

## Supplement 1: Evidence summaries and GRADE profiles

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

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**Evidence Summary 1: Transfusion Ratios in Massively Bleeding Critically Ill adults**

## High vs. low ratio FFP:RBC transfusion in massively bleeding patients

### 1. Massive bleeding in trauma patients

Certainty assessment						№ of patients		Effect		Certainty	Importance
№ of studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	High ratio	Low ratio	Relative (95% CI)	Absolute (95% CI)		
<b>Early mortality- observational studies</b>											
19 obs	serious <sup>a</sup>	not serious <sup>b</sup>	not serious	not serious	none	421/2412 (17.5%)	946/3680 (25.7%)	<b>RR 0.51</b> (0.39 to 0.65)	<b>126 fewer per 1,000</b> (from 157 fewer to 90 fewer)	⊕○○○ VERY LOW	CRITICAL
<b>30 day mortality - observational studies</b>											
33 obs	serious <sup>a</sup>	not serious <sup>b</sup>	not serious	not serious	none	1380/5003 (27.6%)	2411/7108 (33.9%)	<b>RR 0.63</b> (0.54 to 0.73)	<b>126 fewer per 1,000</b> (from 156 fewer to 92 fewer)	⊕○○○ VERY LOW	CRITICAL
<b>24 hour mortality - RCTs</b>											
1 RCT	not serious	not serious	not serious	serious <sup>c</sup>	none	43/338 (12.7%)	58/342 (17.0%)	<b>RR 0.75</b> (0.52 to 1.08)	<b>42 fewer per 1,000</b> (from 81 fewer to 14 more)	⊕⊕⊕○ MODERATE	CRITICAL
<b>30 day mortality - RCTs</b>											
2 RCTs	not serious	serious <sup>d</sup>	not serious	serious <sup>c</sup>	none	88/378 (23.3%)	94/377 (24.9%)	<b>RR 0.93</b> (0.72 to 1.20)	<b>17 fewer per 1,000</b> (from 70 fewer to 50 more)	⊕⊕○○ LOW	CRITICAL
<b>Stroke</b>											
1 RCT	not serious	not serious	not serious	very serious <sup>e</sup>	none	9/338 (2.7%)	11/342 (3.2%)	<b>RR 0.83</b> (0.35 to 1.97)	<b>5 fewer per 1,000</b> (from 21 fewer to 31 more)	⊕⊕○○ LOW	CRITICAL
<b>Myocardial infarction</b>											
1 RCT	not serious	not serious	not serious	very serious <sup>e</sup>	none	0/338 (0.0%)	2/342 (0.6%)	<b>RR 0.20</b> (0.01 to 4.20)	<b>5 fewer per 1,000</b> (from 6 fewer to 19 more)	⊕⊕○○ LOW	CRITICAL
<b>ARDS/TRALI</b>											

## High vs. low ratio FFP:RBC transfusion in massively bleeding patients

1 RCT	not serious	not serious	not serious	serious <sup>c</sup>	none	56/338 (16.6%)	66/342 (19.3%)	<b>RR 0.86</b> (0.62 to 1.19)	<b>27 fewer per 1,000</b> (from 73 fewer to 37 more)	⊕⊕⊕○ MODERATE	CRITICAL
<b>TACO/CHF</b>											
1 RCT	not serious	not serious	not serious	very serious <sup>e</sup>	none	1/338 (0.3%)	0/342 (0.0%)	<b>RR 3.04</b> (0.12 to 74.25)	<b>0 fewer per 1,000</b> (from 0 fewer to 0 fewer)	⊕⊕○○ LOW	IMPORTANT
<b>Infections/Sepsis</b>											
1 RCT	not serious	not serious	not serious	serious <sup>c</sup>	none	155/338 (45.9%)	146/342 (42.7%)	<b>RR 1.07</b> (0.91 to 1.27)	<b>30 more per 1,000</b> (from 38 fewer to 115 more)	⊕⊕⊕○ MODERATE	IMPORTANT
<b>Venous thromboembolism</b>											
1 RCT	not serious	not serious	not serious	serious <sup>c</sup>	none	42/338 (12.4%)	37/342 (10.8%)	<b>RR 1.15</b> (0.76 to 1.74)	<b>16 more per 1,000</b> (from 26 fewer to 80 more)	⊕⊕⊕○ MODERATE	IMPORTANT
<b>Clinical hemostasis -exanguination</b>											
2 RCTs	serious <sup>f</sup>	serious <sup>d</sup>	not serious	not serious	none	320/375 (85.3%)	296/374 (79.1%)	<b>RR 0.70</b> (0.51 to 0.96)	<b>237 fewer per 1,000</b> (from 388 fewer to 32 fewer)	⊕⊕○○ LOW	IMPORTANT

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

### Explanations

- Many studies included patients who died very early, before plasma may have been available, resulting in confounding.
- Though I<sup>2</sup> values are high, indicating statistical heterogeneity, it is of questionable clinical significance as virtually all studies favour high ratio transfusion.
- Wide confidence intervals which do not exclude significant benefit nor harm.
- Significant statistical heterogeneity (I<sup>2</sup> >70%) with studies demonstrating serious inconsistency of unequivocal clinical importance.
- Very wide confidence intervals resulting in very serious imprecision.
- Risk of bias in determining number of patients who had clinical hemostasis



## High vs. low ratio FFP:RBC transfusion in massively bleeding patients

### 2. Massive bleeding in non-trauma patients

Certainty assessment						No of patients		Effect		Certainty	Importance
No of studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	High ratio	Low ratio	Relative (95% CI)	Absolute (95% CI)		
<b>Mortality - Mixed population</b>											
2 obs	not serious <sup>a</sup>	not serious	not serious	serious <sup>b</sup>	none	121/437 (27.7%)	91/316 (28.8%)	<b>RR 0.96</b> (0.76 to 1.21)	<b>12 fewer per 1,000</b> (from 69 fewer to 60 more)	⊕○○○ VERY LOW	CRITICAL
<b>Mortality - Cardiac and vascular surgery</b>											
3 obs	serious <sup>c</sup>	serious <sup>d</sup>	not serious	serious <sup>b</sup>	none	85/471 (18.0%)	149/758 (19.7%)	<b>RR 0.92</b> (0.73 to 1.16)	<b>16 fewer per 1,000</b> (from 53 fewer to 31 more)	⊕○○○ VERY LOW	CRITICAL
<b>Mortality - Obstetric</b>											
2 obs	not serious	not serious	not serious	very serious <sup>e</sup>	none	0/141 (0.0%)	0/152 (0.0%)	not pooled	see comment	-	CRITICAL

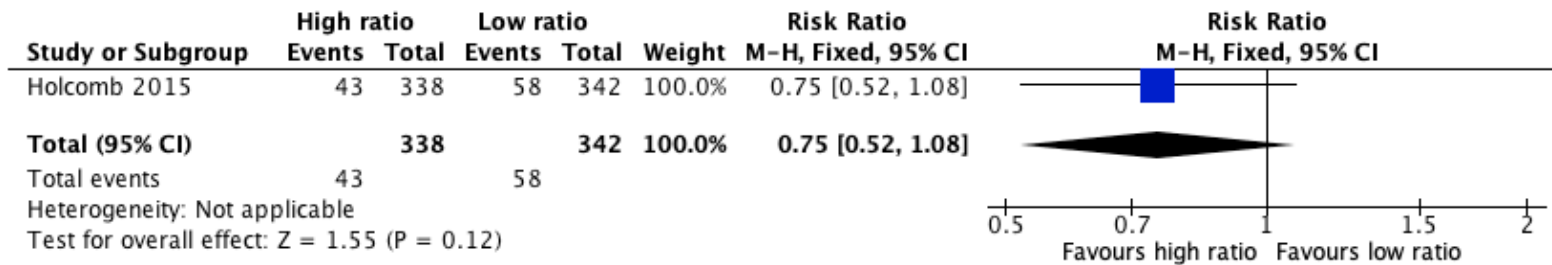
CI: Confidence interval; RR: Risk ratio; MD: Mean difference

#### Explanations

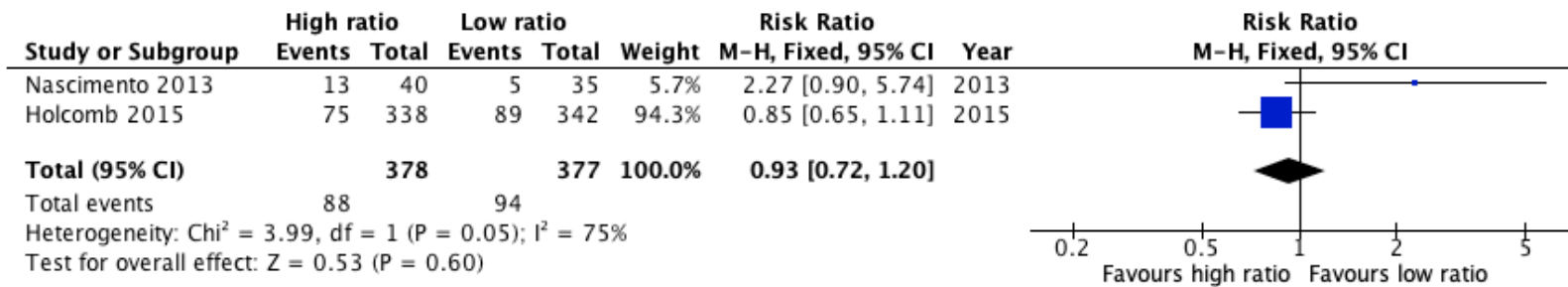
- Largest study (Etchill 2017) excluded patients who died within one hour, possibly reducing the effect of survivorship bias.
- Wide confidence intervals which do not exclude significant benefit nor harm.
- Many studies included patients who died very early, before plasma may have been available, resulting in confounding.
- Significant statistical heterogeneity ( $I^2 > 70\%$ ) with studies demonstrating serious inconsistency of unequivocal clinical importance.
- No events reported resulting in very serious imprecision; overall certainty not rated

## High vs. low ratio FFP:RBC transfusion in massively bleeding patients

### 1. a) Early mortality (24-48 hours), trauma patients, RCTS

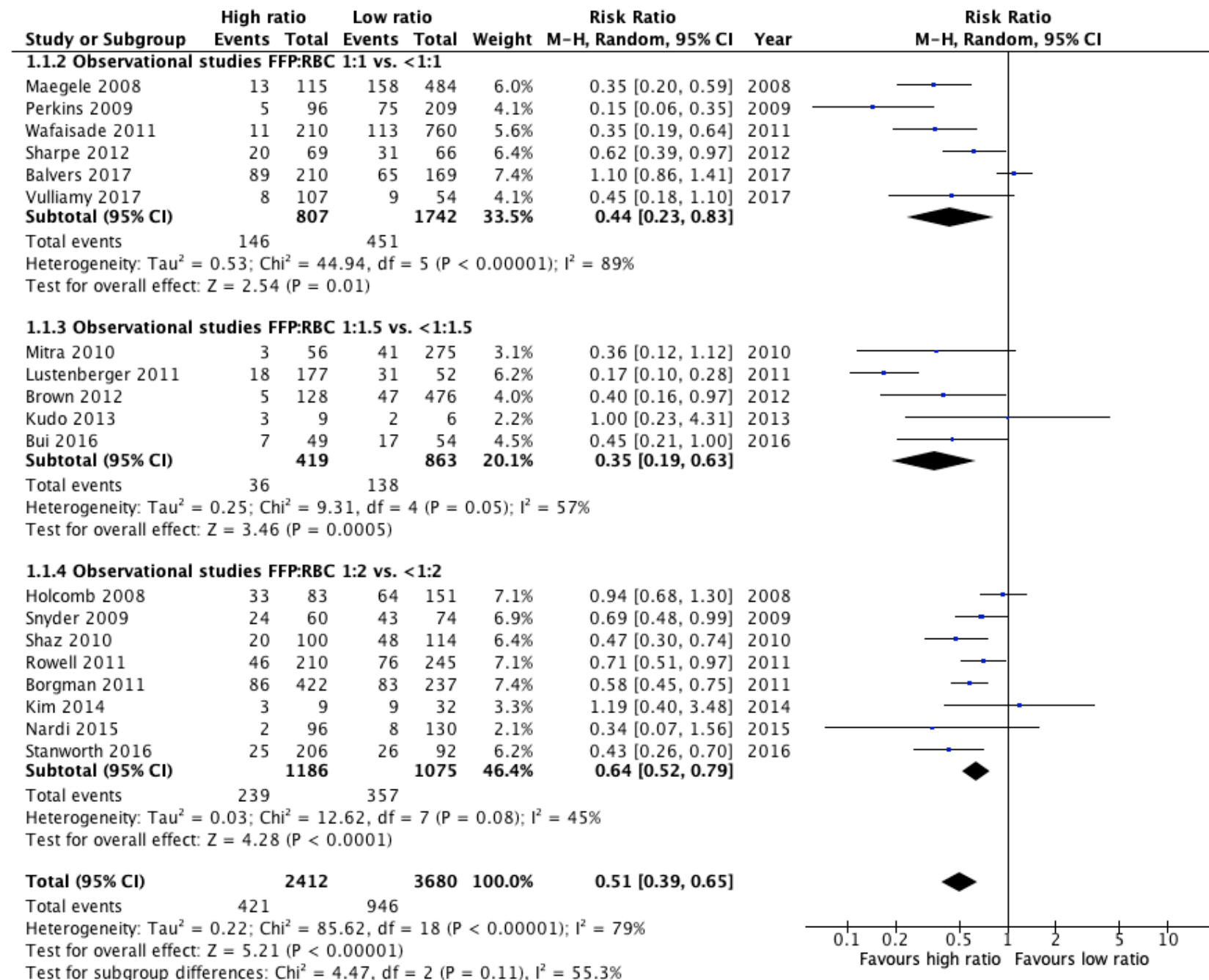


### b) Late mortality (28-30 days, hospital mortality), trauma patients, RCTs



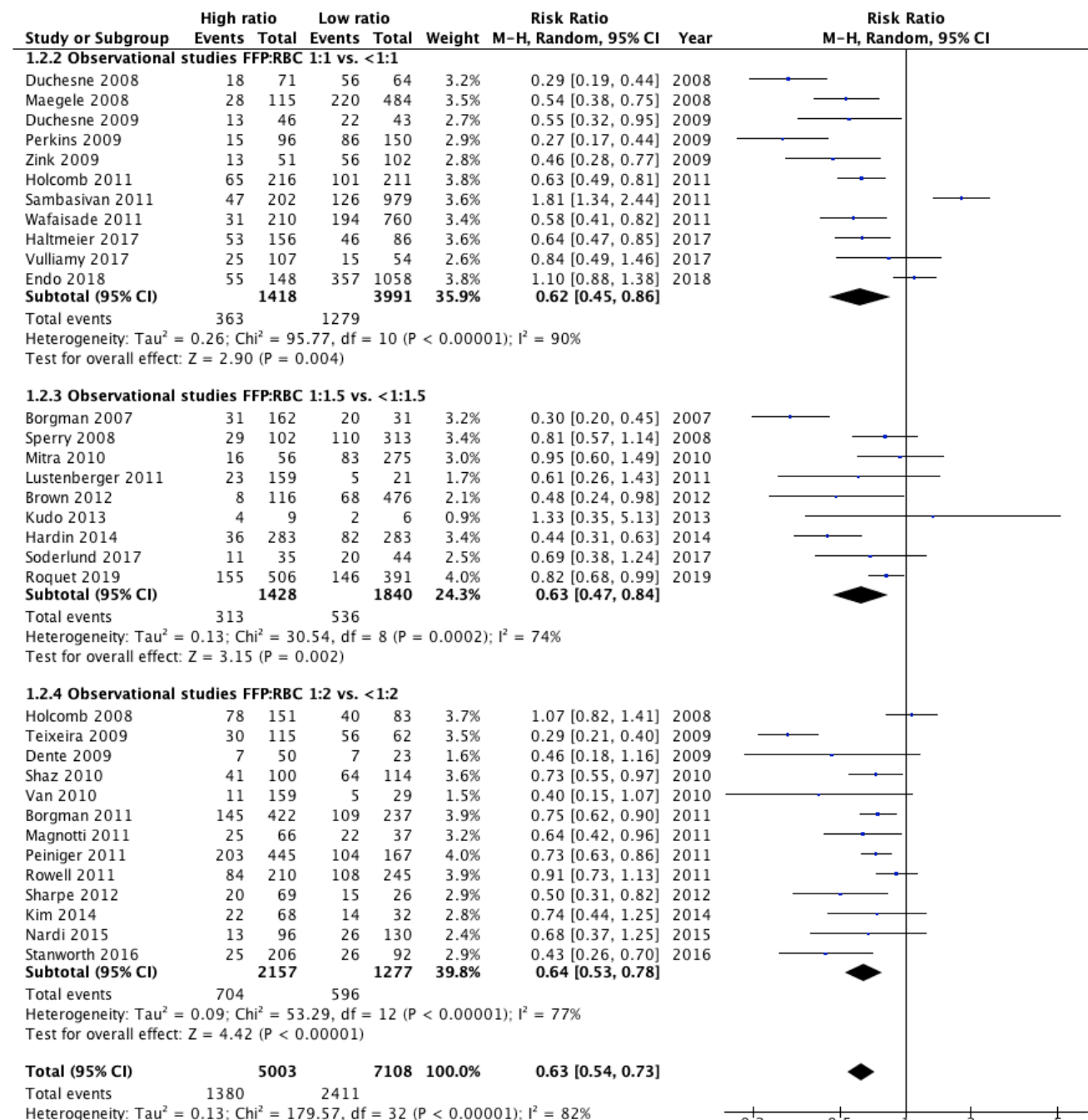
## High vs. low ratio FFP:RBC transfusion in massively bleeding patients

### 2. a) Early mortality (24-48 hours), trauma patients, observational studies



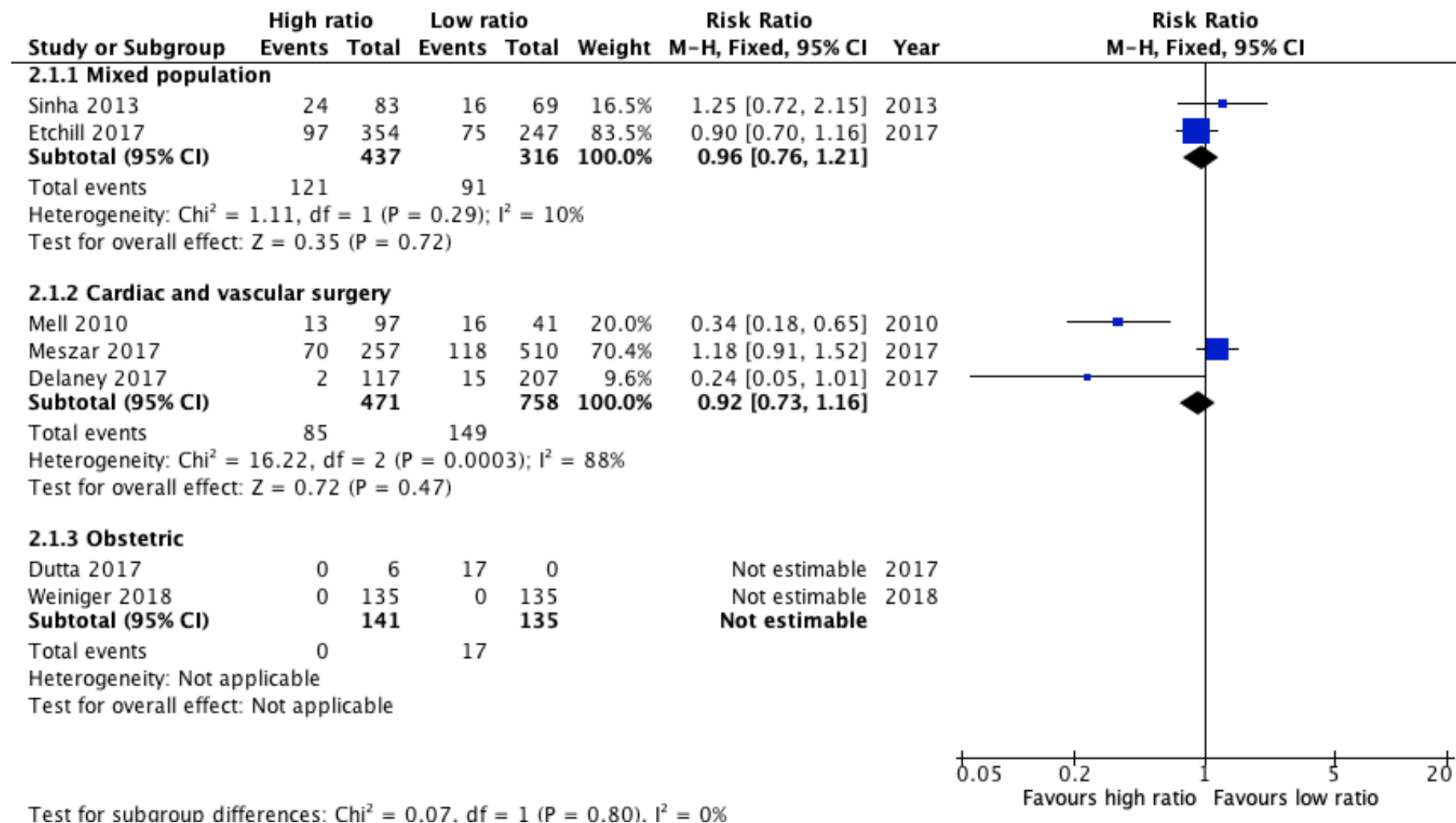
## High vs. low ratio FFP:RBC transfusion in massively bleeding patients

### b) Late mortality (28-30 days, hospital mortality), trauma patients, observational studies



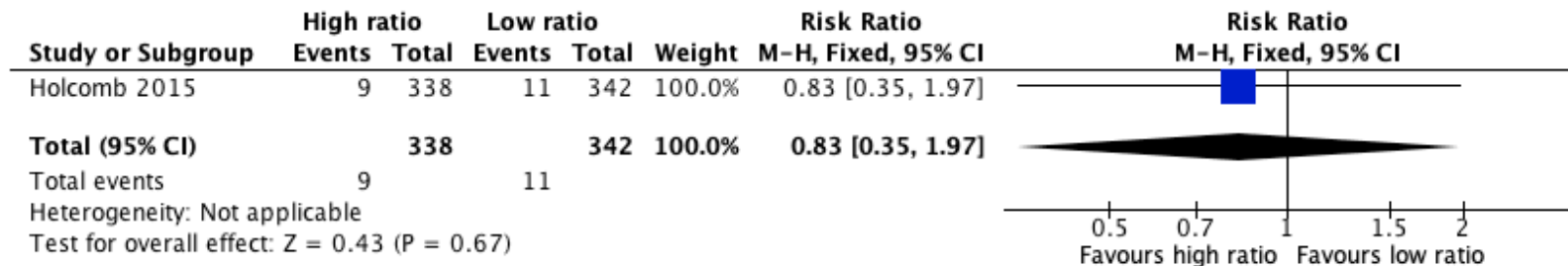
## High vs. low ratio FFP:RBC transfusion in massively bleeding patients

### 3. Late mortality (28-30 days, hospital mortality), non-trauma patients, observational studies

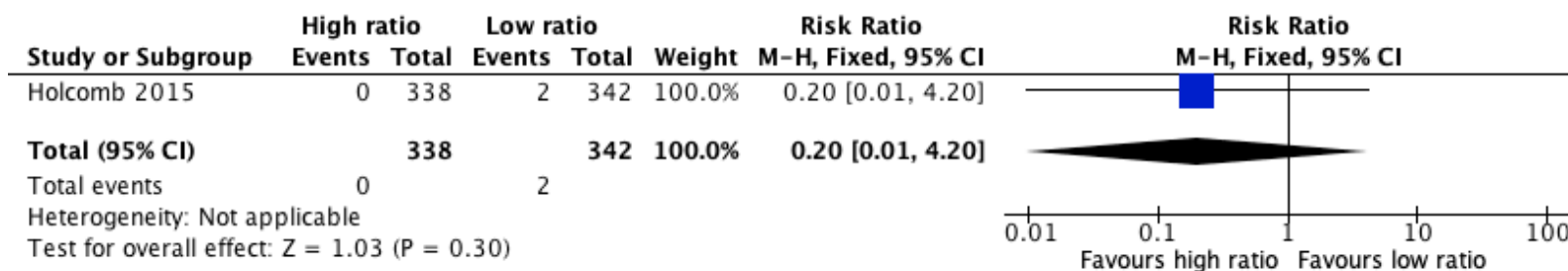


## High vs. low ratio FFP:RBC transfusion in massively bleeding patients

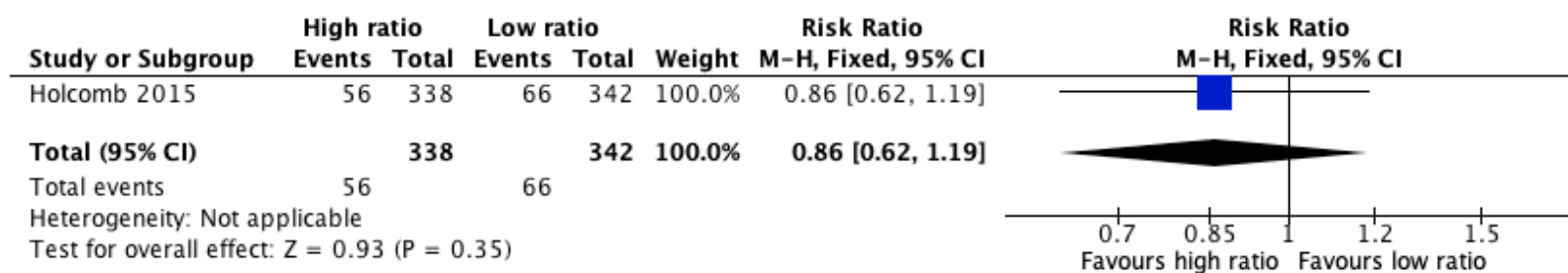
### 3. Stroke, trauma patients, RCTs



### 4. Myocardial infarction, trauma patients, RCTs

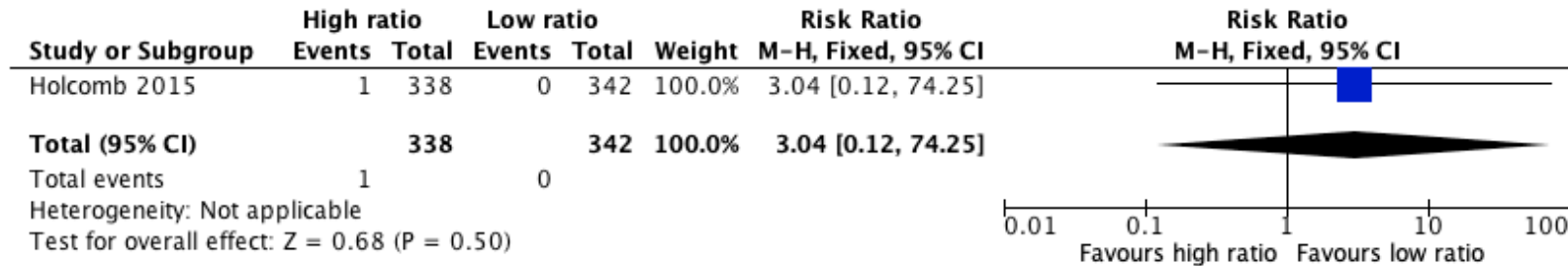


### 5. ARDS/TRALI, trauma patients, RCTs

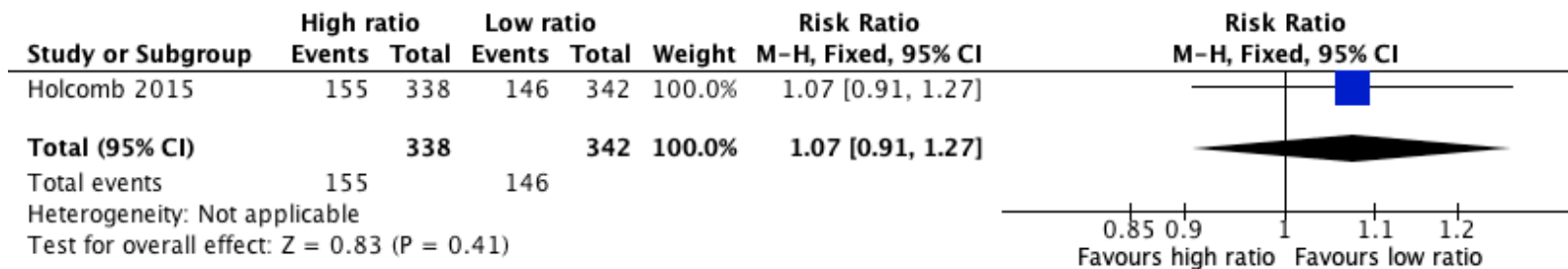


## High vs. low ratio FFP:RBC transfusion in massively bleeding patients

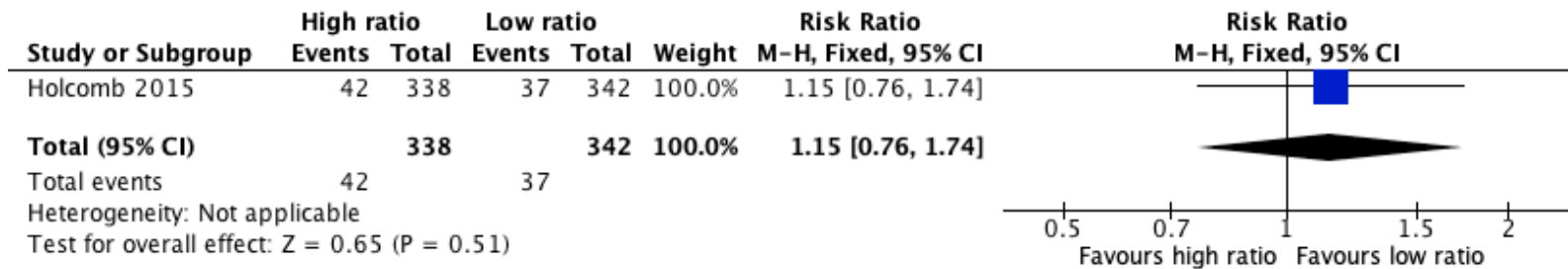
### 6. TACO/CHF, trauma patients, RCTs



### 7. Infections/sepsis, trauma patients, RCTs

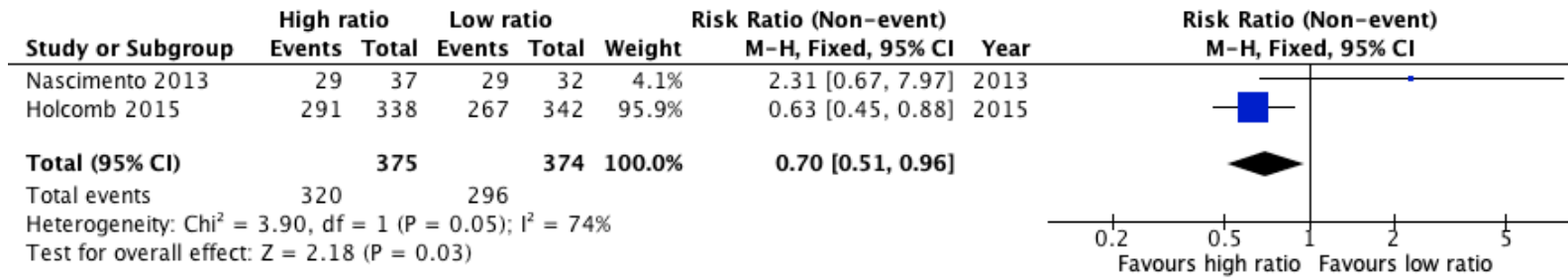


### 8. Venous thromboembolism, trauma patients, RCTs



## High vs. low ratio FFP:RBC transfusion in massively bleeding patients

### 9. Clinical hemostasis, trauma patients, RCTs





**Evidence Summary 2: Cold-stored platelets in massively bleeding, critically ill adults**

## Cold stored platelets in critically ill bleeding patients

Certainty assessment						No of patients		Effect		Certainty	Importance
No of studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Cold platelets	Regular platelets	Relative (95% CI)	Absolute (95% CI)		
<b>Mortality - Cryopreserved platelets</b>											
1 RCT	serious <sup>a</sup>	not serious	not serious	very serious <sup>b</sup>	none	7/25 (28.0%)	4/19 (21.1%)	<b>RR 1.33</b> (0.45 to 3.89)	<b>69 more per 1,000</b> (from 116 fewer to 608 more)	⊕○○○ VERY LOW	CRITICAL
<b>Bleeding - Cold-stored platelets</b>											
1 RCT	serious <sup>a</sup>	not serious	not serious	very serious <sup>b</sup>	none	17	22	-	<b>MD 274 lower</b> (327.99 lower to 220.01 lower)	⊕○○○ VERY LOW	IMPORTANT
<b>Thromboembolic events - Cold-stored platelets</b>											
1 RCT	serious <sup>a</sup>	not serious	not serious	very serious <sup>b</sup>	none	3/17 (17.6%)	7/22 (31.8%)	<b>RR 0.55</b> (0.17 to 1.83)	<b>143 fewer per 1,000</b> (from 264 fewer to 264 more)	⊕○○○ VERY LOW	IMPORTANT
<b>RBCs transfused - Cold-stored platelets</b>											
1 RCT	serious <sup>a</sup>	not serious	not serious	very serious <sup>b</sup>	none	17	22	-	<b>MD 0.5 lower</b> (1.03 lower to 0.03 higher)	⊕○○○ VERY LOW	IMPORTANT
<b>Plasma transfused - Cold-stored platelets</b>											
1 RCT	serious <sup>a</sup>	not serious	not serious	very serious <sup>b</sup>	none	17	22	-	<b>MD 1.8 lower</b> (2.43 lower to 1.17 lower)	⊕○○○ VERY LOW	IMPORTANT
<b>Platelets transfused - Cold-stored platelets</b>											
1 RCT	serious <sup>a</sup>	not serious	not serious	very serious <sup>b</sup>	none	17	22	-	<b>MD 0.2 lower</b> (0.3 lower to 0.1 lower)	⊕○○○ VERY LOW	IMPORTANT

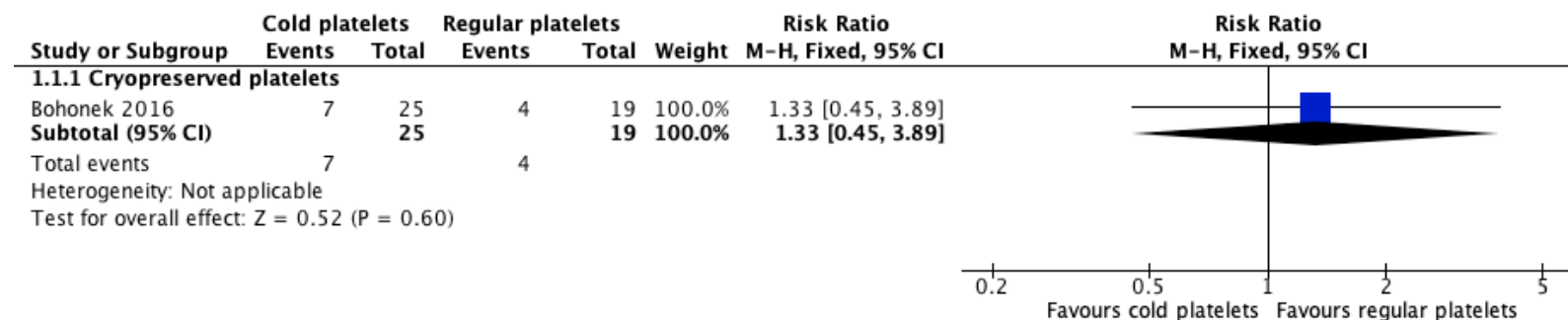
CI: Confidence interval; RR: Risk ratio; MD: Mean difference

### Explanations

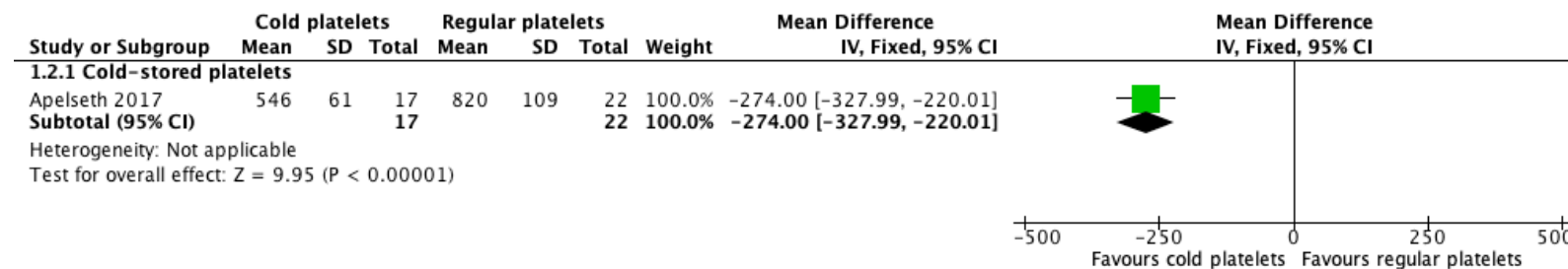
- a. Methods of studies are poorly reported. Due to the absence of clear methods and protocols, we judge the studies to be at high risk of bias, particularly selective reporting.  
b. Very small number of patients included in single study, resulting in very serious imprecision.

## Cold stored platelets in critically ill bleeding patients

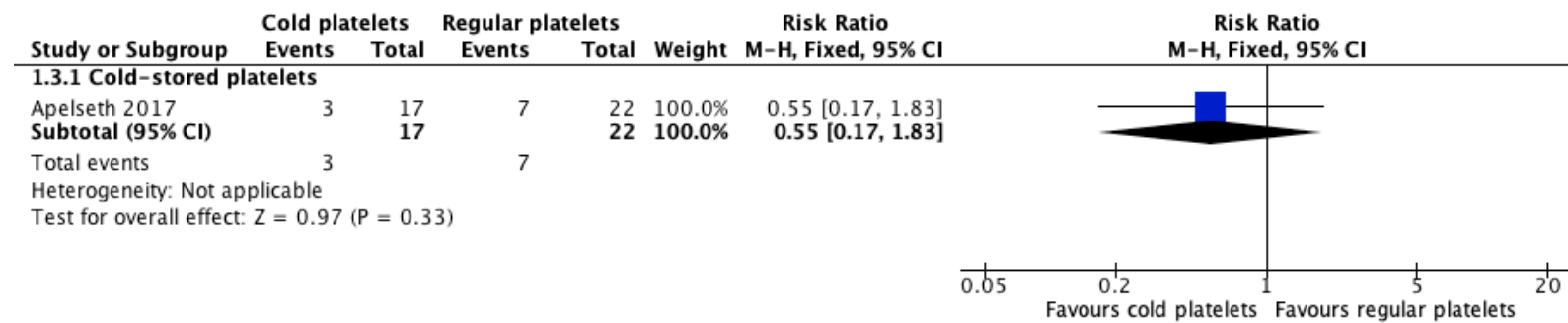
### 1. Mortality - cryopreserved platelets



### 2. Bleeding - cold-stored platelets

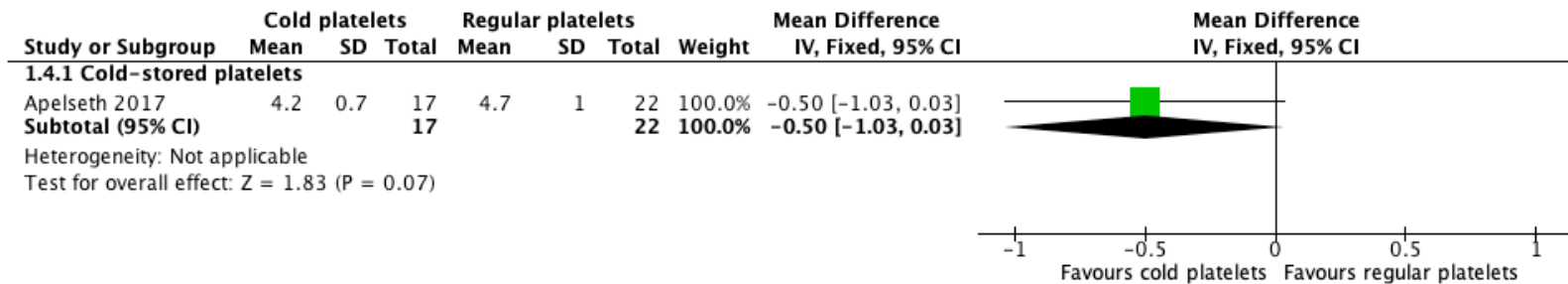


### 3. Thromboembolic events - cold-stored platelets

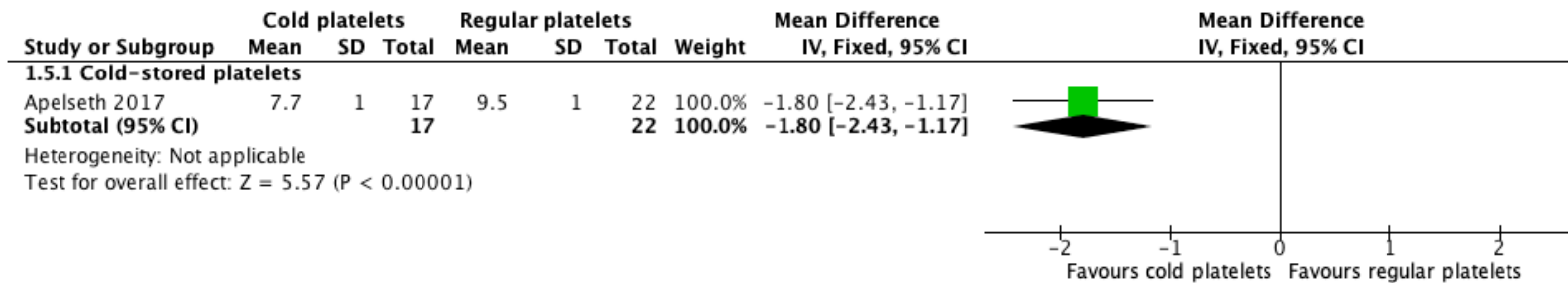


## Cold stored platelets in critically ill bleeding patients

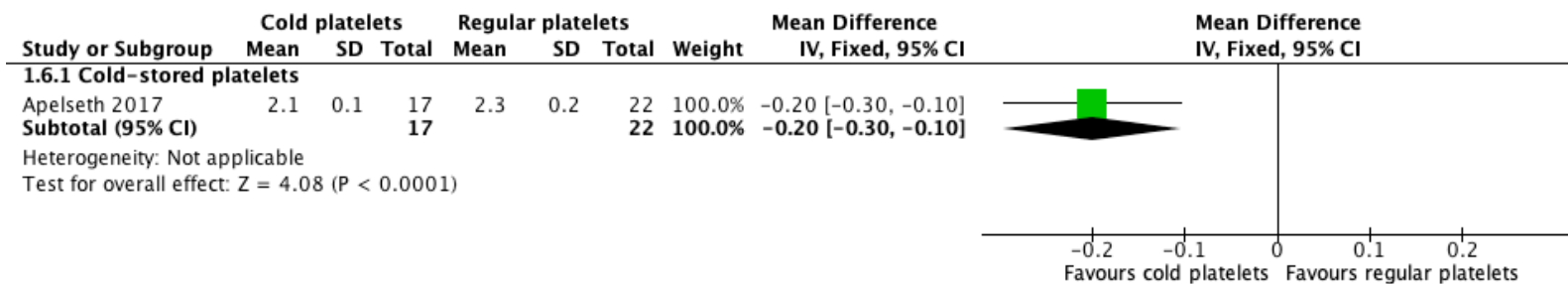
### 4. RBCs transfused - cold-stored platelets



### 5. Plasma transfused - cold-stored platelets



### 6. Platelets transfused - cold-stored platelets



**Evidence Summary 3: Prothrombin complex vs. fresh frozen plasma in massively bleeding, critically ill adults**

## PCC vs. FFP in massively bleeding patients

### Cardiac Surgery

#### ETD Cardiac Surgery

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Massive Transfusion Protocol with Prothrombin	plasma	Relative (95% CI)	Absolute (95% CI)		
<b>Cardiac Surgery- Mortality</b>												
5	observational studies	serious <sup>a</sup>	not serious	not serious	very serious <sup>b</sup>	none <sup>c</sup>	47/539 (8.7%)	44/524 (8.4%)	<b>RR 1.05</b> (0.71 to 1.56)	<b>4 more per 1,000</b> (from 24 fewer to 47 more)	⊕○○○ VERY LOW	CRITICAL
<b>Cardiac Surgery - Stroke</b>												
5	observational studies	serious <sup>a</sup>	serious <sup>d</sup>	not serious	serious <sup>b</sup>	none <sup>c</sup>	27/539 (5.0%)	22/524 (4.2%)	<b>RR 1.20</b> (0.70 to 2.05)	<b>8 more per 1,000</b> (from 13 fewer to 44 more)	⊕○○○ VERY LOW	CRITICAL
<b>Cardiac Surgery- Reoperation</b>												
4	observational studies	serious <sup>a</sup>	not serious	not serious	serious <sup>e</sup>	none <sup>c</sup>	88/512 (17.2%)	151/784 (19.3%)	<b>RR 0.86</b> (0.67 to 1.11)	<b>27 fewer per 1,000</b> (from 64 fewer to 21 more)	⊕○○○ VERY LOW	IMPORTANT
<b>Cardiac Surgery-RRT</b>												
2	observational studies	serious <sup>a</sup>	not serious	not serious	very serious <sup>b</sup>	none <sup>c</sup>	15/270 (5.6%)	7/280 (2.5%)	<b>RR 2.34</b> (0.98 to 5.60)	<b>33 more per 1,000</b> (from 1 fewer to 115 more)	⊕○○○ VERY LOW	IMPORTANT
<b>Cardiac Surgery-RBC transfusion</b>												
4	observational studies	serious <sup>a</sup>	not serious	not serious	not serious	none <sup>c</sup>	381/488 (78.1%)	442/498 (88.8%)	<b>RR 0.88</b> (0.83 to 0.93)	<b>107 fewer per 1,000</b> (from 151 fewer to 62 fewer)	⊕○○○ VERY LOW	IMPORTANT

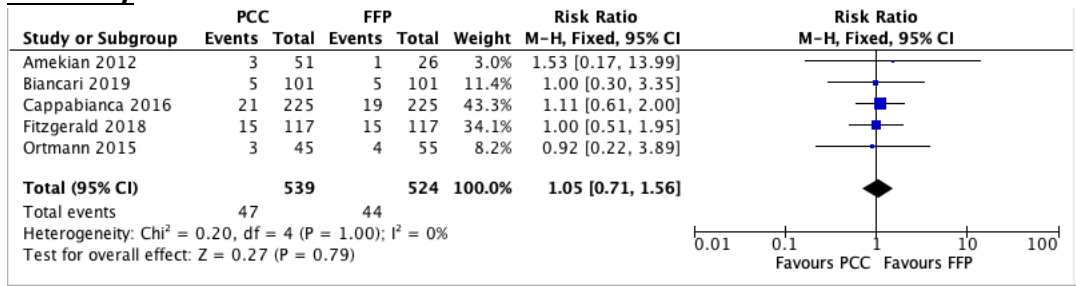
Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Massive Transfusion Protocol with Prothrombin	plasma	Relative (95% CI)	Absolute (95% CI)		
<b>Cardiac Surgery- RBC units transfused</b>												
4	observational studies	serious <sup>a</sup>	serious	not serious	serious <sup>e</sup>	none <sup>c</sup>	422	407	-	MD 1.16 lower (1.59 lower to 0.73 lower)	⊕○○○ VERY LOW	IMPORTANT
<b>Cardiac Surgery- Chest Drain output (24 hours)</b>												
2	observational studies	serious <sup>a</sup>	serious <sup>d</sup>	not serious	very serious <sup>b</sup>	none <sup>c</sup>	276	251	-	MD 72.88 higher (75.87 lower to 221.64 higher)	⊕○○○ VERY LOW	IMPORTANT
<b>Cardiac Surgery- ICU LOS- Hours</b>												
1	observational studies	serious <sup>a</sup>	not serious	not serious	very serious	none <sup>c</sup>	225	225	-	MD 18 lower (43.14 lower to 7.14 higher)	⊕○○○ VERY LOW	IMPORTANT
<b>Cardiac Surgery-Hospital LOS (Days)</b>												
1	observational studies	serious <sup>a</sup>	not serious	not serious	very serious <sup>b</sup>		225	225	-	MD 2.7 lower (4.68 lower to 0.72 lower)	-	IMPORTANT

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

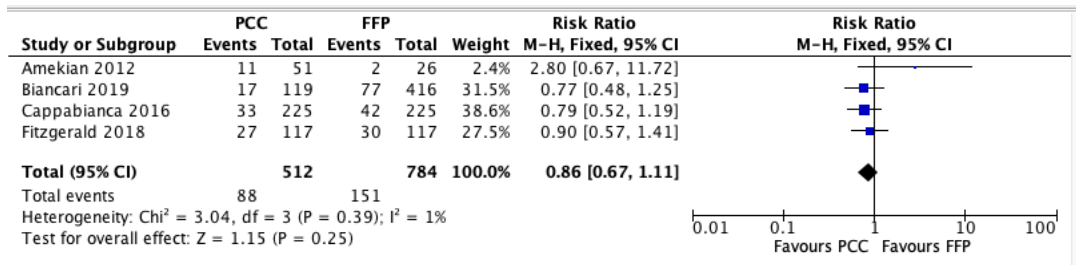
## Explanations

- a. Studies included were at a high risk of bias. The majority of studies were retrospective cohorts.
- b. Rated down for imprecision due to wide confidence intervals and small number of events.
- c. Could not formally assess for publication bias due to small number of studies.
- d. Rated down for significant heterogeneity with point estimates on both sides of the line of no effect.
- e. Rated down for imprecision due to wide confidence intervals.

