Supplemental Digital Content

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Supplementary Table 1. Systematic review search terms

Database	Query	
PubMed	(warfarin OR "vitamin K antagonist" OR VKA OR coumarin OR Coumadin OR anticoagulation OR anticoagulant) AND ("prothrombin complex concentrate" OR PCC) AND (dose or dosing) Filters: from 2000 - 2022	379
EMBASE	SEARCH QUERY (('warfarin'/exp OR 'warfarin' OR 'vitamin k antagonists'/exp OR 'vitamin k antagonists' OR 'vka' OR 'coumarin'/exp OR 'coumarin' OR 'coumadin'/exp OR 'coumadin' OR 'anticoagulation'/exp OR 'anticoagulation' OR 'anticoagulant agent'/exp OR 'anticoagulant agent') AND ([article]/lim OR [review]/lim) AND [humans]/lim) AND ('prothrombin complex concentrate' OR 'pcc') AND ('dose' OR 'dosing')	482
MEDLINE (OVID)	((warfarin or vitamin K antagonists or VKA or VKAs or coumarin or Coumadin or phenprocoumon or acenocoumarol) and (4-factor prothrombin complex concentrate or prothrombin complex concentrate or 4-PCC or PCC)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	568

Supplementary Table 2. Studies included in the meta-analysis.

Author, Year	Country	Design	Participants	PCC used	Target INR		Fixed-Dos Regimen*	Study Population (n)		Indications for Fixed-Dose			Indications for Variable-Dose			NOS
					INR <2	INR <1.5		Fixed-Dose	Variable-Dose	ECH	ICH	Urgent Intervention	ECH	ICH	Urgent Intervention	
van Aart et al., 2006	Netherlands	Prospective RCT	Single Center	Cofact	Yes (INR < 2.1)	Yes	500 IU/ 7 IU IU/kg	47	46	13	2	32	14	8	24	3‡
Khorsand et al., 2011	Netherlands	Prospective cohort†	Multicenter	Cofact	Yes	Yes	Emergency Surgery: 520 IU ECH: 1040 IU	35	32	18	0	17	19	0	13	8
Khorsand et al., 2012	Netherlands	Prospective observational, two-cohort	Multicenter	Cofact	Yes	No	ECH: 1040 IU	101	139	101	0	0	139	0	0	7
Abdoellakhan et al., 2017	Netherlands	Retrospective Cohort	Single Center	Cofact	No	Yes	1000 IU (Additional 500 IU)	28	25	0	28	0	0	25	0	9
Scott et al. ,2018	USA	Retrospective Cohort	Single Center	Kcentra	No	Yes	1000 IU (Additional 1000 IU)	30	31	0	30	0	0	31	0	9
Zemrak et al., 2019	USA	Retrospective Cohort	Single Center	Kcentra	Yes	Yes, (INR < 1.6)	**ICH:** INR > 2: 15 IU/kg INR ≥ 2: 25 IU/kg **Non-ICH:** INR < 4: 15 IU/kg INR ≥ 4: 25 IU/kg	83	122	17	49	17	32	72	18	8
Bitonti et al., 2020	USA	Prospective cohort†	Multicenter	Kcentra	Yes	Yes	INR < 7.5 :1500 IU INR > 7.5: 2000 IU Weight > 100 kg: 2000 IU	24	30	14	9	1	10	19	1	8
Dietrich et al., (EMJ), 2020	USA	Retrospective Cohort	Multicenter	Kcentra	Yes	Yes, (INR < 1.4)	INR < 7.5: 1500 IU INR ≥7.5: 2000 IU Weight ≥100 kg: 2000 IU	75	116	43	8	24	50	37	29	7
Gilbert et al., 2020	USA	Retrospective Cohort	Single Center	Kcentra	No	Yes, (INR < 1.6)	ICH (1500 IU) ECH (1000 IU) Weight > 100 kg (Additional 500 IU)	30	30	9	15	6	8	11	11	8
Kim et al., 2020	USA	Retrospective Cohort	Single Center	Kcentra	Yes	No	2000 IU (Additional 2000 IU)	34	38	12	13	11	14	14	16	8
Elsamadisi et al., 2021	USA	Retrospective Cohort	Single Center	Kcentra	Yes	Yes	Weight ≥ 100 kg 2000 IU (Additional 500–1000 IU)	19	25	8	2	9	6	12	7	8
Bizzell et al., 2021	USA	Retrospective Cohort	Single Center	Kcentra	Yes	Yes	Weight > 100 kg: 2000 - 2500 IU INR > 5: 2000 - 2500 IU ICH: 2000 - 2500 IU Other: 1500 IU	63	50	18	20	23	13	7	25	8
Dietrich et al., (EMJ), 2021	USA	Retrospective Cohort	Multicenter	Kcentra	No	Yes	2000 IU	42	48	15	21	9	17	28	27	7
Dietrich et al., (Pharm), 2021	USA	Retrospective Cohort	Multicenter	Kcentra	No	Yes, INR ≤1.4	INR < 7.5: 1500 IU INR ≥7.5: 2000 IU Weight ≥100 kg: 2000 IU	53	72	0	42	0	0	48	0	8
McMahon et al., 2021	USA	Retrospective Cohort	Single Center	Kcentra	No	Yes	INR ≤6: 1000 IU INR ≥6.1: 2000 IU ICH: 2000 IU Weight ≥100 kg: 2000 IU (Additional 500 IU)	124	102	38	20	66	26	34	42	8
Stoecker et al., 2021	USA	Prospective RCT	Single Center	Kcentra	No	Yes	1500 IU (Additional 500 IU)	34	37	16	16	2	15	22	3	5‡
Abdoellakhan et al., 2022	Netherlands	Prospective RCT	Multicenter	Cofact/Kcentra			Fixed: 1000 IU	80	79	80	0	0	79	0	0	5‡
Bajdas et al., 2022	USA	Retrospective Cohort	Multicenter	Kcentra	No	Yes	INR 2–6: 1000 IU Weight ≤100 kg: 1000 IU	90	175	57	0	33	94	0	81	9
Riha et al., 2023	USA	Retrospective Cohort	Single Center		No	Yes	1500 IU	27	19	0	27	0	0	19	0	7

ICH, intracranial hemorrhage
ECH, extracranial hemorrhage

Supplementary Table 3. Primary meta-analyses comparing fixed- versus variable-dose regimens of 4-PCC administration.

Variable	Subgroup	Number of studies	Fixed dose	Variable dose	OR/SMD*	95% CI	p-value	I^2
Age (years)	RCT	2	73.4 ± 1.6 (n=127)	74.4 ± 3.3 (n=125)	-0.03	[-0.8, 0.7]	0.9	89%
	Cohort	14	72.2 ± 1.3 (n=831)	73 ± 1.2 (n=1035)	-0.04	[-0.2, 0.1]	0.5	43.5%
Sex (male)	RCT	3	55.3% (89/161)	60.5% (98/162)	0.8	[0.5, 1.4]	0.4	24.1%
	Cohort	15	54.3% (451/831)	57.5% (595/1035)	0.9	[0.7, 1.04]	0.1	0%
Patient weight (kg)	RCT	2	73.3 ± 2.7 (n=127)	75.9 ± 2.4 (n=125)	-0.1	[-0.3, 0.2]	0.5	0%
	Cohort	13	86.1 ± 3.4 (n=796)	89 ± 2.6 (n=1003)	-0.02	[-0.2, 0.1]	0.8	61.1%
Indications								
ECH	RCT	3	67.7% (109/161)	66.7% (108/162)	1.1	[0.6, 2]	0.9	0%
	Cohort	15	42.1% (350/831)	41.4% (428/1035)	1.3	[1.02, 1.6]	**0.03**	0%
ICH	RCT	3	11.2% (18/161)	18.5% (30/162)	0.5	[0.2, 1.1]	0.1	0%
	Cohort	15	30.9% (257/831)	32.7% (338/1035)	0.7	[0.5, 1.2]	0.2	52.7%
Emergency intervention (surgery)	RCT	3	21.1% (34/161)	16.7% (27/162)	1.6	[0.8, 3.4]	0.6	0%
	Cohort	15	26% (216/831)	26.1% (270/1035)	0.9	[0.7, 1.3]	0.7	32.1%
Baseline INR	RCT	2	5.6 ± 1.2 (n=127)	5.9 ± 1.2 (n=125)	-0.08	[-0.3, 0.2]	0.5	0%
	Cohort	12	3.7 ± 0.2 (n=767)	3.7 ± 0.3 (n=967)	0.03	[-0.2, 02]	0.7	74.4%
Total PCC dose (IU)	Cohort	14	1537.3 ± 114.2 (n=831)	2222.2 ± 105.7 (n=1035)	-1.02	[-1.3, -0.8]	**< 0.0001**	83.1%
PCC dose by weight (IU/kg)	Cohort	8	22.1 ± 1.4 (n=399)	27.7 ± 2.8 (n=501)	-0.5	[-1.03, 0.0002]	0.05	92.3%
Door-to-needle time (min)	Cohort	2	115.4 ± 14.9 (n=129)	141.4 ± 34.2 (n=164)	-0.6	[-1.4, 02]	0.2	86.7%
Order-to-needle time (min)	Cohort	4	39 ± 2.8 (n=202)	72.03 ± 14.2 (n=280)	-0.4	[-0.6, -0.2]	**< 0.0001**	0%
Post-treatment INR	Cohort	11	1.48 ± 0.05 (n=677)	1.42 ± 0.6 (n=791)	0.2	[-0.2, 0.5]	0.7	88.5%
Clinical hemostasis	Cohort	5	74.1% (320/432)	61.6% (355/576)	1.7	[1.05, 2.8]	**0.03**	0%
INR <2 achieved	RCT	2	84.3% (97/115)	94.1% (111/118)	0.3	[0.02, 4.3]	0.3	80.7%
	Cohort	10	88.8% (468/527)	92.4% (537/581)	0.7	[0.4, 1.2]	0.2	20.8%
INR <1.5 achieved	RCT	2	66.7% (44/66)	88.6% (62/70)	0.3	[0.09, 0.8]	**0.02**	35.4%
	Cohort	15	64.6% (478/740)	74.3% (684/918)	0.6	[0.5, 0.8]	**0.0001**	14.2%
PCC-to-INR (min)	Cohort	4	147.4 ± 50.2 (n=240	192.5 ± 56.9 (n=313)	-0.3	[-0.5, -0.1]	**0.001**	0%
Additional 4-PCC	RCT	3	17.4% (28/161)	2.5% (4/162)	8.6	[3, 24.6]	**< 0.0001**	0%
	Cohort	14	5.2% (40/767)	3.1% (30/967)	1.5	[0.8, 2.6]	0.2	0%
FFP	RCT	2	5.5% (7/127)	0.8% (1/125)	4.7	[0.7, 30.6]	0.1	0%
	Cohort	12	16.3% (118/726)	17.8% (166/930)	0.8	[0.5, 1.2]	0.3	50.1%
vitamin K	RCT	2	97.1% (133/137)	95.9% (212/221)	1.2	[0.4, 3.7]	0.8	0%
	Cohort	13	83.1% (631/759)	87.6% (767/876)	0.8	[0.6, 1.04]	0.09	0%
Other blood products†	Cohort	5	55.5% (126/227)	59.3% (220/371)	0.8	[04, 1.6]	0.6	62.4%
Overall mortality	RCT	2	4.7% (6/127)	7.2% (9/125)	0.6	[0.2, 1.9]	0.4	0%
	Cohort	15	15.6% (130/831)	18.8% (195/1035)	0.8	[0.6, 1.03]	0.08	24.1%
TEE	RCT	3	1.2% (2/161)	1.8% (3/162)	0.7	[0.1, 3.8]	0.7	0%
	Cohort	13	2.4% (15/617)	4.4% (33/758)	0.5	[0.3, 1]	**0.04**	0%
Length of ICU admission	Cohort	3	26.4% (43/163)	22.1% (42/190)	0.7	[02, 2.9]	0.6	61.3%
Length of hospital stay (days)	Cohort	5	10 ± 2 (n=209)	9.6 ± 1.8 (n=257)	0.02	[-0.3, 0.3]	0.9	48.6%

*Effect size reported as an odds ratio for binary data or Hedges' *g* statistic for continuous data
†Other blood products include cryoprecipitate, packed red blood cells, and platelets
OR, Odds Ratio
CI, confidence interval
INR, international normalized ratio
TEE, thromboembolic events

Supplementary Table 4 Quality of evidence based on GRADE recommendations for overall metanalysis of randomized clinical trials.

