National Clinical Guideline Centre

1

Draft for Consultation

Transfusion

Blood transfusion

NICE guideline

Appendices J-K-L

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Draft for consultation

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1

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Contents

1

Appendices J-K-L

Appendix J: GRADE tables

J.1 Erythropoietin and iron

J.1.1 Erythropoietin versus placebo

Quality assessment							No. of patients		Effect			
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Erythropoietin	Placebo/no erythropoietin	Relative (95% CI)	Absolute	Quality	Importance
All-cause mortality at 30 days												
7	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	Serious[b]	None	24/723 (3.3%)	11/486 (2.3%)	RR 1.55 (0.79 to 3.07)	12 more per 1000 (from 5 fewer to 47 more)	LOW	
Number of patients transfused												
12	Randomised trials	Serious[a]	Very serious[c]	No serious indirectness	No serious imprecision	None	295/971 (30.4%)	348/692 (50.3%)	RR 0.59 (0.53 to 0.67)	206 fewer per 1000 (from 166 fewer to 236 fewer)	VERY LOW	

Quality assessment							No. of patients		Effect			
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Erythropoietin	Placebo/no erythropoietin	Relative (95% CI)	Absolute	Quality	Importance
Number of units transfused per patient (Better indicated by lower values)												
7	Randomised trials	Serious[a]	Very serious[d]	No serious indirectness	Serious[e]	None	501	308	-	MD 0.69 lower (0.89 to 0.49 lower)	VERY LOW	
Serious adverse events												
6	Randomised trials	Serious[a]	Serious[f]	No serious indirectness	Very serious[g]	None	39/541 (7.2%)	25/303 (8.3%)	RR 0.92 (0.57 to 1.5)	7 fewer per 1000 (from 35 fewer to 41 more)	VERY LOW	
Thrombosis												
5	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	Very serious [g]	None	29/566 (5.1%)	13/410 (3.2%)	RR 1.37 (0.73 to 2.56)	12 more per 1000 (from 9 fewer to 49 more)	VERY LOW	
Infection												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	0/158 (0%)	0/162 (0%)	-	-	HIGH	
Length of hospital stay (Better indicated by lower values)												
1	Randomised trials	Serious [a,h]	No serious inconsistency	No serious indirectness	No serious imprecision	None	31	32	-	MD 3.00 lower (3.36 to 2.64 lower)	MODERATE	

(a) Most information is from studies at high risk of bias
(b) Confidence interval crosses one default MID (1.25) and line of no effect
(c) Significant heterogeneity. I^2=62%.
(d) Significant heterogeneity. I^2=60%.
(e) Confidence interval crosses one default MID and line of no effect

(f) Heterogeneity. I^2=30%.
(g) Confidence interval crosses both default MIDs (0.75 and 1.25) and line of no effect
(h) Unclear randomisation and allocation concealment

J.1.2 IV iron versus placebo or no IV iron

Quality assessment							No. of patients		Effect			
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	IV iron	Placebo/no IV iron	Relative (95% CI)	Absolute	Quality	Importance
All-cause mortality at 30 days												
2	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	Very serious[b]	None	11/140 (7.9%)	10/140 (7.1%)	RR 1.1 (0.49 to 2.47)	7 more per 1000 (from 36 fewer to 105 more)	VERY LOW	
Number of patients transfused												
5	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	Serious[c]	None	67/239 (28%)	85/228 (37.3%)	RR 0.77 (0.59 to 0.99)	86 fewer per 1000 (from 4 fewer to 153 fewer)	LOW	
Length of hospital stay (better indicated by lower values)												
1	Randomised trials	Serious[d]	No serious inconsistency	No serious indirectness	Serious[c]	None	100	100	-	MD 0.6 higher (1.34 lower to 2.54 higher)	LOW	
Serious adverse events												
1	Randomised trials	Very serious[e]	No serious inconsistency	No serious indirectness	No serious imprecision	None	0/11 (0%)	0/10 (0%)	Not pooled	Not pooled	LOW	
Infections												
1	Randomised trials	Serious[d]	No serious inconsistency	No serious directness	Very serious[b]	None	16/100 (16%)	13/100 (13%)	RR 1.23 (0.63 to 2.42)	30 more per 1000 (from 48 fewer to 185 more)	VERY LOW	

(a) Most information is from studies at high risk of bias
(b) Confidence interval crosses both default MIDs (0.75 and 1.25) and line of no effect
(c) Confidence interval crosses one default MID and line of no effect
(d) No blinding
(e) 7/38 (18%) patients missing data. Low frequency of events means this could impact on results. Study reports the trial was underpowered for the outcomes under assessment and that it stopped early because of recruitment problems.

J.1.3 Oral iron versus placebo or no oral iron

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Oral iron	Placebo/no oral iron	Relative (95% CI)	Absolute		
Number of patients transfused												
2	Randomised trials	Serious[a]	Serious[b]	No serious indirectness	Very serious[c]	None	33/77 (42.9%)	39/77 (50.6%)	RR 0.84 (0.6 to 1.19)	81 fewer per 1000 (from 203 fewer to 96 more)	VERY LOW	

(a) Most information is from studies at high risk of bias
(b) Significant heterogeneity. I^2=66%.
(c) Confidence interval crosses both default MIDs (0.75 and 1.25) and line of no effect

J.1.4 Erythropoietin plus IV iron versus placebo

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Erythropoietin + IV iron	Placebo	Relative (95% CI)	Absolute		
All-cause mortality at 30 days												
2	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	Very serious[b]	None	0/77 (0%)	1/77 (1.3%)	RR 0.33 (0.01 to 7.93)	9 fewer per 1000 (from 13 fewer to	VERY LOW	

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Erythropoietin + IV iron	Placebo	Relative (95% CI)	Absolute		
										90 more)		
Number of patients transfused												
4	Randomised trials	Serious[a]	Very serious[c]	No serious indirectness	No serious imprecision	None	43/141 (30.5%)	84/142 (59.2%)	RR 0.51 (0.39 to 0.67)	290 fewer per 1000 (from 195 fewer to 361 fewer)	VERY LOW	
Number of units transfused per patient (Better indicated by lower values)												
2	Randomised trials	No serious risk of bias	Very serious[d]	No serious indirectness	No serious imprecision	None	91	91	-	MD 0.76 lower (1 to 0.52 lower)	LOW	
Length of hospital stay (Better indicated by lower values)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[e]	None	37	37	-	MD 2.2 lower (5.1 lower to 0.7 higher)	LOW	
Serious adverse events												
1	Randomised trials	Very serious[f]	No serious inconsistency	No serious indirectness	No serious imprecision	None	0/10 (0%)	0/10 (0%)	Not pooled	Not pooled	LOW	

(a) Most information is from studies at high risk of bias
(b) Confidence interval crosses both default MIDs (0.75 and 1.25) and line of no effect
(c) Significant heterogeneity. I^2=69%.
(d) Significant heterogeneity. I^2=93%.
(e) Confidence interval crosses one default MID and line of no effect
(f) 7/38 (18%) patients missing data. Low frequency of events means this could impact on results. Study reports the trial was underpowered for the outcomes under assessment and that it stopped early because of recruitment problems.

J.1.5 Oral iron versus IV iron

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Oral iron	IV iron	Relative (95% CI)	Absolute		
Number of patients transfused												
2	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	Serious[b]	None	29/115 (25.2%)	23/113 (20.4%)	RR 1.28 (0.83 to 1.95)	57 more per 1000 (from 35 fewer to 193 more)	LOW	CRITICAL
Length of hospital stay (better indicated by lower values)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	62	59	-	MD 0.30 lower (0.79 lower to 0.19 higher)	HIGH	
Deep vein thrombosis												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[c]	None	0/62 (0%)	1/59 (1.7%)	RR 0.32 (0.01 to 7.64)	12 fewer per 1000 (from 17 fewer to 113 more)	LOW	
Quality of life (Better indicated by lower values)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	62	59	-	MD 0.00 higher (0.23 lower to 0.23 higher)	HIGH	

(a) Unclear randomisation, allocation concealment and unclear missing data (Garrido-Martin 2012).
(b) Confidence interval crosses one default MID (1.25) and line of no effect.
(c) Confidence interval crosses one default MID and line of no effect.

J.1.6 Erythropoietin plus IV iron versus IV iron

Quality assessment	No. of patients	Effect	Quality	Importance

No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Erythropoietin + IV iron	IV iron	Relative (95% CI)	Absolute		
All-cause mortality at 30 days												
1	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	None	0/40 (0%)	0/40 (0%)	Not pooled	Not pooled	MODERATE	
Number of patients transfused												
2	Randomised trials	Serious[b]	No serious inconsistency	No serious indirectness	Very serious[c]	None	9/50 (18%)	12/51 (23.5%)	RR 0.76 (0.35 to 1.65)	56 fewer per 1000 (from 153 fewer to 153 more)	VERY LOW	
Serious adverse events												
2	Randomised trials	Serious[b]	No serious inconsistency	No serious indirectness	No serious imprecision	None	0/48 (0%)	0/51 (0%)	Not pooled	Not pooled	MODERATE	

(a) Unclear allocation concealment and blinding
(b) Most information is from studies at high risk of bias
(c) Confidence interval crosses both default MIDs (0.75 and 1.25) and line of no effect

J.1.7 Erythropoietin plus oral iron versus oral iron

Quality assessment							No. of patients		Effect			
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Erythropoietin+ Oral iron	Oral iron	Relative (95% CI)	Absolute	Quality	Importance
All-cause mortality at 30 days												
2	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	Very serious[b]	None	10/437 (2.3%)	12/443 (2.7%)	RR 0.88 (0.39 to 1.96)	3 fewer per 1000 (from 17 fewer to 26 more)	VERY LOW	
Number of patients transfused												
3	Randomised	Serious[a]	No serious	No serious	No serious	None	1/68	32/73	RR 0.06	412 fewer per	MODERATE	

	trials		inconsistency	indirectness	imprecision		(1.5%)	(43.8%)	(0.02 to 0.25)	1000 (from 329 fewer to 430 fewer)		
Length of hospital stay (better indicated by lower values)												
2	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	None	38	43	-	MD 0.22 lower (0.61 lower to 0.18 higher)	MODERATE	
Infections												
1	Randomised trials	Serious[c]	No serious inconsistency	No serious indirectness	Very serious[b]	None	1/16 (6.3%)	2/16 (12.5%)	RR 0.5 (0.05 to 4.98)	62 fewer per 1000 (from 119 fewer to 498 more)	VERY LOW	
Deep vein thrombosis												
1	Randomised trials	Serious[d]	No serious inconsistency	No serious indirectness	Serious[e]	None	16/340 (4.7%)	7/340 (2.1%)	RR 2.29 (0.95 to 5.49)	27 more per 1000 (from 1 fewer to 92 more)	LOW	
Other thrombovascular events												
1	Randomised trials	Serious[d]	No serious inconsistency	No serious indirectness	Very serious[b]	None	12/340 (3.5%)	7/340 (2.1%)	RR 1.71 (0.68 to 4.3)	15 more per 1000 (from 7 fewer to 68 more)	VERY LOW	

(a) Most information is from studies at high risk of bias
(b) Confidence interval crosses both default MIDs (0.75 and 1.25) and line of no effect
(c) Unclear randomisation, blinding and allocation concealment.
(d) Open label. No blinding.
(e) Confidence interval crosses one default MID and line of no effect

J.1.8 Erythropoietin plus oral iron or IV iron versus oral or IV iron

Quality assessment							No. of patients		Effect			
No. of	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	EPO+ IV iron or	Placebo+IV iron	Relative	Absolute	Quality	Importance

studies							oral iron	or oral iron	(95% CI)			
Mortality												
1	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	None	0/58 (0%)	0/52 (0%)	Not pooled	Not pooled	MODERATE	
Serious adverse events												
1	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	Very serious[b]	None	0/58 (0%)	1/52 (1.9%)	RR 0.3 (0.01 to 7.19)	13 fewer per 1000 (from 19 fewer to 119 more)	VERY LOW	
Thrombosis												
1	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	None	0/58 (0%)	0/52 (0%)	Not pooled	Not pooled	MODERATE	

(a) Allocation concealment not reported.
(b) Confidence interval crosses both default MIDs (0.75 and 1.25) and line of no effect.

J.2 Alternatives to blood transfusion in surgical patients - combinations of cell salvage and tranexamic acid

J.2.1 Adults - high risk group

Quality assessment							No. of patients		Effect			
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Intra-operative cell salvage	Standard treatment	Relative (95% CI)	Absolute	Quality	Importance
No. exposed to allogeneic blood												
4	Randomised trials	Very serious[a]	No serious inconsistency	No serious indirectness	Serious[b]	None	49/125 (39.2%)	67/126 (53.2%)	RR 0.74 (0.58 to 0.93)	138 fewer per 1000 (from 37 fewer to 223 fewer)	VERY LOW	
Units of allogeneic blood transfused (Better indicated by lower values)												
4	Randomised trials	Very serious[a]	Serious[c]	No serious indirectness	Serious[b]	None	110	113	-	MD 0.78 lower (1.37 to 0.19 lower)	VERY LOW	

Mortality at up to 30 days												
7	Randomised trials	Very serious[a]	No serious inconsistency	No serious indirectness	Very serious[d]	None	15/210 (7.1%)	19/214 (8.9%)	RR 0.97 (0.64 to 1.47)	3 fewer per 1000 (from 32 fewer to 42 more)	VERY LOW	
Any infection												
4	Randomised trials	Very serious[a]	No serious inconsistency	No serious indirectness	Serious[b]	None	7/124 (5.6%)	19/126 (15.1%)	RR 0.4 (0.18 to 0.87)	90 fewer per 1000 (from 20 fewer to 124 fewer)	VERY LOW	
Hospital length of stay (Better indicated by lower values)												
1	Randomised trials	Very serious[a]	No serious inconsistency	No serious indirectness	Very serious[d]	None	40	40	-	MD 0.2 lower (1.26 lower to 0.86 higher)	VERY LOW	

(a) The majority of the evidence was at very high risk of bias.
(b) The confidence interval crosses one MID.
(c) Downgraded by one increment due to heterogeneity, I2=65%.
(d) The confidence interval crosses both MIDs.

Quality assessment							No. of patients		Effect			
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Post Op CS	Standard treatment	Relative (95% CI)	Absolute	Quality	Importance
No. exposed to allogeneic blood												
4	Randomised trials	Very serious[a]	No serious inconsistency	No serious indirectness	Serious[b]	None	28/126 (22.2%)	53/136 (39%)	RR 0.6 (0.45 to 0.81)	156 fewer per 1000 (from 74 fewer to 214 fewer)	VERY LOW	
Units of allogeneic blood transfused (Better indicated by lower values)												
1	Randomised trials	Very serious[a]	No serious inconsistency	No serious indirectness	Serious[b]	None	30	30	-	MD 1.02 lower (1.19 to 0.85 lower)	VERY LOW	
Mortality at up to 30 days												
1	Randomised trials	Very serious[a]	No serious inconsistency	No serious indirectness	Very serious[c]	None	1/25 (4%)	0/25 (0%)	RR 3 (0.13 to 70.3)	-	VERY LOW	
Any infection												

1	Randomised trials	Very serious[a]	No serious inconsistency	No serious indirectness	Serious[b]	None	1/41 (2.4%)	8/49 (16.3%)	RR 0.15 (0.02 to 1.15)	139 fewer per 1000 (from 160 fewer to 24 more)	VERY LOW	
Hospital length of stay (Better indicated by lower values)												
1	Randomised trials	Very serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	None	41	49	-	MD 7.13 lower (9.12 to 5.14 lower)	LOW	

(a) The majority of the evidence was at very high risk of bias.
(b) The confidence interval crosses one MID.
(c) The confidence interval crosses both MIDs.

Quality assessment							No. of patients		Effect			
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Intra-operative cell salvage + post-operative cell salvage	Standard treatment	Relative (95% CI)	Absolute	Quality	Importance
No. exposed to allogeneic blood												
2	Randomised trials	Very serious[a]	No serious inconsistency	No serious indirectness	Serious[b]	None	49/113 (43.4%)	74/117 (63.2%)	RR 0.69 (0.54 to 0.89)	196 fewer per 1000 (from 70 fewer to 291 fewer)	VERY LOW	
Mortality at up to 30 days												
1	Randomised trials	Very serious[a]	No serious inconsistency	No serious indirectness	Very serious[c]	None	1/99 (1%)	3/97 (3.1%)	RR 0.33 (0.03 to 3.09)	21 fewer per 1000 (from 30 fewer to 65 more)	VERY LOW	
Any infection												
1	Randomised trials	Very serious[a]	No serious inconsistency	No serious indirectness	Very serious[c]	None	2/99 (2%)	2/97 (2.1%)	RR 0.98 (0.14 to 6.82)	0 fewer per 1000 (from 18 fewer to 120 more)	VERY LOW	
Length of hospital stay (Better indicated by lower values)												
1	Randomised trials	Very serious[a]	No serious inconsistency	No serious indirectness	Very serious[c]	None	99	97	-	MD 2.8 higher (2.11 lower to 7.71 higher)	VERY LOW	

(a) The majority of the evidence is at very high risk of bias.
(b) The confidence interval crosses one MID.

(c) *The confidence interval crosses both MIDs.*

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Intra-operative cell salvage +TXA	Intra-operative cell salvage	Relative (95% CI)	Absolute		
No. exposed to allogeneic blood												
5	Randomised trials	Very serious[a]	No serious inconsistency	No serious indirectness	Serious[b]	None	100/255 (39.2%)	144/259 (55.6%)	RR 0.71 (0.6 to 0.85)	161 fewer per 1000 (from 83 fewer to 222 fewer)	VERY LOW	
Units of blood transfused (Better indicated by lower values)												
2	Randomised trials	Very serious[a]	Serious[c]	No serious indirectness	No serious imprecision	None	84	86	-	MD 1.56 lower (1.84 to 1.29 lower)	VERY LOW	
Mortality at 30 days												
4	Randomised trials	Very serious[a]	No serious inconsistency	No serious indirectness	Very serious[d]	None	1/143 (0.7%)	2/209 (1%)	RR 1.04 (0.07 to 16.41)	0 more per 1000 (from 9 fewer to 147 more)	VERY LOW	
Length of stay in hospital (Better indicated by lower values)												
2	Randomised trials	Very serious[a]	No serious inconsistency	No serious indirectness	Very serious[d]	None	123	129	-	MD 0.68 higher (0.81 lower to 2.17 higher)	VERY LOW	

(a) *The majority of the evidence is at very high risk of bias.*
(b) *The confidence interval crosses one MID.*
(c) *Downgraded by one increment due to heterogeneity; I2=61%.*
(d) *The confidence interval crosses both MIDs.*

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Intra-operative cell salvage +TXA	TXA	Relative (95% CI)	Absolute		
No. exposed to allogeneic blood												
1	Randomised	Very	No serious	No serious	Very serious[b]	None	12/34	13/29	RR 0.79 (0.43	94 fewer per 1000	VERY LOW	

	trials	serious[a]	inconsistency	indirectness			(35.3%)	(44.8%)	to 1.45)	(from 256 fewer to 202 more)		
Mortality at 30 days												
1	Randomised trials	Very serious[a]	No serious inconsistency	No serious indirectness	Very serious[b]	None	4/34 (11.8%)	0/29 (0%)	RR 7.71 (0.43 to 137.53)	-	VERY LOW	
Infections												
1	Randomised trials	Very serious[a]	No serious inconsistency	No serious indirectness	Very serious[b]	None	5/34 (14.7%)	4/29 (13.8%)	RR 1.07 (0.32 to 3.6)	10 more per 1000 (from 94 fewer to 359 more)	VERY LOW	
Length of stay in hospital (Better indicated by lower values)												
1	Randomised trials	Very serious[a]	No serious inconsistency	No serious indirectness	Very serious[b]	None	34	29	-	MD 2.1 higher (3.36 lower to 7.56 higher)	VERY LOW	

(a) The majority of the evidence is at very high risk of bias.
(b) The confidence interval crosses both MIDs.

Quality assessment							No. of patients		Effect			
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Post-operative cell salvage +TXA	TXA	Relative (95% CI)	Absolute	Quality	Importance
No. of patients with allogeneic blood transfusion												
1	Randomised trials	Very serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	None	0/17 (0%)	0/17 (0%)	not pooled	not pooled	LOW	

(a) The majority of the evidence is at very high risk of bias.

Quality assessment							No. of patients		Effect			
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Intra-operative cell salvage + post-operative cell salvage +TXA	Intra-operative cell salvage + post-operative cell salvage	Relative (95% CI)	Absolute	Quality	Importance
No. exposed to allogeneic blood												
1	Randomised	Very	No serious	No serious	Very serious[b]	None	13/50	14/50	RR 0.93	20 fewer per	VERY	

	trials	serious[a]	inconsistency	indirectness			(26%)	(28%)	(0.49 to 1.77)	1000 (from 143 fewer to 216 more)	LOW	
Units of blood transfused (Better indicated by lower values)												
1	Randomised trials	Very serious[a]	No serious inconsistency	No serious indirectness	Serious[c]	None	13	14	-	MD 0.25 higher (0.32 lower to 0.82 higher)	VERY LOW	
Mortality at 30 days												
1	Randomised trials	Very serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	None	0/50 (0%)	0/50 (0%)	Not pooled	Not pooled	LOW	

(a) The majority of the evidence was at very high risk of bias.
(b) The confidence interval crosses both MIDs.
(c) The confidence interval crosses one MID.

Quality assessment							No. of patients		Effect			
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Intra-operative cell salvage + post-operative cell salvage +TXA	TXA	Relative (95% CI)	Absolute	Quality	Importance
No. exposed to allogeneic blood												
1	Randomised trials	Very serious[a]	No serious inconsistency	No serious indirectness	Very serious[b]	None	31/102 (30.4%)	33/111 (29.7%)	RR 1.02 (0.68 to 1.54)	6 more per 1000 (from 95 fewer to 161 more)	VERY LOW	
Any infection												
1	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	Very serious[b]	None	6/102 (5.9%)	5/111 (4.5%)	RR 1.31 (0.41 to 4.15)	14 more per 1000 (from 27 fewer to 142 more)	VERY LOW	

(a) The majority of the evidence is at very high risk of bias.
(b) The confidence interval crosses both MIDs.

Quality assessment							No. of patients		Effect			
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	TXA	Standard treatment or placebo- High risk- adults	Relative (95% CI)	Absolute	Quality	Importance

No. of patients needing blood transfusions												
38	Randomised trials	Serious[a]	Serious[b]	No serious indirectness	Serious[c]	None	684/2065 (33.1%)	968/2040 (47.5%)	RR 0.71 (0.63 to 0.81)	138 fewer per 1000 (from 90 fewer to 176 fewer)	VERY LOW	
No. of units of blood transfused - All Patients (Better indicated by lower values)												
17	Randomised trials	Serious[a]	Serious[b]	No serious indirectness	No serious imprecision	None	953	965	-	MD 0.0.83 lower (1.17 to 0.5 lower)	LOW	
Mortality												
31	Randomised trials	Serious[a]	Serious[d]	No serious indirectness	Serious[c]	None	17/1891 (0.9%)	35/1880 (1.9%)	RR 0.52 (0.31 to 0.87)	9 fewer per 1000 (from 2 fewer to 13 fewer)	VERY LOW	
Length of hospital stay (Better indicated by lower values)												
3	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	None	89	93	-	MD 0.08 lower (0.35 lower to 0.18 higher)	MODERATE	
Infections												
1	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	Serious[c]	None	10/50 (20%)	16/50 (32%)	RR 0.62 (0.31 to 1.24)	122 fewer per 1000 (from 221 fewer to 77 more)	LOW	
Thrombotic complications												
10	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	Serious[c]	None	5/503 (1%)	12/483 (2.5%)	RR 0.48 (0.18 to 1.23)	13 fewer per 1000 (from 20 fewer to 6 more)	LOW	

(a) Majority of the evidence was at high risk of bias.
(b) Downgraded by one increment due to heterogeneity, I2=72%.
(c) Confidence interval crosses one MID.
(d) Downgraded by one increment as the point estimate varies widely across studies, unexplained by subgroup analysis.

J.2.2 Adults - moderate risk group

Quality assessment							No. of patients		Effect	Quality	Importance

No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Intra-operative cell salvage	Standard treatment	Relative (95% CI)	Absolute		
No. exposed to allogeneic blood												
3	Randomised trials	Very serious[a]	No serious inconsistency	No serious indirectness	Serious[b]	None	37/192 (19.3%)	48/192 (25%)	RR 0.74 (0.5 to 1.12)	65 fewer per 1000 (from 125 fewer to 30 more)	VERY LOW	

(a) Majority of the evidence was at very high risk of bias.
(b) Confidence interval crosses one MID.

assessment							**patients**					
tudies		**bias**	**stency**	**ness**	**sion**		**erative cell salvage**	**d treatment**	**(95% CI)**	**e**		**ance**
osed to allogeneic blood												
	nised trials	rious[a]		ous indirectness			64 (12%)	77 (16.3%)	(0.41 to 0.83)	r per 1000 (from 28 fewer to 96 fewer)	OW	
allogeneic blood transfused (Better indicated by lower values)												
	nised trials	rious[a]		ous indirectness						2 lower (1.31 to 0.33 lower)	OW	
n												
	nised trials	rious[a]	ous inconsistency	ous indirectness	rious[e]		(1.5%)	(0.7%)	(0.53 to 6.07)	per 1000 (from 3 fewer to 37 more)	OW	
l length of stay (Better indicated by lower values)												
	nised trials	rious[a]	ous inconsistency	ous indirectness	rious[e]					7 lower (1.73 lower to 0.99 higher)	OW	

(a) Majority of the evidence was at very high risk of bias.
(b) Downgraded by one increment due to heterogeneity, I^2= 67%.
(c) Confidence interval crosses one MID.
(d) Downgraded by one increment due to heterogeneity, I^2=88%.
(e) Confidence interval crosses both MIDs.

Quality assessment							No. of patients		Effect			
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intra-operative cell salvage + post-operative cell salvage	Standard treatment	Relative (95% CI)	Absolute	Quality	Importance
No. exposed to allogeneic blood												
2	Randomised trials	Very serious[a]	No serious inconsistency	No serious indirectness	Very serious[b]	None	25/377 (6.6%)	58/720 (8.1%)	RR 0.84 (0.54 to 1.33)	13 fewer per 1000 (from 37 fewer to 27 more)	VERY LOW	
Units of allogeneic blood transfused (Better indicated by lower values)												
1	Randomised trials	Very serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	None	23	54	-	MD 0.81 higher (0.49 higher to 1.13 higher)	LOW	
Infection												
1	Randomised trials	Very serious[a]	No serious inconsistency	No serious indirectness	Very serious[b]	None	1/56 (1.8%)	0/62 (0%)	RR 3.32 (0.14 to 79.77)	-	VERY LOW	
Length of stay (Better indicated by lower values)												
1	Randomised trials	Very serious[a]	No serious inconsistency	No serious indirectness	Serious[c]	None	56	62	-	MD 0.2 higher (0.2 lower to 0.6 higher)	VERY LOW	
Mortality												
1	Randomised trials	Very serious[a]	No serious inconsistency	No serious indirectness	Very serious[b]	None	1/56 (1.8%)	0/62 (0%)	RR 3.32 (0.14 to 79.77)	-	VERY LOW	

(a) Majority of the evidence is at very high risk of bias
(b) Confidence interval crosses both MIDs.
(c) Confidence interval crosses one MID.

Quality assessment							No. of patients		Effect			
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Intra-operative cell salvage +TXA	Intra-operative cell salvage	Relative (95% CI)	Absolute	Quality	Importance

No. exposed to allogeneic blood												
1	Randomised trials	Very serious[a]	No serious inconsistency	No serious indirectness	Serious[b]	None	23/73 (31.5%)	30/74 (40.5%)	RR 0.78 (0.5 to 1.2)	89 fewer per 1000 (from 203 fewer to 81 more)	VERY LOW	
Units of blood transfused (Better indicated by lower values)												
1	Randomised trials	Very serious[a]	No serious inconsistency	No serious indirectness	Very serious[c]	None	73	74	-	MD 0.46 lower (1.1 lower to 0.18 higher)	VERY LOW	
Length of stay in hospital (Better indicated by lower values)												
1	Randomised trials	Very serious[a]	No serious inconsistency	No serious indirectness	Very serious[c]	None	73	74	-	MD 0.72 higher (0.85 lower to 2.29 higher)	VERY LOW	

(a) Majority of the evidence was at very high risk of bias.
(b) Confidence interval crosses one MID.
(c) Confidence interval crosses both MIDs.

Quality assessment							No. of patients		Effect			
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Post-operative cell salvage +TXA	Post-operative cell salvage	Relative (95% CI)	Absolute	Quality	Importance
No. exposed to allogeneic blood												
2	Randomised trials	Very serious[a]	No serious inconsistency	No serious indirectness	Serious[b]	None	4/95 (4.2%)	11/98 (11.2%)	RR 0.37 (0.12 to 1.14)	71 fewer per 1000 (from 99 fewer to 16 more)	VERY LOW	
Thrombotic complications												
1	Randomised trials	Very serious[a]	No serious inconsistency	No serious indirectness	Very serious[c]	None	0/49 (0%)	2/49 (4.1%)	RR 0.2 (0.01 to 4.06)	33 fewer per 1000 (from 40 fewer to 125 more)		

(a) Majority of the evidence is at very high risk of bias.
(b) Confidence interval crosses one MID.
(c) Confidence interval crosses both MIDs.

Quality assessment							No. of patients		Effect			
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Intra-operative cell salvage + post-operative	TXA	Relative (95% CI)	Absolute	Quality	Importance

							cell salvage +TXA					
No. exposed to allogeneic blood												
1	Randomised trials	Very serious[a]	No serious inconsistency	No serious indirectness	Very serious[b]	None	9/96 (9.4%)	13/101 (12.9%)	RR 0.73 (0.33 to 1.63)	35 fewer per 1000 (from 86 fewer to 81 more)	VERY LOW	
Units of blood transfused (Better indicated by lower values)												
1	Randomised trials	Very serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	None	96	101	-	Not pooled	LOW	

(a) Majority of the evidence was at very high risk of bias.
(b) Confidence interval crosses both MIDs.

Quality assessment							No. of patients		Effect			
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	TXA	Standard treatment- Adults- moderate risk	Relative (95% CI)	Absolute	Quality	Importance
No. exposed to allogeneic transfusions												
52	Randomised trials	Serious[a]	Serious[b]	No serious indirectness	No serious imprecision	None	384/2397 (16%)	766/2180 (35.1%)	RR 0.45 (0.38 to 0.53)	193 fewer per 1000 (from 165 fewer to 218 fewer)	LOW	
No. of units of blood transfused - All Patients (Better indicated by lower values)												
9	Randomised trials	Serious[a]	Serious[c]	No serious indirectness	No serious imprecision	None	325	319	-	MD 0.88 lower (1.22 to 0.54 lower)	LOW	
Mortality												
9	Randomised trials	Serious[a]	Serious[d]	No serious indirectness	Very serious[e]	None	1/550 (0.2%)	2/521 (0.4%)	RR 0.73 (0.15 to 3.66)	1 fewer per 1000 (from 3 fewer to 10 more)	VERY LOW	
Length of hospital stay (Better indicated by lower values)												
9	Randomised trials	Serious[a]	Serious[f]	No serious indirectness	Serious[g]	None	667	665	-	MD 0.5 lower (1.09 lower to 0.09	VERY LOW	

Quality assessment							No of patients		Effect	Quality	Importance	
										higher)		
Infections												
6	Randomised trials	Serious[a]	Serious[d]	No serious indirectness	Very serious[e]	None	3/296 (1%)	3/290 (1%)	RR 0.93 (0.22 to 3.93)	1 fewer per 1000 (from 8 fewer to 30 more)	VERY LOW	
Thrombotic complications												
48	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	Serious[f]	None	44/2708 (1.6%)	46/2471 (1.9%)	RR 0.67 (0.43 to 1.04)	6 fewer per 1000 (from 11 fewer to 1 more)	LOW	

(a) Majority of the evidence was at high risk of bias.
(b) Downgraded by one increment due to heterogeneity, I^2=55%.
(c) Downgraded by one increment due to heterogeneity, I^2=77%.
(d) Downgraded by one increment due to heterogeneity; the point estimate varies widely across studies, unexplained by subgroup analysis.
(e) Confidence interval crosses both MIDs.
(f) Downgraded by one increment due to heterogeneity, I^2=61%.
(g) Confidence interval crosses one MID.

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intraop CS+Post op CS	Post op CS	Relative (95% CI)	Absolute	
Number of patients transfused											
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	23/321 (7.2%)	33/321 (10.3%)	RR 0.70 (0.42 to 1.16)	31 fewer per 1000 (from 60 fewer to 16 more)	⊕⊕OO LOW
Units of allogeneic blood transfused (Better indicated by lower values)											
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	23	33	-	MD 2.23 higher (1.92 to 2.54 higher)	⊕⊕⊕O MODERATE

1 Majority of the evidence was at high risk of bias.
2 Confidence interval crosses one MID.

J.2.3 Adults - low risk group

Quality assessment							No. of patients		Effect			
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	TXA	Placebo- Low risk-adults	Relative (95% CI)	Absolute	Quality	Importance
No. of patients receiving allogeneic transfusions (route)												
4	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	Very serious[b]	None	6/315 (1.9%)	7/311 (2.3%)	RR 0.83 (0.3 to 2.29)	4 fewer per 1000 (from 16 fewer to 29 more)	VERY LOW	
No. of patients receiving allogeneic transfusions (route) - Topical TXA												
1	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	Very serious[b]	None	0/200 (0%)	2/200 (1%)	RR 0.2 (0.01 to 4.14)	8 fewer per 1000 (from 10 fewer to 31 more)	VERY LOW	
No. of patients receiving allogeneic transfusions (route) - Oral TXA												
1	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	Very serious[2]	None	6/70 (8.6%)	5/66 (7.6%)	RR 1.13 (0.36 to 3.53)	10 more per 1000 (from 48 fewer to 192 more)	VERY LOW	
Blood loss (type of surgery-topical TXA)) - Orthognathic surgery (Better indicated by lower values)												
1	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	None	0	-	-	MD 0.93 higher (0.73 to 1.2 higher)	MODERATE	
Blood loss (type of surgery-topical TXA)) - Otolaryngeal surgery (Better indicated by lower values)												
2	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	None	0	-	-	MD 0.74 higher (0.73 to 0.76 higher)	MODERATE	

(a) Majority of the evidence was at high risk of bias.
(b) Confidence interval crosses both MIDs.

J.2.4 Children - high risk group

Quality assessment	No. of patients	Effect	Quality	Importance

No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Intra-operative cells salvage +TXA	Intra-operative cell salvage- type of surgery	Relative (95% CI)	Absolute		
Number of patients transfused - Post 2003												
1	Randomised trials	Very serious[a]	No serious inconsistency	No serious indirectness	Very serious[2]	None	14/23 (60.9%)	15/21 (71.4%)	RR 0.85 (0.56 to 1.3)	107 fewer per 1000 (from 314 fewer to 214 more)	VERY LOW	
Total blood transfused - Post 2003 (Better indicated by lower values)												
1	Randomised trials	Very serious[a]	No serious inconsistency	No serious indirectness	Very serious[b]	None	23	21	-	MD 325 lower (685.06 lower to 35.06 higher)	VERY LOW	
Total blood loss - Post 2003 (Better indicated by lower values)												
1	Randomised trials	Very serious[a]	No serious inconsistency	No serious indirectness	Very serious[b]	None	23	21	-	MD 855 lower (1408.15 to 301.85 lower)	VERY LOW	

(a) Majority of the evidence was at very high risk of bias.
(b) Confidence interval crosses both MIDs.

Quality assessment							No. of patients		Effect			
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	TXA	Standard treatment	Relative (95% CI)	Absolute	Quality	Importance
Post-operative blood loss - Post 2003 (Better indicated by lower values)												
1	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	None	96	24	-	MD 16 lower (21.13 to 10.87 lower)	MODERATE	
Length of stay (Better indicated by lower values)												
1	Randomised trials	Serious[b]	No serious inconsistency	No serious indirectness	Serious[b]	None	36	47	-	MD 0.1 higher (0.37 lower to 0.57 higher)	LOW	

(a) Majority of the evidence was at high risk of bias.
(b) Confidence interval crosses one MID.

J.3 Red blood cells

J.3.1 RBC thresholds

J.3.1.1 Restrictive strategy versus liberal strategy (adults)

Quality assessment							No. of patients		Effect			
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Blood transfusions (adults)	Control	Relative (95% CI)	Absolute	Quality	Importance
Number of patients needing transfusion												
23	Randomised trials	Serious[a]	Very serious[b]	No serious indirectness	No serious imprecision	None	1965/3981 (49.4%)	92%	RR 0.65 (0.58 to 0.74)	322 fewer per 1000 (from 239 fewer to 386 fewer)	VERY LOW	
Number of patients needing transfusion (sub-groups) - Peri-operative surgical patients												
11	Randomised trials	Serious[a]	Serious[e]	No serious indirectness	Serious[d]	None	928/2256 (41.1%)	87.8%	RR 0.61 (0.50 to 0.76)	342 fewer per 1000 (from 211 fewer to 439 fewer)	VERY LOW	
Number of patients needing transfusion (sub-groups) - Critical care												
5	Randomised trials	Serious[a]	Serious[f]	No serious indirectness	Serious[d]	None	711/1105 (64.3%)	100%	RR 0.73 (0.64 to 0.84)	270 fewer per 1000 (from 160 fewer to 360 fewer)	VERY LOW	
Number of patients needing transfusion (sub-groups) - Acute blood loss/trauma												
4	Randomised trials	Serious[a]	Serious[g]	No serious indirectness	No serious imprecision	None	300/591 (50.8%)	95.2%	RR 0.58 (0.46 to 0.74)	400 fewer per 1000 (from 248 fewer to 514 fewer)	LOW	

Number of patients needing transfusion (sub-groups) - chemotherapy and stem-cell transplants												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	26/29 (89.7%)	93.6%	RR 0.96 (0.82 to 1.12)	37 fewer per 1000 (from 168 fewer to 112 more)	HIGH	
Number of units of blood transfused in those transfused (Better indicated by lower values)												
10	Randomised trials	Serious[a]	Very serious[c]	No serious indirectness	Serious[d]	None	964	1179	-	MD 1.13 lower (1.67 to 0.59 lower)		
Number of units of blood transfused in those transfused (sub-groups) - Peri-operative surgical patients (Better indicated by lower values)												
5	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	None	172	225	-	MD 0.55 lower (0.91 to 0.18 lower)	MODERATE	
Number of units of blood transfused in those transfused (sub-groups) - Critical care (Better indicated by lower values)												
1	Randomised trials	Serious[h]	No serious inconsistency	No serious indirectness	No serious imprecision	None	280	420	-	MD 1.72 lower (2.45 to 0.99 lower)	MODERATE	
Number of units of blood transfused in those transfused (sub-groups) - Acute blood loss/trauma (Better indicated by lower values)												
3	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	None	457	479	-	MD 2.19 lower (2.58 to 1.8 lower)	MODERATE	
Number of units of blood transfused in those transfused (sub-groups) - Acute coronary syndrome (ACS) (Better indicated by lower values)												
1	Randomised trials	Serious[i]	No serious inconsistency	No serious indirectness	No serious imprecision	None	55	55	-	MD 1.09 lower (1.49 to 0.69 lower)	MODERATE	

(a) Majority of the evidence is from studies at high risk of bias.
(b) Evidence of high heterogeneity with I2 value of 93%.
(c) Evidence of high heterogeneity, I2=84%.
(d) Confidence interval crosses one MID.
(e) I^2=91%.
(f) I^2=83%.
(g) I^2=76%.
(h) Unclear randomisation. No blinding.
(i) Unclear randomisation and allocation concealment.

Quality assessment	No. of patients	Effect	Quality	Importance

No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Length of hospital stay (adults)	Control	Relative (95% CI)	Absolute		
Hospital length of stay- subgroups (better indicated by lower values)												
12	Randomised trials	Serious[a]	Serious[b]	No serious indirectness	Serious[c]	None	2697	2699	-	MD 0.52 lower (1.11 lower to 0.06 higher)	VERY LOW	
Hospital length of stay- subgroups - Peri-operative surgical patients (Better indicated by lower values)												
9	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	None	1811	1813	-	MD 0.01 higher (0.30 lower to 0.32 higher)	MODERATE	
Hospital length of stay- subgroups - Critical care (Better indicated by lower values)												
1	Randomised trials	Serious[d]	No serious inconsistency	No serious indirectness	Serious[c]	None	24	21	-	MD 4.2 lower (6.93 to 1.47 lower)	LOW	
Hospital length of stay- subgroups – ACS (Acute MI) (Better indicated by lower values)												
1	Randomised trials	Serious[d]	No serious inconsistency	No serious indirectness	Serious[c]	None	24	21	-	MD 4.2 lower (6.93 to 1.47 lower)	LOW	
Hospital length of stay- subgroups - Acute blood loss/trauma (Better indicated by lower values)												
1	Randomised trials	Serious[e]	No serious inconsistency	No serious indirectness	No serious imprecision	None	444	445	-	MD 1.9 lower (3.34 to 0.46 lower)	MODERATE	

(a) Majority of the evidence is from studies at high risk of bias.
(b) I^2=55%.
(c) Confidence interval crosses one MID.
(d) Unclear randomisation and allocation concealment.
(e) Unclear blinding.

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Mortality (adults)	Control	Relative (95% CI)	Absolute		
30-day mortality												
20	Randomised trials	Serious a	Serious[b]	No serious indirectness	Serious[c]	None	397/3798 (10.5%)	5.1%	RR 0.92 (0.74 to 1.14)	4 fewer per 1000 (from 13 fewer to 7 more)	VERY LOW	
30-day mortality (sub-groups) - Perioperative surgical patients												

11	Randomised trials	Serious [a]	No serious inconsistency	No serious indirectness	Very serious[d]	None	76/2145 (3.5%)	2.4%	RR 0.90 (0.66 to 1.23)	2 fewer per 1000 (from 8 fewer to 6 more)	VERY LOW	
30-day mortality (sub-groups) - Critical care												
5	randomised trials	Serious [a]	no serious inconsistency	no serious indirectness	Serious[e]	none	289/1105 (26.2%)	25%	RR 0.98 (0.73 to 1.31)	5 fewer per 1000 (from 67 fewer to 77 more)	LOW	
30-day mortality (sub-groups) – ACS (Acute MI)												
2	randomised trials	Serious [a]	no serious inconsistency	no serious indirectness	very serious[d]	none	9/78 (11.5%)	4.8%	RR 3.85 (0.82 to 18)	137 more per 1000 (from 9 fewer to 816 more)	VERY LOW	
30-day mortality (sub-groups) - Acute blood loss/trauma												
2	randomised trials	Serious [a]	no serious inconsistency	no serious indirectness	Serious[c]	none	23/470 (4.9%)	8.8%	RR 0.55 (0.34 to 0.89)	40 fewer per 1000 (from 10 fewer to 58 fewer)	LOW	

(a) Majority of the evidence is from studies at high risk of bias.
(b) Effect sizes on forest plot are not consistent with each other.
(c) Confidence interval crosses one MID.
(d) Confidence interval crosses both default MIDs and line of no effect.
(e) Confidence interval crosses one default MID and line of no effect.

Quality assessment							No. of patients		Effect			
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	New cardiac events (adults)	Control	Relative (95% CI)	Absolute	Quality	Importance
New Cardiac events (MI, CHF) - sub-total analysis - Myocardial infarction												
15	Randomised trials	Serious	No serious inconsistency	No serious indirectness	Very serious[a]	None	77/3197 (2.4%)	1.8%	RR 1.13 (0.76 to 1.67)	2 more per 1000 (from 4 fewer to 12 more)	VERY LOW	
New Cardiac events (MI, CHF)- sub-total analysis - Congestive heart failure												
7	Randomised trials	Serious[b]	Serious[c]	No serious indirectness[d]	Very serious[a]	None	83/2106 (3.9%)	4.2%	RR 1.00 (0.54 to 1.83)	0 fewer per 1000 (from 19 fewer to 35 more)	VERY LOW	

(a) *Confidence interval crosses both MIDs.*
(b) *Majority of the evidence was from studies at high risk of bias.*
(c) *I^2=61%.*
(d) *Pulmonary oedema reported in 3 studies which is a surrogate outcome.*

							No. of patients		Effect			
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Infection - adults	Control	Relative (95% CI)	Absolute	Quality	Importance
Infection (Pneumonia, surgical site infection, septicaemia, UTI, infections not specified) – Pneumonia												
8	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	Serious[b]	None	146/1725 (8.5%)	4.1%	RR 0.9 (0.73 to 1.11)	4 fewer per 1000 (from 11 fewer to 5 more)	LOW	
Infection (Pneumonia, surgical site infection, septicaemia, UTI, infections not specified) - Surgical site/Wound infection												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	56/1069 (5.2%)	6.2%	RR 0.73 (0.52 to 1.01)	17 fewer per 1000 (from 30 fewer to 1 more)	LOW	
Infection (Pneumonia, surgical site infection, septicaemia, UTI, infections not specified) - Septicaemia/Bacteraemia												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	1/114 (0.88%)	0.8%	RR 1 (0.06 to 15.62)	0 fewer per 1000 (from 8 fewer to 117 more)	LOW	
Infection (Pneumonia, surgical site infection, septicaemia, UTI, infections not specified) - Infection (not specified)												
4	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	172/1204 (14.3%)	10%	RR 0.89 (0.74 to 1.07)	11 fewer per 1000 (from 26 fewer to 7 more)	LOW	

(a) *Majority of the evidence was from studies at high risk of bias.*
(b) *Confidence interval crosses one MID.*

Quality assessment							No. of patients		Effect			
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Adverse events (adults)	Control	Relative (95% CI)	Absolute	Quality	Importance
All adverse events (as defined by the study)												
3	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	Serious[b]	None	179/957 (18.7%)	0.2%	RR 0.83 (0.72 to 0.97)	0 fewer per 1000 (from 0 fewer to 1 fewer)	LOW	
Transfusion associated circulatory overload (TACO)												

2	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	None	2/932 (0.21%)	1.8%	RR 0.13 (0.03 to 0.54)	16 fewer per 1000 (from 8 fewer to 17 fewer)	MODERATE	
Transfusion Related Acute Lung Injury (TRALI)												
2	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	None	0/932 (0%)	0%	Not pooled	Not pooled	MODERATE	

(a) Majority of the evidence is from studies at high risk of bias.
(b) Confidence interval crosses one MID.

J.3.1.2 Restrictive strategy versus liberal strategy (children)

Quality assessment							No. of patients		Effect			
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Blood transfusion (children)	Control	Relative (95% CI)	Absolute	Quality	Importance
Total RBC ml/patient (Better indicated by lower values)												
1	Randomised trials	Serious[a]	serious inconsistency[b]	No serious indirectness	No serious imprecision	None	53	54	-	MD 73.0 lower (1.0352 to 0.4248 lower)	MODERATE	
Number of patients needing transfusion –children												
2	Randomised trials	Serious[c]	No serious inconsistency	No serious indirectness	No serious imprecision	None	157/350 (44.9%)	97.2%	RR 0.46 (0.41 to 0.52)	525 fewer per 1000 (from 467 fewer to 573 fewer)	MODERATE	
Number of patients needing transfusion (sub-group)-children - Critical care												
1	Randomised trials	Serious[d]	No serious inconsistency	No serious indirectness	No serious imprecision	None	146/320 (45.6%)	97.8%	RR 0.47 (0.41 to 0.53)	518 fewer per 1000 (from 460 fewer to 577 fewer)	MODERATE	
Number of patients needing transfusion (sub-group)-children - Congenital cardiac disease												
1	Randomised trials	Serious[e]	No serious inconsistency[f]	No serious indirectness	No serious imprecisiond	None	11/30 (36.7%)	96.7%	RR 0.38 (0.24 to 0.61)	600 fewer per 1000 (from 377 fewer to 735 fewer)	MODERATE	
Number of units transfused-children (Better indicated by lower values)												
2	Randomised	Serious[c]	Very serious[b]	No serious	No serious	None	350	340	-	MD 0.65 lower (0.98 to	VERY LOW	

	trials			indirectness	imprecision				0.33 lower)			

(a) Unclear sequence generation and unclear blinding.
(b) I^2=97%.
(c) Most information comes from studies with high risk of bias
(d) Unclear randomisation. No blinding of clinical staff and patients.
(e) Unclear randomisation and allocation concealment.
(f) I^2=93%.

Quality assessment							No. of patients		Effect			
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Mortality (children)	Control	Relative (95% CI)	Absolute	Quality	Importance
Mortality (30 days)												
2	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	14/350 (4%)	3.9%	RR 0.93 (0.46 to 1.87)	3 fewer per 1000 (from 21 fewer to 34 more)	VERY LOW	

(a) Most information is from studies at high risk of bias.
(b) Lacroix 2007- Included infants <1 year.
(c) Confidence interval crosses both default MIDs (0.75 and 1.25) and line of no effect.

Quality assessment							No. of patients		Effect			
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Length of hospital stay (children)	Control	Relative (95% CI)	Absolute	Quality	Importance
ICU length of stay (Better indicated by lower values)												
1	Randomised trials	Serious[a]	No serious inconsistency	Serious[b]	Serious[c]	None	320	317	-	MD 0.4 lower (1.59 lower to 0.79 higher)	VERY LOW	

(a) Unclear randomisation sequence generation.
(b) Not protocol outcome. Length of hospital stay not reported. Study included infants <1 year.
(c) Confidence interval crosses one default MID and line of no effect.

Quality assessment							No. of patients		Effect			
No. of	Design	Risk of	Inconsistency	Indirectness	Imprecision	Other	New cardiac events	Control	Relative	Absolute	Quality	Importance

studies		bias					(children)		(95% CI)			
Pulmonary oedema												
1	Randomised trials	Serious[a]	No serious inconsistency	Serious[b]	Very serious[c]	None	0/320 (0%)	1.6%	RR 0.09 (0.01 to 1.62)	15 fewer per 1000 (from 16 fewer to 10 more)	VERY LOW	

(a) Unclear randomisation sequence generation.
(b) Pulmonary oedema not protocol specified new cardiac event. Included children less than 1 year.
(c) Confidence interval crosses both default MIDs and line of no effect.

Quality assessment							No. of patients		Effect			
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Infection (children)	Control	Relative (95% CI)	Absolute	Quality	Importance
Infection (Nosocomial infections)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	65/320 (20.3%)	24.9%	RR 0.82 (0.61 to 1.09)	45 fewer per 1000 (from 97 fewer to 22 more)	VERY LOW	

(a) Unclear randomisation and blinding.
(b) Not specified type of nosocomial infection. Included infants (<1 year).
(c) Confidence interval crosses one default MID and line of no effect.

J.3.2 RBC targets

Blood transfusions (adults)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Blood transfusions (adults)	Control	Relative (95% CI)	Absolute		
Number of patients needing transfusion (all studies)												

5	randomised trials	serious[1]	serious[2]	no serious indirectness	no serious imprecision	none	644/1169 (55.1%)	91.8%	RR 0.61 (0.55 to 0.67)	358 fewer per 1000 (from 303 fewer to 413 fewer)	⨁⨁⨁◯ LOW	
Number of patients needing transfusion (sub-groups) - Peri-operative surgical patients												
1	randomised trials					none	118/249 (47.4%)	198/253 (78.3%)	RR 0.61 (0.52 to 0.7)	305 fewer per 1000 (from 235 fewer to 376 fewer)		
								78.3%		305 fewer per 1000 (from 235 fewer to 376 fewer)		
Number of units of blood transfused in those transfused (Better indicated by lower values)												
3	randomised trials	serious[1]	serious[3]	no serious indirectness	no serious imprecision	none	748	886	-	MD 1.72 lower (2.41 to 1.02 lower)	⨁⨁⨁◯ LOW	

[1] Majority of the evidence was from studies at high risk of bias.
[2] I^2 value=64%
[3] I^2 value=68%

Length of hospital stay (adults)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Length of hospital stay (adults)	Control	Relative (95% CI)	Absolute		
Hospital length of stay (Better indicated by lower values)												
3	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	886	886	-	MD 2.16 lower (3.81 to 0.5 lower)	⨁⨁◯◯ LOW	

[1] Majority of the evidence is from studies at high risk of bias.
[2] Confidence interval crosses MID

Mortality (adults)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Mortality (adults)	Control	Relative (95% CI)	Absolute		
30-day mortality												
6	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	126/1193 (10.6%)	9.2%	RR 0.78 (0.63 to 0.97)	20 fewer per 1000 (from 3 fewer to 34 fewer)	⊕⊕OO LOW	

[1] Majority of the evidence is from studies at high risk of bias.
[2] Confidence interval crosses one MID.

New cardiac events (adults)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	New cardiac events (adults)	Control	Relative (95% CI)	Absolute		
New Cardiac events (MI, CHF)- sub-total analysis - Myocardial infarction												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	3/418 (0.72%)	2.9%	RR 0.25 (0.07 to 0.88)	22 fewer per 1000 (from 3 fewer to 27 fewer)	⊕⊕OO LOW	
New Cardiac events (MI, CHF)- sub-total analysis - Congestive heart failure												
2	randomised trials	serious[1]	no serious inconsistency	serious[3]	serious[2]	none	22/461 (4.8%)	7.7%	RR 0.48 (0.3 to 0.78)	40 fewer per 1000 (from 17 fewer to 54 fewer)	⊕OOO VERY LOW	

[1] Majority of the evidence is from studies at high risk of bias.
[2] Confidence interval crosses one MID.
[3] One study reports acute pulmonary oedema which is a surrogate outcome for congestive heart failure.

Infection - adults for guiding allogeneic red blood cell transfusion

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Infection - adults	Control	Relative (95% CI)	Absolute		
Infection (Pneumonia, surgical site infection, septicemia,UTI) - Pneumonia												
2	no methodology chosen					none	90/443 (20.3%)	96/477 (20.1%)	RR 0.95 (0.73 to 1.22)	10 fewer per 1000 (from 54 fewer to 44 more)		
								20.5%		10 fewer per 1000 (from 55 fewer to 45 more)		
Infection (Pneumonia, surgical site infection, septicemia,UTI) - Infection (not specified)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	30/249 (12%)	9.9%	RR 1.22 (0.74 to 2.01)	22 more per 1000 (from 26 fewer to 100 more)	⨁⨁⨁◯ VERY LOW	

[1] Evidence from study at high risk of bias.
[2] Confidence interval crosses both MIDs.

Adverse events (adults)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Adverse events (adults)	Control	Relative (95% CI)	Absolute		
All adverse events (as defined by the study)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	179/444 (40.3%)	48.1%	RR 0.84 (0.72 to 0.97)	77 fewer per 1000 (from 14 fewer to 135 fewer)	⨁◯◯◯ VERY LOW	

[1] Evidence from study at high risk of bias.
[2] Adverse event not defined in study.
[3] Confidence interval crosses one MID.

Blood transfusion (children)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Blood transfusion (children)	Control	Relative (95% CI)	Absolute		
Total RBC ml/patient (Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	146	310	-	MD 0.2 higher (0.4 lower to 0.8 higher)	⊕OOO VERY LOW	
Number of patients needing transfusion -children (critical care)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	146/320 (45.6%)	97.8%	RR 0.47 (0.41 to 0.53)	518 fewer per 1000 (from 460 fewer to 577 fewer)	⊕⊕⊕O MODERATE	

[1] Evidence from study at high risk of bias.
[2] Confidence interval crosses both MIDs.

Mortality (children)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Mortality (children)	Control	Relative (95% CI)	Absolute		
Mortality (30 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	14/320 (4.4%)	4.4%	RR 0.99 (0.48 to 2.04)	0 fewer per 1000 (from 23 fewer to 46 more)	⊕OOO VERY LOW	

[1] Evidence from study at high risk of bias.
[2] Confidence interval crosses both MIDs.

Length of hospital stay (children)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Length of hospital stay (children)	Control	Relative (95% CI)	Absolute		
ICU length of stay (Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	320	317	-	MD 0.4 lower (1.59 lower to 0.79 higher)	⊕OOO VERY LOW	

[1] Evidence from study at high risk of bias.
[2] Confidence interval crosses both MIDs.

New cardiac events (children)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	New cardiac events (children)	Control	Relative (95% CI)	Absolute		
Pulmonary oedema												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	None	0/320 (0%)	1.6%	RR 0.09 (0.01 to 1.62)	15 fewer per 1000 (from 16 fewer to 10 more)	⊕OOO VERY LOW	

[1] Evidence from study at high risk of bias.
[2] Study reports acute pulmonary oedema which is a surrogate outcome for congestive heart failure.
[3] Confidence interval crosses one MID.

Infection (children)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Infection (children)	Control	Relative (95% CI)	Absolute		
Infection (Nosocomial infections)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	65/320 (20.3%)	24.9%	RR 0.82 (0.61 to 1.09)	45 fewer per 1000 (from 97 fewer to 22 more)	⊕⊕OO LOW	

[1] Evidence from study at high risk of bias.
[2] Confidence interval crosses one MID.

