### 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:

g.u/			Certainty asse	essment			Nº of p	atients	Ef	fect		
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PCC	Placebo	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
Mortality,	PCC vs Placebo	(follow up: r	nean 90 days)						•			
1	observational studies	serious a	not serious	not serious	not serious	strong association <sup>b</sup>	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 (fo	llow 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)	ФФС	CRITICAL

CI: Confidence interval; OR: Odds ratio

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.

### 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 abso	olute effects*	Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Placebo	Risk with PCC		(Studios)	(OIVIDE)	
Mortality, PCC vs Placebo follow up: mean 90 days	617 per 1,000	<b>373 per 1,000</b> (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	<b>279 per 1,000</b> (194 to 367)	<b>OR 0.24</b> (0.15 to 0.36)	585 (1 observational study)	⊕⊕⊖⊖ LOW ª	

<sup>\*</sup>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

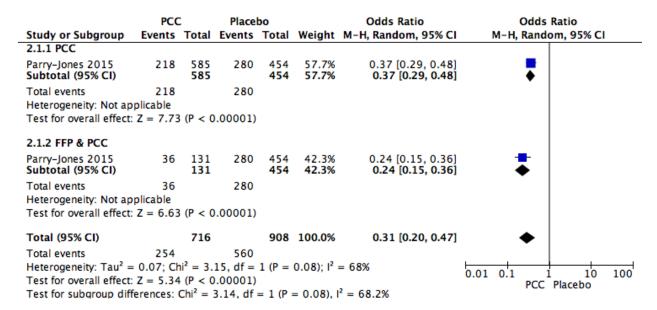
b. A retrospective pooled analysis of 16 stroke registries from Argentina, Australia, Finland, France, Germany, Italy, the Netherlands, the United Kingdom, and the USA.

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

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

FFP: Fresh frozen plasma; I<sup>2</sup>: 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 asse	essment			Nº of p	atients	Ef	fect		
№ of studie s	Study design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecisio n	Other consideration s	PCC	Placebo	Relativ e (95% CI)	Absolut e (95% CI)	Certainty	Importance
Mortality,	follow up											
1	observationa I studies	not seriou s	not serious	not serious	serious <sup>a</sup>	publication bias strongly suspected <sup>b</sup>	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
Hematon	na Volume increas	se > 33% ar	nd or > 6 ml									
2	observationa I studies	not seriou s	not serious	not serious	not serious	publication bias strongly suspected °	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)	⊕⊖⊖ O VERY LOW	IMPORTAN T
Hematon	na volume							•				
1	observationa I studies	not seriou s	not serious	not serious	not serious	publication bias strongly suspected <sup>b</sup>	28	17	-	MD 8.7 mL higher (5.4 lower to 22.8 higher)	⊕⊖⊖ O VERY LOW	IMPORTAN T
Intraventi	ricular extension,	New Interve	entricular hemorrha	ige								
1	observationa I studies	not seriou s	not serious	not serious	serious <sup>a</sup>	publication bias strongly suspected <sup>b</sup>	2/28 (7.1%)	1/17 (5.9%)	OR 1.23 (0.10 to 14.70)	nore per 1,000 (from 53 fewer to 420 more)	⊕⊖⊖ O VERY LOW	IMPORTAN T
								0.0%		0 fewer per 1,000 (from 0 fewer to 0 fewer)		
Modified	Graeb score (cha	nge from ba	seline)									
1	observationa I studies	not seriou s	not serious	not serious	not serious	publication bias strongly suspected <sup>b</sup>	28	17	-	MD 0.5 Score higher (0.74 lower to 1.74 higher)	⊕⊖⊖ O VERY LOW	IMPORTAN T

		essment			№ of patients		Effect						
№ of studie s	Study design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecisio n	Other consideration s	PCC	Placebo	Relativ e (95% CI)	Absolut e (95% CI)	Certainty	Importance	
Length of	ength of stay												
1	observationa I studies	not seriou s	not serious	not serious	serious <sup>a</sup>	publication bias strongly suspected <sup>b</sup>	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

- Wide CI
   Single study to support this outcome
   Two studies to support this outcome

### 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 abs	olute effects*	Relative effect	№ of participants	Certainty of the evidence	Comments
	(95% CI)  Risk with  Placebo	Risk with PCC	(95% CI)	(studies)	(GRADE)	
Mortality, follow up	308 per 1,000	<b>257 per 1,000</b> (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	<b>361 per</b> <b>1,000</b> (229 to 520)	OR 1.22 (0.64 to 2.34)	191 (2 observational studies)	⊕○○○ VERY LOW °	
Hematoma volume	The mean hematoma volume was <b>0</b> 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 <sup>b</sup>	
Intraventricular extension, New	Study population		OR 1.23 (0.10 to 14.70)	45 (1	ФООО	
Interventricular hemorrhage	59 per 1,000	<b>71 per 1,000</b> (6 to 479)	(6110-10-1111-0)	observational study)	VERY LOW a,b	
	Moderate					
	0 per 1,000	<b>0 per 1,000</b> (0 to 0)				
Modified Graeb score (change from baseline)	The mean modified Graeb score (change from baseline) was <b>0</b> 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 <sup>b</sup>	
Length of stay	The mean length of stay was <b>0</b> 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	

### 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	(95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Placebo	Risk with PCC		(studies)	(GIVADE)	

<sup>\*</sup>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

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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

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

CI: Confidence interval; I<sup>2</sup>: 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

	PCC		Nothi	ng		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
5.1.1 Within 5 days							
Purrucker 2015 Subtotal (95% CI)	2	35 <b>35</b>	4	26 <b>26</b>	100.0% 100.0%	0.33 [0.06, 1.98] <b>0.33 [0.06, 1.98]</b>	
Total events	2		4				
Heterogeneity: Not ap							
Test for overall effect:	Z = 1.21	I (P = 0)	.23)				
5.1.2 During acute st	tay						L
Purrucker 2015 Subtotal (95% CI)	6	35 <b>35</b>	4	26 <b>26</b>	100.0% 100.0%	1.14 [0.29, 4.53] 1.14 [0.29, 4.53]	
Total events	6		4				
Heterogeneity: Not ap	plicable						
Test for overall effect:	Z = 0.18	B (P = 0)	.85)				
5.1.3 Until follow up							
Purrucker 2015	9	35	8	26	100.0%	0.78 [0.25, 2.40]	_
Subtotal (95% CI)		35	Ü	26	100.0%	0.78 [0.25, 2.40]	-
Total events	9		8				
Heterogeneity: Not ap	plicable						
Test for overall effect:	Z = 0.44	P = 0	.66)				
							0.01 0.1 1 10 100
						•	PCC Nothing