Certainty assessment							№ of patients		Effect		Certainty	
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Fixed-Dose 4-PCC	Variable-Dose 4-PCC	Relative (95% CI)	Absolute (95% CI)		
Age (follow-up: range 1 Hours to 6 Hours)												
2	randomized trials	not serious	very serious[a]	not serious	not serious	none	127	125	-	SMD **0.03 SD lower** (0.8 lower to 0.7 higher)	⨁⨁◯◯ Low	
Sex												
3	randomized trials	not serious	not serious	not serious	not serious	none	89/161 (55.3%)	98/162 (60.5%)	**OR 0.8** (0.5 to 1.4)	**5 fewer per 100** (from 17 fewer to 8 more)	⨁⨁⨁⨁ High	
Patient weight (assessed with: Kg)												
2	randomized trials	not serious	not serious	not serious	not serious	none	127	125	-	SMD **0.1 SD lower** (0.3 lower to 0.2 higher)	⨁⨁⨁⨁ High	
Baseline INR												
2	randomised trials	not serious	not serious	not serious	not serious	none	127	125	-	SMD **0.08 SD lower** (0.3 lower to 0.2 higher)	⨁⨁⨁⨁ High	
INR <2 achieved												
2	randomized trials	not serious	very serious[a]	not serious	serious[b]	none	97/115 (84.3%)	111/118 (94.1%)	**OR 0.30** (0.02 to 4.30)	**11 fewer per 100** (from 70 fewer to 4 more)	⨁◯◯◯ Very low	
INR <1.5 achieved												
2	randomized trials	not serious	serious[a]	not serious	not serious	strong association	44/66 (66.7%)	62/70 (88.6%)	**OR 0.30** (0.09 to 0.80)	**19 fewer per 100** (from 47 fewer to 2 fewer)	⨁⨁⨁⨁ High	

Certainty assessment							№ of patients		Effect		Certainty	
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Fixed-Dose 4-PCC	Variable-Dose 4-PCC	Relative (95% CI)	Absolute (95% CI)		
Overall Mortality												
2	randomized trials	not serious	not serious	not serious	not serious	none	6/127 (4.7%)	9/125 (7.2%)	**OR 0.6** (0.2 to 1.9)	**3 fewer per 100** (from 6 fewer to 6 more)	⨁⨁⨁⨁ High	
TEE												
3	randomized trials	not serious	not serious	not serious	serious[b]	none	2/161 (1.2%)	3/162 (1.9%)	**OR 0.7** (0.1 to 3.8)	**1 fewer per 100** (from 2 fewer to 5 more)	⨁⨁⨁◯ Moderate	
Additional 4-PCC												
3	randomized trials	not serious	not serious	not serious	very serious[b]	strong association	28/161 (17.4%)	4/162 (2.5%)	**OR 8.6** (3.0 to 24.6)	**15 more per 100** (from 5 more to 36 more)	⨁⨁⨁◯ Moderate	
Additional FFP												
2	randomized trials	not serious	not serious	not serious	very serious[b]	none	7/127 (5.5%)	1/125 (0.8%)	**OR 4.7** (0.7 to 30.6)	**3 more per 100** (from 0 fewer to 19 more)	⨁⨁◯◯ Low	
Additional Vitamin K												
2	randomized trials	not serious	not serious	not serious	serious[b]	none	133/137 (97.1%)	212/221 (95.9%)	**OR 1.2** (0.4 to 3.7)	**1 more per 100** (from 6 fewer to 3 more)	⨁⨁⨁◯ Moderate	

CI: confidence interval; **OR:** odds ratio; **SMD:** standardised mean difference

Explanations

a. Inconsistency was rated based on the heterogeneity statistic I2. It was judged “not serious” when I2 measured below 25%, “serious” when it was between 25-75%, and “very serious” when it exceeded 75%.

b. If the CI around the estimate of the treatment effect is sufficiently narrow. No rate down. If the CI around the estimate of the treatment effect is wide, we rate down by one level. If the CI is very wide, we rate down by two levels.

Supplementary Table 5 Quality of evidence based on GRADE recommendations for overall metanalysis of cohort studies.

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Fixed-Dose 4-PCC	Variable-Dose 4-PCC	Relative (95% CI)	Absolute (95% CI)	
Age (assessed with: Years)											
14	observational studies	serious[a]	not serious	not serious	not serious	strong association	831	1035	-	SMD **0.04 SD lower** (0.2 lower to 0.1 higher)	⨁⨁⨁⨁ High
Sex											
15	observational studies	serious[a]	not serious	not serious	not serious	strong association	451/831 (54.3%)	595/1035 (57.5%)	**OR 0.90** (0.70 to 1.04)	**3 fewer per 100** (from 9 fewer to 1 more)	⨁⨁⨁⨁ High
Patient weight (assessed with: Kg)											
13	observational studies	serious[a]	serious[b]	not serious	not serious	none	796	1003	-	SMD **0.02 SD lower** (0.2 lower to 0.1 higher)	⨁⨁◯◯ Low
Baseline INR											
12	observational studies	serious[a]	serious[b]	not serious	not serious	none	767	967	-	SMD **0.03 SD higher** (0.2 lower to 0.2 higher)	⨁⨁◯◯ Low
Total 4-PCC Dose (assessed with: IU)											
14	observational studies	serious[a]	very serious[b]	not serious	not serious	strong association	831	1035	-	SMD **1.02 SD lower** (1.3 lower to 0.8 lower)	⨁⨁◯◯ Low
PCC Dose/weight											
8	observational studies	serious[a]	very serious[b]	not serious	not serious	strong association	399	501	-	SMD **0.5 SD lower** (1.03 lower to 0.0002 higher)	⨁⨁◯◯ Low
Post-treatment INR											

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Fixed-Dose 4-PCC	Variable-Dose 4-PCC	Relative (95% CI)	Absolute (95% CI)	
11	observational studies	serious[a]	very serious[b]	not serious	not serious	none	677	791	-	SMD **0.2 SD higher** (0.2 lower to 0.5 higher)	⨁◯◯◯ Very low
Door-to-needle time (assessed with: Minutes)											
2	observational studies	serious[a]	very serious[b]	not serious	not serious	none	129	164	-	SMD **0.6 SD lower** (1.4 lower to 0.2 higher)	⨁◯◯◯ Very low
Order-to-needle time (assessed with: Minutes)											
4	observational studies	serious[a]	not serious	not serious	not serious	strong association	202	280	-	SMD **0.4 SD lower** (0.6 lower to 0.2 lower)	⨁⨁⨁⨁ High
PCC-to-INR (assessed with: Minutes											
4	observational studies	serious[a]	not serious	not serious	not serious	strong association	240	313	-	SMD **0.3 SD lower** (0.5 lower to 0.1 lower)	⨁⨁⨁⨁ High
Clinical Hemostasis											
5	observational studies	serious[a]	not serious	not serious	serious[c]	strong association	320/432 (74.1%)	355/576 (61.6%)	**OR 1.70** (1.05 to 2.80)	**12 more per 100** (from 1 more to 20 more)	⨁⨁⨁◯ Moderate
INR <2 achieved											
10	observational studies	serious[a]	not serious	not serious	not serious	none	468/527 (88.8%)	537/581 (92.4%)	**OR 0.7** (0.4 to 1.2)	**3 fewer per 100** (from 9 fewer to 1 more)	⨁⨁⨁◯ Moderate
INR <1.5 achieved											
15	observational studies	serious[a]	not serious	not serious	serious[c]	strong association	478/740 (64.6%)	684/918 (74.5%)	**OR 0.6** (0.5 to 0.8)	**11 fewer per 100** (from 15 fewer to 4 fewer)	⨁⨁⨁◯ Moderate
Overall Mortality											

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Fixed-Dose 4-PCC	Variable-Dose 4-PCC	Relative (95% CI)	Absolute (95% CI)	
15	observational studies	serious[a]	not serious	not serious	not serious	dose response gradient	130/831 (15.6%)	195/1035 (18.8%)	**OR 0.80** (0.60 to 1.03)	**3 fewer per 100** (from 7 fewer to 0 fewer)	⨁⨁⨁⨁ High
Thromboembolic events											
13	observational studies	serious[a]	not serious	not serious	not serious	strong association	15/617 (2.4%)	33/758 (4.4%)	**OR 0.5** (0.3 to 1.0)	**2 fewer per 100** (from 3 fewer to 0 fewer)	⨁⨁⨁⨁ High
ICU Admission											
3	observational studies	serious[a]	serious[b]	not serious	serious[c]	none	43/163 (26.4%)	42/190 (22.1%)	**OR 0.7** (0.2 to 2.9)	**6 fewer per 100** (from 17 fewer to 23 more)	⨁◯◯◯ Very low
Additional 4-PCC											
14	observational studies	serious[a]	not serious	not serious	not serious	none	40/767 (5.2%)	30/967 (3.1%)	**OR 1.5** (0.8 to 2.6)	**1 more per 100** (from 1 fewer to 5 more)	⨁⨁⨁◯ Moderate
Additional FFP											
12	observational studies	serious[a]	serious[b]	not serious	not serious	none	118/726 (16.3%)	166/930 (17.8%)	**OR 0.8** (0.5 to 1.2)	**3 fewer per 100** (from 8 fewer to 3 more)	⨁⨁◯◯ Low
Additional Vitamin K											
13	observational studies	serious[a]	not serious	not serious	not serious[c]	none	631/759 (83.1%)	767/876 (87.6%)	**OR 0.80** (0.60 to 1.04)	**3 fewer per 100** (from 7 fewer to 0 fewer)	⨁⨁⨁◯ Moderate
Additional Blood Products											
5	observational studies	serious[a]	serious[b]	not serious	serious[c]	none	126/227 (55.5%)	220/371 (59.3%)	**OR 0.8** (0.4 to 1.6)	**5 fewer per 100** (from 22 fewer to 11 more)	⨁◯◯◯ Very low
Hospital Stay											

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Fixed-Dose 4-PCC	Variable-Dose 4-PCC	Relative (95% CI)	Absolute (95% CI)	
5	observational studies	serious[a]	serious[b]	not serious	not serious	none	209	257	-	SMD **0.02 SD higher** (0.3 lower to 0.3 higher)	⨁⨁◯◯ Low

CI: confidence interval; **OR:** odds ratio; **SMD:** standardised mean difference

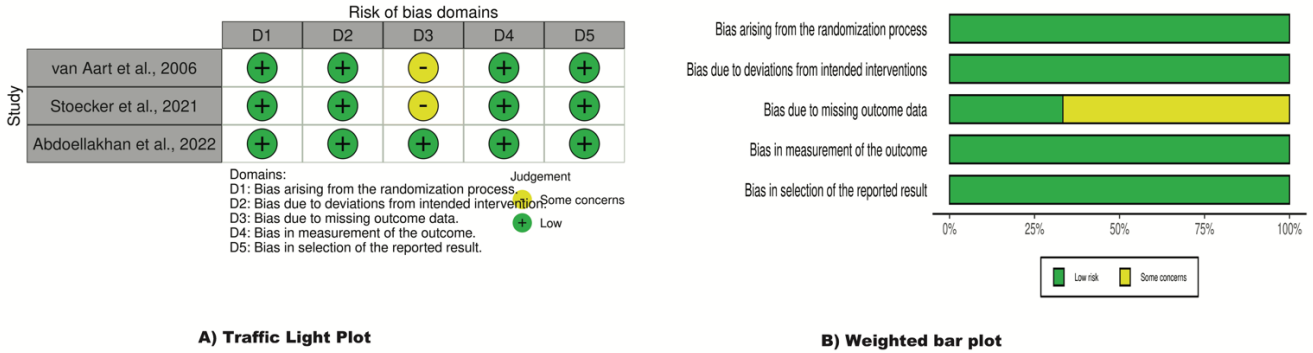
Explanations

a. Most studies are retrospective without confounding adjustments

b. Inconsistency was rated based on the heterogeneity statistic I2. It was judged “not serious” when I2 measured below 25%, “serious” when it was between 25-75%, and “very serious” when it exceeded 75%.

c. If the CI around the estimate of the treatment effect is sufficiently narrow. No rate down If the CI around the estimate of the treatment effect is wide, we rate down by one level. If the CI is very wide, we rate down by two levels.

