Oral Anticoagulants & Reversal Agents Vitamin-K-antagonists and ICH

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Conflict of Interest (CoI)

INCH is an investigator initiated trial (IIT)
Funding: Unrestricted grant from Octapharma AG, Laachen, Switzerland.
The company had no influence on the development of the protocol, conduction, analyses and interpretation of the trial.

Intellectual CoIs	
• Principle investigator of INCH-Study	
• Author of ESO guidelines on ICH management, Int J Stroke 2014;9:840-855	
• Chair of ESO guidelines committee	
Relationships with industry (RWI)	
Company	Relationship
• Octapharma	• Research grant
• Bayer	• Speaker honoraria, consultancy fees
• Boehringer Ingelheim	• Speaker honoraria, consultancy fees
• BMS Pfizer	• Speaker honoraria, consultancy fees
• Daiichy Sanyo	• Consultancy fees

Oral Anticoagulants & Reversal Agents Vitamin-K-antagonists and ICH

1. The INCH trial:
   - PCC vs. FFP - ICH related to VKA
2. Meta-analysis:
   - PCC vs. FFP - major bleedings or need for urgent intervention in patients on VKA

PCC: Prothrombin complex concentrate
FFP: Fresh frozen plasma
VKA: Vitamin-K-antagonists

Background

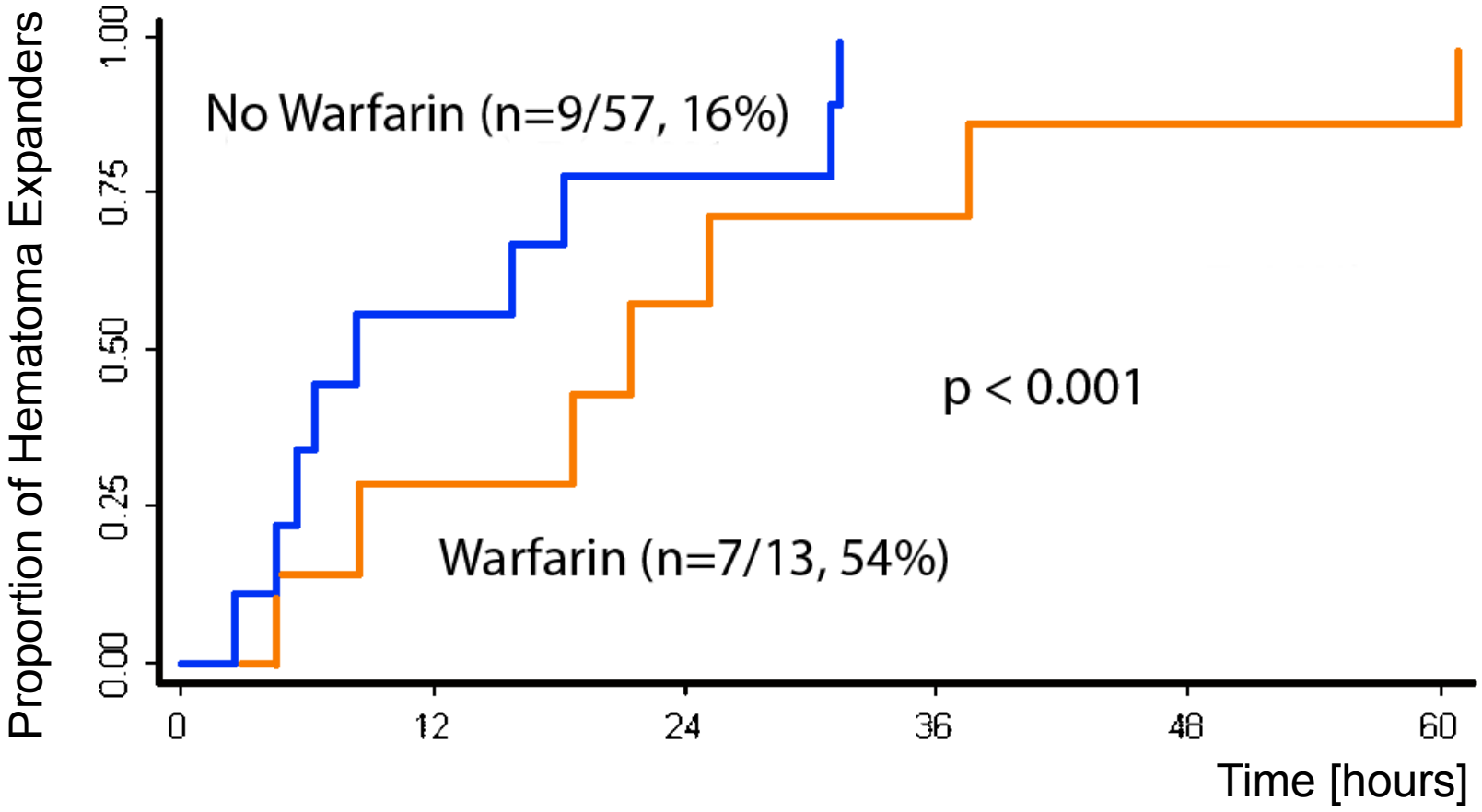
Relevance of VKA-ICH

- Global use of Vitamin-K-antagonists (VKA) in patients with Afib despite an increasing use of DOAC*: about 40%
- Intracranial hemorrhage (ICH) ist the most serious complication in patients treated with VKA:
  - Mortality: up to 60%
  - Main reason for high mortality: hematoma expansion

DOAC: direct oral anticoagulants;FFP: Fresh Frozen Plasma; PCC: Prothrombin Concentrate Complex; INR: international Normalized Ratio; VKA: Vitamin K antagonists; ICH: Intracranial Hemorrhage

