Incidence and Impact of Antithrombotic-related Intracerebral Hemorrhage

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Disclosures

- None

Clinical Relevance

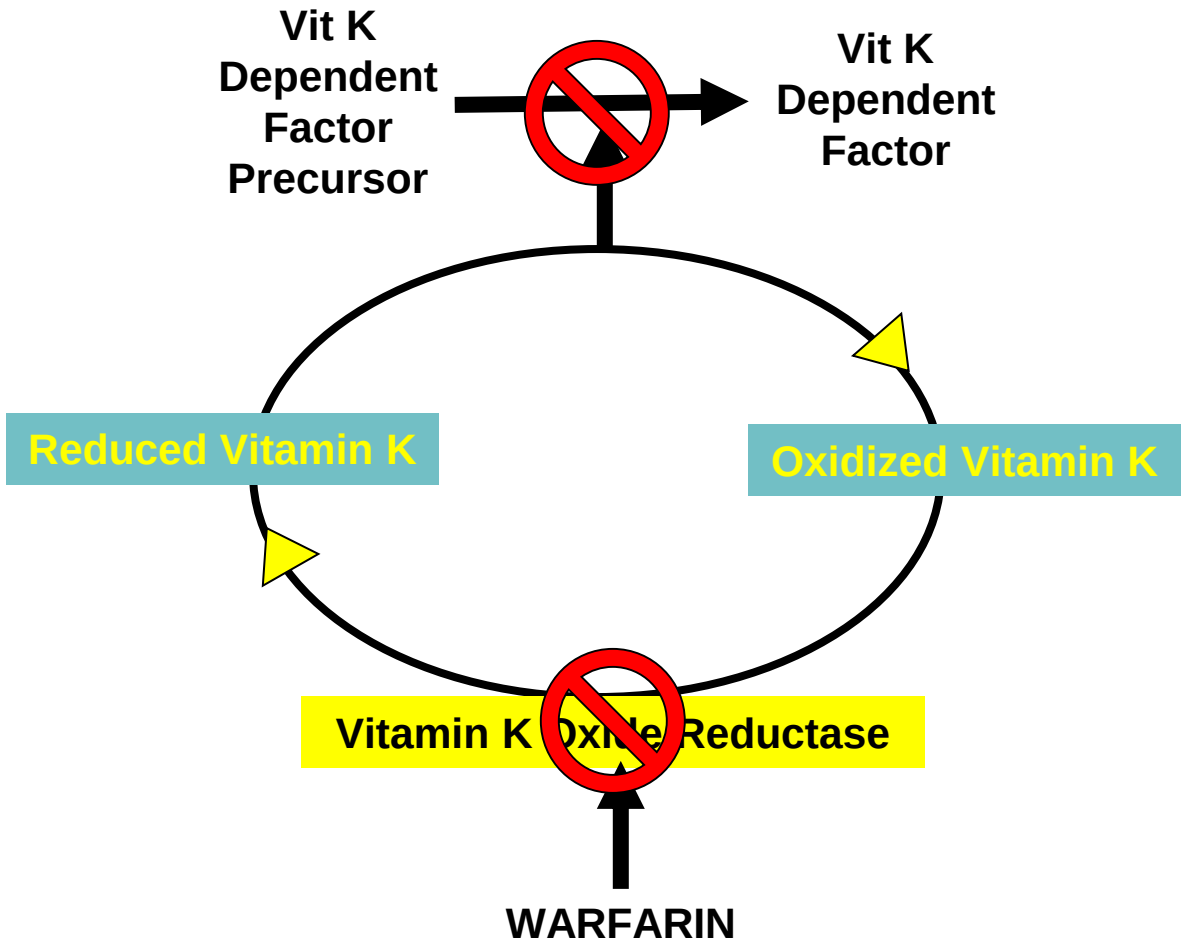
- Antithrombotic associated ICH is expected to become more common
- Introduction of non-vitamin K antagonist oral anticoagulants (NOACs)
- Antithrombotic associated ICH has a higher risk of hematoma expansion, higher mortality and worse outcome