Test for subgroup differences:  $Chi^2 = 1.15$ , df = 2 (P = 0.56),  $I^2 = 0\%$ 

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

_	PCC		Nothi	ng		Odds Ratio	Odds Ratio
Study or Subgroup			Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
5.6.1 Volume increas	e > 33%						
Gerner 2018	35	103	14	43	36.0%	1.07 [0.50, 2.27]	<del>-</del>
Purrucker 2015	11	28	4	17	11.3%		<del>_</del> -
Subtotal (95% CI)		131		60	47.3%	1.25 [0.65, 2.43]	<b>*</b>
Total events	46	_	18				
Heterogeneity: Tau <sup>2</sup> =				1 (P =	0.39); I <sup>2</sup>	= 0%	
Test for overall effect:	Z = 0.67	'(P = 0)	).50)				
E C D Malaura in anno							
5.6.2 Volume increas							
Purrucker 2015	6	28 28	1	17 17	4.2%		
Subtotal (95% CI)	_	28	_	17	4.2%	4.36 [0.48, 39.89]	
Total events	6		1				
Heterogeneity: Not ap							
Test for overall effect:	Z = 1.30	P = 0	).19)				
5.6.3 Volume increas	e > 33%	and or	> 6 ml				
Gerner 2018	35	103	14	43	36.0%	1.07 [0.50, 2.27]	<del></del>
Purrucker 2015	12	28	5	17	12.5%	1.80 [0.50, 6.50]	<del></del>
Subtotal (95% CI)		131		60	48.5%	1.22 [0.64, 2.34]	<b>*</b>
Total events	47		19				
Heterogeneity: Tau2 =	0.00; Cl	$ni^2 = 0.$	47, df =	1 (P =	0.49); I <sup>2</sup>	= 0%	
Test for overall effect:	Z = 0.60	(P = 0)	).55)				
Total (95% CI)		290		137	100.0%	1.30 [0.83, 2.05]	
Total events	99	230	38	137	100.070	1.50 [0.05, 2.05]	
		si <sup>2</sup> – 2		4 (D =	0 66), 12	- 0%	
Heterogeneity: Tau <sup>2</sup> = Test for overall effect:				4 (P =	0.00); I	= 070	0.05 0.2 1 5 20
				- 2 (B	- 0 55)	12 _ 00/	PCC Nothing
Test for subgroup diff	erences:	Cni" =	1.20, 01	= 2 (P	= 0.55),	I = U%	

### 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

Bibliogra	phy:											
			Certainty asse	essment			№ of p	atients	Ef	fect		
№ of studie s	Study design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecisio n	Other consideration s	PCC	FFP	Relativ e (95% CI)	Absolut e (95% CI)	Certainty	Importance
Mortality												
3	observationa I studies	not seriou s	not serious	not serious	not serious	publication bias strongly suspected a	223/61 2 (36.4%)	180/40 0 (45.0%)	OR 0.69 (0.54 to 0.90)	89 fewer per 1,000 (from 26 fewer to 144 fewer)	⊕⊖⊖ O VERY LOW	CRITICAL
Hematom	na expansion, at 3	and 24 h										
1	randomised trials	not seriou s	not serious	not serious	not serious	publication bias strongly suspected <sup>b</sup>	27	23	-	MD 13.89 mL lower (23.45 lower to 4.34 lower)	⊕⊕⊕ MODERATE	IMPORTAN T
INR ≤ 1·2	2, at 3, 7 or 24 h											
1	observationa I studies	not seriou s	not serious	not serious	not serious	publication bias strongly suspected <sup>b</sup>	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	IMPORTAN T
mRS 0-3,	3 months											
1	randomised trials	not seriou s	not serious	not serious	not serious	publication bias strongly suspected <sup>b</sup>	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	IMPORTAN T
NIHSS so	core at day 15 or o	discharge							•			•
1	randomised trials	not seriou s	not serious	not serious	not serious	publication bias strongly suspected <sup>b</sup>	27	23	-	MD 1.3 Score higher (5 lower to 7.6 higher)	⊕⊕⊕ MODERATE	IMPORTAN T
Barthel in	dex at day 90											
1	randomised trials	not seriou s	not serious	not serious	not serious	publication bias strongly suspected <sup>b</sup>	27	23	-	MD 17.5 Score higher (4.26 lower to 39.26 higher)	⊕⊕⊕⊖ MODERATE	IMPORTAN T

			Certainty asse	essment			№ of p	atients	Eff	fect		
№ of studie s	Study design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecisio n	Other consideration s	PCC	FFP	Relativ e (95% CI)	Absolut e (95% CI)	Certainty	Importance
Extended	Extended Glasgow Outcome Scale at day 90											
1	randomised trials	not seriou s	not serious	not serious	not serious	publication bias strongly suspected <sup>b</sup>	27	23	-	MD 0.42 Score lower (1.66 lower to 0.82 higher)	⊕⊕⊕ MODERATE	IMPORTAN T

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

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

### 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 absorption (95% CI)	olute effects*	Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with FFP	Risk with PCC		(Studies)	(GRADL)	
Mortality	450 per 1,000	<b>361 per</b> <b>1,000</b> (306 to 424)	OR 0.69 (0.54 to 0.90)	1012 (3 observational studies)	⊕○○○ VERY LOW ®	
Hematoma expansion, at 3 and 24 h	The mean hematoma expansion, at 3 and 24 h was <b>0</b> 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 Þ	
INR ≤ 1·2, at 3, 7 or 24 h	435 per 1,000	<b>897 per</b> <b>1,000</b> (730 to 966)	OR 11.35 (3.52 to 36.55)	46 (1 observational study)	⊕○○○ VERY LOW <sup>b</sup>	
mRS 0-3, 3 months	391 per 1,000	<b>360 per</b> <b>1,000</b> (113 to 1,000)	<b>RR 0.92</b> (0.29 to 2.88)	50 (1 RCT)	⊕⊕⊕⊖ MODERATE Þ	
NIHSS score at day 15 or discharge	The mean NIHSS score at day 15 or discharge was <b>0</b> 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 <b>0</b> 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 Þ	

