PICO 1: In adult patients with ICH occurring during use of VKA (with an INR above normal) does PCC in comparison to placebo, improve outcomes

Author(s):
Date:
Question: PCC compared to Placebo for ICH occurring during use of VKA
Setting:
Bibliography:

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PCC	Placebo	Relative (95% CI)	Absolute (95% CI)		
Mortality, PCC vs Placebo (follow up: mean 90 days)												
1	observational studies	serious [a]	not serious	not serious	not serious	strong association [b]	218/585 (37.3%)	280/454 (61.7%)	**OR 0.37** (0.29 to 0.48)	**244 fewer per 1,000** (from 181 fewer to 299 fewer)	⨁⨁◯◯ LOW	CRITICAL
Mortality, PCC and FFP vs Placebo (follow up: mean 90 days)												
1	observational studies	serious [a]	not serious	not serious	not serious	strong association	36/131 (27.5%)	280/454 (61.7%)	**OR 0.24** (0.15 to 0.36)	**338 fewer per 1,000** (from 250 fewer to 422 fewer)	⨁⨁◯◯ LOW	CRITICAL

CI: Confidence interval; **OR:** Odds ratio

Explanations

a. Significant differences in baseline characteristics between two groups
b. A retrospective pooled analysis of 16 stroke registries from Argentina, Australia, Finland, France, Germany, Italy, the Netherlands, the United Kingdom, and the USA.

Summary of findings:

PCC compared to Placebo for ICH occurring during use of VKA

Patient or population: ICH occurring during use of VKA
Setting:
Intervention: PCC
Comparison: Placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Placebo	**Risk with PCC**				
Mortality, PCC vs Placebo follow up: mean 90 days	617 per 1,000	**373 per 1,000** (318 to 436)	**OR 0.37** (0.29 to 0.48)	1039 (1 observational study)	⨁⨁◯◯ LOW [a,b]	
Mortality, PCC and FFP vs Placebo (follow up: mean 90 days)	617 per 1,000	**279 per 1,000** (194 to 367)	**OR 0.24** (0.15 to 0.36)	585 (1 observational study)	⨁⨁◯◯ LOW [a]	

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

CI: Confidence interval; **OR:** Odds ratio

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

Explanations

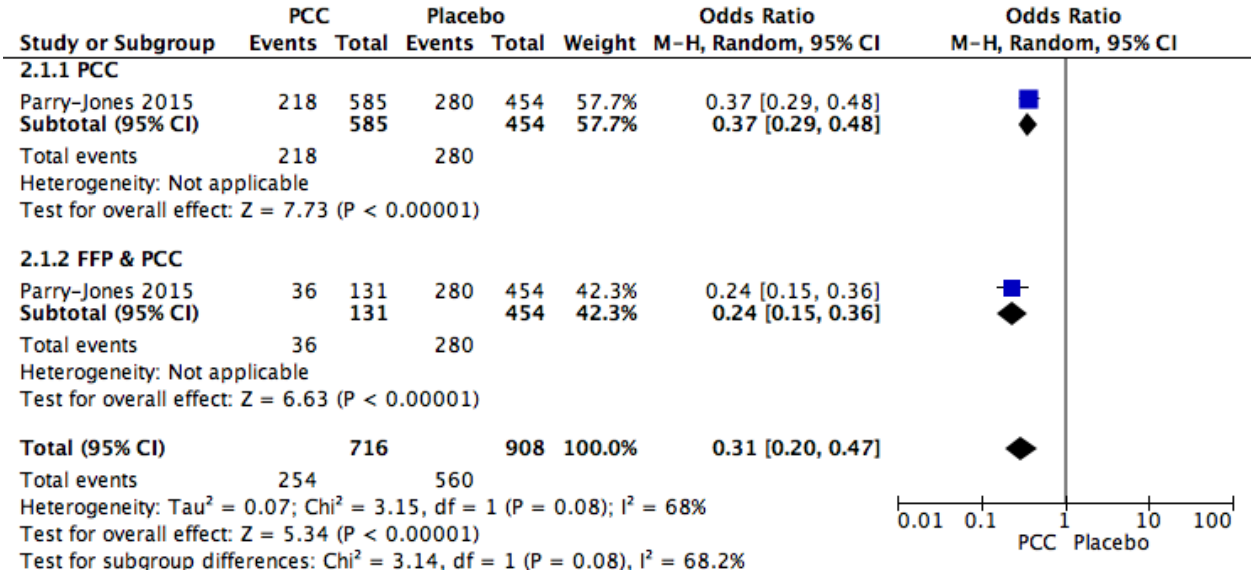
a. Significant differences in baseline characteristics between two groups
b. A retrospective pooled analysis of 16 stroke registries from Argentina, Australia, Finland, France, Germany, Italy, the Netherlands, the United Kingdom, and the USA.

Table: Effect of PCC on all-cause mortality in patients with warfarin-associated intracranial hemorrhage

Outcome	Incidence (%)		n (N)	OR [95% CI]	I^2	P value
	PCC	Control				
PCC vs Control	37% (218/585)	62% (280/454)	1 (1039)	0.37 [0.29, 0.48]	NA	<0.00001
PCC & FFP vs Control	27% (36/131)	62% (280/454)	1 (585)	0.24 [0.15, 0.36]	NA	<0.00001

FFP: Fresh frozen plasma; I^2: Heterogeneity; n: Number of studies; N: Number of patients; p: Statistical significance value; PCC: Prothrombin complex concentrate; OR: Odds Ratio

Figure: Effect of PCC on all-cause mortality in patients with warfarin-associated intracranial hemorrhage



PICO 2: In adult patients with ICH occurring during use of NOAC (with drug levels assumed relevant for an effective anticoagulatory effect) does PCC in comparison to placebo affect the outcomes

Author(s):
Date:
Question: PCC compared to Placebo for ICH occurring during use of NOAC
Setting:
Bibliography:

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PCC	Placebo	Relative (95% CI)	Absolute (95% CI)		
Mortality, follow up												
1	observational studies	not serious	not serious	not serious	serious [a]	publication bias strongly suspected [b]	9/35 (25.7%)	8/26 (30.8%)	**OR 0.78** (0.25 to 2.40)	**50 fewer per 1,000** (from 208 fewer to 208 more)	⨁◯◯◯ VERY LOW	CRITICAL
Hematoma Volume increase > 33% and or > 6 ml												
2	observational studies	not serious	not serious	not serious	not serious	publication bias strongly suspected [c]	47/131 (35.9%)	19/60 (31.7%)	**OR 1.22** (0.64 to 2.34)	**45 more per 1,000** (from 88 fewer to 204 more)	⨁◯◯◯ VERY LOW	IMPORTANT
Hematoma volume												
1	observational studies	not serious	not serious	not serious	not serious	publication bias strongly suspected [b]	28	17	-	MD **8.7 mL higher** (5.4 lower to 22.8 higher)	⨁◯◯◯ VERY LOW	IMPORTANT
Intraventricular extension, New Interventricular hemorrhage												
1	observational studies	not serious	not serious	not serious	serious [a]	publication bias strongly suspected [b]	2/28 (7.1%)	1/17 (5.9%)	**OR 1.23** (0.10 to 14.70)	**13 more per 1,000** (from 53 fewer to 420 more)	⨁◯◯◯ VERY LOW	IMPORTANT
								0.0%		**0 fewer per 1,000** (from 0 fewer to 0 fewer)		
Modified Graeb score (change from baseline)												
1	observational studies	not serious	not serious	not serious	not serious	publication bias strongly suspected [b]	28	17	-	MD **0.5 Score higher** (0.74 lower to 1.74 higher)	⨁◯◯◯ VERY LOW	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PCC	Placebo	Relative (95% CI)	Absolute (95% CI)		
Length of stay												
1	observational studies	not serious	not serious	not serious	serious [a]	publication bias strongly suspected [b]	28	17	-	MD **3.5 Days higher** (0.16 lower to 7.16 higher)	⨁◯◯◯ VERY LOW	

CI: Confidence interval; **OR:** Odds ratio; **MD:** Mean difference

Explanations

a. Wide CI
b. Single study to support this outcome
c. Two studies to support this outcome

Summary of findings:

PCC compared to Placebo for ICH occurring during use of NOAC

Patient or population: ICH occurring during use of NOAC
Setting:
Intervention: PCC
Comparison: Placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Placebo	**Risk with PCC**				
Mortality, follow up	308 per 1,000	**257 per 1,000** (100 to 516)	**OR 0.78** (0.25 to 2.40)	61 (1 observational study)	⨁◯◯◯ VERY LOW [a,b]	
Hematoma Volume increase > 33% and or > 6 ml	317 per 1,000	**361 per 1,000** (229 to 520)	**OR 1.22** (0.64 to 2.34)	191 (2 observational studies)	⨁◯◯◯ VERY LOW [c]	
Hematoma volume	The mean hematoma volume was **0** mL	The mean hematoma volume in the intervention group was 8.7 mL higher (5.4 lower to 22.8 higher)	-	45 (1 observational study)	⨁◯◯◯ VERY LOW [b]	
Intraventricular extension, New Interventricular hemorrhage	**Study population**		**OR 1.23** (0.10 to 14.70)	45 (1 observational study)	⨁◯◯◯ VERY LOW [a,b]	
	59 per 1,000	**71 per 1,000** (6 to 479)				
	Moderate					
	0 per 1,000	**0 per 1,000** (0 to 0)				
Modified Graeb score (change from baseline)	The mean modified Graeb score (change from baseline) was **0** Score	The mean modified Graeb score (change from baseline) in the intervention group was 0.5 Score higher (0.74 lower to 1.74 higher)	-	45 (1 observational study)	⨁◯◯◯ VERY LOW [b]	
Length of stay	The mean length of stay was **0** Days	The mean length of stay in the intervention group was 3.5 Days higher (0.16 lower to 7.16 higher)	-	45 (1 observational study)	⨁◯◯◯ VERY LOW [a,b]	

Summary of findings:

PCC compared to Placebo for ICH occurring during use of NOAC

Patient or population: ICH occurring during use of NOAC
Setting:
Intervention: PCC
Comparison: Placebo

Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Placebo	**Risk with PCC**				

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

CI: Confidence interval; **OR:** Odds ratio; **MD:** Mean difference

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

Explanations

a. Wide CI
b. Single study to support this outcome
c. Two studies to support this outcome

Table: Effect of PCC in patients with NOACs-associated intracranial hemorrhage

Outcome	Incidence (%)		n (N)	MD [95% CI]/ OR [95% CI]	I^2	P value
	PCC	Nothing				
Mortality, within 5 days[1]	6% (2/35)	15% (4/26)	1 (61)	0.33 [0.06, 1.98]	NA	0.23
Mortality, during acute[1] stay	17% (6/35)	15% (4/26)	1 (61)	1.14 [0.29, 4.53]	NA	0.85
Mortality, during FU[1]	26% (9/35)	31% (8/26)	1 (61)	0.78 [0.25, 2.40]	NA	0.66
Length of stay[1]	11±6	7.5±8	1 (61)	3.50 [-0.16, 7.16]	NA	0.06
Intraventricular extension						
New intraventricular hemorrhage[1]	7% (2/28)	6% (1/17)	1 (45)	1.23 [0.10, 14.70]	NA	0.87
Modified Graeb score (change from baseline, increase ≥ 2 points)[1]	18% (5/28)	0% (0/17)	1 (45)	8.19 [0.42, 158.15]	NA	0.08
Modified Graeb score (change from baseline)[1]	0±1.5	-0.5±2.4	1 (40)	0.50 [-0.74, 1.74]	NA	0.43
Hematoma volume, mL[1]	23±24.8	14.3±22.5	1 (45)	8.70 [-5.40, 22.80]		0.23
Hematoma increase						
Volume increase ≥ 33%[1,2]	35% (46/131)	30% (18/60)	2 (191)	1.25 [0.65, 2.43]	0%	0.50
Volume increase ≥ 6 mL[1]	21% (6/28)	6% (1/17)	1 (45)	4.36 [0.48, 39.89]	NA	0.19
Volume increase ≥ 33% and or ≥ 6 mL[1,2]	36% (47/131)	32% (19/60)	2 (191)	1.22 [0.64, 2.34]	0%	0.55
ICH volume[3]	8.3±7.0	NR	1 (5)	NA	NA	NA
Effectiveness of PCC[4]	73% (43/59)	NR	1 (59)	NA	NA	NA
Expansion of ICH[3]	0% (0/5)	NR	1 (5)	NA	NA	NA
Complications of PCC[3]	0% (0/5)	NR	1 (5)	NA	NA	NA
mRS, 3 months[3]	1.8±2.4	NR	1 (5)	NA	NA	NA

