



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

Prof. Dr. Thorsten Steiner

- Department of Neurology, Klinikum Frankfurt Höchst, Germany
- Department of Neurology, Heidelberg University Hospital, Germany
- Department of Clinical Medicine, Copenhagen University, Denmark

# Conflict of Interest (Col)

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 Cols

- 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



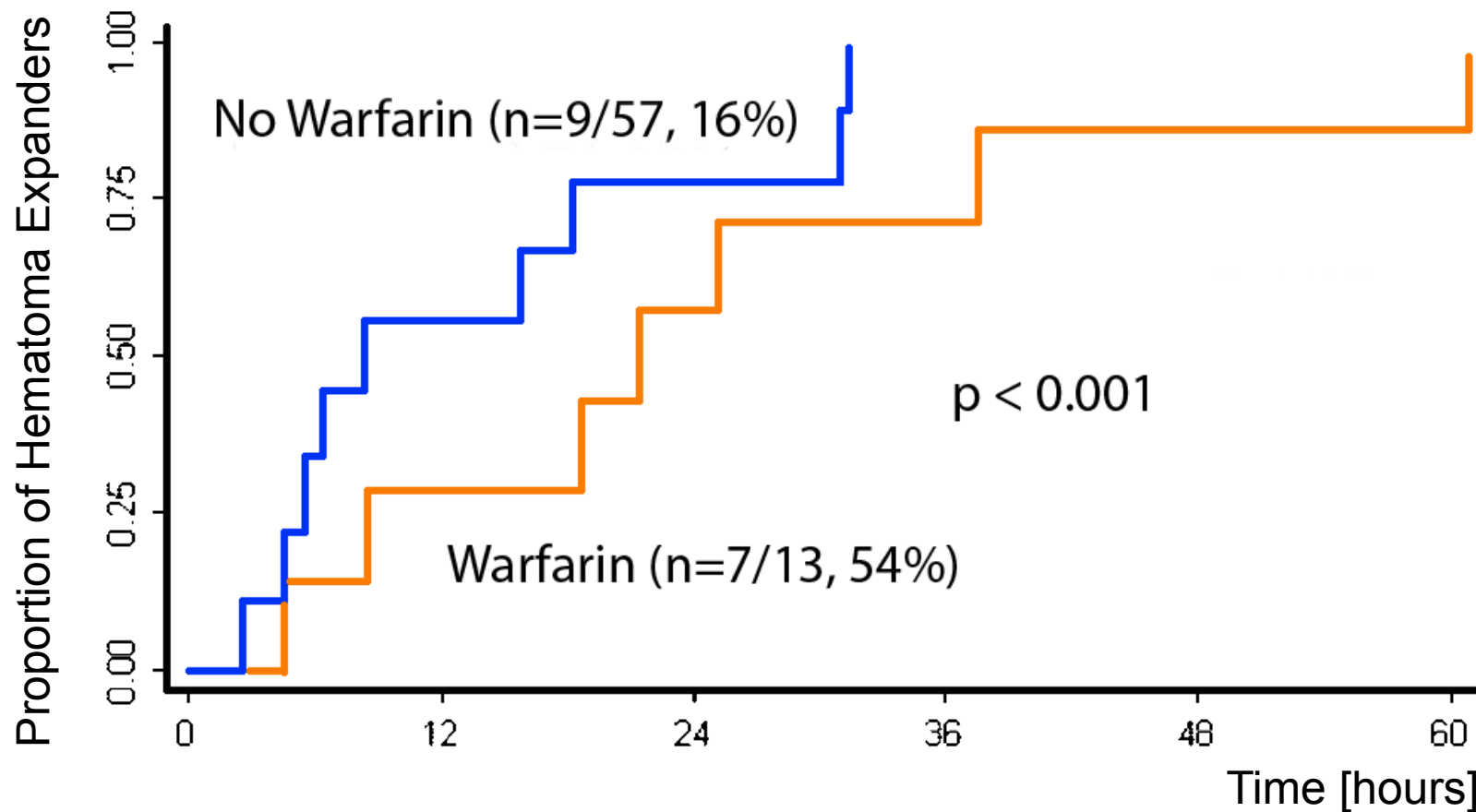
# Background



# 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

# Hematoma growth after spontaneous ICH and Vit-K-antagonists



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



# 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 Griebel, 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*



# Method







# Inclusion criteria

1. Age  $\geq 18$  years
2. ICH by CCT within 12 hours after onset of symptoms or after last seen normal
3. Therapy with VKA, and admission INR  $\geq 2.0$
4. Signed informed consent

