A microscopic view of numerous red blood cells, appearing as reddish-brown, biconcave discs against a lighter background. The cells are densely packed, with some in sharp focus and others blurred in the foreground and background.

# Reversal of anticoagulation in patients with intracranial and subdural hemorrhage

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# Disclosures and Conflicts

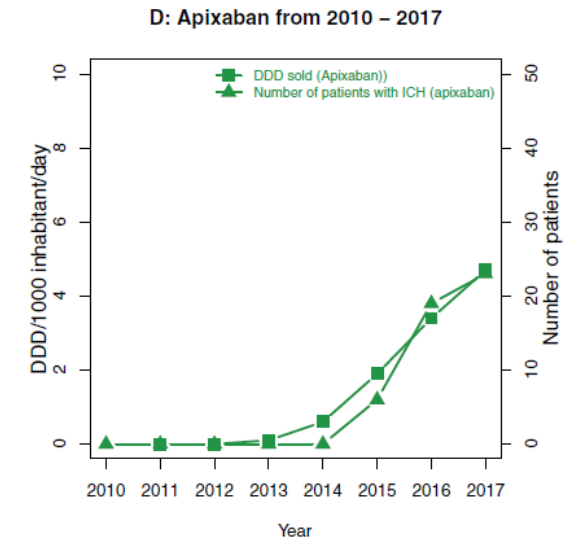
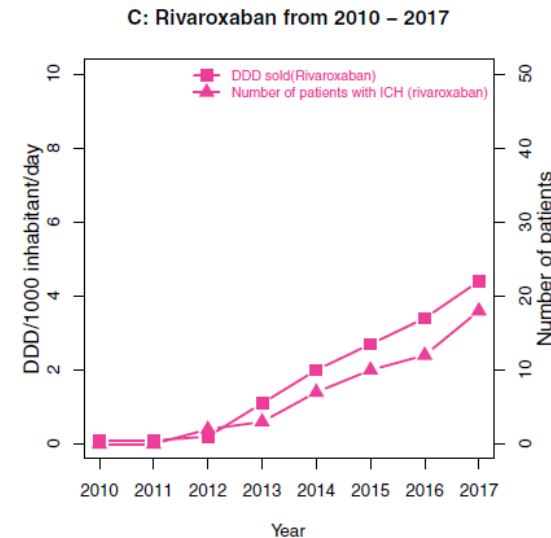
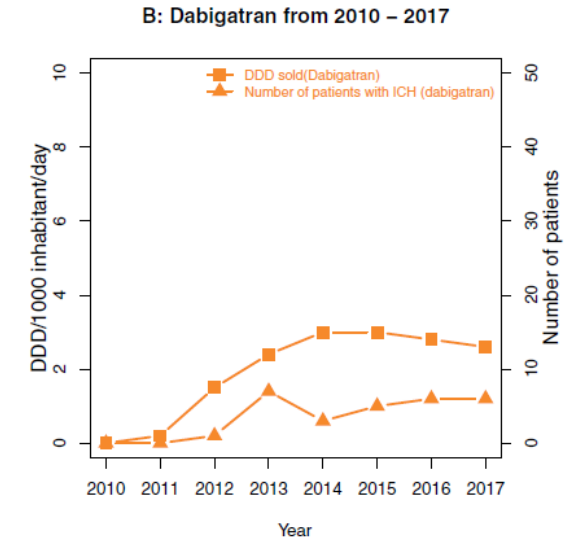
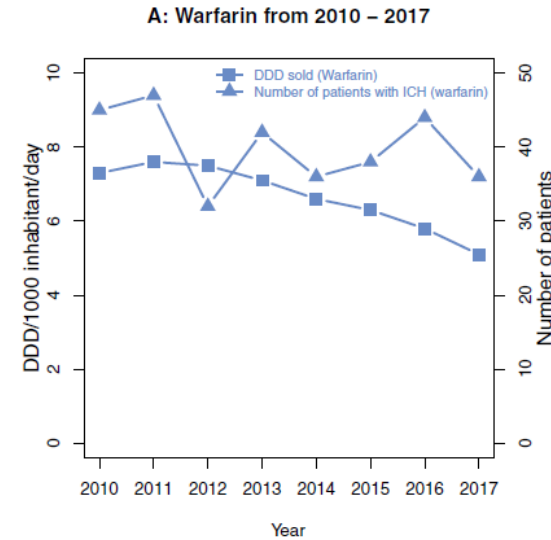
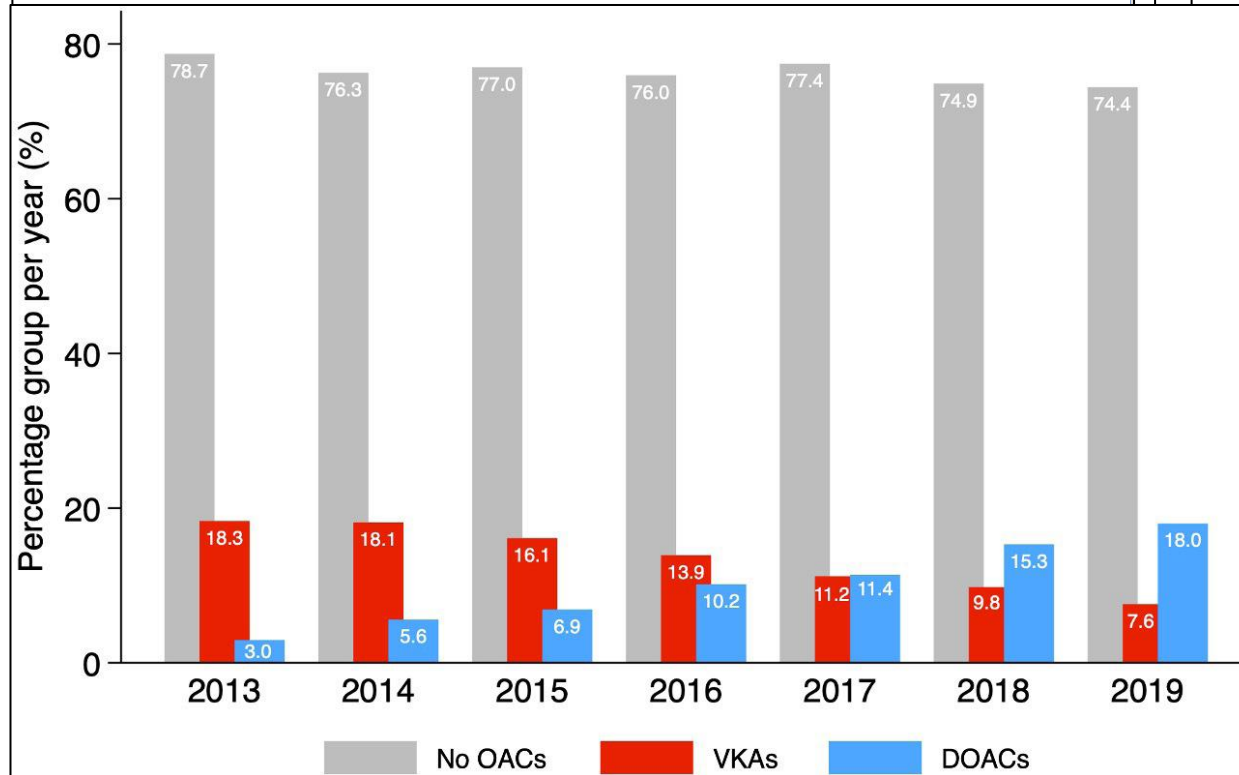
## Disclosures:

- NIH/NINDS: Grant support (current)
- Alzheimer's Association: Grant support (current)
- Consulting fees: Qmetis(current/ongoing relationship)