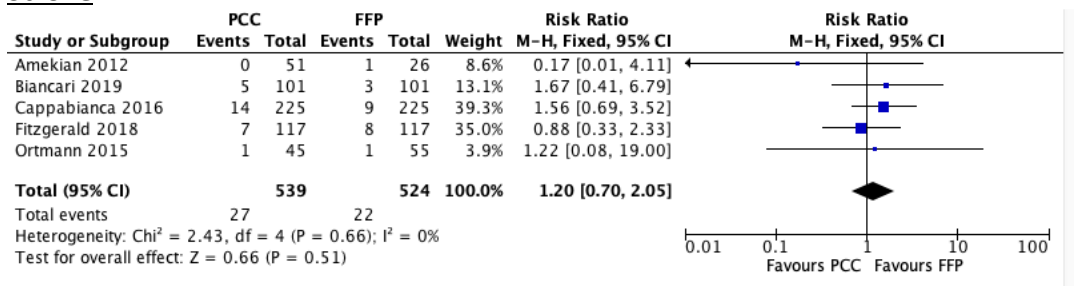
## Mortality



## Reoperation

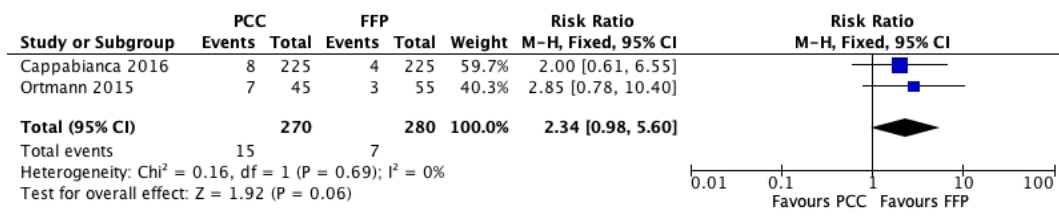


## Stroke

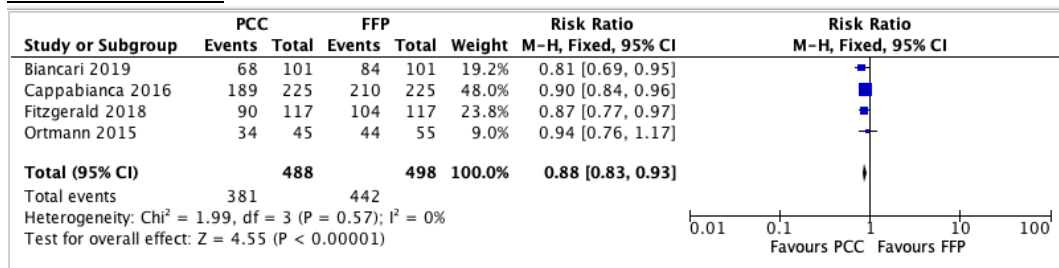


## RRT

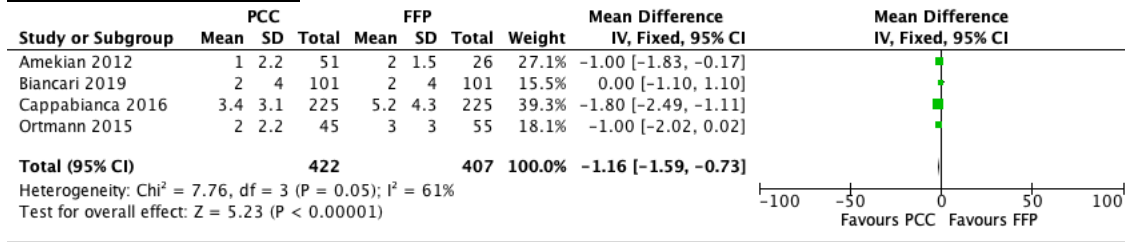




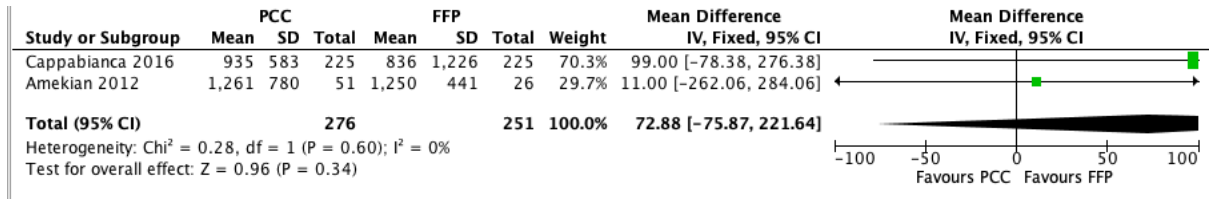
### RBC Transfusion



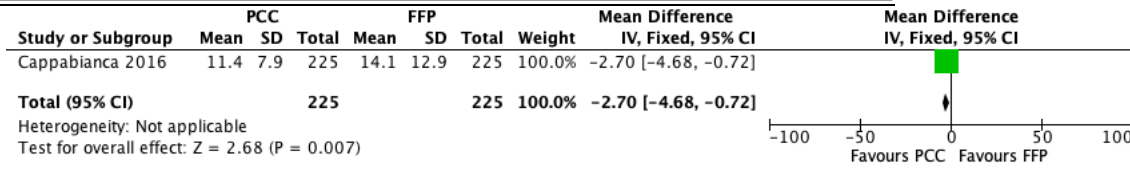
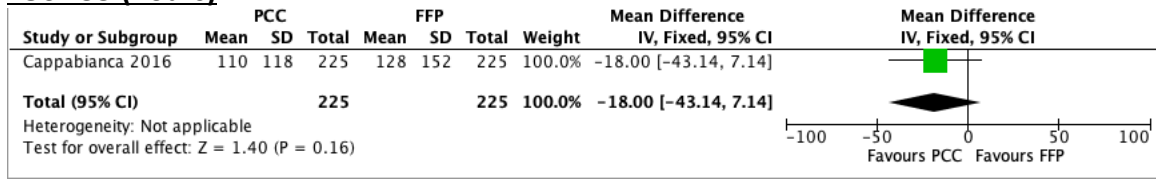
### RBC Transfusion Units



### Chest tube output in 24 hours



### LOS-ICU (hours)



### LOS- Hospital (Days)

## Trauma

### Trauma ETD

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Massive Transfusion Protocol with Prothrombin	plasma	Relative (95% CI)	Absolute (95% CI)		
<b>Trauma- Mortality</b>												
6	observational studies	serious <sup>a</sup>	not serious	not serious	not serious	none <sup>c</sup>	83/462 (18.0%)	241/1175 (20.5%)	<b>RR 0.73</b> (0.58 to 0.92)	<b>55 fewer per 1,000</b> (from 86 fewer to 16 fewer)	⊕○○○ VERY LOW	CRITICAL
<b>Trauma- DVT</b>												
4	observational studies	serious <sup>a</sup>	serious <sup>d</sup>	serious <sup>e</sup>	serious <sup>b</sup>	none <sup>c</sup>	13/364 (3.6%)	31/557 (5.6%)	<b>RR 0.60</b> (0.32 to 1.13)	<b>22 fewer per 1,000</b> (from 38 fewer to 7 more)	⊕○○○ VERY LOW	IMPORTANT
<b>Trauma- Pulmonary Embolism</b>												
2	observational studies	serious <sup>a</sup>	not serious	serious <sup>e</sup>	very serious <sup>b</sup>	none <sup>c</sup>	3/274 (1.1%)	4/314 (1.3%)	<b>RR 0.75</b> (0.17 to 3.31)	<b>3 fewer per 1,000</b> (from 11 fewer to 29 more)	⊕○○○ VERY LOW	IMPORTANT
<b>Trauma- ICU LOS (Mean)</b>												
6	observational studies	serious <sup>a</sup>	not serious	serious <sup>e</sup>	very serious <sup>f</sup>	none <sup>d</sup>	462	1175	-	<b>MD 0.03 lower</b> (0.19 lower to 0.13 higher)	⊕○○○ VERY LOW	IMPORTANT
<b>Trauma-Hospital LOS (Mean)</b>												
6	observational studies	serious <sup>a</sup>	not serious	serious <sup>e</sup>	very serious <sup>f</sup>	none <sup>c</sup>	462	1175	-	<b>MD 2.17 lower</b> (2.82 lower to 1.52 lower)	⊕○○○ VERY LOW	IMPORTANT
<b>Trauma RBC transfusion</b>												

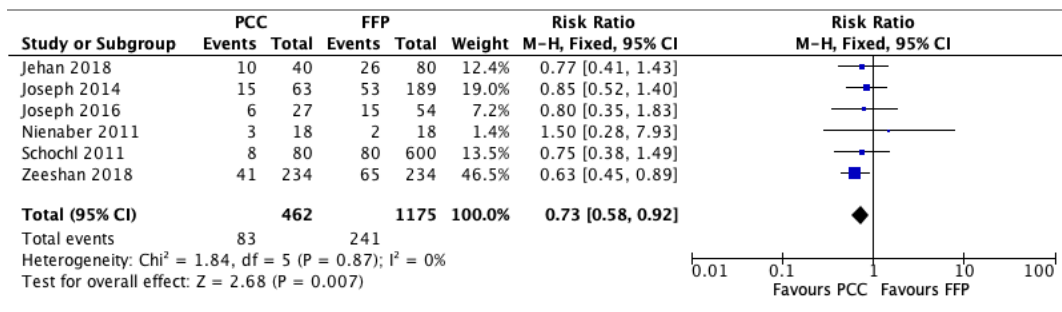
Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Massive Transfusion Protocol with Prothrombin	plasma	Relative (95% CI)	Absolute (95% CI)		
4	observational studies	serious <sup>a</sup>	not serious	serious <sup>e</sup>	serious <sup>g</sup>	none <sup>c</sup>	364	557	-	MD 3.33 lower (3.87 lower to 2.79 lower)	⊕○○○ VERY LOW	IMPORTANT
<b>Trauma-FFP Transfusion Units</b>												
3	observational studies	serious <sup>a</sup>	not serious	serious <sup>e</sup>	serious <sup>g</sup>	none <sup>c</sup>	324	477	-	MD 0.63 lower (0.96 lower to 0.31 lower)	⊕○○○ VERY LOW	IMPORTANT
<b>Trauma-Platelets</b>												
4	observational studies	serious <sup>a</sup>	not serious	serious <sup>e</sup>	very serious <sup>f</sup>	none <sup>c</sup>	364	557	-	MD 0.1 lower (0.44 lower to 0.24 higher)	⊕○○○ VERY LOW	IMPORTANT
<b>Trauma- Sepsis</b>												
1	observational studies	serious <sup>a</sup>	not serious	serious <sup>e</sup>	serious <sup>b</sup>	none <sup>c</sup>	3/18 (16.7%)	6/18 (33.3%)	RR 0.50 (0.15 to 1.70)	167 fewer per 1,000 (from 283 fewer to 233 more)	⊕○○○ VERY LOW	IMPORTANT

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

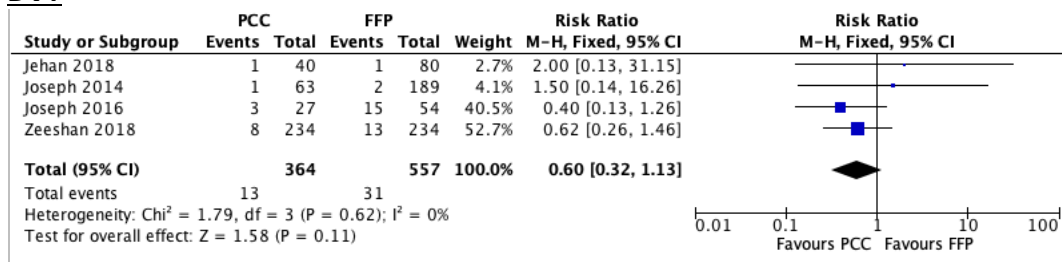
## Explanations

- a. Studies included were at a high risk of bias. The majority of studies were retrospective cohorts.
- b. Rated down for imprecision due to wide confidence intervals and small number of events.
- c. Could not formally assess for publication bias due to small number of studies.
- d. Rated down for significant heterogeneity with point estimates on both sides of the line of no effect.
- e. In some of the studies the intervention group received PCC and FFP, compared to FFP alone.
- f. Rated down for wide confidence intervals, and some studies had to undergo data transformation from median to mean.
- g. Rated down for imprecision as some studies had to undergo data transformation from median to mean.

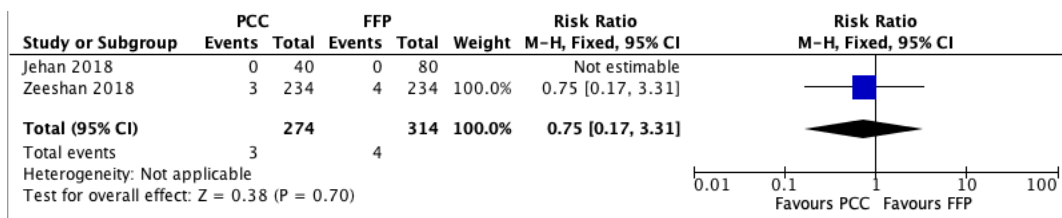
## Mortality



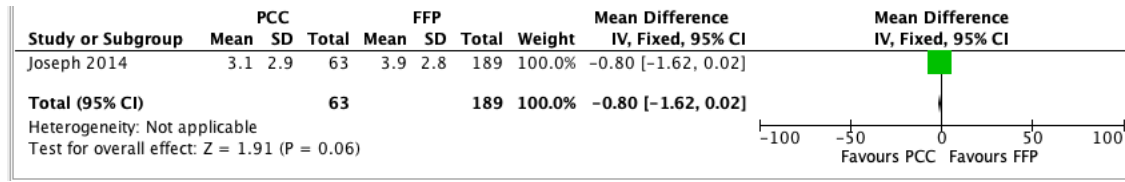
## DVT



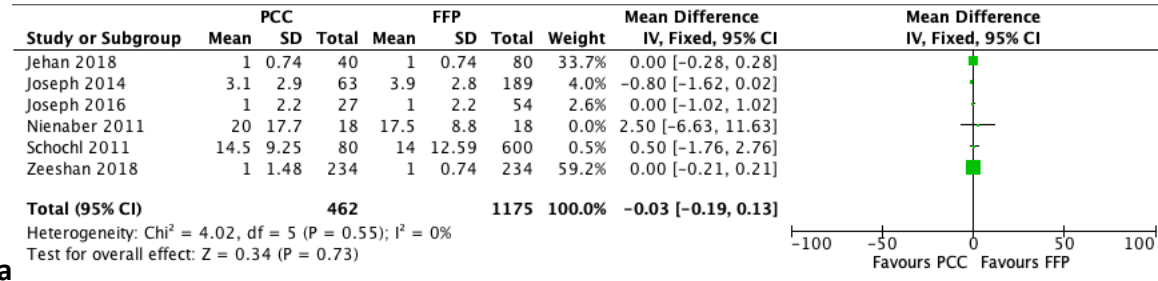
## PE



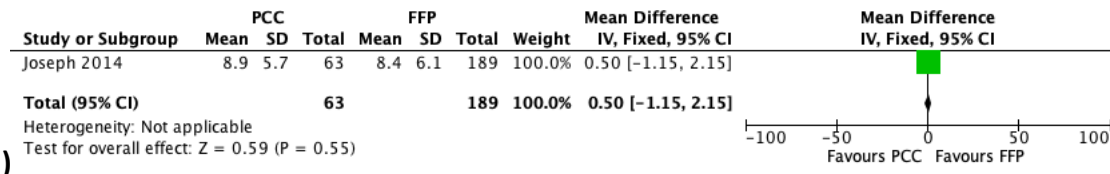
## ICU LOS (Mean)



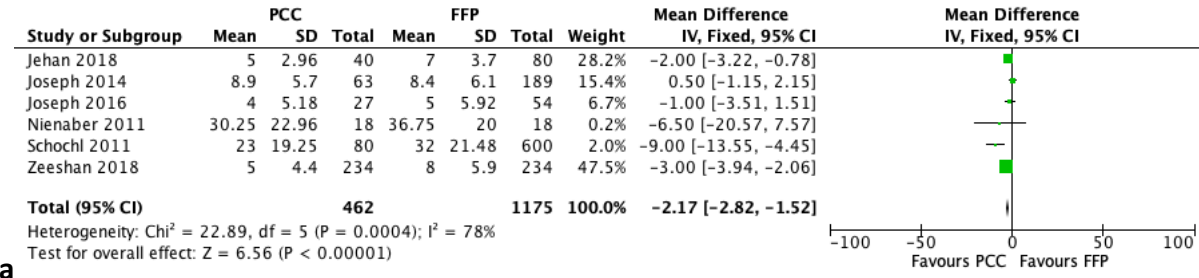
### ICU LOS With all transformed data



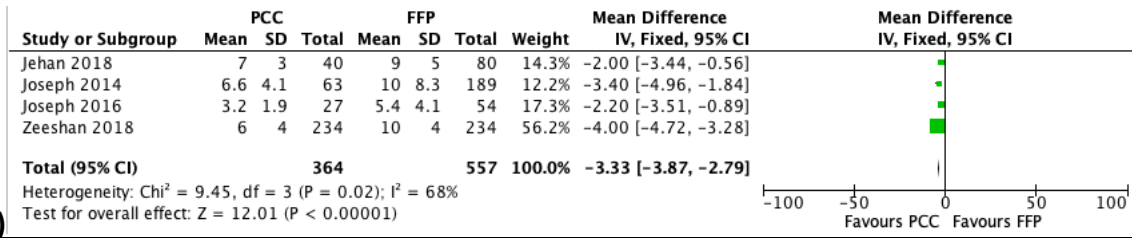
### Hospital LOS (Mean)



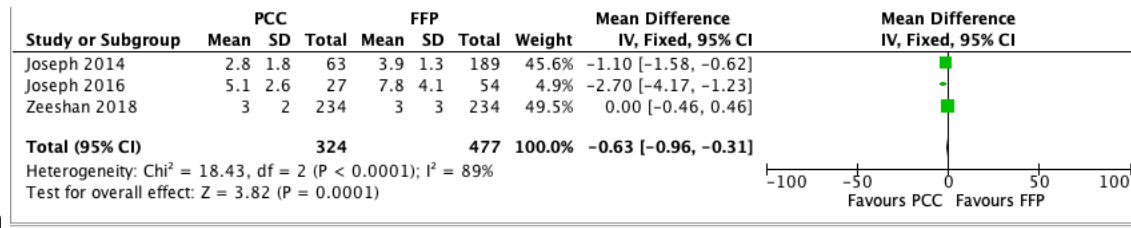
### Hospital LOS with all transformed data



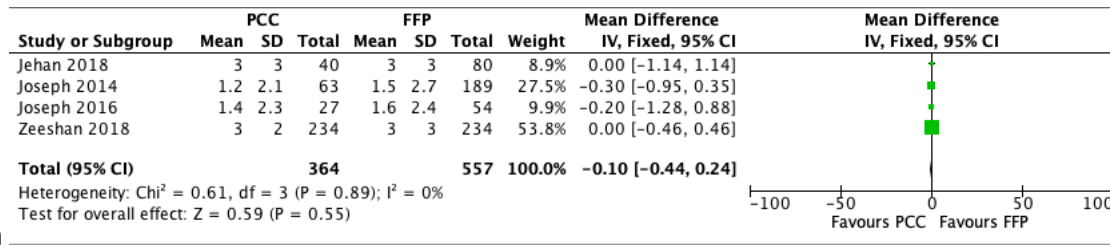
## RBC Transfusion (units)



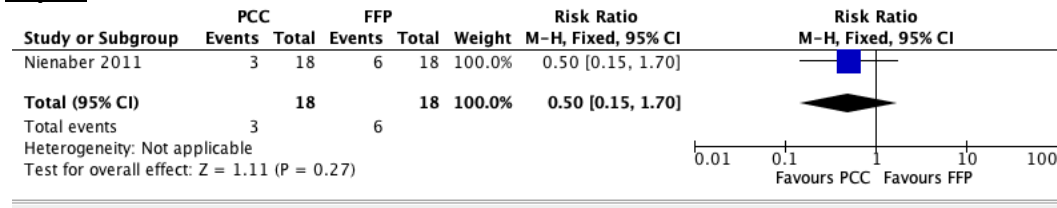
## FFP Transfusion



## Platelet Transfusion



## Sepsis



## GI-Liver Transplant

### Liver Transplant ETD

#### Liver Transplant ETD

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Massive Transfusion Protocol with Prothrombin	plasma	Relative (95% CI)	Absolute (95% CI)		
<b>Liver Transplant-RBC transfusion</b>												
1	observational studies	not serious	not serious	not serious	very serious <sup>a</sup>	none <sup>b</sup>	60	60	-	MD <b>2.03 lower</b> (3.7 lower to 0.36 lower)	⊕○○○○ VERY LOW	IMPORTANT
<b>Liver Transplant-FFP</b>												
1	observational studies	not serious	not serious	not serious	very serious <sup>a</sup>	none <sup>b</sup>	60	60	-	MD <b>3.58 lower</b> (4.73 lower to 2.43 lower)	⊕○○○○ VERY LOW	IMPORTANT
<b>Liver Transplant-Platelet Transfusion</b>												
1	observational studies	not serious	not serious	not serious	very serious <sup>a</sup>	none	60	60	-	MD <b>0.69 higher</b> (1.12 lower to 2.5 higher)	⊕○○○○ VERY LOW	IMPORTANT

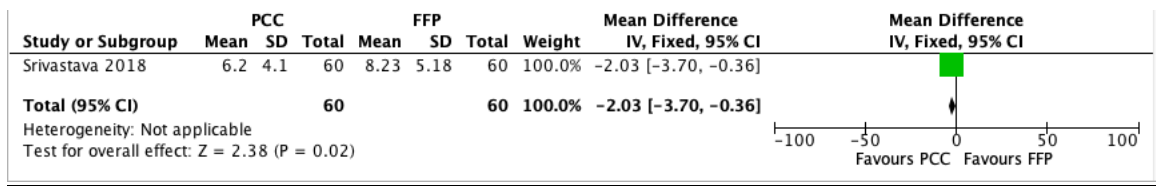
CI: Confidence interval; RR: Risk ratio; MD: Mean difference

### Explanations

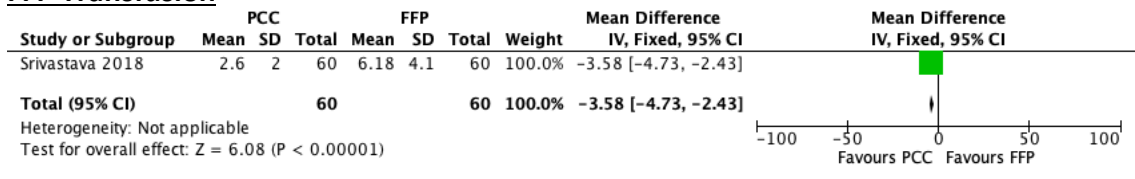
- a. Rated down for imprecision due to wide confidence intervals and small number of events.  
 b. Could not formally assess for publication bias due to small number of studies.

### RBC Transfusion

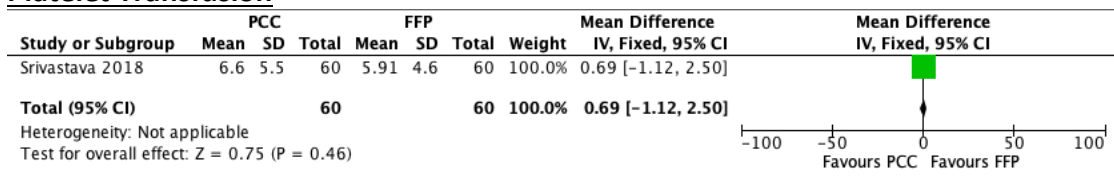




### FFP Transfusion



### Platelet Transfusion



### TBI

TBI ETD

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Massive Transfusion Protocol with Prothrombin	plasma	Relative (95% CI)	Absolute (95% CI)		
<b>TBI- Mortality</b>												
1	observational studies	not serious	not serious	serious <sup>d</sup>	not serious	none <sup>b</sup>	23/74 (31.1%)	68/148 (45.9%)	<b>RR 0.68</b> (0.46 to 0.99)	<b>147 fewer per 1,000</b> (from 248 fewer to 5 fewer)	⊕○○○ VERY LOW	CRITICAL
<b>TBI- VTE</b>												
1	observational studies	serious	not serious	serious <sup>d</sup>	serious <sup>a</sup>	none <sup>b</sup>	3/74 (4.1%)	5/148 (3.4%)	<b>RR 1.20</b> (0.29 to 4.89)	<b>7 more per 1,000</b> (from 24 fewer to 131 more)	⊕○○○ VERY LOW	IMPORTANT
<b>TBI-Progression of ICH</b>												
1	observational studies	not serious	not serious	serious <sup>d</sup>	not serious	none <sup>b</sup>	18/74 (24.3%)	65/148 (43.9%)	<b>RR 0.55</b> (0.36 to 0.86)	<b>198 fewer per 1,000</b> (from 281 fewer to 61 fewer)	⊕○○○ VERY LOW	IMPORTANT
<b>TBI-ICU LOS</b>												
1	observational studies	not serious	not serious	serious	very serious <sup>d</sup>	none <sup>b</sup>	74	148	-	<b>MD 0.6 lower</b> (1.36 lower to 0.16 higher)	⊕○○○ VERY LOW	IMPORTANT
<b>TBI-Hospital LOS</b>												
1	observational studies	not serious	not serious	serious <sup>d</sup>	serious <sup>c</sup>	none <sup>b</sup>	74	148	-	<b>MD 1.1 lower</b> (2.88 lower to 0.68 higher)	⊕○○○ VERY LOW	IMPORTANT
<b>TBI-RBC Transfusion</b>												
1	observational studies	not serious	not serious	serious <sup>d</sup>	serious <sup>c</sup>	none <sup>b</sup>	74	148	-	<b>MD 0.6 lower</b> (1.25 lower to 0.05 higher)	⊕○○○ VERY LOW	IMPORTANT
<b>TBI-FFP Transfusion</b>												

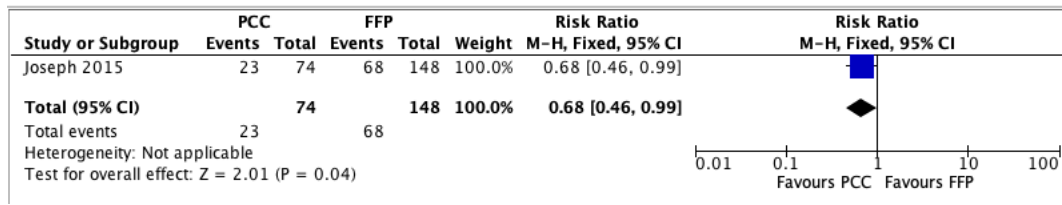
Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Massive Transfusion Protocol with Prothrombin	plasma	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	not serious	not serious	serious <sup>a</sup>	serious <sup>c</sup>		74	148	-	MD 0.9 lower (1.58 lower to 0.22 lower)	-	IMPORTANT
<b>TBI-Platelet transfusion</b>												
1	observational studies	not serious	not serious	serious <sup>a</sup>	not serious	none <sup>b</sup>	74	148	-	MD 0.2 higher (0.29 lower to 0.69 higher)	⊕○○○ VERY LOW	IMPORTANT

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

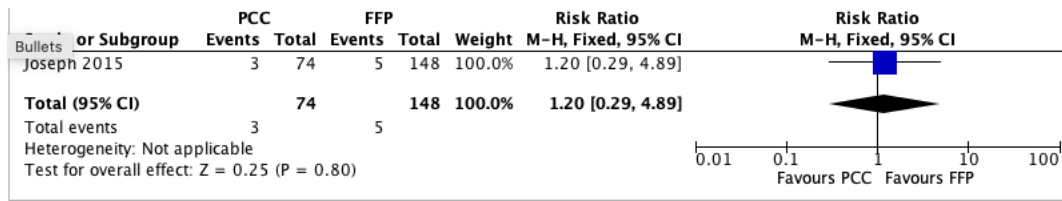
## Explanations

- a. Rated down for imprecision due to wide confidence intervals and small number of events.
- b. Could not formally assess for publication bias due to small number of studies
- c. Rated down for imprecision due to wide confidence intervals.
- d. The study intervention group received PCC and FFP, compared to FFP alone.

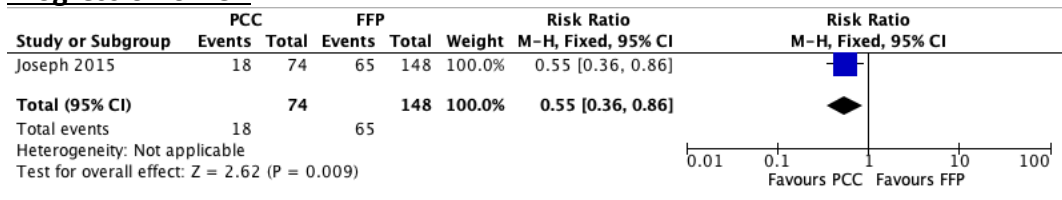
## Mortality



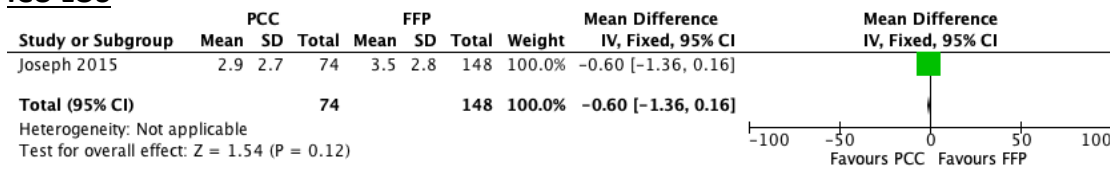
## VTE



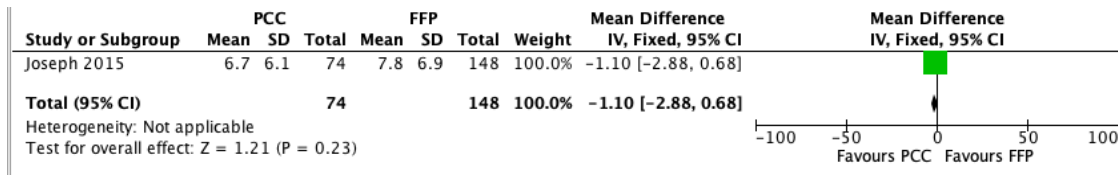
## Progression of ICH



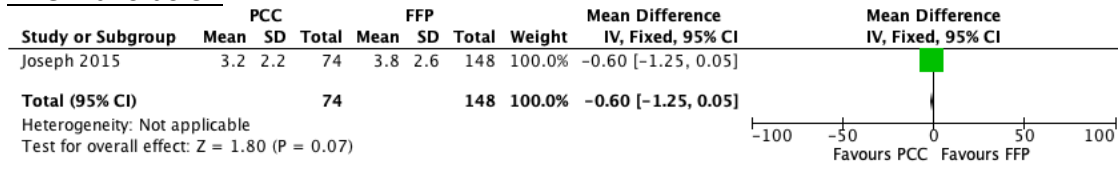
## ICU LOS



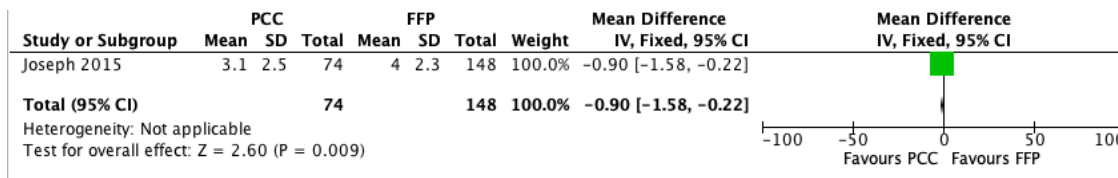
## Hospital LOS



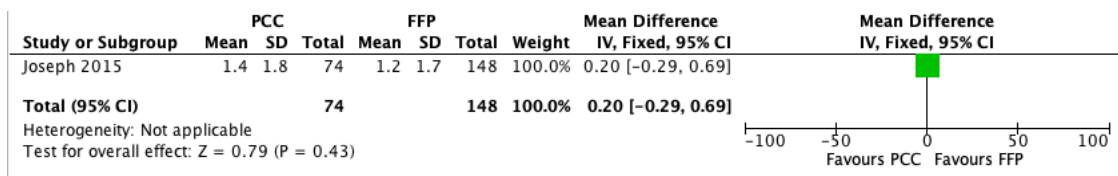
### RBC Transfusion



### FFP Transfusion



### Platelet Transfusion



**Evidence Summary 4: Fibrinogen replacement in massively bleeding, critically ill adults**

## Early/empiric fibrinogen in massively bleeding patients

### 1. Trauma - Randomized controlled trials

Certainty assessment						No of patients		Effect		Certainty	Importance
No of studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Fibrinogen	Control	Relative (95% CI)	Absolute (95% CI)		
<b>All-cause mortality - Trauma (RCT)</b>											
5 RCTs	not serious	serious <sup>a</sup>	not serious	serious <sup>b</sup>	none	20/139 (14.4%)	23/149 (15.4%)	RR 1.02 (0.33 to 3.11)	3 more per 1,000 (from 103 fewer to 326 more)	⊕⊕○○ LOW	CRITICAL
<b>Death due to hemorrhage - Trauma (RCT)</b>											
3 RCTs	not serious	not serious	not serious	very serious <sup>d</sup>	none	5/65 (7.7%)	7/69 (10.1%)	RR 0.77 (0.27 to 2.18)	23 fewer per 1,000 (from 74 fewer to 120 more)	⊕⊕○○ LOW	CRITICAL
<b>Myocardial infarction - Trauma (RCT)</b>											
3 RCTs	not serious	not serious	not serious	very serious <sup>c</sup>	none	0/65 (0.0%)	0/69 (0.0%)	not pooled	see comment	⊕⊕○○ LOW	CRITICAL
<b>ARDS - Trauma (RCT)</b>											
2 RCTs	not serious	not serious	not serious	very serious <sup>d</sup>	none	0/41 (0.0%)	3/45 (6.7%)	RR 0.27 (0.03 to 2.37)	49 fewer per 1,000 (from 65 fewer to 91 more)	⊕⊕○○ LOW	CRITICAL
<b>Renal failure - Trauma (RCT)</b>											
2 RCTs	not serious	not serious	not serious	very serious <sup>d</sup>	none	8/65 (12.3%)	9/74 (12.2%)	RR 1.01 (0.41 to 2.47)	1 more per 1,000 (from 72 fewer to 179 more)	⊕⊕○○ LOW	CRITICAL
<b>Sepsis - Trauma (RCT)</b>											
5 RCTs	not serious	not serious	not serious	serious <sup>b</sup>	none	26/139 (18.7%)	28/149 (18.8%)	RR 1.00 (0.62 to 1.60)	0 fewer per 1,000 (from 71 fewer to 113 more)	⊕⊕⊕○ MODERATE	IMPORTANT
<b>ICU length of stay - Trauma (RCT)</b>											
2 RCTs	not serious	not serious <sup>e</sup>	not serious	serious <sup>f</sup>	none	64	71	-	MD 4.83 lower (8.12 lower to 1.55 lower)	⊕⊕⊕○ MODERATE	IMPORTANT
<b>Hospital length of stay - Trauma (RCT)</b>											

## Early/empiric fibrinogen in massively bleeding patients

3 RCTs	not serious	not serious	not serious	serious <sup>b</sup>	none	94	101	-	MD <b>0.87 lower</b> (3.05 lower to 1.31 higher)	⊕⊕⊕○ MODERATE	IMPORTANT
<b>RBCs transfused - Trauma (RCT)</b>											
6 RCTs	not serious	serious <sup>e</sup>	not serious	serious <sup>b</sup>	none	167	174	-	MD <b>0.68 lower</b> (1.95 lower to 0.59 higher)	⊕⊕○○ LOW	IMPORTANT
<b>Plasma transfused - Trauma (RCT)</b>											
4 RCTs	not serious	very serious <sup>b</sup>	not serious	serious <sup>b</sup>	none	93	94	-	MD <b>0.36 higher</b> (2.21 lower to 2.92 higher)	⊕○○○ VERY LOW	IMPORTANT
<b>Platelets transfused - Trauma (RCT)</b>											
4 RCTs	not serious	serious <sup>e</sup>	not serious	not serious	none	109	119	-	MD <b>0.57 higher</b> (0.31 higher to 0.83 higher)	⊕⊕⊕○ MODERATE	IMPORTANT
<b>Proportion receiving RBCs - Trauma (RCT)</b>											
1 RCT	not serious	not serious	not serious	very serious <sup>d</sup>	none	13/28 (46.4%)	11/25 (44.0%)	RR <b>1.06</b> (0.58 to 1.91)	<b>26 more per 1,000</b> (from 185 fewer to 400 more)	⊕⊕○○ LOW	IMPORTANT
<b>Proportion receiving plasma - Trauma (RCT)</b>											
1 RCT	not serious	not serious	not serious	very serious <sup>d</sup>	none	13/28 (46.4%)	11/25 (44.0%)	RR <b>1.06</b> (0.58 to 1.91)	<b>26 more per 1,000</b> (from 185 fewer to 400 more)	⊕⊕○○ LOW	IMPORTANT
<b>Proportion receiving platelets - Trauma (RCT)</b>											
1 RCT	not serious	not serious	not serious	very serious <sup>d</sup>	none	0/28 (0.0%)	3/25 (12.0%)	RR <b>0.13</b> (0.01 to 2.36)	<b>104 fewer per 1,000</b> (from 119 fewer to 163 more)	⊕⊕○○ LOW	IMPORTANT

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

### Explanations

- Significant heterogeneity with point estimates on both sides of the line of no effect.
- Wide confidence intervals, which do not exclude significant harm or benefit.
- The absence of any deaths means we are unable to estimate the effect for this outcome.
- Very small number of events resulting in very serious imprecision.
- Significant statistical heterogeneity between the included studies not easily explained by study characteristics.
- Statistically significant reduction in length of stay, though small number of patients.



## Early/empiric fibrinogen in massively bleeding patients

### 2. Trauma- observational studies

Certainty assessment						№ of patients		Effect		Certainty	Importance
№ of studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Fibrinogen	Control	Relative (95% CI)	Absolute (95% CI)		
<b>All-cause mortality - Trauma (observational)</b>											
5 Observational Studies	not serious	not serious	not serious	serious <sup>b</sup>	none	391/1246 (31.4%)	237/1312 (18.1%)	<b>RR 1.11</b> (0.87 to 1.42)	<b>20 more per 1,000</b> (from 23 fewer to 76 more)	⊕○○○ VERY LOW	CRITICAL
<b>Death due to hemorrhage - Trauma (Obs)</b>											
1 Observational study	serious <sup>c</sup>	not serious	not serious	serious <sup>b</sup>	none	90/758 (11.9%)	28/269 (10.4%)	<b>RR 1.14</b> (0.76 to 1.70)	<b>15 more per 1,000</b> (from 25 fewer to 73 more)	⊕○○○ VERY LOW	CRITICAL
<b>Sepsis - Trauma (obs)</b>											
2 Observational studies	not serious	not serious	not serious	serious <sup>b</sup>	none	64/312 (20.5%)	58/312 (18.6%)	<b>RR 1.10</b> (0.80 to 1.52)	<b>19 more per 1,000</b> (from 37 fewer to 97 more)	⊕○○○ VERY LOW	IMPORTANT
<b>Surgical intervention - Trauma (obs)</b>											
1 Observational study	serious <sup>c</sup>	not serious	not serious	serious <sup>b</sup>	none	592/758 (78.1%)	195/269 (72.6%)	<b>RR 1.08</b> (0.99 to 1.17)	<b>58 more per 1,000</b> (from 7 fewer to 123 more)	⊕○○○ VERY LOW	IMPORTANT
<b>ICU length of stay - Trauma (Obs)</b>											
4 Observational studies	serious <sup>c</sup>	not serious	not serious	not serious	none	1150	1182	-	<b>MD 1.23 higher</b> (0.02 higher to 2.43 higher)	⊕○○○ VERY LOW	IMPORTANT
<b>Hospital length of stay - Trauma (Obs)</b>											
4 Observational studies	not serious	serious <sup>d</sup>	not serious	not serious	none	1150	1182	-	<b>MD 2.69 lower</b> (5.27 lower to 0.1 lower)	⊕○○○ VERY LOW	IMPORTANT
<b>RBCs transfused - Trauma (obs)</b>											
4 Observational studies	not serious	serious <sup>d</sup>	not serious	not serious	none	1166	711	-	<b>MD 1.16 lower</b> (4.16 lower to 1.85 higher)	⊕○○○ VERY LOW	IMPORTANT

## Early/empiric fibrinogen in massively bleeding patients

Plasma transfused - Trauma (obs)											
4 Observational studies	not serious	very serious <sup>d</sup>	not serious	not serious	none	959	711	-	MD <b>0.12 lower</b> (5.16 lower to 4.93 higher)	⊕○○○ VERY LOW	IMPORTANT
Platelets transfused - Trauma (obs)											
4 Observational studies	not serious	serious <sup>a</sup>	not serious	not serious	none	1166	720	-	MD <b>0.78 higher</b> (0.66 higher to 0.9 higher)	⊕○○○ VERY LOW	IMPORTANT
Proportion receiving RBCs - Trauma (Obs)											
1 Observational study	not serious	not serious	not serious	not serious	none	57/80 (71.3%)	583/601 (97.0%)	RR <b>0.73</b> (0.64 to 0.84)	<b>262 fewer per 1,000</b> (from 349 fewer to 155 fewer)	⊕⊕○○ LOW	IMPORTANT
Proportion receiving platelets - Trauma (obs)											
1 Observational study	not serious	not serious	not serious	not serious	none	7/80 (8.8%)	163/371 (43.9%)	RR <b>0.20</b> (0.10 to 0.41)	<b>351 fewer per 1,000</b> (from 395 fewer to 259 fewer)	⊕⊕○○ LOW	IMPORTANT

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

### Explanations

- Significant heterogeneity with point estimates on both sides of the line of no effect.
- Wide confidence intervals, which do not exclude significant harm or benefit.
- Significant differences in baseline mortality risk between groups despite propensity-matching in Hamada 2020, which is the most-heavily weighted study.
- Significant statistical heterogeneity between the included studies not easily explained by study characteristics.

## Early/empiric fibrinogen in massively bleeding patients

### 3. Obstetric hemorrhage- RCTs

Certainty assessment						No of patients		Effect		Certainty	Importance
No of studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Fibrinogen	Control	Relative (95% CI)	Absolute (95% CI)		
<b>All-cause mortality - Obstetric (RCT)</b>											
1 RCT	not serious	not serious	not serious	very serious <sup>b</sup>	none	0/123 (0.0%)	0/121 (0.0%)	not estimable		⊕⊕○○ LOW	CRITICAL
<b>Bleeding - Obstetric (RCT)</b>											
1 RCT	not serious	not serious	not serious	serious <sup>a</sup>	none	29	28	-	MD 45 lower (110.38 lower to 20.38 higher)	⊕⊕⊕○ MODERATE	IMPORTANT
<b>Surgical intervention - Obstetric bleeding (RCT)</b>											
1 RCT	not serious	not serious	not serious	very serious <sup>c</sup>	none	4/29 (13.8%)	5/28 (17.9%)	RR 0.77 (0.23 to 2.58)	41 fewer per 1,000 (from 138 fewer to 282 more)	⊕⊕○○ LOW	IMPORTANT
<b>Hospital length of stay - Obstetrical bleeding (RCT)</b>											
1 RCT	not serious	not serious	not serious	serious <sup>a</sup>	none	29	28	-	MD 1.61 lower (3.27 lower to 0.05 higher)	⊕⊕⊕○ MODERATE	IMPORTANT
<b>Proportion receiving RBCs - Obstetric bleeding (RCT)</b>											
1 RCT	not serious	not serious	not serious	very serious <sup>c</sup>	none	15/29 (51.7%)	14/28 (50.0%)	RR 1.03 (0.62 to 1.72)	15 more per 1,000 (from 190 fewer to 360 more)	⊕⊕○○ LOW	IMPORTANT
<b>Proportion receiving plasma - Obstetric bleeding (RCT)</b>											
1 RCT	not serious	not serious	not serious	very serious <sup>c</sup>	none	6/29 (20.7%)	8/28 (28.6%)	RR 0.72 (0.29 to 1.82)	80 fewer per 1,000 (from 203 fewer to 234 more)	⊕⊕○○ LOW	IMPORTANT
<b>Proportion receiving platelets - Obstetric bleeding (RCT)</b>											
1 RCT	not serious	not serious	not serious	very serious <sup>c</sup>	none	1/29 (3.4%)	3/28 (10.7%)	RR 0.32 (0.04 to 2.91)	73 fewer per 1,000 (from 103 fewer to 205 more)	⊕⊕○○ LOW	IMPORTANT

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

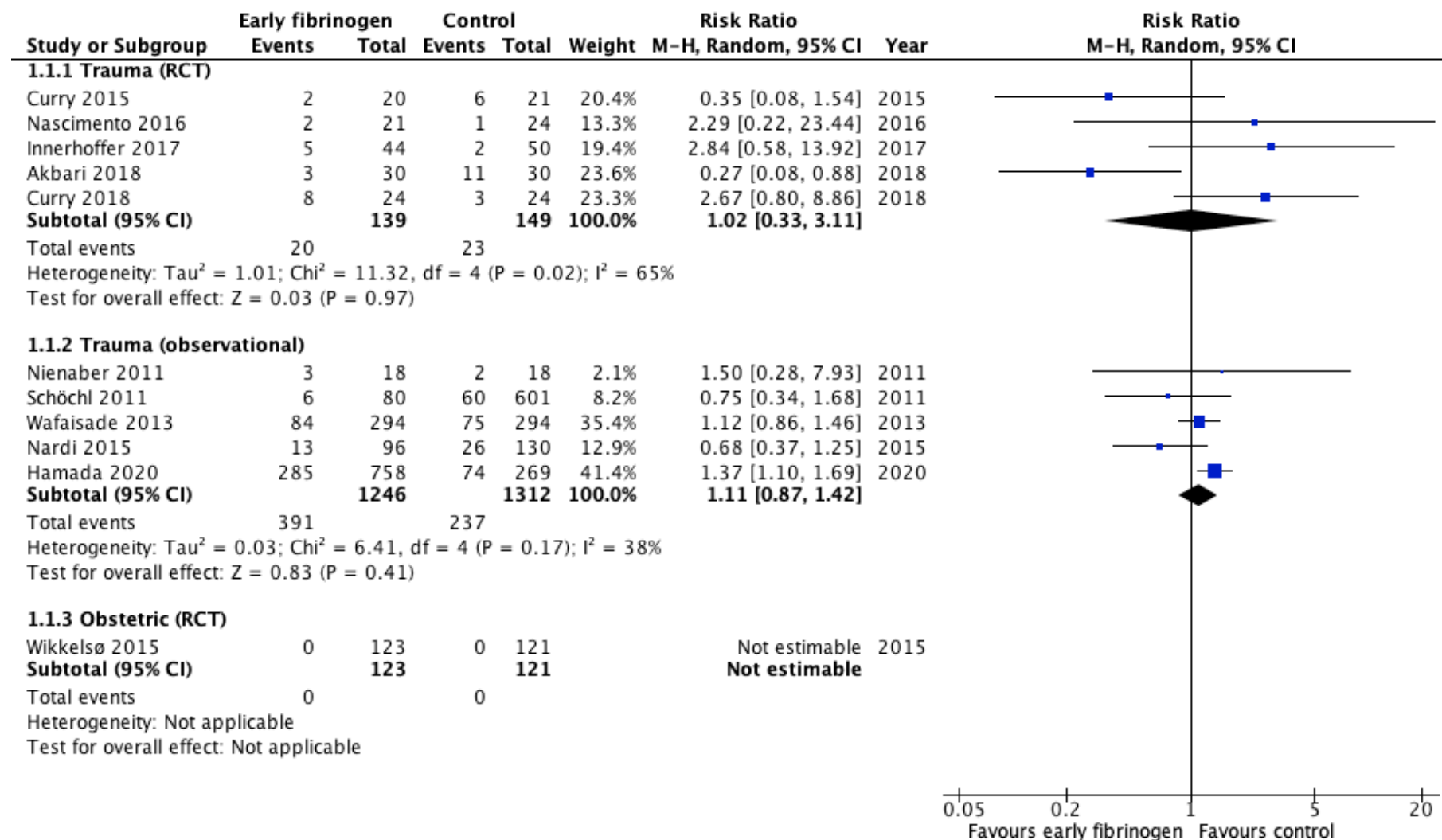
## Early/empiric fibrinogen in massively bleeding patients

### Explanations

- a. Wide confidence intervals, which do not exclude significant harm or benefit.
- b. The absence of any deaths means we are unable to estimate the effect for this outcome.
- c. Very small number of events resulting in very serious imprecision.

## Early/empiric fibrinogen in massively bleeding patients

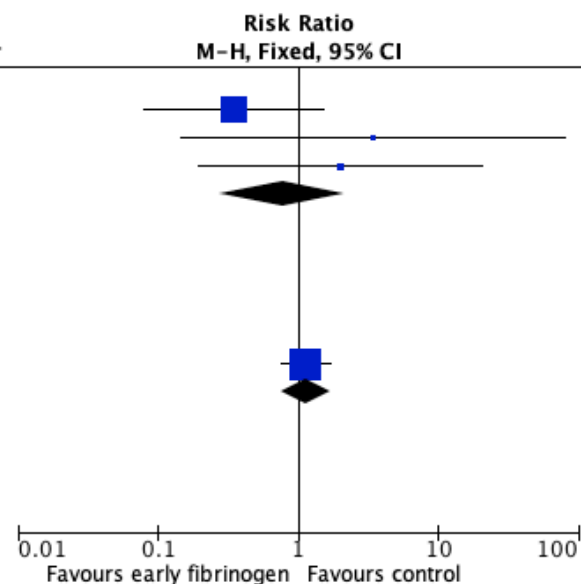
### 1.Mortality



## Early/empiric fibrinogen in massively bleeding patients

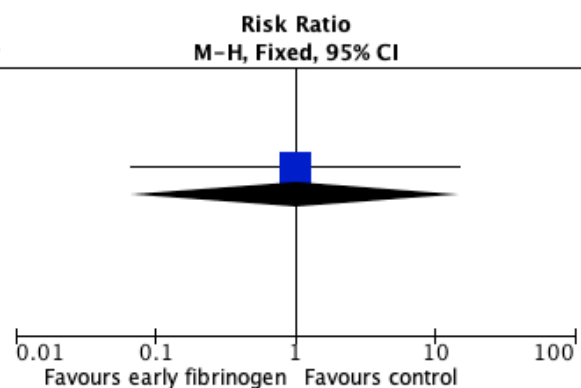
### 2. Deaths due to hemorrhage

Study or Subgroup	Early fibrinogen		Control		Weight	Risk Ratio		Year
	Events	Total	Events	Total		M-H, Fixed, 95% CI		
<b>1.2.1 Trauma (RCT)</b>								
Curry 2015	2	20	6	21	79.9%	0.35 [0.08, 1.54]		2015
Nascimento 2016	1	21	0	24	6.4%	3.41 [0.15, 79.47]		2016
Curry 2018	2	24	1	24	13.7%	2.00 [0.19, 20.61]		2018
<b>Subtotal (95% CI)</b>		<b>65</b>		<b>69</b>	<b>100.0%</b>	<b>0.77 [0.27, 2.18]</b>		
Total events	5		7					
Heterogeneity: $\text{Chi}^2 = 2.59$ , $\text{df} = 2$ ( $P = 0.27$ ); $I^2 = 23\%$								
Test for overall effect: $Z = 0.49$ ( $P = 0.62$ )								
<b>1.2.2 Trauma (observational)</b>								
Hamada 2020	90	758	28	269	100.0%	1.14 [0.76, 1.70]		2020
<b>Subtotal (95% CI)</b>		<b>758</b>		<b>269</b>	<b>100.0%</b>	<b>1.14 [0.76, 1.70]</b>		
Total events	90		28					
Heterogeneity: Not applicable								
Test for overall effect: $Z = 0.64$ ( $P = 0.52$ )								



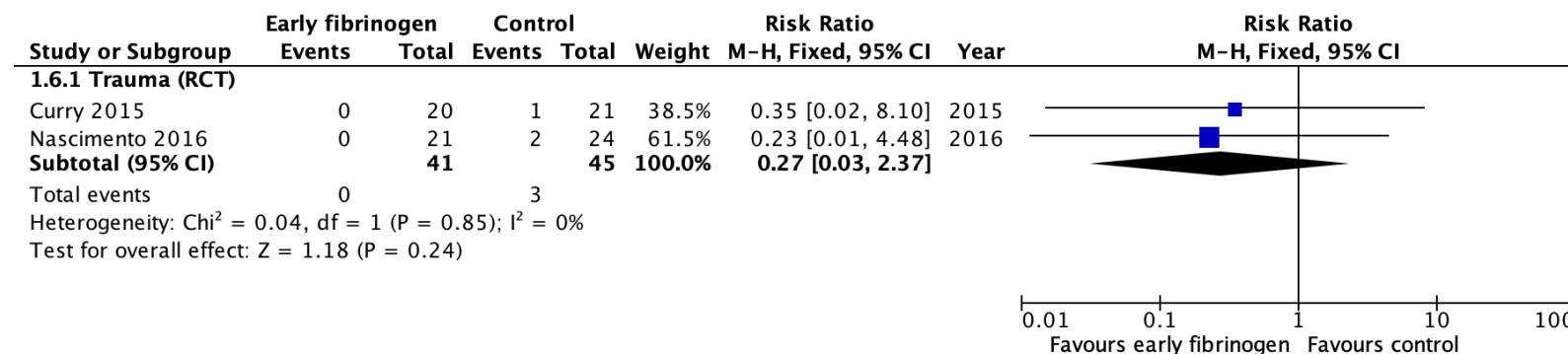
### 3. Stroke

Study or Subgroup	Early fibrinogen		Control		Weight	Risk Ratio		Year
	Events	Total	Events	Total		M-H, Fixed, 95% CI		
<b>1.4.1 Trauma</b>								
Curry 2015	0	20	0	21		Not estimable		2015
Nascimento 2016	0	21	0	24		Not estimable		2016
Curry 2018	1	24	1	24	100.0%	1.00 [0.07, 15.08]		2018
<b>Subtotal (95% CI)</b>		<b>65</b>		<b>69</b>	<b>100.0%</b>	<b>1.00 [0.07, 15.08]</b>		
Total events	1		1					
Heterogeneity: Not applicable								
Test for overall effect: $Z = 0.00$ ( $P = 1.00$ )								

