Stroke

| Study or Subgroup | Restrictive Events | Total | Liberal Events | Total | Weight | Risk Ratio M–H, Fixed, 95% CI | Risk Ratio M–H, Fixed, 95% CI |
|-------------------|--------------------|-------|----------------|-------|--------|-------------------------------|-------------------------------|
| Hebert 1999       | 24                 | 357   | 32             | 356   | 95.4%  | 0.75 [0.45, 1.24]            |                               |
| Walsh 2013        | 0                  | 51    | 1              | 49    | 4.6%   | 0.32 [0.01, 7.68]            |                               |

Total (95% CI) 408 405 100.0% 0.73 [0.44, 1.20]

Total events 24 33
Heterogeneity: Chi² = 0.27, df = 1 (P = 0.61); I² = 0%
Test for overall effect: Z = 1.24 (P = 0.22)

---

5. Myocardial infarction

| Study or Subgroup | Restrictive Events | Total | Liberal Events | Total | Weight | Risk Ratio M–H, Fixed, 95% CI | Risk Ratio M–H, Fixed, 95% CI |
|-------------------|--------------------|-------|----------------|-------|--------|-------------------------------|-------------------------------|
| Hebert 1999       | 2                  | 357   | 12             | 356   | 85.5%  | 0.17 [0.04, 0.74]            |                               |
| Walsh 2013        | 2                  | 51    | 2              | 49    | 14.5%  | 0.96 [0.14, 6.56]            |                               |

Total (95% CI) 408 405 100.0% 0.28 [0.09, 0.85]

Total events 4 14
Heterogeneity: Chi² = 2.05, df = 1 (P = 0.15); I² = 51%
Test for overall effect: Z = 2.25 (P = 0.02)
### 6. ARDS

| Study or Subgroup | Restrictive | Liberal | Risk Ratio |
|-------------------|-------------|---------|------------|
|                   | Events  | Total  | Events  | Total  | Weight | M–H, Fixed, 95% CI |
| Hebert 1999       | 31      | 357    | 48      | 356    | 100.0% | 0.64 [0.42, 0.99]   |
| **Total (95% CI)** | 357    | 356    | 100.0% | 0.64 [0.42, 0.99] |
| Total events      | 31      | 48     |

Heterogeneity: Not applicable

Test for overall effect: \( Z = 2.02 \) (\( P = 0.04 \))
**Question:** Restrictive transfusion strategy compared to liberal transfusion strategy in adult patients receiving cardiac surgery

| certainty assessment | No of patients | Effect | Certainty | Importance |
|----------------------|----------------|--------|-----------|------------|
| **Mortality (long term) (follow up: range 90 days to 6 months)** | | | | |
| 2 RCTs | not serious a | serious b | not serious | serious c | none | 183/3434 (5.3%) | 175/3441 (5.1%) | RR 1.05 (0.86 to 1.28) | 3 more per 1,000 (from 7 fewer to 14 more) | 🌟🌟🌟🌟 LOW CRITICAL |
| **Mortality (short term) (follow up: median 30 days)** | | | | |
| 6 RCTs | not serious a | not serious | not serious | serious d | none | 125/4276 (2.9%) | 132/4280 (3.1%) | RR 0.97 (0.72 to 1.32) | 1 fewer per 1,000 (from 9 fewer to 10 more) | 🌟🌟🌟🌟 MODERATE CRITICAL |
| **Quality of life (follow up: 3 months; assessed with: EQ-5D, SF-12)** | | | | |
| 2 RCTs | not serious a | not serious | not serious | not serious | none | 1363 | 1357 | SMD 0 SD (0.8 lower to 0.8 higher) | 🌟🌟🌟🌟 HIGH CRITICAL |
| **Stroke** | | | | |
| 7 RCTs | not serious a | not serious | not serious | serious d | none | 134/4057 (3.3%) | 118/4073 (2.9%) | RR 1.14 (0.89 to 1.45) | 4 more per 1,000 (from 3 fewer to 13 more) | 🌟🌟🌟🌟 MODERATE IMPORTANT |
| **Acute MI** | | | | |
| 6 RCTs | not serious | not serious | serious e | serious d | none | 168/3513 (4.8%) | 169/3523 (4.8%) | RR 1.00 (0.81 to 1.22) | 0 more per 1,000 (from 9 fewer to 11 more) | 🌟🌟🌟🌟 LOW IMPORTANT |
| **Renal failure** | | | | |
| 6 RCTs | not serious a | not serious | not serious | not serious | none | 111/3071 (3.6%) | 120/3085 (3.9%) | RR 0.98 (0.79 to 1.21) | 1 fewer per 1,000 (from 9 fewer to 9 more) | 🌟🌟🌟🌟 HIGH IMPORTANT |
| **ARDS** | | | | |
CI: Confidence interval; RR: Risk ratio; SMD: Standardised mean difference

Explanations

a. Though clinicians were not blinded in any study, leading to a potential risk of performance bias, outcome assessors were blinded in almost all studies, and our judgement is that the overall study results are at low risk of bias.

b. High I^2 (75%) between the two RCTs, with point estimates on different sides of the line of no effect.

c. We rated down for imprecision, as even with a fixed effect model (done because of the small number of studies) the 95% CI does exclude a potentially important 1.4% absolute increase in the number of deaths.

d. Wide 95% confidence interval which does not rule out a harm or benefit of likely significance to patients.

e. Diagnosing clinically meaningful myocardial infarction is extremely difficult in the post-cardiac surgery population; diagnostic criteria and significance of events is uncertain.

f. Two studies (Murphy 2015, Koch 2017) including the majority of events, reported a composite of pulmonary complications, of which only a small subset was ARDS.

g. Wide variety of infections included across studies (eg. wound infections, pneumonia), likely of varying significance to patients.

Summary statements

1. Restrictive transfusion strategy may result in little to no difference in long-term mortality, though our certainty is limited by inconsistency and imprecision.

2. Restrictive transfusion strategy likely results in little to no difference in short-term mortality, though our certainty is limited by imprecision.

3. Restrictive transfusion strategy results in little to no difference in quality of life.

4. Restrictive transfusion strategy likely results in a small, possibly unimportant increase in stroke, though our certainty is limited by imprecision.

5. Restrictive transfusion strategy results in little to no difference in acute MI, though our certainty is limited by imprecision.

6. Restrictive transfusion strategy likely results in little to no difference in renal failure, though our certainty is limited by imprecision.

7. Restrictive transfusion strategy may result in a small, possibly unimportant, increase in ARDS, though our certainty is limited by indirectness and imprecision.

8. Restrictive transfusion strategy may result in little to no difference in infections, though our certainty is limited by indirectness.
1. Mortality (long term: 90 days or more)

| Study or Subgroup | Restrictive Events | Total Events | Liberal Events | Total Events | Weight | Risk Ratio M–H, Fixed, 95% CI | Year |
|-------------------|-------------------|--------------|----------------|--------------|--------|-------------------------------|------|
| Murphy 2015       | 42                | 1000         | 26             | 1003         | 14.8%  | 1.62 [1.00, 2.62]             | 2015 |
| Mazer 2017        | 141               | 2434         | 149            | 2438         | 85.2%  | 0.95 [0.76, 1.19]             | 2017 |
| **Total (95% CI)** | **3434**          | **3441**     |                |              | 100.0% | 1.05 [0.86, 1.28]             |      |
| Total events      |                  |              |                |              |        | 183                           | 175  |
| Heterogeneity     | Chi² = 3.93, df = 1 (P = 0.05); I² = 75% |                |                |              |        |                               |      |
| Test for overall effect | Z = 0.45 (P = 0.65) |                |                |              |        |                               |      |

2. Mortality (short term: 28-30 days)

| Study or Subgroup | Restrictive Events | Total Events | Liberal Events | Total Events | Weight | Risk Ratio M–H, Random, 95% CI | Year |
|-------------------|-------------------|--------------|----------------|--------------|--------|-------------------------------|------|
| Bracey 1999       | 3                 | 212          | 6              | 216          | 4.7%   | 0.51 [0.13, 2.01]             | 1999 |
| Hajjar 2010       | 15                | 249          | 13             | 253          | 15.3%  | 1.17 [0.57, 2.41]             | 2010 |
| Shehata 2012      | 4                 | 25           | 1              | 25           | 2.0%   | 4.00 [0.48, 33.33]            | 2012 |
| Murphy 2015       | 26                | 1000         | 19             | 1003         | 21.6%  | 1.37 [0.76, 2.46]             | 2015 |
| Koch 2017         | 3                 | 363          | 6              | 354          | 4.7%   | 0.49 [0.12, 1.93]             | 2017 |
| Mazer 2017        | 74                | 2427         | 87             | 2429         | 51.7%  | 0.85 [0.63, 1.15]             | 2017 |
| **Total (95% CI)** | **4276**          | **4280**     |                |              | 100.0% | 0.97 [0.72, 1.32]             |      |
| Total events      |                  |              |                |              |        | 125                           | 132  |
| Heterogeneity     | Tau² = 0.02; Chi² = 5.80, df = 5 (P = 0.33); I² = 14% |                |                |              |        |                               |      |
| Test for overall effect | Z = 0.18 (P = 0.86) |                |                |              |        |                               |      |

3. Quality of life (measured with EQ-5D, SF-12)

| Study or Subgroup | Restrictive Mean | SD | Total | Liberal Mean | SD | Total | Weight | Std. Mean Difference IV, Random, 95% CI | Year |
|-------------------|------------------|----|-------|---------------|----|-------|--------|----------------------------------------|------|
| Murphy 2015       | 0.8              | 0.23| 1000   | 0.8           | 0.23| 1003   | 73.6%  | 0.00 [-0.09, 0.09]                     | 2015 |
| Koch 2017         | 45               | 7   | 363    | 45            | 7   | 354    | 26.4%  | 0.00 [-0.15, 0.15]                     | 2017 |
| **Total (95% CI)** | **1363**         |     | **1357**| **100.0%**    |     |        |        | 0.00 [-0.08, 0.08]                     |      |
| Heterogeneity     | Tau² = 0.00; Chi² = 0.00, df = 1 (P = 1.00); I² = 0% |                |                |              |        |                               |      |
| Test for overall effect | Z = 0.00 (P = 1.00) |                |                |              |        |                               |      |
4. Stroke

| Study or Subgroup     | Restrictive Events | Total | Liberal Events | Total | Weight | Risk Ratio M-H, Random, 95% CI | Year |
|-----------------------|--------------------|-------|----------------|-------|--------|--------------------------------|------|
| Johnson 1992          | 1                  | 20    | 0              | 18    | 0.6%   | 2.71 [0.12, 62.70]             | 1992 |
| Bracey 1999           | 11                 | 212   | 9              | 216   | 8.0%   | 1.25 [0.53, 2.94]              | 1999 |
| Hajjar 2010           | 15                 | 249   | 15             | 253   | 12.4%  | 1.02 [0.51, 2.03]              | 2010 |
| Shehata 2012          | 3                  | 25    | 0              | 25    | 0.7%   | 7.00 [0.38, 128.87]            | 2012 |
| Murphy 2015           | 15                 | 989   | 17             | 985   | 12.5%  | 0.88 [0.44, 1.75]              | 2015 |
| Koch 2017             | 1                  | 363   | 3              | 354   | 1.2%   | 0.33 [0.03, 3.11]              | 2017 |
| Mazer 2017            | 88                 | 2199  | 74             | 2222  | 64.6%  | 1.20 [0.89, 1.63]              | 2017 |

Total (95% CI) 4057 4073 100.0% 1.14 [0.89, 1.45]

Total events 134 118

Heterogeneity: Tau² = 0.00; Chi² = 3.78, df = 6 (P = 0.71); I² = 0%

Test for overall effect: Z = 1.03 (P = 0.30)

5. Myocardial infarction

| Study or Subgroup     | Restrictive Events | Total | Liberal Events | Total | Weight | Risk Ratio M-H, Random, 95% CI | Year |
|-----------------------|--------------------|-------|----------------|-------|--------|--------------------------------|------|
| Johnson 1992          | 0                  | 20    | 1              | 18    | 0.4%   | 0.30 [0.01, 6.97]              | 1992 |
| Bracey 1999           | 1                  | 215   | 0              | 222   | 0.4%   | 3.10 [0.13, 75.61]             | 1999 |
| Shehata 2012          | 1                  | 25    | 0              | 25    | 0.4%   | 3.00 [0.13, 70.30]             | 2012 |
| Murphy 2015           | 3                  | 987   | 4              | 981   | 1.9%   | 0.75 [0.17, 3.32]              | 2015 |
| Mazer 2017            | 162                | 2226  | 164            | 2237  | 96.4%  | 0.99 [0.81, 1.22]              | 2017 |
| Laine 2017            | 1                  | 40    | 0              | 40    | 0.4%   | 3.00 [0.13, 71.51]             | 2017 |

Total (95% CI) 3513 3523 100.0% 1.00 [0.81, 1.22]

Total events 168 169

Heterogeneity: Tau² = 0.00; Chi² = 2.12, df = 5 (P = 0.83); I² = 0%

Test for overall effect: Z = 0.04 (P = 0.97)
6. Renal failure requiring dialysis

| Study or Subgroup | Restrictive Events | Liberal Events | Total Events | Weight | Risk Ratio M–H, Random, 95% CI | Year |
|-------------------|-------------------|----------------|--------------|--------|--------------------------------|------|
| Bracey 1999       | 8                 | 212            | 5            | 216    | 1.63 [0.54, 4.90]              | 1999 |
| Hajjar 2010        | 10                | 249            | 13           | 253    | 0.78 [0.35, 1.75]              | 2010 |
| Shehata 2012      | 0                 | 25             | 1            | 25     | 0.33 [0.01, 7.81]              | 2012 |
| Murphy 2015       | 50                | 989            | 46           | 989    | 1.09 [0.74, 1.61]              | 2015 |
| Koch 2017         | 6                 | 363            | 7            | 354    | 0.84 [0.28, 2.46]              | 2017 |
| Mazer 2017        | 87                | 2222           | 94           | 2237   | 0.93 [0.70, 1.24]              | 2017 |

Total (95% CI) | 4060 | 4074 | 100.0% | 0.98 [0.79, 1.21] |

Total events: 161
Heterogeneity: $\tau^2 = 0.00; \chi^2 = 2.04, \text{df} = 5 (P = 0.84); i^2 = 0\%$
Test for overall effect: $Z = 0.23 (P = 0.82)$

7. ARDS

| Study or Subgroup | Restrictive Events | Liberal Events | Total Events | Weight | Risk Ratio M–H, Fixed, 95% CI | Year |
|-------------------|-------------------|----------------|--------------|--------|--------------------------------|------|
| Hajjar 2010        | 5                 | 249            | 2            | 253    | 2.54 [0.50, 12.97]             | 2010 |
| Murphy 2015       | 127               | 979            | 116          | 982    | 1.10 [0.87, 1.39]              | 2015 |
| Koch 2017         | 23                | 363            | 19           | 354    | 1.18 [0.65, 2.13]              | 2017 |

Total (95% CI) | 1591 | 1589 | 100.0% | 1.13 [0.91, 1.40] |

Total events: 155
Heterogeneity: $\chi^2 = 1.03, \text{df} = 2 (P = 0.60); i^2 = 0\%$
Test for overall effect: $Z = 1.11 (P = 0.27)$
### 8. Infections

| Study or Subgroup | Restrictive Events | Total | Liberal Events | Total | Weight | Risk Ratio M−H, Random, 95% CI | Year |
|-------------------|--------------------|-------|----------------|-------|--------|-------------------------------|------|
| Bracey 1999       | 5                  | 212   | 3              | 216   | 0.9%   | 1.70 [0.41, 7.02]             | 1999 |
| Hajjar 2010        | 29                 | 249   | 25             | 253   | 7.1%   | 1.18 [0.71, 1.95]             | 2010 |
| Shehata 2012      | 3                  | 25    | 0              | 25    | 0.2%   | 7.00 [0.38, 128.87]           | 2012 |
| Murphy 2015       | 210                | 982   | 214            | 983   | 64.1%  | 0.98 [0.83, 1.16]             | 2015 |
| Koch 2017         | 1                  | 363   | 1              | 354   | 0.2%   | 0.98 [0.06, 15.53]            | 2017 |
| Mazer 2017        | 121                | 2428  | 101            | 2429  | 27.4%  | 1.20 [0.93, 1.55]             |      |
| **Total (95% CI)**| **4259**           | **4260** | **100.0%**   |       | 1.06 [0.93, 1.21]            |      |

Total events: 369, 344

Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 3.90$, df = 5 ($P = 0.56$); $I^2 = 0$

Test for overall effect: $Z = 0.85$ ($P = 0.39$)
Narrative Evidence Summary: Restrictive vs. Liberal Transfusions in Patients Undergoing ECMO

Limited direct evidence available as described below
-in general, more transfusions is associated with increased mortality though obviously many confounding issues, eg. lower Hb associated with higher mortality as well
-one cohort study of a centre using a transfusion threshold of 7 g/dL: similar outcomes for ECMO survival survival to ICU and hospital discharge 28 (73.7%), RRT 12 (31.6), bleeding 10 (26.3) similar to rates elsewhere in the literature, but no control group (historical or otherwise) in study

Indirect evidence:
-VV ECMO is most analogous to ARDS, which also has low certainty evidence— should we consider general ICU population as indirect evidence
-this would involve using the same recommendation, but with lower certainty (low certainty mortality, very low for other outcomes)
-alternative is no recommendation (recognizing that clinicians are currently making this decision with no evidence)

-VA ECMO is most commonly used in post-cardiac surgery population, suggest using same recommendation (restrictive transfusion at 7.5 g/dL) and rating down evidence one level (overall low certainty)

1. VV ECMO
Schmidt 2013
-observational study of 10 patients receiving vvECMO for severe ARDS; 3 patients received transfusions (at Hb 5.1 g/dL, 8.6 g/dL, and 7.5 g/dL)
-possible to reduce ECMO blood flow to 60% of baseline value, it was possible after transfusion to reduce flow to 40% while maintaining SaO2>80%

Weingart 2015
-retrospective observational study of 63 patients on vvECMO and interventional lung assist (iLA)
-no difference between transfusion requirements or clinical outcome between ECMO and iLA groups

Voelker 2015
-retrospective analysis of 18 patients seeing vvECMO for severe ARDS, hospital mortality rate 38.9%
-Hb transfusion trigger was 7 g/dL or when physiological transfusion triggers apparent
-greater number of PRBCs in non-survivors compared to survivors (1.97 SD1.47 vs. 0.96 SD0.76)
-greater number of PRBCs/day on ECMO in non-survivors (1.97 SD 1.47 vs 0.96 SD 0.76)
-no differences in APACHE 2 scores but higher mean SOFA and SAPS in non-survivors

Panholzer 2017
-observational study of 46 patients receiving vvECMO for severe ARDS
-all patients received transfusions; non-survivors had a higher mean PRBC transfusions per day (0.9, 05 to 1.6) vs. 04 (0.3 to 1.2), p<0.001

2. VA ECMO
Cahill 2016
-retrospective observational study of cardiac ECMO patients, both pre (n=30) and post (n=31) of a lab testing and transfusion protocol (details not specified)
-transfusions decreased after the protocol (from mean 28 SD 23 to 15 SD 16, p=0.009), with a higher survival (33% pre- to 66% post-transfusion protocol, p=0.014) without a difference in length of ECMO

3. Combined populations

Guttendorf 2014
-retrospective observational study of patients undergoing ECMO at a single centre (vaECMO 146, vvECMO n=66)
-transfusions were significantly higher in patients with in-hospital death (47.84 SD 59.9 vs. 24.13 SD 22.5, p=0.005)

Agerstrand 2015
-retrospective observational study of 38 adults receiving ECMO (34 vv, 2 va, 2 va-v) for severe ARDS after initiation of a blood conservation protocol with a Hb transfusion trigger of 7 g/dL
-survival to ICU and hospital discharge 28 (73.7%), RRT 12 (31.6), bleeding 10 (26.3) similar to rates elsewhere in the literature, but no control group (historical or otherwise) in study

Elbbassi 2017
-single centre retrospective observational study of 29 patients who received ECMO (11 vvECMO, 3VA ECMO, 15 AV ECMO)
-hemoglobin on ECMO was lower in non-survivors vs. survivors (9 SD 2 vs. 10.8 SD 1.54, p=0.02), though no data on transfusion or which variables were adjusted for

Jens 2017
-retrospective study of patients who received ECMO (195 vaECMO, 100 vvECMO)
-transfusion number similar between survivors and non survivors though virtually all received transfusion(129/131 vs. 164/164)
-hemoglobin level 8.85 g/dL on ECMO day 1 or less was predictive for in-hospital mortality rate (sens 63.8 spec 66.4 AUC 65.1) though unclear if this is modified by number of transfusion

Swol 2018
-single-centre retrospective observational study of patient receiving vaECMO (n=5), vvECMO (n=61) or iLA (n=15)
-patients divided into four groups based upon median hematocrit (25% or less, 26-28%, 29-31%, greater than 31%)
-mortality highest in group with HCT>31% (RR 1.73, 95% CI 1.134 to 2.639), with no differences in the other three groups
-in linear regression no relationship between survival and median hematocrit across the entire group, though increased mortality with average number of transfusions per day
**Question:** Restrictive vs. liberal transfusion in acute neurologic conditions

| Certainty assessment | No of patients | Effect | Certainty | Importance |
|-----------------------|----------------|--------|-----------|------------|
|                       |                |        |           |            |
| **Mortality (range: hospital mortality to 6 months)** | | | | |
| 3 RCTs                | not serious    | serious a | not serious | serious b | none | 26/152 (17.1%) | 23/162 (14.2%) | RR 1.20 (0.71 to 2.03) | 28 more per 1,000 (from 41 fewer to 146 more) | + + + | CRITICAL |
|                       |                |         |            |            |      | 26/152 (17.1%) | 23/162 (14.2%) | RR 1.20 (0.71 to 2.03) | 28 more per 1,000 (from 41 fewer to 146 more) | + + + | CRITICAL |
| **Functional recovery (follow up: range 14 days to 6 months; assessed with: Disability rating scale; NIHSS)** | | | | |
| 2 RCTs                | not serious c  | serious a | not serious | serious b | none | 122        | 122        | - | SMD 0.29 lower (0.54 lower to 0.04 lower) | + + + | LOW |
|                       |                |         |            |            |      | 122        | 122        | - | SMD 0.29 lower (0.54 lower to 0.04 lower) | + + + | LOW |
| **Functional recovery (dichotomous) (follow up: range 3 months to 6 months; assessed with: Glasgow outcome score or independent living)** | | | | |
| 3 RCTs                | not serious c  | not serious | not serious | very serious b | none | 79/146 (54.1%) | 83/145 (57.2%) | RR 0.96 (0.79 to 1.16) | 23 fewer per 1,000 (from 120 fewer to 92 more) | + + + | CRITICAL |
|                       |                |         |            |            |      | 79/146 (54.1%) | 83/145 (57.2%) | RR 0.96 (0.79 to 1.16) | 23 fewer per 1,000 (from 120 fewer to 92 more) | + + + | CRITICAL |
| **Stroke**            | | | | |
| 1 RCTs                | not serious    | not serious | not serious | very serious b | none | 11/23 (47.8%) | 9/21 (42.9%) | RR 1.12 (0.58 to 2.14) | 51 more per 1,000 (from 180 fewer to 489 more) | + + + | IMPORTANT |
|                       |                |         |            |            |      | 11/23 (47.8%) | 9/21 (42.9%) | RR 1.12 (0.58 to 2.14) | 51 more per 1,000 (from 180 fewer to 489 more) | + + + | IMPORTANT |
| **ARDS**              | | | | |
| 2 RCTs                | not serious    | not serious e | not serious d | serious b | none | 24/122 (19.7%) | 26/122 (23.0%) | RR 0.85 (0.52 to 1.40) | 34 fewer per 1,000 (from 110 fewer to 92 more) | + + + | IMPORTANT |
|                       |                |         |            |            |      | 24/122 (19.7%) | 26/122 (23.0%) | RR 0.85 (0.52 to 1.40) | 34 fewer per 1,000 (from 110 fewer to 92 more) | + + + | IMPORTANT |
| **Infections**        | | | | |
| 2 RCTs                | not serious    | not serious | serious f | serious b | none | 29/128 (22.7%) | 38/139 (27.3%) | RR 0.79 (0.53 to 1.19) | 57 fewer per 1,000 (from 128 fewer to 52 more) | + + + | IMPORTANT |
|                       |                |         |            |            |      | 29/128 (22.7%) | 38/139 (27.3%) | RR 0.79 (0.53 to 1.19) | 57 fewer per 1,000 (from 128 fewer to 52 more) | + + + | IMPORTANT |

CI: Confidence interval; RR: Risk ratio; SMD: Standardised mean difference; MD: Mean difference
Explanations

a. Moderate statistical heterogeneity not easily explained by study characteristics, with point estimates on both sides of the line of no effect.
b. Wide 95% CI which does not exclude significant benefit or harm of likely significance to patients.
c. Blinded outcome assessment done in all three trials.
d. One study (Naidech 2010) reported "pulmonary edema or respiratory distress" though this data contributed only ~11% of the weight in the analysis and did not have a major impact upon the pooled estimate.
e. Though there is moderate statistical heterogeneity, this is probably explained by quality of outcome measurement: Robertson 2014 had an ARDS outcome adjudication committee; Naidech 2010 reported a composite of "pulmonary edema and respiratory distress." Inclusion or exclusion of the latter study has minimal impact upon the pooled estimate.
f. Both studies included a composite of infections of varying severity and likely of varying importance to patients.

