Supplement 1: Evidence summaries and GRADE profiles

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

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Evidence Summary 1: Transfusion Ratios in Massively Bleeding Critically III adults

1. Massive bleeding in trauma patients

	Certainty assessment						patients		Effect				
Nº of studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	High ratio	Low ratio	Relative (95% CI)	Absolute (95% Cl)	Certainty	Importance		
Early mo	rtality- obso	ervational studies	5										
19 obs serious ^a not serious ^b not serious not serious none 421/2412 (17.5%) 946/3680 (25.7%) RR 0.51 (0.39 to 0.65) 126 fewer per 1,000 (from 157 fewer to 90 fewer) Ch													
						(17.5%)	(23.7%)	(0.59 10 0.05)		VERY LOW			
30 day m	ortality - ob	servational studi	ies	•						-	-		
33 obs	serious ^a	not serious ^b	not serious	not serious	none	1380/500	2411/7108	RR 0.63	126 fewer per 1,000	€000	CRITICAL		
						3 (27.6%)	(33.9%)	(0.54 10 0.73)		VERY LOW			
24 hour r	nortality - R	CTs											
1 RCT	not	not serious	not serious	serious °	none	43/338	58/342	RR 0.75	42 fewer per 1,000	$\oplus \oplus \oplus \bigcirc \bigcirc$	CRITICAL		
	Serious					(12.7%)	(17.0%)	(0.52 10 1.06)		MODERATE			
30 day m	ortality - R	CTs											
2 RCTs	not	serious d	not serious	serious °	none	88/378	94/377	RR 0.93	17 fewer per 1,000	$\oplus \oplus \bigcirc \bigcirc$	CRITICAL		
	Serious					(23.3%)	(24.9%)	(0.72 10 1.20)		LOW			
Stroke													
1 RCT	not	not serious	not serious	very serious	none	9/338	11/342	RR 0.83	5 fewer per 1,000	$\bigoplus \bigoplus \bigcirc \bigcirc \bigcirc \bigcirc$	CRITICAL		
	senous			C		(2.1%)	(3.2%)	(0.35 (0 1.97)	(from 21 lewer to 31 more)	LOW			
Myocard	ial infarctio	n	1	!					1	1			
1 RCT	not	not serious	not serious	very serious	none	0/338	2/342	RR 0.20	5 fewer per 1,000	$\oplus \oplus \bigcirc \bigcirc$	CRITICAL		
	Senous			C		(0.0%)	(0.0%)	(0.01 (0 4.20)		LOW			
ARDS/TF	RALI												

1 RCT	not serious	not serious	not serious	serious ^c	none	56/338 (16.6%)	66/342 (19.3%)	RR 0.86 (0.62 to 1.19)	27 fewer per 1,000 (from 73 fewer to 37 more)	⊕⊕⊕⊖ MODERATE	CRITICAL
TACO/CH	IF										
1 RCT	not serious	not serious	not serious	very serious e	none	1/338 (0.3%)	0/342 (0.0%)	RR 3.04 (0.12 to 74.25)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	$\oplus \oplus \bigcirc \bigcirc \bigcirc$	IMPORTANT
						(000,00)	(0.0.7)	(**************************************	()	LOW	
Infection	s/Sepsis										
1 RCT	not	not serious	not serious	serious ^c	none	155/338	146/342	RR 1.07	30 more per 1,000	$\oplus \oplus \oplus \bigcirc \bigcirc$	IMPORTANT
	serious					(45.9%)	(42.7%)	(0.91 to 1.27)	(from 38 fewer to 115 more)	MODERATE	
Venous t	hromboem	bolism							-		
1 RCT	not	not serious	not serious	serious ^c	none	42/338	37/342	RR 1.15	16 more per 1,000	$\oplus \oplus \oplus \bigcirc \bigcirc$	IMPORTANT
	Serious					(12.4%)	(10.0%)	(0.76 to 1.74)		MODERATE	
Clinical h	nemostasis	-exhanguination									
2 RCTs	serious ^f	serious ^d	not serious	not serious	none	320/375	296/374	RR 0.70	237 fewer per 1,000	$\oplus \oplus \bigcirc \bigcirc \bigcirc$	IMPORTANT
						(00.3%)	(79.1%)	(0.51 (0 0.96)		LOW	

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

Explanations

a. Many studies included patients who died very early, before plasma may have been available, resulting in confounding.

b. Though I2 values are high, indicating statistical heterogeneity, it is of questionable clinical significance as virtually all studies favour high ratio transfusion.

c. Wide confidence intervals which do not exclude significant benefit nor harm.

d. Significant statistical heterogeneity (I2 >70%) with studies demonstrating serious inconsistency of unequivocal clinical importance.

e. Very wide confidence intervals resulting in very serious imprecision.

f. Risk of bias in determining number of patients who had clinical hemostasis

2. Massive bleeding in non-trauma patients

		Certainty as	sessment			№ of patients			Effect		
Nº of studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	High ratio	Low ratio	Relative (95% CI)	Absolute (95% Cl)	Certainty	Importance
Mortality	- Mixed popula	ation									
2 obs	not serious ^a	not serious	not serious	serious ^b	none	121/437	91/316	RR 0.96	12 fewer per 1,000	$\oplus 000$	CRITICAL
						(27.7%)	(20.0%)	(0.76 to 1.21)		VERY LOW	
Mortality	- Cardiac and	vascular surgery									
3 obs	serious ^c	serious ^d	not serious	serious ^b	none	85/471	149/758	RR 0.92	16 fewer per 1,000	$\oplus 000$	CRITICAL
						(10.0%)	(19.7%)	(0.73 10 1.10)	(Irom 53 lewer to 31 more)	VERY LOW	
Mortality	- Obstetric										
2 obs	not serious	not serious	not serious	very serious e	none	0/141 (0.0%)	0/152 (0.0%)	not pooled	see comment	-	CRITICAL

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

Explanations

a. Largest study (Etchill 2017) excluded patients who died within one hour, possibly reducing the effect of survivorship bias.

b. Wide confidence intervals which do not exclude significant benefit nor harm.

c. Many studies included patients who died very early, before plasma may have been available, resulting in confounding.

d. Significant statistical heterogeneity (I2 >70%) with studies demonstrating serious inconsistency of unequivocal clinical importance.

e. No events reported resulting in very serious imprecision; overall certainty not rated

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



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

	atio	Low ra	atio		Risk Ratio		Risk Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	Year	M–H, Fixed, 95% Cl	
Nascimento 2013	13	40	5	35	5.7%	2.27 [0.90, 5.74]	2013		
Holcomb 2015	75	338	89	342	94.3%	0.85 [0.65, 1.11]	2015		
Total (95% CI)		378		377	100.0%	0.93 [0.72, 1.20]		-	
Total events	88		94						
Heterogeneity: Chi ² =	3.99, df	= 1 (P)	= 0.05);	$I^2 = 75$	%		-		
Test for overall effect:	Z = 0.53	B (P = 0)).60)					Favours high ratio Favours low ratio	

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

	Low ra	atio		Risk Ratio		Risk Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	Year	M–H, Random, 95% CI
1.1.2 Observational	studies F	FP:RBC	1:1 vs.	<1:1				
Maegele 2008	13	115	158	484	6.0%	0.35 [0.20, 0.59]	2008	
Perkins 2009	5	96	75	209	4.1%	0.15 [0.06, 0.35]	2009	
Wafaisade 2011	11	210	113	760	5.6%	0.35 [0.19, 0.64]	2011	
Sharpe 2012	20	69	31	66	6.4%	0.62 [0.39, 0.97]	2012	
Balvers 2017	89	210	65	169	7.4%	1.10 [0.86, 1.41]	2017	
Vulliamy 2017	8	107	9	54	4.1%	0.45 [0.18, 1.10]	2017	
Subtotal (95% CI)		807		1742	33.5%	0.44 [0.23, 0.83]		
Total events	146		451	E (B		1. 12 0.001		
Heterogeneity: Tau" =	= 0.53; Ch	$n^2 = 44$	1.94, df =	= 5 (P <	< 0.0000	1); $\Gamma = 89\%$		
lest for overall effect	: Z = 2.54	(P = 0)	.01)					
1.1.3 Observational	studies F	FP:RBC	1:1.5 vs	. <1:1.	5			
Mitra 2010	3	56	41	275	3.1%	0.36 [0.12, 1.12]	2010	
Lustenberger 2011	18	177	31	52	6.2%	0.17 [0.10, 0.28]	2011	
Brown 2012	5	128	47	476	4.0%	0.40 [0.16, 0.97]	2012	
Kudo 2013	3	9	2	6	2.2%	1.00 [0.23, 4.31]	2013	
Bui 2016	7	49	17	54	4.5%	0.45 [0.21, 1.00]	2016	
Subtotal (95% CI)		419		863	20.1%	0.35 [0.19, 0.63]		
Total events	36		138					
Heterogeneity: Tau ² =	= 0.25; Ch	$i^2 = 9.$	31, df =	4 (P =	0.05); I ² :	= 57%		
Test for overall effect	: Z = 3.46	(P = 0)	.0005)					
1.1.4 Observational	studies F	FP:RBC	1:2 vs.	<1:2				
Holcomb 2008	33	83	64	151	7.1%	0.94 [0.68, 1.30]	2008	
Snyder 2009	24	60	43	74	6.9%	0.69 [0.48, 0.99]	2009	
Shaz 2010	20	100	48	114	6.4%	0.47 [0.30, 0.74]	2010	_
Rowell 2011	46	210	76	245	7.1%	0.71 [0.51, 0.97]	2011	
Borgman 2011	86	422	83	237	7.4%	0.58 [0.45, 0.75]	2011	
Kim 2014	3	9	9	32	3.3%	1.19 [0.40, 3.48]	2014	
Nardi 2015	2	96	8	130	2.1%	0.34 [0.07, 1.56]	2015	
Stanworth 2016	25	206	26	92	6.2%	0.43 [0.26, 0.70]	2016	
Subtotal (95% CI)		1186		1075	46.4%	0.64 [0.52, 0.79]		◆
Total events	239	_	357					
Heterogeneity: Tau ² =	= 0.03; Ch	$i^2 = 12$	2.62, df =	= 7 (P =	= 0.08); l ²	² = 45%		
Test for overall effect	: Z = 4.28	(P < 0	.0001)					
Total (95% CI)		2412		3680	100.0%	0.51 [0.39, 0.65]		◆
Total events	421		946					
Heterogeneity: Tau ² =	= 0.22; Ch	$i^2 = 85$	5.62, df =	= 18 (P	< 0.000	01); I ² = 79%		
Test for overall effect	: Z = 5.21	(P < 0	.00001)					Favours high ratio Favours low ratio
Test for subgroup dif	ferences: ($Chi^2 = c$	4.47. df	= 2 (P =	= 0.11), I	² = 55.3%		

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

	High ra	atio	Low ra	tio		Risk Ratio	Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	Year	M–H, Random, 95% Cl
1.2.2 Observational	studies F	FP:RBC	1:1 vs.	<1:1				
Duchesne 2008	18	71	56	64	3.2%	0.29 [0.19, 0.44]	2008	
Maegele 2008	28	115	220	484	3.5%	0.54 [0.38, 0.75]	2008	<u> </u>
Duchesne 2009	13	46	22	43	2.7%	0.55 [0.32, 0.95]	2009	
Perkins 2009	15	96	86	150	2.9%	0.27 [0.17, 0.44]	2009	
Zink 2009	13	51	56	102	2.8%	0.46 [0.28, 0.77]	2009	
Holcomb 2011	65	216	101	211	3.8%	0.63 [0.49, 0.81]	2011	_ —
Sambasivan 2011	47	202	126	979	3.6%	1.81 [1.34, 2.44]	2011	
Wafaisade 2011	31	210	194	760	3.4%	0.58 [0.41, 0.82]	2011	
Haltmeier 2017	53	156	46	86	3.6%	0.64 [0.47, 0.85]	2017	
Vulliamy 2017	25	107	15	54	2.6%	0.84 [0.49, 1.46]	2017	
Endo 2018	55	148	357	1058	3.8%	1.10 [0.88, 1.38]	2018	
Subtotal (95% CI)		1418		3991	35.9%	0.62 [0.45, 0.86]		-
Total events	363		1279					
Heterogeneity: Tau* =	0.26; Cr	$11^{\circ} = 95$	5.77, df =	= 10 (P	< 0.000	01); l* = 90%		
lest for overall effect:	Z = 2.90	(P = 0)	0.004)					
1.2.2 Obconvational	studios E		1.1 5 10	<1.1				
1.2.5 Observational s	studies r	160	1.1.5 VS	. < 1.1.	3 2 20/	0 20 [0 20 0 45]	2007	
Borgman 2007	31	162	20	212	3.2%	0.30 [0.20, 0.45]	2007	
Mitra 2010	29	102	110	313	3.4%	0.61 [0.57, 1.14]	2008	
Milita 2010	10	150	0.5	275	3.0%	0.95 [0.60, 1.49]	2010	
Recurp 2012	25	116	69	476	2.1%	0.01 [0.20, 1.45]	2011	
Kudo 2013	4	110	2	470	0.0%	1 22 [0 25 5 12]	2012	
Hardin 2014	36	283	82	283	3.4%	0.44 [0.31, 0.63]	2013	
Soderlund 2017	11	35	20	44	2.5%	0.69 [0.38, 1.24]	2017	
Roquet 2019	155	506	146	391	4.0%	0.82 [0.68 0.99]	2019	_ _
Subtotal (95% CI)	200	1428	1.0	1840	24.3%	0.63 [0.47, 0.84]	2010	◆
Total events	313		536					-
Heterogeneity: Tau ² =	0.13: Cł	$ni^2 = 30$).54. df =	= 8 (P =	= 0.0002)	$ ^2 = 74\%$		
Test for overall effect:	Z = 3.15	(P = 0)	.002)	- (-	,			
			,					
1.2.4 Observational	studies F	FP:RBC	1:2 vs.	<1:2				
Holcomb 2008	78	151	40	83	3.7%	1.07 [0.82, 1.41]	2008	_
Teixeira 2009	30	115	56	62	3.5%	0.29 [0.21, 0.40]	2009	
Dente 2009	7	50	7	23	1.6%	0.46 [0.18, 1.16]	2009	
Shaz 2010	41	100	64	114	3.6%	0.73 [0.55, 0.97]	2010	_
Van 2010	11	159	5	29	1.5%	0.40 [0.15, 1.07]	2010	
Borgman 2011	145	422	109	237	3.9%	0.75 [0.62, 0.90]	2011	
Magnotti 2011	25	66	22	37	3.2%	0.64 [0.42, 0.96]	2011	
Peiniger 2011	203	445	104	167	4.0%	0.73 [0.63, 0.86]	2011	
Rowell 2011	84	210	108	245	3.9%	0.91 [0.73, 1.13]	2011	
Sharpe 2012	20	69	15	26	2.9%	0.50 [0.31, 0.82]	2012	
Kim 2014	22	68	14	32	2.8%	0.74 [0.44, 1.25]	2014	
Nardi 2015	13	96	26	130	2.4%	0.68 [0.37, 1.25]	2015	
Stanworth 2016	25	206	26	92	2.9%	0.43 [0.26, 0.70]	2016	
Subtotal (95% CI)	70.4	2157	500	12//	59.8%	0.04 [0.53, 0.78]		-
I otal events	704		596	12 (2	- 0.000	01), 12 - 770/		
Test for every " au" =	0.09; Cr	$11^{-} = 53$	0.29, df =	= 12 (P	< 0.000	$(1); \Gamma = 77\%$		
rest for overall effect:	2 = 4.42	(r < 0)	.00001)					
Total (95% CI)		5003		7108	100.0%	0.63 [0.54, 0.73]		▲
Total events	1280	3003	2411	. 100	200.0/0	0.05 [0.54, 0.75]		•
Heterogeneity: Tau ² -	0 13 0	$n^2 = 1.7$	2411 7057 df	- 32 (P < 0.000	$(0.1) \cdot l^2 = 82\%$		
neterogeneity. rau =	0.10, CI	– 1/	5.57, ui	- 32 (. < 0.000	001/,1 = 02/0		ייס איז

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



3. Stroke, trauma patients, RCTs



4. Myocardial infarction, trauma patients, RCTs



5. ARDS/TRALI, trauma patients, RCTs

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	High ratio Lov			tio		Risk Ratio	Risk Ratio			
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% Cl			
Holcomb 2015	56	338	66	342	100.0%	0.86 [0.62, 1.19]				
Total (95% CI)		338		342	100.0%	0.86 [0.62, 1.19]				
Total events	56		66							
Heterogeneity: Not app	plicable						07 085 1 12 15			
Test for overall effect:	Z = 0.93	(P = 0)	.35)				Favours high ratio Favours low ratio			

6. TACO/CHF, trauma patients, RCTs



7. Infections/sepsis, trauma patients, RCTs

	atio	Low ra	atio		Risk Ratio	Risk Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% CI	
Holcomb 2015	155	338	146	342	100.0%	1.07 [0.91, 1.27]		
Total (95% CI)		338		342	100.0%	1.07 [0.91, 1.27]		
Total events	155		146					
Heterogeneity: Not ap	plicable							
Test for overall effect:	Z = 0.83	B (P = 0)	.41)				Favours high ratio Favours low ratio	

8. Venous thromboembolism, trauma patients, RCTs

	High ra	atio	Low ra	tio		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% Cl
Holcomb 2015	42	338	37	342	100.0%	1.15 [0.76, 1.74]	
Total (95% CI)		338		342	100.0%	1.15 [0.76, 1.74]	
Total events	42		37				
Heterogeneity: Not ap	plicable						
Test for overall effect:	Z = 0.65	(P = 0)	.51)				Favours high ratio Favours low ratio

9. Clinical hemostasis, trauma patients, RCTs

	High ratio Low ratio					Risk Ratio (Non-event)		Risk Ratio (Non-event)		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	Year	M–H, Fixed, 95% Cl		
Nascimento 2013	29	37	29	32	4.1%	2.31 [0.67, 7.97]	2013			
Holcomb 2015	291	338	267	342	95.9%	0.63 [0.45, 0.88]	2015			
Total (95% CI)		375		374	100.0%	0.70 [0.51, 0.96]		•		
Total events	320		296							
Heterogeneity: Chi ² =	3.90, df	= 1 (P	= 0.05);	$l^2 = 74$	1%					
Test for overall effect:	Z = 2.18	B (P = 0)).03)					Favours high ratio Favours low ratio		

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

Cold stored platelets in critically ill bleeding patients

		Certainty	assessment			Nº of p	oatients		Effect		
Nº of studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Cold platelets	Regular platelets	Relative (95% Cl)	Absolute (95% Cl)	Certainty	Importance
Mortality	- Cryoprese	erved platelets									
1 RCT	serious ^a	not serious	not serious	very serious ^b	none	7/25 (28.0%)	4/19 (21.1%)	RR 1.33 (0.45 to 3.89)	69 more per 1,000 (from 116 fewer to 608 more)	$\oplus 000$	CRITICAL
								,		VERY LOW	
Bleeding	- Cold-store	ed platelets	-		-		-				-
1 RCT	serious ^a	not serious	not serious	very serious ^b	none	17	22	-	MD 274 lower	$\oplus 000$	IMPORTANT
									(327.99 lower to 220.01 lower)	VERY LOW	
Thrombo	embolic eve	ents - Cold-stored	platelets						•		
1 RCT	serious ^a	not serious	not serious	very serious ^b	none	3/17	7/22	RR 0.55	143 fewer per 1,000	$\oplus 000$	IMPORTANT
						(17.0%)	(31.0%)	(0.17 10 1.63)	(from 264 lewer to 264 more)	VERY LOW	
RBCs tra	nsfused - C	old-stored platele	ts						•		
1 RCT	serious ^a	not serious	not serious	very serious b	none	17	22	-	MD 0.5 lower	⊕000	IMPORTANT
									(1.03 lower to 0.03 higher)	VERY LOW	
Plasma t	ransfused -	Cold-stored plate	lets						•		
1 RCT	serious ^a	not serious	not serious	very serious b	none	17	22	-	MD 1.8 lower	⊕000	IMPORTANT
									(2.43 lower to 1.17 lower)	VERY LOW	
Platelets	transfused	- Cold-stored plat	elets						•		
1 RCT	serious ^a	not serious	not serious	very serious ^b	none	17	22	-	MD 0.2 lower	€000	IMPORTANT
									(U.3 lower to U.1 lower)	VERY LOW	

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

Explanations

a. Methods of studies are poorly reported. Due to the absence of clear methods and protocols, we judge the studies to be at high risk of bias, particularly selective reporting.

b. Very small number of patients included in single study, resulting in very serious imprecision.

Cold stored platelets in critically ill bleeding patients

1. Mortality - cryopreserved platelets



2. Bleeding - cold-stored platelets

	Cold platelets Regular platelets					lets		Mean Difference		Mean Difference		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI		IV, Fixe	d, 95% CI	
1.2.1 Cold-stored pl	atelets											
Apelseth 2017	546	61	17	820	109	22	100.0%	-274.00 [-327.99, -220.01]				
Subtotal (95% CI)			17			22	100.0%	-274.00 [-327.99, -220.01]		-		
Heterogeneity: Not ap	plicable											
Test for overall effect:	Z = 9.9	5 (P <	0.000	01)								
									-500	-250	250	500
									-500	Favours cold platelets	Favours regular platelet	s

3. Thromboembolic events - cold-stored platelets

	Cold plat	telets	Regular pla	telets		Risk Ratio		Risk Ratio			
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fixed, 95% Cl			
1.3.1 Cold-stored pl	atelets										
Apelseth 2017	3	17	7	22	100.0%	0.55 [0.17, 1.83]					
Subtotal (95% CI)		17		22	100.0%	0.55 [0.17, 1.83]					
Total events	3		7								
Heterogeneity: Not ap	plicable										
Test for overall effect:	Z = 0.97	(P = 0.3)	3)								
							0.05		20		
							0.05	Favours cold platelets Favours regular platelet	ts		

Cold stored platelets in critically ill bleeding patients

4. RBCs transfused - cold-stored platelets



5. Plasma transfused - cold-stored platelets

	Cold p	olatel	ets	Regular	r plate	lets		Mean Difference	Mean Difference			
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI			
1.5.1 Cold-stored pl	atelets											
Apelseth 2017 Subtotal (95% CI)	7.7	1	17 17	9.5	1	22 22	100.0% 100.0%	-1.80 [-2.43, -1.17] -1.80 [-2.43, -1.17]				
Heterogeneity: Not ap Test for overall effect:	Heterogeneity: Not applicable Test for overall effect: $Z = 5.57$ (P < 0.00001)											
									-2 -1 0 1 2 Favours cold platelets Favours regular platelets			

6. Platelets transfused - cold-stored platelets

	Cold	plate	lets	Regula	r plate	lets		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
1.6.1 Cold-stored pl	atelets								
Apelseth 2017 Subtotal (95% CI)	2.1	0.1	17 17	2.3	0.2	22 22	100.0% 100.0%	-0.20 [-0.30, -0.10] -0.20 [-0.30, -0.10]	
Heterogeneity: Not ap	plicable								
Test for overall effect:	Z = 4.03	8 (P <	0.000	1)					
									-0.2 -0.1 0 0.1 0.2
									Favours cold platelets Favours regular platelets

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

PCC vs. FFP in massively bleeding patients

Cardiac Surgery

ETD Cardiac Surgery

			Certainty as	ssessment			№ of p	atients	Effec	t		
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Massive Transfusion Protocol with Prothrombin	plasma	Relative (95% Cl)	Absolute (95% Cl)	Certainty	Importance
Cardiac Su	urgery- Mortality											
5	observational studies	serious a	not serious	not serious	very serious _b	none c	47/539 (8.7%)	44/524 (8.4%)	RR 1.05 (0.71 to 1.56)	4 more per 1,000 (from 24 fewer to 47 more)		CRITICAL
Cardiac Su	urgery - Stroke											
5	observational studies	serious a	serious d	not serious	serious b	none c	27/539 (5.0%)	22/524 (4.2%)	RR 1.20 (0.70 to 2.05)	8 more per 1,000 (from 13 fewer to 44 more)		CRITICAL
Cardiac Su	ırgery- Reoperati	on										
4	observational studies	serious a	not serious	not serious	serious e	none c	88/512 (17.2%)	151/784 (19.3%)	RR 0.86 (0.67 to 1.11)	27 fewer per 1,000 (from 64 fewer to 21 more)		IMPORTANT
Cardiac Su	urgery-RRT											
2	observational studies	serious a	not serious	not serious	very serious _b	none c	15/270 (5.6%)	7/280 (2.5%)	RR 2.34 (0.98 to 5.60)	33 more per 1,000 (from 1 fewer to 115 more)		IMPORTANT
Cardiac Su	urgery-RBC trans	fusion						-				
4	observational studies	serious a	not serious	not serious	not serious	none c	381/488 (78.1%)	442/498 (88.8%)	RR 0.88 (0.83 to 0.93)	107 fewer per 1,000 (from 151 fewer to 62 fewer)		IMPORTANT

			Certainty as	ssessment			Nº of p	oatients	Effec	t		
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Massive Transfusion Protocol with Prothrombin	plasma	Relative (95% Cl)	Absolute (95% Cl)	Certainty	Importance
Cardiac Su	urgery- RBC units	s transfused										
4	observational studies	serious a	serious	not serious	serious e	none c	422	407	-	MD 1.16 lower (1.59 lower to 0.73 lower)		IMPORTANT
Cardiac Su	urgery- Chest Dra	in output (24 hou	irs)									
2	observational studies	serious a	serious d	not serious	very serious _b	none c	276	251	-	MD 72.88 higher (75.87 lower to 221.64 higher)		IMPORTANT
Cardiac Su	urgery- ICU LOS-	Hours										
1	observational studies	serious a	not serious	not serious	very serious	none c	225	225	-	MD 18 lower (43.14 lower to 7.14 higher)		IMPORTANT
Cardiac Su	urgery-Hospital L	OS (Days)										
1	observational studies	serious a	not serious	not serious	very serious _b		225	225	-	MD 2.7 lower (4.68 lower to 0.72 lower)	-	IMPORTANT

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

Explanations

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

Mortality

	PCC	2	FFF	,		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% Cl
Amekian 2012	3	51	1	26	3.0%	1.53 [0.17, 13.99]	
Biancari 2019	5	101	5	101	11.4%	1.00 [0.30, 3.35]	
Cappabianca 2016	21	225	19	225	43.3%	1.11 [0.61, 2.00]	
Fitzgerald 2018	15	117	15	117	34.1%	1.00 [0.51, 1.95]	+
Ortmann 2015	3	45	4	55	8.2%	0.92 [0.22, 3.89]	
Total (95% CI)		539		524	100.0%	1.05 [0.71, 1.56]	•
Total events	47		44				
Heterogeneity: Chi ² =	0.20, df	= 4 (P	= 1.00);	$I^2 = 0\%$	6		
Test for overall effect:	Z = 0.27	7 (P = 0)	.79)				Favours PCC Favours FFP

Reoperation

	PCC	2	FFF)		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Amekian 2012	11	51	2	26	2.4%	2.80 [0.67, 11.72]	+
Biancari 2019	17	119	77	416	31.5%	0.77 [0.48, 1.25]	
Cappabianca 2016	33	225	42	225	38.6%	0.79 [0.52, 1.19]	
Fitzgerald 2018	27	117	30	117	27.5%	0.90 [0.57, 1.41]	-
Total (95% CI)		512		784	100.0%	0.86 [0.67, 1.11]	•
Total events	88		151				
Heterogeneity: Chi ² = Test for overall effect:	3.04, df Z = 1.15	= 3 (P) = 0	= 0.39); .25)	$I^2 = 1\%$	5		0.01 0.1 1 10 100 Favours PCC Favours FFP

<u>Stroke</u>

	PCC	2	FFF	,		Risk Ratio		Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fixed, 95% CI	
Amekian 2012	0	51	1	26	8.6%	0.17 [0.01, 4.11]	•	· · · · · · · · · · · · · · · · · · ·	
Biancari 2019	5	101	3	101	13.1%	1.67 [0.41, 6.79]			
Cappabianca 2016	14	225	9	225	39.3%	1.56 [0.69, 3.52]		- +	
Fitzgerald 2018	7	117	8	117	35.0%	0.88 [0.33, 2.33]			
Ortmann 2015	1	45	1	55	3.9%	1.22 [0.08, 19.00]			
Total (95% CI)		539		524	100.0%	1.20 [0.70, 2.05]		•	
Total events	27		22						
Heterogeneity: Chi ² =	2.43, df	= 4 (P	= 0.66);	$I^2 = 0\%$	6		0.01		100
Test for overall effect:	Z = 0.66	6 (P = 0	0.51)				0.01	Favours PCC Favours FFP	100

<u>RRT</u>

	PCC	2	FFF	•		Risk Ratio	Risk Ratio			
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI			
Cappabianca 2016	8	225	4	225	59.7%	2.00 [0.61, 6.55]				
Ortmann 2015	7	45	3	55	40.3%	2.85 [0.78, 10.40]] +			
Total (95% CI)		270		280	100.0%	2.34 [0.98, 5.60]				
Total events	15		7							
Heterogeneity: Chi ² =	0.16, df	= 1 (P	= 0.69);	$I^2 = 0\%$	6		0.01 0.1 1 10	100		
Test for overall effect:	Z = 1.92	P = 0	0.06)				Favours PCC Favours FFP	100		

RBC Transfusion

	PCC	2	FFF	,		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Biancari 2019	68	101	84	101	19.2%	0.81 [0.69, 0.95]	-
Cappabianca 2016	189	225	210	225	48.0%	0.90 [0.84, 0.96]	
Fitzgerald 2018	90	117	104	117	23.8%	0.87 [0.77, 0.97]	=
Ortmann 2015	34	45	44	55	9.0%	0.94 [0.76, 1.17]	-
Total (95% CI)		488		498	100.0%	0.88 [0.83, 0.93]	,
Total events	381		442				
Heterogeneity: Chi ² = Test for overall effect:	1.99, df Z = 4.55	= 3 (P 5 (P < 0	= 0.57); .00001)	$l^2 = 0$ %	5		0.01 0.1 1 10 100 Favours PCC Favours FFP

RBC Transfusion Units

		PCC			FFP			Mean Difference	Mean Difference			
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI			
Amekian 2012	1	2.2	51	2	1.5	26	27.1%	-1.00 [-1.83, -0.17]	•			
Biancari 2019	2	4	101	2	4	101	15.5%	0.00 [-1.10, 1.10]	•			
Cappabianca 2016	3.4	3.1	225	5.2	4.3	225	39.3%	-1.80 [-2.49, -1.11]	•			
Ortmann 2015	2	2.2	45	3	3	55	18.1%	-1.00 [-2.02, 0.02]	1			
Total (95% CI) Heterogeneity: Chi ² =	7.76, d	f = 3	-100 -50 0 50 100									
Test for overall effect.	Z = 5.4	23 (P	< 0.00	001)					Favours PCC Favours FFP			

Chest tube output in 24 hours

		PCC			FFP			Mean Difference		Mean Difference			
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI		IV, Fixed	l, 95% CI		
Cappabianca 2016	935	583	225	836	1,226	225	70.3%	99.00 [-78.38, 276.38]					
Amekian 2012	1,261	780	51	1,250	441	26	29.7%	11.00 [-262.06, 284.06]	←		-		
Total (95% CI)			276			251	100.0%	72.88 [-75.87, 221.64]					
Heterogeneity: Chi ²	= 0.28, di	f = 1 (P = 0.6	50); I ² =	0%		10010/0	12:00 [15:01; 22:01;	100	10	50	100	
Test for overall effec	t: Z = 0.9	6 (P =	0.34)						-100	Favours PCC	Favours FFP	100	

LOS-ICU (hours)



<u>Trauma</u> Trauma ETD

			Certainty as	ssessment			Nº of p	patients	Effec	t		
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Massive Transfusion Protocol with Prothrombin	plasma	Relative (95% Cl)	Absolute (95% Cl)	Certainty	Importance
Trauma- N	lortality											
6	observational studies	serious a	not serious	not serious	not serious	none c	83/462 (18.0%)	241/1175 (20.5%)	RR 0.73 (0.58 to 0.92)	55 fewer per 1,000 (from 86 fewer to 16 fewer)		CRITICAL
Trauma- D	VT											
4	observational studies	serious a	serious d	serious e	serious b	none c	13/364 (3.6%)	31/557 (5.6%)	RR 0.60 (0.32 to 1.13)	22 fewer per 1,000 (from 38 fewer to 7 more)		IMPORTANT
Trauma- P	ulmonary Emboli	sm										
2	observational studies	serious a	not serious	Serious e	very serious b	none c	3/274 (1.1%)	4/314 (1.3%)	RR 0.75 (0.17 to 3.31)	3 fewer per 1,000 (from 11 fewer to 29 more)		IMPORTANT
Trauma- I	CU LOS (Mean)											
6	observational studies	Serious a	not serious	serious e	very serious r	none d	462	1175	-	MD 0.03 lower (0.19 lower to 0.13 higher)		IMPORTANT
Trauma-H	ospital LOS (Mear	n)										
6	observational studies	serious a	not serious	serious e	very serious r	nonê c	462	1175	-	MD 2.17 lower (2.82 lower to 1.52 lower)		IMPORTANT
Trauma R	3C transfusion											

			Certainty as	ssessment			Nº of p	oatients	Effec	t		
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Massive Transfusion Protocol with Prothrombin	plasma	Relative (95% Cl)	Absolute (95% Cl)	Certainty	Importance
4	observational studies	serious a	not serious	serious e	serious g	none 。	364	557	-	MD 3.33 lower (3.87 lower to 2.79 lower)		IMPORTANT
Trauma-FF	P Transfusion U	nits				•						
3	observational studies	serious a	not serious	serious _e	serious g	none c	324	477	-	MD 0.63 lower (0.96 lower to 0.31 lower)		IMPORTANT
Trauma-Pl	atelets											
4	observational studies	serious a	not serious	serious 🛛	very serious r	noné c	364	557	-	MD 0.1 lower (0.44 lower to 0.24 higher)		IMPORTANT
Trauma- S	epsis											
1	observational studies	serious a	not serious	serious 🛛	serious b	noné c	3/18 (16.7%)	6/18 (33.3%)	RR 0.50 (0.15 to 1.70)	167 fewer per 1,000 (from 283 fewer to 233 more)		IMPORTANT

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

Explanations

a. Studies included were at a high risk of bias. The majority of studies were retrospective cohorts. b. Rated down for imprecision due to wide confidence intervals and small number of events.

c. Could not formally assess for publication bias due to small number of studies .

d. Rated down for significant heterogeneity with point estimates on both sides of the line of no effect.
 e. In some of the studies the intervention group received PCC and FFP, compared to FFP alone.
 f. Rated down for imprecision as some studies had to undergo data transformation from median to mean.
 g. Rated down for imprecision as some studies had to undergo data transformation from median to mean.