CI: Confidence interval; I^2: Heterogeneity; MD: Mean difference; mRS: Modified Rankin Scale; n: Number of studies; N: Number of patients; p: Statistical significance value; PCC: Prothrombin complex concentrate; OR: Odds Ratio; 1: Purrucker 2015; 2: Gerner 2018; 3: Dibu et al 2016; 4: Majeed et al 2017

Figure: Effect of PCC on mortality in patients with NOACs induced hemorrhage

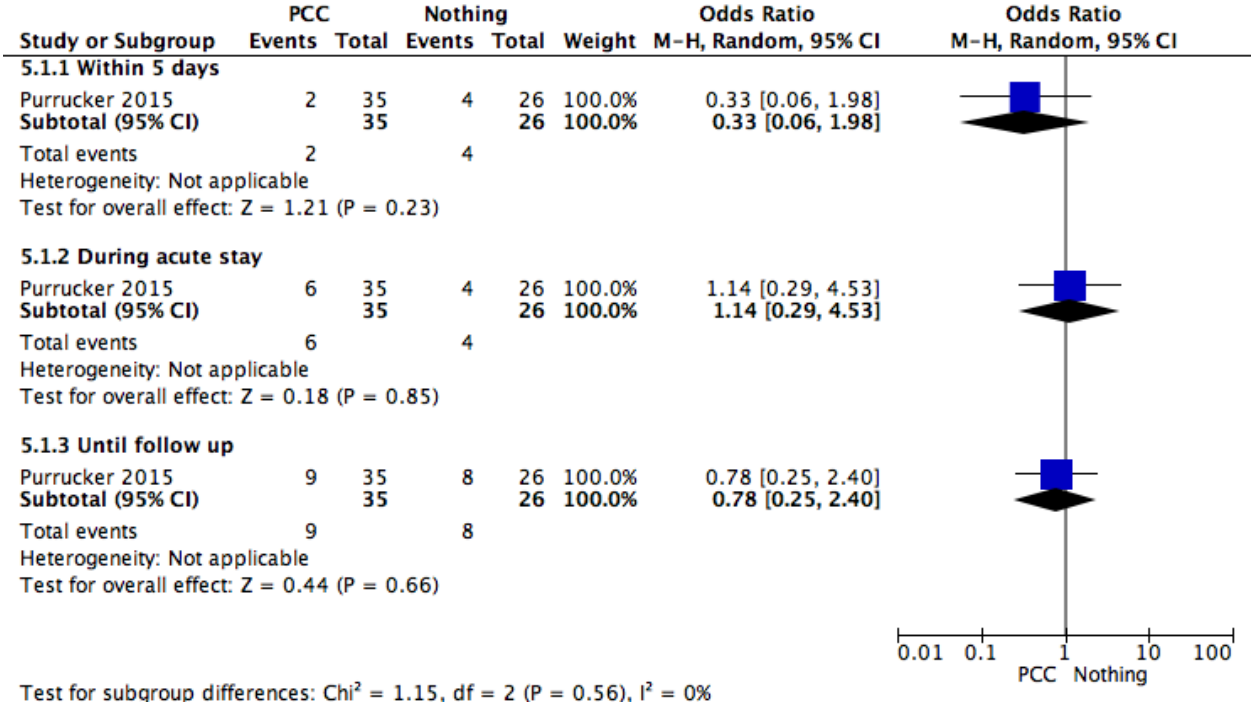
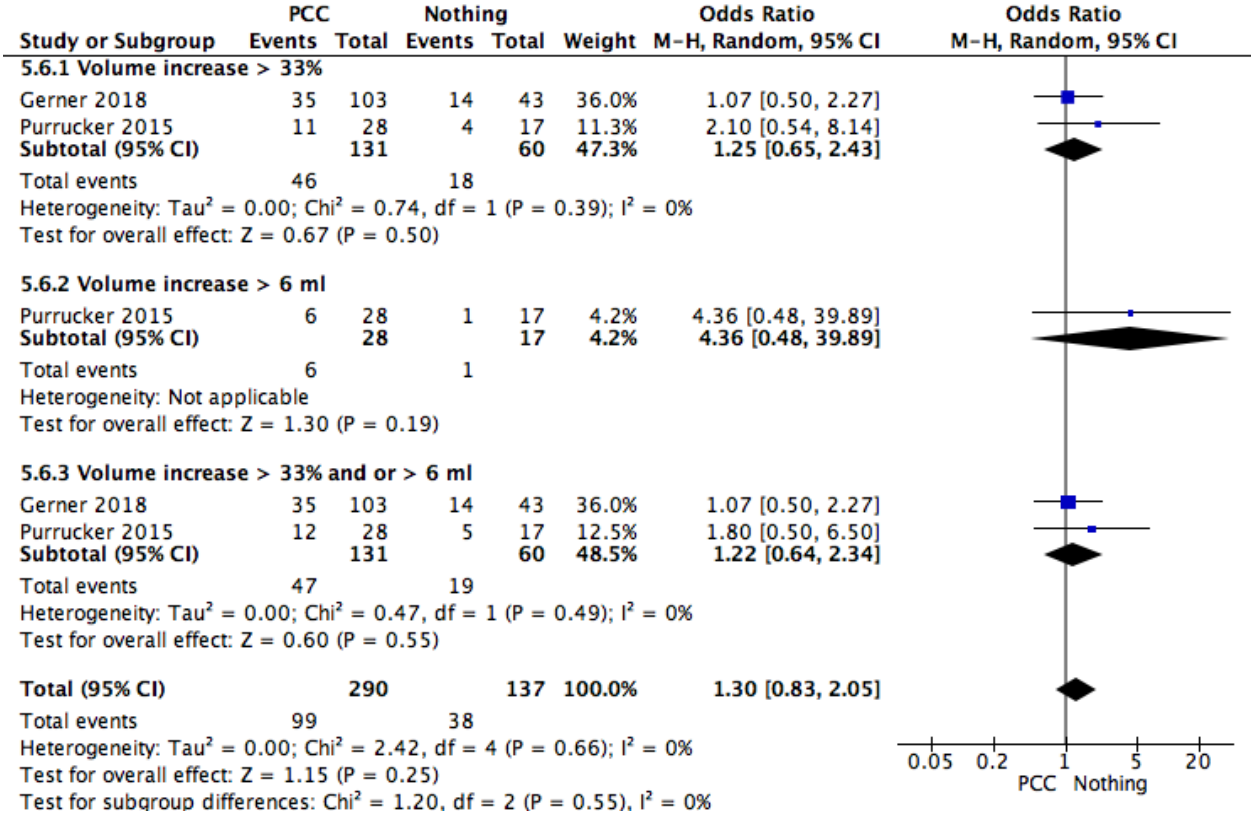


Figure: Effect of PCC on increase of hematoma in patients with NOACs induced hemorrhage



PICO 3: In adult patients with ICH occurring during use of VKA (with an INR above normal) does PCC in comparison to FFP, improve outcomes

Author(s):
Date:
Question: PCC compared to FFP for ICH occurring during use of VKA
Setting:
Bibliography:

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**PCC**	**FFP**	**Relative (95% CI)**	**Absolute (95% CI)**		
Mortality												
3	observational studies	not serious	not serious	not serious	not serious	publication bias strongly suspected [a]	223/612 (36.4%)	180/400 (45.0%)	**OR 0.69** (0.54 to 0.90)	**89 fewer per 1,000** (from 26 fewer to 144 fewer)	⨁◯◯◯ VERY LOW	CRITICAL
Hematoma expansion, at 3 and 24 h												
1	randomised trials	not serious	not serious	not serious	not serious	publication bias strongly suspected [b]	27	23	-	MD **13.89 mL lower** (23.45 lower to 4.34 lower)	⨁⨁⨁◯ MODERATE	IMPORTANT
INR ≤ 1·2, at 3, 7 or 24 h												
1	observational studies	not serious	not serious	not serious	not serious	publication bias strongly suspected [b]	20/23 (87.0%)	10/23 (43.5%)	**OR 11.35** (3.52 to 36.55)	**462 more per 1,000** (from 296 more to 531 more)	⨁◯◯◯ VERY LOW	IMPORTANT
mRS 0-3, 3 months												
1	randomised trials	not serious	not serious	not serious	not serious	publication bias strongly suspected [b]	10/27 (37.0%)	9/23 (39.1%)	**RR 0.92** (0.29 to 2.88)	**31 fewer per 1,000** (from 278 fewer to 736 more)	⨁⨁⨁◯ MODERATE	IMPORTANT
NIHSS score at day 15 or discharge												
1	randomised trials	not serious	not serious	not serious	not serious	publication bias strongly suspected [b]	27	23	-	MD **1.3 Score higher** (5 lower to 7.6 higher)	⨁⨁⨁◯ MODERATE	IMPORTANT
Barthel index at day 90												
1	randomised trials	not serious	not serious	not serious	not serious	publication bias strongly suspected [b]	27	23	-	MD **17.5 Score higher** (4.26 lower to 39.26 higher)	⨁⨁⨁◯ MODERATE	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PCC	FFP	Relative (95% CI)	Absolute (95% CI)		
Extended Glasgow Outcome Scale at day 90												
1	randomised trials	not serious	not serious	not serious	not serious	publication bias strongly suspected [b]	27	23	-	MD **0.42 Score lower** (1.66 lower to 0.82 higher)	⨁⨁⨁◯ MODERATE	IMPORTANT

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

Explanations

a. Three studies to support this outcome
b. Single study to support this outcome

Summary of findings:

PCC compared to FFP for ICH occurring during use of VKA

Patient or population: ICH occurring during use of VKA
Setting:
Intervention: PCC
Comparison: FFP

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with FFP	Risk with PCC				
Mortality	450 per 1,000	**361 per 1,000** (306 to 424)	**OR 0.69** (0.54 to 0.90)	1012 (3 observational studies)	⨁◯◯◯ VERY LOW [a]	
Hematoma expansion, at 3 and 24 h	The mean hematoma expansion, at 3 and 24 h was **0** mL	The mean hematoma expansion, at 3 and 24 h in the intervention group was 13.89 mL lower (23.45 lower to 4.34 lower)	-	50 (1 RCT)	⨁⨁⨁◯ MODERATE [b]	
INR ≤ 1·2, at 3, 7 or 24 h	435 per 1,000	**897 per 1,000** (730 to 966)	**OR 11.35** (3.52 to 36.55)	46 (1 observational study)	⨁◯◯◯ VERY LOW [b]	
mRS 0-3, 3 months	391 per 1,000	**360 per 1,000** (113 to 1,000)	**RR 0.92** (0.29 to 2.88)	50 (1 RCT)	⨁⨁⨁◯ MODERATE [b]	
NIHSS score at day 15 or discharge	The mean NIHSS score at day 15 or discharge was **0** Score	The mean NIHSS score at day 15 or discharge in the intervention group was 1.3 Score higher (5 lower to 7.6 higher)	-	50 (1 RCT)	⨁⨁⨁◯ MODERATE [b]	
Barthel index at day 90	The mean barthel index at day 90 was **0** Score	The mean barthel index at day 90 in the intervention group was 17.5 Score higher (4.26 lower to 39.26 higher)	-	50 (1 RCT)	⨁⨁⨁◯ MODERATE [b]	

