Reversal of anticoagulation in patients with intracranial and subdural hemorrhage

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Disclosures and Conflicts

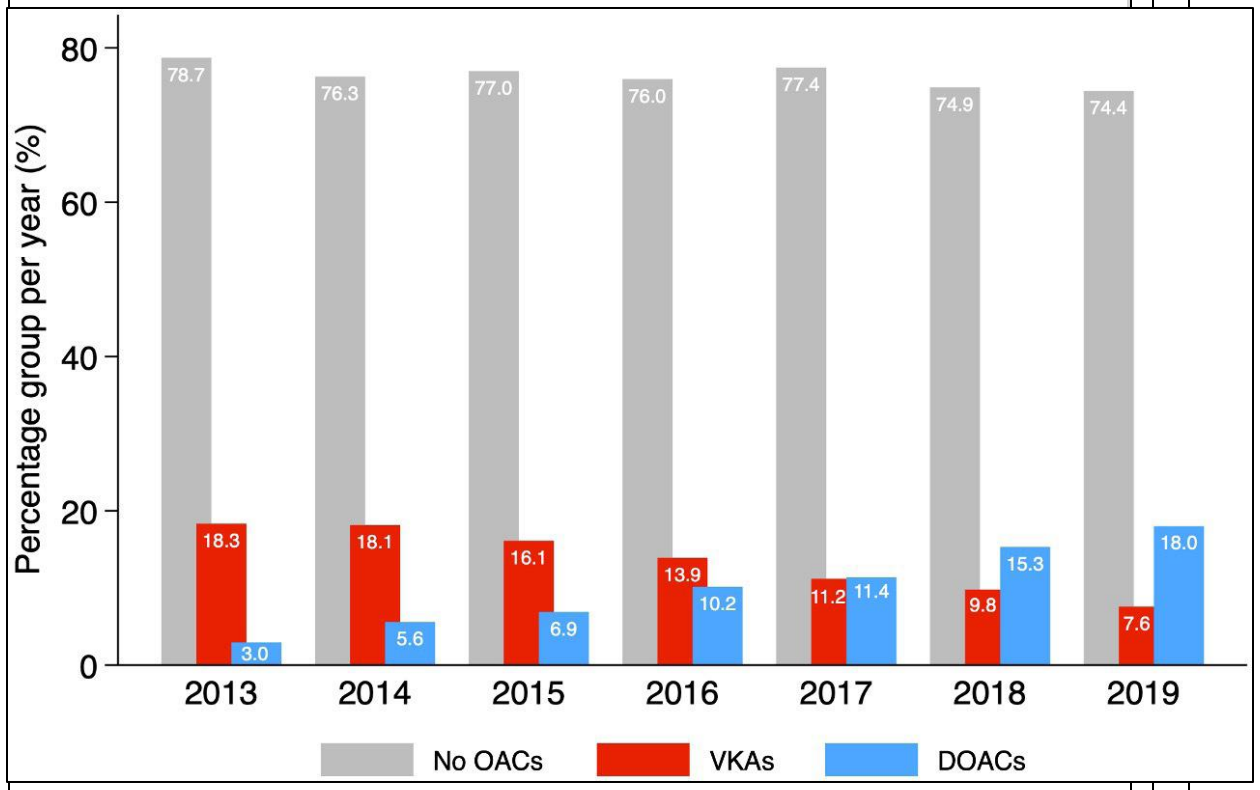
Disclosures:

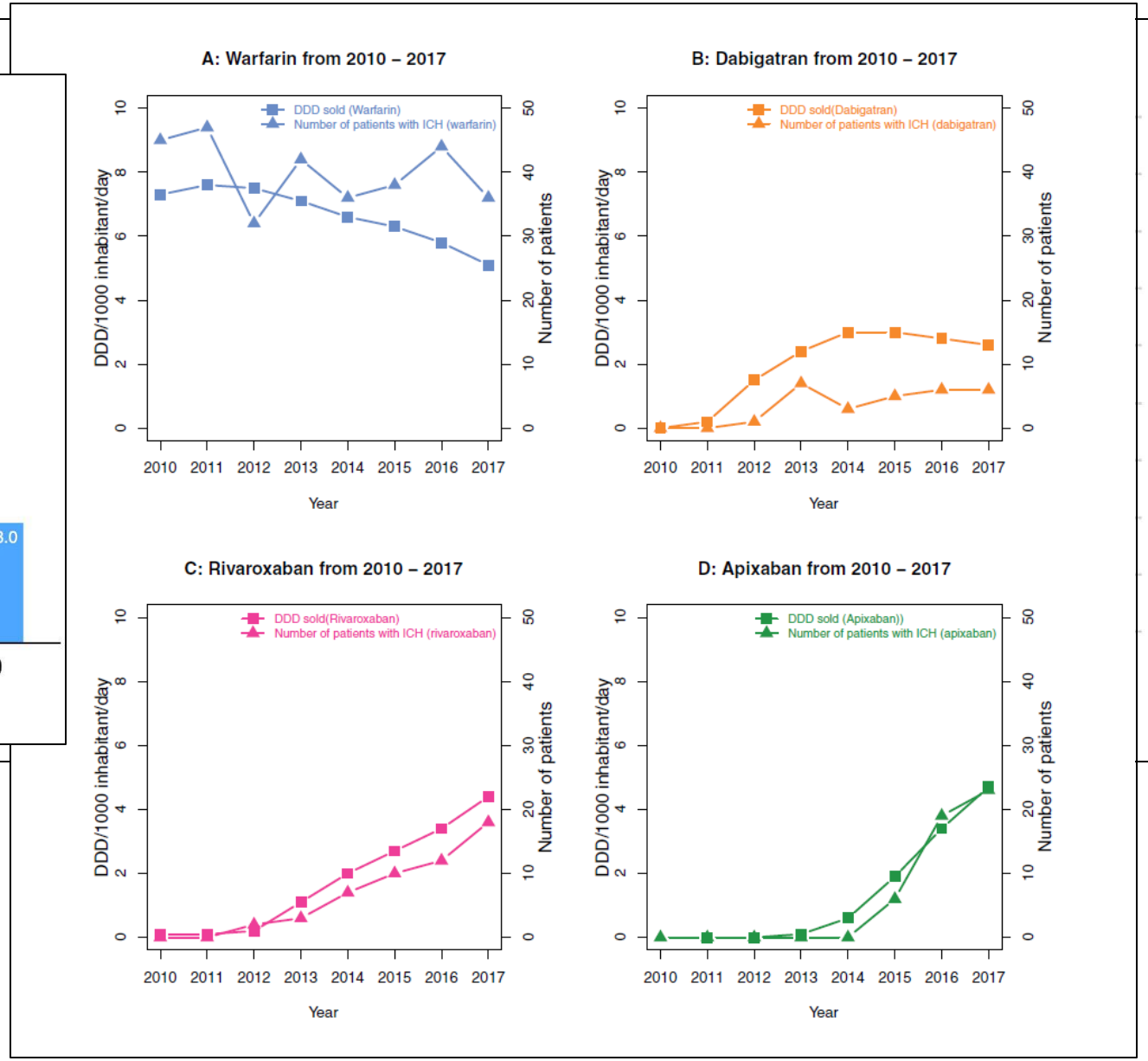
- NIH/NINDS: Grant support (current)
- Alzheimer's Association: Grant support (current)
- Consulting fees: Qmetis(current/ongoing relationship)