Summary statements
1. Restrictive transfusion strategy may increase short-term mortality, though our certainty is limited by inconsistency and imprecision.
2. Restrictive transfusion strategy may result in increased functional recovery (continuous measures), though our certainty is limited by inconsistency and imprecision.
3. Restrictive transfusion strategy may result in little to no difference in functional recovery (dichotomous measures), though our certainty is limited by imprecision.
4. Restrictive transfusion strategy may result in little to no difference in stroke, though our certainty is limited by very significant imprecision.
5. Restrictive transfusion strategy probably results in little to no difference in ARDS, though our certainty is limited by imprecision.
6. Restrictive transfusion strategy may result in little to no difference in infections, though our certainty is limited by indirectness of outcomes and imprecision.
1. Mortality (short term: 28-60 days)

| Study or Subgroup | Restrictive Events | Total | Liberal Events | Total | Weight | Risk Ratio M–H, Fixed, 95% CI | Year |
|-------------------|--------------------|-------|----------------|-------|--------|-----------------------------|------|
| McIntyre 2006     | 5                  | 29    | 5              | 38    | 19.5%  | 1.31 [0.42, 4.10]           | 2006 |
| Robertson 2014    | 14                 | 99    | 17             | 101   | 75.9%  | 0.84 [0.44, 1.61]           | 2014 |
| Gobatto 2019      | 7                  | 24    | 1              | 23    | 4.6%   | 6.71 [0.89, 50.35]          | 2019 |
| **Total (95% CI)**| **152**            |       | **162**        |       | **100.0%** | **1.20 [0.71, 2.03]**      |      |

Total events: 26
Heterogeneity: Chi² = 3.98, df = 2 (P = 0.14); I² = 50%
Test for overall effect: Z = 0.69 (P = 0.49)

2. Functional recovery (continuous, lower is better)

| Study or Subgroup | Restrictive Mean | SD | Total | Liberal Mean | SD | Total | Weight | Std. Mean Difference IV, Fixed, 95% CI | Year |
|-------------------|------------------|----|-------|--------------|----|-------|--------|-----------------------------|------|
| Naidich 2010      | 2                | 11.9 | 23    | 1             | 7.2 | 21    | 18.3%  | 0.10 [-0.49, 0.69]            | 2010 |
| Robertson 2014    | 5                | 5.6  | 99    | 8             | 9.6 | 101   | 81.7%  | -0.38 [-0.66, -0.10]          | 2014 |
| **Total (95% CI)**| **122**          |     | **122**|      |      | **100.0%** | **-0.29 [-0.54, -0.04]**     |      |

Heterogeneity: Chi² = 2.05, df = 1 (P = 0.15); I² = 51%
Test for overall effect: Z = 2.26 (P = 0.02)

3. Functional recovery (dichotomous, fewer is better)

| Study or Subgroup | Restrictive Events | Total | Liberal Events | Total | Weight | Risk Ratio M–H, Fixed, 95% CI | Year |
|-------------------|--------------------|-------|----------------|-------|--------|-----------------------------|------|
| Naidich 2010      | 3                  | 23    | 3              | 21    | 3.8%   | 0.91 [0.21, 4.04]           | 2010 |
| Robertson 2014    | 62                 | 99    | 70             | 101   | 83.8%  | 0.90 [0.74, 1.10]           | 2014 |
| Gobatto 2019      | 14                 | 24    | 10             | 23    | 12.4%  | 1.34 [0.75, 2.39]           | 2019 |
| **Total (95% CI)**| **146**            |       | **145**        |       | **100.0%** | **0.96 [0.79, 1.16]**      |      |

Total events: 79
Heterogeneity: Chi² = 1.65, df = 2 (P = 0.44); I² = 0%
Test for overall effect: Z = 0.44 (P = 0.66)
4. Stroke

| Study or Subgroup | Restrictive | Liberal | Risk Ratio |
|-------------------|-------------|---------|------------|
| Naidech 2010      | 11 23       | 9 21    | 1.12 [0.58, 2.14] |

**Total (95% CI)**

| Study or Subgroup | Restrictive | Liberal | Risk Ratio |
|-------------------|-------------|---------|------------|
| Total events      | 11          | 9       | 1.12 [0.58, 2.14] |

Heterogeneity: Not applicable
Test for overall effect: Z = 0.33 (P = 0.74)

5. ARDS

| Study or Subgroup | Restrictive | Liberal | Risk Ratio |
|-------------------|-------------|---------|------------|
| Naidech 2010      | 8 23        | 3 21    | 2.43 [0.74, 7.99] |
| Robertson 2014    | 16 99       | 25 101  | 0.65 [0.37, 1.15] |

**Total (95% CI)**

| Study or Subgroup | Restrictive | Liberal | Risk Ratio |
|-------------------|-------------|---------|------------|
| Total events      | 24          | 28      | 0.85 [0.52, 1.40] |

Heterogeneity: Chi² = 3.86, df = 1 (P = 0.05); I² = 74%
Test for overall effect: Z = 0.63 (P = 0.53)

6. Infections

| Study or Subgroup | Restrictive | Liberal | Risk Ratio |
|-------------------|-------------|---------|------------|
| McIntyre 2006     | 2 29        | 2 38    | 1.31 [0.20, 8.76] |
| Robertson 2014    | 27 99       | 36 101  | 0.77 [0.51, 1.16] |

**Total (95% CI)**

| Study or Subgroup | Restrictive | Liberal | Risk Ratio |
|-------------------|-------------|---------|------------|
| Total events      | 29          | 38      | 0.79 [0.53, 1.19] |

Heterogeneity: Chi² = 0.30, df = 1 (P = 0.59); I² = 0%
Test for overall effect: Z = 1.14 (P = 0.26)
References

Agerstrand CL, Burkart KM, Abrams DC, Bacchetta MD, Brodie D. Blood conservation in extracorporeal membrane oxygenation for acute respiratory distress syndrome. The Annals of thoracic surgery. 2015 Feb 1;99(2):590-5.

Cahill C, Blumberg N, Schmidt A, Knight P, Melvin A, Massey H, Delehtany J, Zebrak S, Refaai KA, Refaai M. Implementation of a Standardized Laboratory Testing, Clinical Evaluation and Transfusion Protocol for Cardiac Patients Receiving Extracorporeal Membrane Oxygenation (ECMO) is Associated with Decreased Blood Transfusions and Improved Survival. InTRANSFUSION 2016 Sep 1 (Vol. 56, pp. 32A-32A). 111 RIVER ST, HOBOKEN 07030-5774, NJ USA: WILEY-BLACKWELL.

Elabbassi W, Al Aila F, Chowdhury MA, Najib A, Zaid H, Michelin M, Al Nooryani A. The impact of severity of initial illness, determined by SOFA score, and presence of anemia on outcomes among patients requiring Extra Corporal Membrane Oxygenation (ECMO) support: A single center experience. Indian heart journal. 2017 Nov 1;69(6):762-6.

Guttendorf J, Boujoukos AJ, Ren D, Rosenzweig MQ, Hravnak M. Discharge outcome in adults treated with extracorporeal membrane oxygenation. American Journal of Critical Care. 2014 Sep 1;23(5):365-77.

Jenq CC, Tsai FC, Tsai TY, Hsieh SY, Lai YW, Tian YC, Chang MY, Lin CY, Fang JT, Yang CW, Chen YC. Effect of Anemia on Prognosis in Patients on Extracorporeal Membrane Oxygenation. Artificial organs. 2018 Mar 30.

Panholzer B, Meckelburg K, Huenges K, Hoffmann G, von der Brelie M, Haake N, Pilarczyk K, Cremer J, Haneya A. Extracorporeal membrane oxygenation for acute respiratory distress syndrome in adults: an analysis of differences between survivors and non-survivors. Perfusion. 2017 Sep;32(6):495-500.

Schmidt M, Tachon G, Devilliers C, Muller G, Hekimian G, Bréchot N, Merceron S, Luyt CE, Trouillet JL, Chastre J, Leprince P. Blood oxygenation and decarboxylation determinants during venovenous ECMO for respiratory failure in adults. Intensive care medicine. 2013 May 1;39(5):838-46.

Swol J, Marschall C, Strauch JT, Schildhauer TA. Hematocrit and impact of transfusion in patients receiving extracorporeal life support. Perfusion. 2018 Apr 1:0267659118772457.

Voelker MT, Busch T, Bercker S, Fichtner F, Kaisers UX, Laudi S. Restrictive transfusion practice during extracorporeal membrane oxygenation therapy for severe acute respiratory distress syndrome. Artificial organs. 2015 Apr;39(4):374-8.

Weingart C, Lubnow M, Philipp A, Bein T, Camboni D, Müller T. Comparison of coagulation parameters, anticoagulation, and need for transfusion in patients on interventional lung assist or veno-venous extracorporeal membrane oxygenation. Artificial organs. 2015 Sep;39(9):765-73.
**Question**: Restrictive transfusion strategy compared to liberal transfusion strategy in adult ICU patients with malignancy

| Certainty assessment | № of patients | Effect | Certainty | Importance |
|----------------------|---------------|--------|-----------|------------|
|                       | № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Restrictive strategy | Liberal strategy | Relative (95% CI) | Absolute (95% CI) |            |            |
| Mortality (long term) (follow up: range 60 days to 90 days) | 3 | RCTs | serious | not serious | not serious | serious | none | 131/311 (42.1%) | 101/276 (36.6%) | RR 1.26 (1.06 to 1.50) | 95 more per 1,000 (from 22 more to 183 more) | + + + | LOW | CRITICAL |
| Mortality (short term) (follow up: median 30 days) | 2 | RCTs | serious | not serious | not serious | serious | none | 107/252 (42.5%) | 75/246 (30.5%) | RR 1.40 (1.12 to 1.75) | 122 more per 1,000 (from 37 more to 229 more) | + + + | LOW | CRITICAL |
| Stroke | 2 | RCTs | serious | not serious | not serious | serious | none | 6/252 (2.4%) | 2/246 (0.8%) | RR 2.54 (0.59 to 10.86) | 13 more per 1,000 (from 3 fewer to 80 more) | + + + | LOW | IMPORTANT |
| Myocardial infarction | 3 | RCTs | serious | not serious | not serious | serious | none | 6/311 (1.9%) | 4/276 (1.4%) | RR 1.24 (0.39 to 3.92) | 3 more per 1,000 (from 9 fewer to 42 more) | + + + | LOW | IMPORTANT |
| ARDS | 2 | RCTs | not serious | not serious | not serious | very serious | none | 2/252 (0.8%) | 0/246 (0.0%) | RR 4.80 (0.23 to 98.80) | 0 fewer per 1,000 (from 0 fewer to 0 fewer) | + + + | LOW | IMPORTANT |
| Infection | 1 | RCTs | serious | not serious | serious | serious | none | 14/101 (13.9%) | 5/97 (5.2%) | RR 2.69 (1.01 to 7.18) | 87 more per 1,000 (from 1 more to 319 more) | + + + | VERY LOW | IMPORTANT |
| Renal failure requiring renal replacement therapy | | | | | | | | | | | | |

### Meta-analysis results:

**Mortality (long term) (follow up: range 60 days to 90 days)**

- **Restrictive strategy** vs. **Liberal strategy**
- **Relative Risk (RR)**: 1.26 (1.06 to 1.50)
- **Absolute Risk**: 95 more per 1,000 (from 22 more to 183 more)

**Mortality (short term) (follow up: median 30 days)**

- **Restrictive strategy** vs. **Liberal strategy**
- **Relative Risk (RR)**: 1.40 (1.12 to 1.75)
- **Absolute Risk**: 122 more per 1,000 (from 37 more to 229 more)

**Stroke**

- **Restrictive strategy** vs. **Liberal strategy**
- **Relative Risk (RR)**: 2.54 (0.59 to 10.86)
- **Absolute Risk**: 13 more per 1,000 (from 3 fewer to 80 more)

**Myocardial infarction**

- **Restrictive strategy** vs. **Liberal strategy**
- **Relative Risk (RR)**: 1.24 (0.39 to 3.92)
- **Absolute Risk**: 3 more per 1,000 (from 9 fewer to 42 more)

**ARDS**

- **Restrictive strategy** vs. **Liberal strategy**
- **Relative Risk (RR)**: 4.80 (0.23 to 98.80)
- **Absolute Risk**: 0 fewer per 1,000 (from 0 fewer to 0 fewer)

**Infection**

- **Restrictive strategy** vs. **Liberal strategy**
- **Relative Risk (RR)**: 2.69 (1.01 to 7.18)
- **Absolute Risk**: 87 more per 1,000 (from 1 more to 319 more)

### Certainty Assessment:

- **Low**
- **Very Low**
- **Critical**
- **Important**

### Risk of Bias:

- serious
- not serious
Explanations

a. Most data is from single centre studies which tend to have exaggerated effects
b. Even though high value of I² statistic, point estimates and 95% CI of the largest studies are on the same side of the line of no effect, so this heterogeneity is of questionable importance.
c. Though statistically significant, the optimal information size not met; more events needed to demonstrate effects are not due to chance alone.
d. Though standardized definitions of myocardial infarction and stroke were used (eg. elevated troponin, change in EKG, loss of viable myocardium on imaging), the lack of blinding of clinicians could have led to significant detection bias.
e. 95% confidence interval does not exclude significant harm or benefit, with absolute risk numbers likely to be of considerable importance to patients.
f. Extremely small number of ARDS cases in these studies (2), resulting in very significant imprecision.
g. Single study (Almedia 2015) included a wide variety of infections, though difference between groups was largely due to postoperative intra-abdominal infection, making generalization to non-surgical oncology patients difficult.
h. One of the two studies (deZern 2016) did not blind outcome assessors, which could result in detection bias.
i. Both trials assessing risk of bleeding were conducted in hospitalized patients with hematologic malignancy, a population which may have a different risk of bleeding than an ICU population including other malignancies.

Summary statements
1. Restrictive transfusion strategy may result in a moderate to large increase in 60-90 day mortality.
2. Restrictive transfusion strategy may result in a large increase in 30 day mortality.
3. Restrictive transfusion strategy may moderately increase stroke, though our certainty is limited by imprecision and detection bias.
4. Restrictive transfusion strategy may result in little to no difference in myocardial infarction, though our certainty is limited by imprecision and detection bias.
5. We are uncertain about the effect of restrictive transfusion strategy on ARDS, though our certainty is limited by very significant imprecision.
6. We are uncertain about the effect of restrictive transfusion strategy on infections, though our certainty is limited by the indirectness of the outcome definitions.
7. Restrictive transfusion strategy may result in little to no difference in renal failure requiring renal replacement therapy slightly, though our certainty is limited by imprecision.
8. We are uncertain about the effect of restrictive transfusion strategy on bleeding due to indirectness, imprecision, and risk of bias of included trials.
1. Mortality (long term) (60 to 90 days)

| Study or Subgroup | Restrictive Events | Total | Liberal Events | Total | Weight | Risk Ratio M-H, Fixed, 95% CI | Risk Ratio M-H, Fixed, 95% CI |
|-------------------|--------------------|-------|----------------|-------|--------|-------------------------------|-------------------------------|
| Almeida 2015      | 24                 | 101   | 11             | 97    | 11.0%  | 2.10 [1.09, 4.04]             |                               |
| Bergamin 2017     | 106                | 151   | 88             | 149   | 86.5%  | 1.19 [1.00, 1.41]             |                               |
| deZern 2016       | 1                  | 59    | 2              | 30    | 2.6%   | 0.25 [0.02, 2.69]             |                               |
| **Total (95% CI)**| **311**            | **276**| **100.0%**    | **30**| **1.26 [1.06, 1.50]**         |                               |

Total events: 131 (95% CI: 101)
Heterogeneity: Chi² = 4.55, df = 2 (P = 0.10); I² = 56%
Test for overall effect: Z = 2.67 (P = 0.008)

2. Mortality (short term) (30 days or less)

| Study or Subgroup | Restrictive Events | Total | Liberal Events | Total | Weight | Risk Ratio M-H, Fixed, 95% CI | Year                          |
|-------------------|--------------------|-------|----------------|-------|--------|-------------------------------|-------------------------------|
| Almeida 2015      | 23                 | 101   | 8              | 97    | 10.8%  | 2.76 [1.30, 5.87] 2015       |                               |
| Bergamin 2017     | 84                 | 151   | 67             | 149   | 89.2%  | 1.24 [0.99, 1.55] 2017       |                               |
| **Total (95% CI)**| **252**            | **246**| **100.0%**    | **75**| **1.40 [1.12, 1.75]**         |                               |

Total events: 107 (95% CI: 75)
Heterogeneity: Chi² = 4.26, df = 1 (P = 0.04); I² = 77%
Test for overall effect: Z = 2.97 (P = 0.003)

3. Stroke

| Study or Subgroup | Restrictive Events | Total | Liberal Events | Total | Weight | Risk Ratio M-H, Fixed, 95% CI | Risk Ratio M-H, Fixed, 95% CI |
|-------------------|--------------------|-------|----------------|-------|--------|-------------------------------|-------------------------------|
| Almeida 2015      | 3                  | 101   | 0              | 97    | 20.2%  | 6.73 [0.35, 128.52]           |                               |
| Bergamin 2017     | 3                  | 151   | 2              | 149   | 79.8%  | 1.48 [0.25, 8.73]             |                               |
| **Total (95% CI)**| **252**            | **246**| **100.0%**    | **2** | **2.54 [0.59, 10.86]**        |                               |

Total events: 6 (95% CI: 2)
Heterogeneity: Chi² = 0.77, df = 1 (P = 0.38); I² = 0%
Test for overall effect: Z = 1.26 (P = 0.21)
4. Myocardial infarction

| Study or Subgroup | Restrictive | Liberal | Risk Ratio M-H, Fixed, 95% CI |
|-------------------|-------------|---------|-------------------------------|
|                   | Events      | Total   | Events | Total | Weight |  
| Almeida 2015      | 1           | 101     | 0      | 97    | 9.8%    | 2.88 [0.12, 69.91] |
| Bergamin 2017     | 4           | 151     | 4      | 149   | 77.5%   | 0.99 [0.25, 3.87]  |
| deZern 2016       | 1           | 59      | 0      | 30    | 12.7%   | 1.55 [0.07, 36.94] |

Total (95% CI): 311 events
Heterogeneity: Chi² = 0.40, df = 2 (P = 0.82); I² = 0%
Test for overall effect: Z = 0.37 (P = 0.71)

5. ARDS

| Study or Subgroup | Restrictive | Liberal | Risk Ratio M-H, Random, 95% CI |
|-------------------|-------------|---------|-------------------------------|
|                   | Events      | Total   | Events | Total | Weight |  
| Almeida 2015      | 2           | 101     | 0      | 97    | 100.0%  | 4.80 [0.23, 98.80] |
| Bergamin 2017     | 0           | 151     | 0      | 149   | Not estimable |

Total (95% CI): 252 events
Heterogeneity: Not applicable
Test for overall effect: Z = 1.02 (P = 0.31)

6. Infection

| Study or Subgroup | Restrictive | Liberal | Risk Ratio M-H, Random, 95% CI |
|-------------------|-------------|---------|-------------------------------|
|                   | Events      | Total   | Events | Total | Weight |  
| Almeida 2015      | 14          | 101     | 5      | 97    | 100.0%  | 2.69 [1.01, 7.18] |

Total (95% CI): 101 events
Heterogeneity: Not applicable
Test for overall effect: Z = 1.97 (P = 0.05)
7. Renal failure requiring renal replacement therapy

| Study or Subgroup | Restrictive | Liberal | Risk Ratio M-H, Fixed, 95% CI |
|-------------------|-------------|---------|-------------------------------|
|                   | Events      | Total   | Weight |                          |
| Almeida 2015      | 3           | 101     | 2      | 13.5% 1.44 [0.25, 8.44]   |
| Bergamin 2017     | 18          | 151     | 13     | 86.5% 1.37 [0.69, 2.69]   |
| **Total (95% CI)** | **252**     | **246** | **100.0%** | **1.38 [0.73, 2.59]** |

Total events: 21

Heterogeneity: Chi² = 0.00, df = 1 (P = 0.96); I² = 0%

Test for overall effect: Z = 0.99 (P = 0.32)

