Detection and Treatment of Atrial Fibrillation: What's new in prevention and how to choose what's best for my patient.

Edmonton, AB

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WMC Health Sciences Centre

Disclosures and Acknowledgements

Grant-in-Aid
Salary Award

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<u>Speaker's /Adivosry Board Honoraria</u>

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Learning Objectives

- Stroke Diagnosis and Workup
- Cardioembolic Stroke Burden
- Detection of Atrial Fibrillation
- Prevention of Cardioembolic Stroke

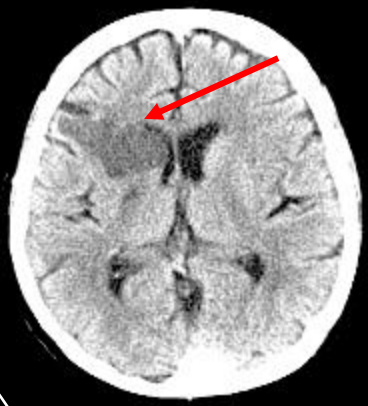
Stroke Diagnosis Requires Brain Scan

85% of stroke is ischemic

Ischemic Stroke Mechanism (Inferred!)

Lacunar Infarct (LACI)

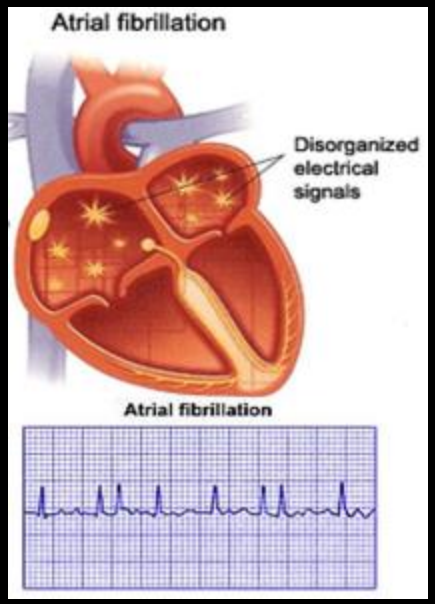
Cortical Infarct (PACI)



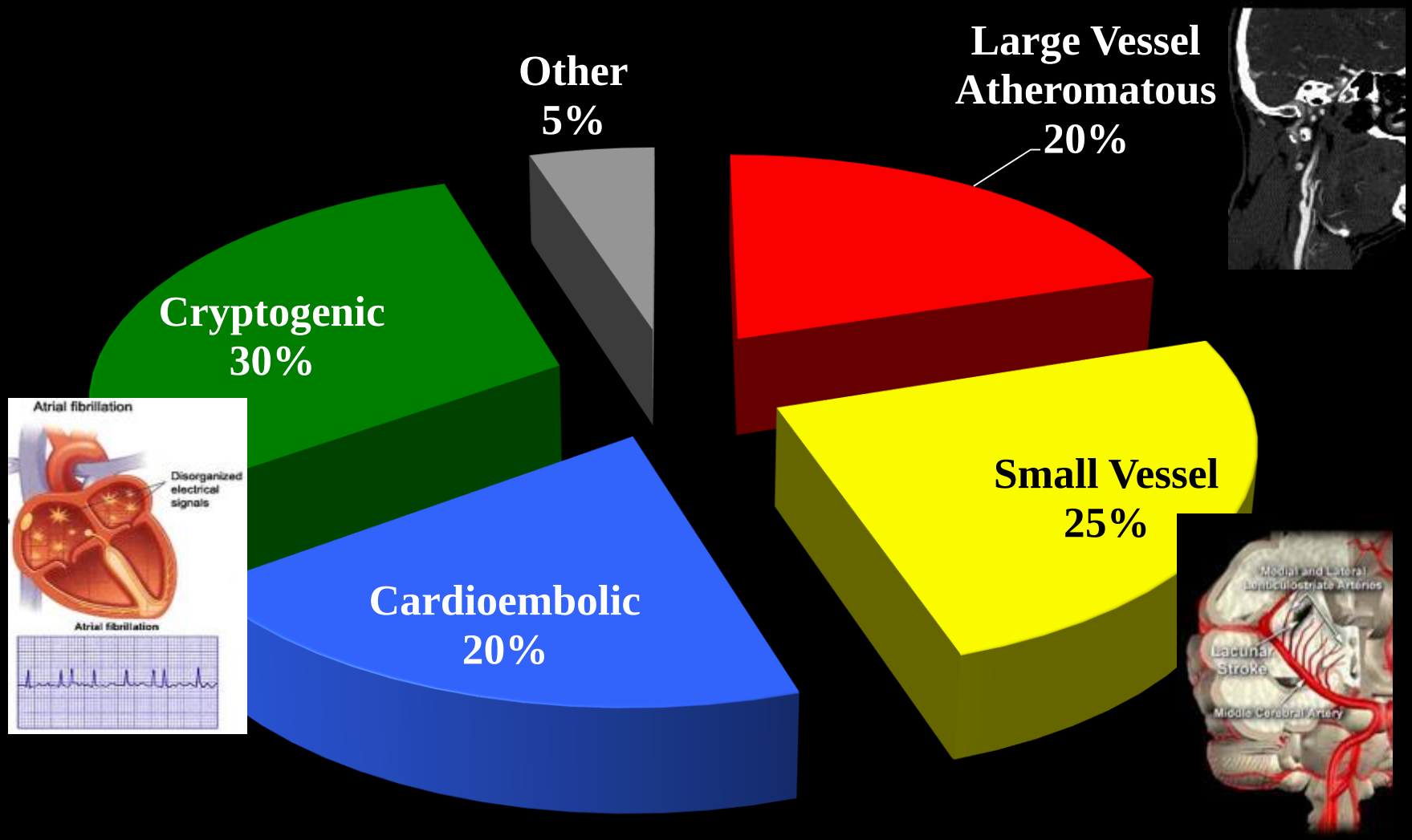
Lipohyalinosis

Artery-artery Embolism

Cardioembolism



This Needs Revision!



Albers GW, et al. Chest 2004; 126 (3 Suppl): 438S–512S
McGrath et al. Stroke 2012; 43: 2048-2054.
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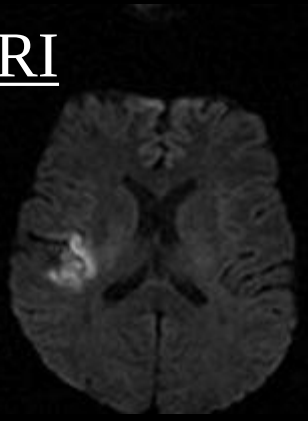
Christmas Day 2013 at UAH

Patient	Presentation	Treatment
86 F	**Stroke + known AF (on warfarin) INR =1.7**	**Dabigatran 110 BID**
88 M	**Stroke + known AF dabigatran (was not taking)**	**Dabigatran 110 BID**
86 M	**Stroke + known AF, on ASA**	**Rivaroxaban 15 mg (eGFR = 35)**
75 F	**TIA + newly diagnosed AF**	**Dabigatran 150 BID**
88 M	***TIA (2nd event)***	***Dabigatran 110 BID x 30 days (DATAS)***
84 F	***'TIA' + 3 previous strokes; cryptogenic***	***Dabigatran 110 BID x 30 days (DATAS)***
84 F	**'Cryptogenic Stroke' (Top of Basilar)**	**ASA+clopidogrel x 30 d**
84 F	**'Cryptogenic Stroke'—Pacemaker!**	**ASA+clopidogrel x 30 d**

Remainder: ICH (2), Lacunar (3), Large Artery Atherosclerosis (2), Vasculitis (1)

