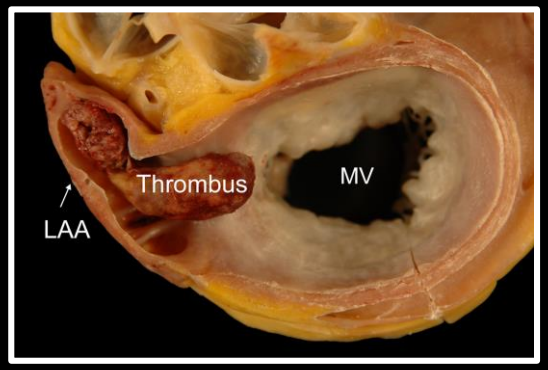
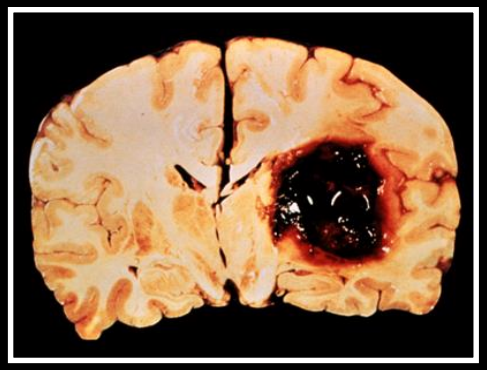
Stroke Prevention in Atrial Fibrillation and Previous Intracerebral Hemorrhage





Ashkan Shoamanesh, MD, FRCPC

Assistant Professor of Medicine (Neurology)

Director, Stroke Fellowship Program

Marta and Owen Boris Chair in Stroke Research and Care

McMaster University

PHRI

Hamilton Health Sciences

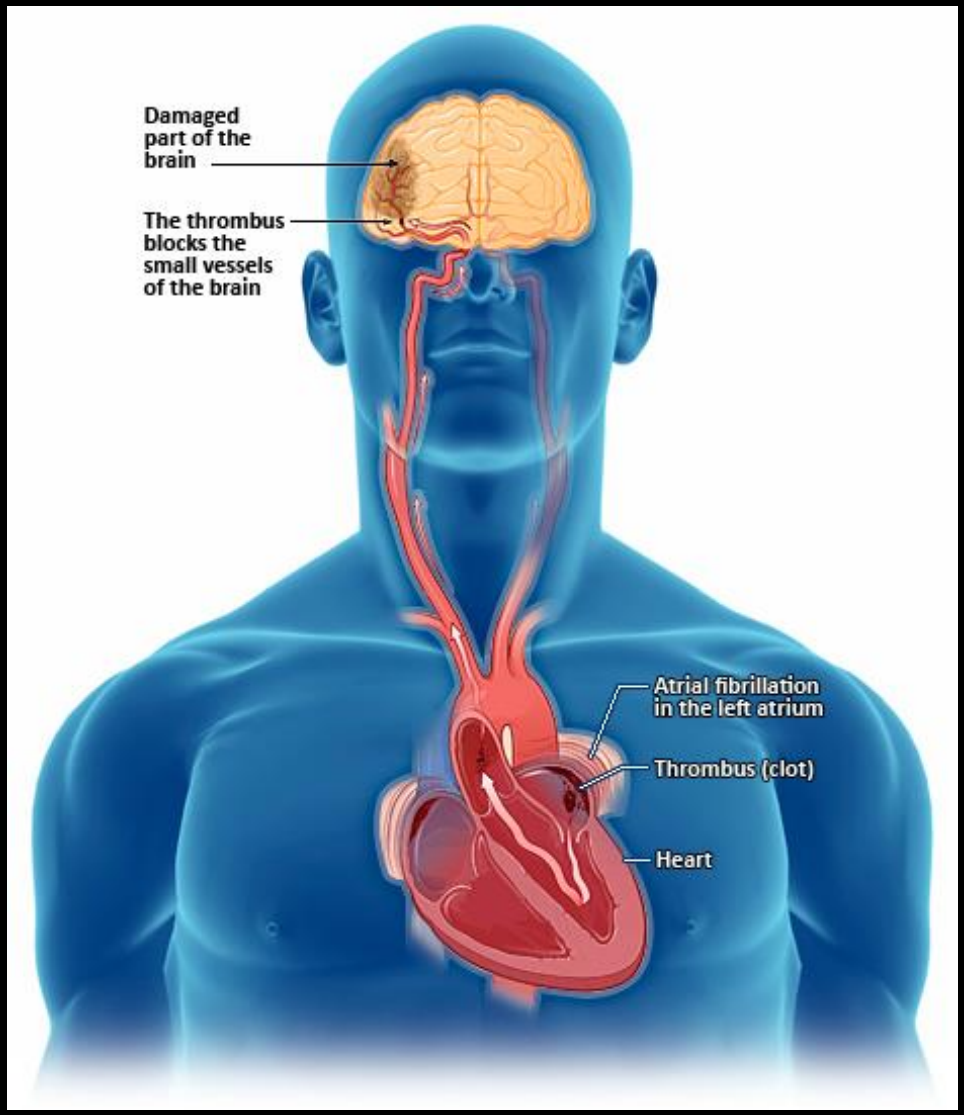
Objectives

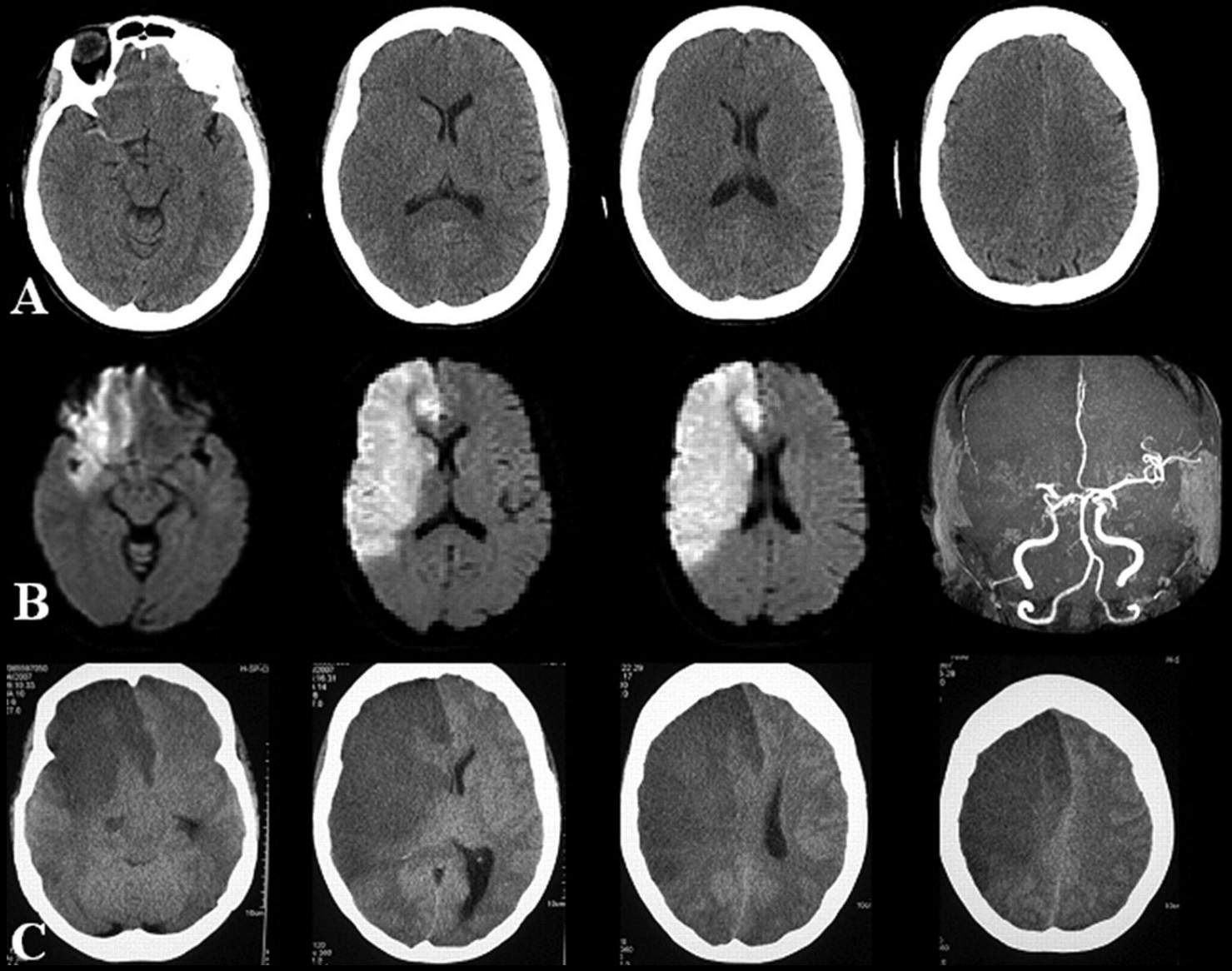
- Introduce clinical dilemma of antithrombotic therapy following ICH in patients with AF.
- Review current evidence and clinical guidelines
- Discuss ongoing randomized controlled trials

Background

- Atrial fibrillation (AF) currently afflicts an estimated 3% of Canadians.

- Primary source of cardioembolic stroke.

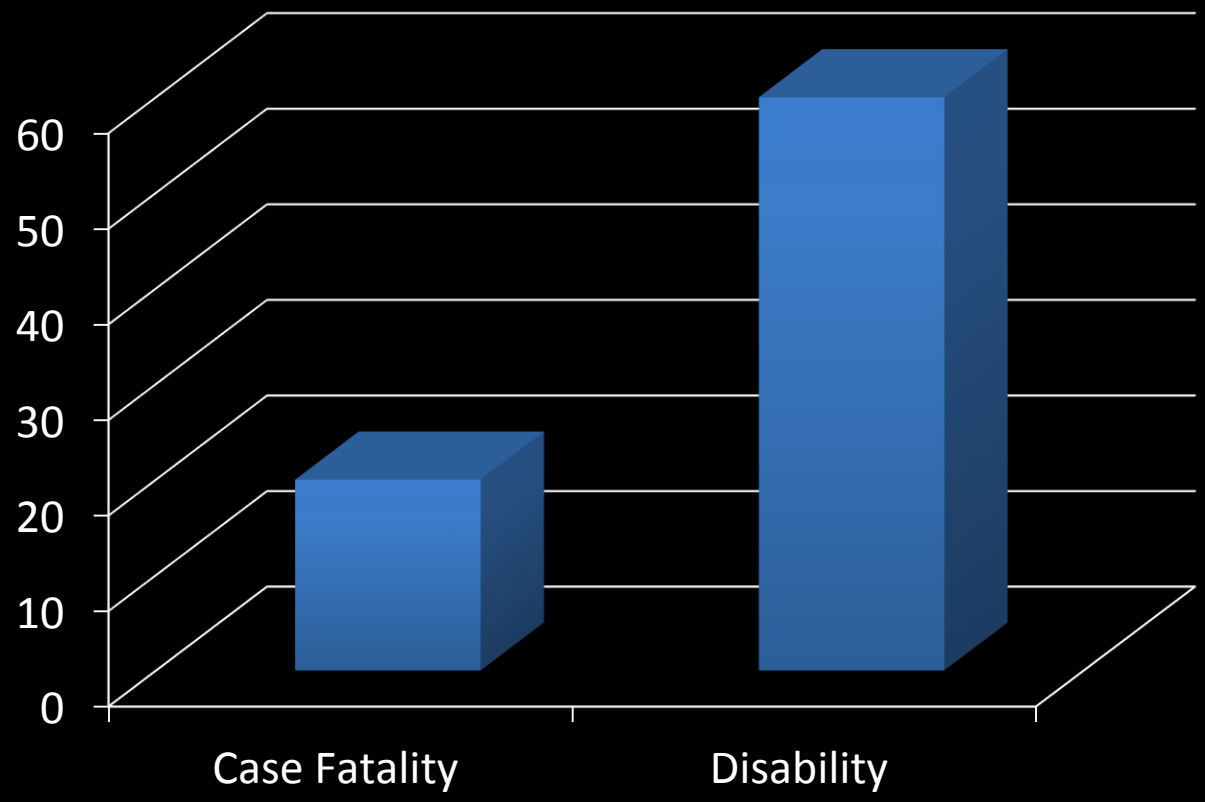




Highest rate of death and long-term disability amongst ischemic stroke subtypes

Stroke Outcomes

Effect of first ischemic stroke in patients with AF (n=597)



AF=atrial fibrillation

Gladstone DJ et al. *Stroke* 2009; 40:235-240

Oral Anticoagulant Therapy Prescription in Patients With Atrial Fibrillation Across the Spectrum of Stroke Risk

