



**JOHNS HOPKINS**  
M E D I C I N E

# Incidence and Impact of Antithrombotic-related Intracerebral Hemorrhage

---

**John J. Lewin III, PharmD, MBA, BCCCP, FASHP, FCCM, FNCS**

Division Director, Critical Care & Surgery Pharmacy Services, The Johns Hopkins Hospital  
Associate Professor, Anesthesiology & Critical Care Medicine, Division of Neurosciences Critical Care;  
Johns Hopkins University School of Medicine  
Clinical Professor, University of Maryland School of Pharmacy

# Disclosures

---

- None

# Clinical Relevance

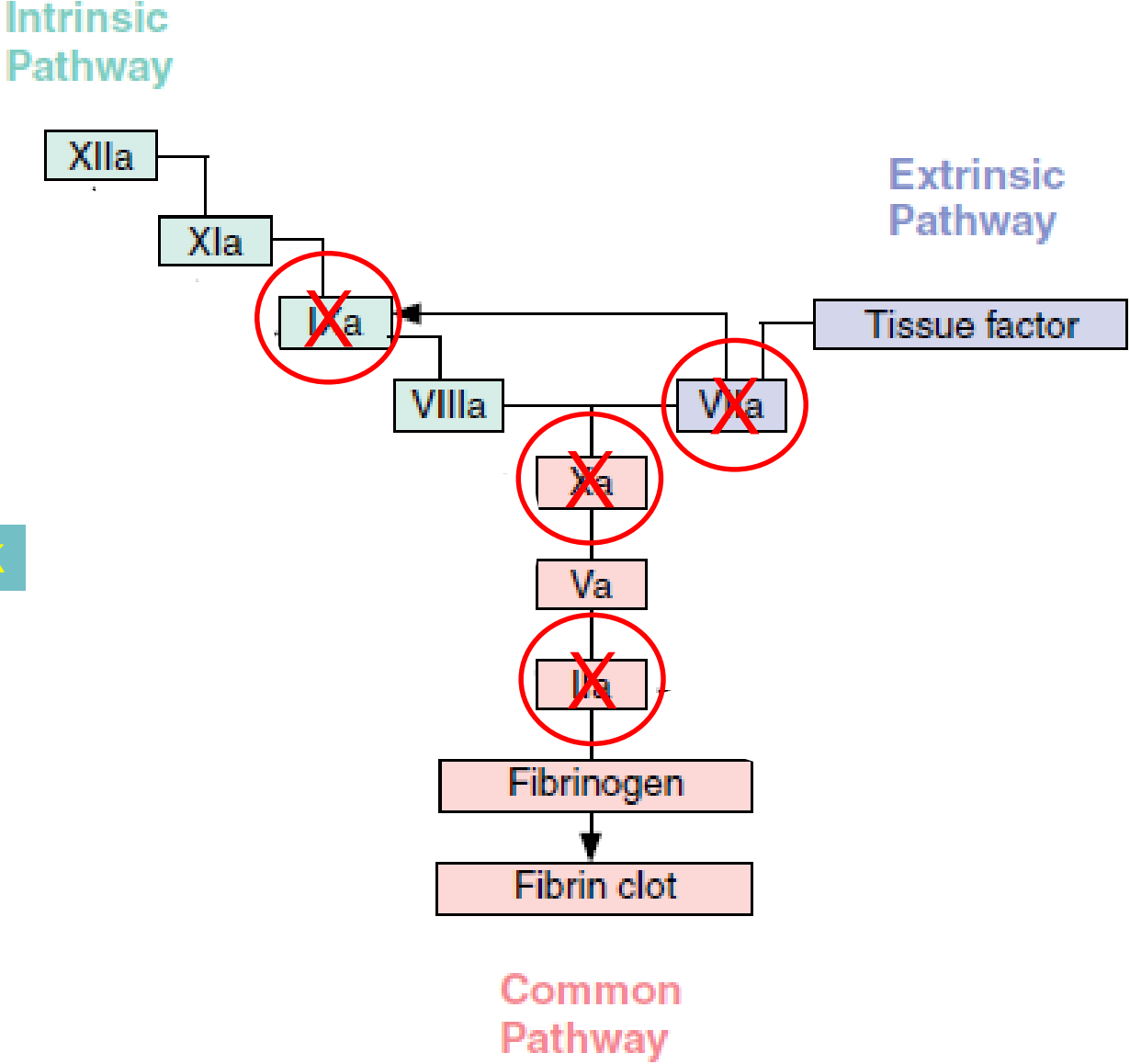
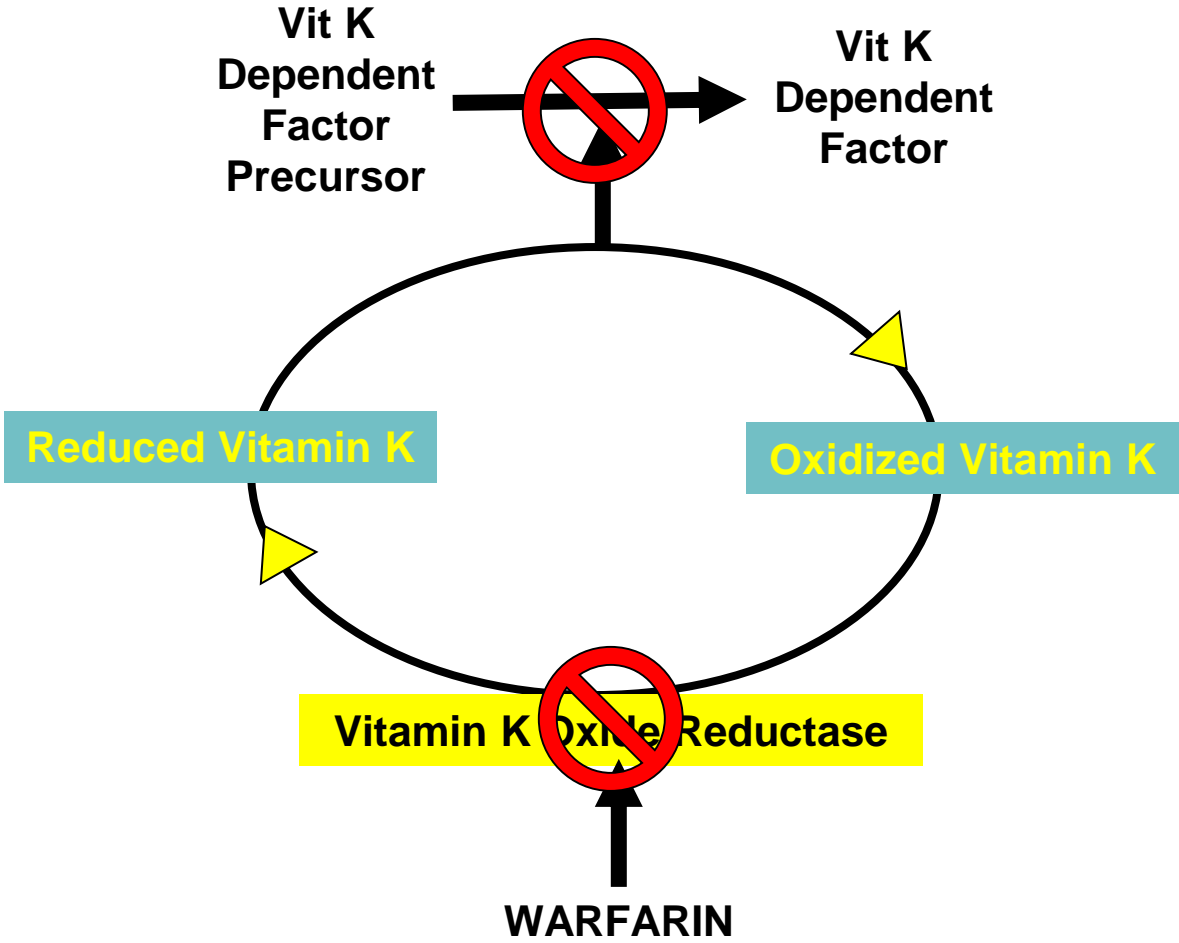
---

- 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

# WARFARIN MECHANISM OF ACTION



Adapted with permission from: Gulseth MP. Am J Health-Syst Pharm. 2008; 65:1520-9.