*Kakkar A, Garfield Registry, ESC 2015

Hematoma growth after spontaneous ICH and Vit-K-antagonists



„Growth"= hematoma expansion > 33% of baseline volume
SICH: spontane intrazerebrale Blutung

Flibotte JJ et al.Neurology. 2004;63:1059-1064

Fresh frozen plasma versus prothrombin complex concentrate in patients with intracranial haemorrhage related to vitamin K antagonists (INCH): a randomised trial

Thorsten Steiner, Sven Poli*, Martin Griebe, Johannes Hüsing, Jacek Hajda, Anja Freiberger, Martin Bendszus, Julian Bösel, Hanne Christensen, Christian Dohmen, Michael Hennerici, Jennifer Kollmer, Henning Stetefeld, Katja E Wartenberg, Christian Weimar, Werner Hacke, Roland Veltkamp*

Steiner T et al. *Lancet Neurol.* 2016;15:566–573

Method

Inclusion criteria

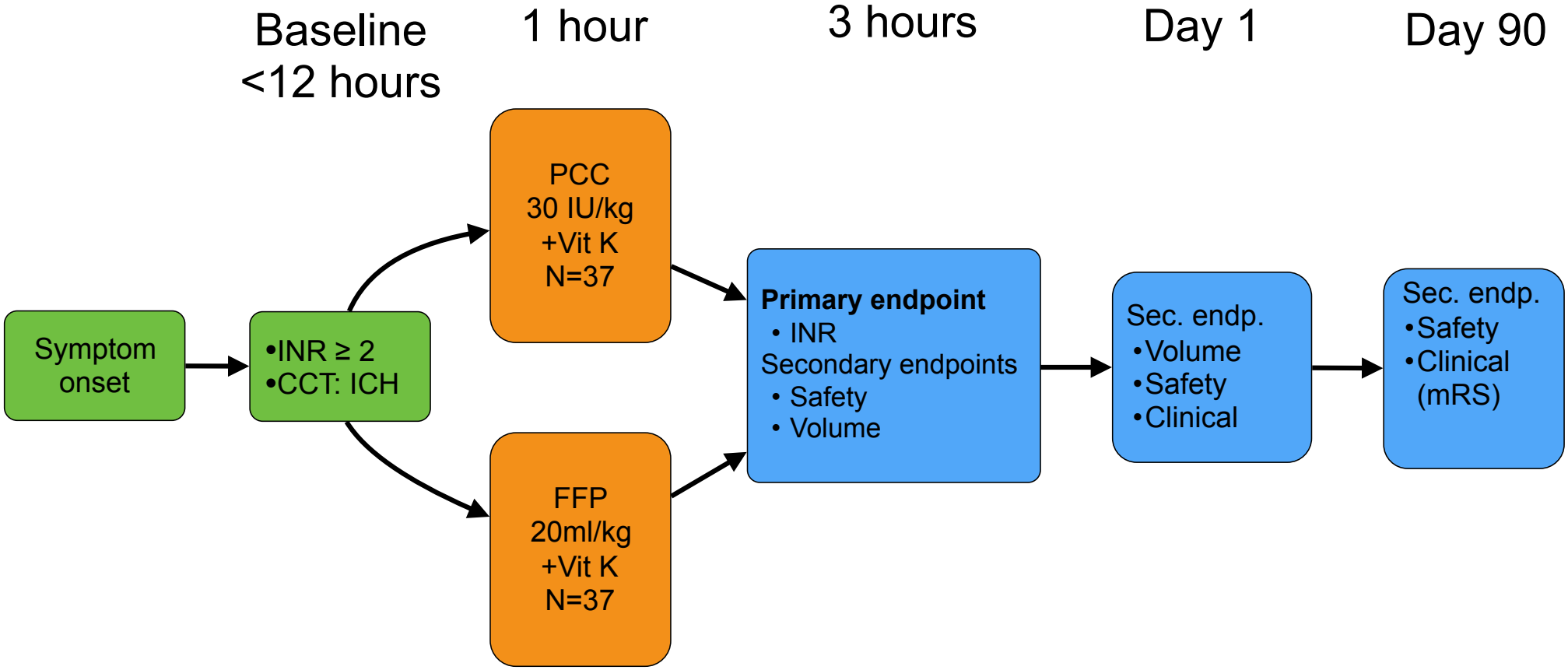
1. Age ≥18 years
2. ICH by CCT within 12 hours after onset of symptoms or after last seen normal
3. Therapy with VKA, and admission INR ≥2·0
4. Signed informed consent

ICH: Intracranial Hemorrhage (subdural, intracerebral)

Exclusion criteria

- Traumatic or secondary intracranial ICH (vascular malformations, transformation of cerebral infarction, cerebral venous thrombosis, tumor, hemophilia or other coagulopathies)
- Glasgow Coma Score ≤ 5
- Moderate to severe premorbid disability (mRS>2).
- Concurrent acute ischemic events
- Congestive heart failure (to prevent cardiac decompensation by fluid overload in the FFP-group)
- History of thrombotic events within the last 30 days
- Liver failure (Child-Pugh-Score C)

