Anticoagulation in Intracerebral Hemorrhage: Risks, Reversal, Resumption

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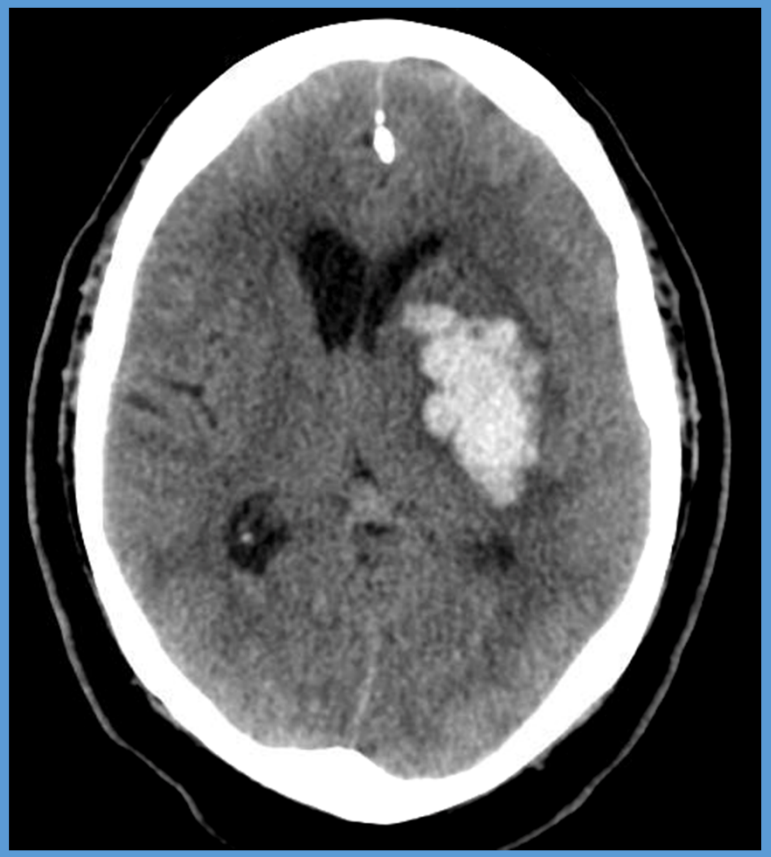
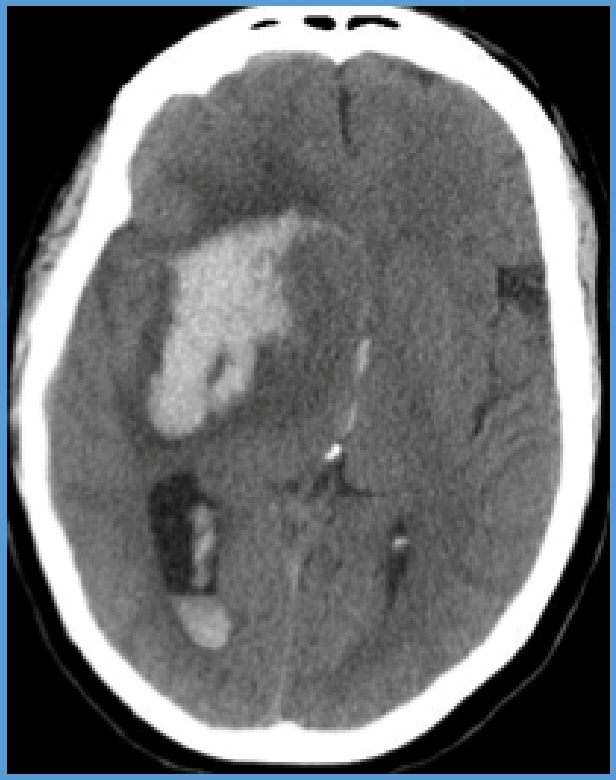
Disclosures

- None relevant to this talk
- **Biogen**- grant support, member of the Advisory Board for CHARM trial
- ***Neurology*** **-** honorarium for editorial work

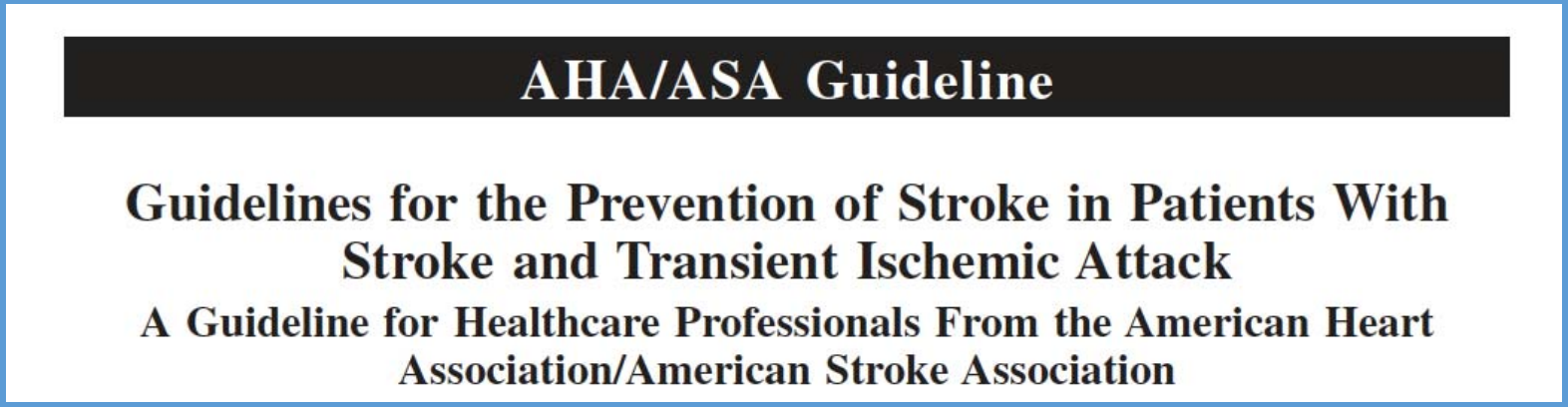


Roadmap for this Talk

- OAT: what's the indication?
- What are the options?
- Lobar v. non-lobar bleeds
- Reversal
- NOACs
- Prognosis and the ICH score
- Next steps



Indications for Anticoagulation (A/C) for Secondary Stroke Prevention



- Atrial Fibrillation (Afib) (CHADS VASc)
- Myocardial Infarction (MI) and thrombus
- Cardiomyopathy: EF<35%, left ventricular assist device (LVAD), etc.
- Mechanical heart valve (not bio-prosthetic)

Kernan. Stroke. 2014;45:00-00.

$CHADS_2$ -> CHA_2DS_2VASc

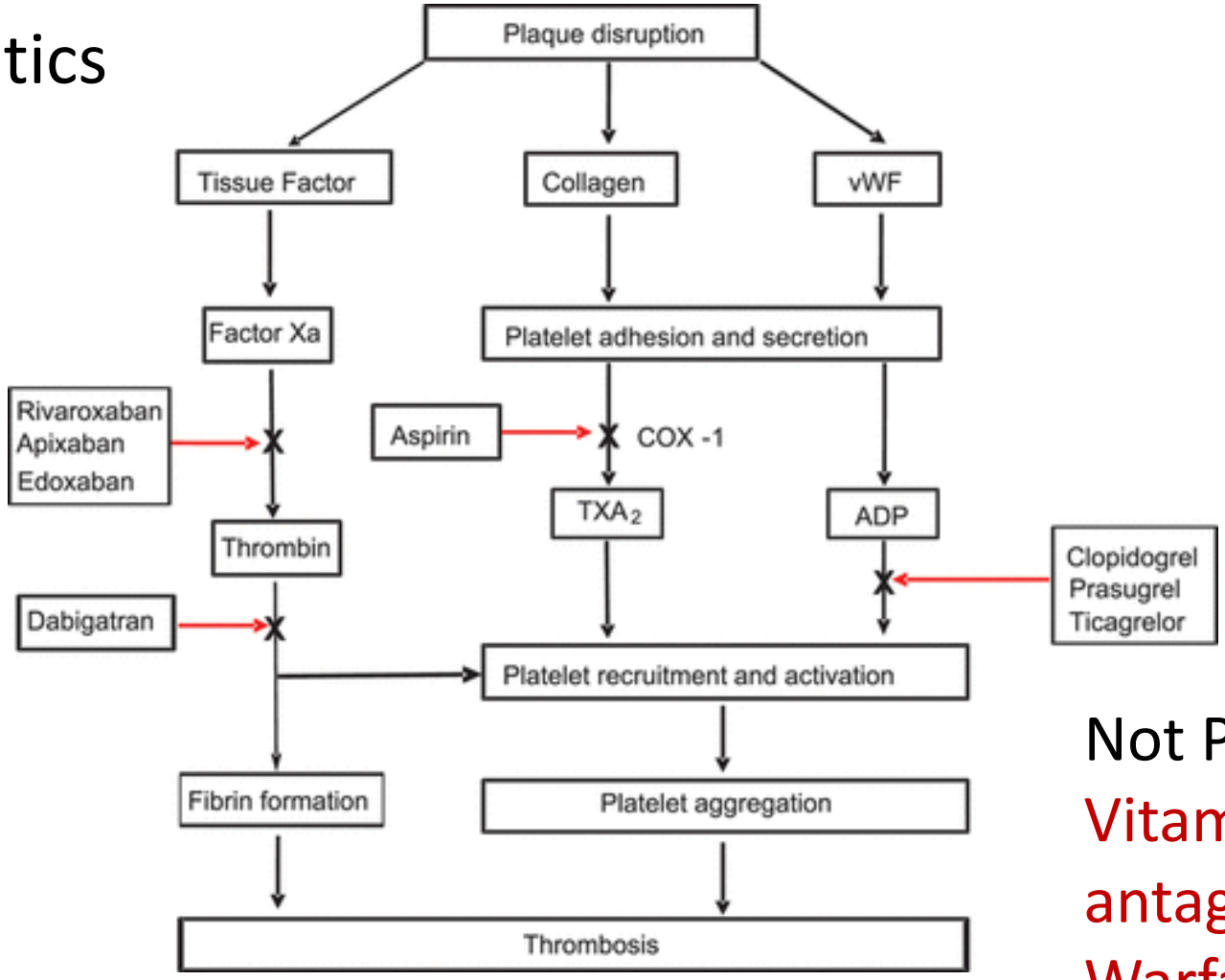
CHADS2 Risk	Score
CHF	1
Hypertension	1
Age > 75	1
Diabetes	1
Stroke or TIA	2