Summary of findings:

PCC compared to FFP for ICH occurring during use of VKA

Patient or population: ICH occurring during use of VKA
Setting:
Intervention: PCC
Comparison: FFP

Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with FFP	**Risk with PCC**				
Extended Glasgow Outcome Scale at day 90	The mean extended Glasgow Outcome Scale at day 90 was **0** Score	The mean extended Glasgow Outcome Scale at day 90 in the intervention group was 0.42 Score lower (1.66 lower to 0.82 higher)	-	50 (1 RCT)	⨁⨁⨁◯ MODERATE [b]	

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

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

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

Explanations

a. Three studies to support this outcome
b. Single study to support this outcome

Table: Effect of FFP compared to PCC on outcomes in patients with warfarin-associated intracranial hemorrhage

Outcome	Incidence (%)		n (N)	OR [95% CI]	I^2	P value
	PCC	FFP				
Mortality, PCC vs FFP	36%	45%	2(1012)	0.69 [0.54, 0.90]	0%	0.005
Mortality, PCC vs FFP+PCC	37%	27%	1(716)	1.57 [1.03, 2.38]	NA	0.04
Incidence of hematoma expansion	22%	37%	1(99)	0.51 [0.21, 1.25]	0%	0.14
Incidence of hematoma expansion leading to death	4%	26%	1(50)	0.11 [0.01, 0.99]	NA	0.05
Extent of hematoma expansion, 3 h	9.7±20.9	23.7±28.4	1(50)	-14.00 [-28.03, 0.03]	NA	0.05
Extent of hematoma expansion, 24 h	8.3±18.3	22.1±27.1	1(50)	-13.80 [-26.85, -0.75]	NA	0.04
Hematoma expansion ≥15% at 3 h	58%	73%	1(48)	0.51 [0.15, 1.73]	NA	0.28
Hematoma expansion ≥33% at 3 h	44%	59%	1(49)	0.55 [0.18, 1.73]	NA	0.31
Hematoma expansion ≥15% at 24 h	44%	70%	1(47)	0.34 [0.10, 1.16]	NA	0.09
Hematoma expansion ≥33% at 24 h	38%	58%	1(96)	0.44 [0.19, 1.02]	NA	0.05
INR ≤1·2 at 3 h	67%	9%	1(50)	21.00 [4.01, 110.06]	NA	0.0003
INR ≤1·2 at 7 h	86%	55%	1(50)	4.88 [1.17, 20.26]	NA	0.03
INR ≤1·2 at 24 h	100%	57%	1(44)	35.72 [1.92, 665.89]	NA	0.02
mRS 0-3 at 15 days	26%	30%	1(50)	0.80 [0.23, 2.76]	NA	0.72
mRS 0-3 at 3 months	29%	32%	1(99)	0.96 [0.39, 2.32]	NA	0.92
Adverse effects						
At least one SAE	59%	43%	1(50)	1.89 [0.61, 5.83]	NA	0.27
Thromboembolic events	26%	9%	1(50)	3.67 [0.68, 19.85]	NA	0.13
-MI	0%	0%	1(50)	Not estimable	NA	NA
-Ischemic stroke	7%	9%	1(50)	0.84 [0.11, 6.49]	NA	0.87
-Pulmonary embolism	15%	0%	1(50)	9.00 [0.46, 176.69]	NA	0.15
-Deep vein thrombosis	4%	0%	1(50)	2.66 [0.10, 68.50]	NA	0.55
NIHSS score at day 15	12.2±11.1	10.9±11.5	1(50)	1.30 [-4.99, 7.59]	NA	0.69
Barthel index at day 90	70.0±37.7	52.5±40.3	1(50)	17.50 [-4.26, 39.26]	NA	0.11
Extended Glasgow Outcome Scale at day 90	4.18±2.23	4.6±2.23	1(50)	-0.42 [-1.66, 0.82]	NA	0.51

FFP: Fresh frozen plasma; I^2: Heterogeneity; n: Number of studies; N: Number of patients; p: Statistical significance value; PCC: Prothrombin complex concentrate; OR: Odds Ratio

Figure: Effect of PCC vs FFP on all-cause mortality in patients with warfarin-associated intracranial hemorrhage

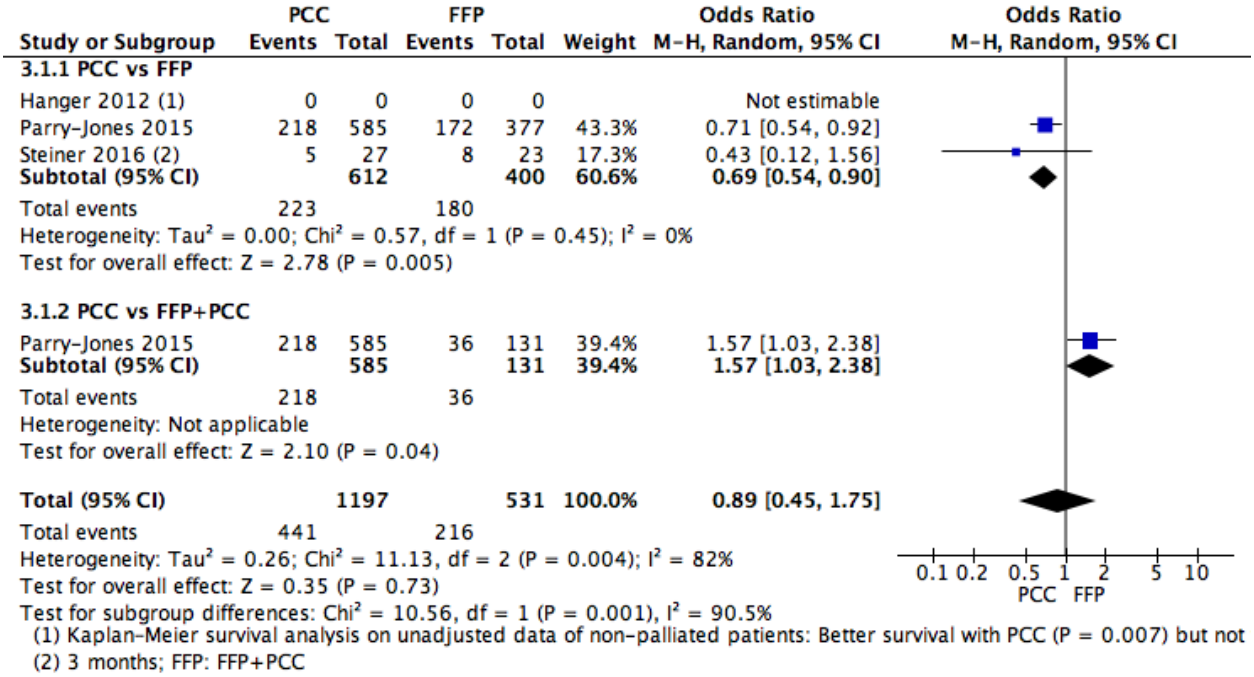


Figure: Effect of PCC vs FFP on incidence of hematoma expansion in patients with warfarin-associated intracranial hemorrhage

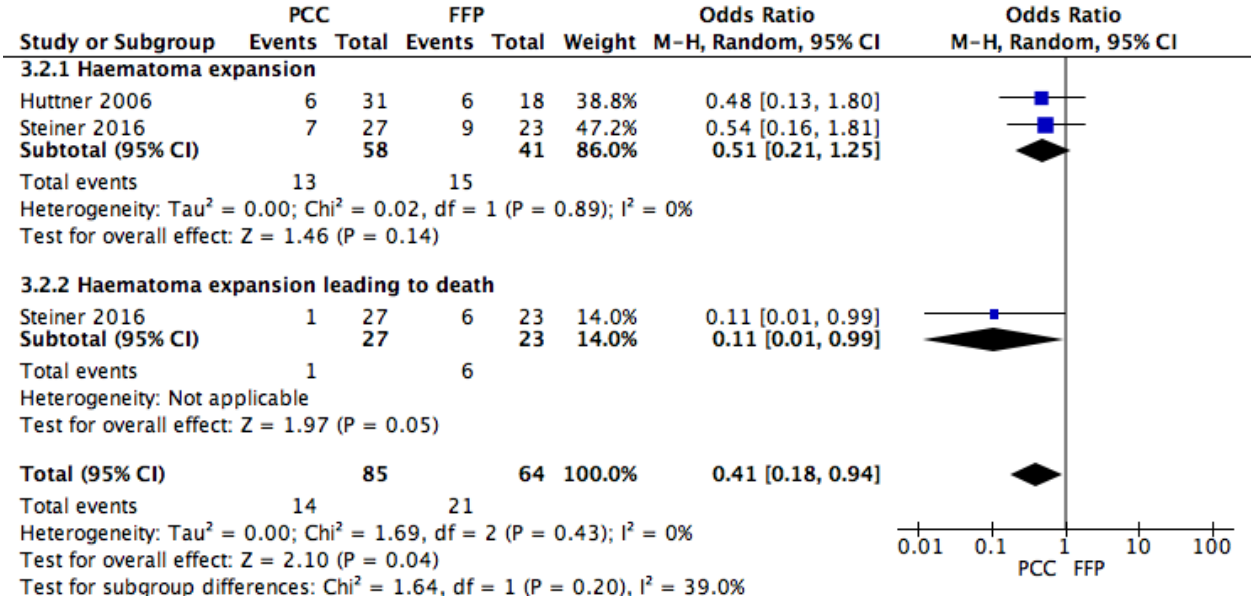


Figure: Effect of PCC vs FFP on extent of hematoma expansion (mL) in patients with warfarin-associated intracranial hemorrhage

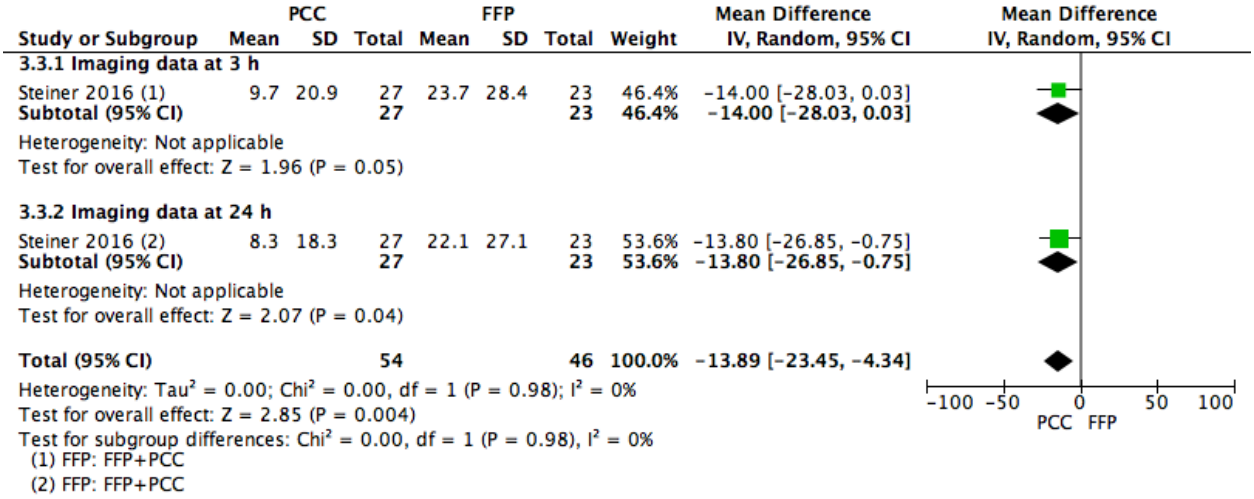


Figure: Effect of PCC vs FFP on % of hematoma expansion in patients with warfarin-associated intracranial hemorrhage