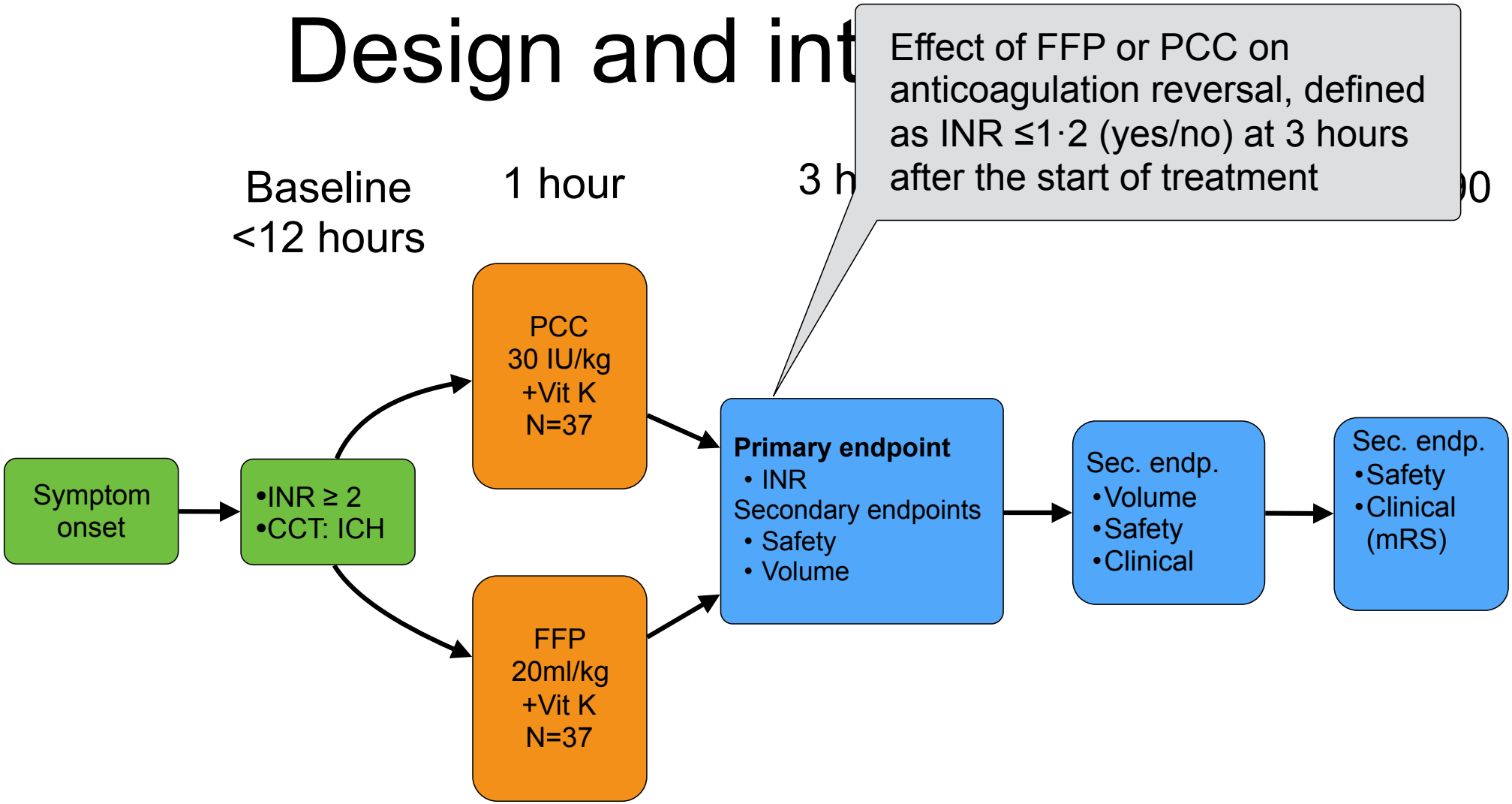
Design and intervention



PCC: 4-factor PCC, Octaplex®, Octapharma, Laachen, Switzerland; FFP: Fresh Frozen Plasma; INR: international Normalized Ratio; VKA: Vitamin K antagonists; ICH: Intracranial Hemorrhage; CCT cerebral computed tomography, mRS: modified Rankin Score

Steiner T et al. Int J Stroke 2011;6:271-277

Design and int



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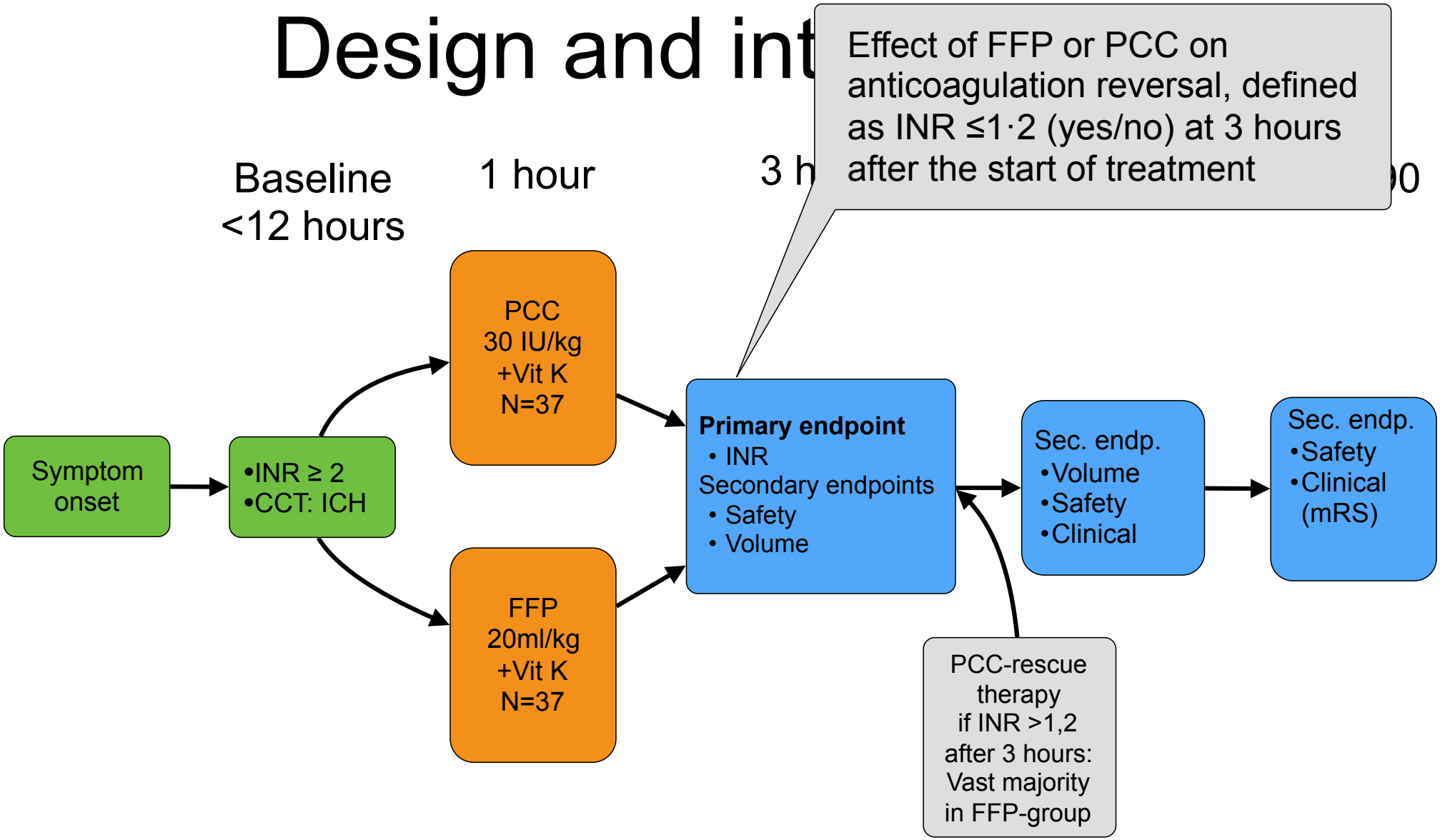