From ESC AF Guidelines
http://escardio.org/guidelines-surveys/esc-guidelines/GuidelinesDocuments/guidelines-afib-FT.pdf

CHA2DS2-VASc Risk	Score
CHF or LVEF ≤ 40%	1
Hypertension	1
Age ≥ 75	2
Diabetes	1
Stroke/TIA/ Thromboembolism	2
Vascular Disease	1
Age 65 - 74	1
Female	1

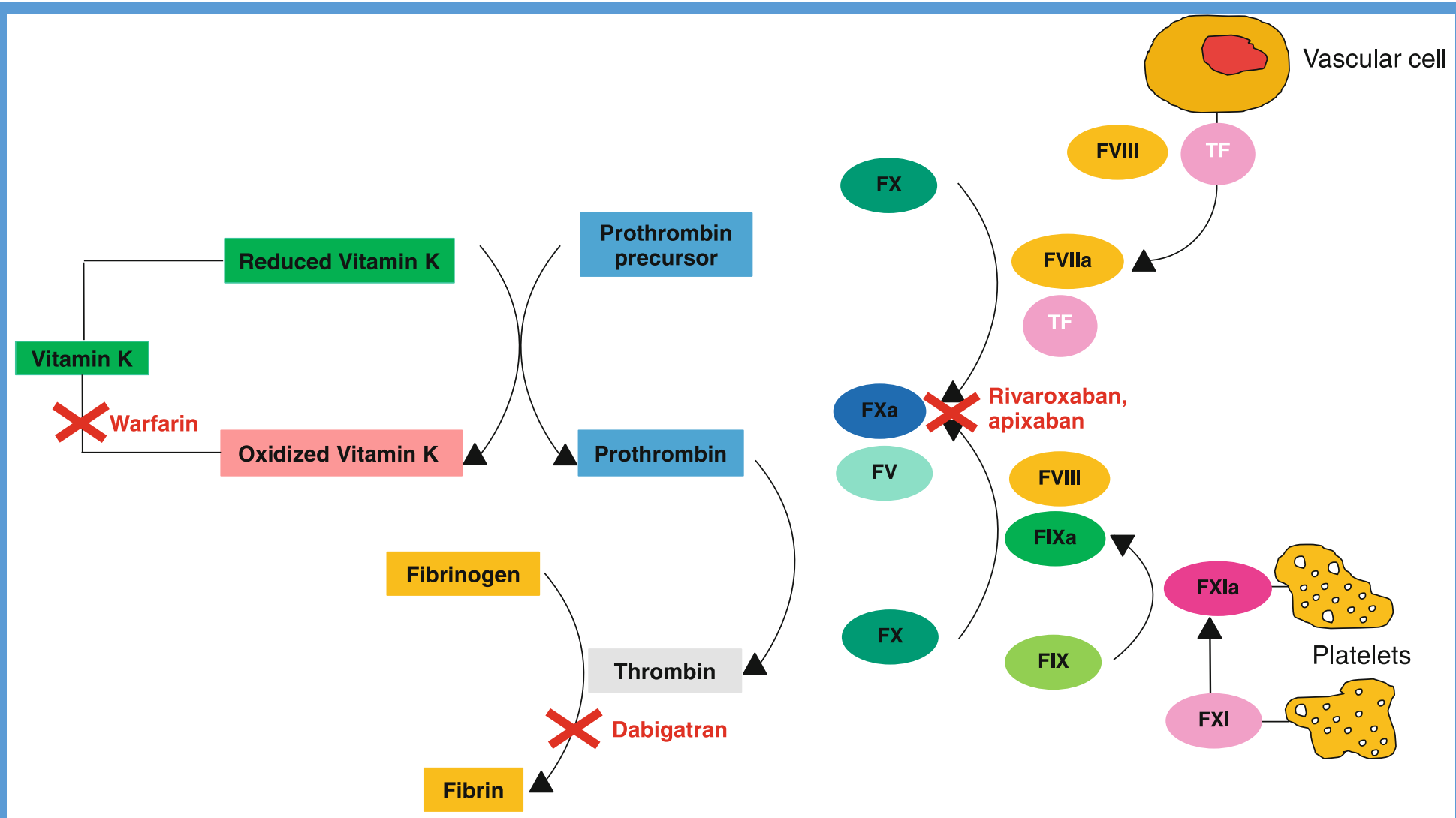
Circulation. 2014;130:e199–e267,
Thromb Haemost. 2012; *107*:1172–9.

Anti-thrombotics



Not Pictured:
Vitamin K antagonist:
Warfarin

Noel C. Chan. Circulation Research. Antithrombotic Agents, Volume: 124, Issue: 3, Pages: 426-436, DOI: (10.1161/CIRCRESAHA.118.313155)



Am J Cardiovasc Drugs (2013) 13:79–85

NOACs: Non-Vitamin K antagonists

- Non-vitamin K antagonist oral anticoagulants (NOACs)
  - Direct thrombin inhibitor (dabigatran)
  - Direct or Indirect Factor X_a inhibitors (rivaroxaban, apixaban, and edoxaban)

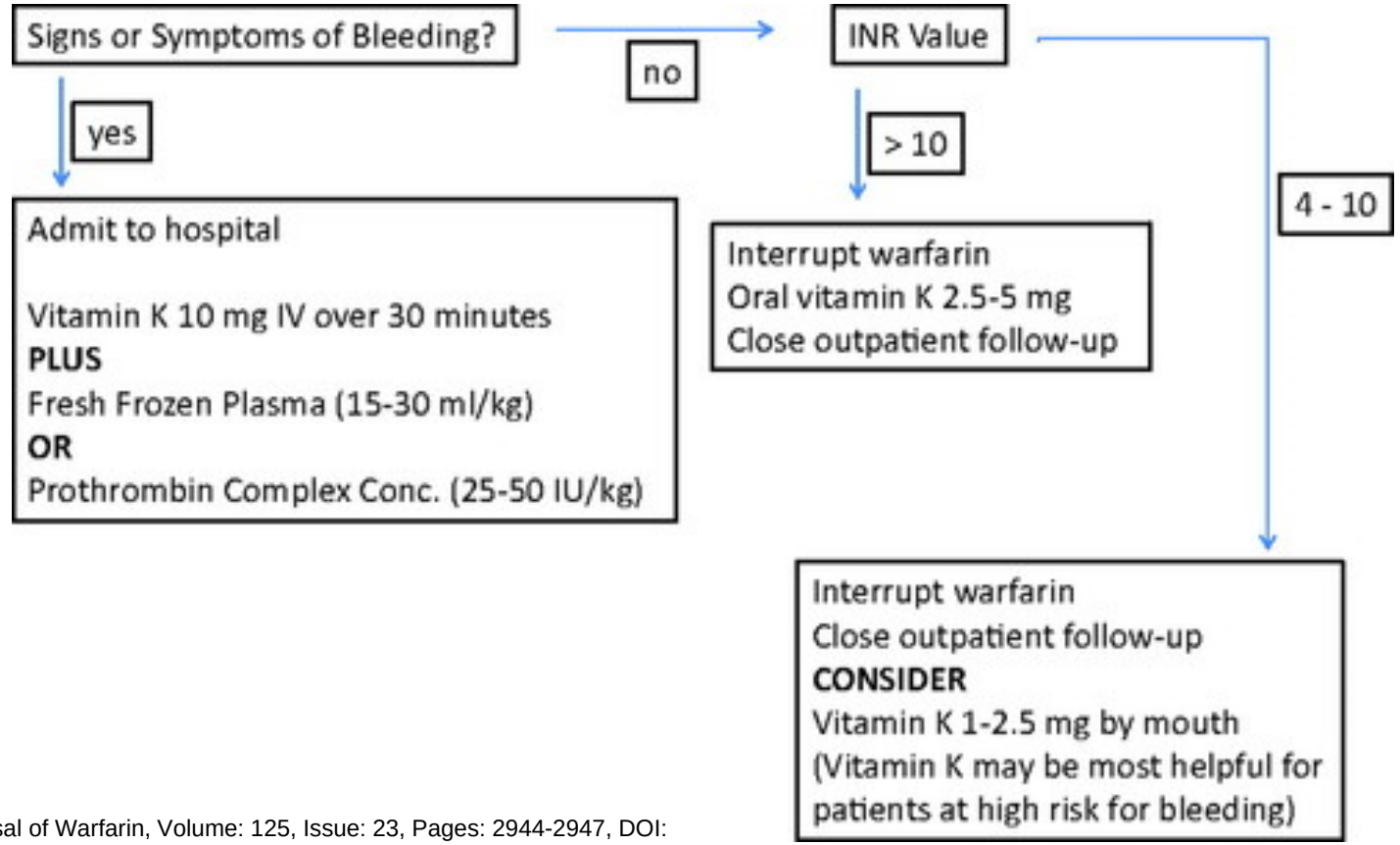
Table 2 – Clinical trial and US Food and Drug Administration dosing of NOACs for stroke prevention in AF.