Insights From the NCDR PINNACLE Registry FREE

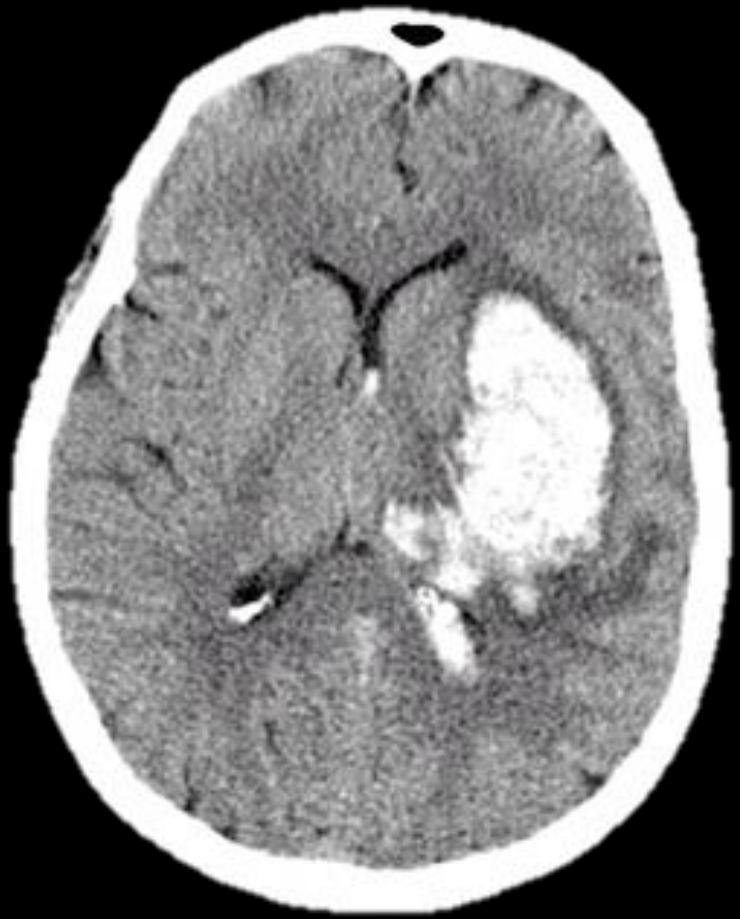
Jonathan C. Hsu, MD, MAS[1]; Thomas M. Maddox, MD, MSc[2,3,4]; Kevin F. Kennedy, MS[5]; David F. Katz, MD[3]; Lucas N. Marzec, MD[3]; Steven A. Lubitz, MD, MPH[6]; Anil K. Gehi, MD[7]; Mintu P. Turakhia, MD, MAS[8,9]; Gregory M. Marcus, MD, MAS[10]

- Cross-sectional registry of outpatients with AF enrolled in the American College of Cardiology National Cardiovascular Data PINNACLE (2008-2012) Registry ~ 430 000 AF patients
- Only 45% received anticoagulation
  - 90.3% Warfarinth
- 26% ASA

- $CHADS_2 \geq 3$ 50% prescribed anticoagulation

JAMA Cardiol. 2016;1(1):55-62. doi:10.1001/jamacardio.2015.0374.

Anticoagulant-Related Intracerebral Hemorrhage



Factors Influencing Physicians' Reported Use of Anticoagulation Therapy in Nonvalvular Atrial Fibrillation: A Cross-Sectional Survey

Cary P. Gross, MD,[1] Eric W. Vogel, MD,[2] Abhay J. Dhond, MD,[1] Cheryl B. Marple, MS, MPH,[3] Roger A. Edwards, ScD,[4*] Ole Hauch, MD,[3] Elizabeth A. Demers, MD,[2] and Michael Ezekowitz, MD[2]

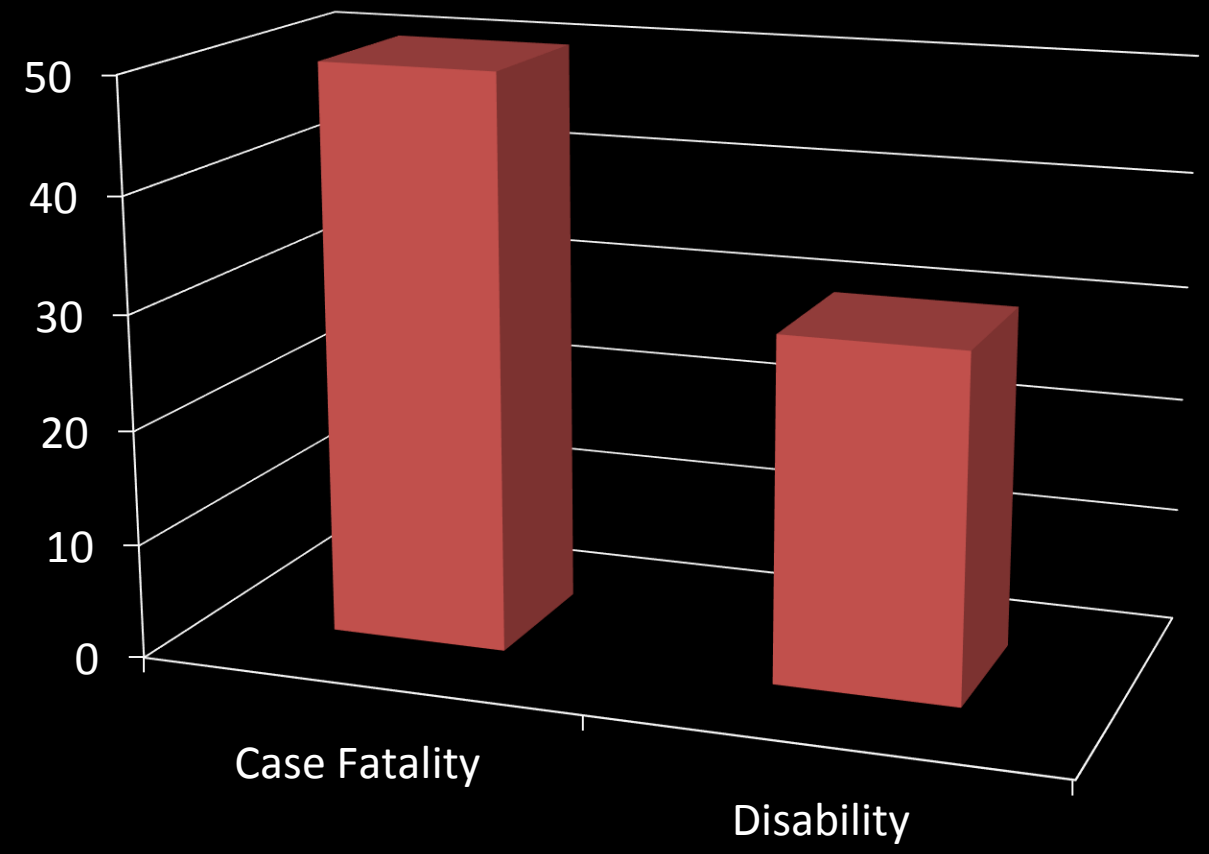
- Physician survey (case vignettes)
- 142 responses from general internists
- Estimates of annual rate of anticoagulant-associated intracerebral hemorrhage were 10-fold higher than literature-based estimates.
- Decision on whether to treat driven not by perceived benefit in a particular case, but rather concern for harm

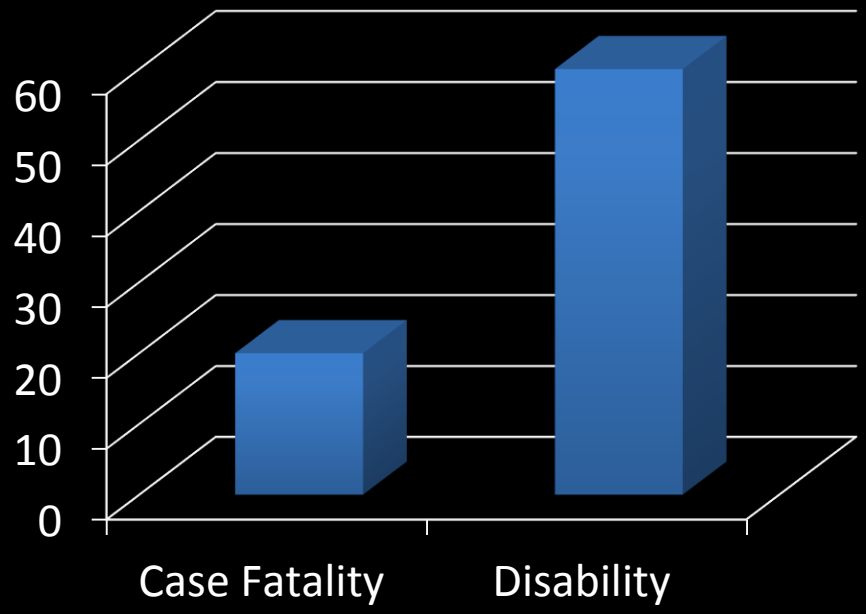
CLINICAL THERAPEUTICS® / VOL. 25, NO. 6, 2003

Incidence, case fatality, and functional outcome of intracerebral haemorrhage over time, according to age, sex, and ethnic origin: a systematic review and meta-analysis

Charlotte J van Asch, Merel JA Luitse, Gabriël JE Rinkel, Ingeborg van der Tweel, Ale Algra, Catharina JM Klijn

Lancet Neurol 2010; 9: 167–76



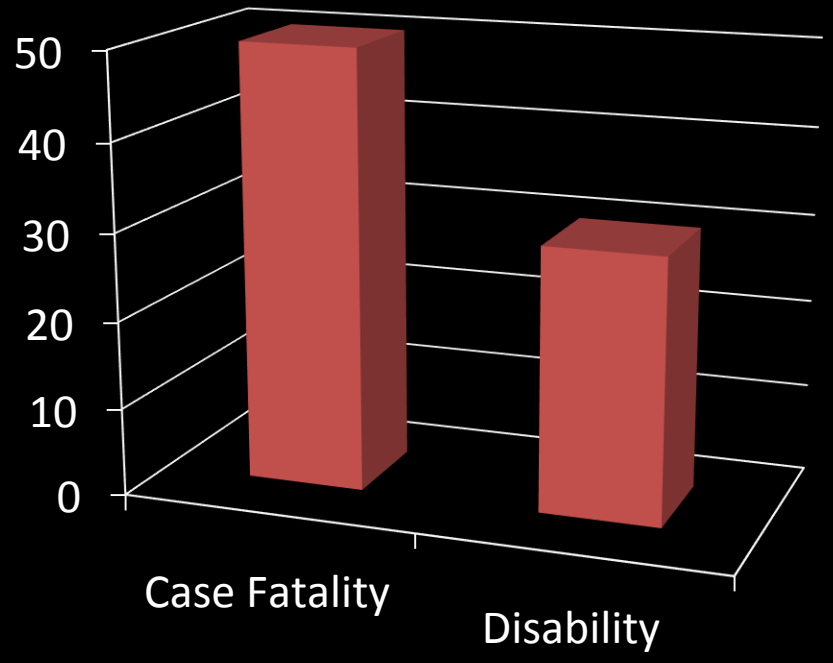


AF-related Ischemic Stroke

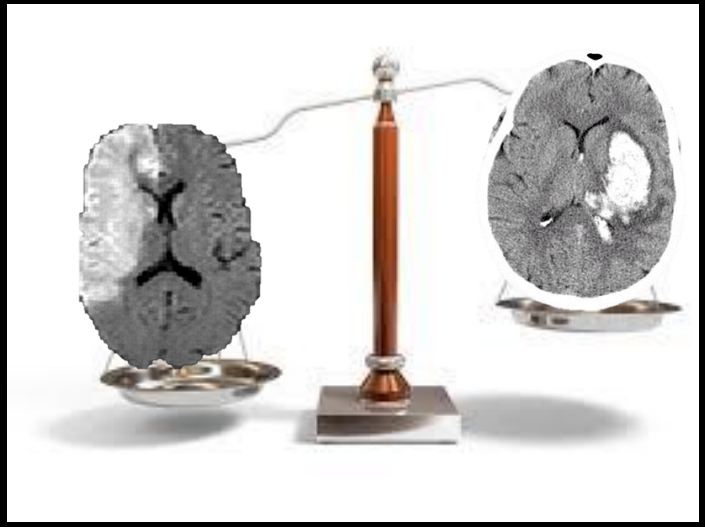
80% death and long-term disability.

Anticoagulant-related ICH

80% death and long-term disability.



- Anticoagulating AF patients after intracerebral hemorrhage poses a challenging clinical dilemma that requires balancing the benefit of reducing thromboembolism against the potential increased risk of recurrent intracerebral hemorrhage.



Guidelines

AHA 2015 (Management Spont. ICH)	**Avoid anticoagulation <u>WITH WARFARIN.</u>** **Anticoagulation after nonlobar ICH and antiplatelet monotherapy after any ICH can be considered particularly where there exists a strong indication** **The usefulness of <u>NOACs</u> in patients with AF and prior ICH uncertain.**
ESO 2014	**In the absence of RCTs to address these treatment dilemmas, we cannot make firm recommendations about whether and when to resume antithrombotic drugs after ICH.**
Canadian Stroke Best Practice Recommendations 2015	**If there is a persisting strong indication for anticoagulation (e.g. atrial fibrillation, mechanical heart valve), the decision about when to restart anticoagulant therapy should be made on a case-by-case basis**

What to do?

- Significant clinical equipoise and variability in practice
  - 2008 Japanese physician survey: 91% of respondents resumed anticoagulation (76% with warfarin).
  - Center dependent in Europe with antithrombotic resumption rate ranging from 11-45%.