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Results

Results

Primary endpoint

INR

Primary endpoint: INR≤1,2 at 3 hours

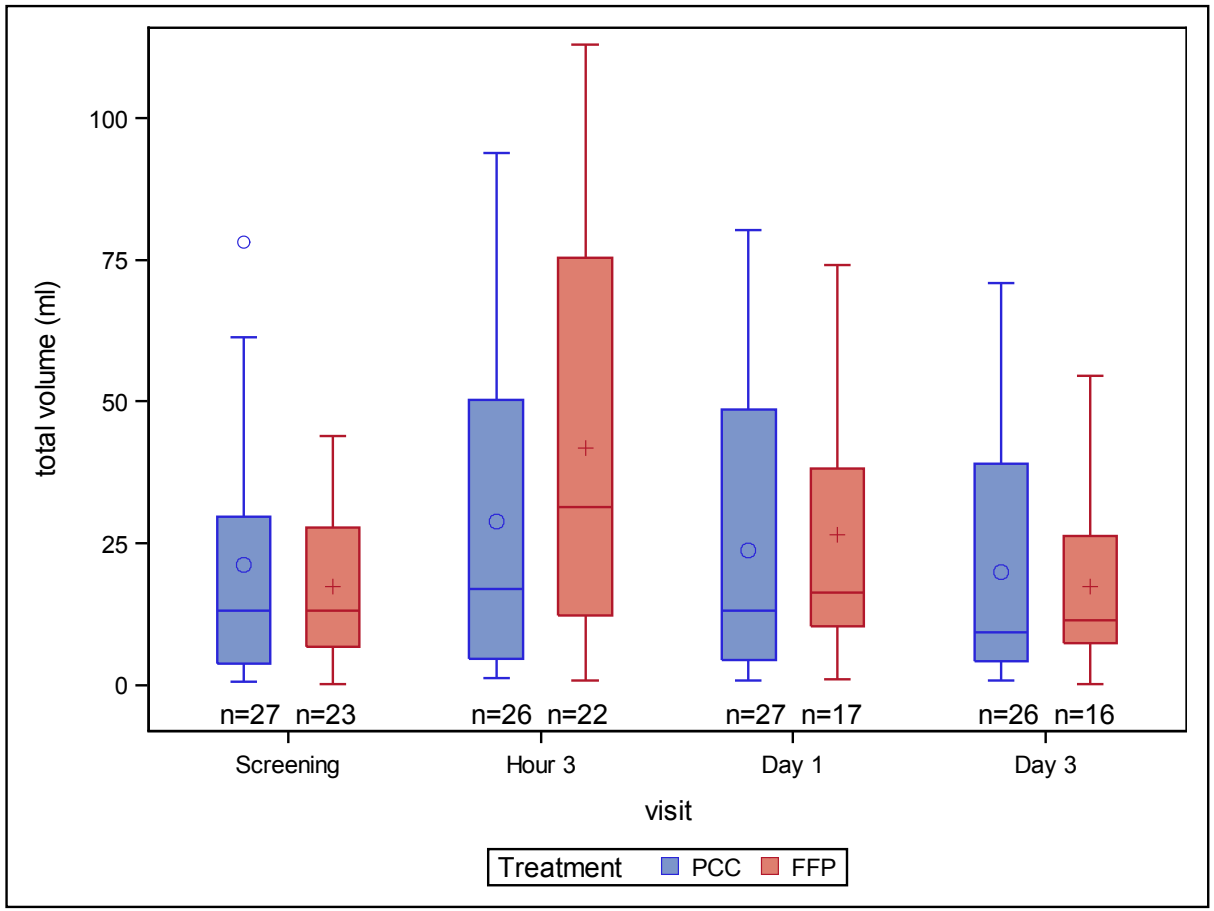
	No		Yes		
	N	**%**	**N**	**%**	**Total**
PCC	9	33,3	**18**	66,7	**27**
FFP	21	91,1	**2**	8,9	**23**
total	30	60,0	20	40,0	50