## Conflicts:

- None relevant to this presentation

# Anticoagulation-associated ICH: increasing trend



Lioutas et al JAMA Neurol. 2020;77(10):1252-1260

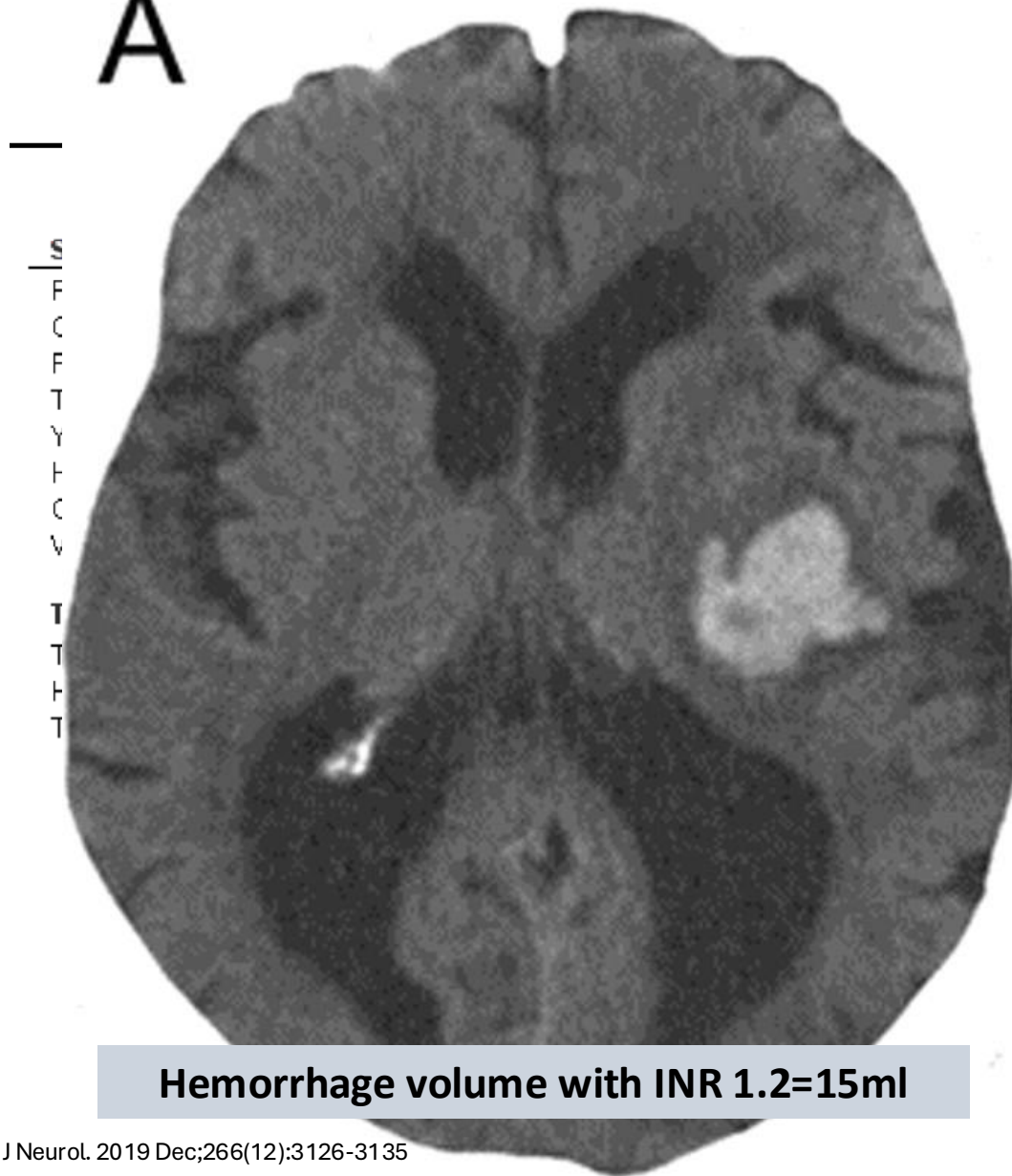
Drescher et al Neuroepidemiology. 2023 Aug 24. doi: 10.1159/000533751