<u>Mortality</u>

	PCC	PCC FFP				Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% Cl
Jehan 2018	10	40	26	80	12.4%	0.77 [0.41, 1.43]	-+-
Joseph 2014	15	63	53	189	19.0%	0.85 [0.52, 1.40]	
Joseph 2016	6	27	15	54	7.2%	0.80 [0.35, 1.83]	
Nienaber 2011	3	18	2	18	1.4%	1.50 [0.28, 7.93]	
Schochl 2011	8	80	80	600	13.5%	0.75 [0.38, 1.49]	
Zeeshan 2018	41	234	65	234	46.5%	0.63 [0.45, 0.89]	
Total (95% CI)		462		1175	100.0%	0.73 [0.58, 0.92]	•
Total events	83		241				
Heterogeneity: Chi ² =	1.84, df	= 5 (P	= 0.87);	$I^2 = 0\%$	6		
Test for overall effect:	Z = 2.68	P = 0	.007)				Favours PCC Favours FFP

<u>DVT</u>

	PCC	C	FFF	,		Risk Ratio		Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fixed, 95% CI	
Jehan 2018	1	40	1	80	2.7%	2.00 [0.13, 31.15]			
Joseph 2014	1	63	2	189	4.1%	1.50 [0.14, 16.26]			
Joseph 2016	3	27	15	54	40.5%	0.40 [0.13, 1.26]			
Zeeshan 2018	8	234	13	234	52.7%	0.62 [0.26, 1.46]			
Total (95% CI)		364		557	100.0%	0.60 [0.32, 1.13]		•	
Total events	13		31						
Heterogeneity: Chi ² =	1.79, df	= 3 (P)	= 0.62);	$I^2 = 0\%$	6		0.01	0.1 1 10	100
rescior overall effect.	2 - 1.30	5(1 = 0)					Favours PCC Favours FFP	

<u>PE</u>

	PCC	2	FFF	>		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% Cl
Jehan 2018	0	40	0	80		Not estimable	
Zeeshan 2018	3	234	4	234	100.0%	0.75 [0.17, 3.31]	
Total (95% CI)		274		314	100.0%	0.75 [0.17, 3.31]	
Total events	3		4				
Heterogeneity: Not ap	plicable						
Test for overall effect:	Z = 0.38	B (P = 0)).70)				Favours PCC Favours FFP

ICU LOS (Mean)

	PCC				FFP			Mean Difference		Me	an Differei	nce	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI		IV,	Fixed, 95%	S CI	
Joseph 2014	3.1	2.9	63	3.9	2.8	189	100.0%	-0.80 [-1.62, 0.02]					
Total (95% CI)			63			189	100.0%	-0.80 [-1.62, 0.02]					
Heterogeneity: Not ap Test for overall effect:	Z = 1.9	1 (P	= 0.06)					-100	-50 Favours	PCC Favo	50 urs FFP	100

-			PCC			FFP			Mean Difference		Mean Difference	
	Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI		IV, Fixed, 95% CI	
-	Jehan 2018	1	0.74	40	1	0.74	80	33.7%	0.00 [-0.28, 0.28]		+	
	Joseph 2014	3.1	2.9	63	3.9	2.8	189	4.0%	-0.80 [-1.62, 0.02]		•	
	Joseph 2016	1	2.2	27	1	2.2	54	2.6%	0.00 [-1.02, 1.02]		ł	
	Nienaber 2011	20	17.7	18	17.5	8.8	18	0.0%	2.50 [-6.63, 11.63]			
	Schochl 2011	14.5	9.25	80	14	12.59	600	0.5%	0.50 [-1.76, 2.76]		t	
	Zeeshan 2018	1	1.48	234	1	0.74	234	59.2%	0.00 [-0.21, 0.21]		•	
	Total (95% CI)			462			1175	100.0%	-0.03 [-0.19, 0.13]			
	Heterogeneity: Chi ² = Test for overall effect:	4.02, d Z = 0.3	f = 5 (4 (P =	P = 0.5 0.73)	5); I ² =	0%				-100	-50 0 50 Favours PCC Favours FFP	100
CO LOS WITH all transformed data												

		PCC			FFP			Mean Difference			Me	an Differe	nce	
	Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI		IV,	Fixed, 95%	6 CI	
	Joseph 2014	8.9	5.7	63	8.4	6.1	189	100.0%	0.50 [-1.15, 2.15]					
	Total (95% CI)	nlicabla		63			189	100.0%	0.50 [-1.15, 2.15]	L		•		
Hospital LOS (Mean)	Test for overall effect:	Z = 0.5	59 (P	= 0.55)					-100	-50 Favours	O PCC Favo	50 ours FFP	100

			PCC			FFP			Mean Difference	Mean Difference
	Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
	Jehan 2018	5	2.96	40	7	3.7	80	28.2%	-2.00 [-3.22, -0.78]	•
	Joseph 2014	8.9	5.7	63	8.4	6.1	189	15.4%	0.50 [-1.15, 2.15]	+
	Joseph 2016	4	5.18	27	5	5.92	54	6.7%	-1.00 [-3.51, 1.51]	+
	Nienaber 2011	30.25	22.96	18	36.75	20	18	0.2%	-6.50 [-20.57, 7.57]	
	Schochl 2011	23	19.25	80	32	21.48	600	2.0%	-9.00 [-13.55, -4.45]	
	Zeeshan 2018	5	4.4	234	8	5.9	234	47.5%	-3.00 [-3.94, -2.06]	
	Total (95% CI)			462			1175	100.0%	-2.17 [-2.82, -1.52]	1
	Heterogeneity: $\text{Chi}^2 = 22.89$, $\text{df} = 5$ (P = 0.0004); $\text{I}^2 = 78\%$								-100 -50 0 50 100	
Hospital LOS with all transformed data	Test for overall effect: $Z = 6.56 (P < 0.00001)$									Favours PCC Favours FFP

				FFP			Mean Difference		Mean I	Difference				
	Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI		IV, Fixe	d, 95% Cl		
	Jehan 2018	7	3	40	9	5	80	14.3%	-2.00 [-3.44, -0.56]			-		
	Joseph 2014	6.6	4.1	63	10	8.3	189	12.2%	-3.40 [-4.96, -1.84]			•		
	Joseph 2016	3.2	1.9	27	5.4	4.1	54	17.3%	-2.20 [-3.51, -0.89]			•		
	Zeeshan 2018	6	4	234	10	4	234	56.2%	-4.00 [-4.72, -3.28]		I	4		
	Total (95% CI)			364			557	100.0%	-3.33 [-3.87, -2.79]			1		
nits)	Heterogeneity: Chi ² = Test for overall effect:	9.45, d Z = 12	f = 3 .01 (I	(P = 0) P < 0.0	.02); I ² 0001)	= 68	%			-100	-50 Favours PC	0 S C Favours FF	50 P	100

RBC Transfusion (units)



			PCC			FFP			Mean Difference		Mean D	oifference	
	Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI		IV, Fixe	d, 95% CI	
	Jehan 2018	3	3	40	3	3	80	8.9%	0.00 [-1.14, 1.14]			+	
	Joseph 2014	1.2	2.1	63	1.5	2.7	189	27.5%	-0.30 [-0.95, 0.35]			+	
	Joseph 2016	1.4	2.3	27	1.6	2.4	54	9.9%	-0.20 [-1.28, 0.88]			+	
	Zeeshan 2018	3	2	234	3	3	234	53.8%	0.00 [-0.46, 0.46]			•	
	Total (95% CI)			364			557	100.0%	-0.10 [-0.44, 0.24]				
	Heterogeneity: Chi ² =	0.61, d	f = 3	(P = 0) = 0.55	.89); I ²	= 0%	6			-100	-50	0 50	100
atelet Transfusion	rescribit overall crieet.	2 - 01.		0.55	·						Favours PCC	Favours FFP	

<u>Sepsis</u>

	PCC		FFF			Risk Ratio		Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fixed, 95% CI	
Nienaber 2011	3	18	6	18	100.0%	0.50 [0.15, 1.70]			
Total (95% CI)		18		18	100.0%	0.50 [0.15, 1.70]			
Total events	3		6						
Heterogeneity: Not ap	plicable						0.01	0 1 1 10	100
Test for overall effect	Z = 1.11	L (P = 0).27)				0.01	Favours PCC Favours FFP	100

GI-Liver Transplant

Liver Transplant ETD

Liver Transplant ETD

			Certainty as	ssessment			Nº of p	atients	Effec	t		
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Massive Transfusion Protocol with Prothrombin	plasma	Relative (95% Cl)	Absolute (95% Cl)	Certainty	Importance
Liver Tran	splant-RBC trans	fusion							-			
1	observational studies	not serious	not serious	not serious	very serious a	none b	60	60	-	MD 2.03 lower (3.7 lower to 0.36 lower)		IMPORTANT
Liver Tran	splant-FFP											
1	observational studies	not serious	not serious	not serious	very serious a	none b	60	60	-	MD 3.58 lower (4.73 lower to 2.43 lower)		IMPORTANT
Liver Tran	splant-Platelet Tr	ansfusion										
1	observational studies	not serious	not serious	not serious	very serious a	none	60	60	-	MD 0.69 higher (1.12 lower to 2.5 higher)		IMPORTANT

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

Explanations

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

RBC Transfusion

	I	РСС			FFP			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Srivastava 2018	6.2	4.1	60	8.23	5.18	60	100.0%	-2.03 [-3.70, -0.36]	•
Total (95% CI) Heterogeneity: Not ap Test for overall effect:	plicable Z = 2.3	88 (P	60 = 0.02)		60	100.0%	-2.03 [-3.70, -0.36]	-100 -50 0 50 100 Favours PCC Favours FFP

FFP Transfusion

	1	РСС			FFP			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Srivastava 2018	2.6	2	60	6.18	4.1	60	100.0%	-3.58 [-4.73, -2.43]	
Total (95% CI) Heterogeneity: Not ap	plicable	NO (D	60	001		60	100.0%	-3.58 [-4.73, -2.43]	
lest for overall effect:	Z = 6.0	J8 (P	< 0.00)001)					Favours PCC Favours FFP

Platelet Transfusion

		PCC			FFP			Mean Difference		Mean D	ifference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI		IV, Fixe	d, 95% CI	
Srivastava 2018	6.6	5.5	60	5.91	4.6	60	100.0%	0.69 [-1.12, 2.50]				
Total (95% CI) Heterogeneity: Not ap Test for overall effect:	plicable Z = 0.7	75 (P	60 = 0.46)		60	100.0%	0.69 [-1.12, 2.50]	-100	-50 Favours PCC	0 50 Favours FFP	100

TBI ETD

			Certainty as	ssessment			N₂ of patients		Effec	t		
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Massive Transfusion Protocol with Prothrombin	plasma	Relative (95% Cl)	Absolute (95% Cl)	Certainty	Importance
TBI- Morta	lity											
1	observational studies	not serious	not serious	serious d	not serious	none b	23/74 (31.1%)	68/148 (45.9%)	RR 0.68 (0.46 to 0.99)	147 fewer per 1,000 (from 248 fewer to 5 fewer)		CRITICAL
TBI- VTE												
1	observational studies	serious	not serious	serious d	serious a	nonê b	3/74 (4.1%)	5/148 (3.4%)	RR 1.20 (0.29 to 4.89)	7 more per 1,000 (from 24 fewer to 131 more)		IMPORTANT
TBI-Progre	ession of ICH											
1	observational studies	not serious	not serious	serious d	not serious	none b	18/74 (24.3%)	65/148 (43.9%)	RR 0.55 (0.36 to 0.86)	198 fewer per 1,000 (from 281 fewer to 61 fewer)		IMPORTANT
TBI-ICU LO	DS			1			1	1	1			
1	observational studies	not serious	not serious	serious	very serious d	none b	74	148	-	MD 0.6 lower (1.36 lower to 0.16 higher)		IMPORTANT
TBI-Hospit	tal LOS											
1	observational studies	not serious	not serious	serious d	serious c	none b	74	148	-	MD 1.1 lower (2.88 lower to 0.68 higher)		IMPORTANT
TBI-RBC T	ransfusion											
1	observational studies	not serious	not serious	serious d	serious c	none b	74	148	-	MD 0.6 lower (1.25 lower to 0.05 higher)		IMPORTANT

			Certainty as	ssessment			Nº of p	oatients	Effec	t		
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Massive Transfusion Protocol with Prothrombin	plasma	Relative (95% Cl)	Absolute (95% Cl)	Certainty	Importance
1	observational studies	not serious	not serious	serious d	serious c		74	148	-	MD 0.9 lower (1.58 lower to 0.22 lower)	-	IMPORTANT
TBI-Platele	et transfusion											
1	observational studies	not serious	not serious	serious d	not serious	none b	74	148	-	MD 0.2 higher (0.29 lower to 0.69 higher)		IMPORTANT

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

Explanations

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

Mortality

	PCO	2	FFF)		Risk Ratio		Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fixed, 95% CI	
Joseph 2015	23	74	68	148	100.0%	0.68 [0.46, 0.99]		-	
Total (95% CI)		74		148	100.0%	0.68 [0.46, 0.99]		•	
Total events	23		68						
Heterogeneity: Not ap	plicable						0.01	01 1 10	100
Test for overall effect:	Z = 2.01	L (P = 0).04)				0.01	Favours PCC Favours FFP	, 100

<u>VTE</u>

	PCC	:	FFF	,		Risk Ratio	Risk Ratio
Bullets or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Joseph 2015	3	74	5	148	100.0%	1.20 [0.29, 4.89]	
Total (95% CI)		74		148	100.0%	1.20 [0.29, 4.89]	
Total events	3		5				
Heterogeneity: Not app	plicable						
Test for overall effect:	Z = 0.25	(P = 0	.80)				Favours PCC Favours FFP

Progression of ICH

	PCC	:	FFF)		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Joseph 2015	18	74	65	148	100.0%	0.55 [0.36, 0.86]	
Total (95% CI)		74		148	100.0%	0.55 [0.36, 0.86]	•
Total events	18		65				
Heterogeneity: Not ap	plicable						
Test for overall effect:	Z = 2.62	(P = 0	.009)				Favours PCC Favours FFP

ICU LOS

	1	PCC			FFP			Mean Difference	N	Aean Difference		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	I	V, Fixed, 95% Cl		
Joseph 2015	2.9	2.7	74	3.5	2.8	148	100.0%	-0.60 [-1.36, 0.16]				
Total (95% CI)			74			148	100.0%	-0.60 [-1.36, 0.16]				
Heterogeneity: Not ap	plicable								-100 -50		50	100
Test for overall effect:	Z = 1.5	64 (P	= 0.12)					Favor	Irs PCC Favours	FFP	200

Hospital LOS

	1	РСС			FFP			Mean Difference		Mea	n Differei	nce	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI		IV, F	ixed, 95%	CI	
Joseph 2015	6.7	6.1	74	7.8	6.9	148	100.0%	-1.10 [-2.88, 0.68]					
Total (95% CI) Heterogeneity: Not ap Test for overall effect:	plicable Z = 1.2	21 (P	74 = 0.23)		148	100.0%	-1.10 [-2.88, 0.68]	-100	-50 Favours	PCC Favo	50 urs FFP	100

RBC Transfusion

		РСС			FFP			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Joseph 2015	3.2	2.2	74	3.8	2.6	148	100.0%	-0.60 [-1.25, 0.05]	•
Total (95% CI) Heterogeneity: Not ap Test for overall effect:	plicable Z = 1.8	30 (P	74 = 0.07)		148	100.0%	-0.60 [-1.25, 0.05]	I -100 -50 0 50 100 Favours PCC Favours FFP

FFP Transfusion

	PCC			FFP				Mean Difference	Mean Difference			nce	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI		IV,	Fixed, 95%	6 CI	
Joseph 2015	3.1	2.5	74	4	2.3	148	100.0%	-0.90 [-1.58, -0.22]					
Total (95% CI)74148Heterogeneity: Not applicable Test for overall effect: Z = 2.60 (P = 0.009)					100.0%	-0.90 [-1.58, -0.22]	-100	-50 Favours	PCC Favo	50 ours FFP	100		

Platelet Transfusion

	PCC			FFP				Mean Difference	Mean Difference				
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI		IV,	Fixed, 95%	5 CI	
Joseph 2015	1.4	1.8	74	1.2	1.7	148	100.0%	0.20 [-0.29, 0.69]					
Total (95% CI)			74			148	100.0%	0.20 [-0.29, 0.69]					
Heterogeneity: Not applicable Test for overall effect: $Z = 0.79$ (P = 0.43)									-100	-50 Favours	PCC Favo	50 urs FFP	100

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

Early/empiric fibrinogen in massively bleeding patients

1. Trauma - Randomized controlled trials

		Cert	ainty assessment			Nº of pat	tients		Effect		Importance	
№ of studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Fibrinogen	Control	Relative (95% Cl)	Absolute (95% Cl)	Certainty		
All-cause mortality - Trauma (RCT)												
5 RCTs	not serious	serious ^a	not serious	serious ^b	none	20/139 (14.4%)	23/149 (15.4%)	RR 1.02 (0.33 to 3.11)	3 more per 1,000 (from 103 fewer to 326 more)		CRITICAL	
Death due	to hemorrh	age - Trauma (RCT)										
3 RCTs	not serious	not serious	not serious	very serious ^d	none	5/65 (7.7%)	7/69 (10.1%)	RR 0.77 (0.27 to 2.18)	23 fewer per 1,000 (from 74 fewer to 120 more)		CRITICAL	
Myocardia	I infarction	- Trauma (RCT)										
3 RCTs	not serious	not serious	not serious	very serious ^c	none	0/65 (0.0%)	0/69 (0.0%)	not pooled	see comment		CRITICAL	
ARDS - Tra	auma (RCT)											
2 RCTs	not serious	not serious	not serious	very serious ^d	none	0/41 (0.0%)	3/45 (6.7%)	RR 0.27 (0.03 to 2.37)	49 fewer per 1,000 (from 65 fewer to 91 more)		CRITICAL	
Renal failu	ıre - Trauma	ı (RCT)										
2 RCTs	not serious	not serious	not serious	very serious ^d	none	8/65 (12.3%)	9/74 (12.2%)	RR 1.01 (0.41 to 2.47)	1 more per 1,000 (from 72 fewer to 179 more)		CRITICAL	
Sepsis - T	rauma (RCT)										
5 RCTs	not serious	not serious	not serious	serious ^b	none	26/139 (18.7%)	28/149 (18.8%)	RR 1.00 (0.62 to 1.60)	0 fewer per 1,000 (from 71 fewer to 113 more)	⊕⊕⊕⊖ MODERATE	IMPORTANT	
ICU length	of stay - Tr	auma (RCT)										
2 RCTs	not serious	not serious •	not serious	serious ^f	none	64	71	-	MD 4.83 lower (8.12 lower to 1.55 lower)	⊕⊕⊕⊖ MODERATE	IMPORTANT	
Hospital le	Hospital length of stay - Trauma (RCT)											

Early/empiric fibrinogen in massively bleeding patients

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

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

a. Significant heterogeneity with point estimates on both sides of the line of no effect.

b. Wide confidence intervals, which do not exclude significant harm or benefit.

c. The absence of any deaths means we are unable to estimate the effect for this outcome.

d. Very small number of events resulting in very serious imprecision.

e. Significant statistical heterogeneity between the included studies not easily explained by study characteristics.

f. Statistically significant reduction in length of stay, though small number of patients.
2. Trauma- observational studies

		Certainty	assessment			№ of patients			Effect		Importance
№ of studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Fibrinogen	Control	Relative (95% CI)	Absolute (95% Cl)	Certainty	Importance
All-cause morta	lity - Traum	a (observational)									
5 Observational Studies	not serious	not serious	not serious	serious ^b	none	391/1246 (31.4%)	237/1312 (18.1%)	RR 1.11 (0.87 to 1.42)	20 more per 1,000 (from 23 fewer to 76 more)	⊕○○○ VERY LOW	CRITICAL
Death due to he	morrhage -	Trauma (Obs)									
1 Observational study	serious ^c	not serious	not serious	serious ^b	none	90/758 (11.9%)	28/269 (10.4%)	RR 1.14 (0.76 to 1.70)	15 more per 1,000 (from 25 fewer to 73 more)		CRITICAL
Sepsis - Trauma	a (obs)										
2 Observational studies	not serious	not serious	not serious	serious ^b	none	64/312 (20.5%)	58/312 (18.6%)	RR 1.10 (0.80 to 1.52)	19 more per 1,000 (from 37 fewer to 97 more)	⊕○○○ VERY LOW	IMPORTANT
Surgical interve	ntion - Trau	ıma (obs)									
1 Observational study	serious ^c	not serious	not serious	serious ^b	none	592/758 (78.1%)	195/269 (72.5%)	RR 1.08 (0.99 to 1.17)	58 more per 1,000 (from 7 fewer to 123 more)	⊕○○○ VERY LOW	IMPORTANT
ICU length of sta	ay - Trauma	ı (Obs)									
4 Observational studies	serious ^c	not serious	not serious	not serious	none	1150	1182	-	MD 1.23 higher (0.02 higher to 2.43 higher)	⊕○○○ VERY LOW	IMPORTANT
Hospital length	of stay - Tra	auma (Obs)									
4 Observational studies	not serious	serious ^d	not serious	not serious	none	1150	1182	-	MD 2.69 lower (5.27 lower to 0.1 lower)	⊕○○○ VERY LOW	IMPORTANT
RBCs transfuse	d - Trauma	(obs)									
4 Observational studies	not serious	serious ^d	not serious	not serious	none	1166	711	-	MD 1.16 lower (4.16 lower to 1.85 higher)	⊕○○○ VERY LOW	IMPORTANT

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

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

Explanations

a. Significant heterogeneity with point estimates on both sides of the line of no effect.b. Wide confidence intervals, which do not exclude significant harm or benefit.

c. Significant differences in baseline mortality risk between groups despite propensity-matching in Hamada 2020, which is the most-heavily weighted study.

d. Significant statistical heterogeneity between the included studies not easily explained by study characteristics.

3. Obstetric hemorrhage- RCTs

		Certa	ainty assessme	nt		№ of patients			Effect		
№ of studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Fibrinogen	Control	Relative (95% CI)	Absolute (95% Cl)	Certainty	Importance
All-cause	mortality	- Obstetric (RCT)									
1 RCT	not serious	not serious	not serious	very serious ^b	none	0/123 (0.0%)	0/121 (0.0%)	not estimable			CRITICAL
Bleeding	- Obstetri	c (RCT)									
1 RCT	not serious	not serious	not serious	serious ^a	none	29	28	-	MD 45 lower (110.38 lower to 20.38 higher)	⊕⊕⊕⊖ MODERATE	IMPORTANT
Surgical	interventio	on - Obstetric ble	eding (RCT)								
1 RCT	not serious	not serious	not serious	very serious ^c	none	4/29 (13.8%)	5/28 (17.9%)	RR 0.77 (0.23 to 2.58)	41 fewer per 1,000 (from 138 fewer to 282 more)		IMPORTANT
Hospital	length of s	tay - Obstetrical	bleeding (RCT)								
1 RCT	not serious	not serious	not serious	serious ^a	none	29	28	-	MD 1.61 lower (3.27 lower to 0.05 higher)	⊕⊕⊕⊖ MODERATE	IMPORTANT
Proportio	on receivin	g RBCs - Obstetr	ric bleeding (RC	T)							
1 RCT	not serious	not serious	not serious	very serious ^c	none	15/29 (51.7%)	14/28 (50.0%)	RR 1.03 (0.62 to 1.72)	15 more per 1,000 (from 190 fewer to 360 more)		IMPORTANT
Proportio	on receivin	g plasma - Obste	etric bleeding (R	CT)							
1 RCT	not serious	not serious	not serious	very serious ^c	none	6/29 (20.7%)	8/28 (28.6%)	RR 0.72 (0.29 to 1.82)	80 fewer per 1,000 (from 203 fewer to 234 more)		IMPORTANT
Proportio	on receivin	g platelets - Obsi	tetric bleeding (RCT)							
1 RCT	not serious	not serious	not serious	very serious ^c	none	1/29 (3.4%)	3/28 (10.7%)	RR 0.32 (0.04 to 2.91)	73 fewer per 1,000 (from 103 fewer to 205 more)		IMPORTANT

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

Explanations

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

	Early fibri	nogen	Cont	rol		Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	Year	M-H, Random, 95% Cl
1.1.1 Trauma (RCT)								
Curry 2015	2	20	6	21	20.4%	0.35 [0.08, 1.54]	2015	
Nascimento 2016	2	21	1	24	13.3%	2.29 [0.22, 23.44]	2016	
Innerhoffer 2017	5	44	2	50	19.4%	2.84 [0.58, 13.92]	2017	
Akbari 2018	3	30	11	30	23.6%	0.27 [0.08, 0.88]	2018	
Curry 2018	8	24	3	24	23.3%	2.67 [0.80, 8.86]	2018	
Subtotal (95% CI)		139		149	100.0%	1.02 [0.33, 3.11]		
Total events	20		23					
Heterogeneity: Tau ² =	= 1.01; Chi ²	= 11.32	, df = 4 ((P = 0.0)	$(2); I^2 = 6$	55%		
Test for overall effect:	Z = 0.03 (F	P = 0.97						
1.1.2 Trauma (obser	vational)							
Nienaber 2011	3	18	2	18	2.1%	1 50 [0 28 7 93]	2011	
Schöchl 2011	6	80	60	601	8.2%	0.75 [0.34, 1.68]	2011	
Wafaisade 2013	84	294	75	294	35.4%	1.12 [0.86, 1.46]	2013	_ _ _
Nardi 2015	13	96	26	130	12.9%	0.68 [0.37, 1.25]	2015	<u>_</u>
Hamada 2020	285	758	74	269	41.4%	1.37 [1.10, 1.69]	2020	
Subtotal (95% CI)		1246		1312	100.0%	1.11 [0.87, 1.42]		•
Total events	391		237					-
Heterogeneity: Tau ² =	0.03: Chi ²	= 6.41.	df = 4 (P	= 0.17	7): $I^2 = 38$	3%		
Test for overall effect:	Z = 0.83 (F	P = 0.41						
		,						
1.1.3 Obstetric (RCT))							
Wikkelsø 2015	0	123	0	121		Not estimable	2015	
Subtotal (95% CI)		123		121		Not estimable		
Total events	0		0					
Heterogeneity: Not ap	plicable							
Test for overall effect:	Not applica	ble						
								Favours early fibrinogen Favours control

2. Deaths due to hemorrhage

	Early fibrii	nogen	Cont	rol		Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	Year	M-H, Fixed, 95% Cl
1.2.1 Trauma (RCT)								
Curry 2015	2	20	6	21	79.9%	0.35 [0.08, 1.54]	2015	
Nascimento 2016	1	21	0	24	6.4%	3.41 [0.15, 79.47]	2016	
Curry 2018	2	24	1	24	13.7%	2.00 [0.19, 20.61]	2018	
Subtotal (95% CI)		65		69	100.0%	0.77 [0.27, 2.18]		
Total events	5		7					
Heterogeneity: Chi ² =	2.59, df = 2	2 (P = 0.	27); I ² =	23%				
Test for overall effect:	Z = 0.49 (P	= 0.62)						
1.2.2 Trauma (observ	vational)							
Hamada 2020	90	758	28	269	100.0%	1.14 [0.76, 1.70]	2020	
Subtotal (95% CI)		758		269	100.0%	1.14 [0.76, 1.70]		◆
Total events	90		28					
Heterogeneity: Not ap	plicable							
Test for overall effect:	Z = 0.64 (P	= 0.52						
								Favours early fibringen Favours control
								rations carly instituigen rations control

3. Stroke

	Early fibrir	nogen	Cont	rol		Risk Ratio				Risk Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	Year		M-H	l, Fixed, 95% (21	
1.4.1 Trauma												
Curry 2015	0	20	0	21		Not estimable	2015					
Nascimento 2016	0	21	0	24		Not estimable	2016			\perp		
Curry 2018	1	24	1	24	100.0%	1.00 [0.07, 15.08]	2018					
Subtotal (95% CI)		65		69	100.0%	1.00 [0.07, 15.08]						
Total events	1		1									
Heterogeneity: Not ap	plicable											
Test for overall effect:	Z = 0.00 (P	= 1.00)										
								0.01	0.1	1	10	100

Favours early fibrinogen Favours control

4. ARDS

	Early fibri	nogen	Cont	rol		Risk Ratio			Ris	« Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	Year		M–H, Fix	ced, 95% CI	
1.6.1 Trauma (RCT)											
Curry 2015	0	20	1	21	38.5%	0.35 [0.02, 8.10]	2015				
Nascimento 2016 Subtotal (95% CI)	0	21 41	2	24 45	61.5% 100.0%	0.23 [0.01, 4.48] 0.27 [0.03, 2.37]	2016				
Total events Heterogeneity: Chi ² = Test for overall effect:	0 0.04, df = 1 : Z = 1.18 (P	1 (P = 0.24)	3 .85); I ² =)	0%							
								0.01 Favo	0.1 Durs early fibrinoger	1 10 1 Favours control	100

5. Thrombosis

	Early fibri	nogen	Cont	rol		Risk Ratio			Risk	Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	Year		M-H, Fixe	ed, 95% CI		
1.6.1 Trauma (obs)												
Wafaisade 2013 Subtotal (95% CI)	20	294 294	10	294 294	100.0% 100.0%	2.00 [0.95, 4.20] 2.00 [0.95, 4.20]	2013					
Total events Heterogeneity: Not ap Test for overall effect:	20 plicable Z = 1.83 (F	P = 0.07)	10									
								0.01 Favou	0.1 rs early fibrinogen	1 Favours cor	10 ntrol	100

Test for subgroup differences: Not applicable

6. Renal failure

	Early fibri	nogen	Cont	rol		Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	Year	r M–H, Fixed, 95% Cl
1.8.1 Trauma (RCT)								
Nascimento 2016	3	21	2	24	22.2%	1.71 [0.32, 9.30]	2016	j <u> </u>
Innerhoffer 2017	5	44	7	50	77.8%	0.81 [0.28, 2.38]	2017	·
Subtotal (95% CI)		65		74	100.0%	1.01 [0.41, 2.47]		
Total events	8		9					
Heterogeneity: Chi ² =	0.54, df = 1	1 (P = 0.	46); I ² =	0%				
Test for overall effect	Z = 0.03 (P	= 0.98)						
								0.1 0.2 0.5 1 2 5 10