	Odds Ratio	**96% CI**	**p**
FFP vs. PCC	30,6	4,7 - 197,9	0.0003

Results

Secondary endpoints

Intracranial hematoma volumes according to treatment group at different time points

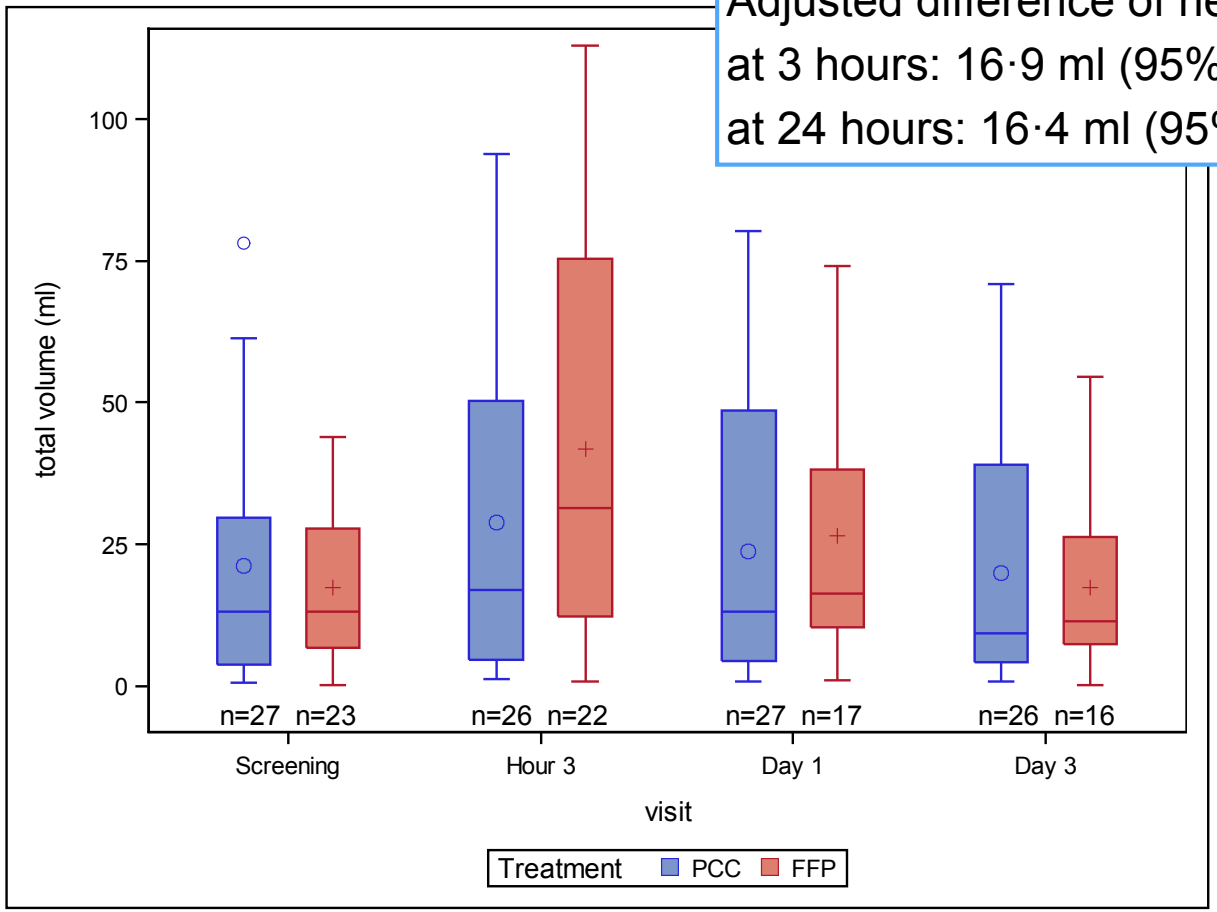


Numbers: number of patients who received CCT at given timepoint.

+ / ◯ : group means and outside values in either treatment group

Intracranial hematoma volumes according to treatment group at different time points

Adjusted difference of hematoma expansion
at 3 hours: 16·9 ml (95%-CI: [2·5; 31·3], p=0·026)
at 24 hours: 16·4 ml (95%-CI: [2·9; 29·9], p=0·018)