#### 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		(Studios)	(OIVIDE)	
Extended Glasgow Outcome Scale at day 90	The mean extended Glasgow Outcome Scale at day 90 was <b>0</b> 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 Þ	

<sup>\*</sup>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

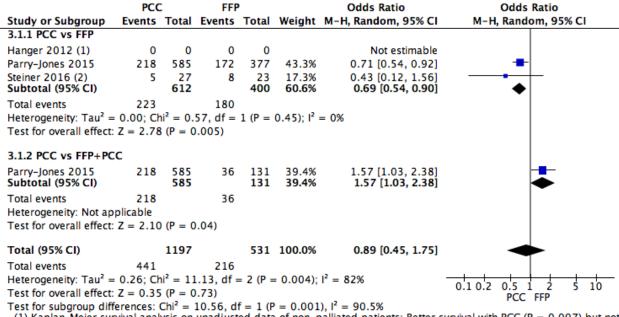
- a. Three studies to support this outcome
- b. Single study to support this outcome

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

Outcome	Incide	ence (%)	n (N)	OR [95% CI]	l <sup>2</sup>	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	22%	37%	1(99)	0.51 [0.21, 1.25]	0%	0.14
expansion						
Incidence of hematoma	4%	26%	1(50)	0.11 [0.01, 0.99]	NA	0.05
expansion leading to death						
Extent of hematoma	9.7±20.9	23.7±28.4	1(50)	-14.00 [-28.03,	NA	0.05
expansion, 3 h				0.03]		
Extent of hematoma	8.3±18.3	22.1±27.1	1(50)	-13.80 [-26.85, -	NA	0.04
expansion, 24 h				0.75]		
Hematoma expansion	58%	73%	1(48)	0.51 [0.15, 1.73]	NA	0.28
≥15% at 3 h						
Hematoma expansion	44%	59%	1(49)	0.55 [0.18, 1.73]	NA	0.31
≥33% at 3 h						
Hematoma expansion	44%	70%	1(47)	0.34 [0.10, 1.16]	NA	0.09
≥15% at 24 h						
Hematoma expansion	38%	58%	1(96)	0.44 [0.19, 1.02]	NA	0.05
≥33% at 24 h	670/	00/	4/50\	24 00 [4 04	<b></b>	0.0000
INR ≤1·2 at 3 h	67%	9%	1(50)	21.00 [4.01,	NA	0.0003
IND <1.2 -+ 7 h	0.00/	F F 0/	1/50\	110.06]	NI A	0.02
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 <i>,</i> 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 NA	0.72
Adverse effects	2370	32/0	1(99)	0.90 [0.39, 2.32]	IVA	0.32
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	0.27
-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	0.15
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,	NA	0.03
Darther much at day 70	/0.0±3/./	J2.J±40.3	1(30)	39.26]	INA	0.11
Extended Glasgow	4.18±2.23	4.6±2.23	1(50)	-0.42 [-1.66, 0.82]	NA	0.51
Outcome Scale at day 90	7.10_2.23	7.042.23	1(30)	3. 12 [ 1.00, 0.02]	14/1	0.51

FFP: Fresh frozen plasma; I<sup>2</sup>: 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



(1) Kaplan-Meier survival analysis on unadjusted data of non-palliated patients: Better survival with PCC (P = 0.007) but not

(2) 3 months; FFP: FFP+PCC

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

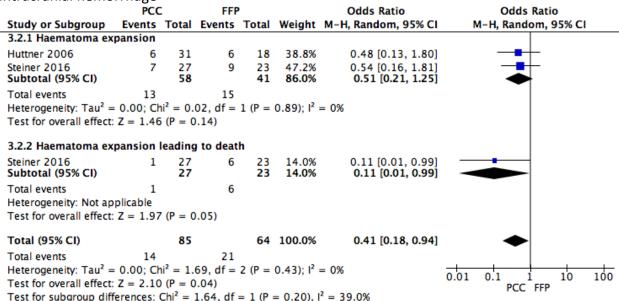


Figure: Effect of PCC vs FFP on extent of hematoma expansion (mL) in patients with warfarin-associated intracranial hemorrhage

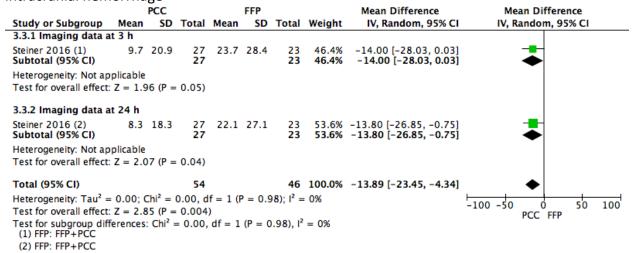


Figure: Effect of PCC vs FFP on % of hematoma expansion in patients with warfarin-associated intracranial hemorrhage