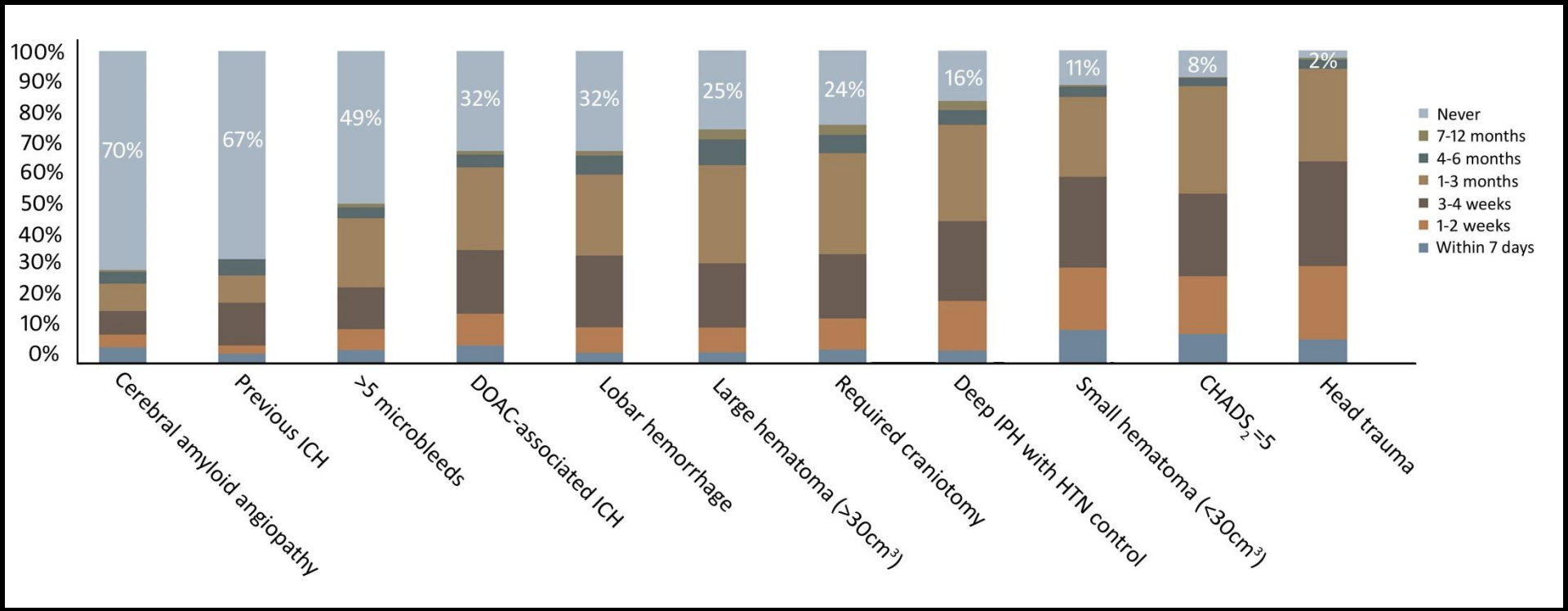
Maeda K, et al. *J Neurol Sci*. 2012;312:82-85
Pasquini M, et al. *Stroke*. 2014;45:2643-2648

N=228

41% Stroke neurologists (CSC, NAVIGATE ESUS investigators)

26% Neurosurgeons (ASNS)

33% Thrombosis (ISTH)



Can Patients Be Anticoagulated After Intracerebral Hemorrhage?: A Decision Analysis

Mark H. Eckman, Jonathan Rosand, Katherine A. Knudsen, Daniel E. Singer and Steven M. Greenberg

- Markov decision analysis assessing quality-adjusted life years among patients receiving either no antithrombotic therapy, aspirin or warfarin after intracerebral hemorrhage in patients with AF

- Suggestion: aspirin is likely the preferred treatment in most cases, on the basis of lower recurrent intracerebral hemorrhage rates, despite a much lower efficacy for ischemic stroke prevention.
  - Deep ICH: Consider restarting anticoagulation
  - Lobar ICH: No antithrombotic therapy or ASA

(*Stroke*. 2003;34:1710-1716.)

Can Patients Be Anticoagulated After Intracerebral Hemorrhage?: A Decision Analysis
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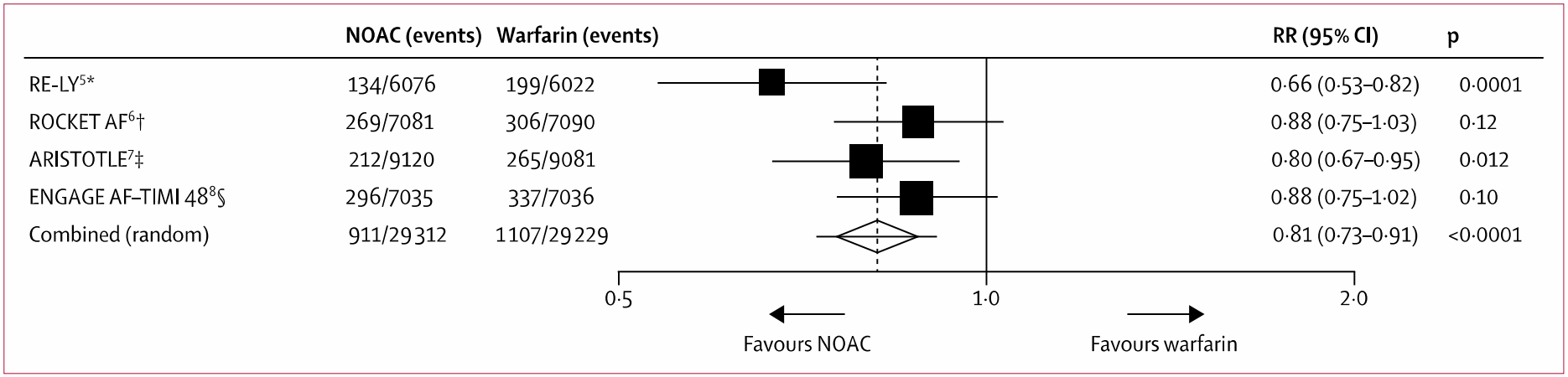
- Limitations:
  - Direct oral anticoagulants not factored into analysis
    - Not available at the time
  - Estimated 2-fold increased rate of ICH with wafarin
    - May not be the case.

(*Stroke*. 2003;34:1710-1716.)

Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials

Christian T Ruff, Robert P Giugliano, Eugene Braunwald, Elaine B Hoffman, Naveen Deenadayalu, Michael D Ezekowitz, A John Camm, Jeffrey I Weitz, Basil S Lewis, Alexander Parkhomenko, Takeshi Yamashita, Elliott M Antman

Lancet 2014; 383: 955–62



	NOAC (events)	Warfarin (events)	RR (95% CI)	p
RE-LY[5]*	134/6076	199/6022	0·66 (0·53–0·82)	0·0001
ROCKET AF[6]†	269/7081	306/7090	0·88 (0·75–1·03)	0·12
ARISTOTLE[7]‡	212/9120	265/9081	0·80 (0·67–0·95)	0·012
ENGAGE AF–TIMI 48[8]§	296/7035	337/7036	0·88 (0·75–1·02)	0·10
Combined (random)	911/29 312	1107/29 229	0·81 (0·73–0·91)	<0·0001

19% reduction in stroke and systemic embolism with direct oral anticaogulants vs. Warfarin

Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials

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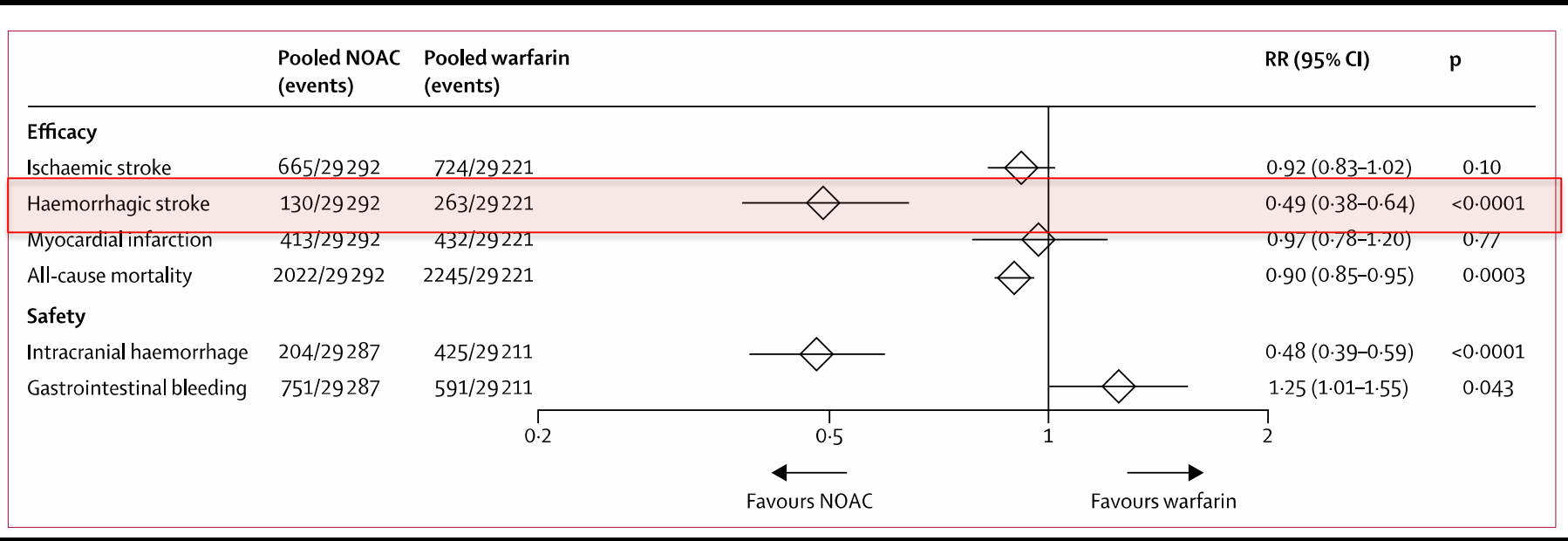

51% reduction in hemorrhagic stroke

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Apixaban in Patients with Atrial Fibrillation

Stuart J. Connolly, M.D., John Eikelboom, M.B., B.S., Campbell Joyner, M.D., Hans-Christoph Diener, M.D., Ph.D., Robert Hart, M.D., Sergey Golitsyn, M.D., Ph.D., Greg Flaker, M.D., Alvaro Avezum, M.D., Ph.D., Stefan H. Hohnloser, M.D., Rafael Diaz, M.D., Mario Talajic, M.D., Jun Zhu, M.D., Prem Pais, M.B., B.S., M.D., Andrzej Budaj, M.D., Ph.D., Alexander Parkhomenko, M.D., Ph.D., Petr Jansky, M.D., Patrick Commerford, M.B., Ch.B., Ru San Tan, M.B., B.S., Kui-Hian Sim, M.B., B.S., Basil S. Lewis, M.D., Walter Van Mieghem, M.D., Gregory Y.H. Lip, M.D., Jae Hyung Kim, M.D., Ph.D., Fernando Lanas-Zanetti, M.D., Antonio Gonzalez-Hermosillo, M.D., Antonio L. Dans, M.D., Muhammad Munawar, M.D., Ph.D., Martin O'Donnell, M.B., Ph.D., John Lawrence, M.D., Gayle Lewis, Rizwan Afzal, M.Sc., and Salim Yusuf, M.B., B.S., D.Phil., for the AVERROES Steering Committee and Investigators*

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Table 3. Rates of Study Outcomes in the Two Treatment Groups.*

Outcome	Apixaban (N=2808)		Aspirin (N=2791)		Hazard Ratio with Apixaban (95% CI)	P Value
	no. of patients with first event	%/yr	*no. of patients with first event*	%/yr		
Stroke†	49	1.6	105	3.4	0.46 (0.33–0.65)	<0.001
Ischemic	35	1.1	93	3.0	0.37 (0.25–0.55)	<0.001
Hemorrhagic	6	0.2	9	0.3	0.67 (0.24–1.88)	0.45
Unspecified	9	0.3	4	0.1	2.24 (0.69–7.27)	0.18
Disabling or fatal	31	1.0	72	2.3	0.43 (0.28–0.65)	<0.001