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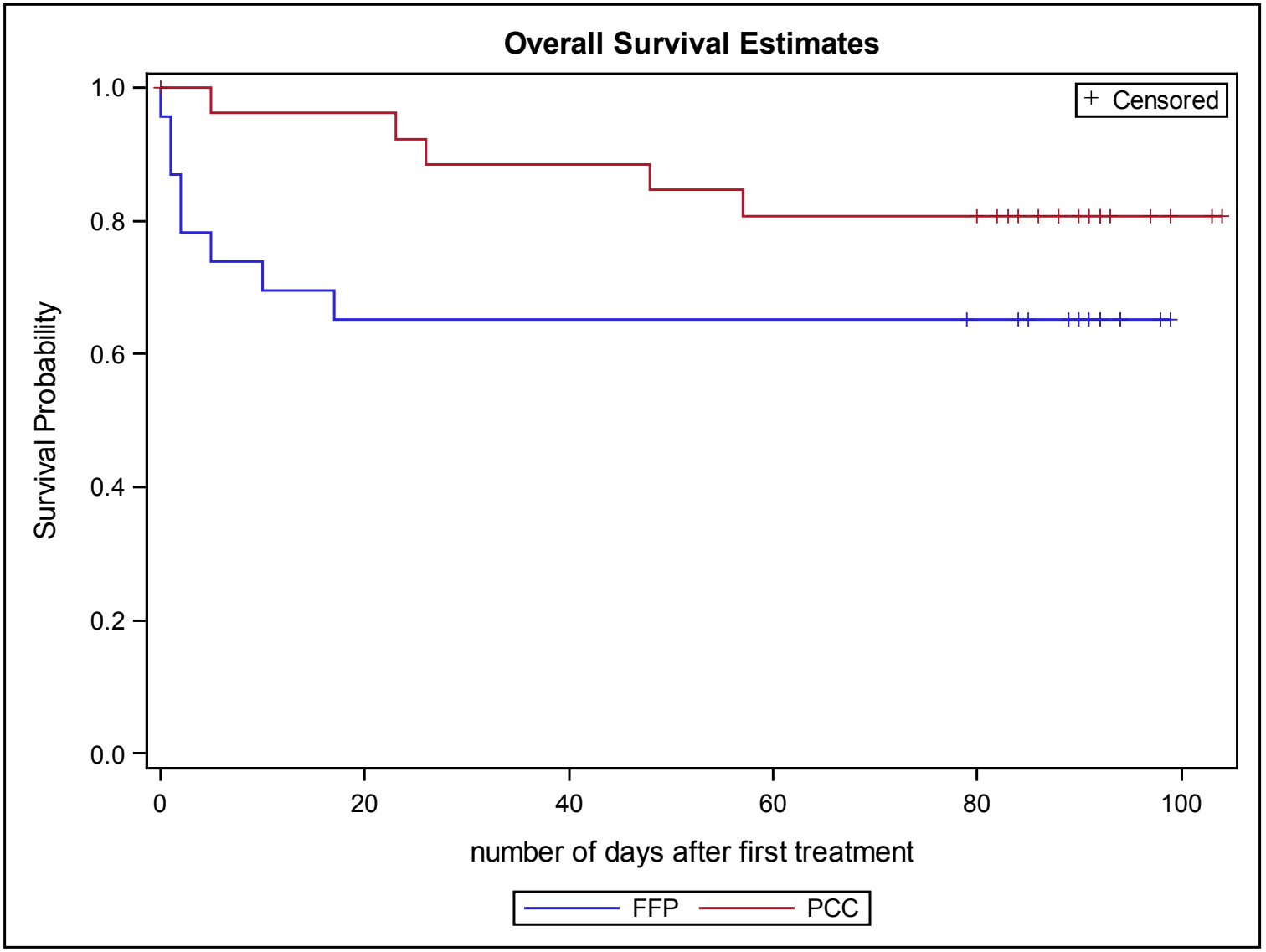
Kaplan-Meier - survival curve



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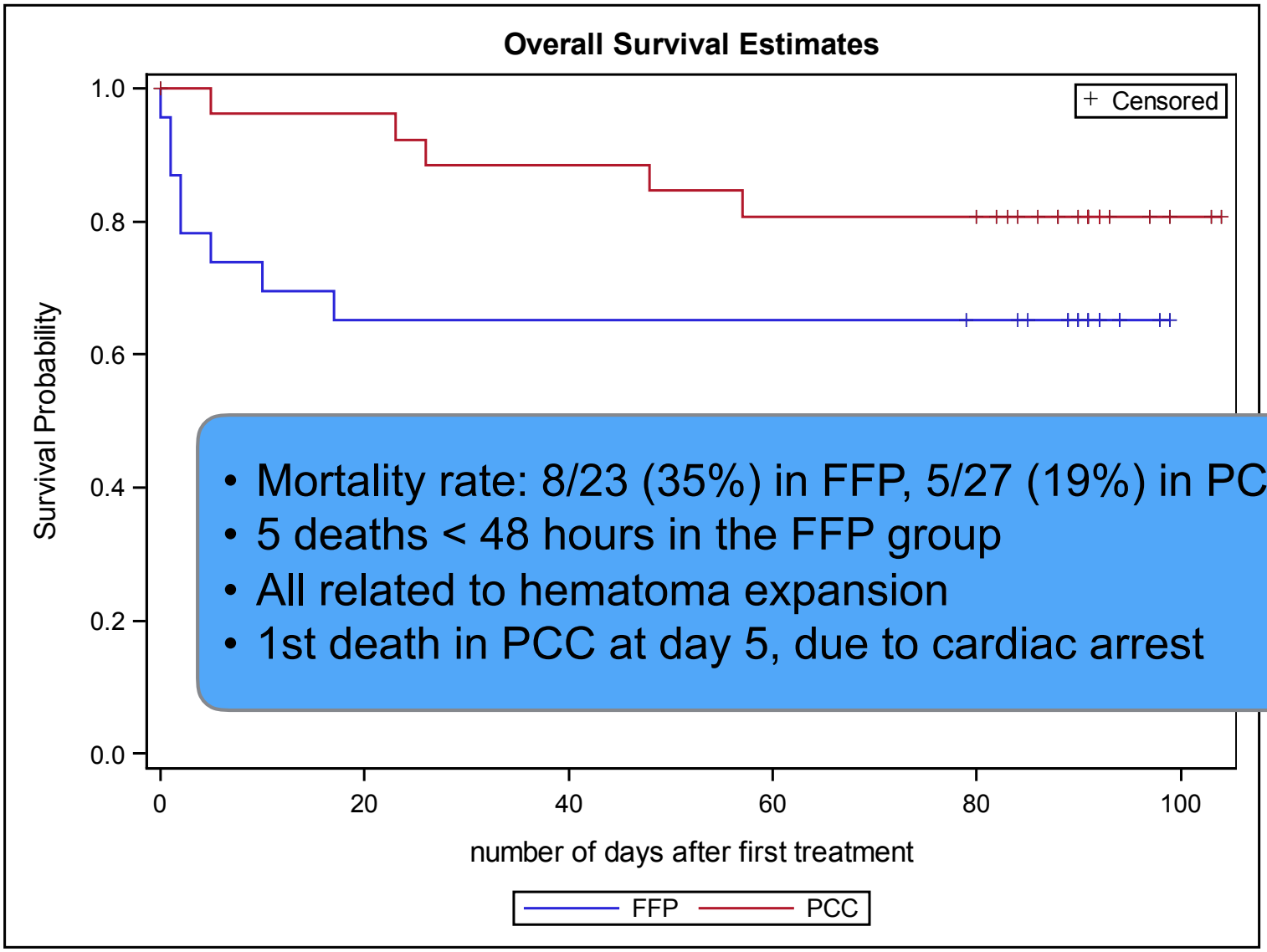