J.3.3 RBC doses

None

J.4 Platelets

J.4.1 Platelet thresholds and targets

J.4.1.1 Prophylactic transfusion versus no prophylactic transfusion - adults who are haematology patients (non-bleeding patients)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Prophylactic transfusion	No prophylactic transfusion - adults who are haematology patients	Relative (95% CI)	Absolute		
Number of patients with bleeding events (WHO grade 2 or higher)												
2	Randomised trials	Serious[a]	Very serious[b]	No serious indirectness	Serious[c]	None	193/493 (39.1%)	57.3%	RR 0.7 (0.61 to 0.8)	172 fewer per 1000 (from 115 fewer to 223 fewer)	VERY LOW	

Number of patients with major bleeding events (WHO grade 3 or 4)											
2	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	None	8/493 (1.6%)	6.3%	RR 0.3 (0.14 to 0.65)	44 fewer per 1000 (from 22 fewer to 54 fewer)	MODERATE	
Serious adverse events (including sepsis and respiratory deterioration)											
1	Randomised trials	Serious[d]	No serious inconsistency	No serious indirectness	Serious[c]	None	20/298 (6.7%)	6%	RR 1.12 (0.6 to 2.07)	7 more per 1000 (from 24 fewer to 64 more)	LOW	
Transfusion related serious adverse event (urticarial and angioedema)											
1	Randomised trials	Serious[d]	No serious inconsistency	No serious indirectness	Very serious[e]	None	1/299 (0.33%)	0%	RR 3.02 (0.12 to 73.84)	-	VERY LOW	
Number of patients needing platelet transfusion											
1	Randomised trials	Serious[d]	No serious inconsistency	No serious indirectness	No serious imprecision	None	266/299 (89%)	58.5%	RR 1.52 (1.37 to 1.69)	304 more per 1000 (from 216 more to 404 more)	MODERATE	
Number of units (platelets) transfused per patient (better indicated by lower values)											
1	Randomised trials	Serious[d]	No serious inconsistency	No serious indirectness	No serious imprecision	None	299	301	-	MD 1.3 higher (0.75 to 1.85 higher)	MODERATE	
Mortality (all cause)											
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[e]	None	5/194 (2.6%)	3.6%	RR 0.73 (0.23 to 2.25)	10 fewer per 1000 (from 28 fewer to 45 more)	LOW	
Side effects of transfusion (not specified)											
1	Randomised trials	No serious risk of bias	No serious inconsistency	Serious[f]	Very serious[e]	None	25/194 (12.9%)	13.7%	RR 0.94 (0.57 to 1.56)	8 fewer per 1000 (from 59 fewer to 77 more)	VERY LOW	

(a) Most information is from studies at high risk of bias.
(b) I^2=92%.
(c) Confidence interval crosses one default MID and line of no effect.
(d) Study at high risk of bias.
(e) Confidence interval crosses both default MIDs and line of no effect.
(f) No pre-specified definition of side-effects.

J.4.1.2 Prophylactic transfusion versus no prophylactic transfusion - children who are haematology patients (non-bleeding patients)

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Prophylactic transfusion	No prophylactic transfusion - children who are haematology patients	Relative (95% CI)	Absolute	Quality	Importance
Number of patients with major bleeding events (WHO grade 3 or 4)												
1	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	Serious[b]	None	10/35 (28.6%)	52.4%	RR 0.55 (0.28 to 1.06)	236 fewer per 1000 (from 377 fewer to 31 more)	LOW	
Mortality (all cause) (3 years)												
1	Randomised trials	Serious[a]	No serious inconsistency	Serious[c]	Very serious[d]	None	12/35 (34.3%)	33.3%	RR 1.03 (0.48 to 2.2)	10 more per 1000 (from 173 fewer to 400 more)	VERY LOW	
Mortality from bleeding (3 years)												
1	Randomised trials	Serious[a]	No serious inconsistency	Serious[e]	Very serious[d]	None	1/35 (2.9%)	9.5%	RR 0.3 (0.03 to 3.11)	67 fewer per 1000 (from 92 fewer to 200 more)	VERY LOW	

(a) Study is at high risk of bias.
(b) Confidence interval crosses one default MID and line of no effect.
(c) Mortality assessed at 3 years, our protocol outcome was mortality at 30 days.
(d) Confidence interval crosses both default MIDs and line of no effect.
(e) Mortality assessed at 3 years, our protocol outcome was mortality at 30 days.

J.4.1.3 Low platelet thresholds versus high platelet thresholds - adults who are haematology patients (non-bleeding patients)

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Low platelet thresholds	High platelet thresholds - Adults who are haematology patients	Relative (95% CI)	Absolute	Quality	Importance
Mortality (all cause)												

4	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	Serious[b]	None	83/329 (25.2%)	23.3%	RR 1.14 (0.9 to 1.45)	33 more per 1000 (from 23 fewer to 105 more)	LOW	
Mortality (all cause) - Patients undergoing chemotherapy												
2	Randomised trials	Serious[a]	Serious[c]	No serious indirectness	No serious imprecision	None	43/172 (25%)	39.1%	RR 1.17 (0.85 to 1.6)	66 more per 1000 (from 59 fewer to 235 more)	LOW	
Mortality (all cause) - Patients undergoing stem-cell transplant												
2	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	Serious[b]	None	40/157 (25.5%)	22.6%	RR 1.12 (0.78 to 1.6)	27 more per 1000 (from 50 fewer to 136 more)	LOW	
Number of patients with bleeding events (WHO grade 2 or higher)												
2	Randomised trials	Serious[a]	No serious inconsistency	Serious[d]	No serious imprecision	None	88/157 (56.1%)	97.5%	RR 0.97 (0.91 to 1.04)	29 fewer per 1000 (from 88 fewer to 39 more)	LOW	
Number of patients with major bleeding events (WHO grade 3 or 4)												
4	Randomised trials	Serious[a]	Serious[e]	Serious[f]	Serious[b]	None	60/329 (18.2%)	17.2%	RR 1.17 (0.84 to 1.64)	29 more per 1000 (from 28 fewer to 110 more)	VERY LOW	
Number of patients with major bleeding events - Patients undergoing chemotherapy												
2	Randomised trials	Serious[a]	Serious[g]	Serious[h]	Serious[b]	None	46/172 (26.7%)	18.5%	RR 1.41 (0.95 to 2.1)	76 more per 1000 (from 9 fewer to 203 more)	VERY LOW	
Number of patients with major bleeding events - Patients undergoing stem-cell transplant												
2	Randomised trials	Serious[a]	No serious inconsistency	Serious[d]	Very serious[i]	None	14/157 (8.9%)	11.7%	RR 0.76 (0.4 to 1.45)	28 fewer per 1000 (from 70 fewer to 53 more)	VERY LOW	
Infections (Bacteraemia)												
1	Randomised trials	Serious[j]	No serious inconsistency	No serious indirectness	Serious[b]	None	31/79 (39.2%)	34.5%	RR 1.14 (0.76 to 1.7)	48 more per 1000 (from 83 fewer to 242 more)	LOW	
Adverse events												
1	Randomised trials	Serious[j]	No serious inconsistency	No serious indirectness	Serious[b]	None	0/37 (0%)	19.5%	RR 0.07 (0 to 1.09)	181 fewer per 1000 (from 195 fewer to 18 more)	LOW	
Number of units (platelets) transfused per patient (Better indicated by lower values)												
3	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	None	250	242	-	MD 1.96 lower (3.03 to 0.89 lower)	MODERATE	

Number of units (platelets) transfused per patient - Patients undergoing chemotherapy (Better indicated by lower values)												
2	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	None	172	161	-	MD 2.09 lower (3.2 to 0.99 lower)	MODERATE	
Number of units (platelets) transfused per patient - Patients undergoing stem-cell transplant (Better indicated by lower values)												
1	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	None	78	81	-	MD 0.2 higher (4.27 lower to 4.67 higher)	MODERATE	

(a) Most information is from studies at high risk of bias.
(b) Confidence interval crosses one default MID and line of no effect.
(c) I^2=66%.
(d) Zumberg 2002 assigned bleeding scores based on modified GIMEMA criteria.
(e) I2=54%.
(f) Heckman 1997 did not use WHO bleeding criteria, but used a standardised toxicity scale (no details reported). Zumberg 2002 assigned bleeding scores based on modified GIMEMA criteria.
(g) I^2=75%.
(h) Heckman 1997 used a standardised toxicity scale to assess severity of bleeding.
(i) Confidence interval crosses both default MIDs and line of no effect.
(j) Study at high risk of bias.

J.4.2 Platelet doses

J.4.2.1 Low platelet dose versus medium platelet dose

Quality assessment							No. of patients		Effect			
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Low dose	Medium dose	Relative (95% CI)	Absolute	Quality	Importance
Number of patients with bleeding (WHO grade 2 and above)												
3	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	None	332/531 (62.5%)	49.2%	RR 1.04 (0.95 to 1.13)	20 more per 1000 (from 25 fewer to 64 more)	MODERATE	
Mortality at 30 days												
3	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	Very serious[b]	None	10/531 (1.9%)	1%	RR 2.04 (0.7 to 5.93)	10 more per 1000 (from 3 fewer to 49 more)	VERY LOW	

Infections											
1	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	Very serious[b]	None	5/417 (1.2%)	1.2%	RR 1.01 (0.3 to 3.48)	0 more per 1000 (from 8 fewer to 30 more)	VERY LOW
Serious adverse event											
1	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	Serious[c]	None	35/417 (8.4%)	6.4%	RR 1.31 (0.81 to 2.13)	20 more per 1000 (from 12 fewer to 72 more)	LOW

(a) Majority of the evidence was from one study where a significant percentage of patients in each group did not receive transfusions within the assigned dose range.
(b) Confidence interval crosses both MIDs.
(c) Confidence interval crosses one MID.

J.4.2.2 High platelet dose versus medium platelet dose

Quality assessment							No. of patients		Effect			
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	High dose	Medium dose	Relative (95% CI)	Absolute	Quality	Importance
Number of patients with bleeding (WHO grade 2 and above)												
2	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	None	305/480 (63.5%)	36.6%	RR 1.02 (0.93 to 1.11)	7 more per 1000 (from 26 fewer to 40 more)	MODERATE	
Mortality at 30 days												
2	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	Very serious[b]	None	7/432 (1.6%)	1%	RR 1.71 (0.51 to 5.81)	7 more per 1000 (from 5 fewer to 48 more)	VERY LOW	
Infections												
1	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	Very serious[b]	None	7/432 (1.6%)	1.2%	RR 1.37 (0.44 to 4.29)	4 more per 1000 (from 7 fewer to 39 more)	VERY LOW	
Serious adverse event												
1	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	Serious[c]	None	36/432 (8.3%)	6.4%	RR 1.31 (0.81 to 2.11)	20 more per 1000 (from 12 fewer to 71 more)	LOW	

(a) Majority of the evidence was from one study where a significant percentage of patients in each group did not receive transfusions within the assigned dose range.
(b) Confidence interval crosses both MIDs.
(c) Confidence interval crosses one MID.

J.4.2.3 Low platelet dose versus high platelet dose

Quality assessment							No. of patients		Effect			
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Low dose	High dose	Relative (95% CI)	Absolute	Quality	Importance
Number of patients with bleeding (WHO grade 2 and above)												
1	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	Serious[b]	None	71/417 (17%)	16.2%	RR 1.05 (0.78 to 1.42)	8 more per 1000 (from 36 fewer to 68 more)	LOW	
Mortality at 30 days												
1	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	Very serious[c]	None	9/417 (2.2%)	1.6%	RR 1.33 (0.5 to 3.54)	5 more per 1000 (from 8 fewer to 41 more)	VERY LOW	
Infections												
1	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	Very serious[c]	None	5/417 (1.2%)	1.6%	RR 0.74 (0.24 to 2.31)	4 fewer per 1000 (from 12 fewer to 21 more)	VERY LOW	
Serious adverse event												
1	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	Very serious[c]	None	35/417 (8.4%)	8.3%	RR 1.01 (0.65 to 1.57)	1 more per 1000 (from 29 fewer to 47 more)	VERY LOW	

(a) Majority of the evidence was from one study where a significant percentage of patients in each group did not receive transfusions within the assigned dose range.
(b) Confidence interval crosses one MID.
(c) Confidence interval crosses both MIDs.

J.5 PCC

J.5.1 PCC thresholds

None

J.5.2 PCC targets

None

J.5.3 PCC doses

J.5.3.1 Low dose PCC (25 IU/kg) versus high dose PCC (40 IU/kg)

Quality assessment							No. of patients		Effect			
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Low dose (25 IU /kg)	High dose (40 IU /kg) [RCT]	Relative (95% CI)	Absolute	Quality	Importance
Mortality												
1	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	Very serious[b]	None	4/29 (13.8%)	20%	RR 0.69 (0.22 to 2.19)	62 fewer per 1000 (from 156 fewer to 238 more)	VERY LOW	
Patients with at least one adverse event												
1	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	Very serious[b]	None	24/29 (82.8%)	83.3%	RR 0.99 (0.79 to 1.25)	8 fewer per 1000 (from 175 fewer to 208 more)	VERY LOW	
Patients with at least one serious adverse event												
1	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	Very serious[b]	None	11/29 (37.9%)	40%	RR 0.95 (0.5 to 1.8)	20 fewer per 1000 (from 200 fewer to 320 more)	VERY LOW	
Patients with at least one thrombotic event												
1	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	Very serious[b]	None	2/29 (6.9%)	6.9%	RR 1 (0.15 to 6.63)	0 fewer per 1000 (from 59 fewer to 388 more)	VERY LOW	
Target INR (<1.2) achieved												
1	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	Serious[c]	None	13/29 (44.8%)	76.7%	RR 0.58 (0.37 to 0.92)	322 fewer per 1000 (from 61 fewer to 483 fewer)	LOW	

(a) Allocation concealment not reported. Open label study.
(b) Confidence interval crosses both default MIDs and line of no effect.
(c) Confidence interval crosses one default MID.

J.5.3.2 Low fixed dose PCC (1040 IU FIX) versus PCC variable dosing regimen (modified GRADE profile)

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Fixed dose (1040 IU)	Variable dose (cohort study)	Relative (95% CI)	Absolute		
Target INR reached (<1.5)												
1	Observational studies	Serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	None	88/101 (87.1%)	89.2%	RR 0.98 (0.89 to 1.07)	18 fewer per 1000 (from 98 fewer to 62 more)	VERY LOW	
Deep vein thrombosis												
1	Observational studies	Serious[a]	No serious inconsistency	No serious indirectness	Very serious[b]	None	0/101 (0%)	0.7%	RR 0.46 (0.02 to 11.12)	4 fewer per 1000 (from 7 fewer to 71 more)	VERY LOW	
Mortality (all cause)												
1	Observational studies	Serious[a]	No serious inconsistency	No serious indirectness	Serious[c]	None	14/101 (13.9%)	25.9%	RR 0.54 (0.31 to 0.94)	119 fewer per 1000 (from 16 fewer to 179 fewer)	VERY LOW	

(a) Observational study and is therefore more prone to selection bias.
(b) Confidence interval crosses both default MIDs and line of no effect.
(c) Confidence interval crosses one default MID.

J.5.3.3 Standard dose PCC (500 IU FIX/7 IU FIX/kg) versus PCC individualised dosing regimen

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Standard dose (500 IU FIX/7 IU/kg)	Individualised dosing regimen [RCT]	Relative (95% CI)	Absolute		
Target INR at 15 minutes after the first dosage of PCC												
1	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	None	20/47 (42.6%)	89.1%	RR 0.48 (0.34 to 0.68)	463 fewer per 1000 (from 285 fewer to 588 fewer)	MODERATE	
serious adverse events												

1	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	Serious[b]	None	2/47 (4.3%)	4.3%	RR 1 (0.15 to 6.81)	0 fewer per 1000 (from 37 fewer to 250 more)	LOW	

(a) Allocation concealment not reported. Open label study.
(b) Confidence interval crosses both default MIDs and line of no effect.

J.6 Monitoring for acute reactions

None

J.7 Electronic decision support

None

J.8 Electronic patient identification

None

J.9 Patient information

None

Appendix K: Forest plots

K.1 Erythropoietin and iron

K.1.1 Erythropoietin versus placebo

Figure 1: All-cause mortality at 30 days

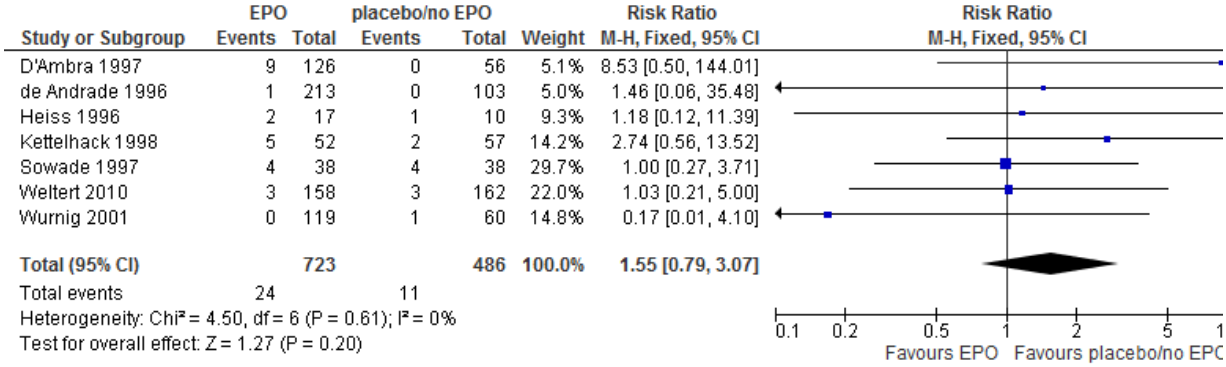


Figure 2: Number of patients transfused

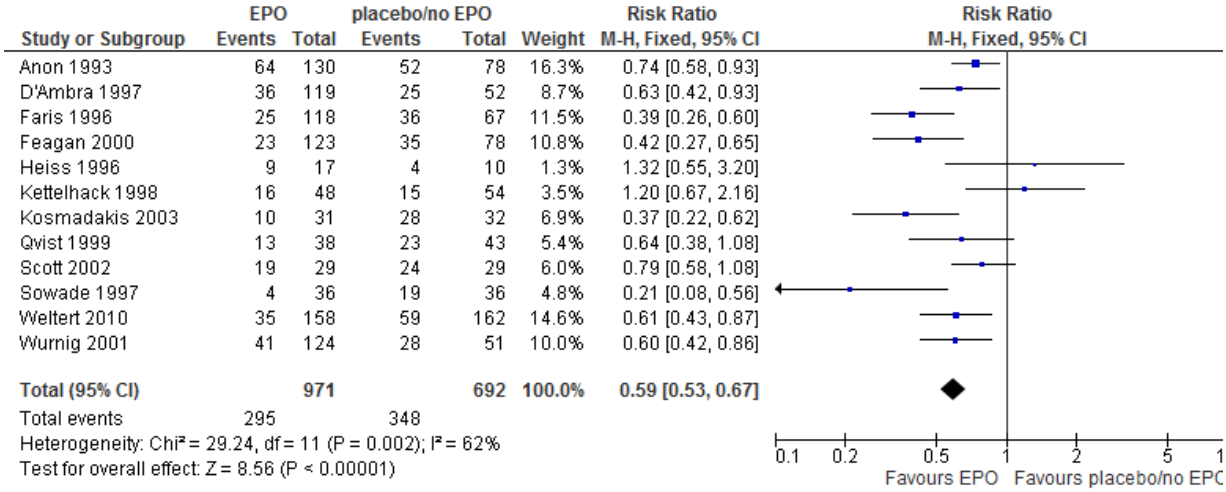
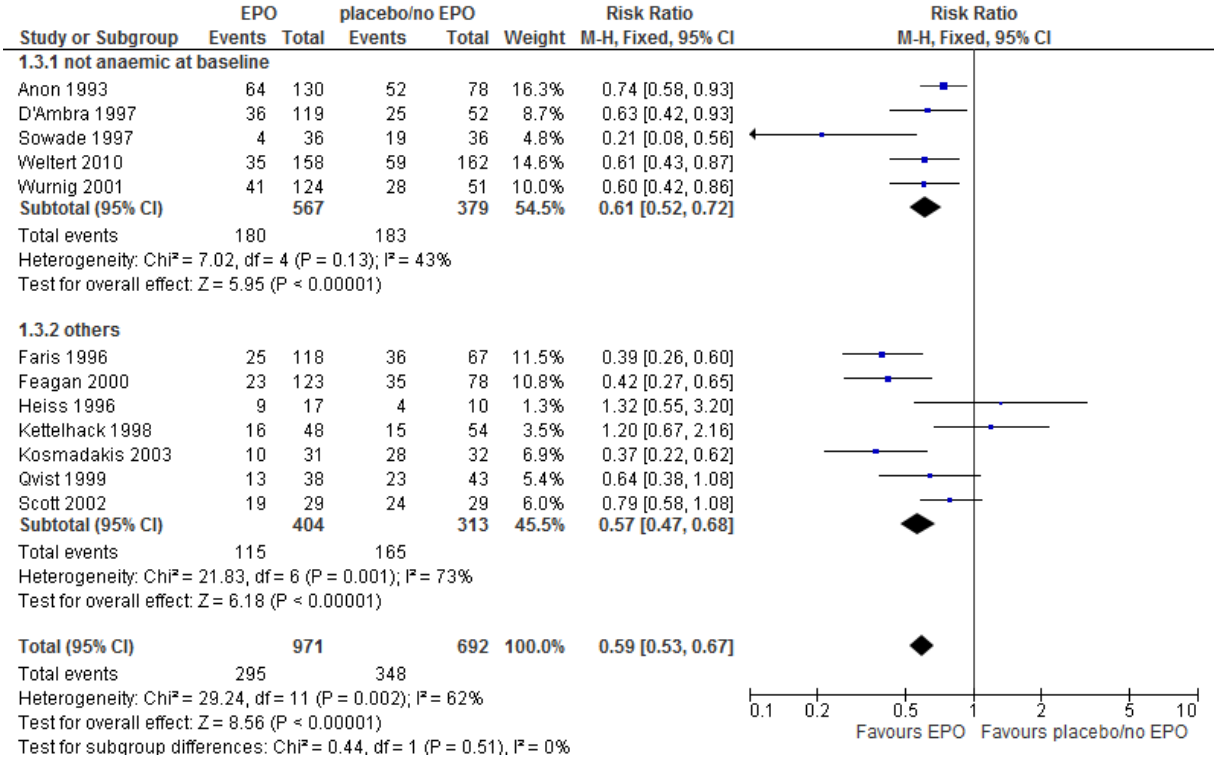
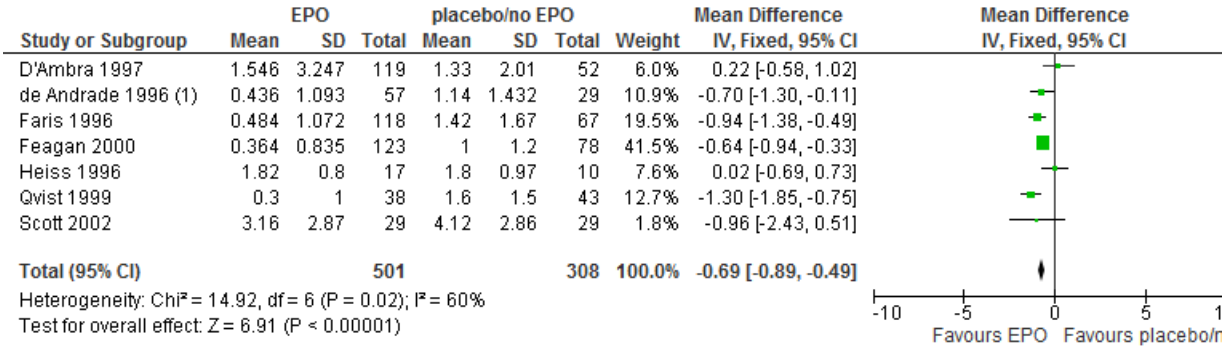


Figure 1: Number of patients transfused – sub-grouped by presence/absence of anaemia at baseline



1

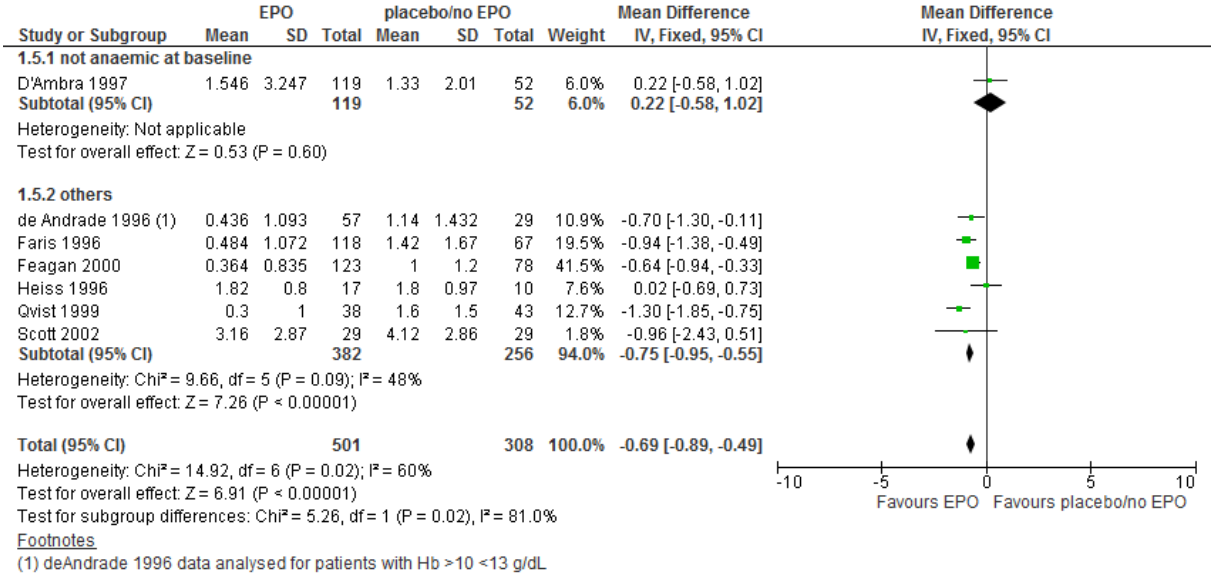
Figure 4: Number of units transfused per patient



(1) deAndrade 1996 data analysed for patients with Hb >10 <13 g/dL

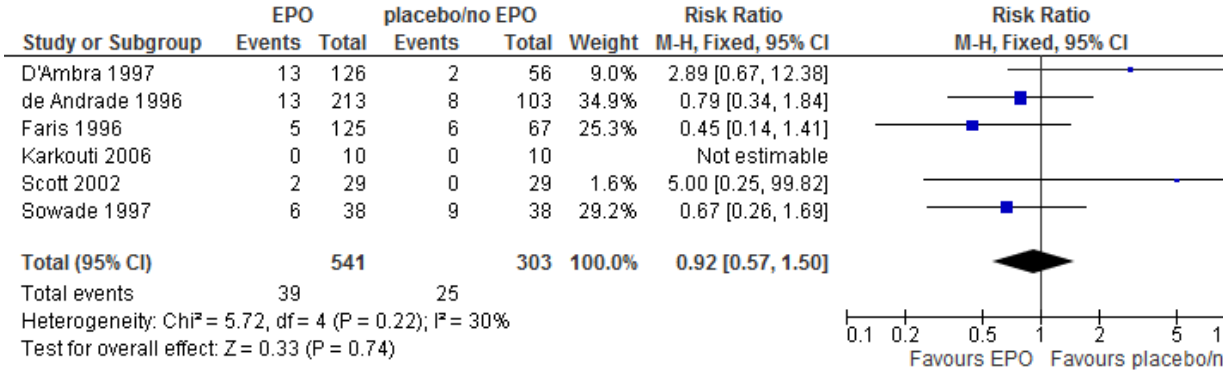
2

Figure 2: Number of units transfused per patient – sub-grouped by presence/absence of anaemia at baseline



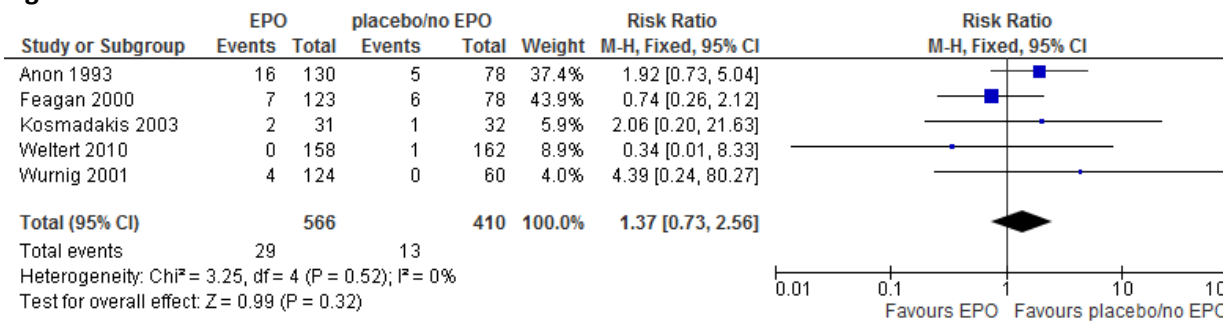
1

Figure 3: Serious adverse events



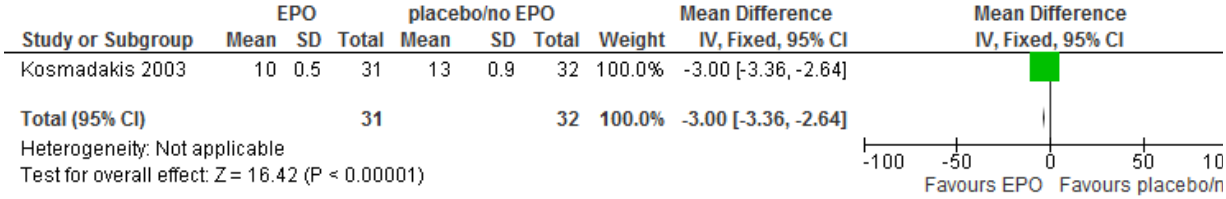
2

Figure 4: Thrombosis



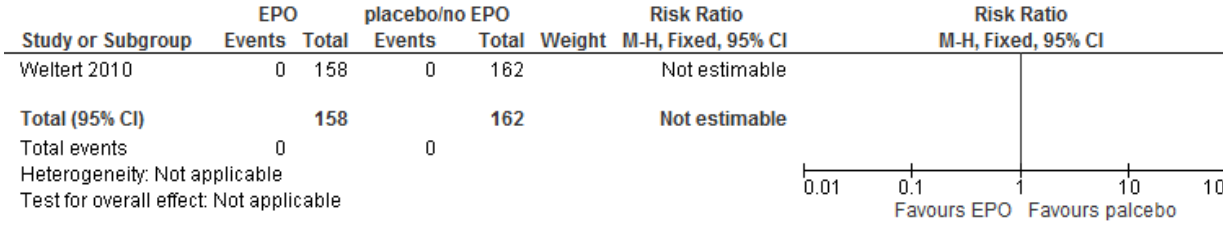
3

Figure 5: Length of hospital stay



1

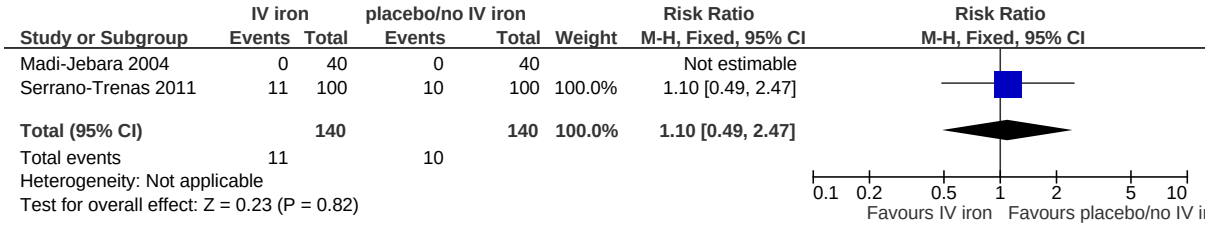
Figure 6: Infection (pneumonia)



2

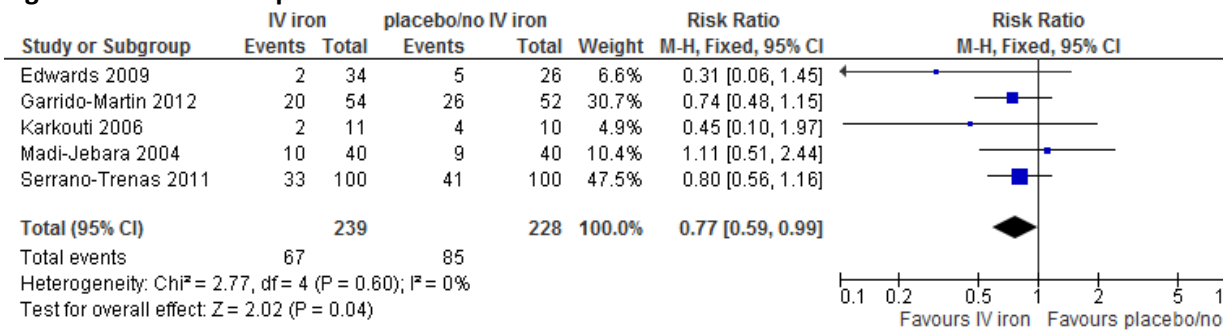
3 **K.1.2 IV iron versus placebo or no IV iron**

Figure 7: All-cause mortality at 30 days



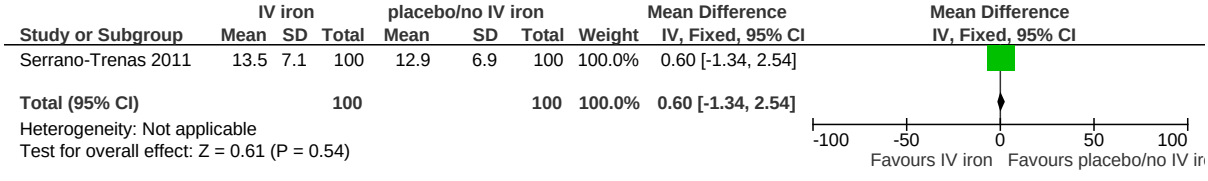
4

Figure 8: Number of patients transfused



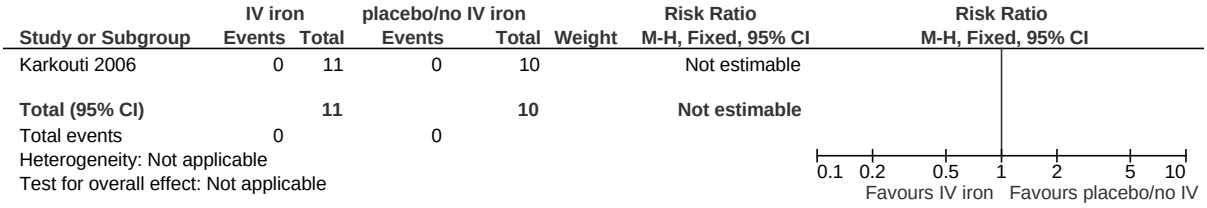
5

Figure 9: Length of hospital stay



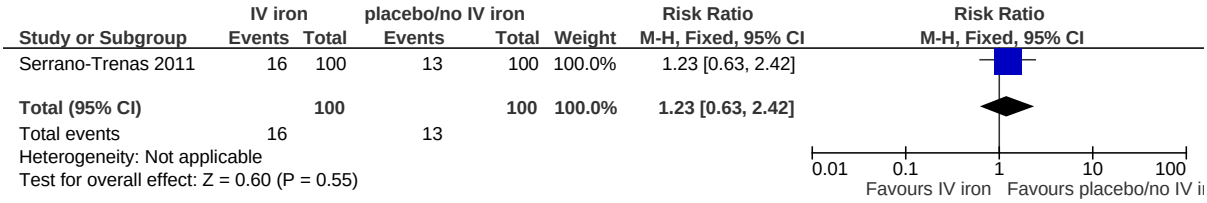
1

Figure 10: Serious adverse events



2

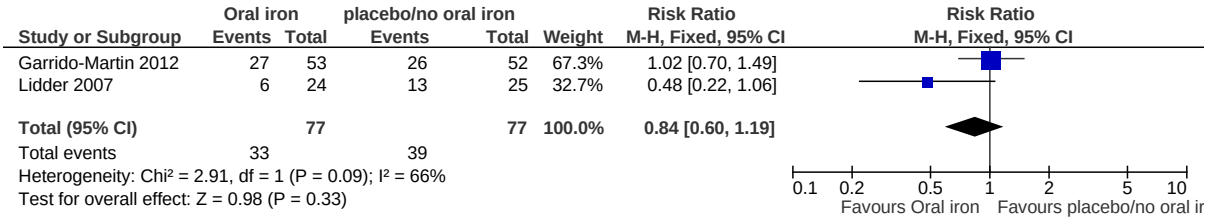
Figure 11: Infections



3

4 K.1.3 Oral iron versus placebo or no oral iron

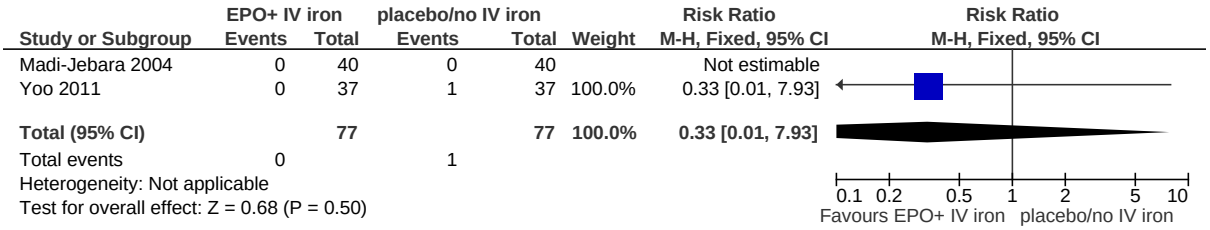
Figure 12: Number of patients transfused



5

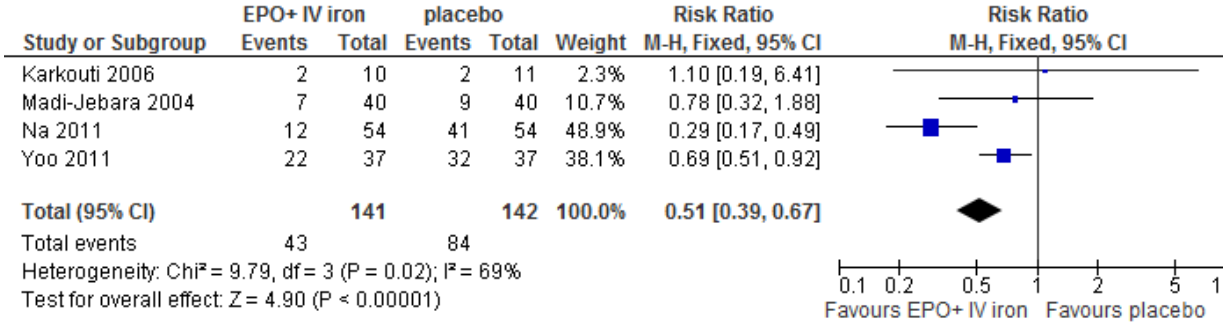
6 K.1.4 Erythropoietin plus IV iron versus placebo

Figure 13: All-cause mortality at 30 days



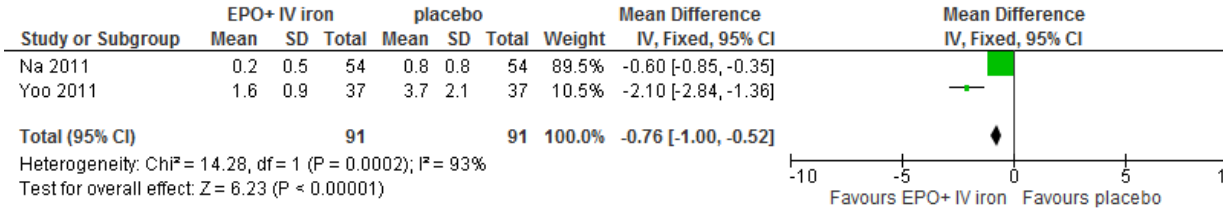
7

Figure 14: Number of patients transfused



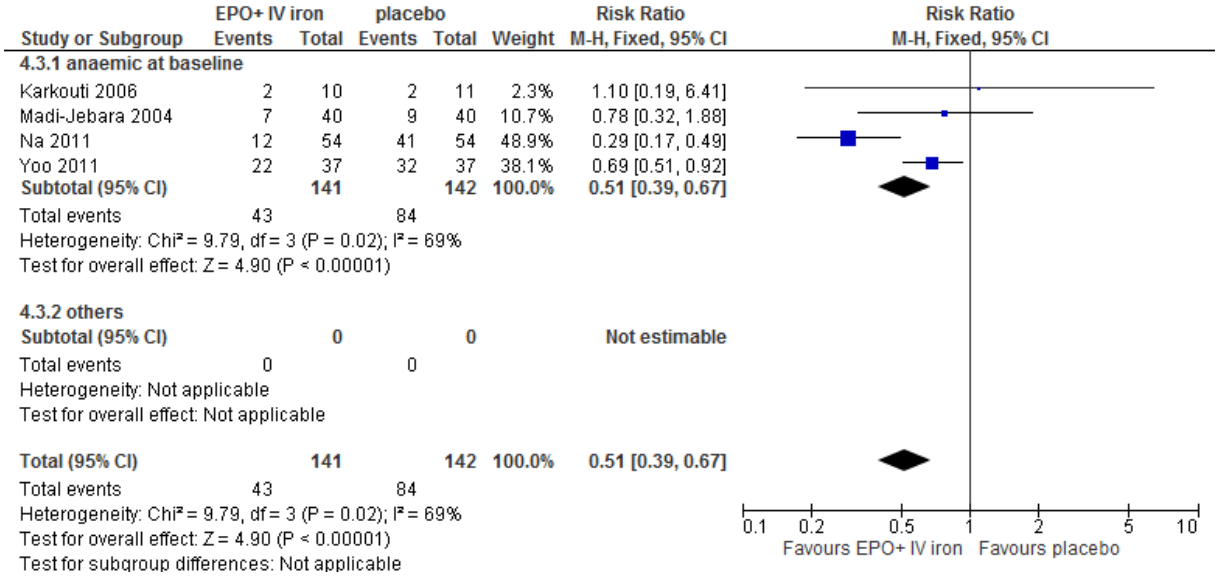
1

Figure 15: Number of units transfused per patient



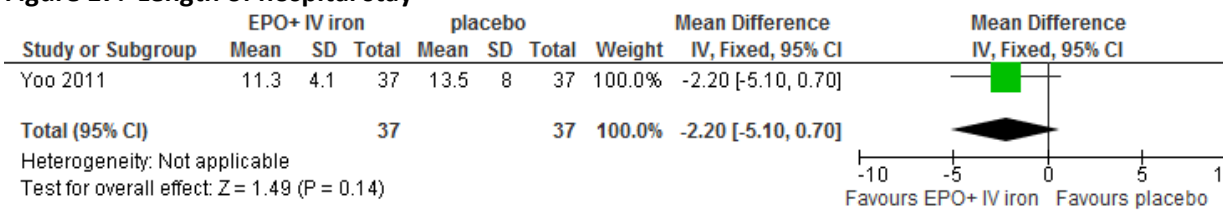
2

Figure 16: Number of units transfused per patient- sub-grouped by presence/absence of anaemia at baseline



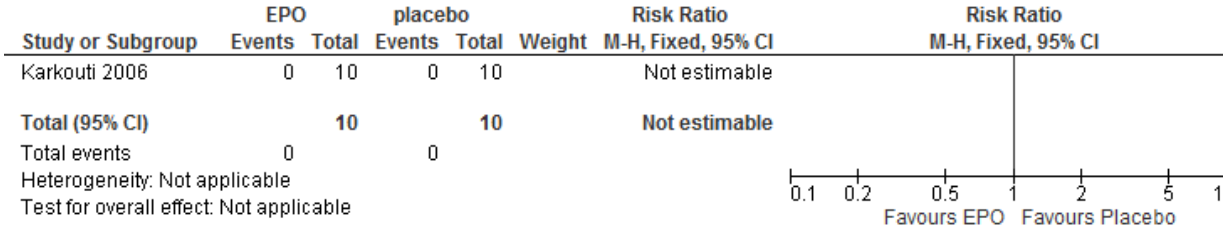
3

Figure 17: Length of hospital stay



1

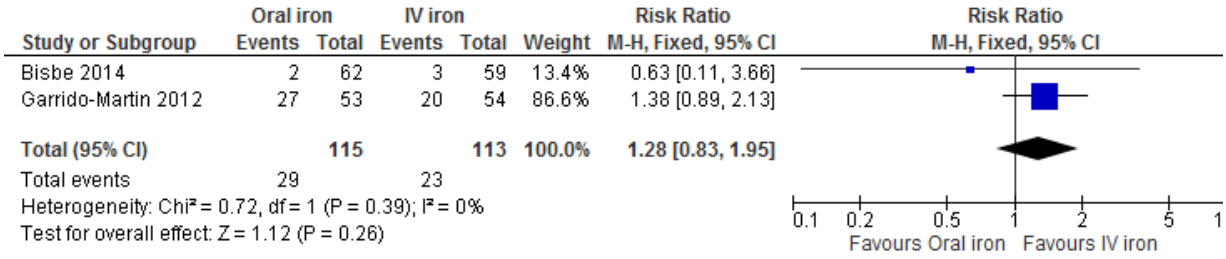
Figure 18: Serious adverse events



2

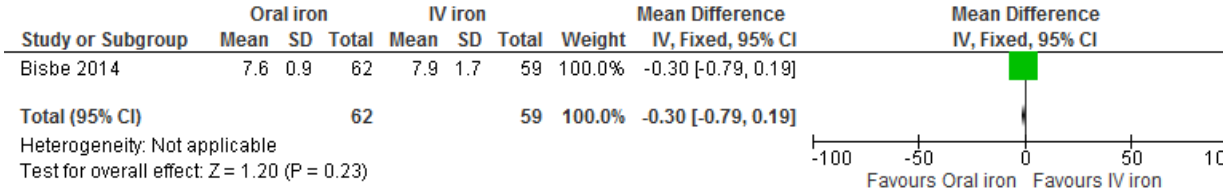
3 **K.1.5 Oral iron versus IV iron**

Figure 19: Number of patients transfused



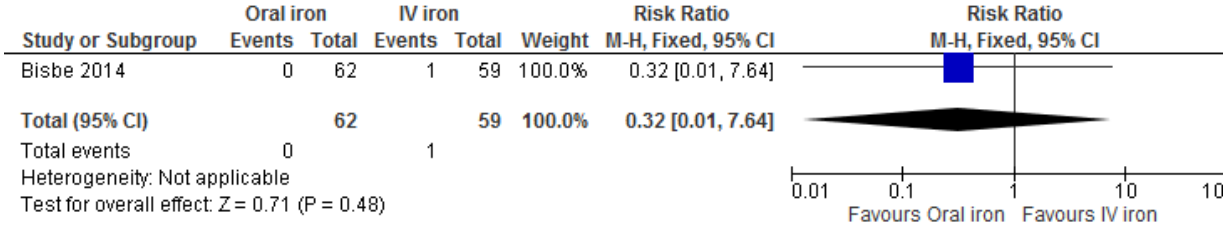
4

Figure 20: Length of hospital stay



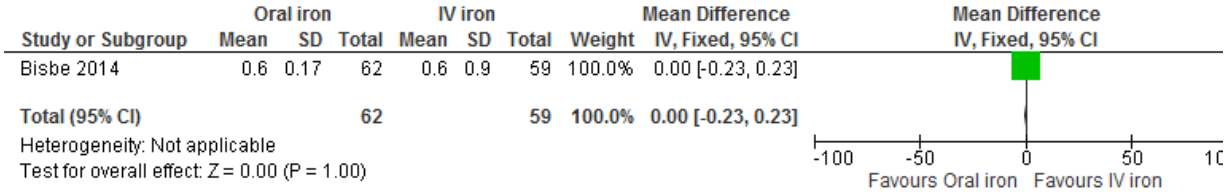
5

Figure 21: Deep vein thrombosis (DVT)



6

Figure 22: Quality of life (Total EQ-5D scores)



K.1.6 Erythropoietin plus IV iron versus IV iron

Figure 23: All-cause mortality at 30 days

Study or Subgroup	EPO+ IV iron Events	Total	IV iron Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Madi-Jebara 2004	0	40	0	40		Not estimable
Total (95% CI)		**40**		**40**		**Not estimable**
Total events	0		0			

Heterogeneity: Not applicable
Test for overall effect: Not applicable

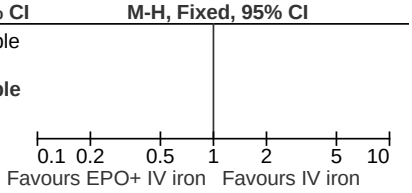


Figure 24: Number of patients transfused

Study or Subgroup	EPO+ IV iron Events	Total	IV iron Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Karkouti 2006	2	10	2	11	19.2%	1.10 [0.19, 6.41]
Madi-Jebara 2004	7	40	10	40	80.8%	0.70 [0.30, 1.66]
Total (95% CI)		**50**		**51**	**100.0%**	**0.76 [0.35, 1.65]**
Total events	9		12			

Heterogeneity: Tau² = 0.00; Chi² = 0.20, df = 1 (P = 0.65); I² = 0%
Test for overall effect: Z = 0.68 (P = 0.49)

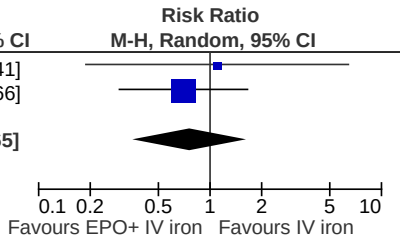
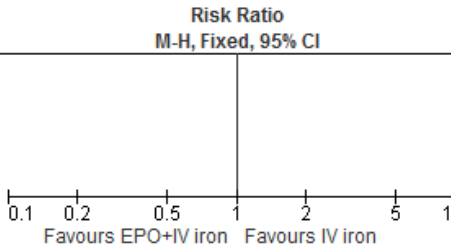


Figure 25: Serious adverse events

Study or Subgroup	EPO+ IV iron Events	Total	IV iron Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Karkouti 2006	0	10	0	10		Not estimable
Kateros 2010	0	38	0	41		Not estimable
Total (95% CI)		**48**		**51**		**Not estimable**
Total events	0		0			

Heterogeneity: Not applicable
Test for overall effect: Not applicable



K.1.7 Erythropoietin plus oral iron versus oral iron

Figure 26: All-cause mortality at 30 days

Study or Subgroup	EPO+ Oral iron Events	Total	Oral iron Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Podesta 2000	9	97	10	103	82.9%	0.96 [0.41, 2.25]
Stowell 2009	1	340	2	340	17.1%	0.50 [0.05, 5.49]
Total (95% CI)		**437**		**443**	**100.0%**	**0.88 [0.39, 1.96]**
Total events	10		12			

Heterogeneity: Chi² = 0.25, df = 1 (P = 0.62); I² = 0%
Test for overall effect: Z = 0.32 (P = 0.75)

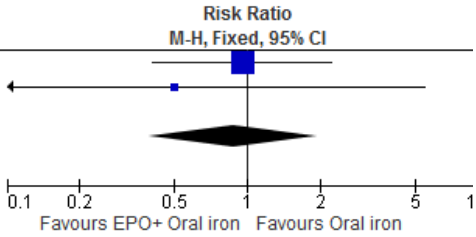
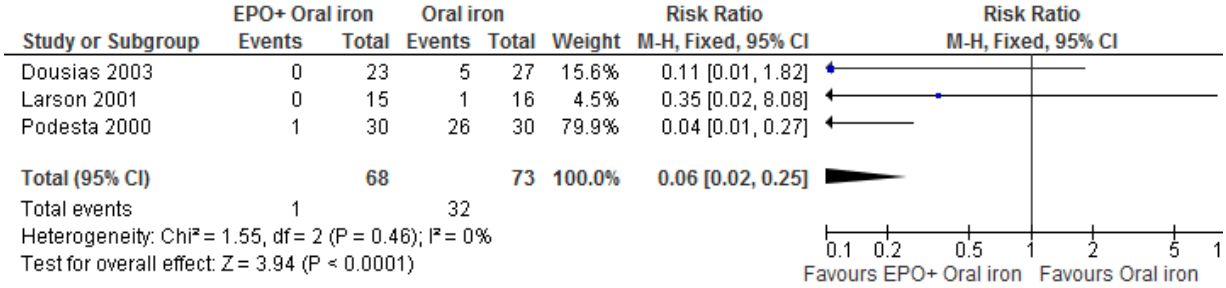
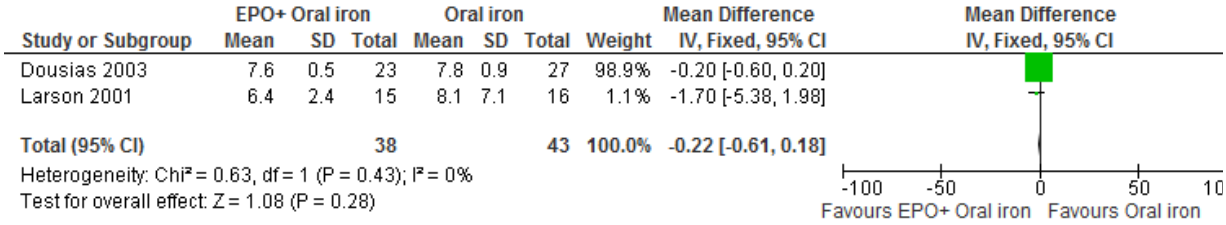


Figure 27: Number of patients transfused



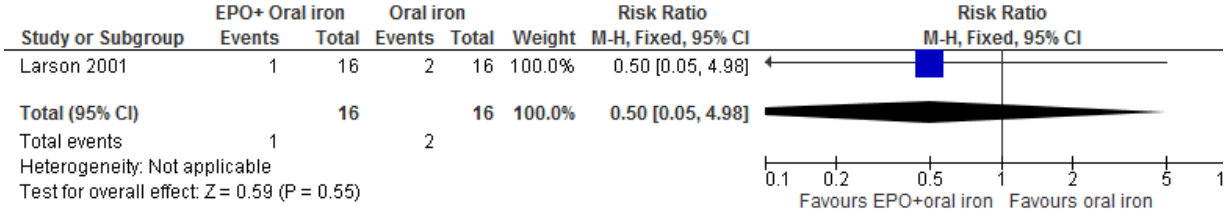
1

Figure 28: Length of hospital stay



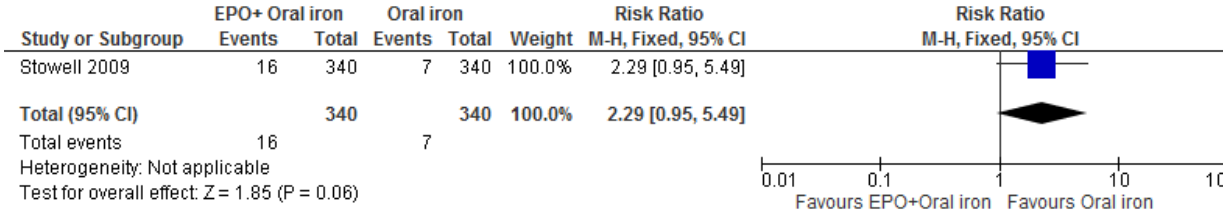
2

Figure 29: Infections



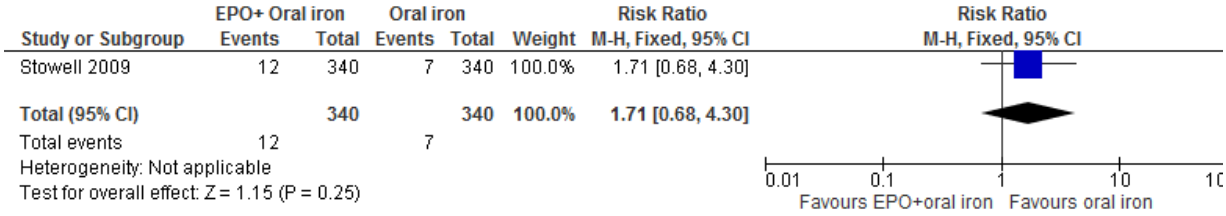
3

Figure 30: Deep vein thrombosis (DVT)



4

Figure 31: Other thrombovascular events



5

K.1.8 Erythropoietin plus oral iron or IV iron versus oral iron or IV iron

Figure 32: Mortality (all-cause)