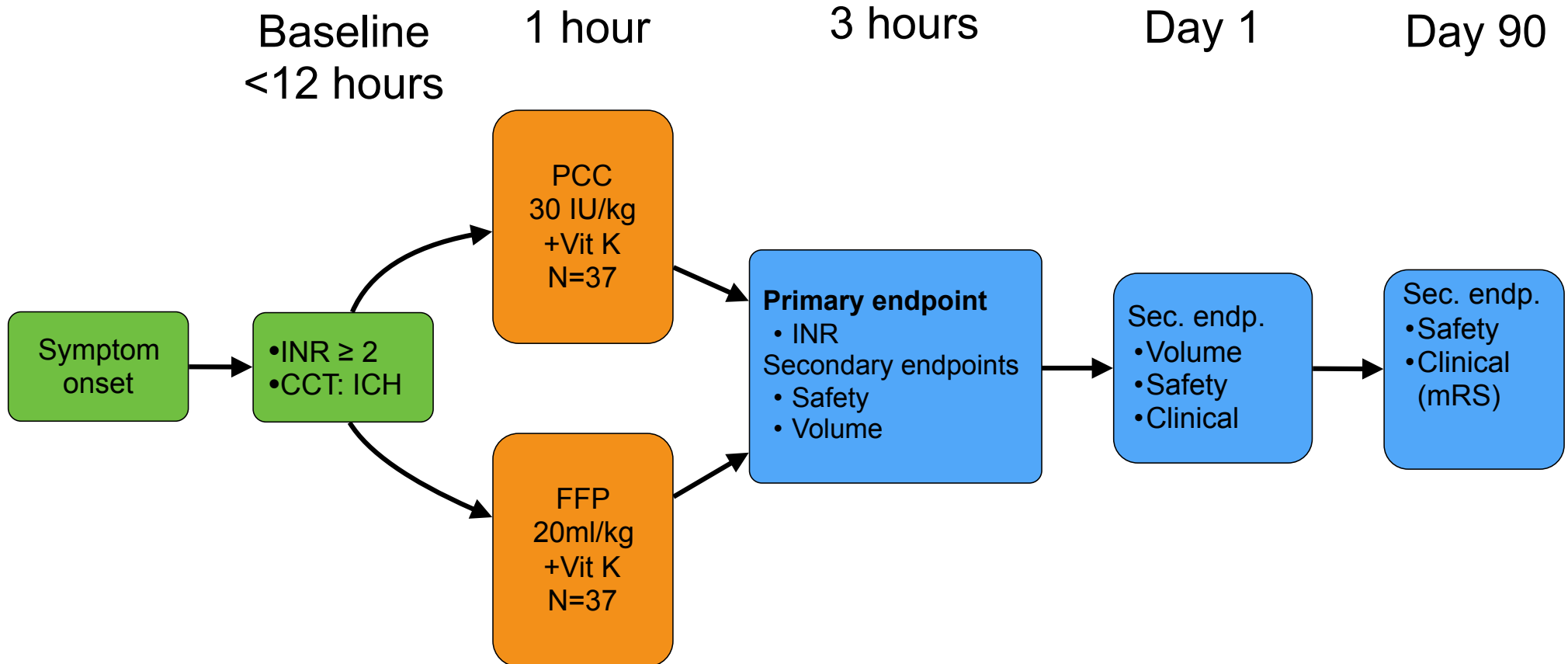
ICH: Intracranial Hemorrhage (subdural, intracerebral)



# Exclusion criteria

- Traumatic or secondary intracranial ICH (vascular malformations, transformation of cerebral infarction, cerebral venous thrombosis, tumor, hemophilia or other coagulopathies)
- Glasgow Coma Score  $\leq 5$
- 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



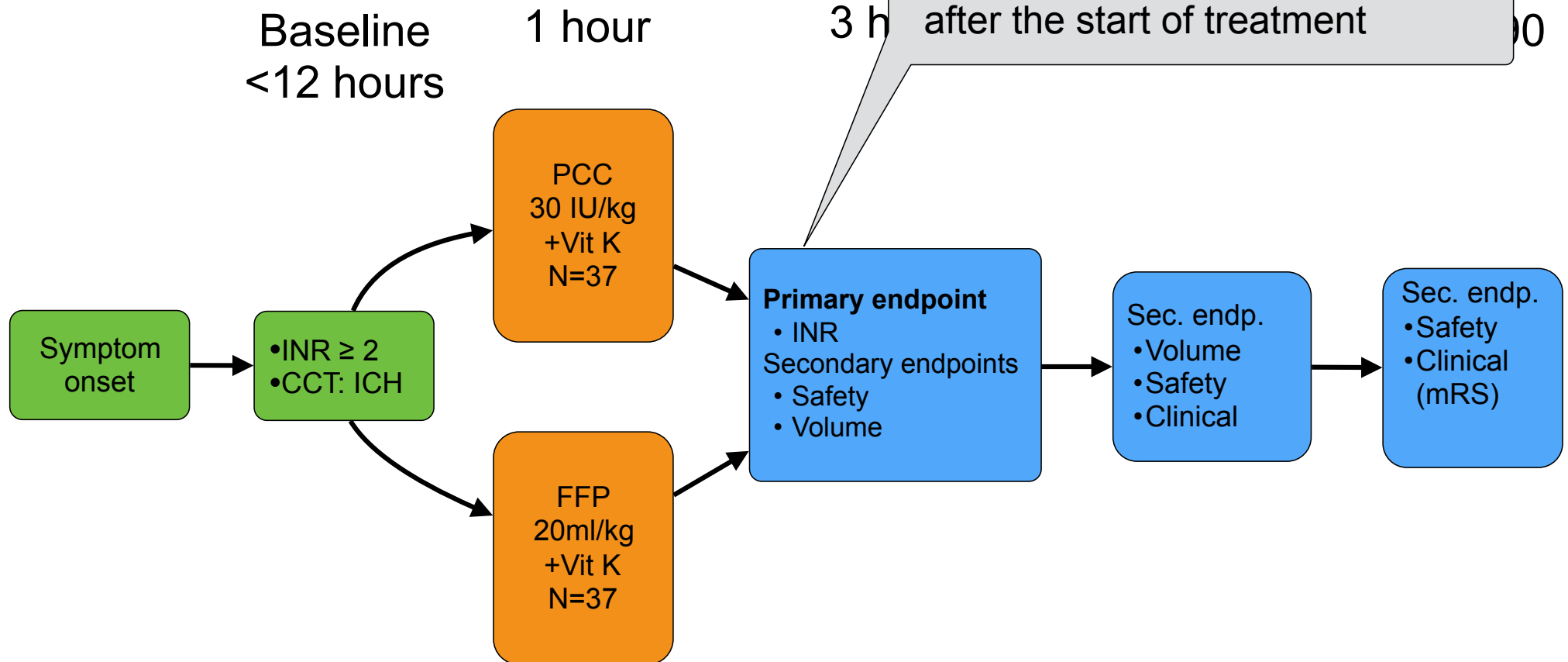
PCC: 4-factor PCC, Octaplex®, Octapharma, Laachen, Switzerland; FFP: Fresh Frozen Plasma; INR: international Normalized Ratio; VKA: Vitamin K antagonists; ICH: Intracranial Hemorrhage; CCT cerebral computed tomography, mRS: modified Rankin Score