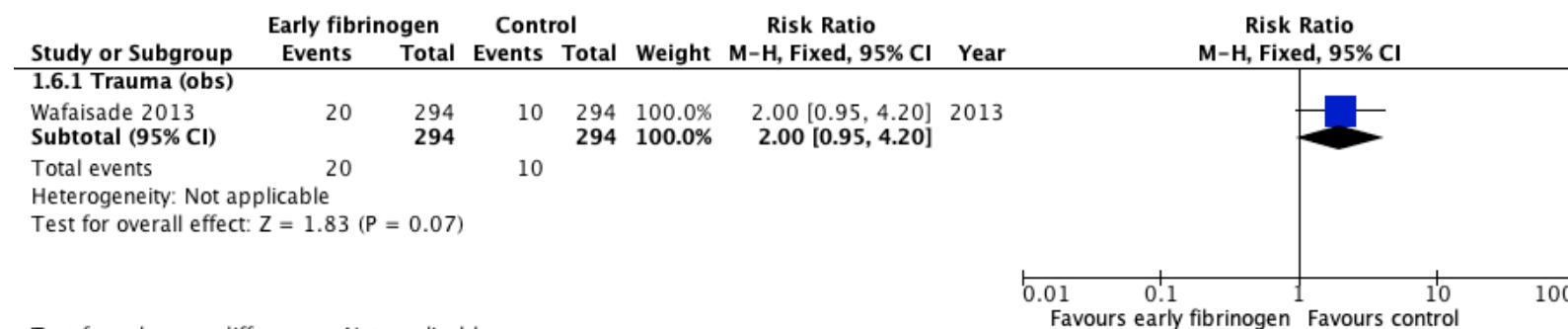


## Early/empiric fibrinogen in massively bleeding patients

### 4. ARDS

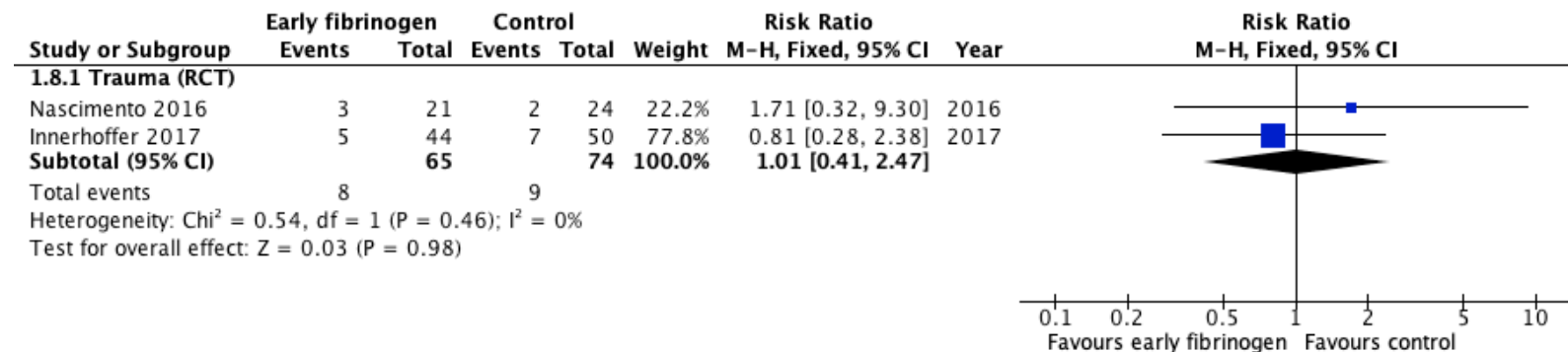


### 5. Thrombosis



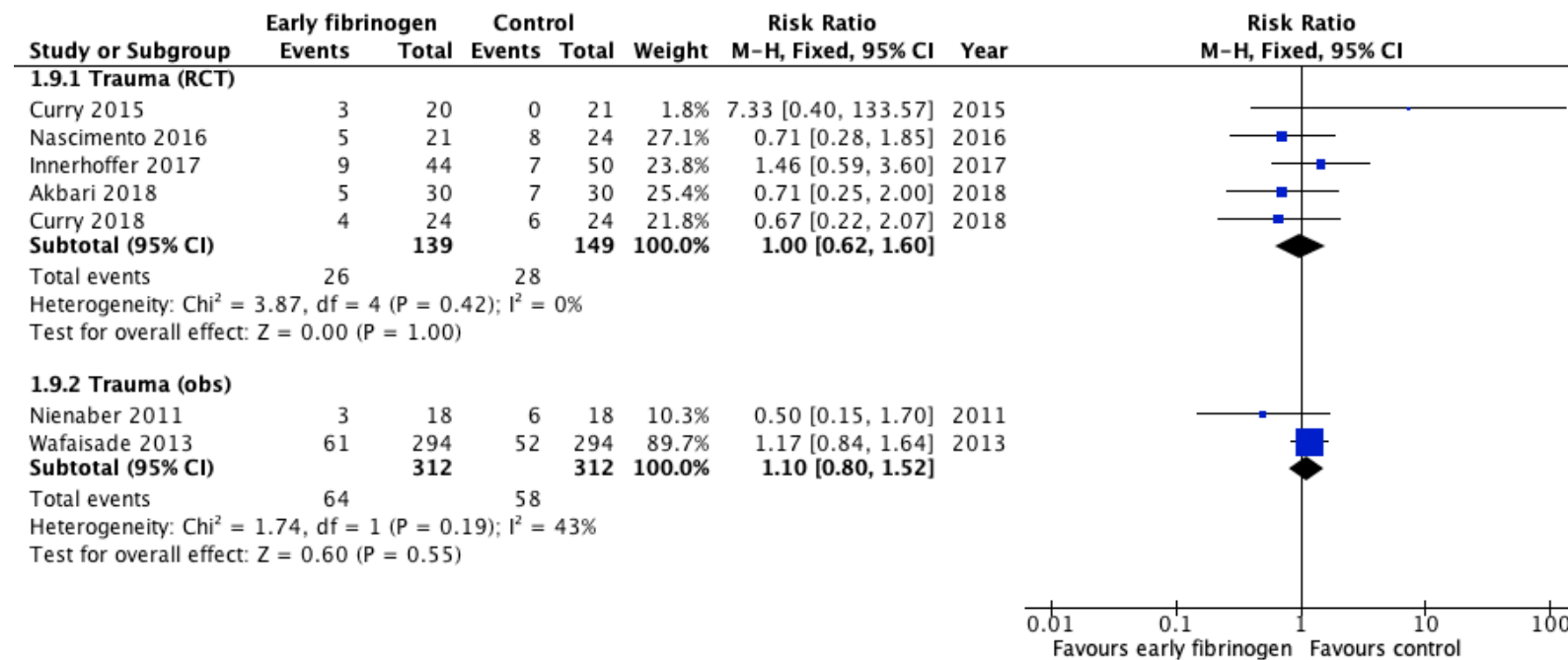
Test for subgroup differences: Not applicable

### 6. Renal failure

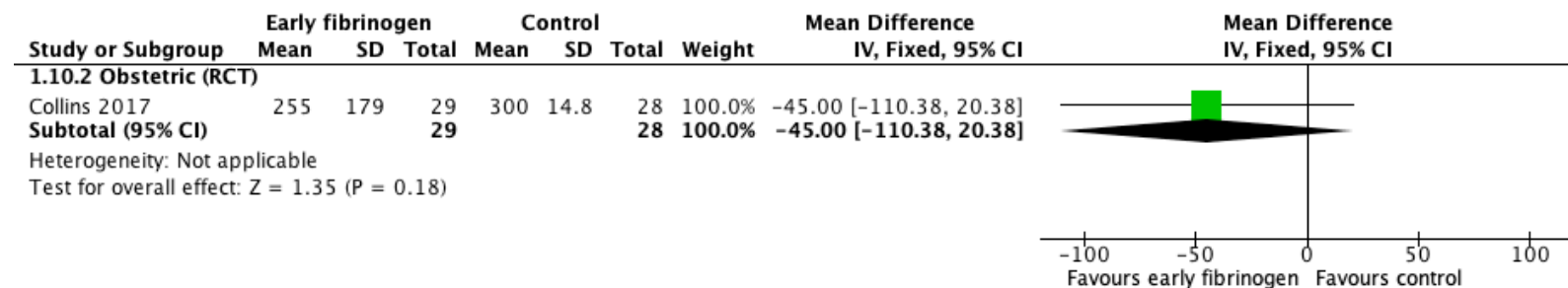


## Early/empiric fibrinogen in massively bleeding patients

### 6. Sepsis



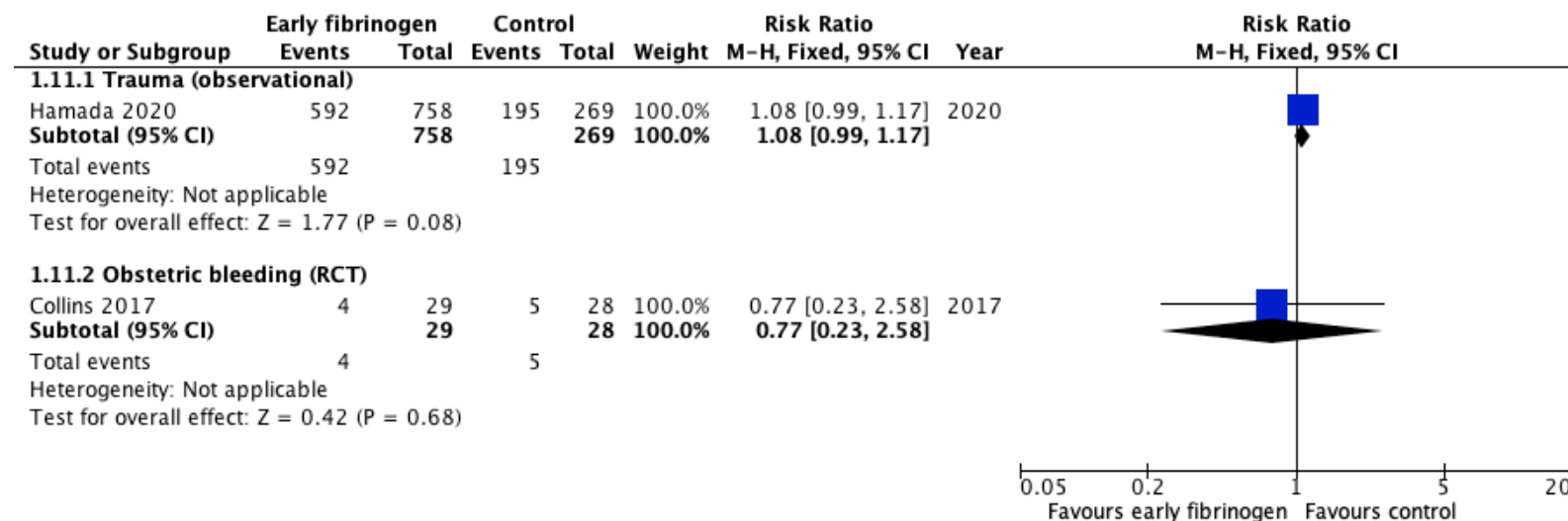
### 7. Bleeding



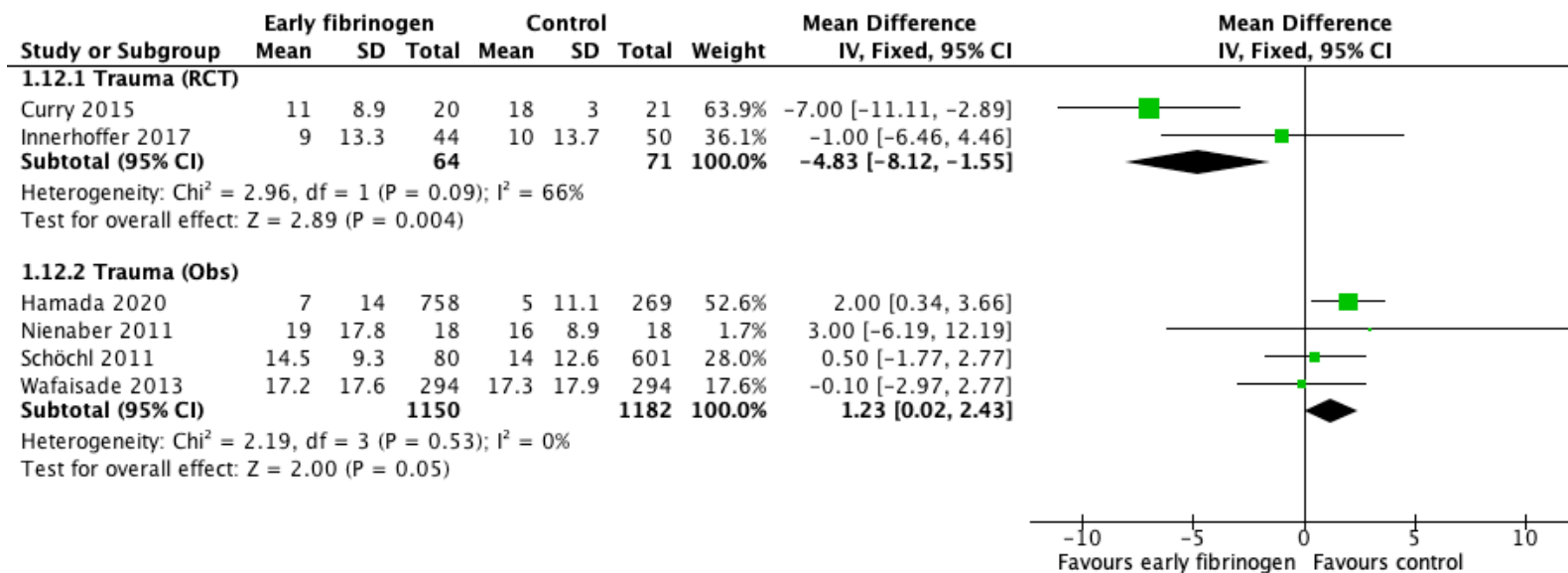


## Early/empiric fibrinogen in massively bleeding patients

### 8. Need for surgical intervention

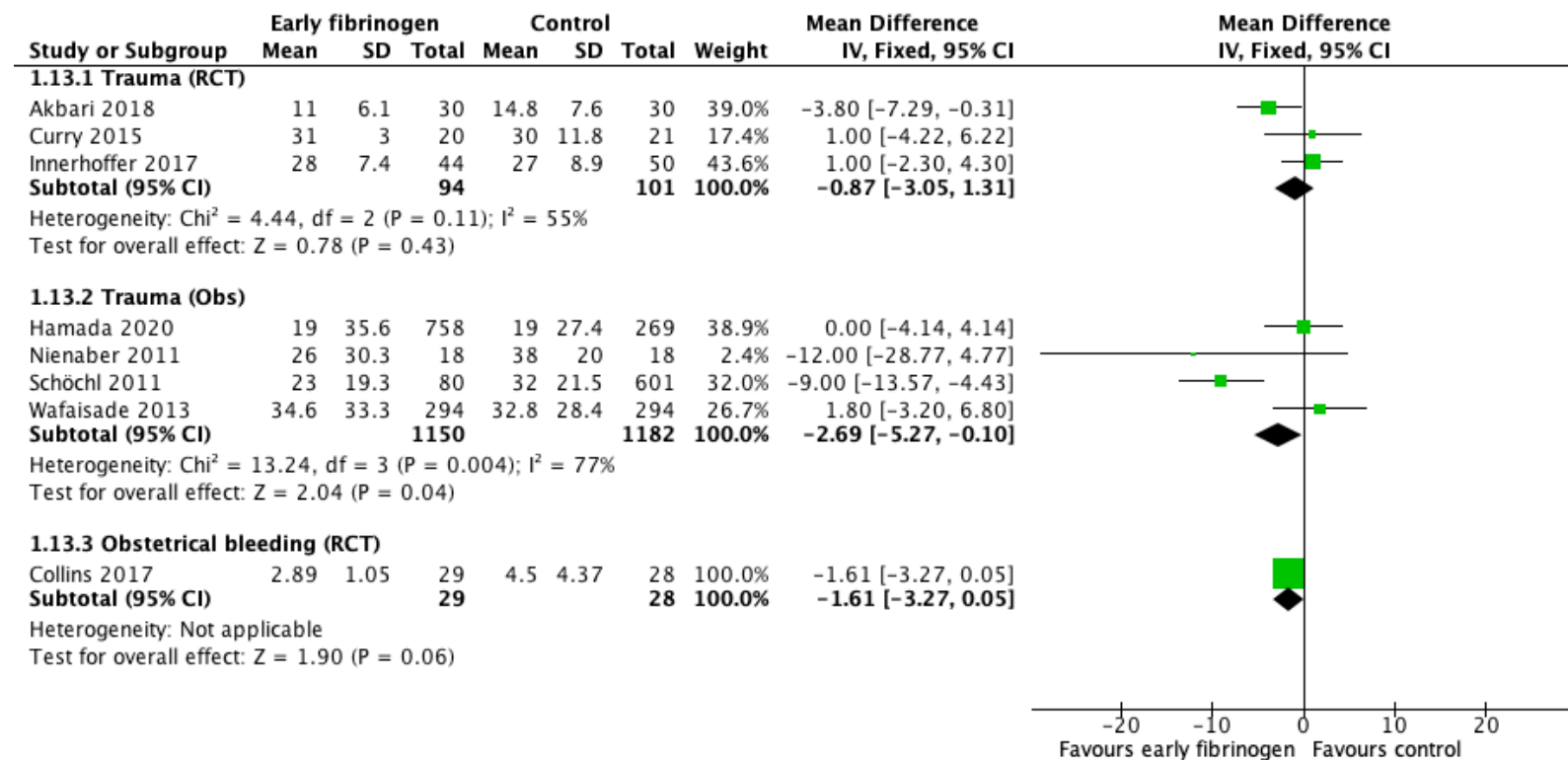


### 9. ICU length of stay



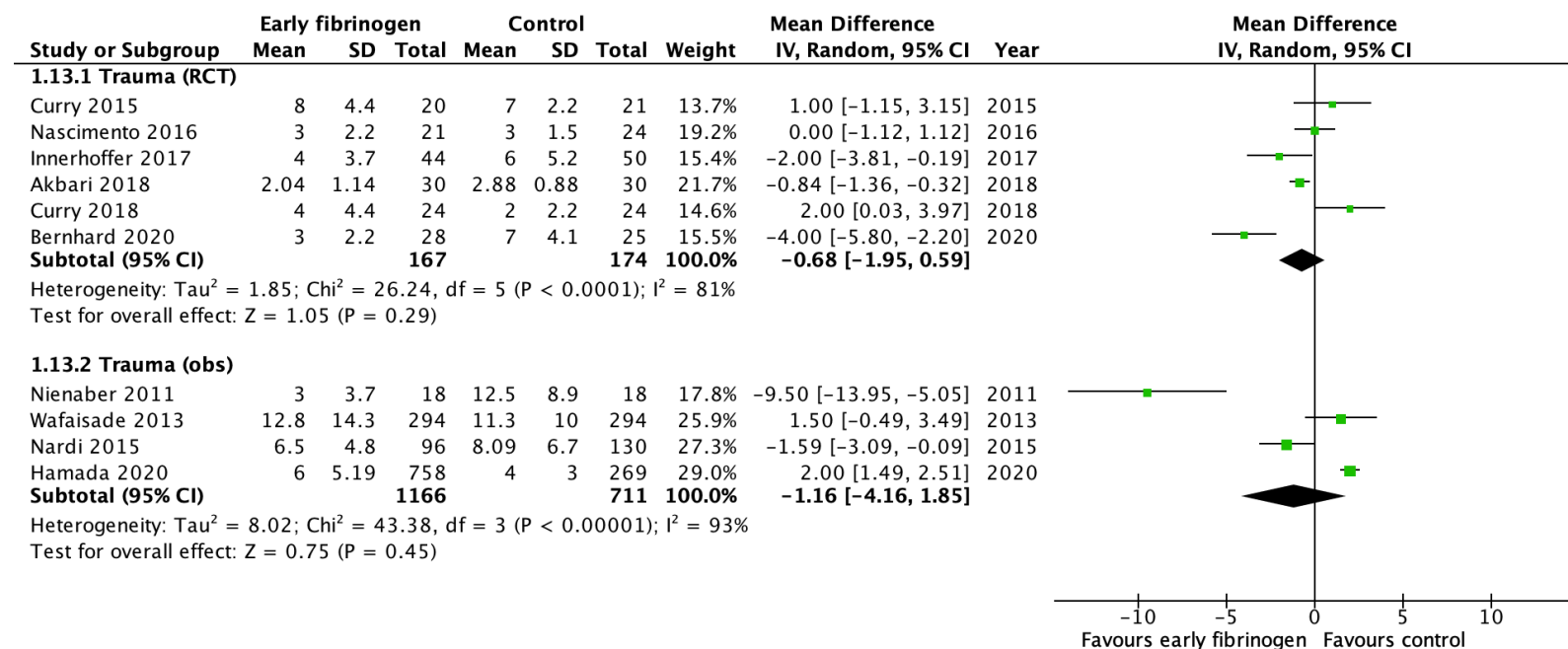
## Early/empiric fibrinogen in massively bleeding patients

### 10. Hospital length of stay

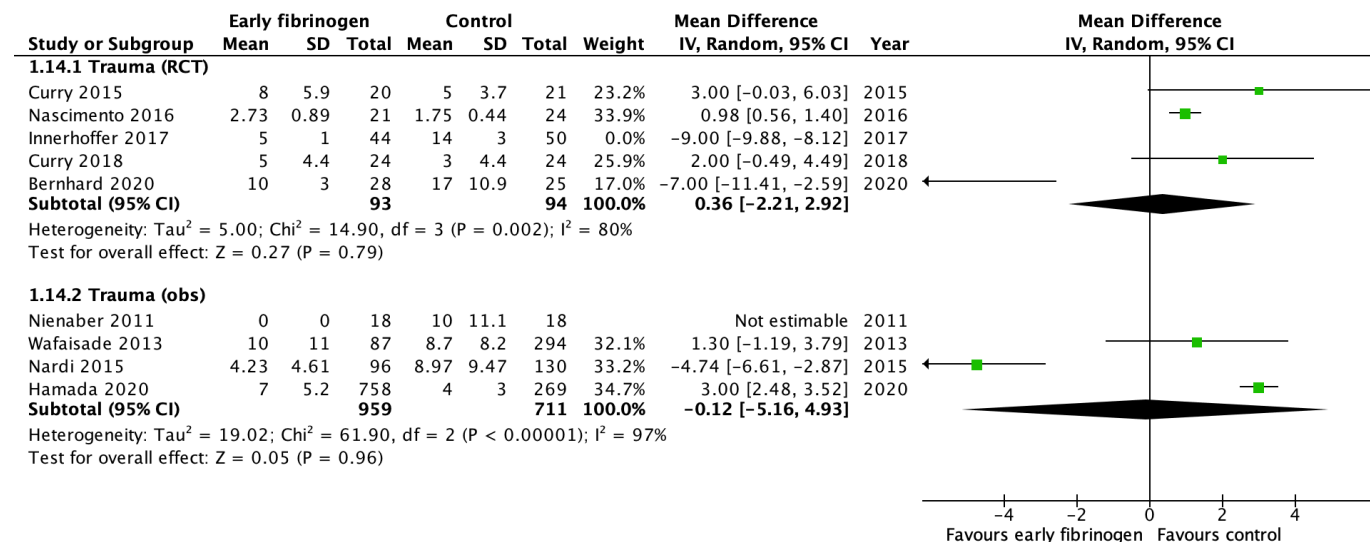


## Early/empiric fibrinogen in massively bleeding patients

### 12. RBCs transfused

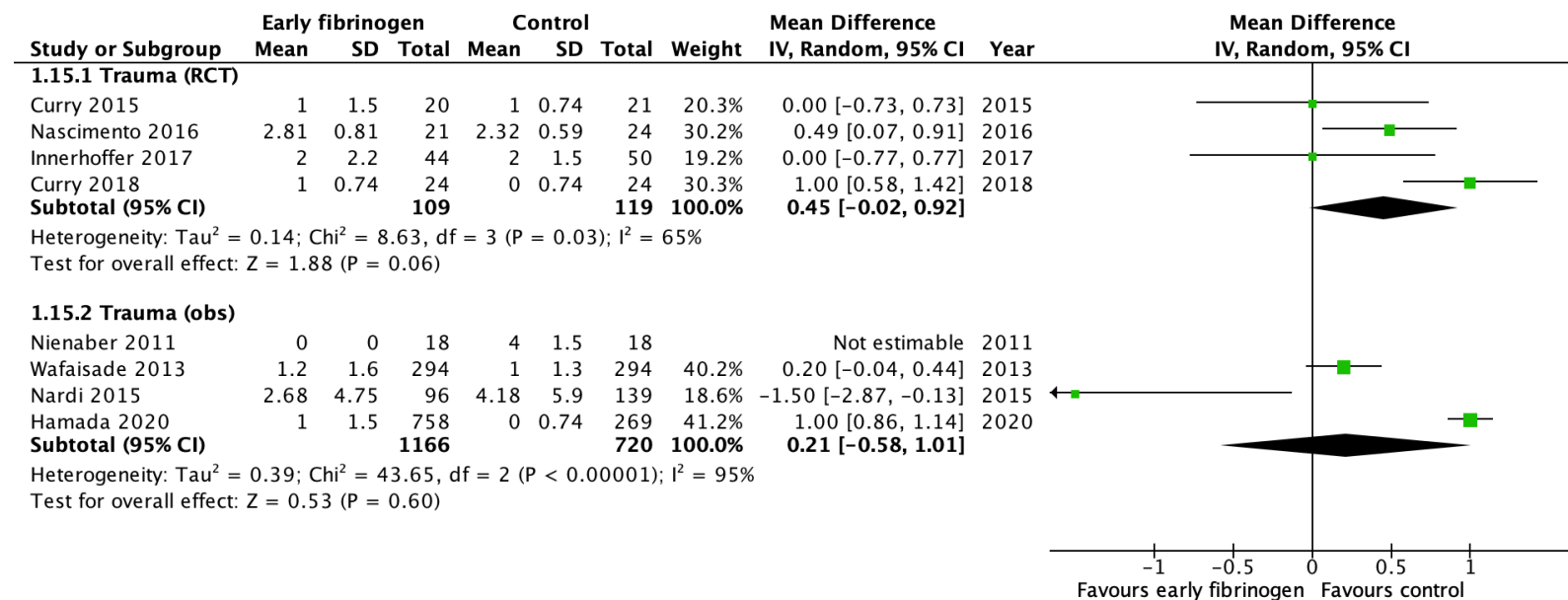


### 13. Plasma transfused

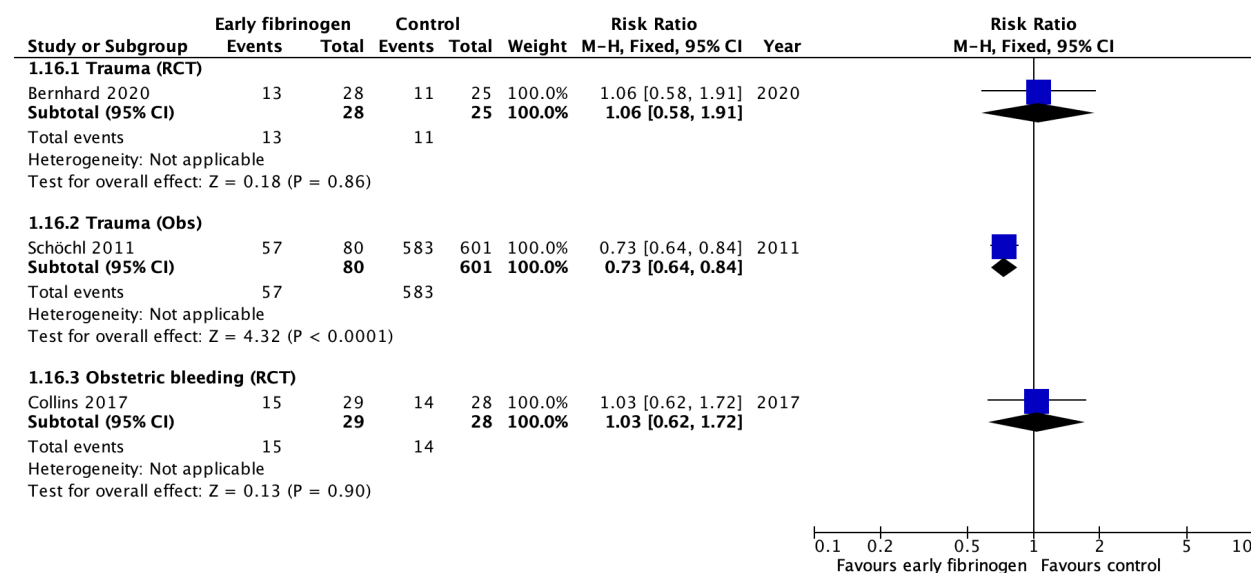


## Early/empiric fibrinogen in massively bleeding patients

### 14. Platelets transfused

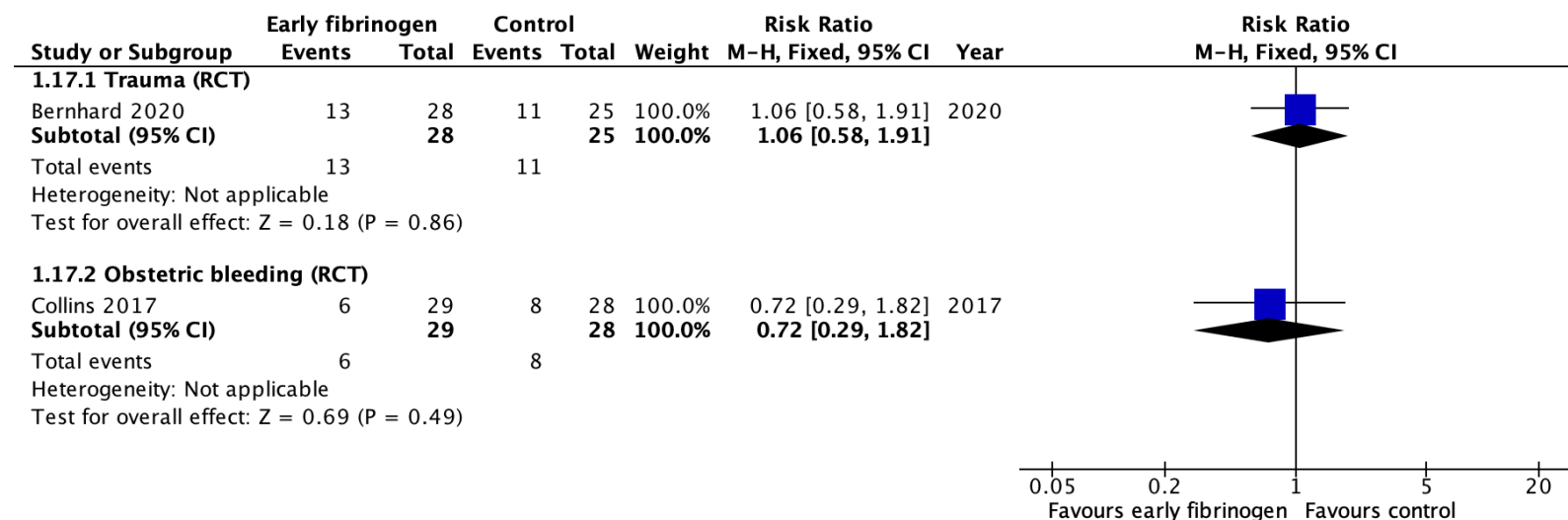


### 15. Proportion receiving RBCs

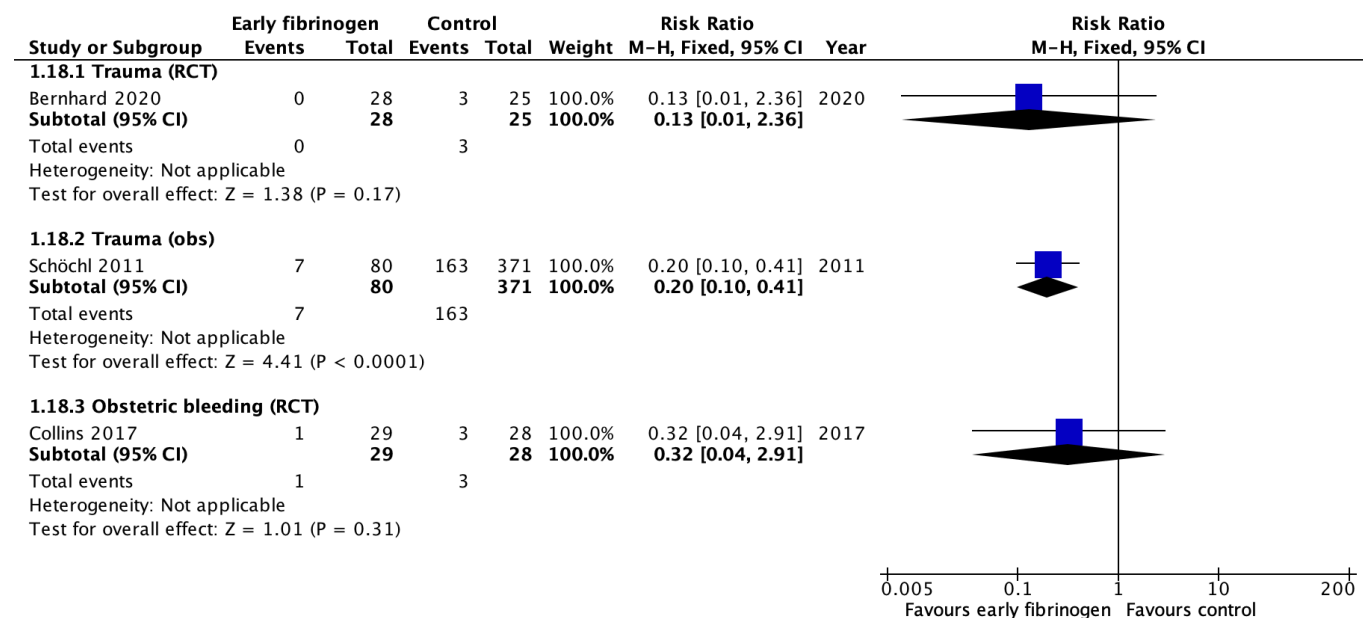


## Early/empiric fibrinogen in massively bleeding patients

### 16. Proportion receiving plasma



### 17. Proportion receiving platelets




**Evidence Summary 5: Combined evidence summary for point of care vs. conventional coagulation testing in massively bleeding, critically ill adults and non-massively bleeding critically ill adults**

# Thromboelastography (TEG) in Massively and Non-massively bleeding Critically Ill patients


## GRADE- Non Massive Bleeding Patients

Author(s): ESICM Guideline Panel


Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TEG	Conventional testing	Relative (95% CI)	Absolute (95% CI)		
<b>CV- Mortality</b>												
7	randomised trials	not serious	serious <sup>a</sup>	not serious	serious <sup>b</sup>	none <sup>c</sup>	17/384 (4.4%)	27/370 (7.3%)	RR 0.60 (0.34 to 1.07)	29 fewer per 1,000 (from 48 fewer to 5 more)	⊕⊕○○ LOW	CRITICAL
<b>CV-Redo Surgery</b>												
10	randomised trials	serious <sup>d</sup>	serious <sup>a</sup>	not serious	serious <sup>b</sup>	publication bias strongly suspected	42/528 (8.0%)	62/524 (11.8%)	RR 0.74 (0.51 to 1.06)	31 fewer per 1,000 (from 58 fewer to 7 more)	⊕○○○ VERY LOW	IMPORTANT
<b>CV-RBC transfusion</b>												
11	randomised trials	serious <sup>d</sup>	serious <sup>a</sup>	not serious	not serious	none <sup>e</sup>	327/595 (55.0%)	377/580 (65.0%)	RR 0.86 (0.76 to 0.98)	91 fewer per 1,000 (from 156 fewer to 13 fewer)	⊕⊕○○ LOW	IMPORTANT
<b>CV-Platelet transfusion</b>												
10	randomised trials	serious <sup>d</sup>	very serious <sup>a,f</sup>	not serious	not serious	none <sup>e</sup>	154/575 (26.8%)	199/560 (35.5%)	RR 0.68 (0.46 to 0.99)	114 fewer per 1,000 (from 192 fewer to 4 fewer)	⊕○○○ VERY LOW	IMPORTANT
<b>CV-FFP transfusion</b>												
8	randomised trials	serious <sup>d</sup>	very serious <sup>a,g</sup>	not serious	not serious	none <sup>e</sup>	91/522 (17.4%)	194/513 (37.8%)	RR 0.46 (0.37 to 0.57)	204 fewer per 1,000 (from 238 fewer to 163 fewer)	⊕○○○ VERY LOW	IMPORTANT
<b>CV-Cryoprecipitate transfusion</b>												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TEG	Conventional	Relative (95% CI)	Absolute (95% CI)		
4	randomised trials	serious <sup>d</sup>	very serious <sup>a,h</sup>	not serious	serious <sup>i</sup>	none <sup>c</sup>	25/177 (14.1%)	49/182 (26.9%)	RR 0.53 (0.35 to 0.79)	127 fewer per 1,000 (from 175 fewer to 57 fewer)	 VERY LOW	IMPORTANT


CV-Hemostasis-12 hour post op bleeding

3	randomised trials	serious <sup>d</sup>	very serious <sup>a,j</sup>	not serious	not serious	none <sup>c</sup>	248	241	-	MD 128.18 lower (172.38 lower to 83.97 lower)	 VERY LOW	IMPORTANT
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
CV-Hemostasis-24 hr post op bleeding

4	randomised trials	serious <sup>d</sup>	serious <sup>a</sup>	not serious	not serious	none <sup>c</sup>	186	190	-	MD 175.25 lower (305.19 lower to 45.32 lower)	 LOW	IMPORTANT
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CV-Hospital LOS

3	randomised trials	serious <sup>d</sup>	very serious <sup>a,k</sup>	not serious	serious <sup>b</sup>	none <sup>c</sup>	167	157	-	MD 0.12 lower (0.45 lower to 0.21 higher)	 VERY LOW	IMPORTANT
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
CV-ICU LOS

6	randomised trials	serious <sup>d</sup>	very serious <sup>a,j</sup>	not serious	not serious	none <sup>c</sup>	333	336	-	MD 4.08 lower (6.33 lower to 1.82 lower)	 VERY LOW	IMPORTANT
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ECMO-Mortality

1	randomised trials	not serious	not serious	not serious	very serious <sup>b,j</sup>	none <sup>c</sup>	2/7 (28.6%)	3/9 (33.3%)	RR 0.86 (0.19 to 3.81)	47 fewer per 1,000 (from 270 fewer to 937 more)	 LOW	CRITICAL
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
ECMO- Rebleeding

1	randomised trials	serious	not serious	not serious	very serious <sup>l,m</sup>	none <sup>l,m</sup>	2/7 (28.6%)	6/9 (66.7%)	RR 0.43 (0.12 to 1.51)	380 fewer per 1,000 (from 587 fewer to 340 more)	 VERY LOW	IMPORTANT
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Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TEG	Conventional	Relative (95% CI)	Absolute (95% CI)		

#### ECMO-Thrombotic Complications

1	randomised trials	serious	not serious	not serious	very serious <sup>i,m</sup>	none <sup>c</sup>	1/9 (11.1%)	5/9 (55.6%)	RR 0.20 (0.03 to 1.39)	444 fewer per 1,000 (from 539 fewer to 217 more)	 VERY LOW	CRITICAL
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CI: Confidence interval; RR: Risk ratio; MD: Mean difference

## Explanations

- Rated down for wide variance in the point estimates
- Rated down as confidence intervals overlaps 1, with no effect.
- Publication bias not formally assessed given few number of studies identified.
- Most studies included in the systematic review by Meco 2020 and Serriano and Murphy 2017, where of unclear or high risk of bias.
- Funnel plot though not asymmetric, given the small number of studies, still could be publication bias present.
- Rated down for considerable heterogeneity (I2 74%)
- Rated down for substantial heterogeneity (I2 68%)
- Rated down for substantial heterogeneity (I2 80%)
- Rated down for few number of events.
- Rated down for substantial heterogeneity (I2 84%)
- Rated down for substantial heterogeneity (I2 69%)
- Rated down for substantial heterogeneity (I2 85%)
- Rated down for overlapping confidence intervals

## GRADE-Massively Bleeding Patients


Author(s): ESICM Guideline Panel

Question: Point of Care compared to Conventional testing (TEG/ROTEM) for transfusions in massive bleeding?


Bibliography: Gurusamy 2011 (Wang 2010, Russo 2010), Kumar 2019, Rout 2019, Gonzalez 2017, Smart 2017

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TEG	Conventional	Relative (95% CI)	Absolute (95% CI)		

#### GI-Cirrhrotic Bleeding-Mortality

2	randomised trials	not serious	not serious	serious <sup>a</sup>	serious <sup>b</sup>	none <sup>c</sup>	31/73 (42.5%)	36/68 (52.9%)	RR 0.82 (0.59 to 1.13)	95 fewer per 1,000 (from 217 fewer to 69 more)	 LOW	CRITICAL
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#### GI-Cirrhrotic Bleeding Rebleeding

2	randomised trials	not serious	serious <sup>d</sup>	not serious	very serious <sup>e</sup>	none <sup>c</sup>	22/62 (35.5%)	27/54 (50.0%)	RR 0.71 (0.47 to 1.07)	145 fewer per 1,000 (from 265 fewer to 35 more)	 VERY LOW	IMPORTANT
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#### GI-Cirrhrotic Bleeding-TRALI

№ of studies	Study design	Certainty assessment					№ of patients		Effect		Certainty	Importance
		Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TEG	Conventional	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	not serious	not serious	not serious	very serious <sup>e</sup>	none <sup>c</sup>	6/49 (12.2%)	23/47 (48.9%)	RR 0.25 (0.11 to 0.56)	367 fewer per 1,000 (from 436 fewer to 215 fewer)	LOW	IMPORTANT

#### GI-Cirrhotic Bleeding-TACO

1	randomised trials	not serious	not serious	not serious	very serious <sup>e</sup>	none <sup>c</sup>	5/49 (10.2%)	10/47 (21.3%)	RR 0.48 (0.18 to 1.30)	111 fewer per 1,000 (from 174 fewer to 64 more)	LOW	IMPORTANT
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#### GI-Cirrhotic Bleeding-ARDS

1	randomised trials	not serious	not serious	not serious	very serious <sup>e</sup>	none <sup>c</sup>	1/49 (2.0%)	9/47 (19.1%)	RR 0.11 (0.01 to 0.81)	170 fewer per 1,000 (from 190 fewer to 36 fewer)	LOW	IMPORTANT
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#### GI-Cirrhotic Bleeding-RBC Transfusion

1	randomised trials	not serious	not serious	not serious	very serious <sup>e</sup>	none <sup>c</sup>	17/30 (56.7%)	16/30 (53.3%)	RR 1.06 (0.67 to 1.68)	32 more per 1,000 (from 176 fewer to 363 more)	LOW	IMPORTANT
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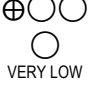
#### GI-Cirrhotic Bleeding-Platelet Transfusion

1	randomised trials	not serious	not serious	not serious	very serious <sup>f</sup>	none <sup>c</sup>	3/30 (10.0%)	21/30 (70.0%)	RR 0.14 (0.05 to 0.43)	602 fewer per 1,000 (from 665 fewer to 399 fewer)	LOW	IMPORTANT
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#### GI-Cirrhotic Bleeding-FFP Transfusion

1	randomised trials	not serious	not serious	not serious	very serious <sup>f</sup>	none <sup>c</sup>	4/30 (13.3%)	14/30 (46.7%)	RR 0.29 (0.11 to 0.77)	331 fewer per 1,000 (from 415 fewer to 107 fewer)	LOW	IMPORTANT
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#### Trauma-Mortality

№ of studies	Study design	Certainty assessment					№ of patients		Effect		Certainty	Importance
		Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TEG	Conventional	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious	not serious	not serious	very serious <sup>e</sup>	none <sup>c</sup>	11/56 (19.6%)	20/55 (36.4%)	RR 0.54 (0.29 to 1.02)	167 fewer per 1,000 (from 258 fewer to 7 more)	 VERY LOW	CRITICAL

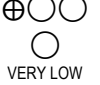
**Liver Transplant- Mortality**

1	randomised trials	not serious	not serious	not serious	very serious <sup>e</sup>	none <sup>c</sup>	2/14 (14.3%)	3/14 (21.4%)	RR 0.67 (0.13 to 3.40)	71 fewer per 1,000 (from 186 fewer to 514 more)	 LOW	CRITICAL
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**Liver Transplant- Blood Loss**

2	randomised trials	serious	not serious	not serious	very serious <sup>f</sup>	none <sup>c</sup>	31	31	-	MD 1.13 lower (1.85 lower to 0.41 lower)	 VERY LOW	IMPORTANT
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**Liver Transplant-RBC Transfusion**

2	randomised trials	serious	very serious <sup>g</sup>	not serious	serious <sup>b</sup>	none <sup>c</sup>	31	31	-	MD 12.22 lower (71.08 lower to 46.64 higher)	 VERY LOW	IMPORTANT
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**Liver Transplant-Platelet Transfusion**

1	randomised trials	serious	not serious	not serious	very serious <sup>e</sup>	none <sup>c</sup>	14	14	-	MD 2.8 lower (14.92 lower to 9.32 higher)	 VERY LOW	IMPORTANT
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**Liver Transplant- FFP Transfusion**

1	randomised trials	serious	not serious	not serious	very serious <sup>f</sup>	none <sup>c</sup>	14	14	-	MD 8.7 lower (16.3 lower to 1.1 lower)	 VERY LOW	IMPORTANT
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
**Liver Transplant-Cryoprecipitate Transfusion**

1	randomised trials	serious	not serious	not serious	very serious <sup>e</sup>	none <sup>c</sup>	14	14	-	MD 2.6 lower (9.94 lower to 4.74 higher)	 VERY LOW	IMPORTANT
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**Liver Transplant Observational- Mortality**

№ of studies	Study design	Certainty assessment					№ of patients		Effect		Certainty	Importance
		Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Point of Care	Conventional testing (TEG/ROTEM)	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious	not serious	not serious	very serious <sup>e</sup>	none <sup>c</sup>	1/34 (2.9%)	1/34 (2.9%)	RR 1.00 (0.07 to 15.34)	0 fewer per 1,000 (from 27 fewer to 422 more)	 VERY LOW	CRITICAL


#### Liver Transplant Observational-RBC Transfusion

1	observational studies	serious	not serious	not serious	very serious <sup>e</sup>	none <sup>c</sup>	28/34 (82.4%)	33/34 (97.1%)	RR 0.85 (0.72 to 1.00)	146 fewer per 1,000 (from 272 fewer to 0 fewer)	 VERY LOW	IMPORTANT
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#### Liver Transplant Observational-Platelet Transfusion

1	observational studies	serious	not serious	not serious	very serious <sup>e</sup>	none <sup>c</sup>	27/34 (79.4%)	19/34 (55.9%)	RR 1.42 (1.01 to 2.00)	235 more per 1,000 (from 6 more to 559 more)	 VERY LOW	IMPORTANT
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#### Liver Transplant Observational-Cryoprecipitate Transfusions

1	observational studies	serious	not serious	not serious	very serious <sup>e</sup>	none <sup>c</sup>	25/34 (73.5%)	19/34 (55.9%)	RR 1.32 (0.92 to 1.89)	179 more per 1,000 (from 45 fewer to 497 more)	 VERY LOW	IMPORTANT
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CI: Confidence interval; RR: Risk ratio; MD: Mean difference

## Explanations

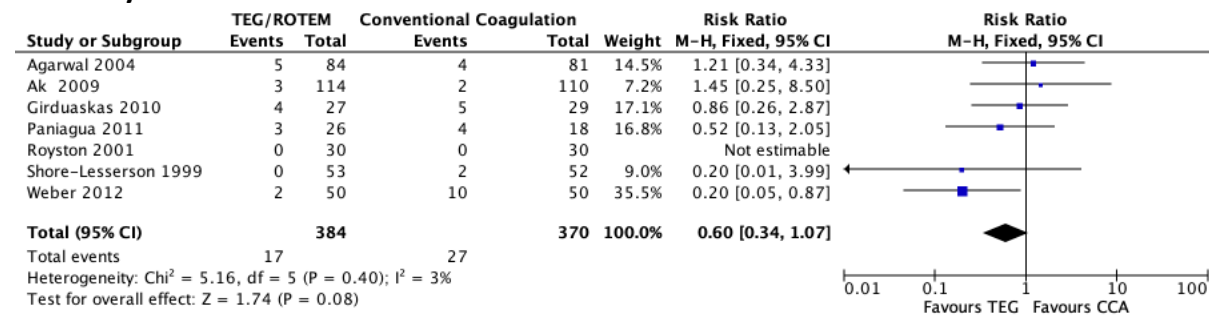
- a. Rated down for indirectness- one study was portal hypertensive bleeding, the other for non-portal hypertensive bleeding in cirrhotic patients
- b. Rated down as for confidence intervals overlap, and encompasses 1.
- c. Publication bias not formally assessed due to the limited number of studies identified
- d. Rated down for substantial heterogeneity
- e. Rated down for overlapping confidence intervals and few number of events
- f. Rated down for few number of events and small sample size
- g. rated down for wide variance in point estimates and substantial heterogeneity