	Dabigatran [2,20]	Rivaroxaban [3,11]	Apixaban [4,10]	Edoxaban [5,12]
Dosing criteria from pivotal clinical trial of stroke prevention in AF				
Pivotal trial for stroke prevention in AF	RE-LY	ROCKET AF	ARISTOTLE	ENGAGE AF-TIMI 48
Renal exclusion in pivotal trial	CrCl < 30 mL/min	CrCl < 30 mL/min	Cr > 2.5 mg/dL or CrCl < 25 mL/min	CrCl < 30 mL/min
Dose adjustment criteria	None	CrCl 30–49 mL/min	>2 of following age ≥80 years, weight ≤60 kg, Cr ≥ 1.5 mg/dL	CrCl 30–50 mL/min, weight ≤60 kg, OR concomitant use of verapamil or quinidine

Steinberg. Trends in Cardiovascular Medicine, Volume 27, Issue 8, November 2017, pp. 573-574

Reversal of Anticoagulation

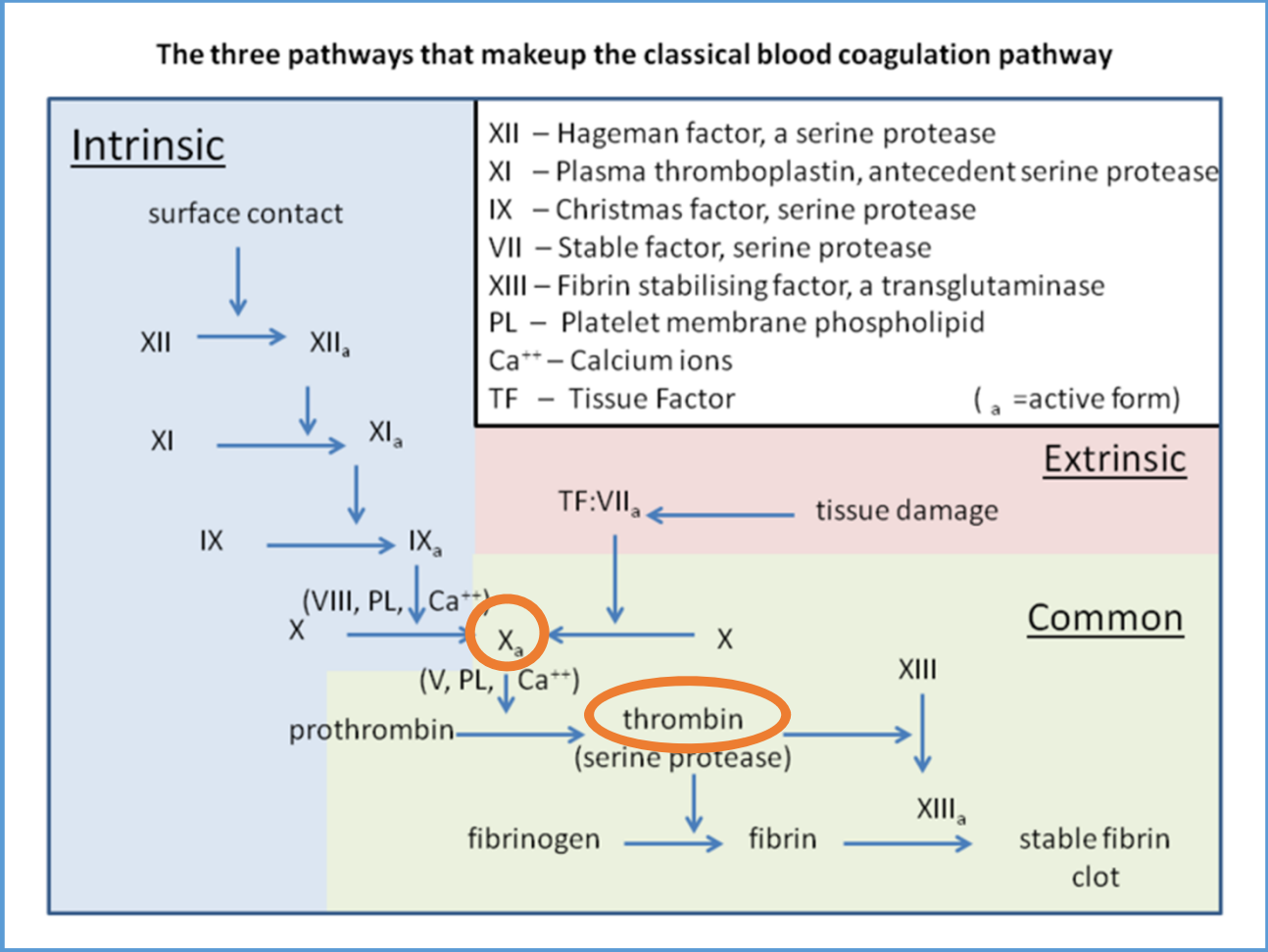
Reversing Warfarin



David A. Garcia. Circulation. Reversal of Warfarin, Volume: 125, Issue: 23, Pages: 2944-2947, DOI: (10.1161/CIRCULATIONAHA.111.081489)

Reversing Warfarin: things to remember

- INR of FFP= 1.6
  - If the INR<1.7, administering FFP is not going to lower INR
- Weighing the risk/benefit to reversal
  - Symptomatic v. asymptomatic ICH
  - ICH size
  - Holding warfarin v. reversing



Idarucizumab for the Reversal of Dabigatran

Pollack CV Jr et al. N Engl J Med 2017;377:431-441.

Reversal of Xa Inhibitors

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Full Study Report of Andexanet Alfa for Bleeding Associated with Factor Xa Inhibitors