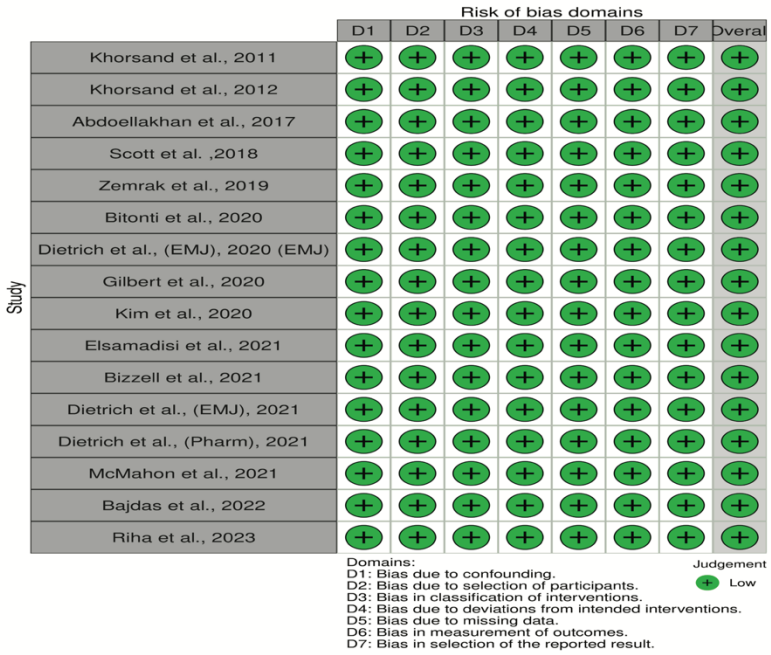
Supplementary Figure 1. RCTs risk-of-bias assessments



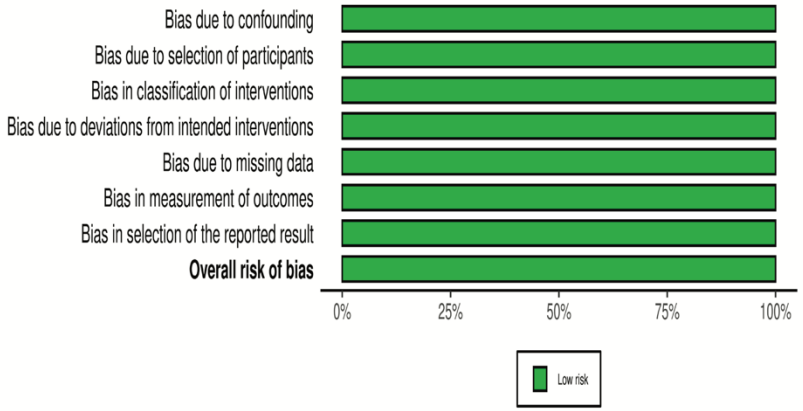
A) Traffic Light Plot **B) Weighted bar plot**

A. Traffic light plot of the domain-level judgments for each RCT.
B. Bar plot of the distribution of risk-of-bias judgments within each bias domain.

Supplementary Figure 2. Cohort studies risk-of-bias assessments



A) Traffic Light Plot



B) Weighted bar plot

A. Traffic light plot of the domain-level judgments for each **Cohort study**.
B. Bar plot of the distribution of risk-of-bias judgments within each bias domain.

Supplementary Table 6. Subgroup meta-analyses based on weight subgroup comparing fixed- versus variable-dose regimens of 4-PCC administration.

Variable	Weight subgroup	Number of studies	Fixed dose	Variable-dose	OR/SMD*	95% CI	p-value	I^2
Age (years)	**< 80 kg**	2	73.3 ± 6 (n=117)	72.8 ± 1.4 (n=164)	-0.01	[-0.6, 0.5]	1	79.1%
	≥ 80 kg	7	73.4. ± 1.9 (n=348)	75 ± 2.5 (n=407)	-0.1	[-0.4, 0.1]	0.3	62.4%
Sex (male)	**< 80 kg**	2	50.4% (59/117)	53.7% (88/164)	0.9	[0.5, 1.4]	0.5	0%
	≥ 80 kg	8	59.4% (221/372)	59.5% (260/437)	1	[0.6, 1.6]	1	56.3%
Patient weight (kg)	**< 80 kg**	2	73.3 ± 6 (n=117)	72.8 ± 1.4 (n=164)	-0.01	[-0.6, 0.5]	0.97	79.1%
	≥ 80 kg	7	93.3 ± 6.3 (n=348)	92 ± 3.9 (n=407)	-0.03	[-0.2, 0.3]	0.3	52.8%
Baseline INR	**< 80 kg**	2	3.5 ± 0.7 (n=117)	3.1 ± 0.3 (n=164)	0.2	[-0.1, 0.5]	0.2	29.5%
	≥ 80 kg	6	3.4 ± 0.2 (n=318)	3.5 ± 0.3 (n=377)	0.02	[-0.3, 0.4]	0.9	77.9%
Total PCC dose	**< 80 kg**	2	1889.5 ± 113.9 (n=117)	2110 ± 83.9 (n=164)	-0.4	[-1, -0.3]	0.3	85.6%
	≥ 80 kg	7	1466.8 ± 144.1 (n=348)	2249 ± 111.3 (n=407)	-1.2	[-1.4, -1]	**< 0.0001**	49.3%
PCC Dose by weight (IU/kg)	**< 80 kg**	2	24 ± 2.7 (n=117)	25.9 ± 1.4 (n=164)	0.2	[-1.6, 1.3]	0.8	96.9%
	≥ 80 kg	3	19.3 ± 1.2 (n=76)	26.1 ± 5.5 (n=74)	-0.4	[-0.4, 1.1]	0.6	94.8%
Order-to-needle time (min)	**≥ 80 kg**	4	35.3 ± 3.2 (n=166)	54.2 ± 5.9 (n=249)	-0.5	[-0.7, -0.3]	**< 0.0001**	0%
Post-treatment INR	**< 80 kg**	2	1.3 ± 0.2 (n=117)	1.3 ± 0.1 (n=164)	-0.2	[-1.1, 0.7]	0.7	91.6%
	≥ 80 kg	5	1.5 ± 0.03 (n=228)	1.3 ± 0.03 (n=201)	0.4	[-0.2, 1]	0.2	86.6%
Clinical hemostasis	**≥ 80 kg**	2	60.7% (130/214)	38.3% (106/277)	2	[1.3, 2.9]	**0.001**	0%
INR <2 achieved	**< 80 kg**	2	91.5% (107/117)	96.3% (158/164)	0.4	[0.1, 1]	0.06	0%
	≥ 80 kg	4	89.2% (173/194)	94.3% (166/176)	0.6	[0.2, 2]	0.4	38.4%
INR <1.5 achieved	**< 80 kg**	2	68.4% (80/117)	70.1% (115/164)	0.9	[0.5, 1.5]	0.6	4.4%
	≥ 80 kg	8	64.5% (240/372)	76.9% (336/437)	0.4	[0.3,0.7]	**0.002**	36.2%
PCC-to-INR (min)	**≥ 80 kg**	2	97.6 ± 2.7 (n=143)	144.7 ± 2.7 (n=127)	-1	[-2.2, 0.2]	0.1	92.3%
Overall mortality	**< 80 kg**	2	14.5% (17/117)	19.5% (32/164)	0.7	[0.3, 1.3]	0.2	0%
	≥ 80 kg	8	17.5% (65/372)	14.6% (64/437)	1.1	[0.8,1.7]	0.5	0.3%
TEE	**< 80 kg**	2	0% (0/117)	2.4% (4/164)	0.3	[0.03, 2.2]	0.2	0%
	≥ 80 kg	6	1.9% (3/158)	1.9% (3/160)	1.1	[0.3, 4.2]	0.9	0%
Length of hospital stay (days)	**< 80 kg**	2	7.1 ± 0.7 (n=117)	7.4 ± 1.6 (n=164)	0.006	[-0.5, 0.5]	1	76.9%
	≥ 80 kg	3	11.1 ± 3.9 (n=85)	12.3 ± 2.8 (n=74)	-0.08	[-0.5, 0.3]	0.7	40.9%
Additional 4-PCC	**< 80 kg**	2	5.2% (6/117)	1.8% (3/164)	2.6	[0.6, 11]	0.2	0%
	≥ 80 kg	7	9.9% (30/308)	5.2% (21/369)	1.6	[0.7, 4]	0.3	30.8%
FFP	**< 80 kg**	2	0 (0/117)	0 (0/164)	1.3	[0.08, 21.5]	0.8	0%
	≥ 80 kg	6	18.6% (59/317)	21.4% (84/393)	1.7	[0.4, 1.4]	0.4	49.8%
Vitamin K	**< 80 kg**	2	81.2% (95/117)	86% (141/164)	0.6	[0.3, 1.2]	0.2	0%
	≥ 80 kg	7	86.3% (297/344)	90.3% (372/412)	0.8	[0.5, 1.3]	0.4	0%

*Effect size reported as an odds ratio for binary data or Hedges' *g* statistic for continuous data
†Other blood products include cryoprecipitate, packed red blood cells, and platelets
OR, odds ratio
CI, confidence interval
INR, international normalized ratio
TEE, thromboembolic events

Supplementary Table 7. Subgroup meta-analyses based on indications subgroup comparing fixed- versus variable-dose regimens of 4-PCC administration.