## Evidence Summary

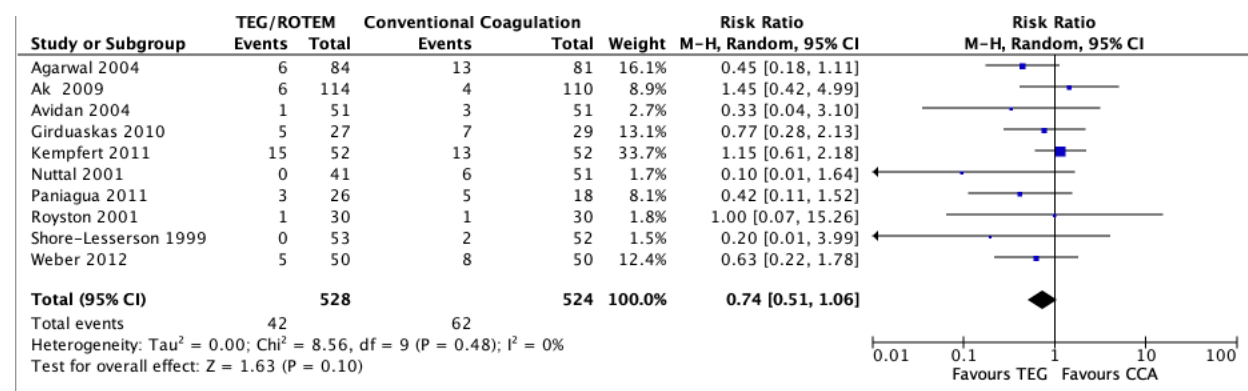
### Non-massively bleeding patients

### CV Surgery

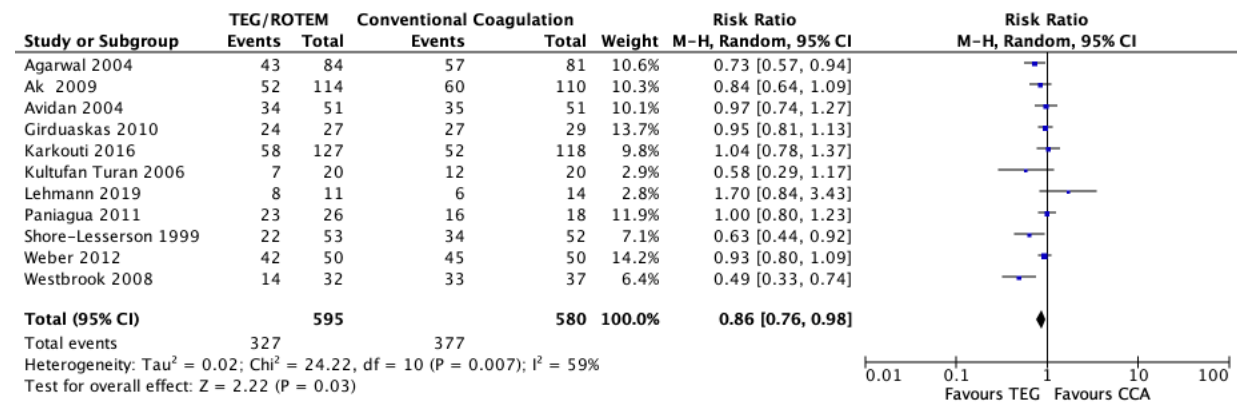
## Mortality



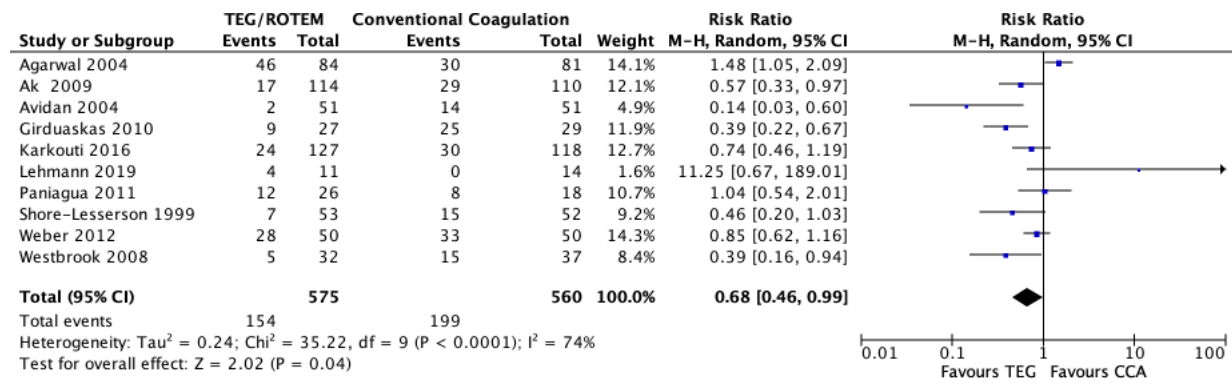
## Redo Surgery



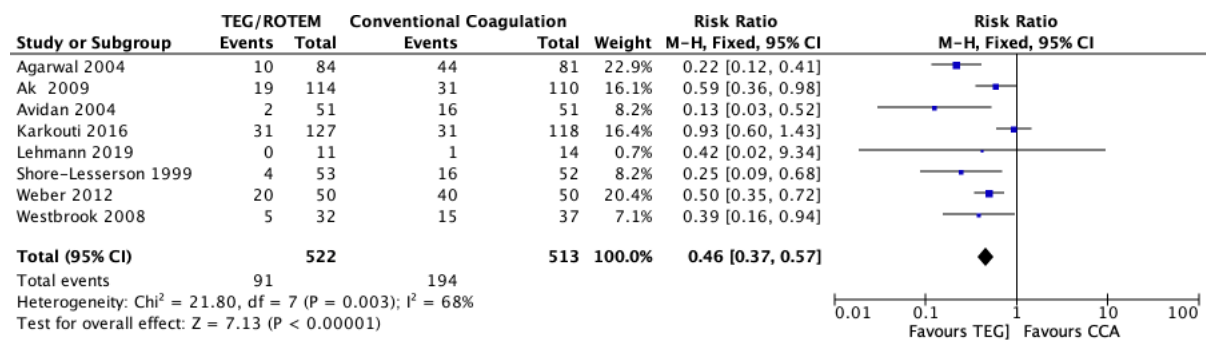
## RBC transfusions



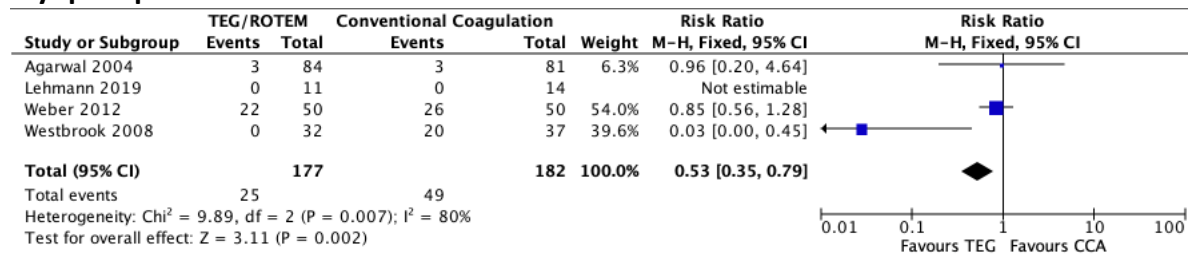
## Platelet transfusions



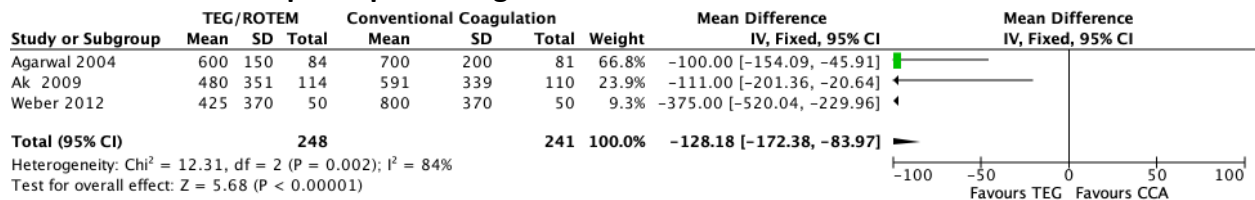
## FFP Transfusions



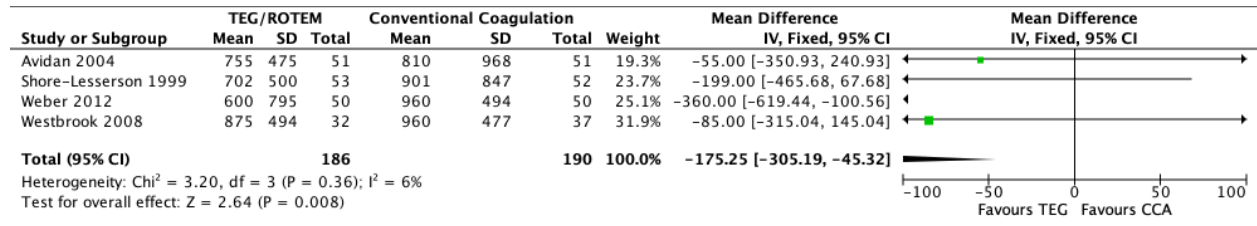
## Cryoprecipitate Transfusion



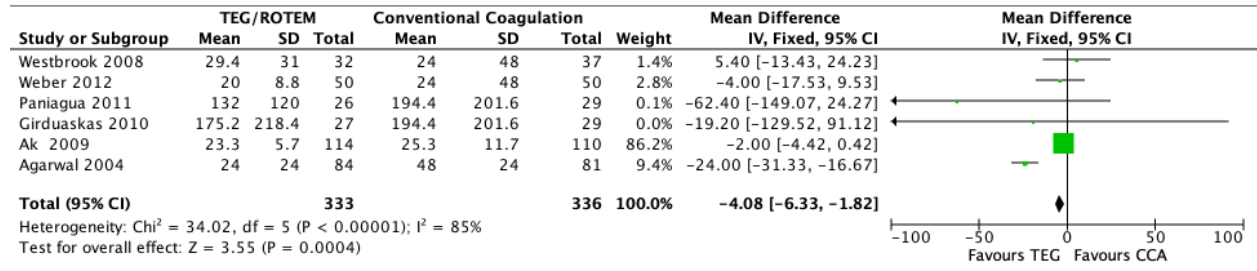
## Hemostasis- 12 hour post op bleeding



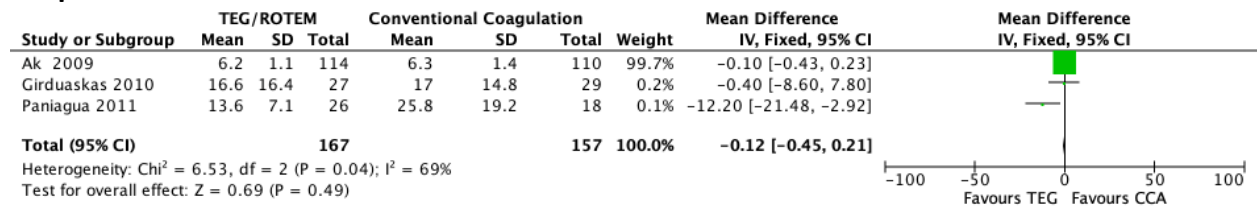
## Hemostasis-24hr post op bleeding



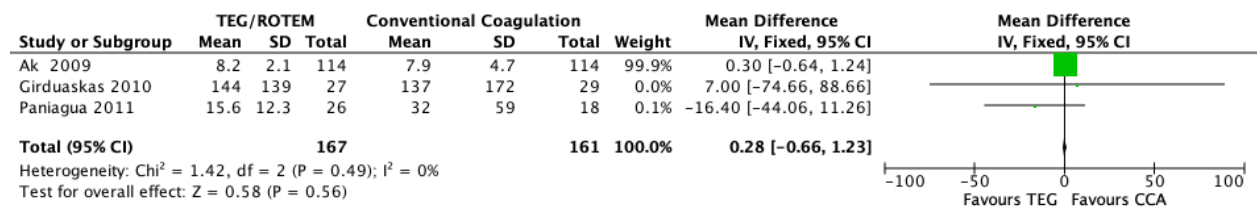
## ICU LOS



## Hospital LOS

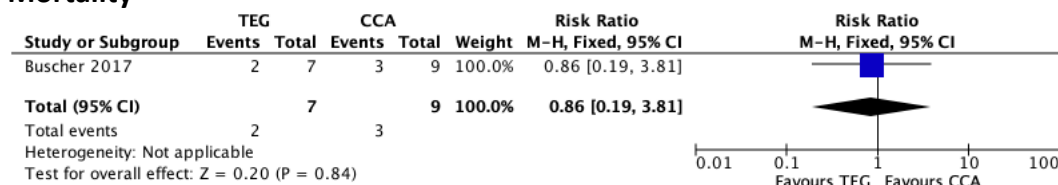


## Duration of Mechanical Ventilation (For your information only, not an included outcome)

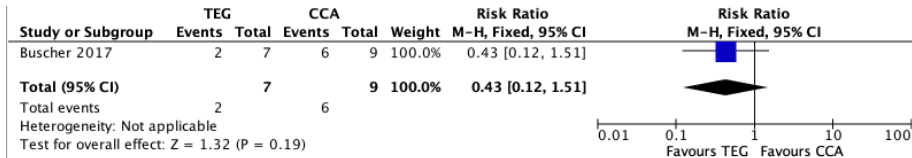


## ECMO

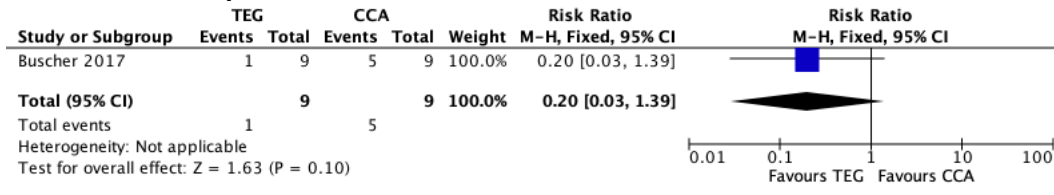
### Mortality



### Rebleeding



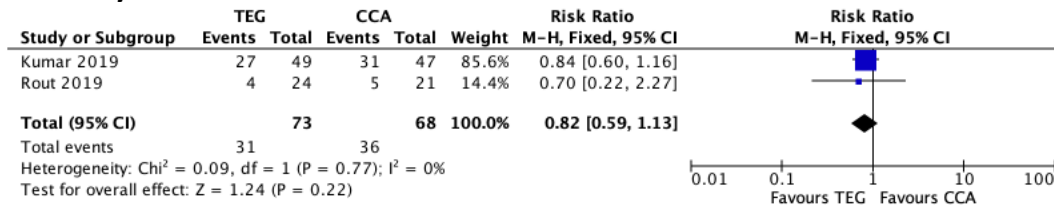
## Thrombotic Complications



## Massively Bleeding

### GI-Cirrhotic Bleeding (variceal/nonvariceal)

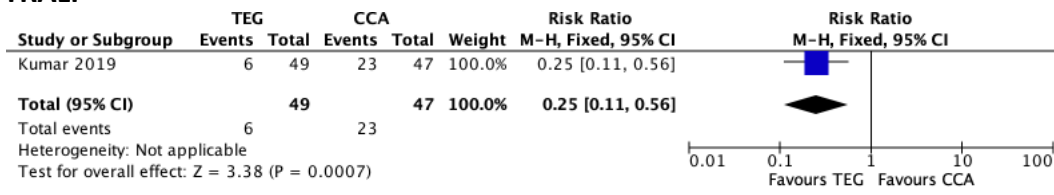
#### Mortality



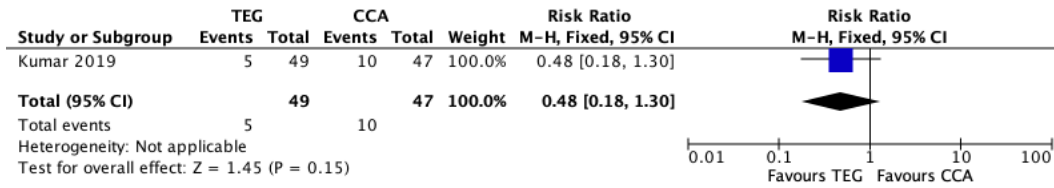
#### Rebleeding



#### TRALI

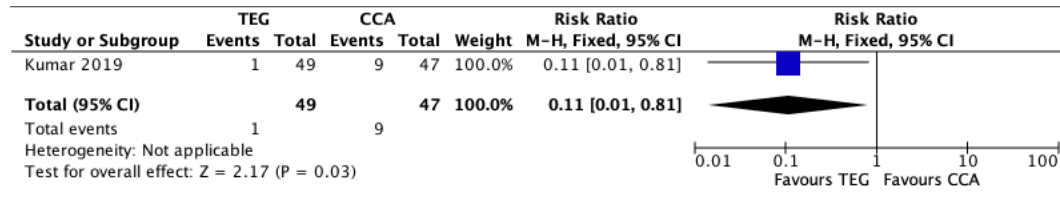


#### TACO

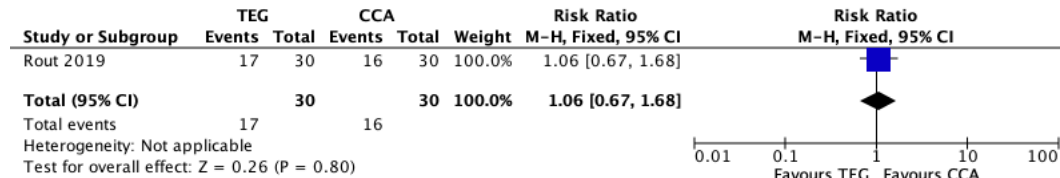


#### ARDS

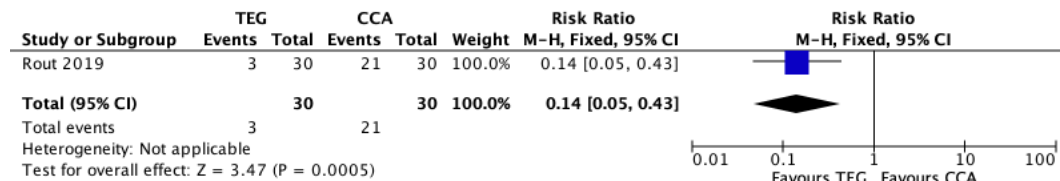




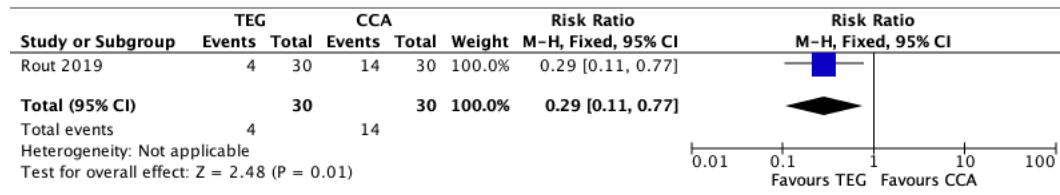
## RBC Transfusion



## Platelet Transfusion

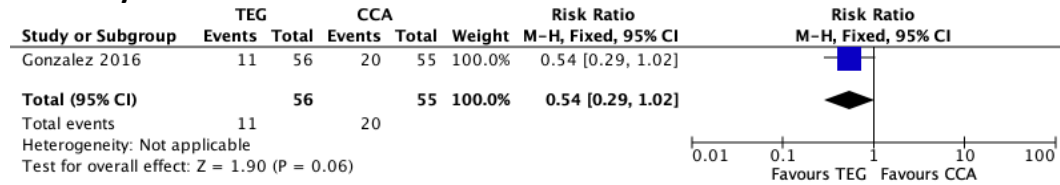


## FFP Transfusion



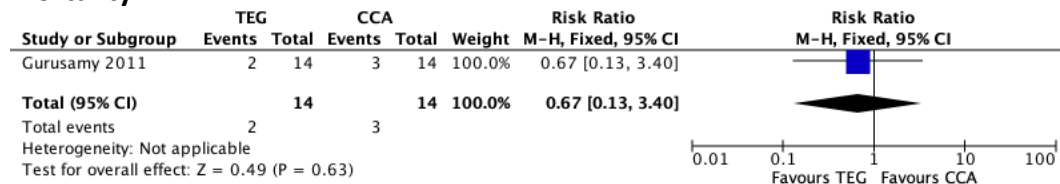
## Trauma

### Mortality

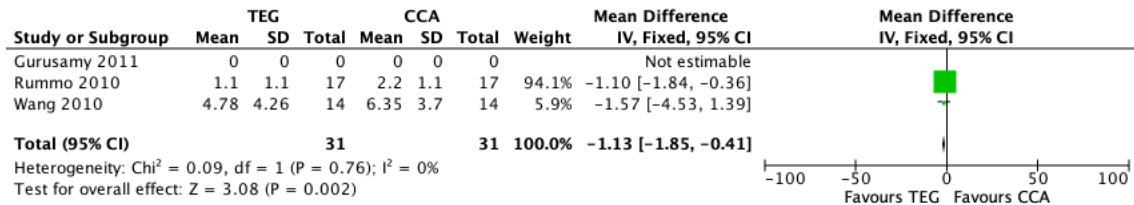


## Liver Transplant

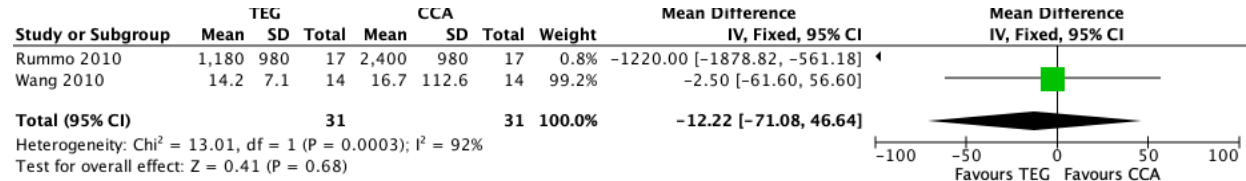
### Mortality



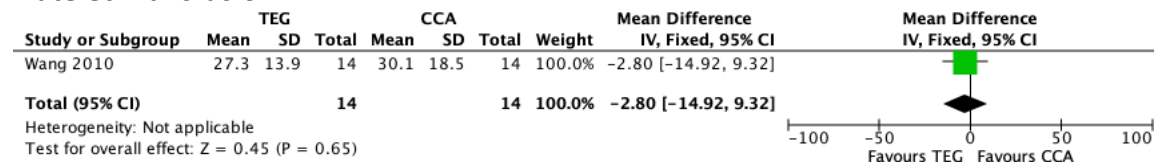
## Blood Loss



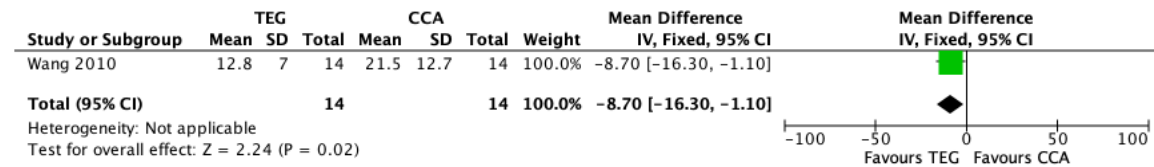
## RBC Transfusion



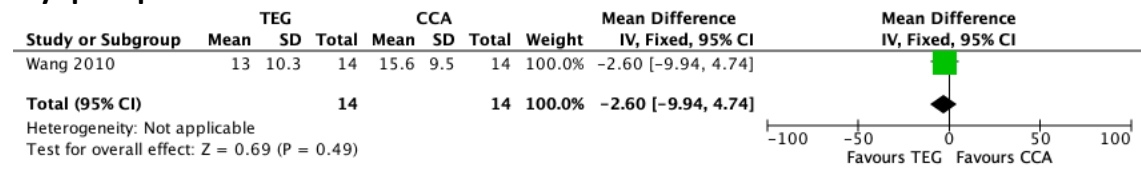
## Platelet Transfusion



## FFP Transfusions

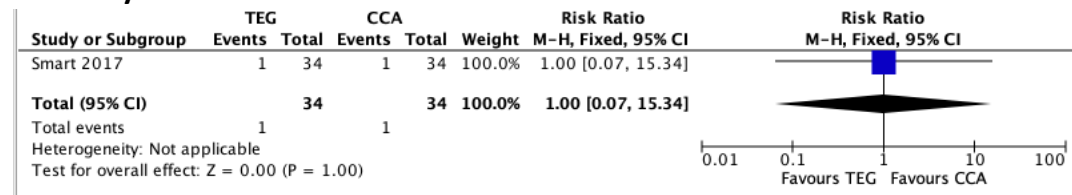


## Cryoprecipitate Transfusion

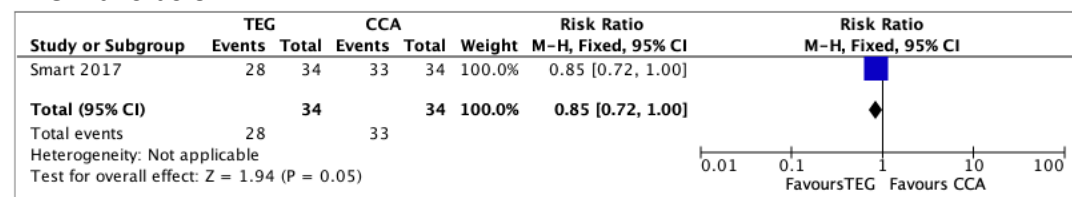


## Liver Transplant- Observational

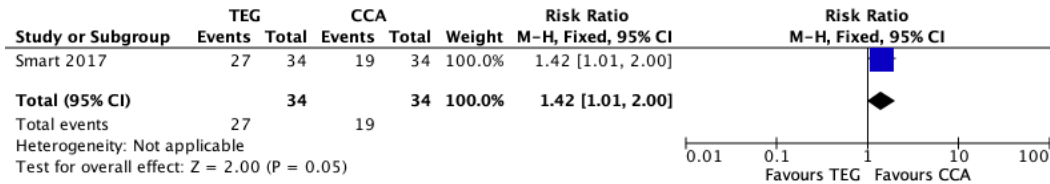
### Mortality



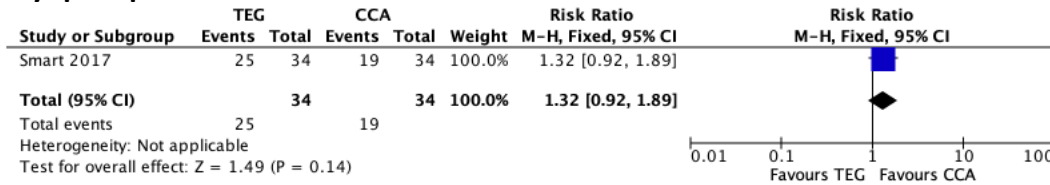
### RBC Transfusion



### Platelet Transfusion



### Cryoprecipitate Transfusion



**Evidence Summary 6: Red blood cell transfusion in non-massively bleeding, critically ill adults**

## Restrictive vs. liberal RBC transfusion in non-massively bleeding patients

### 1. GI Bleeding

Certainty assessment						№ of patients		Effect		Certainty	Importance
№ of studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Restrictive	Liberal	Relative (95% CI)	Absolute (95% CI)		
<b>Mortality - GI bleeding</b>											
4 RCTs	not serious	not serious	not serious	serious <sup>a</sup>	none	37/741 (5.0%)	68/865 (7.9%)	RR 0.63 (0.43 to 0.93)	<b>29 fewer per 1,000</b> (from 45 fewer to 6 fewer)	⊕⊕⊕○ MODERATE	CRITICAL
<b>Quality of life - GI bleeding</b>											
1 RCT	serious <sup>b</sup>	not serious	not serious	serious <sup>c</sup>	none	257	383	-	MD 0.07 lower (0.12 lower to 0.02 lower)	⊕⊕○○ LOW	CRITICAL
<b>Stroke - GI bleeding</b>											
2 RCTs	not serious	not serious	not serious	serious <sup>d</sup>	none	12/701 (1.7%)	29/828 (3.5%)	RR 0.56 (0.29 to 1.09)	<b>15 fewer per 1,000</b> (from 25 fewer to 3 more)	⊕⊕⊕○ MODERATE	CRITICAL
<b>Myocardial infarction - GI bleeding</b>											
1 RCT	not serious	not serious	not serious	very serious <sup>e</sup>	none	8/444 (1.8%)	13/445 (2.9%)	RR 0.62 (0.26 to 1.47)	<b>11 fewer per 1,000</b> (from 22 fewer to 14 more)	⊕⊕○○ LOW	CRITICAL
<b>Acute kidney injury - GI bleeding</b>											
1 RCT	not serious	not serious	serious <sup>f</sup>	serious <sup>d</sup>	none	78/444 (17.6%)	97/445 (21.8%)	RR 0.81 (0.62 to 1.05)	<b>41 fewer per 1,000</b> (from 83 fewer to 11 more)	⊕⊕○○ LOW	CRITICAL
<b>Volume overload/TACO - GI bleeding</b>											
1 RCT	not serious	not serious	not serious	serious <sup>g</sup>	none	2/444 (0.5%)	16/445 (3.6%)	RR 0.13 (0.03 to 0.54)	<b>31 fewer per 1,000</b> (from 35 fewer to 17 fewer)	⊕⊕⊕○ MODERATE	CRITICAL
<b>Post-transfusion sepsis/infection - GI bleeding</b>											

## Restrictive vs. liberal RBC transfusion in non-massively bleeding patients

2 RCTs	not serious	not serious	not serious	serious <sup>d</sup>	none	186/701 (26.5%)	227/82 8 (27.4%)	<b>RR 0.95</b> (0.81 to 1.13)	<b>14 fewer per 1,000</b> (from 52 fewer to 36 more)	⊕⊕⊕○ MODERATE	IMPORTANT
<b>Rebleeding - GI bleeding</b>											
4 RCTs	not serious	not serious	not serious	not serious	none	65/759 (8.6%)	117/88 3 (13.3%)	<b>RR 0.61</b> (0.46 to 0.81)	<b>52 fewer per 1,000</b> (from 72 fewer to 25 fewer)	⊕⊕⊕⊕ HIGH	IMPORTANT
<b>Transfusion reaction - GI bleeding</b>											
2 RCTs	serious <sup>h</sup>	not serious	not serious	serious <sup>g</sup>	none	16/701 (2.3%)	47/828 (5.7%)	<b>RR 0.36</b> (0.21 to 0.63)	<b>36 fewer per 1,000</b> (from 45 fewer to 21 fewer)	⊕⊕○○ LOW	IMPORTANT
<b>Hospital length of stay - GI bleeding</b>											
2 RCTs	not serious	not serious	not serious	not serious	none	701	828	-	<b>MD 1.12 lower</b> (1.66 lower to 0.59 lower)	⊕⊕⊕⊕ HIGH	IMPORTANT
<b>Mean transfusions - GI bleeding</b>											
4 RCTs	not serious	not serious <sup>i</sup>	not serious	not serious	none	741	865	-	<b>MD 1.88 lower</b> (2.37 lower to 1.39 lower)	⊕⊕⊕⊕ HIGH	IMPORTANT
<b>Proportion receiving transfusion - GI bleeding</b>											
2 RCTs	not serious	not serious <sup>i</sup>	not serious	not serious	none	351/701 (50.1%)	630/82 8 (76.1%)	<b>RR 0.67</b> (0.48 to 0.94)	<b>251 fewer per 1,000</b> (from 396 fewer to 46 fewer)	⊕⊕⊕⊕ HIGH	IMPORTANT

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

### Explanations

- Actual number of events is small. Given control group event rate of ~8% and RRR of 37%, the optimal information size is not met, resulting in serious imprecision.
- Significant loss to follow-up for EQ-5D scores in single trial reporting quality of life outcomes.
- Not statistically significant when restricted to patients with Hb <120, or in cluster-adjusted analyses.
- Wide confidence intervals which do not exclude the possibility of significant harm, resulting in serious imprecision.
- Very small number of events, resulting in very serious imprecision.
- Unclear definition of kidney injury, or patient relevance, in single study reporting this outcome.
- Though statistically significant, optimal information size is not met, resulting in serious imprecision.
- Lack of blinding bedside clinicians may result in under-reporting transfusion reactions in restrictive arm.
- Though statistical heterogeneity is present, it is of questionable relevance as all trials favour restrictive transfusion.

## Restrictive vs. liberal RBC transfusion in non-massively bleeding patients

### 2. Obstetric bleeding

Certainty assessment						№ of patients		Effect		Certainty	Importance
№ of studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Restrictive	Liberal	Relative (95% CI)	Absolute (95% CI)		
<b>Quality of life - Obstetric bleeding</b>											
1 RCT	serious <sup>a</sup>	not serious	not serious	serious <sup>b</sup>	none	262	259	-	MD 0.1 lower (3.5 lower to 3.3 higher)	⊕⊕○○ LOW	CRITICAL
<b>Venous thrombosis - Obstetric bleeding</b>											
1 RCT	not serious	not serious	not serious	very serious <sup>c</sup>	none	2/262 (0.8%)	2/259 (0.8%)	RR 0.99 (0.14 to 6.97)	0 fewer per 1,000 (from 7 fewer to 46 more)	⊕⊕○○ LOW	IMPORTANT
<b>Post-transfusion sepsis/infection - Obstetric bleeding</b>											
1 RCT	not serious	not serious	not serious	very serious <sup>c</sup>	none	24/262 (9.2%)	22/259 (8.5%)	RR 1.08 (0.62 to 1.87)	7 more per 1,000 (from 32 fewer to 74 more)	⊕⊕○○ LOW	IMPORTANT
<b>Transfusion reaction - Obstetric bleeding</b>											
1 RCT	serious <sup>d</sup>	not serious	not serious	very serious <sup>c</sup>	none	0/262 (0.0%)	3/259 (1.2%)	RR 0.14 (0.01 to 2.72)	10 fewer per 1,000 (from 11 fewer to 20 more)	⊕○○○ VERY LOW	IMPORTANT
<b>Mean transfusions - Obstetric bleeding</b>											
1 RCT	not serious	not serious	not serious	serious <sup>c</sup>	none	262	259	-	MD 2 higher (0 to 0)	⊕⊕⊕○ MODERATE	IMPORTANT

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

#### Explanations

- Patients were not blinded which may have impacted assessment of quality of life using SF-36.
- Wide confidence intervals which do not exclude the possibility of significant harm, resulting in serious imprecision.
- Very small number of events, resulting in very serious imprecision.
- Lack of blinding bedside clinicians may result in under-reporting transfusion reactions in restrictive arm.

## Restrictive vs. liberal RBC transfusion in non-massively bleeding patients

### 3. Vascular surgery

Certainty assessment						№ of patients		Effect		Certainty	Importance
№ of studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Restrictive	Liberal	Relative (95% CI)	Absolute (95% CI)		
<b>Mortality - Vascular surgery</b>											
1 RCT	not serious	not serious	not serious	very serious <sup>a</sup>	none	2/29 (6.9%)	1/29 (3.4%)	<b>RR 2.00</b> (0.19 to 20.86)	<b>34 more per 1,000</b> (from 28 fewer to 685 more)	⊕⊕○○ LOW	CRITICAL
<b>Myocardial infarction - Vascular surgery</b>											
1 RCT	not serious	not serious	not serious	very serious <sup>a</sup>	none	2/29 (6.9%)	2/29 (6.9%)	<b>RR 1.00</b> (0.15 to 6.63)	<b>0 fewer per 1,000</b> (from 59 fewer to 388 more)	⊕⊕○○ LOW	CRITICAL
<b>Transfusion reaction - Vascular surgery</b>											
1 RCT	serious <sup>b</sup>	not serious	not serious	very serious <sup>a</sup>	none	0/29 (0.0%)	1/29 (3.4%)	<b>RR 0.33</b> (0.01 to 7.86)	<b>23 fewer per 1,000</b> (from 34 fewer to 237 more)	⊕○○○ VERY LOW	IMPORTANT
<b>Mean transfusions - Vascular surgery</b>											
1 RCT	not serious	not serious	not serious	not serious	none	29	29	-	<b>MD 2 lower</b> (3.22 lower to 0.78 lower)	⊕⊕⊕⊕ HIGH	IMPORTANT
<b>Proportion receiving transfusion - Vascular surgery</b>											
1 RCT	not serious	not serious	not serious	not serious	none	19/29 (65.5%)	29/29 (100.0%)	<b>RR 0.66</b> (0.51 to 0.86)	<b>340 fewer per 1,000</b> (from 490 fewer to 140 fewer)	⊕⊕⊕⊕ HIGH	IMPORTANT

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

#### Explanations

a. Very small number of events, resulting in very serious imprecision.

b. Lack of blinding bedside clinicians may result in under-reporting transfusion reactions in restrictive arm.



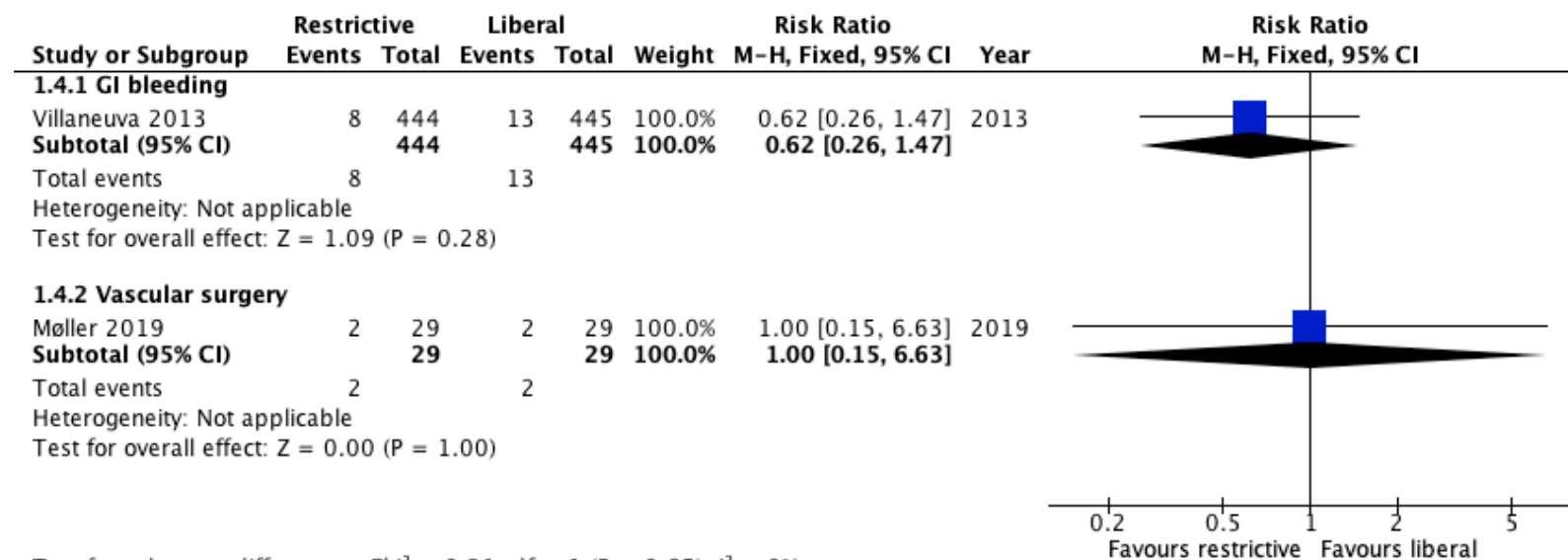


## Restrictive vs. liberal RBC transfusion in non-massively bleeding patients

### 3. Stroke



### 4. Myocardial infarction

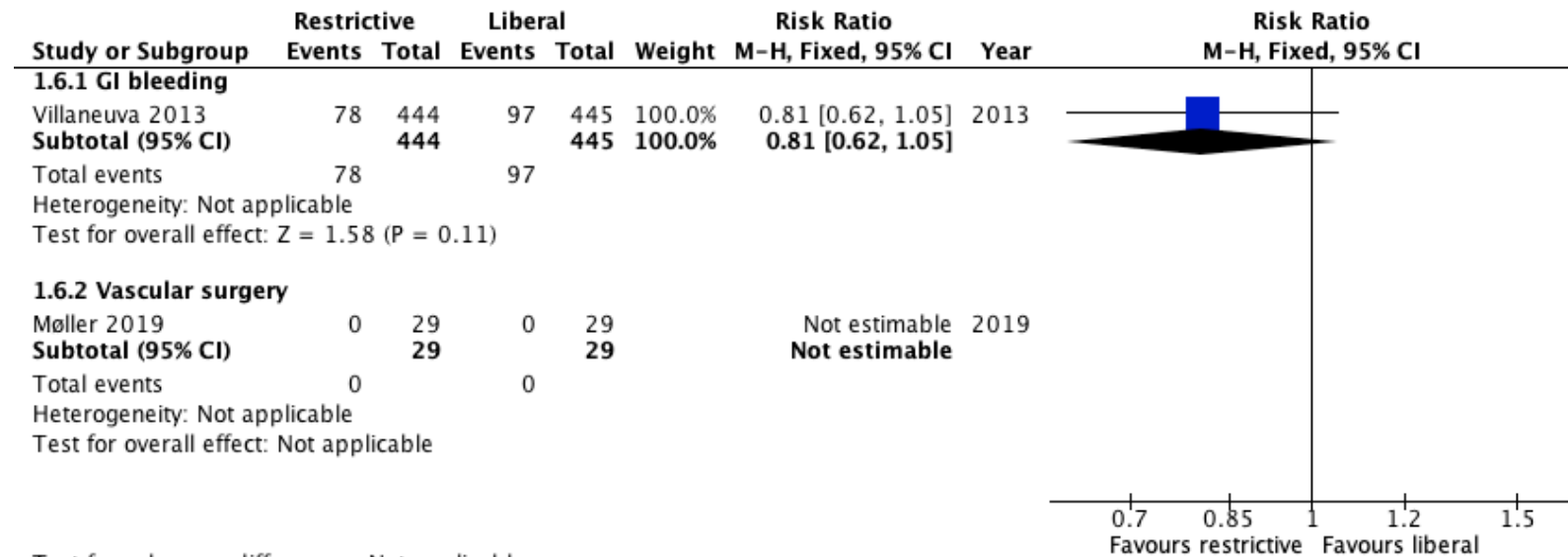


Test for subgroup differences: Chi<sup>2</sup> = 0.21, df = 1 (P = 0.65), I<sup>2</sup> = 0%

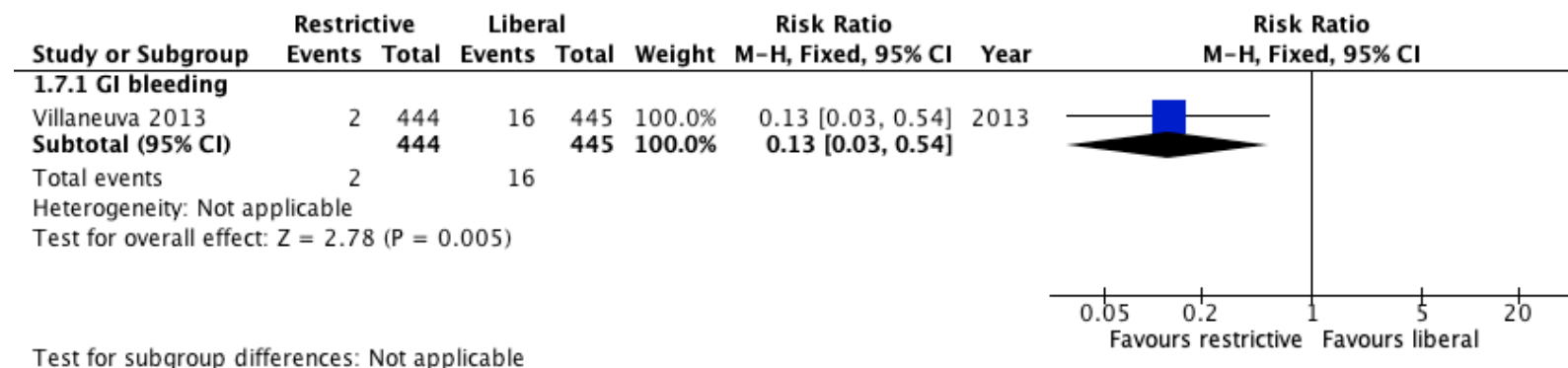
## Restrictive vs. liberal RBC transfusion in non-massively bleeding patients

### 5. ARDS/TRALI - no studies identified

### 6. Acute kidney injury (AKI not specified in Villaneuva 2013; need for RRT in Moller 2019)

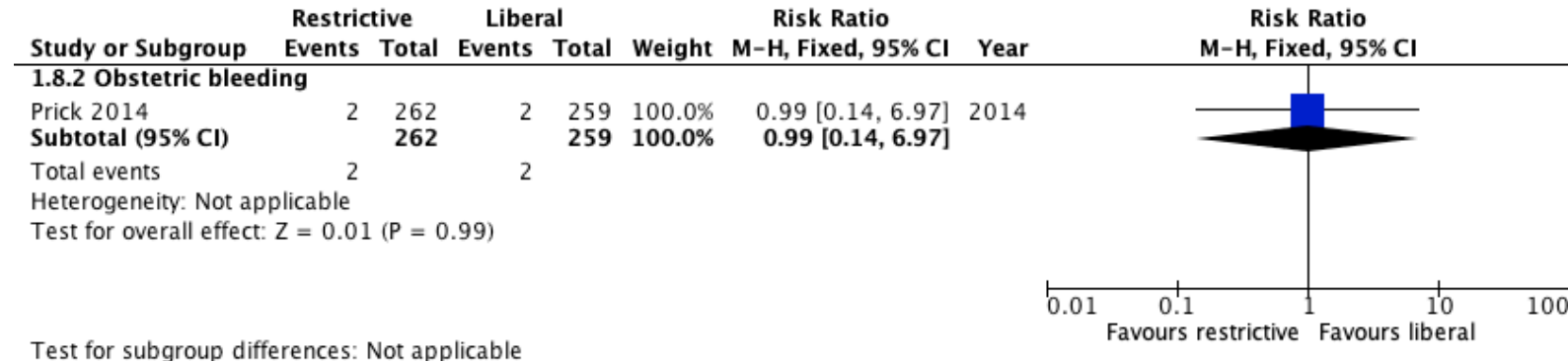


### 7. Volume overload/TACO

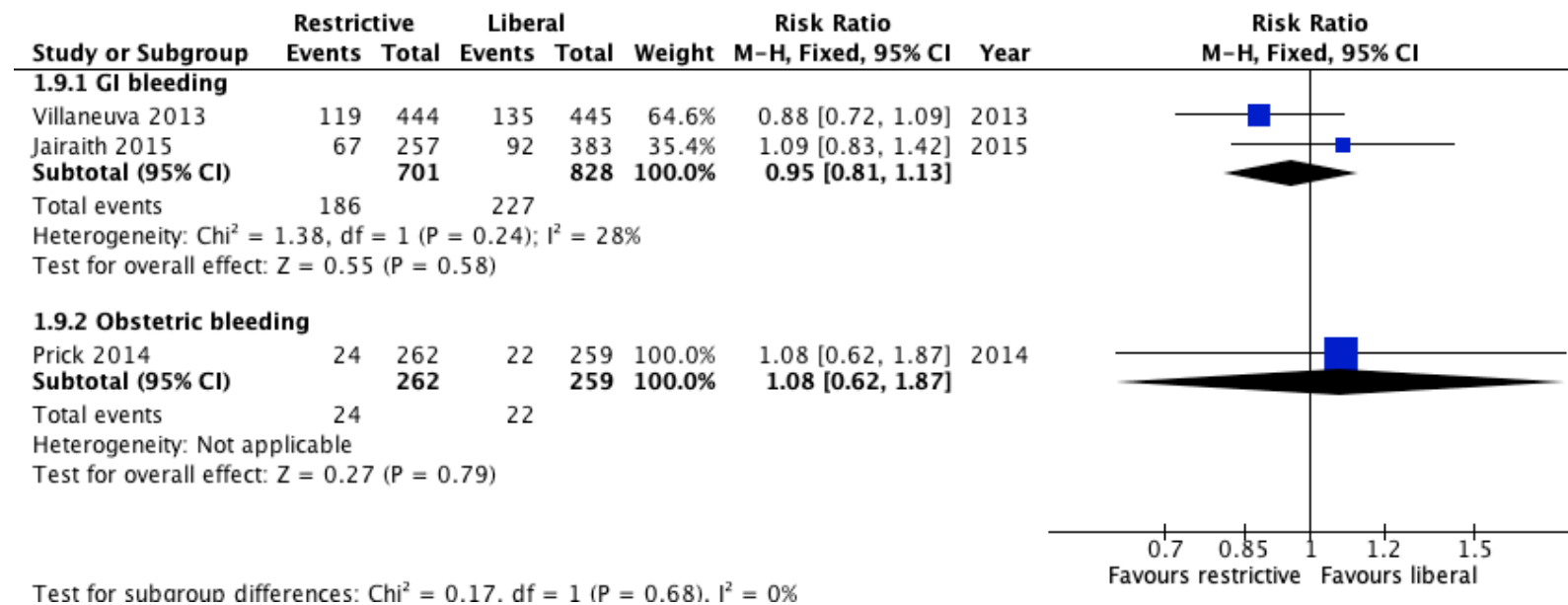


## Restrictive vs. liberal RBC transfusion in non-massively bleeding patients

### 8. Venous thrombosis

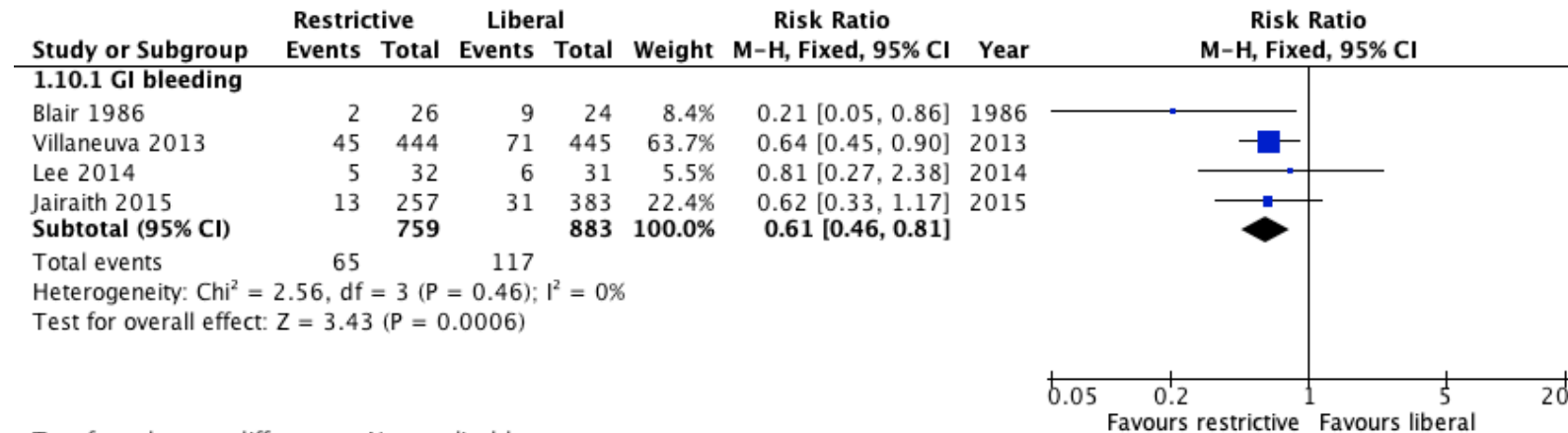


### 9. Post-transfusion sepsis/infection

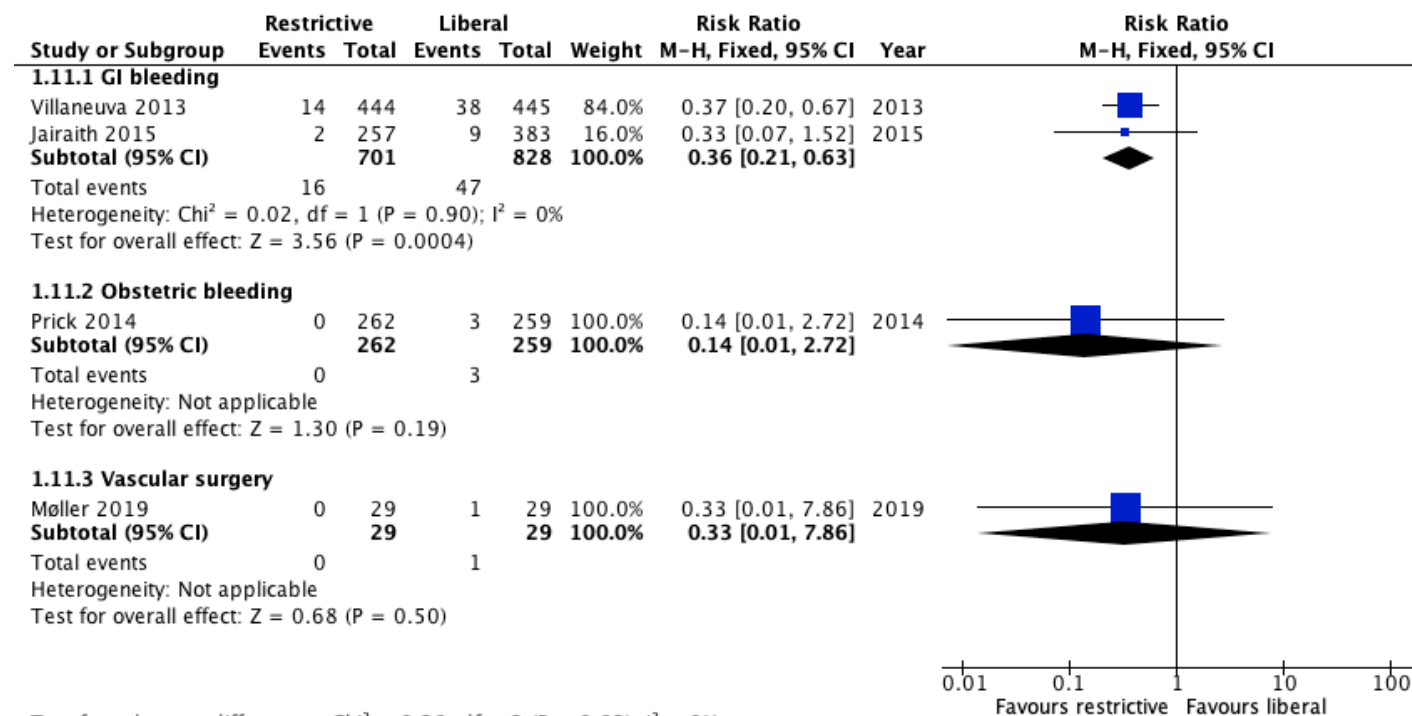


## Restrictive vs. liberal RBC transfusion in non-massively bleeding patients

### 10. Rebleeding (clinical hemostasis)



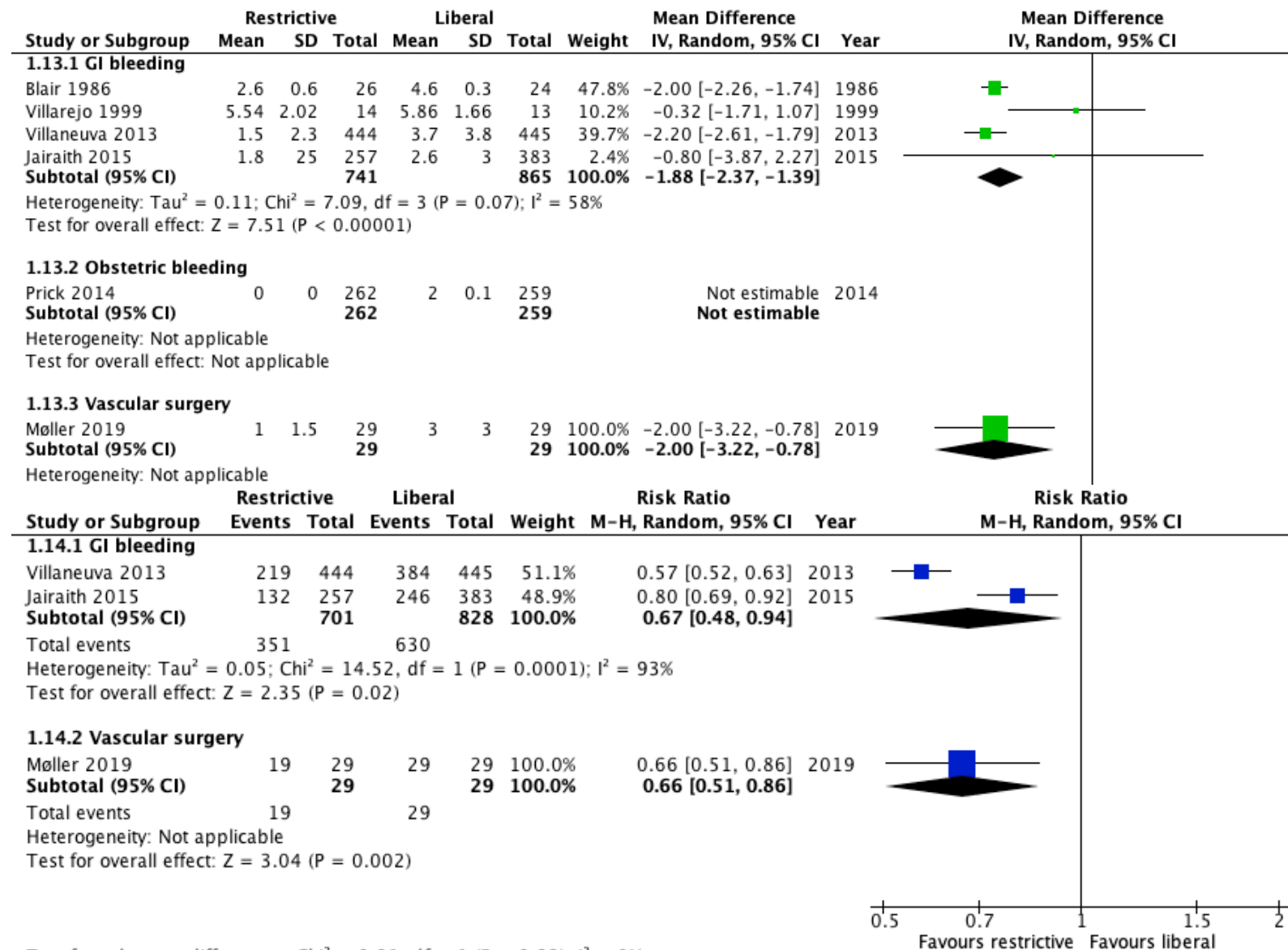
### 11. Transfusion reaction



Test for subgroup differences:  $\text{Chi}^2 = 0.38$ ,  $\text{df} = 2$  ( $P = 0.83$ ),  $I^2 = 0\%$

## Restrictive vs. liberal RBC transfusion in non-massively bleeding patients

### 12. Hospital length of stay



13. Mean number of transfusions

14. Proportion of patients receiving transfusion

Test for subgroup differences: Chi<sup>2</sup> = 0.01, df = 1 (P = 0.93), I<sup>2</sup> = 0%

**Evidence Summary 7: Platelet transfusion in non-massively bleeding, critically ill adults**


*See Evidence Summary 2 for cold-stored platelets in non-massively bleeding critically ill adults*

## Restrictive vs. Liberal Platelet Transfusion Strategy- Evidence Summaries


Restrictive platelet transfusions compared to liberal platelet transfusion for non-massively bleeding patients on anti-platelet therapy

Certainty assessment							N <sub>o</sub> of patients		Effect		Certainty	Importance
N <sub>o</sub> of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Restrictive platelet transfusions	liberal platelet transfusion	Relative (95% CI)	Absolute (95% CI)		
<b>Mortality (3 month)</b>												
1	randomised trials	not serious	not serious	not serious	serious <sup>a</sup>	none <sup>b</sup>	21/93 (22.6%)	31/97 (32.0%)	<b>RR 0.71</b> (0.44 to 1.14)	<b>93 fewer per 1,000</b> (from 179 fewer to 45 more)	⊕⊕⊕⊖ MODERATE	CRITICAL
<b>Mortality-Overall</b>												
2	randomised trials	not serious	not serious	not serious	serious <sup>a</sup>	none <sup>b</sup>	39/205 (19.0%)	48/211 (22.7%)	<b>RR 0.84</b> (0.58 to 1.22)	<b>36 fewer per 1,000</b> (from 96 fewer to 50 more)	⊕⊕⊕⊖ MODERATE	CRITICAL
<b>Modified Rankin Score 4-6 at 3 months</b>												
1	randomised trials	not serious	not serious	not serious	serious <sup>a</sup>	none <sup>b</sup>	52/93 (55.9%)	66/97 (68.0%)	<b>RR 0.82</b> (0.66 to 1.03)	<b>122 fewer per 1,000</b> (from 231 fewer to 20 more)	⊕⊕⊕⊖ MODERATE	CRITICAL
<b>Modified Rankin Score 3-6 at 3 months</b>												
1	randomised trials	not serious	not serious	not serious	serious <sup>a</sup>	none <sup>b</sup>	76/93 (81.7%)	70/97 (72.2%)	<b>RR 1.13</b> (0.97 to 1.32)	<b>94 more per 1,000</b> (from 22 fewer to 231 more)	⊕⊕⊕⊖ MODERATE	CRITICAL
<b>ICH enlargement</b>												
1	randomised trials	not serious	not serious	not serious	serious <sup>a</sup>	none <sup>b</sup>	13/93 (14.0%)	15/97 (15.5%)	<b>RR 0.90</b> (0.46 to 1.80)	<b>15 fewer per 1,000</b> (from 84 fewer to 124 more)	⊕⊕⊕⊖ MODERATE	IMPORTANT
<b>Ischemic Stroke</b>												




1	randomised trials	not serious	not serious	not serious	very serious <sup>c</sup>	none <sup>b</sup>	0/93 (0.0%)	1/97 (1.0%)	<b>RR 0.35</b> (0.01 to 8.42)	<b>7 fewer per 1,000</b> (from 10 fewer to 76 more)	 LOW	CRITICAL
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**MI**

1	randomised trials	not serious	not serious	not serious	very serious <sup>c</sup>	none <sup>b</sup>	1/93 (1.1%)	1/97 (1.0%)	<b>RR 1.04</b> (0.07 to 16.43)	<b>0 fewer per 1,000</b> (from 10 fewer to 159 more)	 LOW	IMPORTANT
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**DVT**

1	randomised trials	not serious	not serious	not serious	very serious <sup>c</sup>	none <sup>b</sup>	0/93 (0.0%)	2/97 (2.1%)	<b>RR 0.21</b> (0.01 to 4.29)	<b>16 fewer per 1,000</b> (from 20 fewer to 68 more)	 LOW	IMPORTANT
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**Pulmonary Embolism**

1	randomised trials	not serious	not serious	not serious	very serious <sup>c</sup>	none <sup>b</sup>	0/93 (0.0%)	1/97 (1.0%)	<b>RR 0.35</b> (0.01 to 8.42)	<b>7 fewer per 1,000</b> (from 10 fewer to 76 more)	 LOW	IMPORTANT
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**Post operative Hemorrhage**

1	randomised trials	not serious	not serious	not serious	very serious <sup>c</sup>	none <sup>b</sup>	17/112 (15.2%)	15/112 (13.4%)	<b>RR 1.13</b> (0.60 to 2.16)	<b>17 more per 1,000</b> (from 54 fewer to 155 more)	 LOW	IMPORTANT
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**ADL- Completely dependent**

1	randomised trials	not serious	not serious	not serious	very serious <sup>c</sup>	none <sup>b</sup>	4/112 (3.6%)	2/114 (1.8%)	<b>RR 2.04</b> (0.38 to 10.89)	<b>18 more per 1,000</b> (from 11 fewer to 174 more)	 LOW	CRITICAL
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**CI:** Confidence interval; **RR:** Risk ratio

**Explanations**

- a. Rated down for imprecision by 1 level because of the small number of events and the 95% CI cross the level of significant
- b. Due to the small number of studies publication bias could not be assessed.
- c. Rated down for imprecision by 2 levels given small sample size, very small number of event and the 95% CI crosses the level of significance.