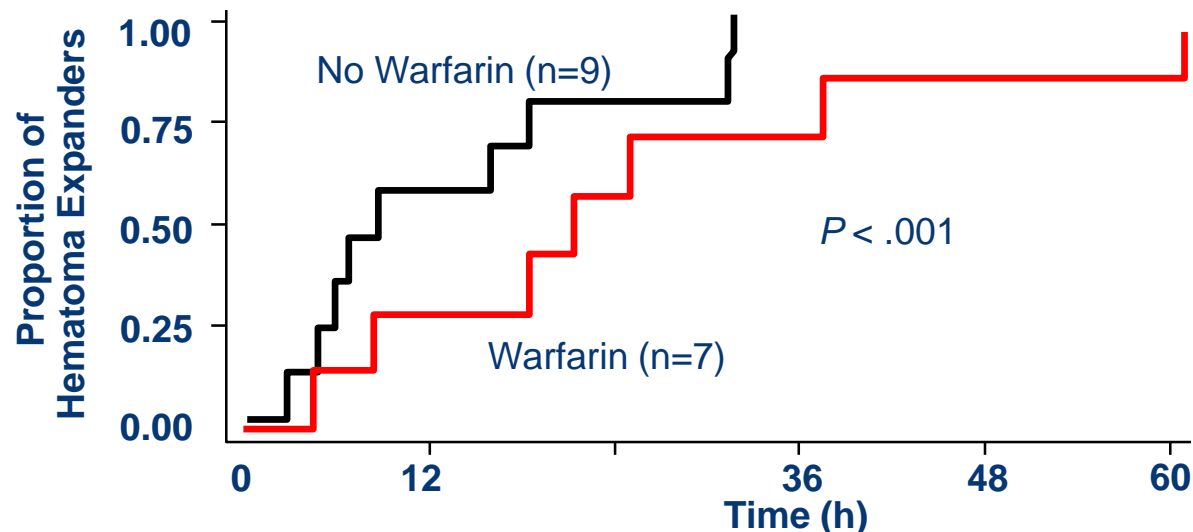
# Warfarin and ICH

---

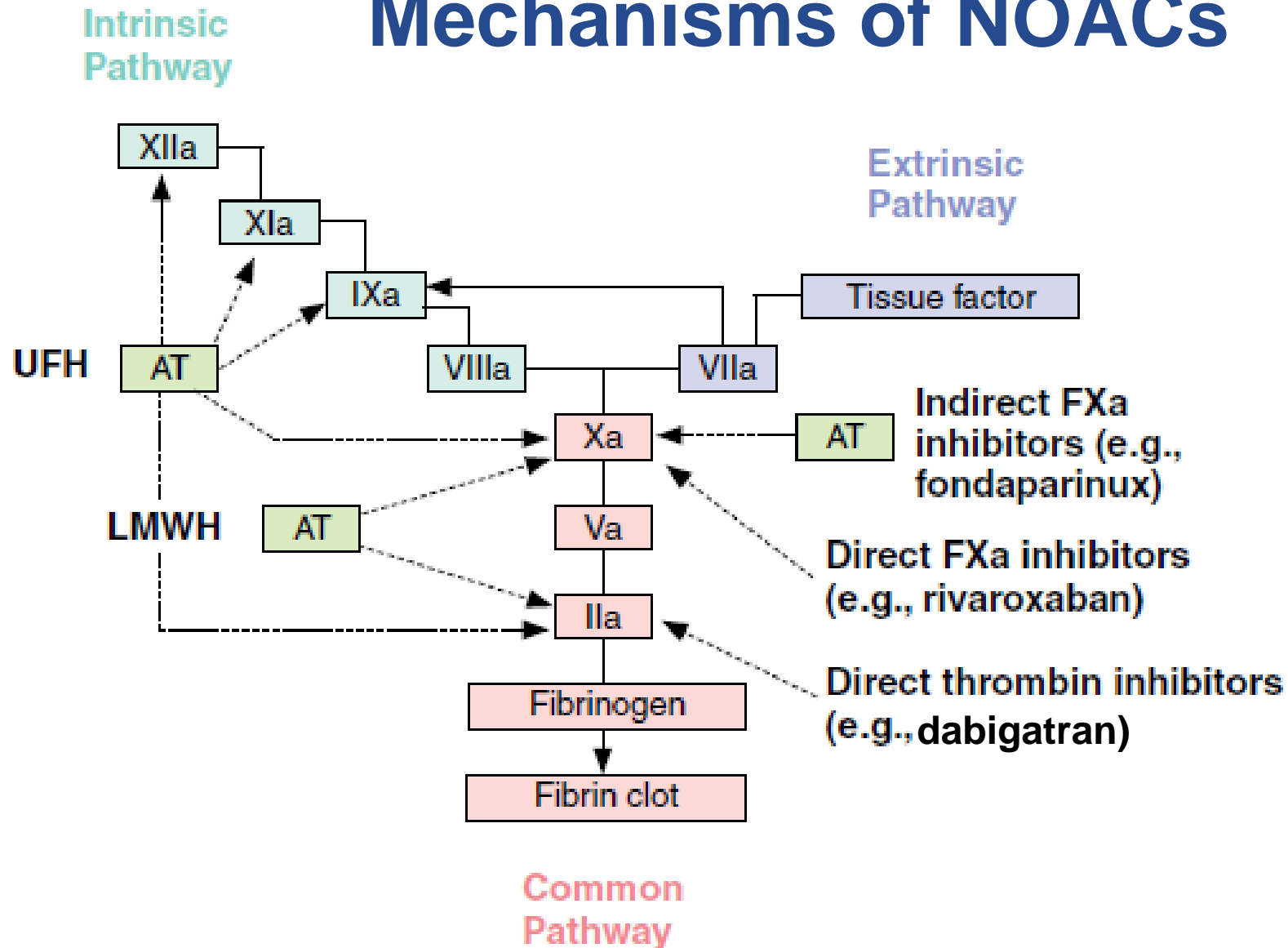
- Warfarin
  - More than doubles the risk of ICH
  - Associated with 12-14% of all ICH
  - Risk of ICH increases with increasing INR, although most occur within the therapeutic range
- 0.3-1.1%/year of patients on warfarin have ICH (baseline risk 0.15%/year)
- 90% of warfarin associated deaths due to 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