Grundtvig Eur Stroke J. 2021 Jun;6(2):143-150

Siepen et al Stroke Vasc Neurol. 2024 Feb 8;svn-2023-002813

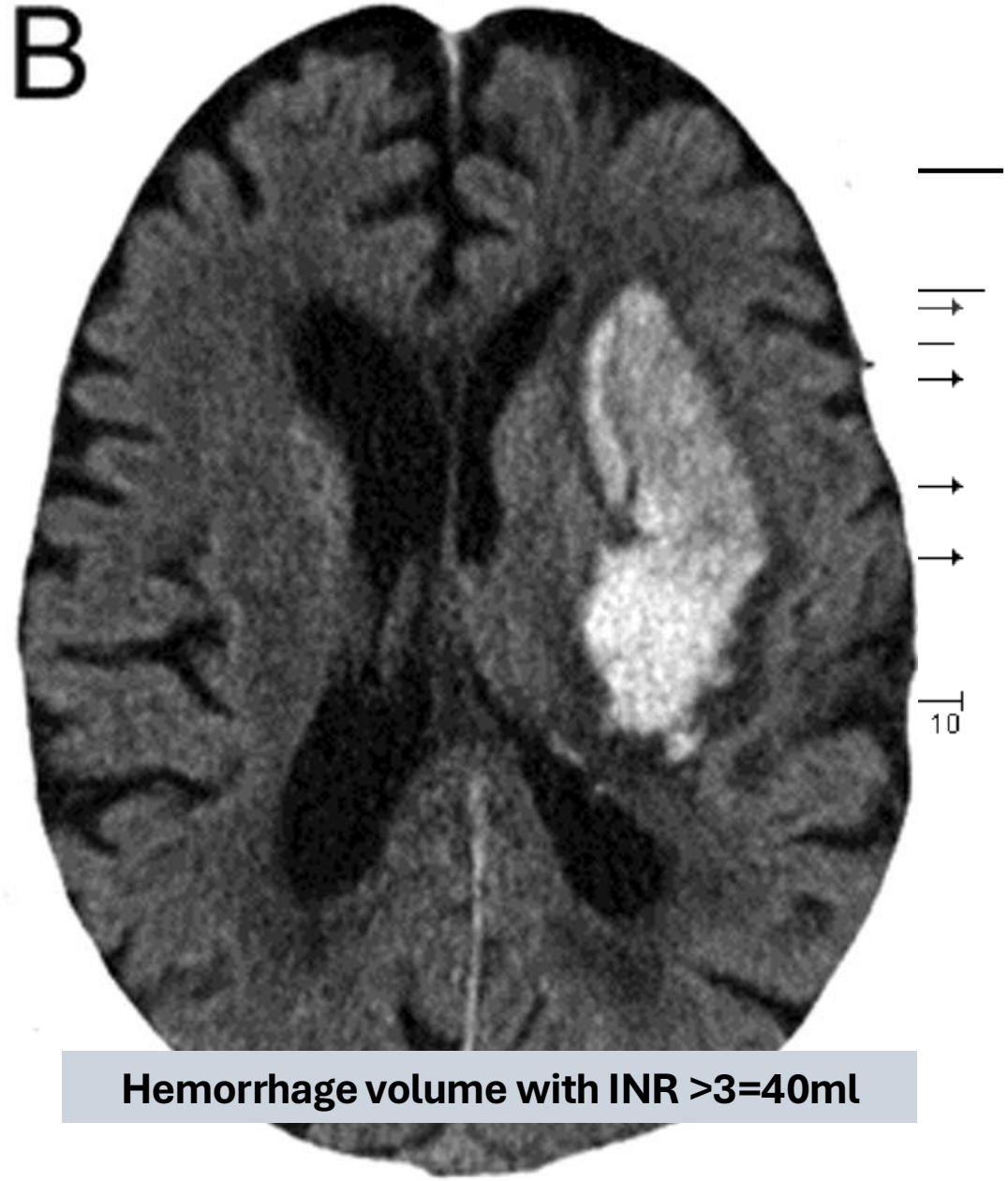
## Size and expansion

# A



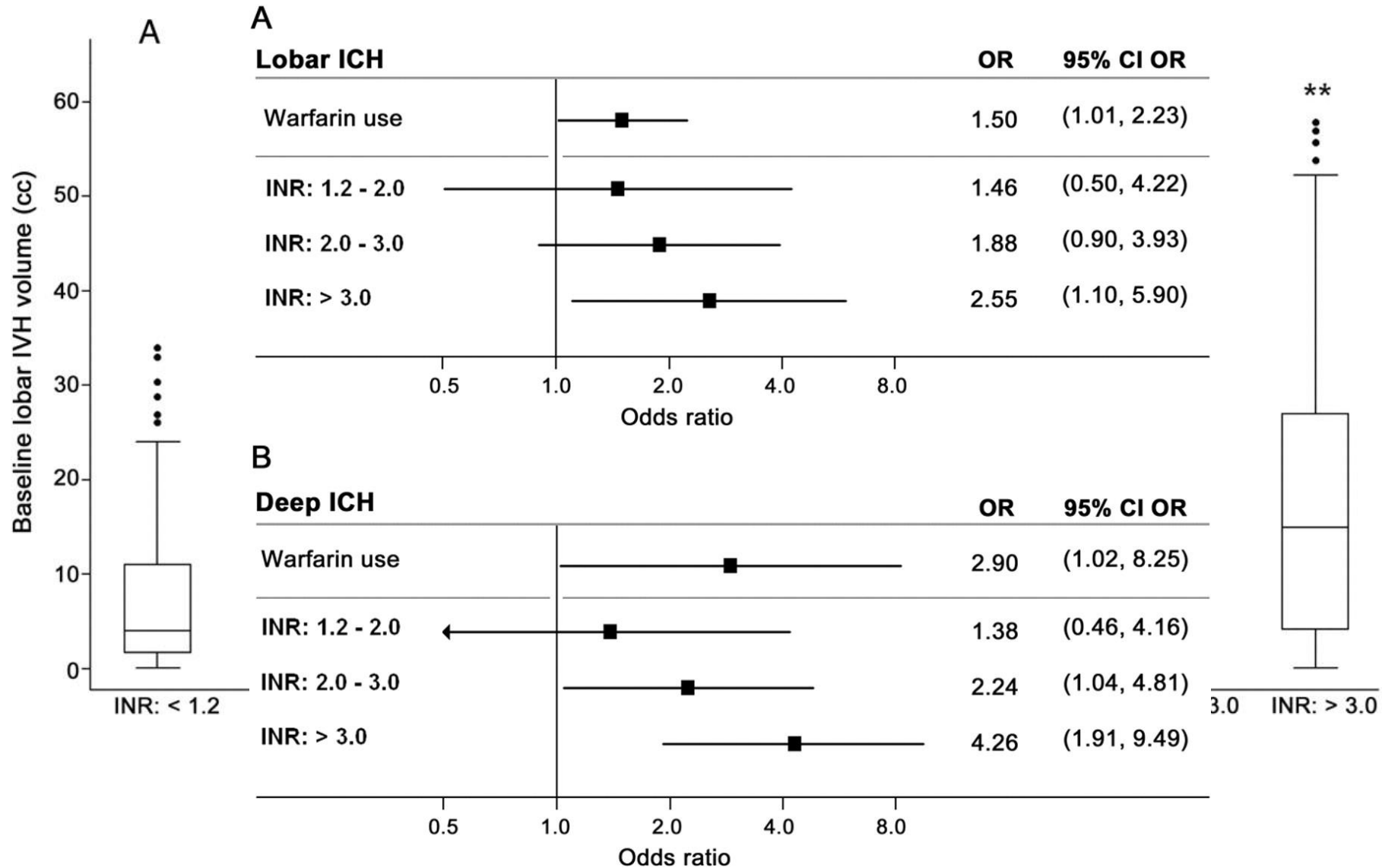
**Hemorrhage volume with INR 1.2=15ml**

# B



**Hemorrhage volume with INR >3=40ml**

# Intraventricular expansion





# Warfarin-associated ICH: outcome

## 3-month mortality

Characteristic	Mean/proportion	Univariate OR (95% CI)	Adjusted OR (95% CI)
Age (per year)	75.7 ± 10.8 y	1.04 (1.01–1.07)	1.03 (0.99–1.07)
Warfarin, %	23	2.91 (1.44–5.90)	2.57 (1.06–6.26)
Antiplatelet agent, %	37	1.46 (0.78–2.73)	
Coronary disease, %	22	1.71 (0.84–3.48)	
Diabetes, %	18	0.77 (0.34–1.72)	
ICH volume per 10 mL	35.4 ± 40.2 mL	1.34 (1.20–1.49)	1.27 (1.11–1.45)
IVH volume per 10 mL	18.6 ± 22.5 mL	2.07 (1.46–2.92)	1.64 (1.17–2.30)
GCS < 9, %	80	8.92 (3.80–20.89)	3.53 (1.20–10.37)
Pulse pressure, mm Hg	85 ± 28	1.00 (0.98–1.01)	
Glucose per 10 mg/dL	149 ± 60 mg/dL	1.08 (0.97–1.21)	
Platelets	231 ± 88 10 <sup>3</sup> /mm <sup>3</sup>	1.00 (0.99–1.01)	
APOE e4, %	29	0.87 (0.36–2.09)	
APOE e2, %	11	5.87 (1.67–20.59)	3.96 (0.70–22.41) <sup>†</sup>
		West	1.01 (0.94–1.08)
		Private insurance	0.890 (0.834–0.949)
		Female sex	0.994 (0.948–1.04)
		History of congestive heart failure	0.972 (0.899–1.05)