Restrictive platelet transfusion strategy compared to liberal platelet transfusion strategy for thrombocytopenic non-massively bleeding patients

Certainty assessment							N <sub>o</sub> of patients		Effect		Certainty	Importance
N <sub>o</sub> of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	restrictive platelet transfusion strategy	liberal platelet transfusion strategy	Relative (95% CI)	Absolute (95% CI)		
<b>Increase in hematoma</b>												
1	observational studies	serious	not serious	serious <sup>a</sup>	very serious <sup>b</sup>	none	7/24 (29.2%)	16/39 (41.0%)	<b>RR 0.71</b> (0.34 to 1.47)	<b>119 fewer per 1,000</b> (from 271 fewer to 193 more)	⊕○○○ VERY LOW	IMPORTANT
<b>No change in hematoma</b>												
1	observational studies	serious	not serious	serious <sup>a</sup>	very serious <sup>b</sup>	none	14/18 (77.8%)	13/24 (54.2%)	<b>RR 1.44</b> (0.92 to 2.24)	<b>238 more per 1,000</b> (from 43 fewer to 672 more)	⊕○○○ VERY LOW	IMPORTANT

CI: Confidence interval; RR: Risk ratio

**Explanations**

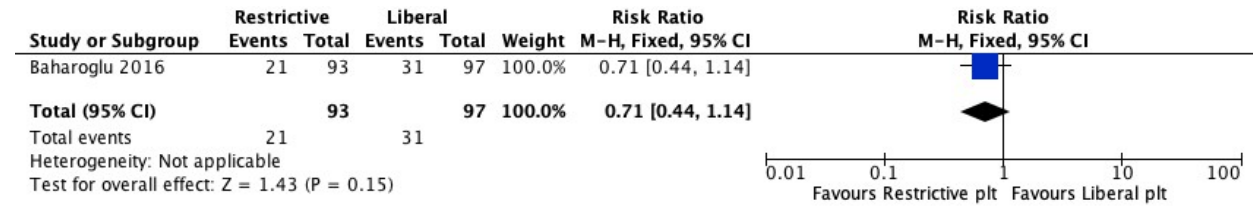
a. Rated down for indirectness.

b. Rated down for two levels for imprecision do to small number of events, and the 95% confidence interval encompasses 1.

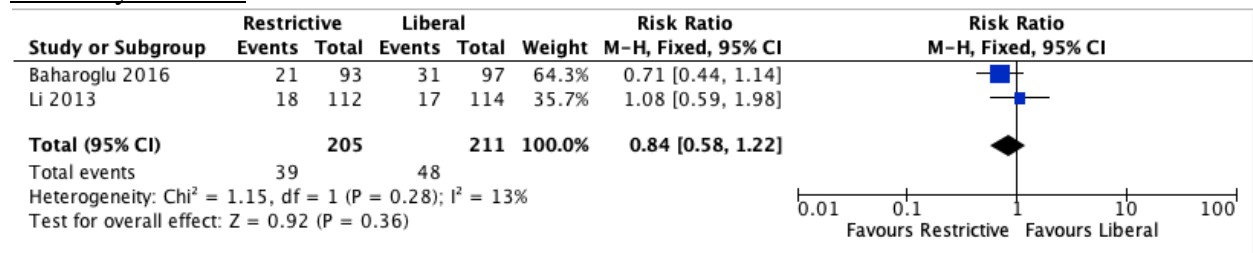
## Restrictive vs. Liberal Platelet Strategy in Non-massively Bleeding Patients On Antiplatelet Therapy

### RCT- Restrictive vs. Liberal Platelet transfusion in patients on antiplatelet therapy

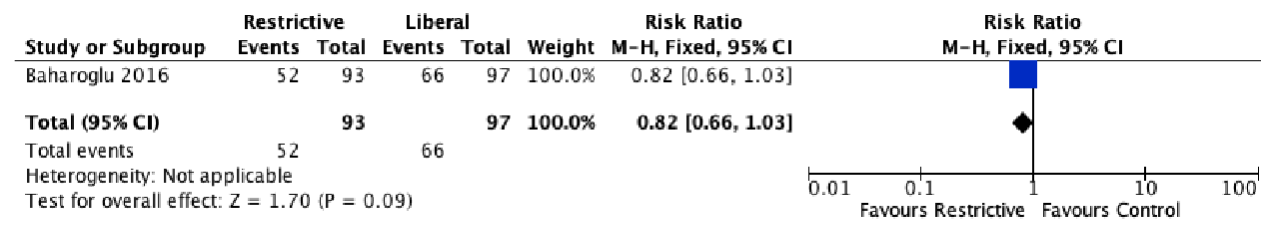
#### Mortality 3 months



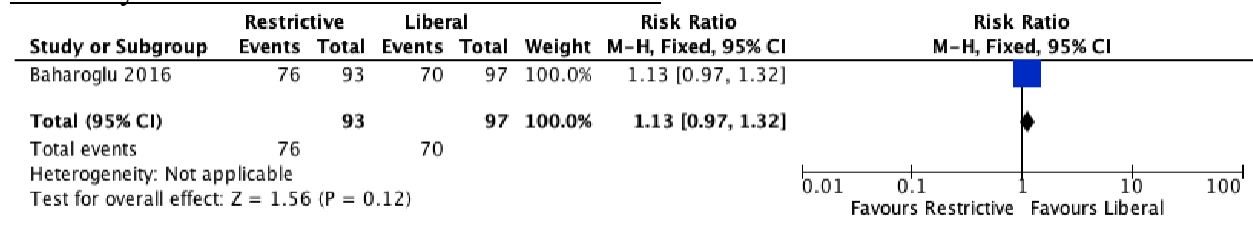
#### Mortality- Overall



#### Disability- Modified Rankin Score 4-6 at 3 months



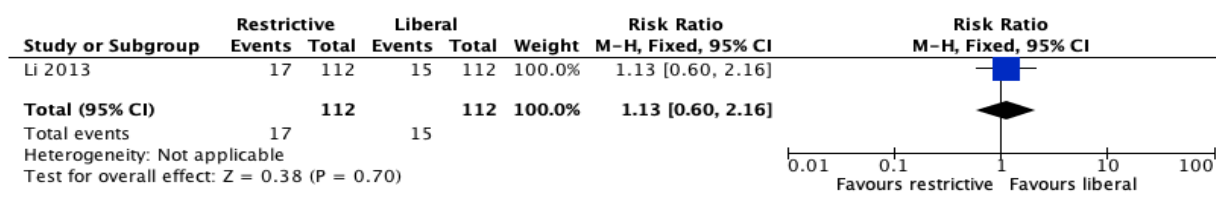
#### Disability- Modified Rankin Score 3-6 at 3 months



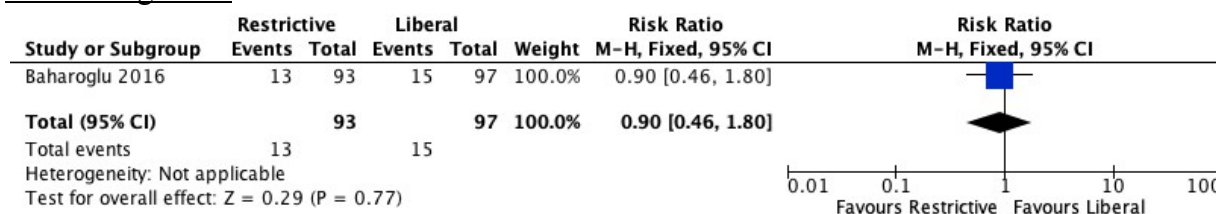
#### Disability- ADL Grade 4- Completely dependent



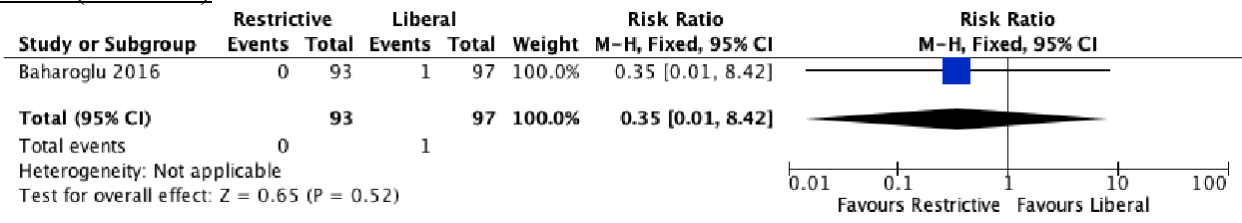
## Postoperative Hemorrhage



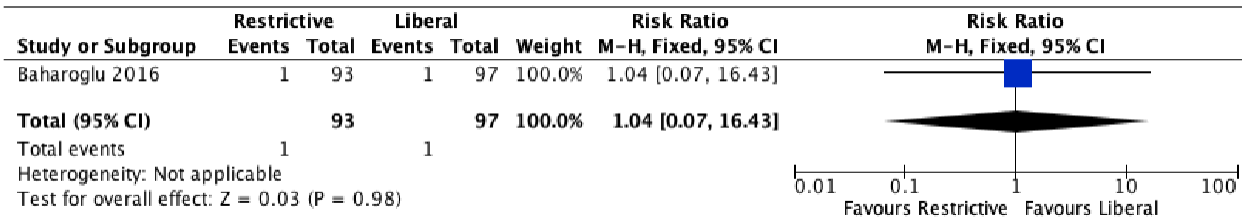
## ICH Enlargement



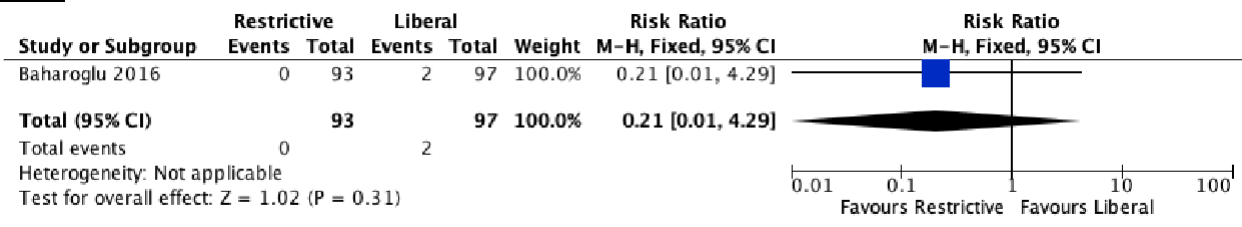
## CVA (Ischemic)



## MI



## DVT



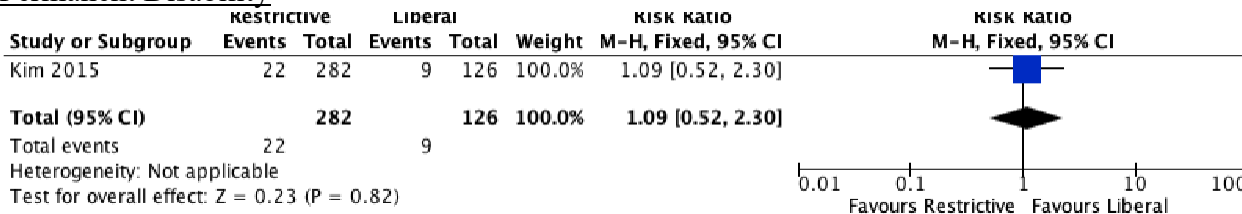
## Observational Studies- Neuro and GI Bleeding

### Neuro

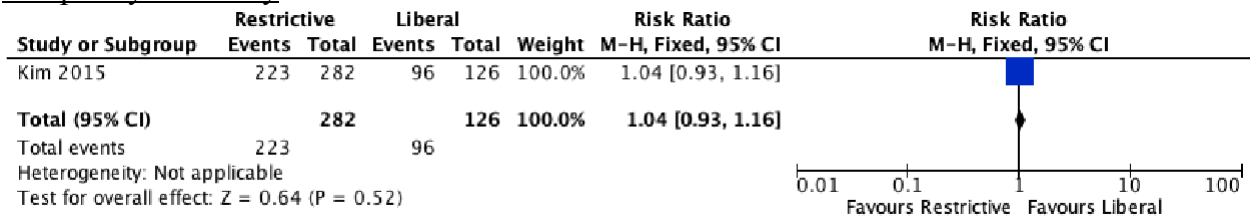
#### Mortality



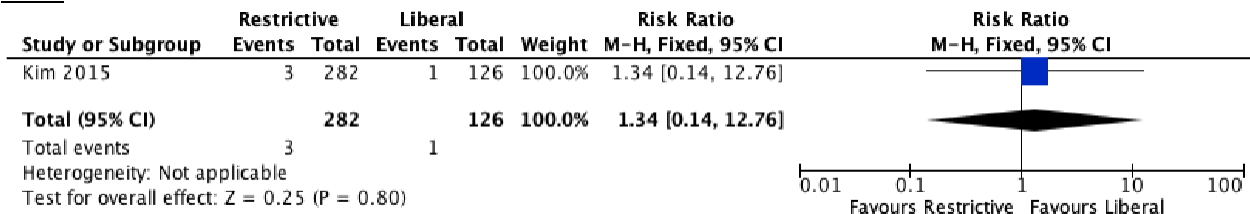
#### Permanent Disability



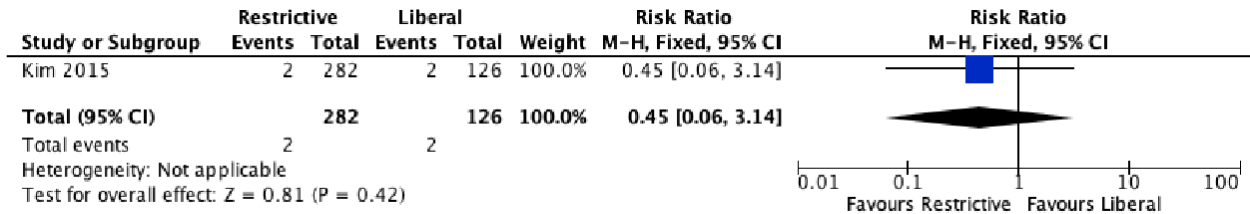
## Temporary Disability



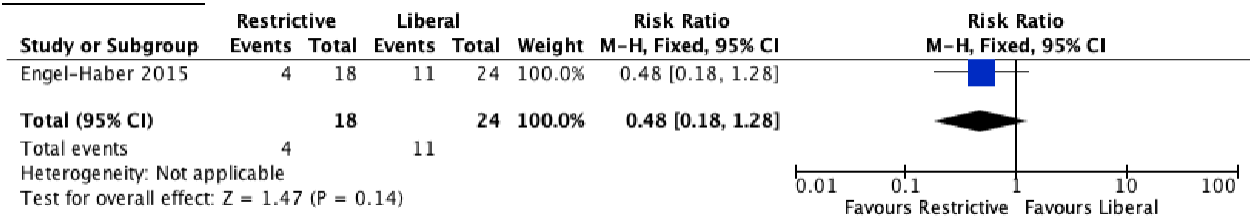
## VTE



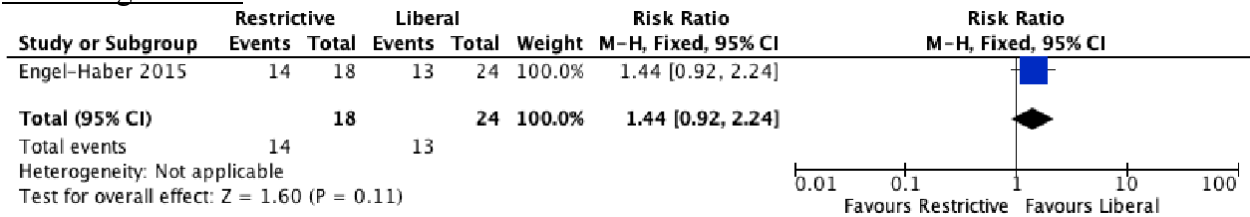
## CVA



## Increase in ICH

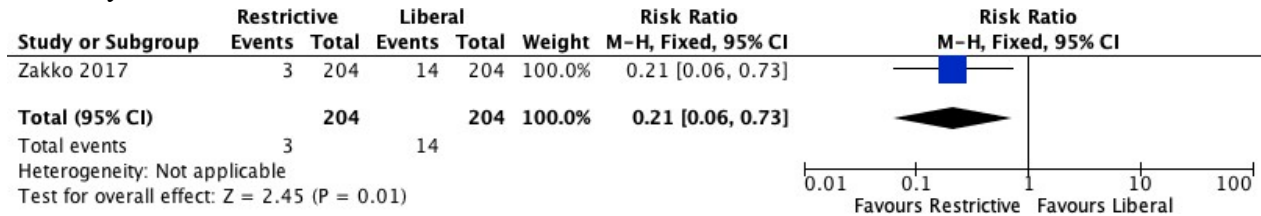


## No Change in ICU

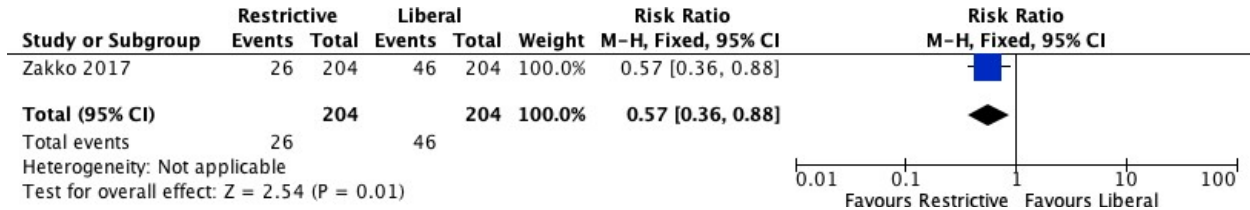


## GI Bleeding

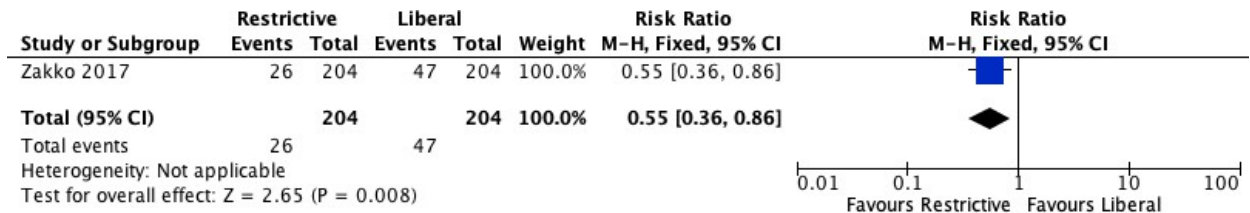
### Mortality



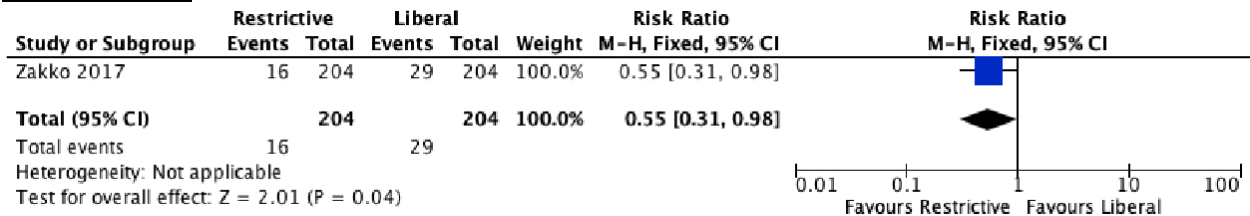
### MI



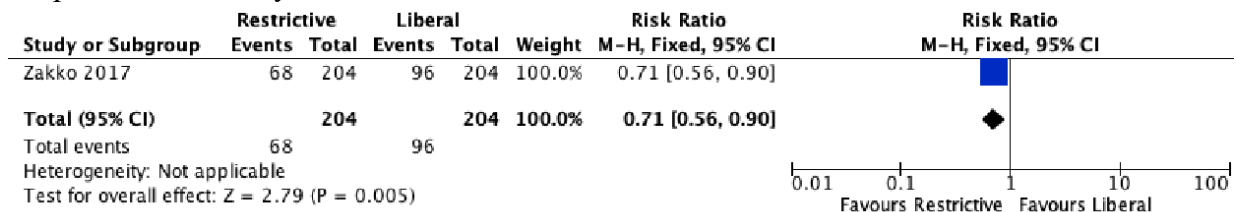
### Major Cardiac Events



### Recurrent GIB



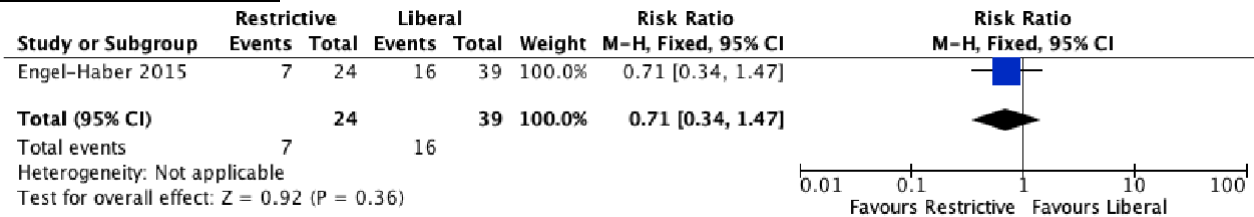
### Hospital LOS > 4 Days



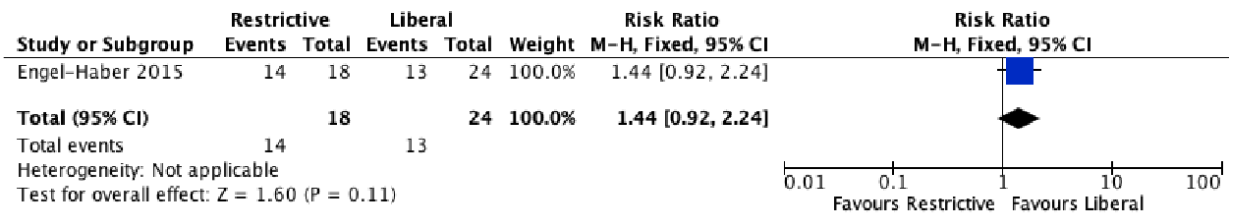
## Restrictive vs. Liberal Platelet Strategy in Non-massively Bleeding Patients

NB: Engel-Haber 2015 did have a cohort not exposed to antiplatelet therapy.

### Increase in hematoma



### No change in hematoma





**Evidence Summary 8: Fibrinogen replacement in non-massively bleeding, critically ill adults**

## Fibrinogen in non-massively bleeding critically ill patients

Certainty assessment						№ of patients		Effect		Certainty	Importance
№ of studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Early fibrinogen	Control	Relative (95% CI)	Absolute (95% CI)		
<b>Mortality - Cardiac surgery</b>											
5 RCT	not serious	not serious	not serious	very serious <sup>a</sup>	none	5/235 (2.1%)	12/234 (5.1%)	<b>RR 0.44</b> (0.17 to 1.19)	<b>29 fewer per 1,000</b> (from 43 fewer to 10 more)	⊕⊕○○ LOW	CRITICAL
<b>Mortality - Vascular surgery</b>											
1 RCT	not serious	not serious	not serious	very serious <sup>a</sup>	none	0/10 (0.0%)	1/10 (10.0%)	<b>RR 0.33</b> (0.02 to 7.32)	<b>67 fewer per 1,000</b> (from 98 fewer to 632 more)	⊕⊕○○ LOW	CRITICAL
<b>Stroke - Cardiac surgery</b>											
3 RCT	not serious	serious <sup>b</sup>	not serious	very serious <sup>a</sup>	none	6/196 (3.1%)	5/192 (2.6%)	<b>RR 1.16</b> (0.36 to 3.72)	<b>4 more per 1,000</b> (from 17 fewer to 71 more)	⊕○○○ VERY LOW	CRITICAL
<b>Stroke - Vascular surgery</b>											
1 RCT	not serious	not serious	not serious	very serious <sup>a</sup>	none	0/10 (0.0%)	0/10 (0.0%)	not pooled	see comment	-	CRITICAL
<b>Myocardial infarction - Cardiac surgery</b>											
3 RCT	not serious	not serious	not serious	very serious <sup>a</sup>	none	3/128 (2.3%)	2/128 (1.6%)	<b>RR 1.40</b> (0.29 to 6.87)	<b>6 more per 1,000</b> (from 11 fewer to 92 more)	⊕⊕○○ LOW	CRITICAL
<b>Myocardial infarction - Non-cardiac surgery</b>											
1 RCT	not serious	not serious	not serious	very serious <sup>a</sup>	none	1/10 (10.0%)	1/10 (10.0%)	<b>RR 1.00</b> (0.07 to 13.87)	<b>0 fewer per 1,000</b> (from 93 fewer to 1,000 more)	⊕⊕○○ LOW	CRITICAL
<b>Acute kidney injury - Cardiac surgery</b>											

## Fibrinogen in non-massively bleeding critically ill patients

3 RCT	not serious	not serious	not serious	very serious <sup>a</sup>	none	11/196 (5.6%)	14/192 (7.3%)	<b>RR 0.77</b> (0.36 to 1.65)	<b>17 fewer per 1,000</b> (from 47 fewer to 47 more)	⊕⊕○○ LOW	CRITICAL
<b>Acute kidney injury - Non-cardiac surgery</b>											
1 RCT	not serious	not serious	not serious	very serious <sup>a</sup>	none	0/10 (0.0%)	1/10 (10.0%)	<b>RR 0.33</b> (0.02 to 7.32)	<b>67 fewer per 1,000</b> (from 98 fewer to 632 more)	⊕⊕○○ LOW	CRITICAL
<b>Venous thrombosis - Cardiac surgery</b>											
4 RCT	not serious	not serious	not serious	very serious <sup>a</sup>	none	1/206 (0.5%)	0/202 (0.0%)	<b>RR 2.85</b> (0.12 to 68.83)	<b>0 fewer per 1,000</b> (from 0 fewer to 0 fewer)	⊕⊕○○ LOW	IMPORTANT
<b>Venous thrombosis - Non-cardiac surgery</b>											
1 RCT	not serious	not serious	not serious	very serious <sup>a</sup>	none	0/10 (0.0%)	1/10 (10.0%)	<b>RR 0.33</b> (0.02 to 7.32)	<b>67 fewer per 1,000</b> (from 98 fewer to 632 more)	⊕⊕○○ LOW	IMPORTANT
<b>Infection - Cardiac surgery</b>											
3 RCT	not serious	not serious	not serious	very serious <sup>a</sup>	none	23/196 (11.7%)	23/192 (12.0%)	<b>RR 0.97</b> (0.57 to 1.67)	<b>4 fewer per 1,000</b> (from 52 fewer to 80 more)	⊕⊕○○ LOW	IMPORTANT
<b>Infection - Non-cardiac surgery</b>											
1 RCT	not serious	not serious	not serious	very serious <sup>a</sup>	none	3/22 (13.6%)	3/21 (14.3%)	<b>RR 0.95</b> (0.22 to 4.21)	<b>7 fewer per 1,000</b> (from 111 fewer to 459 more)	⊕⊕○○ LOW	IMPORTANT
<b>Blood loss - Cardiac surgery</b>											
3 RCT	not serious	not serious <sup>c</sup>	not serious	serious <sup>d</sup>	none	176	172	-	<b>MD 87.76 lower</b> (149.49 lower to 26.03 lower)	⊕⊕⊕○ MODERATE	IMPORTANT
<b>Reoperation - Cardiac surgery</b>											

## Fibrinogen in non-massively bleeding critically ill patients

4 RCT	not serious	not serious	not serious	very serious <sup>a</sup>	none	20/168 (11.9%)	23/168 (13.7%)	<b>RR 0.87</b> (0.54 to 1.42)	<b>18 fewer per 1,000</b> (from 63 fewer to 57 more)	⊕⊕○○ LOW	IMPORTANT
<b>ICU length of stay - Non-cardiac surgery</b>											
1 RCT	not serious	not serious	not serious	very serious <sup>e</sup>	none	19	10	-	<b>MD 0</b> (2.93 lower to 2.93 higher)	⊕⊕○○ LOW	IMPORTANT
<b>Hospital length of stay - Non-cardiac surgery</b>											
1 RCT	not serious	not serious	not serious	very serious <sup>e</sup>	none	10	10	-	<b>MD 1.5 lower</b> (9.96 lower to 6.96 higher)	⊕⊕○○ LOW	IMPORTANT
<b>Proportion receiving RBCs - Cardiac surgery</b>											
3 RCT	not serious	serious <sup>b</sup>	not serious	serious <sup>d</sup>	none	38/128 (29.7%)	61/128 (47.7%)	<b>RR 0.62</b> (0.46 to 0.84)	<b>181 fewer per 1,000</b> (from 257 fewer to 76 fewer)	⊕⊕○○ LOW	IMPORTANT
<b>Proportion receiving plasma - Cardiac surgery</b>											
2 RCT	not serious	serious <sup>b</sup>	not serious	serious <sup>d</sup>	none	9/118 (7.6%)	21/118 (17.8%)	<b>RR 0.44</b> (0.22 to 0.90)	<b>100 fewer per 1,000</b> (from 139 fewer to 18 fewer)	⊕⊕○○ LOW	IMPORTANT
<b>Proportion receiving platelets - Cardiac surgery</b>											
3 RCT	not serious	not serious	not serious	serious <sup>d</sup>	none	13/128 (10.2%)	27/128 (21.1%)	<b>RR 0.50</b> (0.29 to 0.86)	<b>105 fewer per 1,000</b> (from 150 fewer to 30 fewer)	⊕⊕⊕○ MODERATE	IMPORTANT
<b>Mean RBCs transfused - Cardiac surgery</b>											
3 RCT	not serious	serious <sup>b</sup>	not serious	serious <sup>e</sup>	none	176	172	-	<b>MD 0.37 lower</b> (1.6 lower to 0.86 higher)	⊕⊕○○ LOW	IMPORTANT
<b>Mean RBCs transfused - Non-cardiac surgery</b>											

## Fibrinogen in non-massively bleeding critically ill patients

1 RCT	not serious	not serious	not serious	very serious <sup>a</sup>	none	10	10	-	MD <b>1.5 lower</b> (3.15 lower to 0.15 higher)	⊕⊕○○ LOW	IMPORTANT
<b>Mean plasma transfused - Cardiac surgery</b>											
2 RCT	not serious	serious <sup>b</sup>	not serious	serious <sup>e</sup>	none	118	114	-	MD <b>0.42 lower</b> (0.99 lower to 0.14 higher)	⊕⊕○○ LOW	IMPORTANT
<b>Mean platelets transfused - Cardiac surgery</b>											
2 RCT	not serious	not serious	not serious	very serious <sup>e</sup>	none	118	114	-	MD <b>0.01 lower</b> (0.31 lower to 0.29 higher)	⊕⊕○○ LOW	IMPORTANT

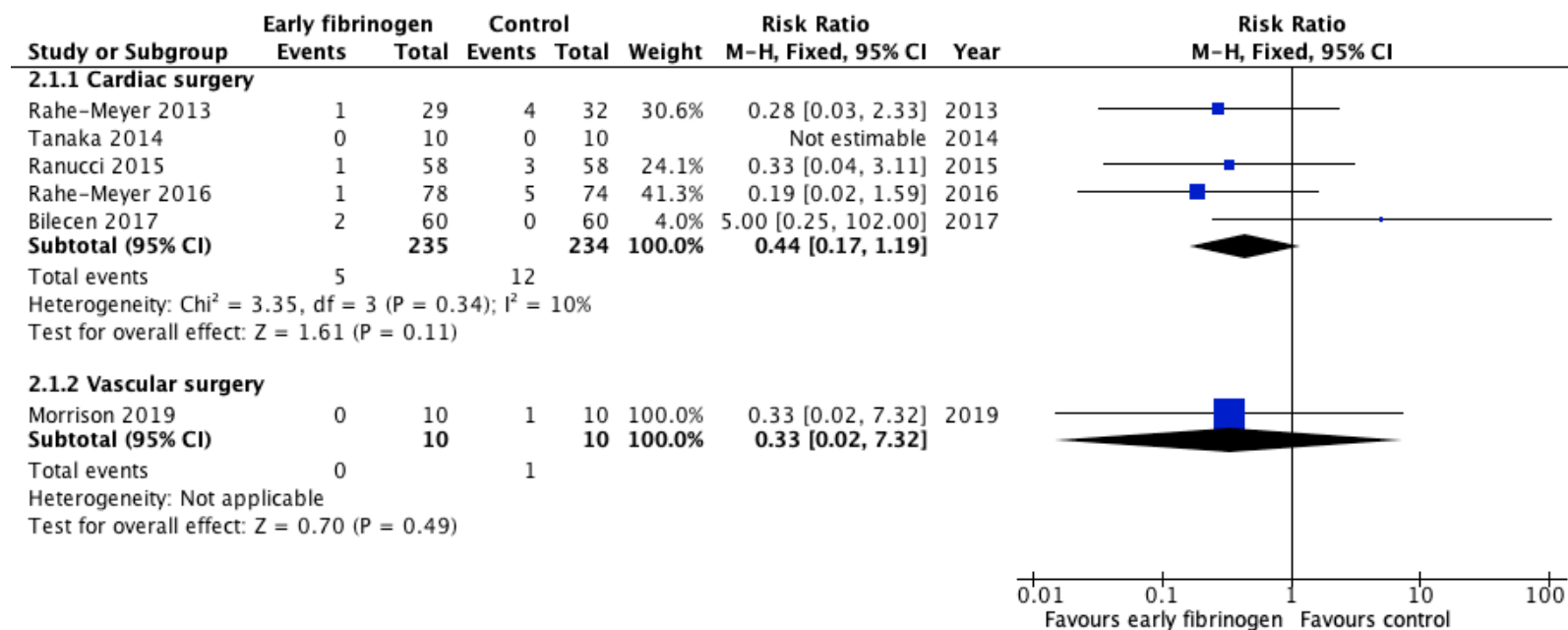
CI: Confidence interval; RR: Risk ratio; MD: Mean difference

### Explanations

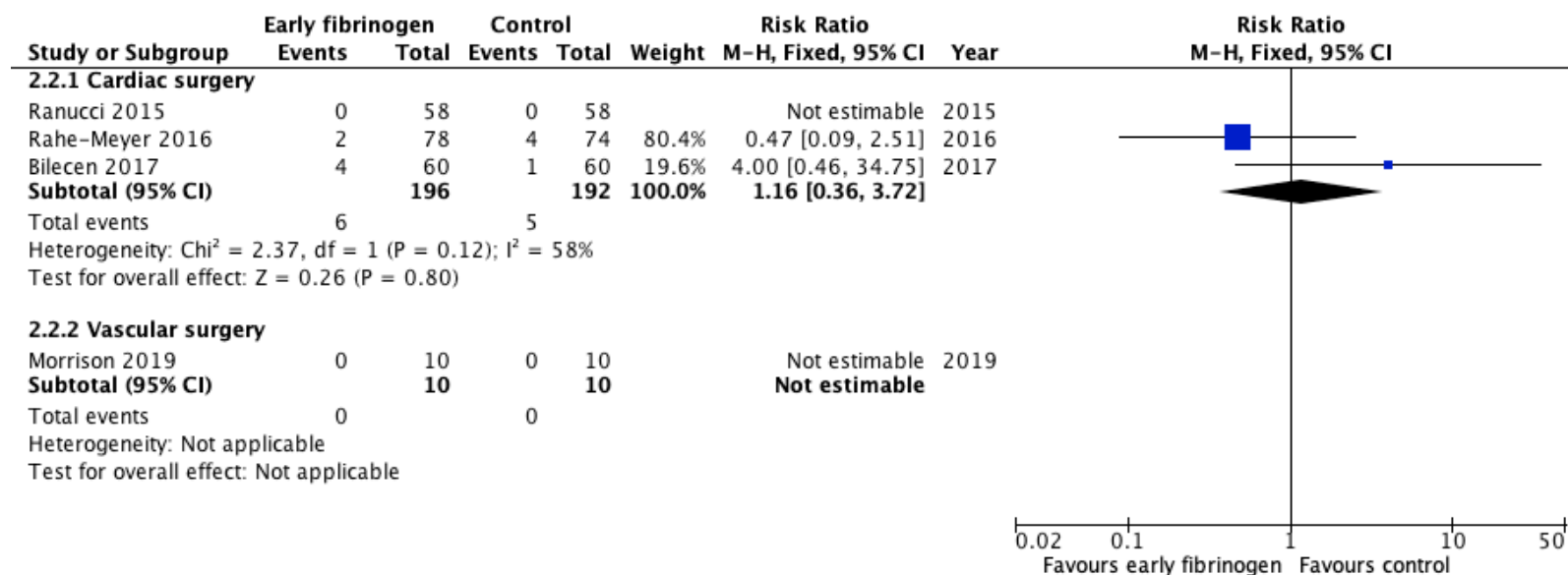
- Few events with very wide confidence intervals which do not exclude significant benefit or harm.
- Significant heterogeneity with point estimates on both sides of the line of no effect.
- Statistical heterogeneity, but of little clinical significance as all point estimates and confidence intervals favour fibrinogen.
- Though statistically significant, but optimal information size is not met, resulting in likely imprecision.
- Small number of patients with very wide confidence intervals resulting in very significant imprecision.