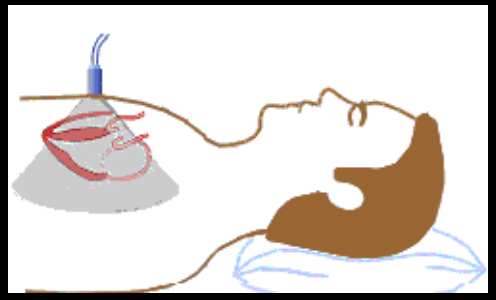
Investigating Stroke Mechanism

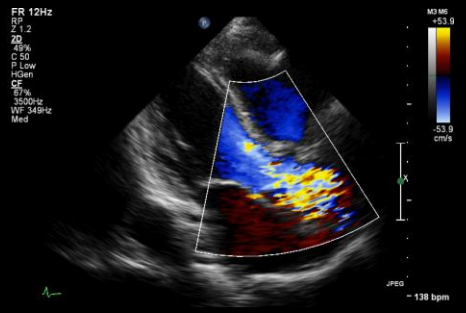
MRI

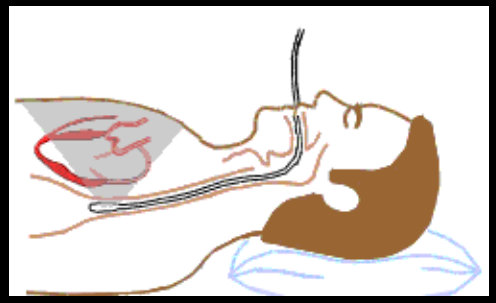


CTA

Echocardiogram

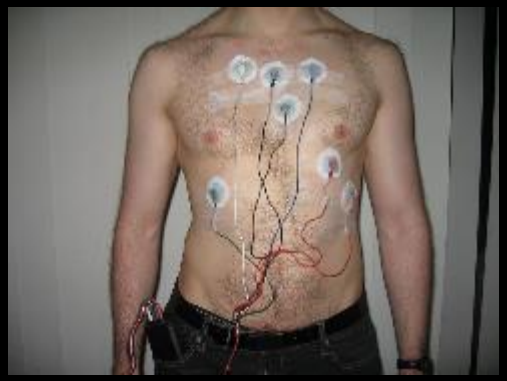






Holter Monitor

AF Detection Rate = 3%

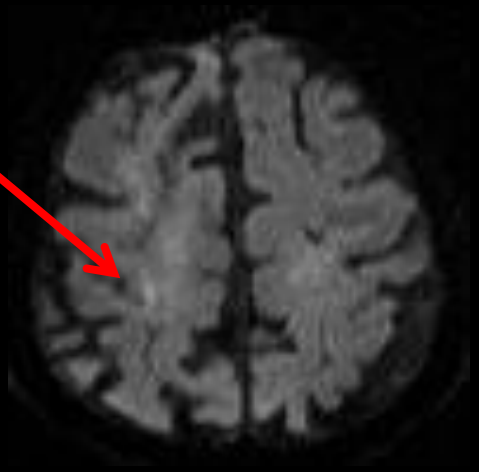


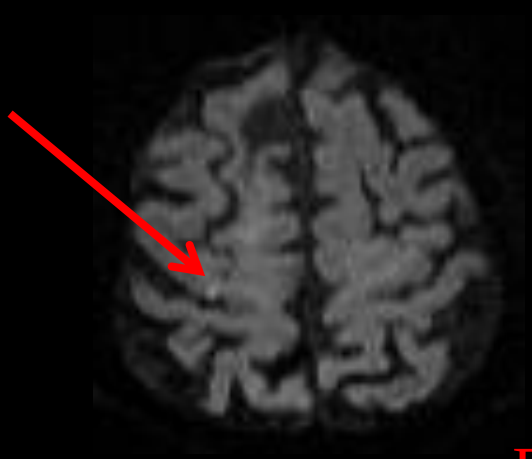
External Loop Recorder

AF Detection Rate = 16%

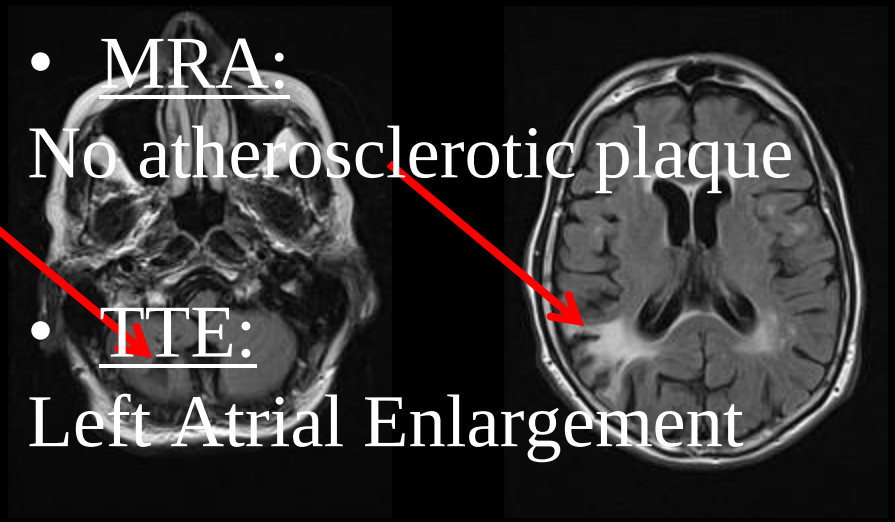
Cryptogenic Stroke??

Acute Stroke (MRI)





Previous Strokes (Three!)