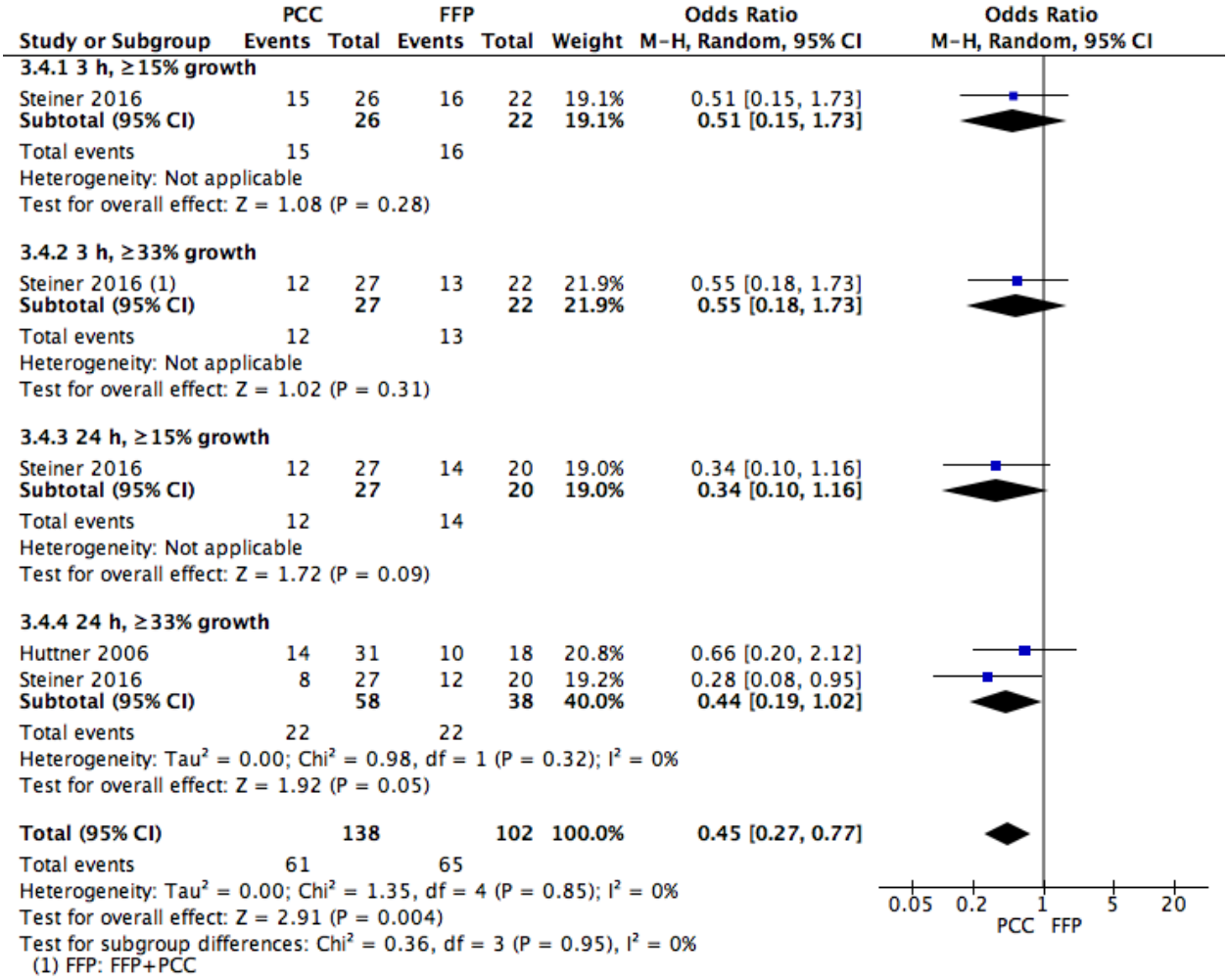


Figure: Effect of PCC vs FFP on INR ≤1·2 in patients with warfarin-associated intracranial hemorrhage

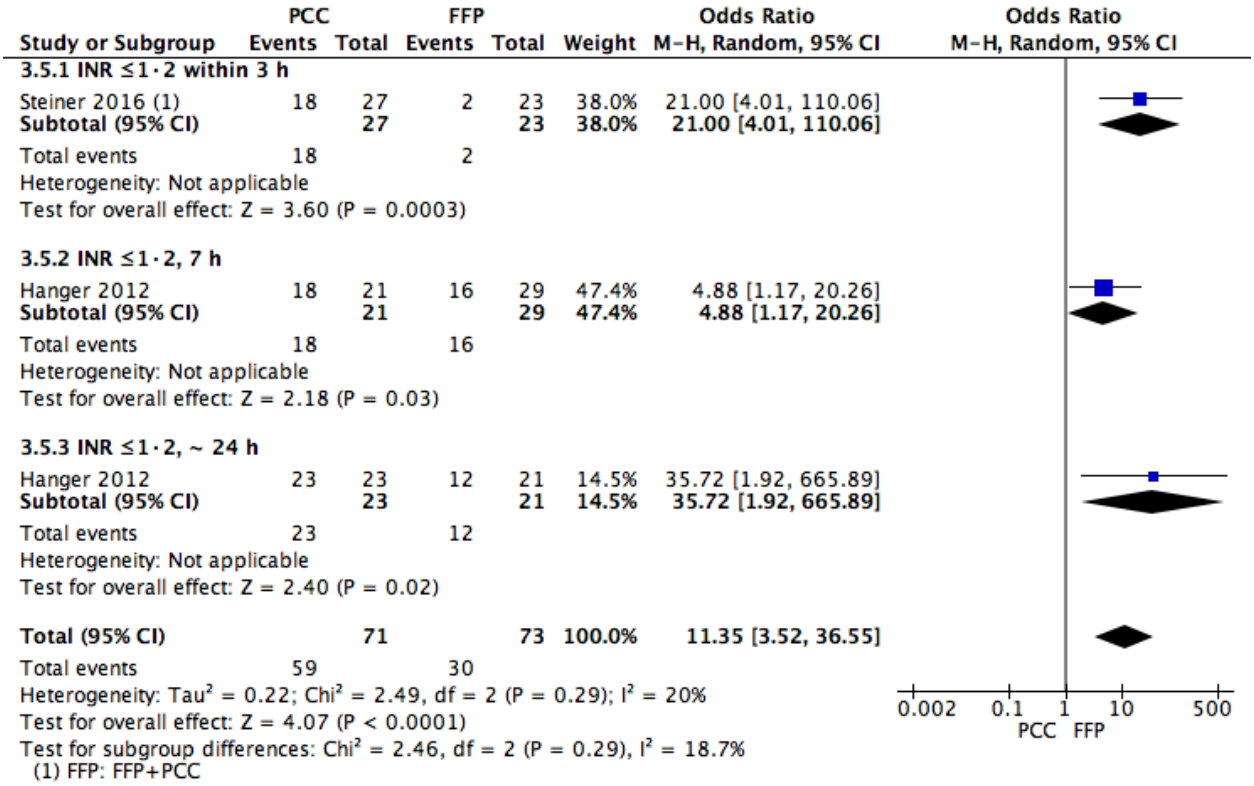


Figure: Effect of PCC vs FFP on mRS score 0-3 in patients with warfarin-associated intracranial hemorrhage

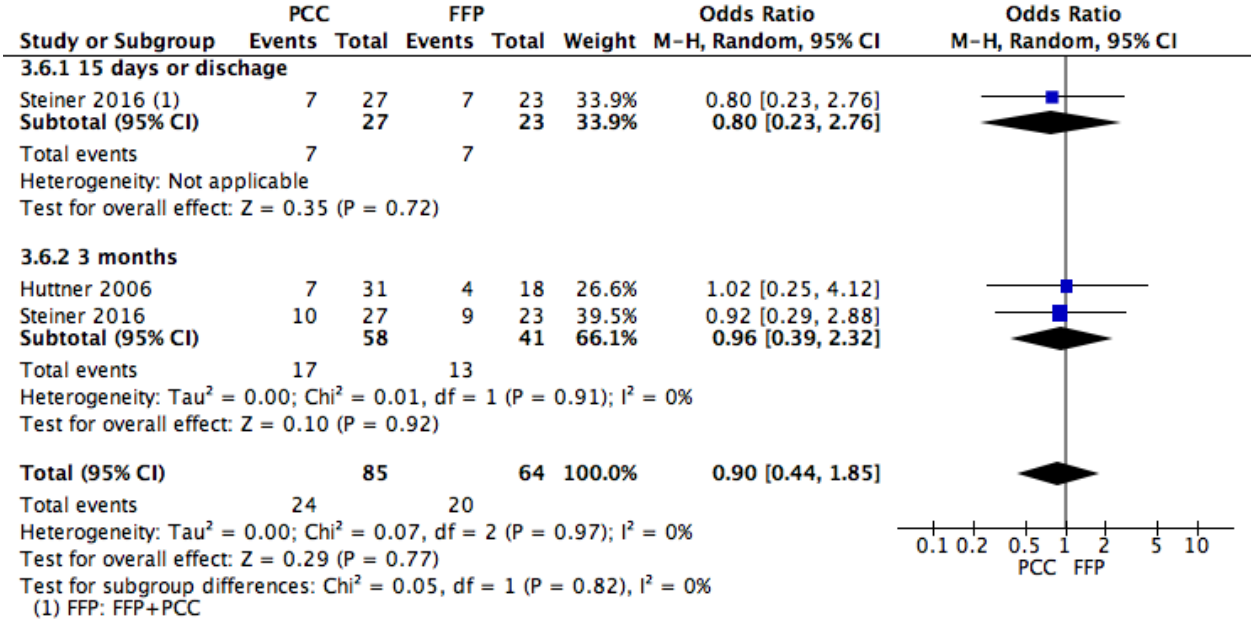


Figure: Effect of PCC vs FFP on adverse events in patients with warfarin-associated intracranial hemorrhage