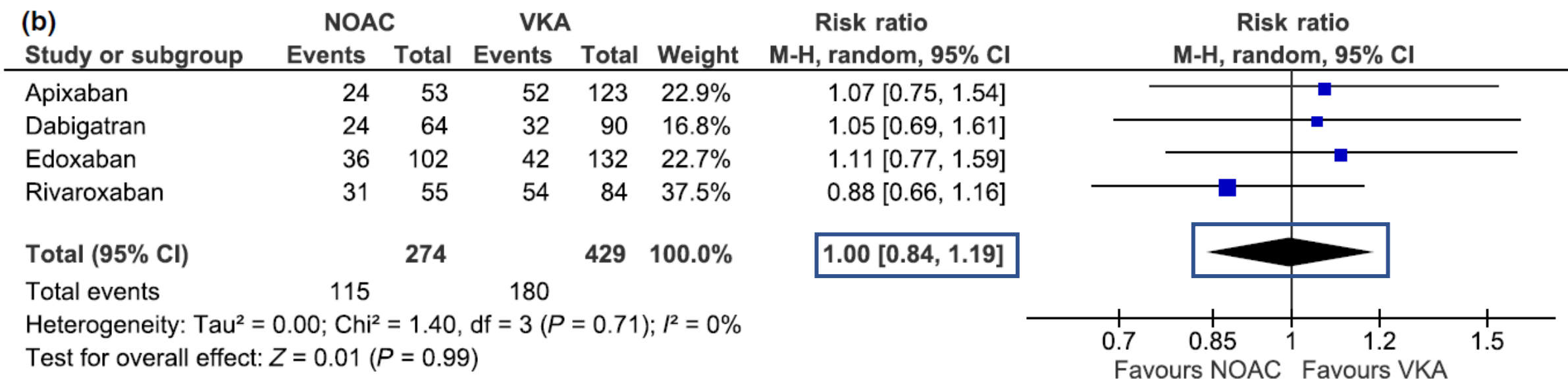
.845

<.001

.814

.465

# NOAC-associated ICH vs Warfarin: outcomes in RCTs



# Warfarin vs NOAC ICH Hospital Mortality

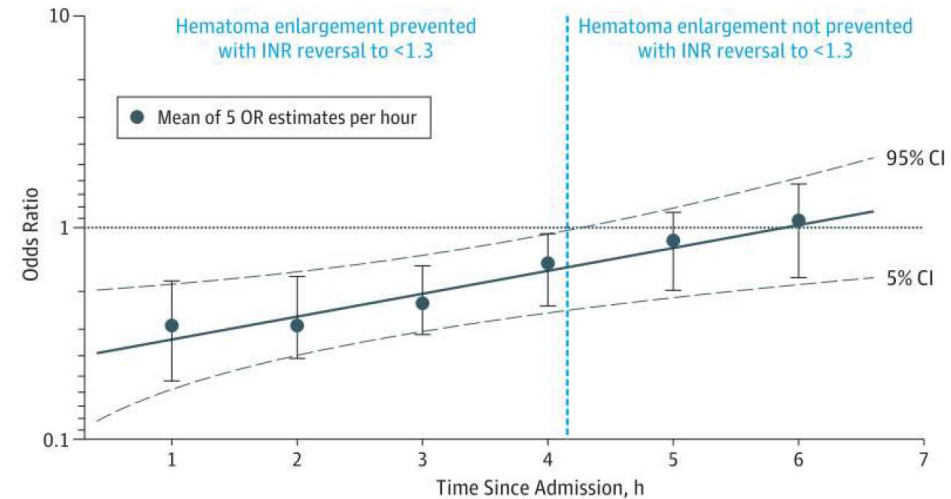
Outcome Measures	Warfarin	NOACs	No OACs
<b>Primary Outcome: In-Hospital Death</b>			
No./total No. (%)	4903/15 036 (32.6)	1305/4918 (26.5)	27 297/121 357 (22.5)
Adjusted RD (97.5% CI), % <sup>a</sup>	[Reference]	-5.7 (-7.3 to -4.2)	-9.0 (-10.1 to -7.9)
Adjusted OR (97.5% CI) <sup>a</sup>	[Reference]	0.75 (0.69 to 0.81)	0.62 (0.58 to 0.65)
Adjusted RD (97.5% CI), % <sup>a</sup>	9.0 (7.9 to 10.1)	3.3 (1.7 to 4.8)	[Reference]
<b>Discharge Home</b>			
No./total No. (%)	2523/15 036 (16.8)	978/4918 (19.9)	32 482/121 357 (26.8)
Adjusted RD (95% CI), % <sup>a</sup>	[Reference]	3.3 (2.0 to 4.5)	3.0 (2.2 to 3.8)
Adjusted OR (95% CI) <sup>a</sup>	[Reference]	1.28 (1.17 to 1.40)	1.24 (1.16 to 1.31)
Adjusted RD (95% CI), % <sup>a</sup>	-3.0 (-3.8 to -2.2)	0.3 (-0.9 to 1.5)	[Reference]
Adjusted OR (95% CI) <sup>a</sup>	0.81 (0.76 to 0.86)	1.04 (0.95 to 1.12)	[Reference]
<b>Modified Rankin Scale Score 0-1<sup>c</sup></b>			
No./total No. (%)	683/9162 (7.5)	270/2939 (9.2)	8813/67 496 (13.1)
Adjusted RD (95% CI), % <sup>a</sup>	[Reference]	1.6 (0.4 to 2.8)	2.0 (1.3 to 2.8)
Adjusted OR (95% CI) <sup>a</sup>	[Reference]	1.27 (1.07 to 1.50)	1.30 (1.16 to 1.46)
Adjusted RD (95% CI), % <sup>a</sup>	-2.0 (-2.8 to -1.3)	-0.4 (-1.6 to 0.7)	[Reference]
Adjusted OR (95% CI) <sup>a</sup>	0.77 (0.69 to 0.86)	0.97 (0.84 to 1.13)	[Reference]

- **2013-2016 GTWG**
- **141,000 ICH hospitalizations**
- **10.6% warfarin (23% INR>3) and 3.5% NOAC-related ICH**

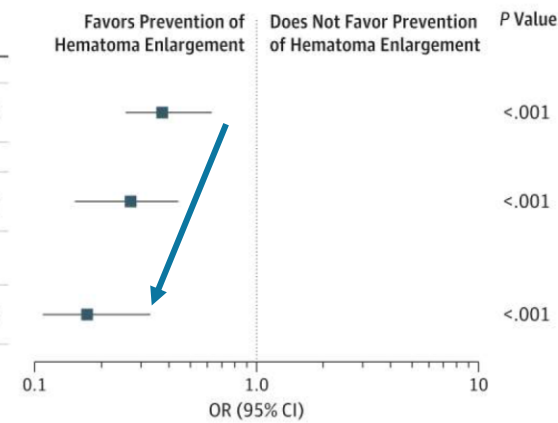


# Vitamin K antagonist: timing and INR goal

Patients With Follow-up Imaging (n = 853) Serial monitoring of coagulation parameters, median (IQR)	With Hematoma Enlargement (n = 307)	Without Hematoma Enlargement (n = 546)	P Value
INR after reversal <sup>i</sup>	1.38 (1.20-1.71)	1.27 (1.16-1.44)	<.001
PTT after reversal, s <sup>i</sup>	34 (31-39)	33 (30-38)	.32
INR at 24 h	1.30 (1.20-1.44)	1.23 (1.13-1.48)	<.001
INR at 48 h	1.23 (1.14-1.38)	1.20 (1.10-1.31)	.002 <sup>b</sup>
INR at 72 h	1.23 (1.13-1.40)	1.19 (1.10-1.30)	.001 <sup>b</sup>



	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)	



FFP	PCCs	rFVIIa
Contains factors II, V, VII, X, and IX	Contains factors II, IX, X, ± VII	Does not replenish most vitamin-K dependent factors
Slow effect (7 to 30 hours) to reverse INR	Rapidly normalizes INR (~ 20 minutes)	Rapidly reverses INR, but may not restore thrombin generation & clotting “pseudo-normalization of INR”
Long processing time	Rapid constitution - Price	Rapid - Price
Require high volumes (6 to 10 units; ~ 2 liters)	High concentration of coagulation factors in small volumes (20-40 ml)	Small volumes
Allergic & infectious transfusion reactions	Risk of thromboembolic complications	Risk of thromboembolic complications

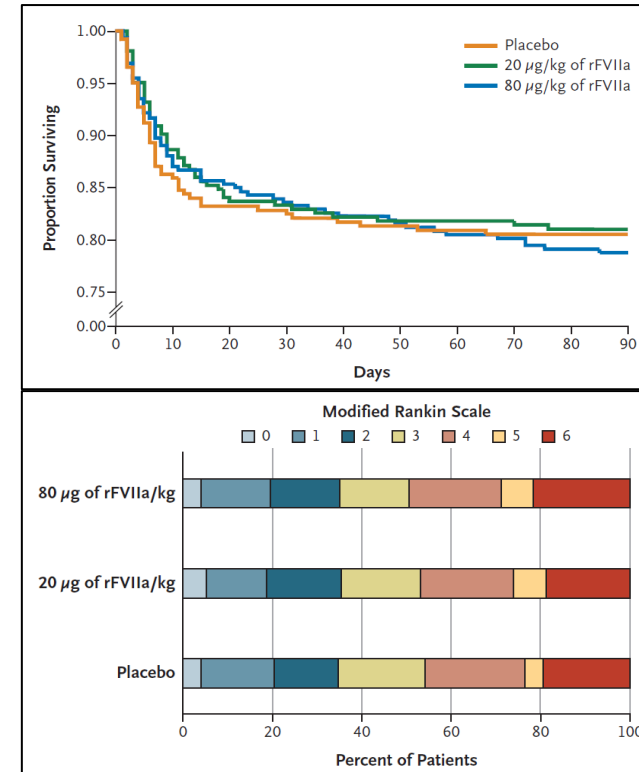
# PCC vs FFP in ICH

	Fresh frozen plasma (n=23)	Prothrombin complex concentrate (n=27)	Treatment effect (95% CI)	p value
<b>Primary outcome</b>				
INR $\leq 1.2$ within 3 h	2 (9%)	18 (67%)	OR 30.6 (4.7 to 197.9)*	0.0003
<b>Secondary clinical outcomes</b>				
Deaths at day 90	8 (35%)	5 (19%)	No proportional hazard assumed	0.14†
Functional independence (mRS score 0–3)				
At day 15 or discharge	7 (30%)	7 (26%)	OR 2.3 (0.5 to 13.1)*	0.31
At day 90	9 (39%)	10 (37%)	OR 1.7 (0.4 to 6.8)*	0.47
NIHSS score at day 15 or discharge	10.9	12.2	–1.9 (–8.3 to 4.4)‡	0.53
Barthel index at day 90	52.5 (40.3)	70.0 (37.7)	–16.0 (–44.9 to 12.8)‡	0.27
Quality of life at day 90§	8.21	9.25	–0.7 (–5.6 to 4.2)‡	0.78
Extended Glasgow Outcome Scale at day 90	4.60	4.18	0.39 (–0.84 to 1.63)‡	0.52
Time until INR $\leq 1.2$ normalisation of INR (min)	1482 (1335–1610)	40 (30–1610)	No proportional hazard assumed	0.050†
<b>Imaging data at 3 h¶</b>				
Haematoma expansion (mL)	23.7 (28.4)	9.7 (20.9)	16.9 (2.5 to 31.3)‡	0.023
$\geq 15\%$ growth	16/22 (73%)**	15/26 (58%)**	OR 2.0 (0.6 to 7.3)*	0.29
$\geq 33\%$ growth	13/22 (59%)**	12 (44%)**	OR 3.8 (1.1 to 16.0)*	0.048
<b>Imaging data at 24 h</b>				
Haematoma expansion (mL)	22.1 (27.1)	8.3 (18.3)	16.4 (2.9 to 29.9)‡	0.018
$\geq 15\%$ growth or death	14/20 (70%)††	12/27 (44%)	OR 3.9 (1.0 to 17.6)*	0.044
$\geq 33\%$ growth or death	12/20 (60%) ††	8/27 (30%)	OR 4.8 (1.3 to 20.4)*	0.024