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

6th WICH & 1st HEADS; Baltimore, 02.05.2017

# Design and int

Effect of FFP or PCC on anticoagulation reversal, defined as INR  $\leq 1.2$  (yes/no) at 3 hours after the start of treatment



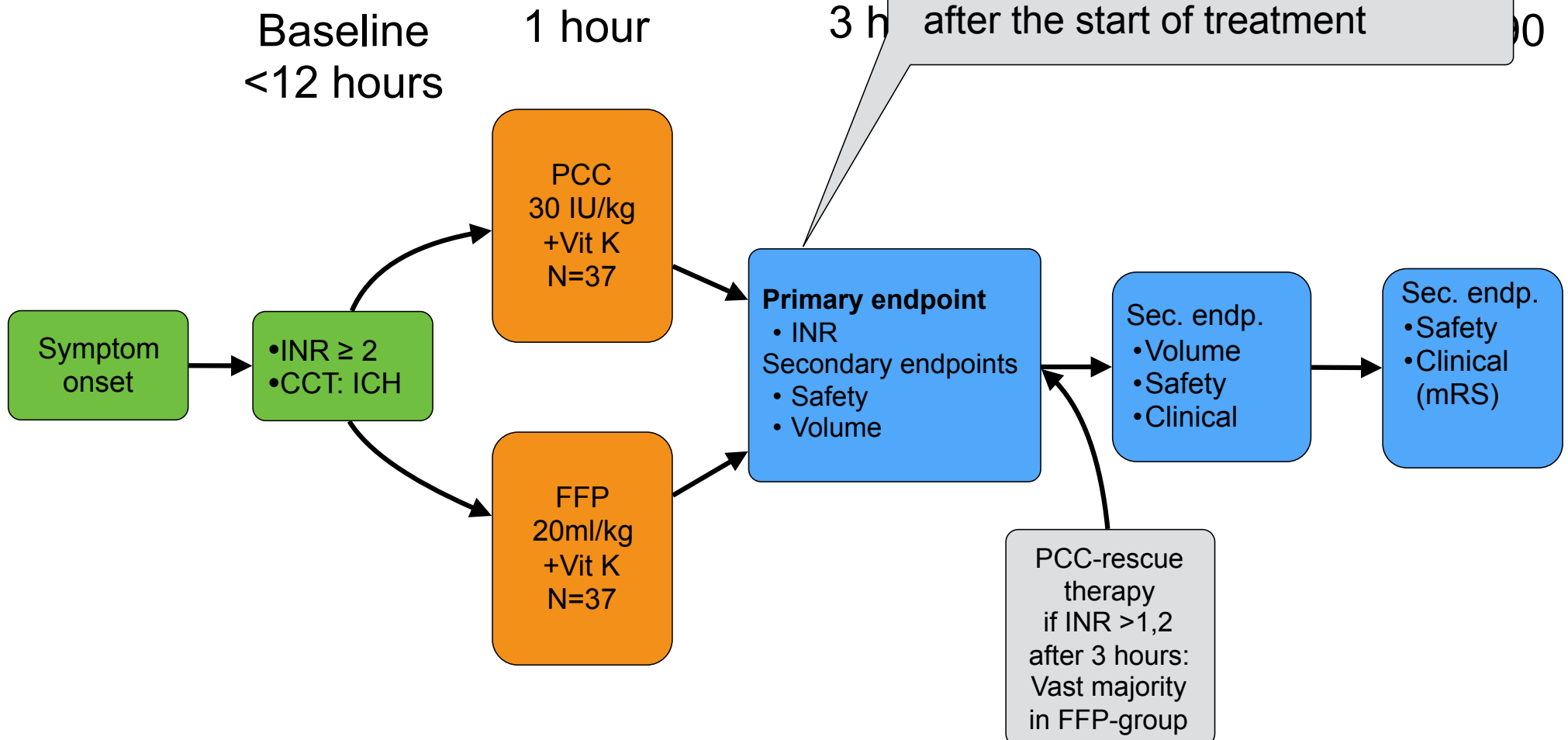
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# Results





