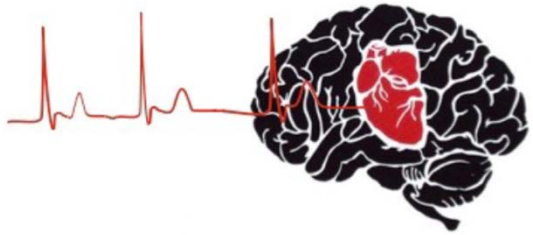
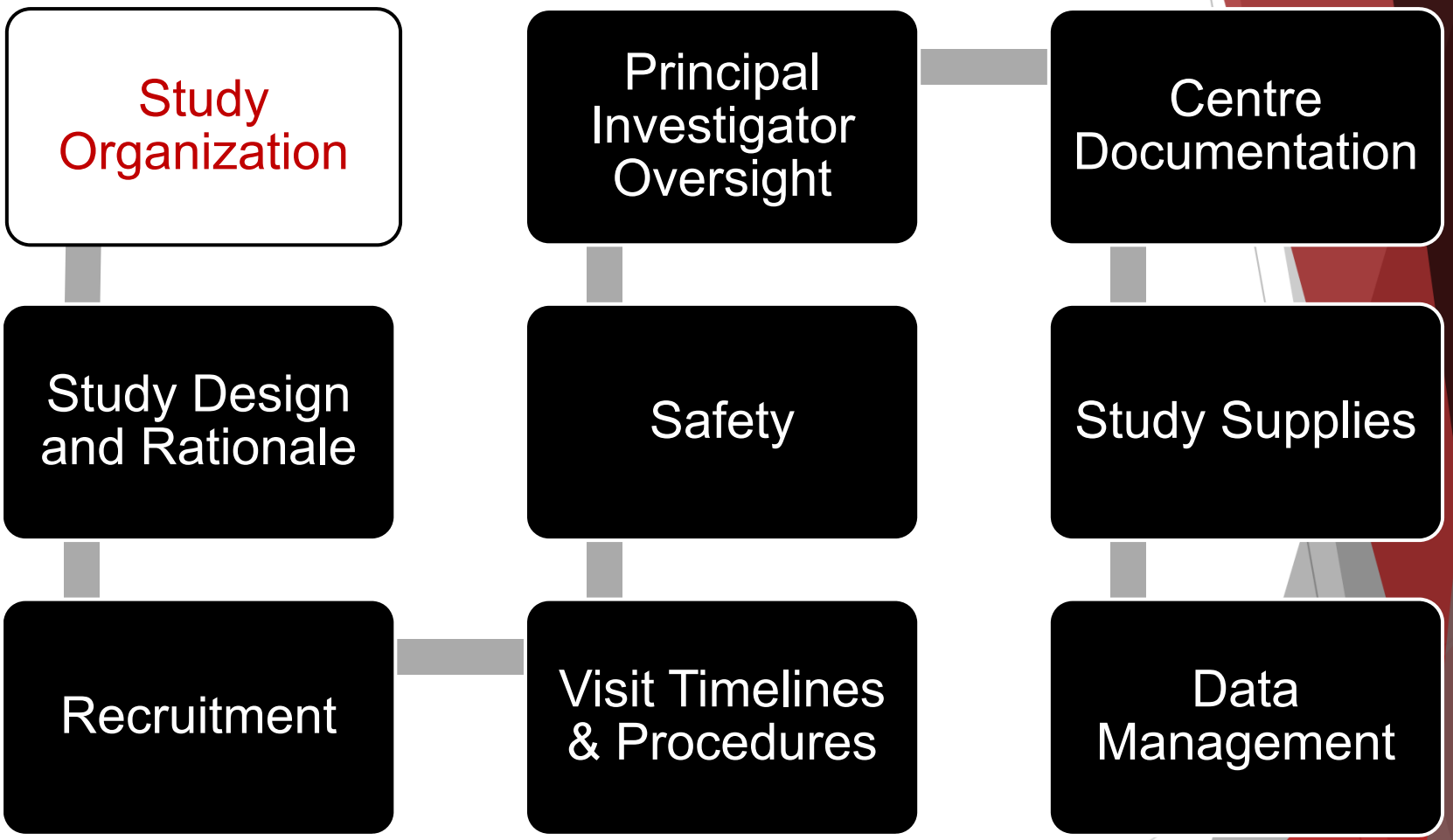
NASPAF-ICH



New Anticoagulant for Stroke Prevention in patients with Atrial Fibrillation and ICH (NASPAF-ICH)