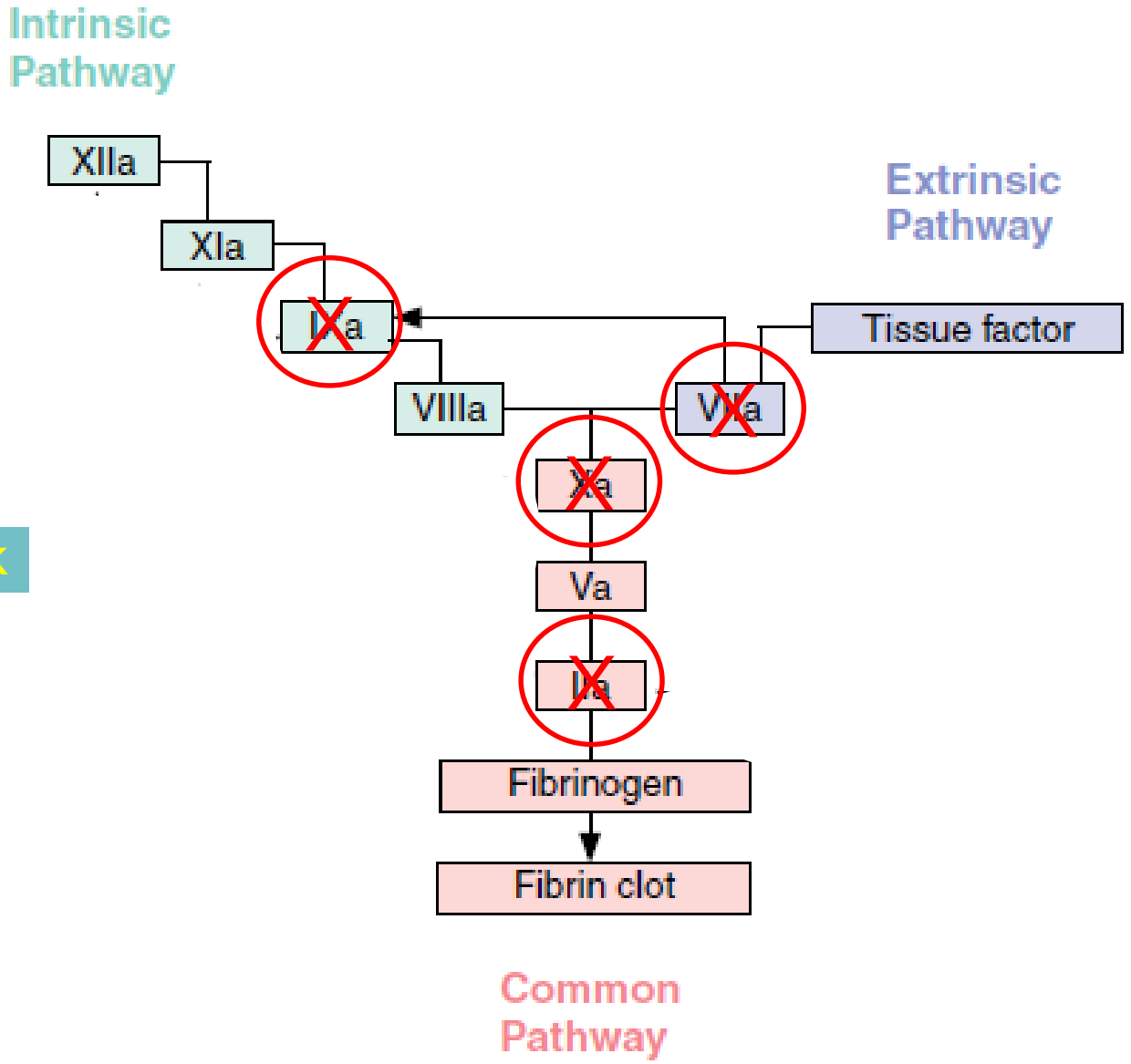
Hematoma Expansion

- Meta analysis of 3 trials (spontaneous ICH, rFVIIa)
- Hematoma growth is an independent predictor of both mortality and functional outcome.
- For every 10% increase in hematoma
  - 5% ↑ death
  - 16% ↑ worse outcome (mRS increase of 1)
  - 18% ↑ worse dependence

Davis SM et al. *Neurology* 2006;66:1175-1181.