# Results

Primary endpoint

INR

## Primary endpoint: INR $\leq$ 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

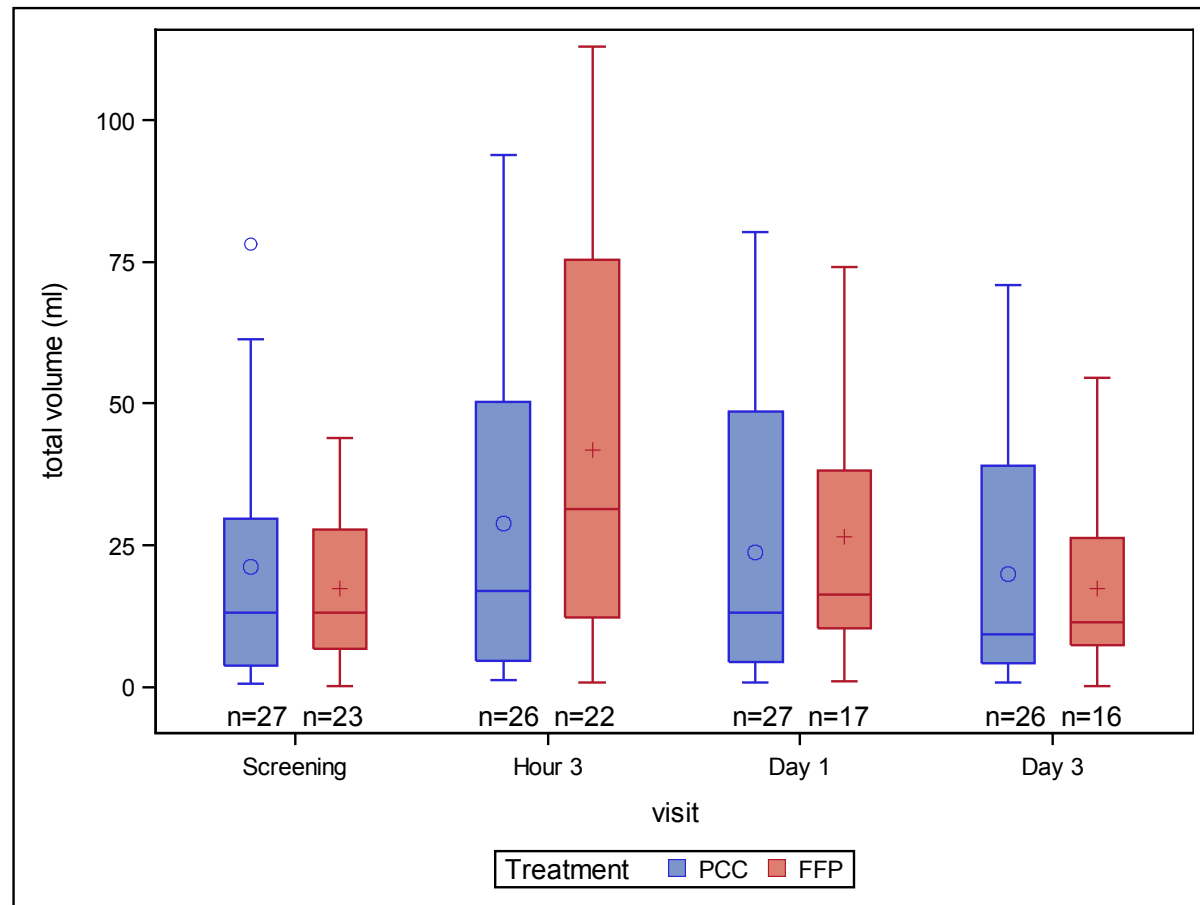




# Results

## Secondary endpoints

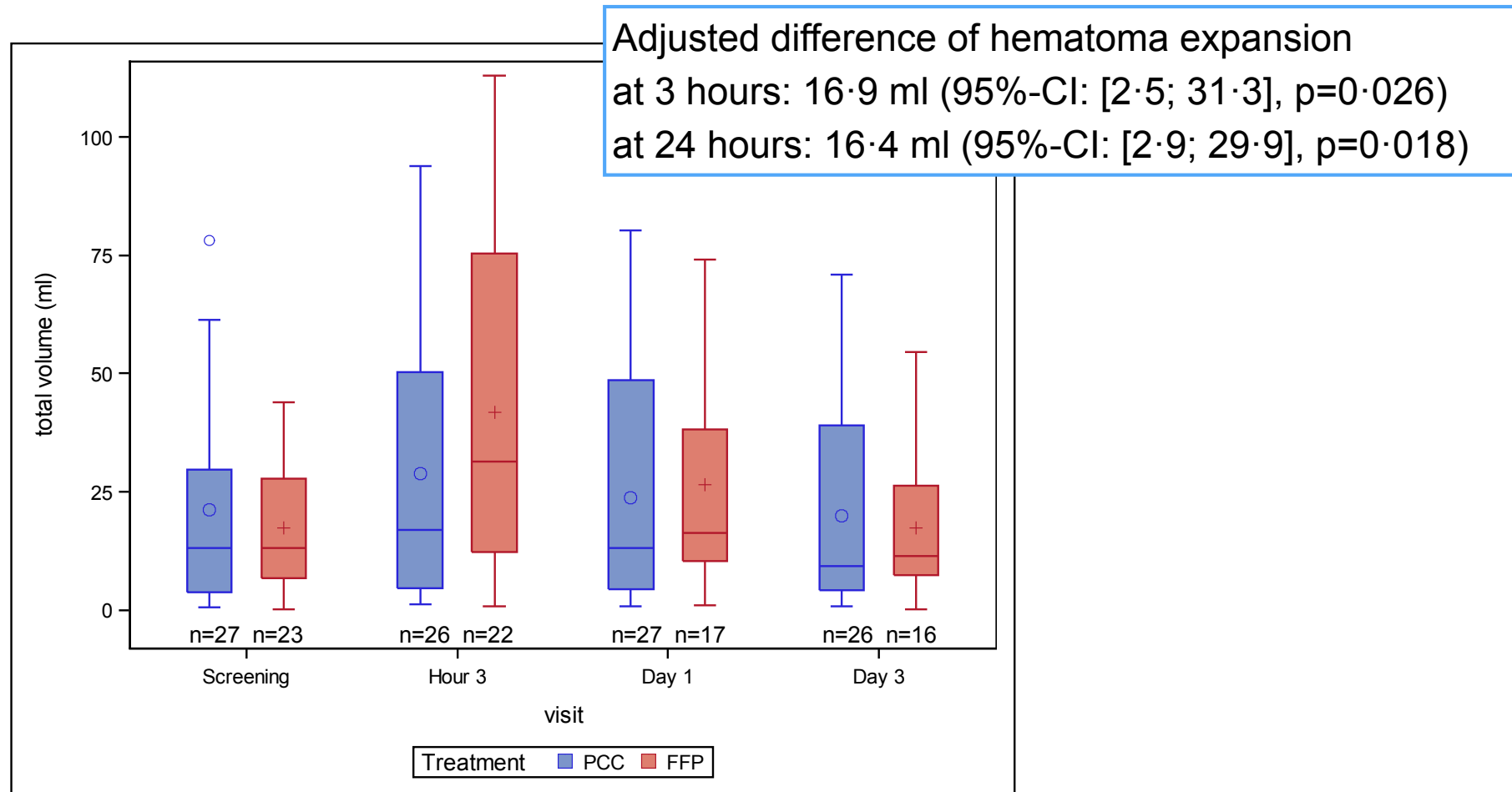
# Intracranial hematoma volumes according to treatment group at different time points