0.1 0.2 0.5 1 2 5 Favours early fibrinogen Favours control

6. Sepsis

	Early fibri	nogen	Cont	rol		Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	Year	ar M-H, Fixed, 95% CI
1.9.1 Trauma (RCT)								
Curry 2015	3	20	0	21	1.8%	7.33 [0.40, 133.57]	2015	5
Nascimento 2016	5	21	8	24	27.1%	0.71 [0.28, 1.85]	2016	6
Innerhoffer 2017	9	44	7	50	23.8%	1.46 [0.59, 3.60]	2017	7
Akbari 2018	5	30	7	30	25.4%	0.71 [0.25, 2.00]	2018	8
Curry 2018	4	24	6	24	21.8%	0.67 [0.22, 2.07]	2018	8
Subtotal (95% CI)		139		149	100.0%	1.00 [0.62, 1.60]		◆
Total events	26		28					
Heterogeneity: Chi ² =	3.87, df =	4 (P = 0.	42); I ² =	0%				
Test for overall effect:	Z = 0.00 (P	P = 1.00)					
1.9.2 Trauma (obs)								
Nienaber 2011	3	18	6	18	10.3%	0.50 [0.15, 1.70]	2011	1
Wafaisade 2013	61	294	52	294	89.7%	1.17 [0.84, 1.64]	2013	3 -
Subtotal (95% CI)		312		312	100.0%	1.10 [0.80, 1.52]		◆
Total events	64		58					
Heterogeneity: Chi ² =	1.74, df =	1 (P = 0.	19); I ² =	43%				
Test for overall effect:	Z = 0.60 (P	P = 0.55)					
								Favours early fibrinogen Favours control

7. Bleeding



8. Need for surgical intervention



9. ICU length of stay

	Early	fibrino	gen	c	ontrol			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
1.12.1 Trauma (RCT)									
Curry 2015	11	8.9	20	18	3	21	63.9%	-7.00 [-11.11, -2.89]	8
Innerhoffer 2017	9	13.3	44	10	13.7	50	36.1%	-1.00 [-6.46, 4.46]	
Subtotal (95% CI)			64			71	100.0%	-4.83 [-8.12, -1.55]	
Heterogeneity: Chi ² =	2.96, df	f = 1 (P)	= 0.09	9); I ² =	66%				
Test for overall effect:	Z = 2.8	9 (P =	0.004)						
1.12.2 Trauma (Obs)									
Hamada 2020	7	14	758	5	11.1	269	52.6%	2.00 [0.34, 3.66]	
Nienaber 2011	19	17.8	18	16	8.9	18	1.7%	3.00 [-6.19, 12.19]	
Schöchl 2011	14.5	9.3	80	14	12.6	601	28.0%	0.50 [-1.77, 2.77]	
Wafaisade 2013	17.2	17.6	294	17.3	17.9	294	17.6%	-0.10 [-2.97, 2.77]	
Subtotal (95% CI)			1150			1182	100.0%	1.23 [0.02, 2.43]	◆
Heterogeneity: Chi ² =	2.19, df	f = 3 (P	= 0.53	3); I ² =	0%				
Test for overall effect:	Z = 2.0	0 (P =	0.05)						
									-10 -5 0 5 10
									Favours early fibrinogen Favours control

10. Hospital length of stay

	Early	fibrino	gen	С	ontrol			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
1.13.1 Trauma (RCT))								
Akbari 2018	11	6.1	30	14.8	7.6	30	39.0%	-3.80 [-7.29, -0.31]	
Curry 2015	31	3	20	30	11.8	21	17.4%	1.00 [-4.22, 6.22]	
Innerhoffer 2017	28	7.4	44	27	8.9	50	43.6%	1.00 [-2.30, 4.30]	
Subtotal (95% CI)			94			101	100.0%	-0.87 [-3.05, 1.31]	◆
Heterogeneity: Chi ² =	4.44, di	f = 2 (P	P = 0.11	1); I ² =	55%				
Test for overall effect	: Z = 0.7	8 (P =	0.43)						
1.13.2 Trauma (Obs))								
Hamada 2020	19	35.6	758	19	27.4	269	38.9%	0.00 [-4.14, 4.14]	_
Nienaber 2011	26	30.3	18	38	20	18	2.4%	-12.00 [-28.77, 4.77]	
Schöchl 2011	23	19.3	80	32	21.5	601	32.0%	-9.00 [-13.57, -4.43]	_
Wafaisade 2013	34.6	33.3	294	32.8	28.4	294	26.7%	1.80 [-3.20, 6.80]	_
Subtotal (95% CI)			1150			1182	100.0%	-2.69 [-5.27, -0.10]	◆
Heterogeneity: Chi ² =	13.24,	df = 3	(P = 0.0)	004); I ²	= 77%	6			
Test for overall effect	: Z = 2.0	4 (P =	0.04)						
1.13.3 Obstetrical b	leeding (RCT)							
Collins 2017	2.89	1.05	29	4.5	4.37	28	100.0%	-1.61 [-3.27, 0.05]	
Subtotal (95% CI)			29			28	100.0%	-1.61 [-3.27, 0.05]	•
Heterogeneity: Not ap	plicable								
Test for overall effect	: Z = 1.9	0 (P =	0.06)						
									-20 -10 0 10 20
									Favours early fibrinogen Favours control

12. RBCs transfused

	Early	fibrino	gen	C	ontrol			Mean Difference		Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	Year	IV, Random, 95% CI
1.13.1 Trauma (RCT))									
Curry 2015	8	4.4	20	7	2.2	21	13.7%	1.00 [-1.15, 3.15]	2015	- +
Nascimento 2016	3	2.2	21	3	1.5	24	19.2%	0.00 [-1.12, 1.12]	2016	+
Innerhoffer 2017	4	3.7	44	6	5.2	50	15.4%	-2.00 [-3.81, -0.19]	2017	
Akbari 2018	2.04	1.14	30	2.88	0.88	30	21.7%	-0.84 [-1.36, -0.32]	2018	+
Curry 2018	4	4.4	24	2	2.2	24	14.6%	2.00 [0.03, 3.97]	2018	
Bernhard 2020	3	2.2	28	7	4.1	25	15.5%	-4.00 [-5.80, -2.20]	2020	
Subtotal (95% CI)			167			174	100.0%	-0.68 [-1.95, 0.59]		\bullet
Heterogeneity: Tau ² =	= 1.85; 0	$Chi^2 = 2$	6.24, 0	lf = 5 (P < 0.0	0001);	$l^2 = 81\%$			
Test for overall effect	Z = 1.0	5 (P =	0.29)							
1.13.2 Trauma (obs)										
Nienaber 2011	3	3.7	18	12.5	8.9	18	17.8%	-9.50 [-13.95, -5.05]	2011	
Wafaisade 2013	12.8	14.3	294	11.3	10	294	25.9%	1.50 [-0.49, 3.49]	2013	+
Nardi 2015	6.5	4.8	96	8.09	6.7	130	27.3%	-1.59 [-3.09, -0.09]	2015	
Hamada 2020	6	5.19	758	4	3	269	29.0%	2.00 [1.49, 2.51]	2020	
Subtotal (95% CI)			1166			711	100.0%	-1.16 [-4.16, 1.85]		
Heterogeneity: Tau ² =	= 8.02; 0	$Chi^2 = 4$	3.38, 0	lf = 3 (P < 0.0	00001)	; $I^2 = 93\%$	6		
Test for overall effect	Z = 0.7	′5 (P =	0.45)							
										-10 -5 0 5 10
										ravours early indrinogen ravours control

13. Plasma transfused

Early fibrinogen Control								Mean Difference		Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	Year	IV, Random, 95% CI
1.14.1 Trauma (RCT))									
Curry 2015	8	5.9	20	5	3.7	21	23.2%	3.00 [-0.03, 6.03]	2015	
Nascimento 2016	2.73	0.89	21	1.75	0.44	24	33.9%	0.98 [0.56, 1.40]	2016	
Innerhoffer 2017	5	1	44	14	3	50	0.0%	-9.00 [-9.88, -8.12]	2017	
Curry 2018	5	4.4	24	3	4.4	24	25.9%	2.00 [-0.49, 4.49]	2018	
Bernhard 2020 Subtotal (95% CI)	10	3	28 93	17	10.9	25 94	17.0% 100.0%	-7.00 [-11.41, -2.59] 0.36 [-2.21, 2.92]	2020	\longleftarrow
1 14 2 Trauma (obs)	z = 0.2	7 (P =	0.79)							
Niensber 2011	0	0	18	10	11 1	18		Not estimable	2011	
Wafaisade 2013	10	11	87	87	8 2	294	32 1%		2013	
Nardi 2015	4 2 3	4 6 1	96	8 97	9 4 7	130	33.2%	-4 74 [-6 61 -2 87]	2015	
Hamada 2020 Subtotal (95% CI)	7	5.2	758 959	4	3	269 711	34.7% 100.0%	3.00 [2.48, 3.52] -0.12 [-5.16, 4.93]	2020	
Heterogeneity: Tau ² =	= 19.02;	Chi ² =	61.90,	df = 2	(P < 0	.00001	L); $I^2 = 97$	%		
Test for overall effect	Z = 0.0	5 (P =	0.96)							
										-4 -2 0 2 4
										Favours early fibrinogen Favours control

14. Platelets transfused



15. Proportion receiving RBCs

	nogen	Control			Risk Ratio		Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	Year	M–H, Fixed, 95% Cl
1.16.1 Trauma (RCT)								
Bernhard 2020	13	28	11	25	100.0%	1.06 [0.58, 1.91]	2020	
Subtotal (95% CI)		28		25	100.0%	1.06 [0.58, 1.91]		\bullet
Total events	13		11					
Heterogeneity: Not ap	plicable							
Test for overall effect:	Z = 0.18 (P	= 0.86)						
1 16 2 Trauma (Obs)								
Schöchl 2011	57	80	592	601	100.0%	0 72 [0 64 0 84]	2011	-
Subtotal (95% CI)	57	80	101	601	100.0%	0.73 [0.64, 0.84]	2011	→
Total events	57		583			- / -		· ·
Heterogeneity: Not ap	plicable							
Test for overall effect:	Z = 4.32 (P	< 0.00	01)					
1.16.3 Obstetric blee	ding (RCT)							
Collins 2017	15	29	14	28	100.0%	1 03 [0 62 1 72]	2017	
Subtotal (95% CI)	15	29	14	28	100.0%	1.03 [0.62, 1.72]	2017	
Total events	15		14					T
Heterogeneity: Not ap	plicable							
Test for overall effect:	Z = 0.13 (P	= 0.90)	1					
								Favours early fibringen Favours control
								· · · · · · · · · · · · · · · · · · ·

16. Proportion receiving plasma

	ogen	Control		Risk Ratio			Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	Year	M–H, Fixed, 95% Cl
1.17.1 Trauma (RCT)								
Bernhard 2020 Subtotal (95% CI)	13	28 28	11	25 25	100.0% 100.0%	1.06 [0.58, 1.91] 1.06 [0.58, 1.91]	2020	
Total events	13		11					
Heterogeneity: Not ap	plicable							
Test for overall effect:	Z = 0.18 (P)	= 0.86)						
1.17.2 Obstetric blee	ding (RCT)							
Collins 2017 Subtotal (95% CI)	6	29 29	8	28 28	100.0% 100.0%	0.72 [0.29, 1.82] 0.72 [0.29, 1.82]	2017	
Total events	6		8					
Heterogeneity: Not ap	plicable							
Test for overall effect:	Z = 0.69 (P)	= 0.49)						
								0.05 0.2 1 5 20 Favours early fibrinogen Favours control

17. Proportion receiving platelets

		Early fibrin	ogen	Conti	rol		Risk Ratio		Risk Ratio
St	udy or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	Year	r M–H, Fixed, 95% Cl
1.	18.1 Trauma (RCT)								
Be	rnhard 2020	0	28	3	25	100.0%	0.13 [0.01, 2.36]	2020)
Su	ıbtotal (95% CI)		28		25	100.0%	0.13 [0.01, 2.36]		
Τc	otal events	0		3					
He	eterogeneity: Not app	olicable							
Te	est for overall effect:	Z = 1.38 (P	= 0.17	ł					
1.	18.2 Trauma (obs)								
Sc	höchl 2011	7	80	163	371	100.0%	0.20 [0.10, 0.41]	2011	
Su	ibtotal (95% CI)		80		371	100.0%	0.20 [0.10, 0.41]		·
Тс	otal events	7		163					
He	eterogeneity: Not app	olicable							
Te	est for overall effect:	Z = 4.41 (P	< 0.00	01)					
1.	18.3 Obstetric blee	ding (RCT)							
Cc	ollins 2017	1	29	3	28	100.0%	0.32 [0.04, 2.91]	2017	7
Su	ıbtotal (95% CI)		29		28	100.0%	0.32 [0.04, 2.91]		
Тс	otal events	1		3					
Hε	eterogeneity: Not app	olicable							
Τe	est for overall effect:	Z = 1.01 (P	= 0.31	1					
									Favours early fibrinogen Favours control
1 e Sci Su To Su To Te Su To He Te	est for overall effect: 18.2 Trauma (obs) höchl 2011 ibtotal (95% CI) otal events eterogeneity: Not app est for overall effect: 18.3 Obstetric blee ollins 2017 ibtotal (95% CI) otal events eterogeneity: Not app est for overall effect:	Z = 1.38 (P 7 olicable Z = 4.41 (P ding (RCT) 1 1 olicable Z = 1.01 (P	= 0.17) 80 80 < 0.000 29 29 = 0.31)	163 163 01) 3 3	371 371 28 28	100.0% 100.0% 100.0% 100.0%	0.20 [0.10, 0.41] 0.20 [0.10, 0.41] 0.32 [0.04, 2.91] 0.32 [0.04, 2.91]	2011 2017	0.005 0.1 1 10 24 Favours early fibrinogen Favours control

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

Thromboelastrography (TEG) in Massively and Non-massively bleeding Critically III patients

GRADE- Non Massive Bleeding Patients Author(s): ESICM Guideline Panel

			Certainty ass	essment		• • •	Nº o	f patients	Ef	fect		
№ of studie s	Study design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecisio n	Other consideration s	TEG	Conventiona I testing	Relativ e (95% Cl)	Absolut e (95% CI)	Certainty	Importance
CV- Mor	tality											
7	randomise d trials	not seriou s	serious a	not serious	serious ^b	none °	17/384 (4.4%)	27/370 (7.3%)	RR 0.60 (0.34 to 1.07)	29 fewer per 1,000 (from 48 fewer to 5 more)		CRITICAL
CV-Red	o Surgery											
10	randomise d trials	seriou S ^d	serious ^a	not serious	serious ^b	publication bias strongly suspected	42/528 (8.0%)	62/524 (11.8%)	RR 0.74 (0.51 to 1.06)	31 fewer per 1,000 (from 58 fewer to 7 more)		IMPORTAN T
CV-RBC	transfusion											
11	randomise d trials	seriou S ^d	serious ^a	not serious	not serious	none °	327/59 5 (55.0%)	377/580 (65.0%)	RR 0.86 (0.76 to 0.98)	91 fewer per 1,000 (from 156 fewer to 13 fewer)		IMPORTAN T
CV-Plate	elet transfusion	n										_
10	randomise d trials	seriou s ^d	very serious _{a.f}	not serious	not serious	none e	154/57 5 (26.8%)	199/560 (35.5%)	RR 0.68 (0.46 to 0.99)	114 fewer per 1,000 (from 192 fewer to 4 fewer)		IMPORTAN T
CV-FFP	transfusion	-				·				-		_
8	randomise d trials	seriou s ^d	very serious _{a.g}	not serious	not serious	none °	91/522 (17.4%)	194/513 (37.8%)	RR 0.46 (0.37 to 0.57)	204 fewer per 1,000 (from 238 fewer to 163 fewer)		IMPORTAN T

CV-Cryoprecipitate transfusion

			Certainty ass	essment			Nº o	of patients	Ef	fect		
№ of studie s	Study design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecisio n	Other consideration s	TEG	Conventional	Relativ e (95% Cl)	Absolut e (95% CI)	Certainty	Importance
4	randomise d trials	seriou s ^d	very serious _{a,h}	not serious	serious ⁱ	none °	25/177 (14.1%)	49/182 (26.9%)	RR 0.53 (0.35 to 0.79)	127 fewer per 1,000 (from 175 fewer to 57 fewer)		IMPORTAN T

CV-Hemostasis-12 hour post op bleeding

3	randomise d trials	seriou s ^d	very serious _{a.j}	not serious	not serious	none °	248	241	-	MD 128.18 lower (172.38 lower to 83.97 lower)	IMPORTAN T
										lower)	

CV-Hemostasis-24 hr post op bleeding

4	randomise d trials	seriou S ^d	serious ^a	not serious	not serious	none c	186	190	-	MD 175.25 lower (305.19 lower to 45.32 lower)		IMPORTAN T
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CV-Hospital LOS

	3	randomise d trials	seriou S ^d	very serious a,k	not serious	serious Þ	none ∘	167	157	-	MD 0.12 lower (0.45 lower to 0.21 higher)		IMPORTAN T
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CV-ICU LOS

6	randomise d trials	seriou S ^d	very serious al	not serious	not serious	none c	333	336	-	MD 4.08 lower (6.33 lower to 1.82 lower)		IMPORTAN T
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ECMO-Mortality

1	randomise d trials	not seriou s	not serious	not serious	very serious ^{b,i}	none °	2/7 (28.6%)	3/9 (33.3%)	RR 0.86 (0.19 to 3.81)	47 fewer per 1,000 (from 270 fewer to 937 more)		CRITICAL
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ECMO- Rebleeding

1	randomise se d trials	seriou s	not serious	not serious	very serious ^{i,m}	none ^{i,m}	2/7 (28.6%)	6/9 (66.7%)	RR 0.43 (0.12 to 1.51)	380 fewer per 1,000 (from 587 fewer to 340 more)		IMPORTAN T
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	Certainty assessment Ne of studie s design Risk of bias y s Indirectnes Imprecisio y s n s							f patients	Ef	fect		
№ of studie s	Study design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecisio n	Other consideration s	TEG	Conventional	Relativ e (95% Cl)	Absolut e (95% CI)	Certainty	Importance
ECMO-T	hrombotic Co	nplication	S									
1	randomise d trials	seriou s	not serious	not serious	very serious ^{i,m}	none °	1/9 (11.1%)	5/9 (55.6%)	RR 0.20 (0.03 to 1.39)	444 fewer per 1,000 (from 539 fewer to		CRITICAL

217 more)

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

Explanations

a. Rated down for wide variance in the point estimates

b. Rated down as confidence intervals overlaps 1, with no effect.

c. Publication bias not formally assessed given few number of studies identified.

- d. Most studies included in the systematic review by Meco 2020 and Serriano and Murphy 2017, where of unclear or high risk of bias.
- E. Funnel plot though not asymetric, given the small number of studies, still could be publication bias present.
 f. Rated down for considerable heterogeneity (I2 74%)
- f. Rated down for considerable heterogeneity (I2 74%)
 g. Rated down for substantial heterogeneity (I2 68%)
 h. Rated down for substantial heterogeneity (I2 80%)
 i. Rated down for substantial heterogeneity (I2 84%)
 k. Rated down for substantial heterogeneity (I2 69%)
 I. Rated down for substantial heterogeneity (I2 85%)
 m. rated down for overlapping confidence intervals

GRADE-Massively Bleeding Patients

Author(s): ESICM Guideline Panel

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

			Certainty asse	essment			Nº o	f patients	Ef	fect		
№ of studie s	Study design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecisio n	Other consideration s	TEG	Conventional	Relativ e (95% CI)	Absolut e (95% Cl)	Certainty	Importance

GI-Cirrhotic Bleeding-Mortality

2	randomised trials	not seriou s	not serious	serious a	serious ^b	none °	31/73 (42.5%)	36/68 (52.9%)	RR 0.82 (0.59 to 1.13)	95 fewer per 1,000 (from 217 fewer to 69	CRITICAL
										more)	

GI-Cirrhotic Bleeding Rebleeding

2	randomised trials	not seriou s	serious ^d	not serious	very serious °	none °	22/62 (35.5%)	27/54 (50.0%)	RR 0.71 (0.47 to 1.07)	145 fewer per 1,000 (from 265 fewer to 35 more)	IMPORTAN T

GI-Cirrhotic Bleeding-TRALI

			Certainty asse	essment			Nº o	f patients	Ef	fect		
№ of studie s	Study design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecisio n	Other consideration s	TEG	Conventional	Relativ e (95% CI)	Absolut e (95% CI)	Certainty	Importance
1	randomised trials	not seriou s	not serious	not serious	very serious º	none °	6/49 (12.2%)	23/47 (48.9%)	RR 0.25 (0.11 to 0.56)	367 fewer per 1,000 (from 436 fewer to 215 fewer)		IMPORTAN T

GI-Cirrhotic Bleeding-TACO

1	randomised trials	not seriou s	not serious	not serious	very serious ∘	none °	5/49 (10.2%)	10/47 (21.3%)	RR 0.48 (0.18 to 1.30)	111 fewer per 1,000 (from 174 fewer to 64 more)	IMPORTAN T
										more)	

GI-Cirrhotic Bleeding-ARDS

1	randomised trials	not seriou s	not serious	not serious	very serious º	none °	1/49 (2.0%)	9/47 (19.1%)	RR 0.11 (0.01 to 0.81)	170 fewer per 1,000 (from 190 fewer to 36 fewer)		IMPORTAN T
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GI-Cirrhotic Bleeding-RBC Transfusion

1	randomised trials	not seriou s	not serious	not serious	very serious °	none °	17/30 (56.7%)	16/30 (53.3%)	RR 1.06 (0.67 to 1.68)	32 more per 1,000 (from 176 fewer to 363 more)	€€OC	IMPORTAN T
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GI-Cirrhotic Bleeding-Platelet Transfusion

1	randomised trials	not seriou s	not serious	not serious	very serious f	none °	3/30 (10.0%)	21/30 (70.0%)	RR 0.14 (0.05 to 0.43)	602 fewer per 1,000 (from 665 fewer to 399 fewer)		IMPORTAN T
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GI-Cirrhotic Bleeding-FFP Transfusion

1	randomised trials	not seriou s	not serious	not serious	very serious f	none °	4/30 (13.3%)	14/30 (46.7%)	RR 0.29 (0.11 to 0.77)	331 fewer per 1,000 (from 415 fewer to 107 fewer)		IMPORTAN T
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Trauma-Mortality

	Certainty assessment Ne of studie s Study design Risk of bias Inconsistenc y Indirectnes Imprecisio n Study s Indirectnes Study n Study s Study							f patients	Ef	fect		
№ of studie s	Study design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecisio n	Other consideration s	TEG	Conventional	Relativ e (95% CI)	Absolut e (95% Cl)	Certainty	Importance
1	randomised trials	seriou s	not serious	not serious	very serious º	none °	11/56 (19.6%)	20/55 (36.4%)	RR 0.54 (0.29 to 1.02)	167 fewer per 1,000 (from 258 fewer to 7 more)		CRITICAL

Liver Transplant- Mortality

1	randomised trials	not seriou s	not serious	not serious	very serious •	none °	2/14 (14.3%)	3/14 (21.4%)	RR 0.67 (0.13 to 3.40)	71 fewer per 1,000 (from 186 fewer to 514 more)		CRITICAL
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Liver Transplant- Blood Loss

2	randomised trials	seriou S	not serious	not serious	very serious ^f	none c	31	31	-	MD 1.13 lower (1.85 lower to 0.41 lower)		IMPORTAN T
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Liver Transplant-RBC Transfusion

2	randomised trials	seriou S	very serious g	not serious	serious ^b	none c	31	31	-	MD 12.22 lower (71.08 lower to 46.64 higher)		IMPORTAN T
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Liver Transplant-Platelet Transfusion

1	randomised trials	seriou S	not serious	not serious	very serious º	none °	14	14	-	MD 2.8 lower (14.92 lower to 9.32 higher)		IMPORTAN T
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Liver Transplant- FFP Transfusion

1	randomised trials	seriou s	not serious	not serious	very serious ^f	none c	14	14	-	MD 8.7 lower (16.3 lower to 1.1 lower)	IMPORTAN T
										lower)	

Liver Transplant-Cryopreciptate Transfusion

1	randomised trials	seriou s	not serious	not serious	very serious ∘	none °	14	14	-	MD 2.6 lower (9.94 lower to 4.74 higher)		IMPORTAN T
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Liver Transplant Observational- Mortality

			Certainty asse	essment			Nº o	f patients	Ef	fect		
№ of studie s	Study design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecisio n	Other consideration s	Point of Care	Conventiona I testing (TEG/ROTEM)	Relativ e (95% Cl)	Absolut e (95% CI)	Certainty	Importance
1	observation al studies	seriou S	not serious	not serious	very serious º	none °	1/34 (2.9%)	1/34 (2.9%)	RR 1.00 (0.07 to 15.34)	0 fewer per 1,000 (from 27 fewer to 422 more)		CRITICAL

Liver Transplant Observational-RBC Transfusion

Liver Transplant Observational-Platelet Transfusion

1	observation al studies	seriou S	not serious	not serious	very serious º	none °	27/34 (79.4%)	19/34 (55.9%)	RR 1.42 (1.01 to 2.00)	235 more per 1,000 (from 6 more to 559 more)		IMPORTAN T
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Liver Transplant Observational-Cryoprecipitate Transfusions

1	observation al studies	seriou s	not serious	not serious	very serious ∘	none ¢	25/34 (73.5%)	19/34 (55.9%)	RR 1.32 (0.92 to 1.89)	179 more per 1,000 (from 45 fewer to 497 more)		IMPORTAN T
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CI: Confidence interval; RR: Risk ratio; MD: Mean difference

Explanations

a. Rated down for indirectness- one study was portal hypertensive bleeding, the other for non-portal hypertensive bleeding in cirrhotic patients

b. Rated down as for confidence intervals overlap, and encompasses 1.

c. Publication bias not formally accessed due to the limited number of studies identified

Rated down for substantial heterogeneity
 Rated down for substantial heterogeneity
 Rated down for overlapping confidence intervals and few number of events
 f. Rated down for few number of events and small sample size

g. rated down for wide variance in point estimates and substantial heterogeneity

Evidence Summary

Non-massively bleeding patients

CV Surgery

Mortality

	TEG/RC	DTEM	Conventional Coag	gulation		Risk Ratio		Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fixed, 95% CI	
Agarwal 2004	5	84	4	81	14.5%	1.21 [0.34, 4.33]			
Ak 2009	3	114	2	110	7.2%	1.45 [0.25, 8.50]			
Girduaskas 2010	4	27	5	29	17.1%	0.86 [0.26, 2.87]			
Paniagua 2011	3	26	4	18	16.8%	0.52 [0.13, 2.05]			
Royston 2001	0	30	0	30		Not estimable			
Shore-Lesserson 1999	0	53	2	52	9.0%	0.20 [0.01, 3.99]	←		
Weber 2012	2	50	10	50	35.5%	0.20 [0.05, 0.87]	-		
Total (95% CI)		384		370	100.0%	0.60 [0.34, 1.07]		•	
Total events	17		27						
Heterogeneity: Chi ² = 5.1	16, df = 5	5 (P = 0)	.40); I ² = 3%					0 1 1 10	100
Test for overall effect: Z	= 1.74 (P	= 0.08	3)				0.01	Favours TEG Favours CCA	100

Redo Surgery

	TEG/RC	ОТЕМ	Conventional Coag	ulation		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M–H, Random, 95% CI
Agarwal 2004	6	84	13	81	16.1%	0.45 [0.18, 1.11]	_
Ak 2009	6	114	4	110	8.9%	1.45 [0.42, 4.99]	
Avidan 2004	1	51	3	51	2.7%	0.33 [0.04, 3.10]	
Girduaskas 2010	5	27	7	29	13.1%	0.77 [0.28, 2.13]	
Kempfert 2011	15	52	13	52	33.7%	1.15 [0.61, 2.18]	
Nuttal 2001	0	41	6	51	1.7%	0.10 [0.01, 1.64]	·
Paniagua 2011	3	26	5	18	8.1%	0.42 [0.11, 1.52]	
Royston 2001	1	30	1	30	1.8%	1.00 [0.07, 15.26]	
Shore-Lesserson 1999	0	53	2	52	1.5%	0.20 [0.01, 3.99]	· · · · · · · · · · · · · · · · · · ·
Weber 2012	5	50	8	50	12.4%	0.63 [0.22, 1.78]	
Total (95% CI)		528		524	100.0%	0.74 [0.51, 1.06]	•
Total events	42		62				
Heterogeneity: Tau ² = 0	.00; Chi ² =	= 8.56,	$df = 9 (P = 0.48); I^2$	= 0%			
Test for overall effect: Z	= 1.63 (P	= 0.10)				Favours TEG Favours CCA

RBC transfusions

	TEG/ROTEM		Conventional Coagulation			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Agarwal 2004	43	84	57	81	10.6%	0.73 [0.57, 0.94]	-
Ak 2009	52	114	60	110	10.3%	0.84 [0.64, 1.09]	
Avidan 2004	34	51	35	51	10.1%	0.97 [0.74, 1.27]	+
Girduaskas 2010	24	27	27	29	13.7%	0.95 [0.81, 1.13]	+
Karkouti 2016	58	127	52	118	9.8%	1.04 [0.78, 1.37]	+
Kultufan Turan 2006	7	20	12	20	2.9%	0.58 [0.29, 1.17]	
Lehmann 2019	8	11	6	14	2.8%	1.70 [0.84, 3.43]	
Paniagua 2011	23	26	16	18	11.9%	1.00 [0.80, 1.23]	+
Shore-Lesserson 1999	22	53	34	52	7.1%	0.63 [0.44, 0.92]	
Weber 2012	42	50	45	50	14.2%	0.93 [0.80, 1.09]	+
Westbrook 2008	14	32	33	37	6.4%	0.49 [0.33, 0.74]	
Total (95% CI)		595		580	100.0%	0.86 [0.76, 0.98]	•
Total events	327		377				
Heterogeneity: Tau ² = 0.	.02; Chi ² =	= 24.22	df = 10 (P = 0.007)	$I^2 = 599$	%		
Test for overall effect: Z	= 2.22 (P	= 0.03)				Favours TEG Favours CCA

Platelet transfusions

	TEG/ROTEM		Conventional Coagulation			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Agarwal 2004	46	84	30	81	14.1%	1.48 [1.05, 2.09]	
Ak 2009	17	114	29	110	12.1%	0.57 [0.33, 0.97]	
Avidan 2004	2	51	14	51	4.9%	0.14 [0.03, 0.60]	
Girduaskas 2010	9	27	25	29	11.9%	0.39 [0.22, 0.67]	
Karkouti 2016	24	127	30	118	12.7%	0.74 [0.46, 1.19]	
Lehmann 2019	4	11	0	14	1.6%	11.25 [0.67, 189.01]	+
Paniagua 2011	12	26	8	18	10.7%	1.04 [0.54, 2.01]	
Shore-Lesserson 1999	7	53	15	52	9.2%	0.46 [0.20, 1.03]	
Weber 2012	28	50	33	50	14.3%	0.85 [0.62, 1.16]	
Westbrook 2008	5	32	15	37	8.4%	0.39 [0.16, 0.94]	- _
Total (95% CI)		575		560	100.0%	0.68 [0.46, 0.99]	•
Total events	154		199				
Heterogeneity: Tau ² = 0.	24; Chi ² =	= 35.22	df = 9 (P < 0.0001)	$l^2 = 749$	6		
Test for overall effect: Z	= 2.02 (P	= 0.04)				Favours TEG Favours CCA

FFP Transfusions

	TEG/RC	TEM	Conventional Coagulation			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M–H, Fixed, 95% Cl
Agarwal 2004	10	84	44	81	22.9%	0.22 [0.12, 0.41]	
Ak 2009	19	114	31	110	16.1%	0.59 [0.36, 0.98]	
Avidan 2004	2	51	16	51	8.2%	0.13 [0.03, 0.52]	
Karkouti 2016	31	127	31	118	16.4%	0.93 [0.60, 1.43]	-
Lehmann 2019	0	11	1	14	0.7%	0.42 [0.02, 9.34]	
Shore-Lesserson 1999	4	53	16	52	8.2%	0.25 [0.09, 0.68]	
Weber 2012	20	50	40	50	20.4%	0.50 [0.35, 0.72]	
Westbrook 2008	5	32	15	37	7.1%	0.39 [0.16, 0.94]	
Total (95% CI)		522		513	100.0%	0.46 [0.37, 0.57]	•
Total events	91		194				
Heterogeneity: Chi ² = 21	.80, df =	7 (P =	0.003); I ² = 68%				01 01 1 10 100
Test for overall effect: Z	= 7.13 (P	< 0.00	001)			0.	Favours TEG] Favours CCA