# 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



# Mechanisms of NOACs

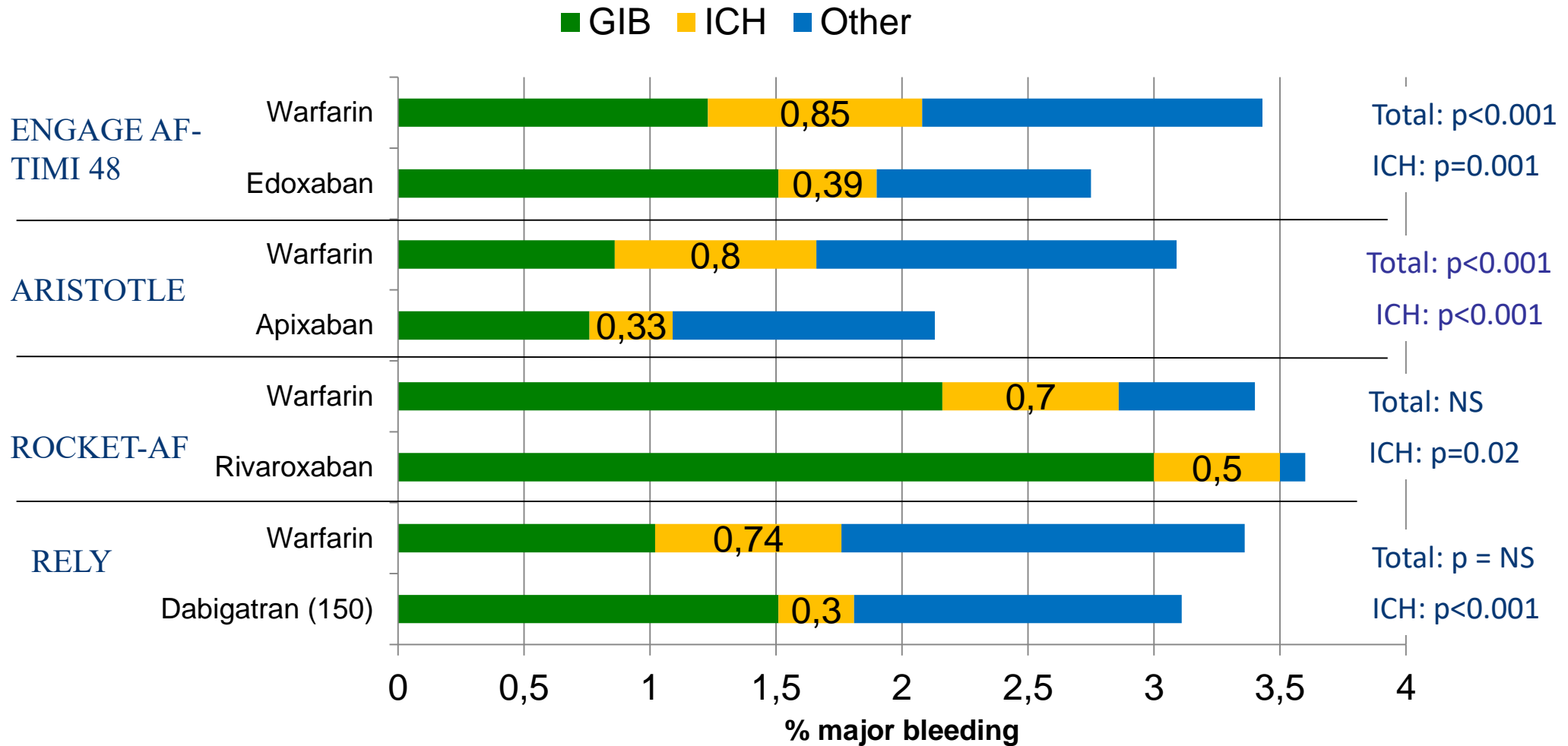




# Properties of NOACs

	Dabigatran	Apixaban	Rivaroxaban	Edoxaban
Direct factor inhibition	Ila	Xa	Xa	Xa
Renal clearance	80%	25%	33%	40%
$t_{1/2}$ 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

# 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

# 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)

# 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)
<b>INR &lt;1.3</b>			
Achieved	432	116 (26.9)	0.37 (0.26-0.59)
Did not achieve	421	191 (45.4)	
<b>INR &lt;1.3 within 4 hours</b>			