Study Organization

Study Principal Investigator

Dr. Ashkan Shoamanesh

Study Co-Principal Investigators

Dr. Oscar Benavente

Dr. Robert Hart

Executive Committee

Dr. Ashkan Shoamanesh

Dr. Robert Hart

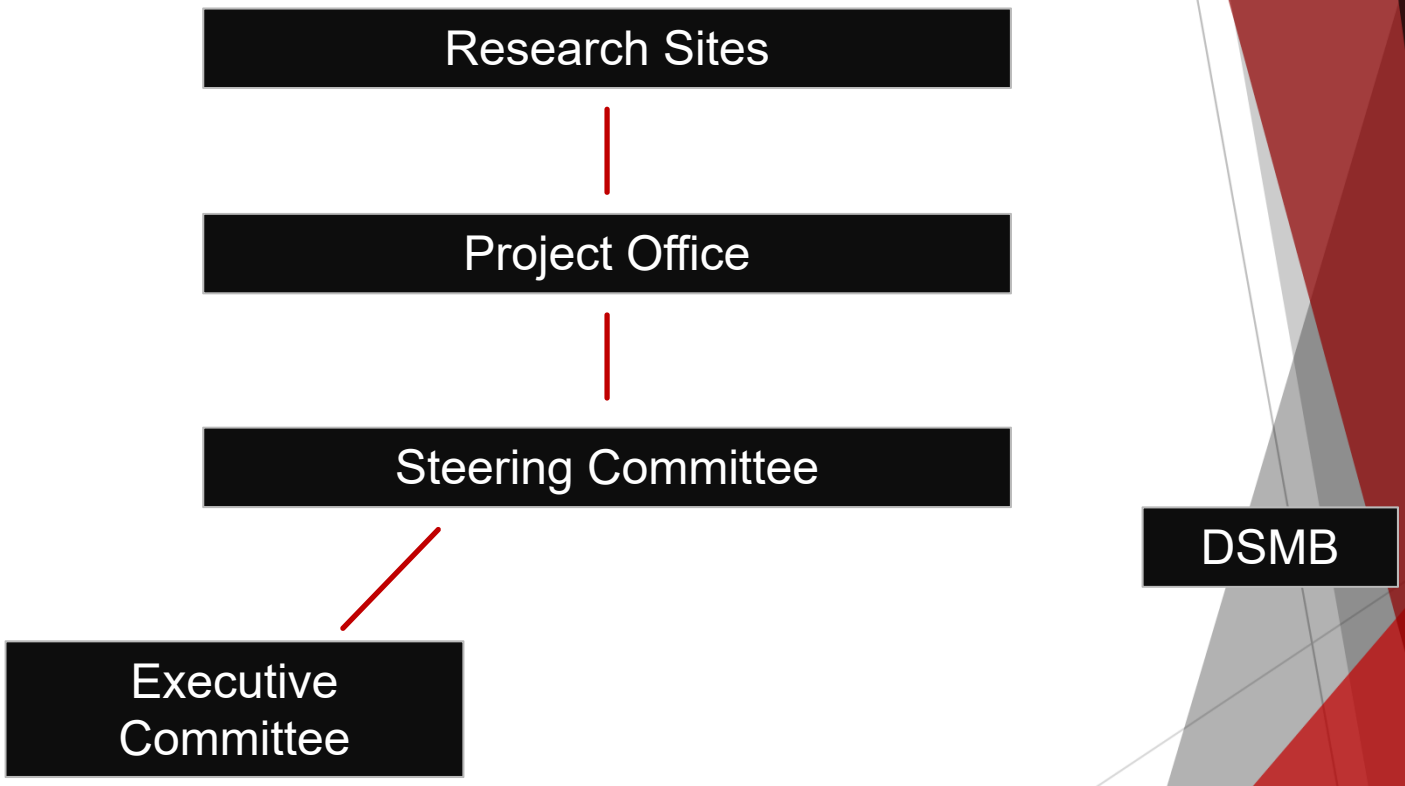
Dr. Oscar Benavente

Dr. Mike Sharma

Dr. Stuart Connolly

Jackie Bosch, PhD

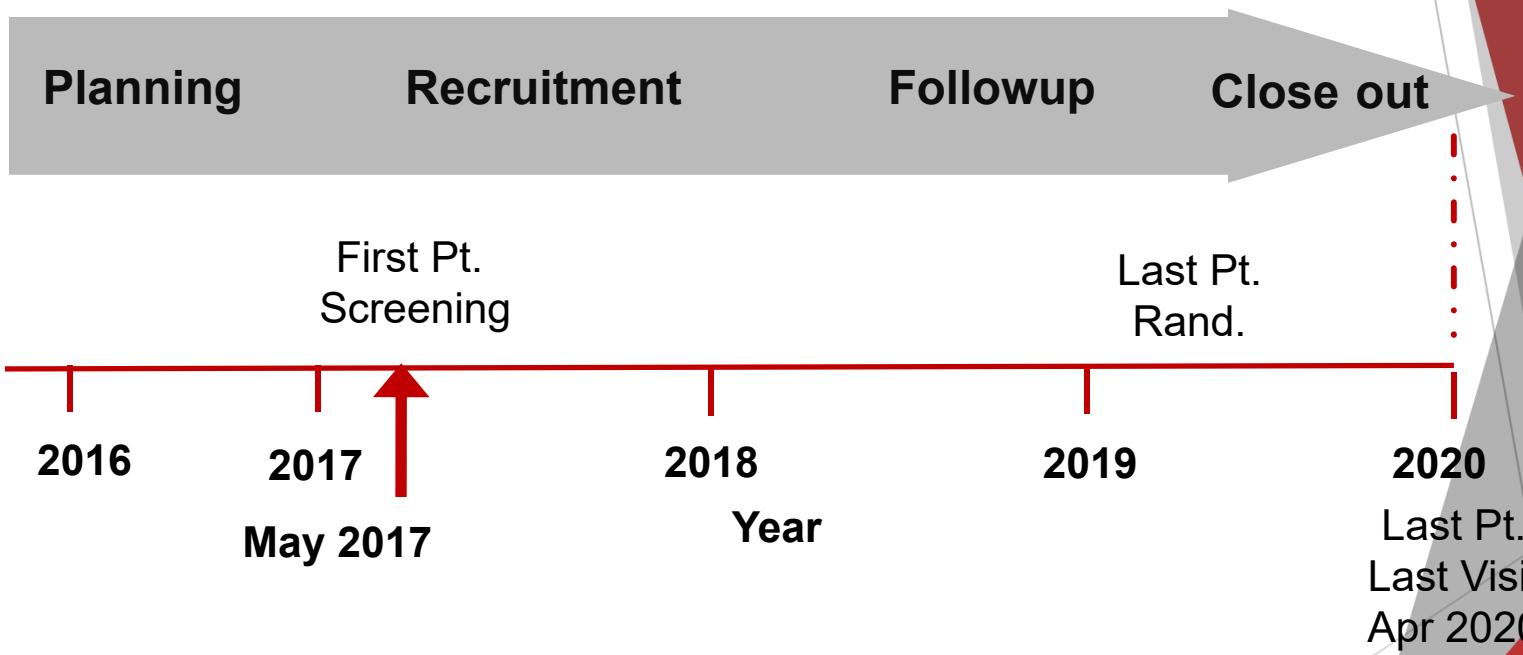
Study Organization

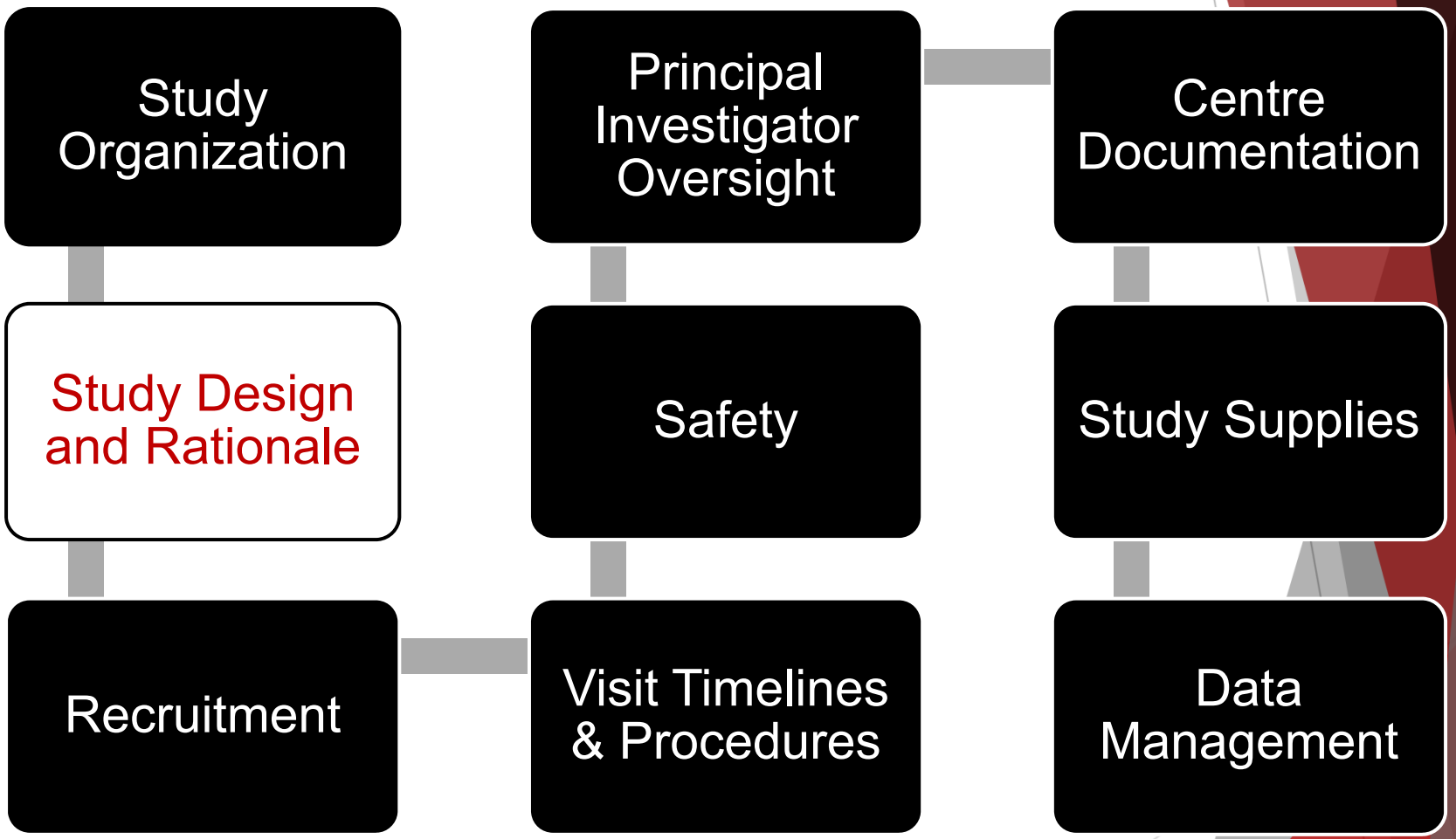


NASPAF-ICH Sites

Site #	PI Name	Location	Site
1	Ashkan Shoamanesh	Hamilton	Hamilton General Hospital
2	Alexander Khaw	London	LHSC-University Hospital
3	David Gladstone	Toronto	Sunnybrook
5	Aleksandra Pikula	Toronto	University Health Network
6	Dariush Dowlatshahi	Ottawa	The Ottawa Hospital Research Institute
7	Shelagh Coutts (Eric Smith)	Calgary	Foothills Medical Centre
8	Ken Butcher	Edmonton	University of Alberta Hospital
9	Thalia S. Field	Vancouver	Vancouver Coastal Health Research Institute
10	Laura Gioia	Montreal	Centre Hospitalier de l'Université de Montréal (CHUM)