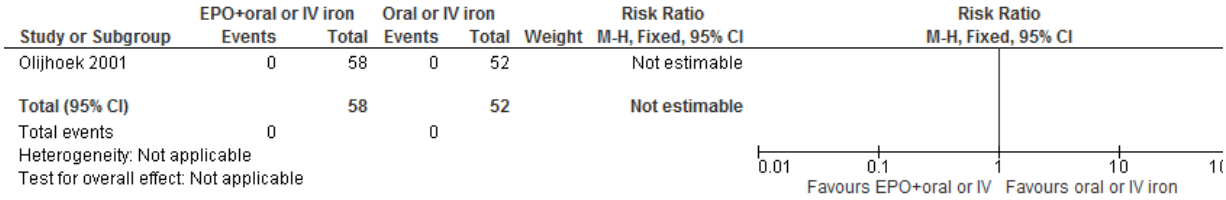


Figure 33: Serious adverse events

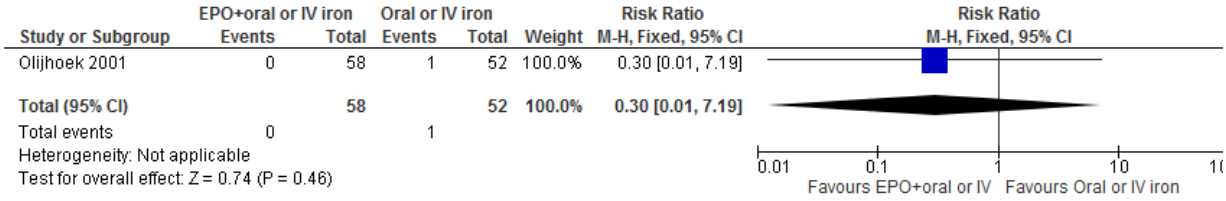
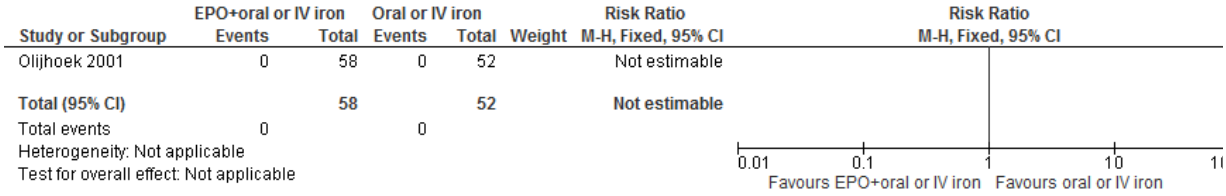


Figure 34: Thrombosis



K.2 Alternatives to blood transfusion in surgical patients- combinations of cell salvage and tranexamic acid

K.2.1 Adults - high risk

Figure 35: ICS versus standard treatment- Number exposed to allogeneic blood

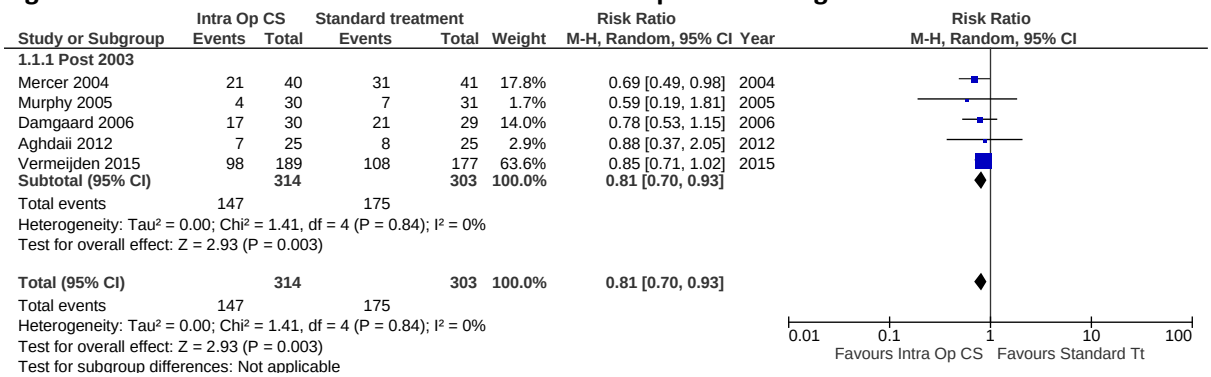
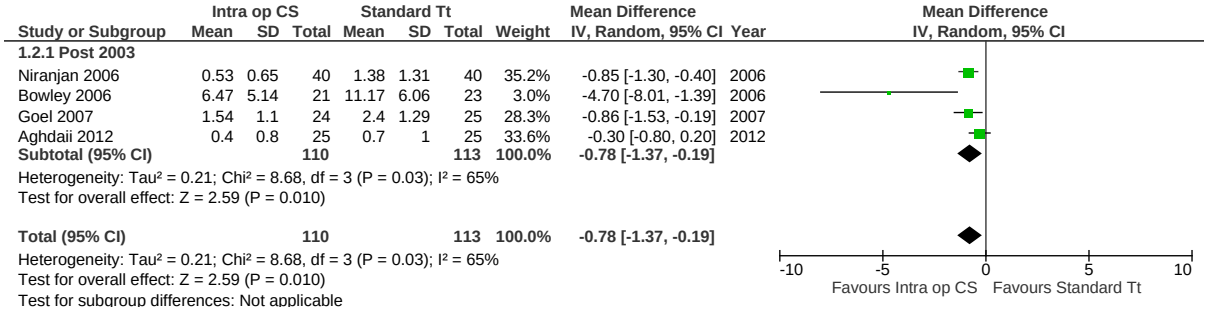
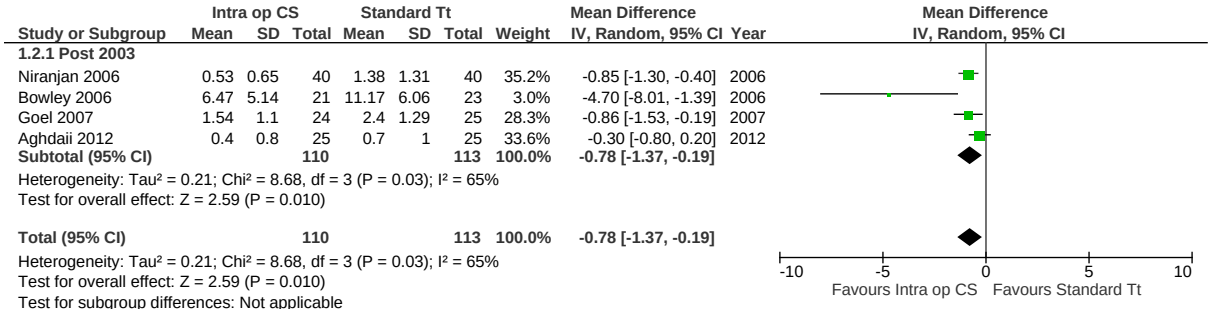


Figure 36: ICS versus standard treatment- Units of allogeneic blood transfused



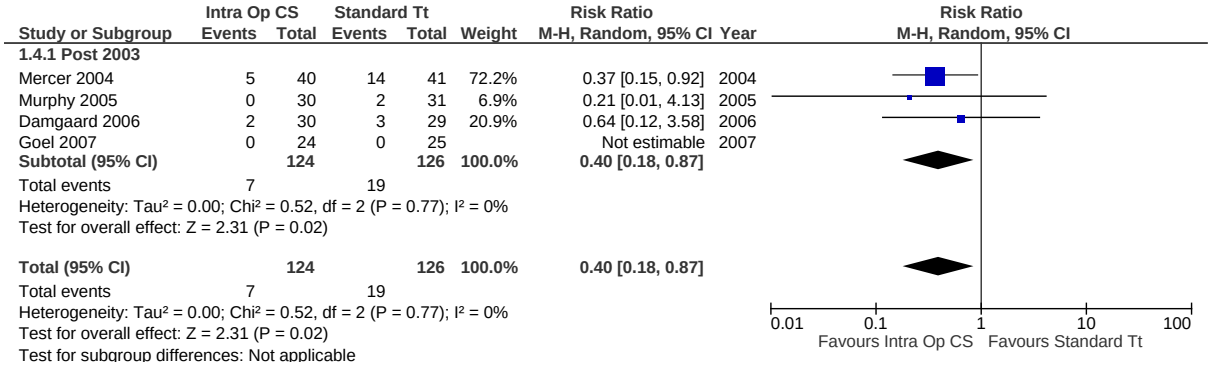
1

Figure 37: ICS versus standard treatment- Mortality at up to 30 days



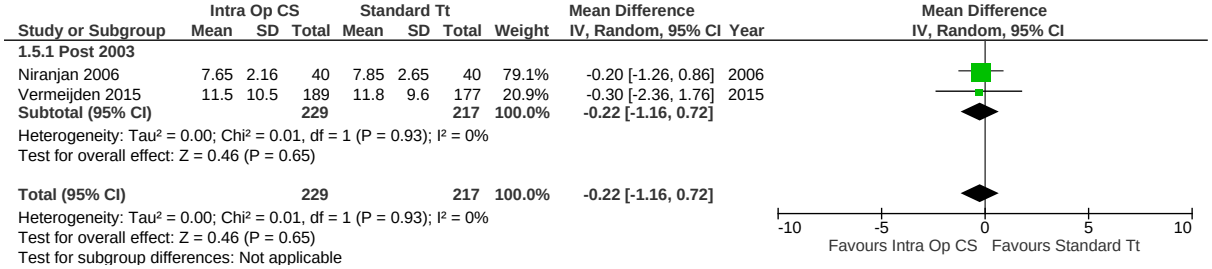
2

Figure 38: ICS versus standard treatment- Infection



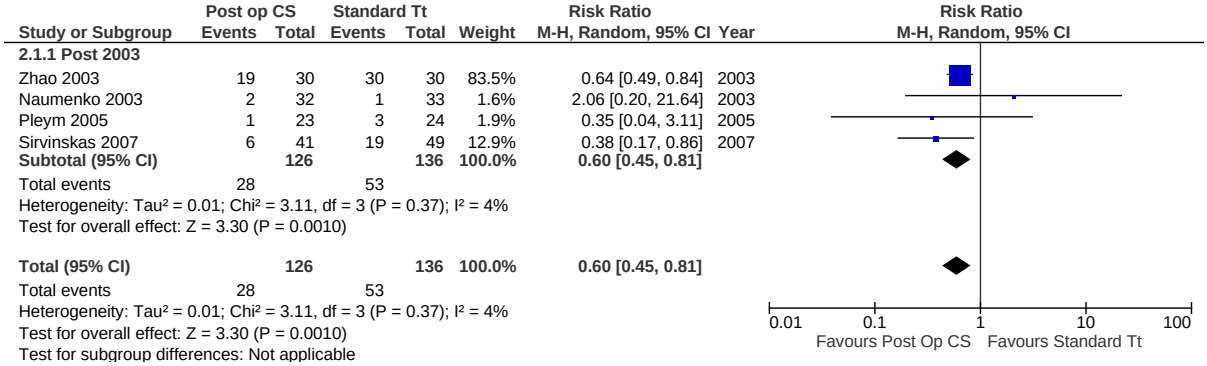
3

Figure 39: ICS versus standard treatment- Length of stay in hospital



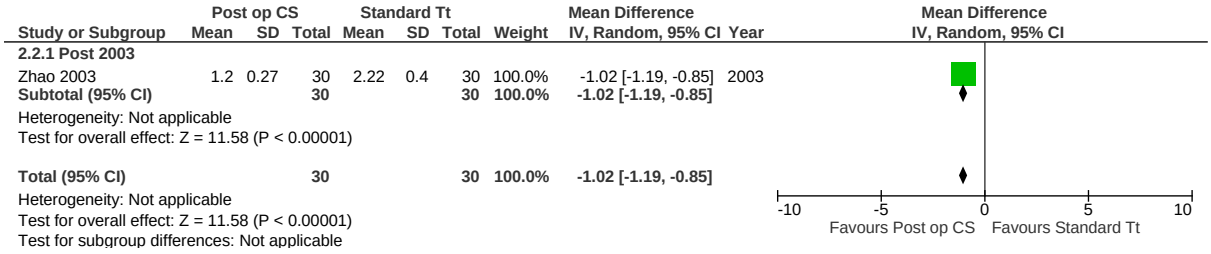
4

Figure 40: PCS versus standard treatment- Number exposed to allogeneic blood



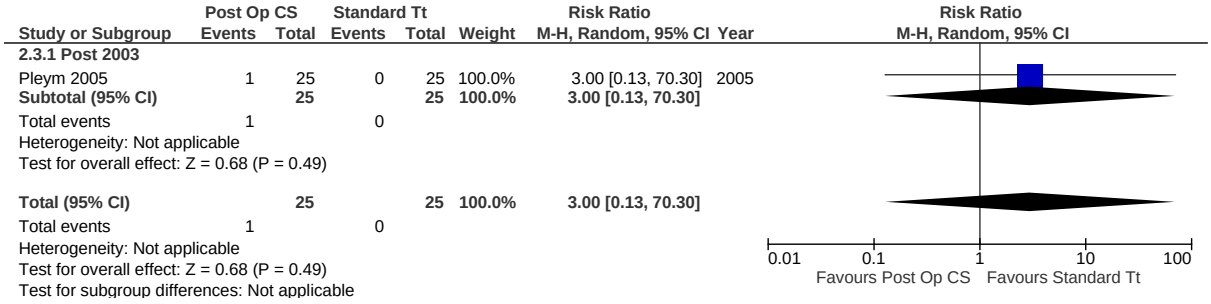
1

Figure 41: PCS versus standard treatment- Units of allogeneic blood transfused



2

Figure 42: PCS versus standard treatment- Mortality at up to 30 days

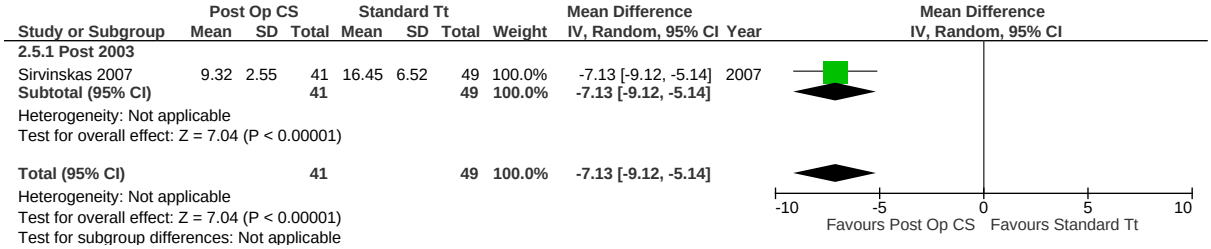


3

Figure 43: PCS versus standard treatment- Infection

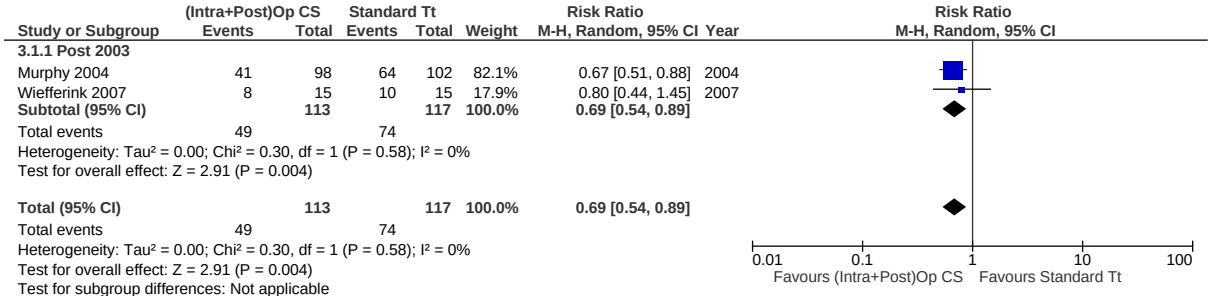
4

Figure 44: PCS versus standard treatment- Length of stay in hospital



1

Figure 45: ICS plus PCS versus standard treatment- Number exposed to allogeneic blood

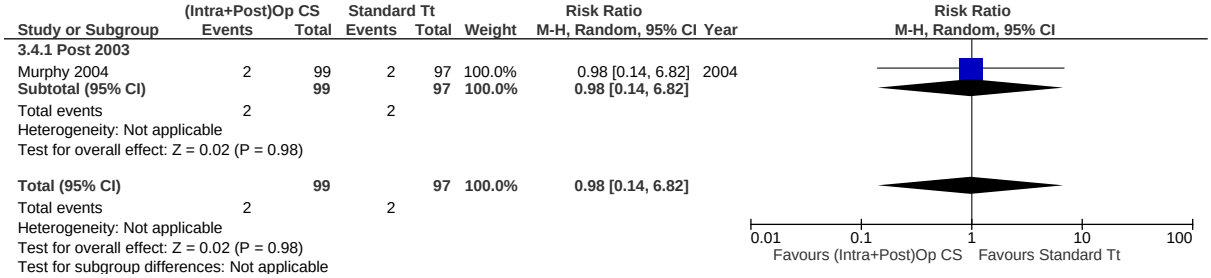


2

Figure 46: ICS plus PCS versus standard treatment- Mortality at up to 30 days

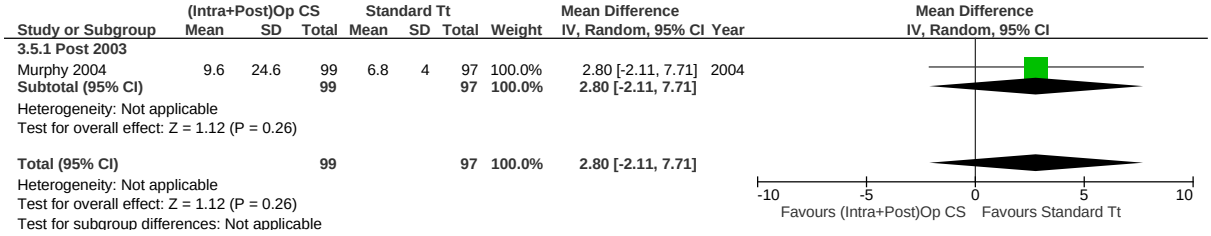
3

Figure 47: ICS plus PCS versus standard treatment- Infection



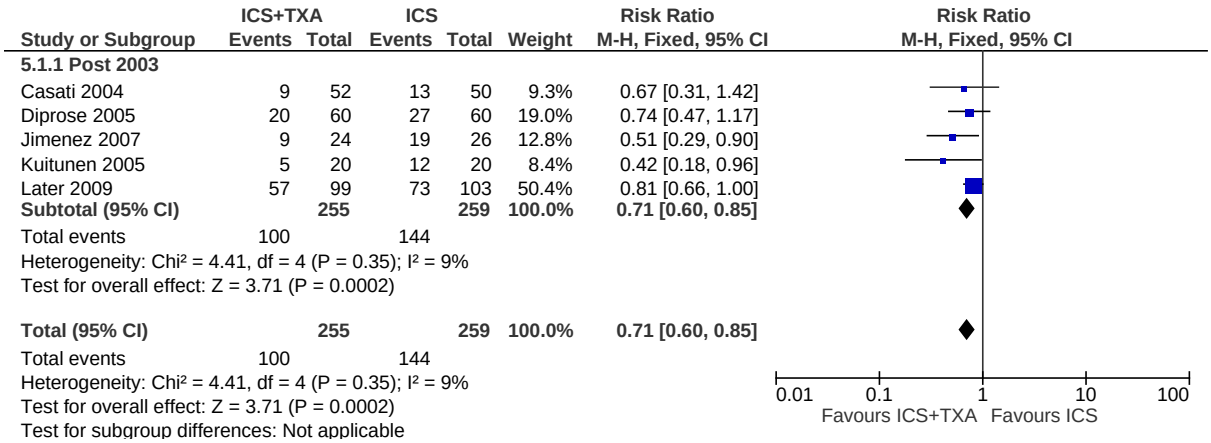
4

Figure 48: ICS plus PCS versus standard treatment- Length of stay in hospital



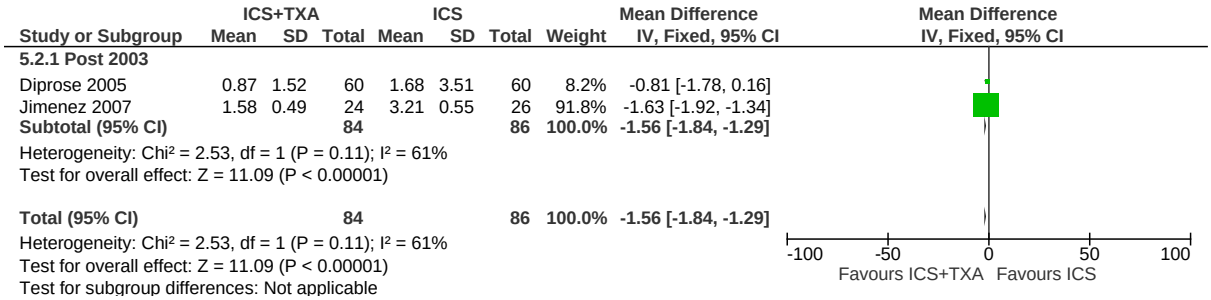
1

Figure 49: ICS plus TXA versus ICS- Number exposed to allogeneic blood



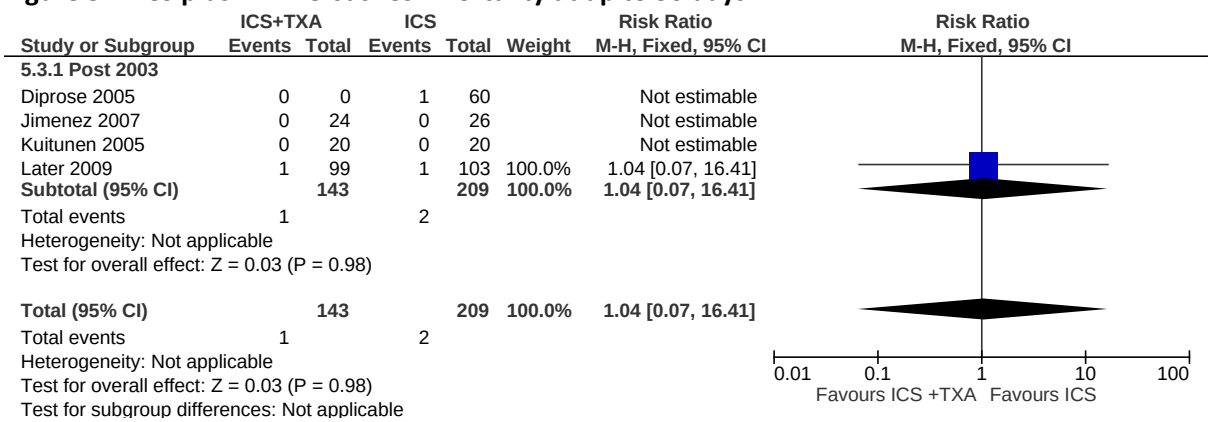
2

Figure 50: ICS plus TXA versus ICS - Units of allogeneic blood transfused



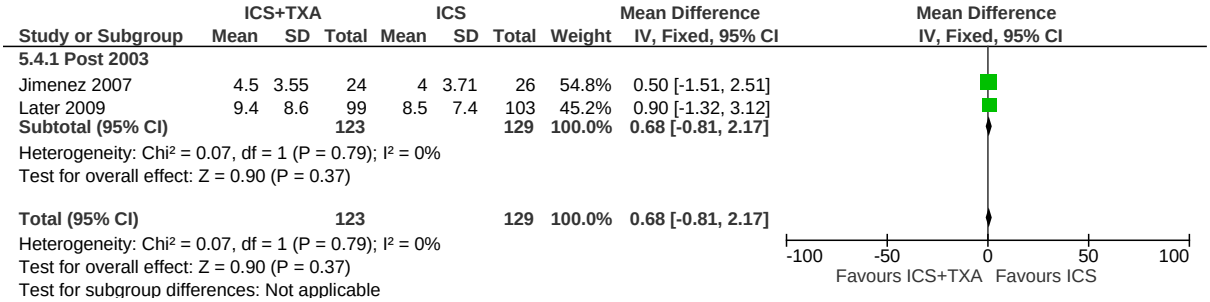
3

Figure 51: ICS plus TXA versus ICS- Mortality at up to 30 days



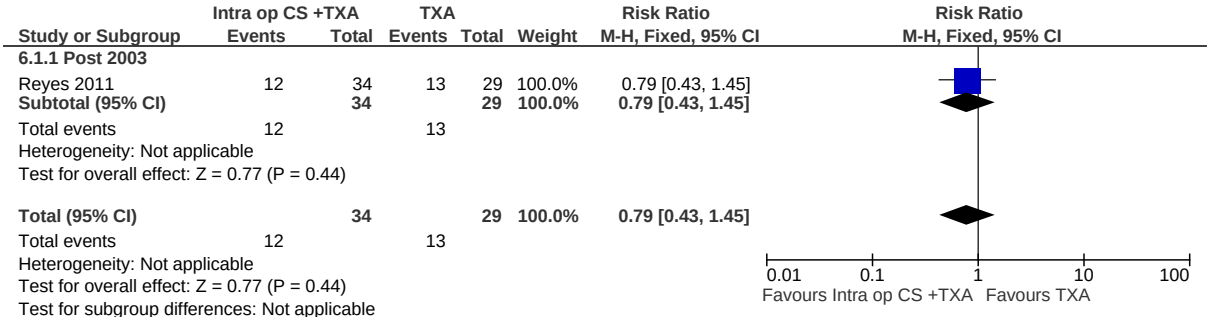
1

Figure 52: ICS plus TXA versus ICS- Length of stay in hospital



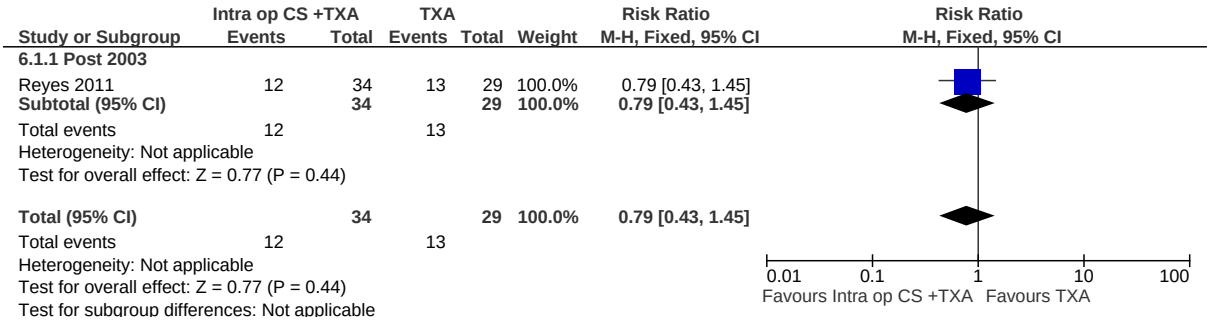
2

Figure 53: ICS plus TXA versus TXA- Number exposed to allogeneic blood



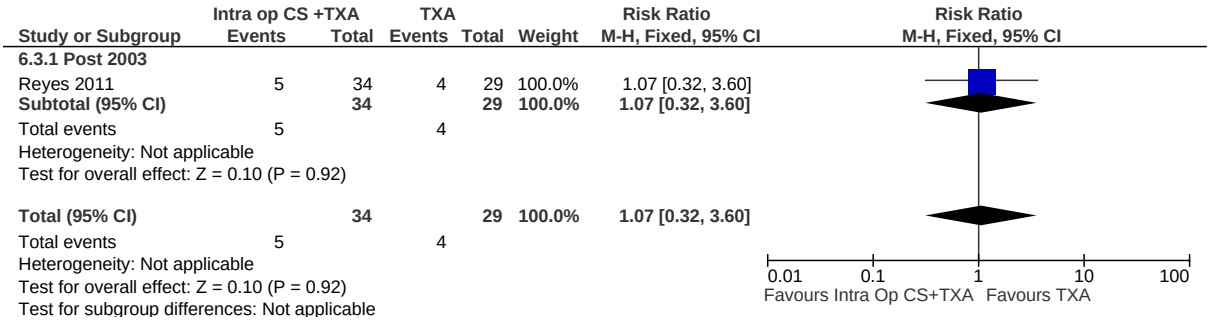
3

Figure 54: ICS plus TXA versus TXA- Mortality at up to 30 days



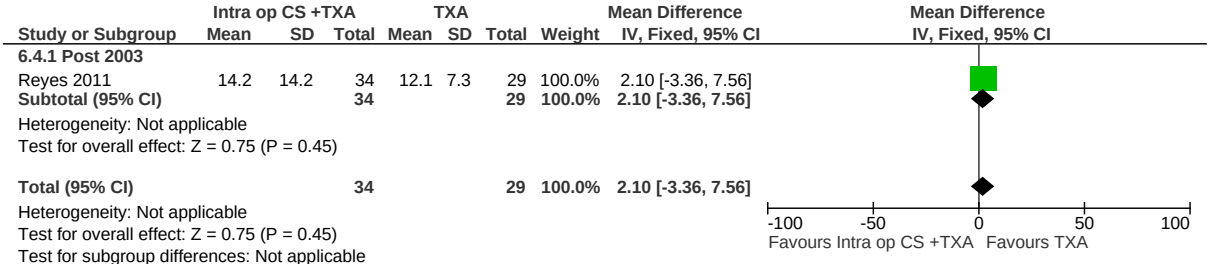
4

Figure 55: ICS plus TXA versus TXA- Infections



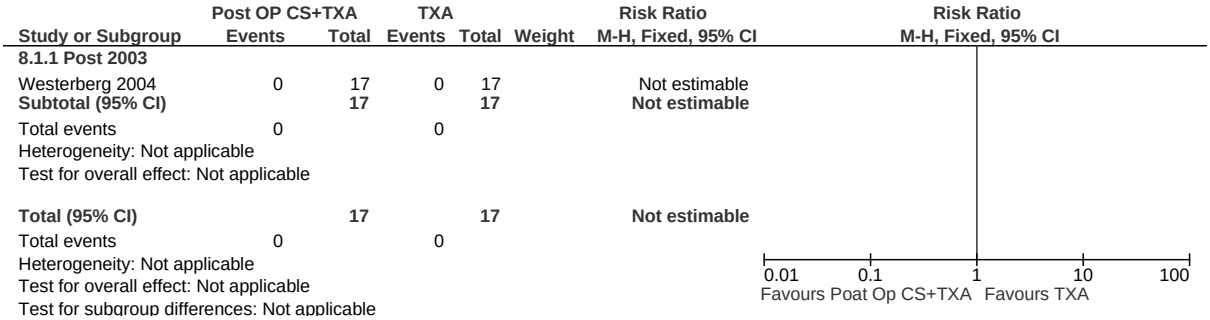
5

Figure 56: ICS+TXA versus TXA- Length of stay in hospital



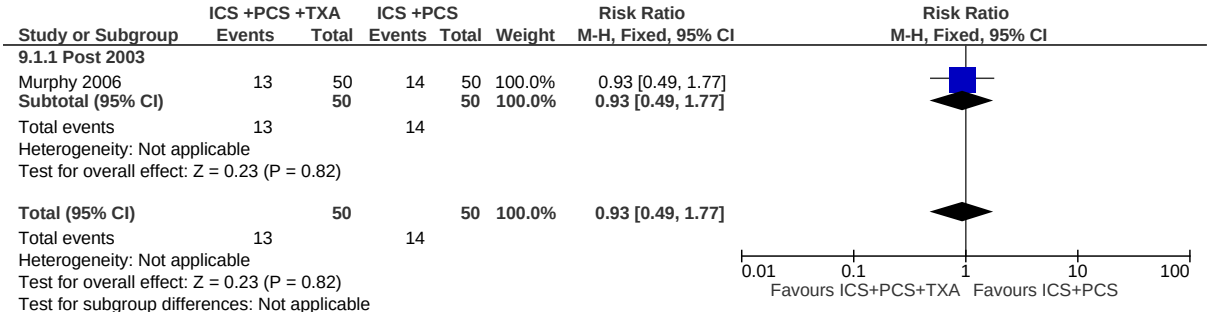
1

Figure 57: PCS plus TXA versus TXA- No. exposed to allogeneic blood



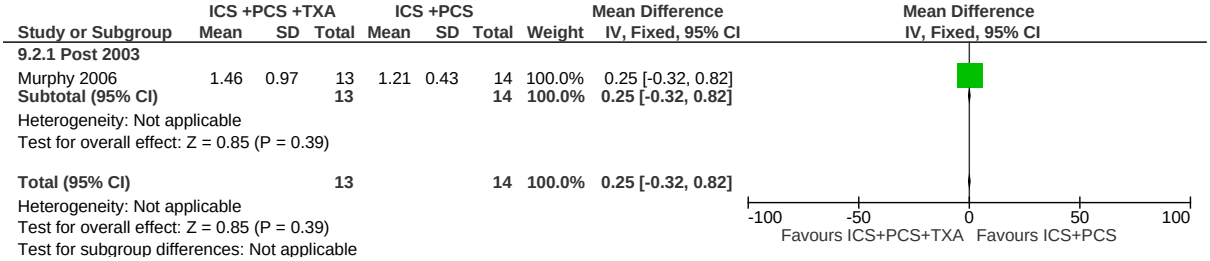
2

Figure 58: ICS plus PCS plus TXA versus ICS plus PCS- Number exposed to allogeneic blood



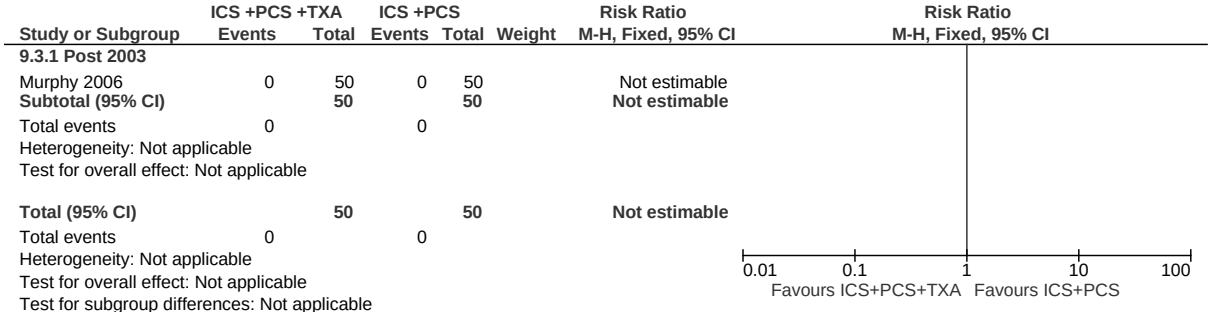
3

Figure 59: ICS plus PCS plus TXA versus ICS plus PCS- Units of allogeneic blood transfused



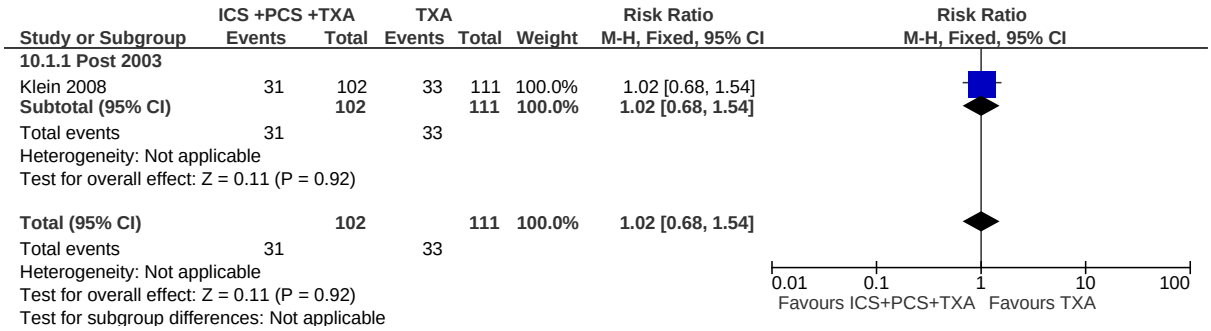
4

Figure 60: ICS plus PCS plus TXA versus ICS plus PCS- Mortality at up to 30 days



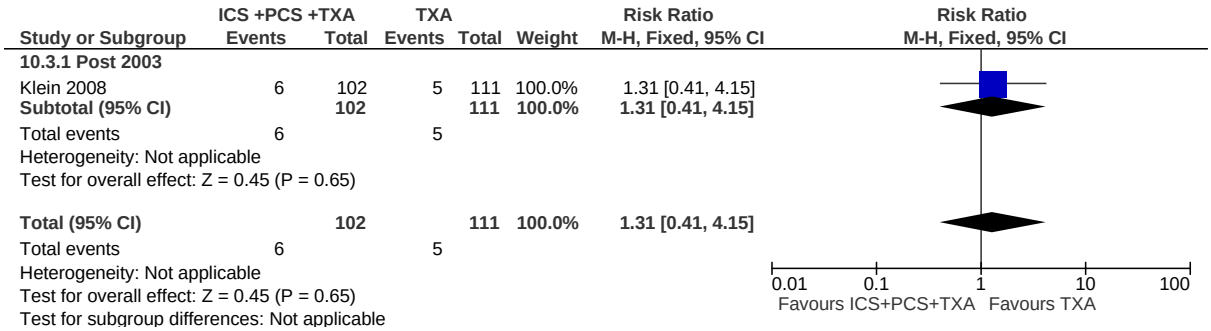
1

Figure 61: ICS plus PCS plus TXA versus TXA- Number exposed to allogeneic blood



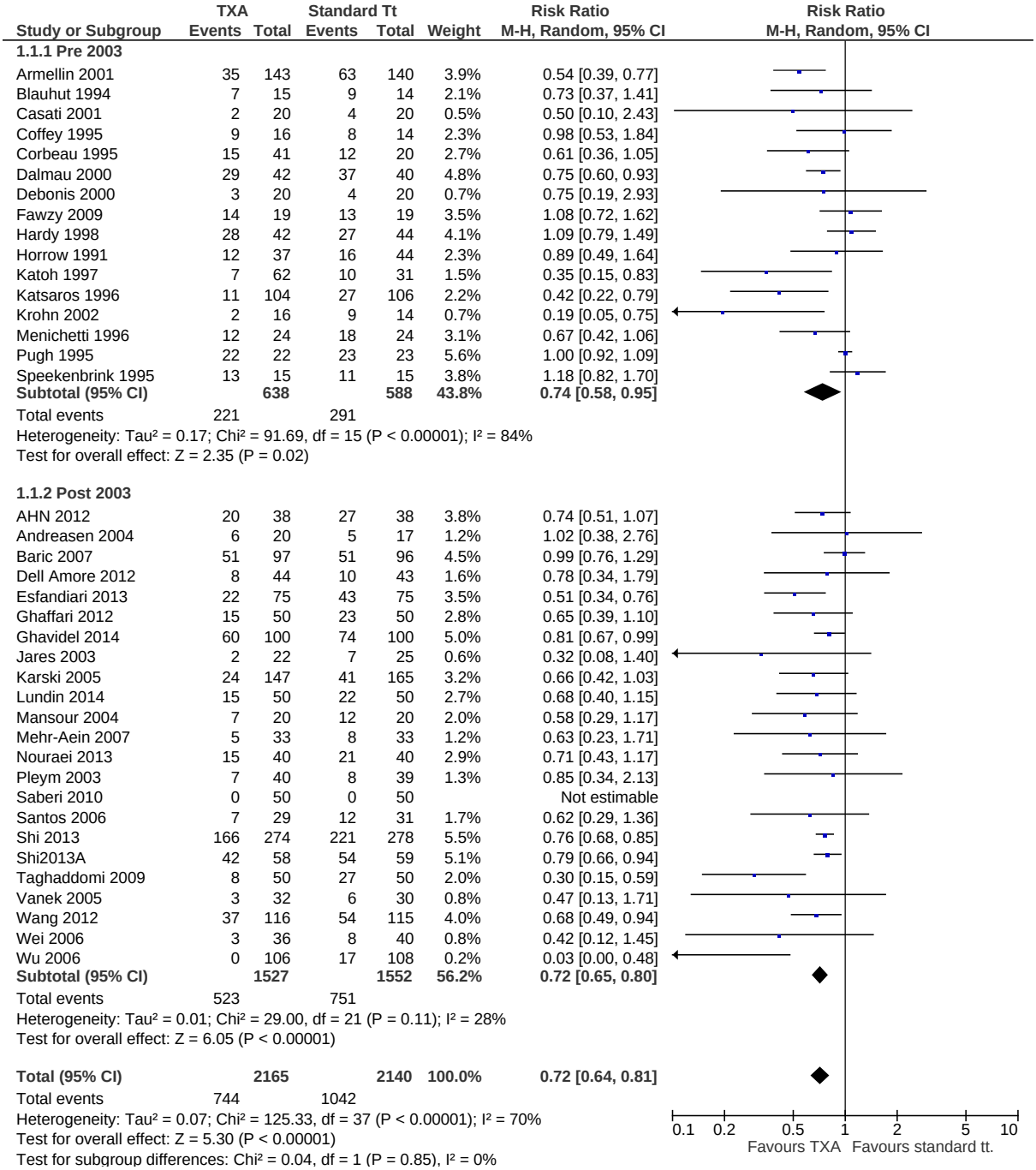
2

Figure 62: ICS plus PCS plus TXA versus TXA- Infection



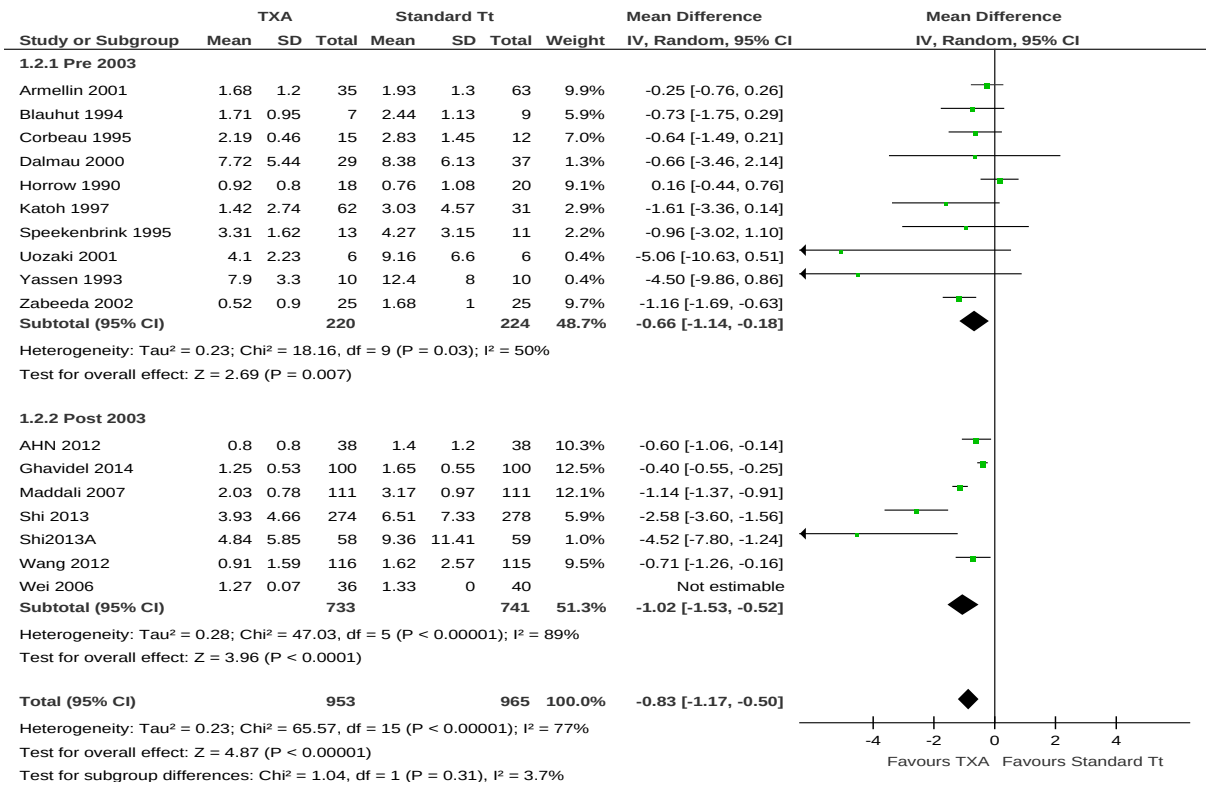
3

Figure 63: TXA versus standard treatment- Number exposed to allogeneic transfusions



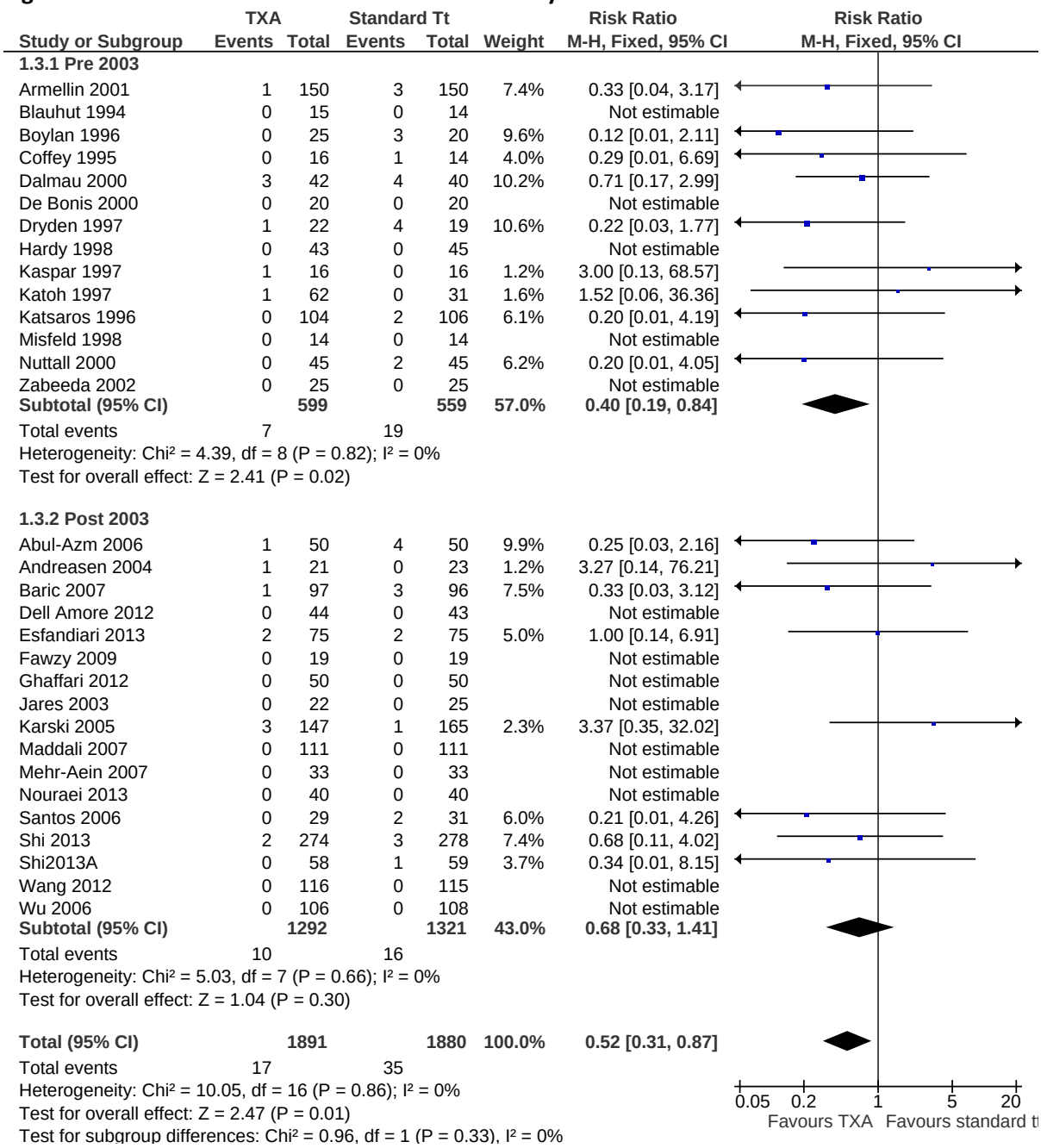
1

Figure 64: TXA versus standard treatment- Units of allogeneic blood transfused



1

Figure 65: TXA versus standard treatment- Mortality



1

Figure 66: TXA versus standard treatment- Length of hospital stay

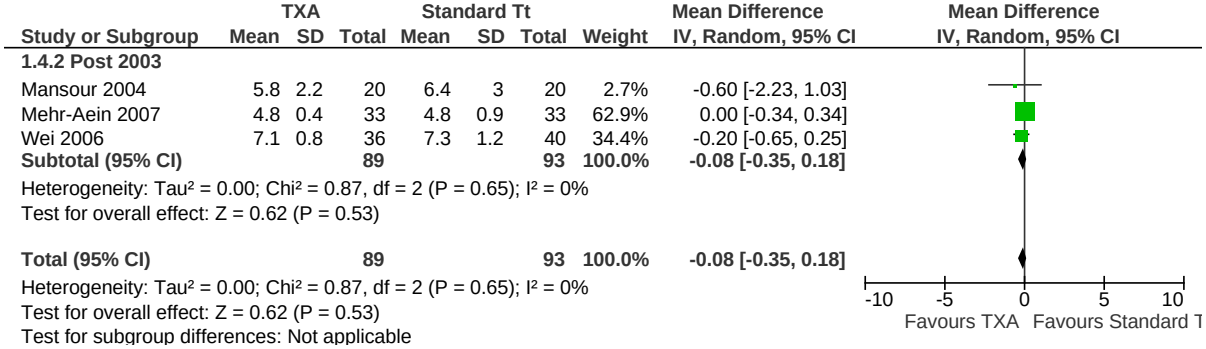


Figure 67: TXA versus standard treatment- Thrombotic complications

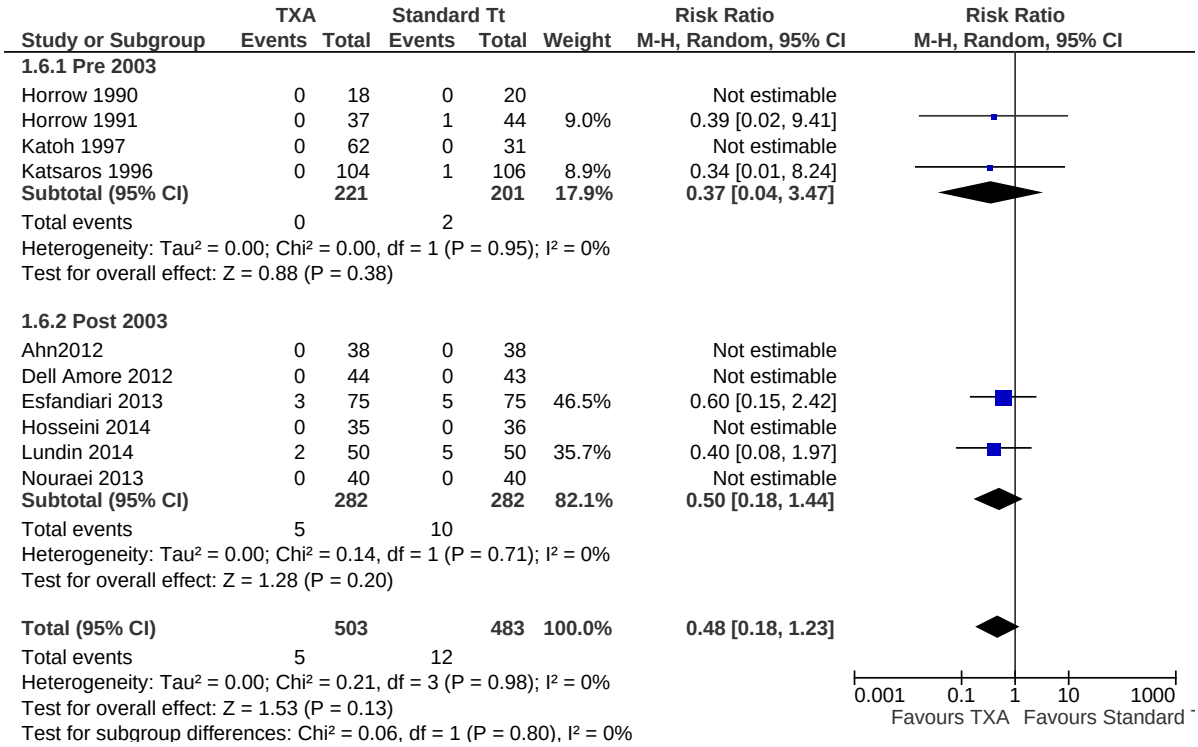
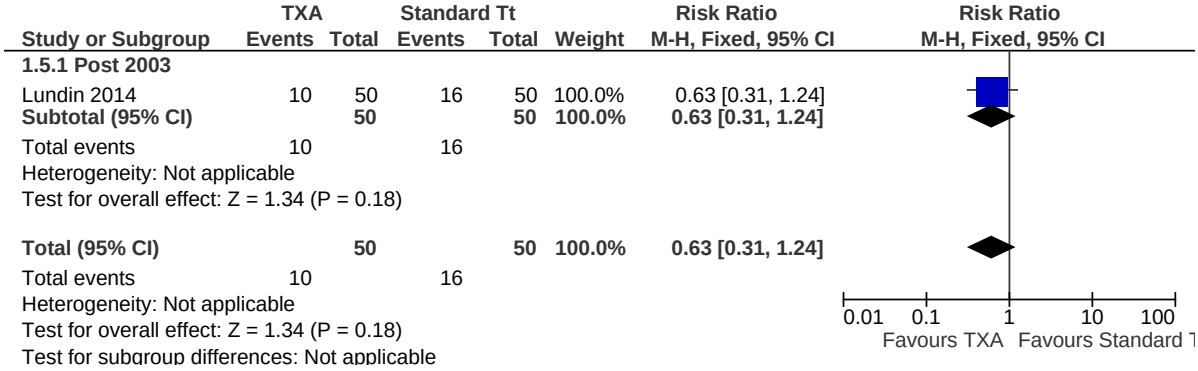