Variable	4-PCC indication	Number of studies	Fixed dose	Variable-dose	OR/SMD*	95% CI	p-value	I^2
Age (years)	**ICH**	5	77.7 ± 0.9 (n=142)	79 ± 2.3 (n=134)	-0.1	[-0.4, 0.2]	0.5	46.7%
	Non-ICH	4	71 ± 0.9 (n=241)	68.9 ± 1.1(n=365)	0.1	[-0.02, 0.3]	0.1	0%
	All Indications	5	69 ± 2.1 (n=244)	72.5 ± 2 (n=301)	-0.3	[-0.5, 0.003]	0.05	51.1%
Sex (male)	**ICH**	5	60.6% (86/142)	54.5% (73/134)	1.4	[0.7, 2.7]	0.3	41.4%
	Non-ICH	4	54.8% (132/241)	54.2% (198/365)	1	[0.6, 1.6]	0.8	50.4%
	All Indications	6	52.2% (140/268)	58.3% (193/331)	0.8	[0.5, 1]	0.1	0%
Patient weight (kg)	**ICH**	6	85 ± 2.4 (n=162)	83.7 ± 2.9 (n=168)	0.1	[-0.1, 0.3]	0.4	0%
	Non-ICH	4	82.4 ± 2 (n=300)	84.9 ± 4.3 (n=392)	-0.1	[-0.4, 0.2]	0.5	69.9%
	All Indications	5	91.9 ± 10.5 (n=244)	87.6 ± 6.3 (n=301)	0.1	[-0.3, 0.5]	0.6	77.7%
Baseline INR	**ICH**	7	3.2 ± 0.3 (n=211)	3.1 ± 0.3 (n=240)	0.03	[-0.2, 0.3]	0.8	43%
	Non-ICH	4	4.4 ± 0.4 (n=243)	4.8 ± 0.3 (n=378)	-0.3	[-0.5, -0.1]	**0.004**	31.7%
	All Indications	4	3.8 ± 0.2 (n=210)	3.3 ± 0.2 (n=263)	0.3	[-0.07, 0.5]	**0.01**	10.3%
Total PCC dose	**ICH**	7	1677.6 ± 134.2 (n=211)	2020.7 ± 81.7 (n=240)	-0.6	[-1.1, -0.1]	**0.02**	82.3%
	Non-ICH	6	1289.6 ± 185.8 (n=352)	2586.9 ± 297.9 (n=456)	-1.6	[-2, -1.2]	**< 0.0001**	81.1%
	All Indications	5	1891.8 ± 138.8 (n=244)	2441.65 ± 230.8 (n=301)	-0.98	[-1.3, -0.7]	**< 0.0001**	60.5%
PCC dose by weight (IU/kg)	**ICH**	4	22.1 ± 1.7 (n=133)	26 ± 1.1 (n=150)	-0.5	[-1.4, 0.3]	0.2	90.7%
	Non-ICH	2	18.1 ± 3.4 (n=32)	33.7 ± 1.7 (n=51)	-1.25	[-1.7, -0.8]	**< 0.0001**	0%
	All Indications	5	22.3 ± 1.6 (n=244)	27.2 ± 4.3 (n=301)	-0.5	[-1.2, 0.11]	0.1	91.7%
Post-treatment INR	**ICH**	6	1.4 ± 0.07 (n=181)	1.3 ± 0.01 (n=209)	0.06	[-0.3, 0.4]	0.8	68.7%
	Non-ICH	4	1.6 ± 0.05 (n=247)	1.5 ± 0.1 (n=262)	0.2	[-0.4, 0.7]	0.5	87.3%
	All Indications	4	1.47 ± 0.08 (n=210)	1.37 ± 0.08 (n=263)	0.3	[-0.1, 0.8]	0.1	82.3%
Door-to-needle time (min)	**Non-ICH**	2	186.3 ± 64 (n=116)	252.± 84.3 (n=158)	-0.8	[-1.3, -0.3]	**0.003**	54.9%
Order-to-needle time (min)	**ICH**	2	35.02 ± 8.1 (n=42)	54.2 ± 15.6 (n=30)	-0.7	[-1.2, -0.3]	**0.003**	0%
	Non-ICH	2	46.3 ± 2.3 (n=100)	77.85 ± 5.1 (n=184)	-0.5	[-0.8, -0.3]	**< 0.0001**	0%
	All Indications	2	58.5 ± 26.6 (n=82)	89.4 ± 43.1 (n=75)	-0.3	[-0.6, 0.01]	**0.04**	0%
Clinical hemostasis	**ICH**	2	76.8% (53/69)	77.4% (82/106)	0.9	[0.4, 2]	0.8	0%
	Non-ICH	5	75.8% (297/392)	61.9% (305/493)	1.9	[1.2, 2.9]	**0.004**	15.1%
INR <2 achieved	**ICH**	4	95.2% (99/104)	96.4% (108/112)	1	[0.3, 3.4]	0.9	0%
	Non-ICH	5	88.6% (217/245)	95.4% (251/263)	0.4	[0.2, 0.9]	**0.03**	0%
	All Indications	5	89.9% (189/215)	89.2% (231/259)	1.01	[0.5, 2.2]	1	33.5%
INR <1.5 achieved	**ICH**	6	80.6% (154/191)	89.3% (184/206)	0.5	[0.2, 1.2]	0.1	36.5%
	Non-ICH	4	58.7% (122/208)	67% (221330)	0.7	[0.5, 1]	0.05	0%
	All Indications	5	54.3% (127/234)	65.5% (192/293)	0.7	[04, 1]	**0.003**	0%
PCC-to-INR (min)	**All Indications**	3	82.1 ± 45 (n=157)	106.6 ± 55.9 (n=191)	-0.2	[-0.4, 0.02]	0.1	0%
Overall mortality	**ICH**	7	19.4% (41/211)	24.2% (58/240)	0.7	[0.4, 1.3]	0.3	31.6%
	Non-ICH	6	11.6% (41/352)	16.2% (74/456)	0.8	[0.4, 1.4]	0.4	34.1%
	All Indications	6	14.2% (38/268)	18.4% (61/331)	0.7	[0.4, 1.1]	0.1	0%
TEE	**ICH**	6	1.6% (3/191)	2.4% (5/206)	0.7	[0.2, 2.9]	0.7	0%
	Non-ICH	4	1.2% (2/168)	3.2% (7/222)	0.5	[0.1, 2.1]	0.3	0%
	All Indications	6	3% (8/268)	4.5% (15/331)	0.6	[0.2, 2.5]	0.5	36.3%
Length of Hospital Stay (days)	**ICH**	4	10.2 ± 2.9 (n=112)	9.5 ± 2.4 (n=103)	0.1	[-0.1, 0.4]	0.3	5.7%
	All Indications	2	7.5 ± 0.9 (n=109)	8.4 ± 0.7 (n=154)	-0.1	[-0.5, 0.3]	0.6	43.6%
Additional 4-PCC	**ICH**	5	15% (22/147)	7.6% (12/157)	1.9	[0.9, 4.1]	0.1	0%
	Non-ICH	4	1% (3/286)	3% (11/367)	0.7	[0.2, 2.3]	0.5	0%
	All Indications	6	3% (8/268)	2.1% (7/331)	1.2	[0.5, 3.2]	0.7	0%
FFP	**Non-ICH**	3	12% (25/208)	9.5% (33/346)	1.3	[0.4, 3.3]	0.8	61.7%
	All Indications	6	16.8% (45/268)	16.9% (56/331)	0.8	[0.4, 1.3]	0.3	10.4%
Vitamin K	**ICH**	3	96% (95/99)	93.9% (92/98)	1.4	[0.4, 4.9]	0.6	0%
	Non-ICH	3	98.2% (222/226)	97.4% (337/346)	1.1	[0.4, 3.4]	0.8	0%
	All Indications	5	73.1% (171/234)	79.5% (233/293)	0.8	[0.5, 1.2]	0.3	0%
Other blood products*	**Non-ICH**	3	61.5% (107/174)	62% (191/308)	0.8	[0.5, 1.6]	0.9	42%
	All Indications	2	35.8% (19/53)	46.03% (29/63)	0.7	[0.1, 6.5]	0.8	85.%

*Effect size reported as an odds ratio for binary data or Hedges' *g* statistic for continuous data
†Other blood products include cryoprecipitate, packed red blood cells, and platelets
OR, odds ratio
CI, confidence interval
INR, international normalized ratio
TEE, thromboembolic events

CI, confidence interval

4-PCC, four-factor prothrombin complex concentrate

ICH, intracranial hemorrhage

INR, international normalized ratio

Wt, weight

Supplementary Table 8. Subgroup meta-analyses based on baseline INR subgroup comparing fixed- versus variable-dose regimens of 4-PCC administration.

Variable	Baseline INR	Number of studies	Fixed dose	Variable-dose	OR/SMD*	95% CI	p-value	I^2
Age (years)	**INR < 4**	8	73.5 ± 2.03 (n=441)	74.7 ± 2.1 (n=469)	-0.1	[-0.3, 0.1]	0.3	46.9%
	INR ≥ 4	3	71.8 ± 1.6 (n=164)	71.1 ± 1.2 (n=196)	0.01	[-0.1, 0.3]	0.5	0%
Sex (male)	**INR < 4**	8	56.7% (250/441)	61.6% (289/469)	0.8	[0.6, 1.2]	0.3	38.2%
	INR ≥ 4	3	48.8% (80/164)	52% (102/196)	0.9	[0.6, 1.3]	0.5	0%
Patient weight (kg)	**INR < 4**	8	88.1 ± 5.9 (n=441)	86.5 ± 4 (n=469)	0.06	[-0.2, -0.3]	0.6	57.1%
	INR ≥ 4	2	84 ± 6.2 (n=129)	87.2 ± 1.6 (n=164)	-0.2	[-0.6, 0.2]	0.07	54.8%
Baseline INR	**INR < 4**	8	3.2 ± 0.1 (n=441)	3 ± 0.1 (n=469)	0.1	[-0.03, 0.3]	0.1	40%
	INR ≥ 4	3	4.8 ± 0.1 (n=164)	4.9 ± 0.3 (n=196)	-0.2	[-0.5, 0.1]	0.3	46.5%
Total PCC dose	**INR < 4**	8	1632.5 ± 115.3 (n=441)	2223 ± 49.4 (n=469)	-1.02	[-1.4, -0.6]	**< 0.0001**	84.2%
	INR ≥ 4	3	1162.2 ± 161.2 (n=164)	1734.7 ± 51.4 (n=196)	-1.2	[-1.9, -0.5]	**0.0006**	85.5%
PCC dose by weight (IU/kg)	**INR < 4**	5	20.3 ± 0.3 (n=245)	24.5 ± 2.3 (n=288)	-0.6	[-1.3, 0.1]	0.1	92.2%
Post-treatment INR	**INR < 4**	7	1.4 ± 0.07 (n=411)	1.3 ± 0.05 (n=438)	0.3	[-0.2, 0.7]	0.2	89.7%
	INR ≥ 4	4	1.6 ± 0.06 (n=232)	1.8 ± 0.2 (n=268)	0.07	[-0.2, 0.3]	0.6	39.2%
Door-to-needle time (min)	**INR ≥ 4**	2	115.4 ± 14.9 (n=129)	141.4 ± 34.2 (n=164)	-0.6	[-1.4, 0.2]	0.2	86.7%
Order-to-needle time (min)	**INR < 4**	3	45.5 ± 15.8 (n=109)	70.5 ± 26.7 (n=94)	-0.4	[-0.8, 0.1]	**0.005**	14.7%
Clinical hemostasis	**INR < 4**	2	76.3% (158/207)	73.7% (165/224)	1.2	[0.5, 2.6]	0.7	69%
INR <2 achieved	**INR < 4**	5	89.1% (245/275)	92.6% (226/244)	0.8	[0.3, 1.9]	0.6	32.9%
	INR ≥ 4	2	87.4% (104/119)	92.8% (142/153)	0.6	[0.2, 1.3]	0.2	0%
INR <1.5 achieved	**INR < 4**	8	64.6% (263/407)	77.8% (326/419)	0.5	[0.3, 0.9]	**0.01**	45.3%
	INR ≥ 4	3	55.7% (73/131)	67.7% (109/161)	0.4	[0.1, 1.3]	0.1	36.8%
PCC-to-INR time (min)	**INR < 4**		116.4 ± 24.2 (n=331)	156.2 ± 25.1 (n=347)	-0.5	[-1.2, 0.1]	0.08	92.7%
Overall mortality	**INR < 4**	8	18.1% (80/441)	20.9% (98/469)	0.8	[0.5, 1.2]	0.3	28.1%
	INR ≥ 4	3	15.9% (26/164)	25% (49/196)	0.6	[0.3, 1.3]	0.2	37.2%
TEE	**INR < 4**	7	4.1% (13/317)	6.3% (23/367)	0.7	[0.2, 1.8]	0.4	27.9%
	INR ≥ 4	3	1.2% (2/164)	3.1% (6/196)	0.4	[0.1, 1.9]	0.3	0%
Length of hospital stay (days)	**INR < 4**	2	6.7 ± 1 (n=69)	6 ± 0.7 (n=67)	0.06	[-0.5, 0.6]	0.8	55.3%
Additional 4-PCC	**INR < 4**	8	5.7% (25/441)	3% (15/506)	1.3	[0.6, 2.7]	0.5	0%
	INR ≥ 4	3	6.1% (10/164)	1% (2/196)	4.1	[2.6, 14.9]	**0.04**	0%
FFP	**INR < 4**	7	18.4% (76/414)	28% (126/450)	0.4	[0.3, 0.6]	**< 0.0001**	0%
Vitamin K	**INR < 4**	8	81.2% (358/441)	85.1% (399/469)	0.9	[0.6, 1.3]	0.5	0%
	INR ≥ 4	2	100 % (136/136)	100% (171/171)	0.9	[0.1, 14.4]	0.9	0%
Other blood products†	**INR < 4**	2	30.4% (31/102)	35.4% (52/147)	1.04	[0.3, 4.1]	1	74.4%
	INR ≥ 4	2	61.9% (112/181)	64.7% (141/218)	0.9	[0.6, 1.3]	0.6	0%

*Effect size reported as an odds ratio for binary data or Hedges' *g* statistic for continuous data

†other blood products include cryoprecipitate, packed red blood cells, and platelets

OR, odds ratio

CI, confidence interval

4-PCC, four-factor prothrombin complex concentrate

ICH, intracranial hemorrhage

INR, international normalized ratio

Supplementary Table 9. Subgroup meta-analyses based on overall dose subgroup comparing fixed- versus variable-dose regimens of 4-PCC administration.