63% RRR in ischemic stroke

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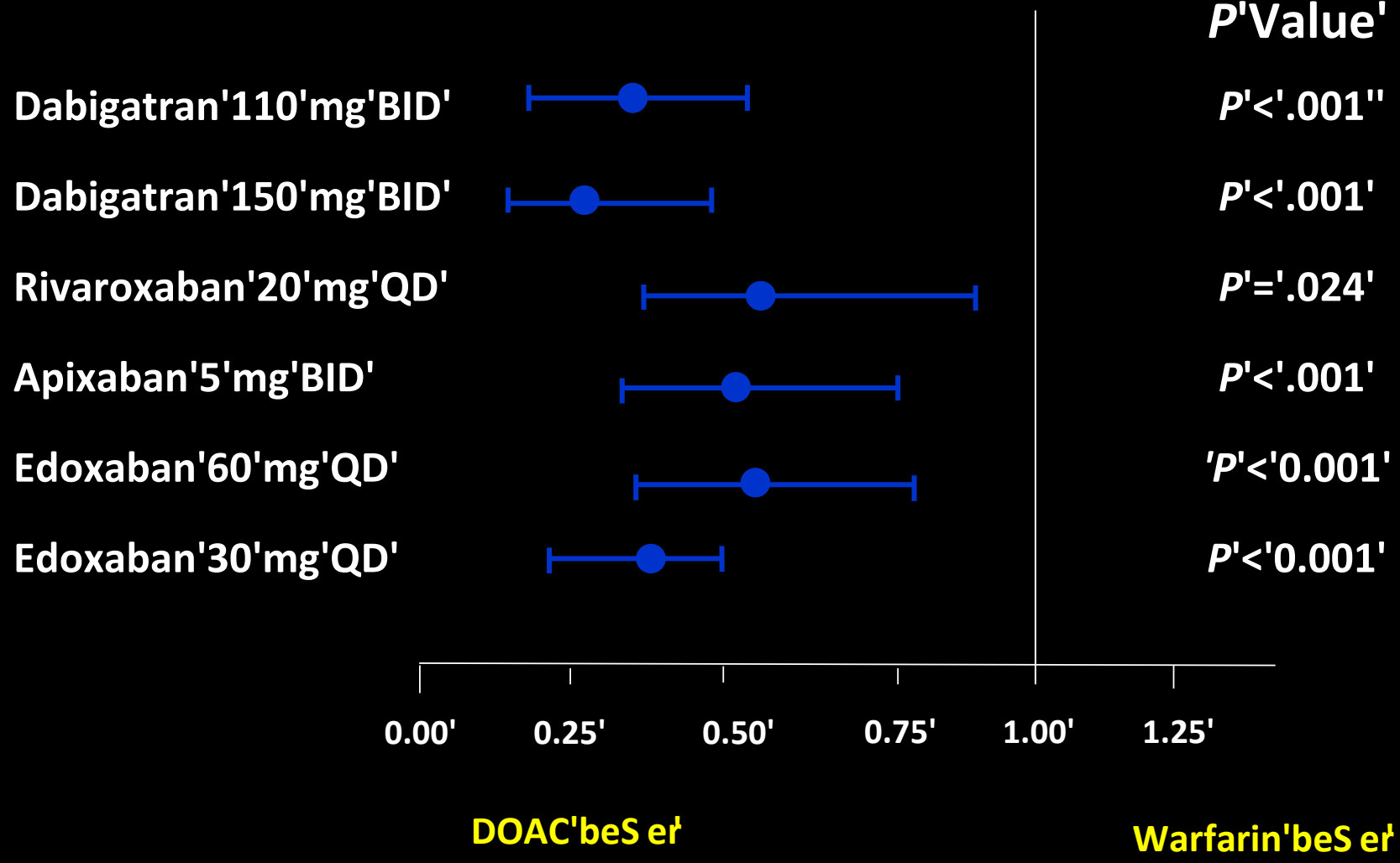
Similar intracerebral hemorrhage rates

DOACs vs. warfarin phase III RCTs in atrial fib: Intracerebral hemorrhage

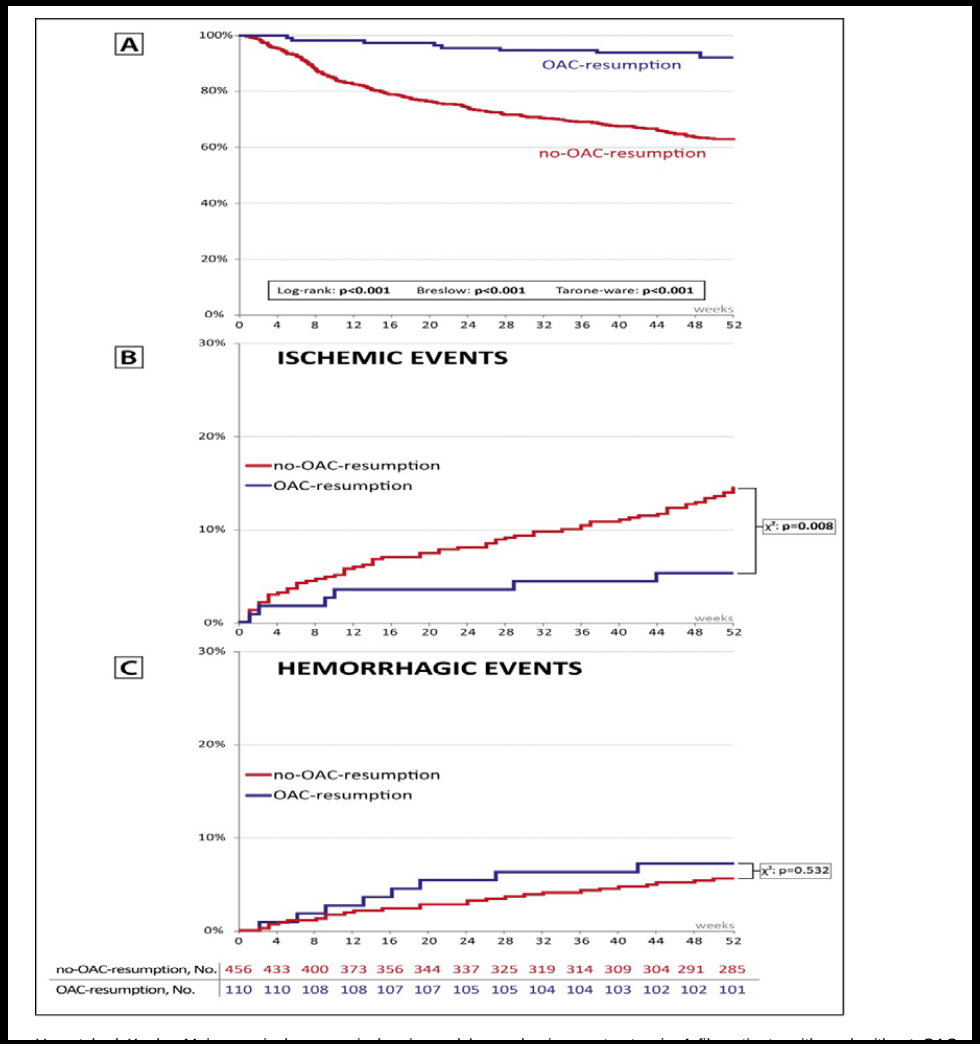


Connolly SJ, et al. N Engl J Med. 2009;361:1139–1151.
Patel MR, et al. N Engl J Med. 2011;365:883–891.
Granger C, et al. N Engl J Med. 2011;365:981–992.
Giugliano RP, et al. N Engl J Med 2013; online Nov 19

Courtesy of Dr. Robert G. Hart

Real-World Data: Recurrent ICH

Anticoagulant Reversal, Blood Pressure Levels, and Anticoagulant Resumption in Patients With Anticoagulation-Related Intracerebral Hemorrhage



110 of 556 (20%) patients with AF and ICH restarted on anticoagulation

19 centers, 2006-2010

Anticoagulant Reversal, Blood Pressure Levels, and Anticoagulant Resumption in Patients With Anticoagulation-Related Intracerebral Hemorrhage

eTable 9. Propensity-matched Cox regression analyses of long-term mortality in A-fib patients.

Patients with atrial fibrillation (n=261)	No. of patients	No. of events (%)	Hazard ratio (95%CI)	*P* Value	Adjusted Hazard ratio 95%CI)	*P* Value
Overall	261	56 (21.5%)				
OAC resumption	108	9 (8.3%)	0.233 (0.114-0.476)	**<0.001**	0.258 (0.125-0.534)	**<0.001**
No OAC resumption	153	47 (30.7%)	1 (reference)		1 (reference)	

Cox regression analysis included all OAC-ICH patients with A-fib after propensity matching. Hazard ratio model was adjusted for events (new ischemic, recurrent hemorrhagic) during 1 year of follow-up and by propensity score (age, ICH volume, IVH, hematoma growth, NIHSS, $CHADS_2$ score as well as pre- and discharge-mRS). Assumption of proportionality was tested by locally weighted scatterplot smoothing of partial Schoenfeld residuals and PH testing. All covariates met the assumption. Significant parameters are expressed in bold.

74% RR in long-term mortality

Anticoagulant Reversal, Blood Pressure Levels, and Anticoagulant Resumption in Patients With Anticoagulation-Related Intracerebral Hemorrhage

eTable 8. Propensity-matched analysis of event and incidence rates in A-fib patients – new ischemic stroke *versus* recurrent ICH.

Patients with atrial fibrillation	No. of Patients	No. of events (%)	*P* Value	Incidence rate per 100 patient years (95%CI)	*P* Value
New cerebral Infarction	261	20 (7.7%)		8.7 (3.8-12.6)	
According to treatment					
OAC resumption	108	4 (3.7%)	**0.04**	3.9 (1.9-5.8)	**0.02**
No OAC resumption	153	16 (10.5%)		12.7 (6.5-19.1)	
Recurrent ICH	261	9 (3.4%)		3.9 (1.4-6.5)	
According to treatment					
OAC resumption	108	4 (3.7%)	0.55	3.9 (1.9-5.8)	0.92
No OAC resumption	153	5 (3.3%)		3.9 (2.2-5.7)	

Analysis included all OAC-ICH patients with A-fib after propensity matching. Given are: total number of patients for analysis, raw number of events and incidence rates (per 100 patient-years) calculated for time on each specific treatment (OAC *versus* no-OAC as defined) during 1 year of follow-up. Significant parameters are expressed in bold.

65% RR new cerebral infarcts

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No difference in recurrent ICH rate

Restarting Anticoagulant Treatment After Intracranial Hemorrhage in Patients With Atrial Fibrillation and the Impact on Recurrent Stroke, Mortality, and Bleeding

A Nationwide Cohort Study

Peter Brønnum Nielsen, MSc, PhD; Torben Bjerregaard Larsen, MD, PhD; Flemming Skjøth, MSc, PhD; Anders Gorst-Rasmussen, MSc, PhD; Lars Hvilsted Rasmussen, MD, PhD; Gregory Y.H. Lip, MD

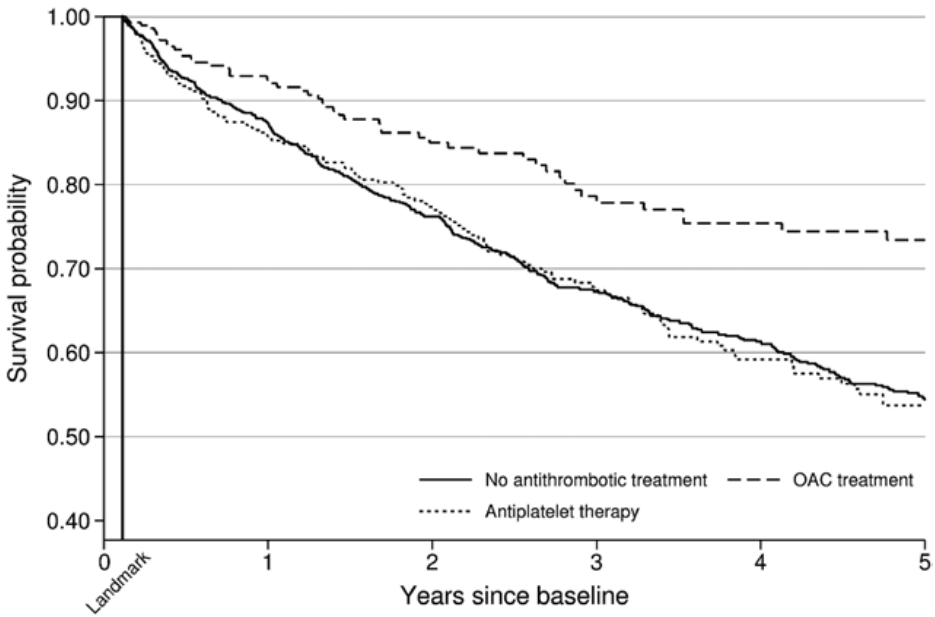
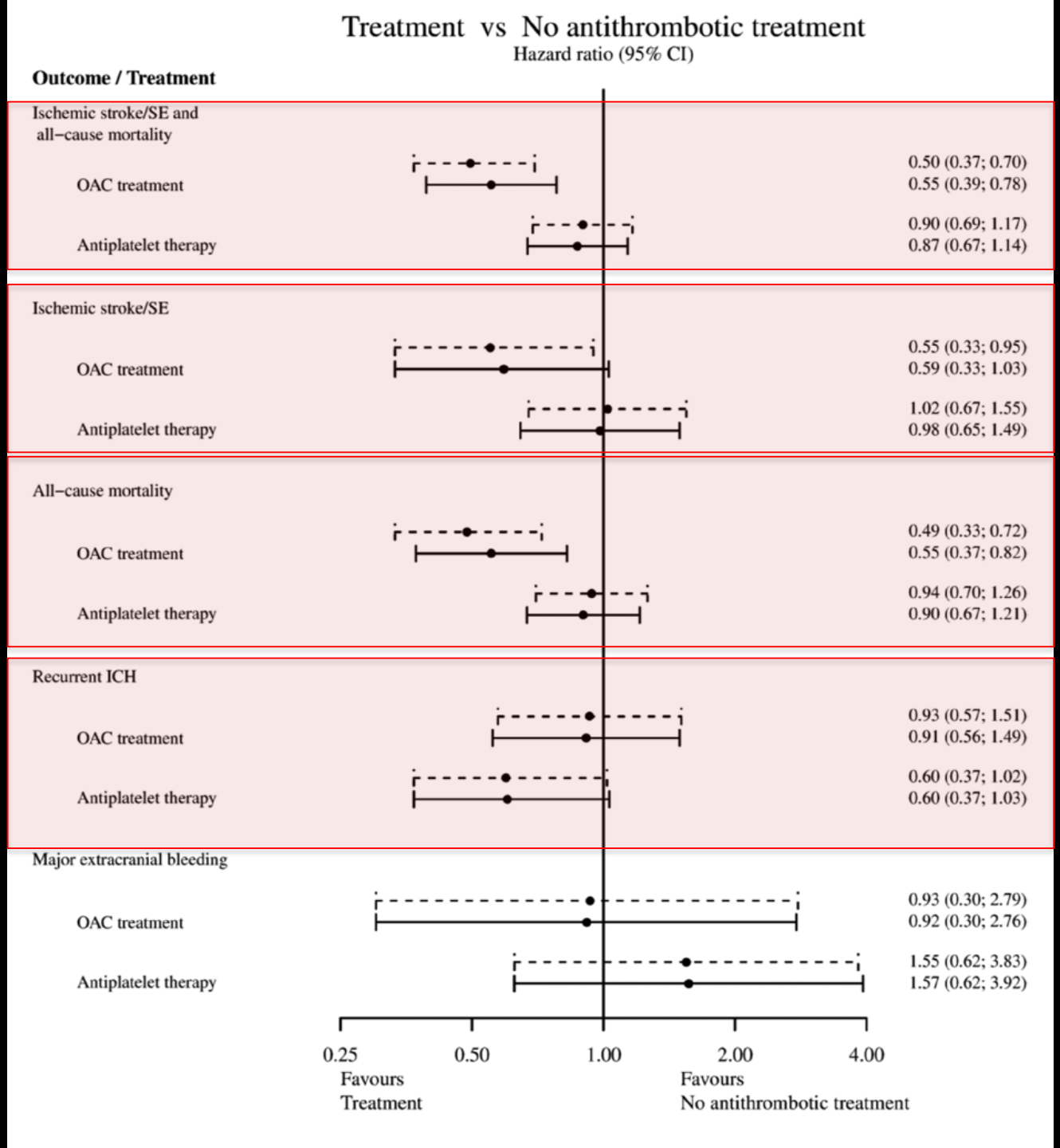