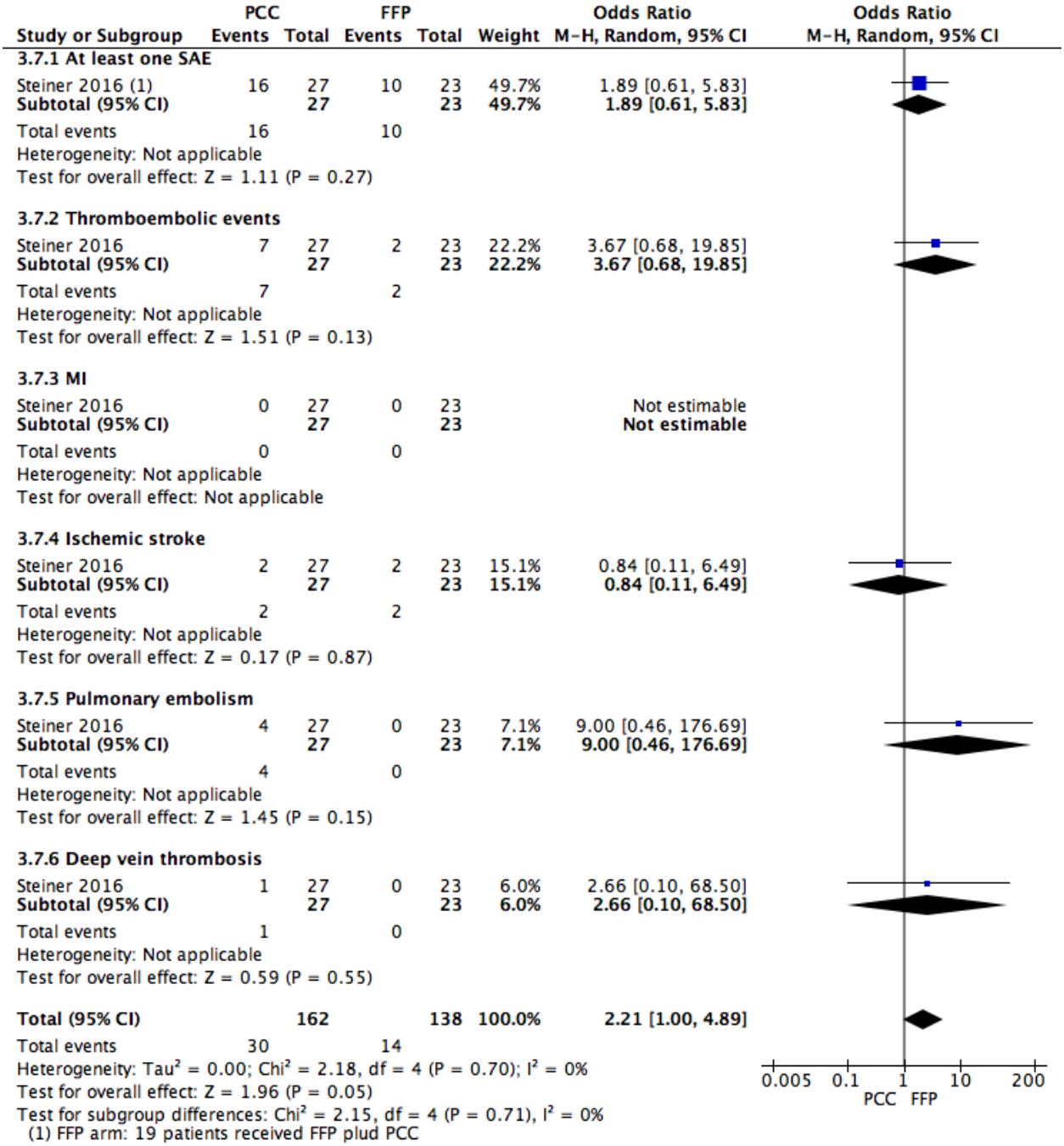
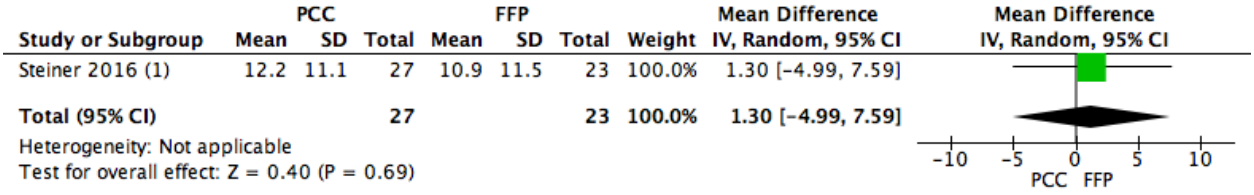
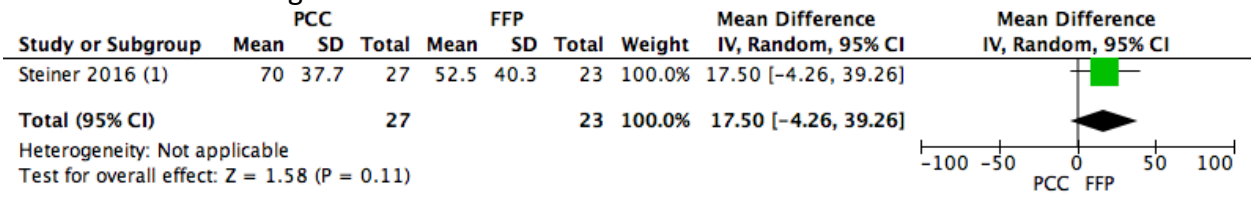


Figure: Effect of PCC vs FFP on NIHSS score at day 15 or discharge in patients with warfarin-associated intracranial hemorrhage



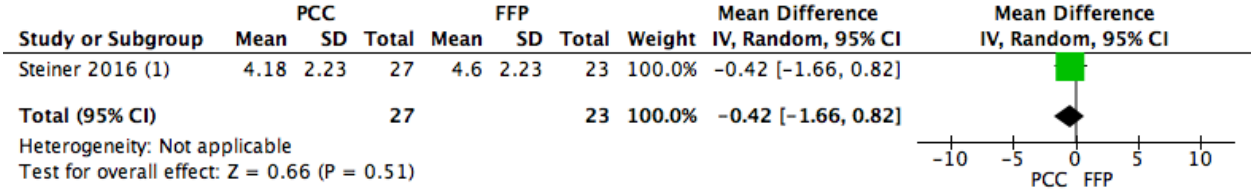
(1) 15 days or discharge; FFP: FFP+PCC

Figure: Effect of PCC vs FFP on Barthel index at day 90 in patients with warfarin-associated intracranial hemorrhage



(1) FFP: FFP+PCC

Figure: Effect of PCC vs FFP on Extended Glasgow Outcome Scale at day 90 in patients with warfarin-associated intracranial hemorrhage



(1) 15 days or discharge; FFP: FFP+PCC

PICO 6: In adult patients with ICH occurring during use of VKA (with an INR above normal) does use of Vit K in comparison to FFP improve outcomes

Author(s):
Date:
Question: Vit K compared to FFP for ICH occurring during use of VKA
Setting:
Bibliography:

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Vit K**	**FFP**	**Relative (95% CI)**	**Absolute (95% CI)**		
Mortality												
1	observational studies	not serious	not serious	not serious	not serious	publication bias strongly suspected [a]	Kaplan–Meier survival analysis on unadjusted data, non-palliated patients: No significant difference in survival between Vit K or FFP.				⨁◯◯◯ VERY LOW	CRITICAL
Incidence of hematoma enlargement												
1	observational studies	not serious	not serious	not serious	serious [b]	publication bias strongly suspected strong association [a]	3/6 (50.0%)	6/18 (33.3%)	**OR 2.00** (0.31 to 13.06)	**167 more per 1,000** (from 199 fewer to 534 more)	⨁◯◯◯ VERY LOW	IMPORTANT
Extent of hematoma enlargement												
1	observational studies	not serious	not serious	not serious	serious [b]	publication bias strongly suspected [a]	4/6 (66.7%)	10/18 (55.6%)	**OR 1.60** (0.23 to 11.08)	**111 more per 1,000** (from 332 fewer to 377 more)	⨁◯◯◯ VERY LOW	IMPORTANT
INR < or = 1.4												
1	observational studies	not serious	not serious	not serious	serious [b]	publication bias strongly suspected [a]	0/6 (0.0%)	7/18 (38.9%)	**OR 0.12** (0.01 to 2.42)	**318 fewer per 1,000** (from 217 more to 383 fewer)	⨁◯◯◯ VERY LOW	IMPORTANT
mRS 0-3												
1	observational studies	not serious	not serious	not serious	serious [b]	publication bias strongly suspected [a]	1/6 (16.7%)	4/18 (22.2%)	**OR 0.70** (0.06 to 7.85)	**56 fewer per 1,000** (from 205 fewer to 469 more)	⨁◯◯◯ VERY LOW	IMPORTANT

CI: Confidence interval; **OR:** Odds ratio

Explanations

a. Single study to support this outcome
b. Wide confidence interval

Summary of findings:

Vit K compared to FFP for ICH occurring during use of VKA

Patient or population: ICH occurring during use of VKA
Setting:
Intervention: Vit K
Comparison: FFP

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with FFP	Risk with Vit K				
Mortality	Kaplan–Meier survival analysis on unadjusted data, non-palliated patients: No significant difference in survival between Vit K or FFP.			(1 observational study)	⨁◯◯◯ VERY LOW [a]	
Incidence of hematoma enlargement	333 per 1,000	**500 per 1,000** (134 to 867)	**OR 2.00** (0.31 to 13.06)	24 (1 observational study)	⨁◯◯◯ VERY LOW [a,b]	
Extent of hematoma enlargement	556 per 1,000	**667 per 1,000** (223 to 933)	**OR 1.60** (0.23 to 11.08)	24 (1 observational study)	⨁◯◯◯ VERY LOW [a,b]	
INR < or = 1.4	389 per 1,000	**71 per 1,000** (6 to 606)	**OR 0.12** (0.01 to 2.42)	24 (1 observational study)	⨁◯◯◯ VERY LOW [a,b]	
mRS 0-3	222 per 1,000	**167 per 1,000** (17 to 692)	**OR 0.70** (0.06 to 7.85)	24 (1 observational study)	⨁◯◯◯ VERY LOW [a,b]	

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

CI: Confidence interval; **OR:** Odds ratio

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

Explanations

a. Single study to support this outcome
b. Wide confidence interval

Table: Effect of Vit K compared to FFP on outcomes in patients with warfarin-associated intracranial hemorrhage

Outcome	Incidence (%)		n (N)	OR [95% CI]	I^2	P value
	Vit K	FFP				
Mortality, Vit K vs FFP	Kaplan–Meier survival analysis on unadjusted data, non-palliated patients: No significant difference in survival between Vit K and FFP (Hanger 2012)					
Incidence of hematoma expansion	50%	33%	1(24)	2.00 [0.31, 13.06]	NA	0.47
Hematoma expansion >33%	67%	56%	1(24)	1.60 [0.23, 11.08]	NA	0.63
INR ≤1·4	0%	39%	1(24)	0.12 [0.01, 2.42]	NA	0.17
mRS 0-3	17%	22%	1(24)	0.70 [0.06, 7.85]	NA	0.77

FFP: Fresh frozen plasma; I^2: Heterogeneity; n: Number of studies; N: Number of patients; p: Statistical significance value; OR: Odds Ratio

Figure: Effect of Vit K vs FFP on incidence of hematoma enlargement in patients with warfarin-associated intracranial hemorrhage

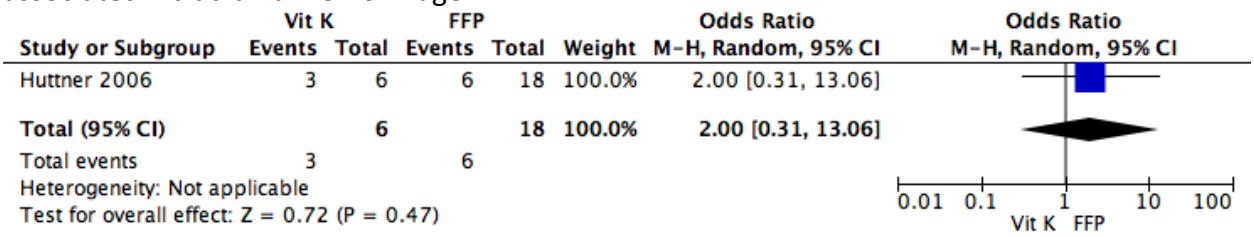
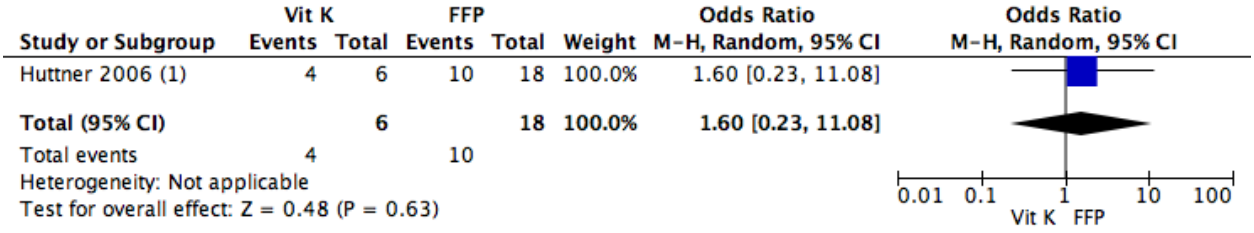