Variable	4-PCC dose	Number of studies	Fixed dose	Variable dose	OR/SMD*	95% CI	p-value	I^2
Age (years)	**1000 – 1500**	4	71.8 ± 2 (n=279)	72.1 ± 3 (n=340)	0.02	[-0.2, 0.2]	0.9	40.1%
	1500 - 2000	7	73.5 ± 2 (n=383)	74.8 ± 2.2 (n=464)	-0.1	[-0.2, 0.05]	0.2	0%
	2000 - 2500	3	71.9 ± 4.1 (n=95)	74.6 ± 1.5 (n=111)	-0.3	[-1, -0.3]	0.4	81.5%
Sex (male)	**1000 - 1500**	4	59.1% (165/279)	59.7% (203/340)	1	[0.5, 1.7]	0.9	60.9%
	1500 - 2000	8	53.8% (206/383)	56.3% (261/464)	0.9	[0.6, 1.2]	0.5	25.7%
	2000 - 2500	3	53.7% (51/95)	61.3% (68/111)	0.7	[0.4, 1.3]	0.3	0%
Patient weight (kg)	**1000 - 1500**	3	85.3 ± 1.8 (n=244)	87.5 ± 2.1 (n=308)	-0.1	[-0.4, 0.2]	0.5	50%
	1500 - 2000	7	81.4 ± 1.7 (n=383)	83.4 ± 1.9 (n=464)	-0.1	[-0.2, 0.1]	0.4	21%
	2000 - 2500	3	101.4 ± 17 (n=95)	88.9 ± 11.7 (n=111)	0.4	[0.1, 0.8]	**0.01**	27.1%
Baseline INR	**1000 - 1500**	4	3.6 ± 0.5 (n=279)	3.7 ± 0.6 (n=340)	-0.03	[-0.5, 0.4]	0.9	86.3%
	1500 - 2000	6	3.8 ± 0.2 (n=353)	3.4 ± 0.2 (n=434)	0.2	[-0.01, 0.3]	0.1	29.7%
	2000 - 2500	2	3.1 ± 0.4 (n=61)	3.01 ± 0.2 (n=73)	0.1	[-0.3, 0.4]	0.7	0%
Total PCC dose	**1000 - 1500**	4	1127.7 ± 93.7 (n=279)	2294.1 ± 42.1 (n=340)	-1.3	[-1.5, -1.2]	**< 0.0001**	0%
	1500 - 2000	7	1623.3 ± 42.9 (n=383)	2154.5 ± 95.6 (n=464)	-0.8	[-1, -0.6]	**< 0.0001**	45.5%
	2000 - 2500	3	2123.6 ± 87.3 (n=95)	2584.8 ± 427.7 (n=111)	-0.8	[-1.8, -0.1]	0.07	89.2%
PCC dose by weight (IU/kg)	**1500 - 2000**	6	20.3 ± 0.4 (n=331)	27.1 ± 0.8 (n=409)	-1	[-1.2, -0.7]	**< 0.0001**	59%
	2000 - 2500	3	25.7 ± 2.5 (n=95)	27.8 ± 7.9 (n=111)	0.2	[-1.1, -1.6]	0.7	95%
Post-treatment INR	**1000 - 1500**	2	1.55 ± 0.02 (n=159)	1.5 ± 0.2 (n=134)	0.2	[-1.1, 1.4]	0.8	95.1%
	1500 - 2000	7	1.4 ± 0.05 (n=383)	1.4 ± 0.07 (n=464)	0.2	[-0.2, 0.5]	0.4	81.2%
	2000-2500	2	1.4 ± 0.2 (n=61)	1.3 ± 0.03 (n=73)	0.2	[-1.6, 2.1]	0.8	95.4%
Door-to-needle time (min)	**1500 - 2000**	2	177.4 ± 79.3(n=108)	224.3 ± 118.9 (n=104)	-0.4	[-0.6; -0.1]	**0.01**	0%
Order-to-needle time (min)	**1500 - 2000**	3	48.8 ± 15.3 (n=120)	80.3 ± 25.4 (n=99)	-0.5	[-0.8, -0.2]	**0.003**	26.3%
INR <2 achieved	**1000 - 1500**	2	85.7% (126/147)	95.2% (118/124)	0.3	[0.1, 0.9]	**0.04**	22.3%
	1500 - 2000	4	86.8% (164/189)	91.2% (196/215)	0.7	[0.4, 1.4]	0.1	0%
	2000 - 2500	3	94.7% (90/95)	89.2% (99/111)	2.1	[0.7, 6.2]	0.2	0%
INR <1.5 achieved	**1000 - 1500**	4	62.5% (157/251)	75.4% (236/313)	0.5	[0.09; 0.9]	**0.03**	47.5%
	1500 - 2000	8	66.8% (233/349)	76.6% (317/414)	0.6	[0.4, 0.9]	**0.01**	4.9%
	2000 - 2500	2	86.6% (39/44)	83.3% (50/60)	1.4	[0.5, 4.5]	0.5	0%
PCC-to-INR time (min)	**1500 - 2000**	3	164.8 ± 66.2 (n=221)	204.4 ± 77.8 (n=288)	-0.3	[-0.5; -0.1]	**0.01**	23.3%
Overall mortality	**1000 - 1500**	4	17.9% (50/279)	14.1% (48/340)	1.2	[0.7, 2.1]	0.6	35.9%
	1500 - 2000	8	14.6% (56/383)	20.9% (97/464)	0.6	[0.4, 0.9]	**0.005**	0%
	2000 - 2500	3	17.9% (17/95)	18.9% (21/111)	0.9	[0.5, 1.9]	0.8	0%
TEE	**1000 - 1500**	2	1.5 % (1/65)	3.2% (2/63)	0.6	[0.1, 4.5]	0.6	0%
	1500 - 2000	8	3.4% (13/383)	5.2% (24/464)	0.6	[0.2, 1.7]	0.4	26.3%
	2000 - 2500	3	1.1% (1/95)	4.5% (5/111)	0.4	[0.1, 2.4]	0.3	0%
Length of hospital stay (days)	**1500 – 2000**	4	9.9 ± 2.9 (n=160)	11.05 ± 1.9 (n=190)	-0.2	[-0.4, 0.1]	0.3	23.7%
	2000 – 2500	2	9.4 ± 2.2 (n=76)	6.7 ± 1 (n=86)	0.2	[-0.1, 0.5]	0.2	0%
Additional 4-PCC	**1000 - 1500**	4	7.8% (19/245)	5.6% (17/302)	1.5	[0.4, 5.9]	0.5	52%
	1500 - 2000	7	5.1% (18/353)	2.3% (10/434)	1.7	[0.7, 3.8]	0.2	0%
	2000 - 2500	3	6.3% (6/95)	4.5% (5/111)	1.4	[0.4, 4.5]	0.6	0%
FFP	**1000 - 1500**	4	16.8% (58/345)	17.4% (78/447)	0.8	[0.3, 2.2]	0.7	79.5%
	1500 - 2000	6	14% (46/328)	17.4% (73/420)	0.6	[0.4, 0.9]	**0.01**	0%
	2000 - 2500	2	26.4% (14/53)	23.8% (15/63)	1.2	[0.5, 2.8]	0.7	0%
vitamin K	**1000-1500**	4	86.% (240/279)	90.6% (308/340)	0.8	[0.5, 1.4]	0.4	0%
	1500-2000	7	82.5% (293/355)	85.9% (377/439)	0.9	[0.6, 1.3]	0.5	0%
	2000-2500	2	86.9% (53/61)	89% (65/73)	0.7	[0.2, 2.3]	0.6	0%
Other blood products†	**1000 - 1500**	2	63.1% (99/157)	61.6% (170/276)	1.1	[0.6, 1.9]	0.8	48.3%
	1500 - 2000	2	59.8% (58/97)	63.1% (70/111)	0.8	[0.4, 1.6]	0.6	21.8%
	2000 - 2500	2	35.9% (19/35)	46% (29/63)	0.8	[0.1, 6.5]	0.8	85%

*effect size reported as an odds ratio for binary data or Hedges' *g* statistic for variable data

†Other blood products include cryoprecipitate, packed red blood cells, and platelets

OR, odds ratio

CI, confidence interval

4-PCC, four-factor prothrombin complex concentrate

ICH, intracranial hemorrhage

INR, international normalized ratio

FFP, fresh frozen plasma

min, minute

Supplementary Table 10. Subgroup meta-analyses Based on Overall Dose & 4-PCC indications (RCTs) subgroups comparing fixed- versus variable-dose regimens of 4-PCC administration.

Variable	4-PCC dose	Number of studies	Fixed dose	Variable-dose	OR/SMD*	95% CI	p-value	I^2
Age (years)	**1500 - 2000**	2	73.4 ± 1.6 (n=127)	74.4 ± 3.3 (n=125)	-0.03	[-0.8, 0.7]	0.9	89%
Sex (male)	**1500 - 2000**	3	55.3% (89/161)	60.5% (98/162)	0.8	[0.5, 1.4]	0.4	24.1%
Patient weight (kg)	**1500 - 2000**	2	73.2 ± 2.7 (n=127)	75.9 ± 2.4 (n=125)	-0.1	[-0.3, 0.2]	0.5	0%
Baseline INR	**All Indications**	2	3.7 ± 0.7 (n=81)	3.9 ± 0.7 (n=83)	-0.1	[-04, 0.2]	0.5	0%
	1500 - 2000	2	5.6 ± 1.2 (n=127)	5.9 ± 1.2 (n=125)	-0.1	[-0.3, 0.2]	0.5	0%
INR <2 achieved	**1500 - 2000**	2	84.3% (97/115)	94.1% (111/118)	0.3	[0.02, 4.3]	0.4	80.7%
INR <1.5 achieved	**1500 - 2000**	2	66.7% (441/66)	88.6% (62/70)	0.3	[0.1, 0.8]	**0.02**	35.4%
Overall mortality	**1500 - 2000**	2	4.7% (6/127)	7.2% (9/125)	0.6	[0.2, 1.9]	0.4	0%
TEE	**All Indications**	2	1.2% (1/81)	1.2% (1/83)	1	[0.1, 10]	0.7	0%
	1500 - 2000	3	1.2% (2/161)	1.9% (3/162)	0.7	[0.1, 3.8]	0.7	0%
Additional 4-PCC	**1500 - 2000**	3	17.4% (28/161)	2.5% (4/162)	8.6	[3, 24.6]	**< 0.0001**	0%
FFP	**1500 - 2000**	2	5.5% (7/127)	0.8% (1/125)	4.7	[0.7, 30.6]	0.1	0%
vitamin K	**1500 – 2000**	2	81.9% (104/127)	87.2% (109/125)	0.6	[0.3, 1.3]	0.2	0%