WARFARIN MECHANSIM OF ACTION





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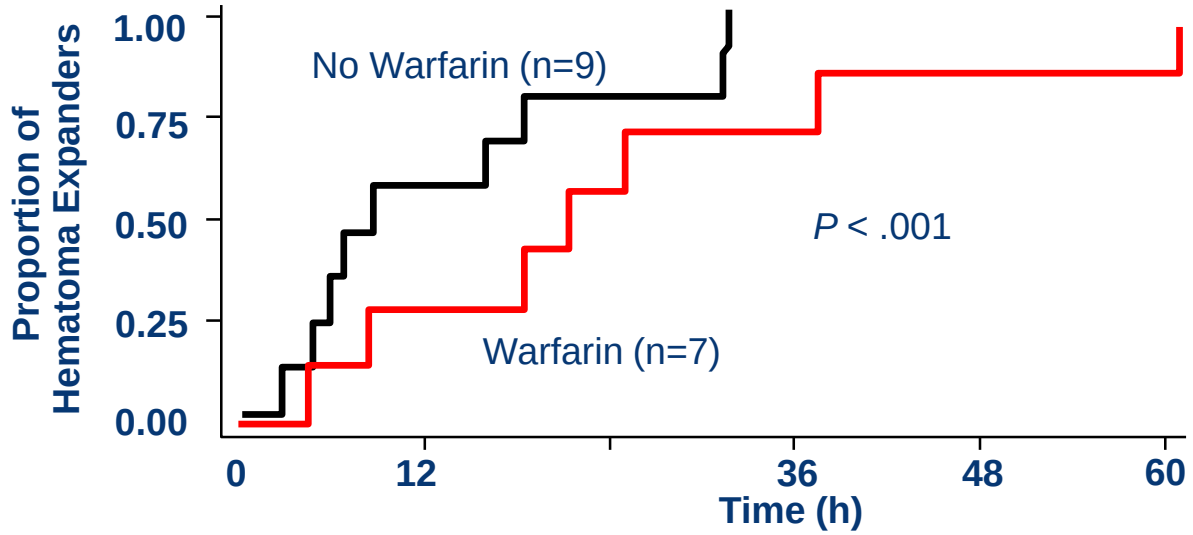
Warfarin and ICH

- Warfarin
  - More than doubles the risk of ICH
  - Associated with 12-14% of all ICH
  - Risk of ICH increases with increasing INR, although most occur within the therapeutic range
- 0.3-1.1%/year of patients on warfarin have ICH (baseline risk 0.15%/year)
- 90% of warfarin associated deaths due to ICH
- Higher volume hematoma, increased rebleeding risk, hematoma expansion for longer time than non-coagulopathic patients
- Higher risk of death and worse functional outcome if ICH on warfarin

Flaherty ML, et al. *Neurology* 2007;68:116-21. Hart RG, et al. *Stroke* 2005;36:1588-93., Flibotte JJ, et a. *Neurology* 2004; 63:059-64.