Conflicts:

- None relevant to this presentation

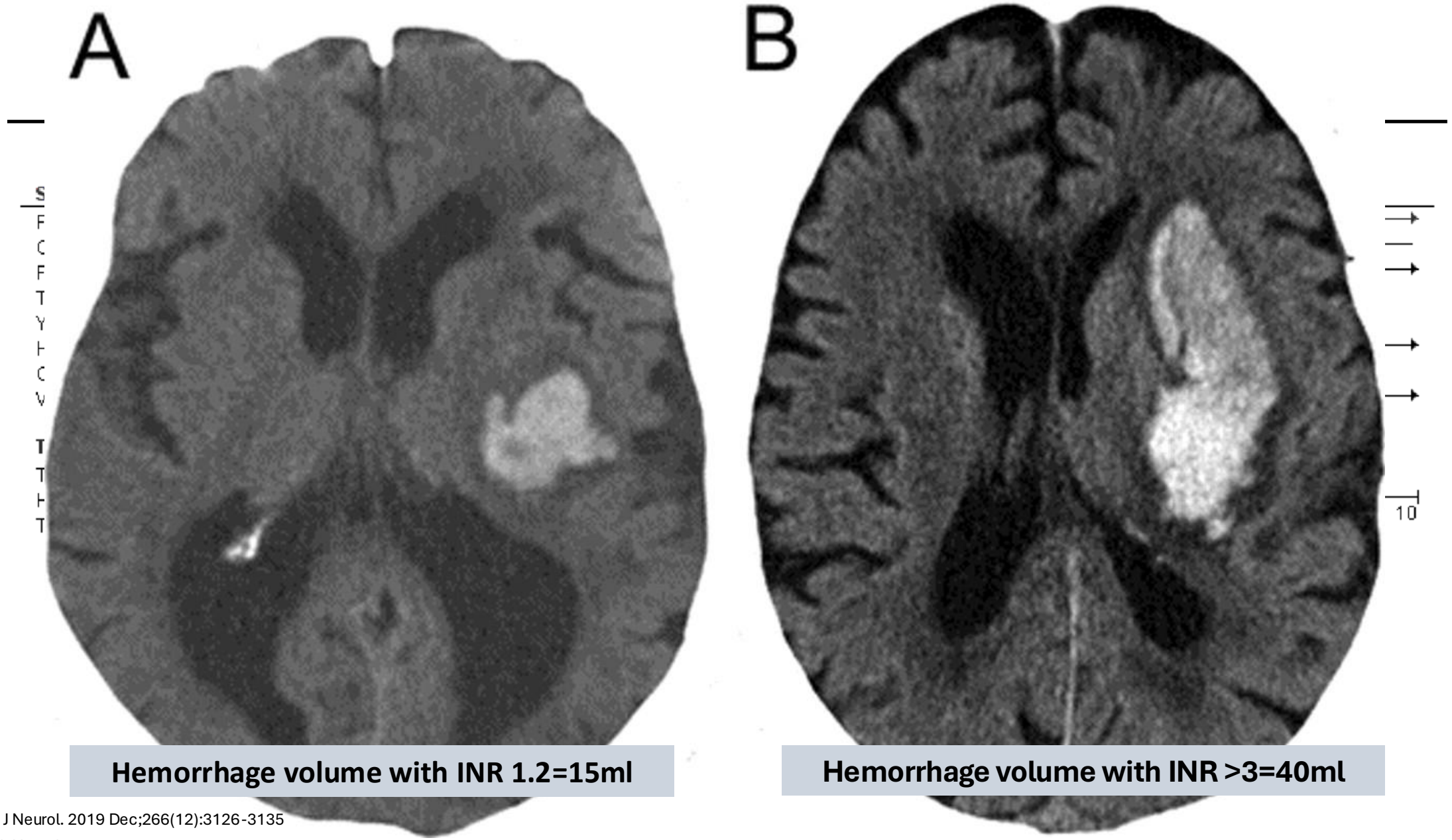
Anticoagulation-associated ICH: increasing trend