Figure 68: Infections



K.2.2 Adults - moderate risk

Figure 69: ICS versus standard treatment- Number exposed to allogeneic blood

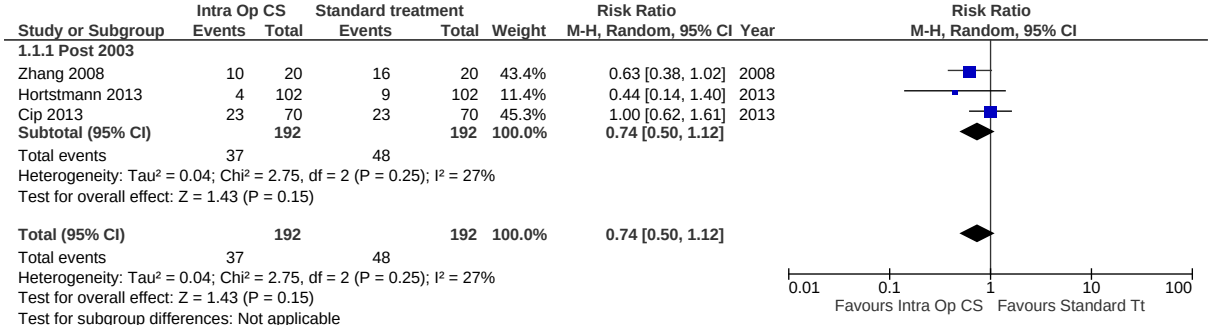


Figure 70: ICS versus standard treatment- Units of allogeneic blood transfused

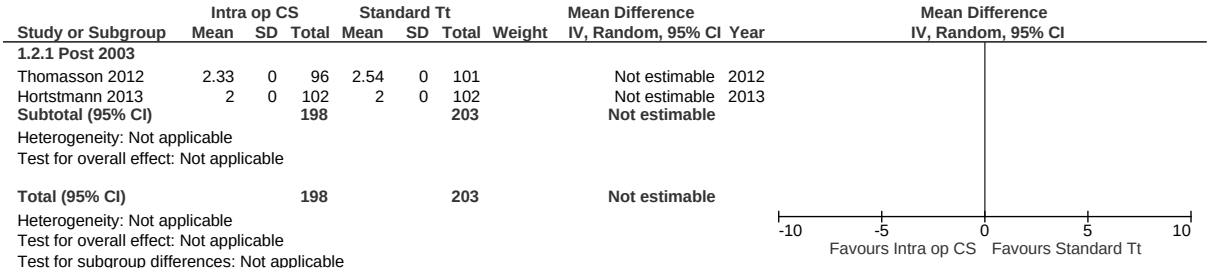


Figure 71: PCS versus standard treatment- Number exposed to allogeneic blood

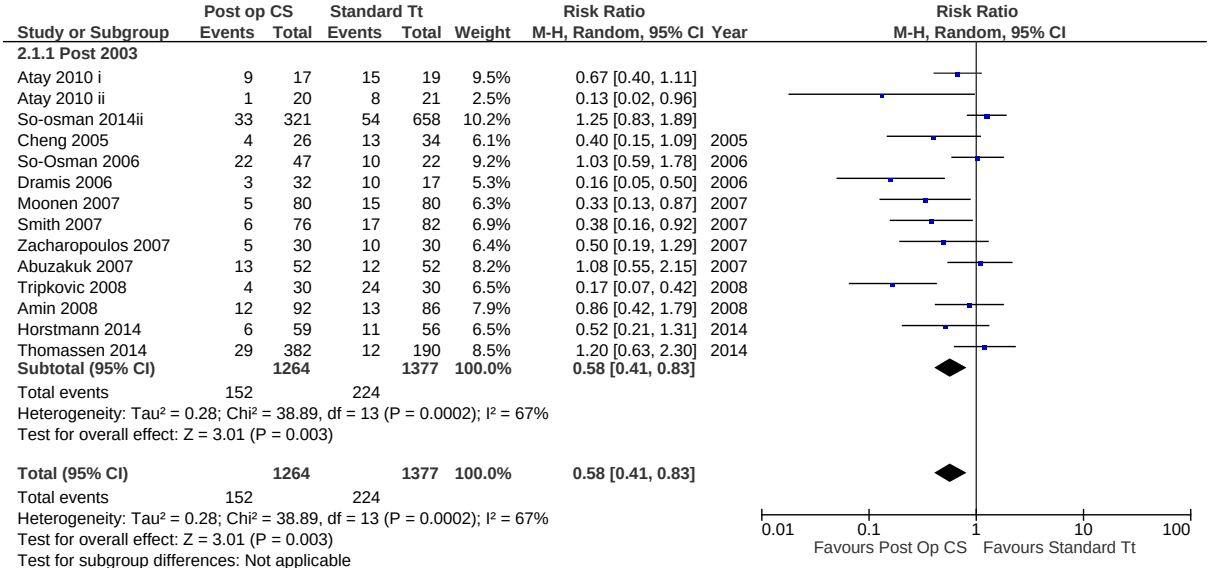


Figure 72: PCS versus standard treatment- Units of allogeneic blood transfused

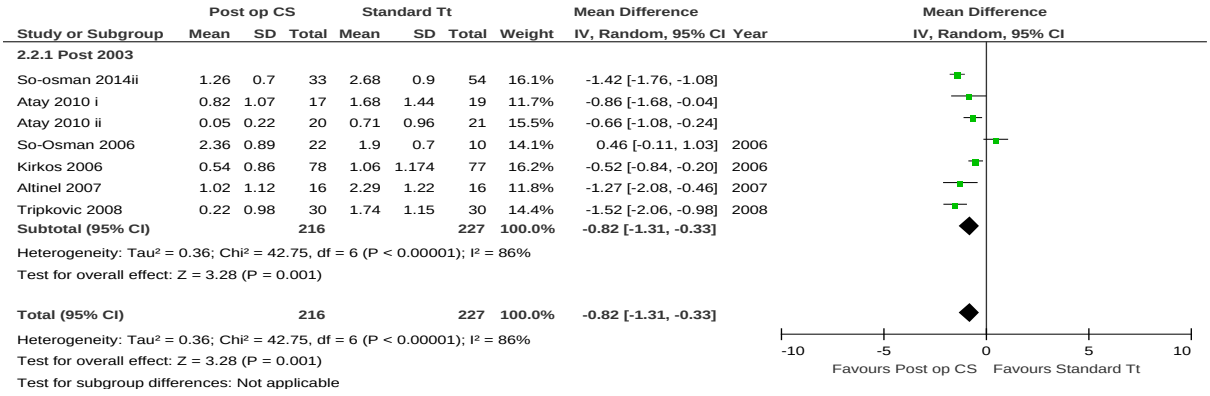
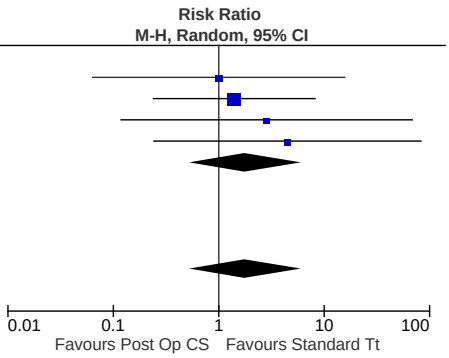


Figure 73: PCS versus standard treatment- Infection

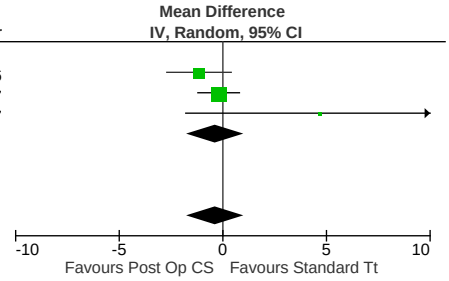
Study or Subgroup	Post Op CS Events	Total	Standard Tt Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
2.3.1 Post 2003							
Moonen 2007	1	80	1	80	19.7%	1.00 [0.06, 15.71]	2007
Amin 2008	3	92	2	86	48.0%	1.40 [0.24, 8.19]	2008
Horstmann 2014	1	59	0	56	14.8%	2.85 [0.12, 68.53]	2014
Thomassen 2014	4	382	0	190	17.6%	4.49 [0.24, 82.93]	2014
Subtotal (95% CI)		**613**		**412**	**100.0%**	**1.79 [0.53, 6.07]**	
Total events	9		3				
Heterogeneity: Tau² = 0.00; Chi² = 0.73, df = 3 (P = 0.87); I² = 0%							
Test for overall effect: Z = 0.93 (P = 0.35)							
Total (95% CI)		**613**		**412**	**100.0%**	**1.79 [0.53, 6.07]**	
Total events	9		3				
Heterogeneity: Tau² = 0.00; Chi² = 0.73, df = 3 (P = 0.87); I² = 0%							
Test for overall effect: Z = 0.93 (P = 0.35)							
Test for subgroup differences: Not applicable							



1

Figure 74: PCS versus standard treatment- Length of hospital stay

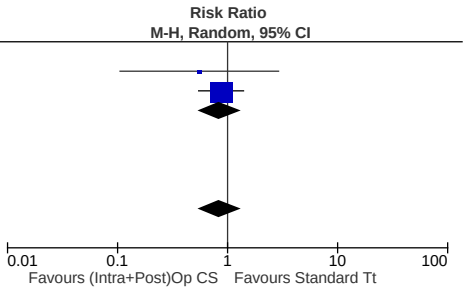
Study or Subgroup	Post Op CS Mean	SD	Total	Standard Tt Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Year
2.4.1 Post 2003									
So-Osman 2006	7.85	3.57	47	9	2.8	22	39.5%	-1.15 [-2.70, 0.40]	2006
Abuzakuk 2007	8.1	2.4	52	8.3	2.8	52	56.3%	-0.20 [-1.20, 0.80]	2007
Altinel 2007	21.2	11.3	16	16.5	6.9	16	4.2%	4.70 [-1.79, 11.19]	2007
Subtotal (95% CI)			**115**			**90**	**100.0%**	**-0.37 [-1.73, 0.99]**	
Heterogeneity: Tau² = 0.59; Chi² = 3.42, df = 2 (P = 0.18); I² = 42%									
Test for overall effect: Z = 0.53 (P = 0.59)									
Total (95% CI)			**115**			**90**	**100.0%**	**-0.37 [-1.73, 0.99]**	
Heterogeneity: Tau² = 0.59; Chi² = 3.42, df = 2 (P = 0.18); I² = 42%									
Test for overall effect: Z = 0.53 (P = 0.59)									
Test for subgroup differences: Not applicable									



2

Figure 75: ICS plus PCS versus standard treatment- Number exposed to allogeneic blood

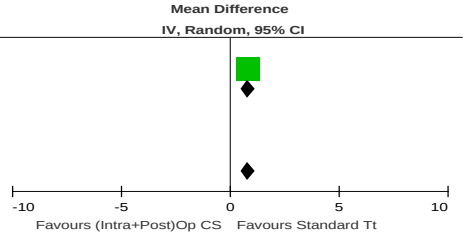
Study or Subgroup	(Intra+Post)Op CS Events	Total	Standard Tt Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
3.1.1 Post 2003							
Horstmann 2014 A	2	56	4	62	7.4%	0.55 [0.11, 2.91]	
So-osman 2014i	23	321	54	658	92.6%	0.87 [0.55, 1.40]	2014
Subtotal (95% CI)		**377**		**720**	**100.0%**	**0.84 [0.54, 1.33]**	
Total events	25		58				
Heterogeneity: Tau² = 0.00; Chi² = 0.27, df = 1 (P = 0.60); I² = 0%							
Test for overall effect: Z = 0.74 (P = 0.46)							
Total (95% CI)		**377**		**720**	**100.0%**	**0.84 [0.54, 1.33]**	
Total events	25		58				
Heterogeneity: Tau² = 0.00; Chi² = 0.27, df = 1 (P = 0.60); I² = 0%							
Test for overall effect: Z = 0.74 (P = 0.46)							
Test for subgroup differences: Not applicable							



3

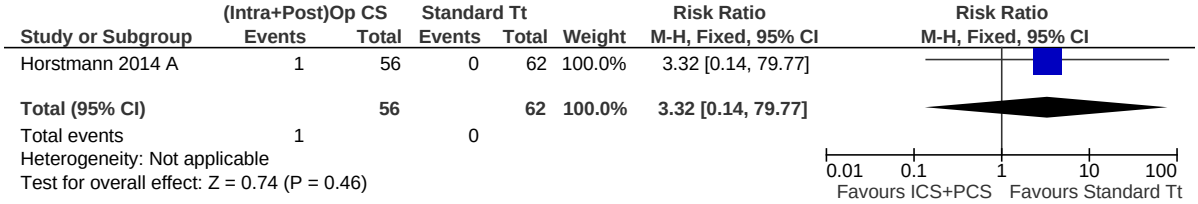
Figure 76: ICS plus PCS versus standard treatment- Units of allogeneic blood transfused

Study or Subgroup	(Intra+Post)Op CS Mean	SD	Total	Standard Tt Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Year
3.2.1 Post 2003									
So-osman 2014i	3.49	0.5	23	2.68	0.9	54	100.0%	0.81 [0.49, 1.13]	2014
Subtotal (95% CI)			**23**			**54**	**100.0%**	**0.81 [0.49, 1.13]**	
Heterogeneity: Not applicable									
Test for overall effect: Z = 5.04 (P < 0.00001)									
Total (95% CI)			**23**			**54**	**100.0%**	**0.81 [0.49, 1.13]**	
Heterogeneity: Not applicable									
Test for overall effect: Z = 5.04 (P < 0.00001)									
Test for subgroup differences: Not applicable									



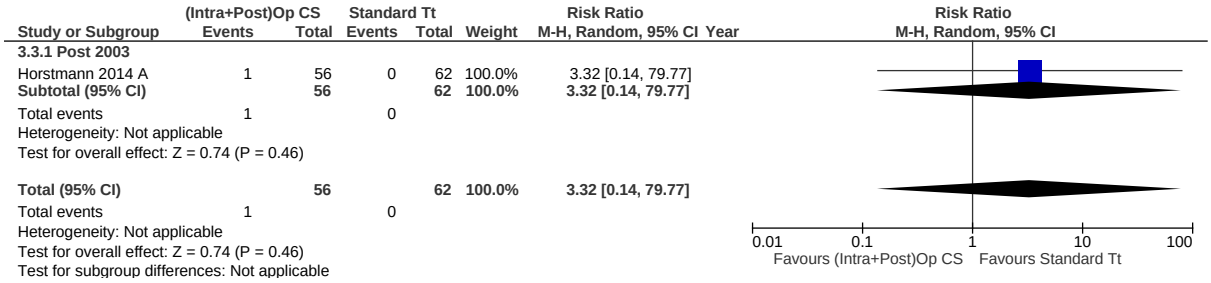
4

Figure 77: ICS plus PCS versus standard treatment- Mortality



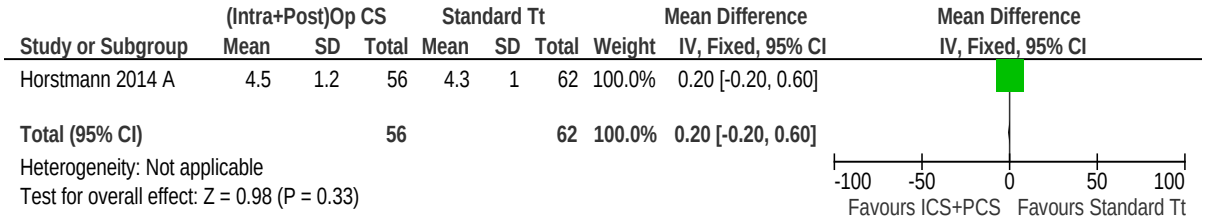
1

Figure 78: ICS plus PCS versus standard treatment- Infection



2

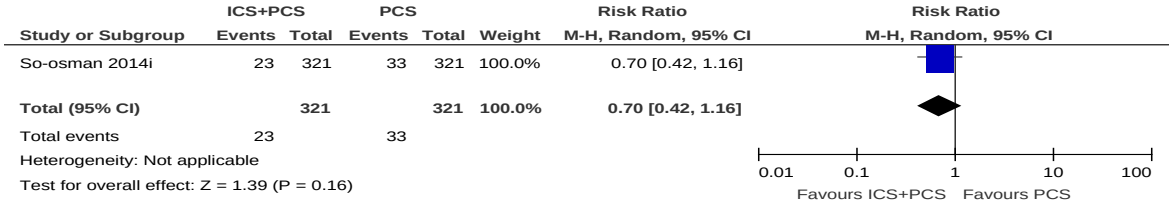
Figure 79: ICS plus PCS versus standard treatment- Length of hospital stay



3

4

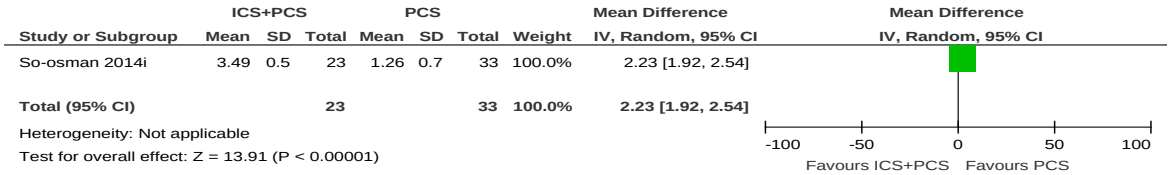
Figure 80: ICS plus PCS versus PCS- No.of patients receiving allogeneic transfusions



5

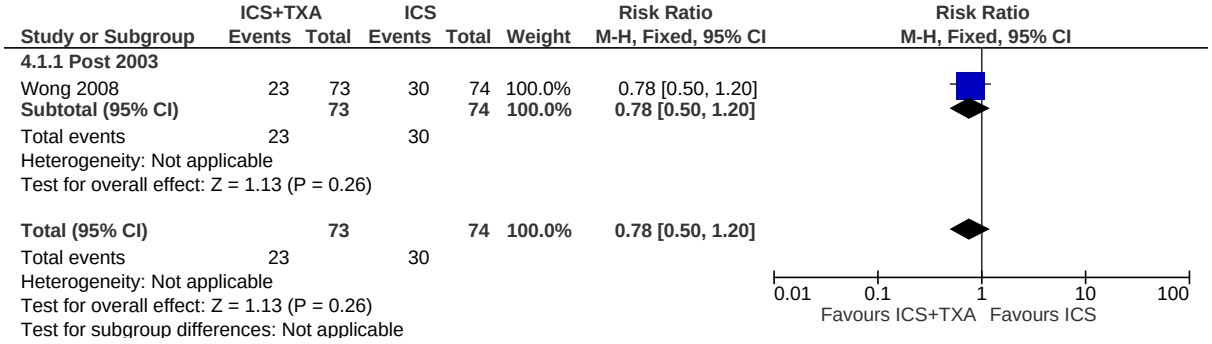
6

Figure 81: ICS plus PCS versus PCS- Units of allogeneic blood transfused



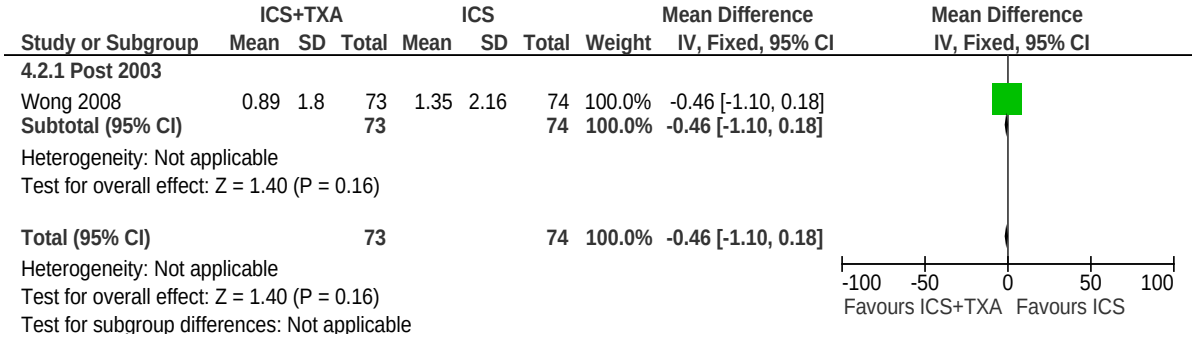
1

Figure 82: ICS plus TXA versus ICS- Number exposed to allogeneic blood



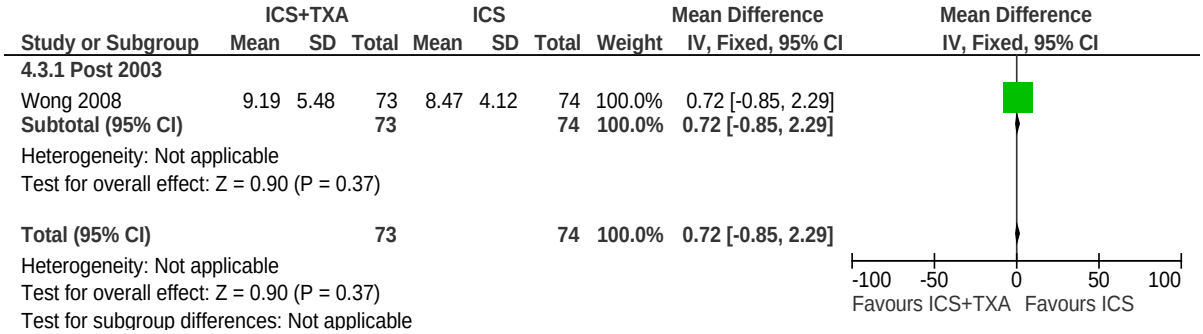
2

Figure 83: ICS plus TXA versus ICS- Units of allogeneic blood transfused



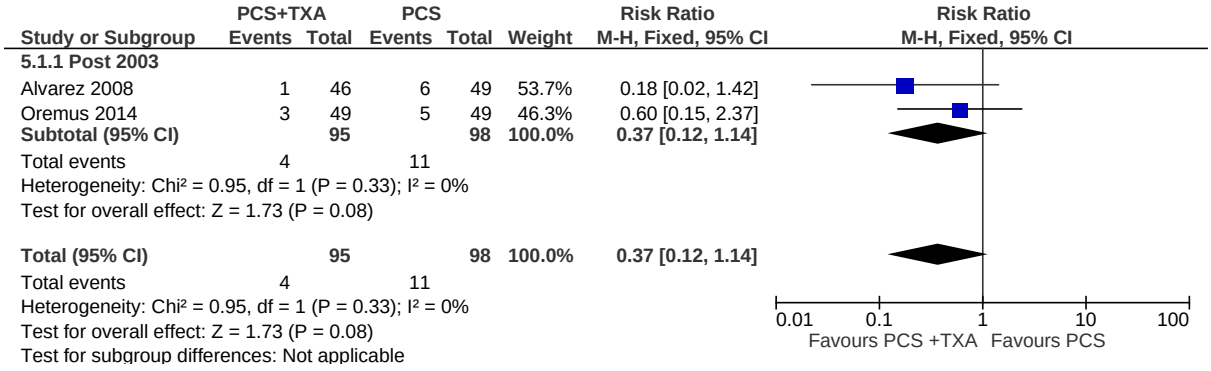
3

Figure 84: ICS plus TXA versus ICS- Length of hospital stay



4

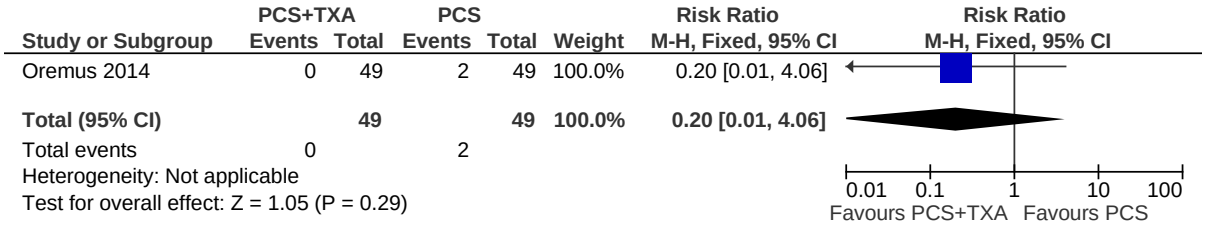
Figure 85: PCS plus TXA versus PCS- Number exposed to allogeneic blood



1

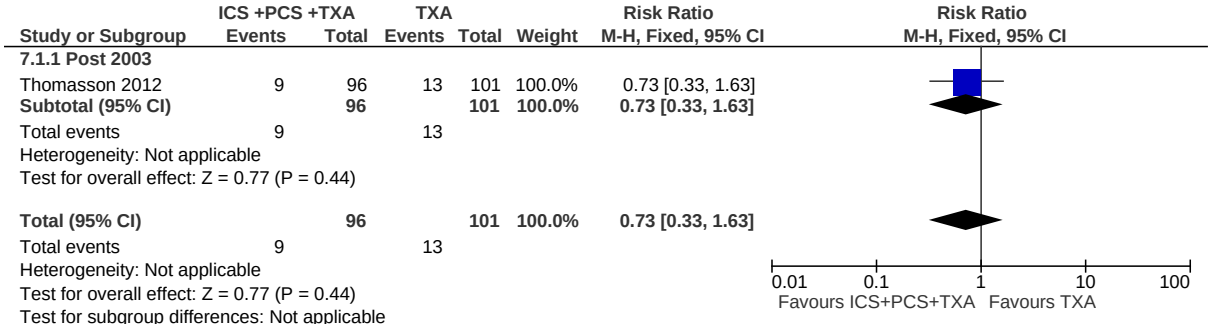
2

Figure 86: PCS plus TXA versus PCS- Thrombotic complications



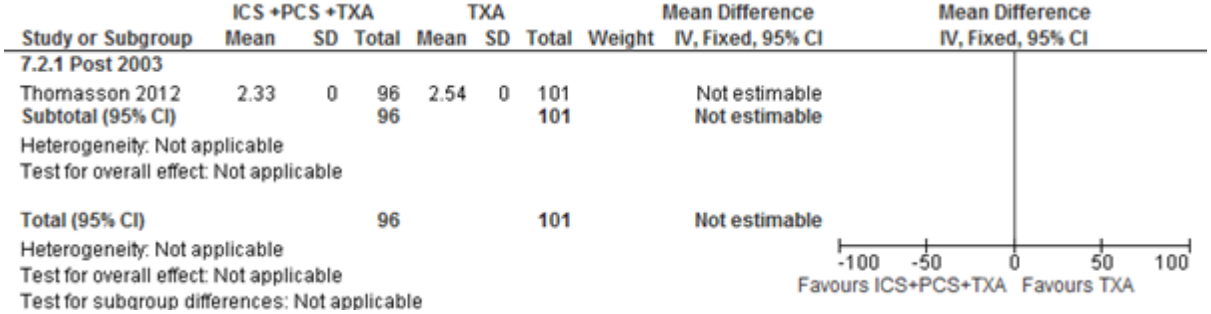
3

Figure 87: ICS plus PCS plus TXA versus TXA- No. exposed to allogeneic blood



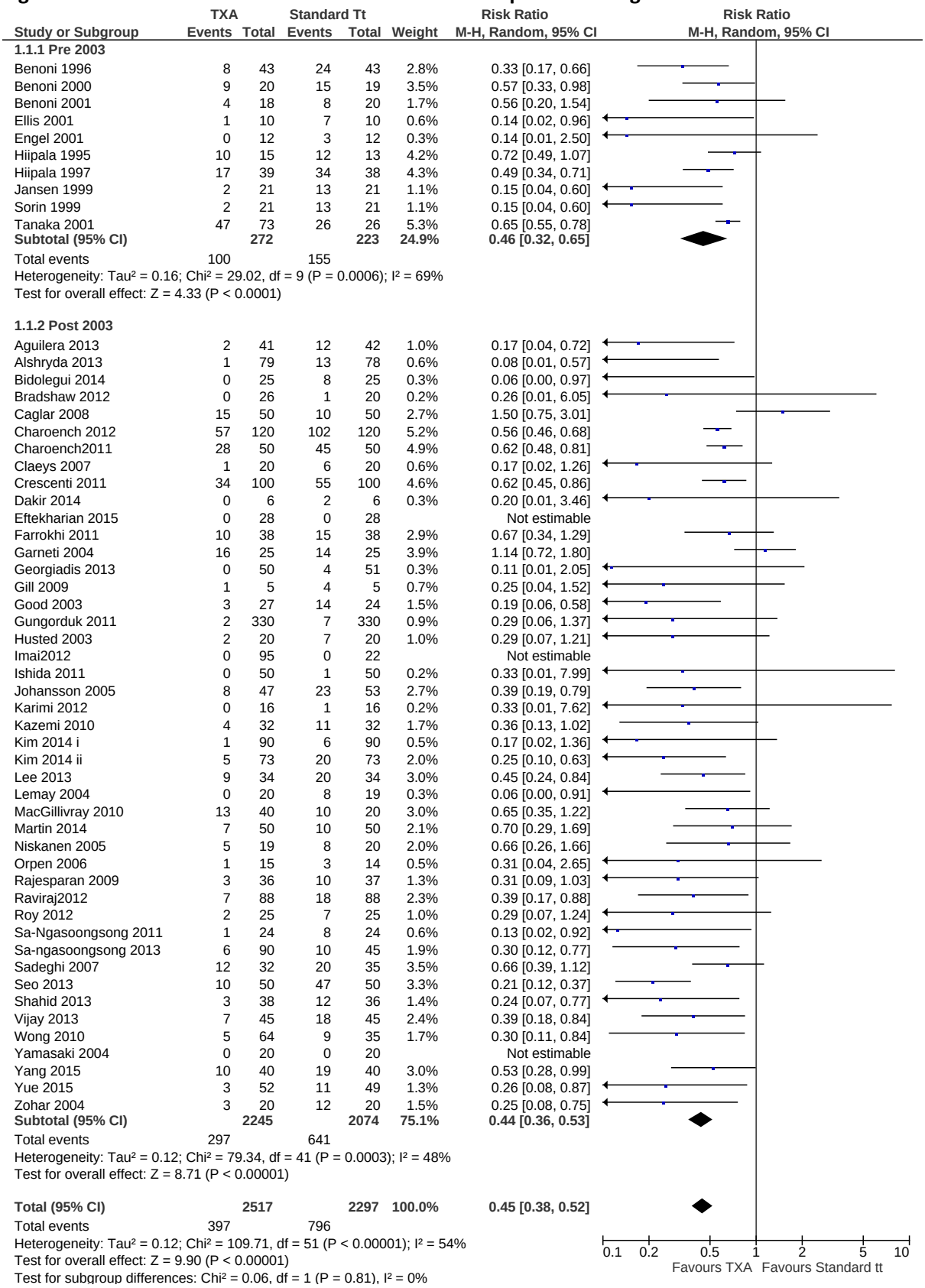
4

Figure 88: ICS plus PCS plus TXA versus TXA- Units of allogeneic blood transfused



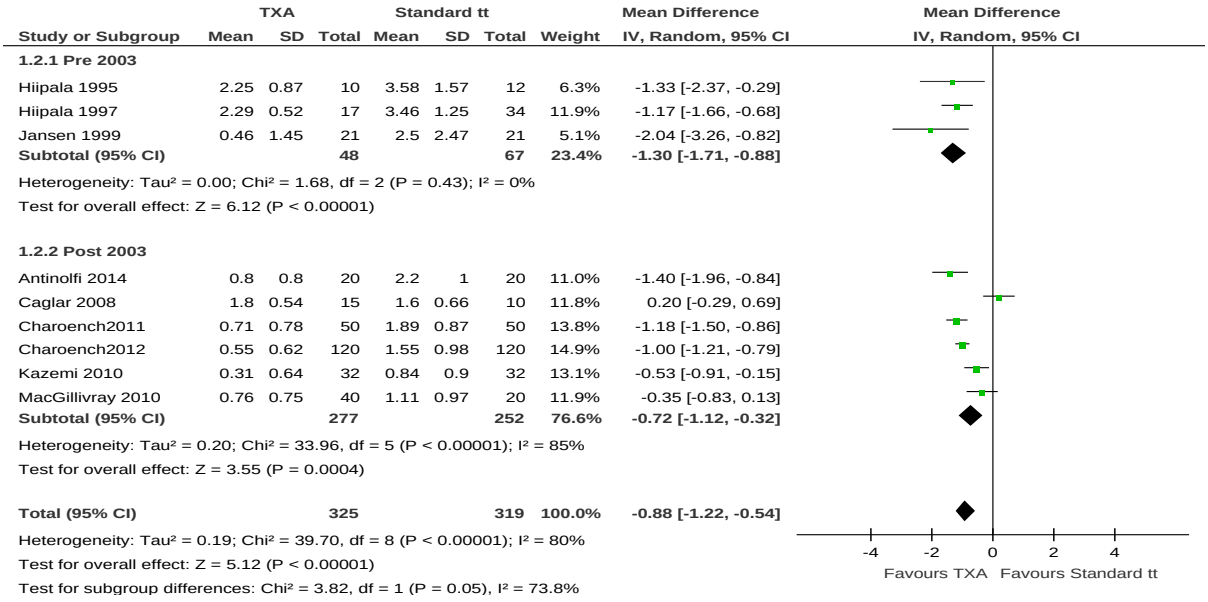
5

Figure 89: TXA versus standard treatment- Number exposed to allogeneic transfusions



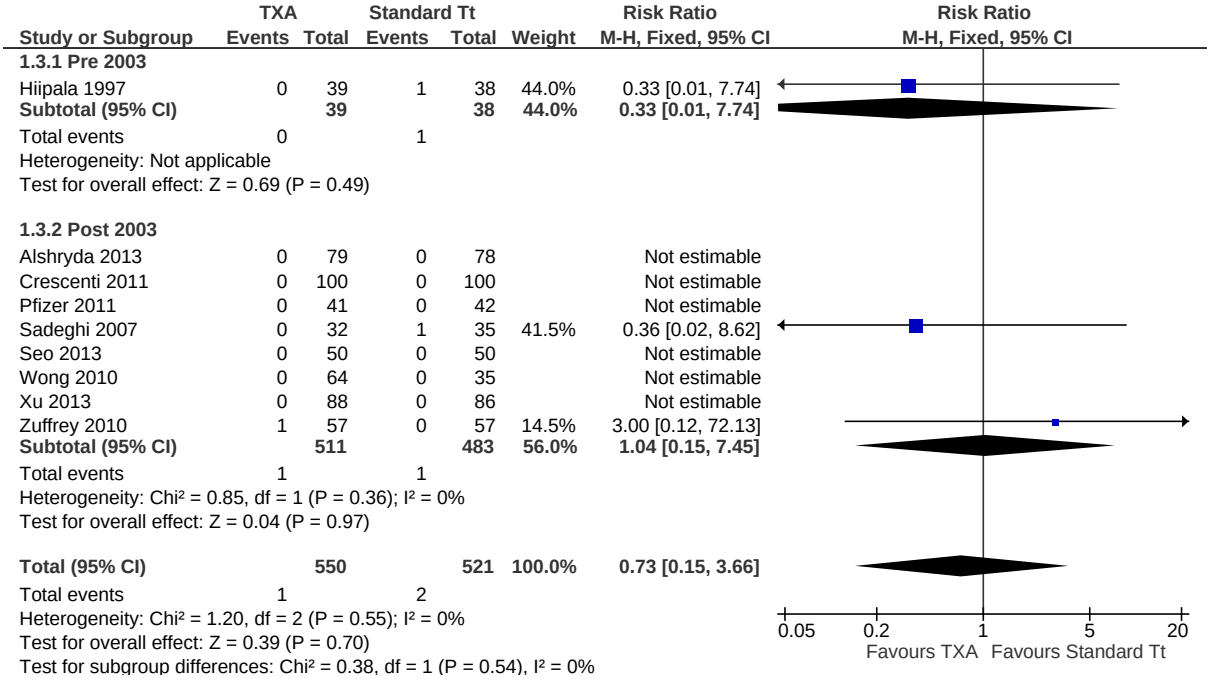
1

Figure 90: TXA versus standard treatment- Units of allogeneic blood transfused



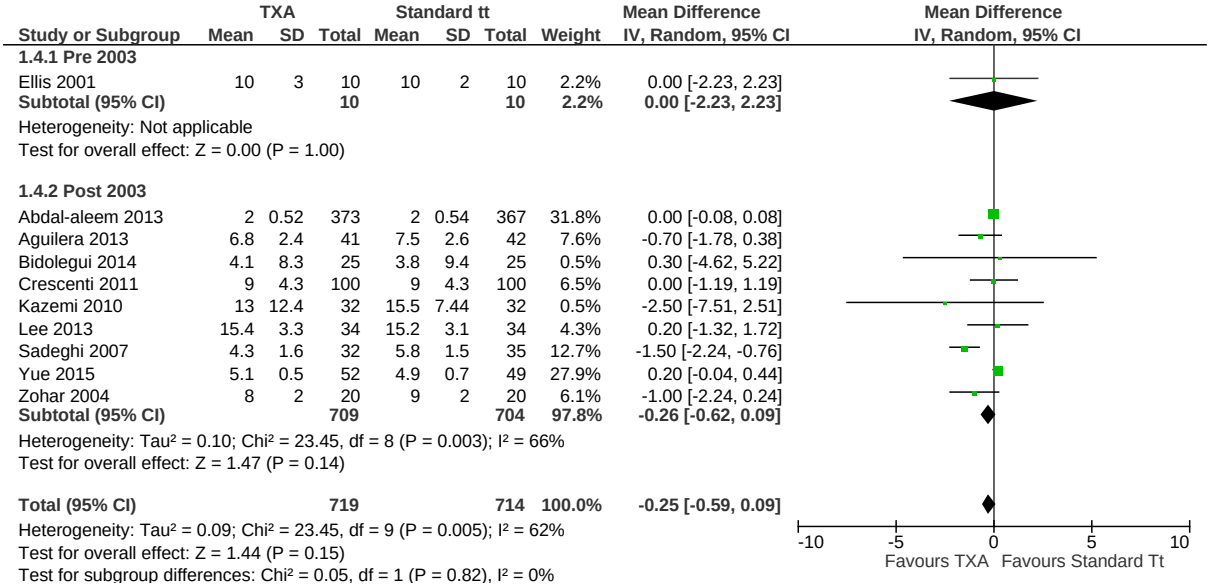
1

Figure 91: TXA versus standard treatment- Mortality



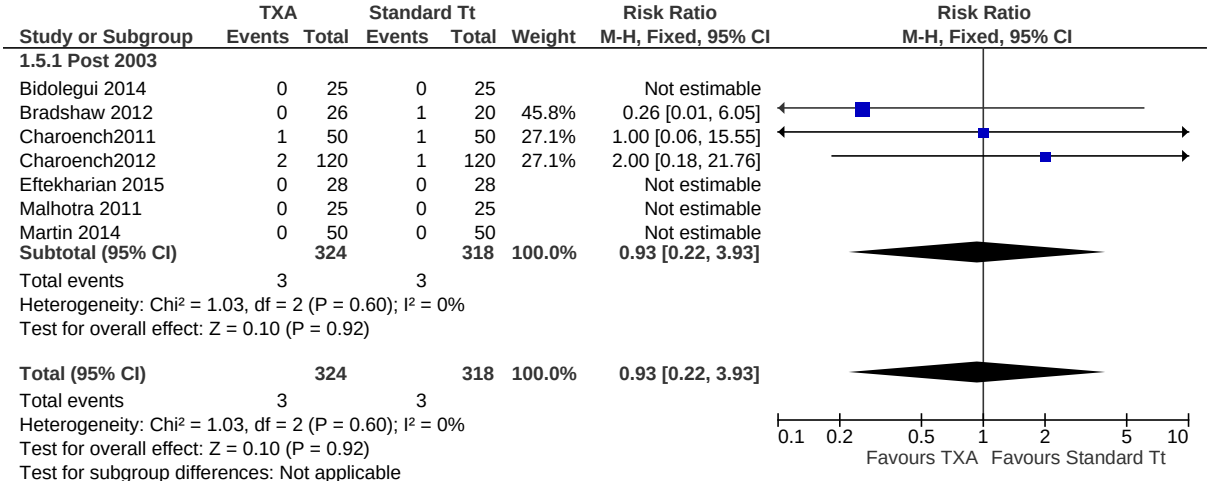
2

Figure 92: TXA versus standard treatment- Length of hospital stay



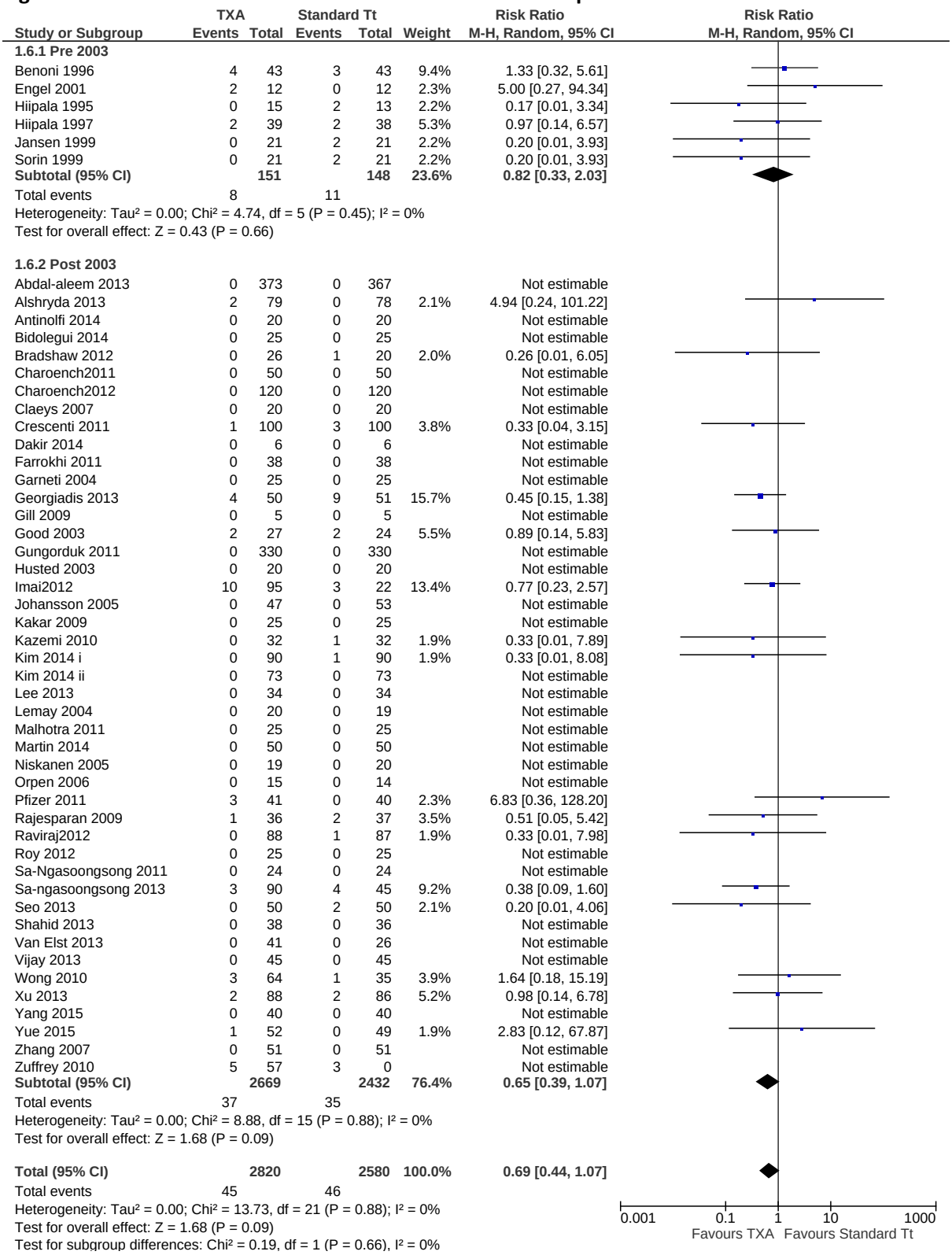
1

Figure 93: TXA versus standard treatment- Infections



2

Figure 94: TXA versus standard treatment- Thrombotic complications



K.2.3 Adult- Low risk group

Figure 95: TXA versus standard treatment- Number exposed to allogeneic blood

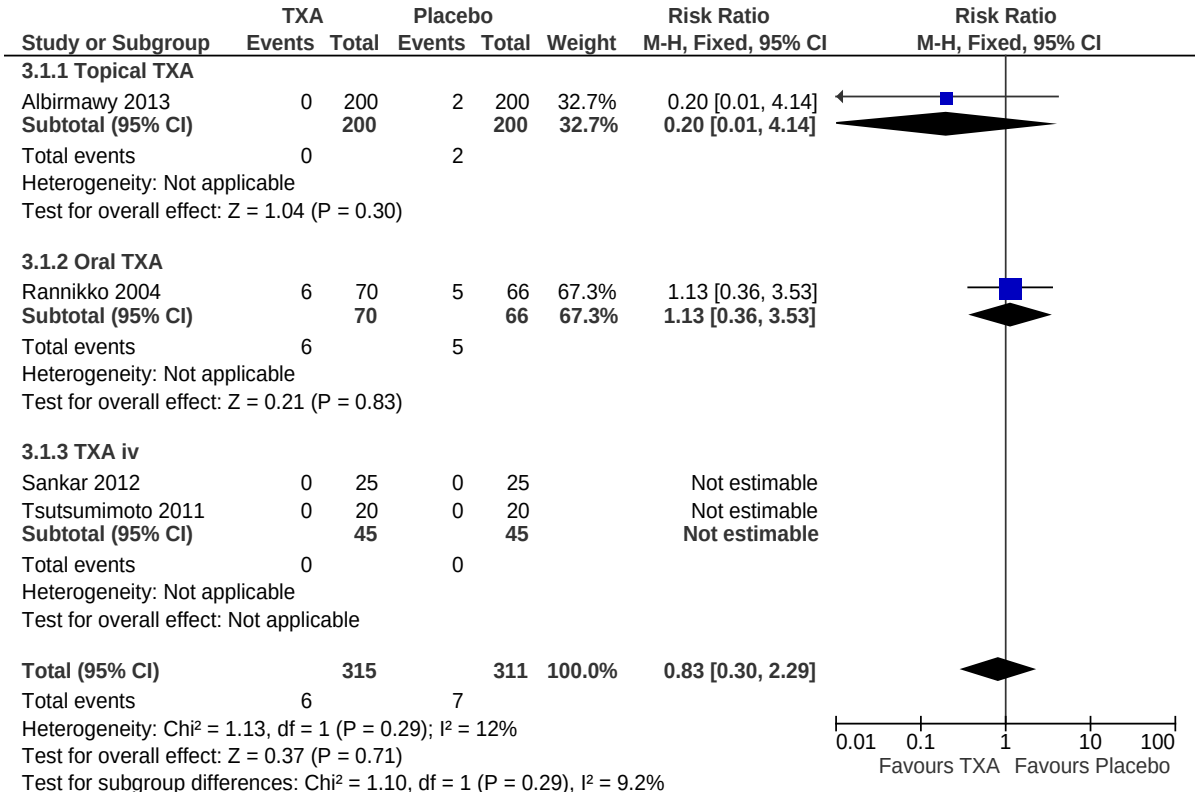


Figure 96: TXA versus standard treatment- Blood loss

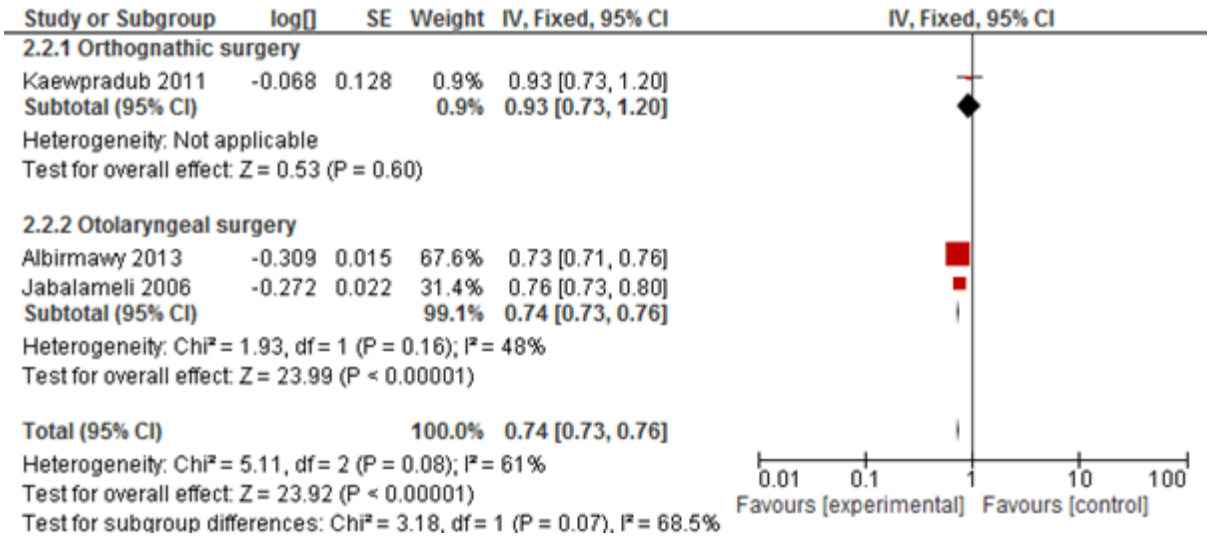
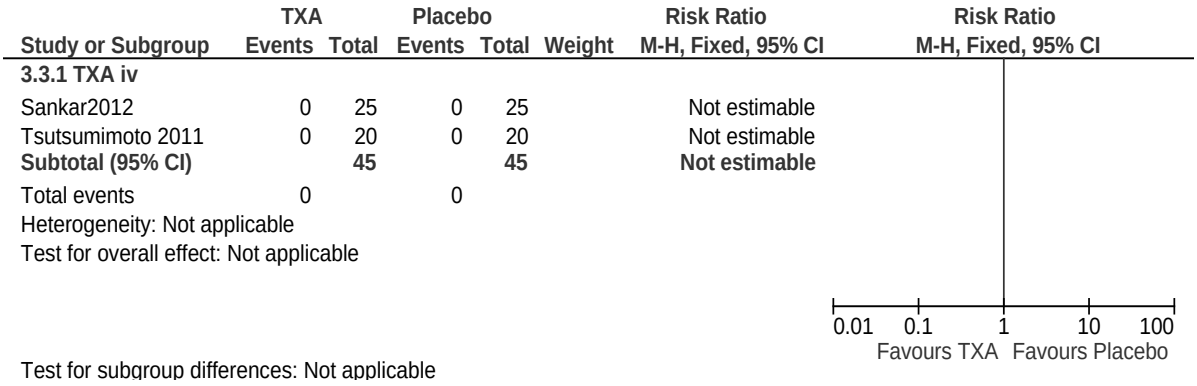


Figure 97: Thrombotic complications



K.2.4 Children - high risk

Figure 98: ICS plus TXA versus ICS- Number exposed to allogeneic blood

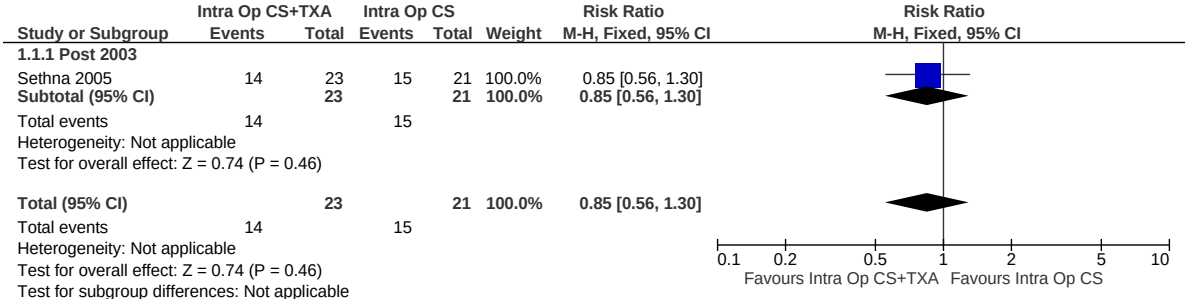


Figure 99: ICS plus TXA versus ICS- Total blood transfused

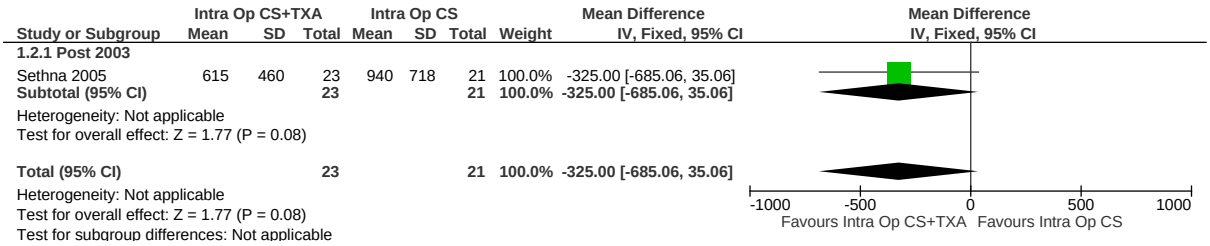


Figure 100: ICS plus TXA versus ICS- Total blood loss

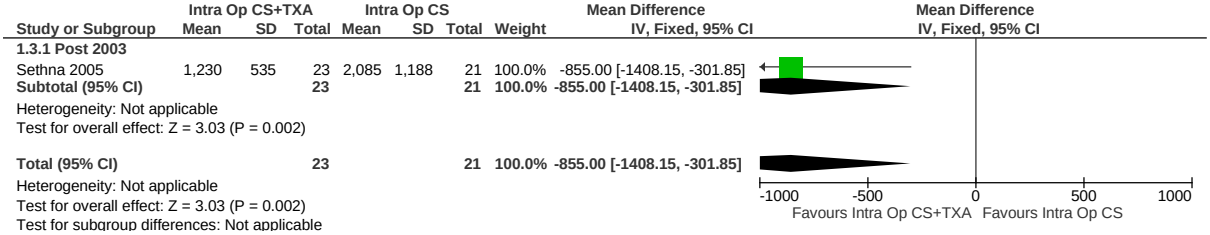
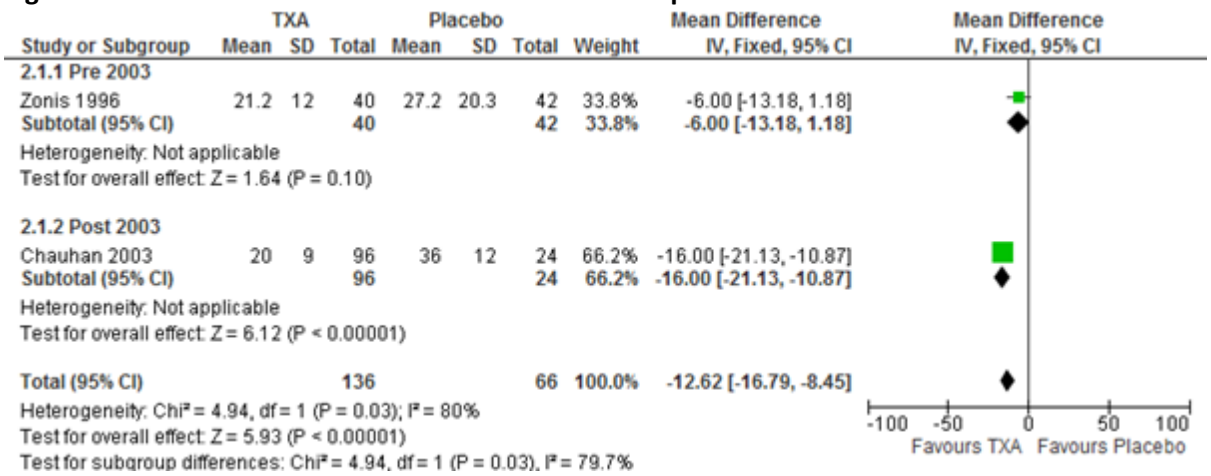
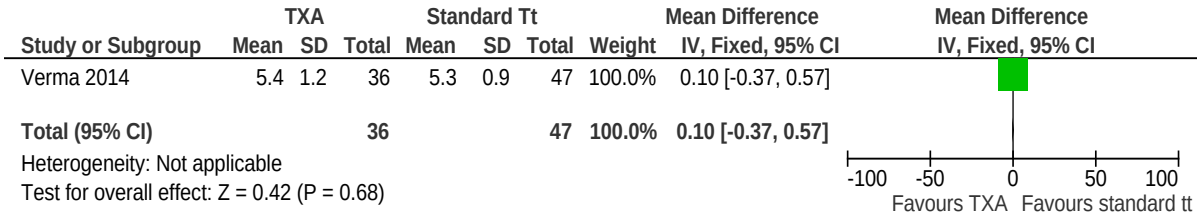