Cryoprecipitate Transfusion

	TEG/RC	ROTEM Conventional Coagulation			Risk Ratio	Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Agarwal 2004	3	84	3	81	6.3%	0.96 [0.20, 4.64]	
Lehmann 2019	0	11	0	14		Not estimable	
Weber 2012	22	50	26	50	54.0%	0.85 [0.56, 1.28]	
Westbrook 2008	0	32	20	37	39.6%	0.03 [0.00, 0.45]	← ■
Total (95% CI)		177		182	100.0%	0.53 [0.35, 0.79]	◆
Total events	25		49				
Heterogeneity: Chi ² =	9.89, df	= 2 (P =	= 0.007); I ² = 80%				
Test for overall effect:	Z = 3.11	(P = 0	.002)			Favours TEG Favours CCA	

Hemostasis- 12 hour post op bleeding

	TEG	/ROT	EM	Conventional Coagulation				Mean Difference	Mean Di	fference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed	l, 95% CI	
Agarwal 2004	600	150	84	700	200	81	66.8%	-100.00 [-154.09, -45.91]	—		
Ak 2009	480	351	114	591	339	110	23.9%	-111.00 [-201.36, -20.64]	+		
Weber 2012	425	370	50	800	370	50	9.3%	-375.00 [-520.04, -229.96]	•		
Total (95% CI)			248			241	100.0%	-128.18 [-172.38, -83.97]	-		
Heterogeneity: Chi ² =	12.31,	df = 2		-100 -50	50	100					
Test for overall effect:	Z = 5.6	68 (P ≺	< 0.000	01)					Favours TEG	Favours CCA	

Hemostasis-24hr post op bleeding

	TEG	/ROT	EM	Conventional Coagulation				Mean Difference	Mean Difference		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI		
Avidan 2004	755	475	51	810	968	51	19.3%	-55.00 [-350.93, 240.93]	← ■ →		
Shore-Lesserson 1999	702	500	53	901	847	52	23.7%	-199.00 [-465.68, 67.68]	•		
Weber 2012	600	795	50	960	494	50	25.1%	-360.00 [-619.44, -100.56]	•		
Westbrook 2008	875	494	32	960	477	37	31.9%	-85.00 [-315.04, 145.04]	←∎ →		
Total (95% CI) Heterogeneity: Chi ² = 3. Test for overall effect: Z	20, df = = 2.64	= 3 (P (P = 0	186 = 0.36) 0.008)	; $I^2 = 6\%$		190	100.0%	-175.25 [-305.19, -45.32]	-100 -50 0 50 100 Favours TEG Favours CCA		

ICU LOS

	TEC	G/ROTE	м	Conventional Coagulation				Mean Difference	Mean Difference		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI		
Westbrook 2008	29.4	31	32	24	48	37	1.4%	5.40 [-13.43, 24.23]	_ _		
Weber 2012	20	8.8	50	24	48	50	2.8%	-4.00 [-17.53, 9.53]			
Paniagua 2011	132	120	26	194.4	201.6	29	0.1%	-62.40 [-149.07, 24.27]	← · · · · · · · · · · · · · · · · · · ·		
Girduaskas 2010	175.2	218.4	27	194.4	201.6	29	0.0%	-19.20 [-129.52, 91.12]	· · · ·		
Ak 2009	23.3	5.7	114	25.3	11.7	110	86.2%	-2.00 [-4.42, 0.42]			
Agarwal 2004	24	24	84	48	24	81	9.4%	-24.00 [-31.33, -16.67]	- 1		
Total (95% CI)			333			336	100.0%	-4.08 [-6.33, -1.82]	•		
Heterogeneity: Chi ² =	34.02, 0	df = 5 (P < 0.0	0001 ; $I^2 =$	85%						
Test for overall effect:	Z = 3.5	5 (P = (0.0004)					Favours TEG Favours CCA			

Hospital LOS

	TEG	ROTE	EM	Convention	Conventional Coagulation			Mean Difference		Mean Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI		IV, Fixed, 95% CI	
Ak 2009	6.2	1.1	114	6.3	1.4	110	99.7%	-0.10 [-0.43, 0.23]			
Girduaskas 2010	16.6	16.4	27	17	14.8	29	0.2%	-0.40 [-8.60, 7.80]			
Paniagua 2011	13.6	7.1	26	25.8	19.2	18	0.1%	-12.20 [-21.48, -2.92]			
Total (95% CI)			167			157	100.0%	-0.12 [-0.45, 0.21]			
Heterogeneity: Chi ² =	6.53, d	f = 2 (P = 0.0	(4); $I^2 = 69\%$					-100	-50 0 50	100
Test for overall effect	z = 0.6	59 (P =	0.49)							Favours TEG Favours CCA	

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

	TEG	/ROTI	EM	Conventior	nal Coagu	lation		Mean Difference		Mean Diff	erence	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI		IV, Fixed, S	95% CI	
Ak 2009	8.2	2.1	114	7.9	4.7	114	99.9%	0.30 [-0.64, 1.24]				
Girduaskas 2010	144	139	27	137	172	29	0.0%	7.00 [-74.66, 88.66]	-	——————————————————————————————————————		
Paniagua 2011	15.6	12.3	26	32	59	18	0.1%	-16.40 [-44.06, 11.26]			-	
Total (95% CI)			167			161	100.0%	0.28 [-0.66, 1.23]				
Heterogeneity: $Chi^2 = 1.42$, $df = 2$ (P = 0.49); $l^2 = 0\%$ Test for overall effect: Z = 0.58 (P = 0.56)									-100	-50 0 Favours TEG F	50 avours CCA	100

<u>ECMO</u>

Mortality

-	TEC		CCA			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Buscher 2017	2	7	3	9	100.0%	0.86 [0.19, 3.81]	
Total (95% CI)		7		9	100.0%	0.86 [0.19, 3.81]	
Total events	2		3				
Heterogeneity: Not ap Test for overall effect:	plicable Z = 0.20) (P = 0	.84)				0.01 0.1 1 10 100 Favours TEG Favours CCA

Rebleeding

	TEC		CC/	4		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Buscher 2017	2	7	6	9	100.0%	0.43 [0.12, 1.51]	
Total (95% CI)		7		9	100.0%	0.43 [0.12, 1.51]	
Total events	2		6				
Heterogeneity: Not ap	oplicable						
Test for overall effect	: Z = 1.32	P = 0).19)				Favours TEG Favours CCA

Thrombotic Complications

	TEC	5	CCA		Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M–H, Fixed, 95% Cl
Buscher 2017	1	9	5	9	100.0%	0.20 [0.03, 1.39]	
Total (95% CI)		9		9	100.0%	0.20 [0.03, 1.39]	
Total events	1		5				
Heterogeneity: Not ap	plicable						
Test for overall effect:	Z = 1.63	8 (P = 0).10)				Favours TEG Favours CCA

Massively Bleeding

GI-Cirrhotic Bleeding (variceal/nonvariceal)

Mortality

•	TEG		CC/	ι		Risk Ratio	Risk Ratio
Study or Subgroup	Events 7	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Kumar 2019	27	49	31	47	85.6%	0.84 [0.60, 1.16]	
Rout 2019	4	24	5	21	14.4%	0.70 [0.22, 2.27]	
Total (95% CI)		73		68	100.0%	0.82 [0.59, 1.13]	•
Total events	31		36				
Heterogeneity: Chi ² =	0.09, df =	1 (P	= 0.77);	$I^2 = 0\%$	5		
Test for overall effect:	Z = 1.24 ((P = 0)	.22)				Favours TEG Favours CCA

Rebleeding

	TEC		CC/	Ą		Risk Ratio		Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fixed, 95% CI	
Kumar 2019	19	38	19	33	70.4%	0.87 [0.56, 1.34]			
Rout 2019	3	24	8	21	29.6%	0.33 [0.10, 1.08]			
Total (95% CI)		62		54	100.0%	0.71 [0.47, 1.07]		•	
Total events	22		27						
Heterogeneity: Chi ² =	2.46, df	= 1 (P	= 0.12);	$l^2 = 59$	9%			01 10	100
Test for overall effect:	Z = 1.63	B (P = 0)	0.10)				0.01	Favours TEG Favours CCA	100

TRALI

	TEG		CC/	4		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% Cl
Kumar 2019	6	49	23	47	100.0%	0.25 [0.11, 0.56]	
Total (95% CI)		49		47	100.0%	0.25 [0.11, 0.56]	◆
Total events	6		23				
Heterogeneity: Not ap	plicable						
Test for overall effect:	Z = 3.38	(P = 0	.0007)				Favours TEG Favours CCA

ТАСО

	TEC	5	cc/	4		Risk Ratio		Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fixed, 95% CI	
Kumar 2019	5	49	10	47	100.0%	0.48 [0.18, 1.30]			
Total (95% CI)		49		47	100.0%	0.48 [0.18, 1.30]		-	
Total events	5		10						
Heterogeneity: Not ap Test for overall effect:	plicable Z = 1.45	5 (P = 0).15)				0.01	0.1 1 10 Favours TEG Favours CCA	100

	TEC	3	CC/	4		Risk Ratio		Risk	Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fixe	ed, 95% CI	
Kumar 2019	1	49	9	47	100.0%	0.11 [0.01, 0.81]				
Total (95% CI)		49		47	100.0%	0.11 [0.01, 0.81]				
Total events	1		9							
Heterogeneity: Not ap	plicable							1	10	100
Test for overall effect:	Z = 2.17	7 (P = 0).03)				0.01 0.	vours TEG	Favours CCA	100

RBC Transfusion

	TEC		CC/	4		Risk Ratio	Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M–H, Fixed, 95% Cl	
Rout 2019	17	30	16	30	100.0%	1.06 [0.67, 1.68]	1 -	
Total (95% CI)		30		30	100.0%	1.06 [0.67, 1.68]	ı 🔶	
Total events	17		16					
Heterogeneity: Not ap	plicable							100
Test for overall effect:	Z = 0.26	5 (P = 0)	.80)				Favours TEG Favours CCA	100

Platelet Transfusion

	TEC		CC/	4		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Rout 2019	3	30	21	30	100.0%	0.14 [0.05, 0.43]	
Total (95% CI)		30		30	100.0%	0.14 [0.05, 0.43]	•
Total events	3		21				
Heterogeneity: Not ap Test for overall effect:	plicable Z = 3.47	7 (P = 0	0.0005)				0.01 0.1 1 10 100 Favours TEG Favours CCA

FFP Transfusion

	TEC	5	CC/	4		Risk Ratio		Risk Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fixed, 95%	CI	
Rout 2019	4	30	14	30	100.0%	0.29 [0.11, 0.77]				
Total (95% CI)		30		30	100.0%	0.29 [0.11, 0.77]				
Total events	4		14							
Heterogeneity: Not ap	plicable						0.01	0.1 1	10	10
Test for overall effect:	Z = 2.48	3 (P = 0)	0.01)					Favours TEG Favours	S CCA	

<u>Trauma</u>

Mortality

-	TEG		CC/	4		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% Cl
Gonzalez 2016	11	56	20	55	100.0%	0.54 [0.29, 1.02]	
Total (95% CI)		56		55	100.0%	0.54 [0.29, 1.02]	◆
Total events	11		20				
Heterogeneity: Not ap	plicable						
Test for overall effect:	Z = 1.90	(P = 0	0.06)				Favours TEG Favours CCA

Liver Transplant

Mortality

-	TEC		CC/	4		Risk Ratio		Risk Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fixed, 95%	CI	
Gurusamy 2011	2	14	3	14	100.0%	0.67 [0.13, 3.40]				
Total (95% CI)		14		14	100.0%	0.67 [0.13, 3.40]				
Total events	2		3							
Heterogeneity: Not app	plicable							0 1 1	10	100
Test for overall effect:	Z = 0.49	$\Theta (P = 0)$).63)				0.01	Favours TEG Favours	s CCA	100

Blood Loss



RBC Transfusion

		TEG			CCA			Mean Difference		Mean Di	tterence	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI		IV, Fixed	, 95% CI	
Rummo 2010	1,180	980	17	2,400	980	17	0.8%	-1220.00 [-1878.82, -561.18]	•		_	
Wang 2010	14.2	7.1	14	16.7	112.6	14	99.2%	-2.50 [-61.60, 56.60]				
Total (95% CI)			31			31	100.0%	-12.22 [-71.08, 46.64]				
Heterogeneity: Chi ² =	13.01, d	df = 1	(P = 0)	.0003);	$I^2 = 922$	%			100	±0 (50	100
Test for overall effect:	Z = 0.4	1 (P =	= 0.68)						-100	Favours TEG	Favours CCA	100

Platelet Transfusion

		TEG			CCA			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Wang 2010	27.3	13.9	14	30.1	18.5	14	100.0%	-2.80 [-14.92, 9.32]	
Total (95% CI) Heterogeneity: Not ap Test for overall effect	plicable Z = 0.4	15 (P =	14 0.65)			14	100.0%	-2.80 [-14.92, 9.32]	-100 -50 0 50 100 Favours TEC, Favours CCA

FFP Transfusions

		ΓEG			CCA			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Wang 2010	12.8	7	14	21.5	12.7	14	100.0%	-8.70 [-16.30, -1.10]	
Total (95% CI)			14			14	100.0%	-8.70 [-16.30, -1.10]	◆
Heterogeneity: Not ap Test for overall effect:	plicable Z = 2.2	24 (P	= 0.02	2)					-100 -50 0 50 100 Favours TEG Favours CCA
Cryoprecipitat	e Tra	ans	fusi	on					
•••		TEG			CCA			Mean Difference	Mean Difference

		TEG			CCA			Mean Difference		Mea	n Differer	ice	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI		IV, F	ixed, 95%	CI	
Wang 2010	13	10.3	14	15.6	9.5	14	100.0%	-2.60 [-9.94, 4.74]			-		
Total (95% CI)			14			14	100.0%	-2.60 [-9.94, 4.74]			•		
Heterogeneity: Not ap Test for overall effect:	Z = 0.6	69 (P =	0.49)						-100	-\$0 Favours 1	EG Favo	5'0 urs CCA	100

Liver Transplant- Observational

Mortality

I		TEG		CC/	4		Risk Ratio		Risk Ratio	
	Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fixed, 95% CI	
ľ	Smart 2017	1	34	1	34	100.0%	1.00 [0.07, 15.34]			
	Total (95% CI)		34		34	100.0%	1.00 [0.07, 15.34]			
	Total events	1		1						
l	Heterogeneity: Not ap	plicable						0.01	0 1 1 10	100
	Test for overall effect:	Z = 0.00) (P = 1	.00)				0.01	Favours TEG Favours CCA	100

RBC Transfusion

	TEC	;	CC/	4		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Smart 2017	28	34	33	34	100.0%	0.85 [0.72, 1.00]	•
Total (95% CI)		34		34	100.0%	0.85 [0.72, 1.00]	↓ ♦
Total events	28		33				
Heterogeneity: Not ap	plicable						
Test for overall effect:	Z = 1.94	(P = 0	0.05)				FavoursTEG Favours CCA

Platelet Transfusion

	TEC		CCA	۱.		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M–H, Fixed, 95% Cl
Smart 2017	27	34	19	34	100.0%	1.42 [1.01, 2.00]	
Total (95% CI)		34		34	100.0%	1.42 [1.01, 2.00]	•
Total events	27		19				
Heterogeneity: Not ap	plicable						
Test for overall effect:	Z = 2.00	(P = 0)	.05)				0.01 0.1 1 10 100
Cryoprecipitat	te Tra	nsfu	sion				
Cryoprecipitat	te Tra	nsfu ធ	sion cc/	Ą		Risk Ratio	Risk Ratio
Cryoprecipitat	te Tra TEC Events	nsfu ^G Total	Sion CC/ Events	A Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% Cl
Cryoprecipital <u>Study or Subgroup</u> Smart 2017	te Tra TEC Events 25	nsfu G Total 34	Sion CC/ Events 19	A Total 34	Weight 100.0%	Risk Ratio M-H, Fixed, 95% CI 1.32 [0.92, 1.89]	Risk Ratio M-H, Fixed, 95% CI
Cryoprecipital Study or Subgroup Smart 2017 Total (95% CI)	te Tra TEC Events 25	nsfu ⁵ ⁷ ³⁴ 34	Sion CC/ Events 19	A <u>Total</u> 34 34	Weight 100.0% 100.0%	Risk Ratio M-H, Fixed, 95% CI 1.32 [0.92, 1.89] 1.32 [0.92, 1.89]	Risk Ratio M-H, Fixed, 95% CI
Cryoprecipitat Study or Subgroup Smart 2017 Total (95% CI) Total events	te Tra TEC Events 25	nsfu ^G Total 34 34	Sion CC/ Events 19	A <u>Total</u> 34 34	Weight 100.0% 100.0%	Risk Ratio M-H, Fixed, 95% CI 1.32 [0.92, 1.89] 1.32 [0.92, 1.89]	Risk Ratio M-H, Fixed, 95% CI
Cryoprecipitat Study or Subgroup Smart 2017 Total (95% CI) Total events Heterogeneity: Not ar	te Tra TEC Events 25 25 25 25	nsfu ⁵ ⁷ 34 34	Sion CC/ Events 19	4 <u>Total</u> 34 34	Weight 100.0% 100.0%	Risk Ratio M-H, Fixed, 95% Cl 1.32 [0.92, 1.89] 1.32 [0.92, 1.89]	Risk Ratio M-H, Fixed, 95% CI
Cryoprecipital Study or Subgroup Smart 2017 Total (95% CI) Total events Heterogeneity: Not agr Test for overall effect	te Tra TEC Events 25 25 25 25 25 25 25 25 25 25 25	nsfu <u>Total</u> 34 34 9 (P = (Sion CC/ Events 19 19	4 <u>Total</u> 34 34	Weight 100.0% 100.0%	Risk Ratio M-H, Fixed, 95% CI 1.32 [0.92, 1.89] 1.32 [0.92, 1.89]	Risk Ratio M-H, Fixed, 95% CI

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

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

1. GI Bleeding

		Certainty a	assessment			№ of patients		Effect			
Nº of studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Restrictive	Liberal	Relative (95% Cl)	Absolute (95% Cl)	Certainty	Importance
Mortality	- GI bleedin	Ig	-		-	-					
4 RCTs	not serious	not serious	not serious	serious ^a	none	37/741 (5.0%)	68/865 (7.9%)	RR 0.63 (0.43 to 0.93)	29 fewer per 1,000 (from 45 fewer to 6 fewer)	⊕⊕⊕⊖ MODERATE	CRITICAL
Quality o	f life - Gl ble	eding							Į.		
1 RCT	serious ^b	not serious	not serious	serious ^c	none	257	383	-	MD 0.07 lower (0.12 lower to 0.02 lower)	⊕⊕⊖⊖ Low	CRITICAL
Stroke - 0	GI bleeding										
2 RCTs	not serious	not serious	not serious	serious ^d	none	12/701 (1.7%)	29/828 (3.5%)	RR 0.56 (0.29 to 1.09)	15 fewer per 1,000 (from 25 fewer to 3 more)	⊕⊕⊕⊖ MODERATE	CRITICAL
Myocard	ial infarction	n - GI bleeding									
1 RCT	not serious	not serious	not serious	very serious e	none	8/444 (1.8%)	13/445 (2.9%)	RR 0.62 (0.26 to 1.47)	11 fewer per 1,000 (from 22 fewer to 14 more)		CRITICAL
Acute kic	lney injury -	GI bleeding									
1 RCT	not serious	not serious	serious ^f	serious ^d	none	78/444 (17.6%)	97/445 (21.8%)	RR 0.81 (0.62 to 1.05)	41 fewer per 1,000 (from 83 fewer to 11 more)		CRITICAL
Volume o	overload/TA	CO - GI bleeding									
1 RCT	not serious	not serious	not serious	serious ^g	none	2/444 (0.5%)	16/445 (3.6%)	RR 0.13 (0.03 to 0.54)	31 fewer per 1,000 (from 35 fewer to 17 fewer)	⊕⊕⊕⊖ MODERATE	CRITICAL
Post-tran	sfusion sep	osis/infection - GI	bleeding								

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

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

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

Explanations

a. Actual number of events is small. Given control group event rate of ~8% and RRR of 37%, the optimal information size is not met, resulting in serious imprecision.

b. Significant loss to follow-up for EQ-5D scores in single trial reporting quality of life outcomes.

- c. Not statistically significant when restricted to patients with Hb <120, or in cluster-adjusted analyses.
- d. Wide confidence intervals which do not exclude the possibility of significant harm, resulting in serious imprecision.

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

f. Unclear definition of kidney injury, or patient relevance, in single study reporting this outcome.

g. Though statistically significant, optimal information size is not met, resulting in serious imprecision.

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

i. Though statistical heterogeneity is present, it is of questionable relevance as all trials favour restrictive transfusion.

2. Obstetric bleeding

		Certainty a	assessment			Nº of p	atients	Effect			
Nº of studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Restricti ve	Liberal	Relative (95% Cl)	Absolute (95% Cl)	Certainty	Importance
Quality o	f life - Obste	etric bleeding								-	-
1 RCT	serious ^a	not serious	not serious	serious ^b	none	262	259	-	MD 0.1 lower	$\bigoplus \bigoplus \bigcirc \bigcirc \bigcirc \bigcirc$	CRITICAL
										LOW	
Venous t	hrombosis ·	· Obstetric bleedi	ng								
1 RCT	not	not serious	not serious	very serious ^c	none	2/262	2/259	RR 0.99	0 fewer per 1,000	$\oplus \oplus \bigcirc \bigcirc$	IMPORTANT
	serious					(0.8%)	(0.8%)	(0.14 to 6.97)	(from 7 fewer to 46 more)	LOW	
Post-tran	sfusion sep	osis/infection - Ot	ostetric bleeding]	•					•	
1 RCT	not	not serious	not serious	very serious ^c	none	24/262	22/259	RR 1.08	7 more per 1,000	$\oplus \oplus \bigcirc \bigcirc \bigcirc$	IMPORTANT
	serious					(9.2%)	(8.5%)	(0.62 to 1.87)	(from 32 fewer to 74 more)	LOW	
Transfus	ion reaction	- Obstetric bleed	ling								
1 RCT	serious ^d	not serious	not serious	very serious ^c	none	0/262	3/259	RR 0.14	10 fewer per 1,000	$\oplus 000$	IMPORTANT
						(0.0%)	(1.2%)	(0.01 to 2.72)	(from 11 fewer to 20 more)	VERY LOW	
Mean tra	nsfusions -	Obstetric bleedin	g			· · · · · · · · · · · · · · · · · · ·					
1 RCT	not	not serious	not serious	serious ^c	none	262	259	-	MD 2 higher	$\oplus \oplus \oplus \bigcirc \bigcirc$	IMPORTANT
	Senous									MODERATE	

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

Explanations

a. Patients were not blinded which may have impacted assessment of quality of life using SF-36.

b. Wide confidence intervals which do not exclude the possibility of significant harm, resulting in serious imprecision.

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

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

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

3. Vascular surgery

		Certainty a	assessment			№ of patients		Effect			
№ of studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Restrictiv e	Liberal	Relative (95% Cl)	Absolute (95% Cl)	Certainty	Importance
Mortality	- Vascular	surgery									
1 RCT	not	not serious	not serious	very serious ^a	none	2/29	1/29	RR 2.00	34 more per 1,000	$\oplus \oplus \bigcirc \bigcirc$	CRITICAL
	Senous					(0.976)	(3.476)	(0.13 (0 20.00)	685 more)	LOW	
Myocard	ial infarctio	n - Vascular surge	ery								
1 RCT	not	not serious	not serious	very serious ^a	none	2/29	2/29	RR 1.00	0 fewer per 1,000	$\oplus \oplus \bigcirc \bigcirc$	CRITICAL
	3611003					(0.370)	(0.378)	(0.13 (0.00)	388 more)	LOW	
Transfus	ion reactior	n - Vascular surge	ry								
1 RCT	serious ^b	not serious	not serious	very serious ^a	none	0/29	1/29	RR 0.33	23 fewer per 1,000	$\oplus 000$	IMPORTANT
						(0.078)	(3.470)	(0.01 (0 7.00)	237 more)	VERY LOW	
Mean tra	nsfusions -	Vascular surgery									
1 RCT	not serious	not serious	not serious	not serious	none	29	29	-	MD 2 lower (3.22 lower to 0.78		IMPORTANT
									lower)	ПОП	
Proportio	on receiving	g transfusion - Vas	scular surgery								
1 RCT	not serious	not serious	not serious	not serious	none	19/29 (65.5%)	29/29 (100.0%)	RR 0.66 (0.51 to 0.86)	340 fewer per 1,000 (from 490 fewer to 140 fewer)	⊕⊕⊕⊕ HIGH	IMPORTANT

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

Explanations

a. Very small number of events, resulting in very serious imprecision.b. Lack of blinding bedside clinicians may result in under-reporting transfusion reactions in restrictive arm.

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

1. Mortality (range 28-90 days)

	Restric	tive	Liber	al		Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	Year	M-H, Fixed, 95% CI
1.1.1 GI bleeding								
Blair 1986	0	26	2	24	4.1%	0.19 [0.01, 3.67]	1986	
Villarejo 1999	0	14	0	13		Not estimable	1999	
Villaneuva 2013	23	444	41	445	64.4%	0.56 [0.34, 0.92]	2013	
Jairaith 2015 Subtotal (95% CI)	14	257 741	25	383 865	31.6% 100.0%	0.83 [0.44, 1.57] 0.63 [0.43, 0.93]	2015	
Total events	37		68			,		•
Heterogeneity: Chi ² =	1.60. df	= 2 (P	= 0.45);	$I^2 = 0\%$	6			
Test for overall effect:	Z = 2.34	P = 0	0.02)					
1.1.3 Vascular surge	ry							
Møller 2019	2	29	1	29	100.0%	2.00 [0.19, 20.86]	2019	
Subtotal (95% CI)		29		29	100.0%	2.00 [0.19, 20.86]		
Total events	2		1					
Heterogeneity: Not ap	plicable							
Test for overall effect:	Z = 0.58	8 (P = 0)).56)					
								Favours restrictive Favours liberal
Test for subgroup diff	erences:	Chi ² =	0.90, df	= 1 (P	= 0.34),	$l^2 = 0\%$		ratears reschedre Taroars inseral

2. Quality of life (measured with EQ-5D or SF-36)

	Re	estrictive			Liberal			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
1.2.1 GI bleeding									
Jairaith 2015 Subtotal (95% CI)	-0.76	0.27	257 257	-0.69	0.32	383 383	100.0% 100.0%	-0.07 [-0.12, -0.02] -0.07 [-0.12, -0.02]	
Heterogeneity: Not ap	plicable								
Test for overall effect	: Z = 2.98	8 (P = 0.0)	03)						
1.2.2 Obstetric blee	ding								
Prick 2014 Subtotal (95% CI)	80	19.7976	262 262	80.1	19.7976	259 259	100.0% 100.0%	-0.10 [-3.50, 3.30] -0.10 [-3.50, 3.30]	
Heterogeneity: Not ap Test for overall effect	plicable : Z = 0.06	6 (P = 0.9	5)						
Test for subgroup dif	ferences:	$Chi^{2} = 0.0$	00, df =	= 1 (P =	0.99), l ² =	= 0%			Favours restrictive Favours liberal

3. Stroke

	Restric	tive	Liber	al		Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	Year	M-H, Fixed, 95% Cl
1.3.1 GI bleeding								
Villaneuva 2013	3	444	6	445	24.5%	0.50 [0.13, 1.99]	2013	
Jairaith 2015 Subtotal (95% CI)	9	257 701	23	383 828	75.5% 100.0%	0.58 [0.27, 1.24] 0.56 [0.29, 1.09]	2015	
Total events	12		29					
Heterogeneity: Chi [*] =	0.04, df	= 1 (P	= 0.85);	$l^{*} = 0\%$	5			
Test for overall effect:	Z = 1.70	(P = 0)	.09)					
Total (95% CI)		701		828	100.0%	0.56 [0.29, 1.09]		
Total events	12		29					
Heterogeneity: Chi ² =	0.04, df	= 1 (P	= 0.85);	$I^2 = 0\%$	5			
Test for overall effect:	Z = 1.70	(P = 0)	.09)				0.1	Favours restrictive Favours liberal
Test for subgroup diff	erences: I	Not app	olicable					

4. Myocardial infarction

	Restrictive		Liberal		Risk Ratio			Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	Year	M-H, Fixed, 95% Cl	
1.4.1 GI bleeding									
Villaneuva 2013 Subtotal (95% CI)	8	444 444	13	445 445	100.0% 100.0%	0.62 [0.26, 1.47] 0.62 [0.26, 1.47]	2013		
Total events	8		13						
Heterogeneity: Not ap	plicable								
Test for overall effect:	Z = 1.09	(P = 0)	.28)						
1.4.2 Vascular surger	ry								
Møller 2019 Subtotal (95% CI)	2	29 29	2	29 29	100.0% 100.0%	1.00 [0.15, 6.63] 1.00 [0.15, 6.63]	2019		
Total events Heterogeneity: Not ap	2 plicable		2						
Test for overall effect:	Z = 0.00	(P = 1)	.00)						
								0.2 0.5 1 2 5 Favours restrictive Favours liberal	

Test for subgroup differences: $Chi^2 = 0.21$, df = 1 (P = 0.65), $I^2 = 0\%$

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

5. ARDS/TRALI - no studies identified

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



7. Volume overload/TACO



Test for subgroup differences: Not applicable

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

8. Venous thrombosis



9. Post-transfusion sepsis/infection

	Restrictive		Liberal		Risk Ratio			Risk Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	Year	M-H, Fixed, 95% Cl		
1.9.1 GI bleeding										
Villaneuva 2013	119	444	135	445	64.6%	0.88 [0.72, 1.09]	2013			
Jairaith 2015	67	257	92	383	35.4%	1.09 [0.83, 1.42]	2015			
Subtotal (95% CI)		701		828	100.0%	0.95 [0.81, 1.13]				
Total events	186		227							
Heterogeneity: $Chi^2 = 1.38$, $df = 1$ (P = 0.24); $I^2 = 28\%$										
Test for overall effect: $Z = 0.55$ (P = 0.58)										
1.9.2 Obstetric bleed	lina									
Prick 2014	24	262	22	259	100.0%	1 08 [0 62 1 87]	2014			
Subtotal (95% CI)	24	262	22	259	100.0%	1.08 [0.62, 1.87]	2014			
Total events	24		22							
Heterogeneity: Not ap	plicable									
Test for overall effect:	Z = 0.27	7 (P = 0)).79)							
								07 085 1 12 15		
								Favours restrictive Favours liberal		
Test for subgroup diff	arancas i	Chi ² – I	0 17 df	-1(P)	-0.68	$I^2 = 0\%$				

Test for subaroup differences: $Chi^{*} = 0.17$. df = 1 (P = 0.68). $I^{*} = 0\%$
Restrictive vs. liberal RBC transfusion in non-massively bleeding patients

10. Rebleeding (clinical hemostasis)

	Restric	tive	Liber	al		Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	Year	M-H, Fixed, 95% CI
1.10.1 GI bleeding								
Blair 1986	2	26	9	24	8.4%	0.21 [0.05, 0.86]	1986	
Villaneuva 2013	45	444	71	445	63.7%	0.64 [0.45, 0.90]	2013	
Lee 2014	5	32	6	31	5.5%	0.81 [0.27, 2.38]	2014	
Jairaith 2015	13	257	31	383	22.4%	0.62 [0.33, 1.17]	2015	
Subtotal (95% CI)		759		883	100.0%	0.61 [0.46, 0.81]		◆
Total events	65		117					
Heterogeneity: Chi ² =	2.56, df	= 3 (P	= 0.46);	$I^2 = 0\%$	6			
Test for overall effect:	Z = 3.43	8 (P = 0)	.0006)					
								Favours restrictive Favours liberal
								ratears rescretive ratears insertin