# rFVIIa

## FAST trial: rFVIIa

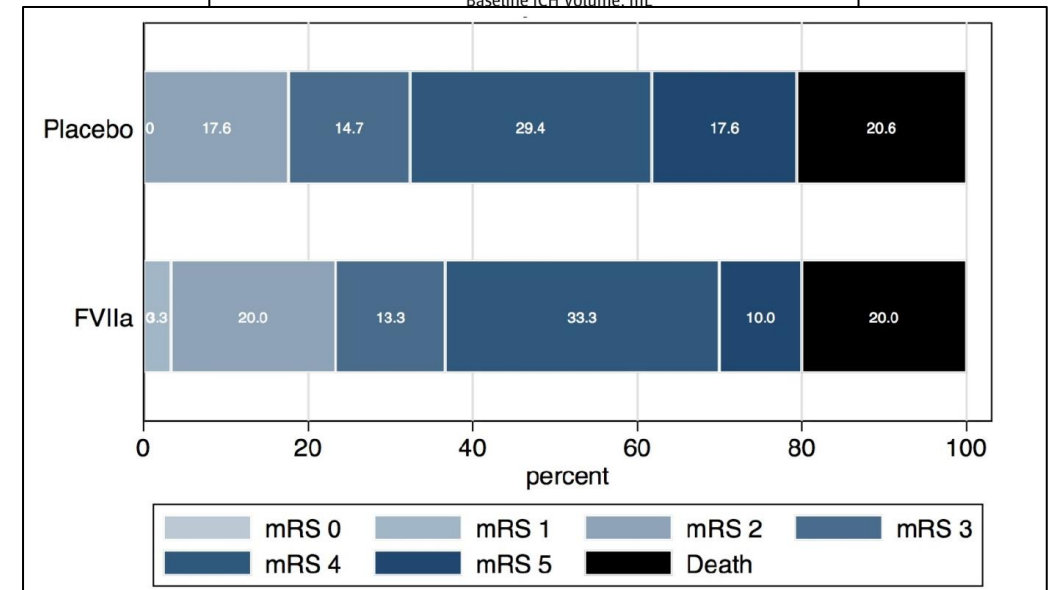
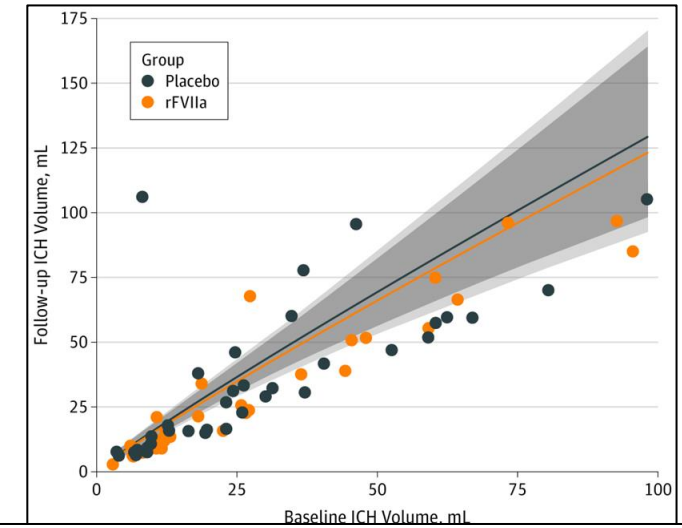
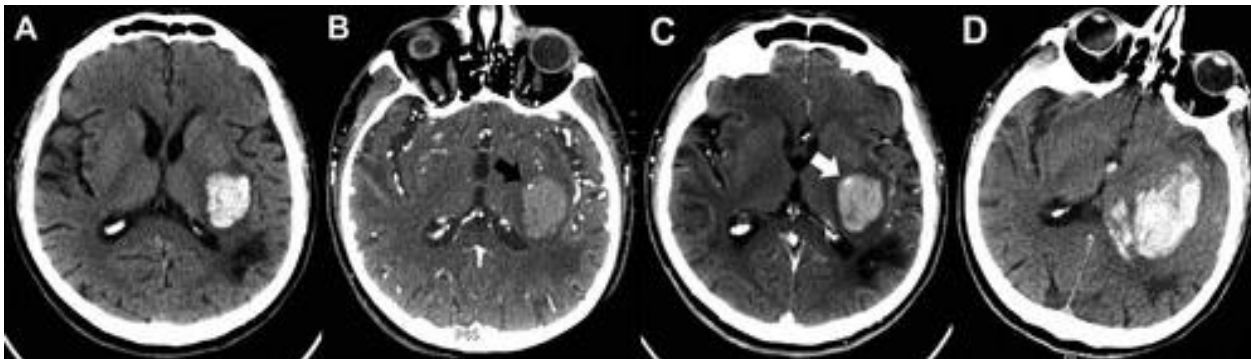
- RCT of 841 patients with supratentorial ICH randomized 1:1:1 to 20µg/kg vs 80µg/kg vs placebo
- Administer within 4 hours
- Significant reduction in ICH growth in the group 80µg/kg vs placebo (11% vs 26%,  $p < 0.0001$ )
- 3.7 (1.7-5.7) vs 7.5 (5.4-9.6) ml,  $p = 0.009$
- No survival or functional benefit



# Hemostatic agents using imaging markers (spot sign)

## SPOTLIGHT/STOP-IT trials

- RCT of 70 patients with supratentorial ICH randomized 1:1 to 80µg/kg rFVIIa vs placebo in patients with CT Angiography confirmed spot sign
- Administer within 4 hours
- No difference in hematoma expansion or functional outcome
- Similar negative trial with Tranexamic acid



# Hematoma growth arrest: Ultra-early administration of hemostatic agents

	Placebo group (n=298)	Intervention group (n=328)
Age, years	60 (12)	61 (12)
Age group, years		
≤70	232 (78%)	241 (73%)
>70	66 (22%)	87 (27%)

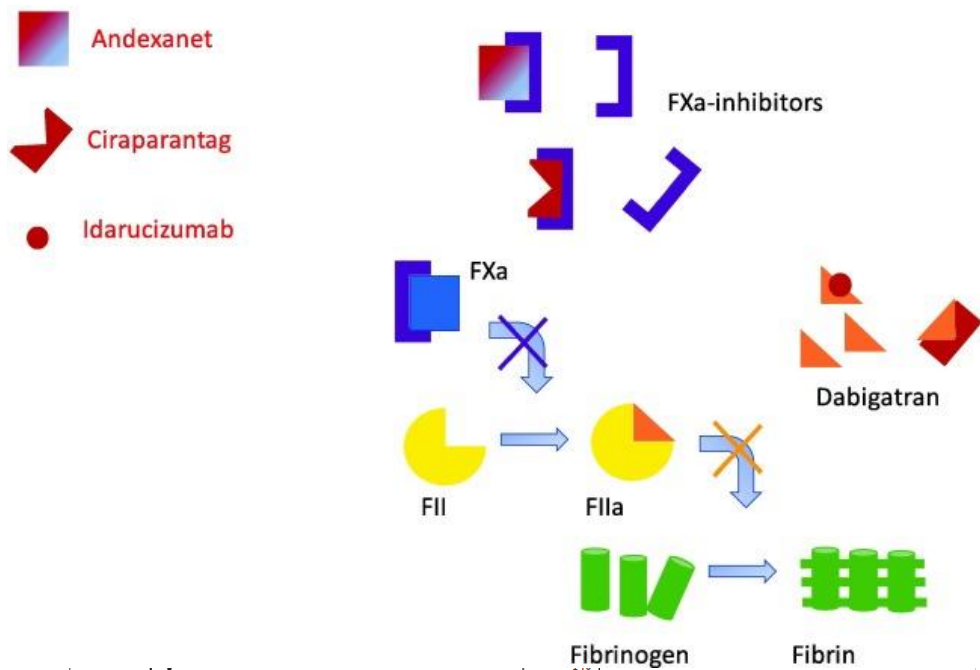
	Placebo group (n=298)	Intervention group (n=328)
(Continued from previous column)		
Location of ICH		
Lobar	41 (14%)	35 (11%)
Deep	254 (85%)	287 (88%)
Infratentorial	3 (1%)	6 (2%)