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

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

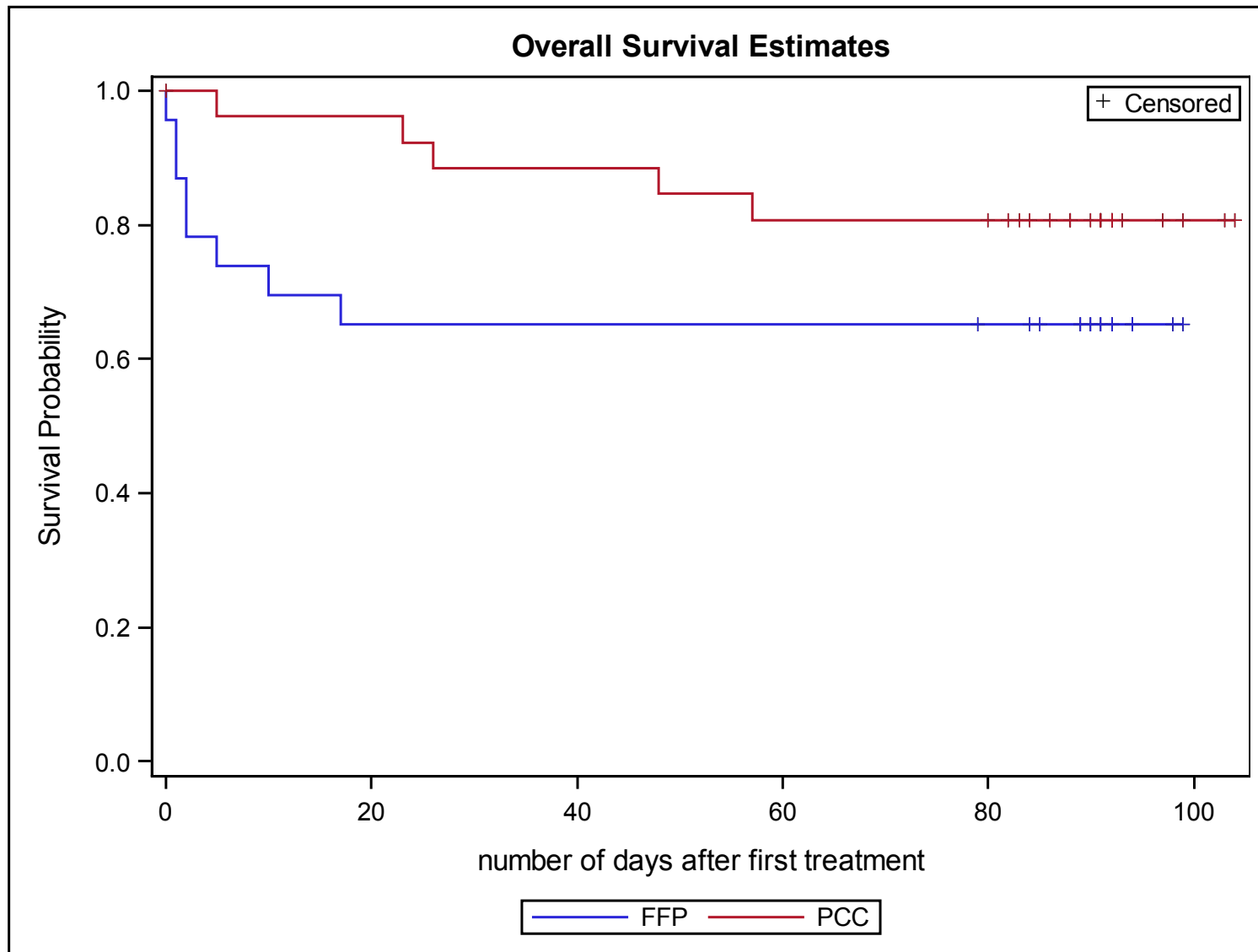