11. Transfusion reaction

	Restric	tive	Liber	ral		Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	Year	M-H, Fixed, 95% Cl
1.11.1 GI bleeding								
Villaneuva 2013	14	444	38	445	84.0%	0.37 [0.20, 0.67]	2013	
Jairaith 2015	2	257	9	383	16.0%	0.33 [0.07, 1.52]	2015	
Subtotal (95% CI)		701		828	100.0%	0.36 [0.21, 0.63]		◆
Total events	16		47					
Heterogeneity: Chi ² =	0.02, df	= 1 (P	= 0.90);	$I^2 = 0\%$	5			
Test for overall effect:	Z = 3.56	$\delta (P = 0)$.0004)					
1 11 2 Obstatuis blas	dina							
1.11.2 Obstetric blee	aing		-					_
Prick 2014	0	262	3	259	100.0%	0.14 [0.01, 2.72]	2014	
Subtotal (95% CI)		262		259	100.0%	0.14 [0.01, 2.72]		
l otal events	0		3					
Heterogeneity: Not ap	plicable		10					
lest for overall effect:	Z = 1.30	(P = 0)).19)					
1.11.3 Vascular surg	erv							
Møller 2019	0	29	1	29	100.0%	0.33 [0.01, 7,86]	2019	
Subtotal (95% CI)	Ŭ	29	-	29	100.0%	0.33 [0.01, 7.86]	2020	
Total events	0		1					
Heterogeneity: Not ap	plicable							
Test for overall effect:	Z = 0.68	B (P = 0)).50)					
								Favours restrictive Favours liberal
Test for subgroup diff	erences.	$Chi^2 = 1$	038 df	- 2 (P	- 0.83)	$l^2 = 0\%$		ravours rescrictive Tavours interal

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

12. Hospital length of stay

	Res	trictive	e	L	iberal			Mean Diff	erence		Mean	Difference		42 Maan number
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Randoi	n, 95% Cl	Year	r IV, Rand	om, 95% Cl		13.Wean number
1.13.1 GI bleeding														of transfusions
Blair 1986	2.6	0.6	26	4.6	0.3	24	47.8%	-2.00 [-2.2	26, -1.74]	1986				
Villarejo 1999	5.54	2.02	14	5.86	1.66	13	10.2%	-0.32 [-1	71, 1.07]	1999				
Villaneuva 2013	1.5	2.3	444	3.7	3.8	445	39.7%	-2.20 [-2.6	51, -1.79]	2013				
Jairaith 2015	1.8	25	257	2.6	3	383	2.4%	-0.80 [-3	87, 2.27]	2015	•			14.Proportion of
Subtotal (95% CI)			741			865	100.0%	-1.88 [-2.:	37, -1.39]		-			patients
Heterogeneity: Tau* =	0.11; 0	$hi^{*} = 7$	'.09, d	f = 3 (F	P = 0.0)7); l* =	58%							receiving
l'est for overall effect:	Z = 7.5	1 (P <	0.000	01)										transfusion
1.13.2 Obstetric blee	dina													
Prick 2014	g	0	262	2	0.1	250		Not	estimable	2014	l			
Subtotal (95% CI)	0	0	262	2	0.1	259		Not	estimable	2014				
Heterogeneity: Not an	plicable													
Test for overall effect:	Not apr	licable												
1.13.3 Vascular surge	ery													
Møller 2019	1	1.5	29	3	3	29	100.0%	-2.00 [-3.2	2, -0.78]	2019				
Subtotal (95% CI)			29			29	100.0%	-2.00 [-3.2	22, -0.78]					
Heterogeneity: Not ap	plicable													
	Res	trictive		Libera	al .			Risk Ratio		_	Risk	Ratio		
Study or Subgroup	Even	ts To	tal Ev	vents	Total	Weigi	nt M-H	, Random, 9	95% CI	/ear	M-H, Rand	om, 95% Cl		
1.14.1 GI bleeding											_			
Villaneuva 2013	2.	19 4	44	384	445	51.1	.%	0.57 [0.52,	0.63] 2	013				
Jairaith 2015	13	32 2	57	246	383	48.9	% •	0.80 [0.69,	0.92] 2	015				
Subtotal (95% CI)		. /	01		828	100.0	%	0.67 [0.48	, 0.94]					
Total events	3	51		630										
Heterogeneity: Tau*	= 0.05;	Chi [*] =	: 14.5	2, df =	1 (P =	= 0.000	01); l ^e =	93%						
Test for overall effect	t: $Z = 2$.35 (P	= 0.02	2)										
1 14 2 Vaccular cur	any													
1.14.2 Vascular Surg	gery	10	20	20	20	100.0		0.00.00.01	0 9 6 1 3	010				
Møller 2019 Subtotal (95% CI)		19	29	29	29	100.0	0% 0/	0.66 [0.51,	0.861	019				
Subtotal (95% CI)		10	29	20	29	100.0	70	0.00 [0.31	, 0.80]					
l otal events		19		29										
Heterogeneity: Not a	pplicabl	e o () D	0.01	0.21										
lest for overall effect	c = 3	.04 (P	= 0.00	02)										
											1			
										0	0.7	1 1.5	ź	
Test for subgroup di	(fa v a n	c. Ch:2	0.0	1 46	1 (0	- 0.03	12 - 00	<i>v</i>		0).5 0.7 Favours restrictive	1 1.5 Favours liberal	ź	

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

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

Restrictive vs. Liberal Platelet Transfusion Strategy- Evidence Summaries

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

			Certainty as	sessment			N₂ of p	atients	Effec	t		
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Restrictive platelet transfusions	liberal platelet transfusion	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
Mortality	(3 month)											
1	randomised trials	not serious	not serious	not serious	serious ^a	none ^b	21/93 (22.6%)	31/97 (32.0%)	RR 0.71 (0.44 to 1.14)	93 fewer per 1,000 (from 179 fewer to 45 more)	MODERATE	CRITICAL
Mortality	-Overall											
2	randomised trials	not serious	not serious	not serious	serious ^a	none ^b	39/205 (19.0%)	48/211 (22.7%)	RR 0.84 (0.58 to 1.22)	36 fewer per 1,000 (from 96 fewer to 50 more)		CRITICAL
Modified	Rankin Score	4-6 at 3 mont	ths									
1	randomised trials	not serious	not serious	not serious	serious ^a	none ^b	52/93 (55.9%)	66/97 (68.0%)	RR 0.82 (0.66 to 1.03)	122 fewer per 1,000 (from 231 fewer to 20 more)	MODERATE	CRITICAL
Modified	Rankin Score	3-6 at 3 mont	ths				-					
1	randomised trials	not serious	not serious	not serious	serious ^a	none ^b	76/93 (81.7%)	70/97 (72.2%)	RR 1.13 (0.97 to 1.32)	94 more per 1,000 (from 22 fewer to 231 more)	MODERATE	CRITICAL
ICH enla	rgement											
1	randomised trials	not serious	not serious	not serious	serious ^a	none ^b	13/93 (14.0%)	15/97 (15.5%)	RR 0.90 (0.46 to 1.80)	15 fewer per 1,000 (from 84 fewer to 124 more)	MODERATE	IMPORTANT
Ischemic	Stroke											

1 randomised not serious not serious not serious very none ^b	0/93 (0.0%) 1/97 (1.0%) RR 0.35 (0.01 to 8.42) 7 fewer 1,000 (from 10 fewer to 76 more) CRITICAL	
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МІ

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

Pulmonary Embolism

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

1 randomised not serious not serious not serious very serious ^c	17/112 15/112 (15.2%) (13.4%)	RR 1.13 (0.60 to 2.16) 17 more per 1,000 (from 54 fewer to 155 more)		IMPORTANT
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ADL- Completely dependent

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

Explanations

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

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

			Certainty ass	essment			N₂ of pa	atients	Effec	t		
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	restrictive platelet transfusion strategy	liberal platelet transfusion strategy	Relative (95% Cl)	Absolute (95% CI)	Certainty	Importance
Increase	in hematoma											
1	observational studies	serious	not serious	serious ^a	very serious ^b	none	7/24 (29.2%)	16/39 (41.0%)	RR 0.71 (0.34 to 1.47)	119 fewer per 1,000 (from 271 fewer to 193 more)	OCO VERY LOW	IMPORTANT

No change in hematoma

1	observational studies	serious	not serious	serious ^a	very serious ^b	none	14/18 (77.8%)	13/24 (54.2%)	RR 1.44 (0.92 to 2.24)	238 more per 1,000 (from 43 fewer to 672 more)	OCO VERY LOW	IMPORTANT
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Cl: Confidence interval; RR: Risk ratio

Explanations

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

<u>Restrictive vs. Liberal Platelet Strategy in Non-massively Bleeding Patients On Antiplatelet</u> <u>Therapy</u>

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

Mortality 3 months

	Restric	tive	Liber	al		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Baharoglu 2016	21	93	31	97	100.0%	0.71 [0.44, 1.14]	
Total (95% CI)		93		97	100.0%	0.71 [0.44, 1.14]	•
Total events	21		31				
Heterogeneity: Not app	plicable						
Test for overall effect:	Z = 1.43	B (P = 0)	.15)				Favours Restrictive plt Favours Liberal plt

Mortality- Overall

	Restrict	ive	Liber	ral		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% Cl
Baharoglu 2016	21	93	31	97	64.3%	0.71 [0.44, 1.14]	
Li 2013	18	112	17	114	35.7%	1.08 [0.59, 1.98]	
Total (95% CI)		205		211	100.0%	0.84 [0.58, 1.22]	•
Total events	39		48				
Heterogeneity: Chi ² =	1.15, df =	= 1 (P =	= 0.28);	$I^2 = 13$	%		
Test for overall effect:	Z = 0.92	(P = 0	.36)				Favours Restrictive Favours Liberal

Disability- Modified Rankin Score 4-6 at 3 months

	Restric	tive	Liber	ral		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Baharoglu 2016	52	93	66	97	100.0%	0.82 [0.66, 1.03]	•
Total (95% CI)		93		97	100.0%	0.82 [0.66, 1.03]	◆
Total events	52		66				
Heterogeneity: Not ap Test for overall effect:	plicable Z = 1.70) (P = 0	.09)				0.01 0.1 1 10 100 Favours Restrictive Favours Control

Disability- Modified Rankin Score 3-6 at 3 months

•	Restrictiv	ve Lik	eral		Risk Ratio	Risk Ratio
Study or Subgroup	Events T	otal Event	s Total	Weight	M-H, Fixed, 95% Cl	M–H, Fixed, 95% Cl
Baharoglu 2016	76	93 7	0 97	100.0%	1.13 [0.97, 1.32]	—
Total (95% CI)		93	97	100.0%	1.13 [0.97, 1.32]	•
Total events	76	7	0			
Heterogeneity: Not ap Test for overall effect:	plicable Z = 1.56 (F	P = 0.12)				0.01 0.1 1 10 100 Favours Restrictive Favours Liberal

Disability- ADL Grade 4- Completely dependent

	Restric	tive	Liber	al		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Li 2013	4	112	2	114	100.0%	2.04 [0.38, 10.89]	
Total (95% CI)		112		114	100.0%	2.04 [0.38, 10.89]	
Total events	4		2				
Heterogeneity: Not app	plicable						
Test for overall effect:	Z = 0.83	B (P = 0)	.41)				Favours restrictive Favours liberal

Postoperative Hemorrhage

	Restric	tive	Liber	al		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Li 2013	17	112	15	112	100.0%	1.13 [0.60, 2.16]	
Total (95% CI)		112		112	100.0%	1.13 [0.60, 2.16]	+
Total events	17		15				
Heterogeneity: Not ap	plicable						
Test for overall effect:	Z = 0.38	(P = 0	.70)				Favours restrictive Favours liberal

ICH Enlargement

	Restric	tive	Liber	al		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Baharoglu 2016	13	93	15	97	100.0%	0.90 [0.46, 1.80]	
Total (95% CI)		93		97	100.0%	0.90 [0.46, 1.80]	+
Total events	13		15				
Heterogeneity: Not ap	plicable						
Test for overall effect:	Z = 0.29	(P = 0)	.77)				Favours Restrictive Favours Liberal

CVA (Ischemic)

	Restric	tive	Liber	al		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M–H, Fixed, 95% Cl	M-H, Fixed, 95% CI
Baharoglu 2016	0	93	1	97	100.0%	0.35 [0.01, 8.42]	
Total (95% CI)		93		97	100.0%	0.35 [0.01, 8.42]	
Total events	0		1				
Heterogeneity: Not app	plicable						
Test for overall effect:	Z = 0.65	(P = 0	.52)				Favours Restrictive Favours Liberal

MI

	Restric	tive	Liber	ral		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M–H, Fixed, 95% Cl
Baharoglu 2016	1	93	1	97	100.0%	1.04 [0.07, 16.43]	
Total (95% CI)		93		97	100.0%	1.04 [0.07, 16.43]	
Total events	1		1				
Heterogeneity: Not ap	plicable						
Test for overall effect:	Z = 0.03	(P = C)	.98)				Favours Restrictive Favours Liberal

DVT

	Restric	tive	Liber	al		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Baharoglu 2016	0	93	2	97	100.0%	0.21 [0.01, 4.29]	
Total (95% CI)		93		97	100.0%	0.21 [0.01, 4.29]	
Total events	0		2				
Heterogeneity: Not ap Test for overall effect:	plicable Z = 1.02	(P = 0	.31)				0.01 0.1 1 10 100 Favours Restrictive Favours Liberal

Observational Studies- Neuro and GI Bleeding

<u>Neuro</u>

<u>Mortality</u>

-	Restrict	ive	Liber	a		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Kim 2015	16	282	15	126	100.0%	0.48 [0.24, 0.93]	
Total (95% CI)		282		126	100.0%	0.48 [0.24, 0.93]	•
Total events	16		15				
Heterogeneity: Not ap Test for overall effect:	Z = 2.16	(P = 0	.03)				0.01 0.1 1 10 100 Favours Restrictive Favours Liberal

Permanent Disability

	Kestric	tive	Liber	ai		KISK KATIO	KISK KATIO
Study or Subgroup	Events	Total	Events	Total	Weight	M–H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
Kim 2015	22	282	9	126	100.0%	1.09 [0.52, 2.30]	
Total (95% CI)		282		126	100.0%	1.09 [0.52, 2.30]	+
Total events	22		9				
Heterogeneity: Not app	plicable						
Test for overall effect:	Z = 0.23	$(\mathbf{P} = 0)$.82)				Favours Restrictive Favours Liberal

Temporary Disability

	Restrictive Liberal				Risk Ratio	Risk Ratio		
Study or Subgroup	Events	Total Events Total Weight M-H, Fixed, 95% Cl M-H, Fixed, 95% Cl		M-H, Fixed, 95% CI				
Kim 2015	223	282	96	126	100.0%	1.04 [0.93, 1.16]		
Total (95% CI)		282		126	100.0%	1.04 [0.93, 1.16]	+	
Total events	223		96					
Heterogeneity: Not ap	plicable							
Test for overall effect:	Z = 0.64	P = 0	.52)				Favours Restrictive Favours Liberal	
VTE								
Study or Subaroup	Restri- Events	tive Total	Libe Events	ral Total	Weight	Risk Ratio M-H Fixed 95% Cl	Risk Ratio	

		nestin	LIVE	LINEI	a		KISK KAUU	KISK KAU	U	
_	Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 9	5% CI	
	Kim 2015	3	282	1	126	100.0%	1.34 [0.14, 12.76]			
	Total (95% CI)		282		126	100.0%	1.34 [0.14, 12.76]			
	Total events	3		1						
	Heterogeneity: Not app	plicable							10	100
	Test for overall effect:	i (P = 0)	.80)				Envours Postrictivo Envo	10 ours Liberal	100	
								ravours resultuve rav	ouis Liberai	

<u>CVA</u>

	Restricti	ive	Liber	al		Risk Ratio	Risk Ratio
Study or Subgroup	Events 1	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% Cl
Kim 2015	2	282	2	126	100.0%	0.45 [0.06, 3.14]	
Total (95% CI)		282		126	100.0%	0.45 [0.06, 3.14]	
Total events	2		2				
Heterogeneity: Not ap	plicable						
Test for overall effect: $Z = 0.81 (P = 0.42)$							Favours Restrictive Favours Liberal

Increase in ICH

	Restric	tive	Liber	ral		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M–H, Fixed, 95% Cl
Engel-Haber 2015	4	18	11	24	100.0%	0.48 [0.18, 1.28]	
Total (95% CI)		18		24	100.0%	0.48 [0.18, 1.28]	-
Total events	4		11				
Heterogeneity: Not ap	plicable						
Test for overall effect:	Z = 1.47	(P = 0)).14)			Favours Restrictive Favours Liberal	

No Change in ICU

-	Restric	tive	Liber	ral		Risk Ratio	Risk Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% (21	
Engel-Haber 2015	14	18	13	24	100.0%	1.44 [0.92, 2.24]	+		
Total (95% CI)		18		24	100.0%	1.44 [0.92, 2.24]	◆		
Total events	14		13						
Heterogeneity: Not ap	plicable						0.01 0.1 1	10 100	
Test for overall effect: $Z = 1.60$ (P = 0.11)							Favours Restrictive Favours	Liberal	

GI Bleeding

<u>Mortality</u>

Restrictive		Libe	ral		Risk Ratio	Risk Ratio			
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI		
Zakko 2017	3	204	14	204	100.0%	0.21 [0.06, 0.73]			
Total (95% CI)		204		204	100.0%	0.21 [0.06, 0.73]			
Total events	3		14						
Heterogeneity: Not app	plicable							100	
Test for overall effect:	Z = 2.45	i (P = 0)	.01)				0.01 0.1 I 10 Eavours Restrictive Eavours Liberal	100	
MI									
	Restric	tive	Liber	al		Risk Ratio	Risk Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI		
Zakko 2017	26	204	46	204	100.0%	0.57 [0.36, 0.88]			
Total (95% CI)		204		204	100.0%	0.57 [0.36, 0.88]	•		
Total events	26		46						
Heterogeneity: Not ap	plicable							100	
Test for overall effect:	Z = 2.54	P = 0	.01)				Favours Restrictive Favours Liberal	100	

Major Cardiac Events

Restrictive		Liberal		Risk Ratio		Risk Ratio		
roup Events Total Events Total Weight M-H, Fixed, 95% CI M-H, Fixed, 95% CI								
26	204	47	204	100.0%	0.55 [0.36, 0.86]			
	204		204	100.0%	0.55 [0.36, 0.86]	•		
26 plicable Z = 2.65	(P = 0	47 .008)				0.01 0.1 1 10 Favours Restrictive Favours Liberal	100	
Doctrict	tiva	Libor			Pick Patio	Pick Patio		
	Events 26 26 26 26 26 26 26 27 26 26 26 26 26 26 26 26 26 26 26 26 26	Events Total 26 204 26 204 26 204 26 204 27 26 28 204 29 204 201 204 26 204 27 205 201 204 202 204 203 204 204 204 205 204 205 204 206 204 207 204 208 204 209 204 200 204 201 204 202 205 203 204 204 204 205 204 205 205 205 205 205 205 205 205 205 205	Events Total Events 26 204 47 26 47 blicable 47 Z = 2.65 (P = 0.008) Restrictive	Events Total Events Total 26 204 47 204 26 47 204 26 47 204 26 47 204 26 47 204 26 47 204 26 47 204 26 47 204 27 205 (P = 0.008) Restrictive	Events Total Events Total Weight 26 204 47 204 100.0% 26 47 204 100.0% 26 47 204 100.0% 26 47 204 100.0% 27 205 9 100.0% 28 47 204 100.0% 29 2.65 (P = 0.008) 100.0%	Events Total Events Total Weight M-H, Fixed, 95% CI 26 204 47 204 100.0% 0.55 [0.36, 0.86] 26 47 204 100.0% 0.55 [0.36, 0.86] 26 47 204 100.0% 0.55 [0.36, 0.86] 26 47 204 200.0% 0.55 [0.36, 0.86] 27 20 47 204 200.0% 28 20.008 8 8 Risk Ratio	Events Total Events Total Weight M-H, Fixed, 95% CI M-H, Fixed, 95% CI 26 204 47 204 100.0% 0.55 [0.36, 0.86] - 26 47 204 100.0% 0.55 [0.36, 0.86] - - 26 47 204 100.0% 0.55 [0.36, 0.86] - - 26 47 - - - - - - 26 47 -	

	restric	.uve	Liber	d.		RISK RALIO	NISK I	latio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixe	d, 95% Cl	
Zakko 2017	16	204	29	204	100.0%	0.55 [0.31, 0.98]			
Total (95% CI)		204		204	100.0%	0.55 [0.31, 0.98]	+		
Total events	16		29						
Heterogeneity: Not ap	plicable							10	100
Test for overall effect:	Z = 2.01	I(P = C)	0.04)				Favours Restrictive	Favours Liberal	100

Hospital LOS > 4 Days

	Restrictive Liberal					Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
Zakko 2017	68	204	96	204	100.0%	0.71 [0.56, 0.90]	
Total (95% CI)		204		204	100.0%	0.71 [0.56, 0.90]	•
Total events	68		96				
Heterogeneity: Not ap Test for overall effect:	plicable Z = 2.79	P = 0	0.005)				0.01 0.1 1 10 100 Favours Restrictive Favours Liberal

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

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

Increase in hematoma

	Restrictive Liberal			al		Risk Ratio	Risk Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% CI		
Engel-Haber 2015	7	24	16	39	100.0%	0.71 [0.34, 1.47]			
Total (95% CI)		24		39	100.0%	0.71 [0.34, 1.47]			
Total events	7		16						
Heterogeneity: Not applicable							0.01 0.1 1 10 100		
Test for overall effect:	P = 0).36)				Favours Restrictive Favours Liberal			

No change in hematoma

	Restrictive Liberal			al		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Engel-Haber 2015	14	18	13	24	100.0%	1.44 [0.92, 2.24]	
Total (95% CI)		18		24	100.0%	1.44 [0.92, 2.24]	◆
Total events	14		13				
Heterogeneity: Not ap Test for overall effect:	plicable Z = 1.60	(P = 0).11)				0.01 0.1 1 10 100 Favours Restrictive Favours Liberal

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

		Certainty	assessment			Nº of pa	itients		Effect				
№ of studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Early fibrinogen	Control	Relative (95% Cl)	Absolute (95% Cl)	Certainty	Importance		
Mortality	- Cardiac	surgery			-								
5 RCT	not serious	not serious	not serious	very serious ^a	none	5/235 (2.1%)	12/234 (5.1%)	RR 0.44 (0.17 to 1.19)	29 fewer per 1,000 (from 43 fewer to 10 more)		CRITICAL		
Mortality	Mortality - Vascular surgery												
1 RCT	not serious	not serious	not serious	very serious ^a	none	0/10	1/10	RR 0.33	67 fewer per 1,000	$\oplus \oplus \bigcirc \bigcirc \bigcirc$	CRITICAL		
	3611003					(0.070)	(10.070)	(0.02 10 7.02)		LOW			
Stroke - (Stroke - Cardiac surgery												
3 RCT	not serious	serious ^b	not serious	very serious ^a	none	6/196 (3.1%)	5/192 (2.6%)	RR 1.16 (0.36 to 3.72)	4 more per 1,000 (from 17 fewer to 71 more)	$\oplus 000$	CRITICAL		
	Sonous					(0.170)	(2.070)	(0.00 10 0.12)		VERY LOW			
Stroke - V	/ascular su	urgery			-								
1 RCT	not serious	not serious	not serious	very serious ^a	none	0/10 (0.0%)	0/10 (0.0%)	not pooled	see comment	-	CRITICAL		
Myocardi	al infarctio	on - Cardiac surge	ery										
3 RCT	not serious	not serious	not serious	very serious ^a	none	3/128	2/128	RR 1.40	6 more per 1,000 (from 11 fewer to 92 more)	$\oplus \oplus \bigcirc \bigcirc \bigcirc$	CRITICAL		
	3611003					(2.370)	(1.070)	(0.23 10 0.07)		LOW			
Myocardi	al infarctio	on - Non-cardiac s	surgery										
1 RCT	not serious	not serious	not serious	very serious ^a	none	1/10	1/10 (10.0%)	RR 1.00	0 fewer per 1,000 (from 93 fewer to 1,000 more)	$\oplus \oplus \bigcirc \bigcirc \bigcirc$	CRITICAL		
	3611043					(10.070)	(10.070)	(0.07 10 10.07)		LOW			
Acute kic	lney injury	- Cardiac surger	у										

3 RCT	not serious	not serious	not serious	very serious ^a	none	11/196 (5.6%)	14/192 (7.3%)	RR 0.77 (0.36 to 1.65)	17 fewer per 1,000 (from 47 fewer to 47 more)		CRITICAL
Acute kidney injury - Non-cardiac surgery									•		
1 RCT	not serious	not serious	not serious	very serious ^a	none	0/10 (0.0%)	1/10 (10.0%)	RR 0.33 (0.02 to 7.32)	67 fewer per 1,000 (from 98 fewer to 632 more)		CRITICAL
Venous t	hrombosis	- Cardiac surger	у		-	-					
4 RCT	not serious	not serious	not serious	very serious ^a	none	1/206 (0.5%)	0/202 (0.0%)	RR 2.85 (0.12 to 68.83)	0 fewer per 1,000 (from 0 fewer to 0 fewer)		IMPORTANT
Venous t	hrombosis	- Non-cardiac su	irgery	-	-						
1 RCT	not serious	not serious	not serious	very serious ^a	none	0/10 (0.0%)	1/10 (10.0%)	RR 0.33 (0.02 to 7.32)	67 fewer per 1,000 (from 98 fewer to 632 more)		IMPORTANT
Infection	- Cardiac	surgery									
3 RCT	not serious	not serious	not serious	very serious ^a	none	23/196 (11.7%)	23/192 (12.0%)	RR 0.97 (0.57 to 1.67)	4 fewer per 1,000 (from 52 fewer to 80 more)		IMPORTANT
Infection	- Non-card	diac surgery							•	•	
1 RCT	not serious	not serious	not serious	very serious ^a	none	3/22 (13.6%)	3/21 (14.3%)	RR 0.95 (0.22 to 4.21)	7 fewer per 1,000 (from 111 fewer to 459 more)		IMPORTANT
Blood los	ss - Cardia	c surgery									
3 RCT	not serious	not serious ^c	not serious	serious ^d	none	176	172	-	MD 87.76 lower (149.49 lower to 26.03 lower)	⊕⊕⊕⊖ MODERATE	IMPORTANT
Reoperat	tion - Card	iac surgery									

4 RCT	not serious	not serious	not serious	very serious ^a	none	20/168 (11.9%)	23/168 (13.7%)	RR 0.87 (0.54 to 1.42)	18 fewer per 1,000 (from 63 fewer to 57 more)		IMPORTANT
ICU leng	th of stay -	Non-cardiac surg	gery						•		
1 RCT	not serious	not serious	not serious	very serious ^e	none	19	10	-	MD 0 (2.93 lower to 2.93 higher)		IMPORTANT
Hospital	length of s	stay - Non-cardiac	surgery		-						
1 RCT	not serious	not serious	not serious	very serious ^e	none	10	10	-	MD 1.5 lower (9.96 lower to 6.96 higher)		IMPORTANT
Proportio	on receivin	g RBCs - Cardiac	surgery	•						-	
3 RCT	not serious	serious ^b	not serious	serious ^d	none	38/128 (29.7%)	61/128 (47.7%)	RR 0.62 (0.46 to 0.84)	181 fewer per 1,000 (from 257 fewer to 76 fewer)		IMPORTANT
Proportio	on receivin	g plasma - Cardia	ac surgery								
2 RCT	not serious	serious ^b	not serious	serious ^d	none	9/118 (7.6%)	21/118 (17.8%)	RR 0.44 (0.22 to 0.90)	100 fewer per 1,000 (from 139 fewer to 18 fewer)		IMPORTANT
Proportio	on receivin	g platelets - Card	liac surgery	•	-						
3 RCT	not serious	not serious	not serious	serious ^d	none	13/128 (10.2%)	27/128 (21.1%)	RR 0.50 (0.29 to 0.86)	105 fewer per 1,000 (from 150 fewer to 30 fewer)	⊕⊕⊕⊖ MODERATE	IMPORTANT
Mean RB	Cs transfu	sed - Cardiac sur	rgery								
3 RCT	not serious	serious ^b	not serious	serious ^e	none	176	172	-	MD 0.37 lower (1.6 lower to 0.86 higher)		IMPORTANT
Mean RB	Cs transfu	sed - Non-cardia	c surgery								

1 RCT	not serious	not serious	not serious	very serious ^a	none	10	10	-	MD 1.5 lower (3.15 lower to 0.15 higher)	IMPORTANT
Mean pla	isma trans	fused - Cardiac s	urgery							
2 RCT	not serious	serious ^b	not serious	serious ^e	none	118	114	-	MD 0.42 lower (0.99 lower to 0.14 higher)	IMPORTANT
Mean pla	itelets tran	sfused - Cardiac	surgery			-		-		
2 RCT	not serious	not serious	not serious	very serious ^e	none	118	114	-	MD 0.01 lower (0.31 lower to 0.29 higher)	IMPORTANT

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

Explanations

a. Few events with very wide confidence intervals which do not exclude significant benefit or harm.

b. Significant heterogeneity with point estimates on both sides of the line of no effect.

c. Statistical heterogeneity, but of little clinical significance as all point estimates and confidence intervals favour fibrinogen.

d. Though statistically significant, but optimal information size is not met, resulting in likely imprecision.

e. Small number of patients with very wide confidence intervals resulting in very significant imprecision.