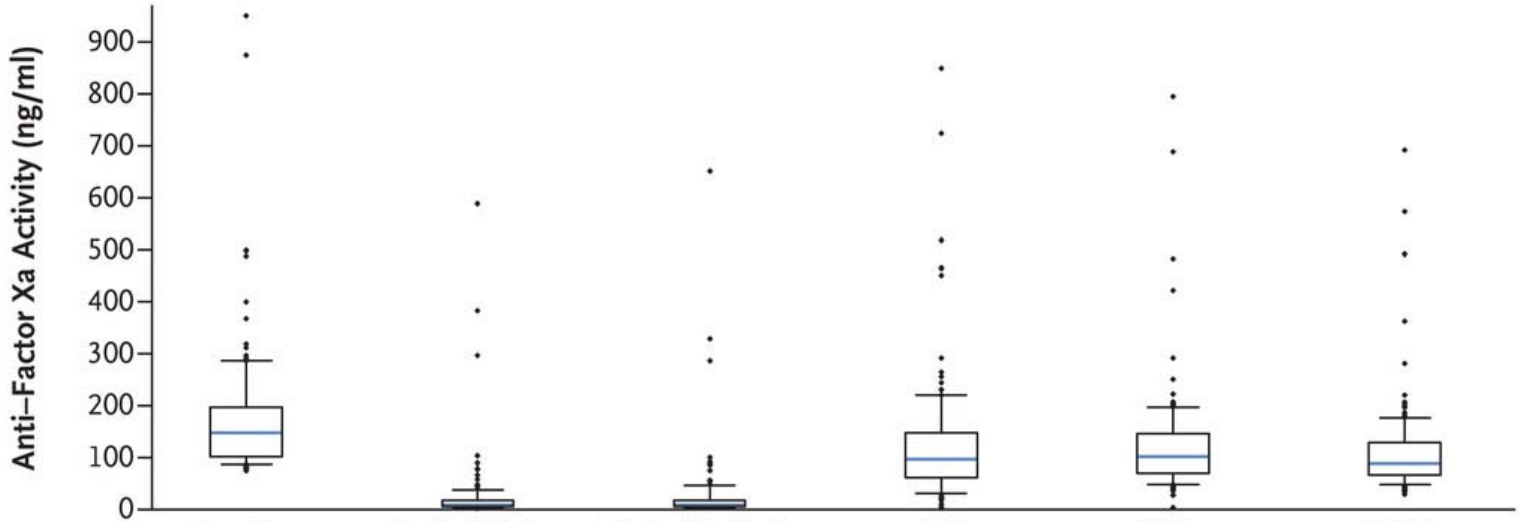
S.J. Connolly, M. Crowther, J.W. Eikelboom, C.M. Gibson, J.T. Curnutte, J.H. Lawrence, P. Yue, M.D. Bronson, G. Lu, P.B. Conley, P. Verhamme, J. Schmidt, S. Middeldorp, A.T. Cohen, J. Beyer-Westendorf, P. Albaladejo, J. Lopez-Sendon, A.M. Demchuk, D.J. Pallin, M. Concha, S. Goodman, J. Leeds, S. Souza, D.M. Siegal, E. Zotova, B. Meeks, S. Ahmad, J. Nakamya, and T.J. Milling, Jr., for the ANNEXA-4 Investigators*

N Engl J Med 2019; 380:1326-1335

Andexanet Alpha for reversal of Xa Inhibitors

- Modified recombinant inactive form of human factor Xa
- Open label, all received drug (n=352)
- Adults (77 ±11) receiving apixaban, rivaroxaban, or edoxaban at any dose or enoxaparin at a dose of at least 1 mg per kilogram of body weight per day
- Presenting with “acute major bleeding”
  - ICH (64%) (GCS>7, ICH<60mL)
  - GIB (26%)
- Primary outcomes: 1)% change in anti-Xa activity, 2)”Good/Excellent hemostasis”

A Patients Who Received Apixaban



	Baseline	End of Bolus	End of Infusion	4 Hr	8 Hr	12 Hr
Median	149.7	11.1	11.5	97.2	104.6	91.2
Percent Change		–92	–92	–32	–34	–38
(95% CI)		(–93 to –91)	(–93 to –91)	(–38 to –29)	(–36 to –27)	(–41 to –34)

Table 2. Timing of Thrombotic Event and Restarting of Anticoagulation.*

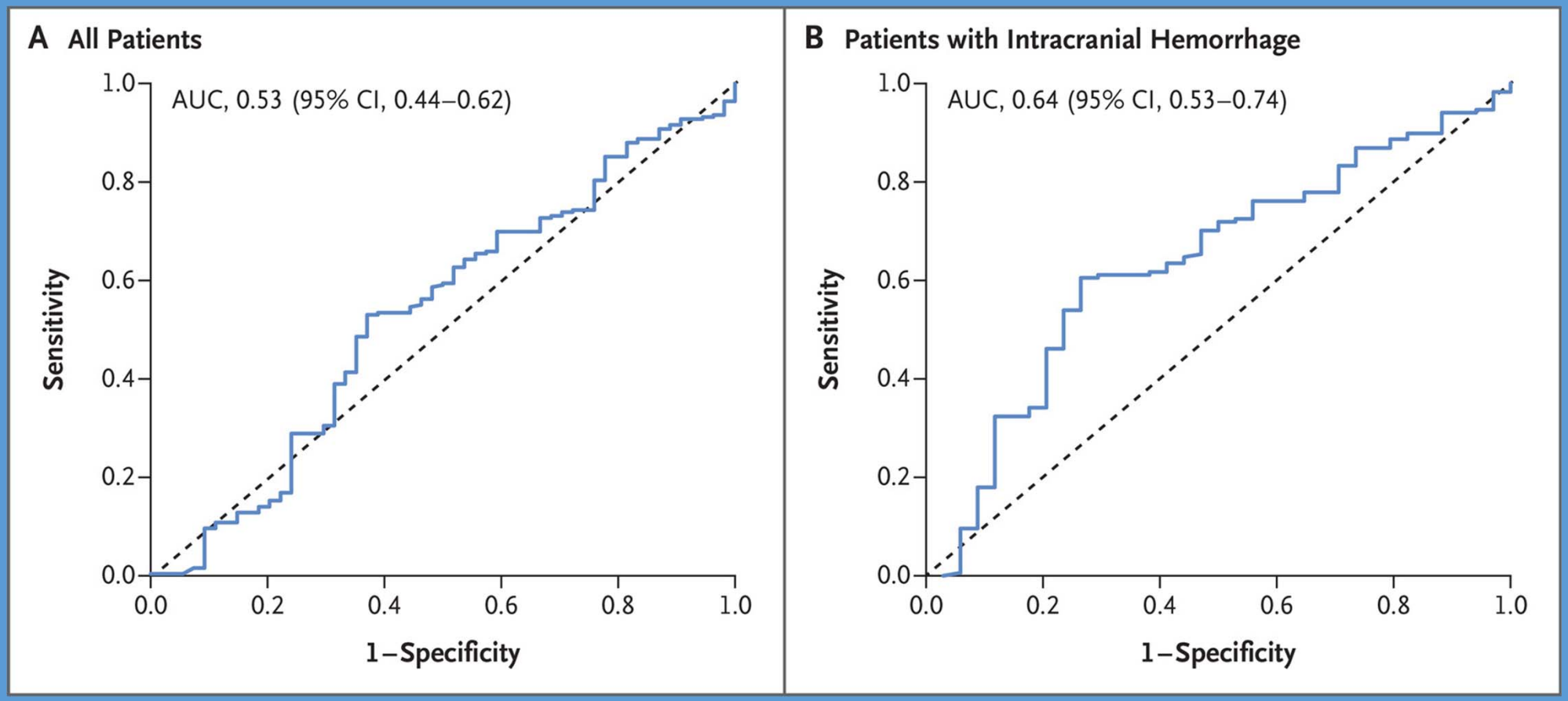
Variable	Safety Population (N=352)			
	Total	<6 Days after Bolus	6–14 Days after Bolus	15–30 Days after Bolus
	number of patients (percent)			
≥1 Thrombotic event within 30 days†	34 (10)	11	11	12
Myocardial infarction	7	6	1	0
Ischemic stroke or stroke of uncertain classification	14	5	6	3
Transient ischemic attack	1	0	0	1
Deep-vein thrombosis	13	1	5	7
Pulmonary embolism	5	1	0	4
Death within 30 days‡	49 (14)	8	21	20
Cardiovascular cause	35	7	15	13
Noncardiovascular cause	12	1	5	6
Uncertain cause	2	0	1	1
Restart of any anticoagulation§	220 (62)	145 (41)	46 (13)	29 (8)
Thrombotic event before restart¶	26 (7)			
Thrombotic event after restart	8 (2)			
Restart of oral anticoagulation‖	100 (28)	31 (9)	37 (11)	32 (9)
Thrombotic event before restart¶	34 (10)			
Thrombotic event after restart	0			

* Thrombotic events that occurred on the day of restarting anticoagulation were considered to have occurred before the restart.
† Some patients had more than one thrombotic event.
‡ Two deaths occurred during study follow-up, but after 30 days.
§ Restart of any anticoagulation includes the use of any form of heparin or low-molecular-weight heparin, fondaparinux, or argatroban, or any oral anticoagulant, including vitamin K antagonists and non–vitamin K antagonists (at any dose and for any duration).
¶ Included are thrombotic events that occurred in patients who never restarted anticoagulation.
‖ Restart of oral anticoagulation includes only the use of vitamin K antagonists or non–vitamin K oral anticoagulants (at any dose and for any duration).