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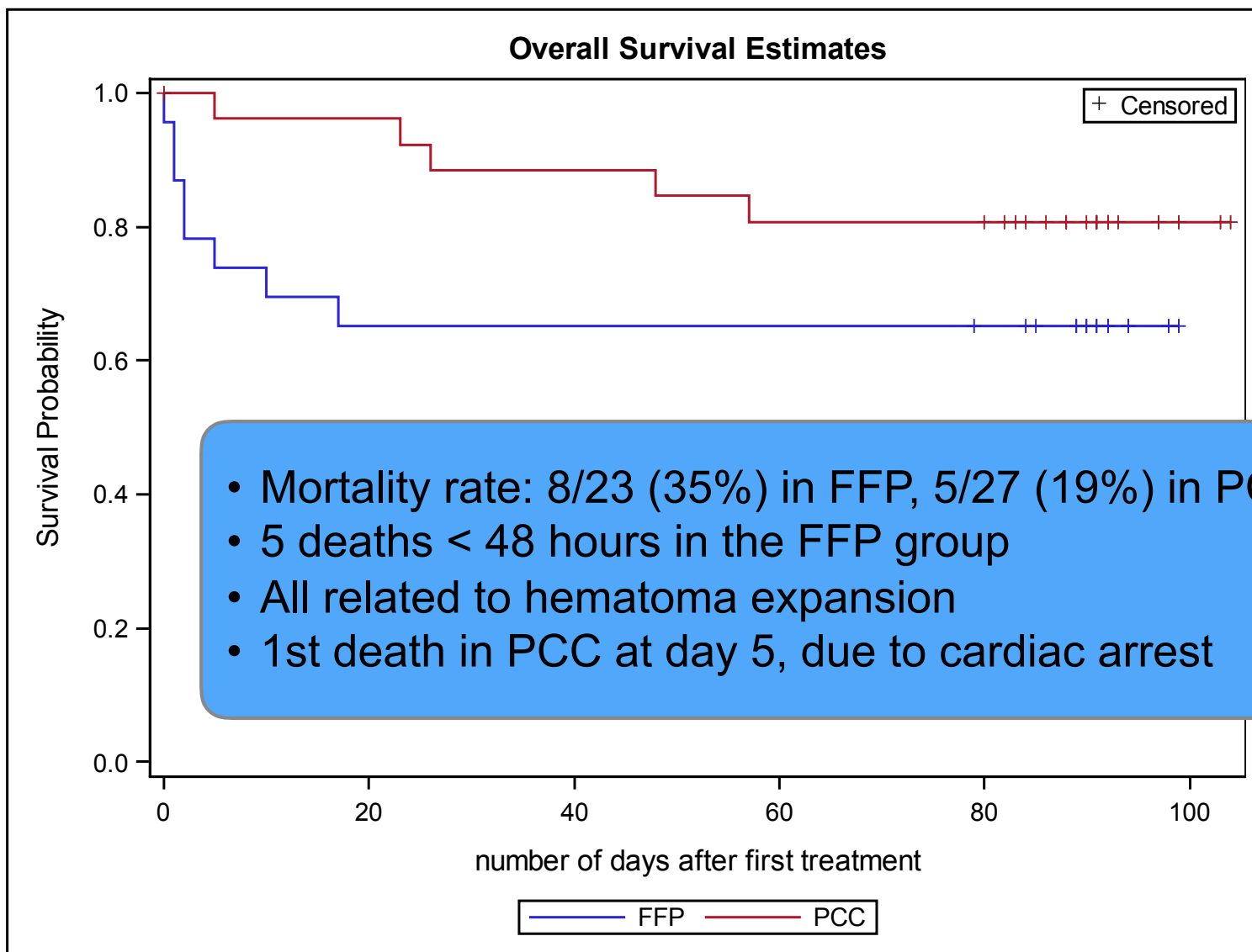
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# Kaplan-Meier - survival curve