Proposed Timelines

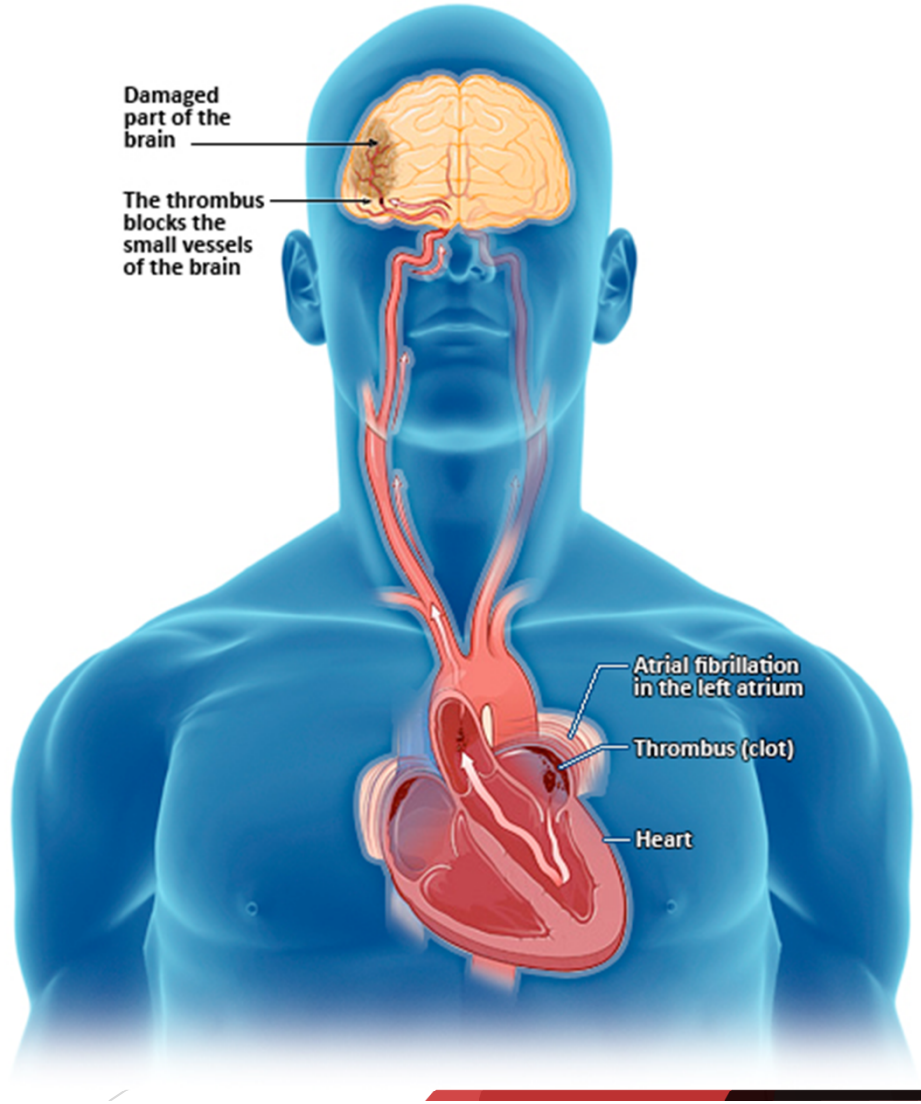


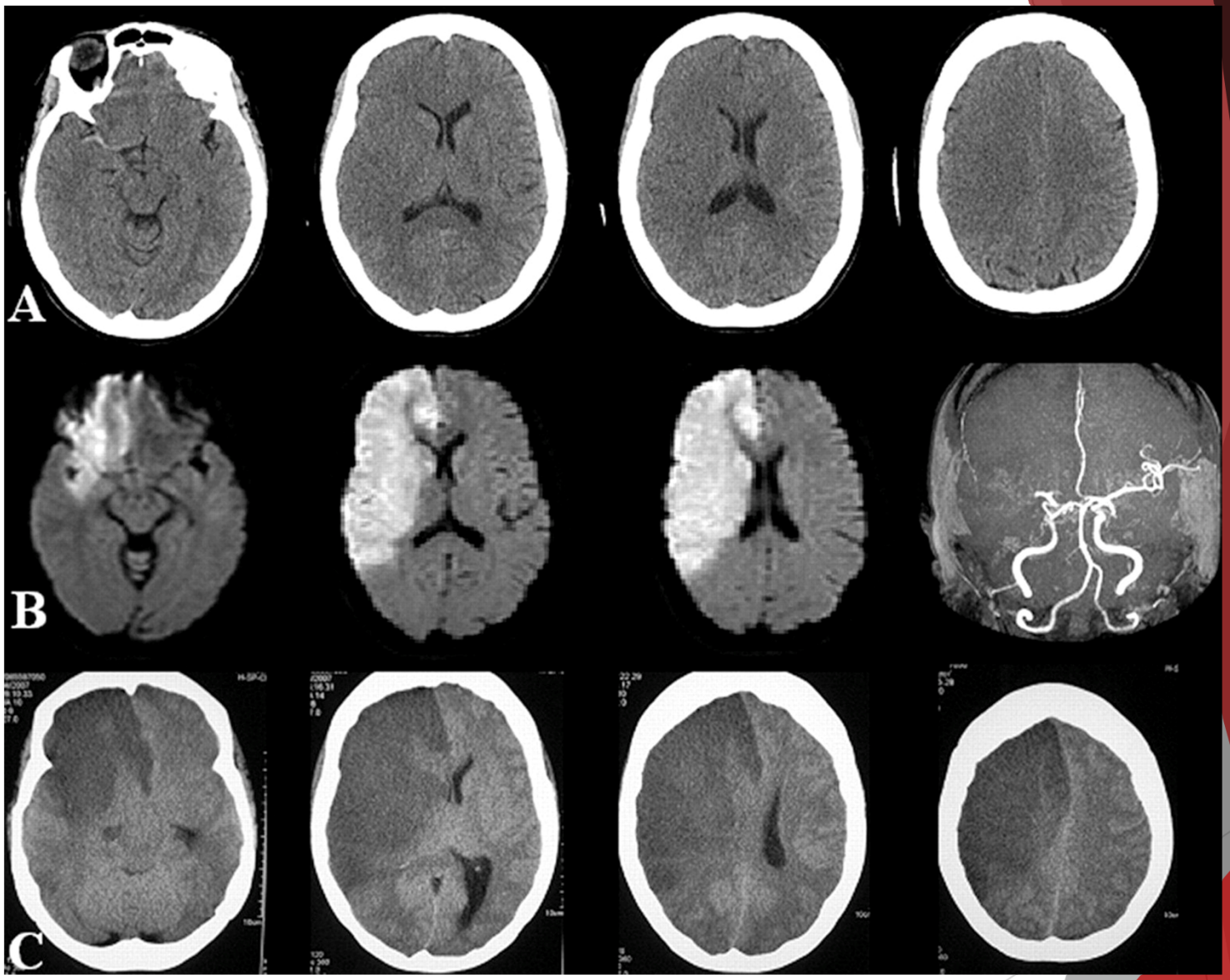

Study Organization
Principal Investigator Oversight
Centre Documentation
Study Design and Rationale
Safety
Study Supplies
Recruitment
Visit Timelines & Procedures
Data Management

Background