8. Bleeding

| Study or Subgroup | Restrictive | Liberal | Risk Ratio M-H, Fixed, 95% CI |
|-------------------|-------------|---------|-------------------------------|
|                   | Events      | Total   | Weight |                          |
| deZern 2016       | 9           | 59      | 5      | 23.8% 0.92 [0.34, 2.49]   |
| Webert 2008       | 22          | 29      | 22     | 76.2% 1.07 [0.79, 1.45]   |
| **Total (95% CI)** | **88**      | **61**  | **100.0%** | **1.03 [0.75, 1.43]** |

Total events: 31

Heterogeneity: Chi² = 0.11, df = 1 (P = 0.75); I² = 0%

Test for overall effect: Z = 0.19 (P = 0.85)
**Question:** Restrictive transfusion strategy compared to liberal transfusion strategy in elderly ICU patients

| Certainty assessment | Nr of patients | Effect | Certainty | Importance |
|----------------------|----------------|--------|------------|------------|
|                      | Nr of patients | Relative (95% CI) | Absolute (95% CI) |            |            |
|                      |                | RR 0.68 (0.44 to 1.05) | 176 fewer per 1,000 (from 309 fewer to 28 more) |            |            |
|                      |                | RR 0.96 (0.57 to 1.62) | 5 fewer per 1,000 (from 54 fewer to 78 more) |            |            |
|                      |                | MD 1 units lower (3.51 lower to 5.51 higher) |            |            |
|                      |                | MD 2 units lower (0.18 lower to 4.18 higher) |            |            |
|                      |                | RR 0.32 (0.01 to 7.68) | 14 fewer per 1,000 (from 20 fewer to 136 more) |            |            |

### Mortality (long term) (follow up: 180 days)

| Nr of studies |Study design |Risk of bias |Inconsistency |Indirectness |Imprecision |Other considerations |Nr of patients |Liberal strategy |Absolute (95% CI) |
|---------------|-------------|-------------|---------------|--------------|-------------|---------------------|---------------|----------------|-----------------|
| 1             |RCTs         |not serious  |not serious    |not serious   |serious a    |none                |19/51 (37.3%) |27/49 (55.1%)   |RR 0.68 (0.44 to 1.05) |
|               |             |serious b    |not serious    |serious a     |none         |52/176 (29.8%)      |22/176 (12.5%) |23/184 (12.5%)  |RR 0.96 (0.57 to 1.62) |
|               |             |not serious  |not serious    |serious a     |none         |51                  |49             |5 fewer per 1,000 (from 54 fewer to 78 more) |
|               |             |serious c    |not serious    |not serious   |serious a    |51                  |49             |MD 1 units lower (3.51 lower to 5.51 higher) |
|               |             |serious d    |not serious    |not serious   |serious a    |51                  |49             |MD 2 units lower (0.18 lower to 4.18 higher) |

### Mortality (short term) (follow up: 30 days)

| Nr of studies |Study design |Risk of bias |Inconsistency |Indirectness |Imprecision |Other considerations |Nr of patients |Liberal strategy |Absolute (95% CI) |
|---------------|-------------|-------------|---------------|--------------|-------------|---------------------|---------------|----------------|-----------------|
| 1             |RCTs         |not serious  |not serious    |not serious   |serious a    |none                |22/176 (12.5%) |23/184 (12.5%)  |RR 0.96 (0.57 to 1.62) |
|               |RCTs         |serious b    |not serious    |serious a     |none         |52/176 (29.8%)      |22/176 (12.5%) |23/184 (12.5%)  |RR 0.96 (0.57 to 1.62) |
|               |RCTs         |not serious  |not serious    |serious a     |none         |51                  |49             |5 fewer per 1,000 (from 54 fewer to 78 more) |
|               |RCTs         |serious c    |not serious    |not serious   |serious a    |51                  |49             |MD 1 units lower (3.51 lower to 5.51 higher) |
|               |RCTs         |serious d    |not serious    |not serious   |serious a    |51                  |49             |MD 2 units lower (0.18 lower to 4.18 higher) |

### Quality of life (follow up: 180 days; assessed with: SF-12)

| Nr of studies |Study design |Risk of bias |Inconsistency |Indirectness |Imprecision |Other considerations |Effect |Certainty | Importance |
|---------------|-------------|-------------|---------------|--------------|-------------|---------------------|--------|----------|------------|
| 1             |RCTs         |serious c    |not serious    |not serious   |serious a    |none                |MD 1 units lower (3.51 lower to 5.51 higher) |CRITICAL |

### Functional recovery (follow up: 180 days; assessed with: Rivermeade Mobility Index)

| Nr of studies |Study design |Risk of bias |Inconsistency |Indirectness |Imprecision |Other considerations |Effect |Certainty | Importance |
|---------------|-------------|-------------|---------------|--------------|-------------|---------------------|--------|----------|------------|
| 1             |RCTs         |serious c    |not serious    |not serious   |serious a    |none                |MD 2 units lower (0.18 lower to 4.18 higher) |CRITICAL |

### Stroke

| Nr of studies |Study design |Risk of bias |Inconsistency |Indirectness |Imprecision |Other considerations |Effect |Certainty | Importance |
|---------------|-------------|-------------|---------------|--------------|-------------|---------------------|--------|----------|------------|
| 1             |RCTs         |serious d    |not serious    |not serious   |serious a    |none                |RR 0.32 (0.01 to 7.68) |IMPORTANT |

### Myocardial infarction
Explanations

a. Wide 95% confidence interval which does not exclude significant benefit or harm of probable significance to patients.
b. Significant inconsistency (I² > 40%) with point estimates on both sides of the line of no effect.
c. Significant loss to follow-up at 180 days (5-10%) which may have biased results.
d. Lack of blinding may have led to detection bias as no standard screening for ischemia was performed.
e. Wide 95% confidence interval with very few events resulting in very significant imprecision.

Summary statements.
1. Restrictive transfusion strategy probably does not increase mortality at 180 days, though our certainty is limited by imprecision.
2. Restrictive transfusion strategy may increase 30 day mortality, though our certainty is limited by inconsistency and imprecision.
3. Restrictive transfusion strategy may result in little to no difference in quality of life, though our certainty is limited by loss to follow up in the single included study and imprecision.
4. Restrictive transfusion strategy may result in a small possibly unimportant effect in functional recovery, though our certainty is limited by loss to follow up in the single included study and imprecision.
5. Restrictive transfusion strategy may not increase stroke, though our certainty is limited by the risk of detection bias and imprecision.
6. Restrictive transfusion strategy may result in little to no difference in, reduction in myocardial infarction, though our certainty is limited by the risk of detection bias and imprecision.
7. Restrictive transfusion strategy may result in no increase need for renal replacement therapy, though our certainty is limited by imprecision.
8. Restrictive transfusion strategy may increase ARDS slightly, though our certainty is limited by very significant imprecision.
1. Mortality (long-term: 180 days)

| Study or Subgroup | Restrictive Events | Total | Liberal Events | Total | Weight | Risk Ratio M-H, Random, 95% CI |
|-------------------|-------------------|-------|----------------|-------|--------|-------------------------------|
| Walsh 2013        | 19                | 51    | 27             | 49    | 100.0% | 0.68 [0.44, 1.05]             |

Total (95% CI) 51 49 100.0% 0.68 [0.44, 1.05]

Total events 19 27

Heterogeneity: Not applicable

Test for overall effect: Z = 1.76 (P = 0.08)

2. Mortality (short-term: 30 days)

| Study or Subgroup | Restrictive Events | Total | Liberal Events | Total | Weight | Risk Ratio M-H, Fixed, 95% CI | Year |
|-------------------|-------------------|-------|----------------|-------|--------|-------------------------------|------|
| 4.2.1 Primary ICU studies |
| Walsh 2013        | 12                | 51    | 16             | 49    | 45.7%  | 0.72 [0.38, 1.36] 2013       |
| Subtotal (95% CI) | 12                | 51    | 16             | 49    | 45.7%  | 0.72 [0.38, 1.36]            |

Total events 12 16

Heterogeneity: Not applicable

Test for overall effect: Z = 1.01 (P = 0.31)

| 4.2.2 ICU study subgroup analyses |
| Nakamura 2015                | 10                | 125   | 7              | 135   | 18.8%  | 1.54 [0.61, 3.93] 2015       |
| Subtotal (95% CI)            | 125               | 135   | 7              | 135   | 18.8%  | 1.54 [0.61, 3.93]            |

Total events 10 7

Heterogeneity: Not applicable

Test for overall effect: Z = 0.91 (P = 0.36)

| 4.2.3 Non–ICU studies |
| Foss 2009                 | 5                 | 60    | 0              | 60    | 1.4%   | 11.00 [0.62, 194.63] 2009    |
| Gregersen 2015            | 21                | 144   | 12             | 140   | 34.1%  | 1.70 [0.87, 3.32] 2015       |
| Subtotal (95% CI)         | 204               | 200   | 12             | 200   | 35.5%  | 2.07 [1.09, 3.92]            |

Total events 26 12

Heterogeneity: Chi² = 1.63, df = 1 (P = 0.20); I² = 38%

Test for overall effect: Z = 2.23 (P = 0.03)

Total (95% CI) 380 384 100.0% 1.35 [0.91, 2.02]

Total events 48 35

Heterogeneity: Chi² = 6.32, df = 3 (P = 0.10); I² = 53%

Test for overall effect: Z = 1.49 (P = 0.14)

Test for subgroup differences: Chi² = 5.44, df = 2 (P = 0.07), I² = 63.2%
3. Quality of life (Measured with SF-12, 180 days)

| Study or Subgroup | Restrictive Mean | SD | Total | Liberal Mean | SD | Total | Weight | Mean Difference IV, Random, 95% CI | Year |
|-------------------|------------------|----|-------|--------------|----|-------|--------|-------------------------------------|------|
| Walsh 2013        | -30              | 11.9 | 51     | -31           | 11.1 | 49     | 100.0% | 1.00 [-3.51, 5.51]                  | 2013 |
| **Total (95% CI)** |                  |     | 51     |              |     | 49     |        | **1.00 [-3.51, 5.51]**              |      |

Heterogeneity: Not applicable
Test for overall effect: Z = 0.43 (P = 0.66)

4. Functional outcome (Measured with Rivermeade Mobility Index, 180 days)

| Study or Subgroup | Restrictive Mean | SD | Total | Liberal Mean | SD | Total | Weight | Mean Difference IV, Random, 95% CI | Year |
|-------------------|------------------|----|-------|--------------|----|-------|--------|-------------------------------------|------|
| Walsh 2013        | -10              | 5.2 | 51     | -12           | 5.9 | 49     | 100.0% | 2.00 [-0.18, 4.18]                  | 2013 |
| **Total (95% CI)** |                  |     | 51     |              |     | 49     |        | **2.00 [-0.18, 4.18]**              |      |

Heterogeneity: Not applicable
Test for overall effect: Z = 1.80 (P = 0.07)

4. Stroke

| Study or Subgroup | Restrictive Events | Total | Liberal Events | Total | Weight | Risk Ratio M-H, Random, 95% CI | Risk Ratio M-H, Random, 95% CI |
|-------------------|--------------------|-------|----------------|-------|--------|-------------------------------|-------------------------------|
| Walsh 2013        | 0                  | 51    | 1              | 49    | 100.0% | 0.32 [0.01, 7.68]             |                               |
| **Total (95% CI)** |                    | 51    |                | 49    |        | **0.32 [0.01, 7.68]**         |                               |

Total events 0
Heterogeneity: Not applicable
Test for overall effect: Z = 0.70 (P = 0.48)
5. Myocardial infarction

| Study or Subgroup   | Restrictive Events | Liberal Events | Risk Ratio M-H, Random, 95% CI |
|---------------------|--------------------|----------------|--------------------------------|
| Walsh 2013          | 2                  | 2              | 0.96 [0.14, 6.56]               |
| Total (95% CI)      | 51                 | 49             | 0.96 [0.14, 6.56]               |

Heterogeneity: Not applicable
Test for overall effect: Z = 0.04 (P = 0.97)

6. Renal failure requiring renal replacement therapy

| Study or Subgroup   | Restrictive Events | Liberal Events | Risk Ratio M-H, Fixed, 95% CI |
|---------------------|--------------------|----------------|--------------------------------|
| Nakamura 2015       | 6                  | 10             | 0.65 [0.24, 1.73]              |
| Total (95% CI)      | 125                | 135            | 0.65 [0.24, 1.73]              |

Heterogeneity: Not applicable
Test for overall effect: Z = 0.87 (P = 0.39)

7. ARDS

| Study or Subgroup   | Restrictive Events | Liberal Events | Risk Ratio M-H, Fixed, 95% CI |
|---------------------|--------------------|----------------|--------------------------------|
| Nakamura 2015       | 3                  | 0              | 7.56 [0.39, 144.83]            |
| Total (95% CI)      | 125                | 135            | 7.56 [0.39, 144.83]            |

Heterogeneity: Not applicable
Test for overall effect: Z = 1.34 (P = 0.18)
Alternative transfusion triggers in the ICU Literature Summary

Reported use of physiologic triggers in OR (Meier 2016)
-European prospective observational study 5803 patients who received at least 1 PRBC in OR
-majority of transfusions (58.9%) at least in part for a physiologic transfusion trigger, rather than Hb alone
-most common physiologic triggers: hypotension (55.4%), tachycardia (30.7%), acidosis (7.8%), arrhythmia (5.1%), ECG changes (2.7%), ScvO2 or SvO2 (3.4%), other (10.2%)

Data from TRACE survey: 25% always use alternative 30% never use 25% sometimes use alternative

These data are consistent with a practice where hypotension and tachycardia are interpreted to indicate that a patient is actively bleeding, and therefore hemoglobin may no longer represent a steady-state marker of a patient's blood volume and oxygen scarring capacity. The studies included in this guideline generally excluded bleeding patients, and our guideline recommendations should not apply in these patients, if indeed hypotension and tachycardia are interpreted as signs of active bleeding (as opposed to ongoing sepsis, pain, agitation, etc.) Similarly, if a patient demonstrates signs of active cardiac ischemia, including changes on EKG, elevated troponin, new wall motion abnormalities on echocardiogram, then a restrictive hemoglobin-based strategy as is suggested in most of our recommendations may no longer apply. In such circumstances that active myocardial ischemia, the recommendation for acute coronary syndromes (conditional recommendation for liberal transfusion threshold) should instead be followed.

There are limited number of studies evaluating physiologic transfusion triggers in comparison to Hb based approaches. The majority of studies are experimental and do not report clinical outcomes. By comparison, there are many studies evaluating various hemoglobin triggers and resulting in more certainty about the impact of transfusion using Hb based thresholds compared to alternative transfusion strategies such as those described below. In the absence of evidence, the use of physiologic transfusion triggers may result in improved or worsened clinical outcomes compared to Hb based transfusion triggers, or increased or decreased use of blood products. In the absence of any evidence, we recommend the use of physiologic transfusion triggers in research settings only.

Transfusion trigger 0: Mitochondrial O2

Transfusion trigger 1: ScvO2
Summary: 4 observational studies (371 patients); no studies reported clinical outcomes between patients using ScvO2 trigger vs. usual Hb trigger; 3 studies (Adamczyk, Surve, Zeroual) in post-operative ICU patients used pre-transfusion ScvO2 to predict increase in ScvO2 post-transfusion. finding a cutoff ~65-70% had reasonable sensitivity and specificity. It remains unclear whether targeting changes in ScvO2 results in improved clinical outcomes.
Samarani 2014 found that a Hb threshold of 7 g/dL did not predict changes in ScvO2 post-transfusion in patients receiving transfusion during or after CV surgery. Samarani 2015 found patients who were weaning from the ventilator at the end of CV surgery had lower ScvO2, but there was no correlation between Hb and ScvO2 levels.

i) Adamczyk 2008
-prospective observational study of 60 hemodynamically patients postoperative general surgery who blood transfusion was considered; ScvO2 and Hb were measured pre- and post-transfusion (29 with ScvO2 <70%, 31 with ScvO2>70%)
-ScvO2 increased in patients with ScvO2<70% (57.8 to 68.5%) but was relatively unchanged in patients with an ScvO2 already >70% (76.8% to 76.5%)
-18 of 33 patients who met standard transfusion trigger criteria had ScvO2>70%, and 13 of 20 patients who did not meet standard transfusion trigger had ScvO2<70%
-no clinical outcomes reported as patients did not receive transfusion based upon ScvO2

ii) Samarani 2014
-retrospective study of 68 patients who received blood transfusion during or immediately after CV surgery, excluding patients with active bleeding, coagulopathy or emergency surgery
-ScvO2 and Hb measured immediately pre and post transfusion
-no correlation between Hb and ScvO2
-ScvO2 of patients transfused when Hb< 7 g/dL (n=44) was no different from ScvO2 in patients transfused with Hb>7 g/dL (69, 59-79 vs. 71, 61-77 respectively; p = 0.90)

iii) Samarani 2015
-prospective observational study of 120 patients undergoing cardiothoracic surgery with a CVC requiring transfusion, in the absence of active bleeding and coagulopathy
-no correlation between Hb and ScvO2 values pre-transfusion
-ScvO2 was lower in patients receiving weaning, even if Hb levels were not statistically different

iv) Surve 2015
-prospective observational study of 70 adult neurointensive care unit patients, with CVC in situ and who required blood transfusion; excluded patients with high FiO2 and high inotropic support (usual practice is transfuse with Hb< 9 g/dL)
-ScvO2 and Hb measured pre and post transfusion
-ROC curve plotted to predict 5% increase in ScvO2, based upon different ScvO2 and Hb cutoff; ScvO2 of 70 had sens 80% spec 87% AUROC 0.893; Hb 8.6 g/dL had sens 79.4% and specificity 60% AUROC 0.622

v) Zeroual 2018
-prospective observational study of 53 patients admitted to a cardiothoracic and vascular ICU who required blood transfusion; excluding actively bleeding and unstable patients
-ScvO2 and Hb collected pre- and post- transfusion
-no correlation between pre-transfusion ScvO2 and Hb level
-to predict ScvO2 increase of 5%, value of ScvO2 of 65% was best (sens 0.68 spec 0.88 AUC 0.82); predicting very large increase in ScvO2 (20%) was best with initial value of ScVO2 of 59% (sens 100 spec 82.3, AUC 0.92)

Transfusion trigger 2: arteriovenous oxygen difference
Summary; 4 observational studies of 417 patients. One study compared clinical outcomes using a-vO2 differences. Fogagnolo studied 113 ICU patients within 24 hours of admission retrospectively assigned patients to high a-vO2 gap pre-transfusion and normal a-vO2 gap pre-transfusion, and then classified transfusions as appropriate or inappropriate based upon these classifications. Inappropriate transfusion by a-vO2 was associated with higher mortality (23/65 vs. 8/48, adjusted for confounders OR was 3.02 [95% CI 1.2 to 6.2]. Orlov 2009 find that in cardiac surgery patients, that an O2ER>30% predicted a reduction in O2ER at 2 hours post-transfusion. Seghal and Mun-ayi did not find a correlation between Hb and O2ER.

i) Seghal 2001
- Prospective observational study of 70 patients undergoing CABG, with arterial and mixed O2 measurements before, in ICU, and 12 hours post-operatively.
- No difference in transfused and non-transfused patients with regard to Hb, CI, O2 delivery, O2 consumption and O2ER

ii) Orlov 2009
- Observational study of 176 patients undergoing cardiac surgery, 74 of whom received transfusions.
- Among patients who received transfusion for low Hb, 43% had normal pre-transfusion O2ER.
- Post-transfusion reduction in O2ER seen in patients with O2ER > 30%, not seen in patients with O2ER > 30% (1.4 +/- 7.0 vs. -3.8 +/- 8 at 2 hours).

iii) Mun’ayi 2013
- Prospective observational study of 58 patients admitted to adult ICU requiring transfusion.
- Mean O2ER (SaO2 - ScvO2).
- No correlation between change in Hb and O2ER.

iv) Fogagnolo 2017
- Prospective observational study of 113 patients with Hb between 7-9 g/dL during first 24 hours after ICU admission.
- Patients divided into “appropriate transfusion” (high a-vO2 gap and transfused, or low a-vO2 gap and not transfused) or “non-appropriate transfusion” (high a-vO2 gap and not transfused, or low a-vO2 gap and transfused).
- Inappropriate transfusion was associated with increased mortality (23/65 vs. 8/48, HR 2.4 [95% CI 1.1 to 4.6]; adjusted for confounders OR for mortality was 3.02 [95% CI 1.2 to 6.2]).