Figure 3. Five-year Kaplan–Meier survival curve for restarting OAC treatment, for receiving antiplatelet therapy, and for not receiving antithrombotic treatment with the use of a landmark at 6 weeks (relative to discharge from hospital) for treatment regimens stratification. OAC indicates oral anticoagulation.

1752 of 6138 (29%) patients with AF and ICH restarted on anticoagulation

Danish National Prescription Registry

(*Circulation*. 2015;132:517-525.



45% RR in IS/SE and all-cause mortality

41% RR in IS/SE

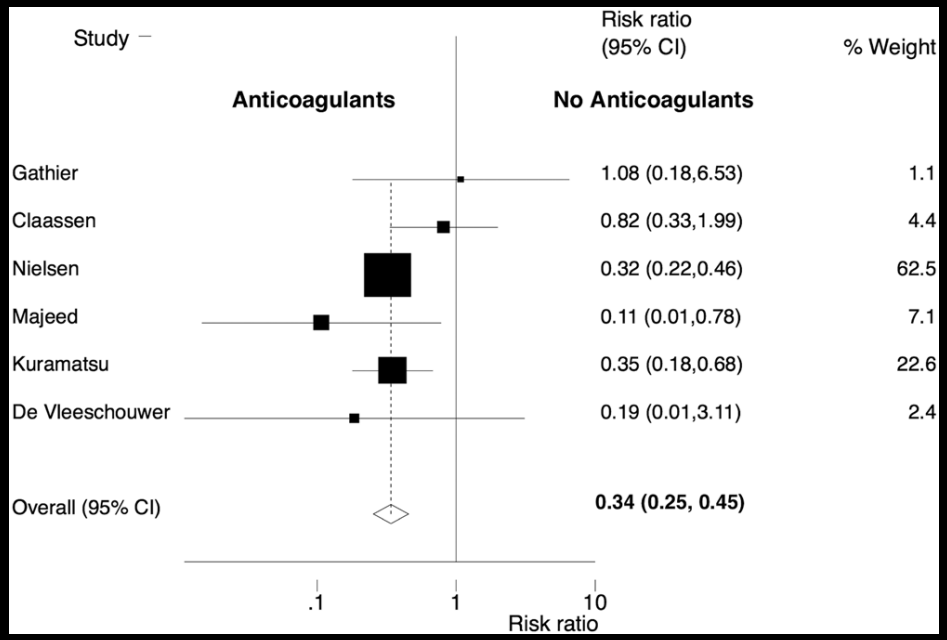
45% RR in all-cause mortality

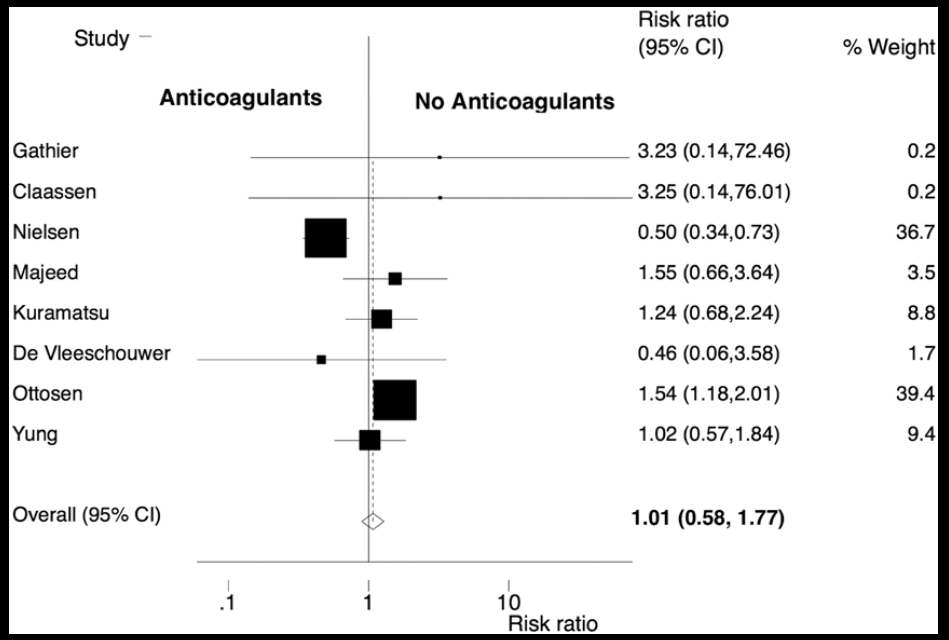
No difference in recurrent ICH rate

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





(Stroke . 2017;48:00-00. DOI: 10.1161/STROKEAHA.116.016327.)

Resumption of Oral Anticoagulation after Intracerebral Hemorrhage is Associated with Decreased Mortality and Favorable Functional Outcome

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], 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], Daniel Woo MD MS[7], Hagen B. Huttner, MD[4], Kevin N Sheth[5]

Ann Neurol. 2017 Oct 13. doi: 10.1002/ana.25079

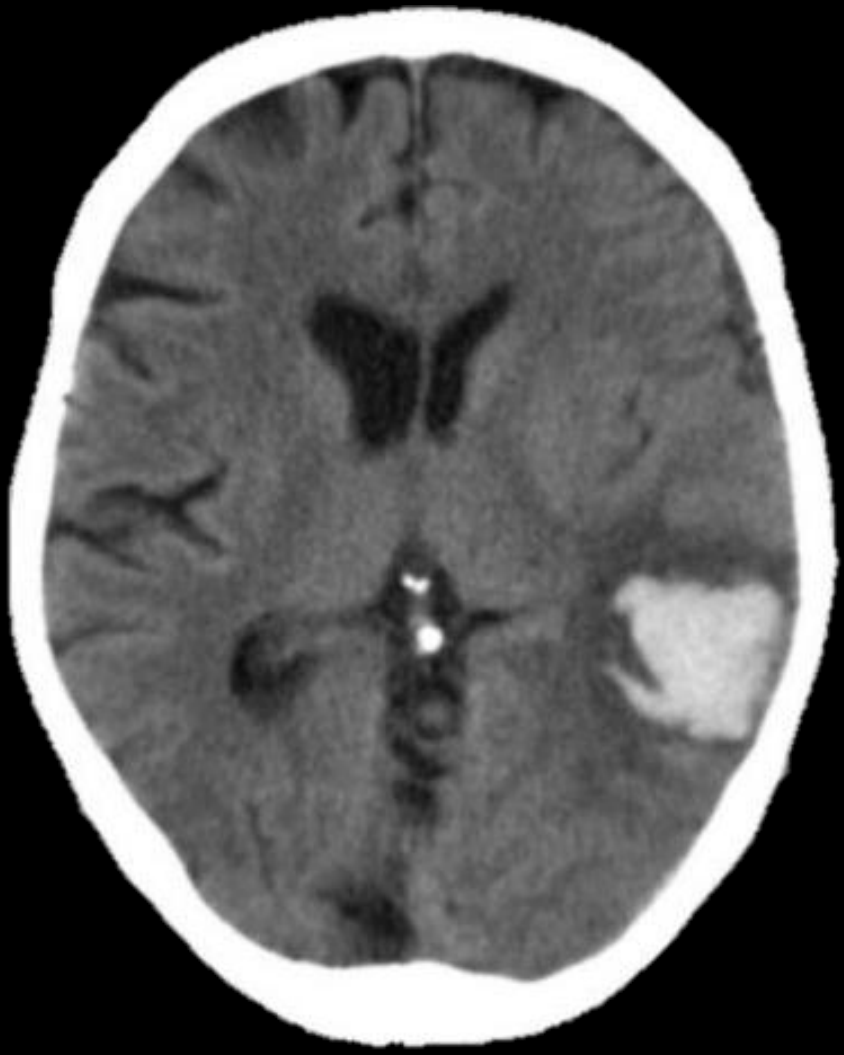
OAT Resumption and Outcomes

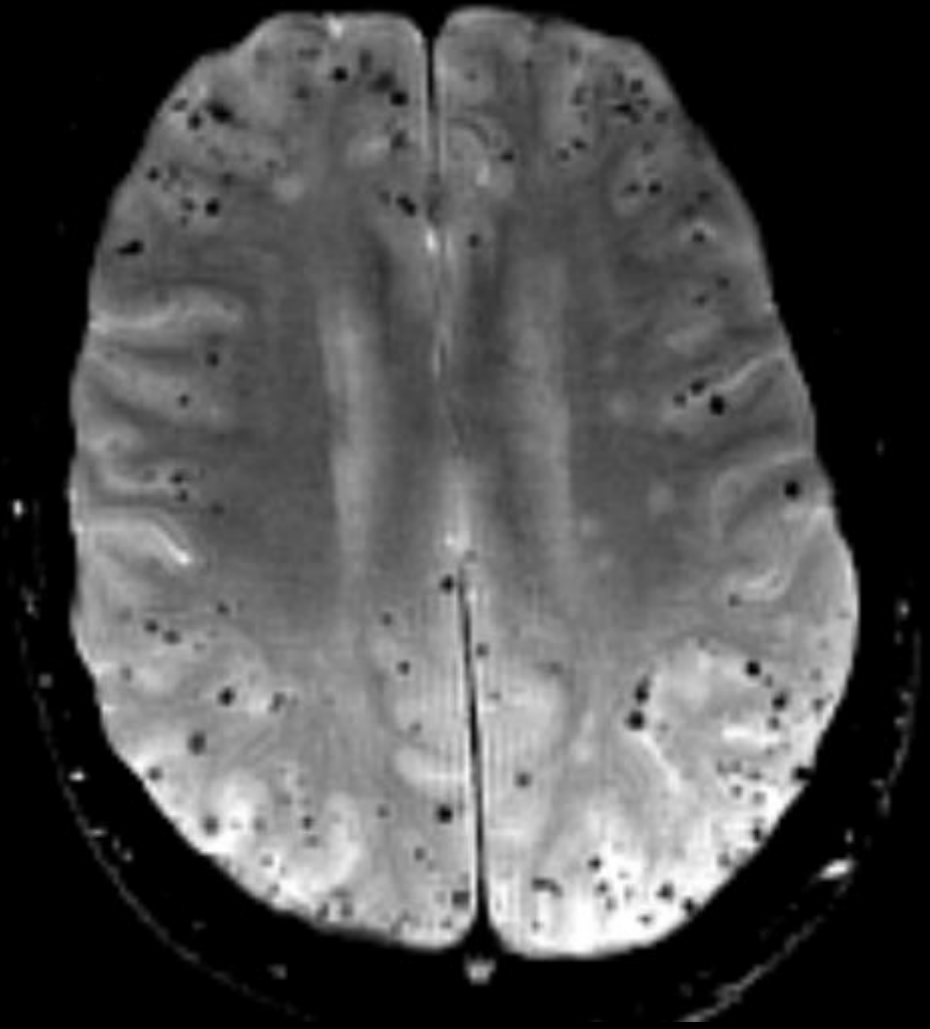
Non-lobar ICH

Outcome at 1 Year	Effect of OAT Resumption		
	HR	95% CI	p
Favorable Outcome (mRS 0 -3)	4.22	2.57-6.94	**<0.0001**
Mortality	0.25	0.14-0.44	**<0.0001**
All-cause Stroke	0.41	0.25-0.67	**0.0004**
- Recurrent ICH	1.17	0.89-1.54	0.27
- Ischemic Stroke	0.39	0.21-0.74	**0.004**