	PCC		FFP	•		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	<b>Events</b>	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
3.4.1 3 h, ≥15% grov	wth						
Steiner 2016 Subtotal (95% CI)	15	26 <b>26</b>	16	22 <b>22</b>	19.1% <b>19.1</b> %	0.51 [0.15, 1.73] <b>0.51 [0.15, 1.73</b> ]	-
Total events	15		16				
Heterogeneity: Not ap Test for overall effect:		(P = 0	.28)				
3.4.2 3 h, ≥33% grov	vth						
Steiner 2016 (1) Subtotal (95% CI)	12	27 <b>27</b>	13	22 <b>22</b>	21.9% <b>21.9</b> %	0.55 [0.18, 1.73] <b>0.55 [0.18, 1.73]</b>	
Total events	12		13				
Heterogeneity: Not ap							
Test for overall effect	Z = 1.02	(P = 0)	.31)				
3.4.3 24 h, ≥15% gro	owth						
Steiner 2016 Subtotal (95% CI)	12	27 <b>27</b>	14	20 <b>20</b>	19.0% <b>19.0</b> %	0.34 [0.10, 1.16] 0.34 [0.10, 1.16]	•
Total events	12		14				
Heterogeneity: Not ap Test for overall effect:		/D - 0	00)				
rest for overall effects	Z = 1.72	(P = 0.	.09)				
3.4.4 24 h, ≥33% gro	owth						
Huttner 2006	14	31	10	18	20.8%	0.66 [0.20, 2.12]	<del></del>
Steiner 2016	8	27	12	20	19.2%	0.28 [0.08, 0.95]	
Subtotal (95% CI)		58		38	40.0%	0.44 [0.19, 1.02]	-
Total events	22	.2 0.0	22	1 (0	0.221.12	00/	
Heterogeneity: Tau <sup>2</sup> = Test for overall effect:				I (P =	0.32); 1	= 0%	
rest for overall effect.	Z = 1.92	(F = 0.	.03)				
Total (95% CI)		138		102	100.0%	0.45 [0.27, 0.77]	<b>◆</b>
Total events	61		65				
Heterogeneity: Tau <sup>2</sup> =				4 (P =	0.85); I <sup>2</sup>	= 0%	0.05 0.2 1 5 20
Test for overall effect: Test for subgroup diff				2 /P	0.05	2 _ 00/	PCC FFP
(1) FFP: FFP+PCC	erences: C	.mr = 0	7.50, UT	= 3 (P	= 0.95), 1	= 076	

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

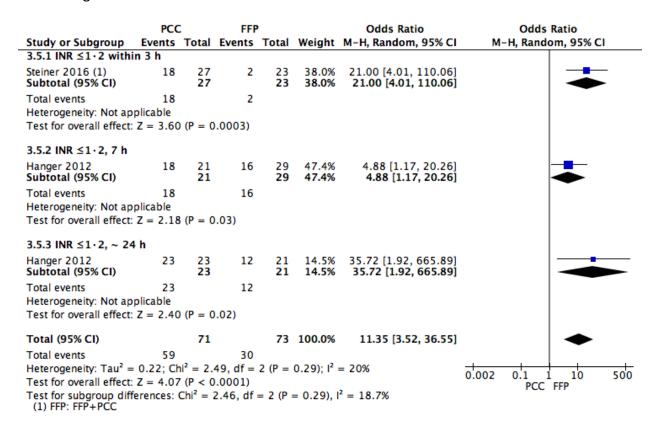


Figure: Effect of PCC vs FFP on mRS score 0-3 in patients with warfarin-associated intracranial hemorrhage

Heilioilliage							
	PCC	:	FFP			Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	<b>Events</b>	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
3.6.1 15 days or disc	hage						
Steiner 2016 (1) Subtotal (95% CI)	7	27 <b>27</b>	7	23 <b>23</b>	33.9% <b>33.9</b> %		
Total events	7		7				
Heterogeneity: Not ap	plicable						
Test for overall effect:	Z = 0.35	(P = 0)	).72)				
3.6.2 3 months							
Huttner 2006	7	31	4	18	26.6%	1.02 [0.25, 4.12]	<del></del>
Steiner 2016 Subtotal (95% CI)	10	27 <b>58</b>	9	23 41	39.5% <b>66.1%</b>		•
Total events	17		13				
Heterogeneity: Tau2 =	0.00; Ch	$ni^2 = 0.$	01, df =	1 (P =	0.91); I <sup>2</sup>	= 0%	
Test for overall effect:	Z = 0.10	(P = 0)	).92)				
Total (95% CI)		85		64	100.0%	0.90 [0.44, 1.85]	•
Total events	24		20				
Heterogeneity: Tau2 =	0.00; Ch	$ni^2 = 0.$	07, df =	2 (P =	0.97); I <sup>2</sup>	= 0%	0.1 0.2 0.5 1 2 5 10
Test for overall effect:	Z = 0.29	P = 0	).77)				PCC FFP
Test for subgroup diff (1) FFP: FFP+PCC	erences:	Chi² = (	0.05, df	= 1 (P	= 0.82),	$I^2 = 0\%$	. 55 111

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

nemormage							
	PCC		FFP	•		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	<b>Events</b>	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
3.7.1 At least one SAI							
Steiner 2016 (1) Subtotal (95% CI)	16	27 <b>27</b>	10	23 23	49.7% <b>49.7</b> %	1.89 [0.61, 5.83] 1.89 [0.61, 5.83]	<b>.</b>
Total events	16		10				
Heterogeneity: Not app	licable						
Test for overall effect: 2	Z = 1.11	(P = 0)	.27)				
3.7.2 Thromboemboli	c events	;					
Steiner 2016 Subtotal (95% CI)	7	27 <b>27</b>	2	23 23	22.2% <b>22.2</b> %	3.67 [0.68, 19.85] 3.67 [0.68, 19.85]	
Total events	7		2				
Heterogeneity: Not app	licable						
Test for overall effect: 7		(P = 0	.13)				
		,	,				
3.7.3 MI							
Steiner 2016 Subtotal (95% CI)	0	27 <b>27</b>	0	23 23		Not estimable Not estimable	
Total events	0		0				
Heterogeneity: Not app	licable						
Test for overall effect: I	Not appl	icable					
3.7.4 Ischemic stroke							
Steiner 2016 Subtotal (95% CI)	2	27 <b>27</b>	2	23 <b>23</b>	15.1% <b>15.1</b> %	0.84 [0.11, 6.49] 0.84 [0.11, 6.49]	<del></del>
Total events	2		2				
Heterogeneity: Not app	licable						
Test for overall effect: 7		(P = 0)	.87)				
3.7.5 Pulmonary embe	olism						
Steiner 2016 Subtotal (95% CI)	4	27 <b>27</b>	0	23 23	7.1% <b>7.1</b> %	9.00 [0.46, 176.69] 9.00 [0.46, 176.69]	
Total events	4		0				
Heterogeneity: Not app	licable						
Test for overall effect: 7		(P = 0)	.15)				
3.7.6 Deep vein thron	ıbosis						
Steiner 2016 Subtotal (95% CI)	1	27 <b>27</b>	0	23 23	6.0% <b>6.0</b> %	2.66 [0.10, 68.50] 2.66 [0.10, 68.50]	
Total events	1		0				
Heterogeneity: Not app	licable						
Test for overall effect: 2	Z = 0.59	(P = 0)	.55)				
Total (95% CI)		162		138	100.0%	2.21 [1.00, 4.89]	•
Total events	30		14				
Heterogeneity: Tau2 =	0.00; Ch	$i^2 = 2$ .	18, df =	4 (P =	0.70); I <sup>2</sup>	= 0%	0.005 0.1 1 10 200
Test for overall effect: 2							0.005 0.1 1 10 200 PCC FFP
Test for subgroup diffe					= 0.71),	$r^2 = 0\%$	
(1) FFP arm: 19 patier	nts receiv	ed FFP	plud PC	С			