# Kaplan-Meier - survival curve





# 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*				
<b>Thromboembolic events</b>						
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
<b>Patients with at least one SAE (N)</b>	2	8	16	0.65	0.16 – 2.49	0.55
<b>SAEs (N)</b>	5	15	23			
<b>SAE classified as haematoma expansion (N)</b>	2	7	7			
<b>SAE classified as haematoma expansion leading to death (N)</b>	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 et al. <u>Lancet</u> . 2015;385:2077-2087	Sarode R et al. <u>Circulation</u> . 2013;128:1234-1243	INCH: Steiner T et al. <u>Lancet Neurol</u> 2016;15:566–573
PCC vs FFP	90 vs 91	107 vs 109	27 vs 23
Population	<ul style="list-style-type: none"> <li>• VKA-reversal in patients needing <u>urgent surgical or invasive interventions</u></li> <li>• INR <math>\geq 2</math></li> </ul>	<ul style="list-style-type: none"> <li>• <u>Major bleeding</u></li> <li>• INR <math>\geq 2</math></li> </ul>	<ul style="list-style-type: none"> <li>• <u>ICH</u></li> <li>• INR <math>\geq 2</math></li> </ul>
PCC dose	25 IU/kg (IX)	25-50 IU /kg	30 IU/kg
Primary endpoint	<ul style="list-style-type: none"> <li>• Effective hemostasis*</li> <li>• Rapid INR reduction**</li> </ul>	<ul style="list-style-type: none"> <li>• Effective hemostasis*</li> <li>• Rapid INR reduction**</li> </ul>	<ul style="list-style-type: none"> <li>• INR <math>\leq 1,2</math> within 3 hours</li> </ul>
Secondary endpoints	<ul style="list-style-type: none"> <li>• Mortality</li> </ul>	<ul style="list-style-type: none"> <li>• Mortality</li> </ul>	<ul style="list-style-type: none"> <li>• Mortality</li> <li>• Hematoma expansion</li> </ul>

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



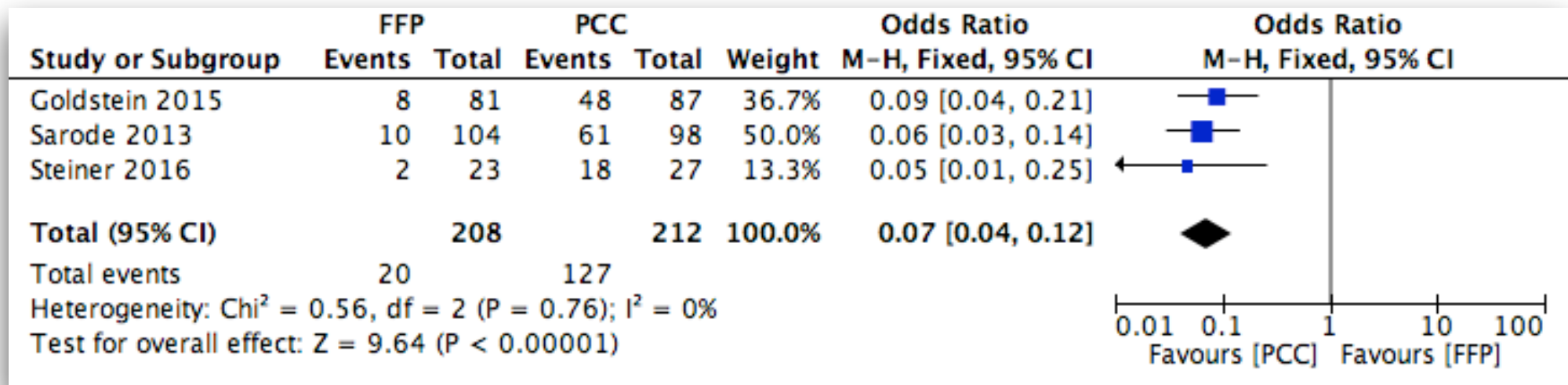
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Quality assessment							Summary of findings					
№ of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute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