*Effect size reported as an odds ratio for binary data or Hedges' *g* statistic for variable data

OR, odds ratio

CI, confidence interval

4-PCC, four-factor prothrombin complex concentrate

ICH, intracranial hemorrhage

Non-ICH, non-intracranial hemorrhage indications

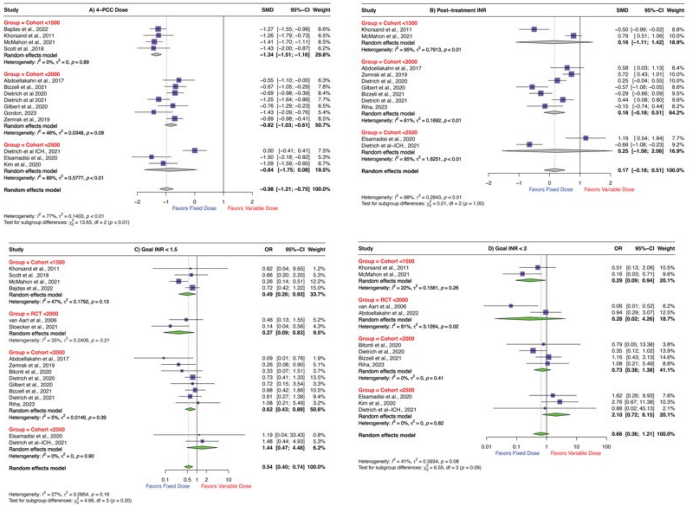
INR, international normalized ratio

wt, weight

FFP, fresh frozen plasma

*Other Blood Products include cryoprecipitate, packed RBCS, and Platelets

Supplementary Figure 3. Forest plots for meta-analyses comparing fixed- versus variable-dose 4-PCC administration by fixed-dose subgroup.



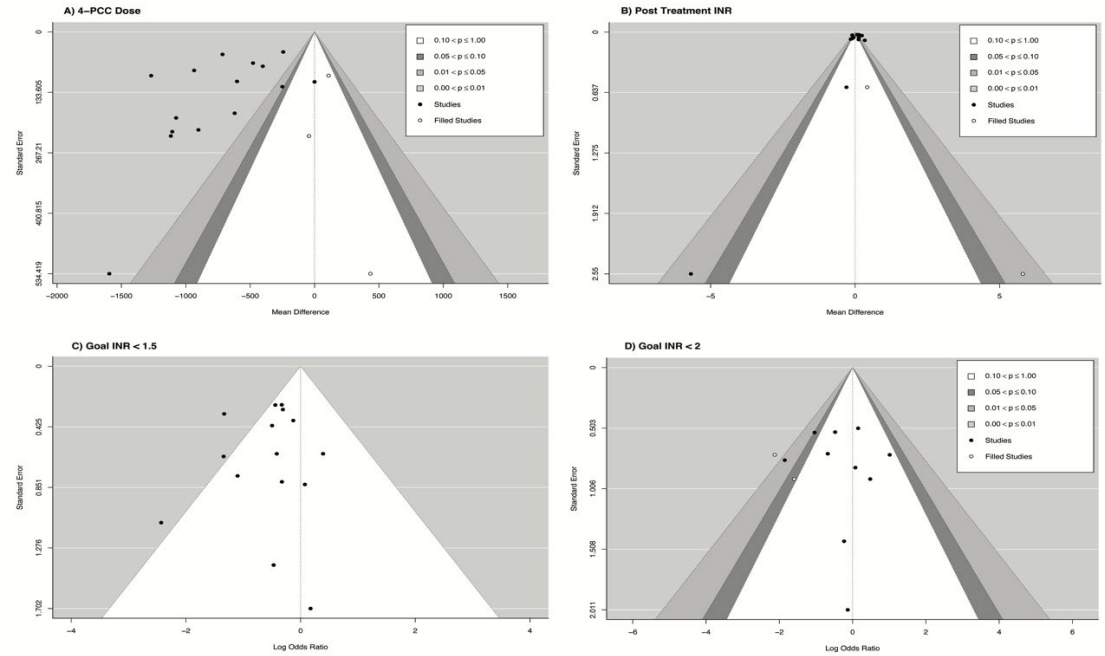
a) 4-PCC Dose administered in fixed-dose strategy versus variable-dose strategy

b) The number of patients achieving overall INR goal

c) The number of patients achieving goal INR < 1.5

d) The number of patients achieving goal INR < 2

Supplementary Figure 4. Funnel plots for overall meta-analyses of fixed- versus variable-dose 4-administration



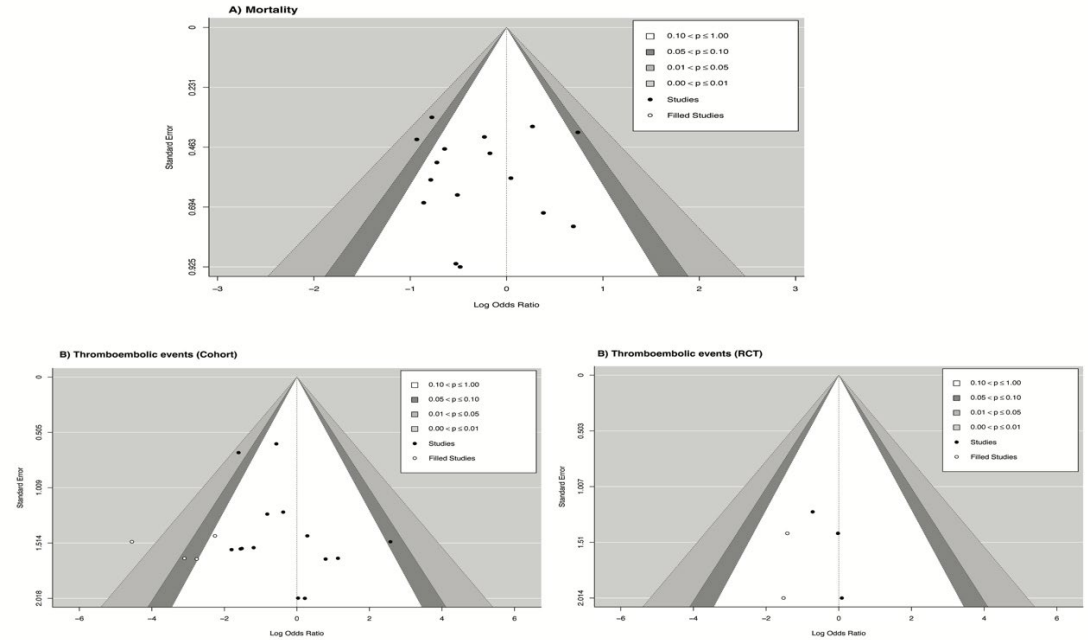
a) 4-PCC Dose administered in fixed-dose strategy versus variable-dose strategy

b) The number of patients achieving overall INR goal

c) The number of patients achieving goal INR < 1.5

d) The number of patients achieving goal INR < 2

Supplementary Figure 5. Funnel plot for overall meta-analyses of fixed-versus variable-dose 4-PCC administration



a) Mortality Rate

b) Thromboembolic events (Cohort & Rcts)

Supplementary Table 11 Quality of evidence based on GRADE recommendations for 4-PCC Dose 1000 – 1500 IU Subgroup.

Certainty assessment							№ of patients		Effect		Certainty	
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	1000 - 1500 IU Fixed-Dose 4-PCC	Variable-Dose 4-PCC	Relative (95% CI)	Absolute (95% CI)		
Total 4-PCC Dose												
4	observational studies	serious[a]	not serious	not serious	not serious	strong association	279	340	-	SMD **1.3 SD lower** (1.5 lower to 1.2 lower)	⨁⨁⨁⨁ High	
INR <2 achieved												
2	observational studies	serious[a]	not serious	not serious	not serious	strong association	126/147 (85.7%)	118/124 (95.2%)	**OR 0.3** (0.1 to 0.9)	**10 fewer per 100** (from 29 fewer to 1 fewer)	⨁⨁⨁⨁ High	
INR <1.5 achieved												
4	observational studies	serious[a]	serious[b]	not serious	not serious	strong association	157/251 (62.5%)	236/313 (75.4%)	**OR 0.50** (0.09 to 0.90)	**15 fewer per 100** (from 54 fewer to 2 fewer)	⨁⨁⨁◯ Moderate	
Overall Mortality												
4	observational studies	serious[a]	not serious	not serious	serious[c]	none	50/279 (17.9%)	48/340 (14.1%)	**OR 1.2** (0.7 to 2.1)	**2 more per 100** (from 4 fewer to 12 more)	⨁⨁◯◯ Low	
TEE												
2	observational studies	serious[a]	not serious	not serious	serious[c]	none	1/65 (1.5%)	2/63 (3.2%)	**OR 0.6** (0.2 to 4.5)	**1 fewer per 100** (from 3 fewer to 10 more)	⨁⨁◯◯ Low	

CI: confidence interval; **OR:** odds ratio; **SMD:** standardised mean difference

Explanations

a. Most studies are retrospective without confounding adjustments

b. when I2 measured below 25%, “serious” when it was between 25-75%, and “very serious” when it exceeded 75%.

c. both the confidence interval and sample size were put into consideration. If the confidence interval for risk ratio exceeded 2.00 and included both benefits and harms, the outcome was deemed to have a “very serious” risk of imprecision. If the confidence interval exceeded 1.00 or if it included both benefits and harms, imprecision was judged to be “serious.”

Supplementary Table 12 Quality of evidence based on GRADE recommendations for 4-PCC Dose 1500 – 2000 IU Subgroup.

Certainty assessment							№ of patients		Effect		Certainty	
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	1500 - 2000 IU Fixed-Dose 4-PCC	Variable-Dose 4-PCC	Relative (95% CI)	Absolute (95% CI)		
Total 4-PCC Dose (assessed with: IU)												
7	observational studies	serious[a]	not serious	not serious	not serious	strong association	383	464	-	SMD **0.8 SD lower** (1 lower to 0.6 lower)	⨁⨁⨁⨁ High	
PCC Dose/weight (assessed with: IU/Kg)												
6	observational studies	serious[a]	serious	not serious	not serious	strong association	331	409	-	SMD **1 SD lower** (1.2 lower to 0.7 higher)	⨁⨁⨁◯ Moderate	
Order-to-needle time (assessed with: Minutes)												
3	observational studies	serious[b]	not serious	not serious	not serious	strong association	120	99	-	SMD **0.5 SD lower** (0.8 lower to 0.2 lower)	⨁⨁⨁⨁ High	
Door-to-needle time (min) (assessed with: Minutes)												
2	observational studies	serious[a]	not serious	not serious	not serious	strong association	108	104	-	SMD **0.4 SD lower** (0.6 lower to 0.1 lower)	⨁⨁⨁⨁ High	
INR <2 achieved												
4	observational studies	serious[a]	not serious	not serious	not serious	none	164/189 (86.8%)	196/215 (91.2%)	**OR 0.7** (0.4 to 1.4)	**3 fewer per 100** (from 11 fewer to 2 more)	⨁⨁⨁◯ Moderate	
INR <1.5 achieved												
8	observational studies	serious[a]	not serious	not serious	not serious	strong association	233/349 (66.8%)	317/414 (76.6%)	**OR 0.6** (0.4 to 0.9)	**10 fewer per 100** (from 20 fewer to 2 fewer)	⨁⨁⨁⨁ High	
INR <1.5 achieved (RCT)												