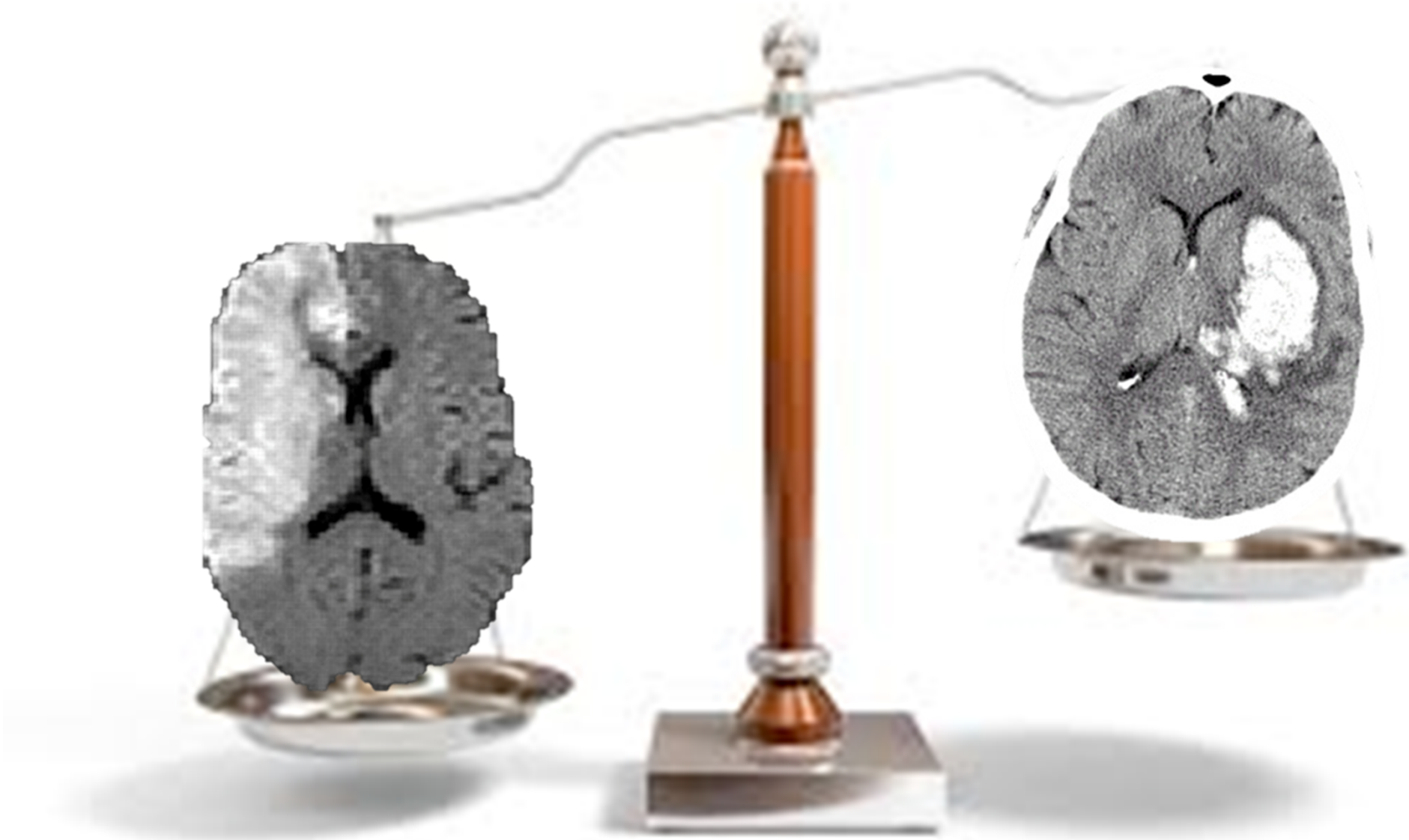
- Atrial fibrillation (AF) currently afflicts an estimated 2.7 million people in the United States and 2-3% of Canadians.

- Primary source of cardioembolic stroke.





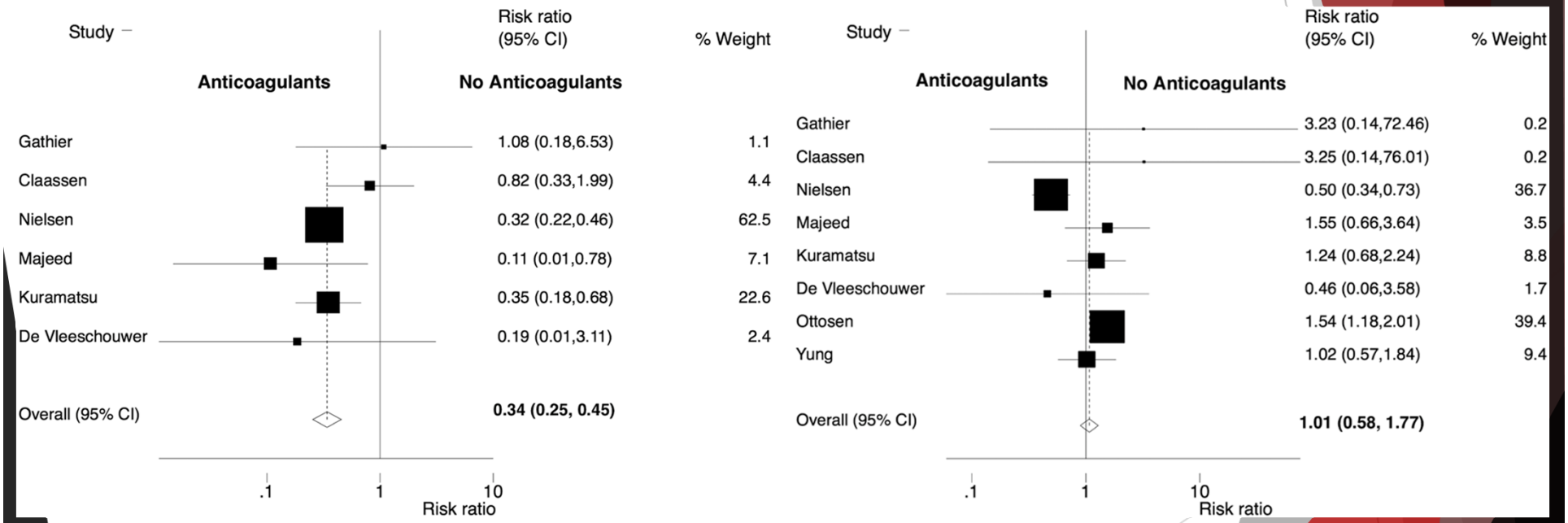
Highest rate of death and long-term disability amongst ischemic stroke subtypes