1. Mortality

	Early fibrinogen		Cont	ol		Risk Ratio		Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	Year	r M–H, Fixed, 95% Cl	
2.1.1 Cardiac surgery	/								
Rahe-Meyer 2013	1	29	4	32	30.6%	0.28 [0.03, 2.33]	2013		
Tanaka 2014	0	10	0	10		Not estimable	2014	•	
Ranucci 2015	1	58	3	58	24.1%	0.33 [0.04, 3.11]	2015	· · · · · · · · · · · · · · · · · · ·	
Rahe-Meyer 2016	1	78	5	74	41.3%	0.19 [0.02, 1.59]	2016	;	
Bilecen 2017	2	60	0	60	4.0%	5.00 [0.25, 102.00]	2017		
Subtotal (95% CI)		235		234	100.0%	0.44 [0.17, 1.19]			
Total events	5		12						
Heterogeneity: Chi ² =	3.35, df = 3	(P = 0.	34); I ² =	10%					
Test for overall effect:	Z = 1.61 (P	= 0.11)							
2.1.2 Vascular surger	Ŷ							_	
Morrison 2019	0	10	1	10	100.0%	0.33 [0.02, 7.32]	2019		
Subtotal (95% CI)		10		10	100.0%	0.33 [0.02, 7.32]			
Total events	0		1						
Heterogeneity: Not ap	plicable								
Test for overall effect:	Z = 0.70 (P	= 0.49							
								0.01 0.1 1 10	100

Favours early fibrinogen Favours control

2. Stroke

Early fibrinogen		Control		Risk Ratio			Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	Year	r M–H, Fixed, 95% Cl
2.2.1 Cardiac surgery	/							
Ranucci 2015	0	58	0	58		Not estimable	2015	5
Rahe-Meyer 2016	2	78	4	74	80.4%	0.47 [0.09, 2.51]	2016	5
Bilecen 2017 Subtotal (95% CI)	4	60 196	1	60 192	19.6% 100.0%	4.00 [0.46, 34.75] 1.16 [0.36, 3.72]	2017	
Total events Heterogeneity: Chi ² = Test for overall effect:	6 2.37, df = 1 Z = 0.26 (P	(P = 0. = 0.80)	5 12); I ² =	58%				
2.2.2 Vascular surger	ry .							
Morrison 2019 Subtotal (95% CI)	0	10 10	0	10 10		Not estimable Not estimable	2019	9
Total events Heterogeneity: Not ap Test for overall effect:	0 plicable Not applicab	ole	0					
								Favours early fibrinogen Favours control

3. Myocardial infarction

Early fibrinogen			Contr	ol		Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	Year	M-H, Fixed, 95% CI
2.3.1 Cardiac surgery	/							
Tanaka 2014	0	10	1	10	60.0%	0.33 [0.02, 7.32]	2014	
Ranucci 2015	0	58	0	58		Not estimable	2015	
Bilecen 2017	3	60	1	60	40.0%	3.00 [0.32, 28.03]	2017	
Subtotal (95% CI)		128		128	100.0%	1.40 [0.29, 6.87]		
Total events	3		2					
Heterogeneity: Chi ² =	1.28, df = 1	(P = 0.	26); I ² =	22%				
Test for overall effect:	Z = 0.41 (P	= 0.68)						
2.3.2 Non-cardiac su	rgery							
Morrison 2019	1	10	1	10	100.0%	1.00 [0.07, 13.87]	2019	
Subtotal (95% CI)		10		10	100.0%	1.00 [0.07, 13.87]		
Total events	1		1					
Heterogeneity: Not ap	plicable							
Test for overall effect:	Z = 0.00 (P	= 1.00)						
								0.01 0.1 1 10 100
								Favours early fibrinogen Favours control
2.3.2 Non-cardiac su Morrison 2019 Subtotal (95% CI) Total events Heterogeneity: Not ap Test for overall effect:	1 1 plicable Z = 0.00 (P	10 10 = 1.00)	1	10 10	100.0% 100.0%	1.00 [0.07, 13.87] 1.00 [0.07, 13.87]	2019	0.01 0.1 1 10 100 Favours early fibrinogen Favours control

4. Venous thrombosis

Early fibrinogen		ogen	Control		Risk Ratio			Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	Year	M-H, Fixed, 95% Cl
2.4.1 Cardiac surgery	/							
Tanaka 2014	0	10	0	10		Not estimable	2014	
Ranucci 2015	0	58	0	58		Not estimable	2015	
Rahe-Meyer 2016	1	78	0	74	100.0%	2.85 [0.12, 68.83]	2016	
Bilecen 2017 Subtotal (95% CI)	0	60 206	0	60 202	100.0%	Not estimable 2.85 [0.12, 68.83]	2017	
Total events	1		0					
Heterogeneity: Not ap	plicable							
Test for overall effect:	Z = 0.64 (P	= 0.52)						
2.4.2 Non-cardiac su	rgery							
Morrison 2019 Subtotal (95% CI)	0	10 10	1	10 10	100.0% 100.0%	0.33 [0.02, 7.32] 0.33 [0.02, 7.32]	2019	
Total events Heterogeneity: Not ap	0 plicable		1					
Test for overall effect:	Z = 0.70 (P	= 0.49)						
								0.01 0.1 1 10 100
								Favours early fibrinogen Favours control

5. Acute Kidney Injury

Early fibrinogen			Control Risk Ratio					Risk Ratio
Study or Subgroup	b Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	Year	M-H, Fixed, 95% Cl
2.5.1 Cardiac surg	ery							
Ranucci 2015	5	58	6	58	42.4%	0.83 [0.27, 2.58]	2015	
Rahe-Meyer 2016	3	78	6	74	43.5%	0.47 [0.12, 1.83]	2016	
Bilecen 2017	3	60	2	60	14.1%	1.50 [0.26, 8.66]	2017	
Subtotal (95% CI)		196		192	100.0%	0.77 [0.36, 1.65]		
Total events	11		14					
Heterogeneity: Chi ²	= 1.07, df = 2	2 (P = 0.	59); I ² =	0%				
Test for overall effe	ct: Z = 0.67 (P	P = 0.50)						
2.5.2 Non-cardiac	surgery							
Morrison 2019	0	10	1	10	100.0%	0.33 [0.02, 7.32]	2019	
Subtotal (95% CI)		10		10	100.0%	0.33 [0.02, 7.32]		
Total events	0		1					
Heterogeneity: Not a	applicable							
Test for overall effe	ct: Z = 0.70 (P	P = 0.49						
								Favours early fibringen Favours control
								ratears carry normogen ratears control

6. Infections/sepsis

Early fibrinogen			Cont	rol		Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	Year	M-H, Fixed, 95% CI
2.6.1 Cardiac surgery	/							
Ranucci 2015	7	58	11	58	47.3%	0.64 [0.27, 1.53]	2015	
Rahe-Meyer 2016	13	78	10	74	44.1%	1.23 [0.58, 2.64]	2016	
Bilecen 2017 Subtotal (95% CI)	3	60 196	2	60 192	8.6% 100.0%	1.50 [0.26, 8.66] 0.97 [0.57, 1.67]	2017	
Total events Heterogeneity: Chi² = Test for overall effect:	23 1.51, df = 2 Z = 0.10 (P	P = 0.92 = 0.92	23 47); I ² =	0%				
2.6.2 Non-cardiac su	rgery							
Lance 2011 Subtotal (95% CI)	3	22 22	3	21 21	100.0% 100.0%	0.95 [0.22, 4.21] 0.95 [0.22, 4.21]	2011	
Total events Heterogeneity: Not ap Test for overall effect:	3 plicable Z = 0.06 (P	= 0.95)	3					
								0.2 0.5 1 2 5

7. Blood loss



8. Reoperation

	Early fibrinogen Cor			rol		Risk Ratio		Ri	sk Ratio			
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	Year		M-H, F	ixed, 95% (21	
2.8.1 Cardiac surgery												
Tanaka 2014	1	10	2	10	8.5%	0.50 [0.05, 4.67]	2014					
Ranucci 2015	0	58	2	58	10.6%	0.20 [0.01, 4.08]	2015					
Esmaeelzadeh 2016	16	40	17	40	72.3%	0.94 [0.56, 1.59]	2016		-			
Bilecen 2017	3	60	2	60	8.5%	1.50 [0.26, 8.66]	2017					
Subtotal (95% CI)		168		168	100.0%	0.87 [0.54, 1.42]				◆		
Total events	20		23									
Heterogeneity: Chi ² = 1	1.60, df = 3	(P = 0.6)	56); I ² =	0%								
Test for overall effect: 2	Z = 0.55 (P	= 0.58)										
								0 01	0 1		10	100
								0.01	V.1	÷	10	100

Favours early fibrinogen Favours control

9. ICU length of stay

Early fibrinogen			Control			Mean Difference			Mean Difference
an S	SD T	Fotal	Mean	SD	Total	Weight	IV, Fixed, 95% CI	Year	IV, Fixed, 95% CI
ery									
4 3	.7	19 19	4	3.9	10 10	100.0% 100.0%	0.00 [-2.93, 2.93] 0.00 [-2.93, 2.93]	2019	
ble 0.00 (P	- 1	00)							
Test for overall effect. $\Sigma = 0.00$ ($\Gamma = 1$.									<u> </u>
1	arly fibr an <u>s</u> ary 4 3 ble 0.00 (P	an SD an SD ary 4 3.7 ble 0.00 (P = 1	an SD Total ary 4 3.7 19 4 3.7 19 19 ble 0.00 (P = 1.00) 100	an <u>SD Total Mean</u> ary 4 3.7 19 4 19 ble 0.00 (P = 1.00)	Inly fibrinogen Contro an <u>SD Total Mean SD</u> ary 4 3.7 19 4 3.9 19 Ible 0.00 (P = 1.00)	Inty fibrinogen Control an SD Total Mean SD Total ary 4 3.7 19 4 3.9 10 19 19 10 10 10 10 ble 0.00 (P = 1.00) 100 10 10 10	Inty fibrinogen Control an SD Total Mean SD Total Weight ary 4 3.7 19 4 3.9 10 100.0% 19 10 100.0% 10 100.0% 10 100.0% ble 0.00 (P = 1.00) 10 100 10 10 10	Inty fibrinogen Control Mean Difference an SD Total Mean SD Total Weight IV, Fixed, 95% CI ary 4 3.7 19 4 3.9 10 100.0% 0.00 [-2.93, 2.93] 19 10 100.0% 0.00 [-2.93, 2.93] 10 100.0% 0.00 [-2.93, 2.93] ble 0.00 (P = 1.00) 100 100 100 100 100	Inty fibrinogen Control Mean Difference an SD Total Mean SD Total Weight IV, Fixed, 95% CI Year ary 4 3.7 19 4 3.9 10 100.0% 0.00 [-2.93, 2.93] 2019 19 10 100.0% 0.00 [-2.93, 2.93] 2019 ble 0.00 (P = 1.00)

10. Hospital length of stay



11. Proportion receiving RBCs

	Early fibrinogen Control					Risk Ratio			Risk Ratio			
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	Year		M-H,	, Fixed, 95%	i CI	
2.9.1 Cardiac surgery	/											
Tanaka 2014	9	10	9	10	14.8%	1.00 [0.75, 1.34]	2014			_ + _		
Ranucci 2015	19	58	32	58	52.5%	0.59 [0.38, 0.92]	2015			■		
Bilecen 2017	10	60	20	60	32.8%	0.50 [0.26, 0.98]	2017					
Subtotal (95% CI)		128		128	100.0%	0.62 [0.46, 0.84]				▶		
Total events	38		61									
Heterogeneity: Chi ² =	10.54, df =	2 (P = 0)).005); I ²	= 81%	6							
Test for overall effect:	Z = 3.07 (P	= 0.002	2)									
								0 05	0 2		<u>Į</u>	20
								0.05	0.2	T	2	20

Favours early fibrinogen Favours control

12. Proportion receiving plasma

	Early fibrir	nogen	Cont	rol		Risk Ratio		Risk Ratio				
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	Year		M-H, Fixed, S	95% CI		
2.10.1 Cardiac surge	ery											
Ranucci 2015	0	58	8	58	39.5%	0.06 [0.00, 1.00]	2015					
Bilecen 2017	9	60	13	60	60.5%	0.69 [0.32, 1.50]	2017		-+=+-			
Subtotal (95% CI)		118		118	100.0%	0.44 [0.22, 0.90]			-			
Total events	9		21									
Heterogeneity: Chi ² =	3.25, df = 1	(P = 0.	$(07); I^2 =$	69%								
Test for overall effect	Z = 2.25 (P	= 0.02)										
								0.002	0 1 1	10	500	

13. Proportion receiving platelets

	Early fibrii	nogen	Cont	rol		Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	Year	M-H, Fixed, 95% CI
2.11.1 Cardiac surge	ry							
Tanaka 2014	4	10	10	10	37.5%	0.43 [0.21, 0.88]	2014	
Ranucci 2015	0	58	4	58	16.1%	0.11 [0.01, 2.02]	2015	
Bilecen 2017	9	60	13	60	46.4%	0.69 [0.32, 1.50]	2017	
Subtotal (95% CI)		128		128	100.0%	0.50 [0.29, 0.86]		◆
Total events	13		27					
Heterogeneity: Chi ² =	1.89, df = 2	2 (P = 0.	39); I ² =	0%				
Test for overall effect:	Z = 2.53 (P	= 0.01))					
								Favours early fibrinogen Favours control

14. Mean RBCs transfused

	Early	fibrino	gen	c	ontrol			Mean Difference		Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	Year	IV, Random, 95% CI
2.12.1 Cardiac surge	ry									
Ranucci 2015	0	0.74	58	1	1.5	58	34.0%	-1.00 [-1.43, -0.57]	2015	
Esmaeelzadeh 2016	1.46	1.16	40	2.54	1.26	40	33.3%	-1.08 [-1.61, -0.55]	2016	_
Rahe-Meyer 2016	1	2.2	78	0	1.5	74	32.7%	1.00 [0.40, 1.60]	2016	
Subtotal (95% CI)			176			172	100.0%	-0.37 [-1.60, 0.86]		
Heterogeneity: Tau ² =	1.11; C	hi² = 34	4.01, d	f = 2 (P	< 0.0	0001);	$I^2 = 94\%$			
Test for overall effect:	Z = 0.59	9 (P = 0)).55)							
2.12.2 Non-cardiac s	urgery									_
Morrison 2019	3.5	1.5	10	5	2.2	10	100.0%	-1.50 [-3.15, 0.15]	2019	
Subtotal (95% CI)			10			10	100.0%	-1.50 [-3.15, 0.15]		
Heterogeneity: Not ap	plicable									
Test for overall effect:	Z = 1.78	8 (P = 0)).07)							
										Favours early fibrinogen Favours control

15. Mean plasma transfused

	Early	fibrino	gen	C	ontrol			Mean Difference		Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	Year	IV, Fixed, 95% CI
2.13.1 Cardiac surge	ry									
Esmaeelzadeh 2016	1.34	1.54	40	3.05	1.39	40	77.5%	-1.71 [-2.35, -1.07]	2016	
Rahe-Meyer 2016	4	4.4	78	0	3	74	22.5%	4.00 [2.81, 5.19]	2016	
Subtotal (95% CI)			118			114	100.0%	-0.42 [-0.99, 0.14]		◆
Heterogeneity: Chi ² =	68.29, d	f = 1 (P < 0.0	0001);	$ ^2 = 9$	9%				
Test for overall effect:	Z = 1.47	7 (P = 0)	0.14)							
										Favours early fibrinogen Favours control

16. Mean platelets transfused

	Early	fibrino	gen	С	ontrol			Mean Difference		Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	Year	IV, Fixed, 95% CI
2.14.1 Cardiac surger	у									
Esmaeelzadeh 2016	0.35	1.16	40	0.37	1.1	40	36.2%	-0.02 [-0.52, 0.48]	2016	
Rahe-Meyer 2016	1	1.5	78	1	0.74	74	63.8%	0.00 [-0.37, 0.37]	2016	_
Subtotal (95% CI)			118			114	100.0%	-0.01 [-0.31, 0.29]		
Heterogeneity: Chi ² = 0	0.00, df	= 1 (P)	= 0.95); $ ^2 = ($	0%					
Test for overall effect:	Z = 0.05	5 (P = 0	0.96)							
										-0.5 -0.25 0 0.25 0.5

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

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

			Certainty ass	essment			N₂ of p	atients	Effec	:t		
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	restrictive plasma transfusion strategy	liberal plasma transfusion strategy	Relative (95% Cl)	Absolute (95% CI)	Certainty	Importance
RCT Mor	tality- 30 Day											
1	randomised trials	not serious a	not serious	not serious	very serious ^b	none ^c	11/30 (36.7%)	11/30 (36.7%)	RR 1.00 (0.51 to 1.94)	0 fewer per 1,000 (from 180 fewer to 345 more)		CRITICAL

Sepsis

1	randomised trials	serious ^d	not serious	not serious	serious ^e	none ^c	4/30 (13.3%)	16/30 (53.3%)	RR 0.25 (0.09 to 0.66)	400 fewer per 1,000 (from 485 fewer to 181	IMPORTANT
										fewer)	

Duration of Hospital Stay in Days

1	randomised trials	serious ^d	not serious	not serious	serious ^e	none ^c	30	30	-	MD 4.4 higher (0.4 higher to 8.4 higher)	⊕⊕⊖O Low	IMPORTANT
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Mortality

1	observational studies	serious ^f	not serious	not serious	serious ^e	none ^c	73/455 (16.0%)	39/178 (21.9%)	RR 0.73 (0.52 to 1.04)	59 fewer per 1,000 (from 105	OCO VERY LOW	CRITICAL
										fewer to 9 more)		

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

Explanations

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

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

Forrest Plots

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

<u>RCT</u>

<u>Mortality</u>

	Restrictive P	lasma	Liberal P	lasma		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M–H, Fixed, 95% Cl	M–H, Fixed, 95% Cl
Akbari 2018	11	30	11	30	100.0%	1.00 [0.51, 1.94]	
Total (95% CI)		30		30	100.0%	1.00 [0.51, 1.94]	↓ ◆
Total events Heterogeneity: Not ap Test for overall effect:	11 plicable Z = 0.00 (P =	1.00)	11				0.01 0.1 1 10 100 Favours Restrictive Favours Liberal

Multiorgan Failure

	Restrictive P	lasma	Liberal P	lasma		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M–H, Fixed, 95% Cl	M–H, Fixed, 95% Cl
Akbari 2018	7	30	8	30	100.0%	0.88 [0.36, 2.11]	
Total (95% CI)		30		30	100.0%	0.88 [0.36, 2.11]	
Total events	7		8				
Heterogeneity: Not ap Test for overall effect:	plicable Z = 0.30 (P =	0.77)					0.01 0.1 1 10 100 Favours Restrictive Favours Liberal

<u>Sepsis</u>

	Restrictive P	lasma	Liberal P	lasma		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M–H, Fixed, 95% Cl	M–H, Fixed, 95% Cl
Akbari 2018	4	30	16	30	100.0%	0.25 [0.09, 0.66]	
Total (95% CI)		30		30	100.0%	0.25 [0.09, 0.66]	
Total events	4		16				
Heterogeneity: Not ap Test for overall effect:	oplicable : Z = 2.80 (P =	0.005)					0.01 0.1 1 10 100 Favours Restrictive Favours Liberal

Duration of Hospital Stay (Days)

	Restrict	Liberal Plasma				Mean Difference	Mean Difference		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% Cl
Akbari 2018	14.8	7.6	30	10.4	8.2	30	100.0%	4.40 [0.40, 8.40]	
Total (95% CI) Heterogeneity: Not app Test for overall effect:	olicable Z = 2.16	(P = 0.	30 .03)			30	100.0%	4.40 [0.40, 8.40]	← -100 -50 0 50 100 Favours Restrictive Favours Liberal

Observational Study- Neuro

<u>Mortality</u>

	Restrictive Plasma					Risk Ratio	Risk Ratio				
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M–H, Fixed, 95% Cl				
Chang 2014	73	455	39	178	100.0%	0.73 [0.52, 1.04]					
Total (95% CI)		455		178	100.0%	0.73 [0.52, 1.04]	◆				
Total events	73		39								
Heterogeneity: Not applicable											
Test for overall effect:	Z = 1.76 (P =	0.08)					Favours Restrictive Plasm Favours Liberal Plasma				

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

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

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

Table 1: Trauma

		Certai	inty assessment			Nº of p	atients		Effect		
№ of studies	Risk of bias	Inconsistency	Indirectness	Imprecision Other considerations		TXA	No TXA	Relative (95% Cl)	Absolute (95% Cl)	Certainty	Importance
Mortality -	Trauma										
1 RCT	not serious	not serious	not serious	not serious	none	1463/10060 (14.5%)	1613/10067 (16.0%)	RR 0.91 (0.85 to 0.97)	14 fewer per 1,000 (from 24 fewer to 5 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
Stroke - T	rauma			•		•					
1 RCT	not serious	not serious	not serious	not serious	none	57/10060 (0.6%)	66/10067 (0.7%)	RR 0.86 (0.61 to 1.23)	1 fewer per 1,000 (from 3 fewer to 2 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Myocardia	al infarction - Tra	uma	-	-	-	-	•			-	
1 RCT	not serious	not serious	not serious	not serious	none	35/10060 (0.3%)	55/10067 (0.5%)	RR 0.64 (0.42 to 0.97)	2 fewer per 1,000 (from 3 fewer to 0 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
Deep venous thrombosis - Trauma											
1 RCT	not serious	not serious	not serious	not serious	none	40/10060 (0.4%)	41/10067 (0.4%)	RR 0.98 (0.63 to 1.51)	0 fewer per 1,000 (from 2 fewer to 2 more)	⊕⊕⊕⊕ HIGH	IMPORTANT
Pulmonar	y embolism - Tra	uma			•					•	
1 RCT	not serious	not serious	not serious	not serious	none	72/10060 (0.7%)	71/10067 (0.7%)	RR 1.01 (0.73 to 1.41)	0 fewer per 1,000 (from 2 fewer to 3 more)	⊕⊕⊕⊕ HIGH	IMPORTANT
Surgical in	ntervention - Trai	uma					-				
1 RCT	not serious	not serious	not serious	not serious	none	4814/10060 (47.9%)	4836/10067 (48.0%)	RR 1.00 (0.97 to 1.03)	0 fewer per 1,000 (from 14 fewer to 14 more)	⊕⊕⊕⊕ HIGH	IMPORTANT
RBC trans	fusion - Trauma		-								
1 RCT	not serious	not serious	not serious	not serious	none	5067/10060 (50.4%)	5160/10067 (51.3%)	RR 0.98 (0.96 to 1.01)	10 fewer per 1,000 (from 21 fewer to 5 more)	⊕⊕⊕⊕ HIGH	IMPORTANT
RBCs tran	nsfused - Trauma	-		-		-	-			-	
1 RCT	not serious	not serious	not serious	not serious	none	10060	10067	-	MD 0.17 lower (0.39 lower to 0.05 higher)	⊕⊕⊕⊕ HIGH	IMPORTANT

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

Table 2: Traumatic brain injury

		Certai	inty assessmen	t		Nº of p	atients		Effect			
Nº of studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ТХА	No TXA	Relative (95% Cl)	Absolute (95% Cl)	Certainty	Importance	
Mortality - Traumatic brain injury												
6 RCTs	not serious	not serious	not serious	serious ^a	none	1074/5382 (20.0%)	1109/5239 (21.2%)	RR 0.88 (0.72 to 1.06)	25 fewer per 1,000 (from 59 fewer to 13 more)	⊕⊕⊕⊖ MODERATE	CRITICAL	
Poor functional outcome - Traumatic brain injury												
5 RCTs	not serious	not serious	not serious	serious ^a	none	214/769 (27.8%)	225/725 (31.0%)	RR 0.89 (0.76 to 1.04)	34 fewer per 1,000 (from 74 fewer to 12 more)	⊕⊕⊕⊖ MODERATE	CRITICAL	
Stroke - T	Fraumatic b	rain injury										
3 RCTs	not serious	not serious	not serious	not serious	none	46/6612 (0.7%)	43/6537 (0.7%)	RR 1.06 (0.70 to 1.60)	0 fewer per 1,000 (from 2 fewer to 4 more)		CRITICAL	
Myocard	al infarctio	n - Traumatic bra	in injury				_					
3 RCTs	not serious	not serious	not serious	not serious	none	19/6612 (0.3%)	23/6537 (0.4%)	RR 0.83 (0.46 to 1.49)	1 fewer per 1,000 (from 2 fewer to 2 more)	⊕⊕⊕⊕ HIGH	CRITICAL	
Renal fai	lure - Traun	natic brain injury	4	4	•	•			5	•		
1 RCT	not serious	not serious	not serious	not serious	none	100/6359 (1.6%)	84/6280 (1.3%)	RR 1.18 (0.88 to 1.57)	2 more per 1,000 (from 2 fewer to 8 more)	⊕⊕⊕⊕ HIGH	CRITICAL	
Sepsis -	Traumatic b	rain injury										
1 RCT	not serious	not serious	not serious	not serious	none	411/6359 (6.5%)	412/6280 (6.6%)	RR 0.99 (0.86 to 1.12)	1 fewer per 1,000 (from 9 fewer to 8 more)	⊕⊕⊕⊕ HIGH	CRITICAL	
Deep ver	ious throm	oosis - Traumatic	brain injury									
4 RCTs	not serious	not serious	not serious	not serious	none	22/6708 (0.3%)	22/6621 (0.3%)	RR 0.98 (0.55 to 1.74)	0 fewer per 1,000 (from 1 fewer to 2 more)	⊕⊕⊕⊕ HIGH	CRITICAL	
Pulmona	ry embolisr	n - Traumatic bra	in injury									

4 RCTs	not serious	not serious	not serious	not serious	none	35/6708 (0.5%)	34/6621 (0.5%)	RR 0.99 (0.62 to 1.59)	0 fewer per 1,000 (from 2 fewer to 3 more)	⊕⊕⊕⊕ HIGH	CRITICAL		
Surgical	Surgical intervention - Traumatic brain injury												
4 RCTs	not serious	not serious	not serious	serious ^a	none	31/327 (9.5%)	33/332 (9.9%)	RR 0.96 (0.61 to 1.51)	4 fewer per 1,000 (from 39 fewer to 51 more)	⊕⊕⊕⊖ MODERATE	IMPORTAN T		
Progress	Progressive intracranial hemorrhage - Traumatic brain injury												
3 RCTs	not serious	not serious	not serious	not serious	none	80/311 (25.7%)	105/316 (33.2%)	RR 0.78 (0.61 to 0.99)	73 fewer per 1,000 (from 130 fewer to 3 fewer)	⊕⊕⊕⊕ HIGH	IMPORTAN T		
Seizure -	Traumatic I	brain injury	!		•				1	!	•		
2 RCTs	not serious	not serious	not serious	not serious	none	213/6705 (3.2%)	189/6589 (2.9%)	RR 1.11 (0.92 to 1.35)	3 more per 1,000 (from 2 fewer to 10 more)	⊕⊕⊕⊕ HIGH	IMPORTAN T		
RBC tran	sfusion - Tr	aumatic brain inj	jury										
2 RCTs	not serious	not serious	not serious	serious ^a	none	72/253 (28.5%)	85/257 (33.1%)	RR 0.86 (0.66 to 1.12)	46 fewer per 1,000 (from 112 fewer to 40 more)	⊕⊕⊕⊖ MODERATE	IMPORTAN T		
ICU lengt	th of stay - 1	Fraumatic brain i	njury										
2 RCTs	not serious	not serious	not serious	serious ^b	none	170	159	-	MD 2.85 higher (0.07 lower to 5.76 higher)	⊕⊕⊕⊖ MODERATE	IMPORTAN T		
Hospital	length of st	ay - Traumatic br	ain injury										
2 RCTs	not serious	not serious	not serious	serious ^a	none	170	159	-	MD 0.3 lower (3.39 lower to 2.79 higher)		IMPORTAN T		

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

Explanations

a. Significant imprecision which does not exclude clinically meaningful benefit or harm.b. Borderline statistically significant result, but small sample size resulting in serious imprecision.

1. Mortality

	TXA Control					Risk Ratio		Risk Ratio				
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	Year		M–H, Random, 95% Cl			
1.1.1 Trauma												
Crash-2 2010	1463	10060	1613	10067	100.0%	0.91 [0.85, 0.97]	2010					
Subtotal (95% CI)		10060		10067	100.0%	0.91 [0.85, 0.97]			•			
Total events	1463		1613									
Heterogeneity: Not applie	cable											
Test for overall effect: Z	= 2.92 (P	= 0.004	4)									
1.1.2 Traumatic brain ir	njury											
Crash-2 2010	14	133	24	137	6.5%	0.60 [0.33, 1.11]	2010					
Yutthakasemsunt 2013	12	120	18	120	5.3%	0.67 [0.34, 1.32]	2013					
Fakharian 2017	2	74	3	75	0.8%	0.68 [0.12, 3.93]	2017					
Crash-3 2019	977	4613	992	4514	78.2%	0.96 [0.89, 1.04]	2019					
Chakroun-Walha 2019	27	96	19	84	9.2%	1.24 [0.75, 2.07]	2019					
Subtotal (95% CI)		5036		4930	100.0%	0.94 [0.80, 1.10]			+			
Total events	1032		1056									
Heterogeneity: Tau ² = 0.	01; Chi ²	= 4.48, 6	df = 4 (P	= 0.35)	; I ² = 11%	6						
Test for overall effect: Z	= 0.81 (P	= 0.42)										
								0.1	0.2 0.5 1 2 5 10			
									Favours TXA Favours control			

2. Poor functional outcome

	TX/	4	Cont	rol		Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	Year	M-H, Fixed, 95% Cl
1.10.2 Traumatic brain	injury							
Crash-2 2010	40	133	53	137	51.9%	0.78 [0.56, 1.09]	2010	
Yutthakasemsunt 2013	21	120	28	120	27.8%	0.75 [0.45, 1.24]	2013	
Fakharian 2017	8	74	13	75	12.8%	0.62 [0.27, 1.42]	2017	
Chakroun-Walha 2019 Subtotal (95% CI)	10	96 423	7	84 416	7.4% 100.0%	1.25 [0.50, 3.14] 0.79 [0.61, 1.01]	2019	•
Total events Heterogeneity: Chi ² = 1.	79 32, df = 3	B (P = 0	101).72); l ² =	= 0%				
Test for overall effect: Z	= 1.86 (P	= 0.06	5)					
								0.5 0.7 1 1.5 2

Favours TXA Favours control

3. Stroke

	тх	A	Cont	rol		Risk Ratio		Risk Ratio				
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	Year		M–H, Fixe	ed, 95% CI		
1.3.1 Trauma												
Crash-2 2010	57	10060	66	10067	100.0%	0.86 [0.61, 1.23]	2010		-	ŀ		
Subtotal (95% CI)		10060		10067	100.0%	0.86 [0.61, 1.23]			₹	F		
Total events	57		66									
Heterogeneity: Not applic	able											
Test for overall effect: Z =	= 0.81 (P	= 0.42)										
1.3.2 Traumatic brain in	jury											
Crash-2 2010	0	133	1	137	3.4%	0.34 [0.01, 8.35]	2010			<u> </u>		
Yutthakasemsunt 2013	0	120	0	120		Not estimable	2013		_	L		
Crash-3 2019	46	6359	42	6280	96.6%	1.08 [0.71, 1.64]	2019		-	-		
Subtotal (95% CI)		6612		6537	100.0%	1.06 [0.70, 1.60]			•	•		
Total events	46		43									
Heterogeneity: Chi ² = 0.4	9, df = 1	1 (P = 0.	48); I ² =	0%								
Test for overall effect: Z =	= 0.26 (P	= 0.79										
								0.02	0 1	1 10	50	
								0.02	Favours TXA	Favours control	30	
									rutours IAA	ratours contro	<i>i</i>	

4. Myocardial infarction

	ТХА					Risk Ratio		Risk Ratio				
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	Year		M-H, Fixed, 95% Cl			
1.4.1 Trauma												
Crash-2 2010	35	10060	55	10067	100.0%	0.64 [0.42, 0.97]	2010					
Subtotal (95% CI)		10060		10067	100.0%	0.64 [0.42, 0.97]			•			
Total events	35		55									
Heterogeneity: Not applie	cable											
Test for overall effect: Z	= 2.09 (P	= 0.04)										
1.4.2 Traumatic brain ir	njury											
Crash-2 2010	1	133	0	137	2.0%	3.09 [0.13, 75.17]	2010					
Yutthakasemsunt 2013	0	120	3	120	14.5%	0.14 [0.01, 2.74]	2013	_				
Crash-3 2019	18	6359	20	6280	83.4%	0.89 [0.47, 1.68]	2019					
Subtotal (95% CI)		6612		6537	100.0%	0.83 [0.46, 1.49]			•			
Total events	19		23									
Heterogeneity: Chi ² = 2.0	06, df = 2	P = 0.	36); I ² =	3%								
Test for overall effect: Z	= 0.63 (P	= 0.53)										
								0.002	0 1 1 10	500		
								0.002	Favours TXA Favours control	500		
5. Deep venous thrombosis

	тх	A	Cont	rol		Risk Ratio			Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	Year		M-H, Fixed, 95%	CI
1.5.1 Trauma										
Crash-2 2010	40	10060	41	10067	100.0%	0.98 [0.63, 1.51]	2010			
Subtotal (95% CI)		10060		10067	100.0%	0.98 [0.63, 1.51]			•	
Total events	40		41							
Heterogeneity: Not applie	cable									
Test for overall effect: Z	= 0.11 (P	= 0.91)								
1.5.2 Traumatic brain ir	njury									
Crash-2 2010	0	133	2	137	10.6%	0.21 [0.01, 4.25]	2010			
Yutthakasemsunt 2013	0	120	1	120	6.4%	0.33 [0.01, 8.10]	2013			
Crash-3 2019	19	6359	16	6280	69.2%	1.17 [0.60, 2.28]	2019			
Chakroun-Walha 2019	3	96	3	84	13.8%	0.88 [0.18, 4.22]	2019			
Subtotal (95% CI)		6708		6621	100.0%	0.98 [0.55, 1.74]			-	
Total events	22		22							
Heterogeneity: $Chi^2 = 1.2$	76, df = 3	B (P = 0.	62); I ² =	0%						
Test for overall effect: Z	= 0.09 (P	= 0.93)								
								0 01	0 1 1	10 100
								0.01	Favours TXA Favour	rs control

6. Pulmonary embolism

	тх	A	Cont	rol		Risk Ratio			Risk	Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	Year		M-H, Fix	ed, 95% CI		
1.6.1 Trauma												
Crash-2 2010	72	10060	71	10067	100.0%	1.01 [0.73, 1.41]	2010		-	-		
Subtotal (95% CI)		10060		10067	100.0%	1.01 [0.73, 1.41]				•		
Total events	72		71									
Heterogeneity: Not appli	cable											
Test for overall effect: Z	= 0.09 (P	= 0.93)										
1.6.2 Traumatic brain in	njury											
Crash-2 2010	0	133	0	137		Not estimable	2010					
Yutthakasemsunt 2013	0	120	0	120		Not estimable	2013					
Chakroun-Walha 2019	11	96	2	84	6.2%	4.81 [1.10, 21.10]	2019					
Crash-3 2019	24	6359	32	6280	93.8%	0.74 [0.44, 1.26]	2019			+-		
Subtotal (95% CI)		6708		6621	100.0%	0.99 [0.62, 1.59]				\blacktriangleright		
Total events	35		34									
Heterogeneity: Chi ² = 5.5	57, df = 1	(P = 0.	02); I ² =	82%								
Test for overall effect: Z	= 0.03 (P	= 0.98)										
								0.05	0.2	1	£	20
								0.05	Favours TXA	Favours co	ntrol	20