- 82% had good/excellent hemostasis
- 10% thrombotic events (n=24)
- 14% Deaths (n=49)

The NEW ENGLAND JOURNAL of MEDICINE

Reversal of Xa Inhibitors

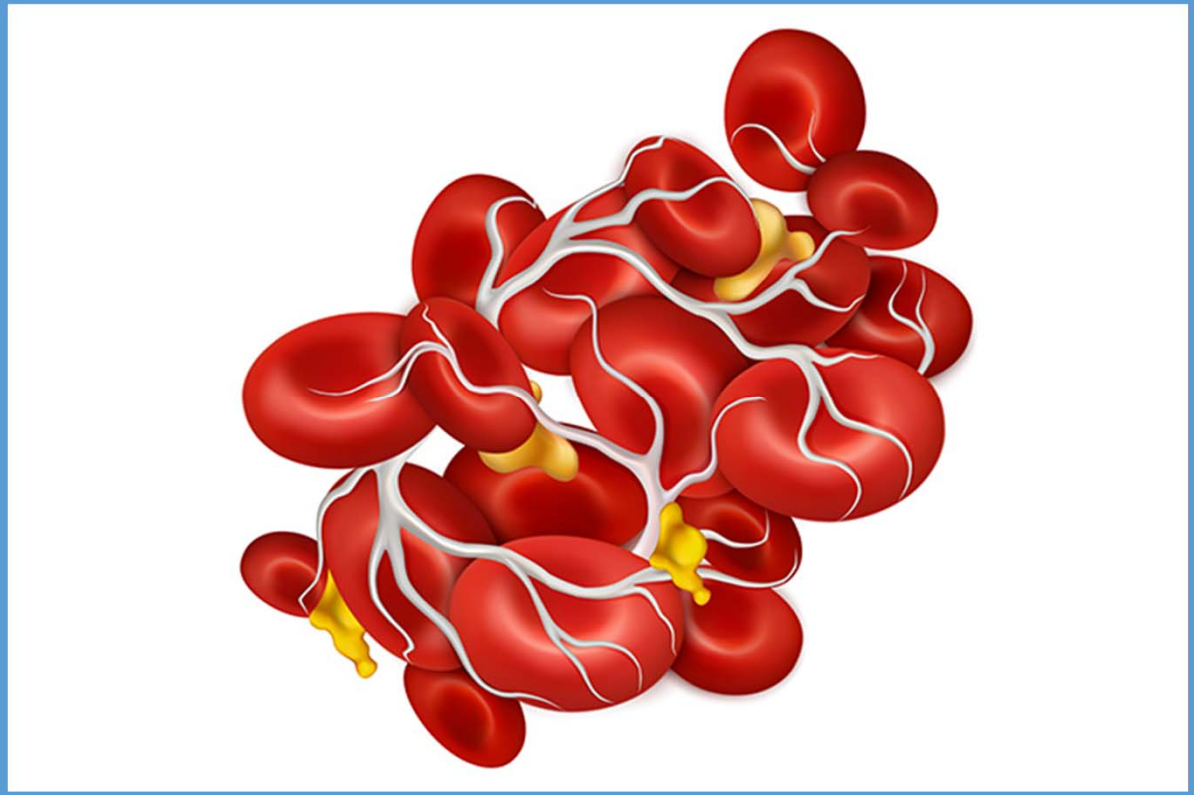


Reversal Summary

- In severe, life threatening bleeding:
  - Associated with Warfarin, PCC is likely best bet
  - Associated with Dabigatran, Praxbind
  - Associated with Xa, Andexanet Alpha if available* or PCC (unproven, incomplete)
- In mild, asymptomatic bleeding:
  - Stop offending agent
  - Consider normalizing INR/Xa v. allowing patient to metabolize drug and monitor closely

*not always formulary, expensive

Resumption of A/C after ICH?



Med Page Today 2020

Systematic Review/Meta-analysis

Long-term antithrombotic treatment in intracranial hemorrhage survivors with atrial fibrillation

Korompoki. Neurology 2017;89:687–696

Prevention of Ischemic Stroke, ICH Recurrence for ICH Survivors

Table 2 Pooled annual event rates for ICH recurrence and IS in different treatment strategies expressed as pooled event rates with 95% CI

	IS event rate (95% CI)	ICH recurrence event rate (95% CI)
VKA	3.2 (2.0-4.9)	4.6 (3.1-6.6)
Antiplatelets	9.5 (7.3-12.0)	3.7 (2.5-5.4)
No antithrombotics	6.1 (4.9-7.6)	4.2 (3.2-5.5)
No VKA (antiplatelets or no antithrombotics)	7.3 (6.2-8.5)	4.0 (3.2-5.0)

Abbreviations: CI = confidence interval; ICH = intracranial hemorrhage; IS = ischemic stroke; VKA = vitamin K antagonist.

Korompoki. Neurology 2017;89:687–696

Systematic Review/Meta-analysis

Original Contribution

Restarting Anticoagulant Therapy After Intracranial Hemorrhage

A Systematic Review and Meta-Analysis

Santosh B. Murthy, MD, MPH; Ajay Gupta, MD; Alexander E. Merkler, MD; Babak B. Navi, MD, MS; Pitchaiah Mandava, MD, PhD, MSEE; Costantino Iadecola, MD; Kevin N. Sheth, MD; Daniel F. Hanley, MD; Wendy C. Ziai, MD, MPH; Hooman Kamel, MD

Murthy Stroke. 2017;48:00-00

Restarting AC after ICH

Study	Indications for AC (%)*						Received AC	AC Type	Time to Restarting AC, d
	NVAF	Prosthetic Heart Valve	VTE	Previous Stroke	Recent MI	Other			
De Vleeschouwer et al[17]	56 (51.9)	30 (27.8)	11 (10.2)	4 (3.7)	2 (1.9)	5 (4.6)	25 (23.1)	VKA	11
Claassen et al[18]	23 (47.9)	12 (25.0)	10 (20.8)	N/A	N/A	3 (6.3)	23 (47.9)	VKA (warfarin)	10
Majeed et al[20]	135 (58.0)	35 (15.0)	37 (16.0)	N/A	N/A	27 (11.0)	45 (34.1)†	VKA (warfarin)	39.2
Yung et al[19]	191 (67.3)	37 (13.0)	31 (10.9)	N/A	N/A	N/A	91 (32.0)	VKA (warfarin)	N/A
Gathier et al[12]	10 (40.0)	2 (8.0)	6 (24.0)	8 (32.0)	2 (8.0)	4 (16.0)	12 (48.0)	VKA	Within 2 mo
Nielsen et al[16]	1752 (100.0)	0	0	0	0	0	509 (29.1)	VKA/NOAC	N/A
Kuramatsu et al[11]	664 (77.8)	67 (7.9)	71 (8.3)	N/A	N/A	51 (6.0)	172 (23.9)	VKA	31
Ottosen et al[15]	1032 (34.7)	78 (2.6)	236 (7.9)	2139 (71.8)	264 (8.9)	30 (1.0)	160 (6.3)‡	VKA/NOAC	Within first 6 mo

AC indicates anticoagulation; MI, myocardial infarction; N/A, not available; NOAC, nonvitamin K oral anticoagulant medications; NVAF, non-valvular atrial fibrillation; VKA, vitamin K antagonists; and VTE, venous thromboembolism.

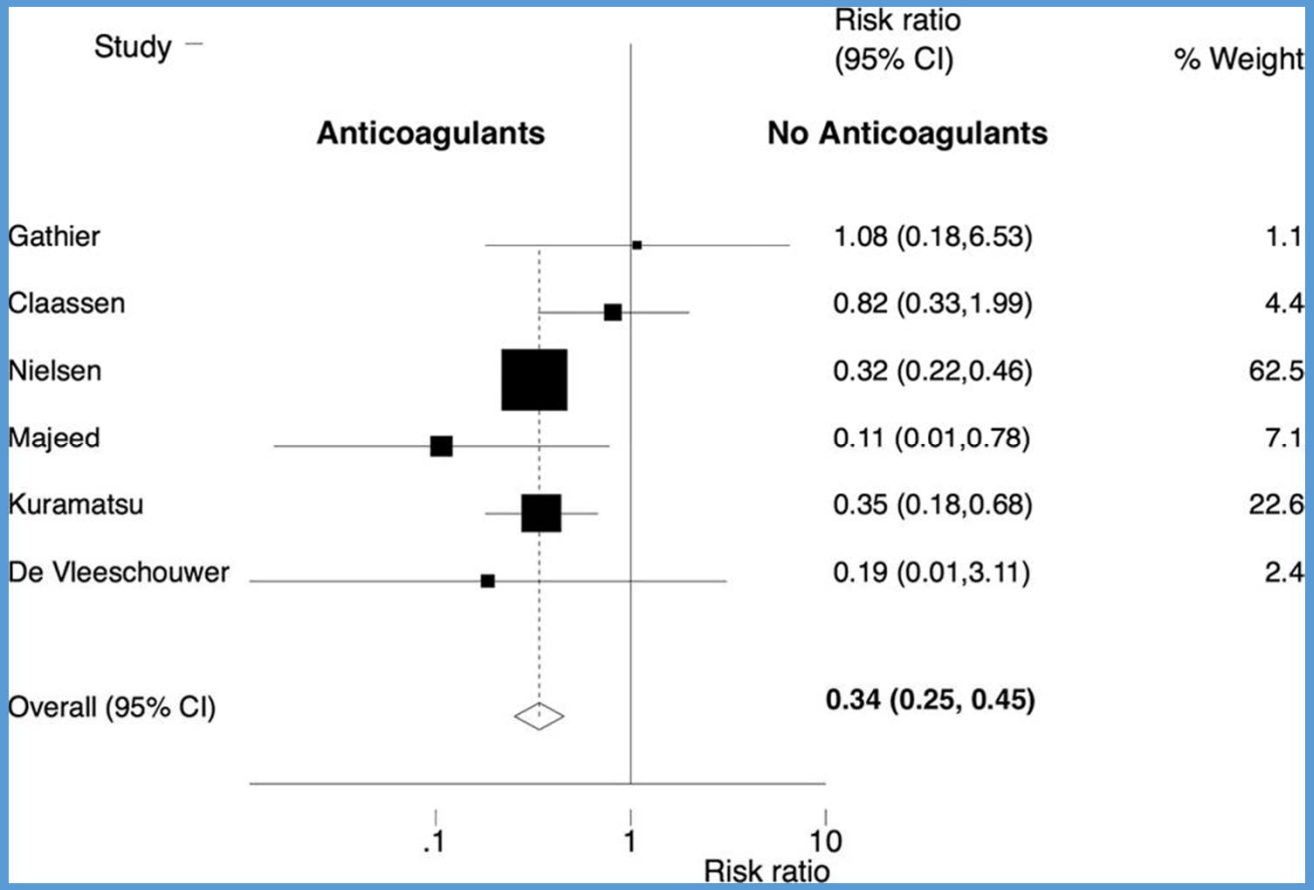
*Sum of all indications may exceed 100% because some patients had multiple indications for AC.