- <u>MRA:</u>

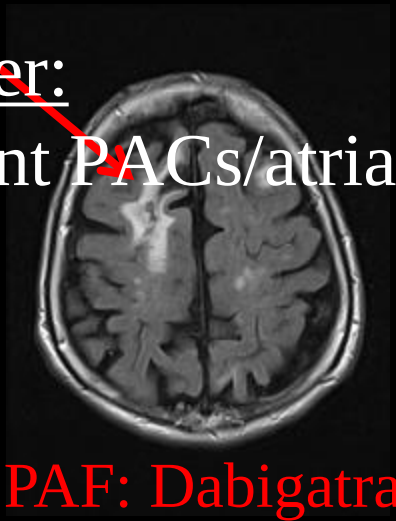
No atherosclerotic plaque

- <u>TTE:</u>

Left Atrial Enlargement

- <u>Holter:</u>

Frequent PACs/atrial ectopy



ELR: 30 seconds of PAF: Dabigatran 110 mg BID

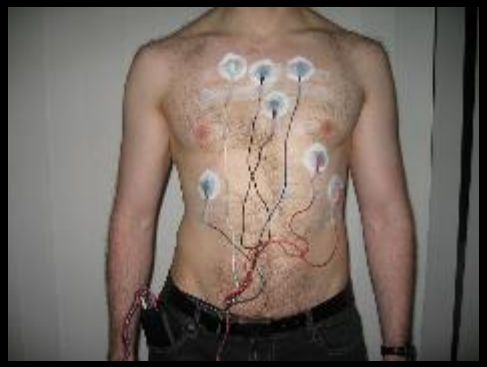
EMBRACE Study

Stroke/TIA and 1 negative Holter
n=572

Accuheart Electrode Belt
(30 days) n=287

Repeat Holter Monior
n=285

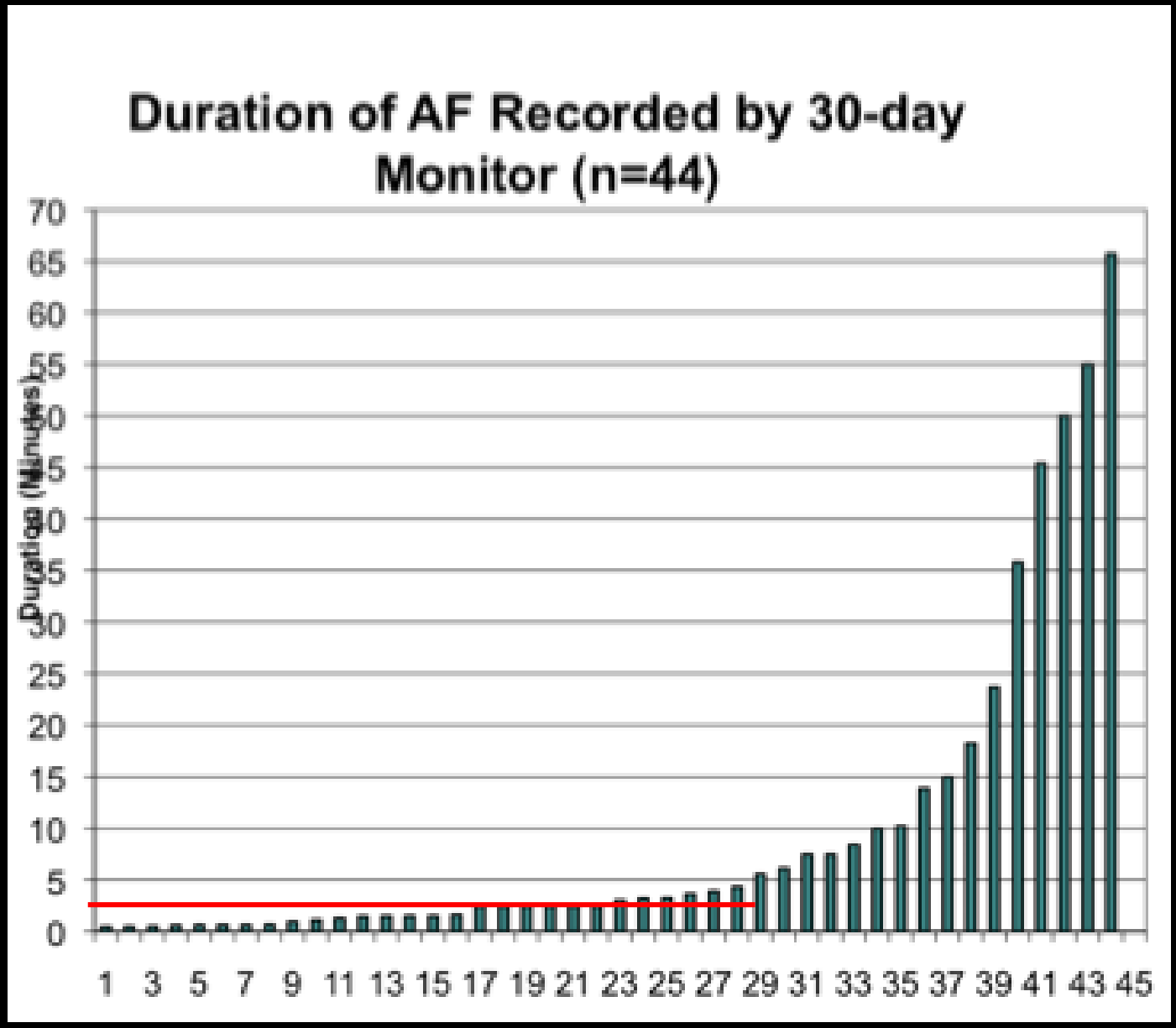
AF Detection: 16%



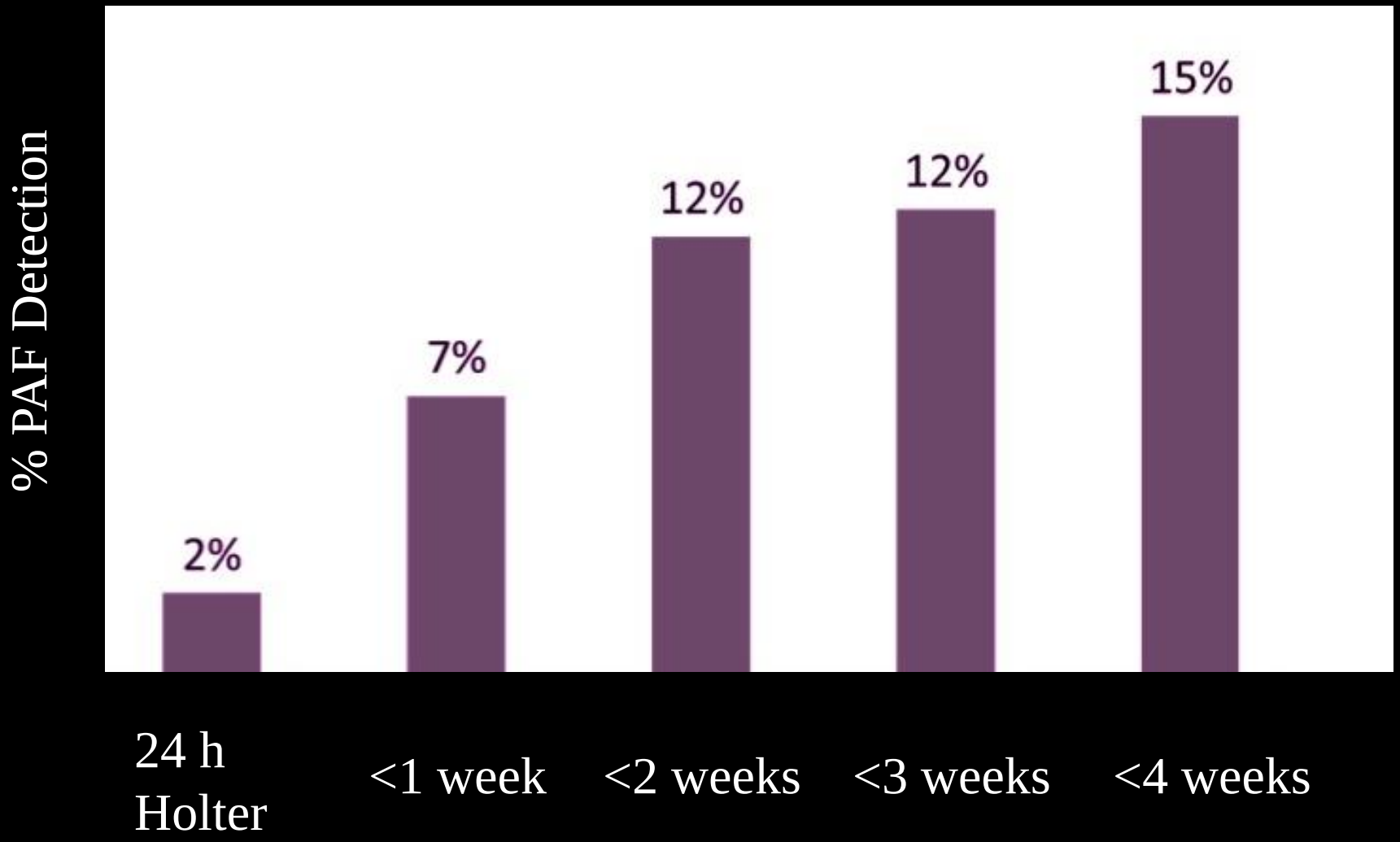
AF Detection: 3%

Gladstone et al, 2013

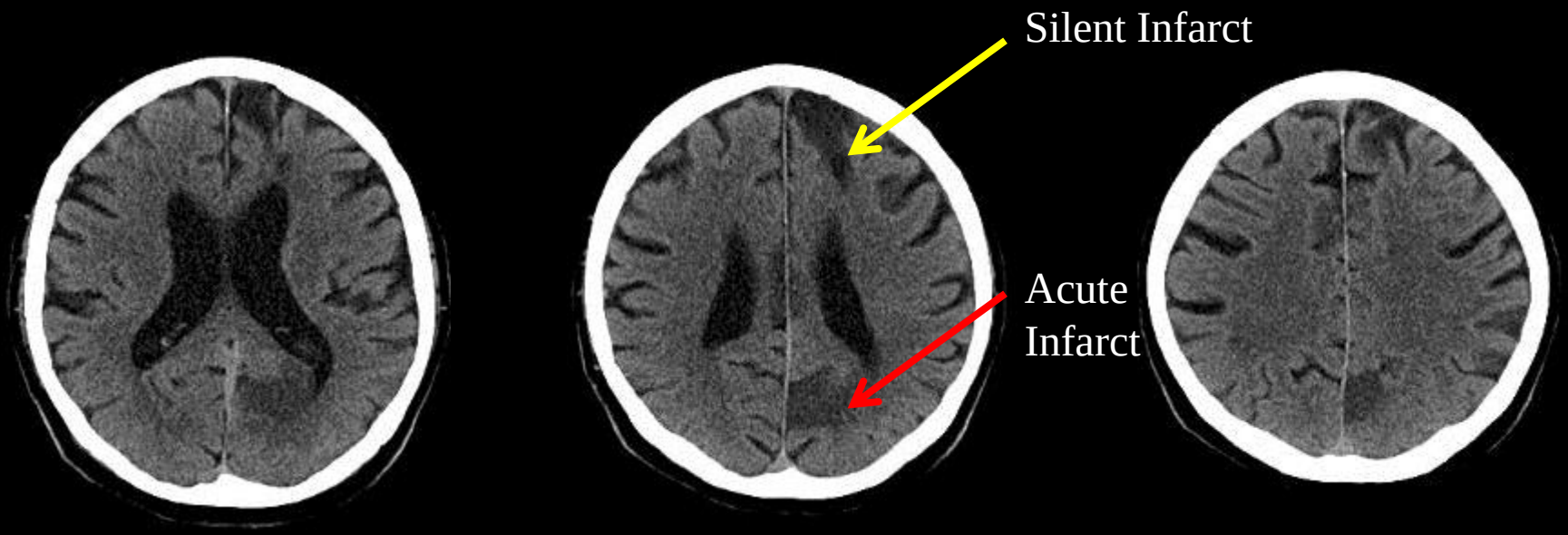