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



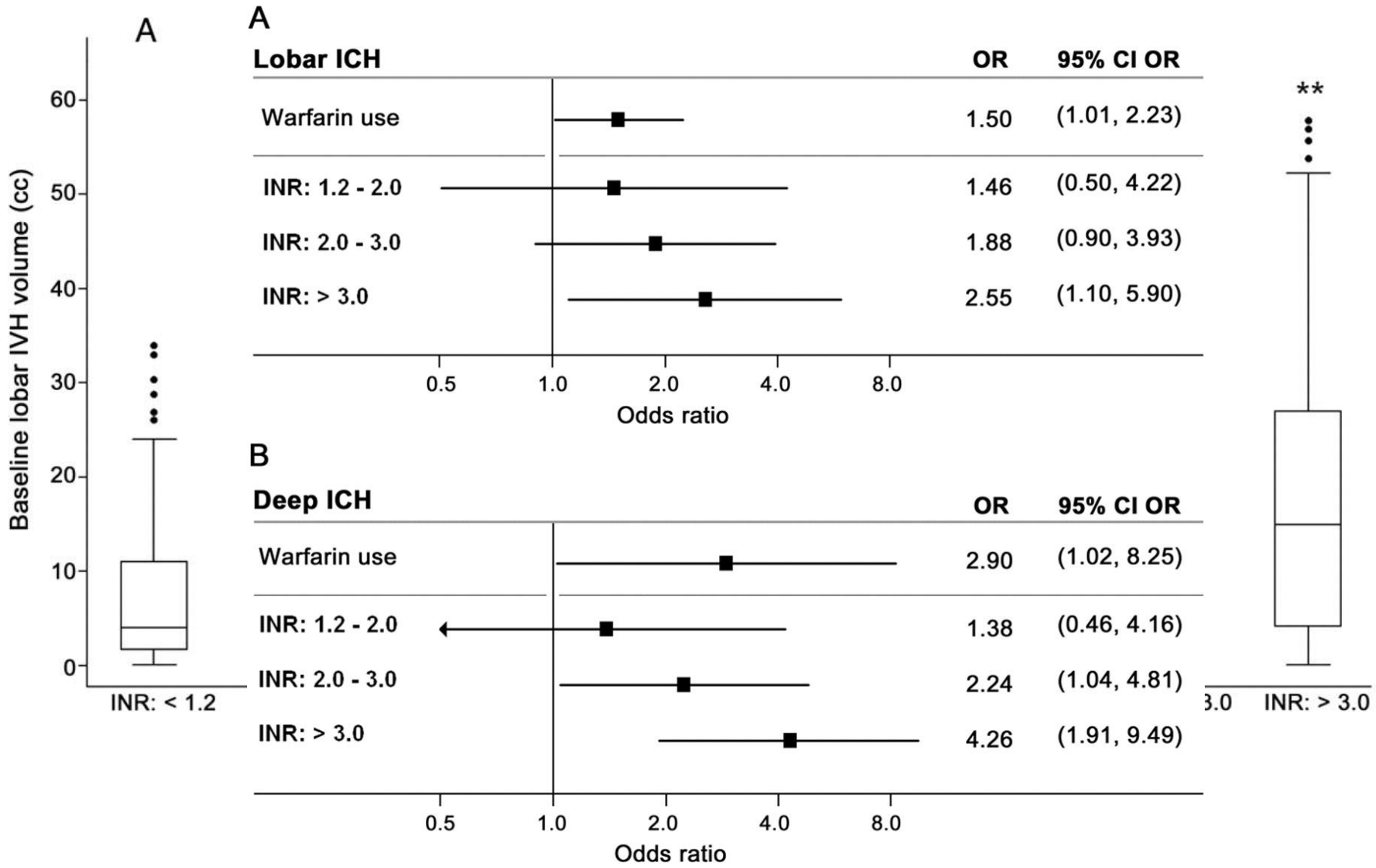
Hemorrhage volume with INR 1.2=15ml

Hemorrhage volume with INR >3=40ml

Seiffge et al. J Neurol. 2019 Dec;266(12):3126-3135

Flaherty et al. Neurology 2008;71:1084-1089

Intraventricular expansion



Biffi et al. Neurology 2011;77:1840-1846

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 10^3/mm^3	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)†
West		1.01 (0.94-1.08)	.845
Private insurance		0.890 (0.834-0.949)	<.001
Female sex		0.994 (0.948-1.04)	.814
History of congestive heart failure		0.972 (0.899-1.05)	.465

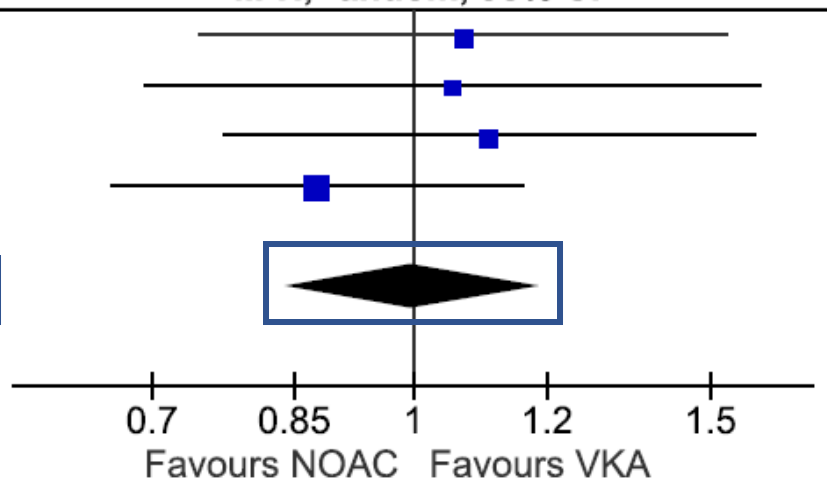
Liotta et al J Stroke Cerebrovasc Dis. 2013 Oct;22(7):1151-5
Flibotte et al. Neurology 2004;63:1059-1064

NOAC-associated ICH vs Warfarin: outcomes in RCTs

(b)	NOAC		VKA			Risk ratio
Study or subgroup	Events	Total	Events	Total	Weight	M-H, random, 95% CI
Apixaban	24	53	52	123	22.9%	1.07 [0.75, 1.54]
Dabigatran	24	64	32	90	16.8%	1.05 [0.69, 1.61]
Edoxaban	36	102	42	132	22.7%	1.11 [0.77, 1.59]
Rivaroxaban	31	55	54	84	37.5%	0.88 [0.66, 1.16]
Total (95% CI)		**274**		**429**	**100.0%**	**1.00 [0.84, 1.19]**
Total events	115		180			

Heterogeneity: Tau² = 0.00; Chi² = 1.40, df = 3 (*P* = 0.71); I^2 = 0%

Test for overall effect: *Z* = 0.01 (*P* = 0.99)