†Data on 132 patients with cardiac indications who were restarted on AC were available.

‡Data were available on 2543 patients who survived.

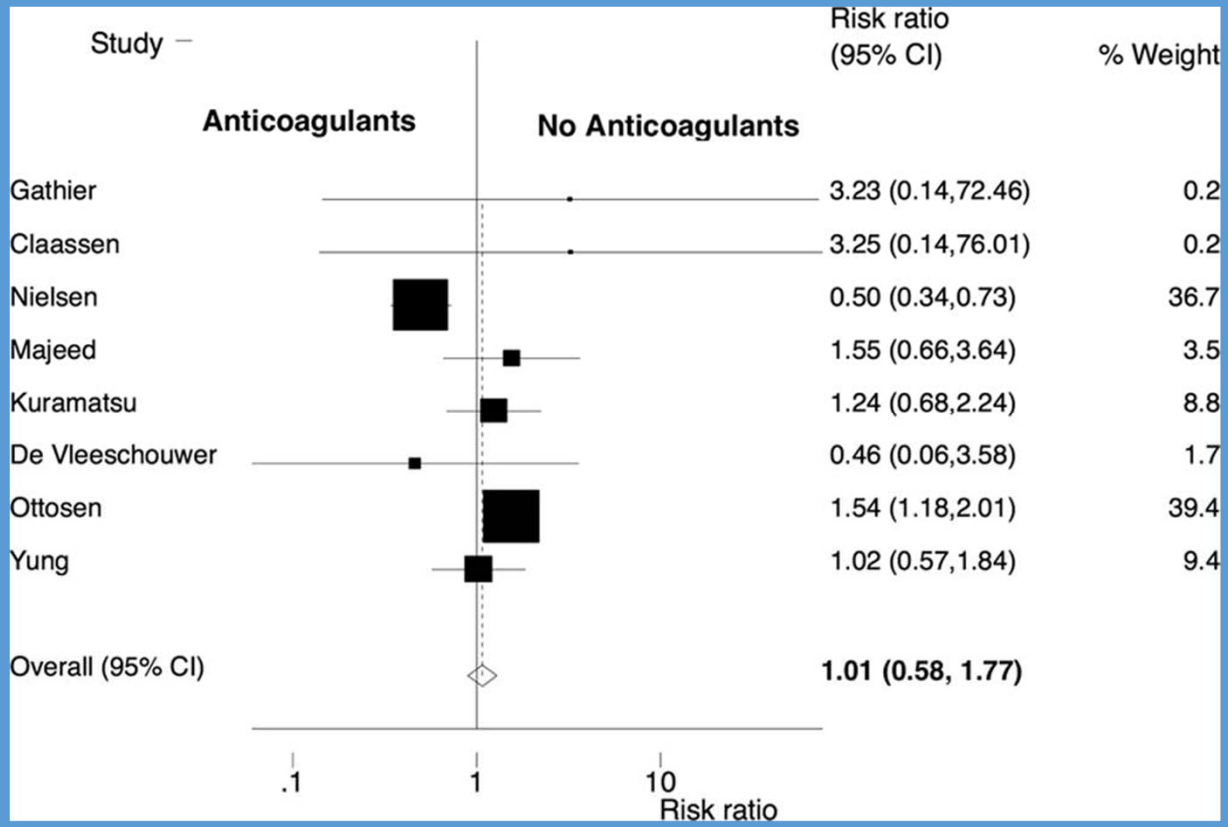
Murthy Stroke. 2017;48:00-00

Relative Risk of Recurrent Ischemic Stroke



Murthy Stroke. 2017;48:00-00

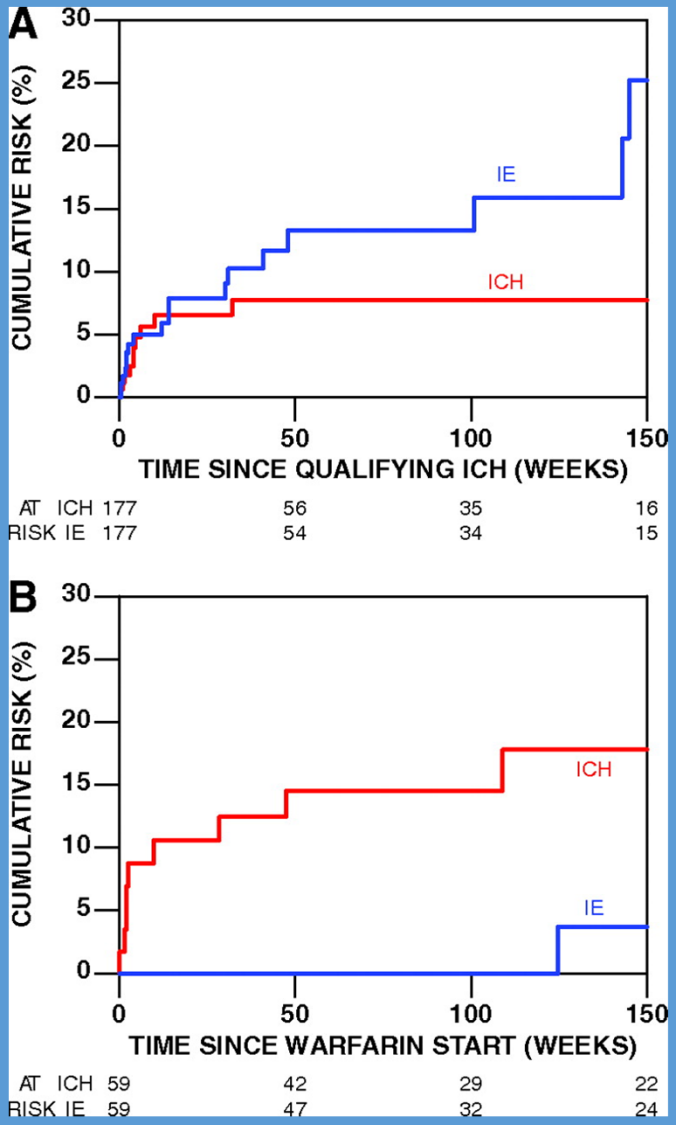
Relative Risk of Recurrent ICH



Murthy Stroke. 2017;48:00-00

When to Resume Warfarin after ICH?