Restarting Anticoagulant Therapy After Intracranial Hemorrhage

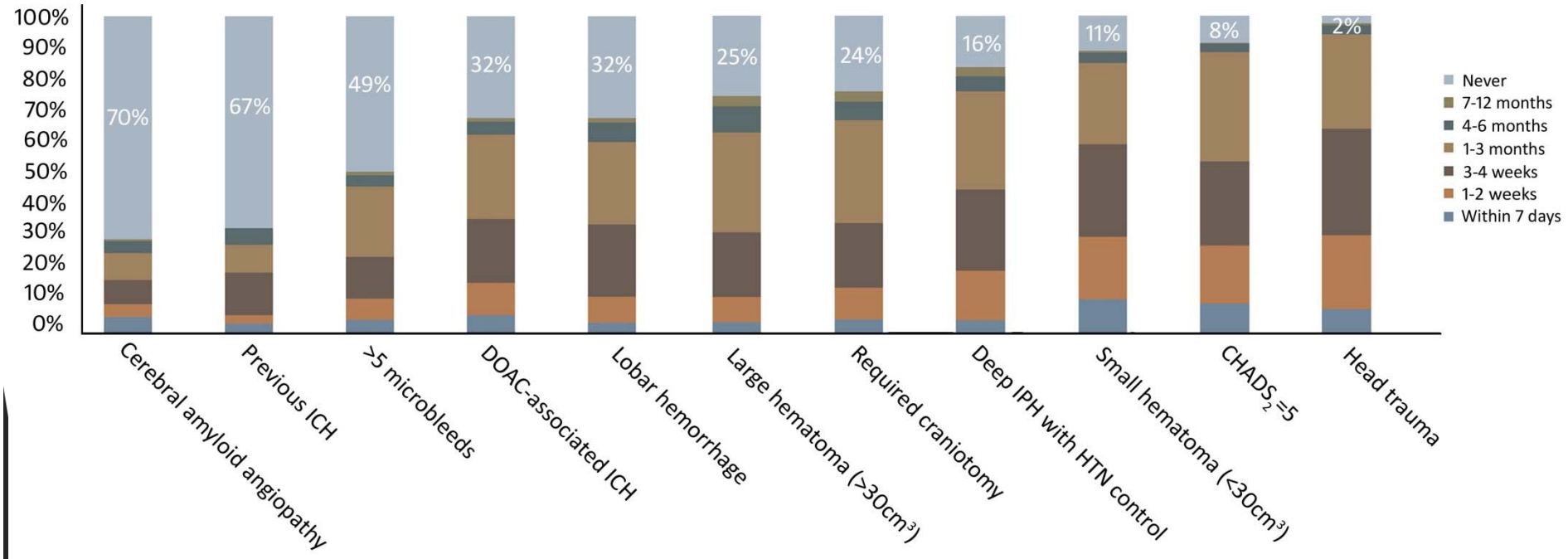
A Systematic Review and Meta-Analysis

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.)

N=228
41% Stroke neurologists (CSC, NAVIGATE ESUS investigators)
26% Neurosurgeons (ASNS)
33% Thrombosis (ISTH)

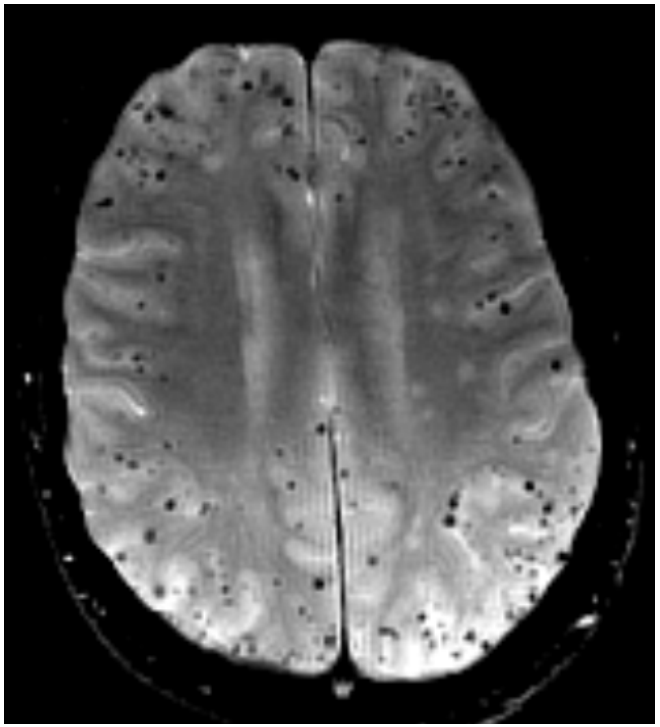


30-98% resumption rate depending on the clinical scenario

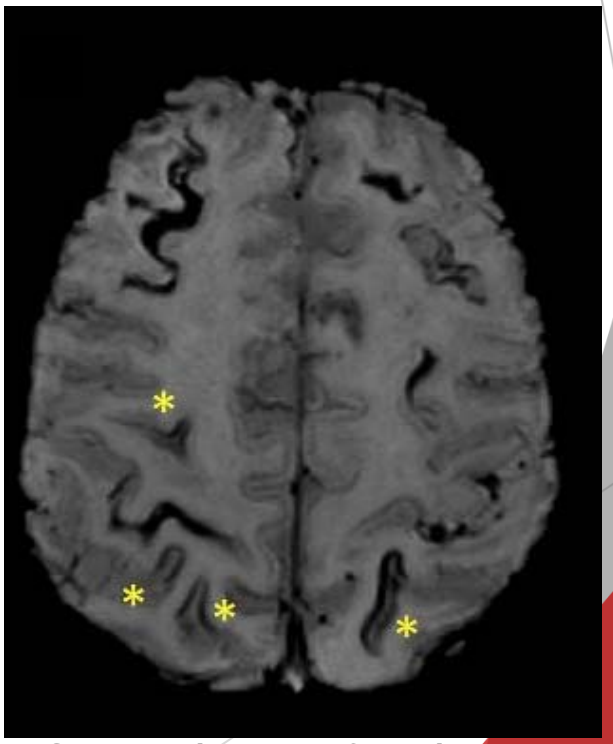
PLoS ONE 13(1): e0191137

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]*



Strictly lobar CMBs



Cortical superficial siderosis

ANN NEUROL 2017;82:755-765

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]*

TABLE 5. Oral Anticoagulation Resumption and Outcomes following Lobar Intracerebral Hemorrhage related to Possible versus Probable CAA N=190

	Possible CAA			Probable CAA		
Outcome[a]	**HR**	**95% CI**	***p***	**HR**	**95% CI**	***p***
Mortality	0.27	0.08–0.86	0.028[b]	0.30	0.10–0.92	0.037[b]
Favorable outcome, mRS 0–3	3.40	1.22–9.46	0.020[b]	3.11	1.08–8.97	0.038[b]

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

ANN NEUROL 2017;82:755-765

Leading Opinion

Cerebral amyloid angiopathy, cerebral microbleeds and implications for anticoagulation decisions: The need for a balanced approach