Figure: Effect of Vit K vs FFP on extent of hematoma enlargement > 33% in patients with warfarin-associated intracranial hemorrhage



(1) PCC alone or with FFP or Vit K

Figure: Effect of Vit K vs FFP on INR ≤ **1.4** in patients with warfarin-associated intracranial hemorrhage

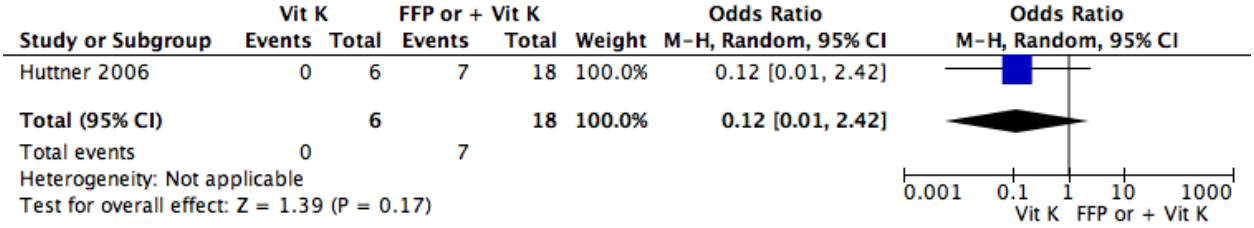
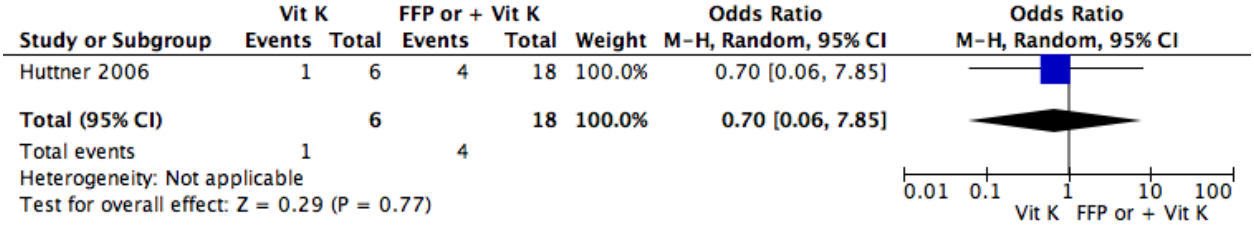


Figure: Effect of Vit K vs FFP on mRS 0-3 in patients with warfarin-associated intracranial hemorrhage



PICO 7: In adult patients with ICH occurring during use of VKA (with an INR above normal) does use of Vit K in comparison to PCC improve outcomes

Author(s):
Date:
Question: Vit K compared to PCC for ICH occurring during use of VKA
Setting:
Bibliography:

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vit K	PCC	Relative (95% CI)	Absolute (95% CI)		
Mortality												
2	observational studies	not serious	not serious	not serious	serious [a]	publication bias strongly suspected [b]	1/4 (25.0%)	1/11 (9.1%)	**OR 3.33** (0.16 to 70.91)	**159 more per 1,000** (from 75 fewer to 785 more)	⨁◯◯◯ VERY LOW	CRITICAL
Incidence of hematoma enlargement												
2	observational studies	not serious	not serious	not serious	serious [a]	publication bias strongly suspected strong association [b]	3/10 (30.0%)	7/42 (16.7%)	**OR 2.85** (0.57 to 14.27)	**196 more per 1,000** (from 64 fewer to 574 more)	⨁◯◯◯ VERY LOW	IMPORTANT
Extent of hematoma enlargement < 33%												
1	observational studies	not serious	not serious	not serious	serious [a]	publication bias strongly suspected [c]	4/6 (66.7%)	14/31 (45.2%)	**OR 2.43** (0.39 to 15.27)	**215 more per 1,000** (from 209 fewer to 475 more)	⨁◯◯◯ VERY LOW	IMPORTANT
INR = or < 1.4												
1	observational studies	not serious	not serious	not serious	not serious	publication bias strongly suspected [c]	0/6 (0.0%)	26/31 (83.9%)	**OR 0.02** (0.00 to 0.33)	**745 fewer per 1,000** (from -- to 207 fewer)	⨁◯◯◯ VERY LOW	IMPORTANT
mRS												
1	observational studies	not serious	not serious	not serious	serious [a]	publication bias strongly suspected [c]	1/6 (16.7%)	7/31 (22.6%)	**OR 0.69** (0.07 to 6.88)	**58 fewer per 1,000** (from 206 fewer to 442 more)	⨁◯◯◯ VERY LOW	IMPORTANT

CI: Confidence interval; **OR:** Odds ratio

Explanations

a. Wide confidence interval
b. Two studies to support this outcome
c. One study to support this outcome

Summary of findings:

Vit K compared to PCC for ICH occurring during use of VKA

Patient or population: ICH occurring during use of VKA
Setting:
Intervention: Vit K
Comparison: PCC

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with PCC	Risk with Vit K				
Mortality	91 per 1,000	**250 per 1,000** (16 to 876)	**OR 3.33** (0.16 to 70.91)	15 (2 observational studies)	⨁◯◯◯ VERY LOW [a,b]	
Incidence of hematoma enlargement	167 per 1,000	**363 per 1,000** (102 to 741)	**OR 2.85** (0.57 to 14.27)	52 (2 observational studies)	⨁◯◯◯ VERY LOW [a,b]	
Extent of hematoma enlargement < 33%	452 per 1,000	**667 per 1,000** (243 to 926)	**OR 2.43** (0.39 to 15.27)	37 (1 observational study)	⨁◯◯◯ VERY LOW [a,c]	
INR = or < 1.4	839 per 1,000	**94 per 1,000** (0 to 632)	**OR 0.02** (0.00 to 0.33)	37 (1 observational study)	⨁◯◯◯ VERY LOW [c]	
mRS	226 per 1,000	**168 per 1,000** (20 to 667)	**OR 0.69** (0.07 to 6.88)	37 (1 observational study)	⨁◯◯◯ VERY LOW [a,c]	

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

CI: Confidence interval; **OR:** Odds ratio

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

Explanations

a. Wide confidence interval
b. Two studies to support this outcome
c. One study to support this outcome

Table: Effect of Vit K compared to PCC on outcomes in patients with warfarin-associated intracranial hemorrhage

Outcome	Incidence (%)		n (N)	OR [95% CI]	I^2	P value
	Vit K	PCC				
Mortality, Vit K vs PCC+Vit K	25%	9%	1(15)	3.33 [0.16, 70.91]	NA	0.44
Mortality, Vit K vs PCC	25%	50%	1(6)	0.33 [0.01, 11.94]	NA	0.55
Incidence of hematoma expansion, Vit K vs PCC+Vit K	30%	17%	1(52)	2.85 [0.57, 14.27]	NA	0.20
Incidence of hematoma expansion, Vit K vs PCC	0%	0%	1(6)	Not estimable	NA	NA
Extent of hematoma expansion ≥33%, Vit K vs PCC+Vit K	67%	45%	1(37)	2.43 [0.39, 15.27]	NA	0.34
INR ≤1·4, Baseline, Vit K+PCC vs PCC	2.70±2.44	6.23±2.08	1(13)	-3.53 [-6.75, -0.31]	NA	0.03
INR ≤1·4, 10 min, Vit K+PCC vs PCC	1.13±0.13	1.36±0.15	1(13)	-0.23 [-0.45, -0.01]	NA	0.04
INR ≤1·4, 12-24 h, Vit K+PCC vs PCC	1.06±0.09	2.07±0.33	1(13)	-1.01 [-1.47, -0.55]	NA	< 0.0001
INR at Baseline, Vit K vs PCC	2.69±0.38	6.23±2.08	1(6)	-3.54 [-6.45, -0.63]	NA	0.02
INR at 10 min, Vit K vs PCC	2.69±0.38	1.36±0.15	1(6)	1.33 [0.90, 1.76]	NA	<0.00001
INR at 12-24 h Vit K vs PCC	1.28±0.06	2.07±0.33	1(6)	-0.79 [-1.25, -0.33]	NA	0.0008
INR ≤1·4	0%	84%	1(37)	0.02 [0.00, 0.33]	NA	0.007
mRS 0-3	17%	23%	1(37)	0.69 [0.07, 6.88]	NA	0.75

I^2: Heterogeneity; n: Number of studies; N: Number of patients; p: Statistical significance value; PCC: Prothrombin complex concentrate; OR: Odds Ratio

Figure: Effect of Vit K vs PCC on mortality in patients with warfarin-associated intracranial hemorrhage

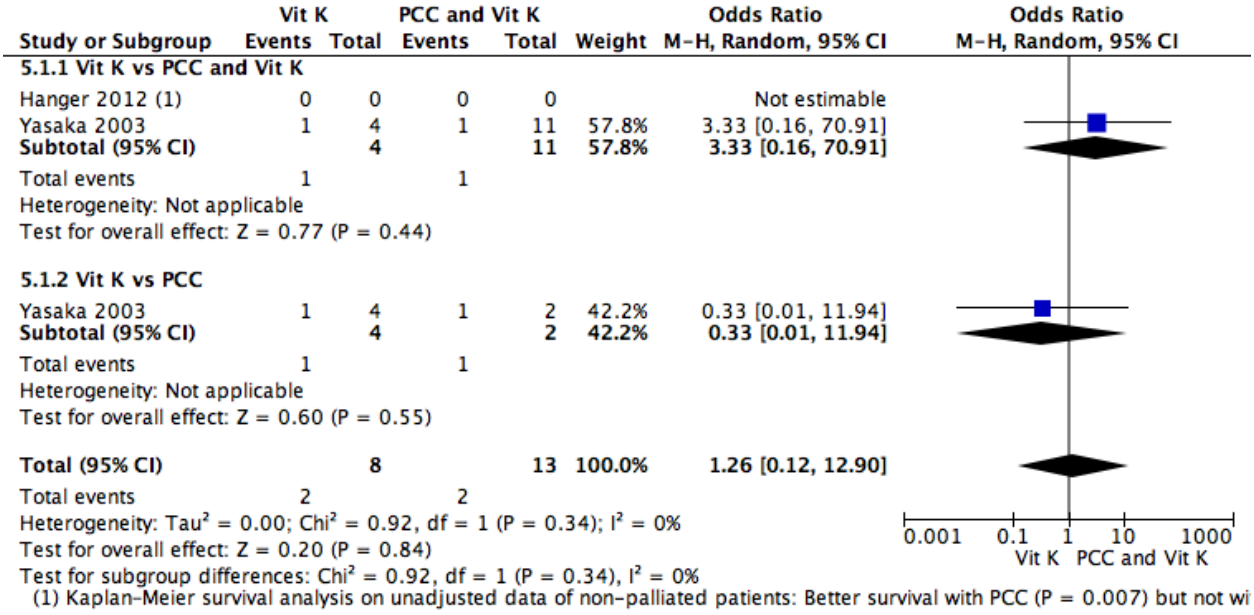


Figure: Effect of Vit K vs PCC on incidence of hematoma enlargement in patients with warfarin-associated intracranial hemorrhage