7. Progressive intracranial hemorrhage

	TX/	4	Cont	rol		Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	Year	M-H, Fixed, 95% CI
1.7.2 Traumatic brain ir	njury							
Crash-2 2010	44	123	56	126	53.2%	0.80 [0.59, 1.09]	2010	
Yutthakasemsunt 2013	21	114	32	115	30.6%	0.66 [0.41, 1.08]	2013	
Fakharian 2017	15	74	17	75	16.2%	0.89 [0.48, 1.66]	2017	
Subtotal (95% CI)		311		316	100.0%	0.78 [0.61, 0.99]		
Total events	80		105					
Heterogeneity: Chi ² = 0.6	57, df = 2	2 (P = 0)).72); I ² =	= 0%				
Test for overall effect: Z =	= 2.07 (P	= 0.04	4)					
								05 07 1 15 2
								Favours TXA Favours control

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



9. Sepsis/infection



10. Seizure

	TX/	A	Cont	rol		Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	Year	M–H, Fixed, 95% Cl
1.10.1 Traumatic bra	in injury	,						
Crash-3 2019 Subtotal (95% CI)	206	6359 6359	186	6280 6280	100.0% 100.0%	1.09 [0.90, 1.33] 1.09 [0.90, 1.33]	2019	
Total events Heterogeneity: Not ap Test for overall effect:	206 plicable Z = 0.90	0 (P = 0	186).37)					

11. Renal failure



Page 8 of 10

0.85

1.1 1.2

Favours TXA Favours control

11. RBC Transfusion

	тх	A	Cont	rol		Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	Year	M-H, Fixed, 95% CI
1.12.1 Trauma								
Crash-2 2010 Subtotal (95% CI)	5067	10060 10060	5160	10067 10067	100.0% 100.0%	0.98 [0.96, 1.01] 0.98 [0.96, 1.01]	2010	•
Total events Heterogeneity: Not applic	5067 able		5160					
Test for overall effect: Z =	= 1.26 (P	= 0.21)						
1.12.2 Traumatic brain i	injury							
Crash-2 2010	41	133	51	137	59.6%	0.83 [0.59, 1.16]	2010	
Yutthakasemsunt 2013 Subtotal (95% CI)	31	120 253	34	120 257	40.4% 100.0%	0.91 [0.60, 1.38] 0.86 [0.66, 1.12]	2013	
Total events	72		85					
Heterogeneity: Chi" = 0.1	13, at = 1	(P = 0)	72); I* =	0%				
lest for overall effect: Z =	= 1.12 (P	= 0.26)						
								0.7 0.85 1 1.2 1.5 Favours TXA Favours control

12. RBCs transfused

		TXA		0	Contro	I		Mean Difference		Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	Year	IV, Fixed, 95% CI
1.13.1 Trauma										
Crash-2 2010 Subtotal (95% CI)	3.05	7.7	10060 10060	3.22	8.02	10067 10067	100.0% 100.0%	-0.17 [-0.39, 0.05] -0.17 [-0.39, 0.05]	2010	
Heterogeneity: Not ap Test for overall effect:	plicable Z = 1.5	53 (P	= 0.13)							
										-0.5 -0.25 0 0.25 0.5 Favours TXA Favours control

13. ICU length of stay

		ТХА		С	ontrol			Mean Difference			Mean Dif	fference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	Year		IV, Fixed,	, 95% CI	
1.14.1 Traumatic brain	injury												
Fakharian 2017	11.9	13.7	74	10.2	9.9	75	57.5%	1.70 [-2.14, 5.54]	2017				
Chakroun-Walha 2019	16.9	16.8	96	12.5	13.8	84	42.5%	4.40 [-0.07, 8.87]	2019		ł		—
Subtotal (95% CI)			170			159	100.0%	2.85 [-0.07, 5.76]					
Heterogeneity: Chi ² = 0.	81, df =	: 1 (P =	= 0.37)	$; I^2 = 0$	%								
Test for overall effect: Z	= 1.91	(P = 0)	.06)										
										10		Į į	10
										-10	Favours TXA	Favours control	10

14. Hospital length of stay

		ТХА		С	ontrol			Mean Difference		Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	Year	IV, Fixed, 95% CI
1.15.1 Traumatic brain	injury									
Fakharian 2017	13.5	14.3	74	14.5	11.2	75	56.1%	-1.00 [-5.13, 3.13]	2017	_
Chakroun-Walha 2019	15	15.5	96	14.4	16.3	84	43.9%	0.60 [-4.07, 5.27]	2019	_
Subtotal (95% CI)			170			159	100.0%	-0.30 [-3.39, 2.79]		
Heterogeneity: Chi ² = 0.	25, df =	= 1 (P =	= 0.61)	$ I^2 = 0$	%					
Test for overall effect: Z	= 0.19	(P = 0)	.85)							

-4 -2 0 2 4 Favours TXA Favours control Evidence Summary 11: Tranexamic acid in critically ill patients with subarachnoid hemorrhage, non-traumatic intracranial hemorrhage, postpartum hemorrhage, and post-cardiac surgery

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

Table 1: Cardiac surgery

		Certa	inty assessmen	t		№ of p	atients		Effect		
№ of studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TXA	no TXA	Relative (95% Cl)	Absolute (95% Cl)	Certainty	Importance
Mortality	- Cardiac	surgery									
36 RCTs	not serious	not serious	not serious	not serious	none	40/4419 (0.9%)	53/4354 (1.2%)	RR 0.75 (0.50 to 1.13)	3 fewer per 1,000 (from 6 fewer to 2 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Post-ope	rative blee	ding - Cardiac su	rgery								
56 RCTs	not serious	not serious ^a	not serious	not serious	none	5273	5015	-	MD 268.52 lower (314.99 lower to 222.04 lower)	⊕⊕⊕ HIGH	IMPORTANT
Surgical	interventic	on - Cardiac surge	ery								
25 RCTs	not serious	not serious	not serious	not serious	none	69/3797 (1.8%)	140/3778 (3.7%)	RR 0.53 (0.40 to 0.71)	17 fewer per 1,000 (from 22 fewer to 11 fewer)	⊕⊕⊕⊕ HIGH	IMPORTANT
Seizure -	Cardiac si	urgery	-	•	•						
7 RCTs	not serious	not serious	not serious	not serious	none	20/2794 (0.7%)	4/2821 (0.1%)	RR 4.11 (1.44 to 11.72)	4 more per 1,000 (from 1 more to 15 more)	⊕⊕⊕⊕ HIGH	IMPORTANT
RBC tran	sfusion - C	Cardiac surgery									
25 RCTs	not serious	not serious	not serious	not serious	none	1272/3755 (33.9%)	1843/373 8 (49.3%)	RR 0.67 (0.60 to 0.74)	163 fewer per 1,000 (from 197 fewer to 128 fewer)	⊕⊕⊕⊕ HIGH	IMPORTANT

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

Explanations

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

Table 2: Obstetric bleeding

		Certa	inty assessmer	t		Nº of pa	atients		Effect		
№ of studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TXA	no TXA	Relative (95% Cl)	Absolute (95% Cl)	Certainty	Importance
Mortality	- Obstetrio	c bleeding									
2 RCTs	not serious	not serious	not serious	not serious ^a	none	227/10108 (2.2%)	256/1005 7 (2.5%)	RR 0.88 (0.74 to 1.05)	3 fewer per 1,000 (from 7 fewer to 1 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Stroke - 0	Obstetric b	leeding									
2 RCTs	not serious	not serious	not serious	not serious	none	8/10104 (0.1%)	6/10057 (0.1%)	RR 1.33 (0.46 to 3.82)	0 fewer per 1,000 (from 0 fewer to 2 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Myocardi	al infarctio	on - Obstetric ble	eding								
2 RCTs	not serious	not serious	not serious	not serious	none	2/10104 (0.0%)	3/10057 (0.0%)	RR 0.66 (0.11 to 3.97)	0 fewer per 1,000 (from 0 fewer to 1 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Deep ven	ous throm	bosis - Obstetric	bleeding								
2 RCTs	not serious	not serious	not serious	not serious	none	3/10104 (0.0%)	7/10057 (0.1%)	RR 0.43 (0.11 to 1.65)	0 fewer per 1,000 (from 1 fewer to 0 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
Pulmona	ry embolis	m - Obstetric ble	eding								
2 RCTs	not serious	not serious	not serious	not serious	none	17/10104 (0.2%)	20/10057 (0.2%)	RR 0.85 (0.44 to 1.61)	0 fewer per 1,000 (from 1 fewer to 1 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Sepsis -	Obstetric k	bleeding									
1 RCT	not serious	not serious	not serious	not serious	none	180/10032 (1.8%)	185/9985 (1.9%)	RR 0.97 (0.79 to 1.19)	1 fewer per 1,000 (from 4 fewer to 4 more)	⊕⊕⊕⊕ HIGH	IMPORTANT
Renal fai	lure - Obst	etric bleeding									
1 RCT	not serious	not serious	not serious	not serious	none	129/10032 (1.3%)	118/9985 (1.2%)	RR 1.09 (0.85 to 1.39)	1 more per 1,000 (from 2 fewer to 5 more)	⊕⊕⊕⊕ HIGH	IMPORTANT
Seizure -	Obstetric	bleeding									
1 RCT	not serious	not serious	not serious	not serious	none	33/10032 (0.3%)	43/9985 (0.4%)	RR 0.76 (0.49 to 1.20)	1 fewer per 1,000 (from 2 fewer to 1 more)	⊕⊕⊕⊕ HIGH	IMPORTANT

Surgical	interventic	on - Obstetric ble	eding (hysterect	tomy)							
2 RCTs	not serious	not serious	not serious	serious ^b	none	358/10104 (3.5%)	353/1005 7 (3.5%)	RR 0.93 (0.46 to 1.89)	2 fewer per 1,000 (from 19 fewer to 31 more)	⊕⊕⊕⊖ MODERATE	IMPORTANT
RBC tran	sfusion - C	Obstetric bleeding	g								
2 RCTs	not serious	not serious	not serious	not serious	none	5471/1010 8 (54.1%)	5439/100 57 (54.1%)	RR 1.00 (0.98 to 1.03)	0 fewer per 1,000 (from 11 fewer to 16 more)		IMPORTANT

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

Explanations

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

Table 3: Subarachnoid hemorrhage

		Certair	nty assessment			Nº of p	atients	1	Effect		
Nº of studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TXA	no TXA	Relative (95% Cl)	Absolute (95% Cl)	Certainty	Importance
Mortality	- Subarachnoic	l hemorrhage									
10 RCTs	not serious	not serious	not serious	serious ^a	none	368/1400 (26.3%)	366/1393 (26.3%)	RR 1.01 (0.88 to 1.16)	3 more per 1,000 (from 32 fewer to 42 more)	⊕⊕⊕⊖ MODERATE	CRITICAL
Poor fund	ctional outcome	e - Subarachnoid	hemorrhage								
5 RCTs	serious ^b	not serious	not serious	serious ^a	none	508/1254 (40.5%)	486/1247 (39.0%)	RR 1.05 (0.95 to 1.15)	19 more per 1,000 (from 19 fewer to 58 more)		CRITICAL
Rebleedi	ng - Subarachn	oid hemorrhage									
10 RCTs	not serious	not serious ^c	not serious	serious ^d	none	157/1400 (11.2%)	273/1393 (19.6%)	RR 0.60 (0.44 to 0.80)	78 fewer per 1,000 (from 110 fewer to 39 fewer)	⊕⊕⊕⊖ MODERATE	IMPORTANT
Stroke - S	Subarachnoid h	emorrhage									
7 RCTs	serious ^b	not serious ^c	not serious	serious ^d	none	324/1307 (24.8%)	273/1299 (21.0%)	RR 1.29 (1.01 to 1.67)	61 more per 1,000 (from 2 more to 141 more)		CRITICAL

CI: Confidence interval; RR: Risk ratio

Explanations

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

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

c. Unclear in several studies whether blinded outcome assessment, leading to an uncertain risk of detection bias.

d. Though moderate statistical heterogeneity, it is of questionable clinical significance as almost all trials have similar point estimates with the majority of the 95% CI on the same side of the line of effect.

Table 4: Non-traumatic ICH

		Certa	inty assessmer	ıt		Nº of ∣	patients		Effect		
№ of studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ТХА	no TXA	Relative (95% Cl)	Absolute (95% Cl)	Certainty	Importance
Mortality	- Non-trau	imatic ICH									
3 RCTs	not serious	not serious	not serious	serious ^a	none	266/1227 (21.7%)	259/1222 (21.2%)	RR 1.02 (0.88 to 1.19)	4 more per 1,000 (from 25 fewer to 40 more)	⊕⊕⊕⊖ MODERATE	CRITICAL
Poor functional outcome - Non-traumatic ICH											
2 RCTs	not serious	not serious	not serious	serious ^a	none	836/1211 (69.0%)	853/1214 (70.3%)	RR 0.98 (0.93 to 1.04)	14 fewer per 1,000 (from 49 fewer to 28 more)	⊕⊕⊕⊖ MODERATE	CRITICAL
Stroke - N	Non-traum	atic ICH									
2 RCTs	not serious	not serious	not serious	serious ^a	none	17/1211 (1.4%)	12/1214 (1.0%)	RR 1.42 (0.68 to 2.96)	4 more per 1,000 (from 3 fewer to 19 more)	⊕⊕⊕⊖ MODERATE	CRITICAL
Myocardi	al infarction	on - Non-traumati	c ICH	1	1						
2 RCTs	not serious	not serious	not serious	serious ^a	none	11/1211 (0.9%)	6/1214 (0.5%)	RR 1.84 (0.68 to 4.95)	4 more per 1,000 (from 2 fewer to 20 more)	⊕⊕⊕⊖ MODERATE	CRITICAL
Deep ven	ous throm	nbosis - Non-trau	matic ICH								
1 RCT	not serious	not serious	not serious	serious ^a	none	19/1161 (1.6%)	14/1164 (1.2%)	RR 1.36 (0.69 to 2.70)	4 more per 1,000 (from 4 fewer to 20 more)	⊕⊕⊕⊖ MODERATE	CRITICAL
Pulmona	ry embolis	m - Non-traumati	c ICH								
2 RCTs	not serious	not serious	not serious	serious ^a	none	20/1211 (1.7%)	24/1214 (2.0%)	RR 0.84 (0.47 to 1.50)	3 fewer per 1,000 (from 10 fewer to 10 more)	⊕⊕⊕⊖ MODERATE	CRITICAL
Venous t	hrombosis	s - Non-traumatic	ІСН								
2	not serious	not serious	not serious	serious ^a	none	40/1177 (3.4%)	37/1172 (3.2%)	RR 1.07 (0.69 to 1.65)	2 more per 1,000 (from 10 fewer to 21 more)	⊕⊕⊕⊖ MODERATE	CRITICAL

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

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

Explanations

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

1a. Mortality - cardiac surgery

	TX/	4	Place	bo		Risk Ratio		Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI	Year	r IV, Random, 95% CI	
2.1.1 Cardiac surgery									
Blauhut 1994	0	16	0	14		Not estimable	1994	4	
Corbeau 1995	1	41	0	14	1.7%	1.07 [0.05, 24.90]	1995	5	
Shore-Lesserson 1996	0	17	0	13		Not estimable	1996	5	
Katsaros 1996	0	104	2	106	1.8%	0.20 [0.01, 4.19]	1996	5	
Brown 1997	1	60	0	30	1.7%	1.52 [0.06, 36,34]	1997	7	
Drvden 1997	1	22	4	19	3.8%	0.22 [0.03, 1.77]	1997	7	
Katoh 1997	1	62	0	31	1.7%	1.52 [0.06, 36,36]	1997	7	
Hardy 1998	0	43	0	45		Not estimable	1998	3	
Nutall 2000	0	45	0	43		Not estimable	2000)	
Armellin 2001	0	143	0	140		Not estimable	2001	1	
Kojima 2001	0	11	0	11		Not estimable	2001	1	
Casati 2001	õ	20	õ	20		Not estimable	2001	1	
Zabeeda 2002	õ	25	õ	25		Not estimable	2002		
lares 2003	õ	22	õ	25		Not estimable	2003	3	
Casati 2004	1	52	2	50	3.0%	0.48 [0.04, 5,14]	2004	· · · · · · · · · · · · · · · · · · ·	
Andreasen 2004	0	21	0	23	5.070	Not estimable	2004	4	
Diprose 2005	õ	62	1	61	1.6%	0.33 [0.01, 7.90]	2005	<u> </u>	
Karski 2005	š	147	1	165	3.3%	3.37 [0.35, 32.02]	2005	<u> </u>	
Kuitunen 2005	õ	20	0	20	3.3/0	Not estimable	2005	5	
Vanek 2005	õ	32	õ	30		Not estimable	2005	5	
Wei 2006	õ	36	ő	40		Not estimable	2006	5	
Murphy 2006	õ	50	õ	50		Not estimable	2006	5	
Santos 2006	õ	29	2	31	1.9%	0.21 [0.01, 4.26]	2006		
Maddali 2007	õ	111	0	111	2.5/0	Not estimable	2007	7	
limenez 2007	õ	24	õ	26		Not estimable	2007	7	
Mehr-Aein 2007	õ	33	ő	33		Not estimable	2007	7	
Later 2009	1	99	1	103	2.2%	1.04 [0.07, 16,41]	2009	a	
Hashemi 2011	Ô	50	0	50	2.270	Not estimable	2011		
Wang 2012	ő	116	õ	115		Not estimable	2012		
Shi jia-3 JAMA 2013	2	285	3	285	5 3%	0 67 [0 11 3 96]	2013		
Shi jia-2 ATS 2013	0	58	1	59	1.6%	0.34 [0.01 8 15]	2013		
Esfandiari 2013	2	75	2	75	4 5%	1 00 [0 14 6 91]	2013		
Shi ila =1 CIS 2013	1	55	1	55	2.2%	1 00 [0 06 15 59]	2013		
Myles 2017	26	2310	33	2320	63.9%	0 79 [0 47 1 32]	2017	ź	
Altun 2017	20	18	0	10	03.570	Not estimable	2017		
Wang 2017	0	105	0	106		Not estimable	2017	,	
Subtotal (95% CI)	0	4419	0	4354	100.0%	0.75 [0.50. 1.13]	2017	· •	
Total events	40		53		_00.070			•	
Heterogeneity: $T_{2}\mu^{2} = 0$	00. Chi ² –	5 75 /	f = 14 (P	- 0 97	$1^{2} = 0^{4}$				
Test for overall effect: 7	= 1 38 (P	= 0.17	– 14 (r	- 0.97	,, i = 0∞				
resciol overall effect. Z	- 1.30 (F	- 0.17)							
								0.01 0.1 1 10	10
								Favours TXA Favours placebo	

1b. Mortality - obstetrical bleeding



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

2.1.4 Subarachnoid hen	norrhage										
van Rossum 1977	15	26	11	25	6.0%	1.31 [0.76, 2.28] 1977	,				
Chandra 1978	1	20	5	19	0.5%	0.19 [0.02, 1.48] 1978	; —				
Maurice 1978	5	38	13	41	2.2%	0.41 [0.16, 1.05] 1978	3				
Kaste 1979	4	32	4	32	1.1%	1.00 [0.27, 3.66] 1979)				
Fodstad 1981	11	30	9	29	3.6%	1.18 [0.58, 2.42] 1981					
Vermeulen 1984	82	241	89	238	24.2%	0.91 [0.72, 1.16] 1984	ŀ				
Tsementzis 1990	19	50	14	50	5.7%	1.36 [0.77, 2.40] 1990)		—		
Roos 2000	76	229	75	233	21.4%	1.03 [0.79, 1.34] 2000)		_ + _		
Hillman 2002	27	254	32	251	7.7%	0.83 [0.52, 1.35] 2002					
Post 2020	128	480	114	475	27.7%	1.11 [0.89, 1.38] 2020)				
Subtotal (95% CI)		1400		1393	100.0%	1.01 [0.88, 1.16]			•		
Total events	368		366								
Heterogeneity: $Tau^2 = 0$.	01; Chi ² =	10.21, d	df = 9 (P	= 0.33); $I^2 = 12\%$	6					
Test for overall effect: Z	= 0.16 (P =	= 0.87)									
2.1.5 Non-traumatic IC	н										
Sprigg 2014	3	16	2	8	0.9%	0.75 [0.16, 3.62] 2014	Ļ				
Sprigg 2018	250	1161	249	1164	95.4%	1.01 [0.86, 1.18] 2018	3				
Meretoja 2020	13	50	8	50	3.7%	1.63 [0.74, 3.58] 2020)		— —		
Subtotal (95% CI)		1227		1222	100.0%	1.02 [0.88, 1.19]			•		
Total events	266		259								
Heterogeneity: $Tau^2 = 0$.	00; $Chi^2 =$	1.51, df	= 2 (P =	= 0.47);	$I^2 = 0\%$						
Test for overall effect: Z	= 0.28 (P =	= 0.78)									
							0.01	0.1	1	10	100
								Favour	s TXA Favours c	ontrol	

Page 8 of 20

2a. Poor functional outcome



2b. Quality of life

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

Non-traumatic ICH:

TICH trial: Euro QoL visual analogue scale: 66.3 (17.0) in TXA vs. 73.3 (15.3) in control (p=0.28). TICH-2 trial: EQ5D scores were identical between groups 0.34 (0.4)

3a. Bleeding - cardiac surgery

		ТХА		PI	acebo)		Mean Difference		Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	Year	IV, Random, 95% CI
2.3.1 Cardiac surgery										
Horrow 1990	496	228	18	750	314	20	1.7%	-254.00 [-427.30, -80.70]	1990	
Horrow 1991	328	175	37	462	205	44	2.1%	-134.00 [-216.76, -51.24]	1991	
Blauhut 1994	403	52	16	453	52	14	2.3%	-50.00 [-87.30, -12.70]	1994	
Horrow 1995	393	200	121	552	271	27	2.0%	-159.00 [-267.25, -50.75]	1995	
Corbeau 1995	766	304	41	1.083	452	20	1.5%	-317.00 [-535.86, -98.14]	1995	
Penta de Penpo 1995	534	288	15	724	280	15	1.6%	-190.00 [-393.27, 13.27]	1995	
Karski 1995	423	44	99	985	105	48	2.3%	-562.00 [-592.94, -531.06]	1995	-
Coffey 1995	711	96	16	1.160	168	14	2.1%	-449.00 [-548.79, -349.21]	1995	
Speekenbrink 1995	915	215	15	1 325	295	15	1 7%	-410 00 [-594 73 -225 27]	1995	
Pugh 1995	375	215	22	615	319	23	1.8%	-240.00 [-398.33 -81.67]	1995	
Shore-Lesserson 1996	649	391	17	923	496	13	1 1%	-274 00 [-601 48 53 48]	1996	
Menichetti 1996	747	400	24	881	600	24	1.1%	-134 00 [-422 50 154 50]	1996	
Katsaros 1996	474	24	104	001	51	106	2 2%	-432 00 [-442 75 -421 25]	1006	
Roum 1007	960	24	104	1 202	620	20	2.3/0	-432.00 [-442.73, -421.23]	1990	
Katab 1007	241	2 1	60	202	029	21	1.1/0	-542.00 [-655.07, -28.95]	1997	
Raton 1997	241	212	02	392	22	31	2.3%	-151.00 [-171.84, -150.16]	1997	-
Dryden 1997	550	217	22	8/1	041	19	1.2%	-321.00 [-623.15, -18.85]	1997	
PINOSKY 1997	600	49	20	1,060	127	19	2.2%	-460.00 [-521.01, -398.99]	1997	-
mardy 1998	888	//2	43	1,119	884	45	1.0%	-231.00 [-577.34, 115.34]	1998	
Nutali 2000	618	375	45	890	896	43	1.2%	-2/2.00 [-561.35, 17.35]	2000	
Kojima 2001	930	60	11	1,580	240	11	1.9%	-650.00 [-796.19, -503.81]	2001	
Jozaki 2001	646	380	7	846	510	7	0.7%	-200.00 [-671.15, 271.15]	2001	
Armellin 2001	447	262	143	720	357	140	2.2%	-273.00 [-346.08, -199.92]	2001	
Casati 2001	400	113	20	650	231	20	2.0%	-250.00 [-362.70, -137.30]	2001	
Zabeeda 2002	194	135	25	488	238	25	2.0%	-294.00 [-401.26, -186.74]	2002	
Pleym 2003	475	274	40	713	243	39	2.0%	-238.00 [-352.13, -123.87]	2003	
ares 2003	420	143	22	550	111	25	2.2%	-130.00 [-203.92, -56.08]	2003	
Casati 2004	464	199	52	704	377	50	2.0%	-240.00 [-357.67, -122.33]	2004	
Andreasen 2004	730	281	21	880	659	23	1.2%	-150.00 [-444.92, 144.92]	2004	
Diprose 2005	510	341	62	860	563	61	1.8%	-350.00 [-514.82, -185.18]	2005	
Karski 2005	520	265	147	790	410	165	2.2%	-270.00 [-345.82, -194.18]	2005	
Vanek 2005	410	119	32	620	154	30	2.2%	-210.00 [-278.82, -141.18]	2005	
Kuitunen 2005	802	48	20	995	63	20	2.3%	-193.00 [-227.71, -158.29]	2005	-
Santos 2006	500	230	29	800	393	31	1.8%	-300.00 [-461.70, -138.30]	2006	
Murphy 2006	410	119	50	620	154	50	2.2%	-210.00 [-263.94, -156.06]	2006	
Wei 2006	440	248	36	655	311	40	2.0%	-215.00 [-340.90, -89.10]	2006	
Maddali 2007	633	183	111	981	267	111	2.2%	-348.00 [-408.22, -287.78]	2007	
Mehr-Aein 2007	320	38	33	480	72	33	2.3%	-160.00 [-187.78, -132.22]	2007	-
limenez 2007	464	369	24	1.037	659	26	1.2%	-573.00 [-866.19, -279.81]	2007	
Taghaddomi 2009	471	182	50	844	363	50	2.0%	-373 00 [-485 55 -260 45]	2009	
ater 2009	760	400	90	860	548	103	1 9%	-100 00 [-231 94 31 94]	2009	
Hashemi 2011	355	179	50	540	347	50	2.0%	-185 00 [-293 22 -76 78]	2005	
Nana 2012	654	224	130	201	205	120	2.0%	-237.00 [-200.67 -173.331	2012	
Anny 2012	751	480	130	720	4/0	130	1.6%	22 00 [-180 08 222 09]	2012	
4accani 2012	274	1.92	100	501	749	20	7 10/0	_127.00 [-109.00, 233.08]	2012	[
rassalli 2012	5/4	103	100	1 025	200	20	2.1%	-127.00 [-214.32, -39.48]	2012	
Jancouri 2012	282	157	30	1,033	607	30	1 /0/	-540.00 [-724.76, 44.76]	2012	
Mansoull 2012	1 060	13/	20	1 450	09/	50	1.4%	-355.00 [-614.00, -505.34]	2012	
Shi jia 2 ATS 2013	1,069	202	200	1,450	900	29	1.5%	-361.00 [-052.81, -109.19]	2013	
mijia-3 JAMA 2013	323	212	285	1,257	691	285	2.1%	-2/6.00 [-3/8.05, -1//.95]	2013	
sni jia –1 CJS 2013	930	556	55	1,210	0/4	55	1.5%	-280.00 [-510.91, -49.09]	2013	
standiari 2013	432	210	75	649	235	75	2.2%	-217.00 [-288.33, -145.67]	2013	
Alizadeh Ghavidel 2014	450	361	100	650	384	100	2.1%	-200.00 [-303.30, -96.70]	2014	
araoni 2014	781	617	24	720	518	12	0.9%	61.00 [-322.18, 444.18]	2014	
Yanartas 2015	350	815	34	400	963	32	0.8%	-50.00 [-481.71, 381.71]	2015	
Myles 2017	600	304	2310	830	407	2320	2.3%	-230.00 [-250.69, -209.31]	2017	-
Wang 2017	860	385	105	985	431	106	2.0%	-125.00 [-235.25, -14.75]	2017	
Altun 2017	306	57	18	972	134	10	2.1%	-666.00 [-753.13, -578.87]	2017	
Subtotal (95% CI)			5273			5015	100.0%	-268.52 [-314.99, -222.04]		◆
Heterogeneity: Tau ² = 24	573.92;	Chi ² =	= 1652	.77, df :	= 55	(P < 0.0)	00001); I ²	= 97%		
Fest for overall effect: Z =	11.32 ((P < 0	.00001	.)						
										-1000 -500 0 500 1000
										Favours TXA Favours placebo

3b. Rebleeding events

2.9.2 Subarachnoid hemorrhage



Favours TXA Favours control

3c. Need for surgical intervention

	ТХ/	4	Cont	rol		Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	Year	M-H, Random, 95% Cl
2.8.1 Cardiac surgery								
Penta de Peppo 1995	1	15	0	15	0.8%	3.00 [0.13, 68.26]	1995	
Pugh 1995	0	23	2	23	0.9%	0.20 [0.01, 3.95]	1995	
Speekenbrink 1995	0	15	0	15		Not estimable	1995	
Shore-Lesserson 1996	0	17	0	13		Not estimable	1996	
Katsaros 1996	1	104	5	106	1.8%	0.20 [0.02, 1.72]	1996	
Brown 1997	0	60	0	30		Not estimable	1997	
Hardy 1998	1	43	3	45	1.6%	0.35 [0.04, 3.23]	1998	· · · · · · · · · · · · · · · · · · ·
Uozaki 2001	1	7	1	7	1.2%	1.00 [0.08, 13.02]	2001	
Armellin 2001	4	143	5	140	4.8%	0.78 [0.21, 2.86]	2001	
Casati 2001	0	20	0	20		Not estimable	2001	
Pleym 2003	0	40	1	40	0.8%	0.33 [0.01, 7.95]	2003	· · · · · · · · · · · · · · · · · · ·
Jares 2003	0	25	1	25	0.8%	0.33 [0.01, 7.81]	2003	· · · · · · · · · · · · · · · · · · ·
Andreasen 2004	1	23	6	23	1.9%	0.17 [0.02, 1.28]	2004	
Casati 2004	1	52	3	50	1.6%	0.32 [0.03, 2.98]	2004	· · · · · · · · · · · · · · · · · · ·
Diprose 2005	5	60	7	60	6.7%	0.71 [0.24, 2.13]	2005	
Murphy 2006	1	50	0	50	0.8%	3.00 [0.13, 71.92]	2006	
Maddali 2007	3	111	3	111	3.2%	1.00 [0.21, 4.85]	2007	· · · · · · · · · · · · · · · · · · ·
Mehr-Aein 2007	0	33	1	33	0.8%	0.33 [0.01, 7.90]	2007	· · · · · · · · · · · · · · · · · · ·
Hashemi 2011	1	50	1	50	1.1%	1.00 [0.06, 15.55]	2011	
Wang 2012	0	116	2	115	0.9%	0.20 [0.01, 4.09]	2012	
Greiff 2012	6	30	9	33	9.7%	0.73 [0.30, 1.82]	2012	
Shi jia-2 ATS 2013	5	274	19	279	8.5%	0.27 [0.10, 0.71]	2013	_
Esfandiari 2013	1	75	1	75	1.1%	1.00 [0.06, 15.69]	2013	
Alizadeh Ghavidel 2014	5	100	5	100	5.5%	1.00 [0.30, 3.35]	2014	· · · · · · · · · · · · · · · · · · ·
Myles 2017	32	2311	65	2320	45.5%	0.49 [0.32, 0.75]	2017	
Subtotal (95% CI)		3797		3778	100.0%	0.53 [0.40, 0.71]		\bullet
Total events	69		140					
Heterogeneity: $Tau^2 = 0.0$	0; Chi ² =	11.27,	df = 20 ((P = 0.94)	4); $I^2 = 0$ %	6		
Test for overall effect: Z =	4.38 (P -	< 0.000	1)					
2 8 3 Obstatric bleading	(hystore)	tomy						
Duclov Poutborg 2011	~		C	70	E 20/	0.20 [0.01 4.00]	2011	
MOMAN trial 2017	250	10022	2	72	5.2%	0.20[0.01, 4.09]	2011	. · · · ·
Subtotal (95% CI)	220	10032 10104	221	9985 10057	94.8% 100.0%	0.93 [0.46, 1.89]	2017	
Total events	358	10101	252	20001	20010/0			•
Heterogeneity: $Tau^2 - 0.1$	3. Chi ² –	1 11 d	f = 1 (P -	= 0 29).	$l^2 = 10\%$			
Test for overall effect: $Z =$	0.19 (P =	= 0.85)	. – エ () -	0.23),	10/0			
		/						
								Favours TXA Favours control