**Transfusion trigger 3 Cerebral oxygenation**

**Summary:** 1 RCT (204 patients), 2 observational studies (37 patients). Only one study compared cerebral oxygenation transfusion trigger to hemoglobin transfusion trigger, though it was intraoperative CV surgery patients, and non-transfusion means of improving oxygenation were also employed: Rogers et al randomized patients in 1:1 fashion to two tissue oxygenation strategies: one “generic” strategy using transfusion threshold Hct 23, the other “patient-specific” using regional cerebral O2 monitoring with transfusion threshold Hct 18%, with goal of maintaining INVOS values >50% or >70% from baseline. This target could be met with altering anesthetic, gas flow, transfusion etc. At ~1 week and 3 months, no difference in most areas of cognitive function. Similar RBC transfusion rates, biomarkers of brain, kidney, myocardial injury, and costs similar. McCredie used SctO2 monitoring in 24 patient with TBI, finding fractional tissue oxygen extraction pre and post-transfusion was not different, despite change significant increases in hemoglobin. Muthuchellappan found rSO2 increased following transfusion with a decrease in cerebral fractional of oxygen extraction in both hemispheres.

i) McCredie 2017
- Prospective observational study of 24 ICU patients with severe TBI requiring transfusion, excluding patients with advice hemorrhage hypotension, GCS3, intoxication.
- SctO2 monitor recording (one on each temporal region, continuous SpO2, measuring fractional tissue oxygen extraction (SpO2-Sct))/SpO2 pre and post transfusion.
- Majority of patients had a Hb > 6 g/dL; post-transfusion FTOE in patients with Hb <7 g/dL was not different than in those with Hb >7 g/dL; no difference in FTOE between pre and post-
transfusion on either side (left 0.69 pre to 0.7 post; right 0.69 pre to 0.71 post) despite statical changes in Hb pre to post transfusion

ii) Muthuchellappan 2017
-prospective observational study of 13 adult neuro-ICU patients before, at the end, and 6, 12, 18, and 24 hours post-transfusion using rSO2 senses, and SCVO2
-rSO2 increased following RBC transfusion on both sides of the brain up to 24 hours
-decrease in cerebral fractionation oxygen extraction up to 24 hours post (35+/- 9% to 28+/- 6%, p=0.021)
-similarly changes see in CFOE for both injured and uninjured hemispheres of the brain

iii) Rogers 2017
-randomized controlled trial at 3 centres, 204 patients randomized 1:1 to ‘generic’ or ‘patient-specific’ algorithm for tissue oxygenation during cardiac surgery
-“generic” algorithm used globes measures of O2 utilization and intraoperative hematocrit transfusion threshold of 23%
-“ patient-specific” algorithm used regional O2 saturation using INVO5000, combined with restrictive transfusion HCT of 18%; goal was to maintain INVOS values of >50% or at >70% baselines value; if this could not bobtained by modifying pump flow, gas exchange, or depth of anaesthesia, RCTS could be transfused above HCT 18%
-primary outcome was cognitive function between 4-7 days post-op and at 3 months
-no difference between groups in there core cognitive domains; only difference was verbal fluency scores were slightly higher in NIRS group; RBC transfusion, biomarkers of brain, kidney, myocardial injury, and costs were similar
**Transfusion trigger 4: Tissue oxygenation & lactate**

*Summary: 5 observational studies (296 patients). Only one study compared tissue oxygenation to hemoglobin transfusion trigger: Loucas reviewed 100 patients undergoing CVsx who received transfusion, 50 with standard transfusion criteria, 50 with InSpectra tissue monitor; the group using the tissue monitor had lower transfusion rates (30% vs. 18%) without a difference in other outcomes or length of stay. Parimi reviewed 111 trauma patients with non-massive transfusion, and found lactate of 2.9 as predictive of need for transfusion (AUC 0.66) and bicarbonate 22 mmol/L (AUC 0.61). 3 studies (Torella, Zogheib, Powell) looked for correlations between changes in Hb and tissue oxygenation, all three finding changes in tissue oxygenation.*

i) Torella 2002
- prospective observational study of 30 patients undergoing acute normovolaemic haemodilution during vascular surgery; measurement of tissue oxygenation using NIRS of forehead (CsO2) and left calf (PsO2)
- Hb concentration changes correlated with changes in CsO2 and PsO2

ii) Zogheib 2011
- prospective observational study of 42 post-operative cardiac surgery patients, not in shock, transfused; StO2 and ScvO2 measured before and after transfusion
- no change observed with basic continuous StO2 monitoring before and after transfusion but StO2 peak changed (90+/- 7 to 93 +/- 4 p=0.04)
- ScVO2 changed (61.6% +/- 8.5% to 66.2% +/- 9.7%, p= 0.001)

iii) Loukas 2011
- retrospective chart review of 100 patients undergoing cardiac surgery (CABG or valve); 50 using standard hemodynamic monitors and standard transfusion criteria; 50 using InSpectra tissue oxygen monitor intra- and post-operatively
- transfusion rates were lower in the tissue monitoring group (30% conventional, 18% tissue) without a difference in other outcomes or length of stay

iv) Powell 2012
- observational study of trauma and elective surgery patients admitted to ICU who received transfusion
- 13 patients, perfused capillary density did not change from baseline to 1 hour, but did change at 3 hours, MAP was unchanged

v) Parimi 2018
- single centre retrospective study of 111 adult trauma patients who received minor transfusion (2 or fewer units) during first hour of admission; patients were divided into two groups, one with “indication for transfusion” and another with “possibly unnecessary” transfusion
- lactate levers were different in the indicated vs unnecessary group (6.7 vs. 4.7 p=0.006), as were bicarbonate (20.9 vs. 22.6), but hemoglobin levels were similar (note: levels in the abstract are reversed!)
- optimal cutoff value for predicting appropriate transfusion was lactate of 2.9 mg/dL (AUC 0.66) and bicarbonate 22 mmol/L (AUC 0.61)
Transfusion trigger 5: veno-arterial CO2 gradient

Summary: Two observational studies (118 patients) examined v-aPCO2 gradient as a transfusion trigger, neither comparing use of v-aCO2 gradient to hemoglobin transfusion trigger. Navarro utility of v-aPCO2 to predict a rise of 5% in SvO2, finding v-aPCO2 AUC 0.82. Taha studied cardiac surgery patients and found deltaPCO2/(arteriovenous oxygen content difference) correlated with moderate and severe blood loss, and improved after transfusion.

i) Navarro 2015
- observational study of 73 patients within 12 hours of admission to ICU
- V-a PCO2, hb, SvO2 were measured; “responders” had a rise >5% SvO2, “non-responders” had a rise <5% SvO2 after transfusion
- pre-transfusion V-aPCO2 cutoff of >=6 had sensitive 66% and specificity (AOC 0.82, 95% CI 0.73-0.91) for predicting responder vs. non-responders

ii) Taha 2015
- observational study of 45 postoperative patient in cardiac ICU, stratified by blood loss (mild 500-1000 mL first 24 hours; moderate 1000 mL to 1500 mL; severe >1500 mL), with measurements of ScvO2 and Ca-CvO2
- deltaPCO2/(arteriovenous oxygen content difference) correlated with moderate and severe blood loss, and improved after transfusion
Transfusion trigger 6: symptoms

Summary: Carson randomized 84 patients with hip fracture undergoing surgery to restrictive + symptoms transfusion vs liberal transfusion. Fewer transfusions in restrictive/symptomatic group, and other outcomes (mortality, MI, mobility, discharge disposition, complications) were similar between groups.

i) Carson 1998
- RCT of 84 patients with hip fracture undergoing surgical repair with post-op Hb less than 10 g/dL were assigned to symptomatic transfusion (symptoms of anemia or Hb < 8 g/dL) vs threshold transfusion (keeping Hb >10 g/dL)
- fewer transfusions in symptom transfusion group (median 2 [1,2] v. 0 [0,2])
- in-hospital, 30-day, 60 day mortality similar; MI similar; death or inability to walk across the room or 10 feet without assistance; pneumonia, VTE, discharge destination, residence at 60 days, length of stay were all similar
References:

Adamczyk S, Robin E, Barreau O, Fleyfel M, Tavernier B, Lebuffe G, Vallet B. Apport de la saturation veineuse centrale en oxygène dans la décision transfusionnelle postopératoire. InAnnales francaises d’anesthésie et de réanimation 2009 Jun 1 (Vol. 28, No. 6, pp. 522-530). Elsevier Masson.

Carson JL, Terrin ML, Barton FB, Aaron R, Greenburg AG, Heck DA, Magaziner J, Merlino FE, Bunce G, McClelland B, Duff A. A pilot randomized trial comparing symptomatic vs. hemoglobin-level-driven red blood cell transfusions following hip fracture. Transfusion. 1998 Jun;38(6):522-9.

Fogagnolo A, Spadaroa S, Cretur J, Cavalcante E, Taccone FS, Vola CA. Can arterio-venous-oxygen content difference be a target to guide transfusion in critically ill patients? Intensive Care Medicine Experimental 2017 5(Suppl 2):0041

Loukas A, Matadial C, Yapor J, Martinez-Ruiz R. Tissue oxygen monitoring leads to lower rates of blood transfusions. Critical Care. 2011 Feb;15(1):P425.

McCredie VA, Piva S, Santos M, Xiong W, de Oliveira Manoel AL, Rigamonti A, Hare GM, Chapman MG, Baker AJ. The impact of red blood cell transfusion on cerebral tissue oxygen saturation in severe traumatic brain injury. Neurocritical care. 2017 Apr 1;26(2):247-55.

Meier J, Filipescu D, Kozek-Langenecker S, Llau Pitarch J, Mallett S, Martus P, Matot I, ETPOS collaborators, Accurso G, Adelmann D, Ahrens N. Intraoperative transfusion practices in Europe. BJA: British Journal of Anaesthesia. 2016 Jan 19;116(2):255-61.

Mung’ayi V, Sharif T, Odaba DS. Blood transfusion and oxygen extraction ratio in patients admitted to the general intensive care unit: A quasi experimental study. African Journal of Emergency Medicine. 2014 Jun 1;4(2):66-70.

Muthuchellappan R, Shaikh NA, Surve RM, Ganne UR, Philip M. Regional cerebral tissue oxygen saturation changes following blood transfusion in neuro-intensive care unit patients—a pilot observational study. Transfusion Medicine. 2018 Jan 10.

Navarro JL, Sanchez-Calzada A, Gastelum R, Delgado L, Torres O, Romano P, Monares E, Gilberto C, Franco J. Venoarterial carbon dioxide gradient utility as a criterion for blood transfusion at the intensive care unit. Intensive care medicine experimental. 2015 Dec 1;3(S1):A221.

Orlov D, O’farrell R, McCluskey SA, Carroll J, Poonawala H, Hozhabri S, Karkouti K. The clinical utility of an index of global oxygenation for guiding red blood cell transfusion in cardiac surgery. Transfusion. 2009 Apr;49(4):682-8.

Parimi N, Fontaine MJ, Yang S, Hu PF, Li HC, Mackenzie CF, Kozar RA, Miller C, Scalea TM, Stein DM. Blood Transfusion Indicators Following Trauma in the Non-Massively Bleeding Patient. Annals of Clinical & Laboratory Science. 2018 May 1;48(3):279-85.

Powell S, Franzen D, Thacker L, Hogan C. RED BLOOD CELL TRANSFUSION IMPROVES MICROVASCULAR PERFUSION IN SURGICAL CRITICALLY ILL PATIENTS IN A DELAYED FASHION. InCRITICAL CARE MEDICINE 2012 Dec 1 (Vol. 40, No. 12, pp. U275-U275). 530 WALNUT ST, PHILADELPHIA, PA 19106-3621 USA: LIPPINCOTT WILLIAMS & WILKINS.
Rogers CA, Stoica S, Ellis L, Stokes EA, Wordsworth S, Dabner L, Clayton G, Downes R, Nicholson E, Bennett S, Angelini GD. Randomized trial of near-infrared spectroscopy for personalized optimization of cerebral tissue oxygenation during cardiac surgery. BJA: British Journal of Anaesthesia. 2017 Jul 19;119(3):384-93.

Samarani G, Zeroual N, Saour M, Ruiz R, Gaudard P, Colson P. B41 DON’T LET ME DOWN: ADVANCES IN THORACIC SURGERY: Central Venous Oxygen Saturation As A Potential Trigger For Blood Transfusion In Cardiovascular Surgery Patients: An Observational Study. American Journal of Respiratory and Critical Care Medicine. 2015;191:1.

Samarani G, Zeroual N, Saour M, Sandra G, Ruiz R, Gaudard P, Colson P. Central venous oxygen saturation as trigger for blood transfusion in cardiovascular surgery patients: an observational study. Oral session EACTA 2014.

Sehgal LR, Zebala LP, Takagi I, Curran RD, Votapka TV, Caprini JA. Evaluation of oxygen extraction ratio as a physiologic transfusion trigger in coronary artery bypass graft surgery patients. Transfusion. 2001 May;41(5):591-5.

Surve RM, Muthuchellappan R, Rao GS, Philip M. The effect of blood transfusion on central venous oxygen saturation in critically ill patients admitted to a neurointensive care unit. Transfusion Medicine. 2016 Oct;26(5):343-8.

Taha A, Shafie A, Mostafa M, Syed N, Hon H, Marktanner R. Evaluation of the quotient of the venoarterial carbon dioxide gradient and the arteriovenous oxygen content difference as a transfusion trigger parameter in hemodynamically stable patients with significant anemia. Critical Care. 2015 Dec;19(1):P331.

Torella F, Haynes SL, McCollum CN. Cerebral and peripheral near-infrared spectroscopy: an alternative transfusion trigger?. Vox sanguinis. 2002 Oct;83(3):254-7.

Zeroual N, Samarani G, Gallais J, Culas G, Saour M, Mourad M, Gaudard P, Colson PH. ScvO2 changes after red-blood-cell transfusion for anaemia in cardiothoracic and vascular ICU patients: an observational study. Vox sanguinis. 2018 Feb;113(2):136-42.

Zogheib E, Walczak K, Guinot P, Badoux L, Duwat A, Lorne E, Remadi JP, Caus T, Dupont H. STO2 CHANGES AFTER TRANSFUSION OF PACKED RED BLOOD CELLS IN CRITICAL CARE PATIENTS. InINTENSIVE CARE MEDICINE 2011 Sep 1 (Vol. 37, pp. S155-S155). 233 SPRING ST, NEW YORK, NY 10013 USA: SPRINGER.
**Question:** Iron compared to No Iron for anemia in non-bleeding critically ill adult patients

| Certainty assessment | № of patients | Effect | Certainty | Importance |
|----------------------|---------------|--------|------------|------------|
|                       | № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Iron (95% CI) | No Iron (95% CI) | Relative (95% CI) | Absolute (95% CI) | |
| **Mortality**         | 5            | randomised trials | not serious | serious a | not serious | serious b | none | 27/294 (9.2%) | 25/300 (8.3%) | RR 1.10 (0.67 to 1.82) | 8 more per 1,000 (from 27 fewer to 66 more) | CRITICAL |
| **In-hospital Infection - RCT** | 3 | randomised trials | not serious | not serious | not serious | serious b | none c | 109/242 (45.0%) | 116/245 (47.3%) | RR 0.95 (0.79 to 1.14) | 24 fewer per 1,000 (from 99 fewer to 66 more) | MODERATE |
| **RBC transfusion - RCT** | 6 | randomised trials | not serious | serious d | not serious | serious e | none f | 183/401 (45.6%) | 187/352 (53.1%) | RR 0.86 (0.75 to 0.99) | 74 fewer per 1,000 (from 133 fewer to 5 fewer) | IMPORTANT |
| **Mean number of units transfused** | 3 | randomised trials | not serious | serious f | not serious | serious g | none h | 189 | 134 | MD 0.19 lower (0.39 lower to 0.01 higher) | IMPORTANT |

CI: Confidence interval; RR: Risk ratio; MD: Mean difference

**Explanations**

a. There are inconsistencies in the point estimate of the effect for mortality across studies.
b. Rated down one level for imprecision for wide confidence intervals that encompasses the line of no effect.
c. Not assessed due to limited number of studies identified
d. Rated down for inconsistency in the point estimates across studies.
e. Rated down 1 level for imprecision for wide confidence intervals.
f. Rated down 1 level for inconsistency due to the statistical heterogeneity across studies, I² 60%.
## Summary of findings:

**Iron compared to No Iron for anemia in non-bleeding critically ill adult patients**

**Patient or population:** anemia in non-bleeding critically ill adult patients  
**Intervention:** Iron  
**Comparison:** No Iron

| Outcomes                  | Anticipated absolute effects* (95% CI) | Relative effect (95% CI) | No of participants (studies) | Certainty of the evidence (GRADE) | Comments                                                                 |
|---------------------------|---------------------------------------|--------------------------|------------------------------|----------------------------------|--------------------------------------------------------------------------|
| Mortality                 | Risk with No Iron 83 per 1,000 (56 to 152) | Risk with Iron 92 per 1,000 (67 to 182) | RR 1.10 (0.67 to 1.82) | 594 (5 RCTs) | ★★★★ LOW a,b | Iron may result in little to no difference in mortality, estimate is limited due to imprecision of the data in 5 RCTs. |
| In-hospital Infection - RCT | Risk with No Iron 473 per 1,000 (374 to 540) | Risk with Iron 450 per 1,000 (395 to 505) | RR 0.95 (0.79 to 1.14) | 487 (3 RCTs) | ★★★★ MODERATE b,c | Iron probably does not increase in-hospital Infection compared to placebo, based on moderate certainty of evidence that is limited by imprecision. |
| RBC transfusion - RCT     | Risk with No Iron 531 per 1,000 (398 to 526) | Risk with Iron 457 per 1,000 (398 to 526) | RR 0.86 (0.75 to 0.99) | 753 (6 RCTs) | ★★★★ LOW c,d,e | The evidence suggests that iron results in little to no difference in RBC transfusion based on low certainty of evidence limited by imprecision and inconsistency. |
| Mean number of units transfused | The mean number of units transfused was 0 | The mean number of units transfused in the intervention group was 0.19 lower (0.39 lower to 0.01 higher) | - | 323 (3 RCTs) | ★★★★ LOW b,c,d,e | The evidence suggests that iron results in little to no difference in mean number of units transfused based on low certainty of evidence limited by inconsistency and imprecision. |

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).*

**CI:** Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

**GRADE Working Group grades of evidence**

- **High certainty:** We are very confident that the true effect lies close to that of the estimate of the effect.  
- **Moderate certainty:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.  
- **Low certainty:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.  
- **Very low certainty:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

### Explanations

- a. There are inconsistencies in the point estimate of the effect for mortality across studies.  
- b. Rated down one level for imprecision for wide confidence intervals that encompass the line of no effect.  
- c. Not assessed due to limited number of studies identified  
- d. Rated down for inconsistency in the point estimates across studies.  
- e. Rated down 1 level for imprecision for wide confidence intervals.  
- f. Rated down 1 level for inconsistency due to the statistical heterogeneity across studies, I² 60%.
### Forest Plots

#### Mortality

| Study or Subgroup | Iron | | No Iron | | Total | | Weight | | Risk Ratio | | Risk Ratio |
|-------------------|------|---|---------|---|-------|---|-------|---|-------------|---|-------------|
|                   | Events Total | | Events Total | | | | M-H, Fixed, 95% CI | | M-H, Fixed, 95% CI |
| Madi-Jebrara 2004 | 0 | 40 | 0 | 40 | | Not estimable | | |
| Pieracci 2014     | 7 | 75 | 2 | 75 | 8.1% | 3.50 [0.75, 16.30] | | |
| Litton 2016       | 7 | 70 | 6 | 70 | 24.3% | 1.17 [0.41, 3.30] | | |
| van Iperen 2000   | 4 | 12 | 7 | 12 | 28.3% | 0.57 [0.22, 1.45] | | |
| Pieracci 2009     | 9 | 97 | 10 | 103 | 39.3% | 0.96 [0.41, 2.25] | | |
| **Total (95% CI)** | 294 | 300 | | 100.0% | | 1.10 [0.67, 1.82] | | |

Total events 27 25
Heterogeneity: Chi² = 4.20, df = 3 (P = 0.24); I² = 29%
Test for overall effect: Z = 0.39 (P = 0.70)

#### Hospital Acquired Infections

| Study or Subgroup | Iron | | No Iron | | Total | | Weight | | Risk Ratio | | Risk Ratio |
|-------------------|------|---|---------|---|-------|---|-------|---|-------------|---|-------------|
|                   | Events Total | | Events Total | | | | M-H, Fixed, 95% CI | | M-H, Fixed, 95% CI |
| **1.2.1 RCT**     | | | | | | | | | | |
| Litton 2016       | 0 | 0 | 0 | 0 | | Not estimable | | |
| Pieracci 2009     | 45 | 97 | 48 | 100 | 37.9% | 0.97 [0.72, 1.30] | | |
| Pieracci 2014     | 44 | 75 | 52 | 75 | 41.7% | 0.85 [0.66, 1.08] | | |
| **Subtotal (95% CI)** | 242 | 245 | | 92.5% | | 0.95 [0.79, 1.14] | | |

Total events 109 116
Heterogeneity: Chi² = 1.80, df = 2 (P = 0.41); I² = 0%
Test for overall effect: Z = 0.53 (P = 0.60)

| Study or Subgroup | Iron | | No Iron | | Total | | Weight | | Risk Ratio | | Risk Ratio |
|-------------------|------|---|---------|---|-------|---|-------|---|-------------|---|-------------|
| **1.2.2 Observational Data** | | | | | | | | | | |
| Peters 2018       | 6 | 26 | 14 | 52 | 7.5% | 0.86 [0.37, 1.97] | | |
| **Subtotal (95% CI)** | 26 | 52 | | 7.5% | | 0.86 [0.37, 1.97] | | |

Total events 6 14
Heterogeneity: Not applicable
Test for overall effect: Z = 0.36 (P = 0.72)

**Total (95% CI)** 268 297 100.0% 0.94 [0.79, 1.13]

Total events 115 130
Heterogeneity: Chi² = 1.80, df = 3 (P = 0.61); I² = 0%
Test for overall effect: Z = 0.62 (P = 0.54)
Test for subgroup differences: Chi² = 0.06, df = 1 (P = 0.81); I² = 0%
## RBC transfusions

### 1.3.1 RCT

| Study or Subgroup | Iron Events | Total | No Iron Events | Total | Weight | Risk Ratio M-H, Fixed, 95% CI | Risk Ratio M-H, Fixed, 95% CI |
|-------------------|-------------|-------|----------------|-------|--------|------------------------------|------------------------------|
| Garrido-Martin 2012 | 47          | 107   | 26            | 52    | 17.1%  | 0.88 [0.62, 1.24]            |                              |
| Litton 2016       | 38          | 70    | 39            | 70    | 19.0%  | 0.97 [0.72, 1.31]            |                              |
| Madi-Jebrara 2004 | 10          | 40    | 9             | 40    | 4.4%   | 1.11 [0.51, 2.44]            |                              |
| Pieracci 2009     | 29          | 97    | 46            | 103   | 21.8%  | 0.67 [0.46, 0.97]            |                              |
| Pieracci 2014     | 47          | 75    | 55            | 75    | 26.8%  | 0.85 [0.68, 1.07]            |                              |
| van Iperen 2000   | 12          | 12    | 12            | 12    | 6.1%   | 1.00 [0.86, 1.17]            |                              |
| **Subtotal (95% CI)** | **401**    | **352** | **95.1%**    | **404** | **100.0%** | **0.86 [0.75, 0.99]**     |                              |

Total events: 183/187

Heterogeneity: Chi² = 6.43, df = 5 (P = 0.27); I² = 22%

Test for overall effect: Z = 2.10 (P = 0.04)

### 1.3.2 Observational Data

| Study or Subgroup | Iron Events | Total | No Iron Events | Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|-------------------|-------------|-------|----------------|-------|--------|------------------------------|
| Peters 2018       | 9           | 26    | 15             | 52    | 4.9%   | 1.20 [0.61, 2.37]            |
| **Subtotal (95% CI)** | **26**    | **52** | **4.9%**      | **52** | **4.9%** | **1.20 [0.61, 2.37]**       |

Total events: 9/15

Heterogeneity: Not applicable

Test for overall effect: Z = 0.53 (P = 0.60)

**Total (95% CI)** 427/404 100.0%

Heterogeneity: Chi² = 6.46, df = 6 (P = 0.37); I² = 7%

Test for overall effect: Z = 1.87 (P = 0.06)

Test for subgroup differences: Chi² = 0.88, df = 1 (P = 0.35), I² = 0%

### Mean Difference

| Study or Subgroup | Mean | SD  | Total | Mean | SD  | Total | Weight | Mean Difference IV, Fixed, 95% CI | Mean Difference IV, Fixed, 95% CI |
|-------------------|------|-----|-------|------|-----|-------|--------|---------------------------------|---------------------------------|
| Garrido-Martin 2012 | -0.085 | 0.74 | 107   | -0.01 | 0.73 | 52    | 66.0%  | -0.08 [-0.32, 0.17]          |                                 |
| Litton 2016       | -0.27 | 1.11 | 70    | 0.016 | 1.15 | 70    | 27.8%  | -0.29 [-0.66, 0.09]          |                                 |
| van Iperen 2000   | 1.07  | 1.04 | 12    | 2.06  | 0.93 | 12    | 6.2%   | -0.99 [-1.78, -0.20]         |                                 |