- Mortality rate: 8/23 (35%) in FFP, 5/27 (19%) in PCC, p=0.14
- 5 deaths < 48 hours in the FFP group
- All related to hematoma expansion
- 1st death in PCC at day 5, due to cardiac arrest

Results

Secondary endpoints

Safety

Safety

Safety parameter	FFP (N=23)		PCC (N=27)	Odds Ratio FFP+PCC vs. PCC	95% CI	p (Fisher's exact test)
	FFP N=4	+ PCC (after 3 hours) N=19*				
Thromboembolic events						
Myocardial infarction	0	0	0	N/A	N/A	N/A
Ischaemic stroke	1**	1**	2	N/A	N/A	N/A
Pulmonary embolism	0	0	4**	N/A	N/A	N/A
Deep vein thrombosis	0	0	1	N/A	N/A	N/A
Patients with at least one SAE (N)	2	8	16	0·65	0·16 – 2·49	0·55
SAEs (N)	5	15	23			
SAE classified as haematoma expansion (N)	2	7	7			
SAE classified as haematoma expansion leading to death (N)	2	4	1			

*Rescue therapy after 3 hours when INR >1,2, per protocol **Three within first three days, all other thromboembolic events occurred at day 12 or later, SAE: serious adverse event, N/A: Not applicable

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Discussion

INCH: Summary of results

1. 4-factor-PCC is superior to FFP in normalizing the INR within 3 hours in patients with VKA related ICH
2. PCC significantly reduced hematoma expansion at 3 and 24 hours in patients with VKA related ICH
3. The 5 five deaths within the first 48 hours occurred exclusively in the FFP-group and were due to hematoma expansion
4. Higher volume load by FFP treatment did not induce hematoma expansion through increased blood pressure

Management of ICH patients
New evidence from the INCH trial

1. The INCH trial:
   - Effect of PCC and FFP on hematoma expansion in intracranial haemorrhage related to Vitamin-K-antagonists
2. Meta-analysis:
   - PCC vs. FFP for reversal of anticoagulation of VKA in patients with major bleeding or in need for urgent intervention

Meta-analysis of studies comparing PCC and FFP for reversal of anticoagulation with VKA in patients with major bleeding or in need for urgent intervention

P	In patients with major bleeding or need for urgent intervention who are on vitamin-K antagonist
I	does prothrombin complex concentration (PCC)
C	compared to fresh frozen plasma (FFP)
O	improve outcome: improve mortality at 3 months, improve hemostatic efficacy, hematoma expansion

RCT on 4-factor prothrombin complex concentrate (PCC) versus (FFP)

Authors	Goldstein JN at al. Lancet. 2015;385:2077-2087	Sarode R et al. Circulation. 2013;128:1234-1243	INCH: Steiner T et al. Lancet Neurol 2016;15:566–573
PCC vs FFP	90 vs 91	107 vs 109	27 vs 23
Population	• VKA-reversal in patients needing urgent surgical or invasive interventions • INR ≥ 2	• Major bleeding • INR ≥ 2	• ICH • INR ≥ 2
PCC dose	25 IU/kg (IX)	25-50 IU /kg	30 IU/kg
Primary endpoint	• Effective hemostasis* • Rapid INR reduction**	• Effective hemostasis* • Rapid INR reduction**	• INR ≤ 1,2 within 3 hours
Secondary endpoints	• Mortality	• Mortality	• Mortality • Hematoma expansion

*Predicted blood loss ≤ 30% or 50ml and normal or mildly abnormal haemostasis and no administration of non-study coagulation drugs; **INR ≤1.3 at 0.5 h after the end of infusion

RCT on 4-factor prothrombin complex concenrate (PCC) versus (FFP)

Quality assessment							Summary of findings				
№ of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With placebo	With INR normalization		Risk with placebo	Risk difference with INR normalization
INR normalization											
420 (3 studies)	not serious	not serious	not serious	not serious	none	-	127/212 (59.9%)	20/208 (9.6%)	**OR 0.07** (0.04 to 0.12)	599 per 1.000	**504 fewer per 1.000** (543 fewer to 447 fewer)
Effective hemostasis											
370 (2 studies)	not serious	not serious	not serious	not serious	none	-	158/185 (85.4%)	129/185 (69.7%)	**OR 0.40** (0.24 to 0.68)	854 per 1.000	**153 fewer per 1.000** (270 fewer to 55 fewer)
Hematoma expansion (>=33%) at 24 hours											
47 (1 study)	not serious [a]	not serious	not serious	serious [a]	none	-	8/27 (29.6%)	12/20 (60.0%)	**OR 3.56** (1.05 to 12.04)	296 per 1.000	**304 more per 1.000** (10 more to 539 more)
Hematoma expansion (>=33%) at 3 hours											
49 (1 study)	not serious [a]	not serious	not serious	serious [a]	none	-	12/27 (44.4%)	13/22 (59.1%)	**OR 1.81** (0.58 to 5.64)	444 per 1.000	**147 more per 1.000** (128 fewer to 374 more)
Mortality											
438 (3 studies)	not serious	not serious [b]	not serious	serious [a]	none	-	12/224 (5.4%)	26/214 (12.1%)	**OR 2.67** (1.28 to 5.58)	54 per 1.000	**78 more per 1.000** (14 more to 186 more)