Stroke Patients: Brief Paroxysmal AF

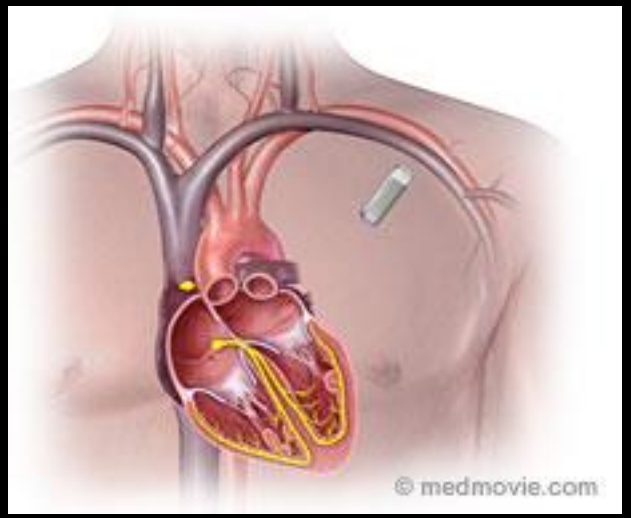


EMBRACE: Time To PAF Detection



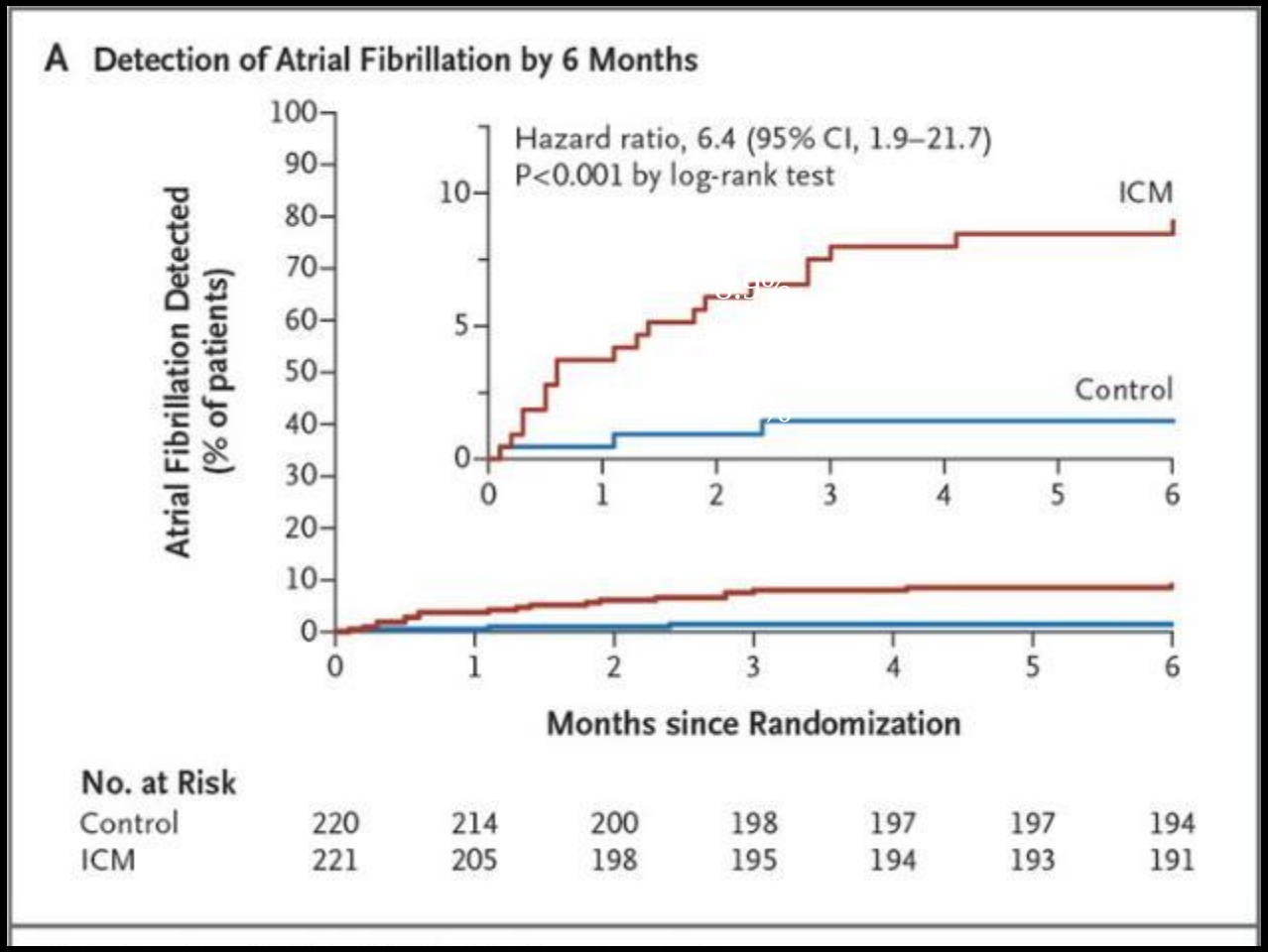
AF: Killing Us Softly





1 min PAF: Dabigatran 150 mg BID

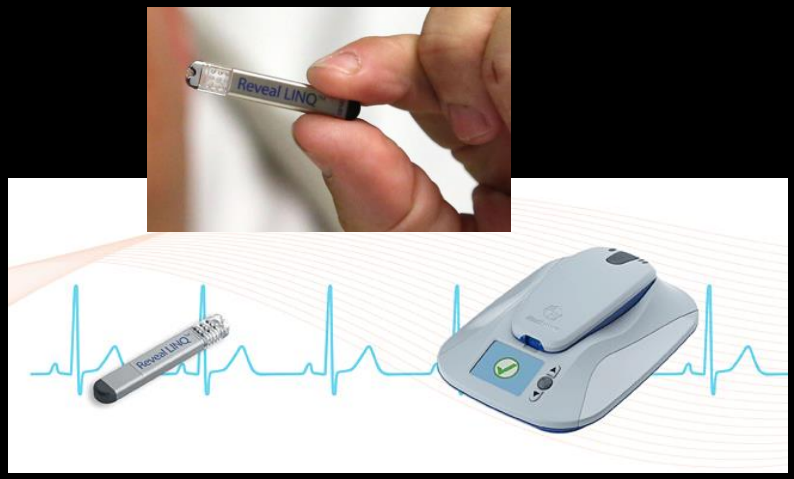
Crystal AF Study



- 12.4% PAF at 1 year
- median time from randomization to AF detection 84 days

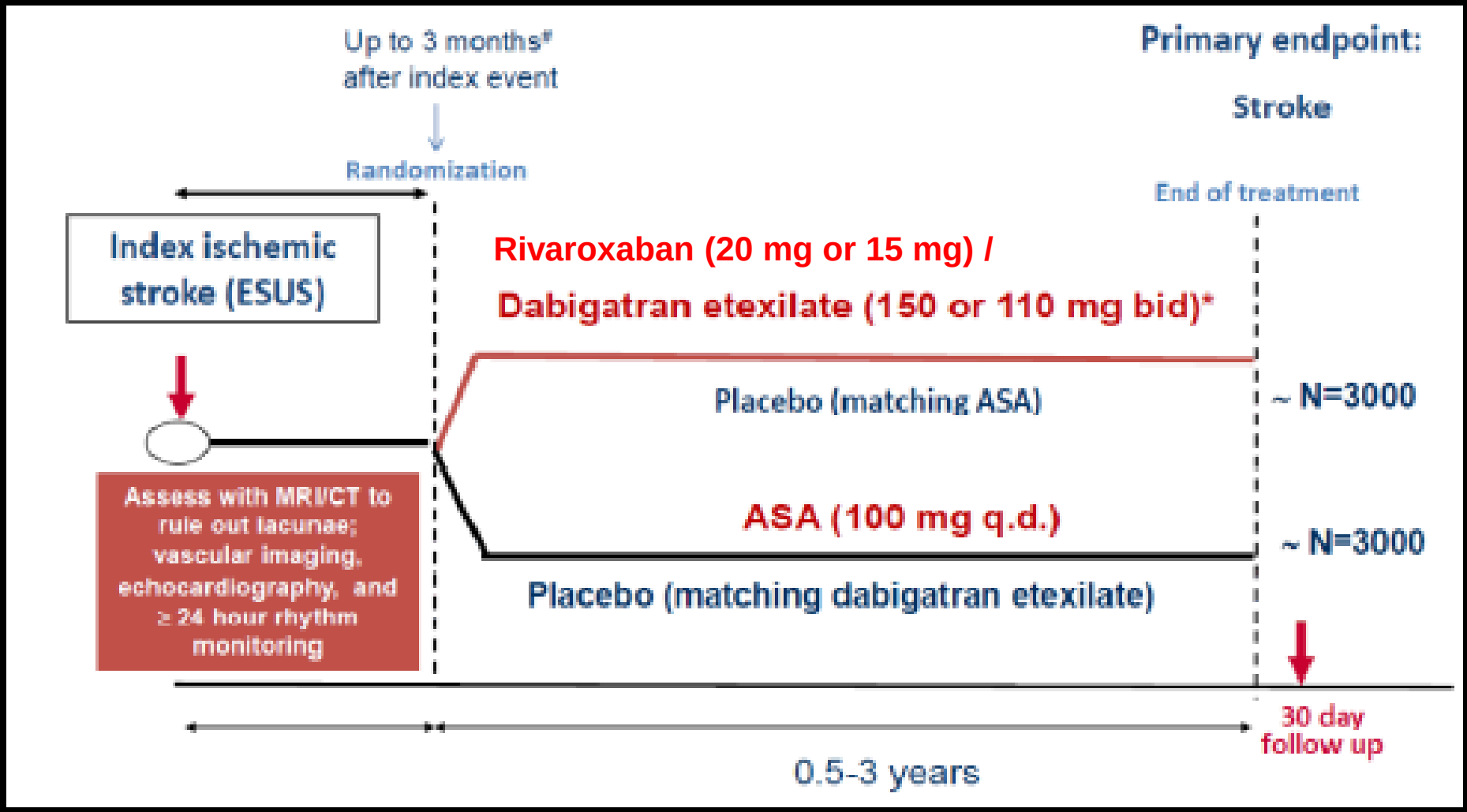
Investigational Approaches to Cryptogenic Stroke

- PER DIEM: Randomized trial, 1:1
  - 30 days monitoring with ELR (Cardiophone)