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

		PCC			FFP			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Steiner 2016 (1)	12.2	11.1	27	10.9	11.5	23	100.0%	1.30 [-4.99, 7.59]	_
Total (95% CI)			27			23	100.0%	1.30 [-4.99, 7.59]	
Heterogeneity: Not ap Test for overall effect:			0.69)						-10 -5 0 5 10 PCC FFP
(1) 15 days or discha	arge; FF	P: FFP+	-PCC						

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

	PCC			FFP			Mean Difference	Mean Difference
Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
70	37.7	27	52.5	40.3	23	100.0%	17.50 [-4.26, 39.26]	+
		27			23	100.0%	17.50 [-4.26, 39.26]	•
olicable		0.11)						-100 -50 0 50 100 PCC FFP
	Mean 70 licable	70 37.7	Mean SD Total 70 37.7 27 27 licable	Mean         SD         Total         Mean           70         37.7         27         52.5           27         27	Mean         SD         Total         Mean         SD           70         37.7         27         52.5         40.3           27           Listable	Mean         SD         Total         Mean         SD         Total           70         37.7         27         52.5         40.3         23           27         23	Mean         SD         Total         Mean         SD         Total         Weight           70         37.7         27         52.5         40.3         23         100.0%           discable         27         23         100.0%	Mean         SD         Total         Mean         SD         Total         Weight         IV, Random, 95% CI           70         37.7         27         52.5         40.3         23         100.0%         17.50 [-4.26, 39.26]           27         23         100.0%         17.50 [-4.26, 39.26]           discable

(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

		PCC			FFP	Ü		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Steiner 2016 (1)	4.18	2.23	27	4.6	2.23	23	100.0%	-0.42 [-1.66, 0.82]	-
Total (95% CI)			27			23	100.0%	-0.42 [-1.66, 0.82]	•
Heterogeneity: Not ap Test for overall effect:			0.51)						-10 -5 0 5 10 PCC FFP

(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

			Certainty asse	ssment			Nº of p	atients	Ef	fect		
№ of studie s	Study design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecisio n	Other consideration s	Vit K	FFP	Relativ e (95% CI)	Absolut e (95% CI)	Certainty	Importance
Mortality												
1	observationa I studies	not seriou s	not serious	not serious	not serious	publication bias strongly suspected <sup>a</sup>	unadjuste	leier surviva d data, non- t difference i	palliated pa	tients: No	⊕⊖⊖ O VERY LOW	CRITICAL
Incidence	e of hematoma en	argement										
1	observationa I studies	not seriou s	not serious	not serious	serious <sup>b</sup>	publication bias strongly suspected strong association <sup>a</sup>	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	IMPORTAN T
Extent of	hematoma enlarg	ement										
1	observationa I studies	not seriou s	not serious	not serious	serious <sup>b</sup>	publication bias strongly suspected <sup>a</sup>	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	IMPORTAN T
INR < or	= 1.4							I.	I.	u u		•
1	observationa I studies	not seriou s	not serious	not serious	serious <sup>b</sup>	publication bias strongly suspected <sup>a</sup>	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	IMPORTAN T
mRS 0-3												•
1	observationa I studies	not seriou s	not serious	not serious	serious <sup>b</sup>	publication bias strongly suspected <sup>a</sup>	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	IMPORTAN T

CI: Confidence interval; OR: Odds ratio

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

### 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 ab	solute effects* (95% CI)	Relative effect	№ of participants	Certainty of the	Comments
	Risk with FFP	Risk with Vit K	(95% CI)	(studies)	(GRADE)	
Mortality	data, non-pallia	urvival analysis on unadjusted ted patients: No significant rvival between Vit K or FFP.		(1 observational study)	⊕○○○ VERY LOW a	
Incidence of hematoma enlargement	333 per 1,000	<b>500 per 1,000</b> (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	<b>667 per 1,000</b> (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	<b>71 per 1,000</b> (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	<b>167 per 1,000</b> (17 to 692)	OR 0.70 (0.06 to 7.85)	24 (1 observational study)	⊕⊖⊖⊖ VERY LOW a,b	

<sup>\*</sup>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

- 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

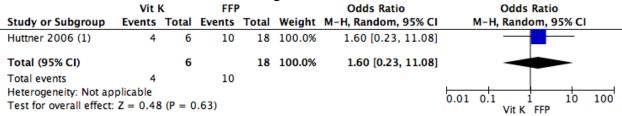
Outcome	Incide	ence (%)	n (N)	OR [95% CI]	l <sup>2</sup>	P value					
	Vit K	FFP									
Mortality, Vit K vs FFP		Kaplan-Meier survival analysis on unadjusted data, non-palliated patients: No									
	significant dif	significant difference in survival between Vit K and FFP (Hanger 2012)									
Incidence 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<sup>2</sup>: 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 warfarinassociated intracranial hemorrhage

	Vit K FFP		•		Odds Ratio	Odds Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Huttner 2006	3	6	6	18	100.0%	2.00 [0.31, 13.06]	_
Total (95% CI)		6		18	100.0%	2.00 [0.31, 13.06]	
Total events	3		6				
Heterogeneity: Not ap Test for overall effect:		2 (P = 0	).47)				0.01 0.1 1 10 100 Vit K FFP

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  $INR \leq 1.4$  in patients with warfarin-associated intracranial hemorrhage