Certainty assessment							№ of patients		Effect		Certainty	
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	1500 - 2000 IU Fixed-Dose 4-PCC	Variable-Dose 4-PCC	Relative (95% CI)	Absolute (95% CI)		
2	randomized trials	not serious	serious[b]	not serious	not serious	none	44/66 (66.7%)	62/70 (88.6%)	**OR 0.3** (0.1 to 0.8)	**19 fewer per 100** (from 45 fewer to 2 fewer)	⨁⨁⨁◯ Moderate	
Overall Mortality												
8	observational studies	serious[a]	not serious	not serious	not serious	strong association	56/383 (14.6%)	97/464 (20.9%)	**OR 0.6** (0.4 to 0.9)	**7 fewer per 100** (from 11 fewer to 2 fewer)	⨁⨁⨁⨁ High	
Overall Mortality (RCT)												
2	randomized trials	not serious	not serious	not serious	not serious	none	6/127 (4.7%)	9/125 (7.2%)	**OR 0.6** (0.2 to 1.9)	**3 fewer per 100** (from 6 fewer to 6 more)	⨁⨁⨁⨁ High	
TEE												
8	observational studies	serious[a]	serious[b]	not serious	not serious	none	13/383 (3.4%)	24/464 (5.2%)	**OR 0.6** (0.2 to 1.7)	**2 fewer per 100** (from 4 fewer to 3 more)	⨁⨁◯◯ Low	
TEE (RCT)												
3	randomized trials	not serious	not serious	not serious	serious[c]	none	2/161 (1.2%)	3/162 (1.9%)	**OR 0.7** (0.1 to 3.8)	**1 fewer per 100** (from 2 fewer to 5 more)	⨁⨁⨁◯ Moderate	

CI: confidence interval; **OR:** odds ratio; **SMD:** standardised mean difference

Explanations

a. Most studies are retrospective without confounding adjustments

b. Inconsistency was rated based on the heterogeneity statistic I2. It was judged “not serious” when I2 measured below 25%, “serious” when it was between 25-75%, and “very serious” when it exceeded 75%.

c. If the CI around the estimate of the treatment effect is sufficiently narrow. No rate down If the CI around the estimate of the treatment effect is wide, we rate down by one level. If the CI is very wide, we rate down by two levels.

Supplementary Table 13 Quality of evidence based on GRADE recommendations for 4-PCC Dose 2000 – 2500 IU Subgroup.

Certainty assessment							№ of patients		Effect		Certainty	
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	2000 - 2500 IU Fixed-Dose 4-PCC	Variable-Dose 4-PCC	Relative (95% CI)	Absolute (95% CI)		
INR <2 achieved												
3	observational studies	serious[a]	not serious	not serious	serious[c]	none	90/95 (94.7%)	99/111 (89.2%)	**OR 2.1** (0.7 to 6.2)	**5 more per 100** (from 4 fewer to 9 more)	⨁⨁◯◯ Low	
INR <1.5 achieved												
2	observational studies	serious[a]	not serious	not serious	serious[c]	none	39/44 (88.6%)	50/60 (83.3%)	**OR 1.4** (0.5 to 4.5)	**4 more per 100** (from 12 fewer to 12 more)	⨁⨁◯◯ Low	
Overall Mortality												
3	observational studies	serious[a]	not serious	not serious	not serious	none	17/95 (17.9%)	21/111 (18.9%)	**OR 0.9** (0.5 to 1.9)	**2 fewer per 100** (from 8 fewer to 12 more)	⨁⨁⨁◯ Moderate	
TEE												
3	observational studies	serious[a]	not serious	not serious	not serious	none	1/95 (1.1%)	5/111 (4.5%)	**OR 0.4** (0.1 to 2.4)	**3 fewer per 100** (from 4 fewer to 6 more)	⨁⨁⨁◯ Moderate	

CI: confidence interval; **OR:** odds ratio; **SMD:** standardised mean difference

Explanations

a. Most studies are retrospective without confounding adjustments

b. Inconsistency was rated based on the heterogeneity statistic I2. It was judged “not serious” when I2 measured below 25%, “serious” when it was between 25-75%, and “very serious” when it exceeded 75%.

c. If the CI around the estimate of the treatment effect is sufficiently narrow. No rate down If the CI around the estimate of the treatment effect is wide, we rate down by one level. If the CI is very wide, we rate down by two levels.

Supplementary Table 14 Quality of evidence based on GRADE recommendations for patients Weight < 80 Subgroup.

Certainty assessment							№ of patients		Effect		Certainty	
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Fixed-Dose 4-PCC	Variable-Dose 4-PCC	Relative (95% CI)	Absolute (95% CI)		
INR <2 achieved												
2	observational studies	serious[a]	not serious	not serious	not serious	none	107/117 (91.5%)	158/164 (96.3%)	**OR 0.4** (0.1 to 1.0)	**5 fewer per 100** (from 24 fewer to 0 fewer)	⨁⨁⨁◯ Moderate	
INR <1.5 achieved												
2	observational studies	serious[a]	not serious	not serious	not serious	none	80/117 (68.4%)	115/164 (70.1%)	**OR 0.9** (0.5 to 1.5)	**2 fewer per 100** (from 16 fewer to 8 more)	⨁⨁⨁◯ Moderate	
Overall Mortality												
2	observational studies	serious[a]	not serious	not serious	not serious	none	17/117 (14.5%)	32/164 (19.5%)	**OR 0.7** (0.3 to 1.3)	**5 fewer per 100** (from 13 fewer to 4 more)	⨁⨁⨁◯ Moderate	
TEE												
2	observational studies	serious[a]	not serious	not serious	serious[c]	none	0/117 (0.0%)	4/164 (2.4%)	**OR 0.30** (0.03 to 2.20)	**2 fewer per 100** (from 2 fewer to 3 more)	⨁⨁◯◯ Low	

CI: confidence interval; **OR:** odds ratio; **SMD:** standardised mean difference

Explanations

a. Most studies are retrospective without confounding adjustments

b. Inconsistency was rated based on the heterogeneity statistic I2. It was judged “not serious” when I2 measured below 25%, “serious” when it was between 25-75%, and “very serious” when it exceeded 75%.

c. If the CI around the estimate of the treatment effect is sufficiently narrow. No rate down If the CI around the estimate of the treatment effect is wide, we rate down by one level. If the CI is very wide, we rate down by two levels.

d. If the CI around the estimate of the treatment effect is sufficiently narrow. No rate down If the CI around the estimate of the treatment effect is wide, we rate down by one level. If the CI is very wide, we rate down by two levels.

Supplementary Table 15 Quality of evidence based on GRADE recommendations for patients Weight ≥ 80 Subgroup.

Certainty assessment							№ of patients		Effect		Certainty	
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Fixed-Dose 4-PCC	Variable-Dose 4-PCC	Relative (95% CI)	Absolute (95% CI)		
Clinical Hemostasis												
2	observational studies	serious[a]	not serious	not serious	not serious	none	130/214 (60.7%)	106/277 (38.3%)	**OR 2.0** (1.3 to 2.9)	**17 more per 100** (from 6 more to 26 more)	⨁⨁⨁◯ Moderate	
INR <2 achieved												
4	observational studies	not serious	not serious	not serious	not serious	none	173/194 (89.2%)	166/176 (94.3%)	**OR 0.6** (0.2 to 2.0)	**3 fewer per 100** (from 17 fewer to 3 more)	⨁⨁⨁⨁ High	
INR <1.5 achieved												
8	observational studies	not serious	not serious	not serious	not serious	none	240/372 (64.5%)	336/437 (76.9%)	**OR 0.4** (0.3 to 0.7)	**20 fewer per 100** (from 27 fewer to 7 fewer)	⨁⨁⨁⨁ High	
Overall Mortality												
8	observational studies	serious[a]	not serious	not serious	not serious	none	65/372 (17.5%)	64/437 (14.6%)	**OR 1.1** (0.8 to 1.7)	**1 more per 100** (from 3 fewer to 8 more)	⨁⨁⨁◯ Moderate	
TEE												
6	observational studies	serious[a]	not serious	not serious	not serious	none	3/158 (1.9%)	3/160 (1.9%)	**OR 1.1** (0.3 to 4.2)	**0 fewer per 100** (from 1 fewer to 6 more)	⨁⨁⨁◯ Moderate	

CI: confidence interval; **OR:** odds ratio; **SMD:** standardised mean difference

Explanations

a. Most studies are retrospective without confounding adjustments

b. Inconsistency was rated based on the heterogeneity statistic I2. It was judged “not serious” when I2 measured below 25%, “serious” when it was between 25-75%, and “very serious” when it exceeded 75%.

Supplementary Table 16 Quality of evidence based on GRADE recommendations for INR < 4 Subgroup.

ertainty assessment							№ of patients		Effect		Certainty	
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Fixed-Dose 4-PCC	Variable-Dose 4-PCC	Relative (95% CI)	Absolute (95% CI)		
Order-to-needle time												
3	observational studies	serious[a]	not serious	not serious	not serious	strong association	109	94	-	SMD **0.4 SD lower** (0.8 lower to 0.1 higher)	⨁⨁⨁⨁ High	
Clinical Hemostasis												
2	observational studies	serious[a]	serious[b]	not serious	not serious	none	158/207 (76.3%)	165/224 (73.7%)	**OR 1.2** (0.5 to 2.6)	**3 more per 100** (from 15 fewer to 14 more)	⨁⨁◯◯ Low	
INR <2 achieved												
5	observational studies	serious[a]	serious[b]	not serious	not serious	none	245/275 (89.1%)	226/244 (92.6%)	**OR 0.8** (0.3 to 1.9)	**2 fewer per 100** (from 14 fewer to 3 more)	⨁⨁◯◯ Low	
INR <1.5 achieved												
8	observational studies	serious[a]	serious[b]	not serious	not serious	strong association	263/407 (64.6%)	326/419 (77.8%)	**OR 0.5** (0.3 to 0.9)	**14 fewer per 100** (from 27 fewer to 2 fewer)	⨁⨁⨁◯ Moderate	
Overall Mortality												
8	observational studies	serious[a]	serious[b]	not serious	not serious	none	80/441 (18.1%)	98/469 (20.9%)	**OR 0.8** (0.5 to 1.2)	**3 fewer per 100** (from 9 fewer to 3 more)	⨁⨁◯◯ Low	
TEE												
7	observational studies	serious[a]	serious[b]	not serious	not serious	none	13/317 (4.1%)	23/367 (6.3%)	**OR 0.7** (0.2 to 1.8)	**2 fewer per 100** (from 5 fewer to 4 more)	⨁⨁◯◯ Low	
Additional 4-PCC												
8	observational studies	serious[a]	not serious	not serious	not serious	none	25/441 (5.7%)	15/506 (3.0%)	**OR 1.3** (0.6 to 2.7)	**1 more per 100** (from 1 fewer to 5 more)	⨁⨁⨁◯ Moderate	

CI: confidence interval; **OR:** odds ratio; **SMD:** standardised mean difference

Explanations

a. Most studies are retrospective without confounding adjustments

b. Inconsistency was rated based on the heterogeneity statistic I2. It was judged “not serious” when I2 measured below 25%, “serious” when it was between 25-75%, and “very serious” when it exceeded 75%.

Supplementary Table 17 Quality of evidence based on GRADE recommendations for INR ≥ 4 Subgroup.