4. Stroke

		ТХА	Cor	trol		Risk Ratio			Risk Ratio
Study or Subgroup	Even	ts Tota	l Events	Total	Weight	M-H, Random, 9	95% CI		M-H, Random, 95% Cl
2.10.2 Obstetric bleedi	ng								
Ducloy-Bouthors 2011		0 72	2 0	72		Not est	imable		
WOMAN trial 2017		8 10032	2 6	9985	100.0%	1.33 [0.46,	, 3.82]		
Subtotal (95% CI)		10104	1	10057	100.0%	1.33 [0.46	, 3.82]		
Total events		8	6						
Heterogeneity: Not appli	cable								
Test for overall effect: Z	= 0.52	P = 0.6	0)						
2 10 2 Subarachnoid ham	orrhood								
Endstad 1078	ormage 2	- 22	0	22 0	70/ 70	NO [O 20 120 22] 1	1079		
Fodstad 1978	2	20	3	23 0.	7% 7.0 7%	2 58 [0 76 8 77] 1	1978		
Vermeulen 1984	59	241	36	238 18.	6%	1.62 [1.11, 2.35]	1984		
Tsementzis 1990	22	50	11	50 11.	1%	2.00 [1.09, 3.68] 1	1990		_ _
Roos 2000	79	229	84	233 24.	2%	0.96 [0.75, 1.23] 2	2000		+
Hillman 2002	45	254	33	251 17.	0%	1.35 [0.89, 2.04] 2	2002		+
Post 2020	108	480	106	475 24.	7%	1.01 [0.80, 1.28] 2	2020		+ .
Subtotal (95% CI)		1307	12	299 100.	0%	1.29 [1.01, 1.67]			•
Total events	324	12 52 1	273	0.04) 12	F. C. 0/				
Heterogeneity: $1 \text{ au}^2 = 0.05$	s; Chi ⁻ =	= 13.52, d	r = 6 (P =	0.04); 1- =	= 56%				
Test for overall effect. $Z = $	2.01 (P	= 0.04)							
2.10.4 Non-traumatic ICH	ł								
Sprigg 2018	16	1161	11 1	164 92.	8%	1.46 [0.68, 3.13] 2	2018		
Meretoja 2020	1	50	1	50 7.	2% 1	.00 [0.06, 15.55] 2	2020		
Subtotal (95% CI)		1211	12	214 100.	0%	1.42 [0.68, 2.96]			-
Total events	17		12						
Heterogeneity: $Tau^2 = 0.00$); Chi ² =	= 0.07, df	= 1 (P = 0)	$(1.80); I^2 =$	0%				
Test for overall effect: $Z = 0$	0.93 (P	= 0.35)							
								1	
							0	.01	0.1 1 10

5. Myocardial infarction

ТХА		Cont	rol		Risk Ratio	Risk Ratio			
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl		M–H, Fixed, 95% Cl	
2.11.1 GI bleeding									
Engquist 1979 Subtotal (95% CI)	2	102 102	0	102 102	100.0% 100.0%	5.00 [0.24, 102.87] 5.00 [0.24, 102.87]			
Total events	2		0						
Heterogeneity: Not appl	icable								
Test for overall effect: Z	= 1.04 (P	= 0.30)						
2.11.2 Obstetric bleed	ing								
Ducloy–Bouthors 2011	0	72	0	72		Not estimable			
WOMAN trial 2017	2	10032	3	9985	100.0%	0.66 [0.11, 3.97]			
Subtotal (95% CI)		10104		10057	100.0%	0.66 [0.11, 3.97]			
Total events	2		3						
Heterogeneity: Not appl	icable								
Test for overall effect: Z	= 0.45 (P	= 0.65)						
2.11.4 Non-traumatic	ІСН								
Meretoja 2020	0	50	0	50		Not estimable			
Sprigg 2018	11	1161	6	1164	100.0%	1.84 [0.68, 4.95]			
Subtotal (95% CI)		1211		1214	100.0%	1.84 [0.68, 4.95]			
Total events	11		6						
Heterogeneity: Not appl	icable								
Test for overall effect: Z	= 1.20 (P	= 0.23)						
							0.002	0 1 1 10 500	
							0.002	Favours TXA Favours control	

6a. Thrombosis — DVT

	TXA	۱	Cont	rol		Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	Year	M–H, Fixed, 95% Cl
2.12.1 GI bleeding								
Engquist 1979	4	102	2	102	66.8%	2.00 [0.37, 10.68]	1979	
Barer 1983	1	256	0	260	16.6%	3.05 [0.12, 74.44]	1983	
Holstein 1987	1	164	0	164	16.7%	3.00 [0.12, 73.11]	1987	
Subtotal (95% CI)		522		526	100.0%	2.34 [0.61, 8.94]		
Total events	6		2					
Heterogeneity: $Chi^2 = 0$.	08, df = 2	P = 0	.96); I ² =	0%				
Test for overall effect: Z	= 1.24 (P	= 0.21)					
2.12.2 Obstetric bleedi	ing							
Ducloy-Bouthors 2011	0	72	0	72		Not estimable	2011	
WOMAN trial 2017	3	10032	7	9985	100.0%	0.43 [0.11, 1.65]	2017	
Subtotal (95% CI)		10104		10057	100.0%	0.43 [0.11, 1.65]		
Total events	3		7					
Heterogeneity: Not appli	icable							
Test for overall effect: Z	= 1.23 (P	= 0.22)					
2.12.3 SAH								
Post 2020	0	480	2	475	100.0%	0.20 [0.01, 4.11]	2020	
Subtotal (95% CI)		480		475	100.0%	0.20 [0.01, 4.11]		
Total events	0		2					
Heterogeneity: Not appli	icable							
Test for overall effect: Z	= 1.05 (P	= 0.30)					
2.12.4 Non-traumatic	ІСН							
Sprigg 2018	19	1161	14	1164	100.0%	1.36 [0.69, 2.70]	2018	
Subtotal (95% CI)		1161		1164	100.0%	1.36 [0.69, 2.70]		•
Total events	19		14					
Heterogeneity: Not appli	icable							
Test for overall effect: Z	= 0.88 (P	= 0.38)					
								0.01 0.1 1 10 100
								Favours TXA Favours control

6b. Thrombosis - pulmonary embolism

	ТХА	\	Cont	rol		Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	Year	M–H, Fixed, 95% Cl
2.13.1 GI bleeding								
Engquist 1979	5	102	2	102	33.4%	2.50 [0.50, 12.59]	1979	
Barer 1983	5	256	2	260	33.2%	2.54 [0.50, 12.97]	1983	
Holstein 1987	1	164	2	164	33.4%	0.50 [0.05, 5.46]	1987	_
Bagneko 2011	0	22	0	25		Not estimable	2011	
Subtotal (95% CI)		544		551	100.0%	1.84 [0.69, 4.94]		
Total events	11		6					
Heterogeneity: $Chi^2 = 1$.	43, df = 2	P = 0	.49); I ² =	0%				
Test for overall effect: Z	= 1.22 (P	= 0.22)					
2.13.2 Obstetric bleedi	ng							
Ducloy-Bouthors 2011	0	72	0	72		Not estimable	2011	
WOMAN trial 2017	17	10032	20	9985	100.0%	0.85 [0.44, 1.61]	2017	— <mark>—</mark> —
Subtotal (95% CI)		10104		10057	100.0%	0.85 [0.44, 1.61]		\bullet
Total events	17		20					
Heterogeneity: Not appli	cable							
Test for overall effect: Z	= 0.51 (P	= 0.61)					
2.13.3 SAH								
Post 2020	6	480	5	475	100.0%	1.19 [0.36, 3.86]	2020	
Subtotal (95% CI)		480		475	100.0%	1.19 [0.36, 3.86]		
Total events	6		5					
Heterogeneity: Not appli	cable							
Test for overall effect: Z	= 0.29 (P	= 0.78)					
2 13 4 Non-traumatic I	сн							
Spring 2018	20	1161	22	1164	93.0%	0 87 [0 48 1 58]	2018	
Morotoia 2020	20	50	25	50	6 1%	0.37 [0.40, 1.30]	2010	•
Subtotal (95% CI)	0	1211	T	1214	100.0%	0.84 [0.47, 1.50]	2020	
Total events	20		24		10010/0			
Heterogeneity: $Chi^2 = 0$	20 34 df - 1	$(\mathbf{P} - 0)$	$56) \cdot 1^2 -$	0%				
Test for overall effect. 7	= 0 59 /P	-0.55)	070				
restion overall effect. Z	- 0.33 (F	- 0.55	,					
								0.05 0.2 1 5 20
								Favours TXA Favours control

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



7. Seizure

	тх	A	Cont	rol		Risk Ratio			Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI	Year		IV, Random, 95% CI
2.5.1 Cardiac surgery									
Greiff 2012	0	30	0	33		Not estimable	2012		
Mansouri 2012	0	30	0	30		Not estimable	2012		
Shi jia-3 JAMA 2013	4	285	2	285	38.5%	2.00 [0.37, 10.83]	2013		
Esfandiari 2013	0	75	0	75		Not estimable	2013		
Shi jia-2 ATS 2013	1	58	0	59	10.9%	3.05 [0.13, 73.39]	2013		
Faraoni 2014	0	12	0	12		Not estimable	2014		
Myles 2017 Subtotal (95% CI)	15	2304 2794	2	2327 2821	50.6% 100.0%	7.57 [1.73, 33.09] 4.11 [1.44, 11.72]	2017		
Total events	20		4						
Heterogeneity: Tau ² =	0.00; Ch	$i^2 = 1.39$	9, df = 2	(P = 0)	.50); I ² =	0%			
Test for overall effect:	Z = 2.64	(P = 0.0)	(80						
2.5.2 Obstetric bleedi	ng								
WOMAN trial 2017	33	10032	43	9985	100.0%	0.76 [0.49, 1.20]	2017		
Subtotal (95% CI)		10032		9985	100.0%	0.76 [0.49, 1.20]			◆
Total events	33		43						
Heterogeneity: Not app	licable								
Test for overall effect:	Z = 1.17	(P = 0.2)	24)						
2.5.2 Non-traumatic									
2.3.3 Non-traumatic		1101		1164	100.00/	0.01 (0.07, 1.00)	2010		
Subtotal (95% CI)	//	1161	85	1164	100.0%	0.91 [0.67, 1.22]	2018		—
Total avents	77	1101	0 5	1104	100.0%	0.91 [0.07, 1.22]			•
Hotorogonoity Not and	//		00						
Test for overall effects	7 = 0.62	(P = 0.5)	2)						
rest for overall effect:	2 = 0.03	(P = 0.5)	(20						
								L	
								0.01	0.1 1 10 100
									Favours TXA Favours control

8. Need for RBC transfusion

	TXA		Contr	ol		Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	Year	M-H, Random, 95% CI
2.15.1 Cardiac surgery								
Penta de Peppo 1995	1	15	3	15	0.2%	0.33 [0.04, 2.85]	1995	←
Speekenbrink 1995	2	15	4	15	0.5%	0.50 [0.11, 2.33]	1995	
Katsaros 1996	11	104	27	106	2.3%	0.42 [0.22, 0.79]	1996	
Shore-Lesserson 1996	10	17	12	13	4.3%	0.64 [0.42, 0.98]	1996	
Pinosky 1997	11	20	9	19	2.4%	1.16 [0.63, 2.15]	1997	
Brown 1997	18	60	20	30	3.9%	0.45 [0.28, 0.71]	1997	
Hardy 1998	28	43	29	45	6.6%	1.01 [0.74, 1.38]	1998	
Armellin 2001	35	143	63	140	5.9%	0.54 [0.39, 0.77]	2001	
Casati 2001	2	20	4	20	0.4%	0.50 [0.10, 2.43]	2001	
Zabeeda 2002	9	25	25	25	3.3%	0.37 [0.22, 0.62]	2002	
Jares 2003	2	22	7	25	0.5%	0.32 [0.08, 1.40]	2003	• • • • • • • • • • • • • • • • • • •
Pleym 2003	7	40	8	40	1.2%	0.88 [0.35, 2.18]	2003	
Andreasen 2004	5	23	6	23	1.0%	0.83 [0.30, 2.35]	2004	
Casati 2004	9	52	13	50	1.7%	0.67 [0.31, 1.42]	2004	
Diprose 2005	20	60	27	60	4.0%	0.74 [0.47, 1.17]	2005	
Murphy 2006	13	50	14	50	2.3%	0.93 [0.49, 1.77]	2006	
Mehr-Aein 2007	5	33	8	33	1.0%	0.63 [0.23, 1.71]	2007	
Later 2009	57	99	73	103	9.5%	0.81 [0.66, 1.00]	2009	
Taghaddomi 2009	8	50	31	50	2.1%	0.26 [0.13, 0.50]	2009	
Hashemi 2011	15	50	29	50	3.6%	0.52 [0.32, 0.84]	2011	
Wang 2012	37	116	54	115	6.1%	0.68 [0.49, 0.94]	2012	
Ahn 2012	20	38	27	38	5.4%	0.74 [0.51, 1.07]	2012	
Esfandiari 2013	22	75	43	75	4.7%	0.51 [0.34, 0.76]	2013	
Shi jia –1 CJS 2013	166	274	221	278	12.9%	0.76 [0.68, 0.85]	2013	-
Myles 2017	759	2311	1086	2320	14.2%	0.70 [0.65, 0.75]	2017	
Subtotal (95% CI)		3755		3738	100.0%	0.67 [0.60, 0.74]		•
Total events	1272		1843					
Heterogeneity: $Tau^2 = 0.0$)2; Chi ² =	42.71,	df = 24 (P = 0.0	1); $I^2 = 4$	4%		
Test for overall effect: Z =	= 7.57 (P	< 0.000	01)					
2.15.3 Obstetric bleed	ina							
Duclov-Bouthors 2011	10	72	13	72	0.29	6 0.77 [0.36, 1.64]	2011	
WOMAN trial 2017	5461	10036	5426	9985	99.89	1.00 [0.98, 1.03]	2017	
Subtotal (95% CI)	5101	10108	5120	10057	7 100.09	6 1.00 [0.98, 1.03]	2017	—
Total events	5471		5439					
Heterogeneity: $Chi^2 = 0$	47. df =	1 (P = 0)	.49): I ² =	0%				
Test for overall effect: 7	= 0.06 (0	P = 0.95)	0.0				
. cottor overall circle 2	0.00 (1	5.75	·					
								0.1 0.2 0.5 1 2 5 10
								Favours TXA Favours control

9. Hospital length of stay

		ТХА		С	ontrol			Mean Difference		Mean Diffe	erence	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI		IV, Fixed, 9	95% CI	
2.16.1 Non-traumati	ic ICH											
Sprigg 2014	19.4	24.5	16	10.8	14	8	5.9%	8.60 [-6.83, 24.03]				
Sprigg 2018	63.12	47.1	1161	63.73	48.1	1164	94.1%	-0.61 [-4.48, 3.26]			_	
Subtotal (95% CI)			1177			1172	100.0%	-0.07 [-3.82, 3.69]		-	•	
Heterogeneity: Chi ² =	1.29, df	f = 1 (f	P = 0.2	6); I ² =	22%							
Test for overall effect:	Z = 0.0	3 (P =	0.97)									
									-20	-10 0	10	20
									-20	Favours TXA Fa	avours contr	ol

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

1. High-dose IV TXA

		Certai	inty assessmen	t		Nº of p	atients		Effect			
№ of studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TXA	no TXA	Relative (95% CI)	Absolute (95% Cl)	Certainty	Importance	
Mortality	at longest	follow-up - High-o	dose IV TXA									
5 RCTs	not serious	not serious ^a	not serious	not serious	none	602/6593 (9.1%)	617/6626 (9.3%)	RR 0.98 (0.88 to 1.09)	2 fewer per 1,000 (from 11 fewer to 8 more)	⊕⊕⊕⊕ HIGH	CRITICAL	
Stroke - H	Stroke - High-dose IV TXA											
4 RCTs	not serious	not serious	not serious	not serious ^b	none	20/6474 (0.3%)	22/6503 (0.3%)	RR 0.92 (0.51 to 1.65)	0 fewer per 1,000 (from 2 fewer to 2 more)	⊕⊕⊕⊕ HIGH	CRITICAL	
Myocardi	al infarctio	n - High-dose IV	ТХА									
2 RCTs	not serious	not serious	not serious	not serious ^b	none	26/6054 (0.4%)	28/6079 (0.5%)	RR 0.93 (0.55 to 1.58)	0 fewer per 1,000 (from 2 fewer to 3 more)	⊕⊕⊕⊕ HIGH	CRITICAL	
Rebleedir	ng - High-d	ose IV TXA										
4 RCTs	not serious	not serious	not serious	not serious ^b	none	503/6611 (7.6%)	548/6645 (8.2%)	RR 0.92 (0.82 to 1.04)	7 fewer per 1,000 (from 15 fewer to 3 more)	⊕⊕⊕⊕ HIGH	IMPORTANT	
Surgical i	interventio	n - High-dose IV 1	ΓΧΑ									
5 RCTs	not serious	not serious ^c	not serious	not serious ^b	none	210/6613 (3.2%)	233/6642 (3.5%)	RR 0.91 (0.76 to 1.09)	3 fewer per 1,000 (from 8 fewer to 3 more)	⊕⊕⊕⊕ HIGH	IMPORTANT	
Seizure -	High-dose	IV TXA										
1 RCT	not serious	not serious	not serious	not serious	none	38/5952 (0.6%)	22/5977 (0.4%)	RR 1.73 (1.03 to 2.93)	3 more per 1,000 (from 0 fewer to 7 more)	⊕⊕⊕⊕ HIGH	IMPORTANT	
Sepsis - H	ligh-dose	ΙΥ ΤΧΑ										
1 RCT	not serious	not serious	not serious	not serious ^b	none	210/5952 (3.5%)	216/5977 (3.6%)	RR 0.98 (0.81 to 1.18)	1 fewer per 1,000 (from 7 fewer to 7 more)	⊕⊕⊕⊕ HIGH	CRITICAL	

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

1 RCT	not serious	not serious	not serious	not serious ^b	none	5953	5978	-	MD 0 (0.03 lower to 0.03	⊕⊕⊕⊕ HIGH	IMPORTANT
									higher)		

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

Explanations

a. Although moderate statistical heterogeneity (I2 >60 %), this is driven by a single older trial (Barer 1983); excluding this trial reduces heterogeneity but has as similar point estimate (RR 1.01, 95% CI 0.91, 1.13). The effect estimate is thus unlikely to be effected by statistical heterogeneity.

b. Though the 95% confidence interval crosses 1, the absolute risk difference in small and possibly of minimal clinical significance.

c. Although moderate statistical heterogeneity (I2 > 60%), this is driven by a single older trial (Holstein 1987); excluding this trial results in a similar estimate of effect (RR 0.96, 95% CI 0.79,

1.15). The effect estimate is thus minimally impacted by the statistical heterogeneity.

2. Low dose IV TXA or enteral TXA only

		Certa	inty assessmen	t		Nº of p	oatients		Effect		Importance		
Nº of studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ТХА	no TXA	Relative (95% Cl)	Absolute (95% Cl)	Certainty			
Mortality	fortality at longest follow-up - Low-dose or enteral TXA only												
7 RCTs	not serious	not serious	not serious	serious ^a	none	19/445 (4.3%)	30/435 (6.9%)	RR 0.62 (0.36 to 1.09)	26 fewer per 1,000 (from 44 fewer to 6 more)	⊕⊕⊕⊖ MODERATE	CRITICAL		
Rebleedi	Rebleeding - Low-dose or enteral TXA only												
5 RCTs	not serious	not serious	not serious	serious ^b	none	30/371 (8.1%)	59/363 (16.3%)	RR 0.5 (0.33 to 0.75)	81 fewer per 1,000 (from 109 fewer to 41 fewer)	⊕⊕⊕⊖ MODERATE	IMPORTANT		
Surgical	interventio	on - Low-dose or e	enteral TXA only	1									
5 RCTs	not serious	not serious	not serious	serious ^b	none	29/302 (9.6%)	49/297 (16.5%)	RR 0.58 (0.38 to 0.88)	69 fewer per 1,000 (from 102 fewer to 20 fewer)	⊕⊕⊕⊖ MODERATE	IMPORTANT		
RBC tran	sfusion - l	_ow-dose or enter	ral TXA only			••							
4 RCTs	not serious	not serious	not serious	serious ^a	none	217/304 (71.4%)	207/299 (69.2%)	RR 1.03 (0.93 to 1.13)	21 more per 1,000 (from 48 fewer to 90 more)	⊕⊕⊕⊖ MODERATE	IMPORTANT		
RBCs tra	nsfused -	Low-dose or ente	ral TXA										
2 RCTs	not serious	not serious	not serious	serious ^b	none	116	111	-	MD 1.12 lower (1.56 lower to 0.67 lower)		IMPORTANT		

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

Explanations

a. Wide 95% confidence intervals do not exclude clinically significant benefit or harm.b. Though statistically significant, optimal information size not met resulting in serious imprecision of the overall estimate.

1. Mortality at longest follow-up

	ТХА	۱.	Cont	rol		Risk Ratio			Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M–H, Fixed, 95% Cl	Year		M–H, Fixed, 95% Cl	
1.1.1 High-dose IV T	XA									
Engquist 1979	11	102	12	102	2.0%	0.92 [0.42, 1.98]	1979			
Barer 1983	16	256	35	260	5.6%	0.46 [0.26, 0.82]	1983			
Holstein 1987	2	164	4	164	0.7%	0.50 [0.09, 2.69]	1987			
Tavakoli 2017	9	115	18	119	2.9%	0.52 [0.24, 1.10]	2017			
Halt–IT 2020	564	5956	548	5981	88.9%	1.03 [0.92, 1.16]	2020			
Subtotal (95% CI)		6593		6626	100.0%	0.98 [0.88, 1.09]			•	
Total events	602		617							
Heterogeneity: Chi ² =	10.93, d	f = 4 (F	P = 0.03); $I^2 = 6$	3%					
Test for overall effect:	Z = 0.36	6 (P = 0)	.72)							
1.1.2 Low–dose or e	nteral TX	A only								
Cormack 1973	3	76	3	74	10.1%	0.97 [0.20, 4.67]	1973			
Biggs 1976	2	103	4	97	13.6%	0.47 [0.09, 2.51]	1976		_	
Berggvist 1980	3	25	5	25	16.6%	0.60 [0.16, 2.25]	1980			
Hawkey 2001	4	103	5	103	16.6%	0.80 [0.22, 2.89]	2001			
, Bagneko 2011	1	22	3	25	9.3%	0.38 [0.04, 3.38]	2011	-		
Saidi 2017	4	67	9	64	30.5%	0.42 [0.14, 1.31]	2017			
Smith 2018	2	49	1	47	3.4%	1.92 [0.18, 20.46]	2018			
Subtotal (95% CI)		445		435	100.0%	0.62 [0.36, 1.09]				
Total events	19		30							
Heterogeneity: Chi ² =	2.08, df	= 6 (P	= 0.91);	$l^2 = 0\%$	ó					
Test for overall effect:	Z = 1.67	P = 0	.10)							
								0.01		100
						2		0.01	Favours TXA Favours control	100

Test for subgroup differences: $Chi^2 = 2.47$, df = 1 (P = 0.12), $I^2 = 59.5\%$

2. Rebleeding

	ТХА	4	Cont	rol		Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M–H, Fixed, 95% Cl	Year	M–H, Fixed, 95% Cl
1.2.1 High-dose IV T	XA							
Engquist 1979	23	102	29	102	5.3%	0.79 [0.49, 1.27]	1979	
Barer 1983	58	256	51	260	9.3%	1.16 [0.83, 1.61]	1983	
Holstein 1987	10	164	19	164	3.5%	0.53 [0.25, 1.10]	1987	
Tavakoli 2017	2	133	1	138	0.2%	2.08 [0.19, 22.62]	2017	
Halt–IT 2020	410	5956	448	5981	81.8%	0.92 [0.81, 1.05]	2020	
Subtotal (95% CI)		6611		6645	100.0%	0.92 [0.82, 1.04]		♦
Total events	503		548					
Heterogeneity: Chi ² =	4.82, df	= 4 (P	= 0.31);	$l^2 = 17$	'%			
Test for overall effect:	Z = 1.37	7 (P = 0)).17)					
1.2.2 Low-dose or e	nteral TX	A only						
Cormack 1973	8	76	11	74	18.7%	0.71 [0.30, 1.66]	1973	
Biggs 1976	7	103	21	97	36.2%	0.31 [0.14, 0.71]	1976	
Hawkey 2001	9	103	10	103	16.7%	0.90 [0.38, 2.12]	2001	
Bagneko 2011	2	22	5	25	7.8%	0.45 [0.10, 2.11]	2011	
Saidi 2017	4	67	12	64	20.5%	0.32 [0.11, 0.94]	2017	
Subtotal (95% CI)		371		363	100.0%	0.50 [0.33, 0.75]		\bullet
Total events	30		59					
Heterogeneity: Chi ² =	4.41, df	= 4 (P	= 0.35);	$l^2 = 9\%$	6			
Test for overall effect:	Z = 3.30	(P = 0)	0.0010)					
								Eavours TXA Eavours control
Test for subgroup diff	arancas	Chi ² -	7 00 df	- 1 (D	- 0.005)	$1^2 - 87.3\%$		ravours INA ravours control

Test for subgroup differences: $Chi^2 = 7.90$, df = 1 (P = 0.005), $l^2 = 87.3\%$

3. Surgical intervention

	ТХА	4	Cont	rol		Risk Ratio			Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M–H, Fixed, 95% Cl	Year		M-H, Fixed, 95% Cl	
1.3.1 High-dose IV T	XA									
Engquist 1979	10	102	18	102	7.7%	0.56 [0.27, 1.14]	1979			
Barer 1983	47	256	40	260	17.1%	1.19 [0.81, 1.75]	1983			
Holstein 1987	3	164	15	164	6.5%	0.20 [0.06, 0.68]	1987			
Tavakoli 2017	4	138	2	138	0.9%	2.00 [0.37, 10.74]	2017			
Halt-IT 2020 Subtotal (95% CI)	146	5953 6613	158	5978 6642	67.9% 100.0%	0.93 [0.74, 1.16] 0.91 [0.76, 1.09]	2020			
Total events	210	0010	233		10010/0	0.012 [011 0, 2100]			•	
Heterogeneity: $Chi^2 =$	10 51 d	f = 4 (1)	$P = 0.03^{\circ}$	$1^{2} = 6$	2%					
Test for overall effect:	Z = 1.06	5 (P = 0)).29)	,,	270					
1.3.2 Low-dose or e	nteral TX	A only								
Biggs 1976	7	103	21	97	43.5%	0.31 [0.14, 0.71]	1976		_	
Bergqvist 1980	7	25	7	25	14.1%	1.00 [0.41, 2.43]	1980			
Hawkey 2001	5	103	6	103	12.1%	0.83 [0.26, 2.64]	2001			
Bagneko 2011	1	22	3	25	5.7%	0.38 [0.04, 3.38]	2011			
Smith 2018	9	49	12	47	24.7%	0.72 [0.33, 1.55]	2018			
Subtotal (95% CI)		302		297	100.0%	0.58 [0.38, 0.88]			•	
Total events	29		49							
Heterogeneity: Chi ² =	4.49, df	= 4 (P	= 0.34);	$ ^2 = 11$.%					
Test for overall effect:	Z = 2.56	6 (P = C)).01)							
									. .	
								0.01	0.1 1 10	100
		- 1.2				2			Favours TXA Favours control	

Test for subgroup differences: $Chi^2 = 3.74$, df = 1 (P = 0.05), $I^2 = 73.2\%$

4. Stroke



Test for subgroup differences: Not applicable

5. Myocardial infarction

	TXA	۸	Cont	rol		Risk Ratio			Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M–H, Fixed, 95% Cl	Year		M–H, Fixed, 95% C	
1.8.1 High-dose IV T	XA									
Engquist 1979	2	102	0	102	1.8%	5.00 [0.24, 102.87]	1979			
Halt-IT 2020	24	5952	28	5977	98.2%	0.86 [0.50, 1.48]	2020			
Subtotal (95% CI)		6054		6079	100.0%	0.93 [0.55, 1.58]			\bullet	
Total events	26		28							
Heterogeneity: Chi ² =	1.27, df	= 1 (P)	= 0.26);	$I^2 = 21$	%					
Test for overall effect:	Z = 0.26	6 (P = 0)	.80)							
								0.002		2 500

Favours TXA Favours control

Test for subgroup differences: Not applicable

6. Deep venous thrombosis



Test for subgroup differences: Not applicable

7. Pulmonary embolism

	ТХА	4	Cont	rol		Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M–H, Fixed, 95% Cl	Year	M–H, Fixed, 95% Cl
1.10.1 High-dose IV	ΤΧΑ							
Engquist 1979	5	102	2	102	9.1%	2.50 [0.50, 12.59]	1979	
Barer 1983	5	256	2	260	9.0%	2.54 [0.50, 12.97]	1983	
Holstein 1987	1	164	2	164	9.1%	0.50 [0.05, 5.46]	1987	
Bagneko 2011	0	22	0	25		Not estimable	2011	
Halt-IT 2020	28	5952	16	5977	72.7%	1.76 [0.95, 3.24]	2020	+- -
Subtotal (95% CI)		6496		6528	100.0%	1.78 [1.06, 3.00]		◆
Total events	39		22					
Heterogeneity: Chi ² =	1.44, df	= 3 (P)	= 0.70);	$l^2 = 0\%$	6			
Test for overall effect:	Z = 2.17	7 (P = 0)).03)					
Barer 1983 Holstein 1987 Bagneko 2011 Halt-IT 2020 Subtotal (95% CI) Total events Heterogeneity: Chi ² = Test for overall effect:	5 1 0 28 39 1.44, df Z = 2.17	256 164 22 5952 6496 = 3 (P 7 (P = 0	2 2 0 16 22 = 0.70); 0.03)	260 164 25 5977 6528 $I^2 = 0\%$	9.0% 9.1% 72.7% 100.0%	2.54 [0.50, 12.97] 0.50 [0.05, 5.46] Not estimable 1.76 [0.95, 3.24] 1.78 [1.06, 3.00]	1983 1987 2011 2020	

Favours TXA Favours control

Test for subgroup differences: Not applicable
TXA in patients with GI bleeding

8. Need for RBC Transfusion

Study or Subgroup 1.14.1 High–dose IV	Events	Total						
1.14.1 High-dose IV	TVA		Events	Total	Weight	M–H, Fixed, 95% Cl	Year	M–H, Fixed, 95% Cl
-	IXA							
Holstein 1987	47	164	54	164	1.3%	0.87 [0.63, 1.21]	1987	
Tavakoli 2017	2	133	1	138	0.0%	2.08 [0.19, 22.62]	2017	<u>+ </u>
Halt–IT 2020	3984	4076	4018	4129	98.6%	1.00 [1.00, 1.01]	2020	
Subtotal (95% CI)		4373		4431	100.0%	1.00 [0.99, 1.01]		Ŧ
Total events	4033		4073					
Heterogeneity: Chi ² =	1.27, df	= 2 (P	= 0.53);	$l^2 = 0\%$	Ś			
Test for overall effect:	Z = 0.71	(P = 0)	.48)					
1.14.2 Low–dose or e	enteral T	XA only	y					
Cormack 1973	68	76	63	74	30.5%	1.05 [0.93, 1.19]	1973	
Biggs 1976	77	103	71	97	35.0%	1.02 [0.87, 1.20]	1976	
Hawkey 2001	58	103	60	103	28.7%	0.97 [0.76, 1.22]	2001	
Bagneko 2011	14	22	13	25	5.8%	1.22 [0.75, 2.00]	2011	
Subtotal (95% CI)		304		299	100.0%	1.03 [0.93, 1.13]		•
Total events	217		207					
Heterogeneity: Chi ² =	0.89, df	= 3 (P	= 0.83);	$l^2 = 0\%$	6			
Test for overall effect:	Z = 0.51	(P = 0)	.61)					
							-	
								Favours TXA Favours control

Test for subgroup differences: $Chi^2 = 0.21$, df = 1 (P = 0.65), $I^2 = 0\%$