_	Vit K		FFP or + Vit K			Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Huttner 2006	0	6	7	18	100.0%	0.12 [0.01, 2.42]	
Total (95% CI)		6		18	100.0%	0.12 [0.01, 2.42]	
Total events	0		7				
Heterogeneity: Not ap Test for overall effect	•	9 (P = 0	).17)				0.001 0.1 1 10 1000 Vit K FFP or + Vit K

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

_	Vit K		FFP or + Vit K		Odds Ratio		Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Huttner 2006	1	6	4	18	100.0%	0.70 [0.06, 7.85]	
Total (95% CI)		6		18	100.0%	0.70 [0.06, 7.85]	
Total events	1		4				
Heterogeneity: Not ap Test for overall effect:		9 (P = 0	).77)				0.01 0.1 1 10 100 Vit K FFP or + Vit K

### 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:

			Certainty asse	ssment			Nº of p	atients	Eff	fect		
№ of studie s	Study design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecisio n	Other consideration s	Vit K	PCC	Relativ e (95% CI)	Absolut e (95% CI)	Certainty	Importance
Mortality												•
2	observationa I studies	not seriou s	not serious	not serious	serious <sup>a</sup>	publication bias strongly suspected <sup>b</sup>	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 en	argement										•
2	observationa I studies	not seriou s	not serious	not serious	serious a	publication bias strongly suspected strong association <sup>b</sup>	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)	⊕⊖⊖ O VERY LOW	IMPORTAN T
Extent of	hematoma enlarg	ement < 33	%									
1	observationa I studies	not seriou s	not serious	not serious	serious ª	publication bias strongly suspected °	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	IMPORTAN T
INR = or	< 1.4								I.			
1	observationa I studies	not seriou s	not serious	not serious	not serious	publication bias strongly suspected °	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)	⊕⊖⊖ O VERY LOW	IMPORTAN T
mRS												
1	observationa I studies	not seriou s	not serious	not serious	serious ª	publication bias strongly suspected °	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	IMPORTAN T

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

#### 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 absorption (95% CI)	olute effects*	Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with PCC	Risk with Vit K		(Stadios)	(011102)	
Mortality	91 per 1,000	<b>250 per 1,000</b> (16 to 876)	<b>OR 3.33</b> (0.16 to 70.91)	15 (2 observational studies)	⊕○○○ VERY LOW a,b	
Incidence of hematoma enlargement	167 per 1,000	<b>363 per 1,000</b> (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	<b>667 per 1,000</b> (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	<b>94 per 1,000</b> (0 to 632)	OR 0.02 (0.00 to 0.33)	37 (1 observational study)	⊕○○○ VERY LOW °	
mRS	226 per 1,000	<b>168 per</b> <b>1,000</b> (20 to 667)	OR 0.69 (0.07 to 6.88)	37 (1 observational study)	⊕○○○ VERY LOW a.c	

<sup>\*</sup>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

- 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	Incide	nce (%)	n (N)	OR [95% CI]	l <sup>2</sup>	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					NA	
expansion, Vit K vs PCC+Vit K	30%	17%	1(52)	2.85 [0.57, 14.27]		0.20
Incidence of hematoma					NA	
expansion, Vit K vs PCC	0%	0%	1(6)	Not estimable		NA
Extent of hematoma					NA	
expansion ≥33%, Vit K vs						
PCC+Vit K	67%	45%	1(37)	2.43 [0.39, 15.27]		0.34
INR ≤1·4, Baseline, Vit K+PCC	2.70±2.44	6.23±2.08	1(13)		NA	0.03
vs PCC				-3.53 [-6.75, -0.31]		
INR ≤1·4, 10 min, Vit K+PCC	1.13±0.13	1.36±0.15	1(13)		NA	0.04
vs PCC				-0.23 [-0.45, -0.01]		
INR ≤1·4, 12-24 h, Vit K+PCC	1.06±0.09	2.07±0.33	1(13)		NA	< 0.0001
vs PCC				-1.01 [-1.47, -0.55]		
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

l²: 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

J	Vit	K	PCC and	Vit K		Odds Ratio	Odds Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI	
5.1.1 Vit K vs PCC ar	nd Vit K							
Hanger 2012 (1)	0	0	0	0		Not estimable		
Yasaka 2003 Subtotal (95% CI)	1	4 4	1	11 11	57.8% <b>57.8</b> %			
Total events	1		1					
Heterogeneity: Not ap	plicable							
Test for overall effect	Z = 0.77	7 (P = 0)	).44)					
5.1.2 Vit K vs PCC								
Yasaka 2003 Subtotal (95% CI)	1	4	1	2 2	42.2% <b>42.2</b> %			
Total events	1		1					
Heterogeneity: Not ap	plicable							
Test for overall effects	Z = 0.60	O(P=0)	).55)					
Total (95% CI)		8		13	100.0%	1.26 [0.12, 12.90]	-	
Total events	2		2					
Heterogeneity: Tau2 =	= 0.00; Cl	$hi^2 = 0.$	92, df = 1	(P = 0.	$34); I^2 =$	0%	0.001 0.1 1 10 1000	
Test for overall effect:							Vit K PCC and Vit K	
Test for subgroup differences: $Chi^2 = 0.92$ , $df = 1$ (P = 0.34), $I^2 = 0\%$ (1) Kaplan-Meier survival analysis on unadjusted data of non-palliated patients: Better survival with PCC (P = 0.007) but not wi								

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

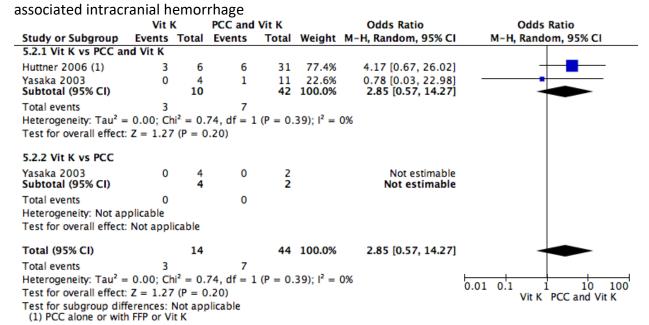


Figure: Effect of Vit K vs PCC on extent of hematoma enlargement > 33% in patients with warfarin-associated intracranial hemorrhage