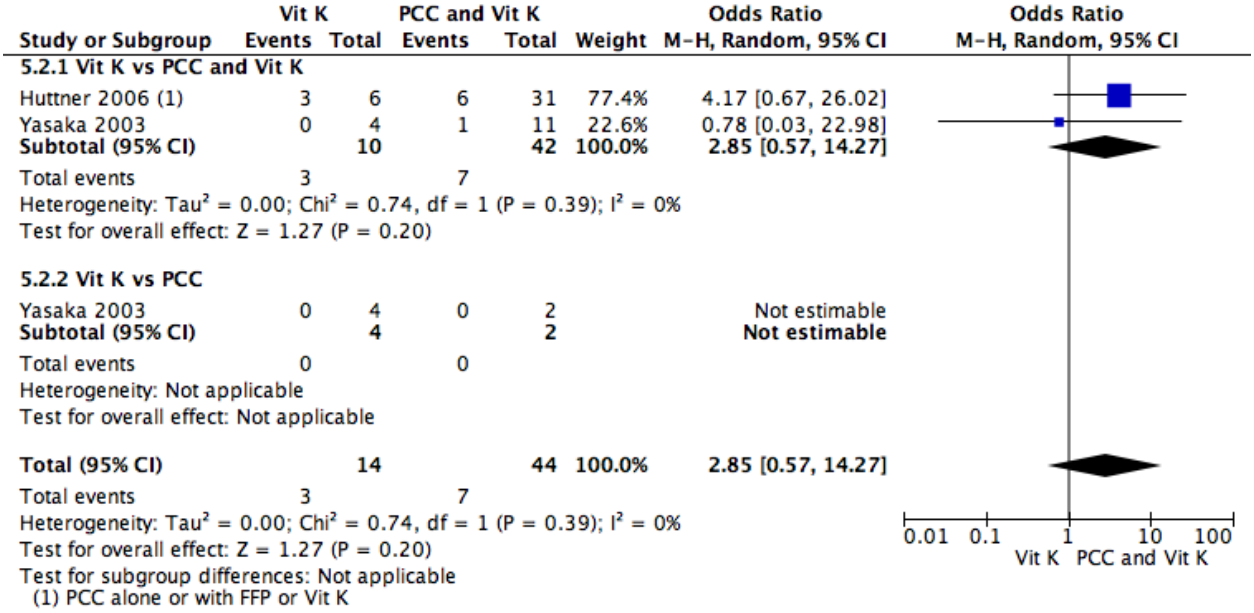


Figure: Effect of Vit K vs PCC on extent of hematoma enlargement > 33% in patients with warfarin-associated intracranial hemorrhage

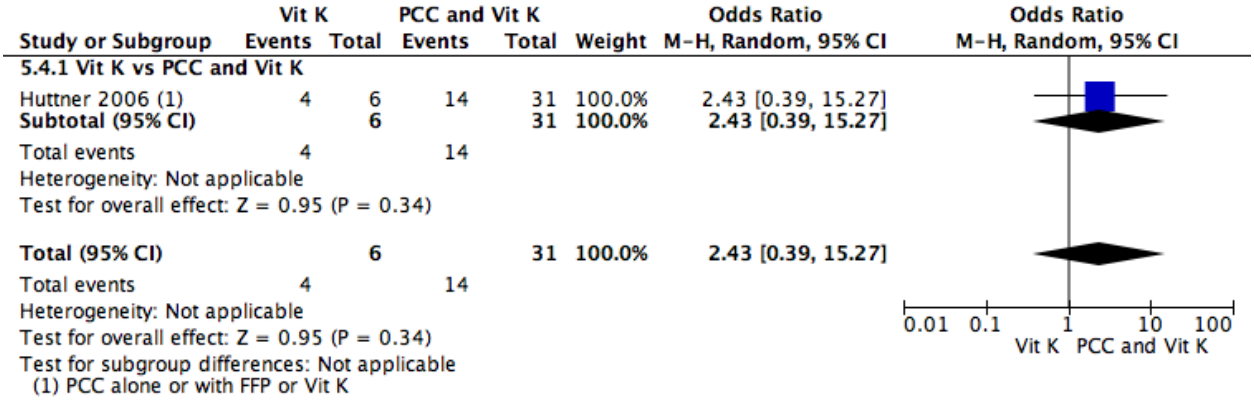


Figure: Effect of Vit K and PCC vs PCC on INR in patients with warfarin-associated intracranial hemorrhage

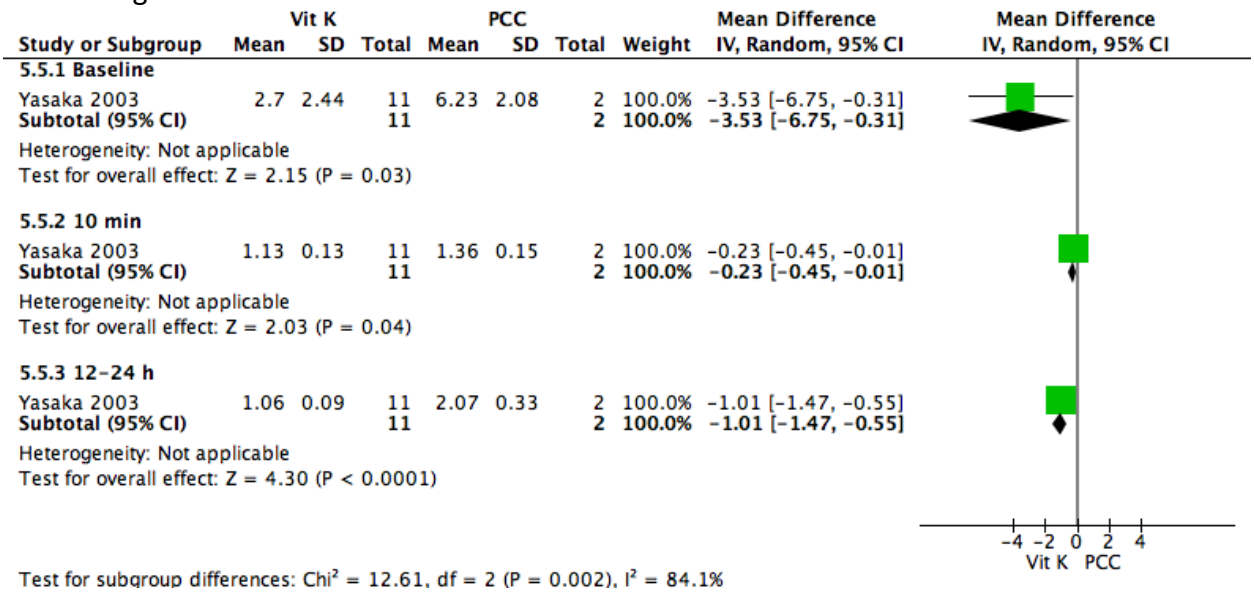


Figure: Effect of Vit K vs PCC on INR in patients with warfarin-associated intracranial hemorrhage

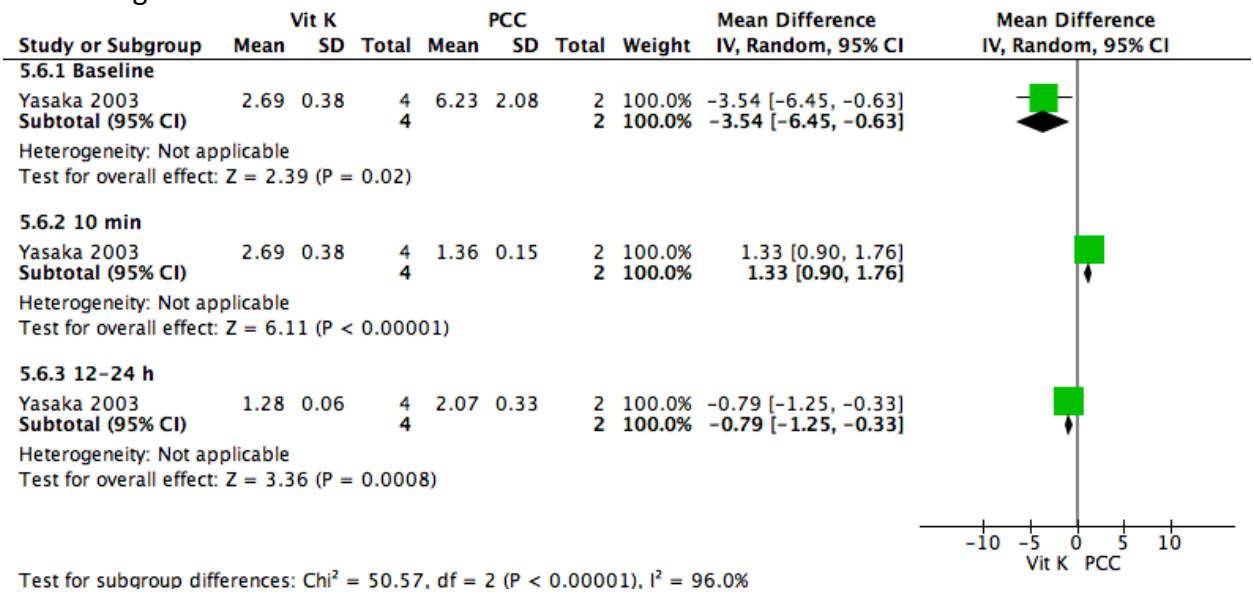


Figure: Effect of Vit K vs PCC on incidence of INR ≤1·4 in patients with warfarin-associated intracranial hemorrhage

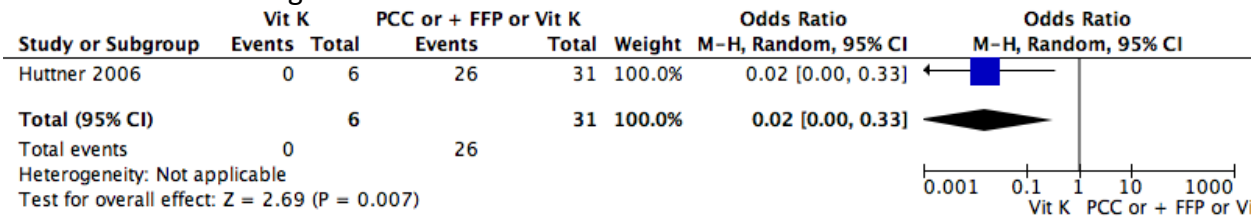
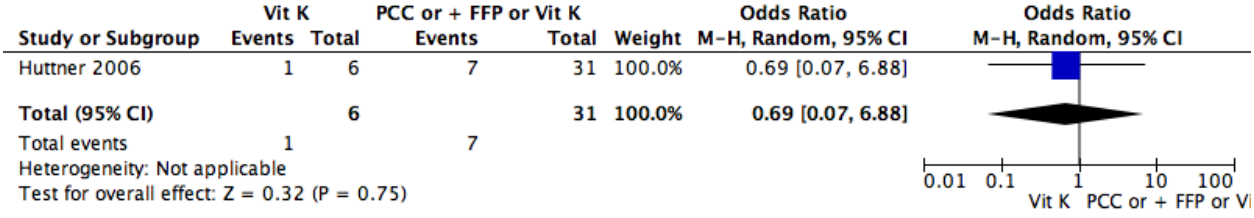


Figure: Effect of Vit K vs PCC on incidence of mRS 0-3 in patients with warfarin-associated intracranial hemorrhage



PICO 9: In adult patients with ICH occurring during use of VKA (with an INR above normal) does use of rFVII in comparison to FFP improve outcomes

Author(s):
Date:
Question: RFVII compared to FFP and Vit K for ICH occurring during use of VKA
Setting:
Bibliography:

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**rFVII**	**FFP and Vit K**	**Relative (95% CI)**	**Absolute (95% CI)**		
Mortality												
1	observational studies	not serious	not serious	not serious	not serious	publication bias strongly suspected strong association [a]	16/45 (35.6%)	6/34 (17.6%)	**OR 2.57** (0.88 to 7.52)	**179 more per 1,000** (from 18 fewer to 441 more)	⨁⨁◯◯ LOW	CRITICAL
INR, 3 and 6 h												
1	observational studies	not serious	not serious	not serious	not serious	publication bias strongly suspected [a]	45	34	-	MD **0.41 lower** (0.55 lower to 0.27 lower)	⨁◯◯◯ VERY LOW	IMPORTANT
Stroke												
1	observational studies	not serious	not serious	not serious	serious [b]	publication bias strongly suspected strong association [a]	1/45 (2.2%)	0/34 (0.0%)	**OR 2.33** (0.09 to 58.88)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⨁◯◯◯ VERY LOW	CRITICAL
Thromembolism												
1	observational studies	not serious	not serious	not serious	serious [b]	publication bias strongly suspected strong association [a]	1/45 (2.2%)	3/34 (8.8%)	**OR 0.23** (0.02 to 2.36)	**66 fewer per 1,000** (from 86 fewer to 98 more)	⨁◯◯◯ VERY LOW	CRITICAL
Transfusion of FFP												
1	observational studies	not serious	not serious	not serious	not serious	publication bias strongly suspected [a]	45	34	-	MD **2 Units lower** (3.53 lower to 0.47 lower)	⨁◯◯◯ VERY LOW	IMPORTANT

CI: Confidence interval; **OR:** Odds ratio; **MD:** Mean difference

Explanations

a. Single study to support this outcome
b. Wide Confidence intervals

Summary of findings:

RFVII compared to FFP and Vit K for ICH occurring during use of VKA

Patient or population: ICH occurring during use of VKA
Setting:
Intervention: rFVII
Comparison: FFP and Vit K

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with FFP and Vit K	Risk with rFVII				
Mortality	176 per 1,000	**355 per 1,000** (159 to 617)	**OR 2.57** (0.88 to 7.52)	79 (1 observational study)	⨁⨁◯◯ LOW [a]	
INR, 3 and 6 h	The mean INR, 3 and 6 h was **0**	The mean INR, 3 and 6 h in the intervention group was 0.41 lower (0.55 lower to 0.27 lower)	-	79 (1 observational study)	⨁◯◯◯ VERY LOW [a]	
Stroke	0 per 1,000	**0 per 1,000** (0 to 0)	**OR 2.33** (0.09 to 58.88)	79 (1 observational study)	⨁◯◯◯ VERY LOW [a,b]	
Thromembolism	88 per 1,000	**22 per 1,000** (2 to 186)	**OR 0.23** (0.02 to 2.36)	79 (1 observational study)	⨁◯◯◯ VERY LOW [a,b]	
Transfusion of FFP	The mean transfusion of FFP was **0** Units	The mean transfusion of FFP in the intervention group was 2 Units lower (3.53 lower to 0.47 lower)	-	79 (1 observational study)	⨁◯◯◯ VERY LOW [a]	

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

CI: Confidence interval; **OR:** Odds ratio; **MD:** Mean difference

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

Explanations

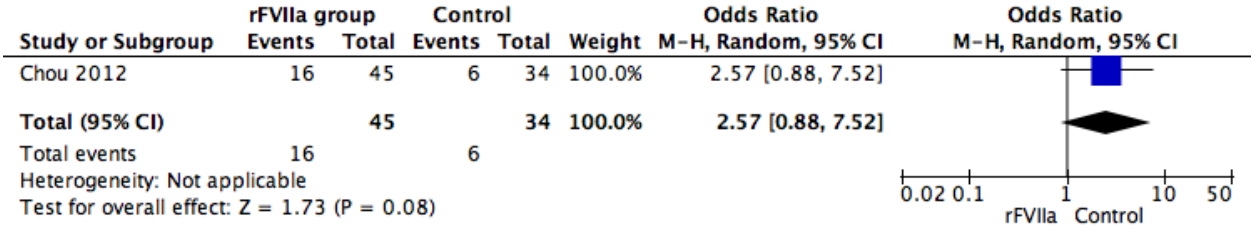
a. Single study to support this outcome
b. Wide Confidence intervals

Table: Effect of rFVII in patients with warfarin-associated intracranial hemorrhage

Outcome	Incidence (%)		n (N)	MD [95% CI]/ OR [95% CI]	I^2	P value
	rFVIIa	FFP and Vit K				
Mortality, in hospital	36% (16/45)	18% (6/34)	1 (79)	2.57 [0.88, 7.52]	NA	0.08
Survival, after hematoma evacuation	38% (17/45)	18% (6/34)	1 (79)	2.83 [0.97, 8.24]	NA	0.05
Survival, after surgical hematoma evacuation	31% (14/45)	12% (4/34)	1 (79)	3.39 [1.00, 11.46]	NA	0.05
Withdrawal of life threatening care	31% (14/45)	18% (6/34)	1 (79)	2.11 [0.71, 6.23]	NA	0.17
Stroke, overall	2% (1/45)	0% (0/34)	1 (79)	2.33 [0.09, 58.88]	NA	0.38
DVT/ PE	2% (1/45)	9% (3/34)	1 (79)	0.23 [0.02, 2.36]	NA	0.22
Transfusion, FFP	3±3.0	5±3.7	1 (79)	-2.00 [-3.53, -0.47]	NA	0.003
Troponin elevation	47% (21/45)	41% (14/34)	1 (79)	1.25 [0.51, 3.07]	NA	0.63
Troponin > 1ng/dL	13% (6/45)	6% (2/34)	1 (79)	2.46 [0.46, 13.04]	NA	0.29
New EKG changes	42% (19/45)	18% (6/34)	1 (79)	3.41 [1.18, 9.86]	NA	0.02
Troponin elevation and EKG changes	4% (2/45)	0% (0/34)	1 (79)	3.97 [0.18, 85.34]	NA	0.38
INR, initial	2.5±1.0	2.2±0.7	1 (79)	0.25 [-0.12, 0.62]	NA	0.36
INR, 3 hr	1.0±0.3	1.6±0.7	1 (79)	-0.65 [-0.88, -0.42]	NA	0.0001
INR, 6 hr	1.1±0.3	1.5±0.3	1 (79)	-0.41 [-0.55, -0.27]	NA	< 0.0001

CI: Confidence interval; DVT/ PE: Deep vein thrombosis or pulmonary embolism; FFP: Fresh frozen plasma; I^2: Heterogeneity; MD: Mean difference; n: Number of studies; N: Number of patients; p: Statistical significance value; OR: Odds Ratio

Figure: Effect of rFVIIa on mortality in patients with warfarin induced intracranial hemorrhage



PICO 12: In adult patients with ICH occurring during use of dabigatran etexilate (with drug levels assumed relevant for an effective anticoagulatory effect) does use of idarucizumab affect

Author(s):
Date:
Question: Idarucizumab compared to Nothing for ICH occurring during use of dabigatran etexilate
Setting:
Bibliography:

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Idarucizumab	Nothing	Relative (95% CI)	Absolute (95% CI)		
Mortality												
1	observational studies	serious [a]	not serious	not serious	not serious	publication bias strongly suspected [b]	16/98 (16.3%)		not estimable		⨁◯◯◯ VERY LOW	CRITICAL
Adverse reactions												
1	observational studies	serious [a]	not serious	not serious	not serious	publication bias strongly suspected [b]	66/301 (21.9%)		not estimable		⨁◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval

Explanations

a. Risk of bias
b. Single study to support this outcome

Summary of findings:

Idarucizumab compared to Nothing for ICH occurring during use of dabigatran etexilate

Patient or population: ICH occurring during use of dabigatran etexilate
Setting:
Intervention: Idarucizumab
Comparison: Nothing

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Nothing	**Risk with Idarucizumab**				
Mortality	0 per 1,000	**0 per 1,000** (0 to 0)	not estimable	98 (1 observational study)	⨁◯◯◯ VERY LOW [a,b]	
Adverse reactions	0 per 1,000	**0 per 1,000** (0 to 0)	not estimable	301 (1 observational study)	⨁◯◯◯ VERY LOW [a,b]	

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

CI: Confidence interval

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

Explanations

a. Risk of bias
b. Single study to support this outcome

Table: Effect of idarucizumab in patients with dabigatran-associated intracranial hemorrhage

Outcome	Incidence (%)		n (N)	OR [95% CI]	I^2	P value
	Idarucizumab	Control				
Mortality	16% (16/98)	NR	1 (98)	NA	NA	NA
Success	100% (98/98)	NR	1 (98)	NA	NA	NA
Adverse reactions[a]	22% (66/301)	NR	1 (301)	NA	NA	NA

a: Considered patients with ICH and other bleeding; I^2: Heterogeneity; n: Number of studies; N: Number of patients; p: Statistical significance value; OR: Odds Ratio

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PICO 13: In adult patients with ICH occurring during use of a fXa inhibitor (with drug levels assumed relevant for an effective anticoagulatory effect) does use of andexanet improve the outcomes

Author(s):
Date:
Question: Andexanet compared to Nothing for ICH occurring during use of a fXa inhibitor
Setting:
Bibliography:

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Andexanet	Nothing	Relative (95% CI)	Absolute (95% CI)		
Mortality												
1	observational studies	serious [a]	not serious	not serious	not serious	publication bias strongly suspected [b]	10/67 (14.9%)		not estimable		⨁◯◯◯ VERY LOW	CRITICAL
Thrombotic event and death, 30 days												
1	observational studies	serious [a]	not serious	not serious	not serious	publication bias strongly suspected [b]	12/67 (17.9%)		not estimable		⨁◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval

Explanations

a. Risk of bias
b. Single study to support this outcome

Summary of findings:

Andexanet compared to Nothing for ICH occurring during use of a fXa inhibitor

Patient or population: ICH occurring during use of a fXa inhibitor
Setting:
Intervention: Andexanet
Comparison: Nothing

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Nothing	**Risk with Andexanet**				
Mortality	0 per 1,000	**0 per 1,000** (0 to 0)	not estimable	67 (1 observational study)	⨁◯◯◯ VERY LOW [a,b]	
Thrombotic event and death, 30 days	0 per 1,000	**0 per 1,000** (0 to 0)	not estimable	67 (1 observational study)	⨁◯◯◯ VERY LOW [a,b]	

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

CI: Confidence interval

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

Explanations

a. Risk of bias
b. Single study to support this outcome

Table: Effect of idarucizumab in patients with dabigatran-associated intracranial hemorrhage

Outcome	Incidence (%)		n (N)	OR [95% CI]	I^2	P value
	Andexanet	Control				
Mortality	15% (10/67)	NR	1 (67)	NA	NA	NA
Thrombotic events and death, during 30 days of follow up	18% (12/67)	NR	1 (67)	NA	NA	NA
Excellent or good hemostatic efficacy, 12 hours after andexanet infusion	79% (37/47)	NR	1 (47)	NA	NA	NA
Change in Xa factor activity in patients receiving rivaroxaban	89%	NA	1 (47)	89% [58-94]	NA	NA
Change in Xa factor activity in patients receiving apixaban	93%	NA	1 (47)	93% [87-94]	NA	NA

CI: Confidence intervals; I^2: Heterogeneity; n: Number of studies; N: Number of patients; p: Statistical significance value; OR: Odds Ratio

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Table: Effect of FFP on all-cause mortality in patients with warfarin-associated intracranial hemorrhage

Outcome	Incidence (%)		n (N)	OR [95% CI]	I^2	P value
	FFP	Control				
FFP vs Control	46% (172/377)	62% (280/454)	1 (831)	0.52 [0.40, 0.69]	NA	<0.00001
FFP & PCC vs Control	27% (36/131)	62% (280/454)	1 (585)	0.24 [0.15, 0.36]	NA	<0.00001

FFP: Fresh frozen plasma; I^2: Heterogeneity; n: Number of studies; N: Number of patients; p: Statistical significance value; PCC: Prothrombin complex concentrate; OR: Odds Ratio

Figure: Effect of FFP vs placebo on mortality in patients with warfarin-associated intracranial hemorrhage