Andreas Charidimou[1,2], Ashkan Shoamanesh[3], Rustam Al-Shahi Salman[4], Charlotte Cordonnier[5], Luke A Perry[6], Kevin N Sheth[7], Alessandro Biffi[1,8], Jonathan Rosand[1,8,9] and Anand Viswanathan[1,2]

International Journal of Stroke, DOI: 10.1177/1747493017741

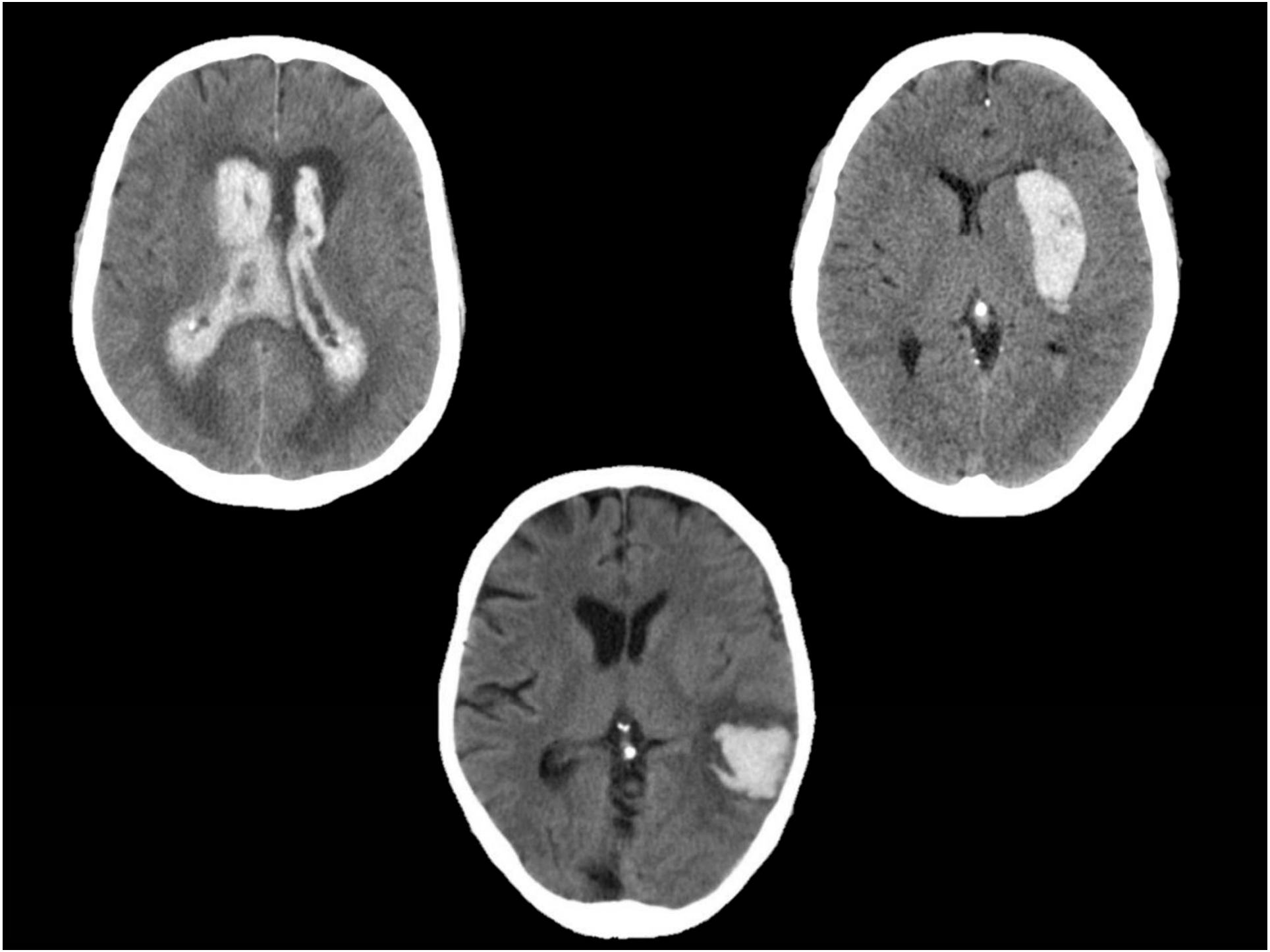
NASPAF-ICH: Aim

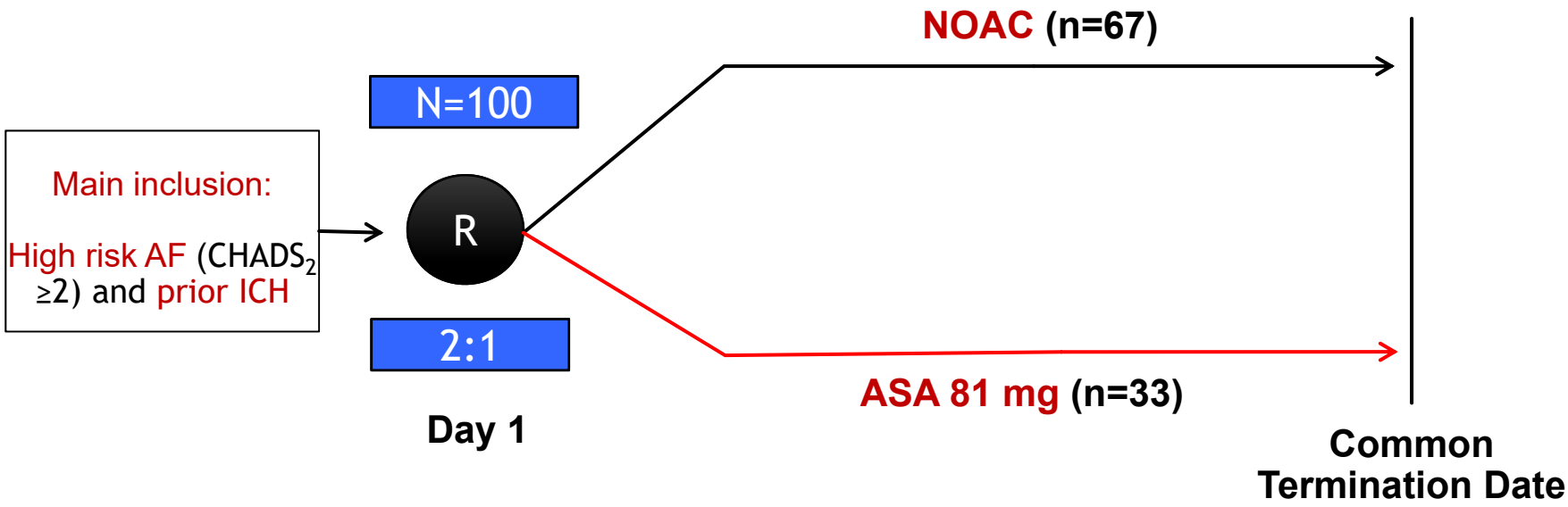
- Open-label, multicenter national phase II randomized pilot study.

- To determine the feasibility of a controlled trial examining the efficacy and safety of NOACs compared with aspirin for stroke prevention in patients with high-risk AF and previous intracerebral hemorrhage (ICH).