	Placebo group	Intervention group	OR (95% CI)*	Two-sided p value
Primary outcome				
mRS at 180 days in the intention-to-treat population				
0-2	134/298 (45%)	151/328 (46%)	1.09 (0.79 to 1.51)	0.61
3	76/298 (26%)	80/328 (24%)	..	..
4-6	88/298 (30%)	97/328 (30%)	..	..
mRS at 180 days in the per-protocol population				
0-2	129/286 (45%)	146/308 (47%)	1.12 (0.80 to 1.56)	0.87
3	75/286 (26%)	79/308 (26%)	..	..
4-6	82/286 (29%)	83/308 (27%)	..	..

	Placebo group (n=298)	Intervention group (n=328)	Relative risk (95% CI)
Life-threatening thromboembolic complications within 4 days*	4 (1%)	15 (<5%)	3.41 (1.14-10.15)
Life-threatening thromboembolic complications within 90 days*†	11 (4%)	21 (6%)	1.73 (0.85-3.54)
Unstable angina	0	0	..
Deep venous thrombosis (not leading to pulmonary embolism)	4 (1%)	7 (2%)	1.59 (0.47-5.38)
Mortality within 180 days	22 (7%)	20 (6%)	0.83 (0.46-1.48)
mRS 5-6 at 180 days	31 (10%)	37 (11%)	1.08 (0.69-1.70)
Myocardial injury without acute coronary syndrome	30 (10%)	49 (15%)	1.48 (0.97-2.27)
Acute myocardial infarction‡	4 (1%)	3 (1%)	0.68 (0.15-3.02)
Acute cerebral infarction‡	11 (4%)	18 (5%)	1.49 (0.71-3.10)



# Thrombin inhibitors (Dabigatran)- ICH reversal

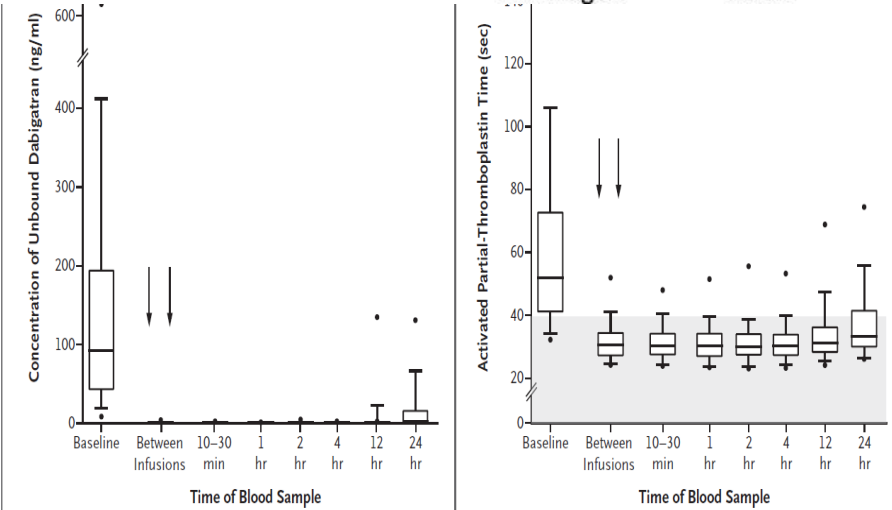


**REVERSE AD trial (single arm)**

- Idarucizumab (Monoclonal antibody)-removes circulating dabigatran from blood
- 503 patients-98 with intracranial hemorrhage (53 ICH, 39 subdural, 26 SAH)-repeat CT not mandatory
- ICH part of Group A→ Primary endpoint: laboratory (Thrombin Time, Ecarin Time)
- 90-day mortality: 16% (no control group)

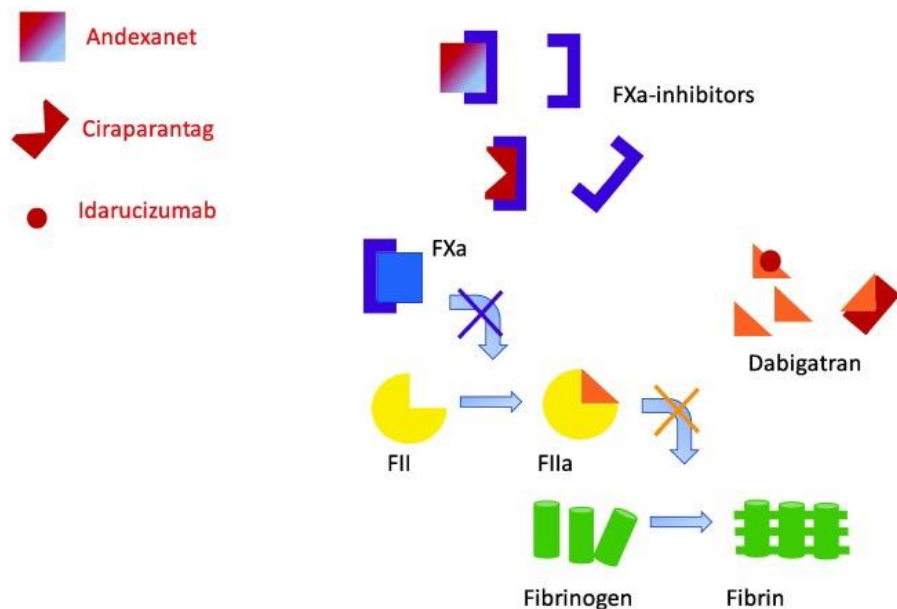
## ICH mortality in the RELY trial (no reversal agent)

	Warfarin, % (n/n)	Dabigatran 150 mg, % (n/n)	Dabigatran 110 mg, % (n/n)
All intracranial	36% (32/90)	35% (13/37)	41% (11/27)
Intracerebral	41% (19/46)	64% (7/11)	64% (9/14)
Spontaneous†	45% (19/42)	64% (7/11)	70% (7/10)
Traumatic	0% (0/4)	0% (0/0)	50% (2/4)



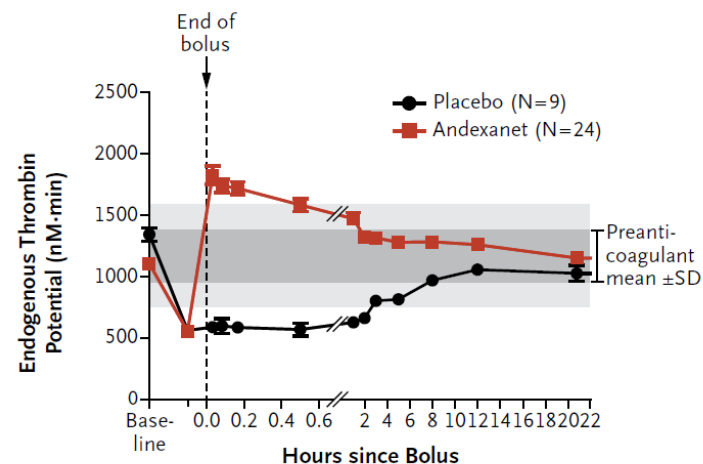
Pollack et al N Engl J Med. 2017 Aug 3;377(5):431-4414  
Hart et al Stroke. 2012;43:1511-1517  
Drug Discov Today. 2022 Oct;27(10):103332