Lobar ICH

Outcome at 1 Year	Effect of OAT Resumption		
	HR	95% CI	p
Favorable Outcome (mRS 0 -3)	4.08	2.48-6.72	**<0.0001**
Mortality	0.29	0.17-0.45	**<0.0001**
All-cause Stroke	0.51	0.37-0.76	**0.0006**
- Recurrent ICH	1.26	0.88-1.71	0.22
- Ischemic Stroke	0.48	0.25-0.75	**0.003**





OAT and Possible vs. Probable CAA

Possible CAA (n=137)

Outcome at 1 Year	Adjusted		
	HR	95% CI	p
Favorable Outcome (mRS 0 -3)	3.40	1.22-9.46	**0.020**
Mortality	0.27	0.08-0.86	**0.028**

Probable CAA (n=55)

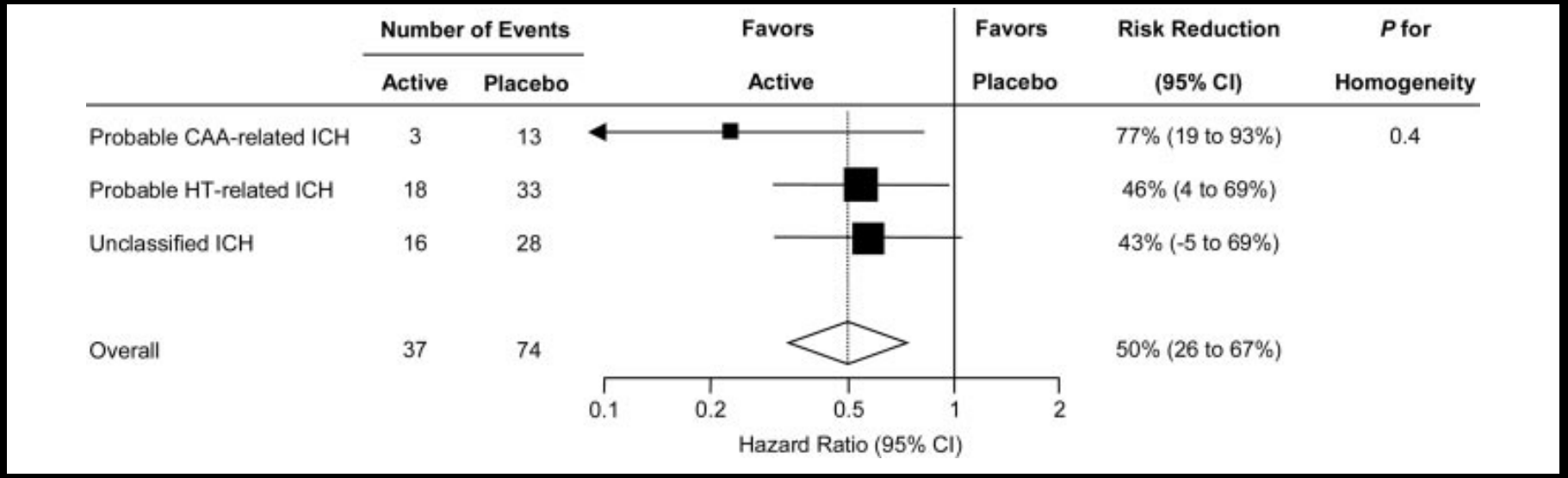
Outcome at 1 Year	Adjusted		
	HR	95% CI	p
Favorable Outcome (mRS 0 -3)	3.11	1.08-8.97	**0.038**
Mortality	0.30	0.10-0.92	**0.037**

Optimization of Safety via BP Control

Effects of Perindopril-Based Lowering of Blood Pressure on Intracerebral Hemorrhage Related to Amyloid Angiopathy

The PROGRESS Trial

Hisatomi Arima, MD; Christophe Tzourio, MD; Craig Anderson, MD; Mark Woodward, PhD; Marie-Germaine Bousser, MD; Stephen MacMahon, PhD; Bruce Neal, MD; John Chalmers, MD; for the PROGRESS Collaborative Group (*Stroke*. 2010;41:394-396.)



Mean reduction of 9/4 mm Hg

Blood-pressure targets in patients with recent lacunar stroke: the SPS3 randomised trial

The SPS3 Study Group*

www.thelancet.com Published online May 29, 2013 http://dx.doi.org/10.1016/S0140-6736(13)60852-1

	Higher-target group (n=1519)		Lower-target group (n=1501)		Hazard ratio (95% CI)	p value
	Number of patients	Rate (% per patient-year)	Number of patients	Rate (% per patient-year)		
Stroke						
All stroke	152	2·77%	125	2·25%	0·81 (0·64–1·03)	0·08
Ischaemic stroke or unknown	131	2·4%	112	2·0%	0·84 (0·66–1·09)	0·19
Intracranial haemorrhage						
All	21*	0·38%	13†	0·23%	0·61 (0·31–1·22)	0·16
Intracerebral	16	0·29%	6	0·11%	0·37 (0·15–0·95)	0·03

Table 2: Primary and secondary outcomes

Timing?

Timing?

AHA 2014	**≥ 1 week**
AHA 2015	**> 4 weeks**
ESO 2015	**2-30 weeks**
EHRA 2015	**4-8 weeks**

Optimal Timing of Resumption of Warfarin After Intracranial Hemorrhage

Ammar Majeed, MD; Yang-Ki Kim, MD; Robin S. Roberts, PhD;
Margareta Holmström, MD, PhD; Sam Schulman, MD, PhD

- Indication
  - AF 48%
  - MV 49%
  - VTE 17%
- Baseline ICH
  - 47% IPH
  - 43% SDH
  - 10% SAH
- Recurrent ICH
  - 67% SDH
  - 33% IPH

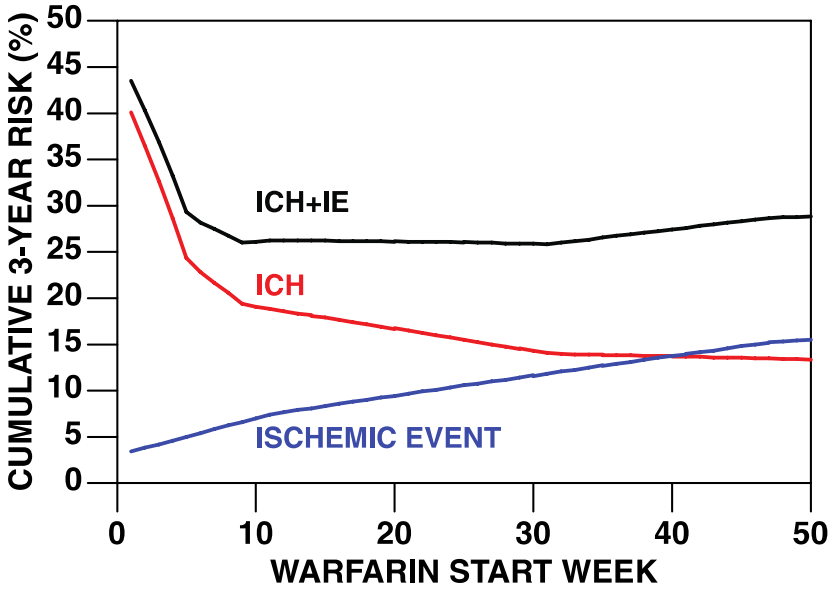
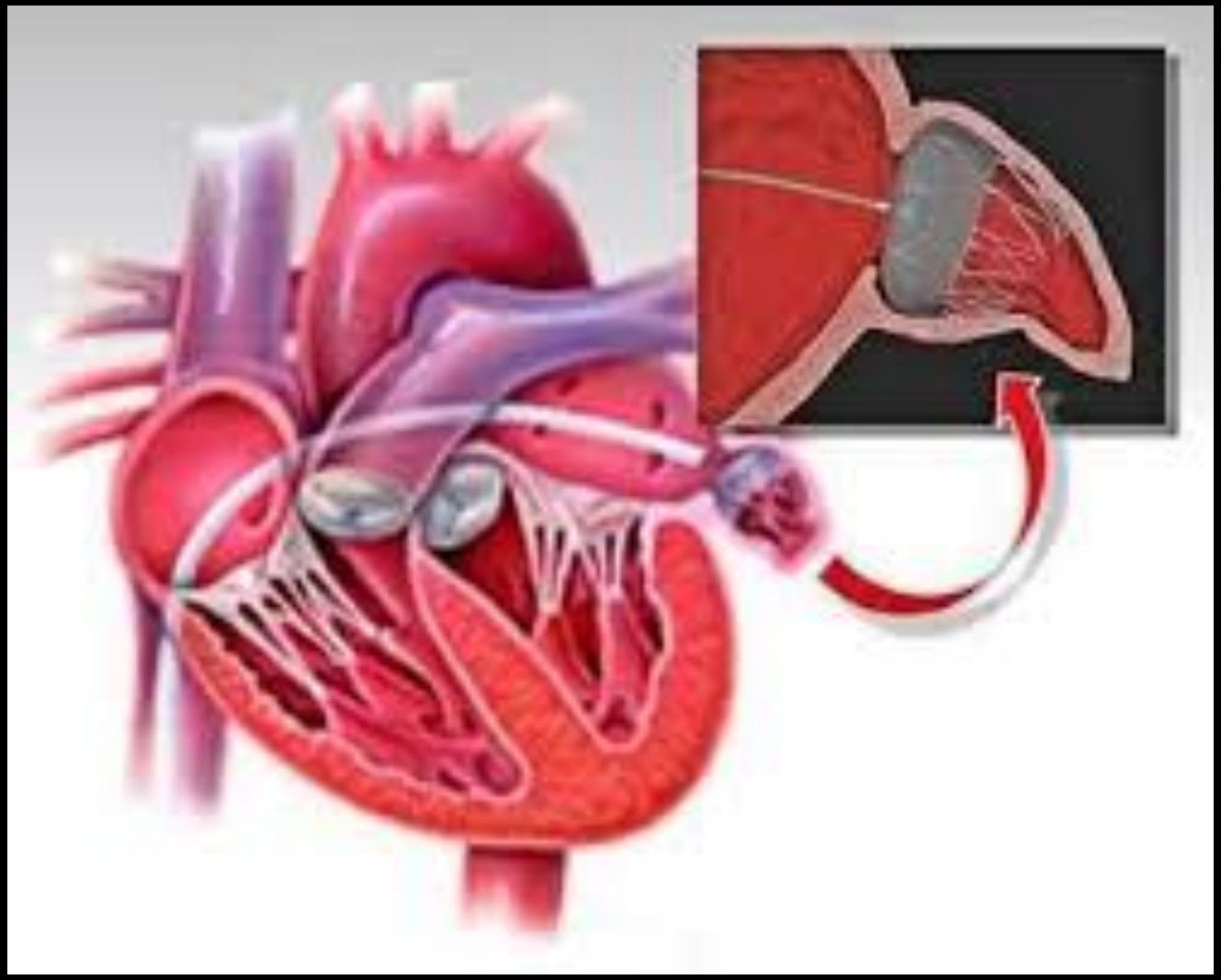


Figure 2. The "total" risk for a treatment horizon of 3 years of recurrent intracranial hemorrhage and of ischemic stroke according to the time point of resumption of anticoagulation.

(*Stroke*. 2010;41:2860-2866.)

Left Atrial Appendage Closure?



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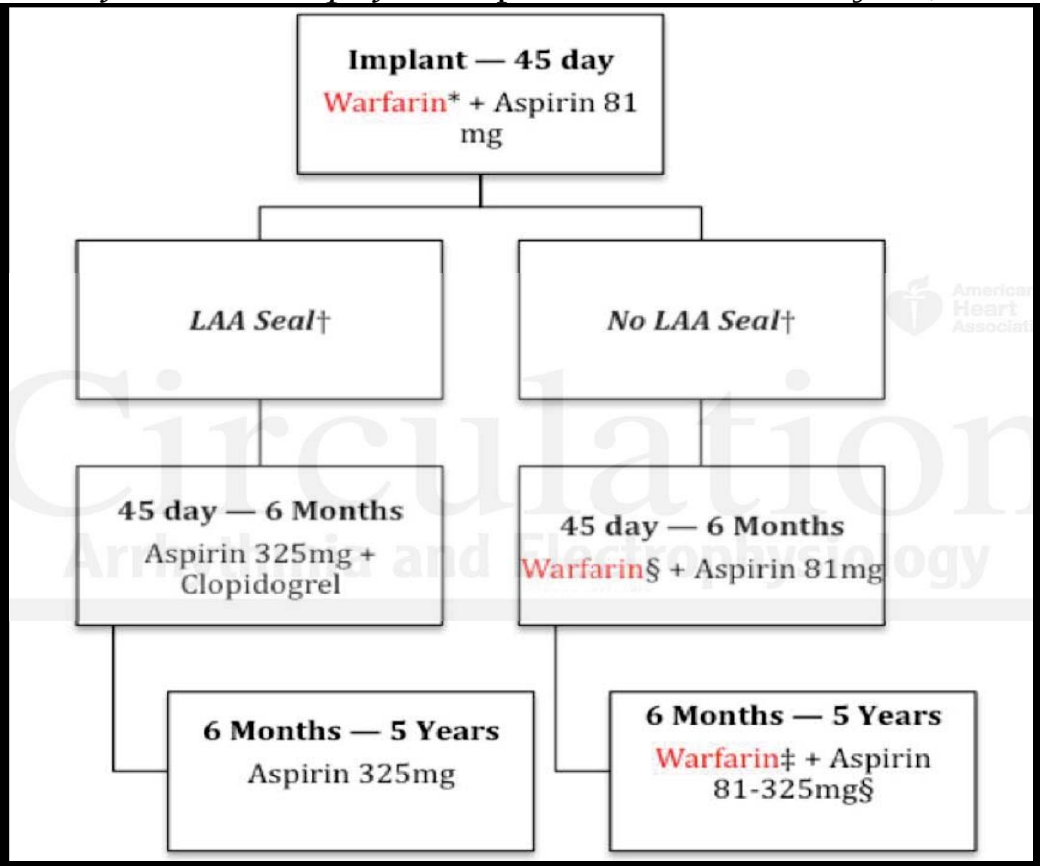