**Total (95% CI)** 189/134 100.0%

Heterogeneity: Chi² = 5.06, df = 2 (P = 0.08); I² = 60%

Test for overall effect: Z = 1.89 (P = 0.06)
| Question: Erythropoietin vs. no erythropoietin in critically ill adults |
| --- |
| **Certainty assessment** | **No of patients** | **Effect** | **Certainty** | **Importance** |
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsistenc y** | **Indirectness** | **Imprecision** | **Other considerations** | **rhEPO** | **no EPO** | **Relative (95% CI)** | **Absolute (95% CI)** |   |
| **Mortality (long term) (follow up: mean 90 days)** | 2 | RCTs | not serious | not serious | not serious | serious a | none | 112/775 (14.5%) | 135/771 (17.5%) | RR 0.84 (0.67 to 1.04) | 28 fewer per 1,000 (from 58 fewer to 7 more) | ⫷⫷⫷ MODERATE CRITICAL |
| **Mortality (short term)** | 6 | RCTs | not serious | serious b | not serious | serious a | none | 209/1568 (13.3%) | 243/1563 (15.5%) | RR 0.80 (0.61 to 1.05) | 31 fewer per 1,000 (from 61 fewer to 8 more) | ⫷⫷ MODERATE CRITICAL |
| **Stroke** | 3 | RCTs | not serious | serious d | not serious | serious a | none | 22/1427 (1.5%) | 34/1420 (2.4%) | RR 0.64 (0.38 to 1.09) | 9 fewer per 1,000 (from 15 fewer to 2 more) | ⫷⫷ MODERATE IMPORTANT |
| **Myocardial infarction** | 2 | RCTs | not serious | not serious | serious e | not serious | none | 25/1378 (1.8%) | 11/1372 (0.8%) | RR 2.26 (1.12 to 4.58) | 10 more per 1,000 (from 1 more to 29 more) | ⫷⫷⫷ MODERATE IMPORTANT |
| **Infections** | 3 | RCTs | not serious | not serious | serious a | serious a | none | 104/1427 (7.3%) | 101/1420 (7.1%) | RR 1.02 (0.79 to 1.31) | 1 more per 1,000 (from 15 fewer to 22 more) | ⫷⫷⫷ MODERATE IMPORTANT |
| **Number of patients who received one or more transfusions** | 6 | RCTs | not serious | not serious | not serious | none | 765/1616 (47.3%) | 849/1587 (53.5%) | RR 0.89 (0.83 to 0.95) | 59 fewer per 1,000 (from 91 fewer to 27 fewer) | ⫷⫷⫷ MODERATE IMPORTANT |

**Mean units transfused per patient**
Explanations

a. Wide 95% confidence intervals which do not exclude a benefit or harm of importance to patients.
b. Significant heterogeneity between mixed ICU and trauma populations (I^2 >70%) without significant heterogeneity within each subgroup. These subgroups are prespecified, within-study subgroups.
c. Although blinding of outcome assessors was not done in one study (Georoupoulos 2005), this study only accounted for ~9% of study weight.
d. Inclusion of multiple "central and peripheral nervous system disorders" in one study (Corwin 2002), which accounts for 1/3 of events.
e. Inclusion of "cardiovascular disorders, general" in one study (Corwin 2002), accounting for a significant number of events (~45% of study weight).
f. Though there was lack of blinding in one study (Georgopoulos) which accounts for ~20% of study weight, the point estimate for this study was not different from the other two studies and therefore unlikely to bias the estimate of effect.
g. Wide variety of infections included in all studies, and poorly described.
h. Though high value of I^2 (81%), post estimates of all studies demonstrate no effect or significant reduction in transfusion, so the heterogeneity is of questionable importance.
i. Though high I^2 value, this is due to a small unblinded single centre study (Iperen 2000) with markedly different results from the other studies (with removal of this study, I^2 =0% and the point estimate remains mostly unchanged)

Summary statements

1. Recombinant human erythropoietin likely results in a small reduction in 90 day mortality, though our certainty is limited by imprecision. The potential beneficial effect upon mortality is more pronounced in trauma patients than in general medical-surgical ICU patients.
2. Recombinant human erythropoietin may result in a small reduction in short-term mortality, though our certainty is limited by imprecision. The potential beneficial effect upon mortality is more pronounced in trauma patients than in general medical-surgical ICU patients.
3. Recombinant human erythropoietin may result in a small possibly unimportant reduction in stroke, though our certainty is limited by imprecision and indirectness.
4. Recombinant human erythropoietin probably results in a small, possibly unimportant, increase in myocardial infarction, though our certainty is limited by indirectness.
5. Recombinant human erythropoietin appears to result in little to no difference in infections, though our certainty is limited by imprecision and indirectness.
6. Recombinant human erythropoietin probably results in a small reduction in the number of patients who receive one or more transfusions, though our certainty is limited by inconsistency, with a larger magnitude of effect in non-trauma patients.
7. Recombinant human erythropoietin results in a small, possibly unimportant, reduction in the number of transfusions per patient.
8. Recombinant human erythropoietin results in a small, possibly unimportant, increase in hemoglobin concentration.
9. Mortality (long term: 90 days or more)

| Study or Subgroup   | EPO Events | Total Events | Control Events | Total Events | Weight % | Risk Ratio M-H, Fixed, 95% CI | Year |
|---------------------|------------|--------------|----------------|--------------|----------|--------------------------------|------|
| 1.1.1 Mixed population |            |              |                |              |          |                                |      |
| Silver 2006         | 8          | 42           | 13             | 44           | 9.4%     | 0.64 [0.30, 1.40]              | 2006 |
| Corwin 2007         | 80         | 331          | 86             | 336          | 63.4%    | 0.94 [0.73, 1.23]              | 2007 |
| **Subtotal (95% CI)** | **373**    | **380**      |                |              | 72.9%    | 0.91 [0.71, 1.16]              |      |
| Total events        | 88         |              |                | 99           |          |                                |      |
| Heterogeneity: Chi² = 0.84, df = 1 (P = 0.36); I² = 0% |
| Test for overall effect: Z = 0.78 (P = 0.44) |

| 1.1.2 Trauma population |            |              |                |              |          |                                |      |
| Corwin 2007            | 24         | 402          | 36             | 391          | 27.1%    | 0.65 [0.39, 1.07]              | 2007 |
| **Subtotal (95% CI)**  | **402**    | **391**      |                |              | 27.1%    | 0.65 [0.39, 1.07]              |      |
| Total events           | 24         |              |                | 36           |          |                                |      |
| Heterogeneity: Not applicable |
| Test for overall effect: Z = 1.71 (P = 0.09) |

**Total (95% CI)**

|            | 775 | 771 | 100.0% | 0.84 [0.67, 1.04] |      |
| Total events | 112 | 135 |        |                   |      |
| Heterogeneity: Chi² = 2.26, df = 2 (P = 0.32); I² = 11% |
| Test for overall effect: Z = 1.57 (P = 0.12) |
| Test for subgroup differences: Chi² = 1.38, df = 1 (P = 0.24), I² = 27.7% |

Favours EPO Favours control
10. Mortality (short term: 28-60 days)

| Study or Subgroup | EPO | Control | Risk Ratio |
|-------------------|-----|---------|------------|
|                   | Events | Total | Events | Total | Weight | M-H, Random, 95% CI | Year |
| **1.2.1 Mixed population** | | | | | | | |
| Corwin 1999 | 24 | 80 | 21 | 80 | 15.5% | 1.14 [0.70, 1.88] | 1999 |
| Iperen 2000 | 2 | 12 | 2 | 12 | 2.2% | 1.00 [0.17, 5.98] | 2000 |
| Corwin 2002 | 96 | 336 | 87 | 336 | 25.3% | 1.10 [0.86, 1.41] | 2002 |
| Georgopoulos 2005 | 5 | 51 | 7 | 48 | 5.4% | 0.67 [0.23, 1.98] | 2005 |
| Silver 2006 | 5 | 42 | 10 | 44 | 6.2% | 0.52 [0.20, 1.41] | 2006 |
| Corwin 2007 | 48 | 331 | 57 | 336 | 20.8% | 0.85 [0.60, 1.22] | 2007 |
| **Subtotal (95% CI)** | 852 | 856 | 75.4% | 1.00 [0.83, 1.19] | | |
| Total events | 180 | 184 | | | | |
| Heterogeneity: Tau² = 0.00; Chi² = 3.84, df = 5 (P = 0.57); I² = 0% | | | | | |
| Test for overall effect: Z = 0.04 (P = 0.97) | | | | | |

| **1.2.2 Trauma population** | | | | | | | |
| Corwin 2002 | 15 | 314 | 33 | 316 | 12.8% | 0.46 [0.25, 0.83] | 2002 |
| Corwin 2007 | 14 | 402 | 26 | 391 | 11.7% | 0.52 [0.28, 0.99] | 2007 |
| **Subtotal (95% CI)** | 716 | 707 | 24.6% | 0.49 [0.32, 0.75] | | |
| Total events | 29 | 59 | | | | |
| Heterogeneity: Tau² = 0.00; Chi² = 0.09, df = 1 (P = 0.76); I² = 0% | | | | | |
| Test for overall effect: Z = 3.26 (P = 0.001) | | | | | |
| **Total (95% CI)** | 1568 | 1563 | 100.0% | 0.80 [0.61, 1.05] | | |
| Total events | 209 | 243 | | | | |
| Heterogeneity: Tau² = 0.06; Chi² = 13.07, df = 7 (P = 0.07); I² = 46% | | | | | |
| Test for overall effect: Z = 1.61 (P = 0.11) | | | | | |
| Test for subgroup differences: Chi² = 8.96, df = 1 (P = 0.003), I² = 88.8% | | | | | |

3. Stroke

| Study or Subgroup | EPO | Control | Risk Ratio |
|-------------------|-----|---------|------------|
|                   | Events | Total | Events | Total | Weight | M-H, Fixed, 95% CI | Year |
| Corwin 2002 | 6 | 650 | 15 | 652 | 43.9% | 0.40 [0.16, 1.03] | 2002 |
| Georgopoulos 2005 | 2 | 49 | 3 | 48 | 8.9% | 0.65 [0.11, 3.74] | 2005 |
| Corwin 2007 | 14 | 728 | 16 | 720 | 47.2% | 0.87 [0.43, 1.76] | 2007 |
| **Total (95% CI)** | 1427 | 1420 | 100.0% | 0.64 [0.38, 1.09] | | |
| Total events | 22 | 34 | | | | |
| Heterogeneity: Chi² = 1.64, df = 2 (P = 0.44); I² = 0% | | | | | |
| Test for overall effect: Z = 1.63 (P = 0.10) | | | | | |
4. Myocardial infarction

| Study or Subgroup | EPO Events | EPO Total | Control Events | Control Total | Weight | Risk Ratio M–H, Fixed, 95% CI | Year |
|-------------------|------------|-----------|----------------|--------------|--------|-------------------------------|------|
| Corwin 2002       | 328        | 650       | 394            | 652          | 46.0%  | 0.84 [0.76, 0.92]            | 2002 |
| Georgopoulos 2005 | 19         | 51        | 28             | 48           | 3.4%   | 0.64 [0.42, 0.98]            | 2005 |
| Silver 2006       | 17         | 42        | 28             | 44           | 3.2%   | 0.64 [0.41, 0.98]            | 2006 |
| Vincent 2006      | 18         | 44        | 12             | 24           | 1.8%   | 0.82 [0.48, 1.40]            | 2006 |
| Corwin 2007       | 122        | 331       | 135            | 336          | 15.7%  | 0.92 [0.76, 1.11]            | 2007 |
| **Subtotal (95% CI)** | **1118**  | **597**   | **1104**       | **70.1%**    |        | **0.83 [0.77, 0.91]**        |      |

Total events: 504
Heterogeneity: $\chi^2 = 3.97$, df = 4 (P = 0.41); $I^2 = 0$
Test for overall effect: $Z = 4.24$ (P < 0.0001)

1.9.2 Trauma patients

| Study or Subgroup | EPO Events | EPO Total | Control Events | Control Total | Weight | Risk Ratio M–H, Fixed, 95% CI | Year |
|-------------------|------------|-----------|----------------|--------------|--------|-------------------------------|------|
| Corwin 2007       | 215        | 402       | 216            | 391          | 25.6%  | 0.97 [0.85, 1.10]            | 2007 |
| Luchette 2012     | 46         | 96        | 36             | 92           | 4.3%   | 1.22 [0.88, 1.70]            | 2012 |
| **Subtotal (95% CI)** | **498**  | **252**   | **483**        | **29.9%**    |        | **1.00 [0.89, 1.13]**        |      |

Total events: 261
Heterogeneity: $\chi^2 = 1.71$, df = 1 (P = 0.19); $I^2 = 42$
Test for overall effect: $Z = 0.08$ (P = 0.93)

**Total (95% CI)**

| Study or Subgroup | EPO Events | EPO Total | Control Events | Control Total | Weight | Risk Ratio M–H, Fixed, 95% CI | Year |
|-------------------|------------|-----------|----------------|--------------|--------|-------------------------------|------|
| Corwin 2002       | 31         | 650       | 30             | 652          | 29.5%  | 1.04 [0.63, 1.69]            | 2002 |
| Georgopoulos 2005 | 26         | 49        | 21             | 48           | 20.9%  | 1.21 [0.80, 1.84]            | 2005 |
| Corwin 2007       | 47         | 728       | 50             | 720          | 49.6%  | 0.93 [0.63, 1.37]            | 2007 |
| **Total (95% CI)** | **1427**  | **849**   | **1420**       | **100.0%**   |        | **1.02 [0.79, 1.31]**        |      |

Total events: 765
Heterogeneity: $\chi^2 = 11.69$, df = 6 (P = 0.07); $I^2 = 49$
Test for overall effect: $Z = 3.48$ (P = 0.0005)
Test for subgroup differences: $\chi^2 = 6.26$, df = 1 (P = 0.01); $I^2 = 84.0$

6. Infections

| Study or Subgroup | EPO Events | EPO Total | Control Events | Control Total | Weight | Risk Ratio M–H, Fixed, 95% CI | Year |
|-------------------|------------|-----------|----------------|--------------|--------|-------------------------------|------|
| Corwin 2002       | 31         | 650       | 30             | 652          | 29.5%  | 1.04 [0.63, 1.69]            | 2002 |
| Georgopoulos 2005 | 26         | 49        | 21             | 48           | 20.9%  | 1.21 [0.80, 1.84]            | 2005 |
| Corwin 2007       | 47         | 728       | 50             | 720          | 49.6%  | 0.93 [0.63, 1.37]            | 2007 |
| **Total (95% CI)** | **1427**  | **849**   | **1420**       | **100.0%**   |        | **1.02 [0.79, 1.31]**        |      |

Total events: 104
Heterogeneity: $\chi^2 = 0.89$, df = 2 (P = 0.64); $I^2 = 0$
Test for overall effect: $Z = 0.16$ (P = 0.87)
7. Proportion of patients who received one or more red blood cell transfusions

| Study or Subgroup | EPO | Control | Risk Ratio |
|-------------------|-----|---------|------------|
|                   | Events | Total | Events | Total | Weight | M–H, Random, 95% CI | Year |
| 1.9.1 Mixed population | | | | | | | |
| Corwin 2002       | 328 | 650 | 394 | 652 | 29.0% | 0.84 [0.76, 0.92] | 2002 |
| Georgopoulos 2005 | 19  | 51  | 28  | 48  | 6.4%  | 0.64 [0.42, 0.98] | 2005 |
| Vincent 2006      | 18  | 44  | 12  | 24  | 4.4%  | 0.82 [0.48, 1.40] | 2006 |
| Silver 2006       | 17  | 42  | 28  | 44  | 6.4%  | 0.64 [0.41, 0.98] | 2006 |
| Corwin 2007       | 122 | 331 | 135 | 336 | 18.7% | 0.92 [0.76, 1.11] | 2007 |
| **Subtotal (95% CI)** | **1118** | **597** | **1104** | **64.8%** | **0.83 [0.77, 0.90]** |
| Total events      | 504 | 597 | | | | | |
| Heterogeneity: Tau² = 0.00; Chi² = 3.97, df = 4 (P = 0.41); I² = 0% |
| Test for overall effect: Z = 4.33 (P < 0.0001) |

1.9.2 Trauma patients

| Study or Subgroup | EPO | Control | Risk Ratio |
|-------------------|-----|---------|------------|
|                   | Events | Total | Events | Total | Weight | M–H, Random, 95% CI | Year |
| Corwin 2007       | 215 | 402 | 216 | 391 | 25.6% | 0.97 [0.85, 1.10] | 2007 |
| Luchette 2012     | 46  | 96  | 36  | 92  | 9.6%  | 1.22 [0.88, 1.70] | 2012 |
| **Subtotal (95% CI)** | **498** | **483** | **35.2%** | **1.03 [0.84, 1.27]** |
| Total events      | 261 | 252 | | | | | |
| Heterogeneity: Tau² = 0.01; Chi² = 1.71, df = 1 (P = 0.19); I² = 42% |
| Test for overall effect: Z = 0.32 (P = 0.75) |

**Total (95% CI)**

| EPO | Control | Risk Ratio |
|-----|---------|------------|
| Events | Total | Events | Total | Weight | M–H, Random, 95% CI | Year |
| **1616** | **1587** | **100.0%** | | | | |
| Total events | 765 | 849 | | | | | |
| Heterogeneity: Tau² = 0.01; Chi² = 11.69, df = 6 (P = 0.07); I² = 49% |
| Test for overall effect: Z = 2.03 (P = 0.04) |
| Test for subgroup differences: Chi² = 3.62, df = 1 (P = 0.06), I² = 72.4% |

8. Mean number of transfusions per patient

| Study or Subgroup | EPO | Control | Std. Mean Difference |
|-------------------|-----|---------|----------------------|
|                   | Mean | SD | Total | Mean | SD | Total | IV, Random, 95% CI | Year |
| Ipren 2000        | 7   | 7  | 12   | 5   | 7  | 12   | 5.5% | 0.28 [-0.53, 1.08] | 2000 |
| Corwin 2002       | 2.4 | 4.79 | 650 | 3  | 5.42 | 652 | 25.0% | -0.12 [-0.23, -0.01] | 2002 |
| Georgopoulos 2005 | 0.64 | 1  | 51   | 2.83 | 3.9 | 48   | 13.4% | -0.77 [-1.18, -0.36] | 2005 |
| Silver 2006       | 1   | 1.87 | 42   | 1.9 | 2.21 | 44   | 12.8% | -0.43 [-0.86, -0.01] | 2006 |
| Corwin 2007       | 4.5 | 4.6 | 733 | 4.3 | 4.8 | 727 | 25.2% | 0.04 [-0.06, 0.15] | 2007 |
| Luchette 2012     | 1.9 | 1   | 96   | 2.5 | 1.7 | 92   | 17.9% | -0.43 [-0.72, -0.14] | 2012 |
| **Total (95% CI)** | **1584** | **1575** | **100.0%** | | | | **-0.24 [-0.45, -0.03]** |
| Heterogeneity: Tau² = 0.04; Chi² = 25.98, df = 5 (P < 0.0001); I² = 81% |
| Test for overall effect: Z = 2.22 (P = 0.03) |
9. Change in hemoglobin concentration

| Study or Subgroup   | EPO Mean | SD  | Total | Control Mean | SD  | Total | Weight | Mean Difference | Year    |
|---------------------|----------|-----|-------|--------------|-----|-------|--------|----------------|---------|
| Corwin 2007         | -1.6     | 1.44| 733   | -1.2         | 1.3 | 727   | 49.3%  | -0.40 [-0.54, -0.26] | 2007    |
| Silver 2006         | -1       | 1.53| 42    | -0.5         | 1.13| 44    | 3.0%   | -0.50 [-1.07, 0.07]  | 2006    |
| Georgopoulos 2005   | -1.32    | 1.45| 650   | -0.94        | 1.36| 652   | 41.8%  | -0.38 [-0.53, -0.23] | 2005    |
| Corwin 2002         | -0.3     | 0.85| 12    | -1.3         | 0.95| 12    | 1.9%   | 1.00 [0.28, 1.72]   | 2000    |
| Total (95% CI)      | 1488     |     | 1483  | 100.0%       |     |       |        | -0.38 [-0.48, -0.28] |         |

Heterogeneity: $\chi^2 = 15.08, \text{ df} = 4 (P = 0.005); I^2 = 73\%$
Test for overall effect: $Z = 7.47 (P < 0.00001)$
**Question**: EPO and Iron compared to Control for non-bleeding critically ill patients

| Certainty assessment | Nr of patients | Effect | Certainty | Importance |
|-----------------------|----------------|--------|-----------|------------|
| Nr of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | EPO and Iron | Control | Relative (95% CI) | Absolute (95% CI) | |
| **Mortality - RCT** | 3 | RCTs | serious a | not serious | not serious | serious b | none c | 5/89 (5.6%) | 8/89 (9.0%) | RR 0.65 (0.29 to 1.47) | 31 fewer per 1,000 (from 64 fewer to 42 more) | + + + + LOW CRITICAL |
| **Major Bleeding (Blood Loss) - RCT** | 2 | RCTs | serious a | serious d | not serious | serious d | none c | 49 | 49 | - | MD 115.66 lower (335.05 lower to 103.72 higher) | + + + + VERY LOW CRITICAL |
| **Renal Failure - RCT** | 2 | RCTs | serious a | serious d | serious e | serious d | none c | 14/49 (28.6%) | 23/47 (48.9%) | RR 0.58 (0.34 to 1.00) | 206 fewer per 1,000 (from 323 fewer to 0 fewer) | + + + + VERY LOW IMPORTANT |
| **RBC transfusion - RCT** | 3 | RCTs | serious a | very serious f | not serious | serious d | none c | 89 | 89 | - | MD 0.38 lower (0.96 lower to 0.21 higher) | + + + + VERY LOW IMPORTANT |

CI: Confidence interval; RR: Risk ratio; MD: Mean difference

**Explanations**: a. Both RCTs are single centre studies. There was concern regarding allocation in one of the studies (Van Iperen, 2000).
b. Rated down 1 level for wide confidence intervals and low number of events.
c. Unable to assess due to the small number of studies identified.
d. Rated down 1 level as the point estimate for each study lay on the side of effect and no effect.
e. Rate down 1 level for indirectness as Yoo (2011) described post operative acute kidney injury and Van Iperen (2000) identified patients who required dialysis.
f. Rated down 1 for inconsistency because of heterogeneity between the studies, I2 40%.
Explanations

a. Both RCTs are single centre studies. There was concern regarding allocation in one of the studies (Van Iperen, 2000).
b. Rated down 1 level for wide confidence intervals and low number of events.
c. Unable to assess due to the small number of studies identified.
d. Rated down 1 level as the point estimate for each study lay on the side of effect and no effect.
e. Rate down 1 level for indirectness as Yoo (2011) described post operative acute kidney injury and Van Iperen (2000) identified patients who required dialysis.
f. Rated down 1 for inconsistency because of heterogeneity between the studies, I2 40%.