# Factor Xa inhibitors: Andexanet

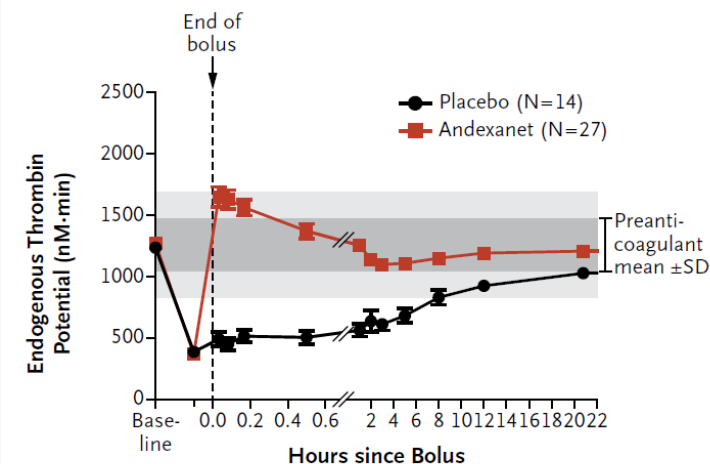


## Thrombin generation

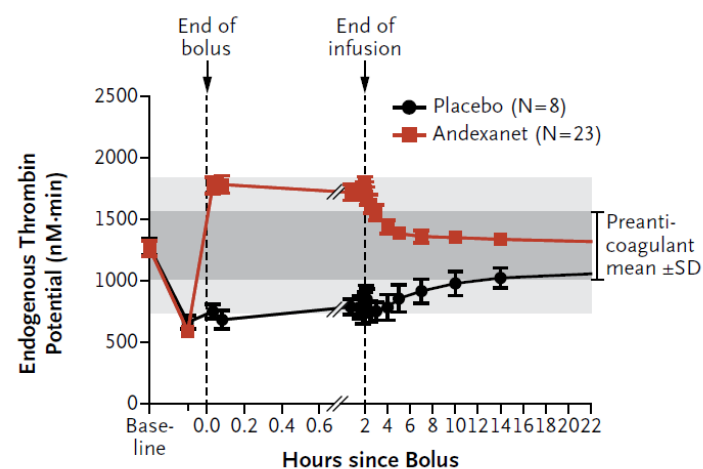
**A** Apixaban Study, Andexanet Bolus



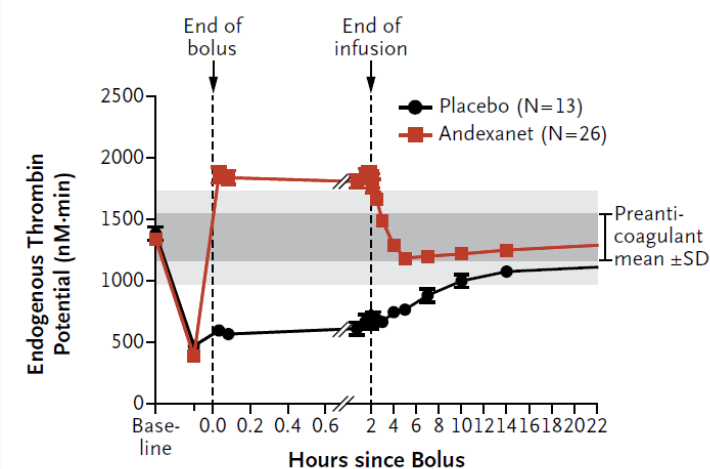
**B** Rivaroxaban Study, Andexanet Bolus



**C** Apixaban Study, Andexanet Bolus plus Infusion



**D** Rivaroxaban Study, Andexanet Bolus plus Infusion



# Factor Xa inhibitors: Andexanet

**Table 3.** Thrombotic Events and Deaths at 30 Days.\*

Event	Andexanet (N = 263)	Usual Care (N = 267)	Increase per 100 Patients (95% CI)†	P Value‡
	<i>no. of patients (%)</i>		<i>percentage points</i>	
≥1 Thrombotic event	27 (10.3)	15 (5.6)	4.6 (0.1 to 9.2)	0.048
Transient ischemic attack	0	0	—	
Ischemic stroke	17 (6.5)	4 (1.5)	5.0 (1.5 to 8.8)	
Myocardial infarction	11 (4.2)	4 (1.5)	2.7 (−0.2 to 6.1)	
Deep-vein thrombosis	1 (0.4)	2 (0.7)	−0.4 (−2.4 to 1.5)	
Pulmonary embolism	1 (0.4)	6 (2.2)	−1.9 (−4.5 to 0.2)	
Arterial systemic embolism	3 (1.1)	2 (0.7)	0.4 (−1.7 to 2.7)	
Death	73 (27.8)	68 (25.5)	2.5 (−5.0 to 10.0)	0.51

# PCC in DOAC-associated ICH

Multicenter observational study, 61 patients with NOAC-related hemorrhage, 57% received PCC

Hematoma expansion: 71% of pts with expansion received PCC vs 57%  $p=0.53$

Association with unfavorable outcome: OR 1.2, CI 0.37-3.87,  $p=0.76$

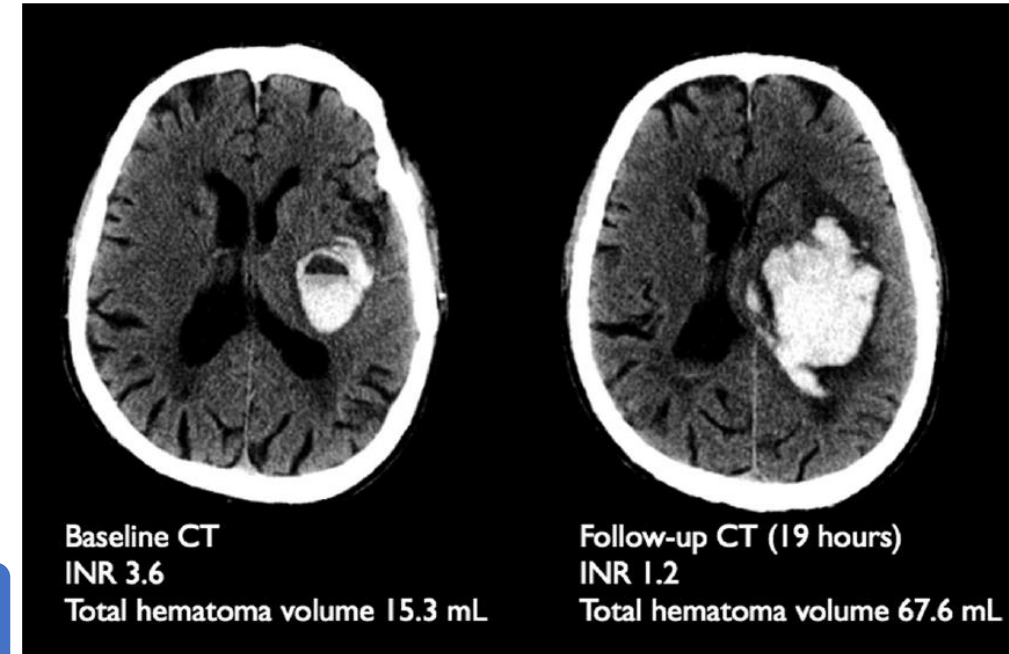
# Does reversal affect outcome?