Katsanos et al Eur J Neur 2018 Oct;25(10):1299-1302

Warfarin vs NOAC ICH Hospital Mortality

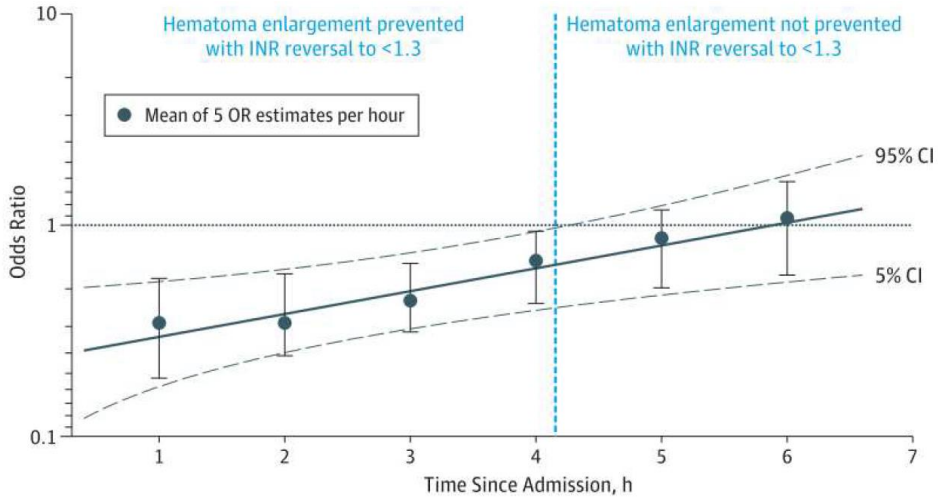
Outcome Measures	Warfarin	NOACs	No OACs
Primary Outcome: In-Hospital Death			
No./total No. (%)	4903/15 036 (32.6)	1305/4918 (26.5)	27 297/121 357 (22.5)
Adjusted RD (97.5% CI), %[a]	[Reference]	−5.7 (−7.3 to −4.2)	−9.0 (−10.1 to −7.9)
Adjusted OR (97.5% CI)[a]	[Reference]	0.75 (0.69 to 0.81)	0.62 (0.58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

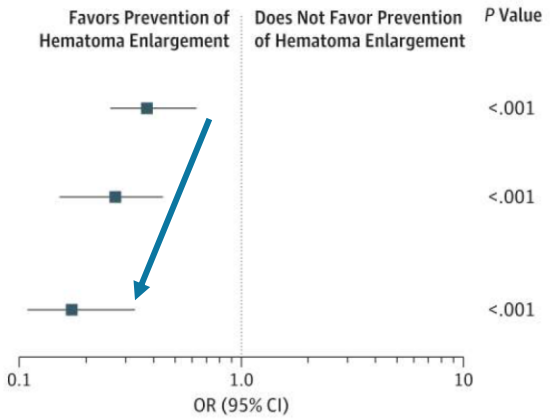
Inohara et al JAMA. 2018 Feb 6;319(5):463-473

Vitamin K antagonist: timing and INR goal

Patients With Follow-up Imaging (n = 853)	With Hematoma Enlargement (n = 307)	Without Hematoma Enlargement (n = 546)	*P* Value
Serial monitoring of coagulation parameters, median (IQR)			
INR after reversal[i]	1.38 (1.20-1.71)	1.27 (1.16-1.44)	<.001
PTT after reversal, s[i]	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[b]
INR at 72 h	1.23 (1.13-1.40)	1.19 (1.10-1.30)	.001[b]



	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 et al JAMA. 2015 Feb 24;313(8):824-36

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

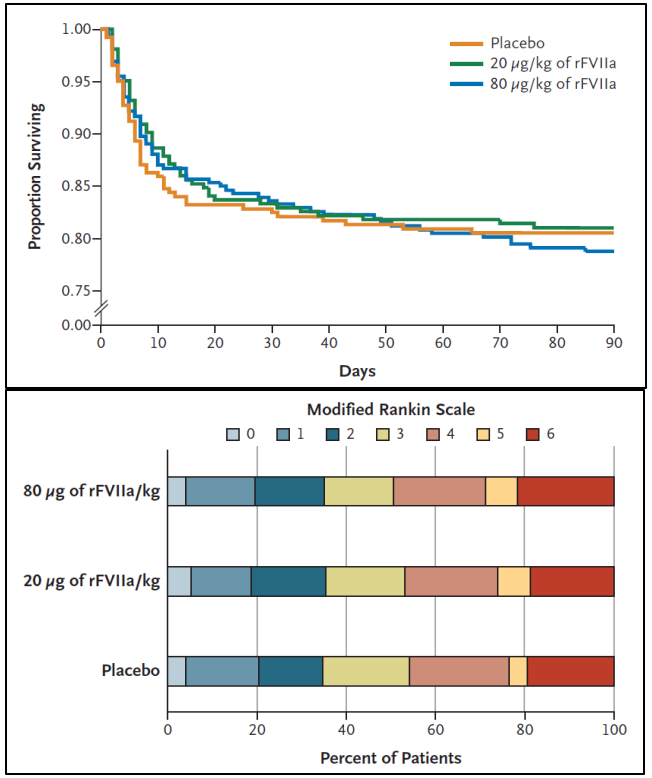
	Fresh frozen plasma (n=23)	Prothrombin complex concentrate (n=27)	Treatment effect (95% CI)	p value
Primary outcome				
INR ≤1·2 within 3 h	2 (9%)	18 (67%)	OR 30·6 (4·7 to 197·9)*	0·0003
Secondary clinical outcomes				
Deaths at day 90	8 (35%)	5 (19%)	No proportional hazard assumed	0·14†
Functional independence (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 ≤1·2 normalisation of INR (min)	1482 (1335–1610)	40 (30–1610)	No proportional hazard assumed	0·050†
Imaging data at 3 h¶				
Haematoma expansion (mL)	23·7 (28·4)	9·7 (20·9)	16·9 (2·5 to 31·3)‡	0·023
≥15% growth‖	16/22 (73%)**	15/26 (58%)**	OR 2·0 (0·6 to 7·3)*	0·29
≥33% growth‖	13/22 (59%)**	12 (44%)**	OR 3·8 (1·1 to 16·0)*	0·048
Imaging data at 24 h				
Haematoma expansion (mL)	22·1 (27·1)	8·3 (18·3)	16·4 (2·9 to 29·9)‡	0·018
≥15% growth or death‖	14/20 (70%)††	12/27 (44%)	OR 3·9 (1·0 to 17·6)*	0·044
≥33% growth or death‖	12/20 (60%) ††	8/27 (30%)	OR 4·8 (1·3 to 20·4)*	0·024