  - 12 months with ILR (Reveal Linq) with centralized wireless monitoring



- Primary outcome: rate of PAF detection
- Secondary outcomes: Cost, compliance, time to detection

Investigational Approaches to Cryptogenic Stroke



Worse Prognosis Following Cardioembolic Stroke

One Year Risk of Death

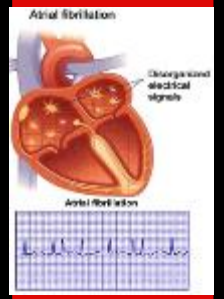
35%
30%
25%
20%
15%
10%
5%
0%

1.4%

Small Vessel

8%

Large Vessel

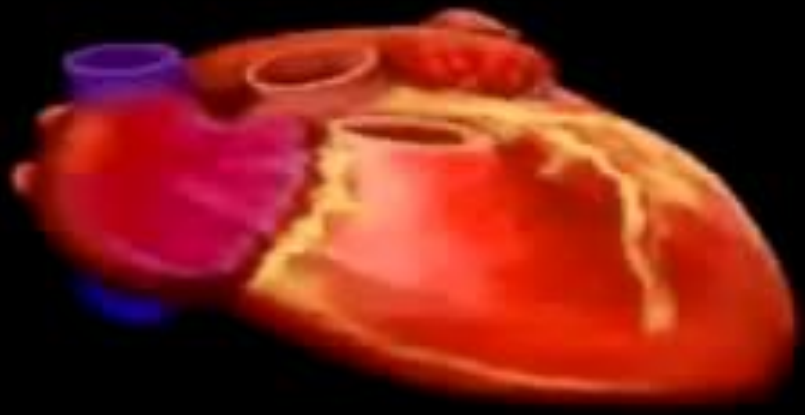


30%

Cardioembolic

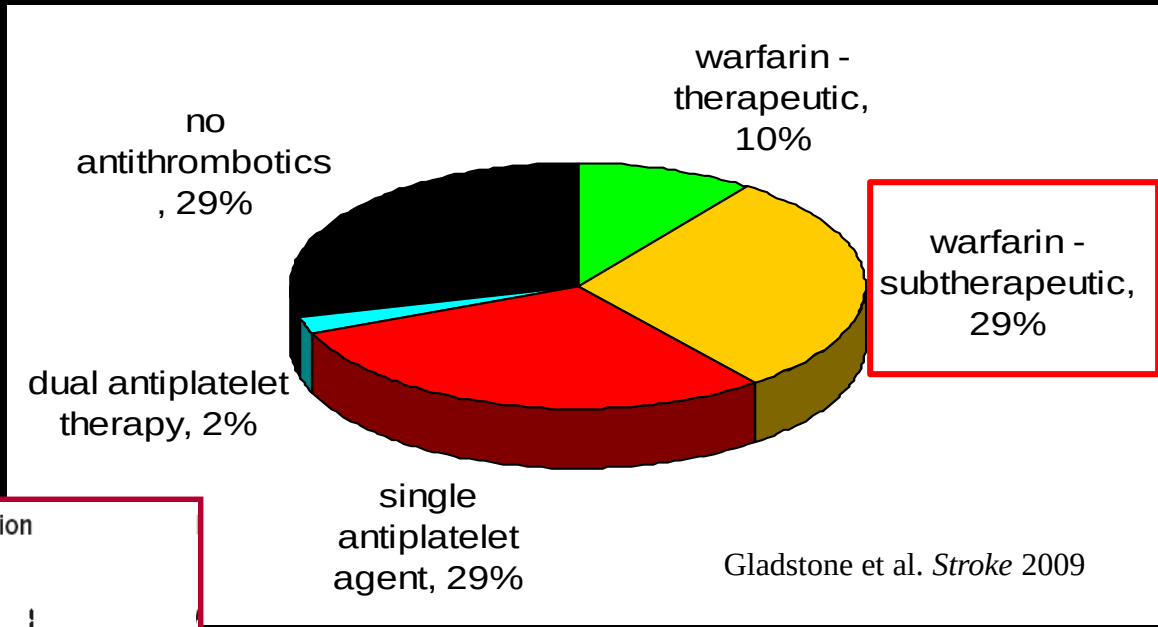
Gladstone DJ et al. *Stroke* 2009; 40:235-240