# Fibrinogen in non-massively bleeding critically ill patients

## 1. Mortality

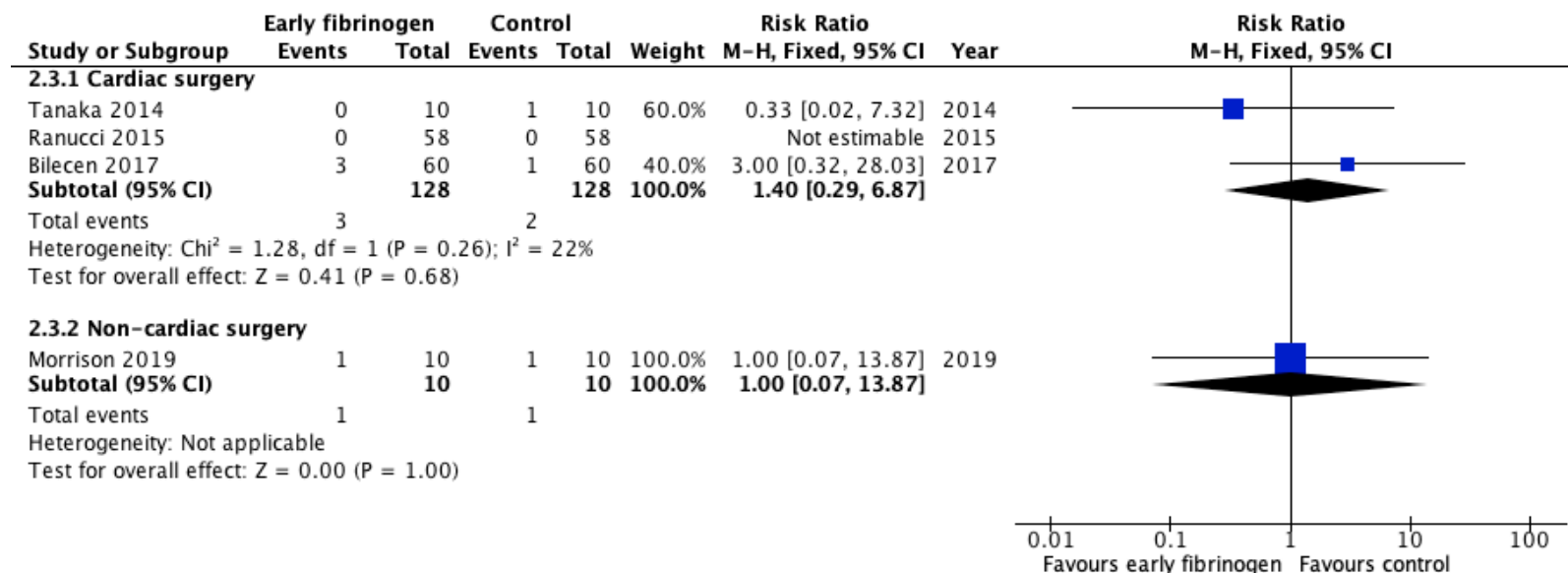


## 2. Stroke

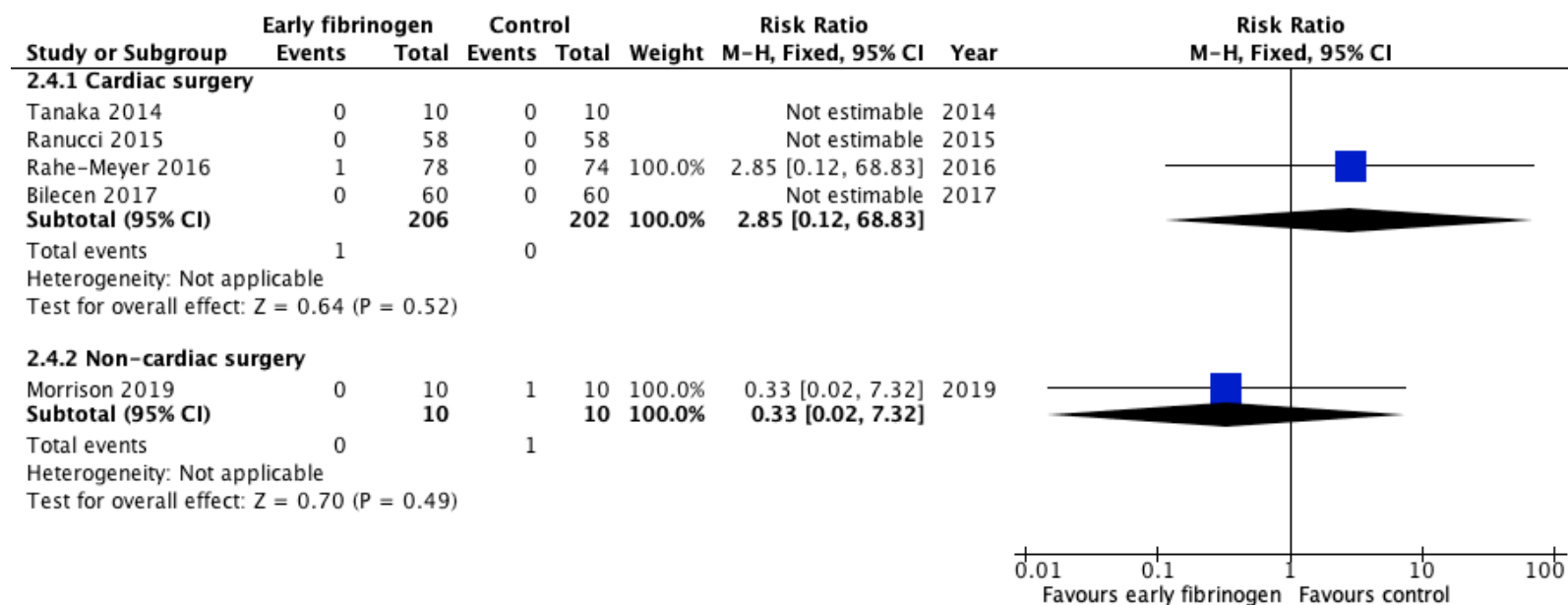


# Fibrinogen in non-massively bleeding critically ill patients

## 3. Myocardial infarction

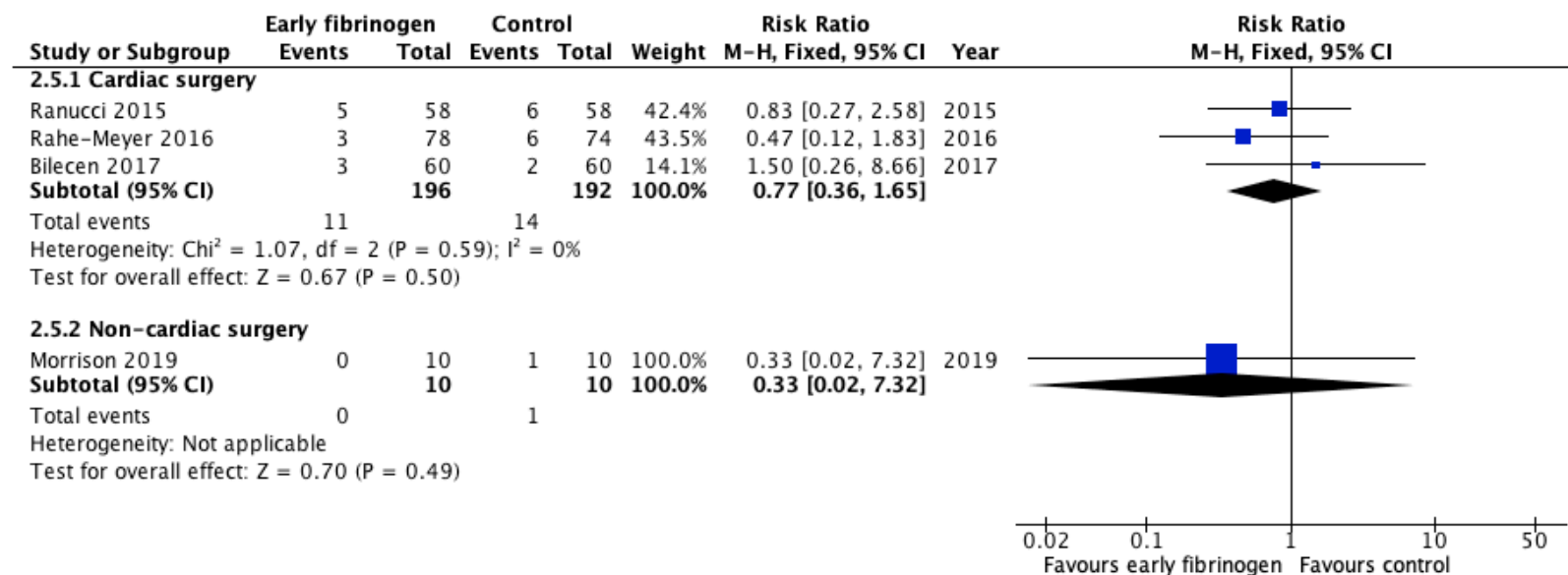


## 4. Venous thrombosis

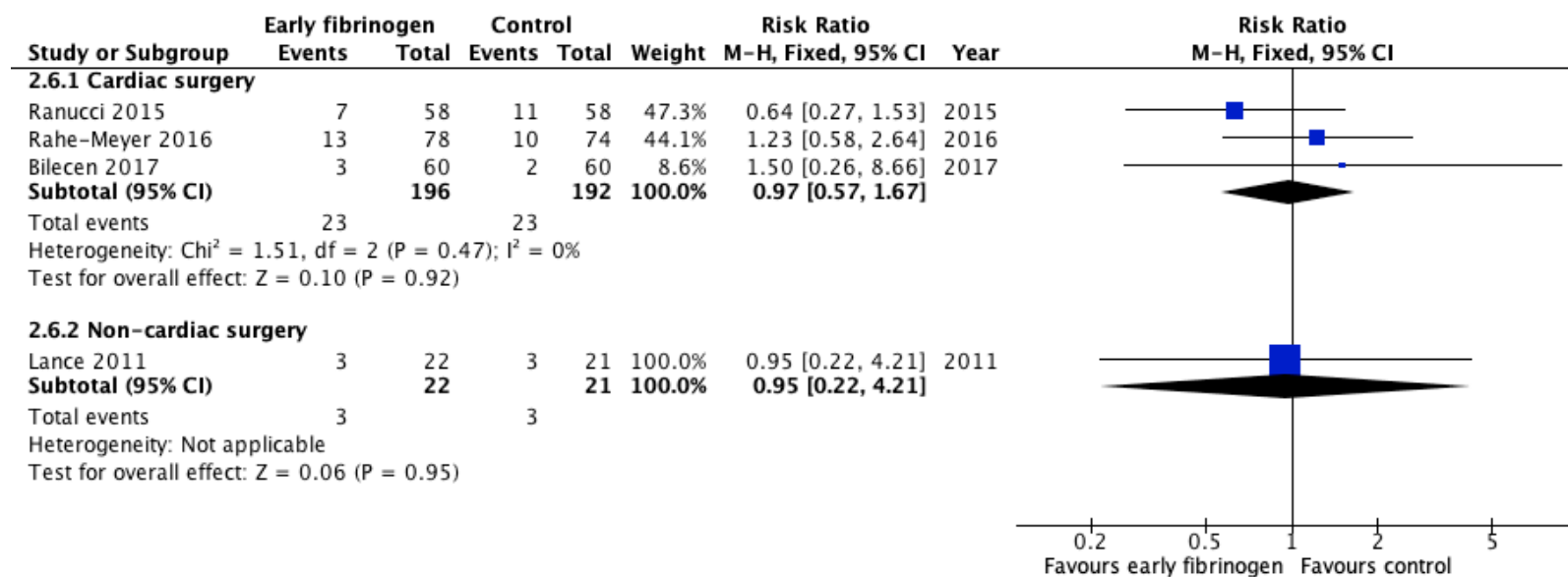


## Fibrinogen in non-massively bleeding critically ill patients

### 5. Acute Kidney Injury



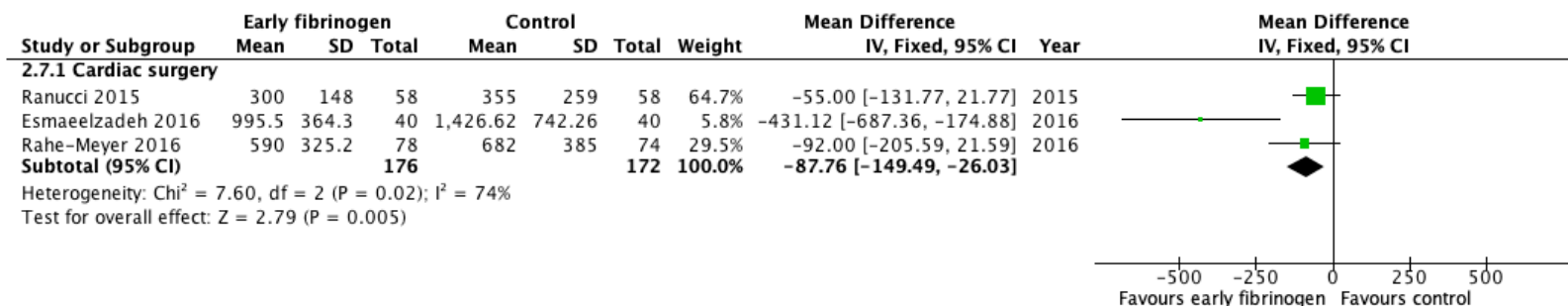
### 6. Infections/sepsis



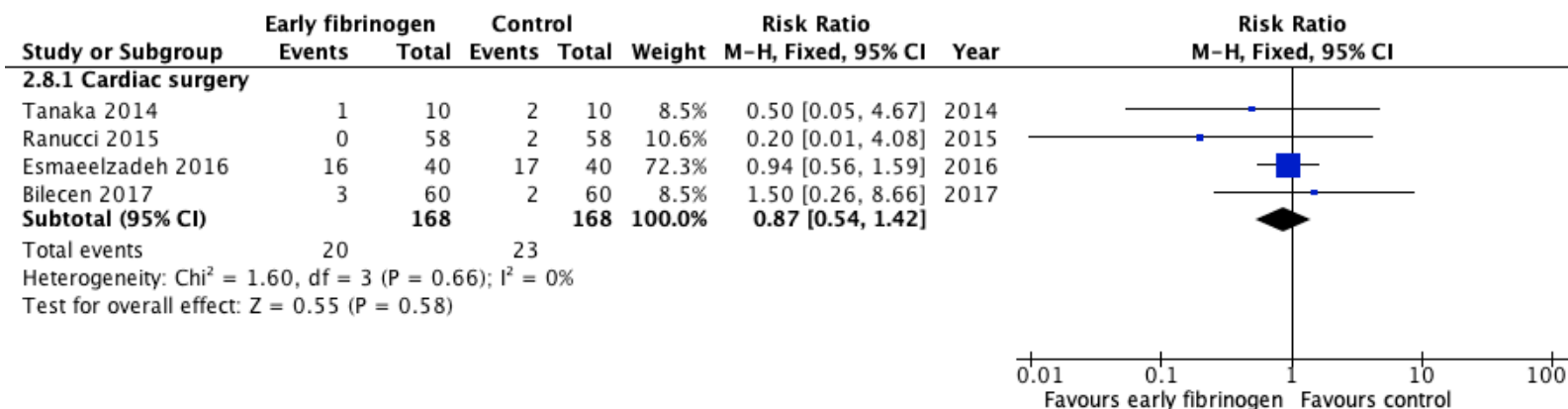


## Fibrinogen in non-massively bleeding critically ill patients

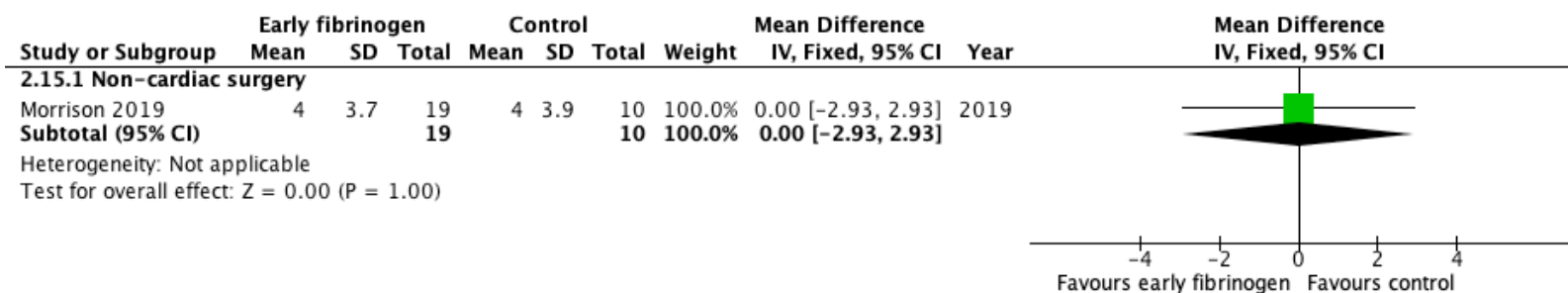
### 7. Blood loss



### 8. Reoperation

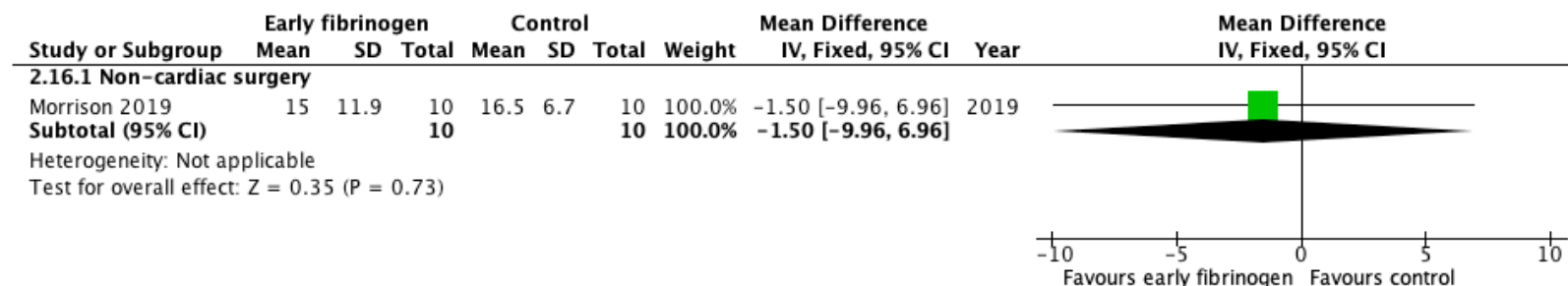


### 9. ICU length of stay

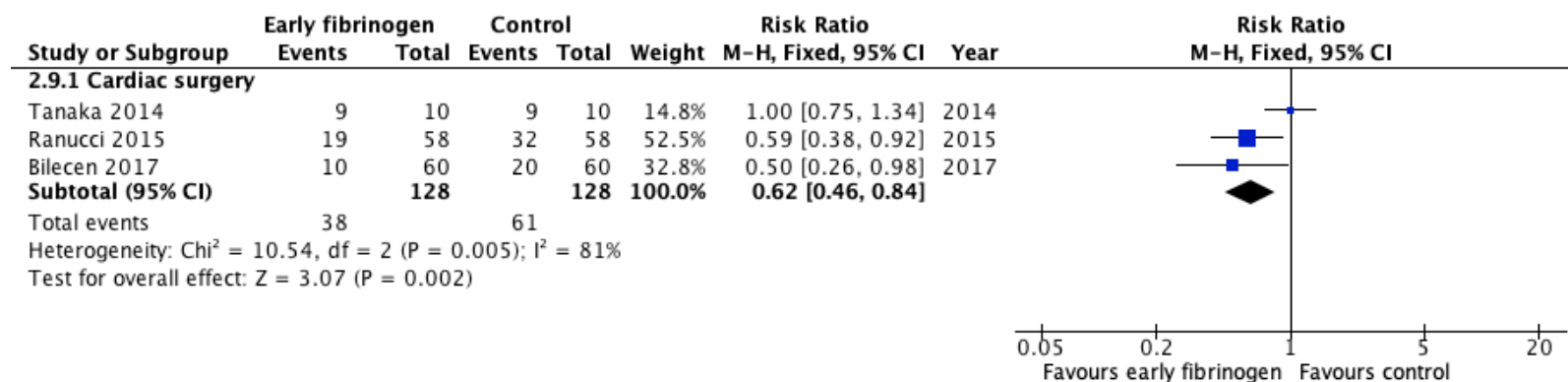


## Fibrinogen in non-massively bleeding critically ill patients

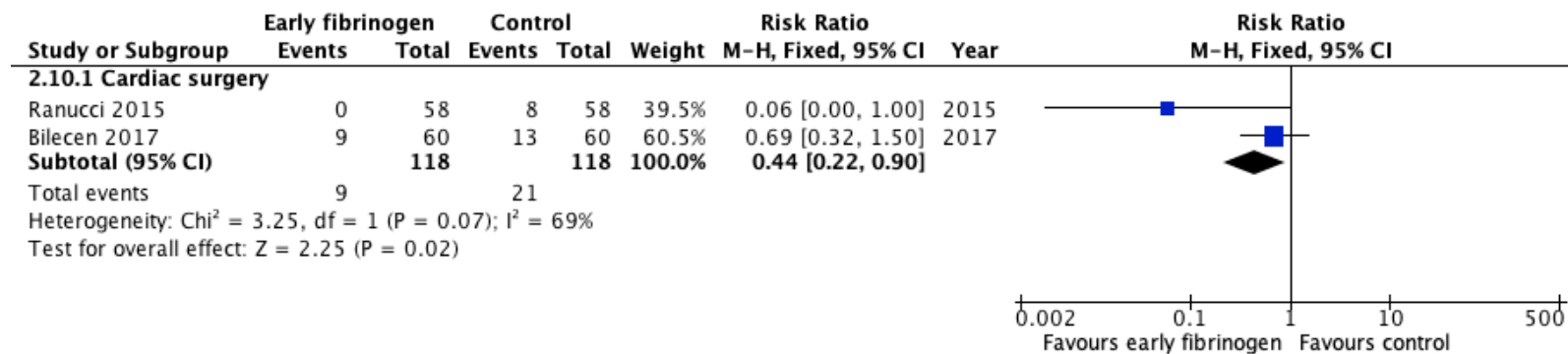
### 10. Hospital length of stay



### 11. Proportion receiving RBCs

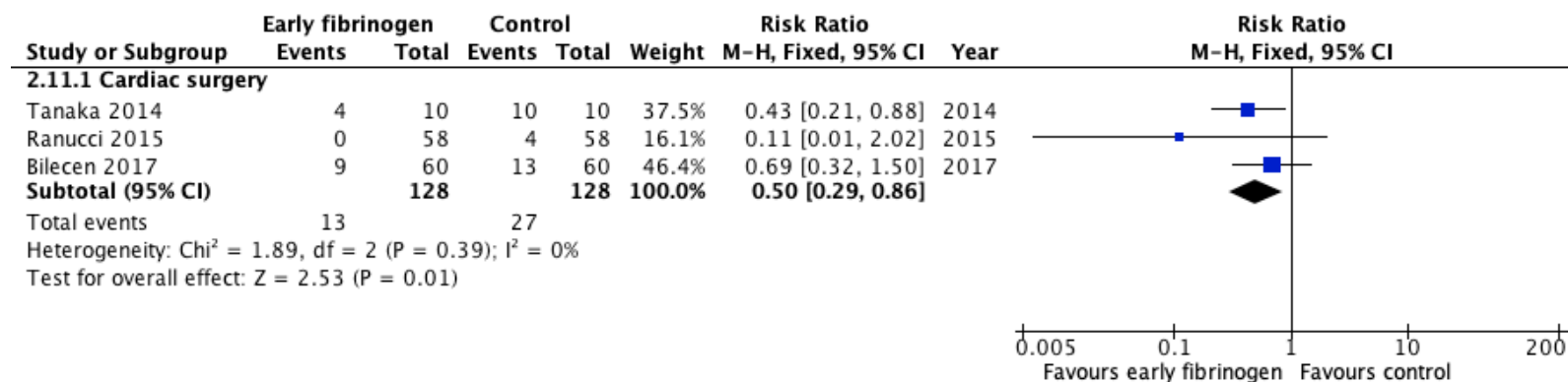


### 12. Proportion receiving plasma

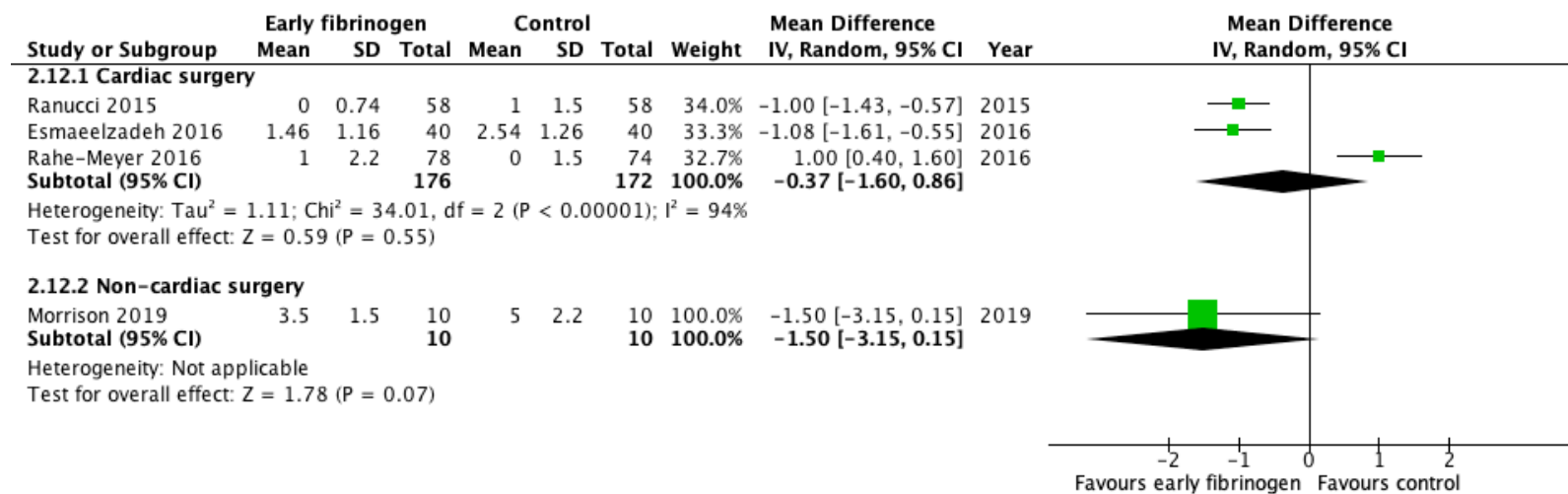


## Fibrinogen in non-massively bleeding critically ill patients

### 13. Proportion receiving platelets



### 14. Mean RBCs transfused

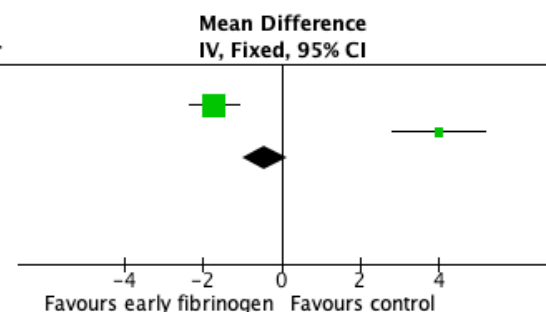


## Fibrinogen in non-massively bleeding critically ill patients

### 15. Mean plasma transfused

Study or Subgroup	Early fibrinogen			Control			Weight	Mean Difference IV, Fixed, 95% CI	Year
	Mean	SD	Total	Mean	SD	Total			
<b>2.13.1 Cardiac surgery</b>									
Esmaelzadeh 2016	1.34	1.54	40	3.05	1.39	40	77.5%	-1.71 [-2.35, -1.07]	2016
Rahe-Meyer 2016	4	4.4	78	0	3	74	22.5%	4.00 [2.81, 5.19]	2016
<b>Subtotal (95% CI)</b>			<b>118</b>			<b>114</b>	<b>100.0%</b>	<b>-0.42 [-0.99, 0.14]</b>	

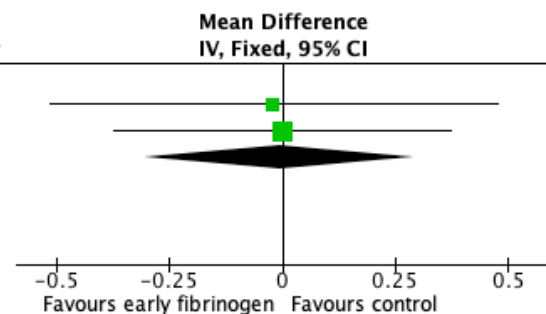
Heterogeneity:  $\text{Chi}^2 = 68.29$ ,  $\text{df} = 1$  ( $P < 0.00001$ );  $I^2 = 99\%$   
 Test for overall effect:  $Z = 1.47$  ( $P = 0.14$ )



### 16. Mean platelets transfused

Study or Subgroup	Early fibrinogen			Control			Weight	Mean Difference IV, Fixed, 95% CI	Year
	Mean	SD	Total	Mean	SD	Total			
<b>2.14.1 Cardiac surgery</b>									
Esmaelzadeh 2016	0.35	1.16	40	0.37	1.1	40	36.2%	-0.02 [-0.52, 0.48]	2016
Rahe-Meyer 2016	1	1.5	78	1	0.74	74	63.8%	0.00 [-0.37, 0.37]	2016
<b>Subtotal (95% CI)</b>			<b>118</b>			<b>114</b>	<b>100.0%</b>	<b>-0.01 [-0.31, 0.29]</b>	

Heterogeneity:  $\text{Chi}^2 = 0.00$ ,  $\text{df} = 1$  ( $P = 0.95$ );  $I^2 = 0\%$   
 Test for overall effect:  $Z = 0.05$  ( $P = 0.96$ )



**Evidence Summary 9: Plasma transfusion in non-massively bleeding, critically ill adults**

## Restrictive plasma transfusion strategy compared to liberal plasma transfusion strategy for non-massively bleeding patients

Certainty assessment							N <sub>o</sub> of patients		Effect		Certainty	Importance
N <sub>o</sub> of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	restrictive plasma transfusion strategy	liberal plasma transfusion strategy	Relative (95% CI)	Absolute (95% CI)		
<b>RCT Mortality- 30 Day</b>												
1	randomised trials	not serious <sup>a</sup>	not serious	not serious	very serious <sup>b</sup>	none <sup>c</sup>	11/30 (36.7%)	11/30 (36.7%)	<b>RR 1.00</b> (0.51 to 1.94)	<b>0 fewer per 1,000</b> (from 180 fewer to 345 more)	⊕⊕○○ LOW	CRITICAL
<b>Sepsis</b>												
1	randomised trials	serious <sup>d</sup>	not serious	not serious	serious <sup>e</sup>	none <sup>c</sup>	4/30 (13.3%)	16/30 (53.3%)	<b>RR 0.25</b> (0.09 to 0.66)	<b>400 fewer per 1,000</b> (from 485 fewer to 181 fewer)	⊕⊕○○ LOW	IMPORTANT
<b>Duration of Hospital Stay in Days</b>												
1	randomised trials	serious <sup>d</sup>	not serious	not serious	serious <sup>e</sup>	none <sup>c</sup>	30	30	-	<b>MD 4.4 higher</b> (0.4 higher to 8.4 higher)	⊕⊕○○ LOW	IMPORTANT
<b>Mortality</b>												
1	observational studies	serious <sup>f</sup>	not serious	not serious	serious <sup>e</sup>	none <sup>c</sup>	73/455 (16.0%)	39/178 (21.9%)	<b>RR 0.73</b> (0.52 to 1.04)	<b>59 fewer per 1,000</b> (from 105 fewer to 9 more)	⊕○○○ VERY LOW	CRITICAL

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

### Explanations

- Akbari 2018 is at a high risk of bias with concerns regarding the lack of blinding and concealment. However, the high risk of bias is unlikely to influence mortality outcome.
- Data rated down two levels for wide confidence intervals and low number of events.
- Publication bias not assessed formally given only one study found.
- Akbari 2018 at high risk of bias for concerns regarding the lack of blinding, appropriate allocation and concealment.
- Dated down one level for wide confidence intervals and low number of events.
- Chang 2017 is a retrospective registry study, outcomes were not adjudicated and concerns regarding follow-up. Therefore rated down one level. However, these concerns are unlikely to effect mortality as an outcome

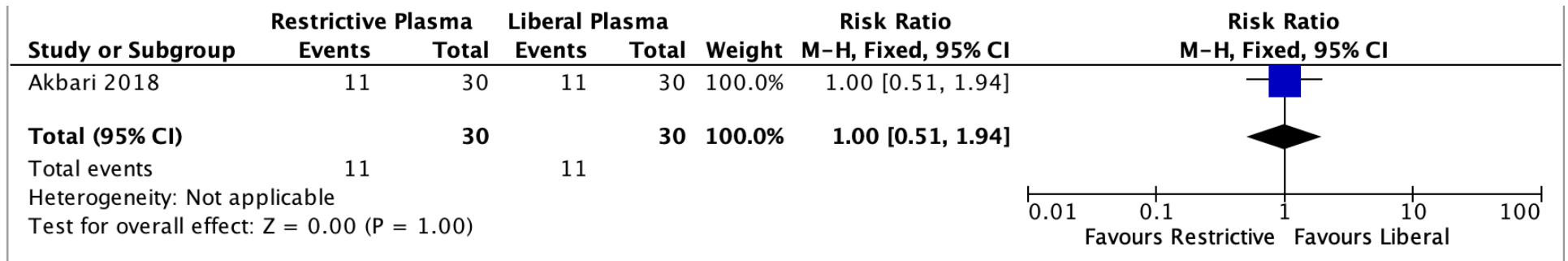
Restrictive vs. Liberal Plasma Transfusion Strategy in non-massively bleeding critically ill patients

Forrest Plots

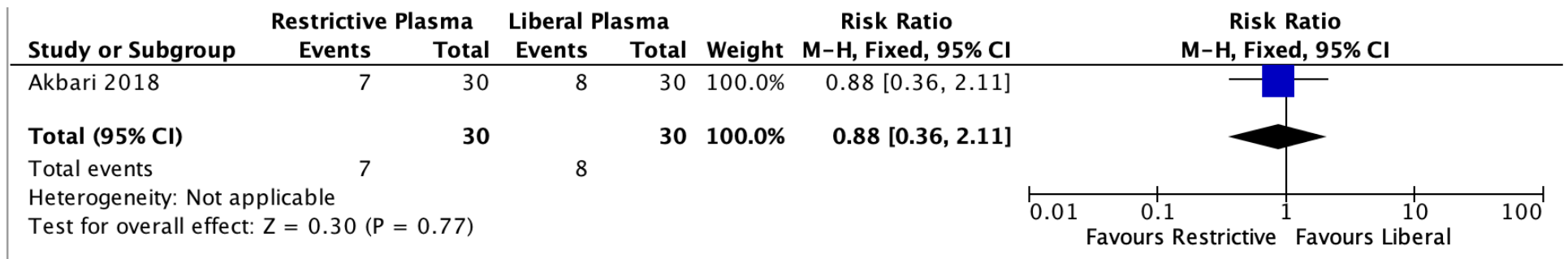
Restrictive vs. Liberal Plasma Transfusions in non-massively bleeding critically ill patients

RCT

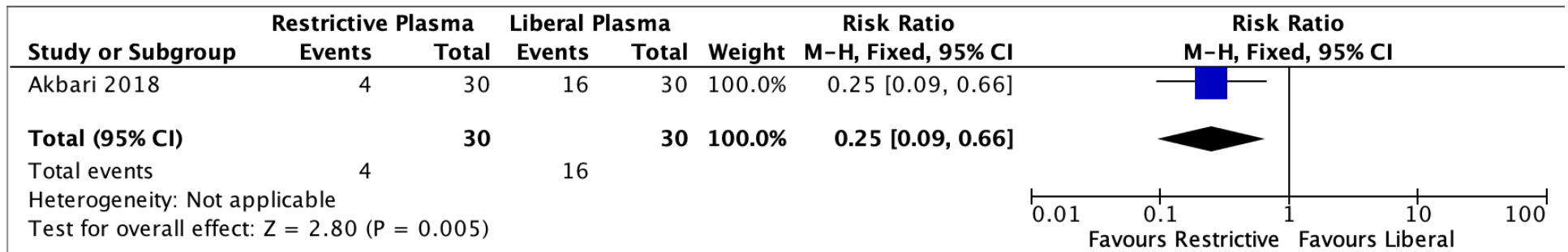
Mortality



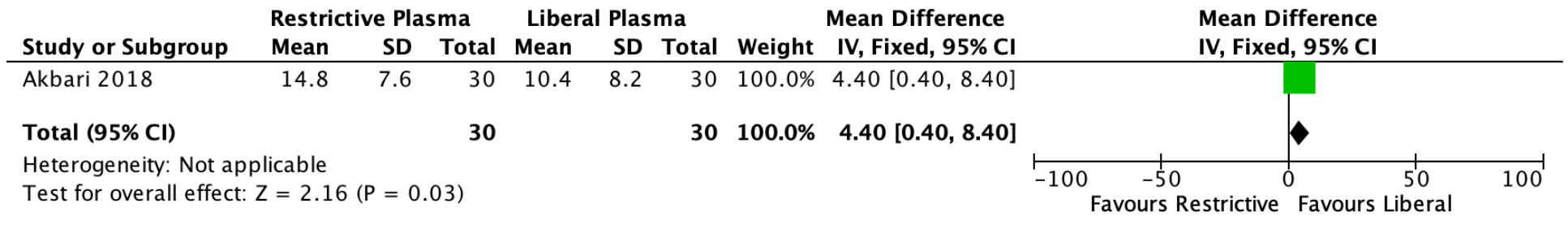
Multiorgan Failure



## Sepsis



## Duration of Hospital Stay (Days)



## Observational Study- Neuro

### Mortality





***Evidence summary: Point of care vs. conventional coagulation testing in non-massively bleeding critically ill adults***

*See evidence summary 5: evidence summaries for point of care vs. conventional coagulation testing in massively bleeding critically ill adults and non-massively bleeding critically ill adults*

**Evidence Summary 10: Tranexamic acid in critically ill patients with traumatic bleeding, including traumatic brain injury**

## TXA in massively bleeding critically ill patients

Table 1: Trauma

Certainty assessment						№ of patients		Effect		Certainty	Importance
№ of studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TXA	No TXA	Relative (95% CI)	Absolute (95% CI)		
<b>Mortality - Trauma</b>											
1 RCT	not serious	not serious	not serious	not serious	none	1463/10060 (14.5%)	1613/10067 (16.0%)	<b>RR 0.91</b> (0.85 to 0.97)	<b>14 fewer per 1,000</b> (from 24 fewer to 5 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
<b>Stroke - Trauma</b>											
1 RCT	not serious	not serious	not serious	not serious	none	57/10060 (0.6%)	66/10067 (0.7%)	<b>RR 0.86</b> (0.61 to 1.23)	<b>1 fewer per 1,000</b> (from 3 fewer to 2 more)	⊕⊕⊕⊕ HIGH	CRITICAL
<b>Myocardial infarction - Trauma</b>											
1 RCT	not serious	not serious	not serious	not serious	none	35/10060 (0.3%)	55/10067 (0.5%)	<b>RR 0.64</b> (0.42 to 0.97)	<b>2 fewer per 1,000</b> (from 3 fewer to 0 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
<b>Deep venous thrombosis - Trauma</b>											
1 RCT	not serious	not serious	not serious	not serious	none	40/10060 (0.4%)	41/10067 (0.4%)	<b>RR 0.98</b> (0.63 to 1.51)	<b>0 fewer per 1,000</b> (from 2 fewer to 2 more)	⊕⊕⊕⊕ HIGH	IMPORTANT
<b>Pulmonary embolism - Trauma</b>											
1 RCT	not serious	not serious	not serious	not serious	none	72/10060 (0.7%)	71/10067 (0.7%)	<b>RR 1.01</b> (0.73 to 1.41)	<b>0 fewer per 1,000</b> (from 2 fewer to 3 more)	⊕⊕⊕⊕ HIGH	IMPORTANT
<b>Surgical intervention - Trauma</b>											
1 RCT	not serious	not serious	not serious	not serious	none	4814/10060 (47.9%)	4836/10067 (48.0%)	<b>RR 1.00</b> (0.97 to 1.03)	<b>0 fewer per 1,000</b> (from 14 fewer to 14 more)	⊕⊕⊕⊕ HIGH	IMPORTANT
<b>RBC transfusion - Trauma</b>											
1 RCT	not serious	not serious	not serious	not serious	none	5067/10060 (50.4%)	5160/10067 (51.3%)	<b>RR 0.98</b> (0.96 to 1.01)	<b>10 fewer per 1,000</b> (from 21 fewer to 5 more)	⊕⊕⊕⊕ HIGH	IMPORTANT
<b>RBCs transfused - Trauma</b>											
1 RCT	not serious	not serious	not serious	not serious	none	10060	10067	-	<b>MD 0.17 lower</b> (0.39 lower to 0.05 higher)	⊕⊕⊕⊕ HIGH	IMPORTANT

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

## TXA in massively bleeding critically ill patients

Table 2: Traumatic brain injury

Certainty assessment						No of patients		Effect		Certainty	Importance
No of studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TXA	No TXA	Relative (95% CI)	Absolute (95% CI)		
<b>Mortality - Traumatic brain injury</b>											
6 RCTs	not serious	not serious	not serious	serious <sup>a</sup>	none	1074/5382 (20.0%)	1109/5239 (21.2%)	<b>RR 0.88</b> (0.72 to 1.06)	<b>25 fewer per 1,000</b> (from 59 fewer to 13 more)	⊕⊕⊕○ MODERATE	CRITICAL
<b>Poor functional outcome - Traumatic brain injury</b>											
5 RCTs	not serious	not serious	not serious	serious <sup>a</sup>	none	214/769 (27.8%)	225/725 (31.0%)	<b>RR 0.89</b> (0.76 to 1.04)	<b>34 fewer per 1,000</b> (from 74 fewer to 12 more)	⊕⊕⊕○ MODERATE	CRITICAL
<b>Stroke - Traumatic brain injury</b>											
3 RCTs	not serious	not serious	not serious	not serious	none	46/6612 (0.7%)	43/6537 (0.7%)	<b>RR 1.06</b> (0.70 to 1.60)	<b>0 fewer per 1,000</b> (from 2 fewer to 4 more)	⊕⊕⊕⊕ HIGH	CRITICAL
<b>Myocardial infarction - Traumatic brain injury</b>											
3 RCTs	not serious	not serious	not serious	not serious	none	19/6612 (0.3%)	23/6537 (0.4%)	<b>RR 0.83</b> (0.46 to 1.49)	<b>1 fewer per 1,000</b> (from 2 fewer to 2 more)	⊕⊕⊕⊕ HIGH	CRITICAL
<b>Renal failure - Traumatic brain injury</b>											
1 RCT	not serious	not serious	not serious	not serious	none	100/6359 (1.6%)	84/6280 (1.3%)	<b>RR 1.18</b> (0.88 to 1.57)	<b>2 more per 1,000</b> (from 2 fewer to 8 more)	⊕⊕⊕⊕ HIGH	CRITICAL
<b>Sepsis - Traumatic brain injury</b>											
1 RCT	not serious	not serious	not serious	not serious	none	411/6359 (6.5%)	412/6280 (6.6%)	<b>RR 0.99</b> (0.86 to 1.12)	<b>1 fewer per 1,000</b> (from 9 fewer to 8 more)	⊕⊕⊕⊕ HIGH	CRITICAL
<b>Deep venous thrombosis - Traumatic brain injury</b>											
4 RCTs	not serious	not serious	not serious	not serious	none	22/6708 (0.3%)	22/6621 (0.3%)	<b>RR 0.98</b> (0.55 to 1.74)	<b>0 fewer per 1,000</b> (from 1 fewer to 2 more)	⊕⊕⊕⊕ HIGH	CRITICAL
<b>Pulmonary embolism - Traumatic brain injury</b>											

## TXA in massively bleeding critically ill patients

4 RCTs	not serious	not serious	not serious	not serious	none	35/6708 (0.5%)	34/6621 (0.5%)	<b>RR 0.99</b> (0.62 to 1.59)	<b>0 fewer per 1,000</b> (from 2 fewer to 3 more)	⊕⊕⊕⊕ HIGH	CRITICAL
<b>Surgical intervention - Traumatic brain injury</b>											
4 RCTs	not serious	not serious	not serious	serious <sup>a</sup>	none	31/327 (9.5%)	33/332 (9.9%)	<b>RR 0.96</b> (0.61 to 1.51)	<b>4 fewer per 1,000</b> (from 39 fewer to 51 more)	⊕⊕⊕○ MODERATE	IMPORTANT
<b>Progressive intracranial hemorrhage - Traumatic brain injury</b>											
3 RCTs	not serious	not serious	not serious	not serious	none	80/311 (25.7%)	105/316 (33.2%)	<b>RR 0.78</b> (0.61 to 0.99)	<b>73 fewer per 1,000</b> (from 130 fewer to 3 fewer)	⊕⊕⊕⊕ HIGH	IMPORTANT
<b>Seizure - Traumatic brain injury</b>											
2 RCTs	not serious	not serious	not serious	not serious	none	213/6705 (3.2%)	189/6589 (2.9%)	<b>RR 1.11</b> (0.92 to 1.35)	<b>3 more per 1,000</b> (from 2 fewer to 10 more)	⊕⊕⊕⊕ HIGH	IMPORTANT
<b>RBC transfusion - Traumatic brain injury</b>											
2 RCTs	not serious	not serious	not serious	serious <sup>a</sup>	none	72/253 (28.5%)	85/257 (33.1%)	<b>RR 0.86</b> (0.66 to 1.12)	<b>46 fewer per 1,000</b> (from 112 fewer to 40 more)	⊕⊕⊕○ MODERATE	IMPORTANT
<b>ICU length of stay - Traumatic brain injury</b>											
2 RCTs	not serious	not serious	not serious	serious <sup>b</sup>	none	170	159	-	<b>MD 2.85 higher</b> (0.07 lower to 5.76 higher)	⊕⊕⊕○ MODERATE	IMPORTANT
<b>Hospital length of stay - Traumatic brain injury</b>											
2 RCTs	not serious	not serious	not serious	serious <sup>a</sup>	none	170	159	-	<b>MD 0.3 lower</b> (3.39 lower to 2.79 higher)	⊕⊕⊕○ MODERATE	IMPORTANT

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

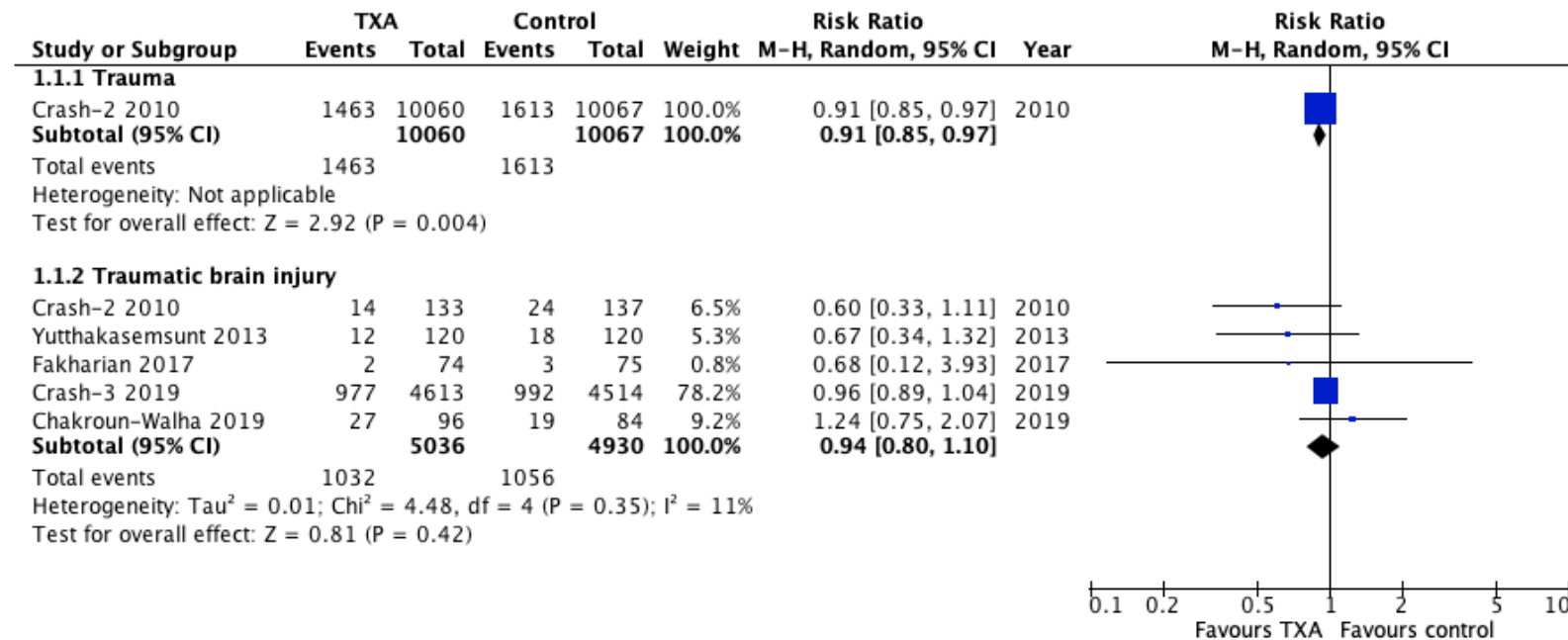
### Explanations

a. Significant imprecision which does not exclude clinically meaningful benefit or harm.

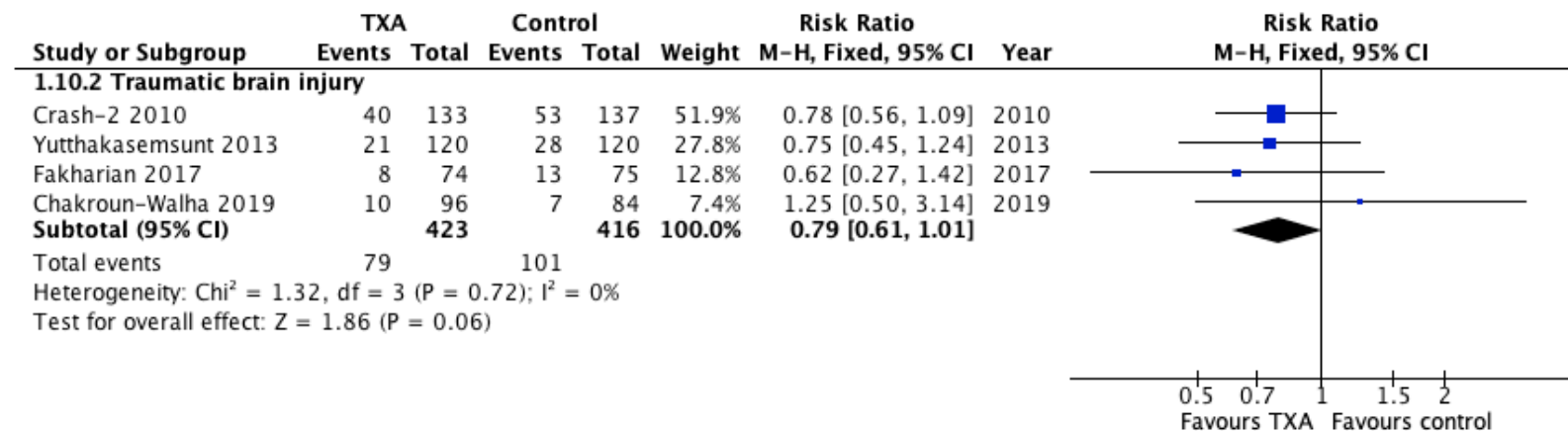
b. Borderline statistically significant result, but small sample size resulting in serious imprecision.

## TXA in massively bleeding critically ill patients

### 1. Mortality

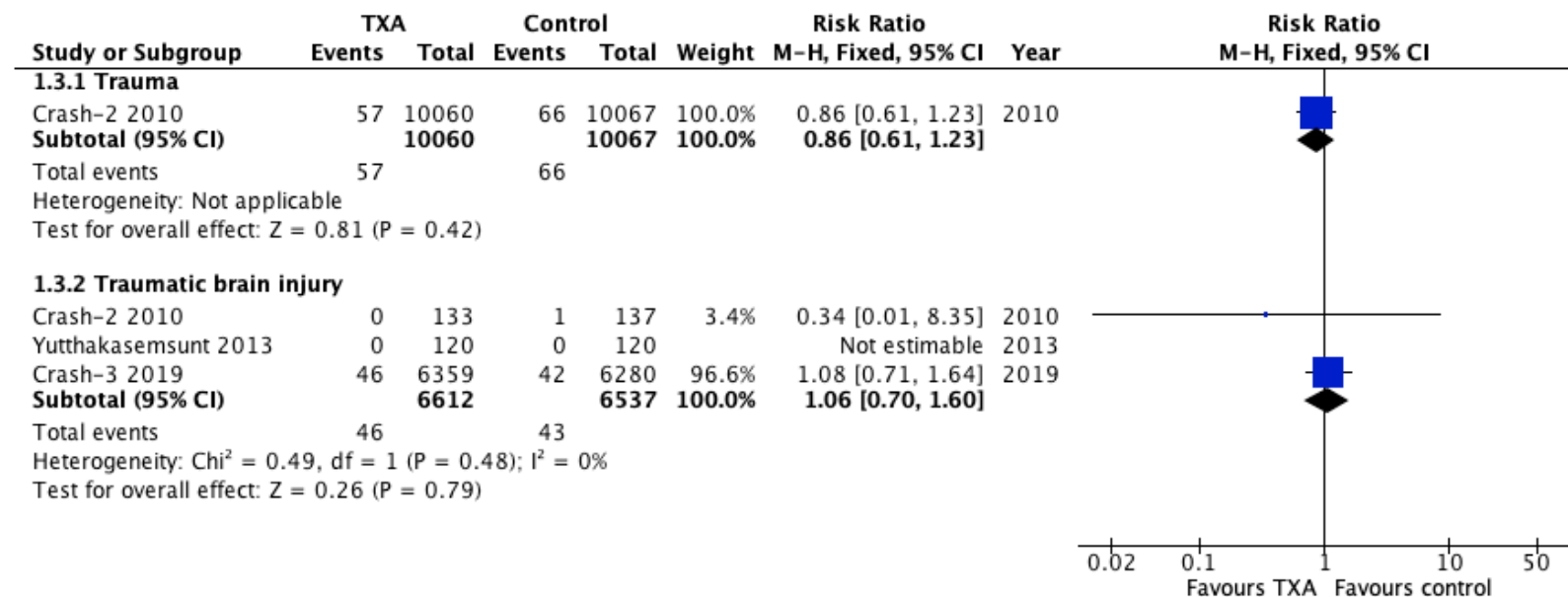


### 2. Poor functional outcome

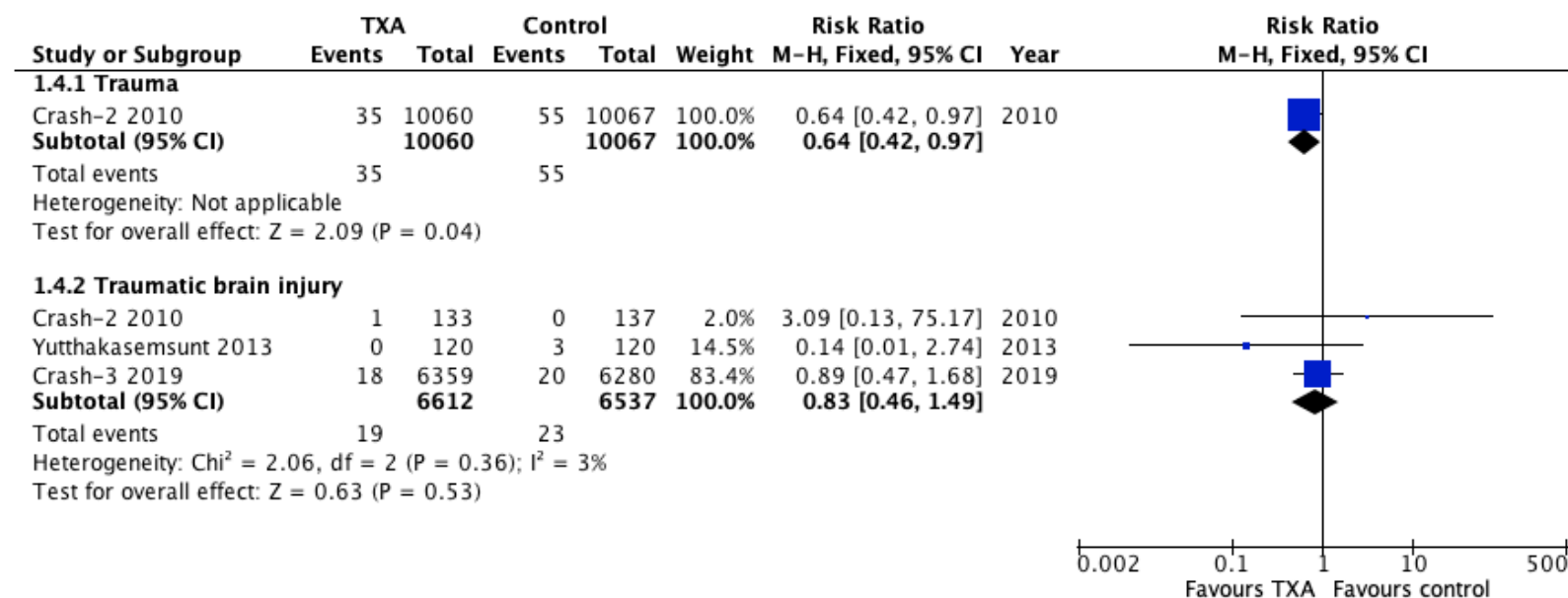


## TXA in massively bleeding critically ill patients

### 3. Stroke



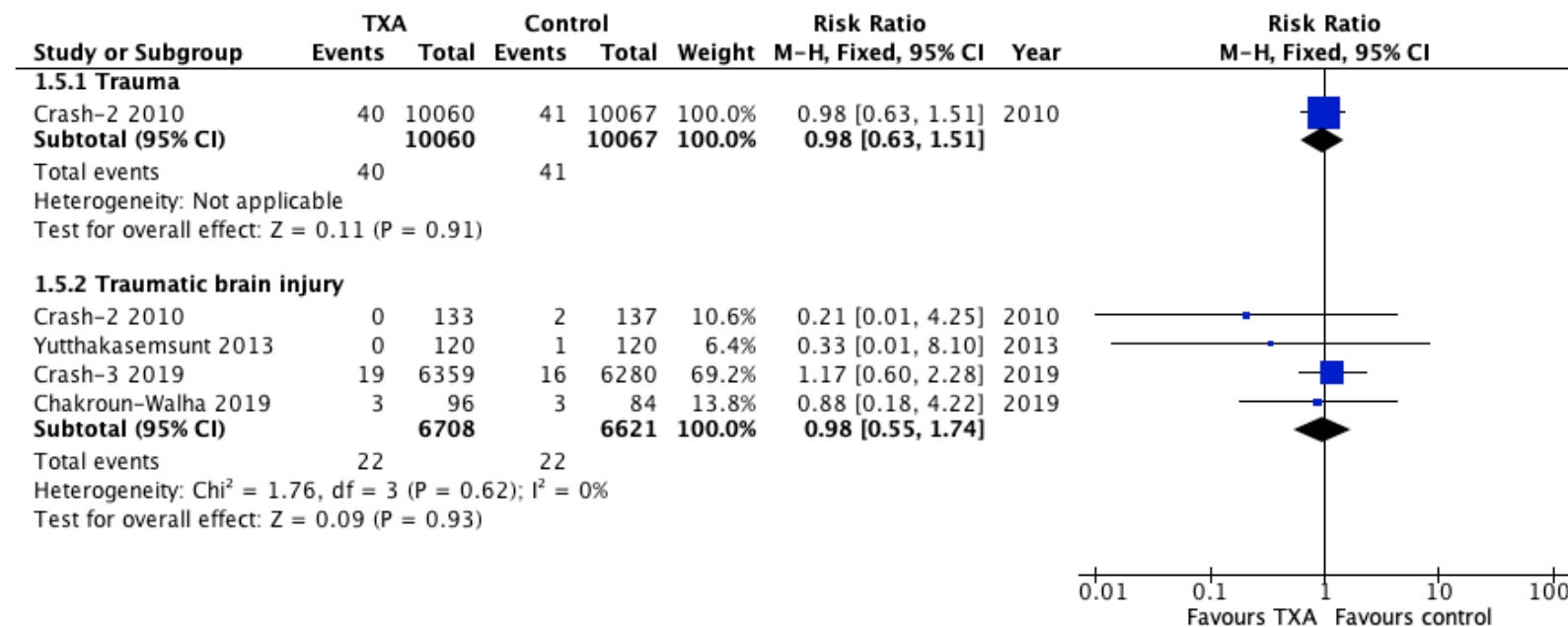
### 4. Myocardial infarction



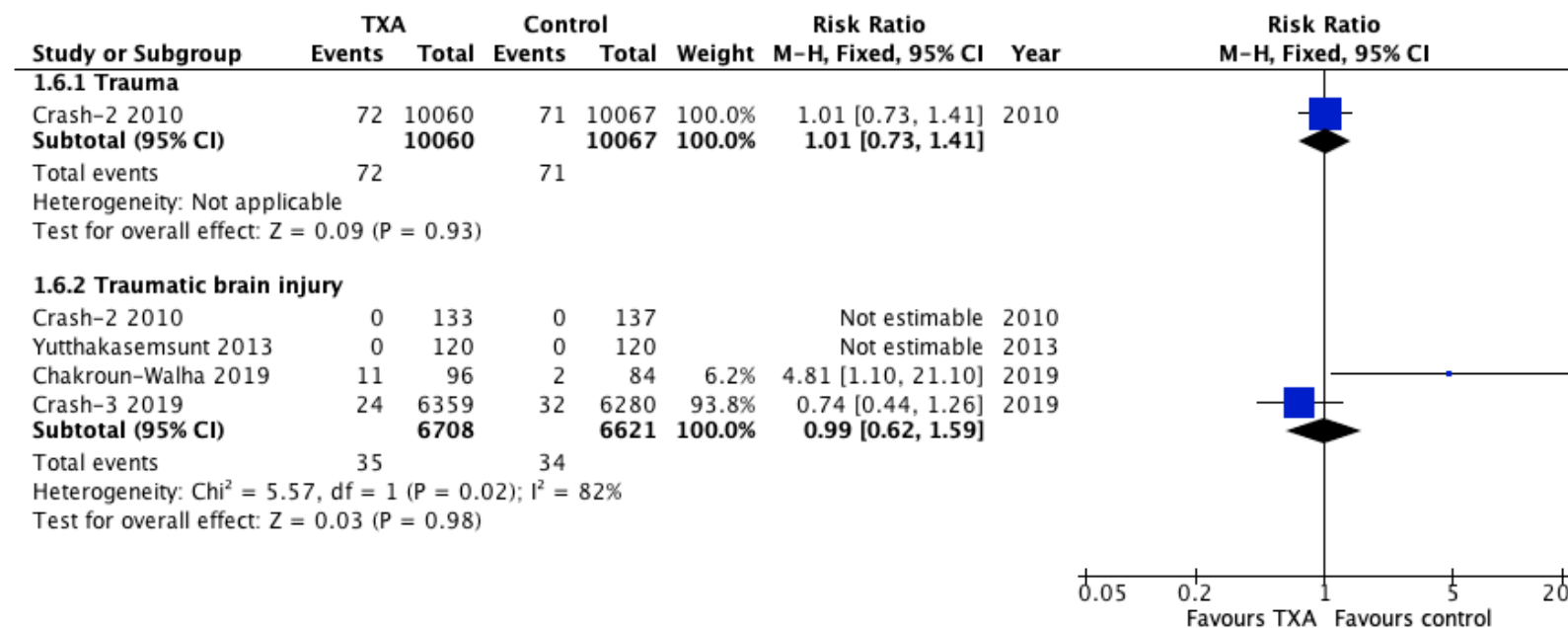


## TXA in massively bleeding critically ill patients

### 5. Deep venous thrombosis

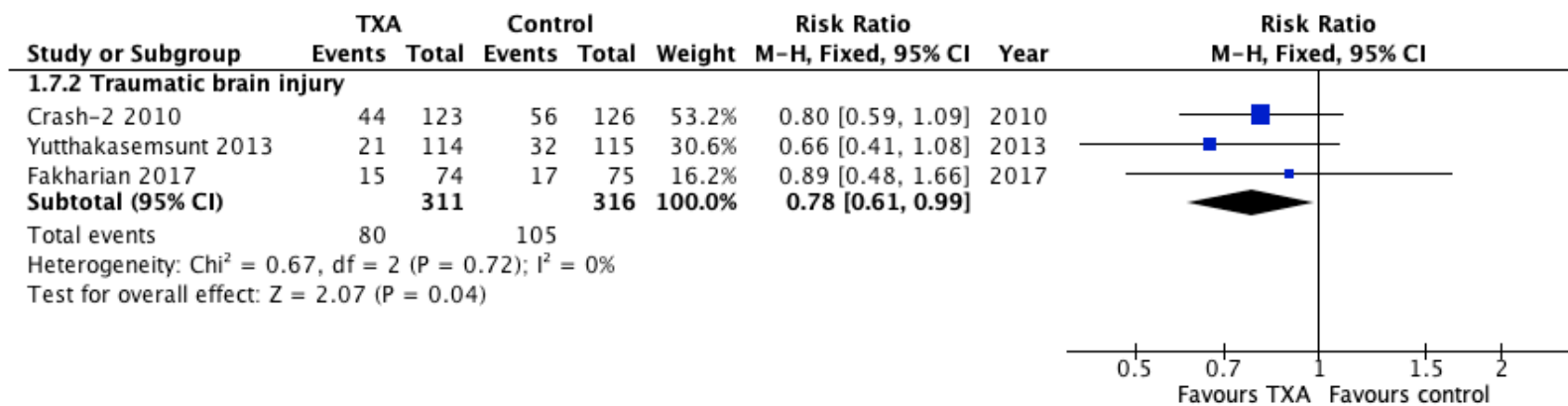


### 6. Pulmonary embolism

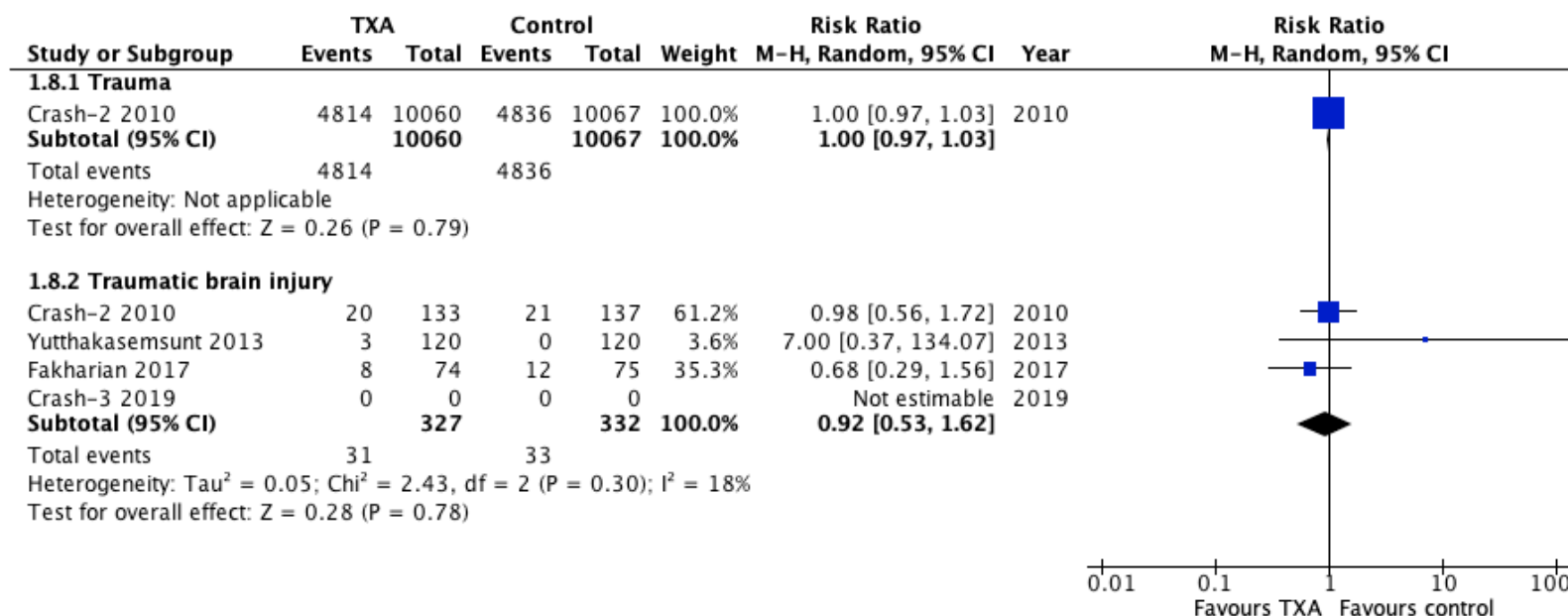


## TXA in massively bleeding critically ill patients

### 7. Progressive intracranial hemorrhage

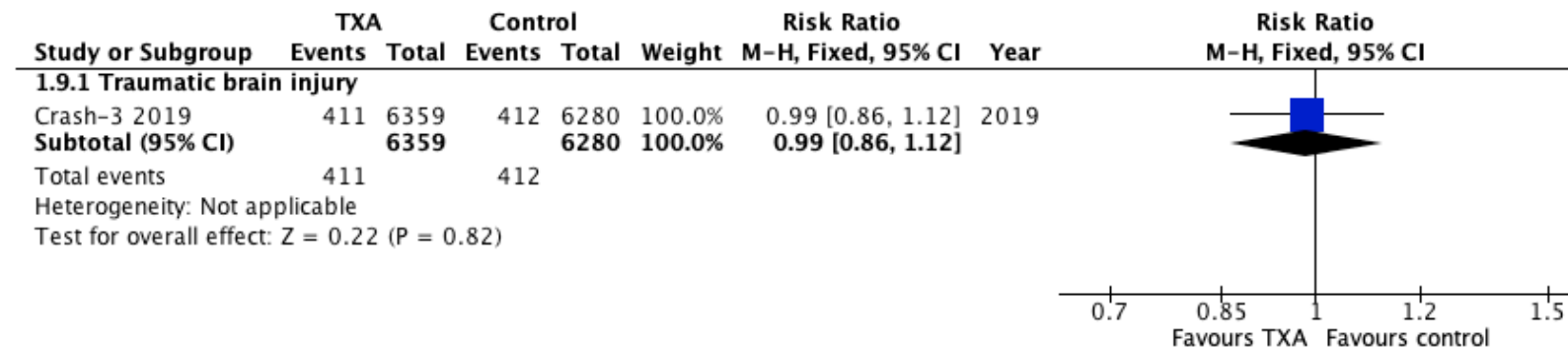


### 8. Surgical intervention (note: though specified as an outcome in the manuscript, CRASH-3 did not report need for neurosurgery in the manuscript)