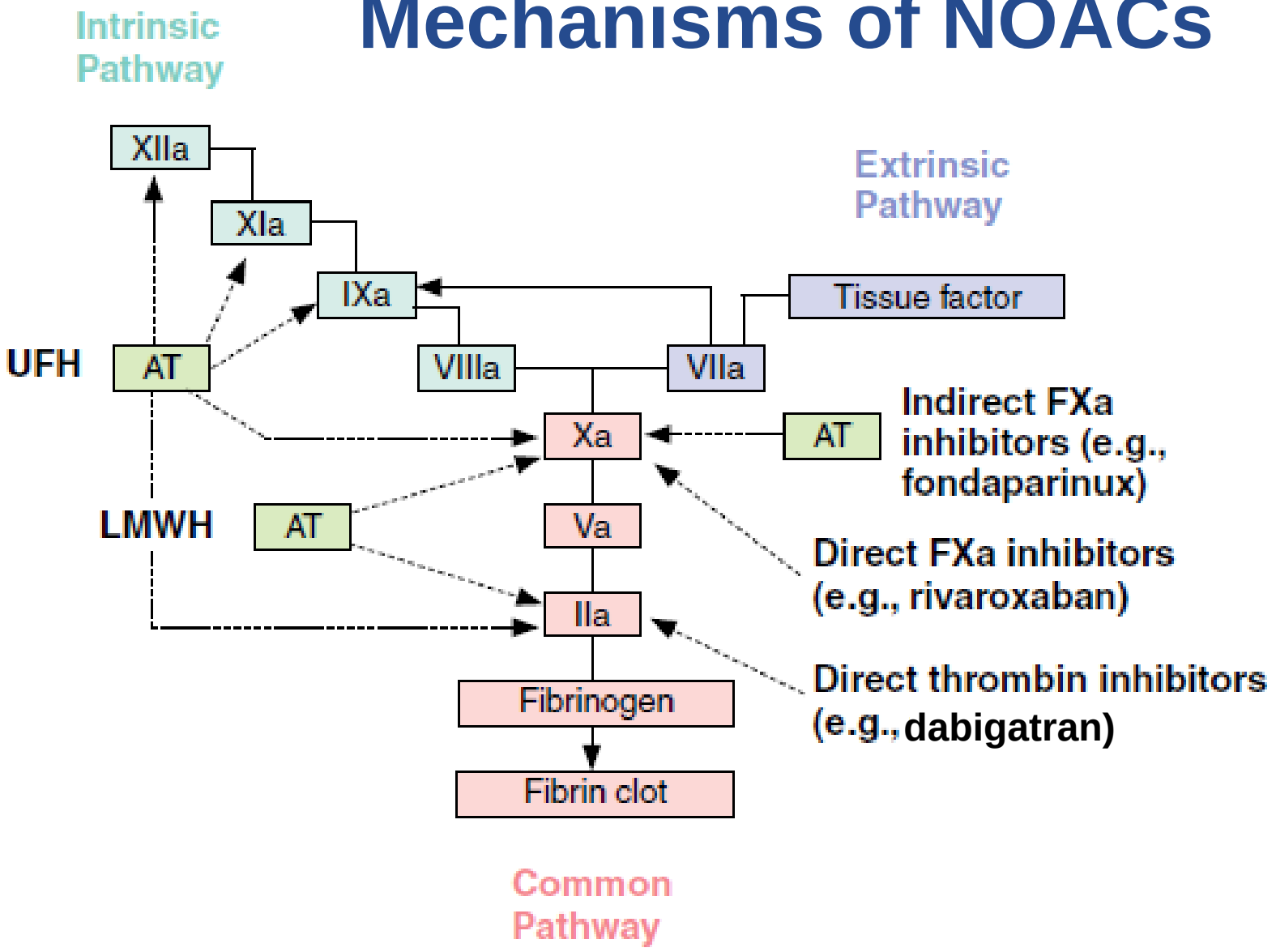
Hematoma Expansion is Prolonged in Warfarin-Related ICH

- 70 consecutive cases in a prospective cohort of ICH patients
- ICH expansion more frequent among warfarin users [7/13 (54%) vs. 9/57 (16%)]
- ICH expansion detected later in hospital course in patients on warfarin
  - Median 21.4 hours vs. 8.4 hours non-warfarin, p<0.001)
- Warfarin sole predictor of ICH expansion (OR 6.2) and predicted 3-month mortality (OR 4.6) when controlling for baseline ICH and IVH volume and GCS