Figure 101: TXA versus standard treatment- Post-operative blood loss



1

Figure 102: Length of hospital stay



2

K.3 Red blood cells

K.3.1 RBC thresholds - adults

Figure 103: Number of patients needing allogeneic transfusions

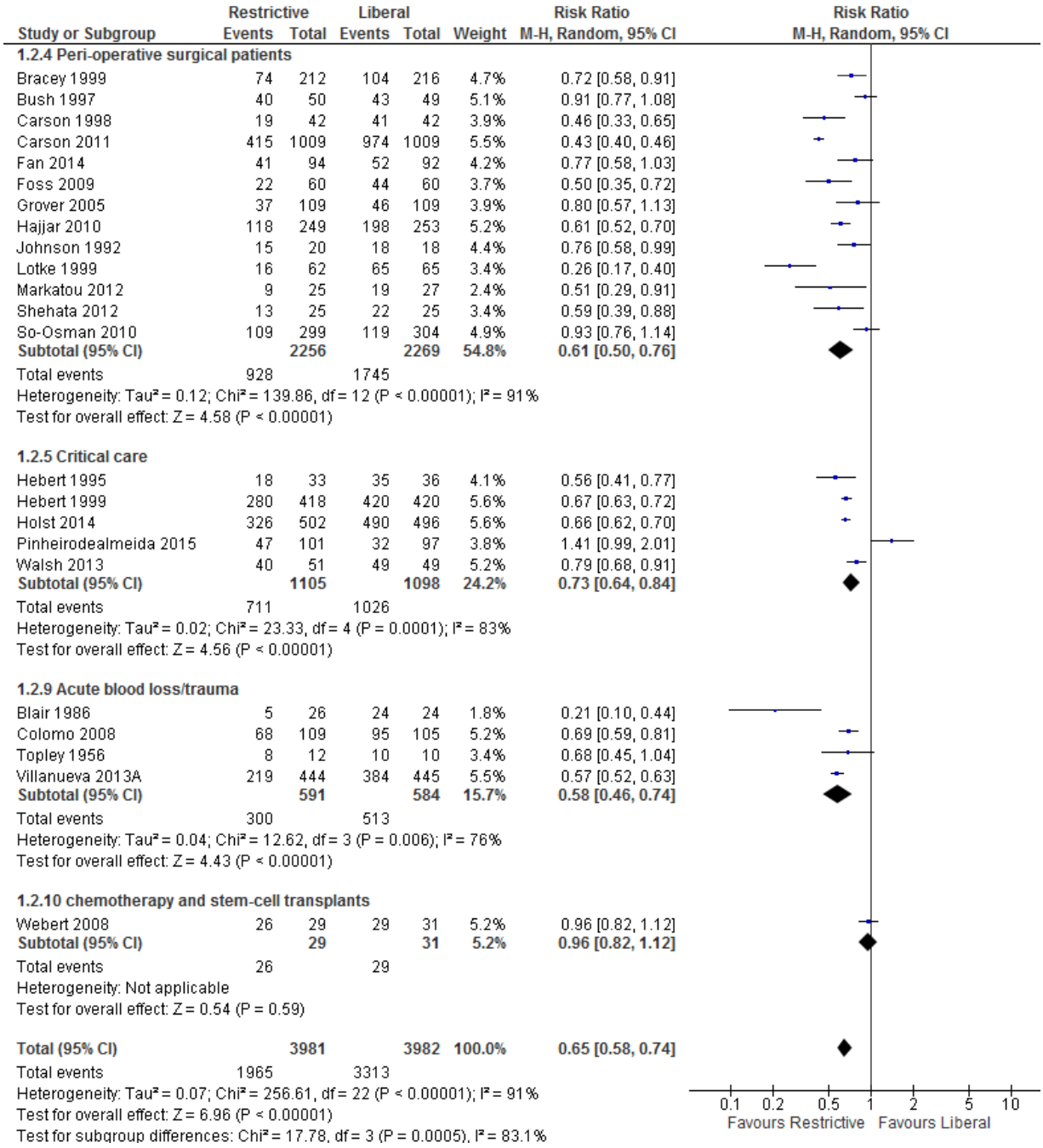
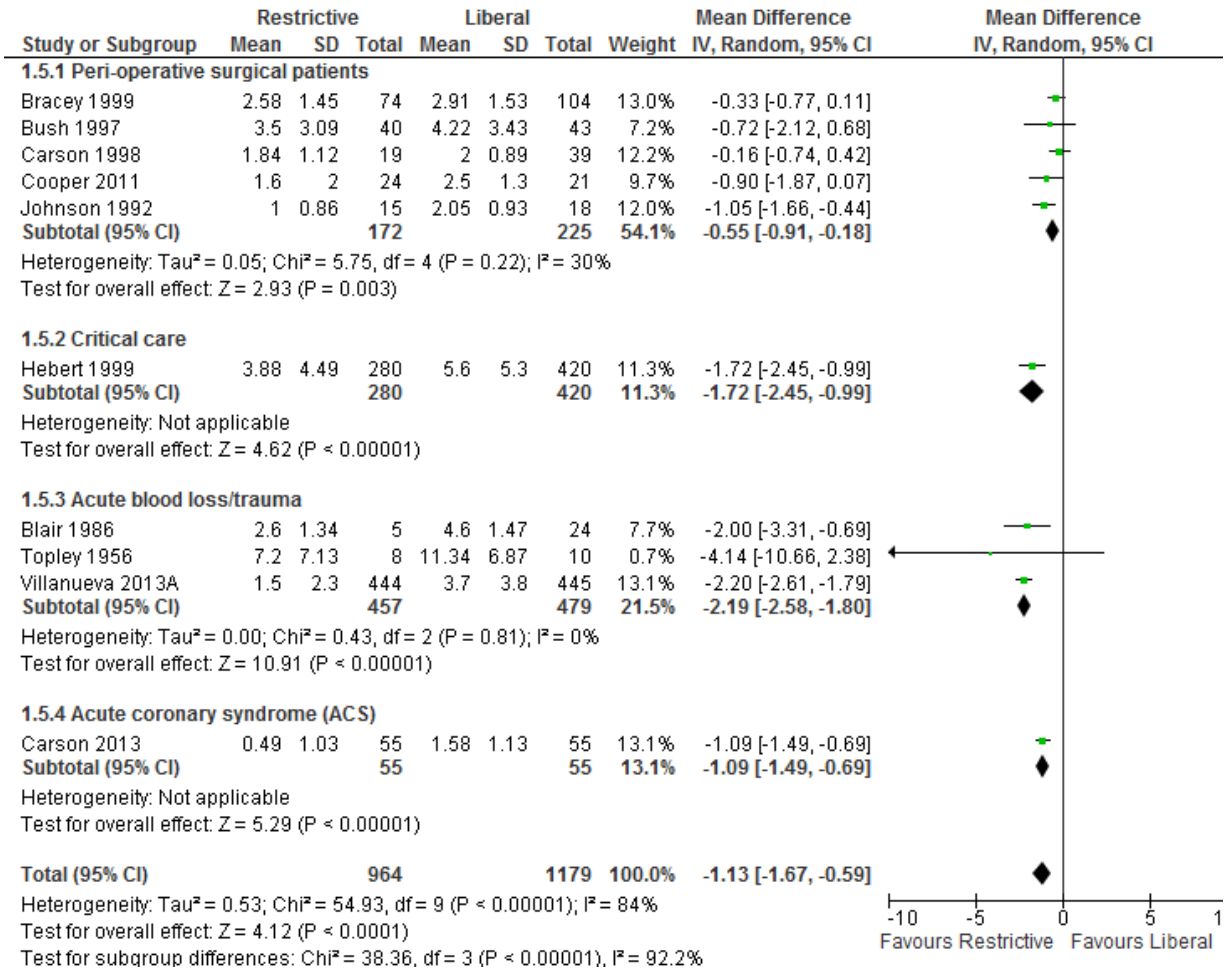
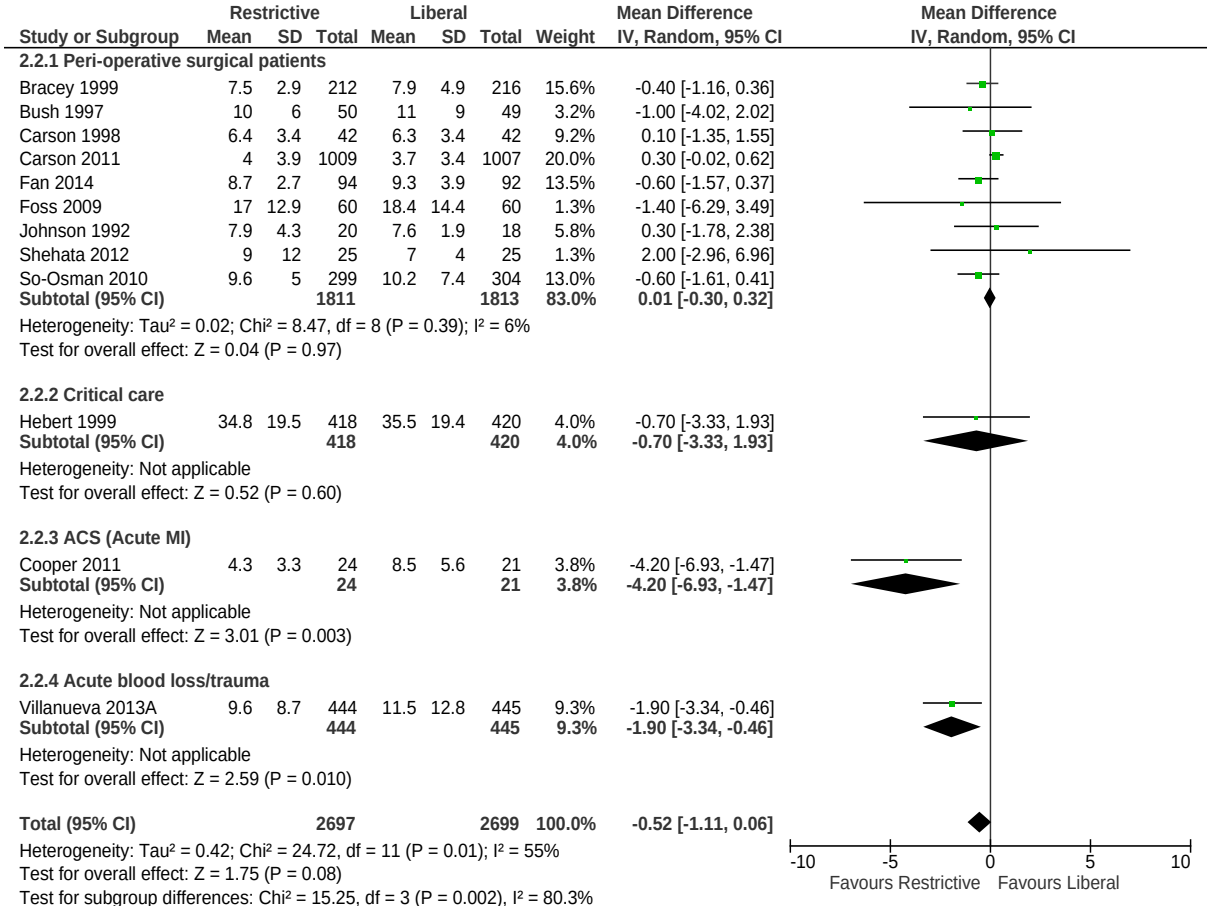


Figure 104: Number of units of blood transfused in those transfused (adults)



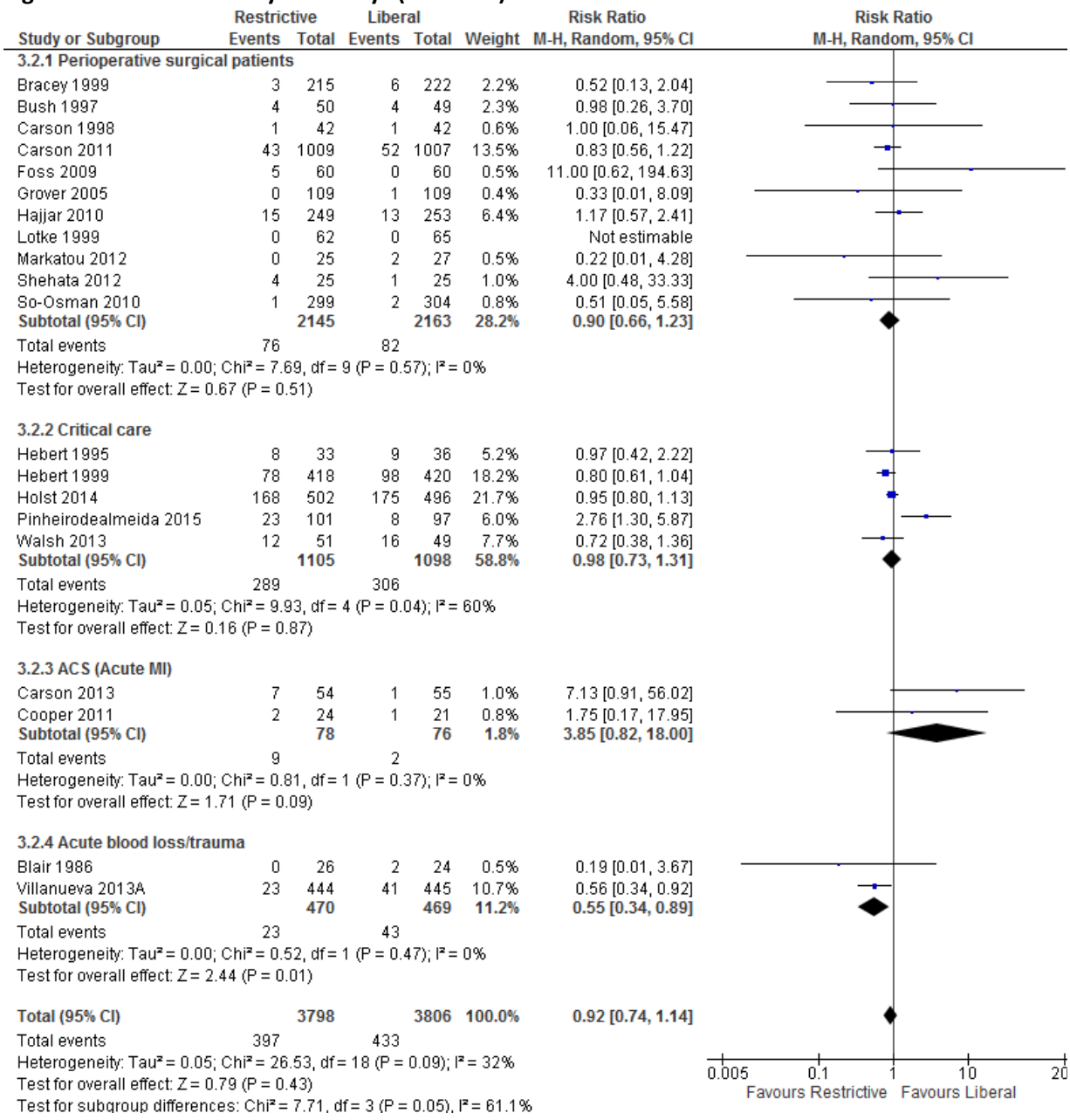
1

Figure 105: Length of stay in hospital (adults)



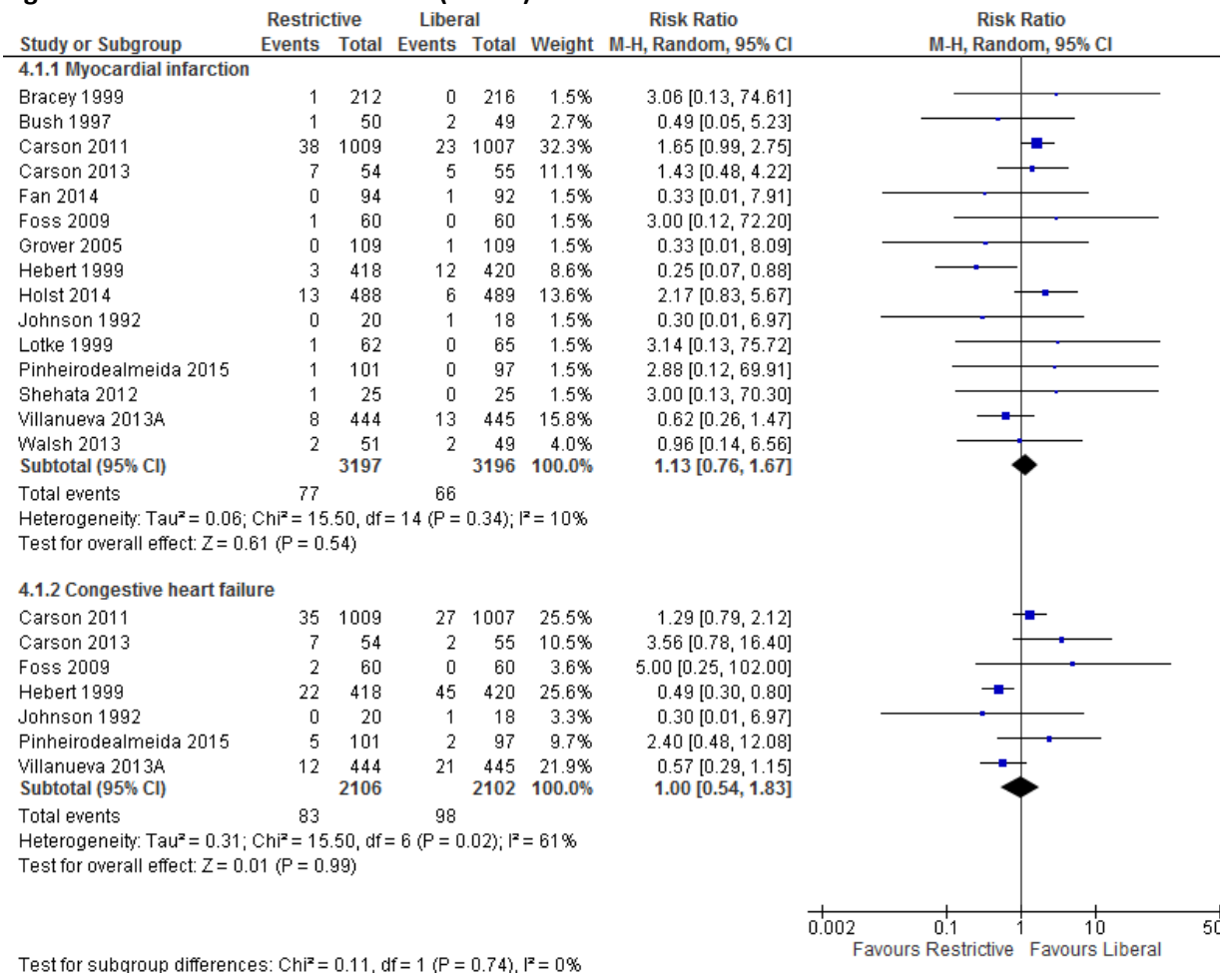
1

Figure 106: Mortality at 30 days (all-cause) -adults



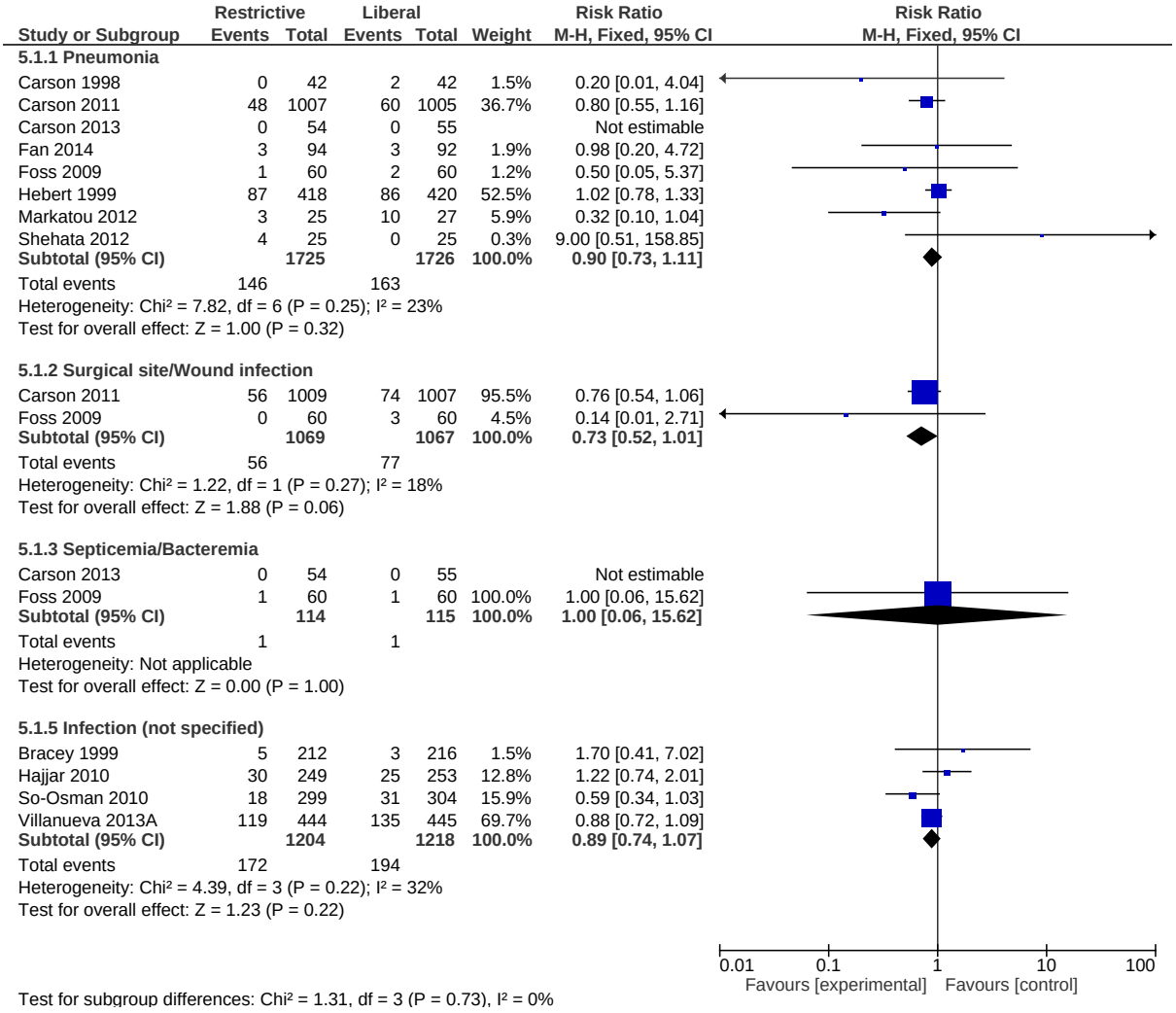
1

Figure 107: New cardiac events (adults)



1

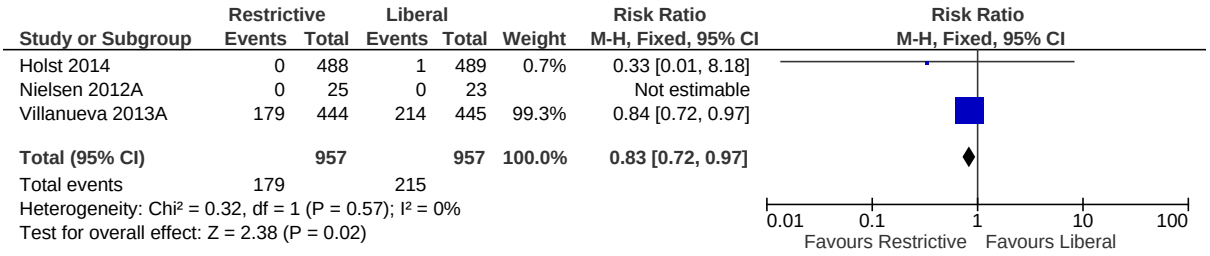
Figure 108: Infections (adults)



Test for subgroup differences: Chi² = 1.31, df = 3 (P = 0.73), I² = 0%

1

Figure 109: Adverse events (adults)



2

Figure 110: Adverse events (adults)-TACO

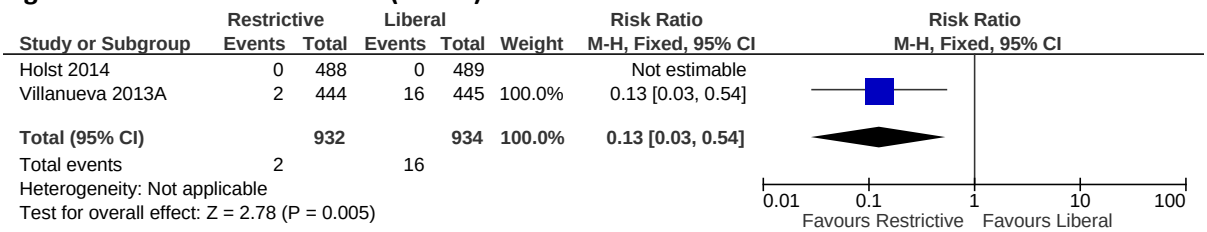
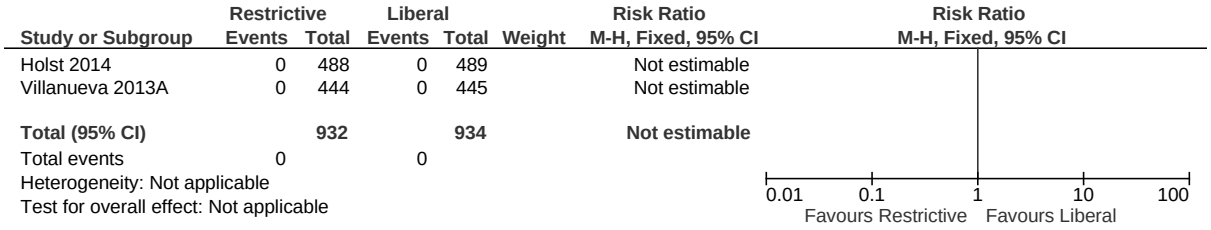


Figure 111: Adverse events (adults)-TRALI



K.3.2 RBC thresholds - children

Figure 112: Total RBC ml/patient (children)

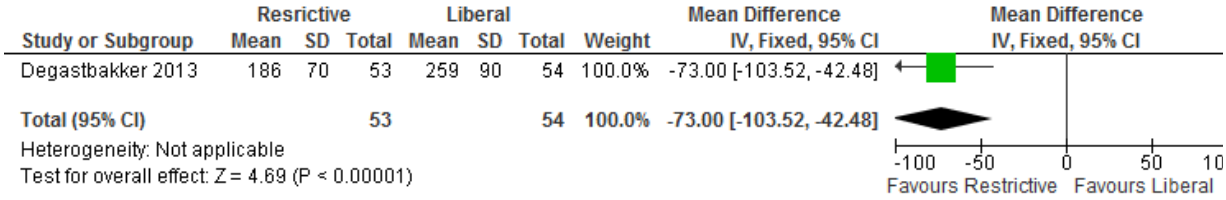


Figure 113: Number of units transfused-children

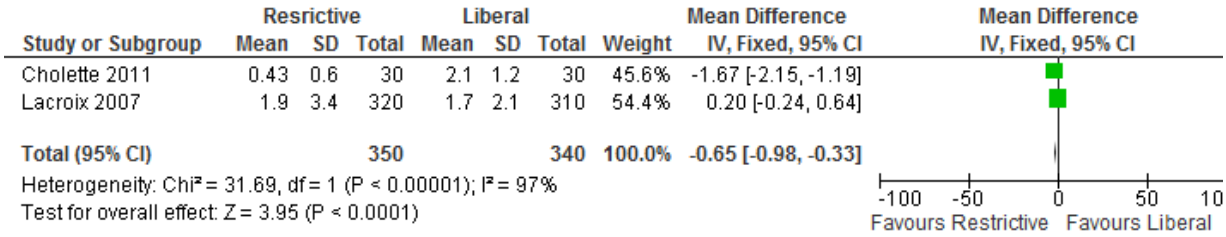


Figure 114: Number of patients needing transfusion -children

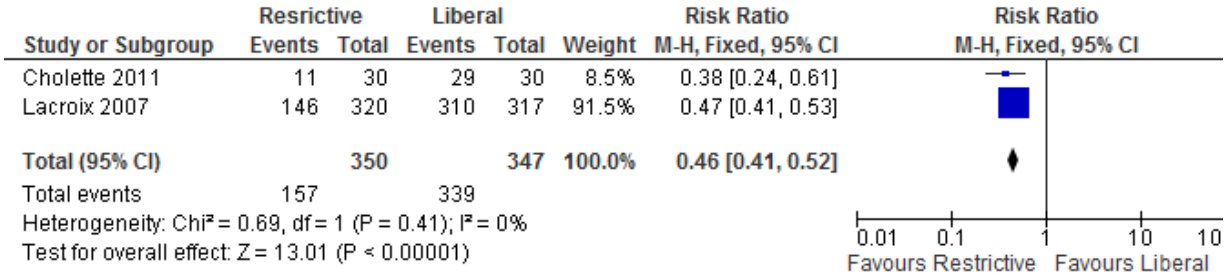
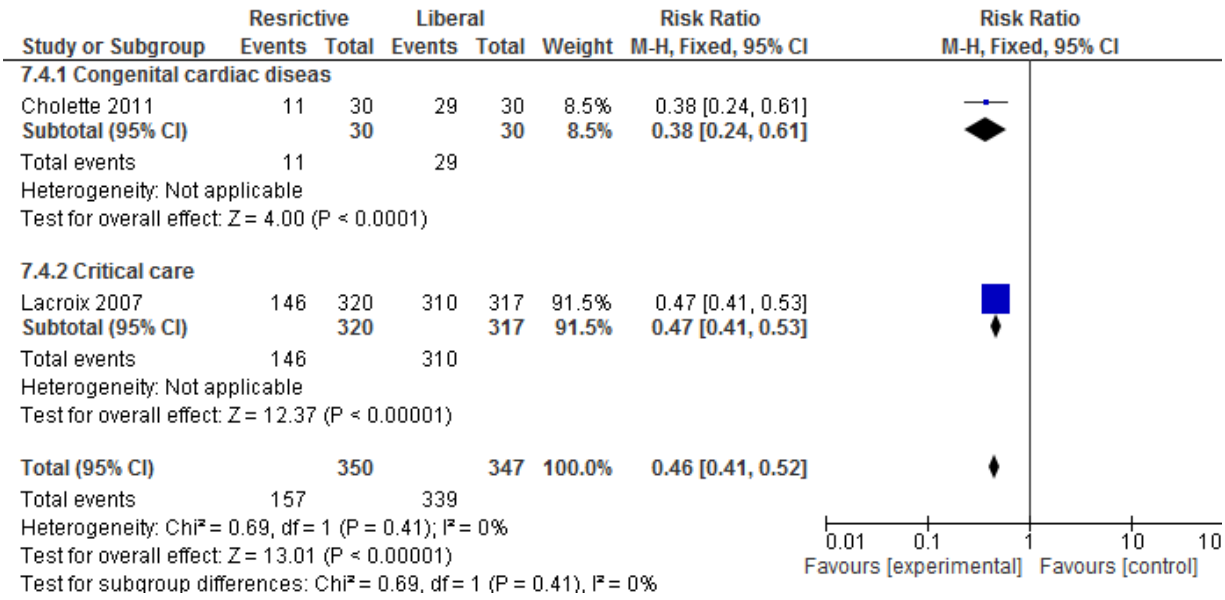
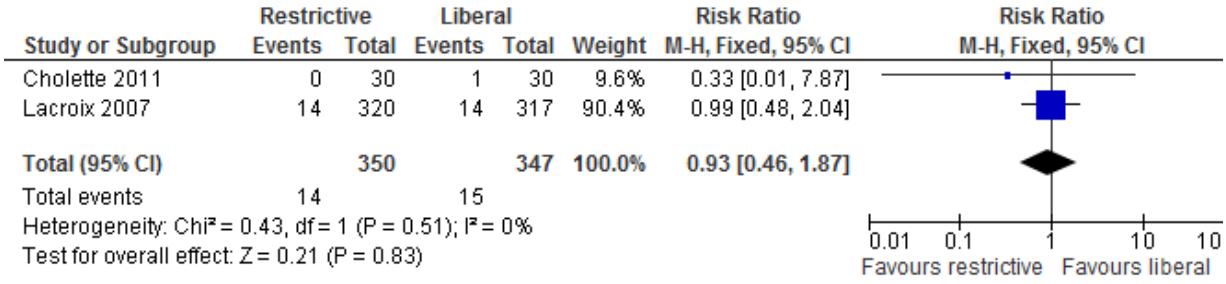


Figure 115: Number of patients needing transfusion -children (sub-group analysis)



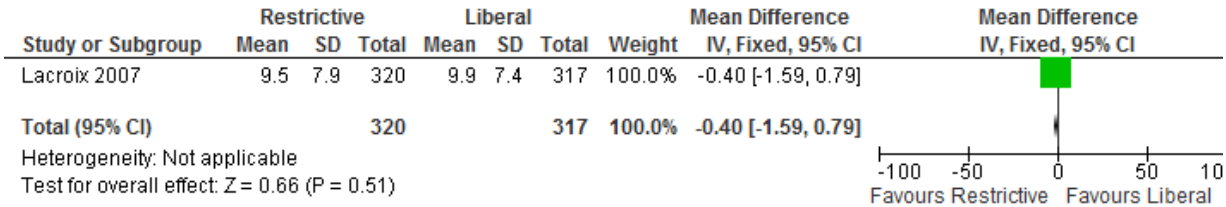
1

Figure 116: Mortality at 30 days (all-cause)- children



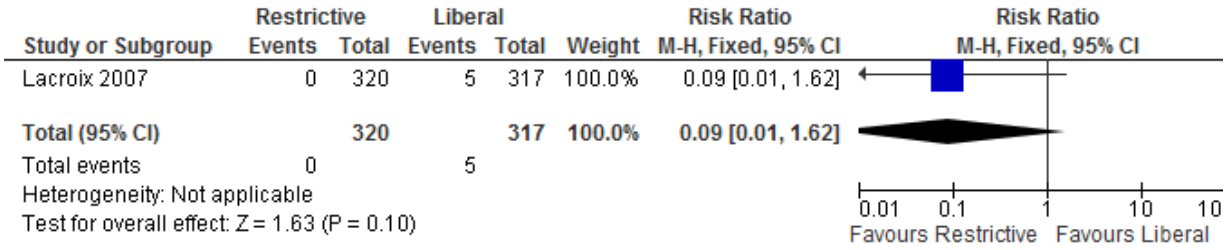
2

Figure 117: ICU length of stay (children)



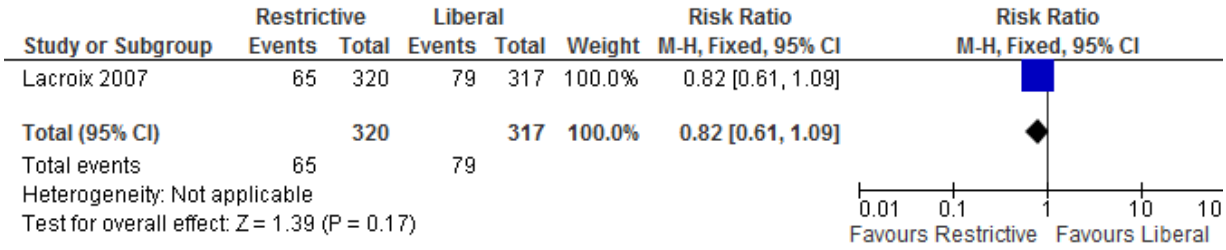
3

Figure 118: Pulmonary oedema (children)



1

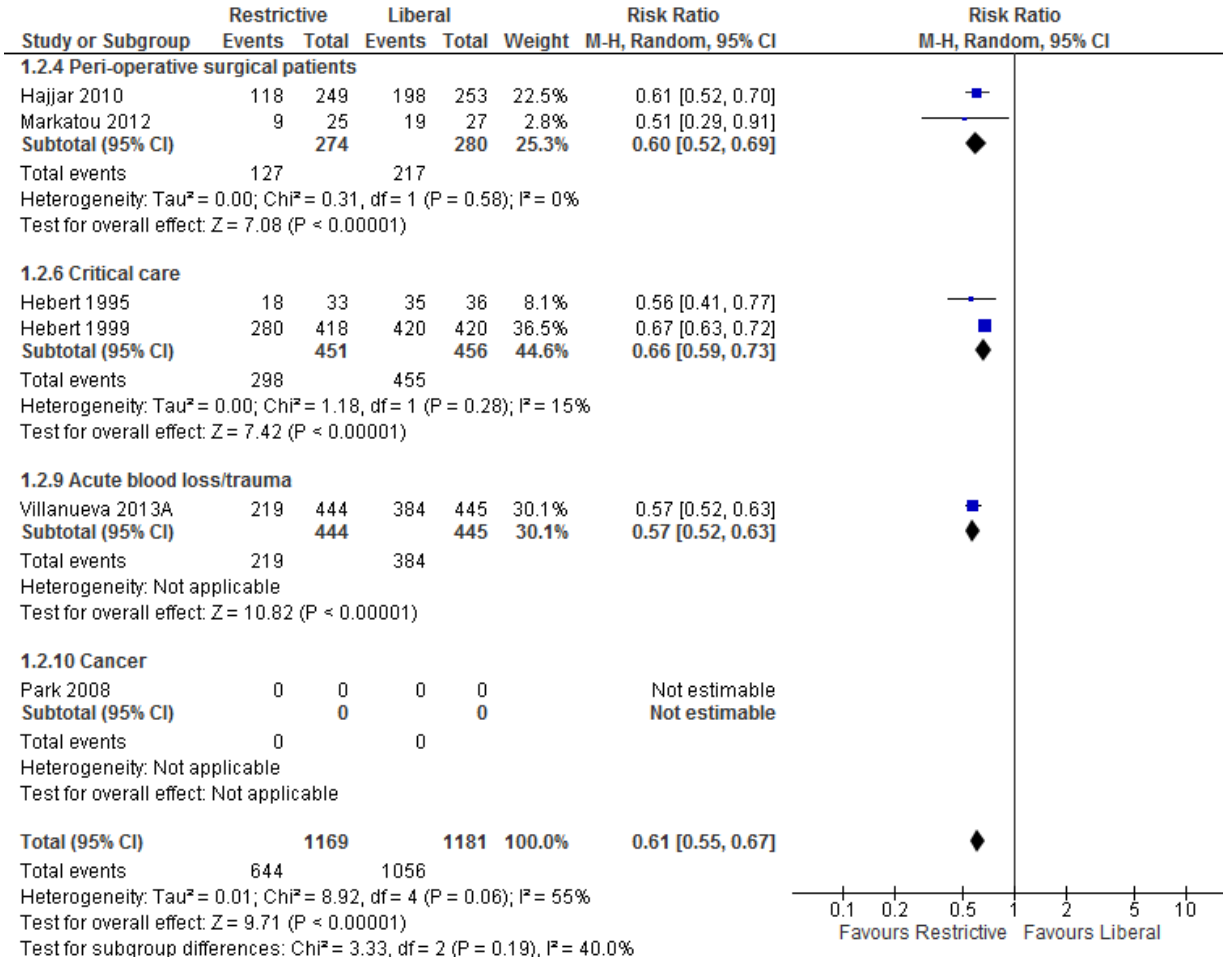
Figure 119: Infections (nosocomial infections) -children



2

K.3.3 Target haemoglobin concentrations for blood transfusion

Figure 120: Number of patients needing transfusions-adults



K.4 Target haemoglobin concentrations for blood transfusion

Figure 121: Number of patients needing transfusions-adults

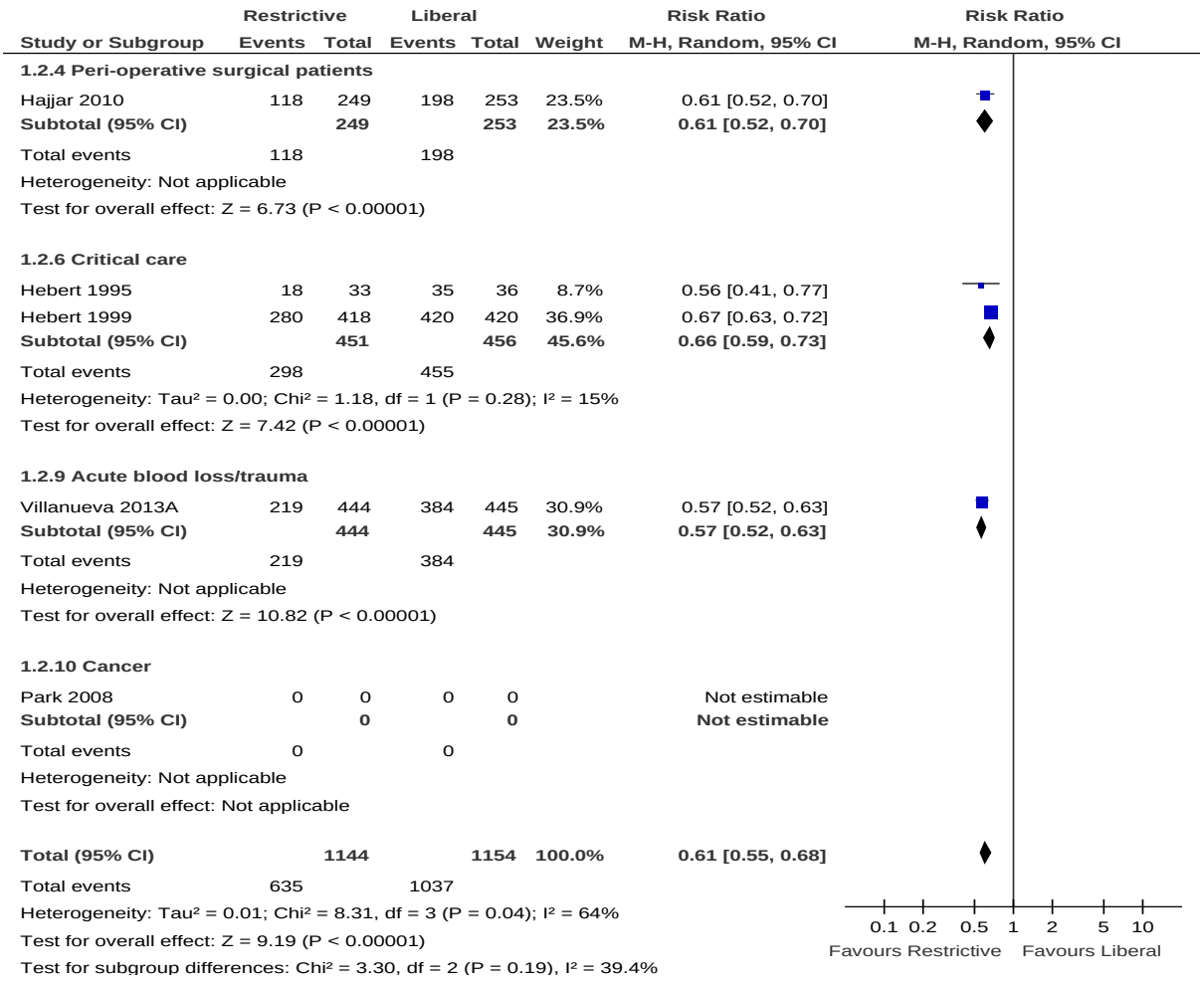


Figure 122: Number of units of blood transfused (in those who were transfused)-adults

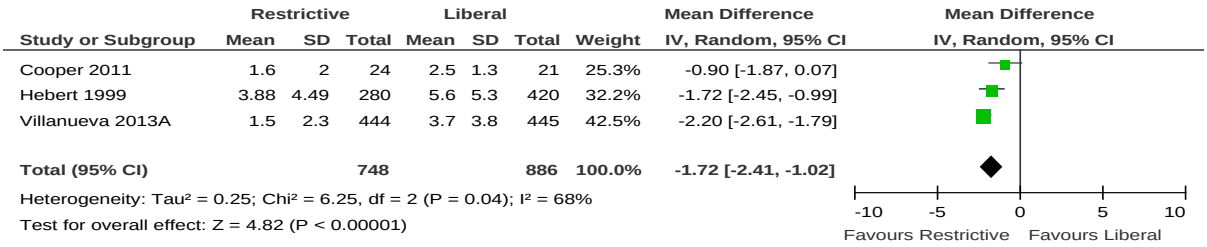
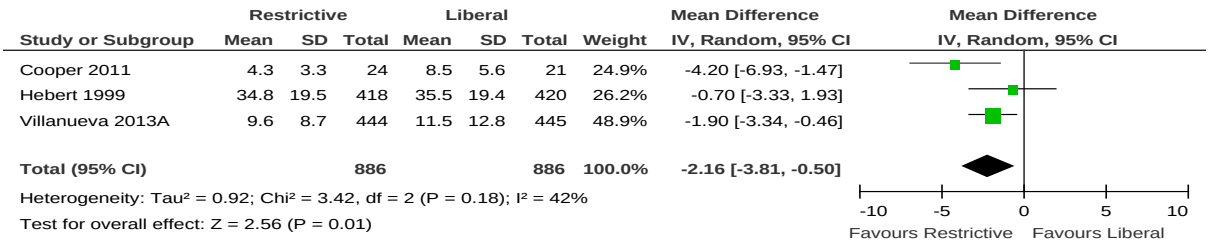
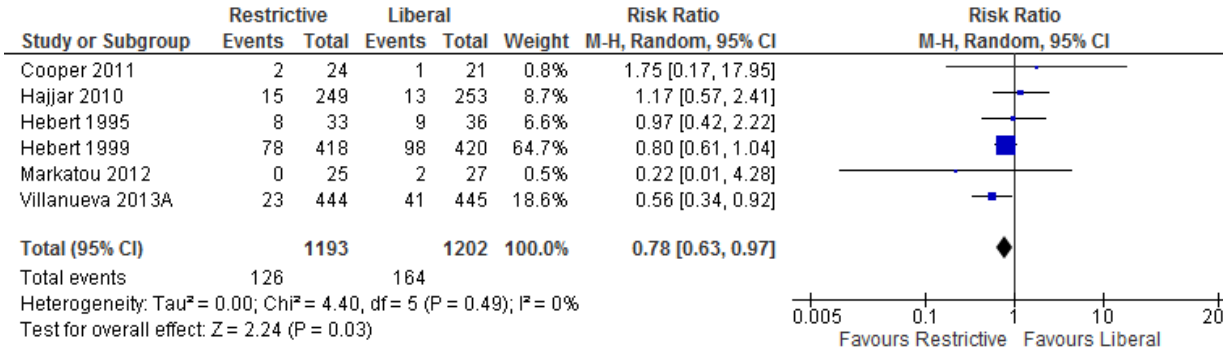


Figure 123: Length of hospital stay-adults



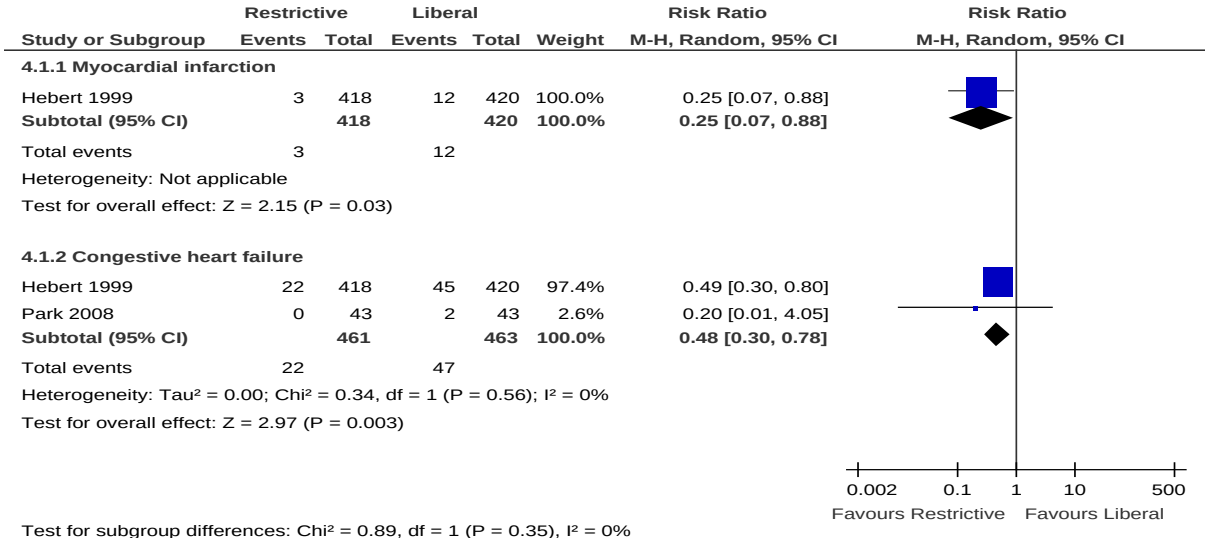
1

Figure 124: Mortality at 30 days (all-cause)-adults



2

Figure 125: New cardiac events-adults



3

Figure 126: Infection-adults

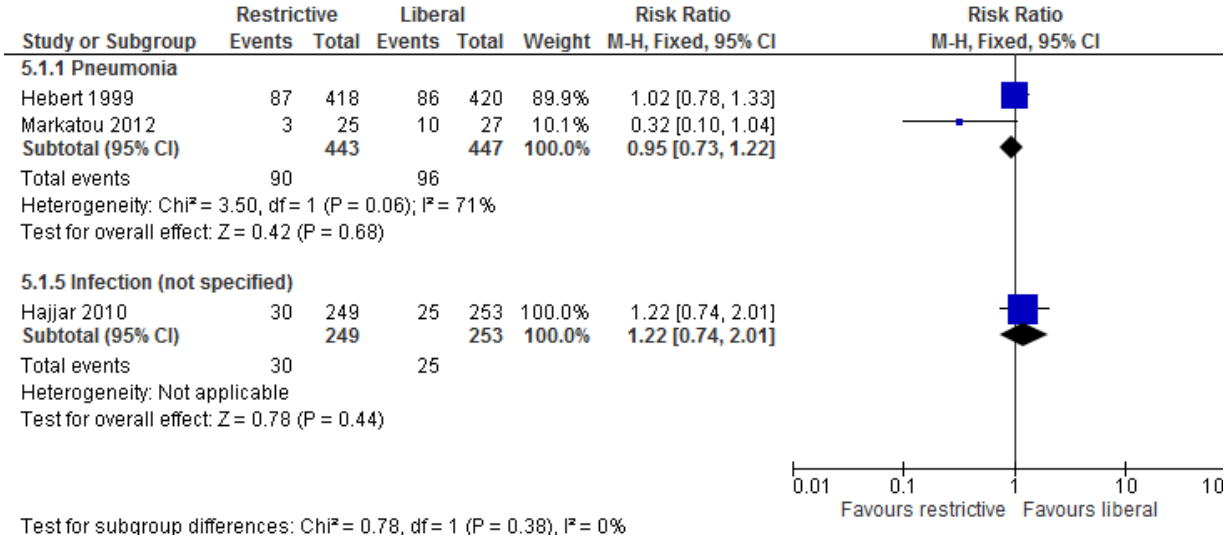


Figure 127: Adverse events (as defined by study)-adults

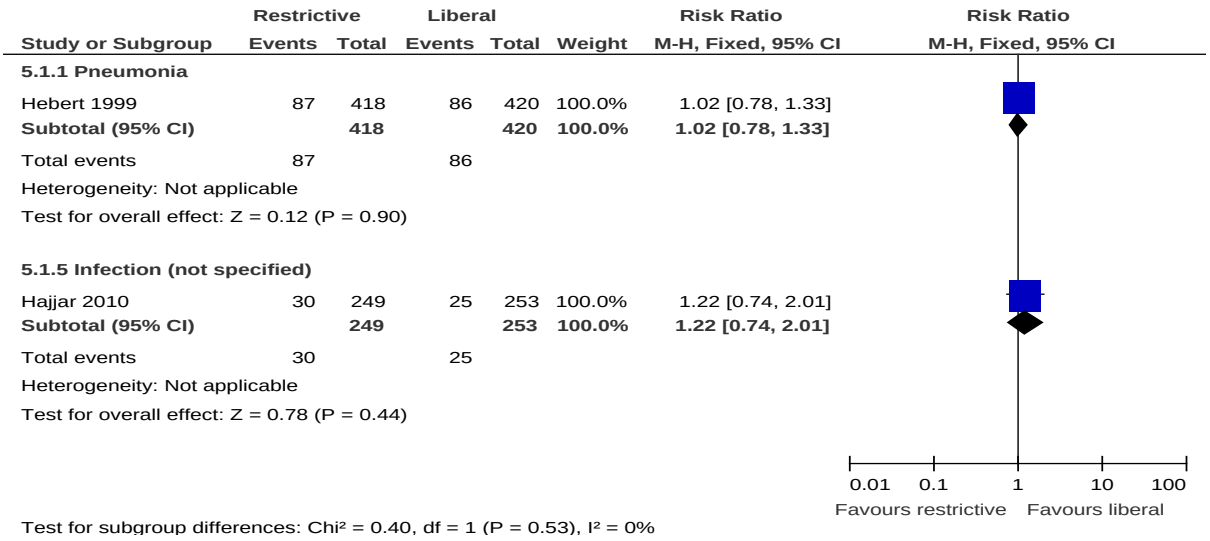


Figure 128: Number of patients needing transfusion- children (critical care)

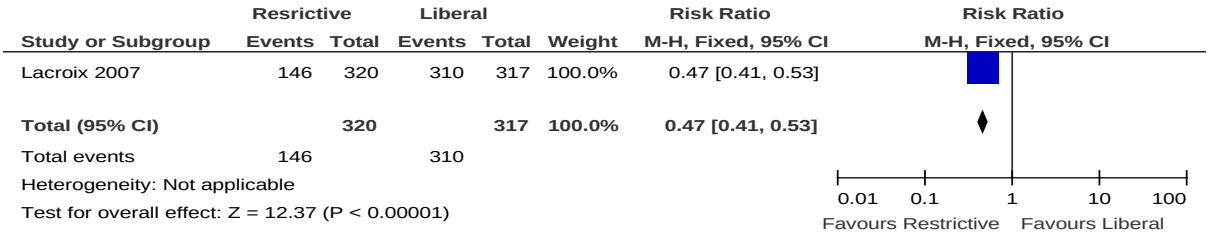


Figure 129: Volume of RBC transfused in ml/patient- children (critical care)

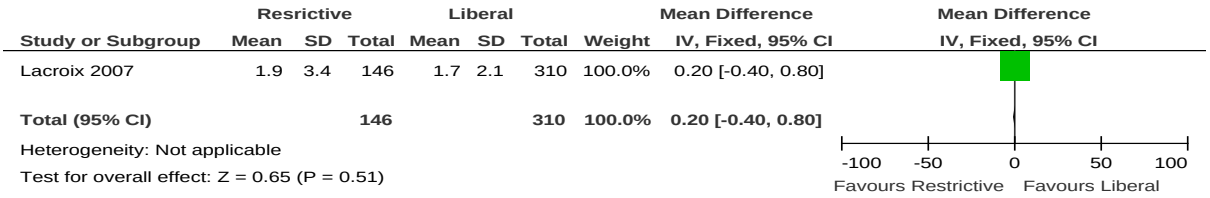


Figure 130: Mortality at 30 days- children (critical care)

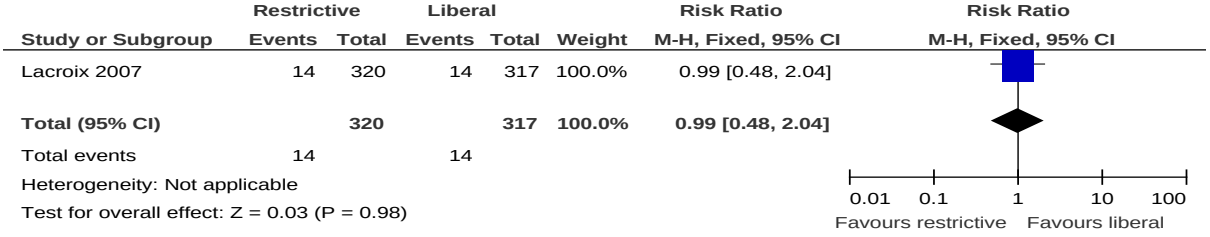
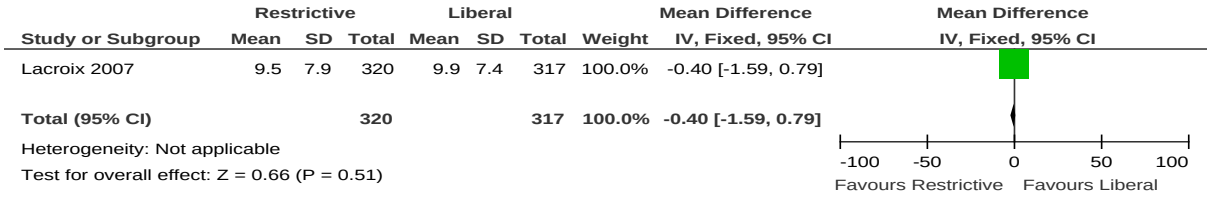
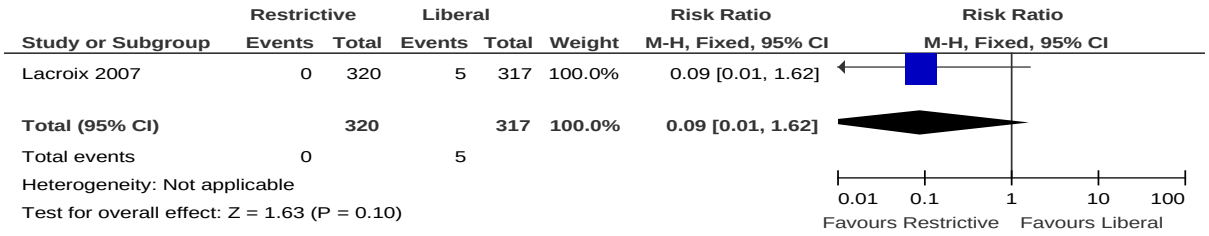


Figure 131: Length of ICU stay-children (critical care)



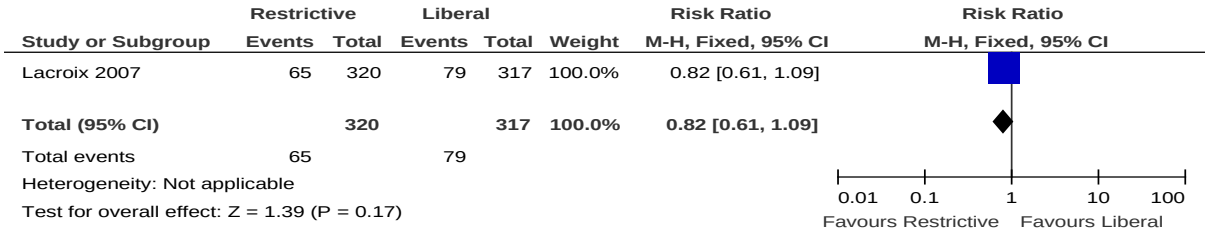
1

Figure 132: Pulmonary oedema- children (critical care)



2

Figure 133: Nosocomial infections- children (critical care)

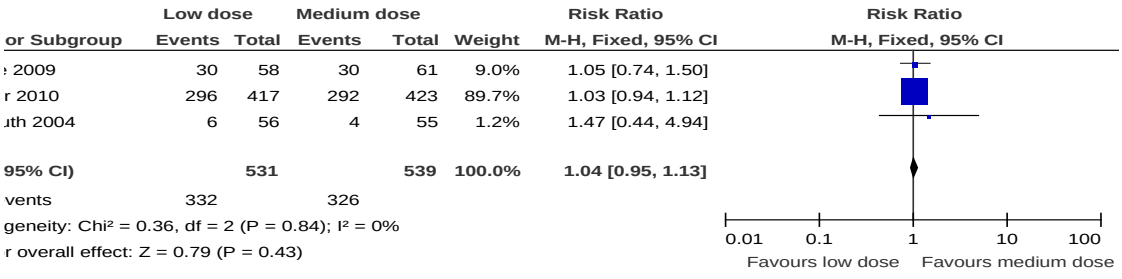


3

4 K.5 Platelets

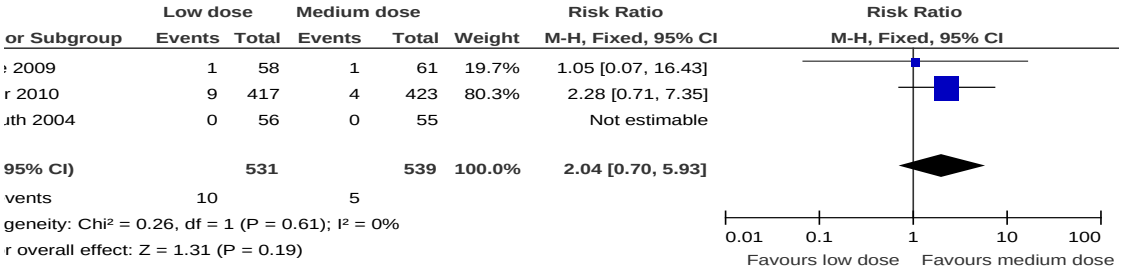
5 K.5.1 Low dose versus medium dose

Figure 134: Number of patients with bleeding (WHO grade 2 and above)