| Outcomes                  | Anticipated absolute effects* (95% CI) | Relative effect (95% CI) | No of participants (studies) | Certainty of the evidence (GRADE) | Comments                                                                 |
|---------------------------|----------------------------------------|--------------------------|-----------------------------|----------------------------------|--------------------------------------------------------------------------|
| Mortality - RCT           | 90 per 1,000                           | 58 per 1,000 (26 to 132) | RR 0.65 (0.29 to 1.47)      | 178 (3 RCTs)                     | EPO and Iron may result in a slight reduction in mortality based on low certainty of evidence which is limited by imprecision and risk of bias. |
| Major Bleeding (Blood Loss) - RCT | The mean major Bleeding (Blood Loss) - RCT was 0 | The mean major Bleeding (Blood Loss) - RCT in the intervention group was 115.66 lower (335.05 lower to 103.72 higher) | -                             | 98 (2 RCTs)                     | EPO and Iron may have little to no effect on major bleeding (Blood Loss), based on very low certainty of evidence limited by risk of bias, inconsistency and imprecision. |
| Renal Failure - RCT       | 489 per 1,000                          | 284 per 1,000 (166 to 489) | RR 0.58 (0.34 to 1.00)      | 96 (2 RCTs)                      | EPO and Iron may have little to no effect on renal failure based on very low certainty of evidence limited by inconsistency and imprecision. |
| RBC transfusion - RCT     | The mean RBC transfusion - RCT was 0    | The mean RBC transfusion - RCT in the intervention group was 0.38 lower (0.96 lower to 0.21 higher) | -                             | 178 (3 RCTs)                     | EPO and Iron may have little to no effect on RBC transfusion but the evidence is very uncertain limited by risk of bias, inconsistency and imprecision. |

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: Confidence interval; RR: Risk ratio; MD: Mean difference

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Summary of findings:

EPO and Iron compared to Control for non-bleeding critically ill patients

Patient or population: non-bleeding critically ill patients

Intervention: EPO and Iron

Comparison: Control
## Forest Plots

### Mortality

| Study or Subgroup      | EPO and Iron | Control | Risk Ratio | Risk Ratio |
|------------------------|--------------|---------|------------|------------|
|                        | Events       | Total   | Weight     | M-H, Fixed, 95% CI | M-H, Fixed, 95% CI |
| 1.1.1 RCT              |              |         |            |             |             |
| Madi-jebara            | 0            | 40      | 0          | 40          | Not estimable |             |
| Van Iperen 2000        | 5            | 12      | 7          | 12          | 29.0% [0.31, 1.63] |             |
| Yoo 2011               | 0            | 37      | 1          | 37          | 6.2% [0.01, 7.93] |             |
| **Subtotal (95% CI)**  | **89**       | **89**  | **35.2%**  | **0.65 [0.29, 1.47]** |             |

Total events 5 8
Heterogeneity: Chi² = 0.22, df = 1 (P = 0.64); I² = 0%
Test for overall effect: Z = 1.04 (P = 0.30)

1.1.2 Observational

| Cladelmas 2012         | 7            | 75      | 14         | 59          | 64.8% [0.17, 0.91] |             |
| Subtotal (95% CI)      | 75           | 59      | 64.8%      | 0.39 [0.17, 0.91] |             |

Total events 7 14
Heterogeneity: Not applicable
Test for overall effect: Z = 2.18 (P = 0.03)

**Total (95% CI)**

164 148 100.0% 0.48 [0.27, 0.87]

### Major Bleeding (Blood Loss)

| Study or Subgroup      | EPO and Iron | Control | Mean Difference | Mean Difference |
|------------------------|--------------|---------|-----------------|-----------------|
|                        | Mean  SD  Total | Mean  SD  Total | IV, Fixed, 95% CI | IV, Fixed, 95% CI |
| 1.2.1 RCT              |              |         |                 |                 |
| Van Iperen 2000        | 1.548 1.309 12 | 1.204 1.030 12 | 5.4% 344.00 [-598.41, 1286.41] | 100% 344.00 [-598.41, 1286.41] |
| Yoo 2011               | 624 380 37 | 766 588 37 | 94.6% -142.00 [-367.58, 83.58] | 100% -142.00 [-367.58, 83.58] |
| **Subtotal (95% CI)**  | **49**       | **49**  | **100.0%**     | **-115.66 [-335.05, 103.72]** |

Heterogeneity: Chi² = 0.97, df = 1 (P = 0.33); I² = 0%
Test for overall effect: Z = 1.03 (P = 0.30)

**Total (95% CI)**

49 49 100.0% -115.66 [-335.05, 103.72]

Heterogeneity: Chi² = 0.97, df = 1 (P = 0.33); I² = 0%
Test for overall effect: Z = 1.03 (P = 0.30)
Test for subgroup differences: Not applicable
## Renal Failure

| Study or Subgroup | EPO and Iron | Control | Risk Ratio M–H, Fixed, 95% CI |
|-------------------|-------------|---------|-----------------------------|
| Van Iperen 2000   | 5 Events, 12 Total | 4 Events, 12 Total | 1.25 [0.44, 3.55] |
| Yoo 2011          | 9 Events, 37 Total | 19 Events, 35 Total | 0.45 [0.24, 0.85] |
| **Subtotal (95% CI)** | **49 Events, 47 Total** | **47 Events, 100.0% Total** | **0.58 [0.34, 1.00]** |

*Total events: 14/23*

Heterogeneity: $\chi^2 = 2.69$, df = 1 ($P = 0.10$); $I^2 = 63$

Test for overall effect: $Z = 1.97$ ($P = 0.05$)

## RBC Transfusion

| Study or Subgroup | EPO and Iron | Control | Mean Difference IV, Fixed, 95% CI |
|-------------------|-------------|---------|----------------------------------|
| Madi-Jebra        | 2.4 Mean, 1.9 SD, Total 40 | 2.3 Mean, 1.9 SD, Total 40 | 0.10 [-0.73, 0.93] |
| Van Iperen 2000   | 7 Mean, 7 SD, Total 12 | 12 Mean, 12 SD, Total 12 | -5.00 [-13.86, 3.86] |
| Yoo 2011          | 2 Mean, 1.8 SD, Total 37 | 2.8 Mean, 1.8 SD, Total 37 | -0.80 [-1.62, 0.02] |
| **Subtotal (95% CI)** | **89 Mean, 100.0% Total** | **89 Mean, 100.0% Total** | **-0.38 [-0.96, 0.21]** |

*Total (95% CI): 89/89*

Heterogeneity: $\chi^2 = 3.33$, df = 2 ($P = 0.19$); $I^2 = 40$

Test for overall effect: $Z = 1.27$ ($P = 0.21$)

Test for subgroup differences: Not applicable
### Question
Should small-volume blood collection tubes be used to prevent anemia in non-bleeding critically ill patients?

| Certainty assessment |  |   |   |   |   |   |   | Certainty | Importance |
|----------------------|---|---|---|---|---|---|---|------------|------------|
| **No of patients**   | **Effect** | **Certainty** | **Importance** |
| **Small tubes** | **Regular tubes** | Relative (95% CI) | Absolute (95% CI) |   | |
| **Mean units transfused** |   |   |   |   |   |   |   |   |   |
| 1 | observational studies | serious a | not serious | not serious | serious b | none | 96 | 110 | - | MD 1.6 units lower (3.14 lower to 0.06 lower) | VERY LOW | IMPORTANT |
| **ICU length of stay** |   |   |   |   |   |   |   |   |   |
| 2 | observational studies | serious a | not serious | not serious | serious b | none | 137 | 125 | - | MD 0.74 days higher (1.97 lower to 3.45 higher) | VERY LOW | IMPORTANT |
| **Daily blood sampling volume** |   |   |   |   |   |   |   |   |   |
| 2 | observational studies | serious a | not serious | not serious | serious b | none | 137 | 125 | - | MD 9.2 mL lower (13.31 lower to 5.09 lower) | VERY LOW | NOT IMPORTANT |
| **Cumulative blood sampling volume** |   |   |   |   |   |   |   |   |   |
| 3 | observational studies | serious a | not serious | not serious | serious b | none | 246 | 243 | - | MD 15.07 mL lower (18.36 lower to 11.67 lower) | VERY LOW | NOT IMPORTANT |

CI: Confidence interval; MD: Mean difference

**Explanations**

a. Studies at significant risk of bias due to likely confounding, issues with measurement and reporting of outcomes.
b. Wide 95% confidence intervals which do not exclude effects of likely significance to patients.
Summary statements
1. Small volume blood collection tubes may reduce units of blood transfused, but we are very uncertain due to risk of bias in the observational studies as well as imprecision due to the small numbers of patients included in the study (optimal information size not reached).
2. Small volume blood collection tubes may have little to no impact on ICU length of stay, but we are very uncertain due to risk of bias in the observational studies as well as imprecision due to the small numbers of patients included in the study (optimal information size not reached).
3. Small volume blood collection tubes may result in a small reduction in daily blood sampling volume, but we are very uncertain due to risk of bias in the observational studies.
4. Small volume blood collection tubes may result in a small reduction in cumulative ICU blood sampling volume, but we are very uncertain due to risk of bias in the observational studies.

Units of blood transfused

| Study or Subgroup | Small tubes | Regular tubes | Mean Difference IV, Fixed, 95% CI |
|-------------------|-------------|---------------|----------------------------------|
| Dolman 2015       | 4.4 3.6 116 | 6 8.2 132    | -1.60 [-3.14, -0.06]             |
| Total (95% CI)    | 116         | 132 100.0%    | -1.60 [-3.14, -0.06]             |

Heterogeneity: Not applicable
Test for overall effect: Z = 2.03 (P = 0.04)

ICU length of stay

| Study or Subgroup | Small tubes | Regular tubes | Mean Difference IV, Fixed, 95% CI |
|-------------------|-------------|---------------|----------------------------------|
| 2.5.1 Medical patients |             |               |                                  |
| Dolman 2015       | 9.7 8.8 23  | 6.6 4 25      | 47.6% 3.10 [-0.82, 7.02]         |
| Subtotal (95% CI) | 23          | 25            | 47.6% 3.10 [-0.82, 7.02]         |

Heterogeneity: Not applicable
Test for overall effect: Z = 1.55 (P = 0.12)

| 2.5.2 Surgical patients |             |               |                                  |
| Dolman 2015             | 9.2 10.1 73 | 10.6 13.8 85  | 52.4% -1.40 [-5.14, 2.34]        |
| Smoller 1989            | 3.7 0 41    | 4.1 0 15      | Not estimable                    |
| Subtotal (95% CI)       | 114         | 100           | 52.4% -1.40 [-5.14, 2.34]        |

Heterogeneity: Not applicable
Test for overall effect: Z = 0.73 (P = 0.46)

| Total (95% CI)          | 137         | 125 100.0%    | 0.74 [-1.97, 3.45]               |

Heterogeneity: Chi² = 2.65, df = 1 (P = 0.10); I² = 62%
Test for overall effect: Z = 0.54 (P = 0.59)
Test for subgroup differences: Chi² = 2.65, df = 1 (P = 0.10), I² = 62.2%
### Daily blood sampling volume

| Study or Subgroup | Small tubes | Regular tubes | Mean Difference IV, Fixed, 95% CI |
|-------------------|-------------|---------------|----------------------------------|
| Smoller 1989      | 32.2        | 55.6          | -9.20 [-13.31, -5.09]            |
| Dolman 2015       | 22.5        | 31.7          | Not estimable                    |

Total (95% CI): 157 small tubes, 147 regular tubes
Heterogeneity: Not applicable
Test for overall effect: Z = 4.39 (P < 0.0001)

### Cumulative ICU blood sampling volume

| Study or Subgroup | Small tubes | Regular tubes | Mean Difference IV, Fixed, 95% CI |
|-------------------|-------------|---------------|----------------------------------|
| Dolman 2015       | 174         | 299           | -125.00 [-194.03, -55.97]        |
| Sanchez-Giron 2008| 5.1         | 19.9          | -14.80 [-18.20, -11.40]          |
| Smoller 1989      | 120.2       | 226.1         | Not estimable                    |

Total (95% CI): 266 small tubes, 265 regular tubes
Heterogeneity: Chi² = 9.77, df = 1 (P = 0.002); I² = 90%
Test for overall effect: Z = 8.71 (P < 0.00001)
**Question:** Should catheter-based blood conservation devices be used to reduce iatrogenic anemia in non-bleeding critically ill patients?

| Certainty assessment | No of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other | No of patients | Effect | Certainty | Importance |
|----------------------|---------------|--------------|--------------|---------------|--------------|-------------|-------|----------------|--------|------------|------------|
| Proportion of patients transfused | 6 | RCTs | serious a | not serious | not serious | serious b | none | 62/290 (21.4%) | RR 0.72 (0.55 to 0.95) | 83 fewer per 1,000 (from 133 fewer to 15 fewer) | ☑️ ☑️ ☑️ | LOW | IMPORTANT |
| Mean number of transfusions | 3 | RCTs | serious a | not serious | not serious | serious b | none | 160 | MD 0.30 higher (0.05 lower to 0.54 higher) | ☑️ ☑️ ☑️ | LOW | IMPORTANT |
| ICU length of stay | 5 | RCTs | serious a | not serious | not serious | serious c | none | 248 | MD 0.14 higher (0.52 lower to 0.81 higher) | ☑️ ☑️ ☑️ | LOW | IMPORTANT |
| Complications | 2 | RCTs | serious a | not serious d | serious e | serious f | none | 7/234 (3.0%) | RR 0.40 (0.17 to 0.91) | 48 fewer per 1,000 (from 66 fewer to 7 fewer) | ☑️ ☑️ ☑️ ☑️ | VERY LOW | IMPORTANT |
| Daily blood sampling volume | 3 | RCTs | serious a | not serious d | not serious | not serious | none | 136 | MD 24.56 lower (25.78 lower to 23.35 lower) | ☑️ ☑️ ☑️ | MODERATE | NOT IMPORTANT |
| Cumulative blood sampling volume | 5 | RCTs | serious a | not serious d | not serious | not serious | none | 206 | MD 47.74 lower (53.66 lower to 41.83 lower) | ☑️ ☑️ ☑️ | MODERATE | NOT IMPORTANT |
| Hemoglobin | 1 | RCTs | serious a | not serious | not serious | serious c | none | 25 | MD 0.7 lower (2.48 lower to 1.08 higher) | ☑️ ☑️ ☑️ | LOW | NOT IMPORTANT |
Explanations

a. Small, single-centre trials with limited methodological reporting makes it difficult to judge risk of bias.
b. Small number of trials; likely underpowered to show a difference; optimal information size not met.
c. Wide 95% confidence intervals which do not exclude results of likely significance to patients.
d. Significant statistical heterogeneity, however all studies appear to be on the same line of no effect, making the heterogeneity of questionable significance.
e. Studies reported a wide variety of complications (infection, thrombosis) of varying degrees of severity.
f. Although statistically significant, there is an extremely small number of events.

Summary statements

1. Blood conservation devices may reduce the proportion of patients transfused, though our certainty is limited by risk of bias in the included studies.
2. Blood conservation devices may result in little to no difference in mean number of transfusions, though our certainty is limited by risk of bias in the included studies and imprecision of the results.
3. Blood conservation devices may result in little to no difference in ICU length of stay, though our certainty is limited by risk of bias in the included studies and imprecision.
4. The evidence is very uncertain about the effect of blood conservation devices on complications, due to risk of bias in included studies, indirectness, and imprecision of the evidence.
5. Blood conservation devices likely reduce cumulative blood sampling volume slightly, though our certainty is limited by potential risk of bias in the included studies.
6. Blood conservation device likely reduces cumulative blood sampling volume slightly, though our certainty is limited by potential risk of bias in the included studies.
7. Blood Conservation Device may result in little to no difference in hemoglobin, though our certainty is limited by risk of bias in the included studies, and imprecision.
Proportion of patients transfused

| Study or Subgroup | Blood conservation device | Control | Risk Ratio M–H, Random, 95% CI |
|-------------------|---------------------------|---------|--------------------------------|
| Harber 2006       | 2                         | 25      | 0.67 [0.12, 3.65]              |
| Madsen 2003       | 17                        | 80      | 0.57 [0.34, 0.94]              |
| Moran 2003        | 2                         | 22      | 0.33 [0.08, 1.36]              |
| Peruzzi 1993      | 16                        | 50      | 1.23 [0.66, 2.28]              |
| Rezende 2010      | 20                        | 62      | 0.72 [0.46, 1.14]              |
| Woda 2009         | 5                         | 51      | 0.94 [0.29, 3.05]              |
| **Total (95% CI)**| **290**                   | **304** | **0.74 [0.55, 0.98]**          |

Total events 62

Heterogeneity: $I^2 = 0.00$, $Q = 5.13$, $df = 5$ ($P = 0.40$); $I^2 = 3$

Test for overall effect: $Z = 2.11$ ($P = 0.03$)

Mean number of transfusions

| Study or Subgroup | Blood conservation device | Control | Mean Difference IV, Fixed, 95% CI |
|-------------------|---------------------------|---------|---------------------------------|
| Peruzzi 1993      | 0.7                       | 50      | 0.30 [-0.37, 0.57]              |
| Rezende 2010      | 1.67                      | 62      | 0.37 [0.09, 0.65]               |
| Thorpe 2009       | 2                         | 48      | 0.00 [-3.08, 3.08]              |
| **Total (95% CI)**| **160**                   | **167** | **0.30 [0.05, 0.54]**           |

Heterogeneity: $Chi^2 = 1.96$, $df = 2$ ($P = 0.16$); $I^2 = 0$

Test for overall effect: $Z = 2.39$ ($P = 0.02$)

Complications

| Study or Subgroup | Blood conservation device | Control | Risk Ratio M–H, Fixed, 95% CI |
|-------------------|---------------------------|---------|--------------------------------|
| Liu 2018          | 2                         | 186     | 0.19 [0.04, 0.84]              |
| Thorpe 2009       | 5                         | 48      | 0.68 [0.24, 1.93]              |
| **Total (95% CI)**| **234**                   | **226** | **0.40 [0.17, 0.91]**          |

Total events 7

Heterogeneity: $Chi^2 = 1.96$, $df = 1$ ($P = 0.16$); $I^2 = 49$

Test for overall effect: $Z = 2.18$ ($P = 0.03$)
### ICU length of stay

| Study or Subgroup | Blood conservation device | Control | Mean Difference |
|-------------------|----------------------------|---------|-----------------|
|                   | Mean | SD  | Total | Mean | SD  | Total | Weight | IV, Random, 95% CI |
| Gleason 1992      | 6.38 | 5.6 | 31    | 6.35 | 5.9 | 37    | 3.9%   | 0.03 [-2.71, 2.77] |
| Harber 2006       | 3.00 | 1.3 | 25    | 3.1  | 1.4 | 25    | 72.5%  | 0.00 [-0.78, 0.78] |
| Macisaac 2003     | 3.1  | 8.6 | 80    | 2.15 | 80  | 80    | 2.9%   | 1.10 [-2.80, 5.00] |
| Peruzzi 1993      | 4.6  | 4.9 | 50    | 4.1  | 3.6 | 50    | 15.5%  | 0.50 [-1.19, 2.19] |
| Rezende 2010      | 14.1 | 12.6 | 62   | 13.1 | 6.1 | 65    | 3.2%   | 1.00 [-2.71, 4.71] |

Total (95% CI) 248

Heterogeneity: Tau² = 0.00; Chi² = 0.74, df = 4 (P = 0.95); I² = 0%
Test for overall effect: Z = 0.42 (P = 0.67)

### Mean daily blood sampling volume

| Study or Subgroup | Blood conservation device | Control | Mean Difference |
|-------------------|----------------------------|---------|-----------------|
|                   | Mean | SD  | Total | Mean | SD  | Total | Weight | IV, Fixed, 95% CI |
| Gleason 1992      | 7.14 | 4.5 | 31    | 11.48 | 6.05 | 37    | 23.4% | -4.34 [-6.85, -1.83] |
| Harber 2006       | 8.25 | 0.2 | 25    | 10.45 | 3.75 | 25    | 67.9% | -3.20 [-3.34, -3.05] |
| Macisaac 2003     | 0.2  | 13.3 | 80    | 21.13 | 80  | 80    | 8.7%  | -20.80 [-24.92, -16.68] |

Total (95% CI) 136

Heterogeneity: Chi² = 350.09, df = 2 (P < 0.00001); I² = 99%
Test for overall effect: Z = 39.64 (P < 0.00001)

### Cumulative blood sampling volume

| Study or Subgroup | Blood conservation device | Control | Mean Difference |
|-------------------|----------------------------|---------|-----------------|
|                   | Mean | SD  | Total | Mean | SD  | Total | Weight | IV, Fixed, 95% CI |
| Gleason 1992      | 35   | 0   | 31    | 69   | 0   | 37    | Not estimable |
| Peruzzi 1993      | 19.4 | 47.4 | 50    | 103.5 | 99.9 | 50    | 3.7% | -84.10 [-114.75, -53.45] |
| Macisaac 2003     | 63   | 227 | 80    | 133  | 352 | 80    | 0.4% | -70.00 [-161.78, 21.78] |
| Harber 2006       | 25   | 5.5 | 25    | 141  | 35  | 25    | 18.1% | -116.00 [-129.89, -102.11] |
| Mahdy 2009        | 15.16 | 5.3 | 20    | 45.11 | 14 | 19    | 77.7% | -29.95 [-36.66, -23.24] |

Total (95% CI) 206

Heterogeneity: Chi² = 125.43, df = 3 (P < 0.00001); I² = 98%
Test for overall effect: Z = 15.82 (P < 0.00001)
### Change in hemoglobin

| Study or Subgroup | Blood conservation device | Control | Mean Difference |
|-------------------|---------------------------|---------|----------------|
|                   | Mean | SD | Total | Mean | SD | Total | IV, Fixed, 95% CI |
| Harber 2006       | 1.3  | 3.5 | 25    | 2.9  | 2.9 | 25    | -0.70 [-2.48, 1.08] |
| **Total (95% CI)** | 25   |     | 25    | 100.0% | -0.70 [-2.48, 1.08] |