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

Mechanisms of NOACs



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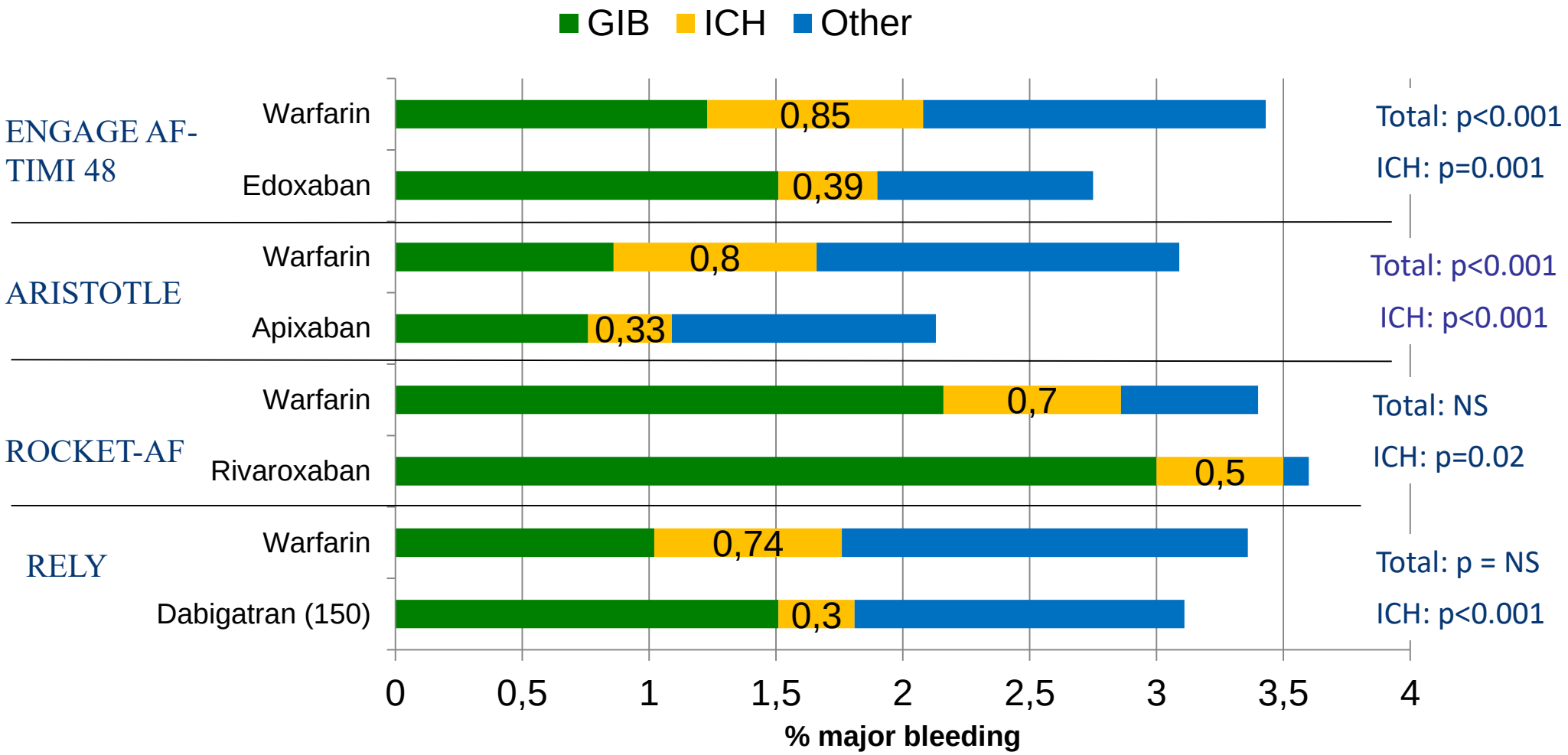
Properties of NOACs

	Dabigatran	Apixaban	Rivaroxaban	Edoxaban
Direct factor inhibition	IIa	Xa	Xa	Xa
Renal clearance	80%	25%	33%	40%
t½ in hours by CrCl (mL/min)				
CrCl > 80	14-17	8-15	5-9h	9-11
CrCl 50 – 79	16.6	14.6	8.7	NA
CrCl 30 – 49	18.7	17.6	9.0	NA
CrCl < 30	27.5	17.3	9.5	NA
Removal by RRT	Yes	Unlikely	Unlikely	Unlikely

Adapted from Kaatz S et al. *Am J Hematol*. 2012; 87(suppl 1):S141–5; Wittkowsky AK. *Pharmacotherapy*. 2011; 31:1175–91.

NOACs vs. warfarin and the risk of ICH



Connolly SJ et al. *N Engl J Med.* 2009; 361:1139-51. Patel MR et al. *N Engl J Med.* 2011; 365:883-91.
Granger CB et al. *N Engl J Med.* 2011; 365:981-92. Giugliano RP et al. N Engl J Med. 2013;369:2093-104.

Outcomes with NOAC-ICH

- Prospective, multicenter observational study in 38 stroke units across Germany
- 61 patients (non-traumatic NOAC-ICH)
  - 45 included in hematoma expansion analysis

Measure	Outcome
Baseline ICH volume, mean (SD)	23.7 mLs (31.3)
Patients with hematoma expansion	38%
New or increased IVH	18%
Mortality at 3 mos.	28%
Poor outcome (mRS 3-6)	65%
Received PCC4	57%
Time from last NOAC intake to Imaging (n=29)	14.3 hrs (IQR 6-22.8)

IQR = interquartile range

Purrucker JC, et al. *JAMA Neurol* 2016;73(2):169-177.