Steiner et al Lancet Neurol 2016; 15: 566–73

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

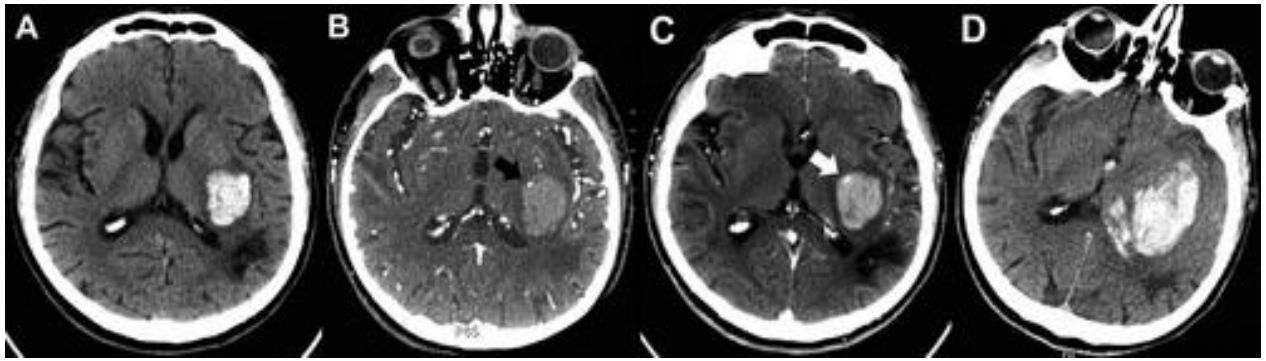


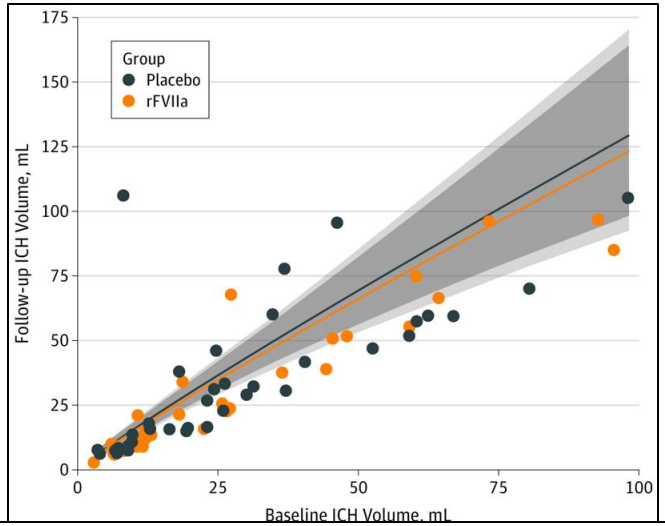
Mayer et al N Engl J Med. 2008 May 15;358(20):2127-37

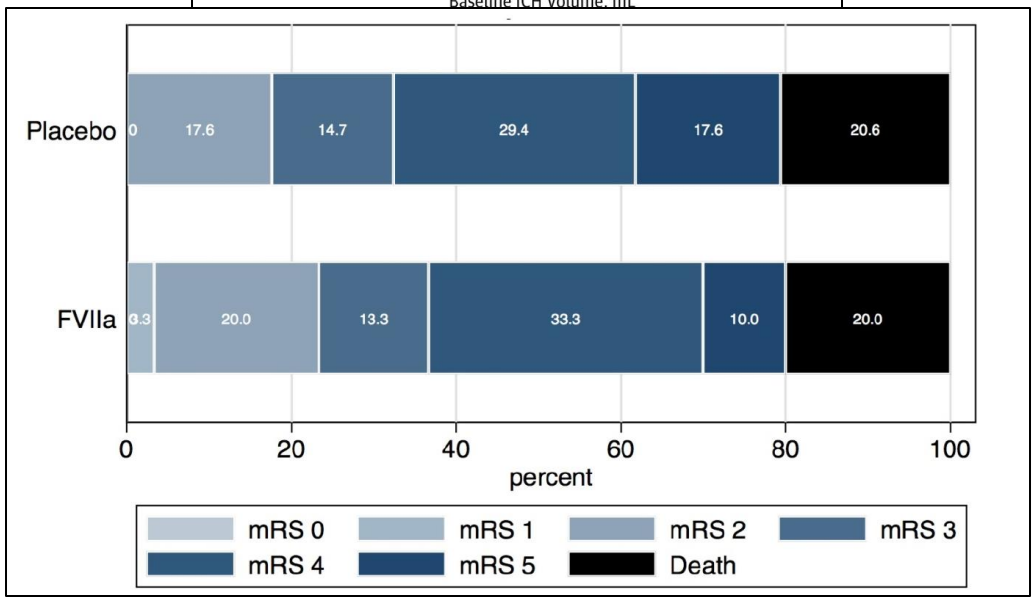
Hemostatic agents using imaging markers (spot sign)