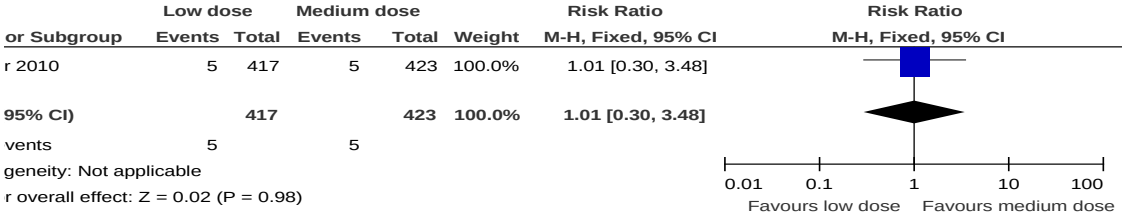
6

Figure 135: All-cause mortality at 30 days



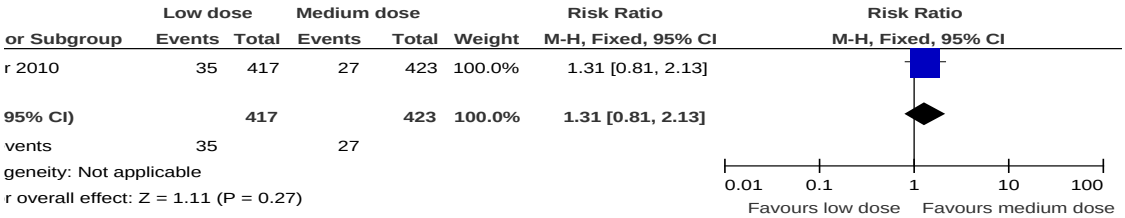
1

Figure 136: Infections



2

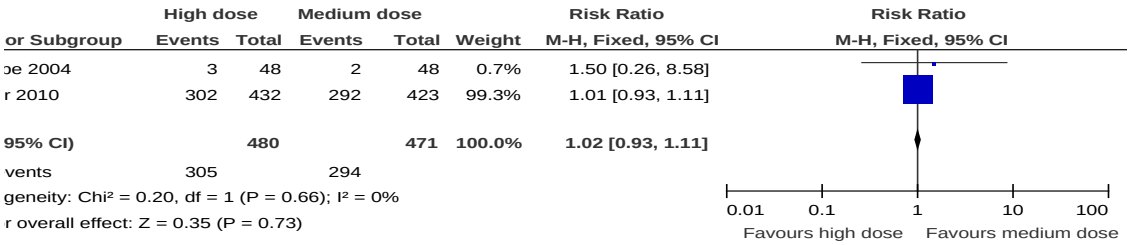
Figure 137: Serious adverse event (any)



3

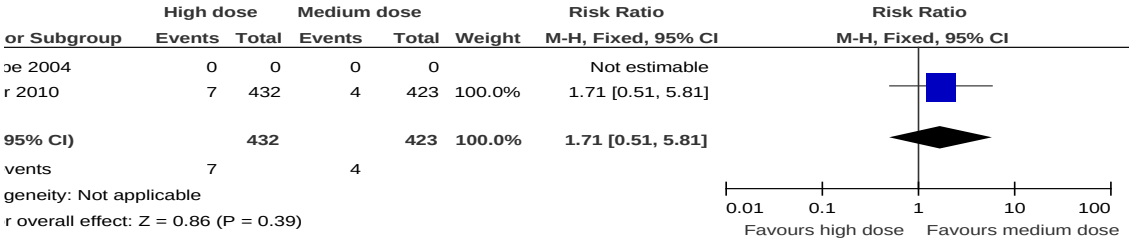
4 K.5.2 High dose versus medium dose

Figure 138: Number of patients with bleeding (WHO grade 2 and above)



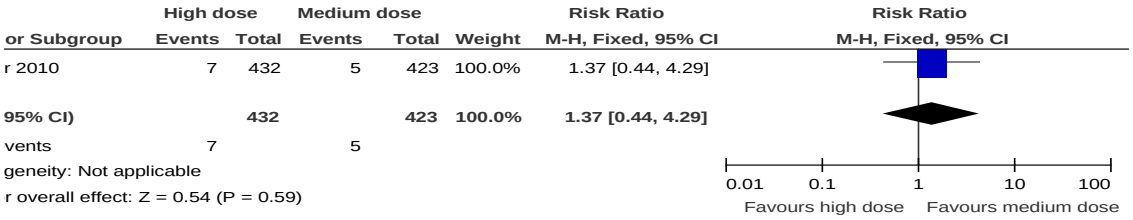
5

Figure 139: All-cause mortality at 30 days



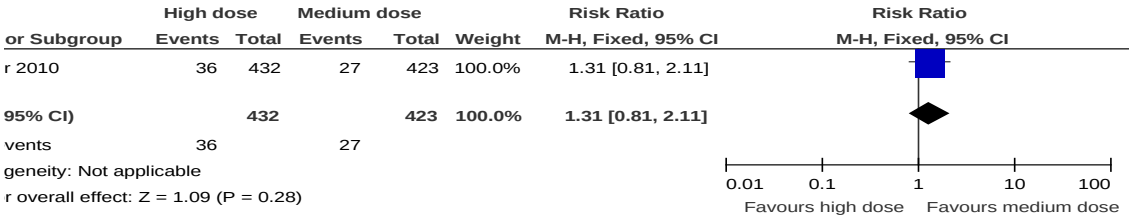
1

Figure 140: Infections



2

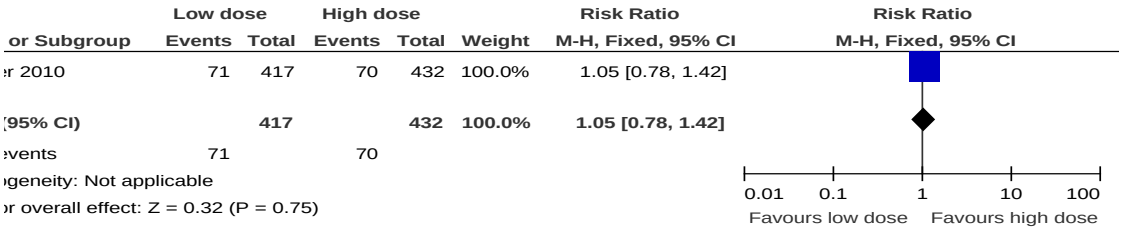
Figure 141: Serious adverse events (any)



3

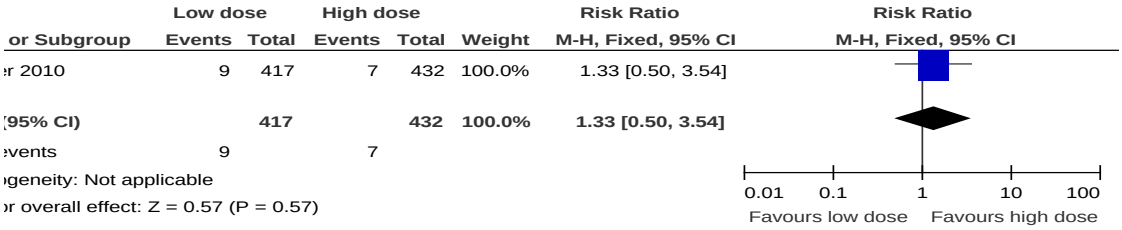
4 **K.5.3 Low dose versus high dose**

Figure 142: Number of patients with bleeding (WHO grade 2 and above)



5

Figure 143: All-cause mortality at 30 days



1

Figure 144: Infections

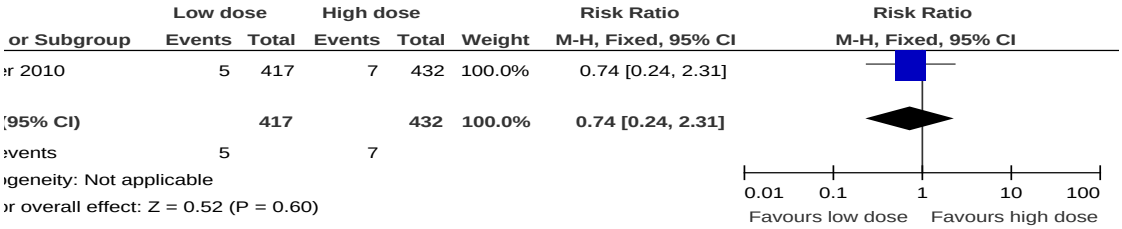


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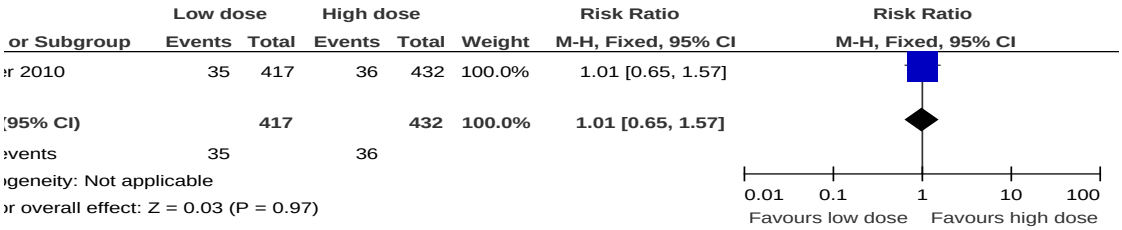
Figure 145: Serious adverse events (any)



3

K.5.4 Platelet thresholds and Targets

Prophylactic transfusion versus no prophylactic transfusion - adults who are haematology patients (non-bleeding patients)

Figure 146: Number of patients with bleeding events (WHO grade 2 or higher)

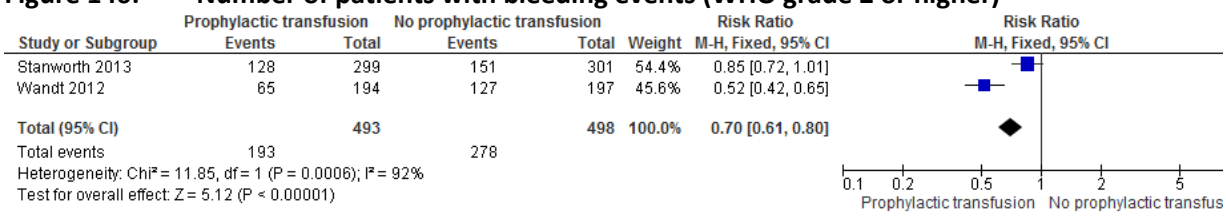


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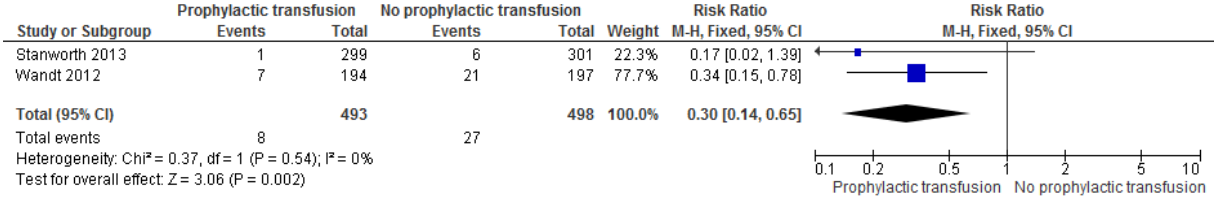
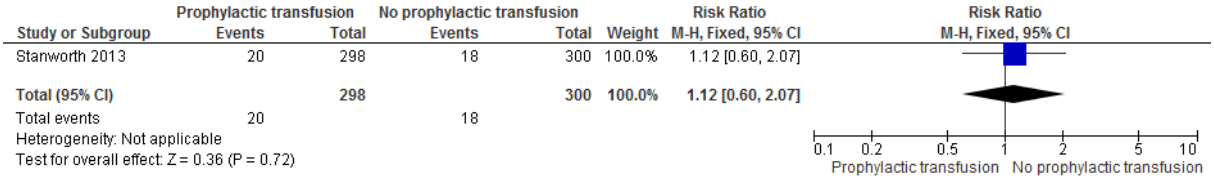
Figure 147: Number of patients with major bleeding events (WHO grade 3 or 4)



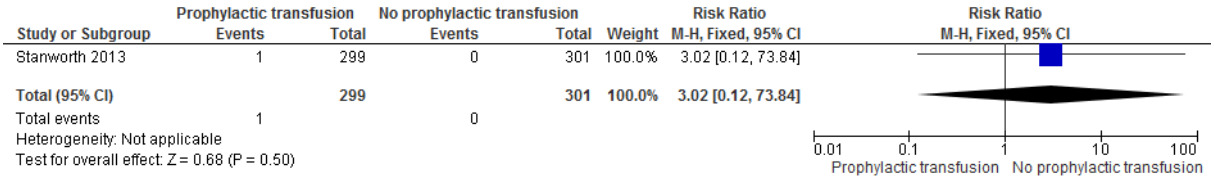
1

Figure 148: Serious adverse events (including sepsis and respiratory deterioration)



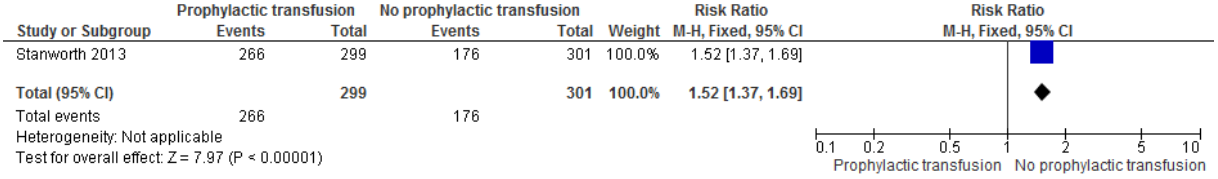
2

Figure 149: Transfusion related serious adverse event (urticarial and angioedema)



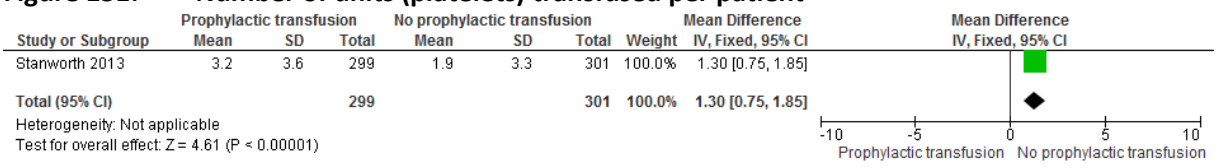
3

Figure 150: Number of patients needing platelet transfusion



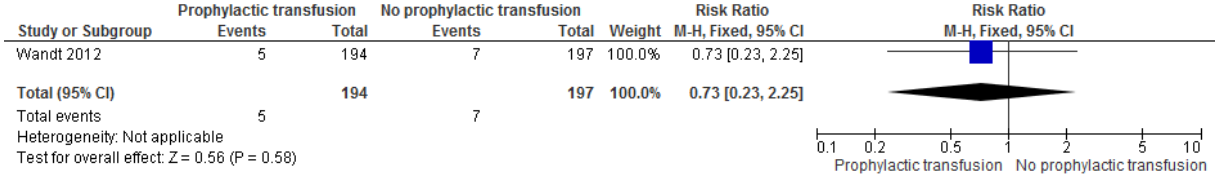
4

Figure 151: Number of units (platelets) transfused per patient



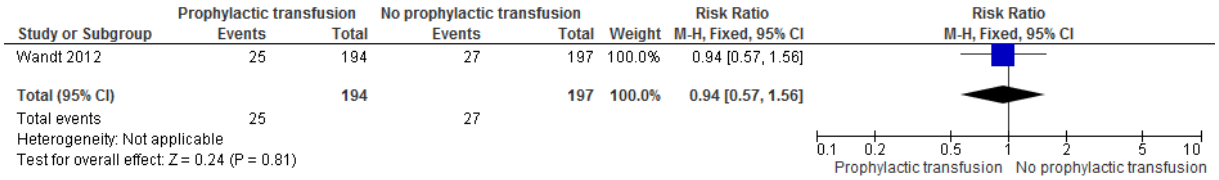
5

Figure 152: Mortality (all cause)



1

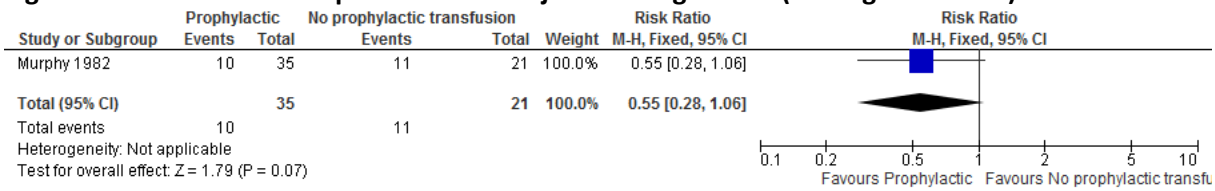
Figure 153: Side effects of transfusion (not specified)



2

3 **K.5.5 Prophylactic transfusion versus no prophylactic transfusion - children who are**
4 **haematology patients (non-bleeding patients)**

Figure 154: Number of patients with major bleeding events (WHO grade 3 or 4)

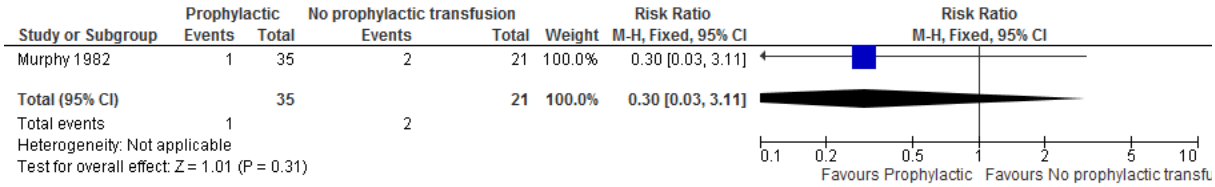


5

Figure 155: Mortality (all cause) 3 years

6

Figure 156: Mortality from bleeding (3 years)



7

K.5.6 Low threshold versus high threshold - adults who are haematology patients (non-bleeding patients)

Figure 157: Mortality (all cause)

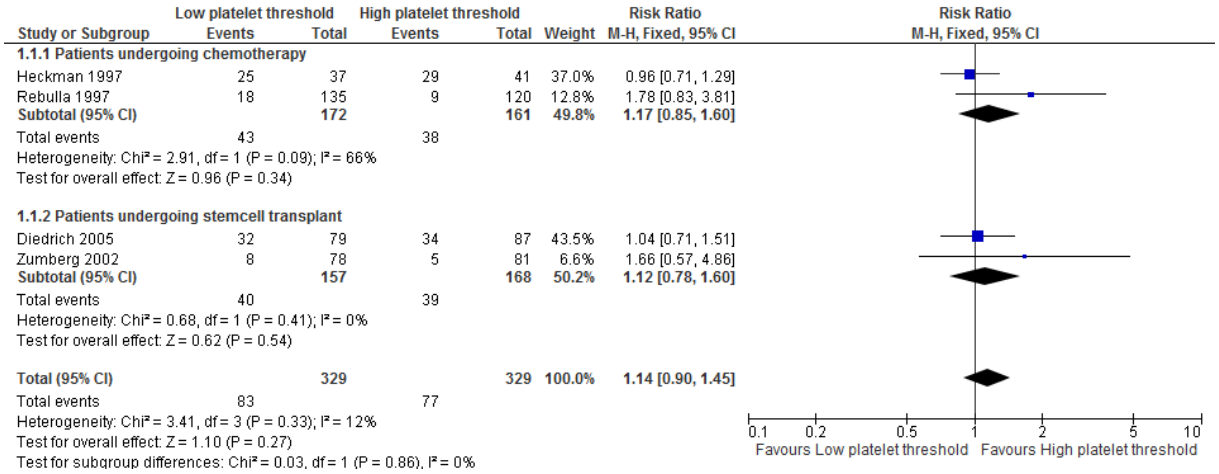


Figure 158: Number of patients with bleeding events (WHO grade 2 or higher)

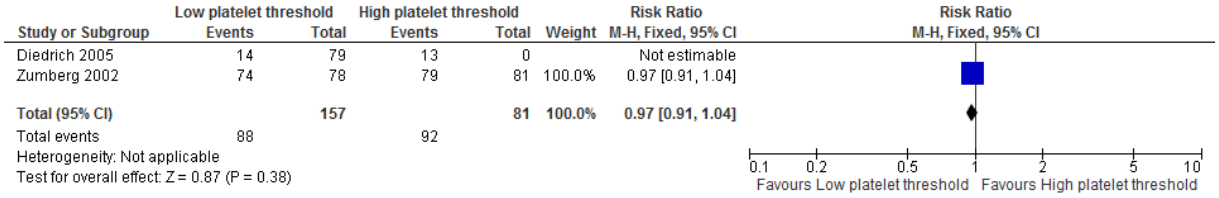


Figure 159: Number of patients with major bleeding events (WHO grade 3 or 4)

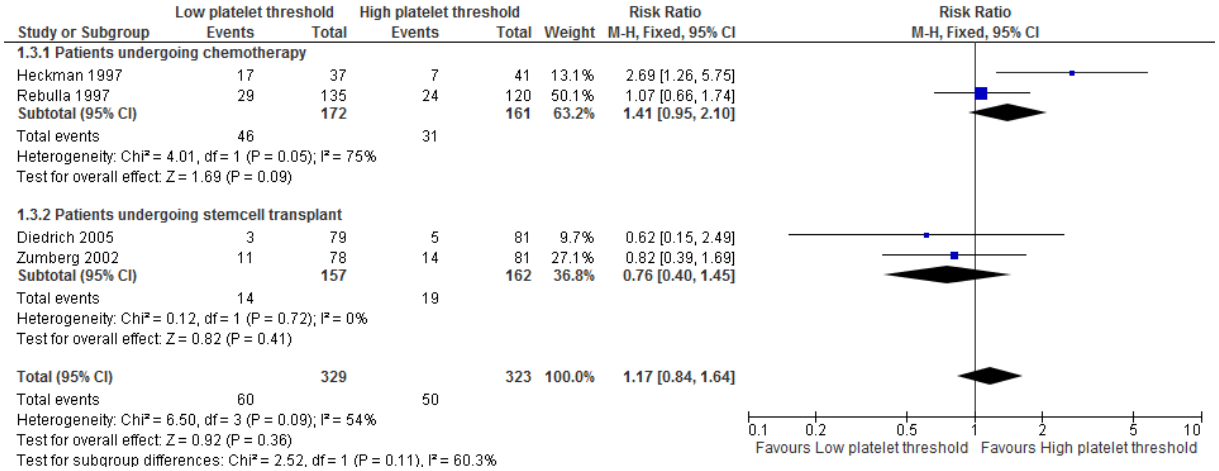
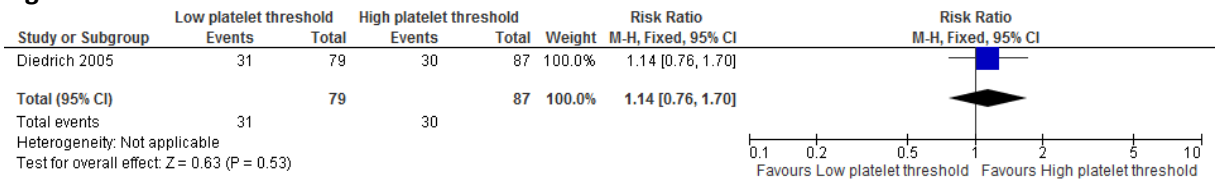
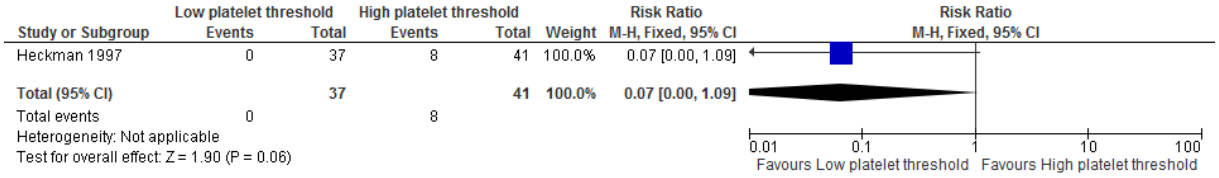


Figure 160: Infections



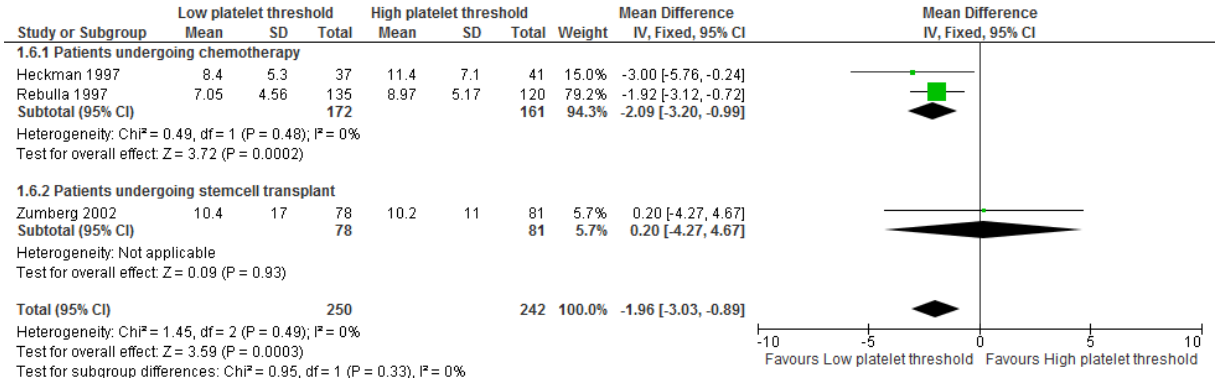
1

Figure 161: Adverse events



2

Figure 162: Number of units (platelets) transfused per patient

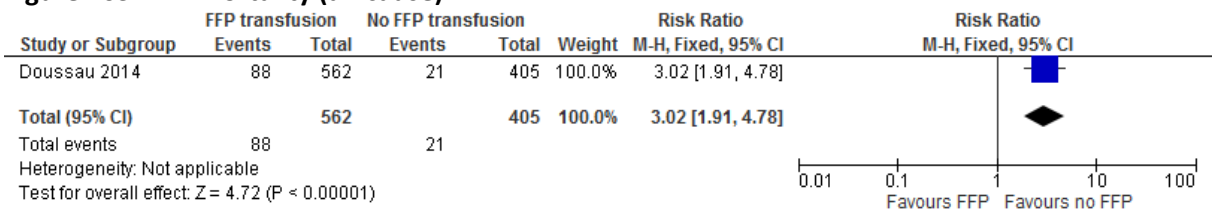


3

4 K.6 Fresh frozen plasma

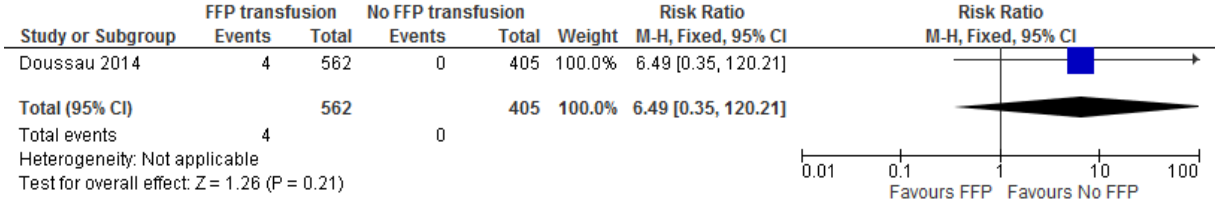
5 K.6.1 Therapeutic FFP transfusion versus no FFP transfusion

Figure 163: Mortality (all-cause)



6

Figure 164: Adverse events



K.7 Prothrombin complex concentrates

K.7.1 Low dose (25 IU/kg) versus high dose (40 IU/kg)

Figure 165: Mortality

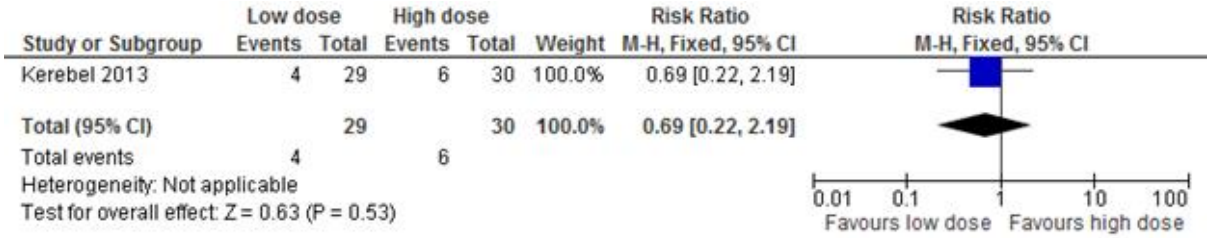


Figure 166: Patients with at least one adverse event

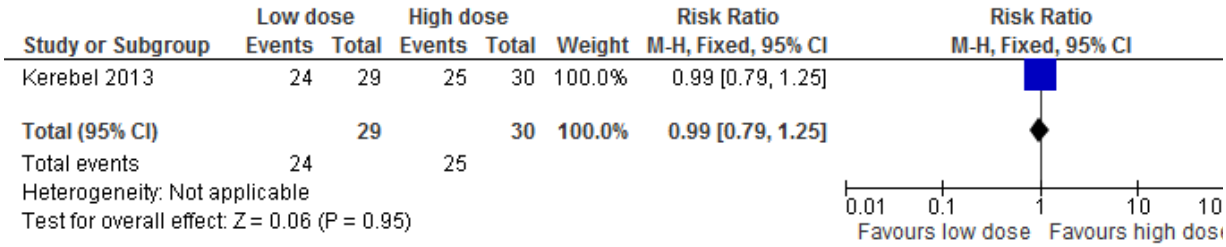


Figure 167: Patients with at least one serious adverse event

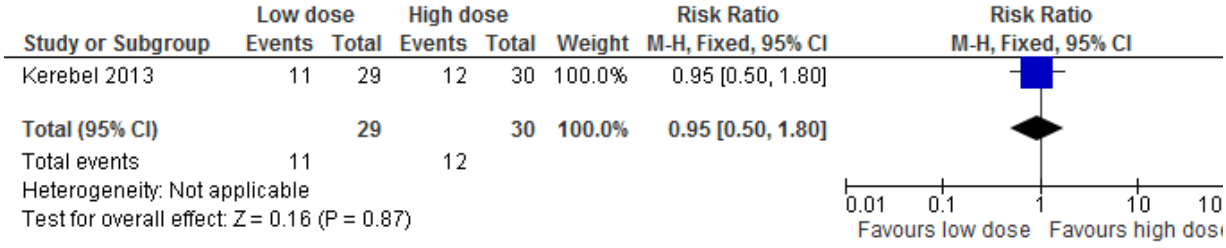
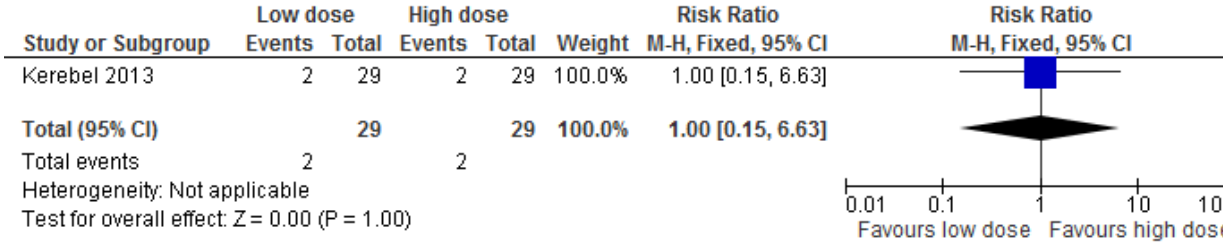
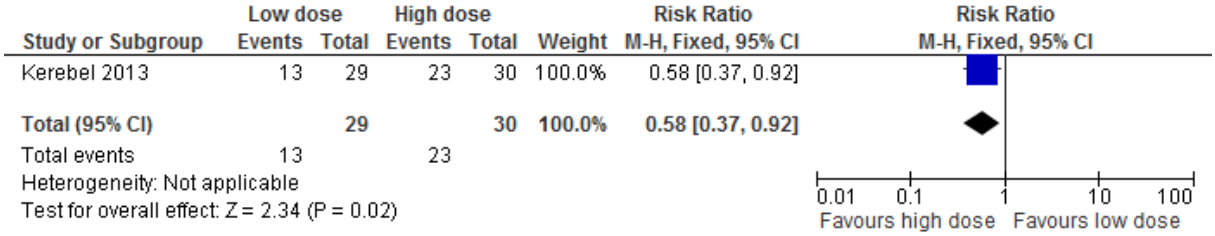


Figure 168: Patients with at least one thrombotic event



1

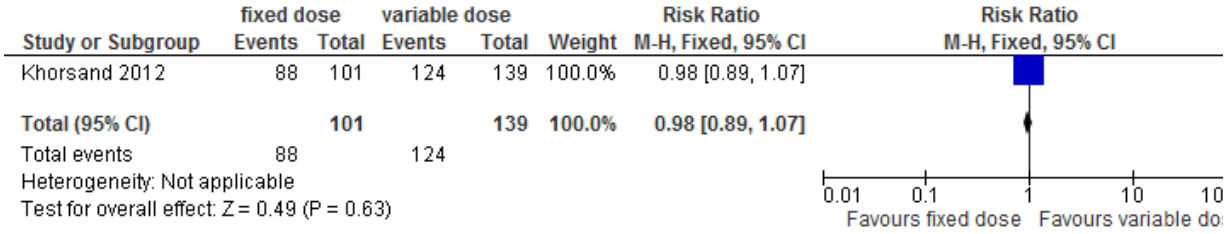
Figure 169: Target INR less than 1.2 achieved



2

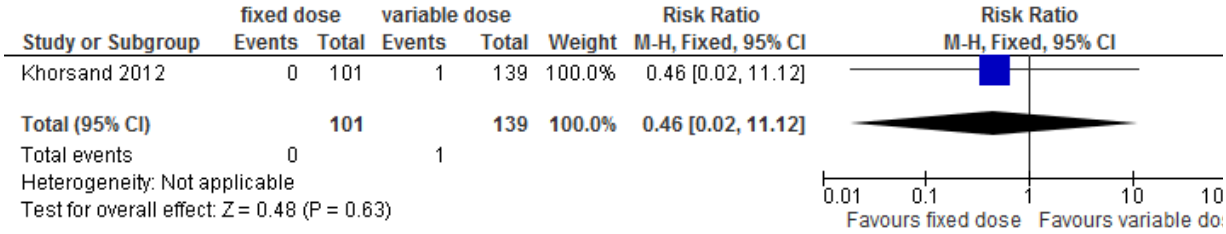
3 ## K.7.2 Low fixed dose (1040 IU FIX) versus variable dose

Figure 170: Target INR reached



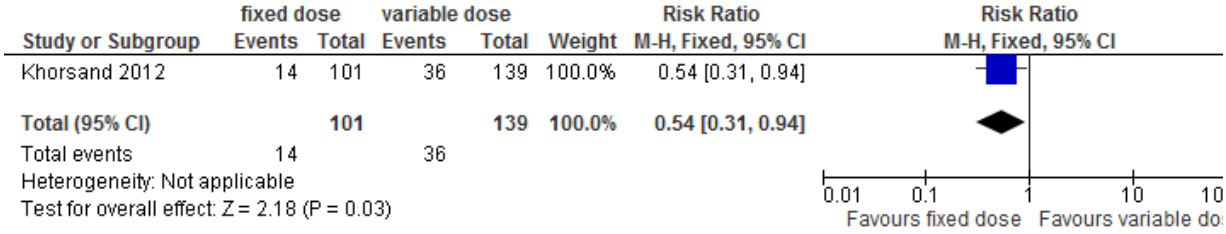
4

Figure 171: Deep Vein Thrombosis (DVT)



5

Figure 172: Mortality



K.7.3 Standard dose (500 IU FIX/7 IU FIX/kg) versus individualised dosing regimen

Figure 173: Target INR at 15 minutes after the first dosage of PCC

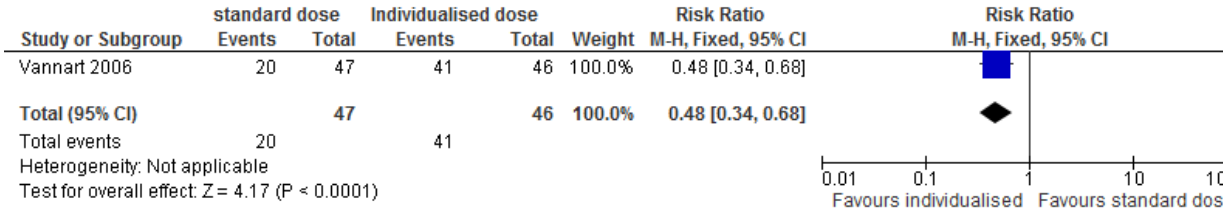
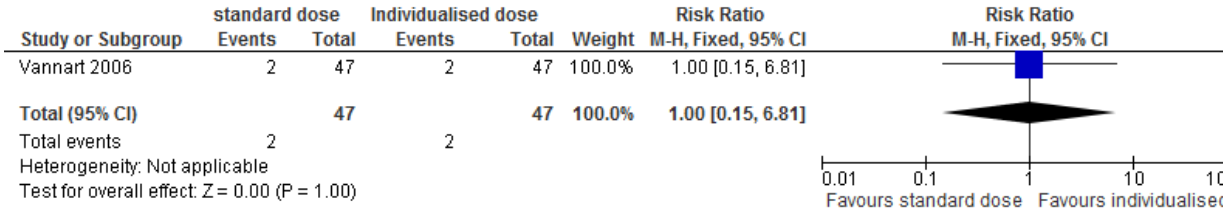


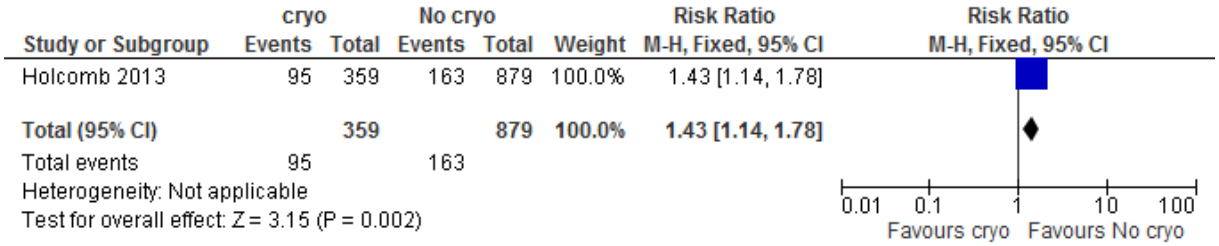
Figure 174: Serious adverse events



K.8 Cryoprecipitate

K.8.1 Cryoprecipitate versus no cryoprecipitate

Figure 175: Mortality at 30 days (all-cause)



Appendix L: Network meta-analysis of alternatives to blood transfusion in surgical patients

L.1 Introduction

The results of conventional meta-analyses of direct evidence alone (as presented in the GRADE profiles in chapter 6 and forest plots in appendix K.2) does not help inform which intervention is most effective as an alternative to blood transfusion in surgical patients. The challenge of interpretation has arisen for two reasons:

- In isolation, each pair-wise comparison does not inform the choice among the different treatments; in addition direct evidence is not available for some pair-wise comparisons in a randomised controlled trial (for example, ICS vs. PCS).
- There are frequently multiple overlapping comparisons (for example, ICS+TXA vs. TXA, ICS+PCS+TXA vs. TXA and ICS+PCS+TXA vs. ICS+PCS), that could potentially give inconsistent estimates of effect.

To overcome these problems, a hierarchical Bayesian network meta-analysis (NMA) was performed. This type of analysis allows for the synthesis of data from direct and indirect comparisons without breaking randomisation and allows for the ranking of different interventions. In this case, in order of efficacy, the outcomes were defined as:

- the number of people who are transfused with allogeneic blood
- the units of allogeneic blood transfused
- length of stay in hospital

The analysis also provided estimates of effect (with 95% credible intervals) for each intervention compared to one another and compared to a single baseline risk (in this case the baseline treatment was standard treatment). These estimates provide a useful clinical summary of the results and facilitate the formation of recommendations based on the best available evidence. Furthermore, these estimates were used to parameterise treatment effectiveness in the de novo cost-effectiveness modelling presented in appendix M.

Conventional fixed effects meta-analysis assumes that the relative effect of one treatment compared to another is the same across an entire set of trials. In a random effects model, it is assumed that the relative effects are different in each trial but that they are from a single common distribution and that this distribution is common across all sets of trials.

Network meta-analysis requires an additional assumption over conventional meta-analysis. The additional assumption is that intervention A has the same effect on people in trials of intervention A compared to intervention B as it does for people in trials of intervention A versus intervention C, and so on. Thus, in a random effects network meta-analysis, the assumption is that intervention A has the same effect distribution across trials of A versus B, A versus C and so on.

This specific method is usually referred to as mixed-treatment comparisons analysis but the term network meta-analysis will be used to refer generically to this kind of analysis. It was agreed that

this would be best since the term “network” better describes the data structure, whereas “mixed treatments” could easily be misinterpreted as referring to combinations of treatments.

L.2 Methods

L.2.1 Study selection and data collection

To estimate the relative risks, an NMA was performed that simultaneously used all the relevant RCT evidence from the clinical evidence review. As with conventional meta-analyses, this type of analysis does not break the randomisation of the evidence, nor does it make any assumptions about adding the effects of different interventions. The effectiveness of a particular treatment strategy combination will be derived only from randomised controlled trials that had that particular combination in a trial arm.

From the outset, effeorts were made to minimise any clinical or methodological heterogeneity by focusing the analysis on RCTs with comparable routes of administration of treatments, identifying equivalent outcomes and including only RCTs on cell salvage that were conducted after 2003 as this was defining watershed in transfusion practice (also see rationale in section 6.2.3, chapter 6). All of the dosages of drugs in the included RCTs were within the therapeutic range as indicated by the BNF. In consultation with the GDG, it was agreed that an NMA would be performed for alternatives to blood transfusion including combinations of different types of cell salvage and/or tranexamic acid. The evidence on these interventions included multiple comparisons and an NMA would allow the synthesis of the evidence in a more comprehensive way.

As such, five networks of evidence were identified, defined by outcome measure. Three networks were in the high risk group and two were in the moderate risk group (For definitions of risk groups see section 6, Chapter 6.4.2). The networks were as follows:

High risk group:

Network 1: Number of people receiving allogeneic transfusions

Network 2: Units of allogeneic blood transfused

Network 3: Length of stay in hospital

Moderate risk group:

Network 4: Number of people receiving allogeneic transfusions

Network 5: Units of allogeneic blood transfused

L.2.2 Outcome measures

The NMA evidence reviews for interventions considered three clinical efficacy outcomes identified from the clinical evidence review; number of people receiving allogeneic transfusions, units of allogeneic blood transfused and length of stay in hospital. Other outcomes were not considered for the NMA as they were infrequently reported across the studies. The GDG considered the number of people receiving allogeneic transfusions and units of allogeneic blood transfused to be the most important clinical outcomes for testing effectiveness of alternatives to reduce blood transfusion requirements.

L.2.3 Comparability of interventions

The interventions compared in the model were those found in the randomised controlled trials and included in the clinical evidence review already presented in chapter 6 of the full guideline and in appendix H. If an intervention was evaluated in a study that met the inclusion criteria for the network (that is if it reported at least one of the outcomes of interest and matched the inclusion criteria for the meta-analysis) then it was included in the network meta-analysis, otherwise it was excluded.

The treatments included in each network are shown in **Table 1**.

Table 1: Treatments included in network meta-analysis

High risk group			Moderate risk group	
Network 1: Number of people receiving allogeneic transfusions	**Network 2: Units of allogeneic blood transfused**	**Network 3: Length of stay in hospital**	**Network 4: Number of people receiving allogeneic transfusions**	**Network 5: Units of allogeneic blood transfused**
Standard treatment	Standard treatment	Standard treatment	Standard treatment	Standard treatment
TXA	ICS	TXA	TXA	TXA
PCS	TXA	ICS	PCS	PCS
ICS	PCS	PCS	ICS	ICS+PCS
ICS+PCS	ICS+TXA	ICS+PCS	ICS+PCS	
ICS+TXA	-	ICS+TXA	ICS+PCS+TXA	
ICS+PCS+TXA	-	-	PCS+TXA	
-	-	-	ICS+TXA	

Abbreviations: TXA-Tranexamic acid, PCS-Post-operative cell salvage, ICS-Intra-operative cell salvage

The details of these interventions can be found in the clinical evidence review in chapter 11 of the full guideline and evidence tables in appendix H.

L.2.4 Baseline risk

The baseline risk is defined here as the risk of achieving the outcome of interest in the standard treatment group. This figure is useful because it allows the conversion of the results of the NMA from odds ratios to relative risks.

Baseline odds were derived by the logistic regression in WinBUGS. This approach has the advantage that baseline and relative effects are both modelled on the same log odds scale, and also ensures that the uncertainty in the estimation of baseline and relative effects is accounted for in the model. This method produced baseline odds [mean (SD)] as follows:

- -0.06809 (1.188) for number of patients receiving allogeneic transfusions in the high risk group
- -0.5185 (1.444) for number of patients receiving allogeneic transfusions in the moderate risk group

A baseline risk model of mortality was conducted in both risk groups to estimate baseline mortality for the economic model. The method produced baseline relative risk [mean (SD)] of 0.0343 (0.01135) in the high risk group. In the moderate risk group, this was 0.00162 (0.002384). For details of data informing these models, please refer to the full cost- effectiveness analysis (section M.2.1, Appendix M).

L.2.5 Statistical analysis

A hierarchical Bayesian network meta-analysis (NMA) was performed using the software WinBUGS. We adapted a three-arm random effects model template for the networks, from the University of Bristol website (https://www.bris.ac.uk/cobm/research/mpes/mtc.html). This model accounts for the correlation between study level effects induced by multi-arm trials.

In order to be included in the analysis, a fundamental requirement is that each treatment is connected directly or indirectly to every other intervention in the network. For each outcome subgroup, a diagram of the evidence network is presented in section L.3.

The model used was a random effects logistic regression model, with parameters estimated by Markov chain Monte Carlo simulation. As it was a Bayesian analysis, for each parameter the evidence distribution is weighted by a distribution of prior beliefs. These were estimated from the baseline models for the dichotomous outcomes using the following equations.

- Predictive probability of response (MeanA) =mean of mu.new
- Precision (PrecA)=1/(standard deviation of mu.new)^2

A non-informative prior distribution was used to maximise the weighting given to the data for continuous outcomes. These priors were normally distributed with a mean of 0 and standard deviation of 10,000.

For the analyses, a series of 100,000 burn-in simulations were run to allow convergence and then a further 100,000 simulations were run to produce the outputs. For the baseline analyses, a series of 50,000 burn-in simulations were run to allow convergence and then a further 50,000 simulations were run to produce the outputs. Convergence was assessed by examining the history and kernel density plots.

The goodness of fit of the model was tested by calculating the residual deviance. If the residual deviance is close to the number of unconstrained data points (the number of trial arms in the analysis) then the model is explaining the data well.

The results, in terms of relative risk, of pair-wise meta-analyses are presented in the clinical evidence review (Chapter 6).

The aim of the NMA was to calculate treatment specific log odds ratios and relative risks for response to be consistent with the comparative effectiveness results presented elsewhere in the clinical evidence review and for ease of interpretation. Let BO, $\tilde{\theta}$, $\widetilde{\mathrm{OR}}$ and p denote the baseline odds, treatment specific odds, treatment specific log odds ratio and absolute probability respectively. Then:

$$\tilde{\boldsymbol{\theta}} = \boldsymbol{Ln}\left(\widetilde{\boldsymbol{OR}}\right) + \boldsymbol{Ln}(\boldsymbol{BO})$$

And:

$$p = \frac{e^{\tilde{\theta}}}{1 + e^{\tilde{\theta}}}$$

Once the treatment specific probabilities for response were calculated, these were divided by the baseline probability (p_b) to get treatment specific relative risks (rr_b):

$$p_b = \frac{e^{BO}}{1 + e^{BO}}$$

$$rr_b = \frac{p}{p_b}$$

This approach has the advantage that baseline and relative effects are both modelled on the same log odds scale, and also ensures that the uncertainty in the estimation of both baseline and relative effects is accounted for in the model.

The overall ranking of interventions according to their relative risk compared to control group and counting the proportion of simulations of the Markov chain in which each intervention had the highest relative risk.

Due to the skewness of the data, the NMA relative risks and rank results are reported as medians rather than means (as in the direct comparisons) to give a more accurate representation of the 'most likely' value.

A key assumption behind NMA is that the network is consistent. In other words, it is assumed that the direct and indirect treatment effect estimates do not disagree with one another. Discrepancies between direct and indirect estimates of effect may result from several possible causes. First, there is chance and if this is the case then the network meta-analysis results are likely to be more precise as they pool together more data than conventional meta-analysis estimates alone. Second, there could be differences between the trials included in terms of their clinical or methodological characteristics. Differences that could lead to inconsistency include:

- Different populations
- Different interventions
- Difrent routes of administration

This heterogeneity is a problem for network meta-analysis but may be dealt with by subgroup analysis, meta-regression or by carefully defining inclusion criteria. In this analysis, sub-group analyses based on various factors such as haemoglobin status at baseline, different haemoglobin thresholds for blood transfusion and different routes of administration was undertaken to account for heterogeneity in the pair wise meta-analyses. Inconsistency in the network, caused by heterogeneity, was assessed subjectively by comparing the odds ratios for binary outcomes and mean differences for continuous outcomes from the direct evidence (from pair-wise meta-analysis) with the corresponding effects estimated from the combined direct and indirect evidence (from NMA). We assumed the evidence to be inconsistent where the odds ratio or mean difference from the NMA did not fit within the confidence interval of the odds ratio or mean difference from the direct comparison. We further tested for inconsistency by developing inconsistency models for networks of binary outcomes (number of patients transfused). We assumed the evidence to be consistent when the difference in deviance information criterion

(DiC) values between the consistency and the inconsistency models was less then 3-5. No inconsistency was identified.

L.3 Results

A total of 129 studies from the original evidence review met the inclusion criteria for at least one network. Figure 1 – Figure 4 show the four networks created by eligible comparisons for each NMA. The number on the line linking two treatments indicates the number of studies included that assessed that direct comparison.

L.3.1 NMA models

Figure 176: Adults-High risk group: Network for number of patients receiving allogeneic transfusions

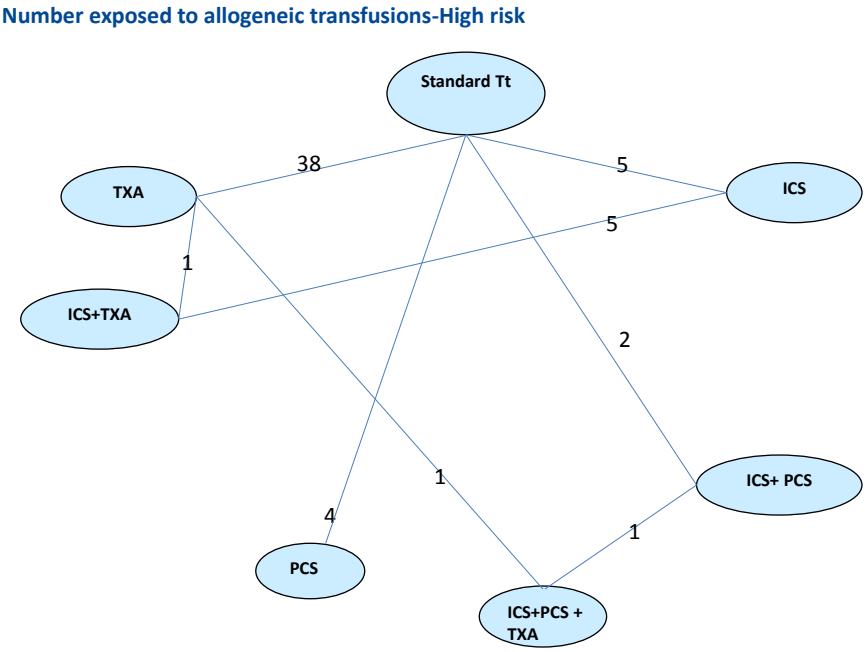
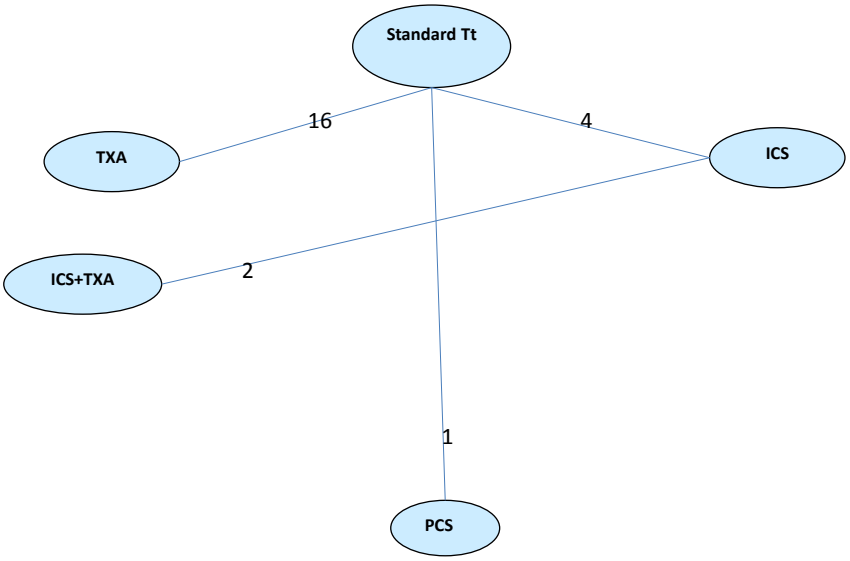


Figure 177: Adults-High risk group: Network for units of allogeneic blood transfused

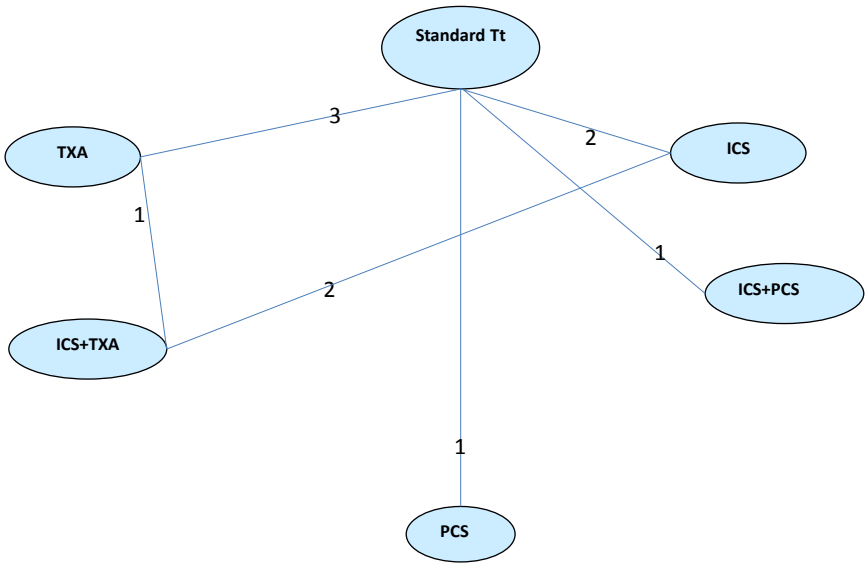
Units of allogeneic blood transfused- High risk



1

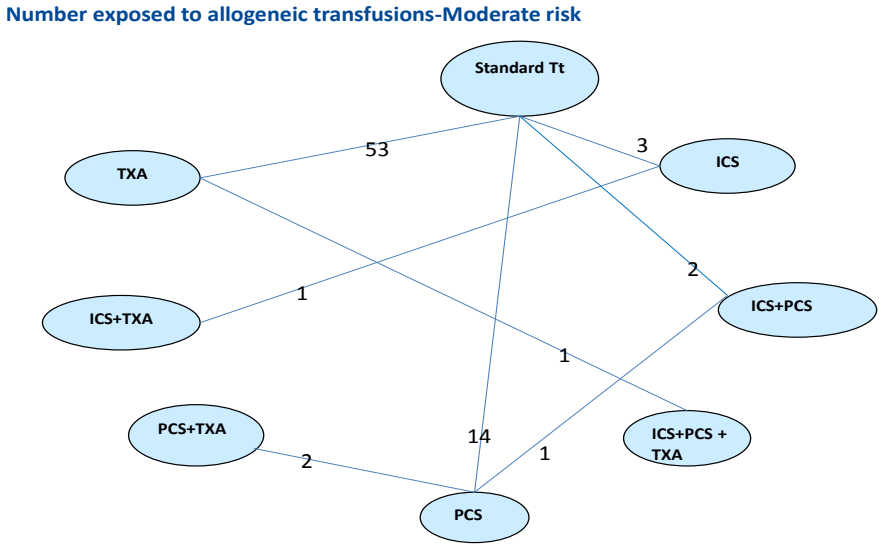
Figure 178: Adults-High risk group: Length of stay in hospital

Length of stay in hospital-High risk



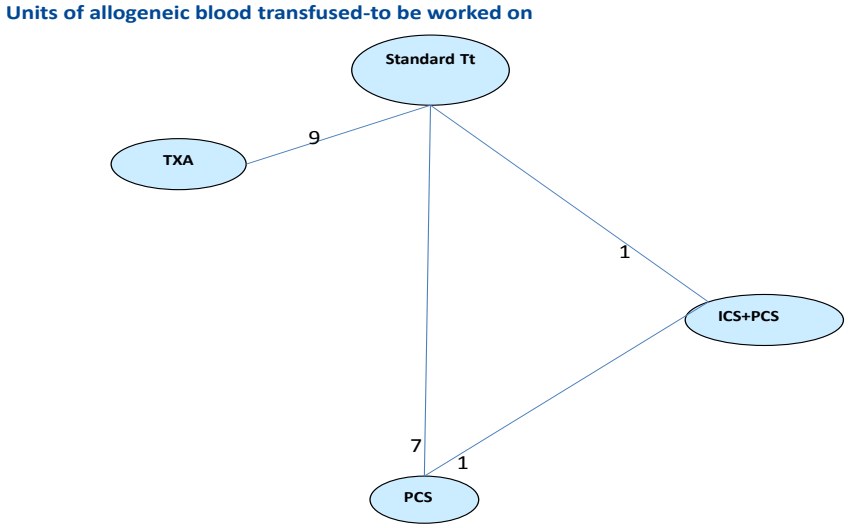
1

Figure 179: Adults-Moderate risk group: Network for number of patients receiving allogeneic transfusions



2

Figure 180: Adults-Moderate risk group: Network for units of allogeneic blood transfused



L.3.2 Trial data

L.3.2.1 High risk group

Trial data from the 56 studies included in the NMA for number of adult patients receiving allogeneic transfusions are shown in Table 2. The trial data from the 23 studies included in the NMA for number of units of allogeneic blood transfused are shown in Table 3. The trial data from the 10 studies included in the NMA for length of stay in hospital are shown in Table 4.