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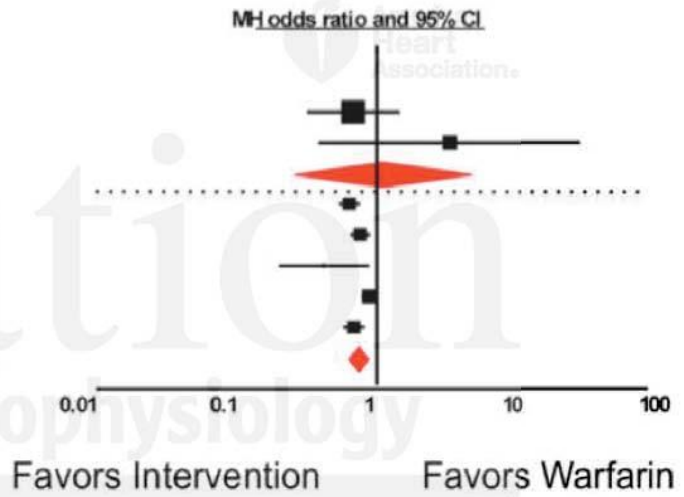
Stroke or Systemic Embolism

Group by Treatment Alternative	Study name	Statistics for each study: MH odds ratio	Lower limit	Upper limit	Z-Value	p-Value	Events / Total: Intervention	Warfarin
Device	PROTECT-AF	0.78	0.37	1.65	-0.64	0.52	18 / 463	12 / 244
Device	PREVAIL	3.66	0.45	30.05	1.21	0.23	7 / 269	1 / 138
Total (95% CI)		1.23	0.30	4.98	0.29	0.77	25 / 732	13 / 382
NOAC	RELY	0.73	0.61	0.88	-3.36	0.00	316 / 12901	199 / 6022
NOAC	ROCKET-AF	0.88	0.74	1.03	-1.56	0.12	269 / 7081	306 / 7090
NOAC	J-ROCKET-AF	0.49	0.24	1.02	-1.90	0.06	11 / 637	22 / 637
NOAC	ENGAGE AF-TIMI 48	1.01	0.88	1.15	0.12	0.91	679 / 14069	337 / 7036
NOAC	ARISTOTLE	0.79	0.66	0.95	-2.50	0.01	212 / 9120	265 / 9081
Total (95% CI)		0.84	0.72	0.97	-2.36	0.02	1487 / 43808	1129 / 29866

Heterogeneity Device: Chi2= 1.88; df= 1; P= 0.17; I^2= 47%

Heterogeneity NOAC: Chi2= 11.39; df= 4; P= 0.023; I^2= 65%



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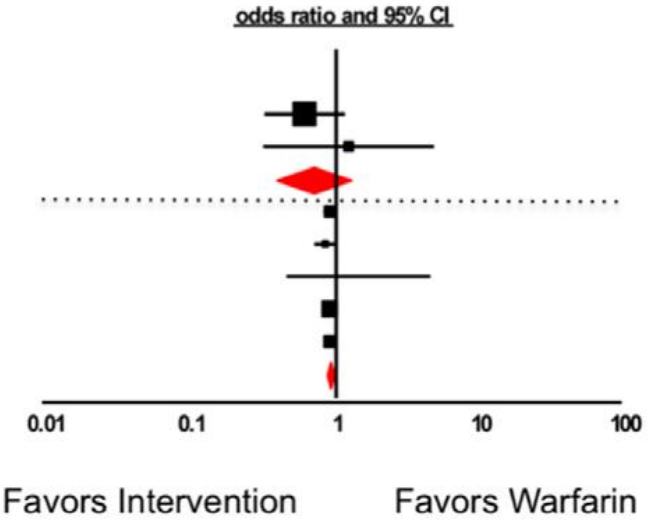
Mortality

Group by Treatment Alternative	Study name	odds ratio	Lower limit	Upper limit	Z-Value	p-Value	Events / Total Intervention	Events / Total Warfarin
Device	PROTECT-AF	0.60	0.31	1.14	-1.56	0.12	21 / 463	18 / 244
Device	PREVAIL	1.20	0.31	4.72	0.26	0.79	7 / 269	3 / 138
Total (95% CI)		0.68	0.38	1.22	-1.29	0.20	28 / 732	21 / 382
NOAC	RELY	0.90	0.80	1.01	-1.86	0.06	884 / 12091	487 / 6022
NOAC	ROCKET-AF	0.83	0.69	1.00	-1.96	0.05	208 / 7061	250 / 7082
NOAC	J-ROCKET-AF	1.40	0.44	4.45	0.58	0.56	7 / 637	5 / 637
NOAC	ENGAGE AF-TIMI 48	0.89	0.81	0.97	-2.59	0.01	1510 / 14069	839 / 7036
NOAC	ARISTOTLE	0.89	0.79	1.00	-2.00	0.05	603 / 9120	669 / 9081
Total (95% CI)		0.89	0.84	0.94	-4.15	0.00	3212 / 42978	2250 / 29858

Heterogeneity Device: Chi2= 0.82; df= 1; P= 0.36; I^2= 0

Heterogeneity NOAC: Chi2= 1.14; df= 4; P= 0.89; I^2= 0



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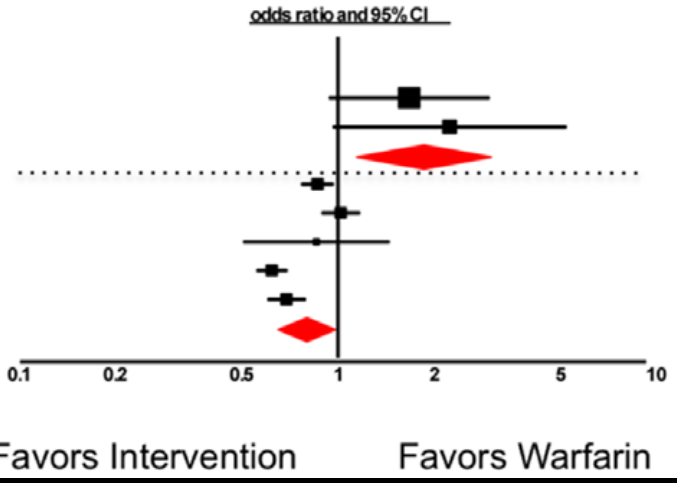
Major Bleeding or Procedure Related Complications

Group by Treatment Alternative	Study name	Statistics for each study: odds ratio	Lower limit	Upper limit	Z-Value	p-Value	Events / Total: Intervention	Warfarin
Device	PROTECT-AF	1.687	0.938	3.034	1.745	0.081	49 / 463	16 / 244
Device	PREVAIL	2.261	0.964	5.303	1.876	0.061	29 / 269	7 / 138
Total (95% CI)		1.853	1.143	3.006	2.501	0.012	78 / 732	23 / 382
NOAC	RELY	0.869	0.767	0.983	-2.230	0.026	741 / 12091	421 / 6022
NOAC	ROCKET-AF	1.027	0.889	1.186	0.360	0.719	395 / 7111	386 / 7125
NOAC	J-ROCKET-AF	0.861	0.503	1.473	-0.546	0.585	26 / 639	30 / 639
NOAC	ENGAGEAF-TIMI 48	0.624	0.554	0.702	-7.842	0.000	672 / 14014	524 / 7012
NOAC	ARISTOTLE	0.694	0.600	0.802	-4.947	0.000	327 / 9088	462 / 9052
Total (95% CI)		0.794	0.647	0.973	-2.222	0.026	2161 / 42943	1823 / 29850

Heterogeneity Device: Chi2= 0.31; df= 1; P= 0.58; I^2= 0

Heterogeneity NOAC: Chi2= 33.27; df= 4; P= 1.05; I^2= 88%



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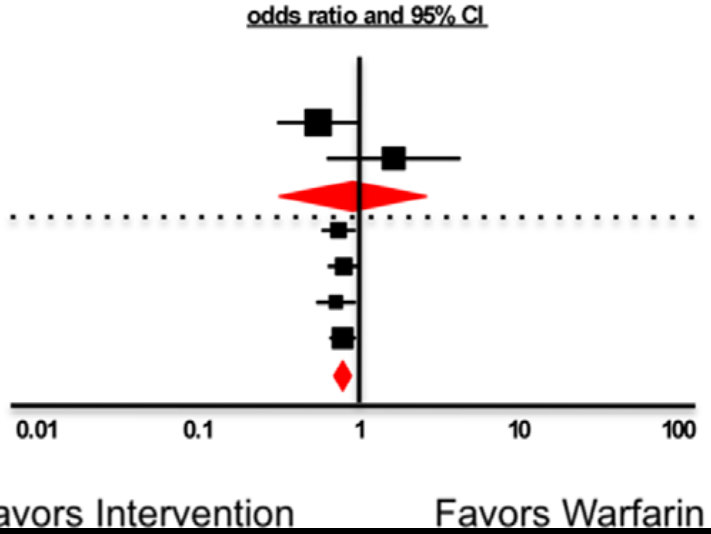
Stroke or Systemic Embolism in the Elderly

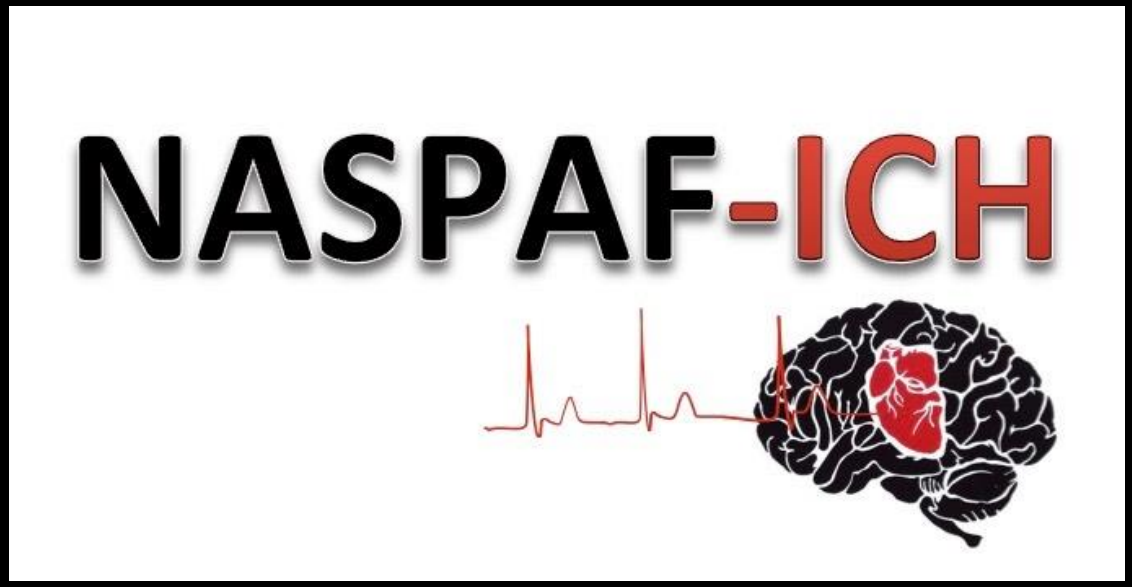
Group by Treatment Alternative	Study name	Statistics for each study: odds ratio	Lower limit	Upper limit	Z-Value	P-Value	Events / Total: Intervention	Warfarin
Device	PROTECT-AF	0.56	0.31	1.01	-1.91	0.06	25 / 228	25 / 138
Device	PREVAIL	1.64	0.62	4.33	1.01	0.31	17 / 160	6 / 89
Total (95% CI)		0.89	0.31	2.56	-0.21	0.83	42 / 388	31 / 227
NOAC	RELY	0.75	0.58	0.96	-2.24	0.03	156 / 4828	101 / 2360
NOAC	ROCKET-AF	0.80	0.63	1.02	-1.77	0.08	125 / 3082	154 / 3082
NOAC	ARISTOTLE	0.72	0.54	0.97	-2.19	0.03	79 / 2743	109 / 2752
NOAC	ENGAGE AF-TIMI 48	0.79	0.65	0.96	-2.33	0.02	184 / 5627	230 / 5610
Total (95% CI)		0.77	0.68	0.87	-4.24	0.00	544 / 16280	594 / 13804