- Observational study (2010)
  - 3 institutions, 3 countries
  - 234 patients with warfarin-associated ICH identified
  - 177 survived the first week
- Warfarin resumed in 45 patients
- Optimal timing appears to be 10-30 weeks



Majeed. Stroke. 2010 Dec;41(12):2860-6

What about Amyloid? Lobar v. non-lobar bleeds

- CAA confers a high risk of recurrence:
  - in the range of 7% (95% CI: 3–12%) per year in well phenotyped patients
- Risk of recurrent ICH may not be uniform
  - Cortical Superficial Siderosis – a recently discovered hemorrhagic MRI signature of CAA– is a potent marker of individuals at highest risk for recurrent ICH
- NOACs might be an attractive option in CAA-related ICH survivors, in view of their 50% lower risk of ICH relative to warfarin
  - Absolute rates of ICH that are similar to aspirin monotherapy

Charidimou. Int J Stroke. 2017 Jan 1:1747493017741384

Functional Outcomes in ICH Survivors

RESEARCH ARTICLE

Oral Anticoagulation and Functional Outcome after Intracerebral Hemorrhage

Alessandro Biffi, MD,[1,2,3*] Joji B. Kuramatsu, MD,[4*] Audrey Leasure, BS,[5] Hooman Kamel, MD,[6] Christina Kourkoulis, BS,[1,2,3] Kristin Schwab, BA,[1,3] Alison M. Ayres, BA,[1,3] Jordan Elm, PhD,[7] M. Edip Gurol, MD, MSc,[1,3] Steven M. Greenberg, MD, PhD,[1,3] Anand Viswanathan, MD, PhD,[1,3] Christopher D. Anderson, MD, MMSc,[1,2,3] Stefan Schwab, MD,[4] Jonathan Rosand, MD, MSc,[1,2,3] Fernando D. Testai, MD, PhD,[8] Daniel Woo, MD, MS,[9] Hagen B. Huttner, MD,[4*] and Kevin N Sheth, MD[5*]

Annals of Neurology Volume 82, Issue 5, pages 755-765, 31 OCT 2017

Functional Outcomes in ICH Survivors

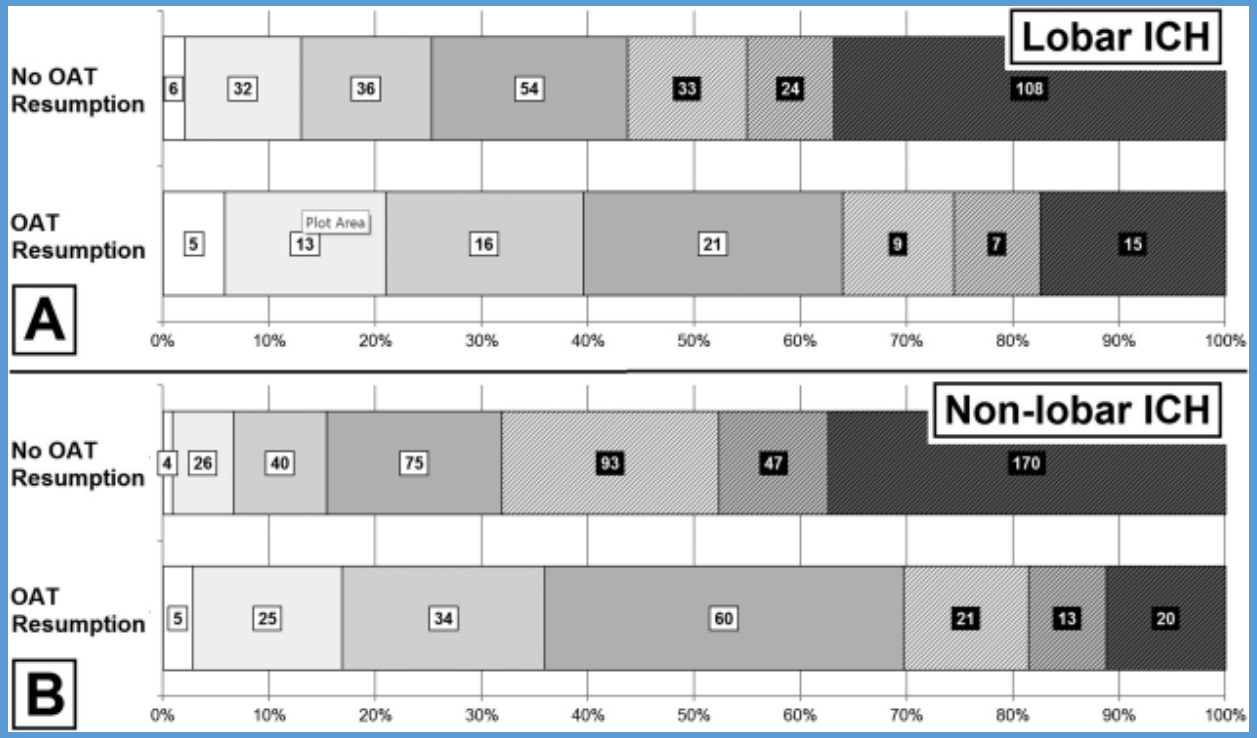
TABLE 3. Oral Anticoagulation Resumption and Outcomes following Intracerebral Hemorrhage

	All ICH			Nonlobar ICH			Lobar ICH		
Outcome[a]	HR	95% CI	*p*	HR	95% CI	*p*	HR	95% CI	*p*
Mortality	0.27	0.19–0.40	<0.0001[b]	0.25	0.14–0.44	<0.0001[b]	0.29	0.17–0.45	<0.0001[b]
Favorable outcome, mRS = 0–3	4.15	2.92–5.90	<0.0001[b]	4.22	2.57–6.94	<0.0001[b]	4.08	2.48–6.72	<0.0001[b]
All-cause stroke	0.47	0.36–0.64	<0.0001[b]	0.41	0.25–0.67	0.0004[b]	0.51	0.37–0.76	0.0006[b]
Recurrent ICH	1.20	0.95–1.58	0.21	1.17	0.89–1.54	0.27	1.26	0.88–1.71	0.22
Ischemic stroke	0.44	0.29–0.66	<0.0001[b]	0.39	0.21–0.74	0.004[b]	0.48	0.25–0.75	0.003[b]

[a]All analyses were adjusted by means of propensity score matching using the following parameters: Glasgow Coma Scale at presentation, ICH volume, presence of intraventricular hemorrhage, discharge mRS, CHA_2DS_2-VASc score, and HAS-BLED score.
[b]Statistically significant.
CI = confidence interval; HR = hazard ratio; ICH = intracerebral hemorrhage; mRS = modified Rankin Scale.

Annals of Neurology Volume 82, Issue 5, pages 755-765, 31 OCT 2017

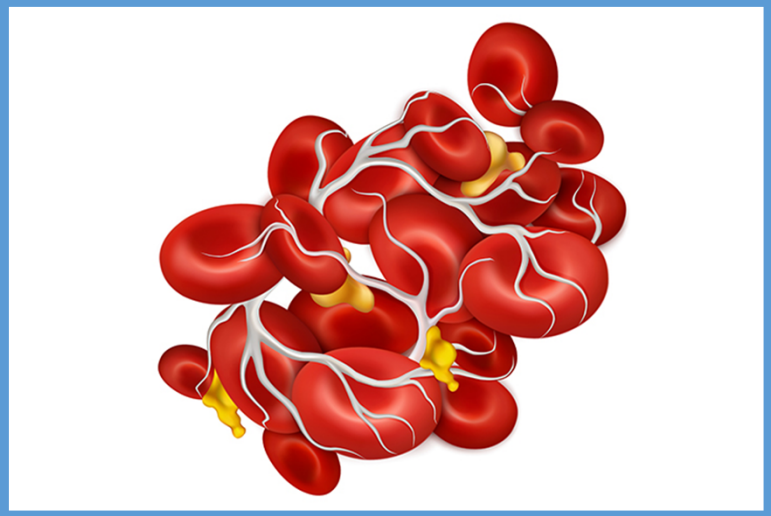
Oral Anticoagulation and Functional Outcome (mRS) after Intracerebral Hemorrhage



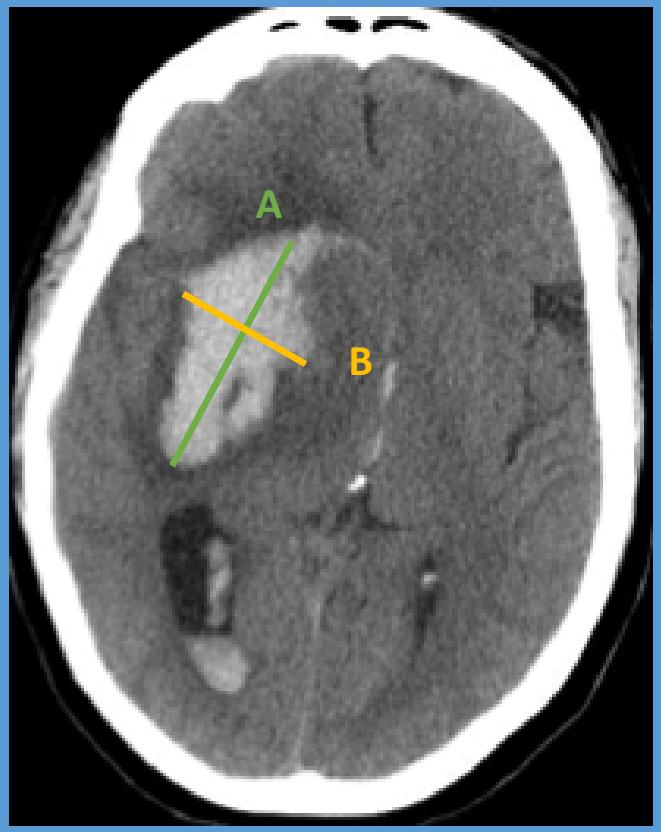
Annals of Neurology Volume 82, Issue 5, pages 755-765, 31 OCT 2017