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

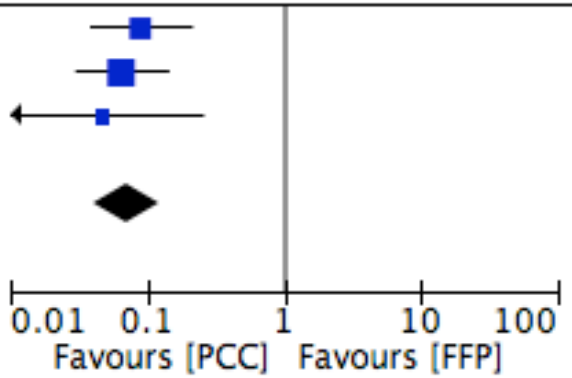
a. INCH small trial
b. Heterogeneity of population between trials

Meta-Analysis of PCC-FFP trials

Outcome: INR-normalization

Study or Subgroup	FFP Events	FFP Total	PCC Events	PCC Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Goldstein 2015	8	81	48	87	36.7%	0.09 [0.04, 0.21]
Sarode 2013	10	104	61	98	50.0%	0.06 [0.03, 0.14]
Steiner 2016	2	23	18	27	13.3%	0.05 [0.01, 0.25]
Total (95% CI)		**208**		**212**	**100.0%**	**0.07 [0.04, 0.12]**
Total events	20		127			

Heterogeneity: $Chi^2 = 0.56$, $df = 2$ ($P = 0.76$); $I^2 = 0\%$
Test for overall effect: $Z = 9.64$ ($P < 0.00001$)



*Mean duration of infusion
- PCC17 (7-288) minutes
- FFP 148 (26 - 928) minutes

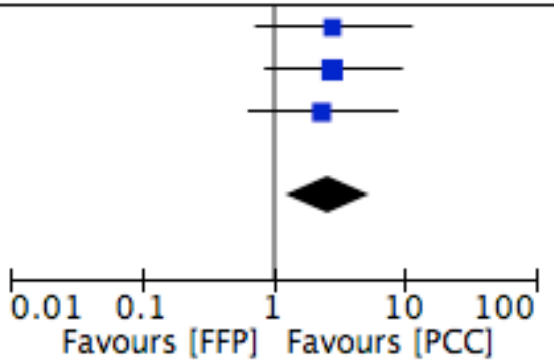
Steiner T, unpublished data 2016

Meta-Analysis of PCC-FFP trials

Outcome: Mortality

Study or Subgroup	FFP Events	FFP Total	PCC Events	PCC Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Goldstein 2015	8	88	3	88	29.5%	2.83 [0.73, 11.06]
Sarode 2013	10	103	4	109	38.0%	2.82 [0.86, 9.30]
Steiner 2016	8	23	5	27	32.5%	2.35 [0.64, 8.57]
Total (95% CI)		**214**		**224**	**100.0%**	**2.67 [1.28, 5.58]**
Total events	26		12			

Heterogeneity: $Chi^2 = 0.05$, df = 2 (P = 0.97); $I^2 = 0\%$
Test for overall effect: Z = 2.61 (P = 0.009)



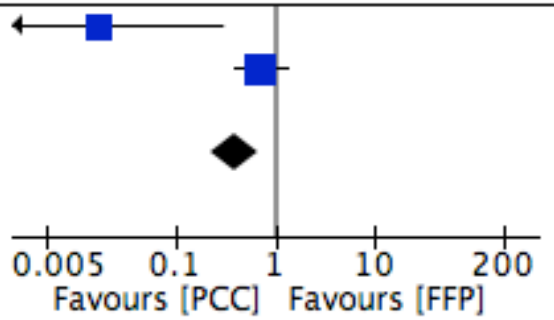
Steiner T, unpublished data 2016

Meta-Analysis of PCC-FFP trials

Outcome: Effective haemostasis

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Goldstein 2015	61	81	87	87	45.5%	0.02 [0.00, 0.29]
Sarode 2013	68	104	71	98	54.5%	0.72 [0.39, 1.31]
Total (95% CI)		**185**		**185**	**100.0%**	**0.40 [0.24, 0.68]**
Total events	129		158			

Heterogeneity: $Chi^2 = 8.45$, df = 1 (P = 0.004); $I^2 = 88\%$
Test for overall effect: Z = 3.42 (P = 0.0006)



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**INR ≤1.3 at 0.5 h after the end of infusion

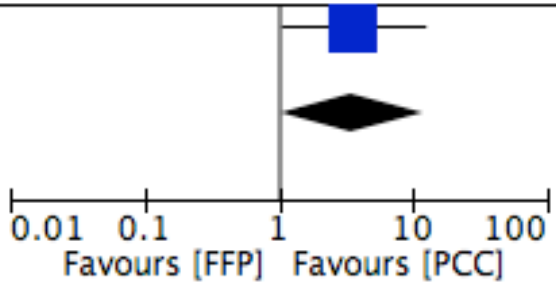
Steiner T, unpublished data 2016

Meta-Analysis of PCC-FFP trials

Outcome: Hematoma expansion

Study or Subgroup	FFP Events	FFP Total	PCC Events	PCC Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Steiner 2016	12	20	8	27	100.0%	3.56 [1.05, 12.04]
Total (95% CI)		**20**		**27**	**100.0%**	**3.56 [1.05, 12.04]**
Total events	12		8			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.04 (P = 0.04)



Steiner T, unpublished data 2016

Oral Anticoagulants & Reversal Agents
Vitamin-K-antagonists and ICH

Conclusion

In patients with major bleeding or in need for urgent intervention

4-factor PCCs compared to FFP

1. significantly faster lower INR
2. significantly decrease mortality at day 30
3. significantly decrease early haematoma expansion at 3 and 24 hours in patients with ICH