Table 2: Study data for number of patients receiving allogeneic transfusions

Study	Treatment	Comparator	Treatment		Comparator	
			Events	N	Events	N
Mercer2004[85]	Standard treatment	ICS	31	41	21	40
Murphy2005[88]	Standard treatment	ICS	7	31	4	30
Damgard2006[35]	Standard treatment	ICS	21	29	17	30
Aghdaii 2012[2]	Standard treatment	ICS	8	25	7	25
Naumenko2003[90]	Standard treatment	PCS	1	33	2	32
Zhao2003[137]	Standard treatment	PCS	30	30	19	30
Pleym2005[96]	Standard treatment	PCS	3	24	1	23
Sirvinkas2007 [110]	Standard treatment	PCS	19	49	6	41
Murphy2004[87]	Standard treatment	ICS+PCS	64	102	41	98
Wiefferink2007[127]	Standard treatment	ICS+PCS	10	15	8	15
Casati2004[24]	ICS	ICS+TXA	13	50	9	52
Diprose2005[38]	ICS	ICS+TXA	27	60	20	60
Jiminez2007[64]	ICS	ICS+TXA	19	26	9	24
Kuitunen2005[75]	ICS	ICS+TXA	12	20	5	20
Later2009[76]	ICS	ICS+TXA	73	103	57	99
Reyes2011[100]	TXA	ICS+TXA	13	29	12	24
Murphy2006[89]	ICS+PCS	ICS+PCS+TXA	14	50	13	50
Klein2008[73]	TXA	ICS+PCS+TXA	33	111	31	102
Ahn2012[4]	Standard treatment	TXA	27	38	20	38
Andreasen2004[10]	Standard treatment	TXA	5	17	6	20
Baric2007[14]	Standard	TXA	51	96	51	97

Study	Treatment	Comparator	Treatment		Comparator	
	treatment					
Dellamore2012[37]	Standard treatment	TXA	10	43	8	44
Ghaffari2012[47]	Standard treatment	TXA	23	50	15	50
Jares2003[63]	Standard treatment	TXA	7	25	2	22
Karski2005[67]	Standard treatment	TXA	41	165	24	147
Mansour2004[82]	Standard treatment	TXA	12	20	7	20
Mehraein2007[83]	Standard treatment	TXA	8	33	5	33
Nouraei2013[93]	Standard treatment	TXA	21	40	15	40
Pleym2003[97]	Standard treatment	TXA	8	39	7	40
Santos2006[105]	Standard treatment	TXA	12	31	7	29
Shi2013[108]	Standard treatment	TXA	221	278	166	274
Shi2013a[109]	Standard treatment	TXA	54	59	42	58
Taghaddomi2009[116]	Standard treatment	TXA	27	50	8	50
Vanek2005[122]	Standard treatment	TXA	6	30	3	32
Wang2012[125]	Standard treatment	TXA	54	115	37	116
Wei2006[126]	Standard treatment	TXA	8	40	3	36
Wu2006[130]	Standard treatment	TXA	17	108	0	106
Armellin2001[12]	Standard treatment	TXA	63	140	35	143
Blauhut1994[19]	Standard treatment	TXA	9	14	7	15
Casati2001[23]	Standard treatment	TXA	4	20	2	20
Coffey1995[30]	Standard treatment	TXA	8	14	9	16
Corbeau1995[31]	Standard treatment	TXA	12	20	15	41
Dalmau2000[34]	Standard treatment	TXA	37	40	29	42

Study	Treatment	Comparator	Treatment		Comparator	
Debonis2000[36]	Standard treatment	TXA	4	20	3	20
Fawzy2009[44]	Standard treatment	TXA	13	19	14	19
Hardy1998[52]	Standard treatment	TXA	27	44	28	42
Horrow1991[56]	Standard treatment	TXA	16	44	12	37
Katoh1997[68]	Standard treatment	TXA	10	31	7	62
Katsaros1996[69]	Standard treatment	TXA	27	106	11	104
Krohn2003[74]	Standard treatment	TXA	9	14	2	16
Menichetti1996[84]	Standard treatment	TXA	18	24	12	24
Speekenbrink1995[115]	Standard treatment	TXA	11	15	13	15
Esfandiari2013[42]	Standard treatment	TXA	43	75	22	75
Lundin2014[79]	Standard treatment	TXA	22	50	15	50
Ghavidel 2014[5]	Standard treatment	TXA	74	100	60	100
Vermeijden2015[123]	Standard treatment	ICS	108	177	98	189

Abbreviations: TXA-Tranexamic acid, PCS-Post-operative cell salvage, ICS-Intra-operative cell salvage

Table 3: Study data for units of allogeneic blood transfused

Study	Treatment	Comparator	Treatment		Comparator	
			Mean	Standard error	Mean	Standard error
Bowley2006[20]	Standard treatment	ICS	11.17	1.2635973	6.47	1.12164
Niranjan2006[91]	Standard treatment	ICS	1.38	0.2071292	0.53	0.102774
Goel2007[49]	Standard treatment	ICS	2.4	0.258	1.54	0.224537
Aghdaii2012[2]	Standard treatment	ICS	0.7	0.2	0.4	0.16
Zhao2003[137]	Standard treatment	PCS	2.22	0.0730297	1.2	0.049295
Diprose2005[38]	ICS	ICS+TXA	1.68	0.4531391	0.87	0.196231

Study	Treatment	Comparator	Treatment		Comparator	
Jiminez2007[64]	ICS	ICS+TXA	3.21	0.1078639	1.58	0.100021
Armellin2001[12]	Standard treatment	TXA	1.93	0.16	1.68	0.208
Blauhut1994[19]	Standard treatment	TXA	2.44	0.38	1.71	0.3591
Corbeau1995[31]	Standard treatment	TXA	2.83	0.42	2.19	0.1188
Dalmau2000[34]	Standard treatment	TXA	8.38	1.01	7.72	1.0102
Horrow1990[55]	Standard treatment	TXA	0.76	0.24	0.92	0.188562
Katoh1997[68]	Standard treatment	TXA	3.03	0.82	1.42	0.34798
Speekenbrink1995[115]	Standard treatment	TXA	4.27	0.95	3.37	0.44
Uozaki2001[121]	Standard treatment	TXA	9.16	2.69	4.1	0.910394
Yassen1993[132]	Standard treatment	TXA	12.4	2.53	7.9	1.043552
Zabeeda2002[134]	Standard treatment	TXA	1.68	0.20	0.52	0.18
Ahn2012[4]	Standard treatment	TXA	1.4	0.19	0.8	0.129777
Maddali2007[81]	Standard treatment	TXA	3.17	0.09	2.03	0.074034
Shi2013[108]	Standard treatment	TXA	6.51	0.44	3.93	0.281521
Shi2013a[108]	Standard treatment	TXA	9.36	1.49	4.84	0.768143
Wang2012[125]	Standard treatment	TXA	1.62	0.24	0.91	0.147628
Ghavidel2014[5]	Standard treatment	TXA	1.65	0.053	1.25	0.055

Abbreviations: TXA-Tranexamic acid, PCS-Post-operative cell salvage, ICS-Intra-operative cell salvage

Table 4: Study data for length of stay

Study	Treatment	Comparator	Treatment		Comparator	
			Mean	Standard error	Mean	Standard error
Niranjan2006[91]	Standard treatment	ICS	7.85	0.419	7.65	0.341526
Sirvinskas2007[110]	Standard treatment	PCS	16.45	0.931	9.32	0.398243

Study	Treatment	Comparator	Treatment		Comparator	
Murphy2004[87]	Standard treatment	ICS+PCS	6.8	0.406	9.6	2.472393
Jimenez2007[64]	ICS	ICS+TXA	4	0.728	4.5	0.724641
Later2009[76]	ICS	ICS+TXA	8.5	0.729	9.4	0.864333
Reyes2011[100]	TXA	ICS+TXA	12.1	1.356	14.2	2.43528
Mansour2004[82]	Standard treatment	TXA	6.4	0.671	5.8	0.491935
Mehraein2007[83]	Standard treatment	TXA	4.8	0.157	4.8	0.069631
Wei2006[126]	Standard treatment	TXA	7.3	0.190	7.1	0.133333
Vermeijden2015[123]	Standard treatment	ICS	11.8	0.72158	11.5	0.763763

Abbreviations: TXA-Tranexamic acid, PCS-Post-operative cell salvage, ICS-Intra-operative cell salvage

L.3.2.2 Moderate risk group

The trial data from the 73 studies included in the NMA for number of patients receiving allogeneic transfusions are shown in Table 5. The trial data from the 16 studies included in the NMA for number of units of allogeneic transfusions received are shown in Table 42.

Table 5: Study data for number of patients receiving allogeneic transfusions

Study	Treatment	Comparator 1	Comparator 2	Treatment		Comparator 1		Comparator 2	
				Events	N	Events	N	Events	N
Zhang2008[136]	Standard treatment	ICS		16	20	10	20	NA	NA
Cip2013[28]	Standard treatment	ICS		23	70	23	70	NA	NA
Horstmann2013[57]	Standard treatment	ICS		9	102	8	102	NA	NA
Atay2010i[13]	Standard treatment	PCS		15	19	9	17	NA	NA
Atay2010ii[13]	Standard treatment	PCS		8	21	1	20	NA	NA
Cheng2005[27]	Standard treatment	PCS		13	34	4	26	NA	NA
Dramis2006[39]	Standard treatment	PCS		10	17	3	32	NA	NA
Soosman2006[112]	Standard treatment	PCS		10	22	22	47	NA	NA
Zacharopoulos2007[135]	Standard treatment	PCS		10	30	5	30	NA	NA

Study	Treatment	Comparator 1	Comparator 2	Treatment		Comparator 1		Comparator 2	
Abuzakuk2007[1]	Standard treatment	PCS		12	52	13	52	NA	NA
Smith2007[111]	Standard treatment	PCS		17	82	6	76	NA	NA
Moonen2007[86]	Standard treatment	PCS		15	80	5	80	NA	NA
Tripkovic2008[120]	Standard treatment	PCS		24	30	4	30	NA	NA
Amin2008[9]	Standard treatment	PCS		13	86	12	92	NA	NA
Thomassen2014[118]	Standard treatment	PCS		12	190	29	382	NA	NA
Horstmann2014[58]	Standard treatment	PCS		11	56	6	59	NA	NA
Soosman2014[113]	Standard treatment	PCS	ICS+PCS	54	658	33	321	23	321
Horstmann2014a[59]	Standard treatment	ICS+PCS		4	62	2	56	NA	NA
Wong2008[129]	ICS	ICS+TXA		30	74	23	73	NA	NA
Alvarez2008[8]	PCS	PCS+TXA		6	49	1	46	NA	NA
Oremus2014[94]	PCS	PCS+TXA		5	49	3	49	NA	NA
Thomassen2012[119]	TXA	ICS+PCS+TXA		13	101	9	96	NA	NA
Aguilera2013[3]	Standard treatment	TXA		12	42	2	41	NA	NA
Benoni1996[15]	Standard treatment	TXA		24	43	8	43	NA	NA
Benoni2000[17]	Standard treatment	TXA		15	19	9	20	NA	NA
Benoni2001[16]	Standard treatment	TXA		8	20	4	18	NA	NA
Bidolegui2014[18]	Standard treatment	TXA		8	25	0	25	NA	NA
Dakir2014[33]	Standard treatment	TXA		2	6	0	6	NA	NA
Ellis2001[40]	Standard treatment	TXA		7	10	1	10	NA	NA
Engel2001[41]	Standard treatment	TXA		3	12	0	12	NA	NA
Hiipala1995[53]	Standard treatment	TXA		12	13	10	15	NA	NA
Hiipala1997[54]	Standard treatment	TXA		34	38	17	39	NA	NA

Study	Treatment	Comparator 1	Comparator 2	Treatment		Comparator 1		Comparator 2	
Jansen1999[62]	Standard treatment	TXA		13	21	2	21	NA	NA
Sorin1999[114]	Standard treatment	TXA		13	21	2	21	NA	NA
Tanaka2001[117]	Standard treatment	TXA		26	26	47	73	NA	NA
Alshryda2013[6]	Standard treatment	TXA		13	78	1	79	NA	NA
Bradshaw2012[21]	Standard treatment	TXA		1	20	0	26	NA	NA
Caglar2008[22]	Standard treatment	TXA		10	50	15	50	NA	NA
Charoeanch2012[25]	Standard treatment	TXA		102	120	57	120	NA	NA
Charoeanch2011[26]	Standard treatment	TXA		45	50	28	50	NA	NA
Claeys2007[29]	Standard treatment	TXA		6	20	1	20	NA	NA
Crescenti2011[32]	Standard treatment	TXA		55	100	34	100	NA	NA
Farrokhi2011[43]	Standard treatment	TXA		15	38	10	38	NA	NA
Garneti2004[45]	Standard treatment	TXA		14	25	16	25	NA	NA
Georgiadis2013[46]	Standard treatment	TXA		4	51	0	50	NA	NA
Gill2009[48]	Standard treatment	TXA		4	5	1	5	NA	NA
Good2003[50]	Standard treatment	TXA		14	24	3	27	NA	NA
Gungorduk2011[51]	Standard treatment	TXA		7	330	2	330	NA	NA
Husted2003[60]	Standard treatment	TXA		7	20	2	20	NA	NA
Ishida2011[61]	Standard treatment	TXA		1	50	0	50	NA	NA
Johansson2005[65]	Standard treatment	TXA		23	53	8	47	NA	NA
Karimi2012[66]	Standard treatment	TXA		1	16	0	16	NA	NA
Kazemi2010[70]	Standard treatment	TXA		11	32	4	32	NA	NA
Kim2014i[71]	Standard	TXA		6	90	1	90	NA	NA

Study	Treatment	Comparator 1	Comparator 2	Treatment		Comparator 1		Comparator 2	
	treatment								
Kim 2014ii[71]	Standard treatment	TXA		20	73	5	73	NA	NA
Lee2013[77]	Standard treatment	TXA		20	34	9	34	NA	NA
Lemay2004[78]	Standard treatment	TXA		8	19	0	20	NA	NA
Macgillvray2010[80]	Standard treatment	TXA		10	20	13	40	NA	NA
Niskanen2005[92]	Standard treatment	TXA		8	20	5	19	NA	NA
Orpen2006[95]	Standard treatment	TXA		3	14	1	15	NA	NA
Rajesparan2009[98]	Standard treatment	TXA		10	37	3	36	NA	NA
Raviraj2012[99]	Standard treatment	TXA		18	88	7	88	NA	NA
Roy2012[101]	Standard treatment	TXA		7	25	2	25	NA	NA
Sa-ngasoongsong2011[102]	Standard treatment	TXA		8	24	1	24	NA	NA
Sa-ngasoongsong2013[103]	Standard treatment	TXA		10	45	6	90	NA	NA
Sadeghi2007[104]	Standard treatment	TXA		20	35	12	32	NA	NA
Seo2013[106]	Standard treatment	TXA		47	50	10	50	NA	NA
Shahid2013[107]	Standard treatment	TXA		12	36	3	38	NA	NA
Vijay2013[124]	Standard treatment	TXA		18	45	7	45	NA	NA
Wong2010[128]	Standard treatment	TXA		9	35	5	64	NA	NA
Zohar2004[138]	Standard treatment	TXA		12	20	3	20	NA	NA
Yang2014[131]	Standard treatment	TXA		19	40	10	40	NA	NA
Yue2015[133]	Standard treatment	TXA		11	49	3	52	NA	NA

Abbreviations: TXA-Tranexamic acid, PCS-Post-operative cell salvage, ICS-Intra-operative cell salvage

Table 6: Study data for units of allogeneic blood transfused

Study	Treatment	Comparator 1	Comparator 2	Treatment		Comparator 1		Comparator 2	
				Mean	SE	Mean	SE	Mean	SE
Altinel 2007[7]	Standard treatment	PCS	NA	2.29	0.31	1.02	0.28	NA	NA
Antinolfi2014[11]	Standard treatment	TXA	NA	2.2	0.22	0.8	0.18	NA	NA
Atay2010i[13]	Standard treatment	PCS	NA	1.68	0.33	0.82	0.26	NA	NA
Atay2010ii[13]	Standard treatment	PCS	NA	0.71	0.21	0.05	0.05	NA	NA
Calgar2008[22]	Standard treatment	TXA	NA	1.6	0.21	1.8	0.14	NA	NA
Charoench2011[26]	Standard treatment	TXA	NA	1.89	0.12	0.71	0.11	NA	NA
Charoench2012[25]	Standard treatment	TXA	NA	1.55	0.09	0.55	0.06	NA	NA
Hiipala1995[53]	Standard treatment	TXA	NA	3.58	0.45	2.25	0.28	NA	NA
Hiipala1997[54]	Standard treatment	TXA	NA	3.46	0.21	2.29	0.13	NA	NA
Jansen1999[62]	Standard treatment	TXA	NA	2.5	0.54	0.46	0.32	NA	NA
Kazemi2010[70]	Standard treatment	TXA	NA	0.84	0.16	0.31	0.11	NA	NA
Kirkos2006[72]	Standard treatment	PCS	NA	1.06	0.13	0.54	0.10	NA	NA
Macgillivray2010[80]	Standard treatment	TXA	NA	1.11	0.22	0.76	0.12	NA	NA
So-osman2006[112]	Standard treatment	PCS	NA	1.9	0.22	2.36	0.19	NA	NA
Soosmonan2014ii[113]	Standard treatment	PCS	ICS+PCS	2.68	0.12	1.26	0.12	3.49	0.10
Tripkovic2008[120]	Standard treatment	PCS	NA	1.74	0.21	0.22	0.18	NA	NA

Abbreviations: TXA-Tranexamic acid, PCS-Post-operative cell salvage, ICS-Intra-operative cell salvage

L.3.3 Network 1: Number of patients receiving allogeneic transfusions (Adults-high risk group)

Table 7 summarises the results of the conventional meta-analyses in terms of odds ratios generated from studies directly comparing different interventions, together with the results of the NMA in terms of odds ratios for every possible treatment comparison.

Table 7: Odds ratios for number of patients receiving allogeneic transfusions (Adults- high risk group)

Comparison		Odds ratio	
		Direct (mean)	NMA (median)
Versus standard treatment	TXA vs. standard treatment	0.48(0.41, 0.57)	0.4523 (0.3797, 0.5359)
	PCS vs. standard treatment	0.29(0.08, 1.14)	0.2092 (0.08271, 0.4785)
	ICS vs. standard treatment	0.61(0.44, 0.86)	0.6287 (0.412, 0.9501)
	ICS+PCS vs. standard treatment	0.44(0.26, 0.75)	0.4591 (0.2529, 0.8438)
	ICS+TXA vs. standard treatment	-	0.317 (0.1785, 0.5555)
	ICS+PCS+TXA vs. standard treatment	-	0.4486 (0.2293, 0.863)
Versus TXA	PCS vs. TXA	-	0.4625 (0.1807, 1.079)
	ICS vs. TXA	-	1.39 (0.8904, 2.164)
	ICS+PCS vs. TXA	-	1.013 (0.5527, 1.895)
	ICS+TXA vs. TXA	0.67(0.24, 1.85)	0.6996 (0.3905, 1.24)
	ICS+PCS+TXA vs. TXA	1.03(0.57, 1.85)	0.9899 (0.5123, 1.897)
Versus PCS	ICS vs. PCS	-	3.003 (1.191, 8.247)
	ICS+PCS vs. PCS	-	2.198 (0.7904, 6.539)
	ICS+TXA vs. PCS	-	1.517 (0.5531, 4.423)
	ICS+PCS+TXA vs. PCS	-	2.146 (0.7407, 6.562)
Versus ICS	ICS+PCS vs. ICS	-	0.728 (0.3492, 1.535)
	ICS+TXA vs. ICS	0.49(0.34, 0.71)	0.5045 (0.3257, 0.765)
	ICS+PCS+TXA vs. ICS	-	0.7125 (0.3249, 1.556)
Versus ICS+PCS	ICS+TXA vs. ICS+PCS	-	0.6896 (0.2966, 1.577)
	ICS+PCS+TXA vs. ICS+PCS	0.9(0.37, 2.17)	0.9746 (0.4659, 2.011)
Versus ICS+TXA	ICS+PCS+TXA vs. ICS+TXA	-	1.409 (0.5999, 3.368)

Abbreviations: TXA-Tranexamic acid, PCS-Post-operative cell salvage, ICS-Intra-operative cell salvage

Figure 181 shows the rank of each intervention compared to the others. Figure 182 shows the median relative risk of each intervention compared to the others. The rank is based on the relative risk compared to baseline and indicates the probability of being the best treatment, second best, third best and so on among the 7 different interventions being evaluated.

Figure 181: Rank order for treatments based on number of patients receiving allogeneic transfusions

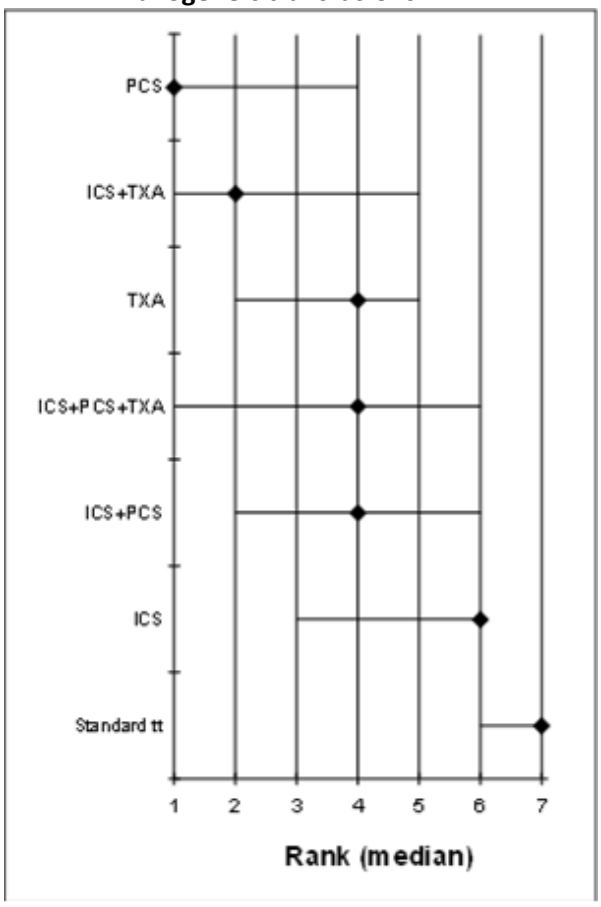
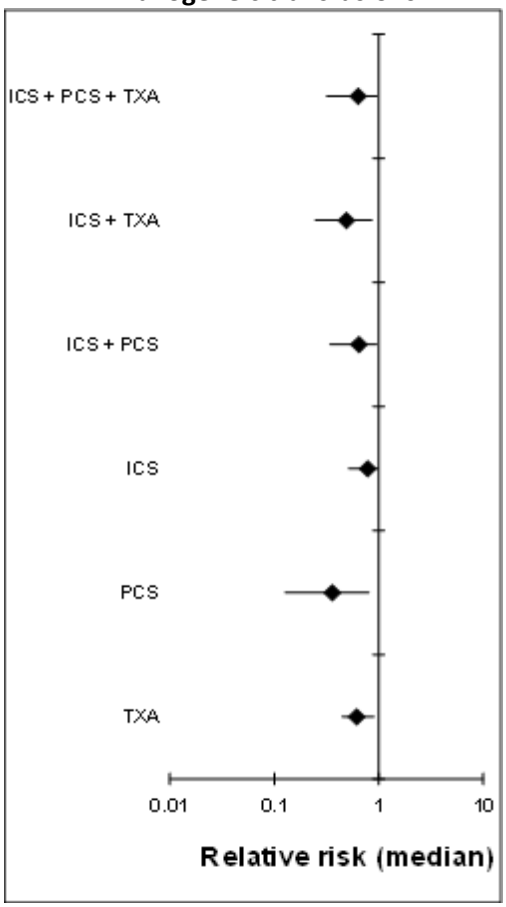


Figure 182: Relative risk (median) for number of patients receiving allogeneic transfusions



Based on the relative risks from the direct comparisons , efficacy as assessed by number of patients receiving allogeneic transfusions favours tranexamic acid, post-operative cell salvage, intra-operative cell salvage and the combination of intra-operative and post-operative cell salvage over standard treatment and the combination of intra-operative cell salvage and tranexamic acid over intra-operative cell salvage. No other treatment effects reached statistical significance.

The random effects model used for the NMA is a relatively good fit, with a residual deviance of 125.8 reported. This corresponds fairly well to the total number of trial arms, 112. The between study variance was 0.2149 (0.01189, 0.4721). No inconsistency was identified between the direct and NMA results for any comparison. All the median odds ratios from the NMA lie within the 95% confidence interval from the direct comparison of the same comparisons (see Table 42). The DiC value from the network was 624.777 and the DiC value from the inconsistency model was 626.856.

Evidence statement:

A network meta-analysis of 56 studies comparing seven treatments suggested that PCS is ranked as the best treatment, ICS+TXA is ranked second, TXA, ICS+PCS+TXA and ICS+PCS are jointly ranked fourth and standard treatment ranked least effective at reducing the number of adult patients receiving allogeneic transfusions in the high risk group, but there was considerable uncertainty.

L.3.4 Network 2: Units of allogeneic blood transfused (Adults- high risk group)

Table 8 summarises the results of the conventional meta-analyses in terms of mean differences generated from studies directly comparing different interventions, together with the results of the NMA in terms of mean differences for every possible treatment comparison.

Table 8: Mean differences for units of allogeneic blood transfused (Adults- high risk group)

Comparison		Mean difference	
		Direct (mean)	NMA (median)
Versus standard treatment	ICS vs. standard treatment	-0.78 (-1.37, -0.19)	-0.818 (-1.671, -0.1148)
	TXA vs. standard treatment	-0.83 (-1.17, -0.50)	-0.8536 (-1.343, -0.4843)
	PCS vs. standard treatment	-1.02 (-1.19, -0.86)	-1.021 (-2.29, 0.2511)
	ICS+TXA vs. standard treatment	-	-2.16 (-3.444, -0.9444)
Versus ICS	TXA vs. ICS	-	-0.03479 (-0.8862, 0.8435)
	PCS vs. ICS	-	-0.2067 (-1.609, 1.375)
	ICS+TXA vs. ICS	-1.56 (-1.84, -1.29)	-1.346 (-2.291, -0.3032)
Versus TXA	PCS vs. TXA	-	-0.1725 (-1.438, 1.243)
	ICS+TXA vs. TXA	-	-1.309 (-2.589, 0.03418)
Versus PCS	ICS+TXA vs. PCS	-	-1.141 (-2.965, 0.6136)

Abbreviations: TXA-Tranexamic acid, PCS-Post-operative cell salvage, ICS-Intra-operative cell salvage

Figure 183 shows the rank of each intervention compared to the others. Figure 184 shows the median of the mean differences of each intervention compared to the others. The rank is based on the mean difference compared to baseline and indicates the probability of being the best treatment, second best, third best and so on among the 5 interventions being evaluated.

Figure 183: Rank order for treatments based on units of allogeneic blood transfused

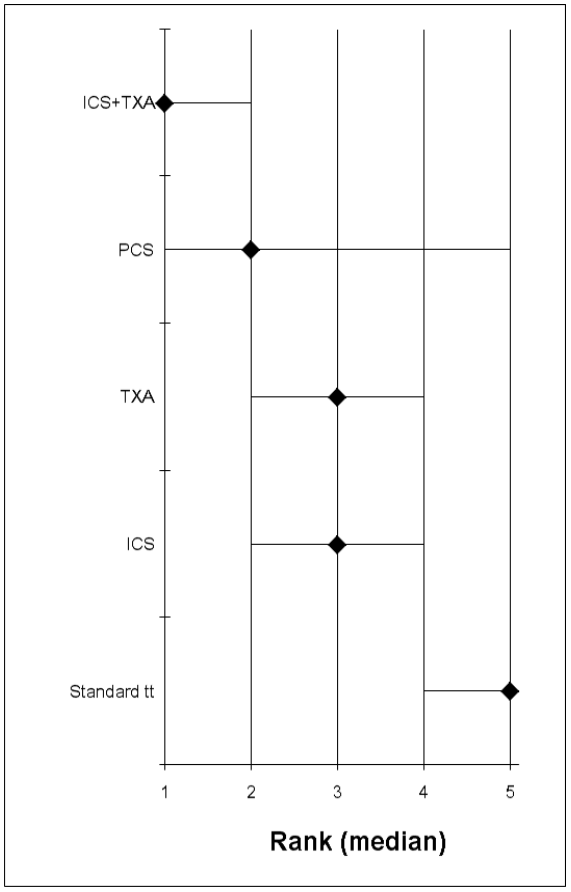
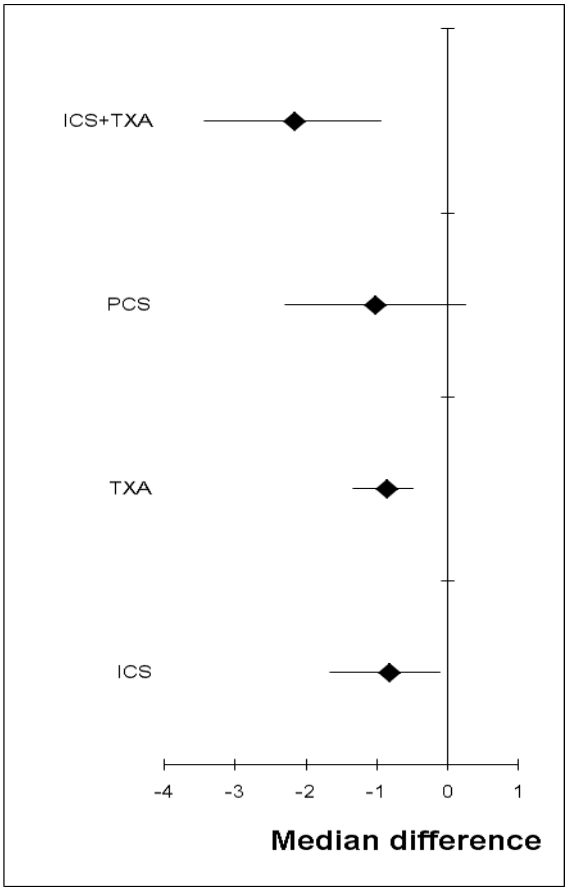


Figure 184: Mean differences (median) for units of allogeneic blood transfused



Based on the direct comparisons (first results column Table 8), efficacy as assessed by reduced number of units of allogeneic transfusions received favours intra-operative cell salvage, post-operative cell salvage, tranexamic acid over standard treatment, and the combination of intra-operative cell salvage and tranexamic acid over intra-operative cell salvage. No other treatment effects reached statistical significance.

The random effects model used for the NMA is a relatively good fit, with a residual deviance of 54.55 reported. This corresponds fairly well to the total number of trial arms, 46. The between study variance was 0.5521 (0.2752, 1.078). The DiC value for the network was 61.454. No inconsistency was identified between the direct and NMA results for any comparison. All the mean differences from the NMA lie within the 95% confidence interval from the direct comparison of the same comparisons.

Evidence statement:

A network meta-analysis of 23 studies comparing five treatments suggested that ICS+TXA is ranked as the best treatment, PCS is ranked second, TXA and ICS are jointly ranked third, and standard treatment ranked least effective at reducing the number of units of allogeneic blood transfusions in adult patients in the high risk group, but there was considerable uncertainty.

L.3.5 Network 3: Length of stay in hospital (Adults- high risk group)

Table 9 summarises the results of the conventional meta-analyses in terms of mean differences generated from studies directly comparing different interventions, together with the results of the NMA in terms of mean differences for every possible treatment comparison.

Table 9: Mean differences for length of stay in hospital (Adults- high risk group)

Comparison		Mean difference	
		Direct (mean)	NMA (median)
Versus standard treatment	TXA vs. standard treatment	-0.08 (-0.35, 0.18)	-0.1266 (-0.9664, 0.4938)
	ICS vs. standard treatment	-0.22 (-1.16, 0.72)	-0.1668 (-1.346 , 1.041)
	PCS vs. standard treatment	-7.13 (-9.12, -5.14)	-7.123 (-9.394, -4.869)
	ICS+PCS vs. standard treatment	2.80 (-2.11, 7.71)	2.83 (-2.182, 7.842)
	ICS+TXA vs. standard treatment	-	0.6375 (-1.306, 2.607)
Versus TXA	ICS vs. TXA	-	-0.03038 (-1.315, 1.428)
	PCS vs. TXA	-	-6.987 (-9.315, -4.577)
	ICS+PCS vs. TXA	-	2.977 (-2.077, 8.056)
	ICS+TXA vs. TXA	2.10 (-3.36, 7.56)	0.7759 (-1.204, 2.864)
Versus ICS	PCS vs. ICS	-	-6.962 (-9.537, -4.427)
	ICS+PCS vs. ICS	-	2.994 (-2.137, 8.15)
	ICS+TXA vs. ICS	0.68 (-0.81, 2.17)	0.8029 (-0.8243, 2.432)
Versus PCS	ICS+PCS vs. PCS	-	9.961 (4.498, 15.46)
	ICS+TXA vs. PCS	-	7.748 (4.834, 10.78)
Versus ICS+PCS	ICS+TXA vs. ICS+PCS	-	-2.196 (-7.537, 3.248)

Abbreviations: TXA-Tranexamic acid, PCS-Post-operative cell salvage, ICS-Intra-operative cell salvage

Figure 185 shows the rank of each intervention compared to the others. Figure 186 shows the median of the mean differences of each intervention compared to the others. The rank is based on the mean difference compared to baseline and indicates the probability of being the best treatment, second best, third best and so on among the 6 different interventions being evaluated.

Figure 185: Rank order for treatments based on length of stay in hospital

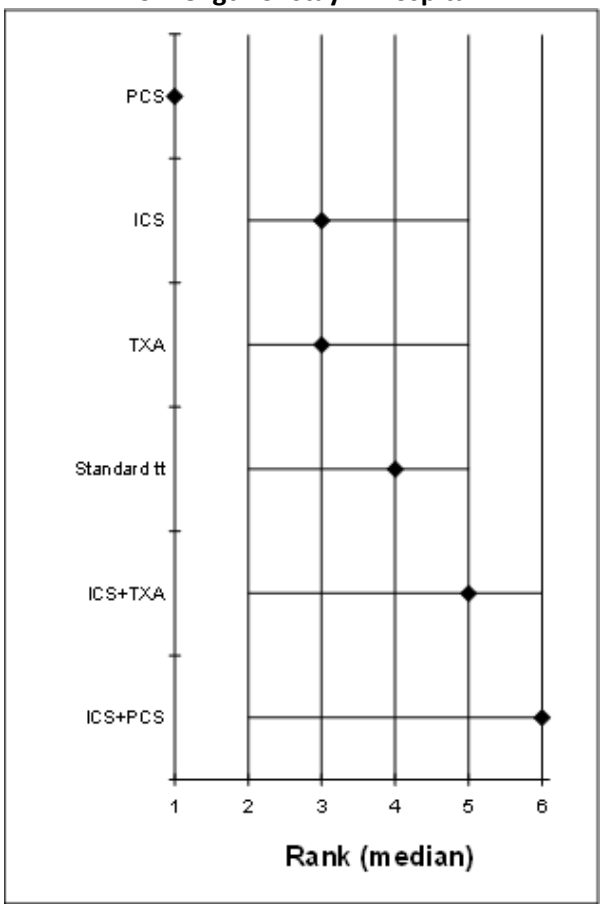
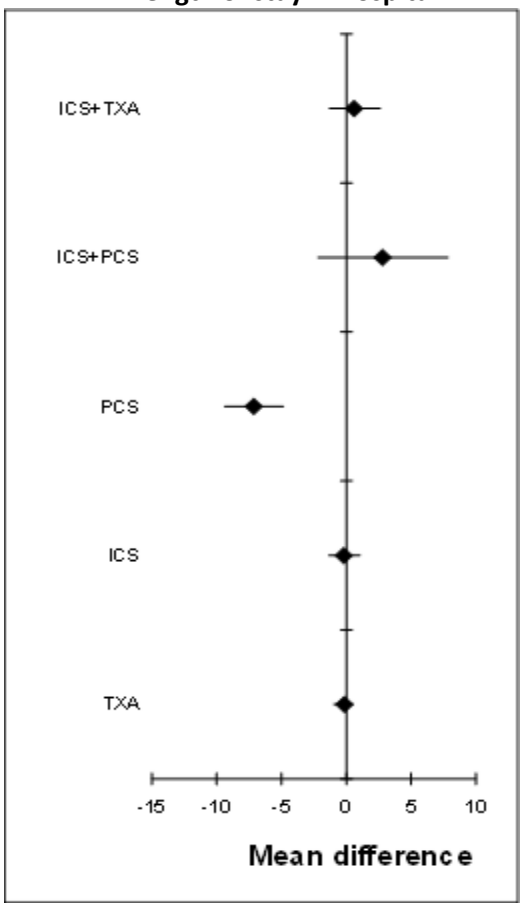


Figure 186: Mean differences (median) for length of stay in hospital



Based on the direct comparisons (first results column Table 9), efficacy as assessed by reduced length of stay in hospital favours post-operative cell salvage over standard treatment. No other treatment effects reached statistical significance.

The random effects model used for the NMA is a relatively good fit, with a residual deviance of 16.82 reported. This corresponds fairly well to the total number of trial arms, 20. The between study variance was 0.261 (0.01098, 1.459). The DiC value for this network was 44.320. No inconsistency was identified between the direct and NMA results for any comparison. All the mean differences from the NMA lie within the 95% confidence interval from the direct comparison of the same comparisons.

Evidence statement:

A network meta-analysis of 10 studies comparing six treatments suggested that PCS is ranked as the best treatment, ICs and TXA are jointly ranked third, standard treatment is ranked fourth,

ICS+TXA is ranked fifth and ICS+PCS is ranked least effective at reducing length of stay in hospital in adult patients in the high risk group, but there was considerable uncertainty.

L.3.6 Network 4: Number of patients receiving allogeneic blood (Adults- moderate risk group)

Table 10 summarises the results of the conventional meta-analyses in terms of risk ratios generated from studies directly comparing different interventions, together with the results of the NMA in terms of risk ratios for every possible treatment comparison.

Table 10: Risk ratios for number of patients receiving allogeneic transfusions (Adults-moderate risk group)

Comparison		Odds ratio	
		Direct (mean)	**NMA (median)**
Versus standard treatment	TXA vs. standard treatment	0.23(0.18, 0.3)	0.1790 (0.1285, 0.2428)
	PCS vs. standard treatment	0.43(0.25, 0.73)	0.4111 (0.2421, 0.6789)
	ICS vs. standard treatment	0.56(0.24, 1.3)	0.655 (0.2171, 1.925)
	ICS+PCS vs. standard treatment	0.83(0.51, 1.35)	0.4954 (0.1385, 1.713)
	ICS+PCS+TXA vs. standard treatment	-	0.1239 (0.01897, 0.7784)
	PCS+TXA vs. standard treatment	-	0.1223 (0.01919, 0.6719)
	ICS+TXA vs. standard treatment	-	0.4382 (0.0562, 3.374)
Versus TXA	PCS vs. TXA	-	2.293 (1.264, 4.181)
	ICS vs. TXA	-	3.654 (1.18, 11.39)
	ICS+PCS vs. TXA	-	2.766 (0.7558, 10.05)
	ICS+PCS+TXA vs. TXA	0.7(0.28, 1.72)	0.6914 (0.1102, 4.311)
	PCS+TXA vs. TXA	-	0.6822 (0.1059, 3.903)
	ICS+TXA vs. TXA	-	2.442 (0.311, 19.47)
Versus PCS	ICS vs. PCS	-	1.591 (0.4809, 5.349)
	ICS+PCS vs. PCS	0.67 (0.39, 1.2)	1.207 (0.3335, 4.359)
	ICS+PCS+TXA vs. PCS	-	0.3014 (0.04394, 2.061)
	PCS+TXA vs. PCS	0.35(0.11, 1.13)	0.2981 (0.05066, 1.535)
	ICS+TXA vs. PCS	-	1.064 (0.1306, 8.837)
Versus ICS	ICS+PCS vs. ICS	-	0.7563 (0.1434, 3.972)
	ICS+PCS+TXA vs. ICS	-	0.1895 (0.02182, 1.628)
	PCS+TXA vs. ICS	-	0.1869 (0.02193, 1.426)
	ICS+TXA vs. ICS	0.67 (0.34, 1.33)	0.6697 (0.1192, 3.782)
Versus ICS+PCS	ICS+PCS+TXA vs. ICS+PCS	-	0.2497 (0.02635, 2.353)
	PCS+TXA vs. ICS+PCS	-	0.2465 (0.02783, 1.981)
	ICS+TXA vs. ICS+PCS	-	0.8879 (0.08067, 9.756)
Versus ICS+PCS+TXA	PCS+TXA vs. ICS+PCS+TXA	-	0.9818 (0.07212, 12.35)
	ICS+TXA vs. ICS+PCS +TXA	-	3.536 (0.2247, 56.38)

Versus PCS+TXA	ICS+TXA vs. PCS +TXA	-	3.62 (0.2495, 56.34)

Abbreviations: TXA-Tranexamic acid, PCS-Post-operative cell salvage, ICS-Intra-operative cell salvage

Figure 187 shows the rank of each intervention compared to the others. Figure 188 shows the median relative risk of each intervention compared to the others. The rank is based on the relative risk compared to baseline and indicates the probability of being the best treatment, second best, third best and so on among the 8 different interventions being evaluated.

Figure 187: Rank order for treatments based on number of patients receiving allogeneic transfusions

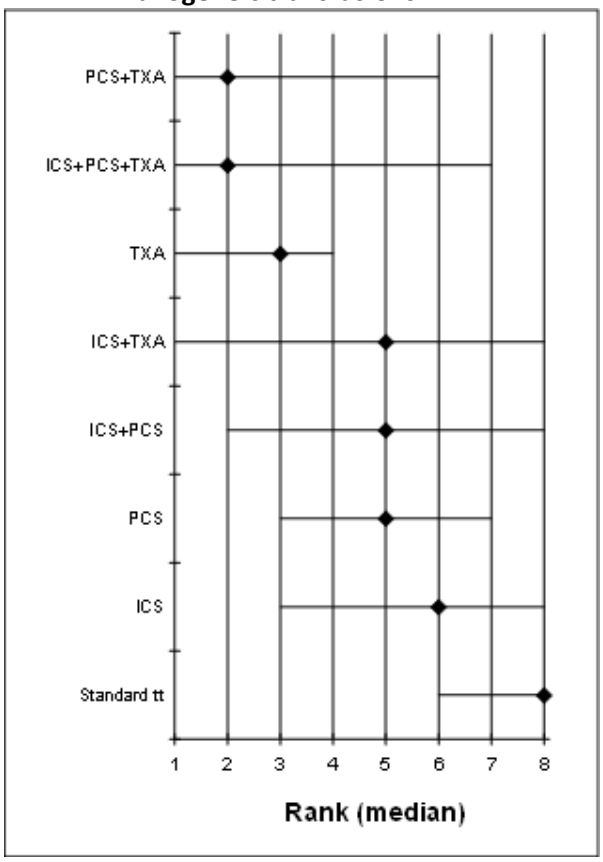
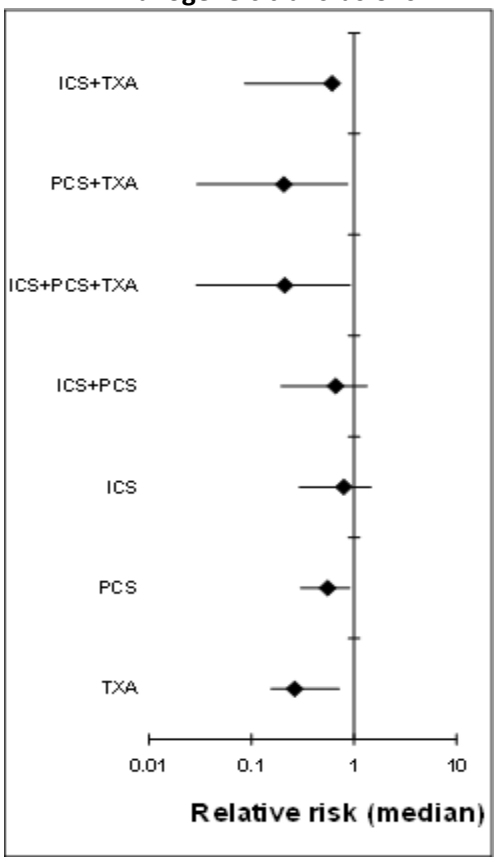


Figure 188: Relative risk (median) for number of patients receiving allogeneic transfusions



Based on the direct comparisons (first results column Table 10), efficacy as assessed by number of patients receiving allogeneic transfusions favours the use of post-operative cell salvage or tranexamic acid over standard treatment. No other treatment effects reached statistical significance.

The random effects model used for the NMA is a relatively good fit, with a residual deviance of 145.2 reported. This corresponds fairly well to the total number of trial arms, 147. The between

study variance was 0.7827 (0.5682, 1.057). On evaluating inconsistency by comparing the odds ratios, the NMA estimated odds ratio for ICS+PCS vs. standard treatment (0.4954 [0.1385, 1.713]) lay outside of the confidence interval of the odds ratio estimated from the direct comparison (0.83[0.51, 1.35]). However, the DiC values generated from the network and the inconsistency models were similar highlighting that there was no inconsistency. The DiC value from the network was 745. 119 and the DiC value from the inconsistency model was 745.202.

Evidence statement:

A network meta-analysis of 73 studies comparing eight treatments suggested that PCS+TXA is ranked as the best treatment, ICS +TXA is ranked second, TXA is ranked fourth, ICS+TXA, ICS+PCS and PCS are jointly ranked fifth, ICS is ranked sixth and standard treatment is ranked least effective at reducing the number of adult patients receiving allogeneic transfusions in the moderate risk group, but there was considerable uncertainty.

L.3.7 Network 5: Units of allogeneic blood transfused (Adults- moderate risk group)

Table summarises the results of the conventional meta-analyses in terms of mean differences generated from studies directly comparing different interventions, together with the results of the NMA in terms of mean differences for every possible treatment comparison.

Table 11: Mean differences for units of allogeneic blood transfused (Adults- Moderate risk group)

Comparison		Mean difference	
		Direct (mean)	NMA (median)
Versus Standard treatment	TXA vs. standard treatment	-0.88 (-1.22, -0.54)	-0.9028 (-1.397, -0.4369)
	PCS vs. standard treatment	-0.82 (-1.31, -0.33)	-0.8217 (-1.364, -0.2834)
	ICS+PCS vs. standard treatment	0.81 (0.49, 1.13)	1.11(-0.1026, 2.313)
Versus TXA	PCS vs. TXA	-	0.0816(-0.6285, 0.8177)
	ICS+PCS vs. TXA	-	2.013(0.7254, 3.317)
Versus PCS	ICS+PCS vs. PCS	2.23 (1.92, 2.54)	1.932(0.7209, 3.136)

(a) Abbreviations: TXA-Tranexamic acid, PCS-Post-operative cell salvage, ICS-Intra-operative cell salvage

Figure 205 shows the rank of each intervention compared to the others. Figure 206 shows the median of the mean differences of each intervention compared to the others. The rank is based on the mean difference compared to baseline and indicates the probability of being the best treatment, second best, third best and so on among the 4 interventions being evaluated.

Figure 189: Rank order for treatments based on units of allogeneic blood transfused

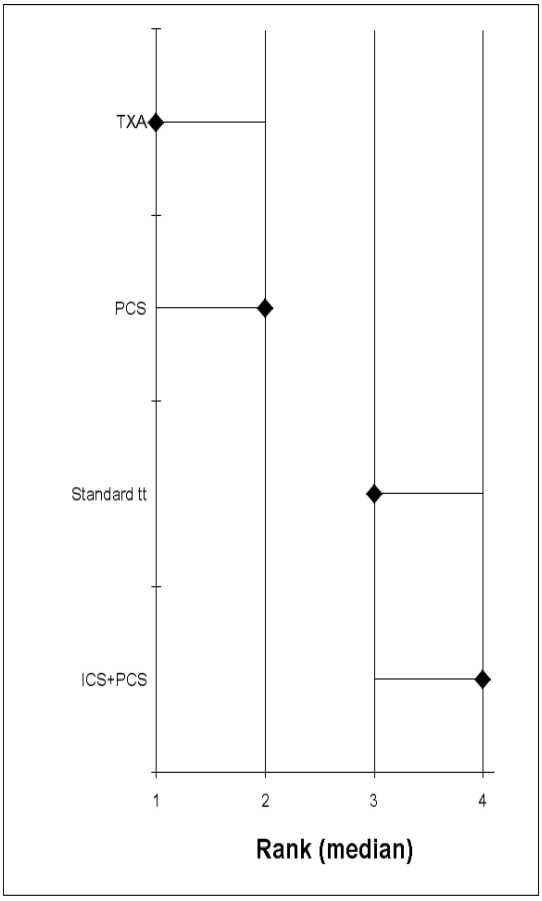
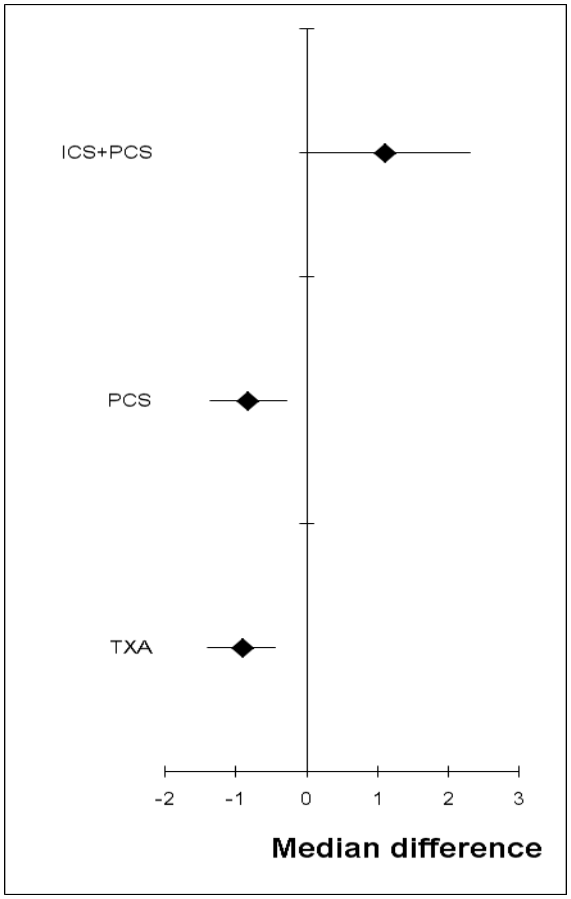


Figure 190: Mean differences (median) for units of allogeneic blood transfused



Based on the direct comparisons (first results column Table 46), efficacy as assessed by reduced number of units of allogeneic transfusions received favours tranexamic acid and post-operative cell salvage over standard treatment, and standard treatment over the combination of intra-operative cell salvage and post-operative cell salvage. No other treatment effects reached statistical significance.

The random effects model used for the NMA is a relatively good fit, with a residual deviance of 33.45 reported. This corresponds fairly well to the total number of trial arms, 33. The DiC value of the network was 8.237. No inconsistency was identified between the direct and NMA results for any comparison. All the mean differences from the NMA lie within the 95% confidence interval from the direct comparison of the same comparisons.

Evidence statement:

A network meta-analysis of 16 studies comparing four treatments suggested that PCS and TXA are jointly ranked as the best treatment, standard treatment is ranked third and the combination of ICS+PCS is ranked least effective at reducing the number of units of allogeneic blood transfusions in adult patients in the moderate risk group, but there was some uncertainty.

L.4 Discussion

Based on the results of conventional meta-analyses of direct evidence, as has been previously presented in chapter 6 and appendix 6.5.2, deciding upon the most effective intervention as an alternative to blood transfusion in surgical patients is challenging. In order to overcome the difficulty of interpreting the conclusions from numerous separate comparisons, network meta-analysis of the direct evidence were performed.

Our analyses were divided into two risk groups- high and moderate risk groups (For details of stratification, please refer section 6.4.2, chapter 6). 73 studies formed 3 networks, each for a different outcome, in the high risk group; 56 studies were included in a network for one outcome in the moderate risk group. Four treatment interventions were evaluated alone or in combination with one another in these analyses.

The findings from the NMA were used to facilitate the GDG in decision making when developing recommendations for alternatives to blood transfusion in surgical patients.

In the first network of number of adult patients receiving allogeneic transfusions in the high risk group, all treatments were found to be superior to standard treatment; ICS+TXA was found to be superior to TXA, ICS, ICS+PCS+TXA, ICS+PCS; TXA alone was found to be superior to ICS, ICS+PCS+TXA, ICS+PCS; ICS+PCS+TXA was found to be superior to ICS, ICS+PCS; ICS+PCS was found to be superior to ICS alone.

In the ranking of treatments PCS was ranked as the best treatment although there is considerable uncertainty about this estimate as the credible intervals are quite wide; the GDG also discussed concerns regarding the applicability of this evidence and highlighted that it may not be an appropriate intervention in all high risk surgeries (for details, please refer the full cost-effectiveness analysis in Appendix M and the LETR). ICS+TXA was ranked second and the GDG noted that in surgical patients who were expected to have very high blood loss, this may well be the most appropriate blood saving intervention. TXA was ranked third, with much smaller credible intervals only spanning three ranking positions.

In the second network of number of units of allogeneic transfusions received in the high risk group, all treatments were found to be superior to standard treatment; ICS+TXA was found to be superior to PCS, TXA, ICS; PCS was found to be superior to TXA,ICS; TXA and ICS were found to be superior to standard treatment.

In the ranking of treatments ICS +TXA was ranked as the best treatment with very precise credible intervals spanning spanning only two ranking interventions; the GDG agreed that ICS+TXA was the most blood saving intervention in the high risk group in terms of number of units transfused. PCS was ranked second ICS+TXA was ranked second, but with very wide credible intervals; TXA and ICs were jointly ranked third.

In the third network of length of stay in hospital in the high risk group, all treatments were found to be superior to ICS+PCS; PCS was found to be superior to ICS, TXA, Standard treatment, ICS+TXA; ICS was found to be superior to TXA, Standard treatment, ICS+TXA; Standard treatment was found to be superior to ICS+TXA.

In the ranking of treatments PCS was ranked as the best treatment with very precise credible intervals. However, the GDG noted that this was based on data from one study where the baseline group had a very high length of stay. ICS and TXA were jointly ranked as the second best interventions having reduced length of stay, with identical credible intervals. Standard treatment was ranked as the third best intervention over ICS+TXA and ICS+PCS, but all three had very wide credible intervals spanning greater than three ranking interventions.