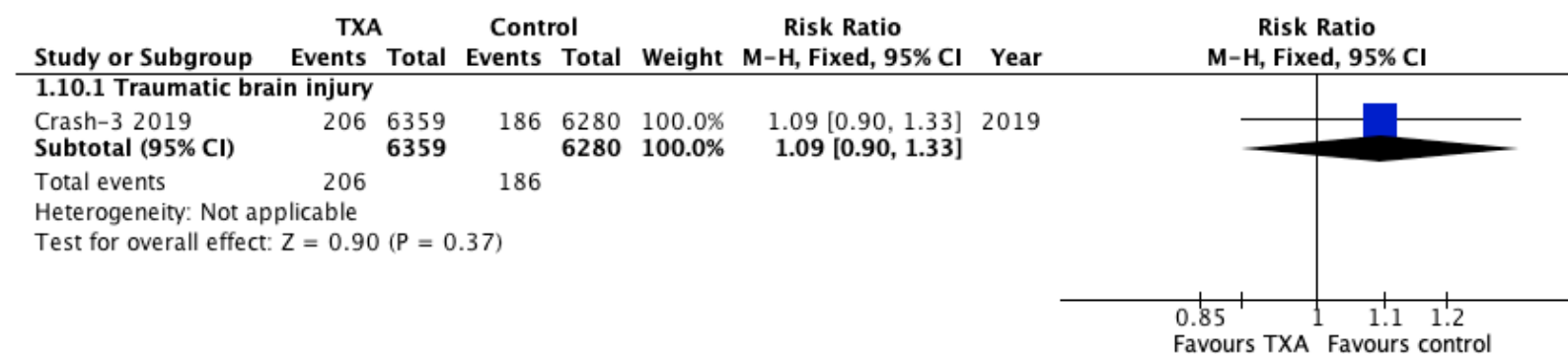


## TXA in massively bleeding critically ill patients

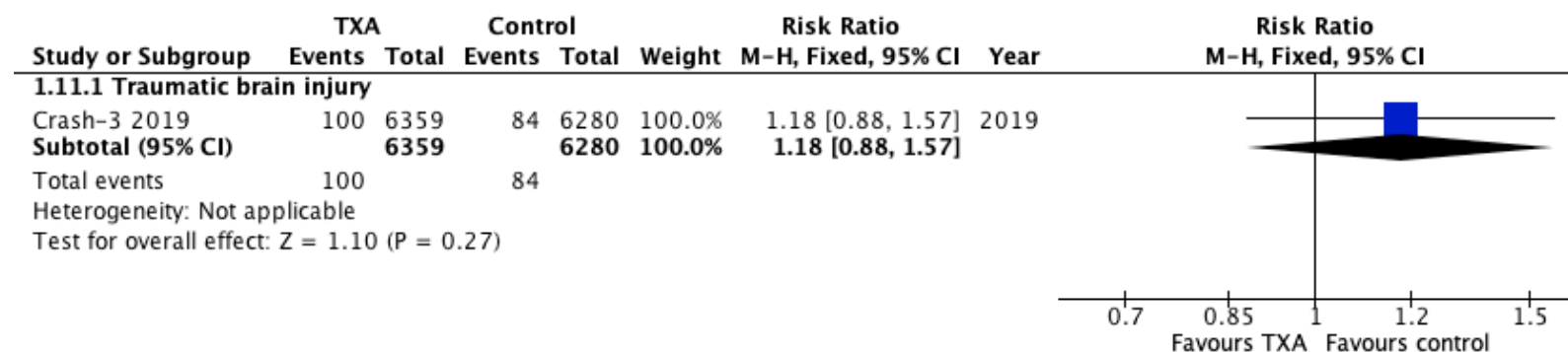
### 9. Sepsis/infection



### 10. Seizure

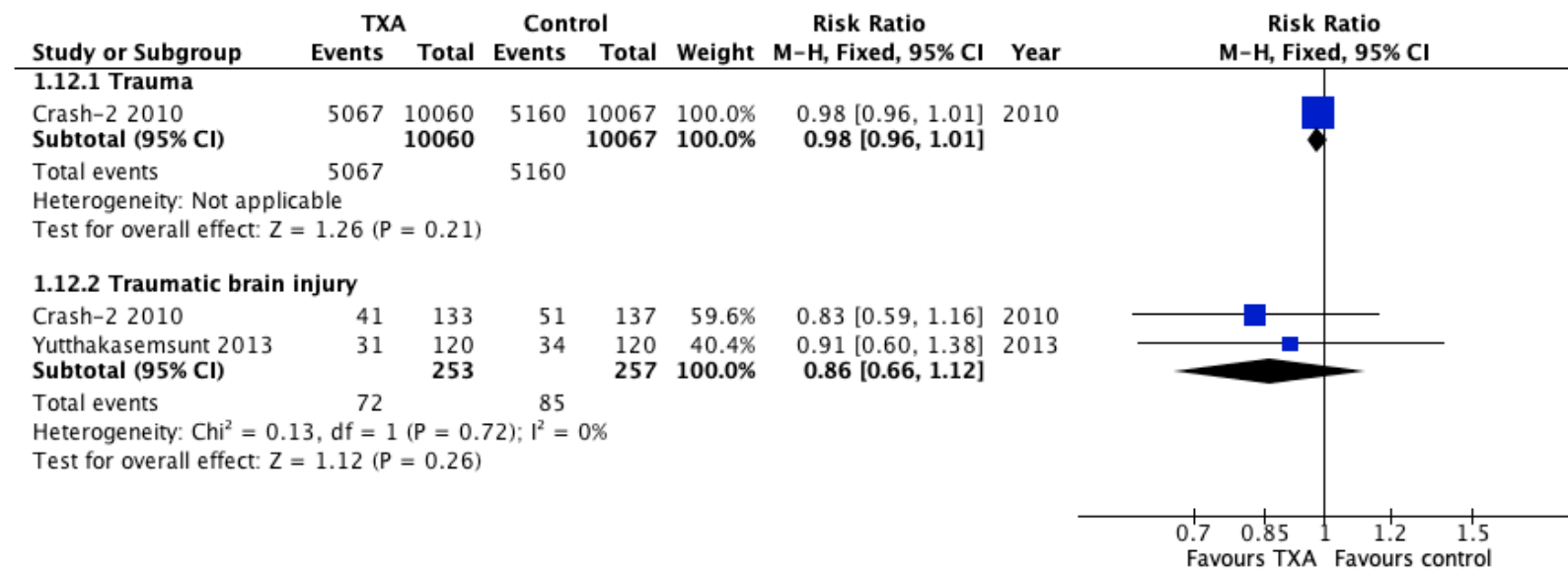


### 11. Renal failure

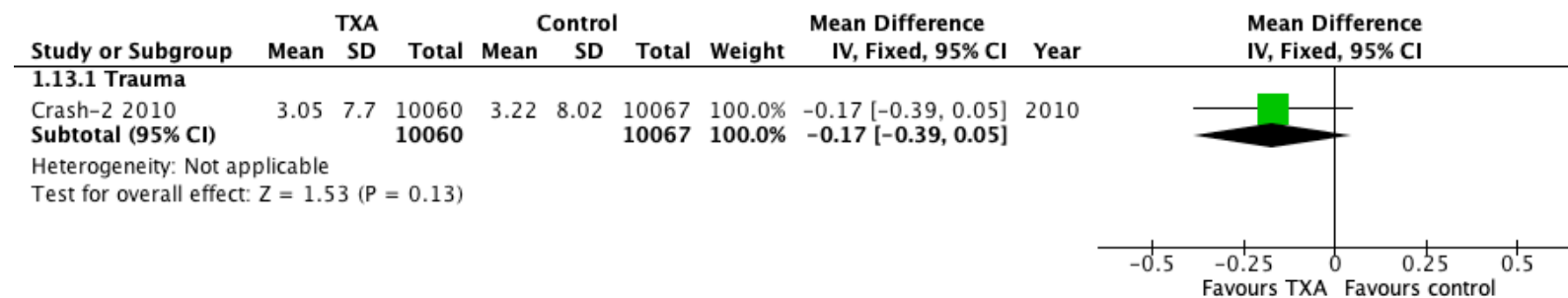


## TXA in massively bleeding critically ill patients

### 11. RBC Transfusion

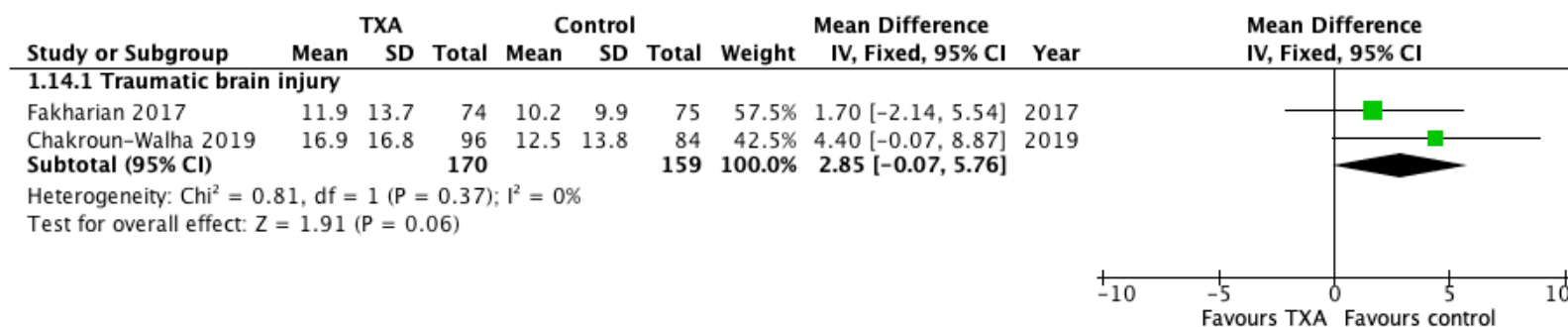


### 12. RBCs transfused

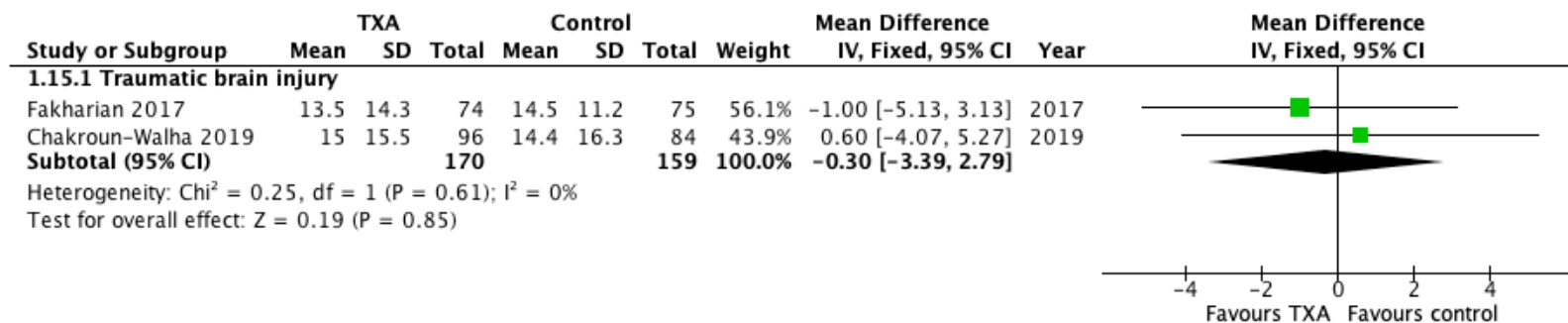


## TXA in massively bleeding critically ill patients

### 13. ICU length of stay



### 14. Hospital length of stay



**Evidence Summary 11: Tranexamic acid in critically ill patients with subarachnoid hemorrhage, non-traumatic intracranial hemorrhage, postpartum hemorrhage, and post-cardiac surgery**

*See evidence summary 12 for tranexamic acid in critically ill patients with GI bleeding*

## TXA in non-massively bleeding critically ill patients

**Table 1: Cardiac surgery**

Certainty assessment						№ of patients		Effect		Certainty	Importance
№ of studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TXA	no TXA	Relative (95% CI)	Absolute (95% CI)		
<b>Mortality - Cardiac surgery</b>											
36 RCTs	not serious	not serious	not serious	not serious	none	40/4419 (0.9%)	53/4354 (1.2%)	<b>RR 0.75</b> (0.50 to 1.13)	<b>3 fewer per 1,000</b> (from 6 fewer to 2 more)	⊕⊕⊕⊕ HIGH	CRITICAL
<b>Post-operative bleeding - Cardiac surgery</b>											
56 RCTs	not serious	not serious <sup>a</sup>	not serious	not serious	none	5273	5015	-	<b>MD 268.52 lower</b> (314.99 lower to 222.04 lower)	⊕⊕⊕⊕ HIGH	IMPORTANT
<b>Surgical intervention - Cardiac surgery</b>											
25 RCTs	not serious	not serious	not serious	not serious	none	69/3797 (1.8%)	140/3778 (3.7%)	<b>RR 0.53</b> (0.40 to 0.71)	<b>17 fewer per 1,000</b> (from 22 fewer to 11 fewer)	⊕⊕⊕⊕ HIGH	IMPORTANT
<b>Seizure - Cardiac surgery</b>											
7 RCTs	not serious	not serious	not serious	not serious	none	20/2794 (0.7%)	4/2821 (0.1%)	<b>RR 4.11</b> (1.44 to 11.72)	<b>4 more per 1,000</b> (from 1 more to 15 more)	⊕⊕⊕⊕ HIGH	IMPORTANT
<b>RBC transfusion - Cardiac surgery</b>											
25 RCTs	not serious	not serious	not serious	not serious	none	1272/3755 (33.9%)	1843/3738 (49.3%)	<b>RR 0.67</b> (0.60 to 0.74)	<b>163 fewer per 1,000</b> (from 197 fewer to 128 fewer)	⊕⊕⊕⊕ HIGH	IMPORTANT

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

### Explanations

a. Although very high value of I-squared (97%) the vast majority of trials demonstrate an effect estimate in favour of TXA without any clear signal of harm.

## TXA in non-massively bleeding critically ill patients

Table 2: Obstetric bleeding

Certainty assessment						No of patients		Effect		Certainty	Importance
No of studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TXA	no TXA	Relative (95% CI)	Absolute (95% CI)		
<b>Mortality - Obstetric bleeding</b>											
2 RCTs	not serious	not serious	not serious	not serious <sup>a</sup>	none	227/10108 (2.2%)	256/10057 (2.5%)	<b>RR 0.88</b> (0.74 to 1.05)	<b>3 fewer per 1,000</b> (from 7 fewer to 1 more)	⊕⊕⊕⊕ HIGH	CRITICAL
<b>Stroke - Obstetric bleeding</b>											
2 RCTs	not serious	not serious	not serious	not serious	none	8/10104 (0.1%)	6/10057 (0.1%)	<b>RR 1.33</b> (0.46 to 3.82)	<b>0 fewer per 1,000</b> (from 0 fewer to 2 more)	⊕⊕⊕⊕ HIGH	CRITICAL
<b>Myocardial infarction - Obstetric bleeding</b>											
2 RCTs	not serious	not serious	not serious	not serious	none	2/10104 (0.0%)	3/10057 (0.0%)	<b>RR 0.66</b> (0.11 to 3.97)	<b>0 fewer per 1,000</b> (from 0 fewer to 1 more)	⊕⊕⊕⊕ HIGH	CRITICAL
<b>Deep venous thrombosis - Obstetric bleeding</b>											
2 RCTs	not serious	not serious	not serious	not serious	none	3/10104 (0.0%)	7/10057 (0.1%)	<b>RR 0.43</b> (0.11 to 1.65)	<b>0 fewer per 1,000</b> (from 1 fewer to 0 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
<b>Pulmonary embolism - Obstetric bleeding</b>											
2 RCTs	not serious	not serious	not serious	not serious	none	17/10104 (0.2%)	20/10057 (0.2%)	<b>RR 0.85</b> (0.44 to 1.61)	<b>0 fewer per 1,000</b> (from 1 fewer to 1 more)	⊕⊕⊕⊕ HIGH	CRITICAL
<b>Sepsis - Obstetric bleeding</b>											
1 RCT	not serious	not serious	not serious	not serious	none	180/10032 (1.8%)	185/9985 (1.9%)	<b>RR 0.97</b> (0.79 to 1.19)	<b>1 fewer per 1,000</b> (from 4 fewer to 4 more)	⊕⊕⊕⊕ HIGH	IMPORTANT
<b>Renal failure - Obstetric bleeding</b>											
1 RCT	not serious	not serious	not serious	not serious	none	129/10032 (1.3%)	118/9985 (1.2%)	<b>RR 1.09</b> (0.85 to 1.39)	<b>1 more per 1,000</b> (from 2 fewer to 5 more)	⊕⊕⊕⊕ HIGH	IMPORTANT
<b>Seizure - Obstetric bleeding</b>											
1 RCT	not serious	not serious	not serious	not serious	none	33/10032 (0.3%)	43/9985 (0.4%)	<b>RR 0.76</b> (0.49 to 1.20)	<b>1 fewer per 1,000</b> (from 2 fewer to 1 more)	⊕⊕⊕⊕ HIGH	IMPORTANT



## TXA in non-massively bleeding critically ill patients

Surgical intervention - Obstetric bleeding (hysterectomy)											
2 RCTs	not serious	not serious	not serious	serious <sup>b</sup>	none	358/10104 (3.5%)	353/1005 7 (3.5%)	<b>RR 0.93</b> (0.46 to 1.89)	<b>2 fewer per 1,000</b> (from 19 fewer to 31 more)	⊕⊕⊕○ MODERATE	IMPORTANT
RBC transfusion - Obstetric bleeding											
2 RCTs	not serious	not serious	not serious	not serious	none	5471/10108 (54.1%)	5439/10057 (54.1%)	<b>RR 1.00</b> (0.98 to 1.03)	<b>0 fewer per 1,000</b> (from 11 fewer to 16 more)	⊕⊕⊕⊕ HIGH	IMPORTANT

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

### Explanations

- a. Though the 95% confidence interval crosses 1, the result is very precise and essentially rules out a clinically meaningful increase in mortality (0.1%).
- b. Wide 95% confidence intervals do not exclude clinically significant benefit or harm.

## TXA in non-massively bleeding critically ill patients

**Table 3: Subarachnoid hemorrhage**

Certainty assessment						No of patients		Effect		Certainty	Importance
No of studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TXA	no TXA	Relative (95% CI)	Absolute (95% CI)		
<b>Mortality - Subarachnoid hemorrhage</b>											
10 RCTs	not serious	not serious	not serious	serious <sup>a</sup>	none	368/1400 (26.3%)	366/1393 (26.3%)	<b>RR 1.01</b> (0.88 to 1.16)	<b>3 more per 1,000</b> (from 32 fewer to 42 more)	⊕⊕⊕○ MODERATE	CRITICAL
<b>Poor functional outcome - Subarachnoid hemorrhage</b>											
5 RCTs	serious <sup>b</sup>	not serious	not serious	serious <sup>a</sup>	none	508/1254 (40.5%)	486/1247 (39.0%)	<b>RR 1.05</b> (0.95 to 1.15)	<b>19 more per 1,000</b> (from 19 fewer to 58 more)	⊕⊕○○ LOW	CRITICAL
<b>Rebleeding - Subarachnoid hemorrhage</b>											
10 RCTs	not serious	not serious <sup>c</sup>	not serious	serious <sup>d</sup>	none	157/1400 (11.2%)	273/1393 (19.6%)	<b>RR 0.60</b> (0.44 to 0.80)	<b>78 fewer per 1,000</b> (from 110 fewer to 39 fewer)	⊕⊕⊕○ MODERATE	IMPORTANT
<b>Stroke - Subarachnoid hemorrhage</b>											
7 RCTs	serious <sup>b</sup>	not serious <sup>c</sup>	not serious	serious <sup>d</sup>	none	324/1307 (24.8%)	273/1299 (21.0%)	<b>RR 1.29</b> (1.01 to 1.67)	<b>61 more per 1,000</b> (from 2 more to 141 more)	⊕⊕○○ LOW	CRITICAL

CI: Confidence interval; RR: Risk ratio

### Explanations

- Though statistically significant, optimal information size not met resulting in serious imprecision of the overall estimate.
- Wide 95% confidence intervals do not exclude clinically significant benefit or harm.
- Unclear in several studies whether blinded outcome assessment, leading to an uncertain risk of detection bias.
- Though moderate statistical heterogeneity, it is of questionable clinical significance as almost all trials have similar point estimates with the majority of the 95% CI on the same side of the line of effect.

## TXA in non-massively bleeding critically ill patients

Table 4: Non-traumatic ICH

Certainty assessment						№ of patients		Effect		Certainty	Importance
№ of studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TXA	no TXA	Relative (95% CI)	Absolute (95% CI)		
<b>Mortality - Non-traumatic ICH</b>											
3 RCTs	not serious	not serious	not serious	serious <sup>a</sup>	none	266/1227 (21.7%)	259/1222 (21.2%)	RR 1.02 (0.88 to 1.19)	4 more per 1,000 (from 25 fewer to 40 more)	⊕⊕⊕○ MODERATE	CRITICAL
<b>Poor functional outcome - Non-traumatic ICH</b>											
2 RCTs	not serious	not serious	not serious	serious <sup>a</sup>	none	836/1211 (69.0%)	853/1214 (70.3%)	RR 0.98 (0.93 to 1.04)	14 fewer per 1,000 (from 49 fewer to 28 more)	⊕⊕⊕○ MODERATE	CRITICAL
<b>Stroke - Non-traumatic ICH</b>											
2 RCTs	not serious	not serious	not serious	serious <sup>a</sup>	none	17/1211 (1.4%)	12/1214 (1.0%)	RR 1.42 (0.68 to 2.96)	4 more per 1,000 (from 3 fewer to 19 more)	⊕⊕⊕○ MODERATE	CRITICAL
<b>Myocardial infarction - Non-traumatic ICH</b>											
2 RCTs	not serious	not serious	not serious	serious <sup>a</sup>	none	11/1211 (0.9%)	6/1214 (0.5%)	RR 1.84 (0.68 to 4.95)	4 more per 1,000 (from 2 fewer to 20 more)	⊕⊕⊕○ MODERATE	CRITICAL
<b>Deep venous thrombosis - Non-traumatic ICH</b>											
1 RCT	not serious	not serious	not serious	serious <sup>a</sup>	none	19/1161 (1.6%)	14/1164 (1.2%)	RR 1.36 (0.69 to 2.70)	4 more per 1,000 (from 4 fewer to 20 more)	⊕⊕⊕○ MODERATE	CRITICAL
<b>Pulmonary embolism - Non-traumatic ICH</b>											
2 RCTs	not serious	not serious	not serious	serious <sup>a</sup>	none	20/1211 (1.7%)	24/1214 (2.0%)	RR 0.84 (0.47 to 1.50)	3 fewer per 1,000 (from 10 fewer to 10 more)	⊕⊕⊕○ MODERATE	CRITICAL
<b>Venous thrombosis - Non-traumatic ICH</b>											
2	not serious	not serious	not serious	serious <sup>a</sup>	none	40/1177 (3.4%)	37/1172 (3.2%)	RR 1.07 (0.69 to 1.65)	2 more per 1,000 (from 10 fewer to 21 more)	⊕⊕⊕○ MODERATE	CRITICAL

## TXA in non-massively bleeding critically ill patients

Seizure - Non-traumatic ICH											
1 RCT	not serious	not serious	not serious	serious <sup>a</sup>	none	77/1161 (6.6%)	85/1164 (7.3%)	<b>RR 0.91</b> (0.67 to 1.22)	<b>7 fewer per 1,000</b> (from 24 fewer to 16 more)	⊕⊕⊕○ MODERATE	CRITICAL
Hospital length of stay - Non-traumatic ICH											
2 RCTs	not serious	not serious	not serious	serious <sup>a</sup>	none	1177	1172	-	<b>MD 0.07 lower</b> (3.82 lower to 3.69 higher)	⊕⊕⊕○ MODERATE	IMPORTANT

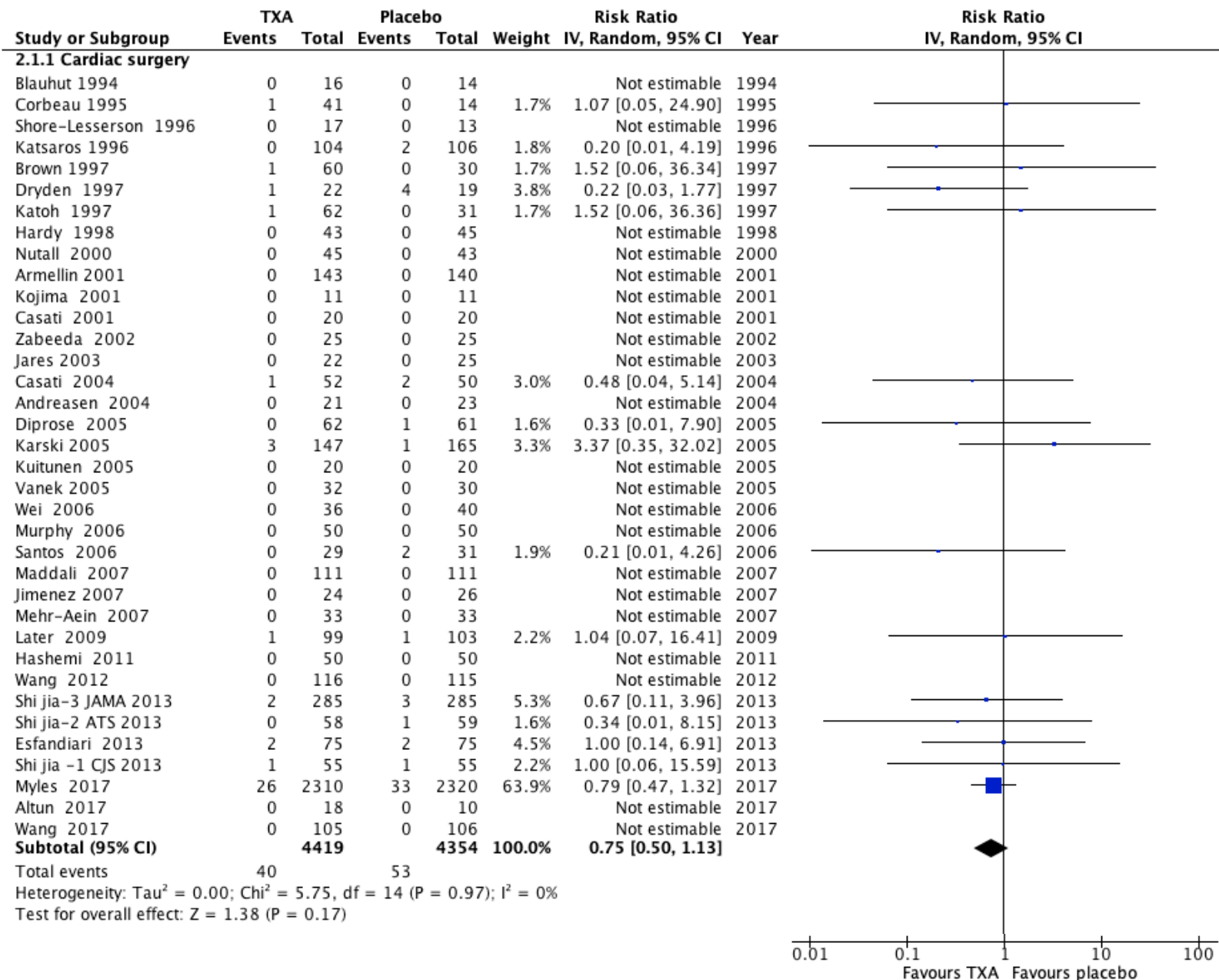
**CI:** Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

### Explanations

a. Wide 95% confidence intervals do not exclude clinically significant benefit or harm.

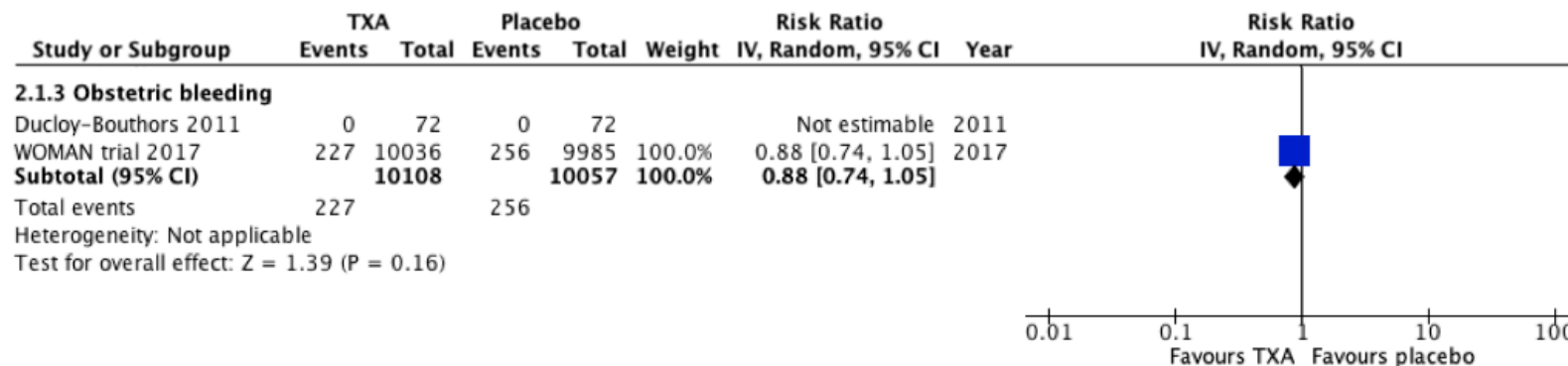
# TXA in non-massively bleeding critically ill patients

## 1a. Mortality - cardiac surgery



## TXA in non-massively bleeding critically ill patients

### 1b. Mortality - obstetrical bleeding



### 1c. Mortality - Subarachnoid hemorrhage and non-traumatic ICH

#### 2.1.4 Subarachnoid hemorrhage

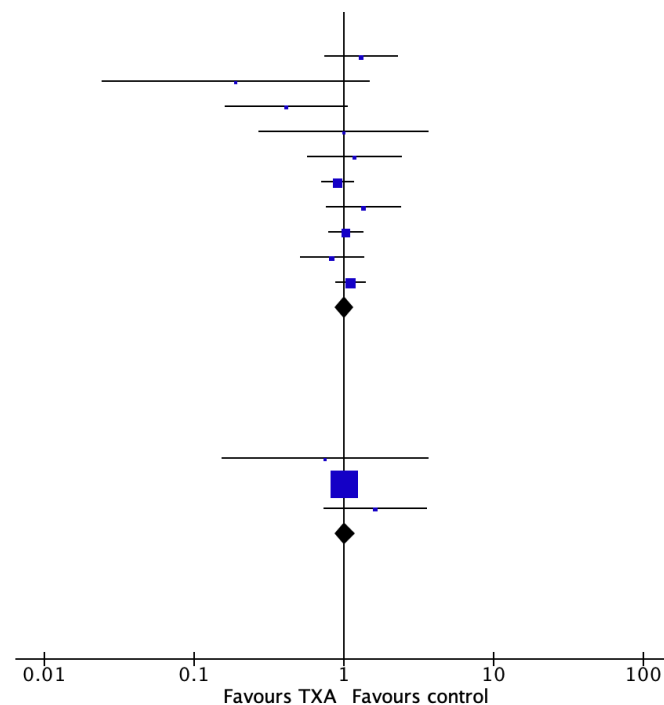
van Rossum 1977	15	26	11	25	6.0%	1.31 [0.76, 2.28]	1977
Chandra 1978	1	20	5	19	0.5%	0.19 [0.02, 1.48]	1978
Maurice 1978	5	38	13	41	2.2%	0.41 [0.16, 1.05]	1978
Kaste 1979	4	32	4	32	1.1%	1.00 [0.27, 3.66]	1979
Fodstad 1981	11	30	9	29	3.6%	1.18 [0.58, 2.42]	1981
Vermeulen 1984	82	241	89	238	24.2%	0.91 [0.72, 1.16]	1984
Tsementzis 1990	19	50	14	50	5.7%	1.36 [0.77, 2.40]	1990
Roos 2000	76	229	75	233	21.4%	1.03 [0.79, 1.34]	2000
Hillman 2002	27	254	32	251	7.7%	0.83 [0.52, 1.35]	2002
Post 2020	128	480	114	475	27.7%	1.11 [0.89, 1.38]	2020
<b>Subtotal (95% CI)</b>		<b>1400</b>		<b>1393</b>	<b>100.0%</b>	<b>1.01 [0.88, 1.16]</b>	

Total events 368 366  
Heterogeneity: Tau<sup>2</sup> = 0.01; Chi<sup>2</sup> = 10.21, df = 9 (P = 0.33); I<sup>2</sup> = 12%  
Test for overall effect: Z = 0.16 (P = 0.87)

#### 2.1.5 Non-traumatic ICH

Sprigg 2014	3	16	2	8	0.9%	0.75 [0.16, 3.62]	2014
Sprigg 2018	250	1161	249	1164	95.4%	1.01 [0.86, 1.18]	2018
Meretoja 2020	13	50	8	50	3.7%	1.63 [0.74, 3.58]	2020
<b>Subtotal (95% CI)</b>		<b>1227</b>		<b>1222</b>	<b>100.0%</b>	<b>1.02 [0.88, 1.19]</b>	

Total events 266 259  
Heterogeneity: Tau<sup>2</sup> = 0.00; Chi<sup>2</sup> = 1.51, df = 2 (P = 0.47); I<sup>2</sup> = 0%  
Test for overall effect: Z = 0.28 (P = 0.78)



## TXA in non-massively bleeding critically ill patients

### 2a. Poor functional outcome

Study or Subgroup	TXA		Control		Weight	Risk Ratio M-H, Random, 95% CI	Year
	Events	Total	Events	Total			
<b>2.3.1 Subarachnoid hemorrhage</b>							
Vermeulen 1984	114	241	112	238	25.1%	1.01 [0.83, 1.21]	1984
Tsementzis 1990	23	50	20	50	4.4%	1.15 [0.73, 1.81]	1990
Roos 2000	114	229	105	233	24.4%	1.10 [0.91, 1.34]	2000
Hillman 2002	64	254	74	251	11.1%	0.85 [0.64, 1.14]	2002
Post 2020	193	480	175	475	35.0%	1.09 [0.93, 1.28]	2020
<b>Subtotal (95% CI)</b>		<b>1254</b>		<b>1247</b>	<b>100.0%</b>	<b>1.05 [0.95, 1.15]</b>	

Total events

508

486

Heterogeneity:  $\text{Tau}^2 = 0.00$ ;  $\text{Chi}^2 = 2.85$ ,  $\text{df} = 4$  ( $P = 0.58$ );  $I^2 = 0\%$

Test for overall effect:  $Z = 0.93$  ( $P = 0.35$ )

#### 2.3.2 Non-traumatic ICH

Sprigg 2018	814	1161	826	1164	98.3%	0.99 [0.94, 1.04]	2018
Meretoja 2020	22	50	27	50	1.7%	0.81 [0.54, 1.22]	2020
<b>Subtotal (95% CI)</b>		<b>1211</b>		<b>1214</b>	<b>100.0%</b>	<b>0.98 [0.93, 1.04]</b>	

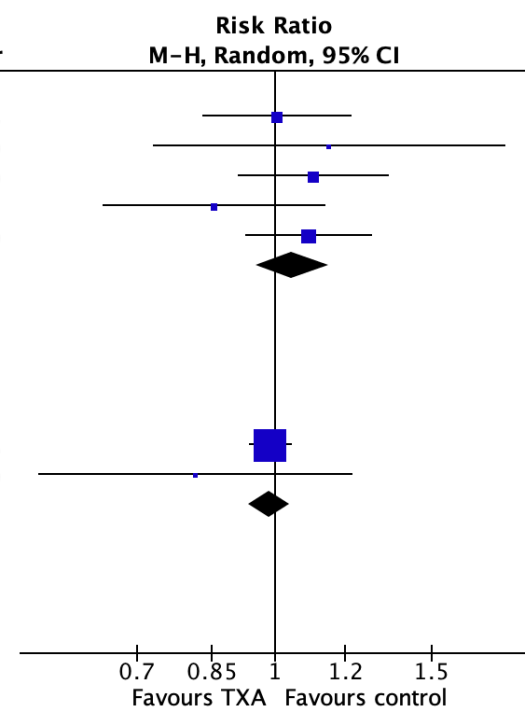
Total events

836

853

Heterogeneity:  $\text{Tau}^2 = 0.00$ ;  $\text{Chi}^2 = 0.87$ ,  $\text{df} = 1$  ( $P = 0.35$ );  $I^2 = 0\%$

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



### 2b. Quality of life

#### Obstetric bleeding:

Woman Trial - EQ5D values were similar between two groups (not reported)

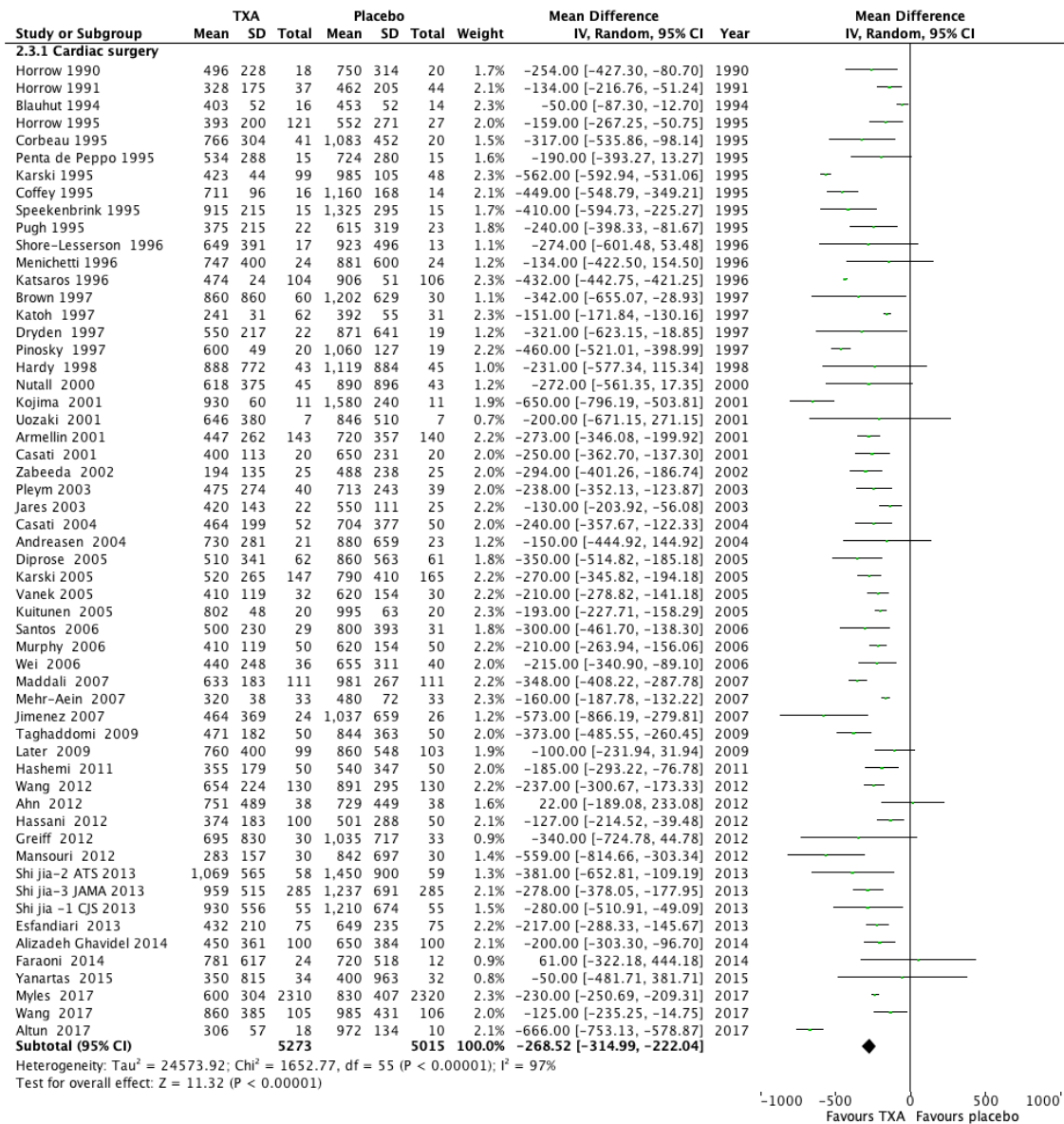
#### Non-traumatic ICH:

TICH trial: Euro QoL visual analogue scale: 66.3 (17.0) in TXA vs. 73.3 (15.3) in control ( $p=0.28$ ).