141 patients receiving PCC in the  
Canadian PCC network

INR normalized to  $<1.5$  within 1 hour in  
72% of patients

Despite reversal, 45.5% of patients  
experienced significant hematoma  
growth

After adjustment, only the GCS score  
and early palliation predicted mortality



# Summary

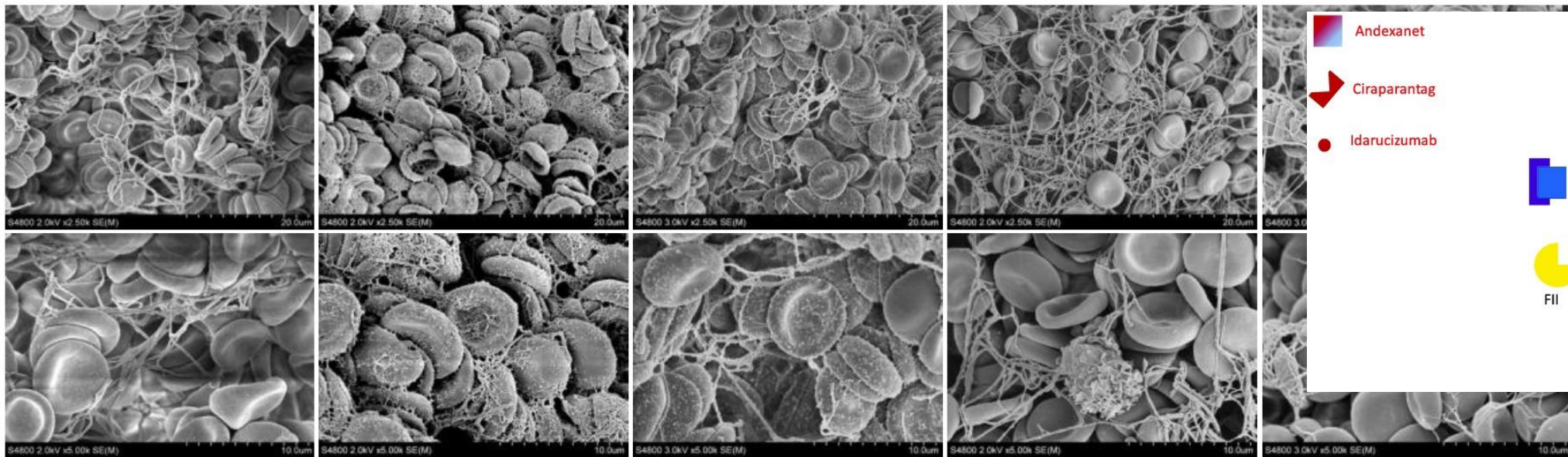
- Anticoagulation-associated ICH (esp DOACs) increasing
- Unfavorable clinicoimaging characteristics, worse outcomes
- For VKA → PCC strongly indicated, goal INR<1.4, TIME MATTERS
- Dabigatran → idarucizumab
- Factor Xa inhibitors → Andexanet pulled out of the US Market.  
Conditionally approved in Europe. Available in Japan → PCC (only available option, not FDA approved)



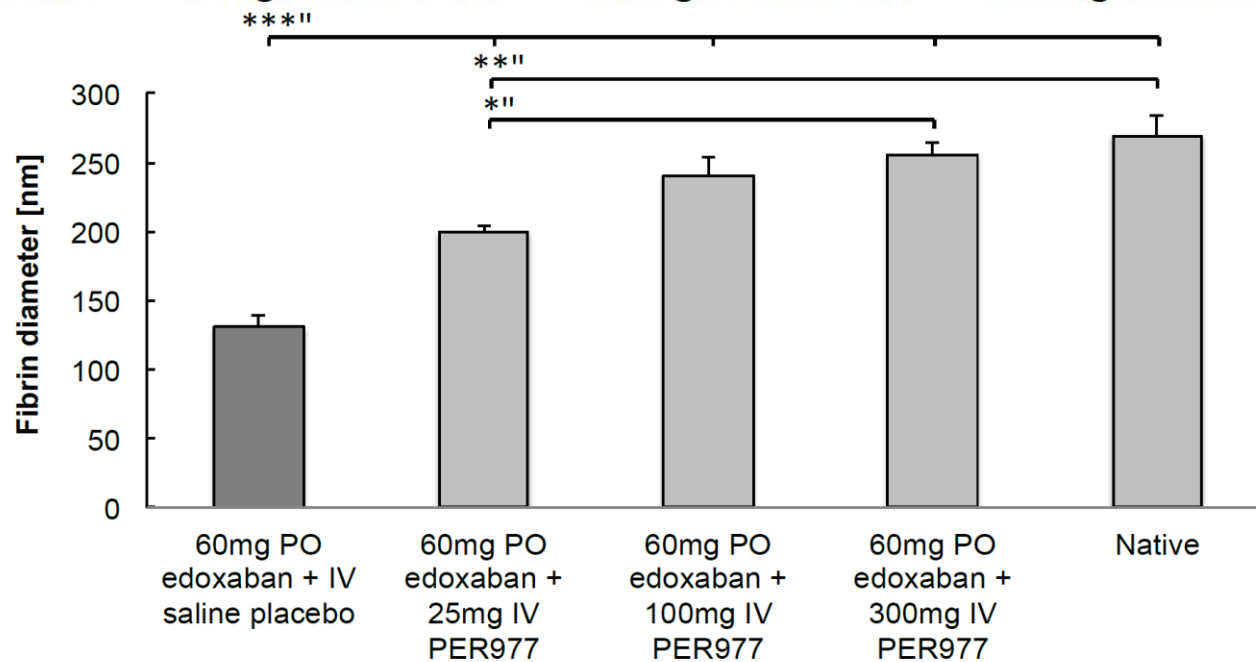


© George Papanas  
Photography

Thank you for your attention!



0 mg Edoxaban p.o., 0 mg PER977 i.v.    60 mg Edoxaban p.o., 0 mg PER977 i.v.    60 mg Edoxaban p.o., 25 mg PER977 i.v.    60 mg Edoxaban p.o., 100 mg PER977 i.v.    60 mg Edoxaban p.o., 300 mg PER977 i.v.



\* p<0.05, \*\* p<0.01, \*\*\* p<0.001

circulation 2012;126:A11395-A11395

Ansell et al N Engl J Med 2014; 371:2141-2142

Drug Discov Today. 2022 Oct;27(10):103332



# Andexanet-instructions for use in clinical practice

In patients with CNS hemorrhage, the benefit of andexanet alfa may be minimal if patient demonstrates stability in mental status over 6 hours.

Patients with ICH volume of above 60 ml **AND** Glasgow Coma Scale (GCS) below 8 have a predicted mortality rate above 90%. Reversal with andexanet alfa may be futile. These cases should be discussed with Stroke/Neurology/Neurosurgery on a case-by-case basis.

Factor Xa Inhibitor	Factor Xa Inhibitor Last Dose	<8 Hours or Unknown	8-18 Hours
Apixaban	≤5 mg	Low dose	Low dose
	>5 mg or unknown	High dose	
Rivaroxaban	≤10 mg	Low dose	
	>10 mg or unknown	High dose	
Edoxaban	Any dose	High dose	High dose

# Hematoma growth arrest: Ultra-early administration of hemostatic agents

## FASTEST trial: rFVIIa <120 minutes from symptom onset

- Post-hoc analysis from FAST and SPOTLIGHT/STOP-IT showed significant functional benefit in those treated within 120min
- Prospective, randomized, placebo-controlled trial of 80µg/kg rFVIIa vs placebo
- Target enrollment: 860 patients
- 18-80 years, <60ml
- Planned use of Mobile Stroke Units to expedite treatment
- (Big) Caveat: only relatively small proportion of acute ICH patients will be eligible for this intervention. The treatment window is too narrow

### FAST trial

Minutes from onset to treatment in patients age ≤ 80	mRS 0-2 FVIIa	mRS 0-2 Placebo	Absolute % in mRS 0-2 in favor of FVIIa at 90 days
≤ 150	42%	42%	0%
≤ 140	46%	41%	5%
≤ 130	49%	41%	9%
≤ 120*	52%	38%	14%

Minutes from onset to treatment in patients age ≤ 70	mRS 0-2 FVIIa	mRS 0-2 Placebo	Absolute % in mRS 0-2 in favor of FVIIa at 90 days
≤ 150	53%	39%	14%
≤ 140	59%	38%	21%
≤ 130	62%	38%	24%
≤ 120	69%	33%	36%

### SPOTLIGHT and STOP-IT

Minutes from onset to treatment in patients age ≤ 80	mRS 0-2 FVIIa	mRS 0-2 Placebo	Absolute % in mRS 0-2 in favor of FVIIa at 90 days
≤ 150	42%	32%	10%
≤ 140	47%	30%	17%
≤ 130	50%	25%	25%
≤ 120	50%	20%	30%