In the fourth network of number of adult patients receiving allogeneic transfusions in the moderate risk group, all treatments were found to be superior to standard treatment; PCS+TXA was found to be superior to ICS+PCS+TXA, TXA, ICS+TXA, ICS+PCS, PCS, ICS; ICS+PCS+TXA was found to be superior to TXA, ICS+TXA, ICS+PCS, PCS; TXA alone was found to be superior to ICS+TXA, ICS+PCS, PCS, ICS; ICS+TXA was found to be superior to ICS+PCS, PCS, ICS; ICS+PCS was found to be superior to PCS, ICS; PCS was found to be superior to ICS.

In the ranking of treatments PCS+TXA was ranked first and ICS+PCS+TXA was ranked second, although both rankings had very wide credible intervals spanning greater than five treatment ranking interventions. TXA was ranked third, but with much smaller credible intervals only spanning three ranking positions. ICS +TXA and ICS+PCS were jointly ranked fifth with very wide credible intervals spanning greater than six treatment ranking interventions. PCS was also ranked fifth, but had smaller credible intervals spanning four treatment ranking interventions. ICs was ranked sixth but again, had very wide credible intervals.

All four networks seem to fit well, as demonstrated by residual deviance and no inconsistencies in the networks were found.

In summary, the three outcomes chosen for this analysis were considered to be among the most important for assessing efficacy of alternatives to blood transfusion in adult surgical patients in the high and moderate risk groups. All of these outcomes contributed to the cost effectiveness analysis (see Appendix M).

L.5 Conclusion

This analysis allowed us to combine findings from many different comparisons presented in the reviews for alternatives to blood transfusion even when direct comparative data was lacking.

Overall, the GDG agreed that results of the four networks in the high and moderate risk groups were not conclusive. It was acknowledged that the combination of intra-operative cell salvage and tranexamic acid and, tranexamic acid alone were likely to be the most effective blood saving interventions and therefore appropriate as alternatives to blood transfusion in adult surgical patients.

It should be noted that this analysis does not take into account the adverse effect profile of these treatments, but known profiles have been taken into account in the development of the associated recommendations. For details of the rationale and discussion around the discussion leading to recommendations, please refer the section linking the evidence to the recommendations (section 4.5, chapter 4).

L.6 WinBUGS codes

L.6.1 WinBUGS code for assessment of baseline risk of receiving allogeneic transfusions (High risk group)

```
# Baseline random effects model
model{                    # *** PROGRAM STARTS
for (i in 1:ns){           # LOOP THROUGH STUDIES
   r[i] ~ dbin(p[i],n[i])                # Likelihood
   logit(p[i]) <- mu[i]                        # Log-odds of response
   mu[i] ~ dnorm(m,tau.m)     # Random effects model
 }
mu.new ~ dnorm(m,tau.m)             # predictive dist. (log-odds)
m ~ dnorm(0,.0001)            # vague prior for mean
var.m <- 1/tau.m              # between-trial variance
tau.m <- pow(sd.m,-2)   # between-trial precision = (1/between-trial variance)
sd.m ~ dunif(0,5)             # vague prior for between-trial SD
#tau.m ~ dgamma(0.001,0.001)
#sd.m <- sqrt(var.m)
logit(R) <- m                 # posterior probability of response
logit(R.new) <- mu.new        # predictive probability of response
}

 Data
list(ns=48)  # ns=number of studies

r[]        n[]
31         41
7          31
21         29
```

1	8	25
2	1	33
3	30	30
4	3	24
5	19	49
6	64	102
7	10	15
8	27	38
9	5	17
10	51	96
11	10	43
12	23	50
13	7	25
14	41	165
15	12	20
16	8	33
17	21	40
18	8	39
19	12	31
20	221	278
21	54	59
22	27	50
23	6	30
24	54	115
25	8	40
26	17	108
27	63	140
28	9	14
29	4	20

```
8 14
12 20
37 40
4 20
13 19
27 44
16 44
10 31
27 106
9 14
18 24
11 15
43 75
22 50
74 100
108 177
END

 Inits
list(mu=c( 0,0,0,0,0,  0,0,0,0,0,  0,0,0,0,0,  0,0,0,0,0,  0,0,0,0,0,  0,0,0,0,0,  0,0,0,0,0,  0,0,0,0,0,
0,0,0,0,0,0,0,0,0), sd.m=1, m=0)
list(mu = c(1,-1,-1,-1,-1,  -1,-1,-1,-1,-1,  -1,-1,-1,-1,-1,  -1,-1,-1,-1,-1,  -1,-1,-1,-1,-1,  -1,-1,-1,-1,-1,
-1,-1,-1,-1,-1,  -1,-1,-1,-1,-1,  -1,-1,-1,-1,-1,-1,-1,-1,-1), sd.m=2, m= -1)
list(mu = c(1,1,1,1,1,  1,1,1,1,1,  1,1,1,1,1,  1,1,1,1,1,  1,1,1,1,1,  1,1,1,1,1,  1,1,1,1,1,  1,1,1,1,1,
1,1,1,1,1,1,1,1,1), sd.m = 0.5, m = 1)
```

L.6.2 WinBUGS code for number of adult patients receiving allogeneic transfusions (High risk group)

```
NUMBER TRANSFUSED HIGH RISK
# Binomial likelihood, logit link
```

```
# Random effects model for multi-arm trials
model{                          # *** PROGRAM STARTS
for(i in 1:ns){                 # LOOP THROUGH STUDIES
   w[i,1] <- 0    # adjustment for multi-arm trials is zero for control arm
   delta[i,1] <- 0           # treatment effect is zero for control arm
   mu[i] ~ dnorm(0,.0001)          # vague priors for all trial baselines
   for (k in 1:na[i]) {           # LOOP THROUGH ARMS
      r[i,k] ~ dbin(p[i,k],n[i,k]) # binomial likelihood
      logit(p[i,k]) <- mu[i] + delta[i,k]  # model for linear predictor
      rhat[i,k] <- p[i,k] * n[i,k] # expected value of the numerators
#Deviance contribution
      dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k]))
         +  (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-rhat[i,k])))        }
#  summed residual deviance contribution for this trial
   resdev[i] <- sum(dev[i,1:na[i]])
   for (k in 2:na[i]) {           # LOOP THROUGH ARMS
# trial-specific LOR distributions
      delta[i,k] ~ dnorm(md[i,k],taud[i,k])
# mean of LOR distributions (with multi-arm trial correction)
      md[i,k] <-  d[t[i,k]] - d[t[i,1]] + sw[i,k]
# precision of LOR distributions (with multi-arm trial correction)
      taud[i,k] <- tau *2*(k-1)/k
# adjustment for multi-arm RCTs
      w[i,k] <- (delta[i,k] - d[t[i,k]] + d[t[i,1]])
# cumulative adjustment for multi-arm trials
      sw[i,k] <- sum(w[i,1:k-1])/(k-1)
     }
 }
totresdev <- sum(resdev[])         # Total Residual Deviance
```

```
d[1]<-0      # treatment effect is zero for reference treatment
# vague priors for treatment effects
for (k in 2:nt){  d[k] ~ dnorm(0,.0001) }
sd ~ dunif(0,5)     # vague prior for between-trial SD
tau <- pow(sd,-2)   # between-trial precision = (1/between-trial variance)
# Provide estimates of treatment effects T[k] on the natural (probability) scale
# Given a Mean Effect, meanA, for 'standard' treatment A,
# with precision (1/variance) precA
A ~ dnorm(meanA,precA)
for (k in 1:nt) { logit(T[k]) <- A + d[k]  }
rr [1] < -1
for (k in 2:nt)  {rr[k]<-T[k]/T[1] }
for (c in 1:(nt-1))
{  for (k in (c+1):nt)
{  lor[c,k] <- d[k] - d[c]
log(or[c,k]) <- lor[c,k]
lrr[c,k] <- log(rr[k]) - log(rr[c])
log(rrisk[c,k]) <- lrr[c,k] }}
for (k in 1:nt) {
rk[k]<-rank(rr[],k)
best[k]<-equals(rank(rr[],k),1)}

}                          # *** PROGRAM ENDS

 Data
# ns= number of studies; nt=number of treatments
list(ns=56, nt=7, meanA=-0.07213, precA=0.708544479588251)

r[,1]      r[,2]      n[,1]      n[,2]      t[,1]      t[,2]      na[]
```

1	31	21	41	40	1	4	2
2	7	4	31	30	1	4	2
3	21	17	29	30	1	4	2
4	8	7	25	25	1	4	2
5	1	2	33	32	1	3	2
6	30	19	30	30	1	3	2
7	3	1	24	23	1	3	2
8	19	6	49	41	1	3	2
9	64	41	102	98	1	5	2
10	10	8	15	15	1	5	2
11	13	9	50	52	4	6	2
12	27	20	60	60	4	6	2
13	19	9	26	24	4	6	2
14	12	5	20	20	4	6	2
15	73	57	103	99	4	6	2
16	13	12	29	24	2	6	2
17	14	13	50	50	5	7	2
18	33	31	111	102	2	7	2
19	27	20	38	38	1	2	2
20	5	6	17	20	1	2	2
21	51	51	96	97	1	2	2
22	10	8	43	44	1	2	2
23	23	15	50	50	1	2	2
24	7	2	25	22	1	2	2
25	41	24	165	147	1	2	2
26	12	7	20	20	1	2	2
27	8	5	33	33	1	2	2
28	21	15	40	40	1	2	2
29	8	7	39	40	1	2	2

1	12	7	31	29	1	2	2
2	221	166	278	274	1	2	2
3	54	42	59	58	1	2	2
4	27	8	50	50	1	2	2
5	6	3	30	32	1	2	2
6	54	37	115	116	1	2	2
7	8	3	40	36	1	2	2
8	17	0	108	106	1	2	2
9	63	35	140	143	1	2	2
10	9	7	14	15	1	2	2
11	4	2	20	20	1	2	2
12	8	9	14	16	1	2	2
13	12	15	20	41	1	2	2
14	37	29	40	42	1	2	2
15	4	3	20	20	1	2	2
16	13	14	19	19	1	2	2
17	27	28	44	42	1	2	2
18	16	12	44	37	1	2	2
19	10	7	31	62	1	2	2
20	27	11	106	104	1	2	2
21	9	2	14	16	1	2	2
22	18	12	24	24	1	2	2
23	11	13	15	15	1	2	2
24	43	22	75	75	1	2	2
25	22	15	50	50	1	2	2
26	74	60	100	100	1	2	2
27	108	98	177	189	1	4	2
28							
29	END						

```
 Initial Values
list(
d=c(NA,0,0,0,0,0,0),
sd=.2,
mu=c(2,0,3,0,2,-2,2,-2,-1,3,2,-2,1,3,1,1,2,-3,2,-2,-2,1,0,-3,3,0,-3,-2,-3,-2,3,-3,0,-1,-3,2,1,3,-
2,2,2,0,1,2,0,0,-2,1,-2,-2,-3,-2,1,2,1,2))
list(
d=c(NA,1,1,1,1,1,1),
sd=.1,
mu=c(2,1,3,1,2,0,2,0,-1,3,2,0,1,3,1,1,2,-3,2,0,0,1,1,-3,3,1,-3,0,-3,0,3,-3,1,-1,-
3,2,1,3,0,2,2,1,1,2,1,1,0,1,0,0,-3,0,1,2,1,2))
list(
d=c(NA,0.5,0.5,0.5,0.5,0.5,0.5),
sd=.15,
mu=c(2,0.5,3,0.5,2,-2,2,1,-1,3,2,1,1,3,1,1,2,-3,2,1,1,1,0.5,-3,3,0.5,-3,1,-3,1,3,-3,0.5,-1,-
3,2,1,3,1,2,2,0.5,1,2,0.5,0.5,1,1,1,1,-3,-2,1,2,1,2))
```

L.6.3 WinBUGS code for inconsistency model for number of adult patients receiving allogeneic transfusions (High risk group)

```
High risk number transfused
56 trials
7 treatments

# Binomial likelihood, logit link, inconsistency model
# Random effects model
model{                    # *** PROGRAM STARTS
for(i in 1:ns){           # LOOP THROUGH STUDIES
   delta[i,1]<-0          # treatment effect is zero in control arm
   mu[i] ~ dnorm(0,.0001)  # vague priors for trial baselines
   for (k in 1:na[i])  {   # LOOP THROUGH ARMS
      r[i,k] ~ dbin(p[i,k],n[i,k]) # binomial likelihood
```

```
      logit(p[i,k]) <- mu[i] + delta[i,k]  # model for linear predictor
#Deviance contribution
      rhat[i,k] <- p[i,k] * n[i,k] # expected value of the numerators
      dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k]))
        +  (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-rhat[i,k])))
     }
# summed residual deviance contribution for this trial
  resdev[i] <- sum(dev[i,1:na[i]])
  for (k in 2:na[i]) {  # LOOP THROUGH ARMS
# trial-specific LOR distributions
      delta[i,k] ~ dnorm(d[t[i,1],t[i,k]] ,tau)
     }
 }
totresdev <- sum(resdev[])   # Total Residual Deviance
for (c in 1:(nt-1)) {  # priors for all mean treatment effects
   for (k in (c+1):nt)  { d[c,k] ~ dnorm(0,.0001) }
 }
sd ~ dunif(0,5)  # vague prior for between-trial standard deviation
var <- pow(sd,2) # between-trial variance
tau <- 1/var     # between-trial precision
} # *** PROGRAM ENDS


 Data
# High risk number transfused
# nt=no. treatments, ns=no. studies
list(nt=7,ns=56 )

r[,1]     r[,2]     n[,1]     n[,2]     t[,1]     t[,2]     na[]
```

1	31	21	41	40	1	4	2
2	7	4	31	30	1	4	2
3	21	17	29	30	1	4	2
4	8	7	25	25	1	4	2
5	1	2	33	32	1	3	2
6	30	19	30	30	1	3	2
7	3	1	24	23	1	3	2
8	19	6	49	41	1	3	2
9	64	41	102	98	1	5	2
10	10	8	15	15	1	5	2
11	13	9	50	52	4	6	2
12	27	20	60	60	4	6	2
13	19	9	26	24	4	6	2
14	12	5	20	20	4	6	2
15	73	57	103	99	4	6	2
16	13	12	29	24	2	6	2
17	14	13	50	50	5	7	2
18	33	31	111	102	2	7	2
19	27	20	38	38	1	2	2
20	5	6	17	20	1	2	2
21	51	51	96	97	1	2	2
22	10	8	43	44	1	2	2
23	23	15	50	50	1	2	2
24	7	2	25	22	1	2	2
25	41	24	165	147	1	2	2
26	12	7	20	20	1	2	2
27	8	5	33	33	1	2	2
28	21	15	40	40	1	2	2
29	8	7	39	40	1	2	2

1	12	7	31	29	1	2	2
2	221	166	278	274	1	2	2
3	54	42	59	58	1	2	2
4	27	8	50	50	1	2	2
5	6	3	30	32	1	2	2
6	54	37	115	116	1	2	2
7	8	3	40	36	1	2	2
8	17	0	108	106	1	2	2
9	63	35	140	143	1	2	2
10	9	7	14	15	1	2	2
11	4	2	20	20	1	2	2
12	8	9	14	16	1	2	2
13	12	15	20	41	1	2	2
14	37	29	40	42	1	2	2
15	4	3	20	20	1	2	2
16	13	14	19	19	1	2	2
17	27	28	44	42	1	2	2
18	16	12	44	37	1	2	2
19	10	7	31	62	1	2	2
20	27	11	106	104	1	2	2
21	9	2	14	16	1	2	2
22	18	12	24	24	1	2	2
23	11	13	15	15	1	2	2
24	43	22	75	75	1	2	2
25	22	15	50	50	1	2	2
26	74	60	100	100	1	2	2
27	108	98	177	189	1	4	2
28							
29	END						

INITS

```
# chain 1
list(sd=1, mu=c(2,0,3,0,2, -2,2,-2,-1,3, 2,-2,1,3,1, 1,2,-3,2,-2, -2,1,0,-3,3, 0,-3,-2,-3,-2, 3,-
3,0,-1,-3, 2,1,3,-2,2, 2,0,1,2,0, 0,-2,1,-2,-2, 2,1,1, 2,2,3),
d=structure(.Data=c(NA,0,1,0,0,-2,0, NA,NA,0,0,2,0,0, NA,NA,NA,0,0,0,0, NA,NA,NA,NA,0,0,0,
NA,NA,NA,NA,NA,0,0, NA,NA,NA,NA,NA,NA,0), .Dim = c(6,7)))

# chain 2
list(sd=1.5, mu=c(2,1,3,1,2, 0,2,0,-1,3, 2,0,1,3,1, 1,2,-3,2,0, 0,1,1,-3,3, 1,-3,0,-3,0, 3,-3,1,-1,-
3, 2,1,3,0,2, 2,1,1,2,1, 1,0,1,0,0, 2,3,1, -2,1,2),
d = structure(.Data =c(NA,0,1,0,0,-1,2, NA,NA,1,0.5,2,0,0, NA,NA,NA,2,1,1,0,
NA,NA,NA,NA,0.5,2,0,
NA,NA,NA,NA,NA,2,0, NA,NA,NA,NA,NA,NA,1 ), .Dim = c(6,7)))

# chain 3
list(sd=3, mu=c(2,0.5,3,0.5,2, -2,2,1,-1,3, 2,1,1,3,1, 1,2,-3,2,1, 1,1,0.5,-3,3, 0.5,-3,1,-3,1,
3,-3,0.5,-1,-3, 2,1,3,1,2, 2,0.5,1,2,0.5, 0.5,1,1,1,1, 2,1,0, -1,0,1),
d = structure(.Data =c(NA,0,1,0,0,-2,0, NA,NA,0,1,-2,0,-1, NA,NA,NA,2,0,1,0,
NA,NA,NA,NA,0,1,2,
NA,NA,NA,NA,NA,1,1, NA,NA,NA,NA,NA,NA,-1), .Dim = c(6,7)))
```

L.6.4 WinBUGS code for number of units of receiving allogeneic blood transfusions (High risk group)

```
UNITS TRANSFUSED - HIGH RISK
# Normal likelihood, identity link
# Random effects model for multi-arm trials
```

```
model{                          # *** PROGRAM STARTS
for(i in 1:ns){                  #   LOOP THROUGH STUDIES
   w[i,1] <- 0    # adjustment for multi-arm trials is zero for control arm
   delta[i,1] <- 0           # treatment effect is zero for control arm
   mu[i] ~ dnorm(0,.0001)          # vague priors for all trial baselines
   for (k in 1:na[i]) {           #  LOOP THROUGH ARMS
      var[i,k] <- pow(se[i,k],2)   # calculate variances
      prec[i,k] <- 1/var[i,k]      # set precisions
      y[i,k] ~ dnorm(theta[i,k],prec[i,k]) # binomial likelihood
      theta[i,k] <- mu[i] + delta[i,k]  # model for linear predictor
#Deviance contribution
      dev[i,k] <- (y[i,k]-theta[i,k])*(y[i,k]-theta[i,k])*prec[i,k]
     }
#  summed residual deviance contribution for this trial
   resdev[i] <- sum(dev[i,1:na[i]])
   for (k in 2:na[i]) {           # LOOP THROUGH ARMS
# trial-specific LOR distributions
      delta[i,k] ~ dnorm(md[i,k],taud[i,k])
# mean of LOR distributions, with multi-arm trial correction
      md[i,k] <-  d[t[i,k]] - d[t[i,1]] + sw[i,k]
# precision of LOR distributions (with multi-arm trial correction)
      taud[i,k] <- tau *2*(k-1)/k
# adjustment, multi-arm RCTs
      w[i,k] <- (delta[i,k] - d[t[i,k]] + d[t[i,1]])
# cumulative adjustment for multi-arm trials
      sw[i,k] <- sum(w[i,1:k-1])/(k-1)
     }
 }
totresdev <- sum(resdev[])          #Total Residual Deviance
```

```
d[1]<-0      # treatment effect is zero for control arm
# vague priors for treatment effects
for (k in 2:nt){  d[k] ~ dnorm(0,.0001) }
sd ~ dunif(0,5)     # vague prior for between-trial SD
tau <- pow(sd,-2)   # between-trial precision = (1/between-trial variance)
# Provide estimates of treatment effects T[k] on the natural scale
# Given a Mean Effect, meanA, for 'standard' treatment A,
# with precision (1/variance) precA
A ~ dnorm(meanA,precA)
for (k in 1:nt) { T[k] <- A + d[k]  }
for (k in 1:nt) {
rk[k]<-rank(d[],k)
best[k]<-equals(rank(d[],k),1)}
for (c in 1:(nt-1))
{  for (k in (c+1):nt)
{  D[c,k] <- d[k] - d[c]}}
}                              # *** PROGRAM ENDS
 Data
# ns= number of studies; nt=number of treatments
list(ns=23, nt=5, meanA=-1, precA=1)


t[,1]    t[,2]    y[,1]    y[,2]    se[,1]    se[,2]    na[]
1        2        11.17    6.47     1.263597349    1.121639956    2
1        2        1.38     0.53     0.207129187    0.102774024    2
1        2        2.4      1.54     0.258     0.22453656     2
1        2        0.7      0.4      0.2       0.16      2
1        4        2.22     1.2      0.073029674    0.04929503     2
2        5        1.68     0.87     0.453139052    0.196231156    2
```

1	2	5	3.21	1.58	0.107863874	0.100020831	2
2	1	3	0.87	0.41	0.109870053	0.077770507	2
3	1	3	1.57	0.8	0.400891863	0.278854801	2
4	1	3	1.7	0.8	0.402492236	0.171791138	2
5	1	3	7.75	5.33	0.996117463	0.890330329	2
6	1	3	0.76	0.92	0.241495342	0.188561808	2
7	1	3	3.03	1.42	0.82079623	0.347980348	2
8	1	3	3.13	2.87	0.852056336	0.490577891	2
9	1	3	9.16	4.1	2.694438717	0.910393688	2
10	1	3	12.4	7.9	2.529822128	1.043551628	2
11	1	3	1.68	0.52	0.2	0.18	2
12	1	3	1.4	0.8	0.194665705	0.129777137	2
13	1	3	3.17	2.03	0.092068326	0.074034324	2
14	1	3	6.51	3.93	0.439624185	0.281520895	2
15	1	3	9.36	4.84	1.485455474	0.768142632	2
16	1	3	1.62	0.91	0.239653736	0.147627794	2
17	1	3	1.65	1.25	0.053	0.055	2

END

Initial Values

#chain 1

list(d=c(NA, 0,0,0,0), sd=1, mu=c(0,0,0,0,0,0,0,0,0,0,0,1,1,1, 0, 0, 0, 0, 0, 1,1,1,0))

#chain 2

list(d=c(NA, -1,-3,1,-1), sd=4, mu=c(0,3,0,-1,0,2,1,0,-3,0,-2,1,1,1, 2, 0, 0, 1, 1,1,1,2,0))

#chain 3

list(d=c(NA, 2,2,2,2), sd=2, mu=c(2,3,1,-1,1,2,0,0,-3,0,2,1,-1,1,-2, 0, 0,-1,-1,1,1,-1,0))

L.6.5 WinBUGS code for length of stay in hospital (High risk group)

LENGTH OF STAY - HIGH RISK

```
# Normal likelihood, identity link
# Random effects model for multi-arm trials
model{                          # *** PROGRAM STARTS
for(i in 1:ns){                 #   LOOP THROUGH STUDIES
   w[i,1] <- 0    # adjustment for multi-arm trials is zero for control arm
   delta[i,1] <- 0           # treatment effect is zero for control arm
   mu[i] ~ dnorm(0,.0001)          # vague priors for all trial baselines
   for (k in 1:na[i]) {           #  LOOP THROUGH ARMS
      var[i,k] <- pow(se[i,k],2)   # calculate variances
      prec[i,k] <- 1/var[i,k]      # set precisions
      y[i,k] ~ dnorm(theta[i,k],prec[i,k]) # binomial likelihood
      theta[i,k] <- mu[i] + delta[i,k]  # model for linear predictor
#Deviance contribution
      dev[i,k] <- (y[i,k]-theta[i,k])*(y[i,k]-theta[i,k])*prec[i,k]
     }
#  summed residual deviance contribution for this trial
   resdev[i] <- sum(dev[i,1:na[i]])
   for (k in 2:na[i]) {           # LOOP THROUGH ARMS
# trial-specific LOR distributions
      delta[i,k] ~ dnorm(md[i,k],taud[i,k])
# mean of LOR distributions, with multi-arm trial correction
      md[i,k] <-  d[t[i,k]] - d[t[i,1]] + sw[i,k]
# precision of LOR distributions (with multi-arm trial correction)
      taud[i,k] <- tau *2*(k-1)/k
# adjustment, multi-arm RCTs
      w[i,k] <- (delta[i,k] - d[t[i,k]] + d[t[i,1]])
# cumulative adjustment for multi-arm trials
      sw[i,k] <- sum(w[i,1:k-1])/(k-1)
     }
```

```
 }
totresdev <- sum(resdev[])          #Total Residual Deviance
d[1]<-0      # treatment effect is zero for control arm
# vague priors for treatment effects
for (k in 2:nt){  d[k] ~ dnorm(0,.0001) }
sd ~ dunif(0,5)     # vague prior for between-trial SD
tau <- pow(sd,-2)   # between-trial precision = (1/between-trial variance)
# Provide estimates of treatment effects T[k] on the natural scale
# Given a Mean Effect, meanA, for 'standard' treatment A,
# with precision (1/variance) precA
A ~ dnorm(meanA,precA)
for (k in 1:nt) { T[k] <- A + d[k]  }
for (k in 1:nt) {
rk[k]<-rank(d[],k)
best[k]<-equals(rank(d[],k),1)}
for (c in 1:(nt-1))
{  for (k in (c+1):nt)
{  D[c,k] <- d[k] - d[c]}}
}                              # *** PROGRAM ENDS

 Data
# ns= number of studies; nt=number of treatments
list(ns=10, nt=6, meanA=-1, precA=1)

t[,1]    t[,2]    y[,1]    y[,2]    se[,1]    se[,2]    na[]
1        3        7.85     7.65     0.41900179     0.341525987     2
1        4        16.45    9.32     0.931428571    0.398243093     2
1        5        6.8      9.6      0.406138466    2.472393026     2
3        6        4        4.5      0.727590861    0.724640716     2
```

```
3	6	8.5	9.4	0.729143666	0.864332521	2
2	6	12.1	14.2	1.355575969	2.435279909	2
1	2	6.4	5.8	0.670820393	0.491934955	2
1	2	4.8	4.8	0.15666989	0.069631062	2
1	2	7.3	7.1	0.18973666	0.133333333	2
1	3	11.8	11.5	0.721580187	0.763762616	2

END
 Initial Values
#chain 1
list(d=c( NA, 0,0,0,0,0), sd=1, mu=c(1,0, 0, 0, 0, 0, 1,1,0,2))
#chain 2
list(d=c( NA, -3,1,-1,-3,-1), sd=4, mu=c(1, 2, 0, 0, 1, 1,1,1,0,1))
#chain 3
list(d=c( NA, 2,2,2,2,2), sd=2, mu=c(-2, 1, 0, 0,-1,-1,1,1,0,1))
```

L.6.6 WinBUGS code for assessment of baseline risk of receiving allogeneic transfusions (Moderate risk group)

```
# Binomial likelihood, logit link
# Baseline random effects model
model{                    # *** PROGRAM STARTS
for (i in 1:ns){           # LOOP THROUGH STUDIES
   r[i] ~ dbin(p[i],n[i])                # Likelihood
   logit(p[i]) <- mu[i]                        # Log-odds of response
   mu[i] ~ dnorm(m,tau.m)     # Random effects model
 }
mu.new ~ dnorm(m,tau.m)             # predictive dist. (log-odds)
m ~ dnorm(0,.0001)           # vague prior for mean
```

```
var.m <- 1/tau.m              # between-trial variance
tau.m <- pow(sd.m,-2)   # between-trial precision = (1/between-trial variance)
sd.m ~ dunif(0,5)             # vague prior for between-trial SD
#tau.m ~ dgamma(0.001,0.001)
#sd.m <- sqrt(var.m)
logit(R) <- m                 # posterior probability of response
logit(R.new) <- mu.new        # predictive probability of response
}

 Data
list(ns=69)  # ns=number of studies

r[]     n[]
16      20
23      70
9       102
15      19
8       21
13      34
10      17
10      22
10      30
12      52
17      82
15      80
24      30
13      86
12      190
11      56
```

1	54	658
2	4	62
3	12	42
4	24	43
5	15	19
6	8	20
7	8	25
8	2	6
9	7	10
10	3	12
11	12	13
12	34	38
13	13	21
14	13	21
15	26	26
16	13	78
17	1	20
18	10	50
19	102	120
20	45	50
21	6	20
22	55	100
23	15	38
24	14	25
25	4	51
26	4	5
27	14	24
28	7	330
29	7	20

```
1       1       50
2       23      53
3       1       16
4       11      32
5       6       90
6       20      73
7       20      34
8       8       19
9       10      20
10      8       20
11      3       14
12      10      37
13      18      88
14      7       25
15      8       24
16      10      45
17      20      35
18      47      50
19      12      36
20      18      45
21      9       35
22      12      20
23      19      40
24      11      49
25
26      END
27      Inits
28      list(mu=c( 0,0,0,0,0,  0,0,0,0,0,  0,0,0,0,0,  0,0,0,0,0,  0,0,0,0,0,  0,0,0,0,0,  0,0,0,0,0,  0,0,0,0,0,
29      0,0,0,0,0,  0,0,0,0,0, 0,0,0,0,0, 0,0,0,0,0, 0,0,0,0,0, 0,0,1,1), sd.m=1, m=0)
```

```
list(mu = c(1,-1,-1,-1,-1,  -1,-1,-1,-1,-1,  -1,-1,-1,-1,-1,  -1,-1,-1,-1,-1,  -1,-1,-1,-1,-1,  -1,-1,-1,-1,-1,
-1,-1,-1,-1,-1,  -1,-1,-1,-1,-1,  -1,-1,-1,-1,-1,  -1,-1,-1,-1,-1,  -1,-1,-1,-1,-1, -1,-1,-1,-1,-1, -1,-1,-1,-1,-
1, -1,-1,2,1), sd.m=2, m= -1)

list(mu = c(1,1,1,1,1,  1,1,1,1,1,  1,1,1,1,1,  1,1,1,1,1,  1,1,1,1,1,  1,1,1,1,1,  1,1,1,1,1,  1,1,1,1,1,
1,1,1,1,1,  1,1,1,1,1,  1,1,1,1,1, 1,1,1,1,1, 1,1,1,1,1, 1,1,0,0), sd.m = 0.5, m = 1)
```

L.6.7 WinBUGS code for number of adult patients receiving allogeneic transfusions (Moderate risk group)

```
NUMBER TRANSFUSED MODERATE RISK
# Binomial likelihood, logit link
# Random effects model for multi-arm trials
model{                          # *** PROGRAM STARTS
for(i in 1:ns){                 # LOOP THROUGH STUDIES
  w[i,1] <- 0    # adjustment for multi-arm trials is zero for control arm
  delta[i,1] <- 0           # treatment effect is zero for control arm
  mu[i] ~ dnorm(0,.0001)          # vague priors for all trial baselines
  for (k in 1:na[i]) {          # LOOP THROUGH ARMS
    r[i,k] ~ dbin(p[i,k],n[i,k]) # binomial likelihood
    logit(p[i,k]) <- mu[i] + delta[i,k]  # model for linear predictor
    rhat[i,k] <- p[i,k] * n[i,k] # expected value of the numerators
#Deviance contribution
    dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k]))
      +  (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-rhat[i,k])))        }
#  summed residual deviance contribution for this trial
  resdev[i] <- sum(dev[i,1:na[i]])
  for (k in 2:na[i]) {          # LOOP THROUGH ARMS
# trial-specific LOR distributions
    delta[i,k] ~ dnorm(md[i,k],taud[i,k])
```

```
# mean of LOR distributions (with multi-arm trial correction)
      md[i,k] <-  d[t[i,k]] - d[t[i,1]] + sw[i,k]
# precision of LOR distributions (with multi-arm trial correction)
      taud[i,k] <- tau *2*(k-1)/k
# adjustment for multi-arm RCTs
      w[i,k] <- (delta[i,k] - d[t[i,k]] + d[t[i,1]])
# cumulative adjustment for multi-arm trials
      sw[i,k] <- sum(w[i,1:k-1])/(k-1)
     }
 }
totresdev <- sum(resdev[])          # Total Residual Deviance
d[1]<-0      # treatment effect is zero for reference treatment
# vague priors for treatment effects
for (k in 2:nt){  d[k] ~ dnorm(0,.0001) }
sd ~ dunif(0,5)     # vague prior for between-trial SD
tau <- pow(sd,-2)   # between-trial precision = (1/between-trial variance)
# Provide estimates of treatment effects T[k] on the natural (probability) scale
# Given a Mean Effect, meanA, for 'standard' treatment A,
# with precision (1/variance) precA
A ~ dnorm(meanA,precA)
for (k in 1:nt) { logit(T[k]) <- A + d[k]  }
rr [1] < -1
for (k in 2:nt)  {rr[k]<-T[k]/T[1] }
for (c in 1:(nt-1))
{  for (k in (c+1):nt)
{  lor[c,k] <- d[k] - d[c]
log(or[c,k]) <- lor[c,k]
lrr[c,k] <- log(rr[k]) - log(rr[c])
log(rrisk[c,k]) <- lrr[c,k] }}
```

```
for (k in 1:nt) {
rk[k]<-rank(rr[],k)
best[k]<-equals(rank(rr[],k),1)}

}                    # *** PROGRAM ENDS
 Data
# ns= number of studies; nt=number of treatments
list(ns=73, nt=8, meanA=-0.5185, precA=0.479585024669854)
```

r[,1]	r[,2]	r[,3]	n[,1]	n[,2]	n[,3]	t[,1]	t[,2]	t[,3]	na[]
16	10	NA	20	20	NA	1	4	NA	2
23	23	NA	70	70	NA	1	4	NA	2
9	8	NA	102	102	NA	1	4	NA	2
15	9	NA	19	17	NA	1	3	NA	2
8	1	NA	21	20	NA	1	3	NA	2
13	4	NA	34	26	NA	1	3	NA	2
10	3	NA	17	32	NA	1	3	NA	2
10	22	NA	22	47	NA	1	3	NA	2
10	5	NA	30	30	NA	1	3	NA	2
12	13	NA	52	52	NA	1	3	NA	2
17	6	NA	82	76	NA	1	3	NA	2
15	5	NA	80	80	NA	1	3	NA	2
24	4	NA	30	30	NA	1	3	NA	2
13	12	NA	86	92	NA	1	3	NA	2
12	29	NA	190	382	NA	1	3	NA	2
11	6	NA	56	59	NA	1	3	NA	2
54	33	23	658	321	321	1	3	5	3
4	2	NA	62	56	NA	1	5	NA	2
30	23	NA	74	73	NA	4	8	NA	2
6	1	NA	49	46	NA	3	7	NA	2

1	5	3	NA	49	49	NA	3	7	NA	2
2	13	9	NA	101	96	NA	2	6	NA	2
3	12	2	NA	42	41	NA	1	2	NA	2
4	24	8	NA	43	43	NA	1	2	NA	2
5	15	9	NA	19	20	NA	1	2	NA	2
6	8	4	NA	20	18	NA	1	2	NA	2
7	8	0	NA	25	25	NA	1	2	NA	2
8	2	0	NA	6	6	NA	1	2	NA	2
9	7	1	NA	10	10	NA	1	2	NA	2
10	3	0	NA	12	12	NA	1	2	NA	2
11	12	10	NA	13	15	NA	1	2	NA	2
12	34	17	NA	38	39	NA	1	2	NA	2
13	13	2	NA	21	21	NA	1	2	NA	2
14	13	2	NA	21	21	NA	1	2	NA	2
15	26	47	NA	26	73	NA	1	2	NA	2
16	13	1	NA	78	79	NA	1	2	NA	2
17	1	0	NA	20	26	NA	1	2	NA	2
18	10	15	NA	50	50	NA	1	2	NA	2
19	102	57	NA	120	120	NA	1	2	NA	2
20	45	28	NA	50	50	NA	1	2	NA	2
21	6	1	NA	20	20	NA	1	2	NA	2
22	55	34	NA	100	100	NA	1	2	NA	2
23	15	10	NA	38	38	NA	1	2	NA	2
24	14	16	NA	25	25	NA	1	2	NA	2
25	4	0	NA	51	50	NA	1	2	NA	2
26	4	1	NA	5	5	NA	1	2	NA	2
27	14	3	NA	24	27	NA	1	2	NA	2
28	7	2	NA	330	330	NA	1	2	NA	2
29	7	2	NA	20	20	NA	1	2	NA	2

1	1	0	NA	50	50	NA	1	2	NA	2
2	23	8	NA	53	47	NA	1	2	NA	2
3	1	0	NA	16	16	NA	1	2	NA	2
4	11	4	NA	32	32	NA	1	2	NA	2
5	6	1	NA	90	90	NA	1	2	NA	2
6	20	5	NA	73	73	NA	1	2	NA	2
7	20	9	NA	34	34	NA	1	2	NA	2
8	8	0	NA	19	20	NA	1	2	NA	2
9	10	13	NA	20	40	NA	1	2	NA	2
10	8	5	NA	20	19	NA	1	2	NA	2
11	3	1	NA	14	15	NA	1	2	NA	2
12	10	3	NA	37	36	NA	1	2	NA	2
13	18	7	NA	88	88	NA	1	2	NA	2
14	7	2	NA	25	25	NA	1	2	NA	2
15	8	1	NA	24	24	NA	1	2	NA	2
16	10	6	NA	45	90	NA	1	2	NA	2
17	20	12	NA	35	32	NA	1	2	NA	2
18	47	10	NA	50	50	NA	1	2	NA	2
19	12	3	NA	36	38	NA	1	2	NA	2
20	18	7	NA	45	45	NA	1	2	NA	2
21	9	5	NA	35	64	NA	1	2	NA	2
22	12	3	NA	20	20	NA	1	2	NA	2
23	19	10	NA	40	40	NA	1	2	NA	2
24	11	3	NA	49	52	NA	1	2	NA	2

```
END

 Initial Values
list(
```

d=c(NA,0,0,0,0,0,0,0),

sd=.2,

mu=c(2,0,3,0,2, -2,2,-2,-1,3, 2,-2,1,3,1, 1,2,-3,2,-2, -2,1,0,-3,3, 0,-3,-2,-3,-2, 3,-3,0,-1,-3, 2,1,3,-2,2, 2,0,1,2,0, 0,-2,1,-2,-2, -3,1,-2,1,2, 2,0,1,2,0, 0,-1,2,0,-1, 1,1,1,1,1, 2,2,3))

list(

d=c(NA,1,1,1,1,1,1,1),

sd=.1,

mu=c(2,1,3,1,2, 0,2,0,-1,3, 2,0,1,3,1, 1,2,-3,2,0, 0,1,1,-3,3, 1,-3,0,-3,0, 3,-3,1,-1,-3, 2,1,3,0,2, 2,1,1,2,1, 1,0,1,0,0, -3,0,1,2,0, 2,0,3,0,2, -2,2,-2,-1,3, 2,0,3,0,2, -2,1,2))

list(

d=c(NA,0.5,0.5,0.5,0.5,0.5,0.5,0.5),

sd=.15,

mu=c(2,0.5,3,0.5,2, -2,2,1,-1,3, 2,1,1,3,1, 1,2,-3,2,1, 1,1,0.5,-3,3, 0.5,-3,1,-3,1, 3,-3,0.5,-1,-3, 2,1,3,1,2, 2,0.5,1,2,0.5, 0.5,1,1,1,1, -3,-2,1,2, 0, 2,0,3,0,2, -2,2,-2,-1,3, 2,0,3,0,2, -1,0,1))

L.6.8 WinBUGS code for inconsistency model for number of adult patients receiving allogeneic transfusions (Moderate risk group)

Moderate risk number transfused

73 tr**ials (including one 3-arm-trial**),

8 treatments

```
# Binomial likelihood, logit link, inconsistency model
# Random effects model
model{                  # *** PROGRAM STARTS
for(i in 1:ns){          # LOOP THROUGH STUDIES
   delta[i,1]<-0         # treatment effect is zero in control arm
   mu[i] ~ dnorm(0,.0001)  # vague priors for trial baselines
   for (k in 1:na[i])  {   # LOOP THROUGH ARMS
```

```
      r[i,k] ~ dbin(p[i,k],n[i,k]) # binomial likelihood
      logit(p[i,k]) <- mu[i] + delta[i,k]  # model for linear predictor
#Deviance contribution
      rhat[i,k] <- p[i,k] * n[i,k] # expected value of the numerators
      dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k]))
        +  (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-rhat[i,k])))
     }
# summed residual deviance contribution for this trial
  resdev[i] <- sum(dev[i,1:na[i]])
  for (k in 2:na[i]) {  # LOOP THROUGH ARMS
# trial-specific LOR distributions
      delta[i,k] ~ dnorm(d[t[i,1],t[i,k]] ,tau)
     }
 }
totresdev <- sum(resdev[])   # Total Residual Deviance
for (c in 1:(nt-1)) {  # priors for all mean treatment effects
   for (k in (c+1):nt)  { d[c,k] ~ dnorm(0,.0001) }
 }
sd ~ dunif(0,5)  # vague prior for between-trial standard deviation
var <- pow(sd,2) # between-trial variance
tau <- 1/var     # between-trial precision
} # *** PROGRAM ENDS


 Data
# Moderate risk number transfused
# nt=no. treatments, ns=no. studies
list(nt=8,ns=73 )
```

1	r[,1]	r[,2]	r[,3]	n[,1]	n[,2]	n[,3]	t[,1]	t[,2]	t[,3]	na[]
2	16	10	NA	20	20	NA	1	4	NA	2
3	23	23	NA	70	70	NA	1	4	NA	2
4	9	8	NA	102	102	NA	1	4	NA	2
5	15	9	NA	19	17	NA	1	3	NA	2
6	8	1	NA	21	20	NA	1	3	NA	2
7	13	4	NA	34	26	NA	1	3	NA	2
8	10	3	NA	17	32	NA	1	3	NA	2
9	10	22	NA	22	47	NA	1	3	NA	2
10	10	5	NA	30	30	NA	1	3	NA	2
11	12	13	NA	52	52	NA	1	3	NA	2
12	17	6	NA	82	76	NA	1	3	NA	2
13	15	5	NA	80	80	NA	1	3	NA	2
14	24	4	NA	30	30	NA	1	3	NA	2
15	13	12	NA	86	92	NA	1	3	NA	2
16	12	29	NA	190	382	NA	1	3	NA	2
17	11	6	NA	56	59	NA	1	3	NA	2
18	54	33	23	658	321	321	1	3	5	3
19	4	2	NA	62	56	NA	1	5	NA	2
20	30	23	NA	74	73	NA	4	8	NA	2
21	6	1	NA	49	46	NA	3	7	NA	2
22	5	3	NA	49	49	NA	3	7	NA	2
23	13	9	NA	101	96	NA	2	6	NA	2
24	12	2	NA	42	41	NA	1	2	NA	2
25	24	8	NA	43	43	NA	1	2	NA	2
26	15	9	NA	19	20	NA	1	2	NA	2
27	8	4	NA	20	18	NA	1	2	NA	2
28	8	0	NA	25	25	NA	1	2	NA	2
29	2	0	NA	6	6	NA	1	2	NA	2

1	7	1	NA	10	10	NA	1	2	NA	2
2	3	0	NA	12	12	NA	1	2	NA	2
3	12	10	NA	13	15	NA	1	2	NA	2
4	34	17	NA	38	39	NA	1	2	NA	2
5	13	2	NA	21	21	NA	1	2	NA	2
6	13	2	NA	21	21	NA	1	2	NA	2
7	26	47	NA	26	73	NA	1	2	NA	2
8	13	1	NA	78	79	NA	1	2	NA	2
9	1	0	NA	20	26	NA	1	2	NA	2
10	10	15	NA	50	50	NA	1	2	NA	2
11	102	57	NA	120	120	NA	1	2	NA	2
12	45	28	NA	50	50	NA	1	2	NA	2
13	6	1	NA	20	20	NA	1	2	NA	2
14	55	34	NA	100	100	NA	1	2	NA	2
15	15	10	NA	38	38	NA	1	2	NA	2
16	14	16	NA	25	25	NA	1	2	NA	2
17	4	0	NA	51	50	NA	1	2	NA	2
18	4	1	NA	5	5	NA	1	2	NA	2
19	14	3	NA	24	27	NA	1	2	NA	2
20	7	2	NA	330	330	NA	1	2	NA	2
21	7	2	NA	20	20	NA	1	2	NA	2
22	1	0	NA	50	50	NA	1	2	NA	2
23	23	8	NA	53	47	NA	1	2	NA	2
24	1	0	NA	16	16	NA	1	2	NA	2
25	11	4	NA	32	32	NA	1	2	NA	2
26	6	1	NA	90	90	NA	1	2	NA	2
27	20	5	NA	73	73	NA	1	2	NA	2
28	20	9	NA	34	34	NA	1	2	NA	2
29	8	0	NA	19	20	NA	1	2	NA	2

```
1   10  13  NA  20  40  NA  1  2  NA  2
2   8   5   NA  20  19  NA  1  2  NA  2
3   3   1   NA  14  15  NA  1  2  NA  2
4   10  3   NA  37  36  NA  1  2  NA  2
5   18  7   NA  88  88  NA  1  2  NA  2
6   7   2   NA  25  25  NA  1  2  NA  2
7   8   1   NA  24  24  NA  1  2  NA  2
8   10  6   NA  45  90  NA  1  2  NA  2
9   20  12  NA  35  32  NA  1  2  NA  2
10  47  10  NA  50  50  NA  1  2  NA  2
11  12  3   NA  36  38  NA  1  2  NA  2
12  18  7   NA  45  45  NA  1  2  NA  2
13  9   5   NA  35  64  NA  1  2  NA  2
14  12  3   NA  20  20  NA  1  2  NA  2
15  19  10  NA  40  40  NA  1  2  NA  2
16  11  3   NA  49  52  NA  1  2  NA  2
17
18  END
19  INITS
20
21  # chain 1
22  list(sd=1, mu=c(2,0,3,0,2, -2,2,-2,-1,3, 2,-2,1,3,1, 1,2,-3,2,-2, -2,1,0,-3,3, 0,-3,-2,-3,-2, 3,-
23  3,0,-1,-3, 2,1,3,-2,2, 2,0,1,2,0, 0,-2,1,-2,-2, -3,1,-2,1,2, 2,0,1,2,0, 0,-1,2,0,-1, 1,1,1,1,1, 2,2,3),
24  d=structure(.Data=c(NA,0,1,0,0,-2,0,0, NA,NA,0,0,2,0,0,-2, NA,NA,NA,0,0,0,0,0,
25  NA,NA,NA,NA,0,0,0,0,
26  NA,NA,NA,NA,NA,0,0,1, NA,NA,NA,NA,NA,NA,0,0, NA,NA,NA,NA,NA,NA,NA,0), .Dim = c(7,8)))
27
28  # chain 2
29  list(sd=1.5, mu=c(2,1,3,1,2, 0,2,0,-1,3, 2,0,1,3,1, 1,2,-3,2,0, 0,1,1,-3,3, 1,-3,0,-3,0, 3,-3,1,-1,-
30  3, 2,1,3,0,2, 2,1,1,2,1, 1,0,1,0,0, -3,0,1,2,0, 2,0,3,0,2, -2,2,-2,-1,3, 2,0,3,0,2, -2,1,2),
```

```
d = structure(.Data =c(NA,0,1,0,0,-1,2,0,    NA,NA,1,0.5,2,0,0,-2,    NA,NA,NA,2,1,1,0,0,
NA,NA,NA,NA,0.5,2,0,1,
NA,NA,NA,NA,NA,2,0,1,    NA,NA,NA,NA,NA,NA,1,0,      NA,NA,NA,NA,NA,NA,NA,1), .Dim = c(7,8)))

# chain 3
list(sd=3,  mu=c(2,0.5,3,0.5,2,   -2,2,1,-1,3,    2,1,1,3,1,    1,2,-3,2,1,    1,1,0.5,-3,3,   0.5,-3,1,-3,1,
3,-3,0.5,-1,-3,   2,1,3,1,2,  2,0.5,1,2,0.5,   0.5,1,1,1,1,  -3,-2,1,2, 0,   2,0,3,0,2,   -2,2,-2,-1,3,
2,0,3,0,2,   -1,0,1),
d = structure(.Data =c(NA,0,1,0,0,-2,0,0,    NA,NA,0,1,-2,0,-1,0,    NA,NA,NA,2,0,1,0,2,
NA,NA,NA,NA,0,1,2,0,
NA,NA,NA,NA,NA,1,1,1,    NA,NA,NA,NA,NA,NA,-1,2,      NA,NA,NA,NA,NA,NA,NA,2), .Dim =
c(7,8)))
```

L.6.9 WinBUGS code for number of units of receiving allogeneic blood transfusions (Moderate risk group)

```
Units Transfused - Moderate risk

# Normal likelihood, identity link
# Random effects model for multi-arm trials
model{                          # *** PROGRAM STARTS
for(i in 1:ns){                 #   LOOP THROUGH STUDIES
   w[i,1] <- 0    # adjustment for multi-arm trials is zero for control arm
   delta[i,1] <- 0           # treatment effect is zero for control arm
   mu[i] ~ dnorm(0,.0001)          # vague priors for all trial baselines
   for (k in 1:na[i]) {           #  LOOP THROUGH ARMS
      var[i,k] <- pow(se[i,k],2)   # calculate variances
      prec[i,k] <- 1/var[i,k]      # set precisions
      y[i,k] ~ dnorm(theta[i,k],prec[i,k]) # binomial likelihood
      theta[i,k] <- mu[i] + delta[i,k]  # model for linear predictor
#Deviance contribution
      dev[i,k] <- (y[i,k]-theta[i,k])*(y[i,k]-theta[i,k])*prec[i,k]
```

```
      }
#  summed residual deviance contribution for this trial
   resdev[i] <- sum(dev[i,1:na[i]])
   for (k in 2:na[i]) {           # LOOP THROUGH ARMS
# trial-specific LOR distributions
      delta[i,k] ~ dnorm(md[i,k],taud[i,k])
# mean of LOR distributions, with multi-arm trial correction
      md[i,k] <-  d[t[i,k]] - d[t[i,1]] + sw[i,k]
# precision of LOR distributions (with multi-arm trial correction)
      taud[i,k] <- tau *2*(k-1)/k
# adjustment, multi-arm RCTs
      w[i,k] <- (delta[i,k] - d[t[i,k]] + d[t[i,1]])
# cumulative adjustment for multi-arm trials
      sw[i,k] <- sum(w[i,1:k-1])/(k-1)
     }
  }
totresdev <- sum(resdev[])          #Total Residual Deviance
d[1]<-0      # treatment effect is zero for control arm
# vague priors for treatment effects
for (k in 2:nt){  d[k] ~ dnorm(0,.0001) }
sd ~ dunif(0,5)     # vague prior for between-trial SD
tau <- pow(sd,-2)   # between-trial precision = (1/between-trial variance)
# Provide estimates of treatment effects T[k] on the natural scale
# Given a Mean Effect, meanA, for 'standard' treatment A,
# with precision (1/variance) precA
A ~ dnorm(meanA,precA)
for (k in 1:nt) { T[k] <- A + d[k]  }
for (k in 1:nt) {
rk[k]<-rank(d[],k)
```

```
best[k]<-equals(rank(d[],k),1)}
for (c in 1:(nt-1))
{  for (k in (c+1):nt)
{  D[c,k] <- d[k] - d[c]}}
}                          # *** PROGRAM ENDS


 Data
# ns= number of studies; nt=number of treatments
list(ns=16, nt=4, meanA=-1, precA=1)

t[,1]   t[,2]   t[,3]   y[,1]   y[,2]   y[,3]   se[,1]   se[,2]   se[,3]   na[]
1       3       NA      1.68    0.82    NA      0.330358657   0.259513119   NA      2
1       3       NA      0.71    0.05    NA      0.209489175   0.049193496   NA      2
1       3       NA      1.9     2.36    NA      0.221359436   0.189748638   NA      2
1       3       NA      1.06    0.54    NA      0.133789717   0.097375825   NA      2
1       3       NA      2.29    1.02    NA      0.305    0.28    NA      2
1       3       NA      1.74    0.22    NA      0.209960314   0.178922702   NA      2
1       3       4       2.68    1.26    3.49    0.122474487   0.121854359   0.104257207   3
1       2       NA      3.58    2.25    NA      0.453219961   0.275118156   NA      2
1       2       NA      3.46    2.29    NA      0.214373231   0.126118525   NA      2
1       2       NA      2.5     0.46    NA      0.538998189   0.316415941   NA      2
1       2       NA      1.6     1.8     NA      0.208710326   0.1394274     NA      2
1       2       NA      1.89    0.71    NA      0.12303658    0.110308658   NA      2
1       2       NA      1.55    0.55    NA      0.089461351   0.056597998   NA      2
1       2       NA      0.84    0.31    NA      0.159099026   0.113137085   NA      2
1       2       NA      1.11    0.76    NA      0.216898594   0.118585412   NA      2
1       2       NA      2.2     0.8     NA      0.223606798   0.178885438   NA      2
```

END

Initial Values

#chain 1

list(d=c(NA, 0,0,0), sd=1, mu=c(0,0,0,0,0, 0,0,0,0,0, 0,1,1,1, 0, 0))

#chain 2

list(d=c(NA, -1,-3,1), sd=4, mu=c(0,3,0,-1,0, 2,1,0,-3,0, -2,1,1,1, 2, 0))

#chain 3

list(d=c(NA, 2,2,2), sd=2, mu=c(2,3,1,-1,1, 2,0,0,-3,0, 2,1,-1,1,-2, 0))

L.6.10 WinBUGS code for assessment of baseline risk of mortality (High risk group)- *for use in economic model*

```
# Binomial likelihood, logit link
# Baseline random effects model
model{                    # *** PROGRAM STARTS
for (i in 1:ns){           # LOOP THROUGH STUDIES
   r[i] ~ dbin(p[i],n[i])                # Likelihood
   logit(p[i]) <- mu[i]                        # Log-odds of response
   mu[i] ~ dnorm(m,tau.m)     # Random effects model
 }
mu.new ~ dnorm(m,tau.m)             # predictive dist. (log-odds)
m ~ dnorm(0,.0001)           # vague prior for mean
var.m <- 1/tau.m             # between-trial variance
tau.m <- pow(sd.m,-2)   # between-trial precision = (1/between-trial variance)
```

```
sd.m ~ dunif(0,5)            # vague prior for between-trial SD
#tau.m ~ dgamma(0.001,0.001)
#sd.m <- sqrt(var.m)
logit(R) <- m                # posterior probability of response
logit(R.new) <- mu.new       # predictive probability of response
}
 Data
list(ns=24)  # ns=number of studies

r[]     n[]
1       41
15      23
1       40
2       29
0       25
3       97
4       50
0       23
3       96
1       165
2       31
3       278
1       59
3       150
3       20
1       14
4       40
4       19
0       16
```

```
0	31
2	106
2	45
2	75
5	177
END
 Inits
list(mu=c( 0,0,0,0,0,   0,0,0,0,0,   0,0,0,0,0,   0,0,0,0,0,  0,0,0,0), sd.m=1, m=0)
list(mu = c(1,-1,-1,-1,-1,   -1,-1,-1,-1,-1,   -1,-1,-1,-1,-1,    -1,-1,-1,-1,-1,  -1,-1,-1,-1), sd.m=2, m= -1)
list(mu = c(1,1,1,1,1,   1,1,1,1,1,   1,1,1,1,1,  1,1,1,1,1,   1,1,1,1), sd.m = 0.5, m = 1)
```

L.6.11 WinBUGS code for assessment of baseline risk of mortality (Moderate risk group)- *for use in economic model*

```
# Binomial likelihood, logit link
# Baseline random effects model
model{                    # *** PROGRAM STARTS
for (i in 1:ns){             # LOOP THROUGH STUDIES
   r[i] ~ dbin(p[i],n[i])                 # Likelihood
   logit(p[i]) <- mu[i]                          # Log-odds of response
   mu[i] ~ dnorm(m,tau.m)     # Random effects model
 }
mu.new ~ dnorm(m,tau.m)              # predictive dist. (log-odds)
m ~ dnorm(0,.0001)            # vague prior for mean
var.m <- 1/tau.m              # between-trial variance
tau.m <- pow(sd.m,-2)   # between-trial precision = (1/between-trial variance)
sd.m ~ dunif(0,5)             # vague prior for between-trial SD
#tau.m ~ dgamma(0.001,0.001)
#sd.m <- sqrt(var.m)
```

```
logit(R) <- m                # posterior probability of response
logit(R.new) <- mu.new       # predictive probability of response
}
 Data
list(ns=10)  # ns=number of studies

r[]     n[]
0       62
1       38
0       78
0       100
0       42
1       35
0       50
0       35
0       86
0       57

END
 Inits
list(mu=c( 0,0,0,0,0,   0,0,0,0,0), sd.m=1, m=0)
list(mu = c(1,-1,-1,-1,-1,   -1,-1,-1,-1,-1), sd.m=2, m= -1)
list(mu = c(1,1,1,1,1,   1,1,1,1,1), sd.m = 0.5, m = 1)
```

1

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