TICH-2 trial: EQ5D scores were identical between groups 0.34 (0.4)

# TXA in non-massively bleeding critically ill patients

## 3a. Bleeding - cardiac surgery





## TXA in non-massively bleeding critically ill patients

### 3b. Rebleeding events

#### 2.9.2 Subarachnoid hemorrhage

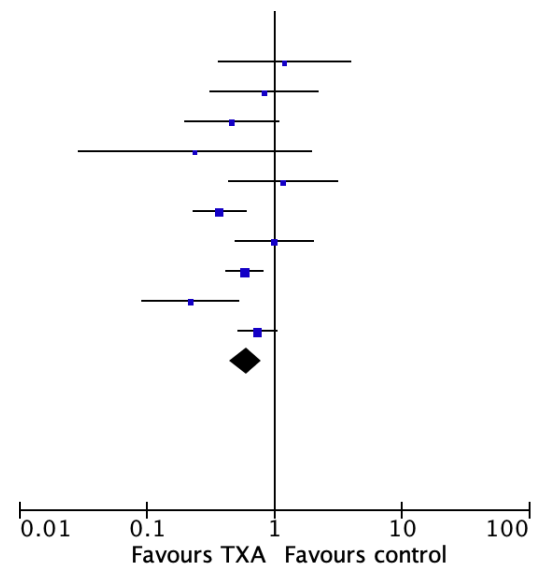
van Rossum 1977	5	26	4	25	4.9%	1.20 [0.36, 3.97]	1977
Fodstad 1978	6	30	7	29	6.8%	0.83 [0.32, 2.17]	1978
Maurice 1978	6	38	14	41	8.2%	0.46 [0.20, 1.08]	1978
Chandra 1978	1	20	4	19	1.8%	0.24 [0.03, 1.94]	1978
Kaste 1979	7	32	6	32	6.7%	1.17 [0.44, 3.09]	1979
Vermeulen 1984	21	241	56	238	15.3%	0.37 [0.23, 0.59]	1984
Tsementzis 1990	12	50	12	50	10.4%	1.00 [0.50, 2.01]	1990
Roos 2000	44	229	77	233	19.2%	0.58 [0.42, 0.80]	2000
Hillman 2002	6	254	27	251	7.9%	0.22 [0.09, 0.52]	2002
Post 2020	49	480	66	475	18.5%	0.73 [0.52, 1.04]	2020
<b>Subtotal (95% CI)</b>	<b>1400</b>		<b>1393</b>	<b>100.0%</b>		<b>0.60 [0.44, 0.80]</b>	

Total events

157                      273

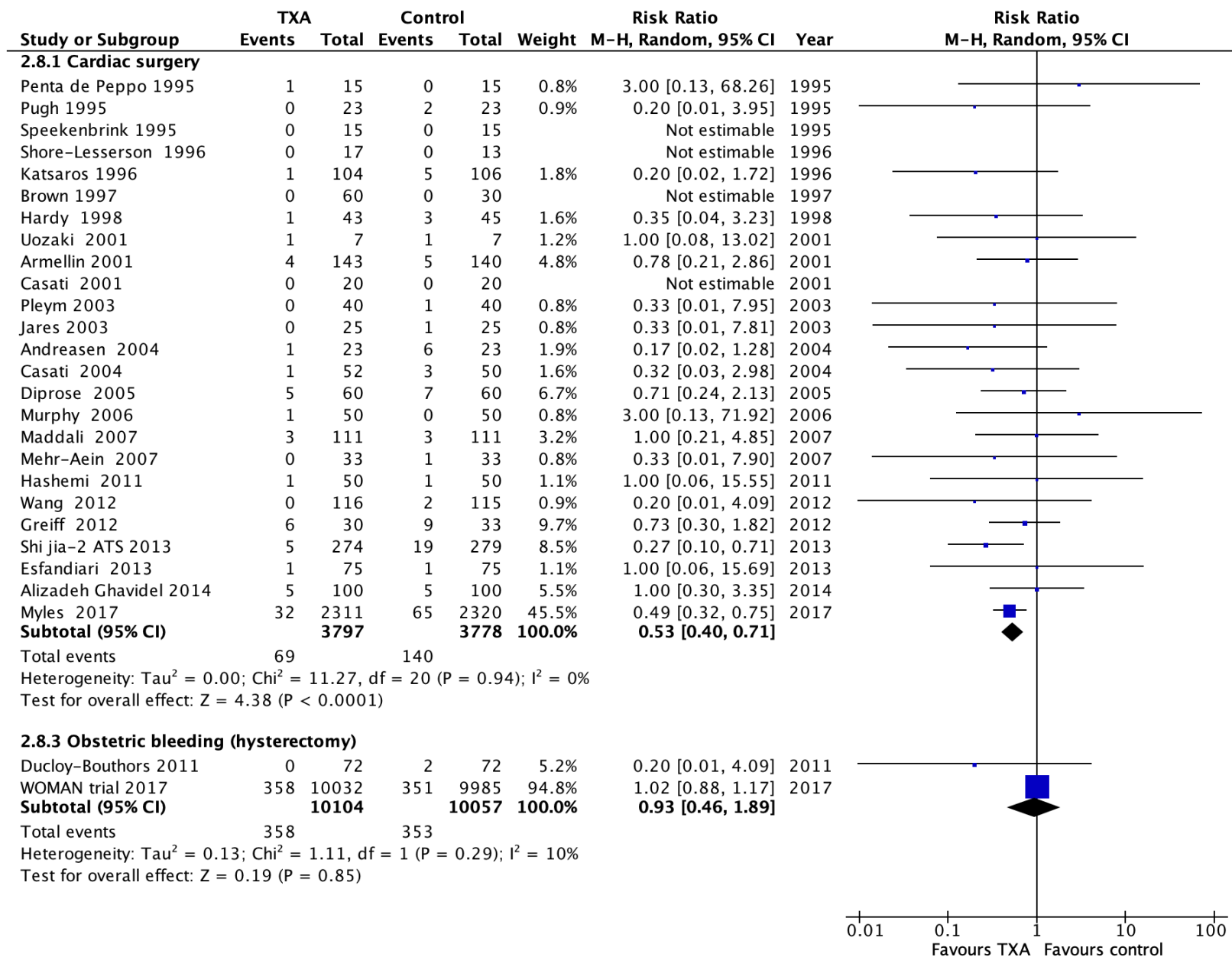
Heterogeneity:  $\tau^2 = 0.09$ ;  $\chi^2 = 17.43$ ,  $df = 9$  ( $P = 0.04$ );  $I^2 = 48\%$

Test for overall effect:  $Z = 3.42$  ( $P = 0.0006$ )



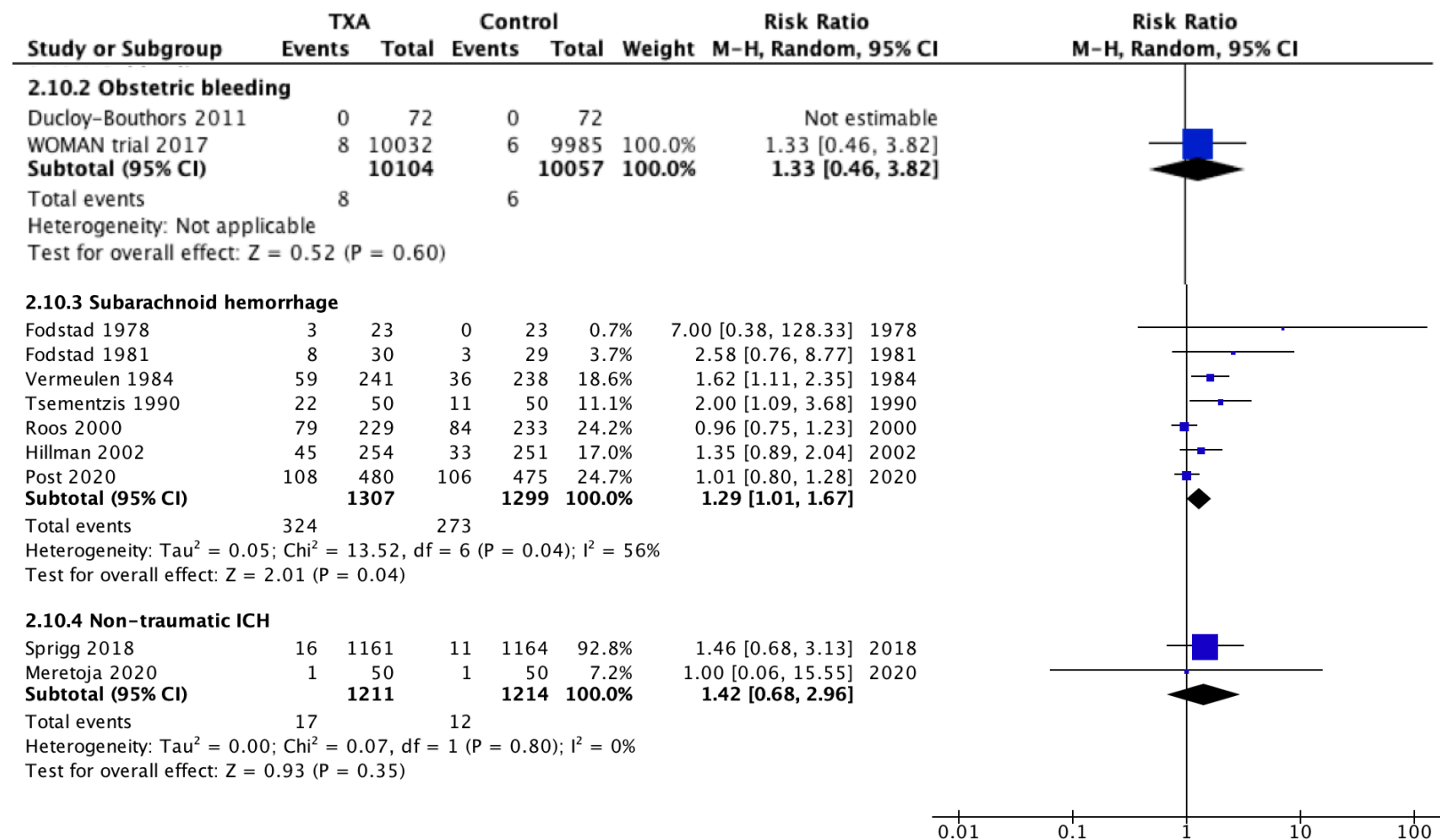
## TXA in non-massively bleeding critically ill patients

### 3c. Need for surgical intervention



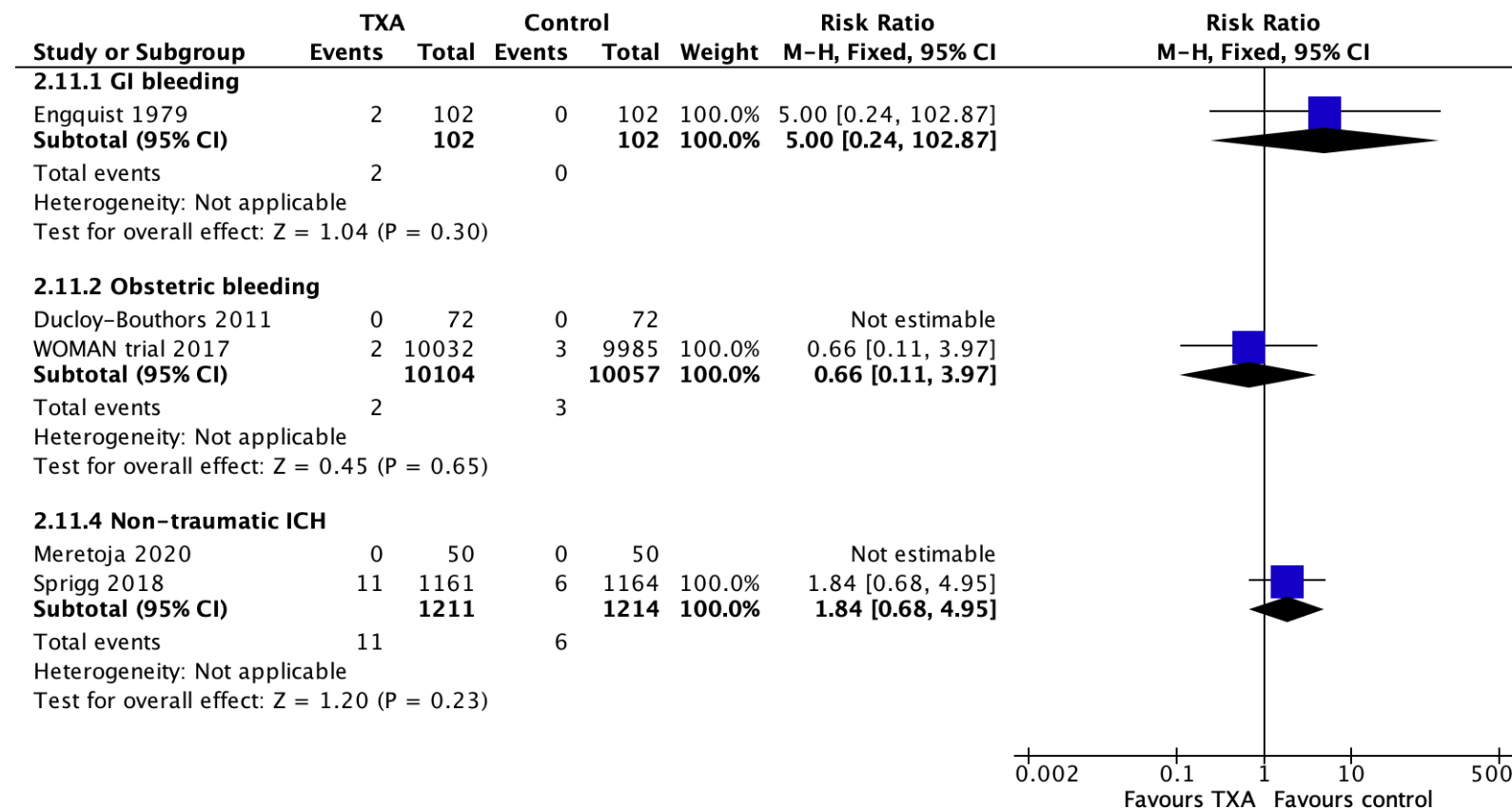
# TXA in non-massively bleeding critically ill patients

## 4. Stroke



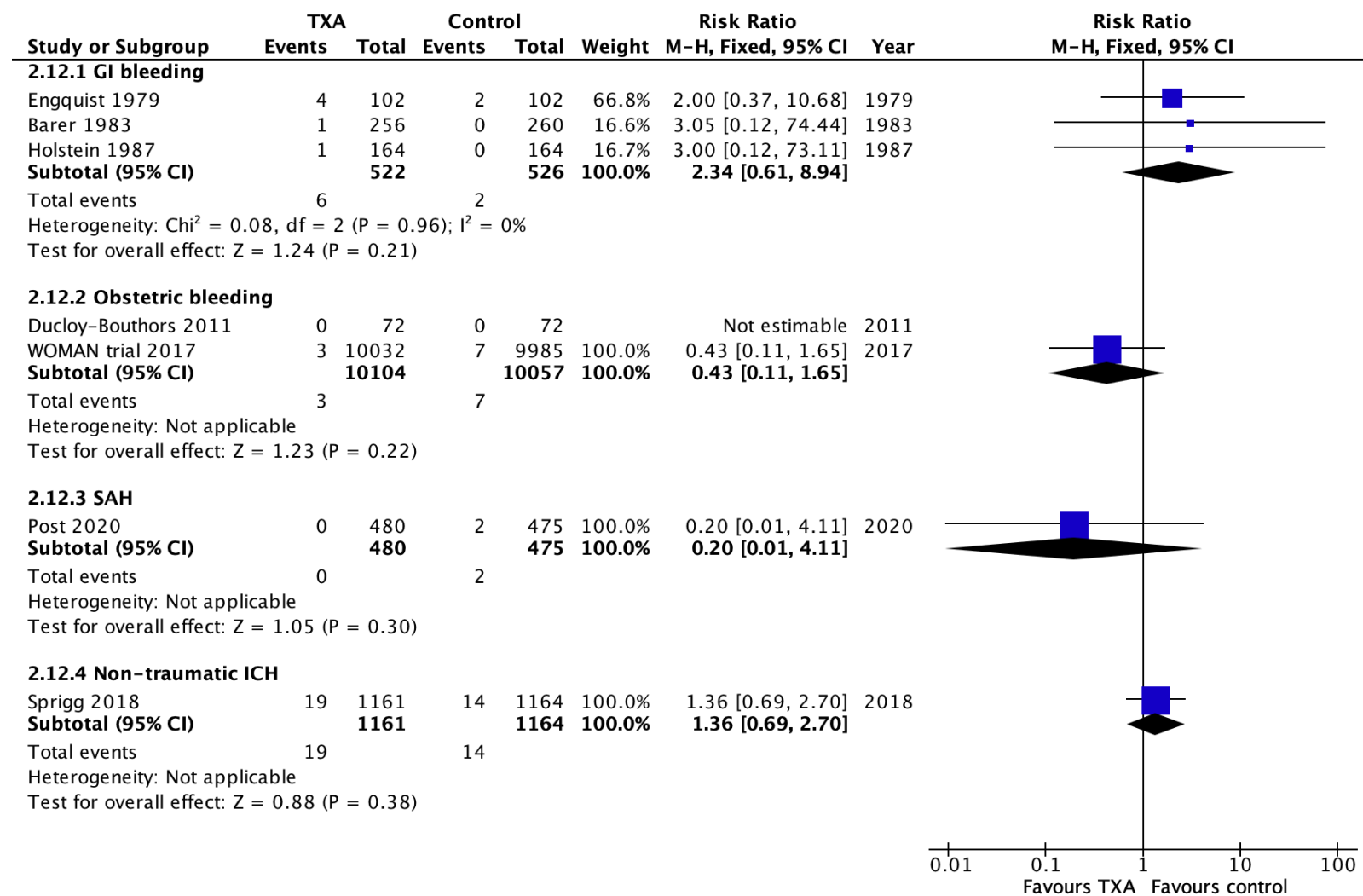
## TXA in non-massively bleeding critically ill patients

### 5. Myocardial infarction



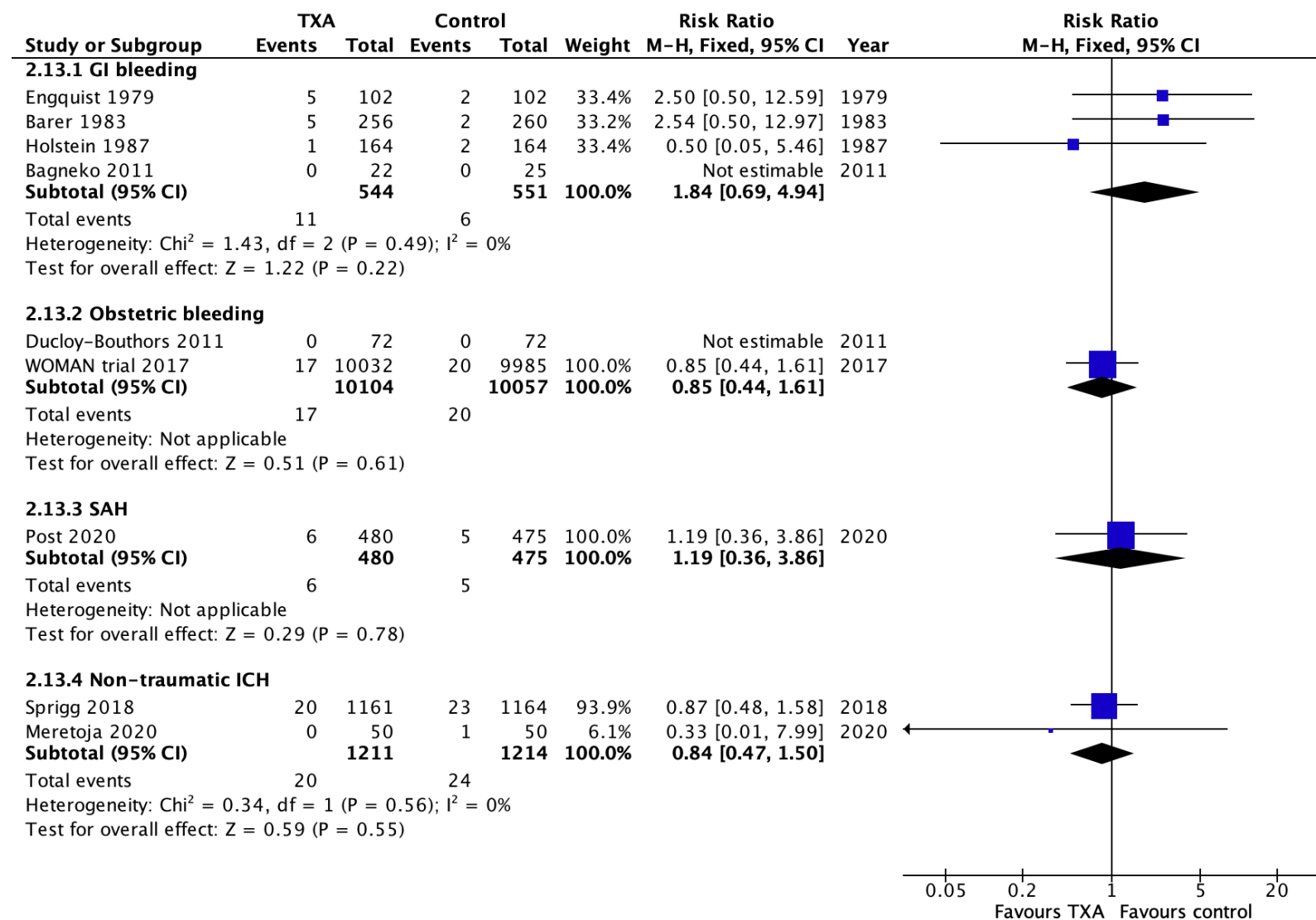
## TXA in non-massively bleeding critically ill patients

### 6a. Thrombosis — DVT



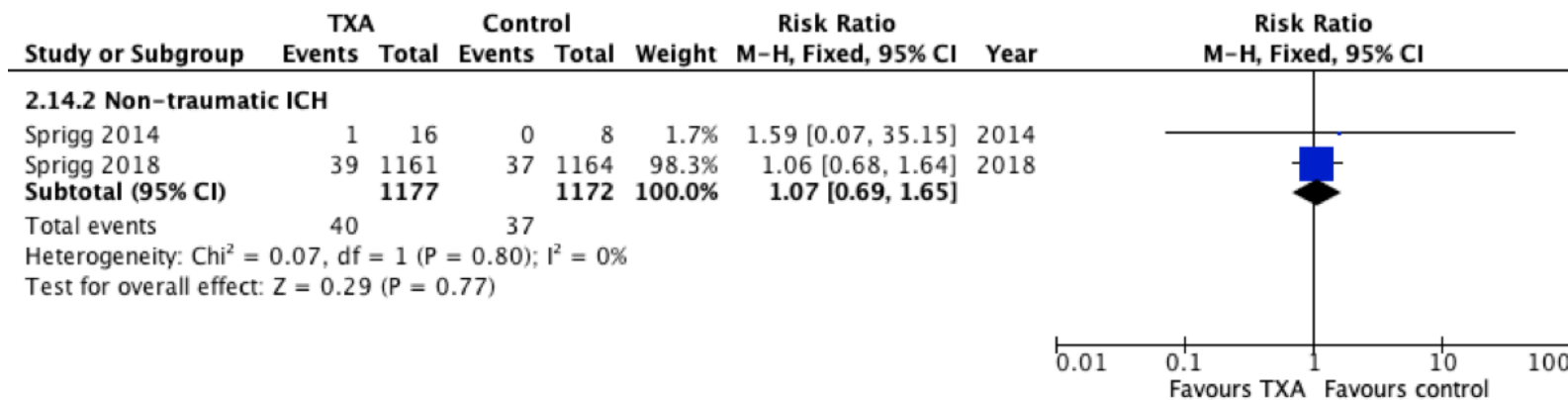
## TXA in non-massively bleeding critically ill patients

### 6b. Thrombosis - pulmonary embolism



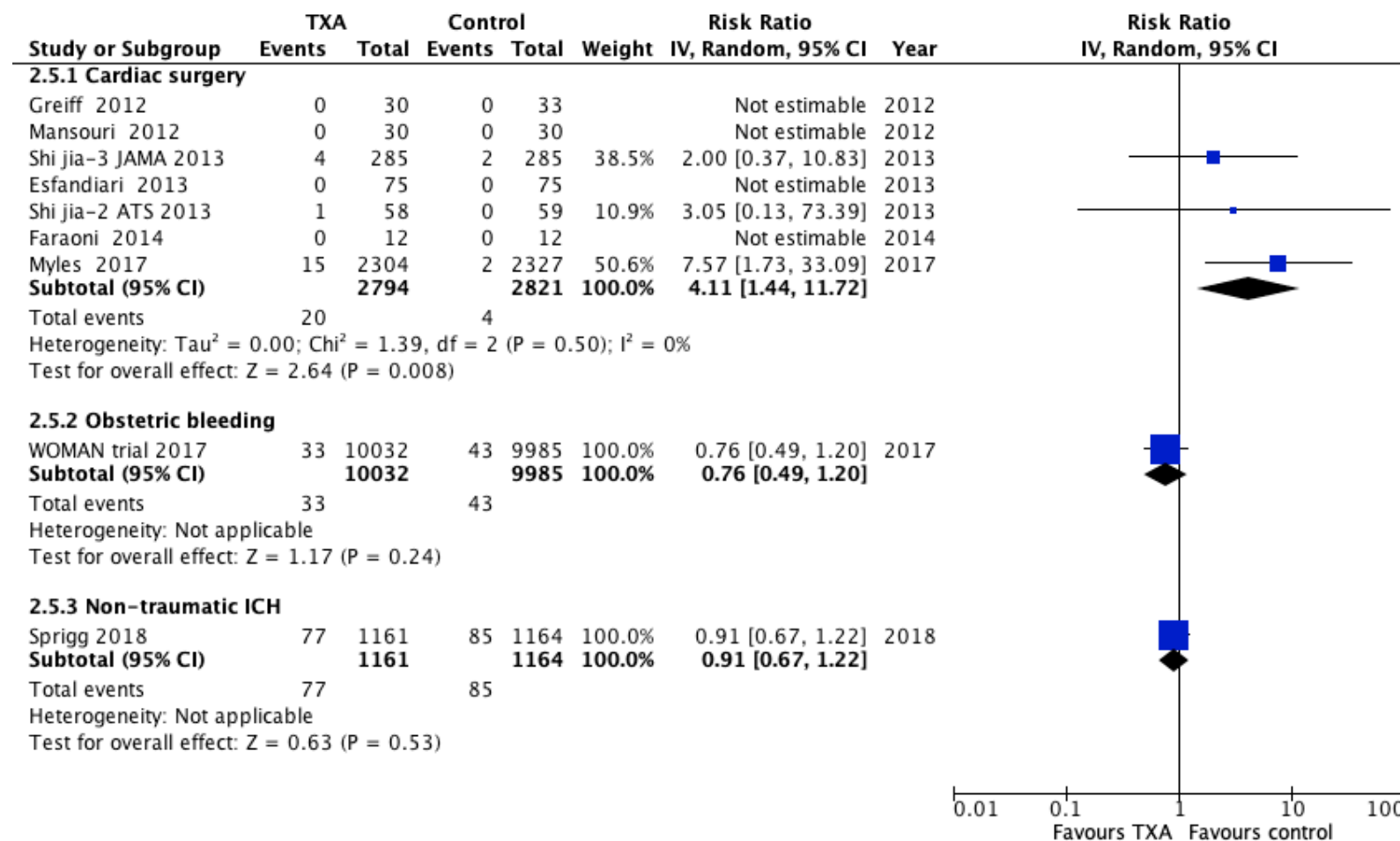
## TXA in non-massively bleeding critically ill patients

### 6c. Thrombosis - venous thrombosis not otherwise specified or combined DVT/PE



## TXA in non-massively bleeding critically ill patients

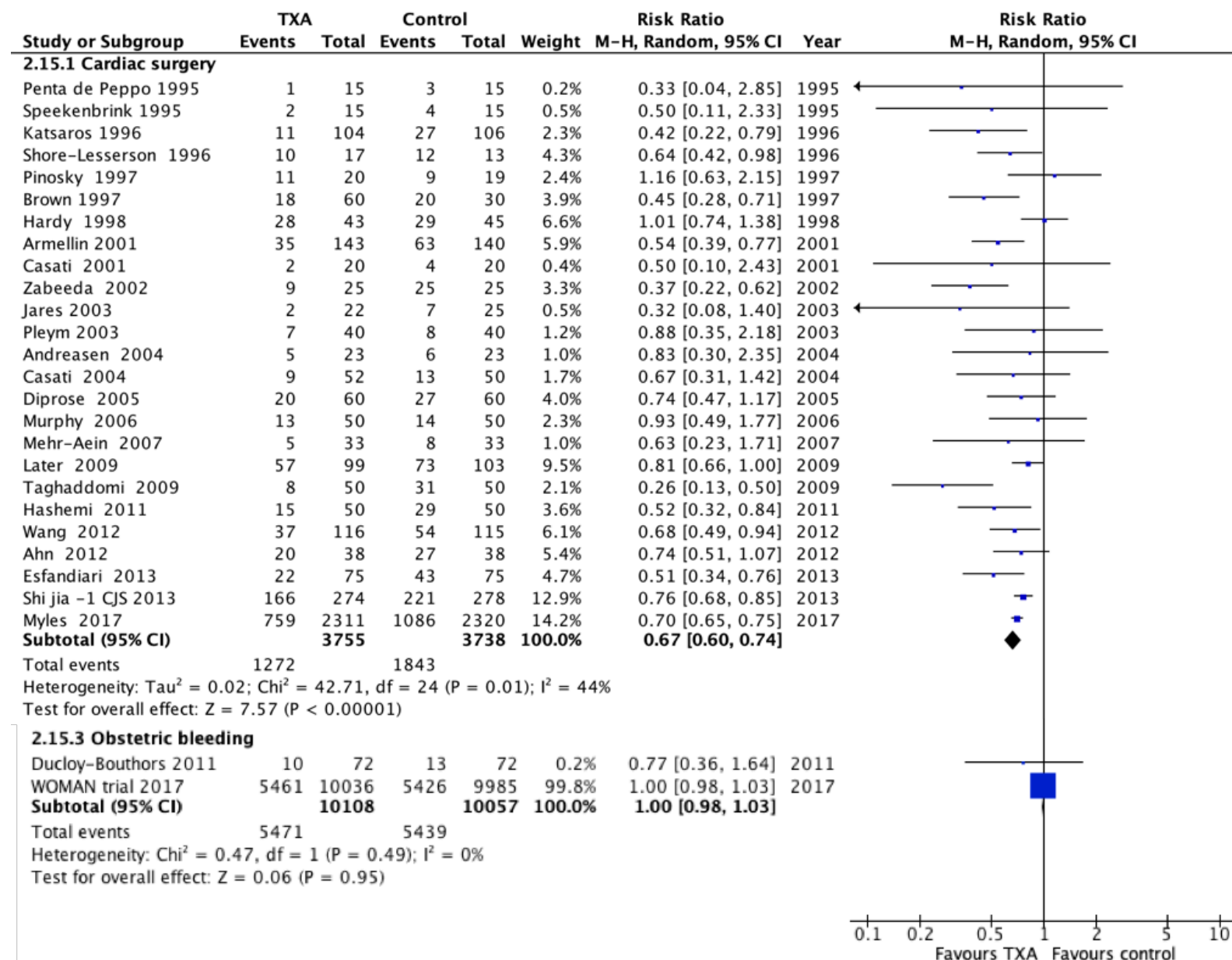
### 7. Seizure





# TXA in non-massively bleeding critically ill patients

## 8. Need for RBC transfusion



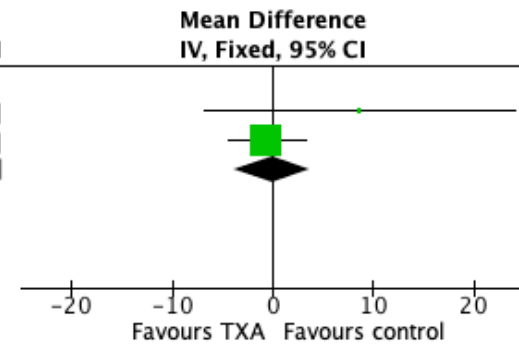
## TXA in non-massively bleeding critically ill patients

### 9. Hospital length of stay

Study or Subgroup	TXA			Control			Weight	Mean Difference IV, Fixed, 95% CI
	Mean	SD	Total	Mean	SD	Total		
<b>2.16.1 Non-traumatic ICH</b>								
Sprigg 2014	19.4	24.5	16	10.8	14	8	5.9%	8.60 [-6.83, 24.03]
Sprigg 2018	63.12	47.1	1161	63.73	48.1	1164	94.1%	-0.61 [-4.48, 3.26]
<b>Subtotal (95% CI)</b>			<b>1177</b>			<b>1172</b>	<b>100.0%</b>	<b>-0.07 [-3.82, 3.69]</b>

Heterogeneity:  $\text{Chi}^2 = 1.29$ ,  $\text{df} = 1$  ( $P = 0.26$ );  $I^2 = 22\%$

Test for overall effect:  $Z = 0.03$  ( $P = 0.97$ )



**Evidence Summary 12: Tranexamic acid in critically ill patients with gastrointestinal bleeding**

## TXA in patients with GI bleeding

### 1. High-dose IV TXA

Certainty assessment						№ of patients		Effect		Certainty	Importance
№ of studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TXA	no TXA	Relative (95% CI)	Absolute (95% CI)		
<b>Mortality at longest follow-up - High-dose IV TXA</b>											
5 RCTs	not serious	not serious <sup>a</sup>	not serious	not serious	none	602/6593 (9.1%)	617/6626 (9.3%)	<b>RR 0.98</b> (0.88 to 1.09)	<b>2 fewer per 1,000</b> (from 11 fewer to 8 more)	⊕⊕⊕⊕ HIGH	CRITICAL
<b>Stroke - High-dose IV TXA</b>											
4 RCTs	not serious	not serious	not serious	not serious <sup>b</sup>	none	20/6474 (0.3%)	22/6503 (0.3%)	<b>RR 0.92</b> (0.51 to 1.65)	<b>0 fewer per 1,000</b> (from 2 fewer to 2 more)	⊕⊕⊕⊕ HIGH	CRITICAL
<b>Myocardial infarction - High-dose IV TXA</b>											
2 RCTs	not serious	not serious	not serious	not serious <sup>b</sup>	none	26/6054 (0.4%)	28/6079 (0.5%)	<b>RR 0.93</b> (0.55 to 1.58)	<b>0 fewer per 1,000</b> (from 2 fewer to 3 more)	⊕⊕⊕⊕ HIGH	CRITICAL
<b>Rebleeding - High-dose IV TXA</b>											
4 RCTs	not serious	not serious	not serious	not serious <sup>b</sup>	none	503/6611 (7.6%)	548/6645 (8.2%)	<b>RR 0.92</b> (0.82 to 1.04)	<b>7 fewer per 1,000</b> (from 15 fewer to 3 more)	⊕⊕⊕⊕ HIGH	IMPORTANT
<b>Surgical intervention - High-dose IV TXA</b>											
5 RCTs	not serious	not serious <sup>c</sup>	not serious	not serious <sup>b</sup>	none	210/6613 (3.2%)	233/6642 (3.5%)	<b>RR 0.91</b> (0.76 to 1.09)	<b>3 fewer per 1,000</b> (from 8 fewer to 3 more)	⊕⊕⊕⊕ HIGH	IMPORTANT
<b>Seizure - High-dose IV TXA</b>											
1 RCT	not serious	not serious	not serious	not serious	none	38/5952 (0.6%)	22/5977 (0.4%)	<b>RR 1.73</b> (1.03 to 2.93)	<b>3 more per 1,000</b> (from 0 fewer to 7 more)	⊕⊕⊕⊕ HIGH	IMPORTANT
<b>Sepsis - High-dose IV TXA</b>											
1 RCT	not serious	not serious	not serious	not serious <sup>b</sup>	none	210/5952 (3.5%)	216/5977 (3.6%)	<b>RR 0.98</b> (0.81 to 1.18)	<b>1 fewer per 1,000</b> (from 7 fewer to 7 more)	⊕⊕⊕⊕ HIGH	CRITICAL

## TXA in patients with GI bleeding

<b>Renal failure - High-dose IV TXA</b>											
1 RCT	not serious	not serious	not serious	not serious <sup>b</sup>	none	142/5951 (2.4%)	157/5978 (2.6%)	<b>RR 0.91</b> (0.73 to 1.14)	<b>2 fewer per 1,000</b> (from 7 fewer to 4 more)	⊕⊕⊕⊕ HIGH	IMPORTANT
<b>Deep venous thrombosis - High-dose IV TXA</b>											
4 RCTs	not serious	not serious	not serious	not serious	none	29/6474 (0.4%)	14/6503 (0.2%)	<b>RR 2.01</b> (1.08 to 3.72)	<b>2 more per 1,000</b> (from 0 fewer to 6 more)	⊕⊕⊕⊕ HIGH	IMPORTANT
<b>Pulmonary embolism - High-dose IV TXA</b>											
5 RCTs	not serious	not serious	not serious	not serious	none	39/6496 (0.6%)	22/6528 (0.3%)	<b>RR 1.78</b> (1.06 to 3.00)	<b>3 more per 1,000</b> (from 0 fewer to 7 more)	⊕⊕⊕⊕ HIGH	IMPORTANT
<b>RBC transfusion - High-dose IV TXA</b>											
3 RCTs	not serious	not serious	not serious	not serious <sup>b</sup>	none	4033/437 3 (92.2%)	4073/443 1 (91.9%)	<b>RR 1.00</b> (0.99 to 1.01)	<b>0 fewer per 1,000</b> (from 9 fewer to 9 more)	⊕⊕⊕⊕ HIGH	IMPORTANT
<b>Plasma transfusion - High-dose IV TXA</b>											
1 RCT	not serious	not serious	not serious	not serious <sup>b</sup>	none	910/4076 (22.3%)	993/4129 (24.0%)	<b>RR 0.93</b> (0.86 to 1.01)	<b>17 fewer per 1,000</b> (from 34 fewer to 2 more)	⊕⊕⊕⊕ HIGH	IMPORTANT
<b>Platelet transfusion - High-dose IV TXA</b>											
1 RCT	not serious	not serious	not serious	not serious <sup>b</sup>	none	219/4076 (5.4%)	255/4129 (6.2%)	<b>RR 0.87</b> (0.73 to 1.04)	<b>8 fewer per 1,000</b> (from 17 fewer to 2 more)	⊕⊕⊕⊕ HIGH	IMPORTANT
<b>RBCs transfused - High-dose IV TXA</b>											
1 RCT	not serious	not serious	not serious	not serious <sup>b</sup>	none	5953	5978	-	<b>MD 0.1 lower</b> (0.19 lower to 0.01 lower)	⊕⊕⊕⊕ HIGH	IMPORTANT
<b>Plasma transfused - High-dose IV TXA</b>											
1 RCT	not serious	not serious	not serious	not serious <sup>b</sup>	none	5953	5978	-	<b>MD 0.1 lower</b> (0.19 lower to 0.01 lower)	⊕⊕⊕⊕ HIGH	IMPORTANT
<b>Platelets transfused - High-dose IV TXA</b>											

## TXA in patients with GI bleeding

1 RCT	not serious	not serious	not serious	not serious <sup>b</sup>	none	5953	5978	-	MD 0 (0.03 lower to 0.03 higher)	⊕⊕⊕⊕ HIGH	IMPORTANT
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CI: Confidence interval; RR: Risk ratio; MD: Mean difference

### Explanations

- Although moderate statistical heterogeneity ( $I^2 > 60\%$ ), this is driven by a single older trial (Barer 1983); excluding this trial reduces heterogeneity but has as similar point estimate (RR 1.01, 95% CI 0.91, 1.13). The effect estimate is thus unlikely to be effected by statistical heterogeneity.
- Though the 95% confidence interval crosses 1, the absolute risk difference is small and possibly of minimal clinical significance.
- Although moderate statistical heterogeneity ( $I^2 > 60\%$ ), this is driven by a single older trial (Holstein 1987); excluding this trial results in a similar estimate of effect (RR 0.96, 95% CI 0.79, 1.15). The effect estimate is thus minimally impacted by the statistical heterogeneity.

## TXA in patients with GI bleeding

### 2. Low dose IV TXA or enteral TXA only

Certainty assessment						№ of patients		Effect		Certainty	Importance
№ of studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TXA	no TXA	Relative (95% CI)	Absolute (95% CI)		
<b>Mortality at longest follow-up - Low-dose or enteral TXA only</b>											
7 RCTs	not serious	not serious	not serious	serious <sup>a</sup>	none	19/445 (4.3%)	30/435 (6.9%)	<b>RR 0.62</b> (0.36 to 1.09)	<b>26 fewer per 1,000</b> (from 44 fewer to 6 more)	⊕⊕⊕○ MODERATE	CRITICAL
<b>Rebleeding - Low-dose or enteral TXA only</b>											
5 RCTs	not serious	not serious	not serious	serious <sup>b</sup>	none	30/371 (8.1%)	59/363 (16.3%)	<b>RR 0.5</b> (0.33 to 0.75)	<b>81 fewer per 1,000</b> (from 109 fewer to 41 fewer)	⊕⊕⊕○ MODERATE	IMPORTANT
<b>Surgical intervention - Low-dose or enteral TXA only</b>											
5 RCTs	not serious	not serious	not serious	serious <sup>b</sup>	none	29/302 (9.6%)	49/297 (16.5%)	<b>RR 0.58</b> (0.38 to 0.88)	<b>69 fewer per 1,000</b> (from 102 fewer to 20 fewer)	⊕⊕⊕○ MODERATE	IMPORTANT
<b>RBC transfusion - Low-dose or enteral TXA only</b>											
4 RCTs	not serious	not serious	not serious	serious <sup>a</sup>	none	217/304 (71.4%)	207/299 (69.2%)	<b>RR 1.03</b> (0.93 to 1.13)	<b>21 more per 1,000</b> (from 48 fewer to 90 more)	⊕⊕⊕○ MODERATE	IMPORTANT
<b>RBCs transfused - Low-dose or enteral TXA</b>											
2 RCTs	not serious	not serious	not serious	serious <sup>b</sup>	none	116	111	-	<b>MD 1.12 lower</b> (1.56 lower to 0.67 lower)	⊕⊕⊕○ MODERATE	IMPORTANT

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

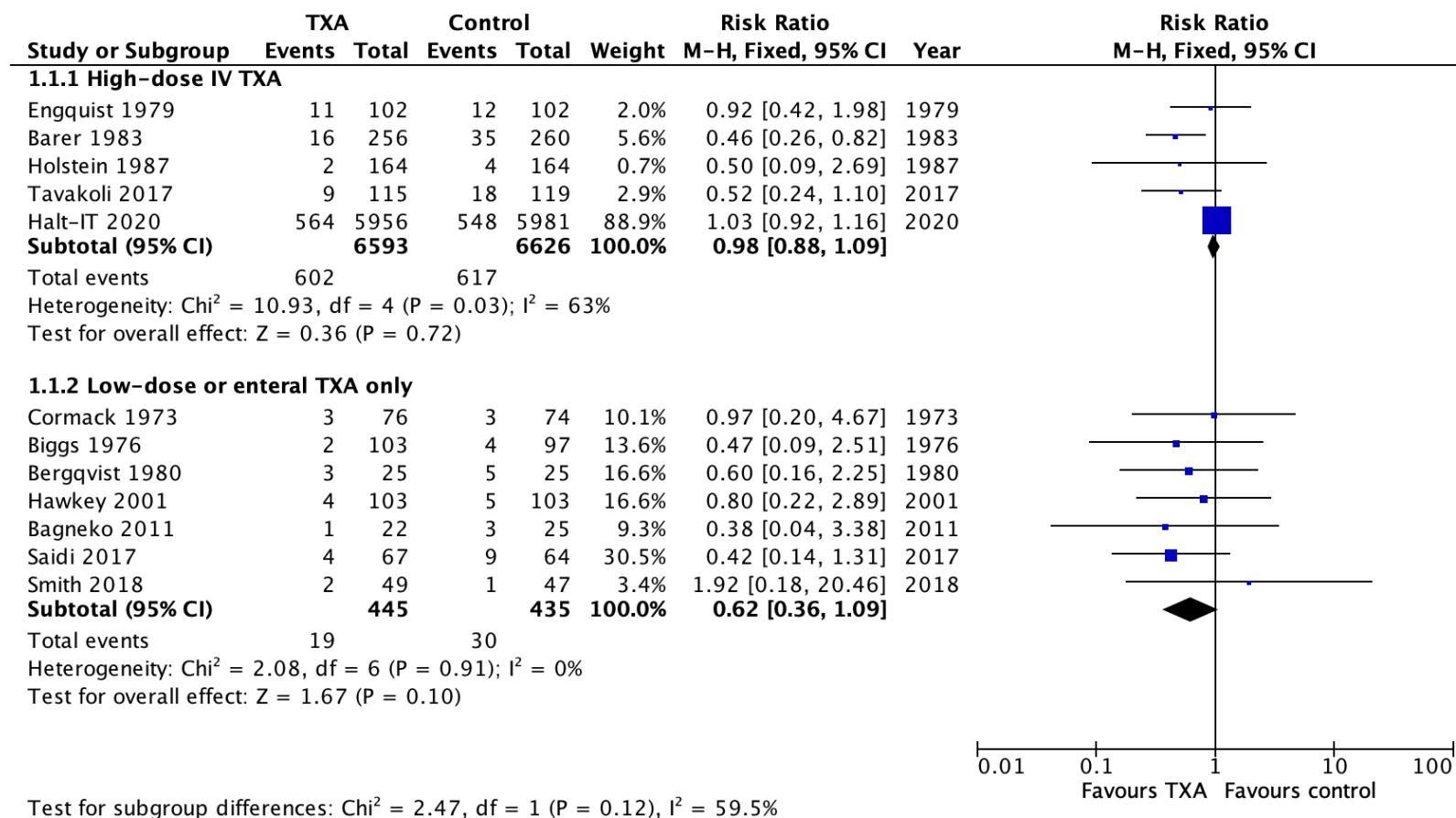
#### Explanations

a. Wide 95% confidence intervals do not exclude clinically significant benefit or harm.

b. Though statistically significant, optimal information size not met resulting in serious imprecision of the overall estimate.

## TXA in patients with GI bleeding

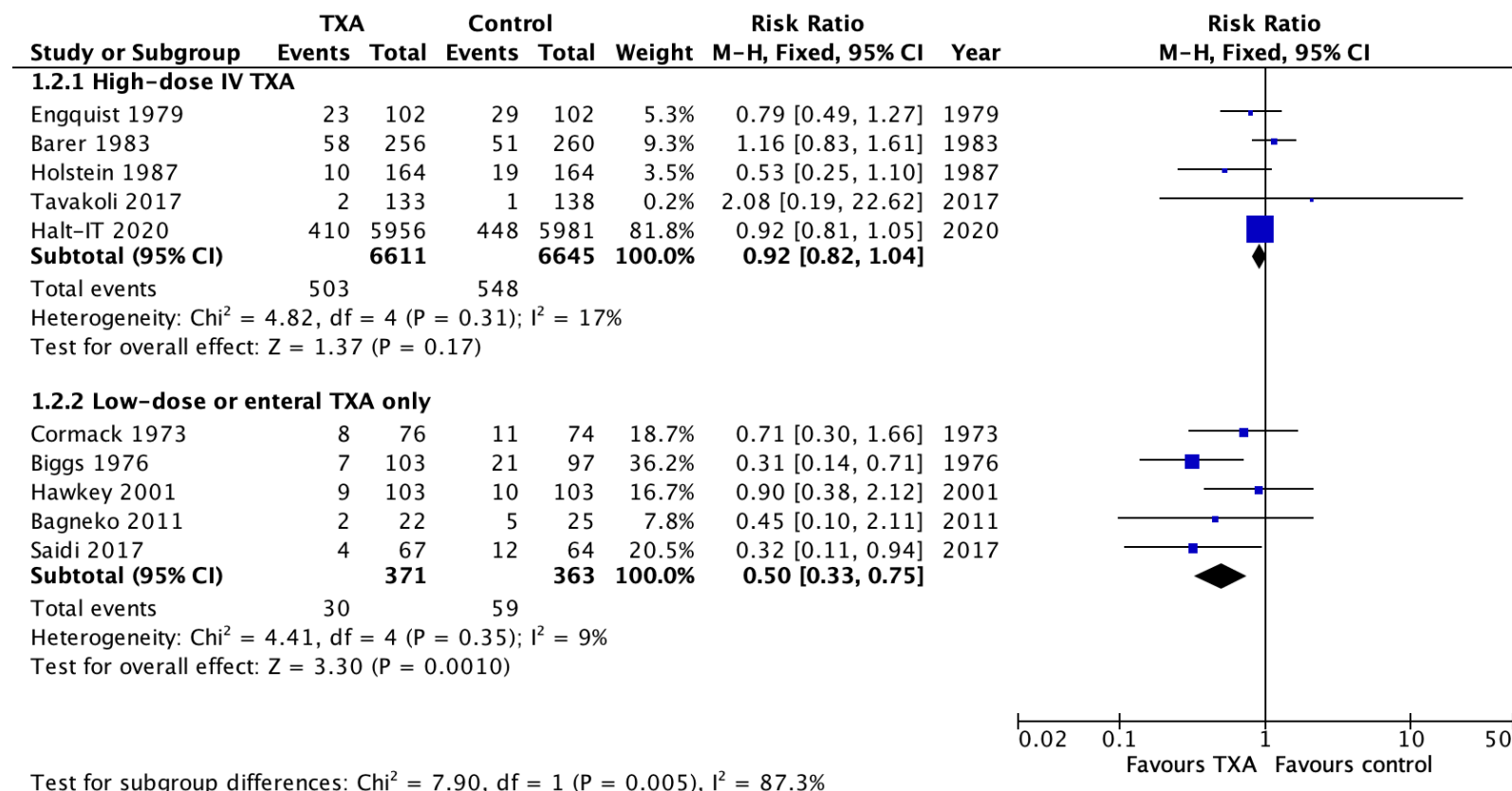
### 1. Mortality at longest follow-up





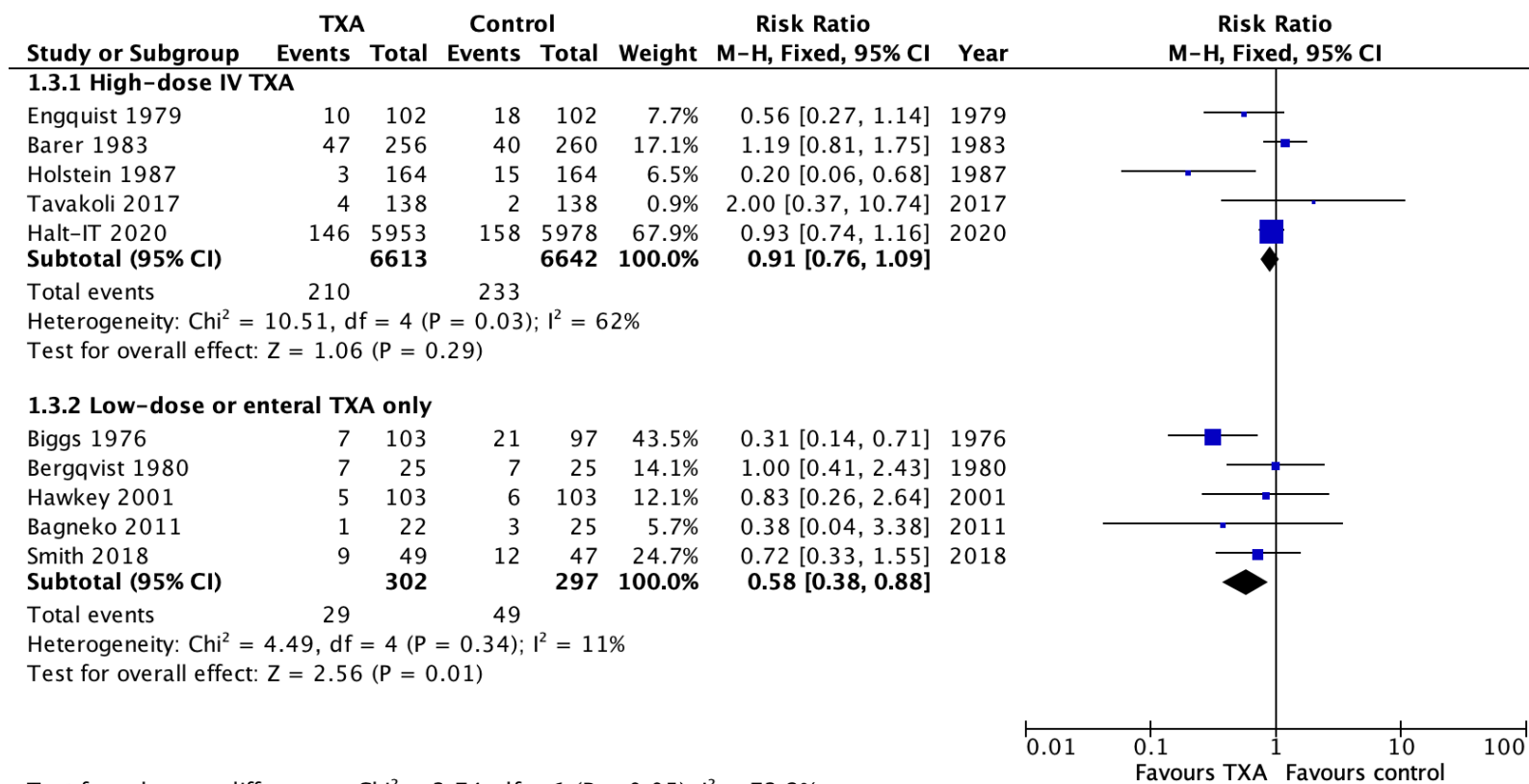
## TXA in patients with GI bleeding

### 2. Rebleeding



## TXA in patients with GI bleeding

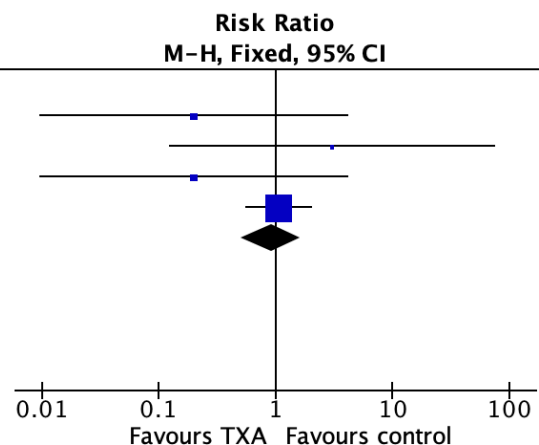
### 3. Surgical intervention



## TXA in patients with GI bleeding

### 4. Stroke

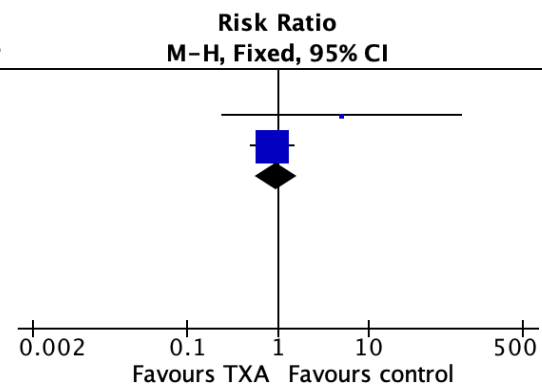
Study or Subgroup	TXA		Control		Weight	Risk Ratio M-H, Fixed, 95% CI	Year
	Events	Total	Events	Total			
<b>1.7.1 High-dose IV TXA</b>							
Engquist 1979	0	102	2	102	10.7%	0.20 [0.01, 4.11]	1979
Barer 1983	1	256	0	260	2.1%	3.05 [0.12, 74.44]	1983
Holstein 1987	0	164	2	164	10.7%	0.20 [0.01, 4.13]	1987
Halt-IT 2020	19	5952	18	5977	76.6%	1.06 [0.56, 2.02]	2020
<b>Subtotal (95% CI)</b>		<b>6474</b>		<b>6503</b>	<b>100.0%</b>	<b>0.92 [0.51, 1.65]</b>	
Total events	20		22				
Heterogeneity: $\text{Chi}^2 = 2.68$ , $\text{df} = 3$ ( $P = 0.44$ ); $I^2 = 0\%$							
Test for overall effect: $Z = 0.28$ ( $P = 0.78$ )							



Test for subgroup differences: Not applicable

### 5. Myocardial infarction

Study or Subgroup	TXA		Control		Weight	Risk Ratio M-H, Fixed, 95% CI	Year
	Events	Total	Events	Total			
<b>1.8.1 High-dose IV TXA</b>							
Engquist 1979	2	102	0	102	1.8%	5.00 [0.24, 102.87]	1979
Halt-IT 2020	24	5952	28	5977	98.2%	0.86 [0.50, 1.48]	2020
<b>Subtotal (95% CI)</b>		<b>6054</b>		<b>6079</b>	<b>100.0%</b>	<b>0.93 [0.55, 1.58]</b>	
Total events	26		28				
Heterogeneity: $\text{Chi}^2 = 1.27$ , $\text{df} = 1$ ( $P = 0.26$ ); $I^2 = 21\%$							
Test for overall effect: $Z = 0.26$ ( $P = 0.80$ )							

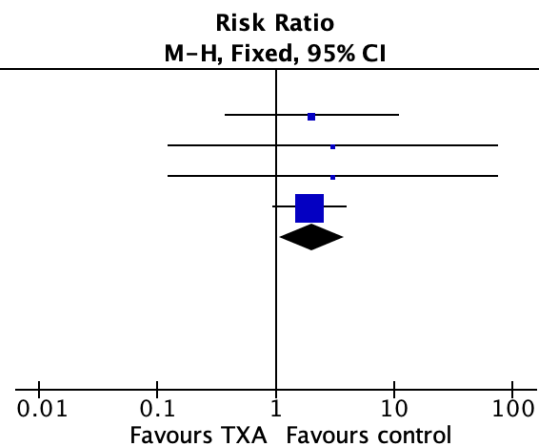


Test for subgroup differences: Not applicable

## TXA in patients with GI bleeding

### 6. Deep venous thrombosis

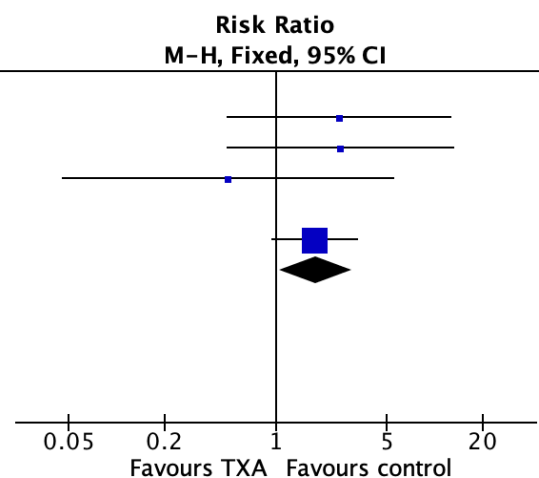
Study or Subgroup	TXA		Control		Weight	Risk Ratio M-H, Fixed, 95% CI	Year
	Events	Total	Events	Total			
<b>1.9.1 High-dose IV TXA</b>							
Engquist 1979	4	102	2	102	13.4%	2.00 [0.37, 10.68]	1979
Barer 1983	1	256	0	260	3.3%	3.05 [0.12, 74.44]	1983
Holstein 1987	1	164	0	164	3.3%	3.00 [0.12, 73.11]	1987
Halt-IT 2020	23	5952	12	5977	80.0%	1.92 [0.96, 3.86]	2020
<b>Subtotal (95% CI)</b>		<b>6474</b>		<b>6503</b>	<b>100.0%</b>	<b>2.01 [1.08, 3.72]</b>	
Total events	29		14				
Heterogeneity: $\text{Chi}^2 = 0.14$ , $\text{df} = 3$ ( $P = 0.99$ ); $I^2 = 0\%$							
Test for overall effect: $Z = 2.21$ ( $P = 0.03$ )							



Test for subgroup differences: Not applicable

### 7. Pulmonary embolism

Study or Subgroup	TXA		Control		Weight	Risk Ratio M-H, Fixed, 95% CI	Year
	Events	Total	Events	Total			
<b>1.10.1 High-dose IV TXA</b>							
Engquist 1979	5	102	2	102	9.1%	2.50 [0.50, 12.59]	1979
Barer 1983	5	256	2	260	9.0%	2.54 [0.50, 12.97]	1983
Holstein 1987	1	164	2	164	9.1%	0.50 [0.05, 5.46]	1987
Bagneko 2011	0	22	0	25		Not estimable	2011
Halt-IT 2020	28	5952	16	5977	72.7%	1.76 [0.95, 3.24]	2020
<b>Subtotal (95% CI)</b>		<b>6496</b>		<b>6528</b>	<b>100.0%</b>	<b>1.78 [1.06, 3.00]</b>	
Total events	39		22				
Heterogeneity: $\text{Chi}^2 = 1.44$ , $\text{df} = 3$ ( $P = 0.70$ ); $I^2 = 0\%$							
Test for overall effect: $Z = 2.17$ ( $P = 0.03$ )							



Test for subgroup differences: Not applicable

## TXA in patients with GI bleeding

### 8. Need for RBC Transfusion