Summary of Resumption of OAT

- Must weigh risks of ischemic stroke versus recurrence of ICH
- Careful blood pressure control is probably helpful
- May be reasonable to resume OAT in ICH survivors
  - Lobar v. non-lobar locations
- Active area of research



Prognosis and and the ICH Score

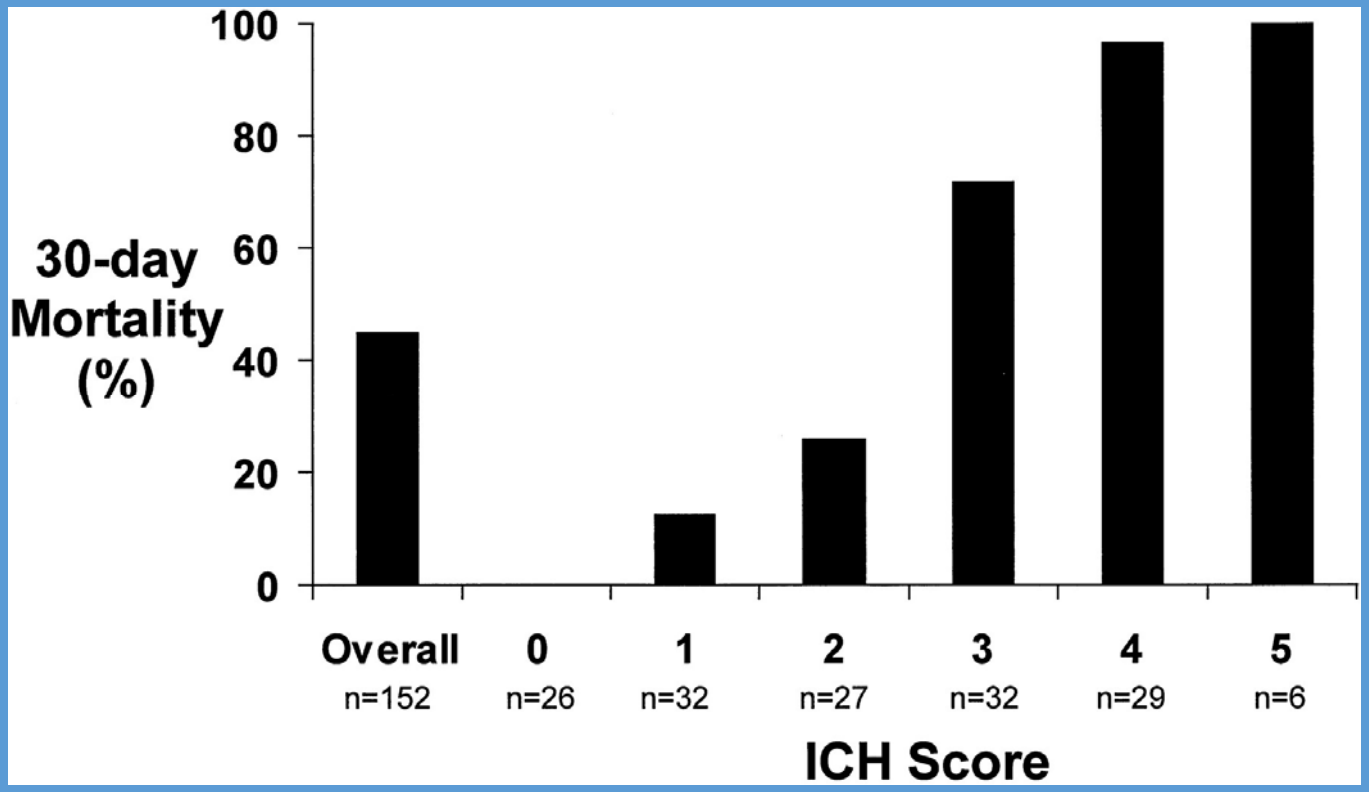


(AxBxC)/2

Glasgow Coma Score	3-4	+2
	5-12	+1
	13-15	**0**
Age ≥ 80	**No**	**0**
	Yes	+1
ICH Volume ≥ 30ml	**No**	**0**
	Yes	+1
Intraventricular Hemorrhage	**No**	**0**
	Yes	+1
Infratentorial Origin of Hemorrhage	**No**	**0**
	Yes	+1

Hemphill. Stroke. 2001;32:891-897

The ICH Score and 30-day mortality



J. Claude Hemphill III et al. Stroke. 2001;32:891-897

Predicting Outcome after ICH

Early subjective clinical judgment of physicians correlates more closely with 3-month outcome after ICH than prognostic scales

Table 3 Correlation with 3-month outcome of clinician predictions compared to ICH outcome scales

		ICH score		FUNC score	
Clinician group	r^a	r^a	p	r^b	p
Total patient cohort (n = 121)					
All physicians	0.75	0.62	0.057	−0.56	0.009
Attendings (n = 91)	0.78		0.02		0.003
Trainees (n = 30)	0.64		0.87		0.56
Nurses	0.72		0.16		0.03
For survivors at 3 mo (n = 78)					
All physicians	0.62	0.34	0.02	−0.33	0.02
Attendings (n = 59)	0.72		0.002		0.001
Trainees (n = 19)	0.21		0.61		0.64
Nurses	0.58		0.06		0.05
Without comfort care bias[c] (n = 89)					
All physicians	0.68	0.50	0.07	−0.42	0.01
Attendings (n = 65)	0.73		0.02		0.004
Trainees (n = 24)	0.52		0.91		0.60
Nurses	0.64		0.17		0.04

Abbreviation: ICH = intracerebral hemorrhage.

[a] *r* represents the Spearman rank correlation coefficient vs 3-month actual outcome as measured by the modified Rankin Scale. A perfect coefficient with an absolute value of 1 occurs when the 2 tested variables are a perfect monotonic function of the other. The listed *p* values represent the probabilities that differences in *r* for the ICH score and FUNC score with respect to those for the clinician groups are due to chance.

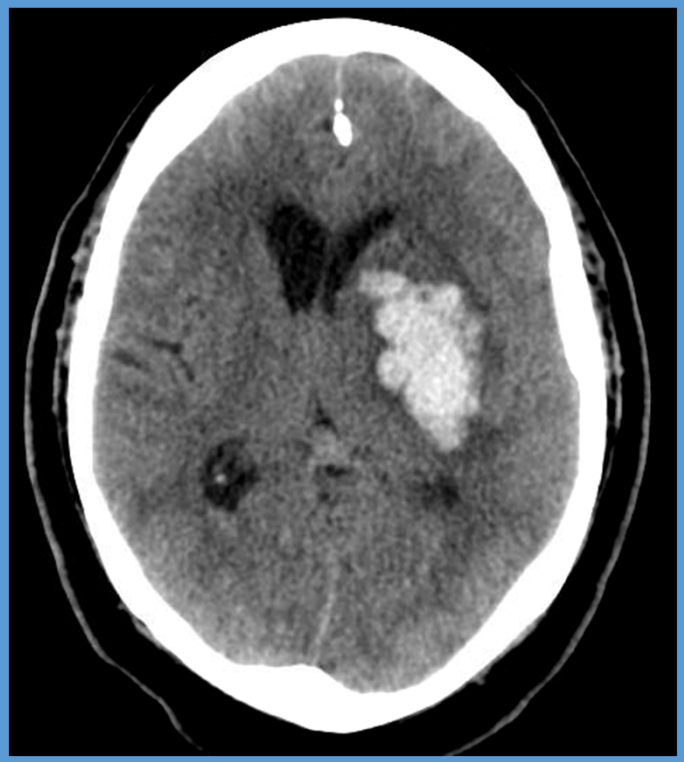
[b] Because a high FUNC score value is ideally supposed to correlate with an eventual low modified Rankin Scale value, the Spearman rank correlation coefficients calculated for FUNC scores are negative. The absolute value can be compared with the other calculated *r* values.

[c] Patients for whom either a physician or a nurse indicated on the prediction form that he or she would be inclined to recommend comfort care to the family were excluded from this analysis.

Hwang.Neurology. 2016 Jan 12; 86(2): 126–133.

Next Steps

- TIMING trial (ongoing, est. 5/2021)
  - Swedish Stroke Register of ischemic stroke patients
  - Randomization (n=3000) (1:1) within 72 h from ischemic stroke onset to either early (≤ 4 days) or delayed (≥ 5-10 days) start of NOAC therapy[1]
- ASPIRE trial (ongoing, est. 4/2024)
  - Anticoagulation in ICH Survivors for Prevention and Recovery
  - Resumption of anti-thrombotic (aspirin vs apixaban) in ICH survivors



1. Asberg. Trials. 2017 Dec 2;18(1):581

Thank you

- Questions?