Cardioembolic Stroke Mechanism and Outcome

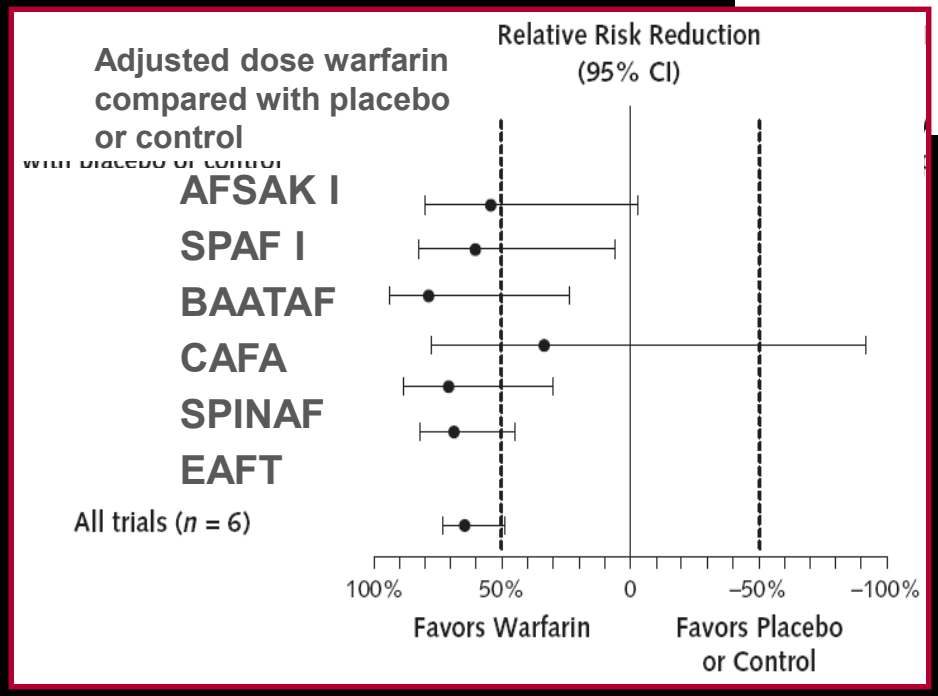


Why the Evidence-Practice Disconnect?