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

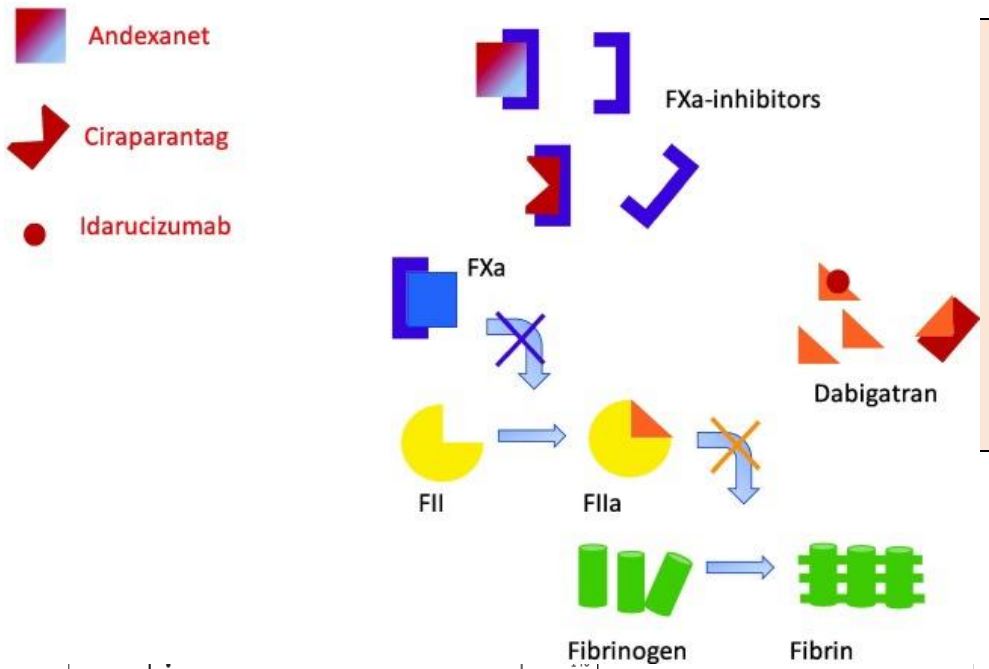






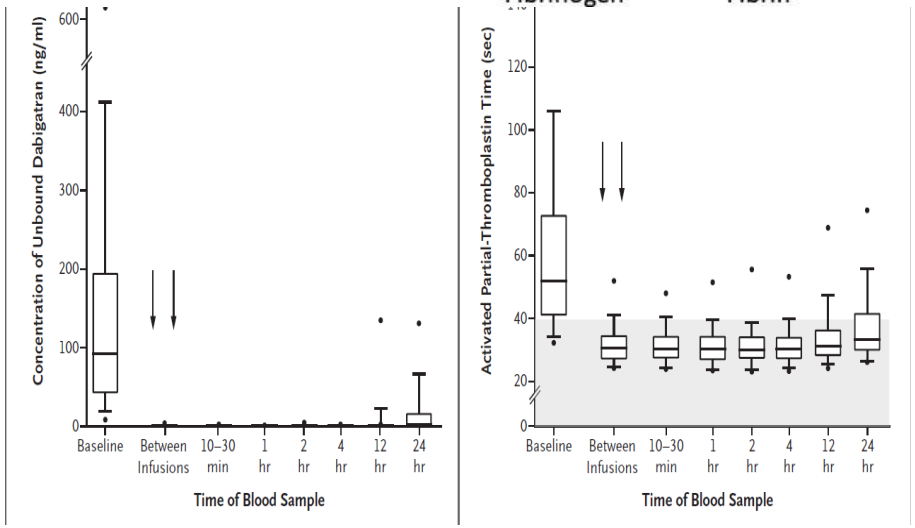
Wada et al Stroke. 2007 Apr;38(4):1257-62
Gladstone et al JAMA Neurol. 2019 Aug 19;76(12):1493–501

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)

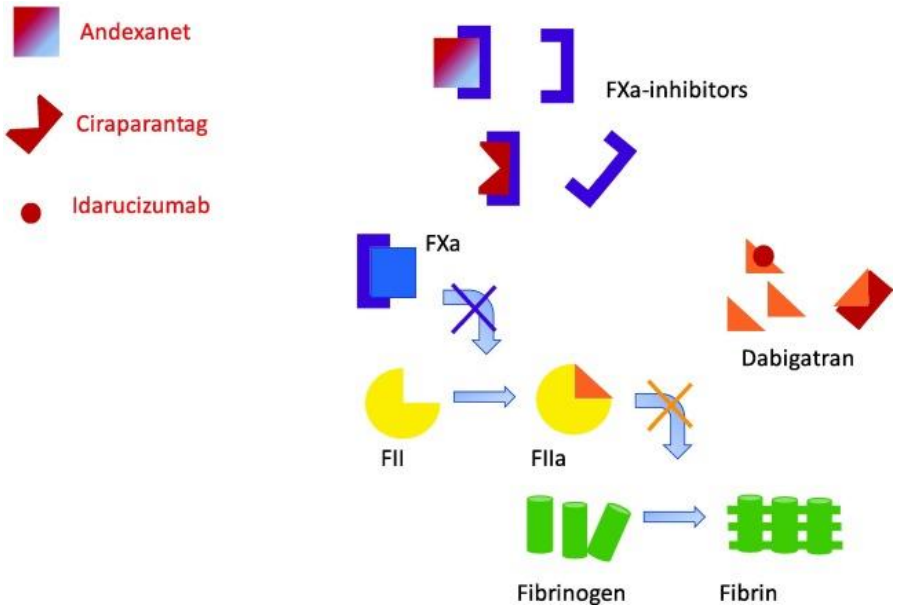


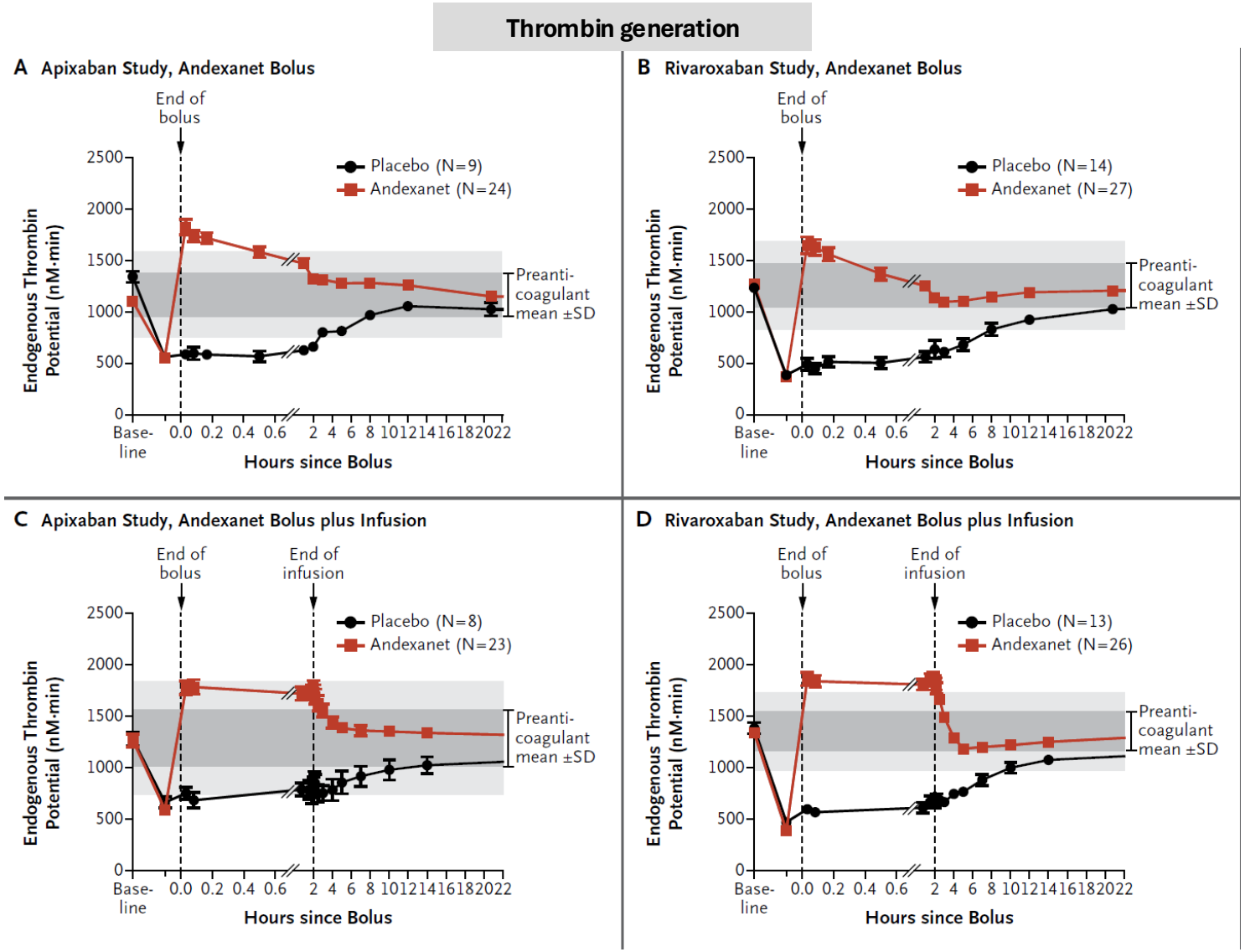
ICH mortality in the RELY trial (no reversal agent)