Outcomes with NOAC-ICH

- Comparison of NOAC-ICH vs VKA-ICH
- Multi-center international collaborative across 13 centers

Measure	NOAC-ICH (n=97)	VKA-ICH (n=403)	Comparison
Median baseline ICH volume (mL)	14.4 (IQR 3.6-38.4)	10.6 (IQR 4-27.9)	p = 0.78
All cause mortality	33%	31%	p = 0.64*
Hematoma expansion	40%	34%	p = 0.45
Functional outcome at discharge	OR = 0.47 (95% CI 0.18-1.119, p = 0.11)		

IQR = interquartile range
*adjusted Cox hazard ration 0.93 (95% CI 0.52-1.64)

Wilson D et al. *Neurology* 2017;88:1-8.

Time to Correction Matters (VKA-ICH)

- Retrospective cohort of 19 German tertiary care centers
- n=1176 (functional outcomes), n=853 assessable for hematoma enlargement (36%)

	No. of Patients	Patients With Hematoma Enlargement, No. (%)	OR (95% CI)
INR <1.3			
Achieved	432	116 (26.9)	0.37 (0.26-0.59)
Did not achieve	421	191 (45.4)	
INR <1.3 within 4 hours			
Achieved	217	43 (19.8)	0.27 (0.15-0.43)
Did not achieve	636	264 (41.5)	
INR <1.3 within 4 hours and systolic BP <160 mm Hg within 4 hours			
Achieved	193	35 (18.1)	0.17 (0.11-0.33)
Did not achieve	498	220 (44.2)	

Kuramatsu JB, et al. JAMA 2015;313(8):824-36.

Practical aspects

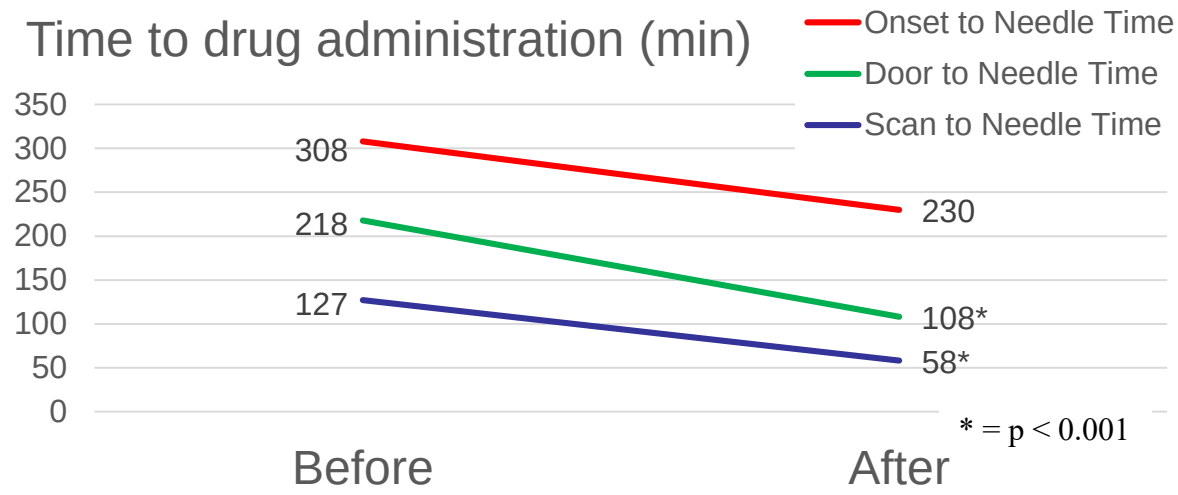
1. Hematoma growth a predictor of mortality and functional outcomes
2. Time to anticoagulant reversal matters

What are we doing in our own institutions to expedite reversal?

Reducing delays in therapy

Single center UK stroke center cohort. 42 patient with VKA-ICH

Before (n=19)		**After** (n= 23)
• Delays in obtaining INR	→	• Implemented POC INR testing
• Delays getting approval from hematology	→	• Stroke physicians authorized to approve/prescribe via protocol
• Logistic delays obtaining PCC from hematology	→	• Stored PCC in ED



Parry-Jones A. *BMJ Quality Improvement Reports* 2015; 4(1):1-4

Summary

- Oral anticoagulants worsen outcomes associated with ICH
- Timing to correction matters
- Newer therapies for reversal promise to more quickly reverse oral anticoagulant effects
- Practical aspects of implementation should not be overlooked