Heterogeneity: Not applicable

Test for overall effect: Z = 0.77 (P = 0.44)
**Question:** Prophylactic platelet transfusion compared to no platelet transfusion in critically ill patients without bleeding

| Certainty assessment | Nr of patients | Effect | | |
|-----------------------|----------------|--------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|
|                       | Platelet transfusion | No platelet transfusion | Relative (95% CI) | Absolute (95% CI) | Certainty | Importance |
| Mortality             |                |                |                  |                   |         |          |
| 2                     | observational studies | not serious | not serious | serious a | none | 117/1075 (10.9%) | 114/1012 (11.3%) | RR 0.85 (0.66 to 1.08) | 17 fewer per 1,000 (from 38 fewer to 9 more) | ⋁ ᵏ ᵏ ᵏ | VERY LOW | CRITICAL |
| ARDS (TRALI)          |                |                |                  |                   |         |          |
| 1                     | observational studies | not serious | not serious | very serious b | none | 2/90 (2.2%) | 0/27 (0.0%) | RR 1.54 (0.08 to 31.11) | 0 fewer per 1,000 (from 0 fewer to 0 fewer) | ⋁ ᵏ ᵏ ᵏ | VERY LOW | CRITICAL |
| Major Bleeding        |                |                |                  |                   |         |          |
| 1                     | observational studies | not serious | not serious | very serious b | none | 1/90 (1.1%) | 0/27 (0.0%) | RR 0.92 (0.04 to 22.03) | 0 fewer per 1,000 (from 0 fewer to 0 fewer) | ⋁ ᵏ ᵏ ᵏ | VERY LOW | IMPORTANT |
| Infections (nosocomial) |                |                |                  |                   |         |          |
| 1                     | observational studies | not serious | not serious | not serious | none | 154/621 (24.8%) | 5.0% | OR 2.53 (1.99 to 3.21) | 68 more per 1,000 (from 45 more to 95 more) | ⋁ ⋁ ⋁ | LOW | IMPORTANT |

CI: Confidence interval; RR: Risk ratio; OR: Odds ratio

**Explanations**

a. Wide 95% confidence intervals which do not exclude potential harm or benefit of likely significance to patients.

b. Very wide 95% confidence interval which does not exclude potential harm or benefit of likely significance to patients, and very few events overall.
| Outcomes               | Anticipated absolute effects* (95% CI) | Relative effect (95% CI) | No of participants (studies) | Certainty of the evidence (GRADE) | Comments                                                                                                                                 |
|-----------------------|---------------------------------------|--------------------------|------------------------------|-----------------------------------|----------------------------------------------------------------------------------------------------------------------------------------|
|                       | No platelet transfusion | Platelet transfusion   |                               |                                   |                                                                                                                                       |
| Mortality             | 113 per 1,000 (74 to 122)            | 96 per 1,000 (66 to 108) | RR 0.85 (0.66 to 1.08)       | 2087 (2 observational studies)   | ⬤ ⬤ ⬤ ⬤ VERY LOW[^a^] We are uncertain about the effect of prophylactic platelet transfusion on mortality due to observational study design imprecision. |
| ARDS (TRALI)          | 0 per 1,000 (0 to 0)                 | 0 per 1,000 (0 to 0)     | RR 1.54 (0.08 to 31.11)     | 117 (1 observational study)      | ⬤ ⬤ ⬤ ⬤ VERY LOW[^b^] We are uncertain about the effect of prophylactic platelet transfusion on ARDS (TRALI) due to observational study design imprecision. |
| Major Bleeding        | 0 per 1,000 (0 to 0)                 | 0 per 1,000 (0 to 0)     | RR 0.92 (0.04 to 22.03)     | 117 (1 observational study)      | ⬤ ⬤ ⬤ ⬤ VERY LOW[^b^] We are uncertain about the effect of prophylactic platelet transfusion on major bleeding due to observational study design and imprecision. |
| Infections (nosocomial) | Low                                  |                          |                              |                                   |                                                                                                                                       |
|                       | 50 per 1,000                           |                          |                              |                                   |                                                                                                                                       |
|                       | 118 per 1,000 (95 to 145)             |                          |                              |                                   |                                                                                                                                       |
|                       | Moderate                               |                          |                              |                                   |                                                                                                                                       |
|                       | 100 per 1,000                          |                          |                              |                                   |                                                                                                                                       |
|                       | 219 per 1,000 (181 to 263)            |                          |                              |                                   |                                                                                                                                       |
|                       | High                                   |                          |                              |                                   |                                                                                                                                       |
|                       | 150 per 1,000                          |                          |                              |                                   |                                                                                                                                       |
|                       | 309 per 1,000 (260 to 362)            |                          |                              |                                   |                                                                                                                                       |

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: Confidence interval; RR: Risk ratio; OR: Odds ratio
GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Forest Plots

Mortality

| Study or Subgroup | prophylactic plt transf | no transf | Total | Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|-------------------|-------------------------|-----------|-------|-------|--------|-----------------------------|
| Salman 2006       | 27                      | 90        | 117   | 101   | 10.0%  | 0.62 [0.38, 1.03]           |
| Warner 2017       | 90                      | 85        | 175   | 154   | 93.5%  | 0.89 [0.68, 1.17]           |
| Total (95% CI)    | 1075                    | 1012      | 100.0%| 0.85  | 0.66, 1.06 |

Total events: 117 / 114
Heterogeneity: CH² = 1.57, df = 1 (P = 0.21), I² = 38%
Test for overall effect: Z = 1.35 (P = 0.18)

TRALI

| Study or Subgroup | prophylactic plt transf | no transf | Total | Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|-------------------|-------------------------|-----------|-------|-------|--------|-----------------------------|
| Salman 2006       | 2                       | 90        | 92    | 0     | 0%     | 1.54 [0.98, 2.41]           |
| Total (95% CI)    | 90                      | 27        | 100.0%| 1.54  | 0.88, 1.11 |

Total events: 2 / 0
Heterogeneity: Not applicable
Test for overall effect: Z = 0.28 (P = 0.78)

Major Bleeding
Prospective cohort study of patients with thrombocytopenia in the ICU

**AIM:**
The aim of this analysis was to describe the prevalence and clinical significance of thrombocytopenia complicating critical illness. Specifically, we aimed to explore the associations among thrombocytopenia, bleeding, and patient survival in the ICU. We also aimed to provide a detailed description of the clinical use of PLT transfusions in general ICUs.

**Methodology:**
multicentre observational cohort study conducted in all patients admitted to the UK general ICUs over 8 weeks. Daily data was collected on frequency if thrombocytopenia and plt transfusion and clinical outcomes such as bleeding and mortality.

**Data collection:**
- Data were collected prospectively from patient records for the 24 hours before admission and every subsequent day in the ICU until discharge, death, or 30 days (for patients remaining in the ICU at this time).
- Data collected included hematology and coagulation test results, all procedures, the occurrence of clinically significant hemorrhage during each 24-hour period (defined either as estimated total cumulative blood loss >300 mL, 1 unit of red blood cells [RBCs], or bleeding from a critical site such as intracranial, using a previously described definition), and all blood component transfusions including PLT transfusions.

**Results:**
- 1923 pts from 29 ICUs included.
- Period prevalence of severe thrombocytopenia (<50) for the entire ICU stay was 12.4% (234/1881) and 13.7% (263/1914) when the first 24 hrs were included.
- 35.4% of patients who had severe thrombocytopenia died in ICU.
- 169 patients/1914 received plt transfusion (medium number of units per admission was 2, IQR 1-3).
- Patients who received plt transfusion, 40% of pts had a plt account of >50 with no clinical sign of bleeding.
**Question:** Platelets compared to no platelets in critically ill patients prior to invasive procedures

| Certainty assessment | № of patients | Effect | Certainty | Importance |
|----------------------|---------------|--------|-----------|------------|
|                      | № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other | Platelets | No platelets | Relative (95% CI) | Absolute (95% CI) |
| **Mortality - RCTs**  |              | RCTs | not serious | not serious | serious a | very serious b | none | 11/35 | 15/35 | RR 0.73 (0.39 to 1.36) | 116 fewer per 1,000 (from 261 fewer to 154 more) | ✫ ✫ ✫ ✔ ✔ ✔ ✔ ✔ ✔ ✔ CRITICAL |
| **Major Bleeding - RCTs** |              | RCTs | not serious c | not serious | serious a | very serious b | none | 3/35 | 2/37 | RR 1.59 (0.28 to 8.93) | 32 more per 1,000 (from 39 fewer to 429 more) | ✫ ✫ ✫ ✔ ✔ ✔ ✔ ✔ ≈ ≈ ✔ ✔ ✔ ✔ ✔ ✔ ✔ ✔ ✔ ✔ IMPORTANT |

CI: Confidence interval; RR: Risk ratio

**Explanations**

a. Indirectness of intervention: one study (Veelo 2012) used correction with both FFP and platelets vs. no correction; unclear how much of the effects seen are due to platelets alone.
b. Very wide 95% confidence intervals resulting in very serious imprecision.
c. Though single study (Veelo 2012) was stopped early for low number of events, as opposed to significant benefit or harm, and this is unlikely to have biased results.
### Platelets compared to no platelets in critically ill patients prior to invasive procedures

**Patient or population:** critically ill patients prior to invasive procedures  
**Intervention:** platelets  
**Comparison:** no platelets

| Outcomes          | Anticipated absolute effects* (95% CI) | Relative effect (95% CI) | No of participants (studies) | Certainty of the evidence (GRADE) | Comments                                                                 |
|-------------------|---------------------------------------|--------------------------|------------------------------|----------------------------------|--------------------------------------------------------------------------|
|                   | Risk with no platelets                | Risk with platelets      |                              |                                  |                                                                          |
| Mortality - RCTs  | 429 per 1,000                         | 313 per 1,000 (167 to 583) | RR 0.73 (0.39 to 1.36)       | 70 (1 RCT)                       | We are uncertain about the effect of platelets on mortality due to indirectness of intervention and very serious imprecision. |
| Major Bleeding - RCTs | 54 per 1,000                       | 86 per 1,000 (15 to 483) | RR 1.59 (0.28 to 8.93)       | 72 (1 RCT)                       | We are uncertain about the effect of platelets on major bleeding due to indirectness of intervention and very serious imprecision. |

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).*

**CI:** Confidence interval; **RR:** Risk ratio

**GRADE Working Group grades of evidence**

- **High certainty:** We are very confident that the true effect lies close to that of the estimate of the effect.
- **Moderate certainty:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
- **Low certainty:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
- **Very low certainty:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

### Explanations

- **a.** Indirectness of intervention: one study (Veelo 2012) used correction with both FFP and platelets vs. no correction; unclear how much of the effects seen are due to platelets alone.
- **b.** Very wide 95% confidence intervals resulting in very serious imprecision.
- **c.** Though single study (Veelo 2012) was stopped early for low number of events, as opposed to significant benefit or harm, and this is unlikely to have biased results.
## Forest Plots

### Mortality (Hospital)

| Study or Subgroup | Platelet transfusion | Total | No platelet transfusion | Total | Risk Ratio  | Risk Ratio  |
|-------------------|----------------------|-------|--------------------------|-------|-------------|-------------|
|                   | Events               | Total | Events                   | Total | M-H, Fixed, 95% CI | M-H, Fixed, 95% CI |
| 1.6.1 RCTs        | 11                   | 35    | 15                       | 35    | 0.73 [0.39, 1.36] |             |
| Subtotal (95% CI) |                      | 35    |                          | 35    | 0.73 [0.39, 1.36] |             |
| Total events      | 11                   | 35    |                          | 35    | 0.73 [0.39, 1.36] |             |

Heterogeneity: Not applicable
Test for overall effect: Z = 0.98 (P = 0.33)

Test for subgroup differences: Not applicable
### Mortality (Hospital- RCT and observational data)

| Study or Subgroup | Platelet transfusion Events | Total | No platelet transfusion Events | Total | Weight | Risk Ratio M–H, Fixed, 95% CI |
|-------------------|-----------------------------|-------|-------------------------------|-------|--------|----------------------------|
| **1.6.1 RCTs**    |                             |       |                               |       |        |                             |
| Veelo 2012        | 11                          | 35    | 15                            | 35    | 29.5%  | 0.73 [0.39, 1.36]           |
| **Subtotal (95% CI)** |                             | **35** |                               | **35** | **29.5%** | **0.73 [0.39, 1.36]** |
| Total events      | 11                          | 15    |                               | 11    | 15     |                             |

Heterogeneity: Not applicable
Test for overall effect: Z = 0.98 (P = 0.33)

| **1.6.2 Observational studies** |                             |       |                               |       |        |                             |
|--------------------------------|-----------------------------|-------|-------------------------------|-------|--------|----------------------------|
| Warner 2017                   | 44                          | 203   | 182                           | 1857  | 70.5%  | 2.21 [1.65, 2.97]           |
| **Subtotal (95% CI)**         |                             | **203** |                               | **1857** | **70.5%** | **2.21 [1.65, 2.97]** |
| Total events                  | 44                          | 182   |                               | 44    | 182    |                             |

Heterogeneity: Not applicable
Test for overall effect: Z = 5.26 (P < 0.00001)

**Total (95% CI)**

| Total events | 55                          | 197   |                               | 55    | 197    |                             |

Heterogeneity: Chi² = 9.90, df = 1 (P = 0.002); I² = 90%
Test for overall effect: Z = 4.32 (P < 0.00001)
Test for subgroup differences: Chi² = 9.89, df = 1 (P = 0.002), I² = 89.9%

### Major Bleeding (RCTs)

| Study or Subgroup | Platelet transfusion Events | Total | No platelet transfusion Events | Total | Weight | Risk Ratio M–H, Fixed, 95% CI |
|-------------------|-----------------------------|-------|-------------------------------|-------|--------|----------------------------|
| **1.1.1 RCTs**    |                             |       |                               |       |        |                             |
| Veelo 2012        | 3                           | 35    | 2                             | 37    | 100.0% | 1.59 [0.28, 8.93]           |
| **Subtotal (95% CI)** |                             | **35** |                               | **37** | **100.0%** | **1.59 [0.28, 8.93]** |
| Total events      | 3                           | 2     |                               | 3     | 2      |                             |

Heterogeneity: Not applicable
Test for overall effect: Z = 0.52 (P = 0.60)

**Total (95% CI)**

| Total events | 3                           | 2     |                               | 3     | 2      |                             |

Heterogeneity: Not applicable
Test for overall effect: Z = 0.52 (P = 0.60)
Test for subgroup differences: Not applicable
## Mortality (RCTs and Observational)

| Study or Subgroup       | Platelet transfusion | No platelet transfusion | Risk Ratio | Risk Ratio |
|-------------------------|----------------------|-------------------------|------------|------------|
|                         | Events   | Total | Events   | Total | Weight | M-H, Fixed, 95% CI | M-H, Fixed, 95% CI |
| **1.1.1 RCTs**          |          |       |          |       |        |                      |                      |
| Veelo 2012              | 3        | 35    | 2        | 37    | 4.1%   | 1.59 [0.28, 8.93]  |                      |
| **Subtotal (95% CI)**   | 35       |   | 37       |  | 4.1%   | 1.59 [0.28, 8.93]  |                      |
| Total events            | 3        |       | 2        |       |        |                      |                      |
| Heterogeneity: Not applicable |
| Test for overall effect: $Z = 0.52$ (P = 0.60) |
| **1.1.2 Observational studies** |
| Auzinger 2007           | 1        | 25    | 0        | 35    | 0.9%   | 4.15 [0.18, 97.97] |                      |
| Warner 2017             | 56       | 203   | 231      | 1857  | 95.1%  | 2.22 [1.72, 2.86]  |                      |
| **Subtotal (95% CI)**   | 228      |     | 1892     | 95.9% | 2.24   | [1.74, 2.88]       |                      |
| Total events            | 57       |       | 231      |       |        |                      |                      |
| Heterogeneity: $\chi^2 = 0.15$, df = 1 (P = 0.70); $I^2 = 0\%$ |
| Test for overall effect: $Z = 6.23$ (P < 0.00001) |
| **Total (95% CI)**      | 263      |     | 1929     | 100.0%| 2.21   | [1.72, 2.84]       |                      |
| Total events            | 60       |       | 233      |       |        |                      |                      |
| Heterogeneity: $\chi^2 = 0.30$, df = 2 (P = 0.86); $I^2 = 0\%$ |
| Test for overall effect: $Z = 6.18$ (P < 0.00001) |
| Test for subgroup differences: $\chi^2 = 0.15$, df = 1 (P = 0.70), $I^2 = 0\%$ |
**Question**: Prophylactic platelet transfusion compared to no platelet transfusion in critically ill patients without bleeding

| Certainty assessment | Nr of patients | Effect | Certainty | Importance |
|----------------------|----------------|--------|-----------|------------|
|                      |                |        | ••••••••• |            |
|                      |                |        | VERY LOW  |            |
|                      |                |        | CRITICAL  |            |
|                      |                |        | IMPORTANT |            |
|                      |                |        | LOW       | IMPORTANT  |

| Nr of | Study | Risk of | Inconsistency | Indirectness | Other considerations | Platelet transfusion | No platelet transfusion | Relative (95% CI) | Absolute (95% CI) | Effect | Certainty | Importance |
|-------|-------|---------|---------------|--------------|----------------------|----------------------|------------------------|-------------------|-------------------|--------|-----------|------------|
| 2     | observational studies | not serious | not serious | not serious | serious \(a\) | none | 117/1075 (10.9%) | 114/1012 (11.3%) | RR 0.85 (0.66 to 1.08) | 17 fewer per 1,000 (from 38 fewer to 9 more) | •••••••• | VERY LOW  | CRITICAL   |
| 1     | observational studies | not serious | not serious | not serious | very serious \(b\) | none | 2/90 (2.2%) | 0/27 (0.0%) | RR 1.54 (0.08 to 31.11) | 0 fewer per 1,000 (from 0 fewer to 0 fewer) | •••••••• | VERY LOW  | CRITICAL   |
| 1     | observational studies | not serious | not serious | not serious | very serious \(b\) | none | 1/90 (1.1%) | 0/27 (0.0%) | RR 0.92 (0.04 to 22.03) | 0 fewer per 1,000 (from 0 fewer to 0 fewer) | •••••••• | VERY LOW  | IMPORTANT  |
| 1     | observational studies | not serious | not serious | not serious | not serious | none | 154/621 (24.8%) | 5.0% | OR 2.53 (1.99 to 3.21) | 68 more per 1,000 (from 45 more to 95 more) | •••••••• | LOW       | IMPORTANT  |

CI: Confidence interval; RR: Risk ratio; OR: Odds ratio

**Explanations**

a. Wide 95% confidence intervals which do not exclude potential harm or benefit of likely significance to patients.
b. Very wide 95% confidence interval which does not exclude potential harm or benefit of likely significance to patients, and very few events overall.
### Prophylactic platelet transfusion compared to no platelet transfusion in critically ill patients without bleeding

| Outcomes            | Anticipated absolute effects* (95% CI) | Relative effect (95% CI) | No of participants (studies) | Certainty of the evidence (GRADE) | Comments                                                                 |
|---------------------|---------------------------------------|--------------------------|-----------------------------|----------------------------------|--------------------------------------------------------------------------|
|                     | No platelet transfusion | Platelet transfusion   |                             |                                  |                                                                          |
| Mortality           | 113 per 1,000 (74 to 122) | 96 per 1,000 (0.66 to 1.08) | RR 0.85 (0.66 to 1.08) | 2087 (2 observational studies) | ⬤ ✦ ✦ ✦ VERY LOW<sup>a</sup> | We are uncertain about the effect of prophylactic platelet transfusion on mortality due to observational study design imprecision. |
| ARDS (TRALI)        | 0 per 1,000 (0 to 0) | 0 per 1,000 (0 to 0) | RR 1.54 (0.08 to 31.11) | 117 (1 observational study) | ⬤ ✦ ✦ ✦ VERY LOW<sup>b</sup> | We are uncertain about the effect of prophylactic platelet transfusion on ARDS (TRALI) due to observational study design imprecision. |
| Major Bleeding      | 0 per 1,000 (0 to 0) | 0 per 1,000 (0 to 0) | RR 0.92 (0.04 to 22.03) | 117 (1 observational study) | ⬤ ✦ ✦ ✦ VERY LOW<sup>b</sup> | We are uncertain about the effect of prophylactic platelet transfusion on major bleeding due to observational study design and imprecision. |
| Infections (nosocomial) | Low         | 118 per 1,000 (95 to 145) | OR 2.53 (1.99 to 3.21) | 621 (1 observational study) | ⬤ ✦ ✦ ✦ LOW | Prophylactic platelet transfusion may increase nosocomial infections slightly, but our certainty is limited due to observational study design. We estimated effect size for high, moderate, and low event rates in the control group based upon previously published data (Alberti 2002, Laupland 2002). |
|                     | Moderate     | 219 per 1,000 (181 to 263) |                     |                                 |                                                                          |
|                     | High         | 309 per 1,000 (260 to 362) |                     |                                 |                                                                          |

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: Confidence interval; RR: Risk ratio; OR: Odds ratio
GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Forest Plots

Mortality

| Study or Subgroup | prophylactic plt transf | no transfusion | Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|-------------------|------------------------|---------------|-------|--------|-----------------------------|
| Salman 2006       | 27                     | 90            | 117   | 1.65   | 0.62 [0.38, 1.03]           |
| Warner 2017       | 90                     | 985           | 114   | 1.00   | 0.89 [0.68, 1.17]           |
| Total (95% CI)    | 1075                   | 1012          | 100.0%| 0.85   | 0.85 [0.66, 1.06]           |

Total events: 117
Heterogeneity: CH² = 1.57, df = 1 (p = 0.21); I² = 38%
Test for overall effect: Z = 1.35 (p = 0.18)

TRALI

| Study or Subgroup | prophylactic plt transf | no transfusion | Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|-------------------|------------------------|---------------|-------|--------|-----------------------------|
| Salman 2006       | 2                      | 90            | 92    | 100.0%| 1.54 [0.88, 1.11]           |
| Total (95% CI)    | 90                     | 27            | 100.0%| 1.54   | 1.54 [0.88, 1.11]           |

Heterogeneity: Not applicable
Test for overall effect: Z = 0.28 (p = 0.78)

Major Bleeding
Narrative Summary of Studies

Stanworth 2012

- **Prospective cohort study of patients with thrombocytopenia in the ICU**
- **AIM:** The aim of this analysis was to describe the prevalence and clinical significance of thrombocytopenia complicating critical illness. Specifically, we aimed to explore the associations among thrombocytopenia, bleeding, and patient survival in the ICU. We also aimed to provide a detailed description of the clinical use of PLT transfusions in general ICUs.
- **Methodology:** multicentre observational cohort study conducted in all patients admitted to the UK general ICUs over 8 weeks. Daily data was collected on frequency if thrombocytopenia and plt transfusion and clinical outcomes such as bleeding and mortality.
- **Data collection:**
  - Data were collected prospectively from patient records for the 24 hours before admission and every subsequent day in the ICU until discharge, death, or 30 days (for patients remaining in the ICU at this time). Data collected included hematology and coagulation test results, all procedures, the occurrence of clinically significant hemorrhage during each 24-hour period (defined either as estimated total cumulative blood loss >300 mL, 1 unit of red blood cells [RBCs], or bleeding from a critical site such as intracranial, using a previously described definition), and all blood component transfusions including PLT transfusions.
- **Results:**
  - 1923pts from 29 ICUs included. Period prevalence of severe thrombocytopenia (<50) for the entire ICU stay was 12.4% (234/1881) and 13.7% (263/19140) When the first 24 hrs were included.
  - 35.4% of patients who had severe thrombocytopenia died in ICU.
  - 169 patients/1914 received plt transfusion (medium number of units per admission was 2, IQR 1-3).
  - Patients who received plt transfusion, 40% of pts had a plt account of >50 with no clinical sign of bleeding.
Arnold 2006

- **AIM:** to describe the indications for plt transfusion, the transfusion triggers employed, and the plt count responses among thrombocytopenic patients and the frequency and severity of bleeding.
- **Methodology:** conducted a retrospective cohort study of all thrombocytopenic adult patients admitted to a 15-bed medical-surgical ICU in Hamilton, Ontario, Canada, between January 2001 and January 2002. Thrombocytopenia was defined as any PLT count less than 150 Å~ 109 per/L, and severe thrombocytopenia was defined as a PLT count less than 50 Å~ 109 per L. Patients were identified from a prior prospective study that enrolled consecutive adult ICU patients with an expected length of stay of at least 72 hours and which excluded patients with an admission diagnosis of trauma, orthopedic or cardiac surgery, pregnancy, and life-support withdrawal.
- **Minor bleeding** was defined as hemorrhage requiring the transfusion of fewer than 2 units of RBCs in 24 hours, bruising, oozing, or petechiae.
- **Major bleeding** was defined as CNS hemorrhage, gross hematuria, hemoptysis, melena, hematochezia, hematemesis, vaginal bleeding, any gross blood loss requiring the transfusion of 2 or more units of RBS in a 24 hour period, bleeding requiring surgery or endoscopy or fatal bleeding.
- Bleeding severity was done in duplicate.
- Each transfusion a patient received was defined as therapeutic (to treat bleeding) or prophylactic (to prevent spontaneous bleeding or bleeding anticipated from an invasive procedure). Indications for transfusion were adjudicated in duplicate.
- **Results:** total 118 patients had thrombocytopenia, 37 patients had major bleeding, 24 had minor bleeding. 43.2% of patients with major bleeding received transfusion of plt, 11/77 of patients without major bleeding. 76 transfusions administered to 27/118 patients, 52 where prophylactic, and administered at a medial plt transfusion of 41 (IQR 20-57) and 24 (31.6%) were therapeutic with a median plt trigger of 51. Prophylactic transfusion for procedure related bleeding accounted for 18 transfusions given and administered at a median plt count of 46.