	Vit K		PCC and	Vit K		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
5.4.1 Vit K vs PCC ar	nd Vit K						
Huttner 2006 (1) Subtotal (95% CI)	4	6 <b>6</b>	14	31 31	100.0% 100.0%	2.43 [0.39, 15.27] 2.43 [0.39, 15.27]	
Total events Heterogeneity: Not ap Test for overall effect:		6 (P = 0	14				
Total (95% CI)		6		31	100.0%	2.43 [0.39, 15.27]	
Total events Heterogeneity: Not ap Test for overall effect: Test for subgroup diff (1) PCC alone or with	Z = 0.95 ferences: I	Not app					0.01 0.1 1 10 100 Vit K PCC and Vit K

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

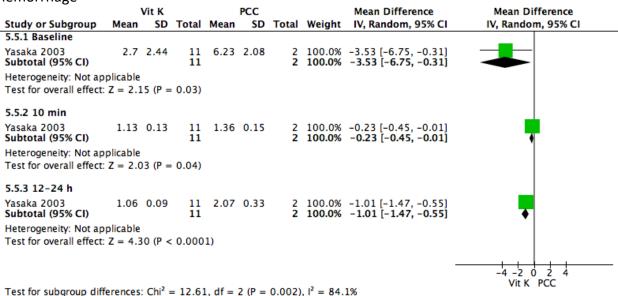


Figure: Effect of Vit K vs PCC on INR in patients with warfarin-associated intracranial hemorrhage

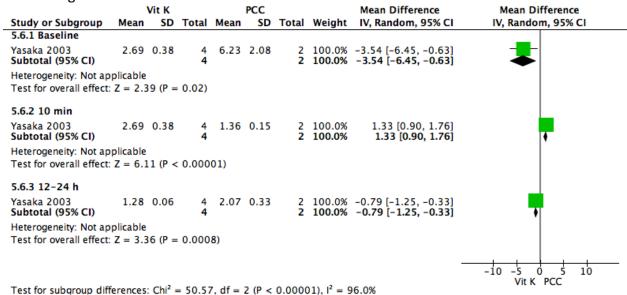


Figure: Effect of Vit K vs PCC on incidence of INR ≤1·4 in patients with warfarin-associated intracranial hemorrhage

	Vit K		PCC or + FFP or Vit K		Odds Ratio		Odds Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Rai	ndom, 95% CI	
Huttner 2006	0	6	26	31	100.0%	0.02 [0.00, 0.33]	<b>←</b>		
Total (95% CI)		6		31	100.0%	0.02 [0.00, 0.33]			
Total events	0		26						
Heterogeneity: Not ap Test for overall effect:		) (P = 0	).007)				0.001 0.1 Vit	1 10 1000 K PCC or + FFP or Vi	

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

	Vit	K	PCC or + FFP o	or Vit K		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Huttner 2006	1	6	7	31	100.0%	0.69 [0.07, 6.88]	
Total (95% CI)		6		31	100.0%	0.69 [0.07, 6.88]	
Total events	1		7				
Heterogeneity: Not ap Test for overall effect:		2 (P = 0	).75)				0.01 0.1 1 10 100 Vit K PCC or + FFP or V

### 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 asse	essment			Nº of p	atients	Ef	fect		
№ of studie s	Study design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecisio n	Other consideration s	rFVII	FFP and Vit K	Relativ e (95% CI)	Absolut e (95% CI)	Certainty	Importance
Mortality									•			
1	observationa I studies	not seriou s	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)	ФФСО	CRITICAL
INR, 3 an	d 6 h											
1	observationa I studies	not seriou s	not serious	not serious	not serious	publication bias strongly suspected <sup>a</sup>	45	34	-	MD <b>0.41</b> lower (0.55 lower to 0.27 lower)	⊕○○ ○ VERY LOW	IMPORTAN T
Stroke									•			
1	observationa I studies	not seriou s	not serious	not serious	serious <sup>b</sup>	publication bias strongly suspected strong association <sup>a</sup>	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
Thromem	bolism					!						
1	observationa I studies	not seriou s	not serious	not serious	serious <sup>b</sup>	publication bias strongly suspected strong association <sup>a</sup>	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)	⊕⊖⊖ O VERY LOW	CRITICAL
Transfusi	on of FFP											
1	observationa I studies	not seriou s	not serious	not serious	not serious	publication bias strongly suspected <sup>a</sup>	45	34	-	MD 2 Units lower (3.53 lower to 0.47 lower)	⊕⊖⊖ O VERY LOW	IMPORTAN T

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

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

#### 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 abse	olute effects*	Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with FFP and Vit K	Risk with rFVII		(Statics)	(OIVIDE)	
Mortality	176 per 1,000	<b>355 per</b> <b>1,000</b> (159 to 617)	OR 2.57 (0.88 to 7.52)	79 (1 observational study)	DOM ₃	
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 <sup>a</sup>	
Stroke	0 per 1,000	<b>0 per 1,000</b> (0 to 0)	OR 2.33 (0.09 to 58.88)	79 (1 observational study)	⊕⊖⊖⊖ VERY LOW a,b	
Thromembolism	88 per 1,000	<b>22 per 1,000</b> (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 <b>0</b> 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 <sup>a</sup>	

<sup>\*</sup>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

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

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

Outcome	Incide	nce (%)	n (N)	MD [95% CI]/ OR		
	rFVIIa	FFP and Vit K		[95% CI]	l <sup>2</sup>	P value
Mortality, in hospital	36%	18%				
	(16/45)	(6/34)	1 (79)	2.57 [0.88, 7.52]	NA	0.08
Survival, after hematoma	38%	18%				
evacuation	(17/45)	(6/34)	1 (79)	2.83 [0.97, 8.24]	NA	0.05
Survival, after surgical	31%	12%				
hematoma evacuation	(14/45)	(4/34)	1 (79)	3.39 [1.00, 11.46]	NA	0.05
Withdrawal of life	31%	18%				
threatening care	(14/45)	(6/34)	1 (79)	2.11 [0.71, 6.23]	NA	0.17
Stroke, overall	2%	0%				
	(1/45)	(0/34)	1 (79)	2.33 [0.09, 58.88]	NA	0.38
DVT/ PE	2%	9%				
	(1/45)	(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%	41%				
	(21/45)	(14/34)	1 (79)	1.25 [0.51, 3.07]	NA	0.63
Troponin > 1ng/dL	13%	6%				
	(6/45)	(2/34)	1 (79)	2.46 [0.46, 13.04]	NA	0.29
New EKG changes	42%	18%				
	(19/45)	(6/34)	1 (79)	3.41 [1.18, 9.86]	NA	0.02
Troponin elevation and	4%	0%				
EKG changes	(2/45)	(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<sup>2</sup>: 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