NASPAF-ICH: Hypothesis

- Feasibility: Enrollment of 100 eligible participants at 15 recruitment sites over 24 months will be feasible with minimal loss-to-follow up.
- Efficacy: Treatment with NOACs will reduce the risk of ischemic stroke compared with aspirin.
- Safety: There will be no significant increase in ICH recurrence with NOACs vs. aspirin





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)

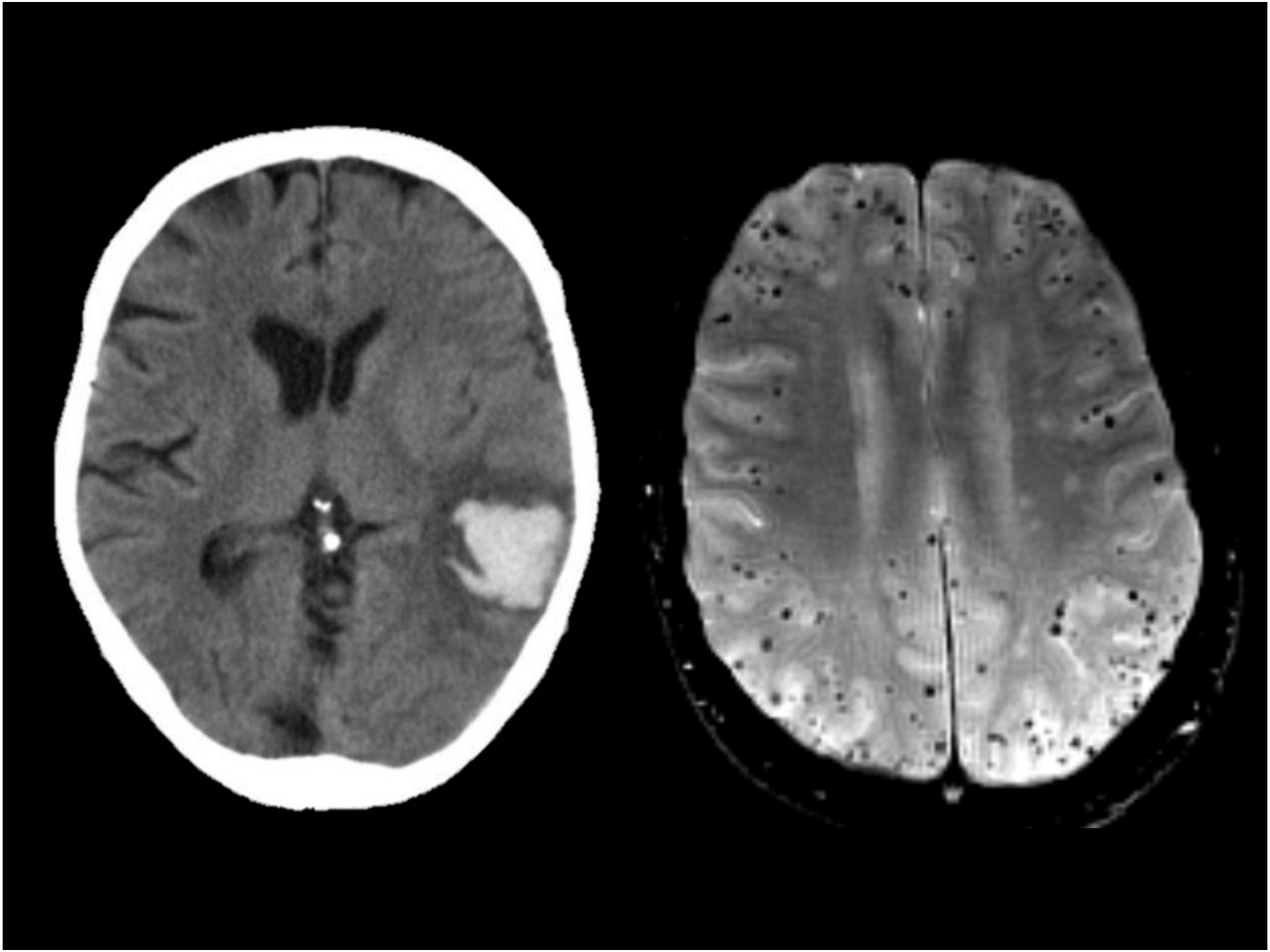
Special procedure: MRI at study entry for post-hoc risk stratification according to burden of CSVD and end study for accrual of CMBs and covert infarcts

Main Exclusion Criteria

- Non-stroke indication for antiplatelet or anticoagulant therapy
- Recent ICH within 14 days (no upper limit on ICH)
- Estimated glomerular filtration rate <30 mL/min
- Platelet count less than 100,000/mm^3 at enrollment or other bleeding diathesis
- Prior symptomatic lobar ICH other than the qualifying event (i.e. ≥2 symptomatic lobar ICH)
- Uncontrollable hypertension consistently above SBP/DBP of 160/100 mmHg
- Known hypersensitivity to either ASA or NOACs
- Inability to adhere to study procedures or unexpected to survive 6 months

Phased Approach to Enrollment

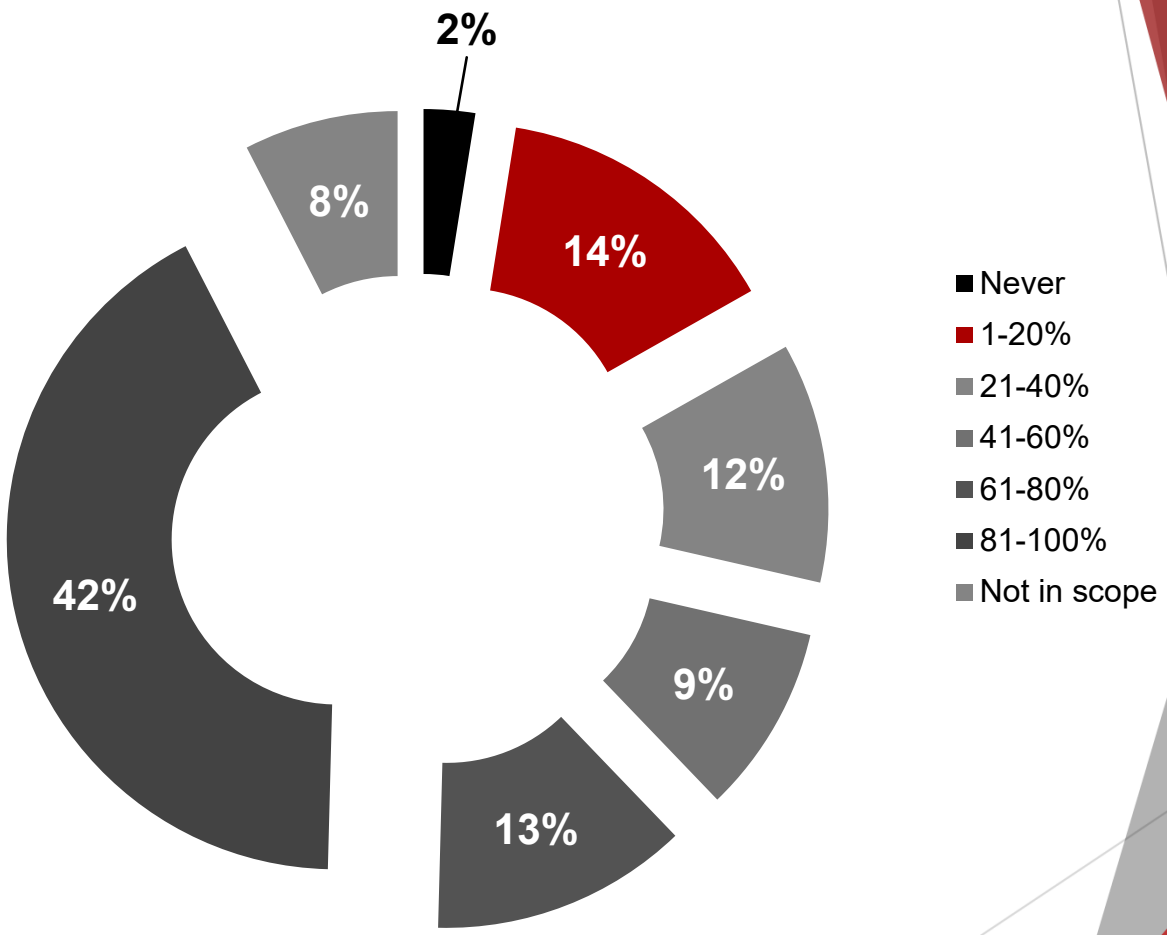
- NASPAF-ICH I (n=15):
  - Exclusion of patients with definite/probable CAA (modified Boston Criteria)
    - **Log participants with definite/probable CAA for inclusion in NASPAF-ICH II**
- NASPAF-ICH II (n=85):
  - Only once NASPAF-ICH I participants have completed an average of 6 months of follow-up and no signal suggesting harm
  - Include patients with definite/probable CAA unless have experienced a previous lobar symptomatic ICH other than the index event