Salman 2006

- **AIM:** 1) to assess the variability in practice of the use of platelet transfusion in critically ill patients with thrombocytopenia but no active bleeding 2. to assess the compliance with published practice guidelines for platelet transfusion; and 3. to compare the
incidence of new bleeding transfusion complications, and overall outcome in critically ill patients without active bleeding who did or did not receive platelet transfusion for the correction of thrombocytopenia.

- **Methodology:**
  - Retrospective cohort jul 1-Nov 30 2004 the investigators identified and review the EMR of patients with plts less then 50 at any time during their ICU admission.
  - Predictor variables included age, gender, Acute Physiology and Chronic Health Evaluation (APACHE) III score [7], international normalized ratio (INR) level, fibrinogen level, activated partial thromboplastin time (APTT) level, serum creatinine level, number of platelet transfusions, indication for platelet transfusion, and mechanism of thrombocytopenia, depending on underlying etiology: increased consumption (distribution or destruction) [8], impaired production, hypersplenism, and concomitant coagulopathy.
  - The main outcome variables included platelet transfusion complications and new bleeding episodes during the ICU stay. Recorded transfusion complications were: 1. Febrile reaction, 2. posttransfusion sepsis, 3. TRALI and TACO, 4. Allergic reaction.
    - Definitions: 1. febrile reactions, defined as a rise in temperature of at least 1 over baseline that achieved a body temperature of 38°C or higher during or up to 4 hours after transfusion,
    - 2. posttransfusion sepsis, considered if the patient had a positive blood culture or sepsis as defined in the Surviving Sepsis Campaign Guidelines [12] and was receiving antibiotic therapy that was not given for prophylactic purposes.
    - TRALI and TACO, as defined by the National Heart, Lung, and Blood Institute. 4. allergic reactions, defined as those associated with laryngeal or skin manifestations (pruritus, urticaria, erythema, flushing), or both, if clinical evaluation supported an allergic cause. New bleeding was defined as a bleeding episode requiring the transfusion of at least 1 unit of RBCs occurring within 24 hours of a platelet transfusion or the lowest platelet count, or a drop in hemoglobin of at least 3 grams regardless of RBC transfusion. Secondary outcomes included hospital mortality and ICU length of stay among survivors.
  - **Analysis:** logistic regression univariant and multivariant
  - **Results:** 117pts with mod to severe thrombocytopenia. 90/117 were transfused. 90 who received plts, 1 had a bleeding incidence, 27 died, 23 had an invasive procedure done, 27 died, LOS 3.65 days, 2 had a febrile reaction, 2, had an allergic reaction and 2 had TRALI, 14/74 pts received plts outside of guidelines. 27 plts did not receive plts and 9 had an invasive procedure done, 13 died, there was no bleeding episodes, and LOS in ICU was 3.86 (117-6.9). In multivariable logistic regression analysis, platelet count (odds ratio [OR], 1.32 per each 103/µL decrease in platelet count; 95% CI, 1.13 to 1.57) and postoperative status (OR, 7.8; 95% CI, 1.91 to 13.32) were independently associated with platelet transfusion. In
contrast, invasive procedures (OR, 0.92; 95% CI, 0.34 to 2.58) were not independently associated with platelet transfusions.

| Additional Outcome       | Transfusion     | No Transfusion  | P value |
|--------------------------|----------------|----------------|---------|
| ICU length of stay (days)| 3.65 (1.63-9.05)| 3.89 (1.71-6.9)| 0.936   |
| Platelet count less than 10 | 15            | 1              | N/A     |

**Warner 2017**

- **AIM:** The objective of this study was to assess the impact of prophylactic platelet transfusion on bleeding complications in critically ill patients with thrombocytopenia
- **Methods:** retrospective cohort study
- **Inclusion Criteria:** Inclusion criteria were age $\geq$ 18 years, ICU admission between January 1, 2009, and December 31, 2013, and the presence of a platelet count measured during ICU admission. For patients with multiple ICU admissions during the study period, only the first admission with a platelet count measurement was included
- **Exclusion Criteria:** Patients were excluded for lack of research authorization and prior inclusion in the study such that no patient was included twice. Patients receiving red blood cell (RBC) transfusion in the 24 hours before measurement of the qualifying platelet count were also excluded to minimize the risk of including those with active bleeding. Similarly, patients receiving RBC transfusion in the interval between platelet count measurement and platelet transfusion were also excluded.
- **Outcomes:** The primary outcome for this investigation was RBC transfusion within 24 hours of the qualifying platelet count value for nonplatelet-transfused patients and within 24 hours of platelet transfusion for platelet-transfused patients. Secondary outcome measures included ICU and hospital-free days (defined as 28 minus the ICU or hospital length of stay in days, with patients dying before discharge and those with ICU or hospital durations greater than 28 days receiving a score of zero), ICU mortality, all-cause mortality within 30 days of ICU discharge, and changes in sequential organ failure assessment (SOFA) score 24 hours after the qualifying platelet count or platelet transfusion for non transfused and transfused patients, respectively.
• **Analysis**: performed matching 1:1 of patients transfused with plts versus those who did not. Then performed propensity matching of the cohort with prespecified analysis

• **Results**: of the matched cohort 985 patients received transfusion and 985 did not. Events for RBS transfusion was 102 in the non transfused, 485 pts in the transfused group, ICU mortality was 90 in the non transfused group and 101 in the transfusion group. All cause 30 day mortality was 162 in the non transfused group and 184 in the transfusion group.

| Additional Outcome | Platelet Transfusion propensity matched cohort N=985, plt count less then 50 N=229 | No platelet transfusion propensity matched cohort N=985, plt count less then 50 N=229 | Mean Rate Ratio (95% CI) | P value |
|--------------------|---------------------------------------------------------------------------------|---------------------------------------------------------------------------------|--------------------------|---------|
| ICU free days, Mean (SD) | 22.7 (8.3) | 20.8 (9.1) | 0.9 (0.9-1.0) | 0.004 |
| Hospital free day, Mean SD | 15.8 (9.4) | 13.0 (9.7) | 0.8 (0.7-0.9) | <0.001 |
| ICU free days, Mean (SD), in pts with plt count less then 50 | 19.9 (10.5) | 18.3 (10.6) | 0.9 (0.8-1.1) | <0.399 |
| Hospital free day, Mean SD, in pts with plt count less then 50 | 10.2 (10.0) | 7.8 (9.4) | 0.8 (0.5-1.1) | 0.141 |

**Habr 2015 (recommend excluding)**
• **AIM:** aimed to address the current practices in platelet transfusion and the risk of bleeding in cancer patients with hypoproliferative thrombocytopenia in a medical intensive care unit.

• **Methods:** This retrospective observational study was carried out over a 7-year period (December 2006 to February 2014) in a 24-bed tertiary medical ICU. Collected data via electronic records. For each patient, the following baseline data were collected: demographics (age and gender), type of malignancy (solid tumor or hematologic malignancy), and the presence of other comorbidities such as chronic organ dysfunctions. The presumed or proved mechanisms of central thrombocytopenia were also collected.

• **Inclusion Criteria:** Adult patients with hematologic malignancies or solid tumors with presumed or proved central thrombocytopenia as defined by a platelet count below 150/L, and who received at least one platelet concentrate during the ICU stay, were included.

• **Exclusion Criteria:** Patients with thrombocytopenia from exclusive peripheral origin were not included.

• **Indications for Transfusions:** Indications of platelet transfusions were distributed into the three following categories: prophylactic, securing an invasive procedure, and therapeutic. Prophylactic transfusions aimed at maintaining platelet count above 10–20 Å~ 10^9/L.

• **RESULTS:** Did split the group into those who had ICU acquired bleed versus those who did not but both groups received transfusions. 300/900 platelet transfusions were for prophylaxis. 257/900 platelets transfusions were for invasive procedure, typically patients who were transfused their counts <20, 5 reactions of resp failure/overload were noted.

---

Ning 2016

• **AIM:** We analyzed a large cohort of critically ill nononcology patients to address several fundamental questions about platelet transfusion practices in the ICU: (1) What is the platelet count threshold for transfusion? (2) What is the expected platelet count increment? (3) What are the predictors of ineffectual platelet transfusions in this population?

• **METHODS:** identified consecutive patients who received one or more platelet transfusions during their ICU admissions from the Transfusion Registry for Utilization, Surveillance, and Tracking (TRUST) research database. Data validation for the TRUST database was done through integrity checks of patients’ medical records, discrepancy verifications of the laboratory information system and blood product inventory, and comparisons of imported and merged data to ensure accuracy and completeness.

• **Inclusion Criteria:** critically ill adults (≥ 18years) admitted to medical/surgical, cardiac, or burn ICUs at three academic centers in Hamilton, Canada between April 2006 and September 2015.

• **Excluded:** Patients with cancer or chemotherapy-induced thrombocytopenia were excluded.
• **RESULTS:** Most admissions (78.7%) were for cardiac surgery. Based on 5,700 analyzable transfusions, the median pretransfusion platelet count was $87 \_ 109/L$ (interquartile range [IQR], 57-130). The pretransfusion platelet count was $50 \_ 109/L$ and $150 \_ 109/L$ for 79.6% and 17.8% of transfusions, respectively. Reasons for transfusion despite a normal platelet count were active bleeding or surgery in patients receiving antiplatelet agents or anticoagulants. The median platelet count increment was $23 \_ 109/L$ (IQR, 7-44), and 21.8% of transfusions were ineffectual. ABO incompatibility, sepsis, liver disease, and red cell and cryoprecipitate transfusions were associated with a poor platelet count increment.

Engele 2016

• **AIM:** The purpose of this prospective cohort study was to investigate the risk of nosocomial infections following transfusion in critically ill patients. We hypothesized that the number of blood products was independently associated with an increased risk of nosocomial infection

• **Methods:** prospective cohort (within the MARS project). Primary outcome was nosocomial infection. Scoring of nosocomial infection was performed daily based on criteria adapted from the Centre of Disease Control that were published previously [17]. These criteria included the source of infection, the causative pathogen and the plausibility of infection (none, possible, probable and definite).

• As per transfusion protocols plts were transfused when: A unit of pooled platelets from 5 donors is transfused prophylactically at a platelet count of 10 or 50 L in case of use of antiplatelet medication

• Scoring of nosocomial infection was performed daily based on criteria adapted from the Centre of Disease Control that were published previously [17]. These criteria included the source of infection, the causative pathogen and the plausibility of infection (none, possible, probable and definite).

• Use propensity matching.

• **RESULTS:** T 3502 pts in the cohort, 621 pts received platelets, out of those with infection 157/476 had received platelets. For non-infected patients 464/3026 had received platelets For nosocomial infection increased with plt transfusion logistic regression showed OR 2.530 (95%CI 1.998-3.205), p<0.001, COX regression HR 1.463, (95%CI 1.184-1.806), p<0.001. Propensity matching took into account the following variables: Corrected for exposure bias (for platelet transfusion) summarized in propensity score including admission type, malignancy, APACHE IV score and sepsis. Also corrected for confounders including APACHE predicted length of stay and mechanical ventilation.
NOTES:

The review my Etchill 2017 in SHOCK provides excellent background information on prophylactic and therapeutic platelet transfusions. A good resource when writing background for the guideline.

Identified two additional references from the Lieberman review. A review article that can be used to write the background for the recommendation.
**Question**: Plasma compared to no plasma in ICU patients prior to invasive procedures

### Certainty assessment

| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | № of patients | Effect | Certainty | Importance |
|--------------|--------------|--------------|---------------|--------------|-------------|----------------------|---------------|--------|------------|------------|
|              |              |              |               |              |             |                      | plasma        | no plasma | Relative (95% CI) | Absolute (95% CI) |              |            |
| **Mortality (Short term)** | | | | | | | | | | | |
| 2 | randomised trials | not serious a | not serious | serious b | serious c | none | 30/73 (41.1%) | 42/73 (57.5%) | RR 0.71 (0.51 to 0.99) | 167 fewer per 1,000 (from 282 fewer to 6 fewer) | ☓ ☓ ☓ | LOW | CRITICAL |
| **Major Bleeding** | | | | | | | | | | | |
| 2 | randomised trials | not serious | not serious | serious b | very serious c | none | 3/73 (4.1%) | 3/75 (4.0%) | RR 1.04 (0.25 to 4.37) | 2 more per 1,000 (from 30 fewer to 135 more) | ☓ ☓ ☓ | VERY LOW | IMPORTANT |

CI: Confidence interval; RR: Risk ratio

**Explanations**

a. Both studies stopped early, however this was due to difficulty with enrolment and low event rates, as opposed to stopping early for benefit or harm which can bias results.
b. Indirectness of intervention: one study (Veelo 2012) contributing >40% of weight in the meta-analysis used correction with both FFP and platelets vs. no correction; unclear how much of the effects seen are due to plasma alone.
c. Wide 95% confidence intervals which do not exclude benefit or harm of probable importance to patients.
## Plasma compared to no plasma in ICU patients prior to invasive procedures

**Patient or population:** ICU patients prior to invasive procedures  
**Intervention:** plasma  
**Comparison:** no plasma

| Outcomes                  | Anticipated absolute effects* (95% CI) | Relative effect (95% CI) | Nº of participants (studies) | Certainty of the evidence (GRADE) | Comments                                                                 |
|---------------------------|---------------------------------------|--------------------------|----------------------------|----------------------------------|--------------------------------------------------------------------------|
| **Mortality (Short term)**| Risk with no plasma 575 per 1,000     | Risk with plasma 408 per 1,000 (293 to 570) | RR 0.71 (0.51 to 0.99)     | 146 (2 RCTs)                     | + + ○ ○ LOW a,b,c                                                      |
|                           |                                       |                          |                            |                                  | Plasma may reduce short term mortality, but our certainty is limited by indirectness of the intervention. |
| **Major Bleeding**        | Risk with no plasma 40 per 1,000       | Risk with plasma 42 per 1,000 (10 to 175) | RR 1.04 (0.25 to 4.37)     | 148 (2 RCTs)                     | + + + + + VERY LOW b,c                                                   |
|                           |                                       |                          |                            |                                  | We are uncertain about the effect of plasma on major bleeding, due to indirectness of the intervention, and very few events leading to very significant imprecision. |

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: Confidence interval; RR: Risk ratio

### GRADE Working Group grades of evidence
- **High certainty:** We are very confident that the true effect lies close to that of the estimate of the effect.
- **Moderate certainty:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
- **Low certainty:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
- **Very low certainty:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.
### Mortality (Hospital)

| Study or Subgroup | Plasma Transfusion (FFP) | no plasma transfusion | Risk Ratio | Risk Ratio |
|-------------------|--------------------------|-----------------------|------------|------------|
|                   | Events       | Total | Events | Total | Weight | M-H, Fixed, 95% CI | M-H, Fixed, 95% CI |
| Mueller 2015      | 19           | 38    | 27     | 38    | 64.3%   | 0.70 [0.48, 1.03]  |
| Veelo 2012        | 11           | 35    | 15     | 35    | 35.7%   | 0.73 [0.39, 1.36]  |
| Total (95% CI)    | 30           | 73    | 42     | 73    | 100.0%  | 0.71 [0.51, 0.99]  |

Heterogeneity: $\chi^2 = 0.01$, $df = 1$ ($p = 0.91$); $I^2 = 0$
Test for overall effect: $Z = 2.00$ ($p = 0.05$)

**Caption**

Forest plot of comparison: 1 plasma transfusion versus no plasma transfusion for invasive procedures in non bleeding critically ill patients, outcome: 1.2 Mortality (Short term).

### Major Bleeding
**AIM:** conducted a multicenter randomized controlled clinical trial in critically ill patients with a coagulopathy who needed to undergo an invasive procedure. Using noninferiority analysis, we aimed to determine whether FFP transfusion could be safely omitted in these patients.

**Methods:** noninferiority RCT

**Results:** Due to slow inclusion, the trial was stopped before the predefined target enrollment was reached. Eighty-one patients were randomly assigned, 40 to FFP and 41 to no FFP transfusion. Incidence of bleeding did not differ between groups, with a total of one major and 13 minor bleedings \((p = 0.08 \text{ for noninferiority})\). FFP transfusion resulted in a reduction of INR to less than in 54\% of transfused patients. **No differences in lung injury scores were observed.** SEE Excel spreadsheet

**Additional Data**

| Additional Outcomes                          | FFP Group N=38 | No FFP N=38 | P value |
|---------------------------------------------|----------------|-------------|---------|
| ICU Length of Stay (days), Median (IQR)     | 12 (6-19)      | 7 (3-17)    | 0.13    |
Veelo 2012

- **AIM:** conducted an RCT of critically ill patients requiring percutaneous tracheotomy who had thrombocytopenia, coagulopathy and been exposure to aspirin. Patients assigned to the “correction” of coagulopathy group did receive platelets and FFP according to their PT.
- **Methods:** open label RCT
- **Specifics:** 12/35 patients received FFP alone, 17/35 patients received platelets alone, 6/35 patients received both FFP and platelets
- **Intervention:** Patients with a prolonged PT with mild coagulation disorders (PT 14.7-29 seconds and or put counts 40-100) assigned to the “correction group” received one or two units of FFP (1 unit of FFP if PT between 14.7-18 seconds, if the PT was between 18-20 seconds the pt received 2 units of FFP). Patients with a low put count and or active use of ASA assigned to the correction group received 5 units of pts prepared from 5 pooled buffy coats. Patients assigned to the no correction group received neither.
- **Results:** The study was terminated early due to the small amount of bleeding events and for reluctance to transfuse patients by the consultant physicians. Minor bleeding in FFP group was 8/38, in no FFP was 5/38. Per protocol analysis
- **Additional Data:**

|                                | Median (IQR) | p-value |
|--------------------------------|--------------|---------|
| **Duration of MV, Median (days)** | 11 (6-16)    | 0.01    |
| **FFP in Units, Median (IQR)**   | 0 (0-1)      | 0.06    |
| **RBCs in Units, Median (IQR)**  | 1 (0-2)      | 0.91    |
| **Platelets in units, Median (IQR)** | 1 (0-2) | 0.43    |

|                                | Median (IQR) | p-value |
|--------------------------------|--------------|---------|
| **VAP**                        | 8 (3)        | 0.001   |
| **FFP in Units, Median (IQR)**  | 2 (0-2)      |         |
| **RBCs in Units, Median (IQR)** | 2(0-3)       |         |
| **Platelets in units, Median (IQR)** | 0 (0-1) |         |
The cost of one FFP and five units of platelet concentrates in our hospital is €172 ($252) and €484 ($709), respectively. A surplus of €14,423 ($21,104) was spent in the "correction" group compared to the "no correction" group. Consequently, a procedure that is not preceded by correction of mild coagulation disorders saves, on average, €465 per patient. (Veelo et al., 2012, page 217)

### Weigand 2009 (excluded after full text review)
- **AIM:** The aim of the prospective study presented here was to demonstrate that coagulopathy, defined by prothrombin time or INR and platelet count, is not decisive for bleeding.
- **Methods:** non-randomized parallel trial (confirmed on clinicaltrials.gov, no clear in manuscript)
- **Intervention:** CVC in coagulopathy

| Additional Outcomes          | Correction n=35 | No Correction N=37 | P value |
|-----------------------------|-----------------|--------------------|---------|
| ICU Length of Stay (days) median (IQR) | 15 (8-29)       | 21 (14-26)         | 0.21    |
| Duration of MV (days) (IQR)  | 11 (7-24)       | 16 (10-21)         | 0.16    |
| FFP in Units                 | N/A             | N/A                | N/A     |
| RBCs in Units                | N/A             | N/A                | N.A     |

*Cost Data From Veelo 2012 page 217*

The cost of one FFP and five units of platelet concentrates in our hospital is €172 ($252) and €484 ($709), respectively. A surplus of €14,423 ($21,104) was spent in the "correction" group compared to the "no correction" group. Consequently, a procedure that is not preceded by correction of mild coagulation disorders saves, on average, €465 per patient. (Veelo et al., 2012, page 217)
• **Inclusion Criteria:** The study included all patients > 18 years of age that were undergoing CVC insertion electively or in case of emergency, who did not meet the exclusion criteria.

• **Exclusion Criteria:** Exclusion criteria were bleeding for other reasons, like gastrointestinal bleeding or trauma. Additionally, pre or post surgery patients were excluded as well as patients undergoing systemic lysis therapy or chemotherapy

• Major bleeding: defined as a drop in hgb >1.5/dl

• **RESULTS:** 34 pts had significant drop in hgb, only 7 had suffered from coagulopathy