J	rFVIIa g	rFVIIa group Control				Odds Ratio	Odds Ratio			
Study or Subgroup	<b>Events Total</b>		<b>Events Total</b>		Weight	M-H, Random, 95% CI	M-H, Random, 95% CI			
Chou 2012	16	45	6	34	100.0%	2.57 [0.88, 7.52]	+			
Total (95% CI)		45		34	100.0%	2.57 [0.88, 7.52]	•			
Total events	16		6							
Heterogeneity: Not ap							0.02 0.1 1 10 50			
Test for overall effect	: Z = 1.73	(P = 0.	08)				rFVIIa Control			

### 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):

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

Setting: Bibliography:

	Certainty assessment							№ of patients Effect		ect		
№ of studie s	Study design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecisio n	Other consideration s	Idarucizuma b	Nothin g	Relative (95% CI)  Absolut e (95% CI)		Certainty	Importanc e
Mortality	Mortality											
1	observation al studies	seriou s ª	not serious	not serious	not serious	publication bias strongly suspected <sup>b</sup>	16/98 (16.3%)		not estimabl e		⊕○○ ○ VERY LOW	CRITICAL
Adverse	reactions	•			•					-		
1	observation al studies	seriou s <sup>a</sup>	not serious	not serious	not serious	publication bias strongly suspected <sup>b</sup>	66/301 (21.9%)		not estimabl e		⊕⊖⊖ O VERY LOW	CRITICAL

CI: Confidence interval

### **Explanations**

a. Risk of biasb. Single study to support this outcome

#### 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 abso	olute effects*	Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Nothing Idarucizumab		(studies)	(CINDL)		
Mortality	0 per 1,000	<b>0 per 1,000</b> (0 to 0)	not estimable	98 (1 observational study)	⊕⊖⊖⊖ VERY LOW a,b	
Adverse reactions	0 per 1,000	<b>0 per 1,000</b> (0 to 0)	not estimable	301 (1 observational study)	⊕⊖⊖⊖ VERY LOW a,b	

<sup>\*</sup>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

- 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]		
	Idarucizumab	Idarucizumab Control			I <sup>2</sup>	P value
Mortality	16%	NR	1 (98)	NA	NA	NA
	(16/98)					
Success	100%			NA	NA	NA
	(98/98)	NR	1 (98)			
Adverse reactions <sup>a</sup>	22%	NR		NA	NA	NA
	(66/301)		1 (301)			

a: Considered patients with ICH and other bleeding; I<sup>2</sup>: Heterogeneity; n: Number of studies; N: Number of patients; p: Statistical significance value; OR: Odds Ratio
Pollack et al 2017

### 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 asse	essment			№ of patients Effect			ect		
№ of studie s	Study design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecisio n	Other consideration s	Andexane t	Nothin g	Relative (95% CI)	Absolut e (95% CI)	Certainty	Importanc e
Mortality		-					-	-		,		
1	observationa I studies	seriou s <sup>a</sup>	not serious	not serious	not serious	publication bias strongly suspected <sup>b</sup>	10/67 (14.9%)		not estimabl e		⊕⊖⊖ O VERY LOW	CRITICAL
Thrombo	tic event and deat	th, 30 days										
1	observationa I studies	seriou s <sup>a</sup>	not serious	not serious	not serious	publication bias strongly suspected <sup>b</sup>	12/67 (17.9%)		not estimabl e		⊕⊖⊖ O VERY LOW	CRITICAL

CI: Confidence interval

- a. Risk of biasb. Single study to support this outcome

#### And examet 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 abs (95% CI)	olute effects*	Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Nothing	Risk with Andexanet		(Statics)	(OIVIDE)	
Mortality	0 per 1,000	<b>0 per 1,000</b> (0 to 0)	not estimable	67 (1 observational study)	⊕○○○ VERY LOW a,b	
Thrombotic event and death, 30 days	0 per 1,000	<b>0 per 1,000</b> (0 to 0)	not estimable	67 (1 observational study)	⊕○○○ VERY LOW a,b	

<sup>\*</sup>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

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

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

Connolly et al

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

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

FFP: Fresh frozen plasma; I<sup>2</sup>: 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

	FFP or	PCC	Place	bo		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	<b>Events</b>	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
1.2.1 FFP							
Parry-Jones 2015 Subtotal (95% CI)	172	377 <b>377</b>	280	454 <b>454</b>	52.2% <b>52.2</b> %	0.52 [0.40, 0.69] <b>0.52 [0.40, 0.69]</b>	•
Total events	172		280				
Heterogeneity: Not ap	plicable						
Test for overall effect:	Z = 4.60	(P < 0)	.00001)				
1.2.2 FFP & PCC							
Parry-Jones 2015 Subtotal (95% CI)	36	131 131	280	454 <b>454</b>	47.8% <b>47.8</b> %	0.24 [0.15, 0.36] 0.24 [0.15, 0.36]	•
Total events	36		280				
Heterogeneity: Not ap	plicable						
Test for overall effect:	Z = 6.63	B (P < 0	.00001)				
Total (95% CI)		508		908	100.0%	0.36 [0.16, 0.78]	•
Total events	208		560				
Heterogeneity: Tau2 =	0.28; Ch	$ni^2 = 9.$	35, df =	1 (P =	0.002); 1	2 = 89%	0.01 0.1 1 10 100
Test for overall effect:	Z = 2.60	P = 0	.009)				FFP or PCC Placebo
Test for subgroup diff	erences:	$Chi^2 = 9$	9.34, df	= 1 (P :	= 0.002),	$I^2 = 89.3\%$	THE OFFICE PROCESS