	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





N Engl J Med 2015;373:2413-24

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†
	no. of patients (%)		*percentage points*	
≥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

Connolly et al N Engl J Med. 2024 May 16;390(19):1745-1755

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

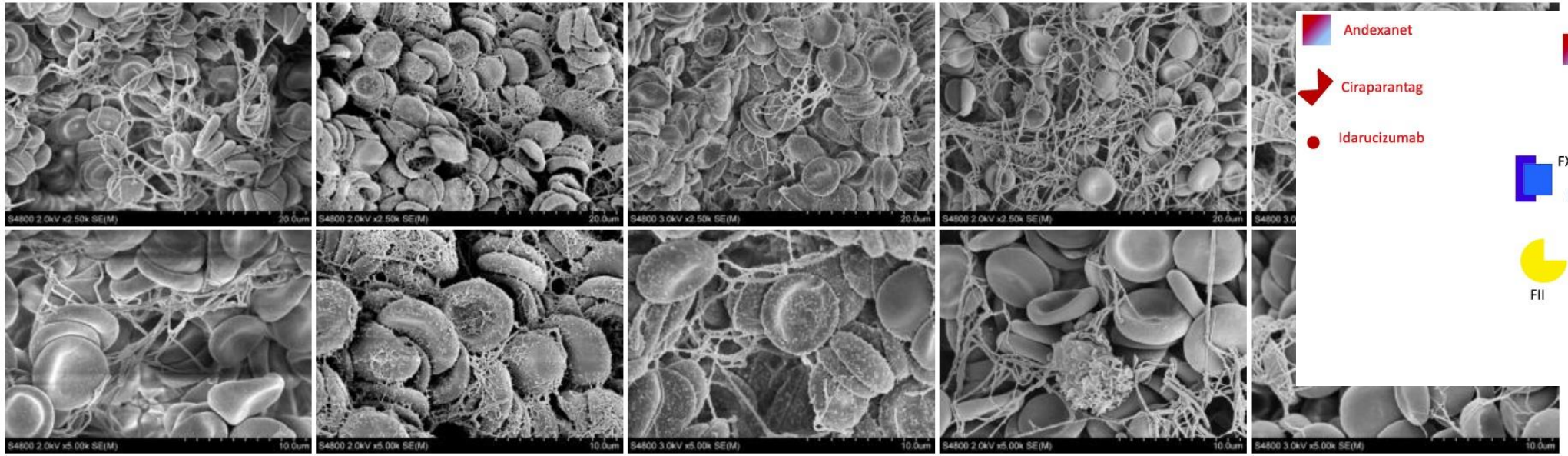
PCC in DOAC-associated ICH

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

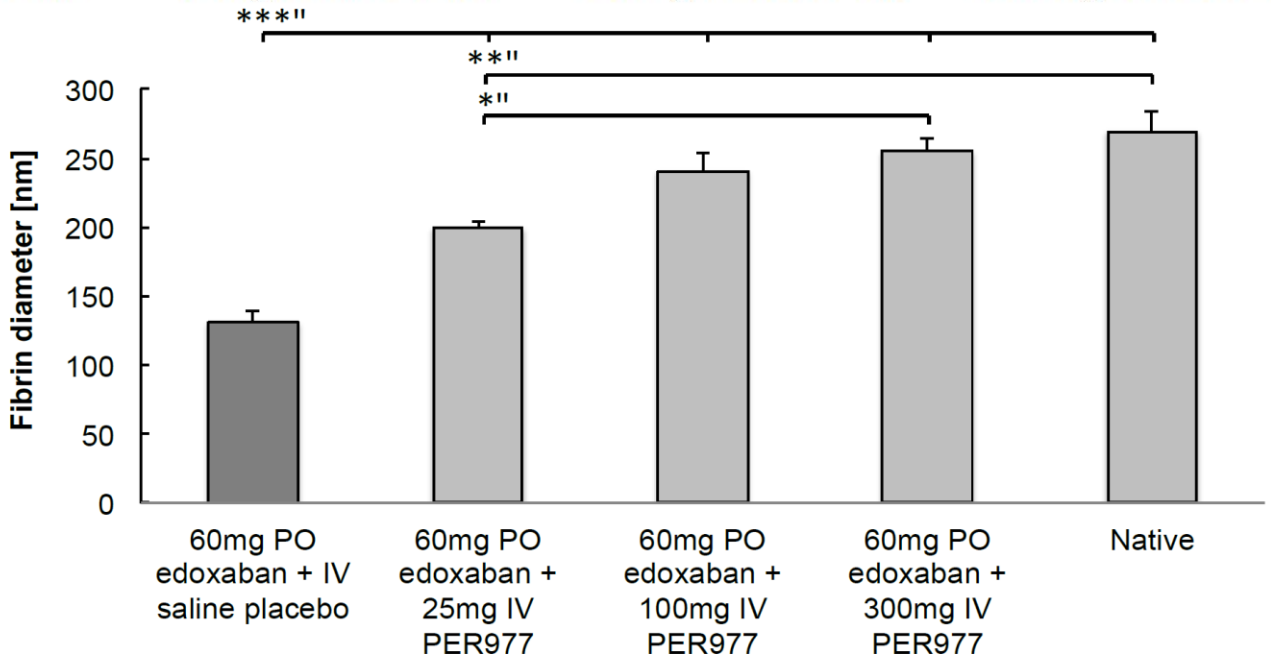
Hematoma expansion: 71% of pts with expansion received PCC vs 57% p=0.53

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

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



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

culation 2012;126:A11395-A11395
Ansell et al N Engl J Med 2014; 371:2141-2142
Drug Discov Today. 2022 Oct;27(10):103332

Hematoma growth arrest future directions: 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%