CI: Confidence interval; OR: Odds ratio

# Meta-Analysis of PCC-FFP trials

## Outcome: INR-normalization



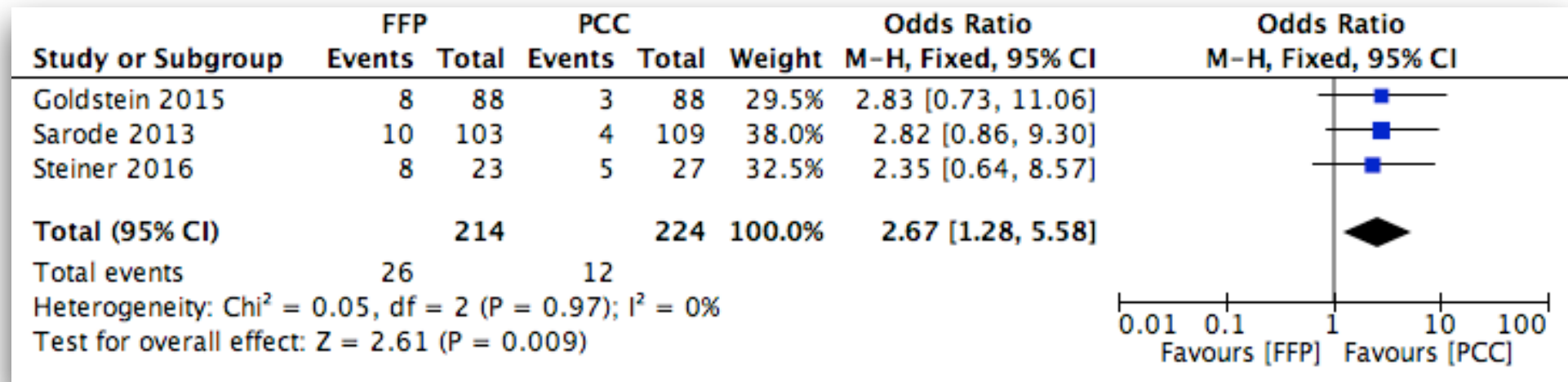
\*Mean duration of infusion  
 • PCC17 (7-288) minutes  
 • FFP 148 (26 - 928) minutes

Steiner T, unpublished data 2016



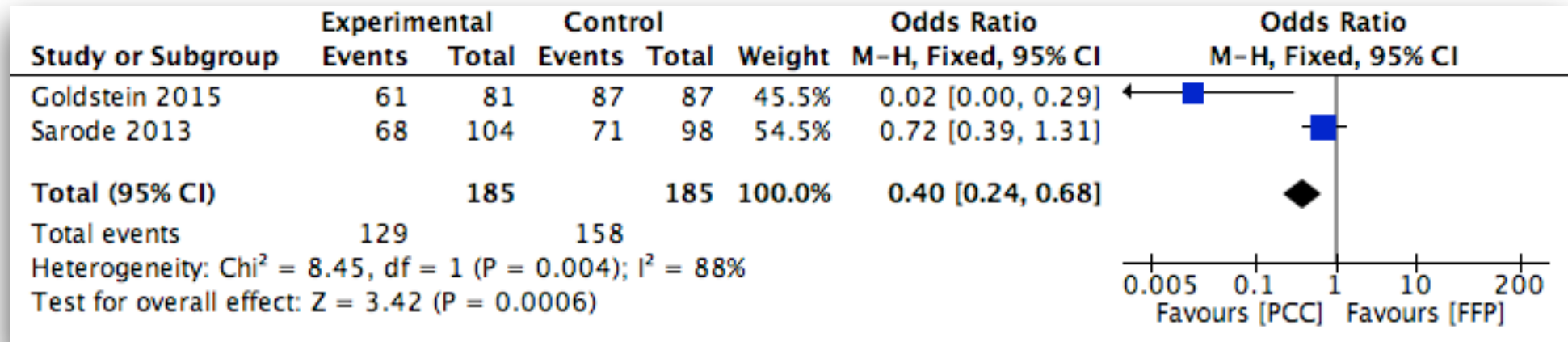
# Meta-Analysis of PCC-FFP trials

## Outcome: Mortality



# Meta-Analysis of PCC-FFP trials

Outcome: Effective haemostasis

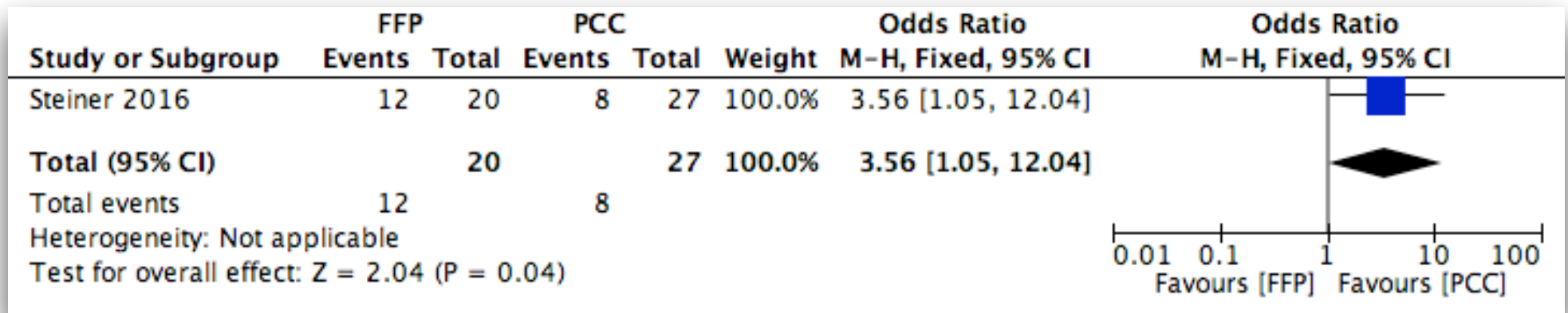


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\*\*INR  $\leq 1.3$  at 0.5 h after the end of infusion

# Meta-Analysis of PCC-FFP trials

Outcome: Hematoma expansion





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## 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