Requisites for Randomization

- Baseline MRI within 3 months (clinical or study)
- Serum creatinine/eGFR within 3 months

In what proportion of ICH patients would you do a clinical MRI in during workup?



NASPAF-ICH: Outcomes

- Primary feasibility: Average recruitment rate amongst sites.
- Efficacy: Composite of ischemic stroke and recurrent ICH, fatal stroke, MI, all-cause mortality, and mRS & MoCA at end of study, and composite of all stroke, myocardial infarct, systemic thromboembolism or death.
- Safety: Major hemorrhage (ISTH criteria)

Anticipated Outcomes

- **Table 2.** NASPAF-ICH: Anticipated Stroke Outcomes

	Ischemic stroke	Recurrent ICH	All stroke
Aspirin	6%/yr	2%/yr	8%/yr
NOAC	2%/yr	2%/yr	4%/yr

Predefined Subgroup Analysis

- Timing of randomization relative to qualifying ICH (2-4 weeks vs. >4 weeks)
- Qualifying ICH topography (lobar vs. deep)
- Presence/absence of prior ICH other than the qualifying event
- CAA vs. non-CAA related ICH
- Cerebral microbleed status at study entry

NASPAF-ICH: Recruitment Rate

5 patients/centre/year

- Estimate 12 eligible patients per high-volume stroke research centre per year, on the basis of an average annual admission rate of 100 ICH cases, 12% suffering non-fatal ICH in the setting of high-risk AF.

- Notwithstanding eligible patients with high risk AF and remote ICH living within the community who are actively being followed in anticoagulation, internal medicine subspecialty, neurology and family medicine outpatient clinics.

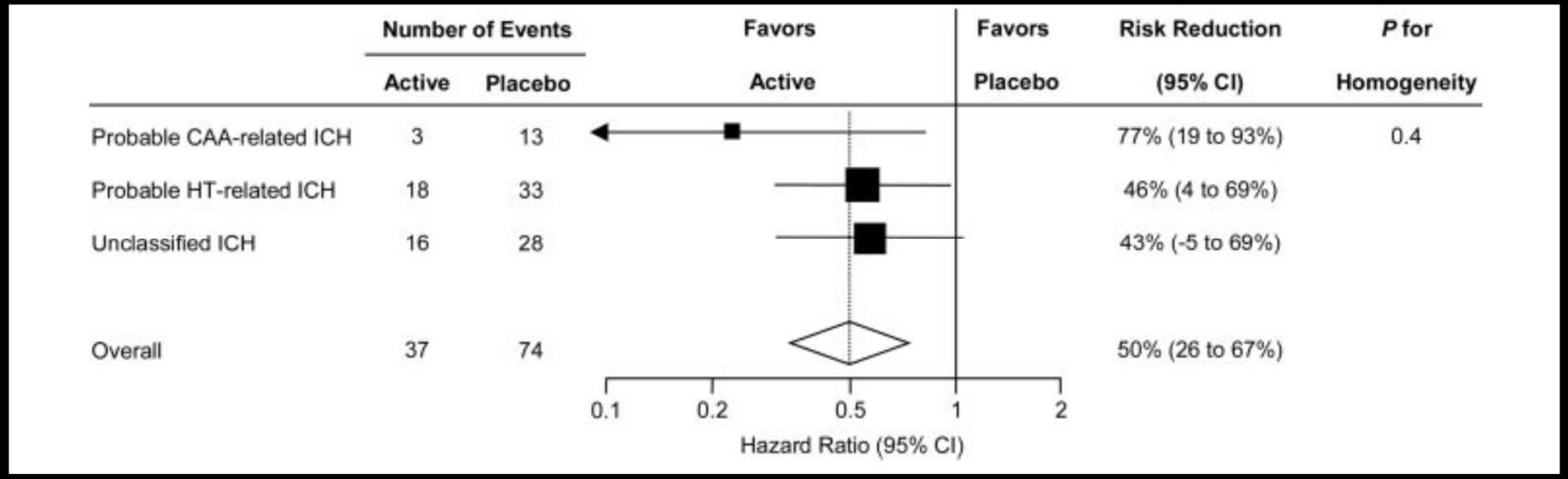
Optimization of Participant Safety

Strict BP control to long-term target < 130/80 mmHg

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**

NASPAF-ICH: Importance

- RCT assessing safety and efficacy of anticoagulant therapy in AF patients after intracerebral hemorrhage.

- Provide the requisite pilot data on recruitment rates, operational feasibility, event rates and treatment effect estimates to design a large, multicenter, phase III, RCT assessing whether NOACs are more efficacious than aspirin for prevention of the composite of ischemic stroke and recurrent ICH in high-risk AF patients with previous ICH

- Provide clarity in an area of clinical practice that is currently inundated with doubt and global/institutional variation in practice.

- Significantly lower the exaggerated perception of ICH risk amongst physicians with potential of improving anticoagulation rates amongst all AF patients.

Study Schedule

Section 2.18 in the study protocol

	Screen	Random	Treatment Phase							
	V1	V2	V3	V4	V5	V6	V7	(V8)	(V9)	EOT
Timelines	-4 to 0 wks[b]	0	1 Mo	2 Mo	3 Mo	4 Mo	5 Mo	6 Mo	7 Mo	
Visit Window (weeks)			±1	±2	±2	±1	±2	±2	±1	±1
Type of Visit	Visit	Visit	Visit	TC	TC	Visit	TC	TC	Visit	Visit
Initiation Procedures										
Informed consent	•									
Eligibility criteria	•									
Demographics	•									
Medical hx and risk factors	•									
Pregnancy test[c]	•									
eGFR[d]	•									
Liver panel	•									
CBC	•									
Coagulation studies	•									
ESR/CRP	•									
Blood pressure at time of ICH	•									
ICH characteristics	•									
Weight/height[e]	•									
MRI brain[f]	•									
Medications										
Concomitant medications		•				•			•	•
1st study drug		•								
Drug dispense		•				•			•	
Drug return + accountability						•			•	•
Efficacy Outcomes										
Ischemic stroke, ICH, fatal stroke, intracranial hemorrhage, MI, STE, and all-cause mortality.		•	•	•	•	•	•	•	•	•
Modified Rankin Score	•									•
MOCA	•									•
Safety Outcomes										
Major hemorrhage		•	•	•	•	•	•	•	•	•
Other adverse events		•	•	•	•	•	•	•	•	•
Vital signs/BP readings	•	•	•	•	•	•	•	•	•	•