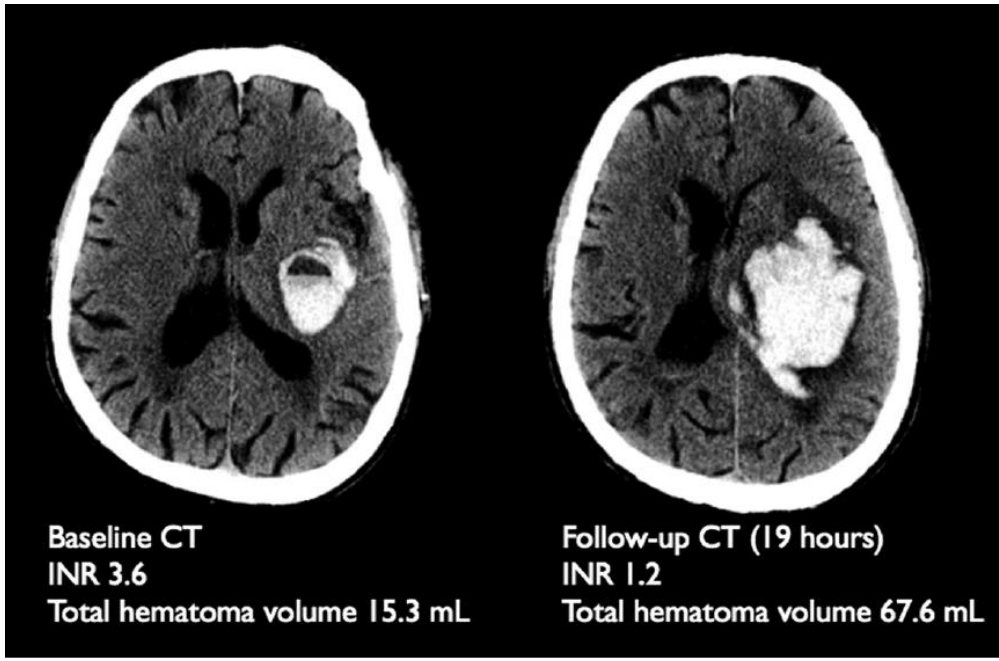
SPOTLIGHT and STOP-IT

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%

Data presented from the study protocol available publicly at UCincinnati by Broderick, Grotta et al

Does reversal affect outcome?

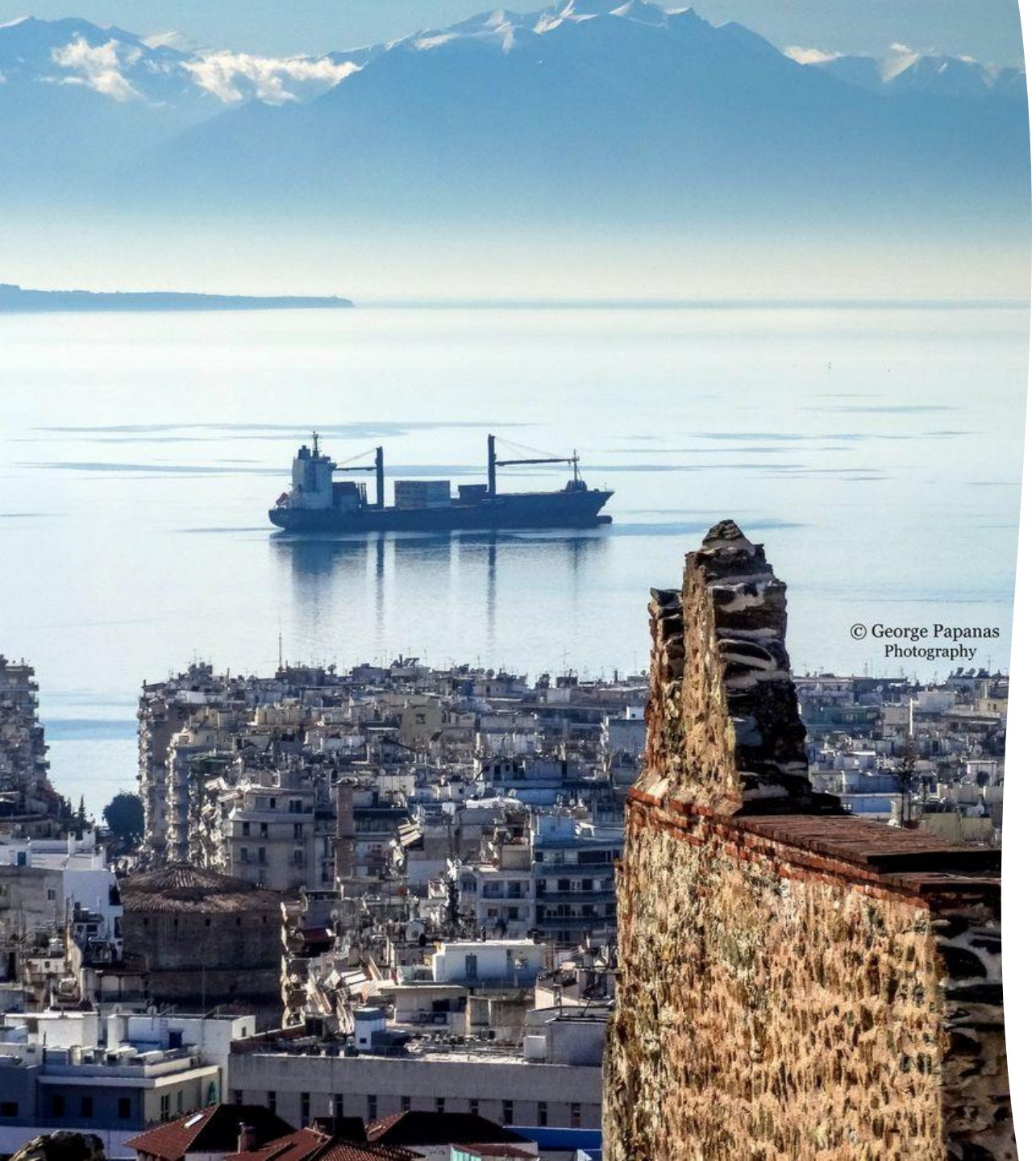
- 141 patients receiving PCC in the Canadian PCC network
- INR normalized to <1.5 within 1 hour in 72% of patients
- Despite reversal, 45.5% of patients experienced significant hematoma growth
- After adjustment, only the GCS score and early palliation predicted mortality



Dowlatshahi et al *Stroke*. 2012;43:1812-1817

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, with caveats (thrombotic complications, ?net benefit, cost and availability)



Thank you for your attention!