Achieved	217	43 (19.8)	0.27 (0.15-0.43)
Did not achieve	636	264 (41.5)	
<b>INR &lt;1.3 within 4 hours and systolic BP &lt;160 mm Hg within 4 hours</b>			
Achieved	193	35 (18.1)	0.17 (0.11-0.33)
Did not achieve	498	220 (44.2)	

# 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

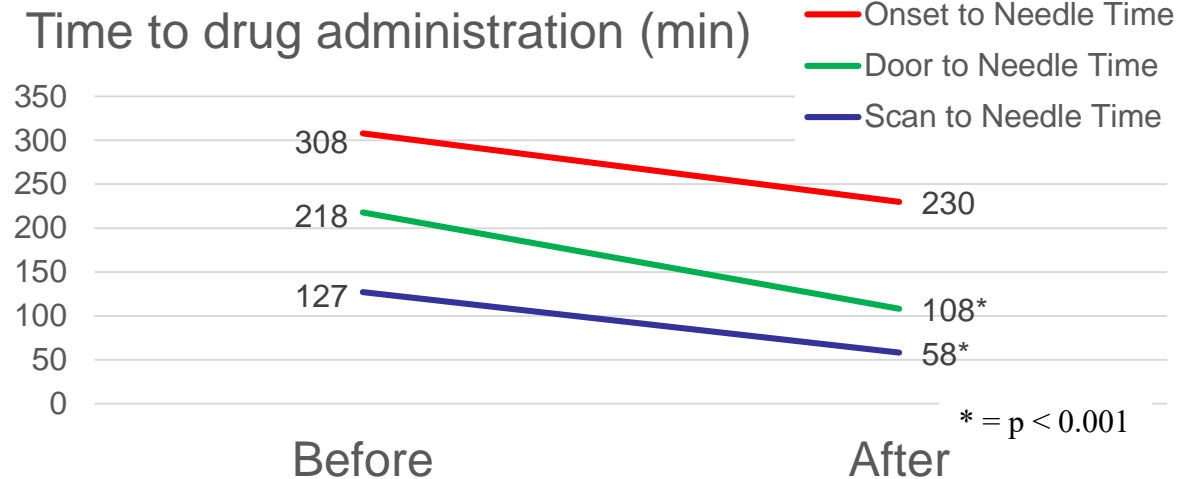
## Before (n=19)

- Delays in obtaining INR
- Delays getting approval from hematology
- Logistic delays obtaining PCC from hematology



## After (n= 23)

- Implemented POC INR testing
- Stroke physicians authorized to approve/prescribe via protocol
- Stored PCC in ED



# 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