Certainty assessment							№ of patients		Effect		Certainty	
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Fixed-Dose 4-PCC	Variable-Dose 4-PCC	Relative (95% CI)	Absolute (95% CI)		
Baseline INR												
3	observational studies	serious[a]	serious[b]	not serious	not serious	none	164	196	-	SMD **0.2 SD lower** (0.5 lower to 0.1 higher)	⨁⨁◯◯ Low	
Total 4-PCC Dose												
3	observational studies	not serious	not serious	not serious	not serious	strong association	164	196	-	SMD **1.2 SD lower** (1.9 lower to 0.5 lower)	⨁⨁⨁⨁ High	
Door-to-needle time (assessed with: Minutes)												
2	observational studies	serious[a]	very serious[b]	not serious	not serious	none	129	164	-	SMD **0.6 SD lower** (1.4 lower to 0.2 higher)	⨁◯◯◯ Very low	
PCC-to-INR												
5	observational studies	serious[a]	very serious[b]	not serious	not serious	none	331	347	-	SMD **0.5 SD lower** (1.2 lower to 0.1 higher)	⨁◯◯◯ Very low	
INR <2 achieved												
2	observational studies	serious[a]	not serious	not serious	not serious	none	104/119 (87.4%)	142/153 (92.8%)	**OR 0.6** (0.2 to 1.3)	**4 fewer per 100** (from 21 fewer to 2 more)	⨁⨁⨁◯ Moderate	
INR <1.5 achieved												
3	observational studies	serious[a]	serious[b]	not serious	not serious	none	73/131 (55.7%)	109/161 (67.7%)	**OR 0.4** (0.1 to 1.3)	**22 fewer per 100** (from 50 fewer to 5 more)	⨁⨁◯◯ Low	
Overall Mortality												

Certainty assessment							№ of patients		Effect		Certainty	
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Fixed-Dose 4-PCC	Variable-Dose 4-PCC	Relative (95% CI)	Absolute (95% CI)		
3	observational studies	serious[a]	serious[b]	not serious	not serious	none	26/164 (15.9%)	49/196 (25.0%)	**OR 0.6** (0.3 to 1.3)	**8 fewer per 100** (from 16 fewer to 5 more)	⨁⨁◯◯ Low	
TEE												
3	observational studies	serious[a]	not serious	not serious	not serious	none	21/164 (12.8%)	6/196 (3.1%)	**OR 0.4** (0.1 to 1.9)	**2 fewer per 100** (from 3 fewer to 3 more)	⨁⨁⨁◯ Moderate	
Additional 4-PCC												
3	observational studies	not serious	not serious	not serious	very serious[c]	strong association	10/164 (6.1%)	2/196 (1.0%)	**OR 4.1** (2.6 to 14.9)	**3 more per 100** (from 2 more to 12 more)	⨁⨁⨁◯ Moderate	

CI: confidence interval; **OR:** odds ratio; **SMD:** standardised mean difference

Explanations

a. Most studies are retrospective without confounding adjustments

b. Inconsistency was rated based on the heterogeneity statistic I2. It was judged “not serious” when I2 measured below 25%, “serious” when it was between 25-75%, and “very serious” when it exceeded 75%.

c. If the CI around the estimate of the treatment effect is sufficiently narrow. No rate down If the CI around the estimate of the treatment effect is wide, we rate down by one level. If the CI is very wide, we rate down by two levels.

Supplementary Table 18 Quality of evidence based on GRADE recommendations for ICH indications Subgroup.

Certainty assessment							№ of patients		Effect		Certainty	
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Fixed-Dose 4-PCC	Variable-Dose 4-PCC	Relative (95% CI)	Absolute (95% CI)		
Order-to-needle time (assessed with: Minutes)												
2	observational studies	serious[a]	not serious	not serious	not serious	none	42	30	-	SMD **0.7 SD lower** (1.2 lower to 0.3 higher)	⨁⨁⨁◯ Moderate	
Clinical Hemostasis												
2	observational studies	serious[a]	not serious	not serious	not serious	none	55/69 (79.7%)	82/106 (77.4%)	**OR 0.9** (0.4 to 2.0)	**2 fewer per 100** (from 20 fewer to 10 more)	⨁⨁⨁◯ Moderate	
INR <2 achieved												
4	observational studies	serious[a]	not serious	not serious	not serious	none	99/104 (95.2%)	108/112 (96.4%)	**OR 1.0** (0.3 to 3.4)	**0 fewer per 100** (from 7 fewer to 2 more)	⨁⨁⨁◯ Moderate	
INR <1.5 achieved												
6	observational studies	serious[a]	serious[b]	not serious	not serious	none	154/191 (80.6%)	184/206 (89.3%)	**OR 0.5** (0.2 to 1.2)	**9 fewer per 100** (from 27 fewer to 2 more)	⨁⨁◯◯ Low	
Overall Mortality												
7	observational studies	serious[a]	serious[b]	not serious	not serious	none	41/211 (19.4%)	58/240 (24.2%)	**OR 0.7** (0.4 to 1.3)	**6 fewer per 100** (from 13 fewer to 5 more)	⨁⨁◯◯ Low	
TEE												
6	observational studies	serious[a]	not serious	not serious	not serious	none	3/191 (1.6%)	5/206 (2.4%)	**OR 0.7** (0.2 to 2.9)	**1 fewer per 100** (from 2 fewer to 4 more)	⨁⨁⨁◯ Moderate	
Additional 4-PCC												

Certainty assessment							№ of patients		Effect		Certainty	
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Fixed-Dose 4-PCC	Variable-Dose 4-PCC	Relative (95% CI)	Absolute (95% CI)		
5	observational studies	serious[a]	not serious	not serious	not serious	none	22/147 (15.0%)	12/157 (7.6%)	**OR 1.9** (0.9 to 4.1)	**6 more per 100** (from 1 fewer to 18 more)	⨁⨁⨁◯ Moderate	

CI: confidence interval; **OR:** odds ratio; **SMD:** standardised mean difference

Explanations

a. Most studies are retrospective without confounding adjustments

b. Inconsistency was rated based on the heterogeneity statistic I2. It was judged “not serious” when I2 measured below 25%, “serious” when it was between 25-75%, and “very serious” when it exceeded 75%.

Supplementary Table 19 Quality of evidence based on GRADE recommendations for Non-ICH Subgroup.

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Fixed-Dose 4-PCC	Variable-Dose 4-PCC	Relative (95% CI)	Absolute (95% CI)	
Door-to-needle time (assessed with: Minutes)											
2	observational studies	serious[a]	serious	not serious	not serious	none	116	158	-	SMD **0.8 SD lower** (1.3 lower to 0.3 higher)	⨁⨁◯◯ Low
Order-to-needle time (assessed with: Minutes)											
2	observational studies	serious[a]	not serious	not serious	not serious	none	100	184	-	SMD **0.5 SD lower** (0.8 lower to 0.3 lower)	⨁⨁⨁◯ Moderate
Clinical Hemostasis											
5	observational studies	serious[a]	not serious	not serious	not serious	none	297/392 (75.8%)	305/493 (61.9%)	**OR 1.9** (1.2 to 2.9)	**14 more per 100** (from 4 more to 21 more)	⨁⨁⨁◯ Moderate
INR <2 achieved											
5	observational studies	serious[a]	not serious	not serious	not serious	none	217/245 (88.6%)	251/263 (95.4%)	**OR 0.4** (0.2 to 0.9)	**6 fewer per 100** (from 15 fewer to 0 fewer)	⨁⨁⨁◯ Moderate
INR <1.5 achieved											
4	observational studies	serious[a]	not serious	not serious	not serious	none	122/208 (58.7%)	221/330 (67.0%)	**OR 0.7** (0.5 to 1.0)	**8 fewer per 100** (from 17 fewer to 0 fewer)	⨁⨁⨁◯ Moderate
Overall Mortality											
6	observational studies	serious[a]	serious[b]	not serious	not serious	none	41/352 (11.6%)	74/456 (16.2%)	**OR 0.8** (0.4 to 1.4)	**3 fewer per 100** (from 9 fewer to 5 more)	⨁⨁◯◯ Low
TEE											

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Fixed-Dose 4-PCC	Variable-Dose 4-PCC	Relative (95% CI)	Absolute (95% CI)	
4	observational studies	serious[a]	not serious	not serious	not serious	none	2/168 (1.2%)	7/222 (3.2%)	**OR 0.5** (0.1 to 2.1)	**2 fewer per 100** (from 3 fewer to 3 more)	⨁⨁⨁◯ Moderate

CI: confidence interval; **OR:** odds ratio; **SMD:** standardised mean difference

Explanations

a. Most studies are retrospective without confounding adjustments

b. Inconsistency was rated based on the heterogeneity statistic I2. It was judged “not serious” when I2 measured below 25%, “serious” when it was between 25-75%, and “very serious” when it exceeded 75%.

Supplementary Table 20 Quality of evidence based on GRADE recommendations for All Indications Subgroup.

Certainty assessment							№ of patients		Effect		Certainty	
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Fixed-Dose 4-PCC	Variable-Dose 4-PCC	Relative (95% CI)	Absolute (95% CI)		
Order-to-needle time												
2	observational studies	serious[a]	not serious	not serious	not serious	none	82	75	-	SMD **0.3 SD lower** (0.6 lower to 0.01 higher)	⨁⨁⨁◯ Moderate	
PCC-to-INR (assessed with: Minutes)												
3	observational studies	serious[a]	not serious	not serious	not serious	none	157	191	-	SMD **0.2 SD lower** (0.4 lower to 0.02 higher)	⨁⨁⨁◯ Moderate	
INR <2 achieved												
5	observational studies	serious[a]	serious[b]	not serious	not serious	none	189/215 (87.9%)	231/259 (89.2%)	**OR 1.01** (0.50 to 2.20)	**0 fewer per 100** (from 9 fewer to 6 more)	⨁⨁◯◯ Low	
INR <1.5 achieved												
5	observational studies	serious[a]	not serious	not serious	not serious	strong association	127/234 (54.3%)	192/293 (65.5%)	**OR 0.7** (0.4 to 1.0)	**8 fewer per 100** (from 22 fewer to 0 fewer)	⨁⨁⨁⨁ High	
Overall Mortality												
6	observational studies	serious[a]	not serious	not serious	not serious	none	38/268 (14.2%)	61/331 (18.4%)	**OR 0.7** (0.4 to 1.1)	**5 fewer per 100** (from 10 fewer to 1 more)	⨁⨁⨁◯ Moderate	
TEE												
6	observational studies	serious[a]	serious[b]	not serious	not serious	none	8/268 (3.0%)	15/331 (4.5%)	**OR 0.6** (0.2 to 2.5)	**2 fewer per 100** (from 4 fewer to 6 more)	⨁⨁◯◯ Low	

Certainty assessment							№ of patients		Effect		Certainty	
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Fixed-Dose 4-PCC	Variable-Dose 4-PCC	Relative (95% CI)	Absolute (95% CI)		
TEE (RCT)												
2	randomized trials	not serious	not serious	not serious	very serious[c]	none	1/81 (1.2%)	1/83 (1.2%)	**OR 1.0** (0.1 to 10.0)	**0 fewer per 1,000** (from 11 fewer to 97 more)	⨁⨁◯◯ Low	

CI: confidence interval; **OR:** odds ratio; **SMD:** standardised mean difference

Explanations

a. Most studies are retrospective without confounding adjustments

b. Inconsistency was rated based on the heterogeneity statistic I2. It was judged “not serious” when I2 measured below 25%, “serious” when it was between 25-75%, and “very serious” when it exceeded 75%.

c. If the CI around the estimate of the treatment effect is sufficiently narrow. No rate down If the CI around the estimate of the treatment effect is wide, we rate down by one level. If the CI is very wide, we rate down by two levels.

Supplementary Table 21. PRISMA Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Introduction
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Abstract
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Introduction
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Introduction
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Methods
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Methods
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Supplementary Material
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Methods
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Methods
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Methods
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Methods

Section and Topic	Item #	Checklist item	Location where item is reported
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Methods
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Methods
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Methods
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Methods
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Methods
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Methods
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Methods
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Methods
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Methods
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Methods
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Results & Supplementary Material
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	NA
Study characteristics	17	Cite each included study and present its characteristics.	Supplementary Material

Section and Topic	Item #	Checklist item	Location where item is reported
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Supplementary Material
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimates and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Results
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Results
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Results & Supplementary Material
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Results
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Results &
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Results
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Results
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Discussion
	23b	Discuss any limitations of the evidence included in the review.	Discussion
	23c	Discuss any limitations of the review processes used.	Discussion
	23d	Discuss implications of the results for practice, policy, and future research.	Discussion
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	N/A
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	N/A
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	Other Information

Section and Topic	Item #	Checklist item	Location where item is reported
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Other Information
Competing interests	26	Declare any competing interests of review authors.	Other Information
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Other Information

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71