Warfarin Data: 28 044 patients:
68% RRR stroke

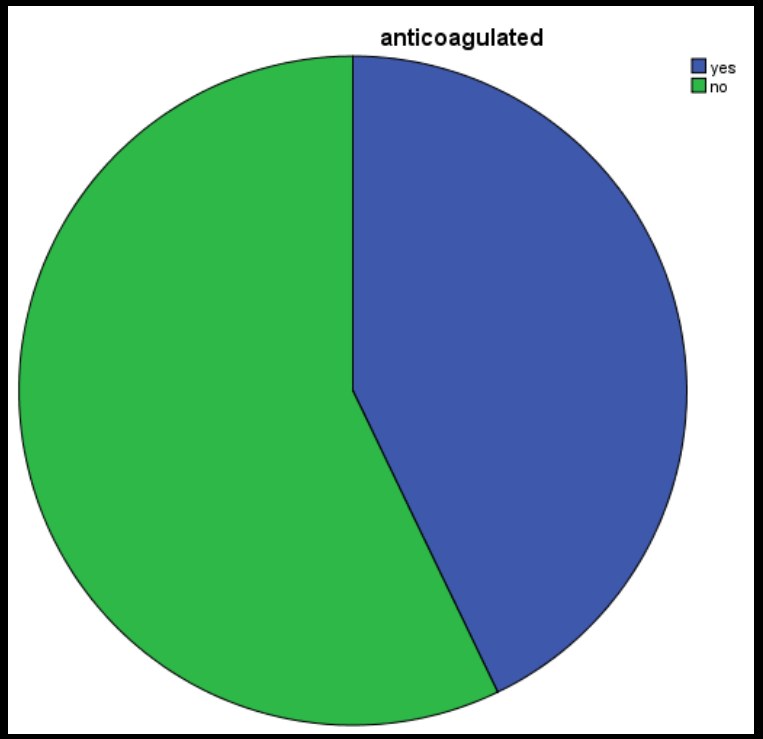


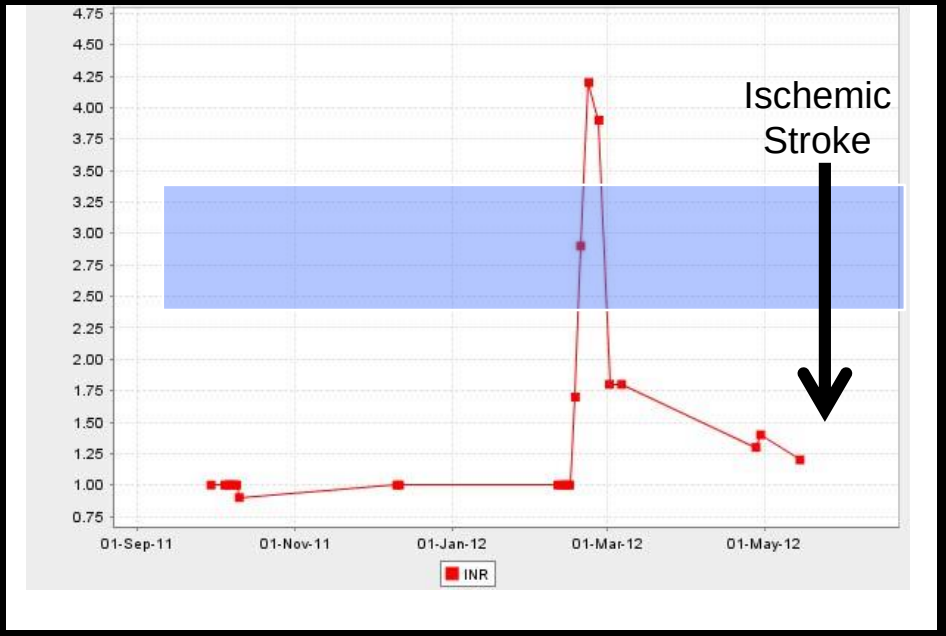
Gladstone et al. *Stroke* 2009



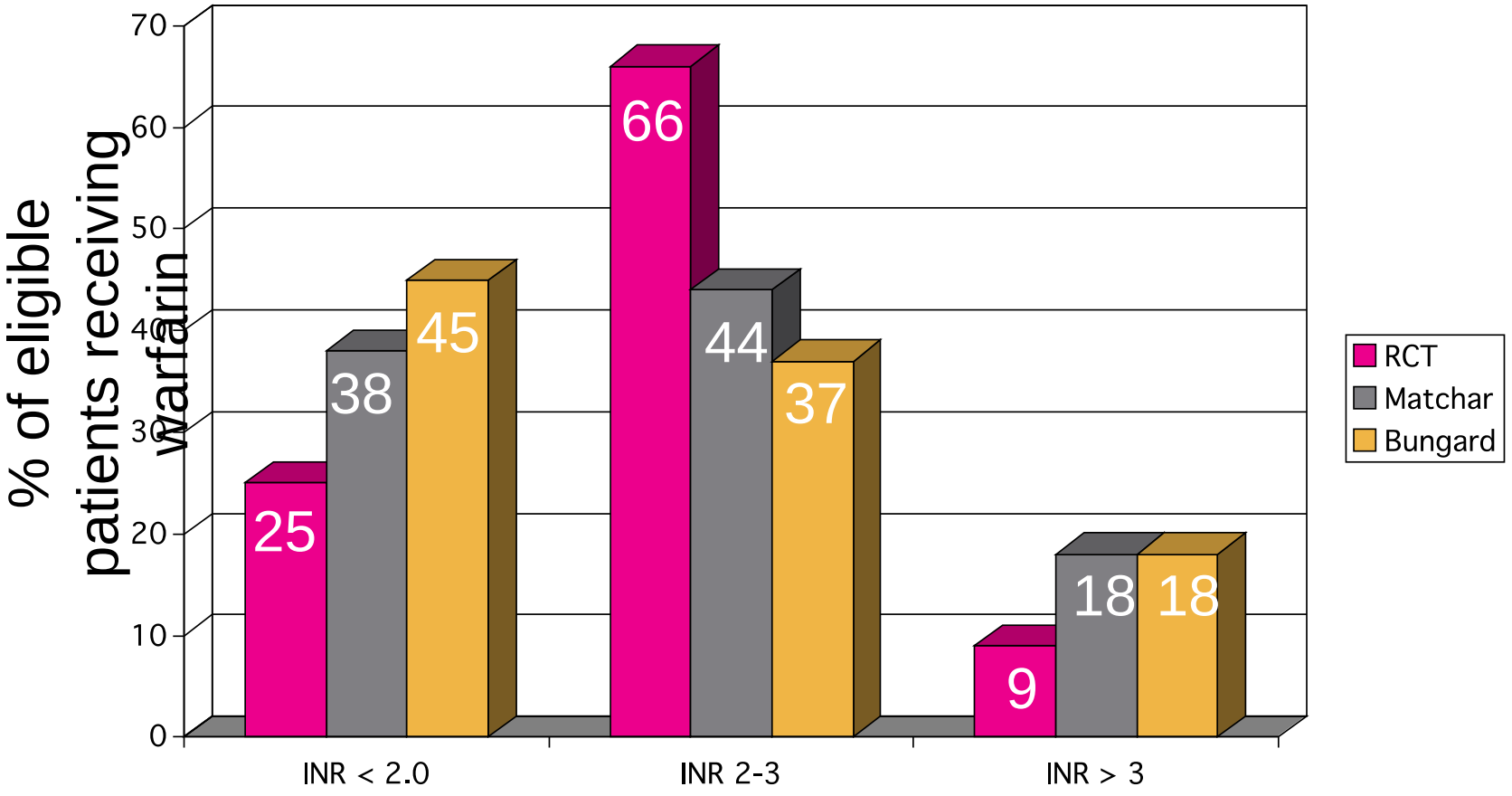
Under-use of OAC in Edmonton

Patients with a known history of AF presenting with stroke/TIA to UAH 2012-13 (n=402)





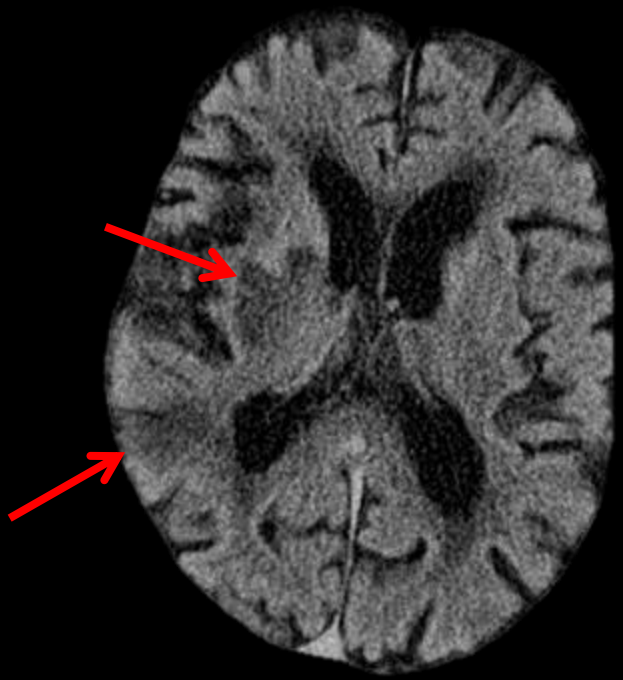
INR Control: Clinical Trials vs. Clinical Practice



INR control is an ongoing challenge in routine clinical practice

RCT: Kalra *et al. BMJ* 2000
Matchar *et al. Am J Med* 2002
Bungard *et al. Pharmacotherapy* 2000

Christmas ‘13: 86 Male, Known AF, Rx: ASA (‘*Protecting*’ The Elderly From OAC Risks)

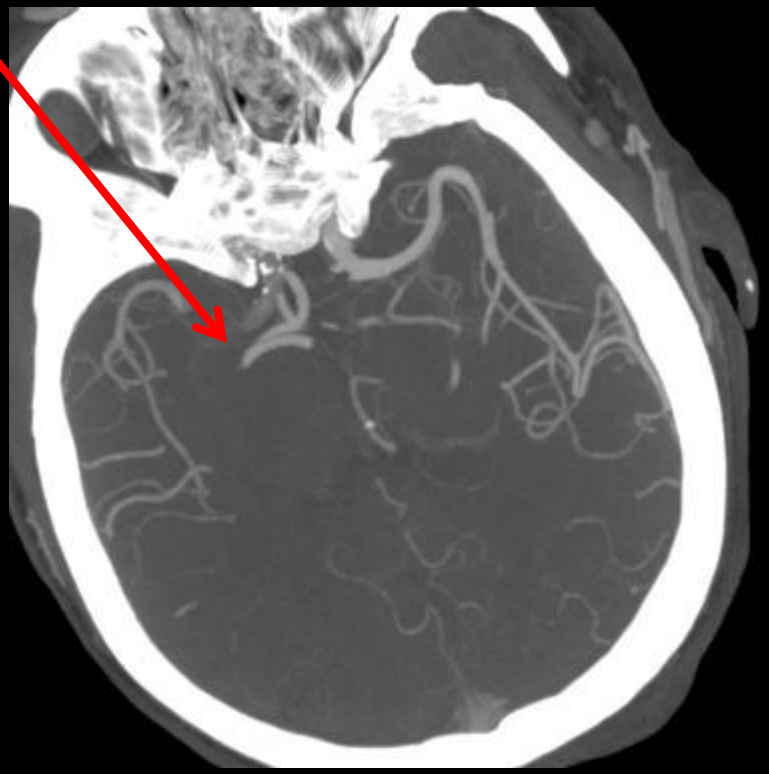


Christmas Dinner

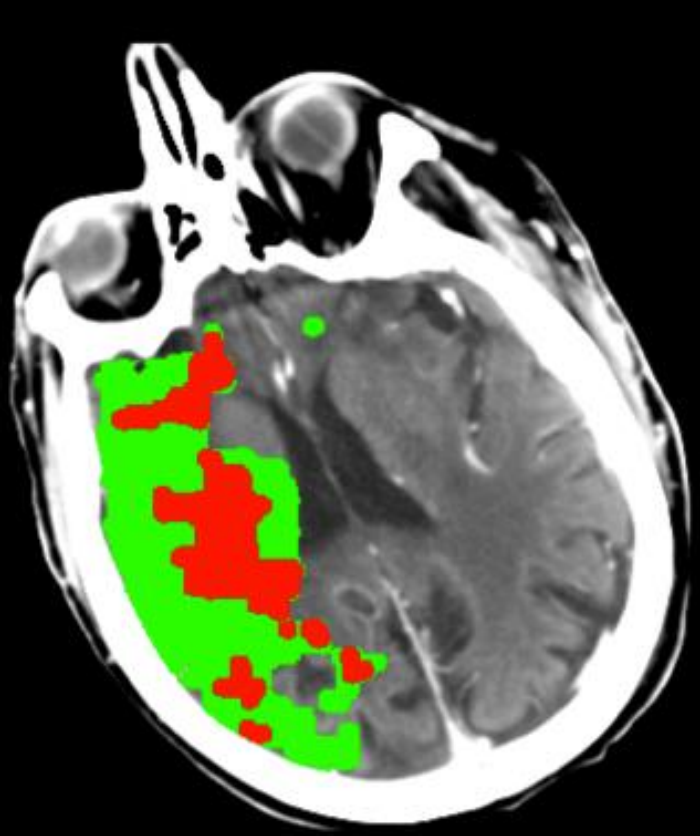
93 Independent Male: Warfarin Discontinued 6 Days Earlier