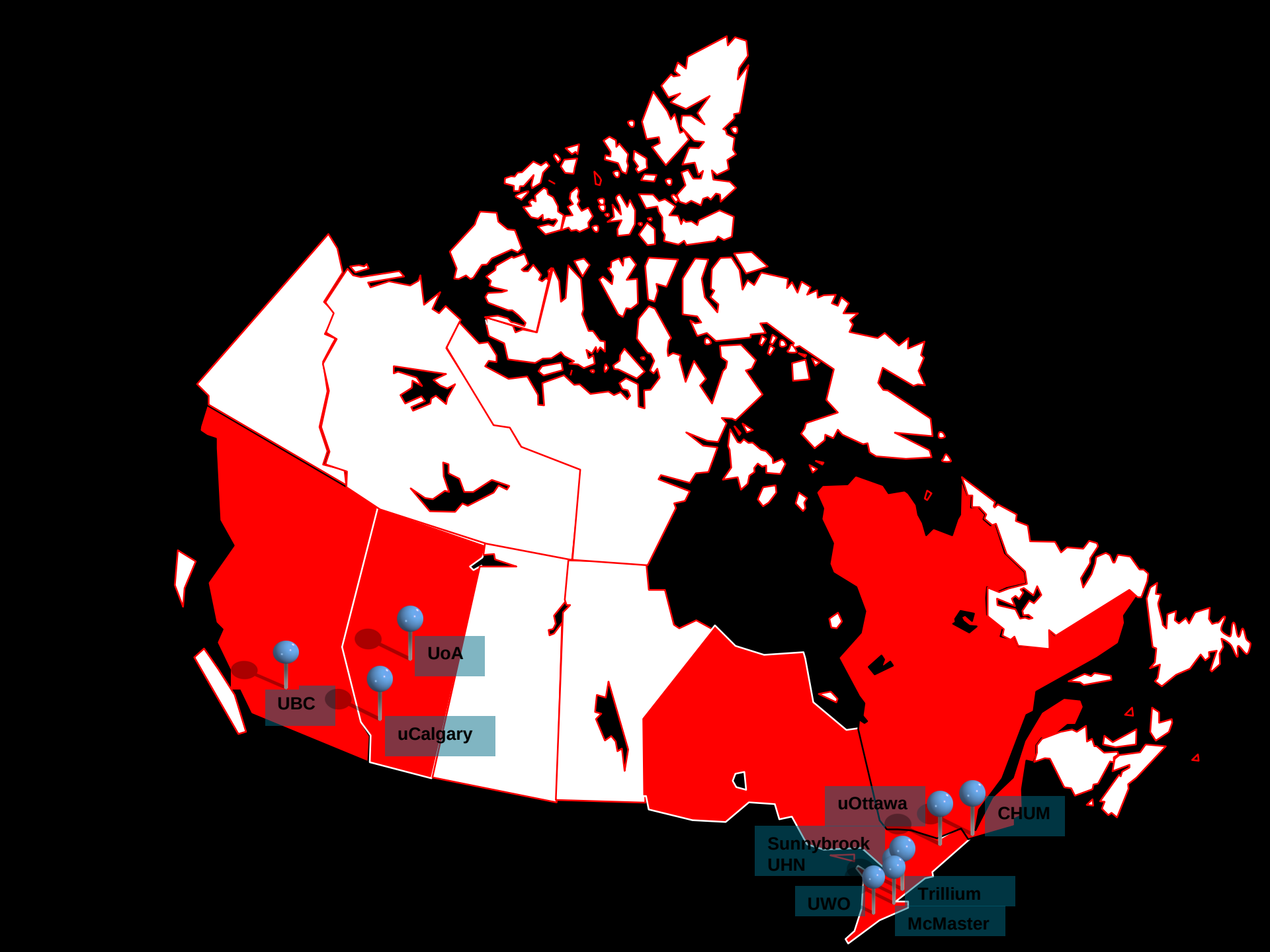
Heterogeneity Device: Chi2= 3.47; df= 1; P= 0.06; I^2= 72%

Heterogeneity NOAC: Chi2= 0.45; df= 3; P= 0.93; I^2= 0



Non-vitamin K Antagonist Anticoagulant for Stroke Prevention in patients with Atrial Fibrillation and ICH




UoA
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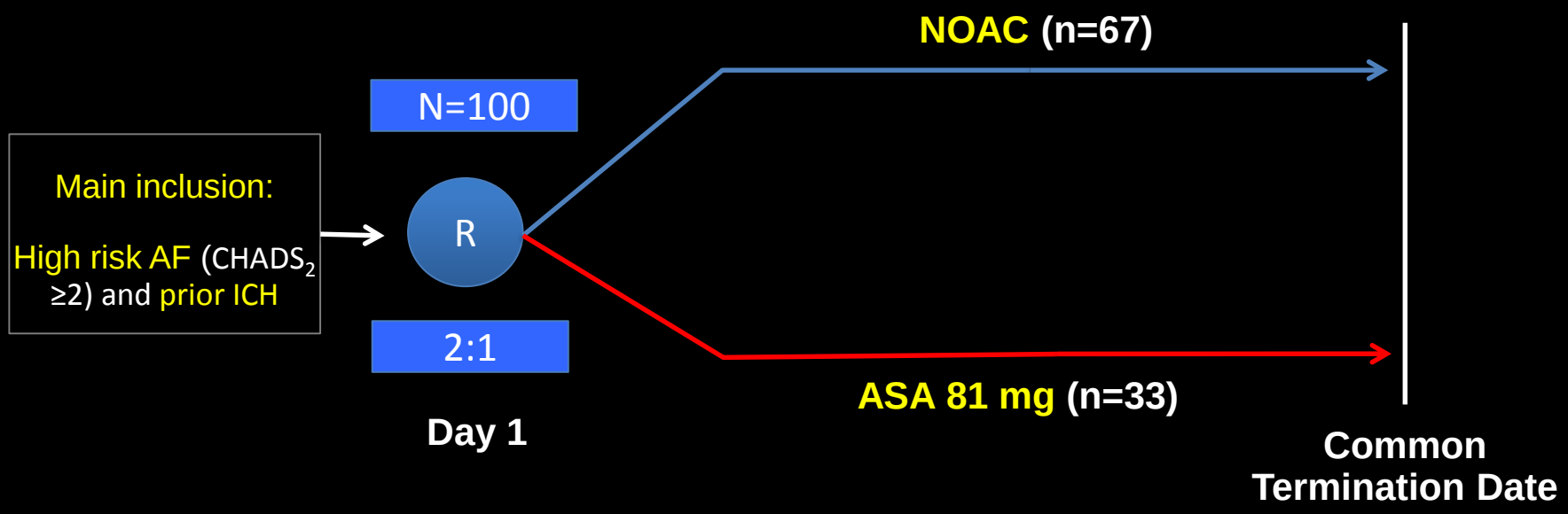
Trillium
UWO
McMaster

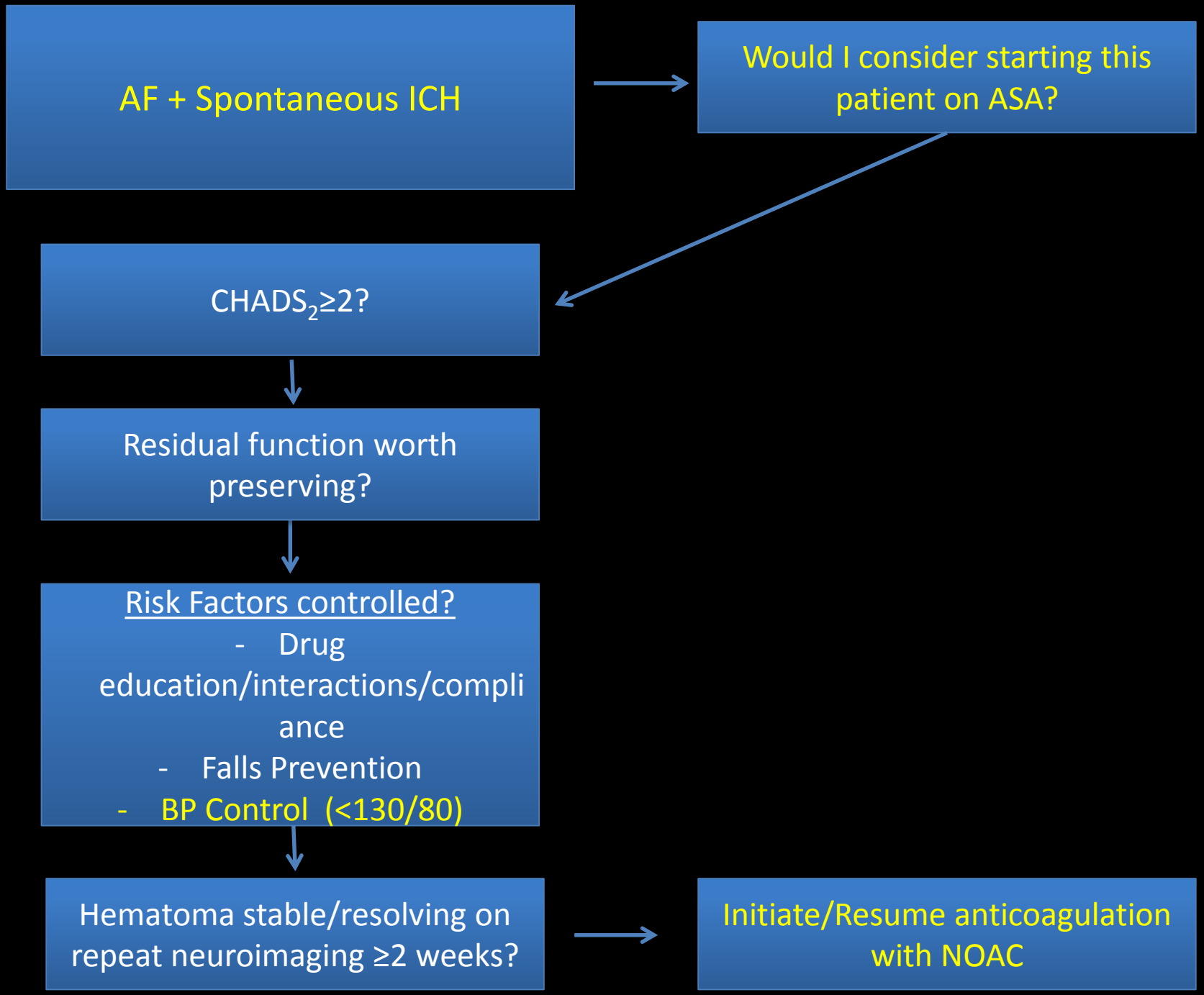


Recruitment period: 24 months
Last participant followed: 6 months

Total study duration: ~ 3 years
Mean follow-up per participant: 12 months (range 6 - 30 months)
Primary outcome: Composite of ischemic stroke and recurrent ICH

Special procedure: MRI at study entry for post-hoc risk stratification according to burden of CSVD.

	APACHE-AF	NASPAF-ICH	SoSTART	ASPIRE
Country	Netherlands	Canada	UK	USA
Participants	n=100, AF and CHA2DS2 VASc≥ 3, 7-90 days after OAC-associated ICH/IVH	n=100, AF and CHADS2≥2, ≥ 14 days after ICH/IVH	n=60, AF and CHA2DS2 VASc ≥ 2, >24 hours after intracranial haemorrhage	n=370, Non-CAA CHA2DS2 VASc ≥ 2
Intervention	Apixaban	Any NOAC	NOAC (any) or VKA	Apixaban
Comparator	Antiplatelet or no antithrombotic drug	Aspirin	Antiplatelet or no antithrombotic drug	Aspirin
Allocation	1:1	2:1	1:1	1:1
Masking	Adjudication only	Adjudication only	Adjudication only	Double blind
1° outcome/fu	Vascular death or non-fatal stroke/ ≥ 12 months	Recruitment rate, Composite of ICH and IS / ≥ 6 months	All symptomatic serious vascular events/ ≥ 12 months	Recurrent stroke and all-cause mortality


AF + Spontaneous ICH
Would I consider starting this patient on ASA?
CHADS2≥2?
Residual function worth preserving?
Risk Factors controlled?
- Drug education/interactions/compliance
- Falls Prevention
- BP Control (<130/80)
Hematoma stable/resolving on repeat neuroimaging ≥2 weeks?
Initiate/Resume anticoagulation with NOAC

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- Robert G. Hart, McMaster University/PHRI
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- Dr. Mukul Sharma, McMaster University/PHRI
- Dr. Stuart J. Connolly, McMaster University/PHRI
- Dr. Jeff Healy, McMaster University/PHRI
- Dr. John W. Eikelboom, McMaster University/PHRI
- Dr. Jackie Bosch, McMaster University/PHRI
- Dr. Guillaume Pare, McMaster University/PHRI
- Dr. Amparo Casanova, McMaster University/PHRI
- Hyejung Jung, McMaster University/PHRI

- **Site-specific Investigators:**
- Dr. David Gladstone, Sunnybrook Health Sciences Centre, University of Toronto
- Dr. Luciana Catanese, Hamliton Health Sciences, McMaster University
- Dr. Dariush Dowlatshahi, Champlain Stroke Network, University of Ottawa
- Dr. Jennifer Mandzia, London Health Sciences Centre, Western University
- Dr. Manu Mehdiratta, Trillium Health Partners, University of Toronto
- Dr. Aleksandra Pikula, University Health Network, University of Toronto
- Drs. Shelagh Coutts and Eric Smith, Foothills Medical Centre, University of Calgary
- Dr. Ken Butcher, University of Alberta Hospital, University of Alberta
- Dr. Thalia Field, Vancouver Coastal Health, University of British Columbia
- Dr. Laura Gioia, Centre Hospitalier de l'Université de Montréal