CT Angiogram

M1 Occlusion

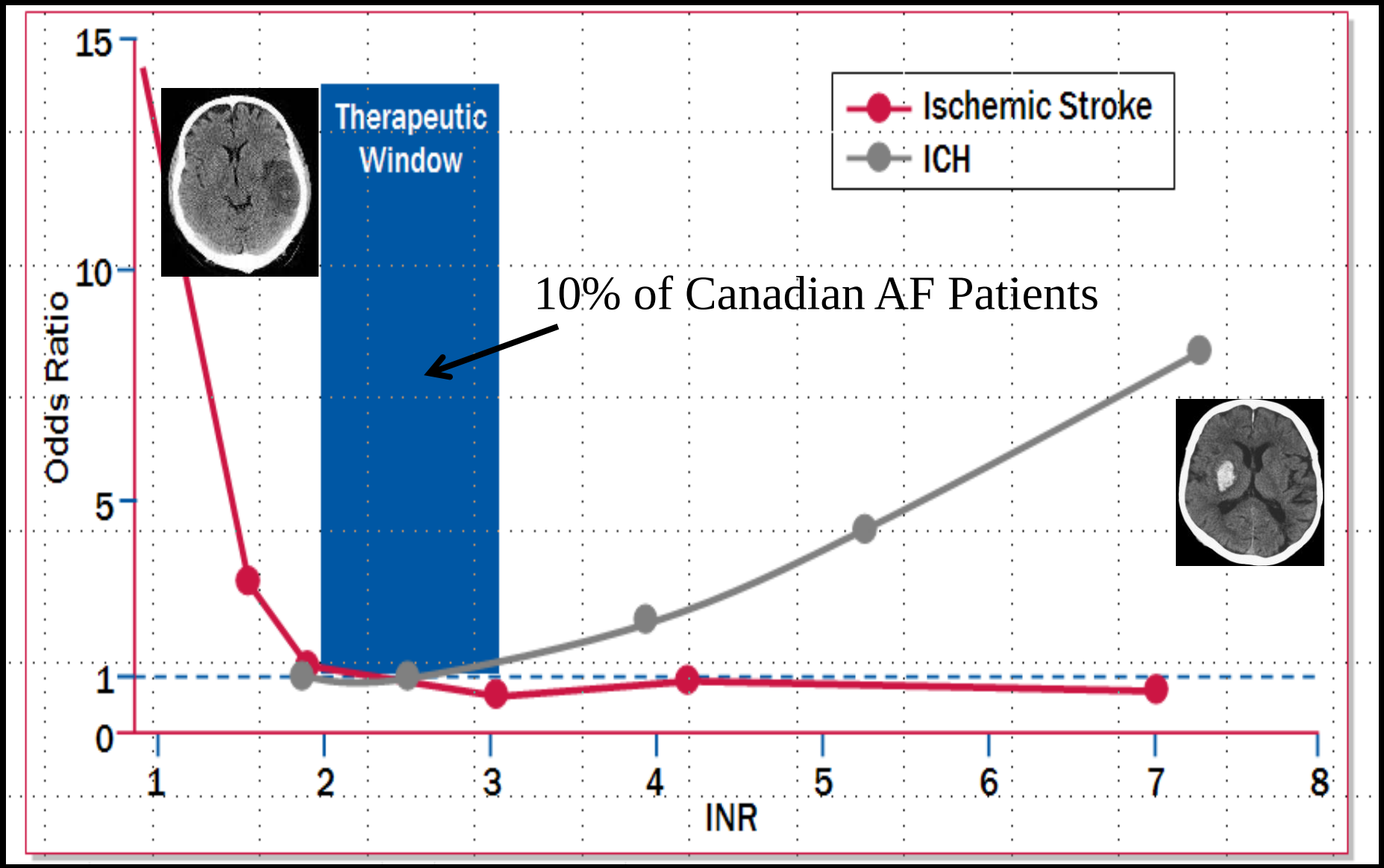


Penumbra Map



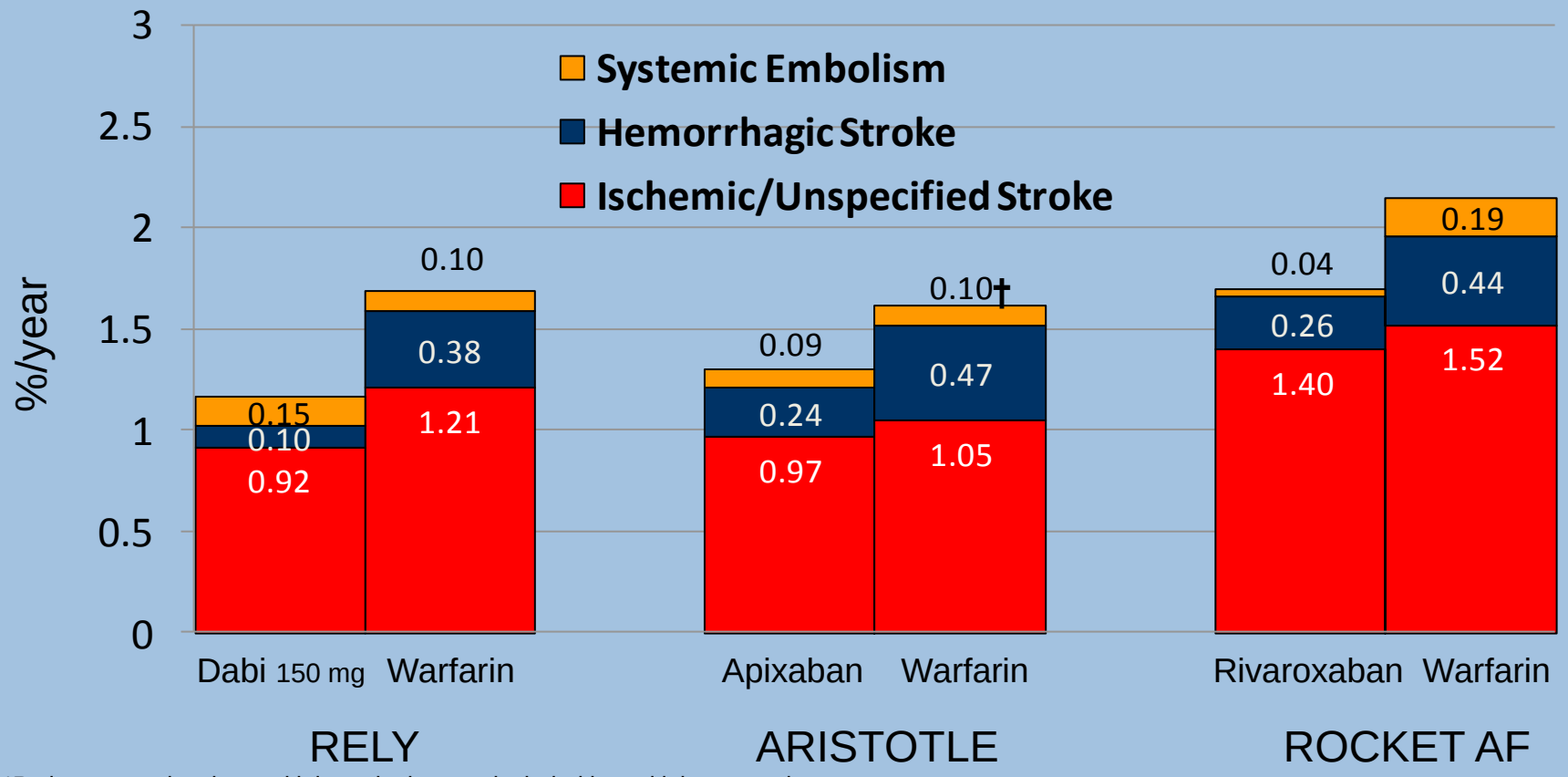
Patient Died 5 Days Later

Anticoagulation and Physician Psychology



Hylek EM et al. *N Engl J Med.* 1996;335:540-546.

AF Trials: Elements of Primary Endpoint: Ischemic Stroke is No. 1!



*Patients experiencing multiple endpoints are included in multiple categories.
†Systemic embolism result reported for RELY refers to pulmonary embolism.

In recent trials, the majority of AF strokes were ischemic

Connolly *N Engl J Med* 2010;363:1876; Patel *N Engl J Med* 2011;365:883; Granger *N Engl J Med* 2011;365:981

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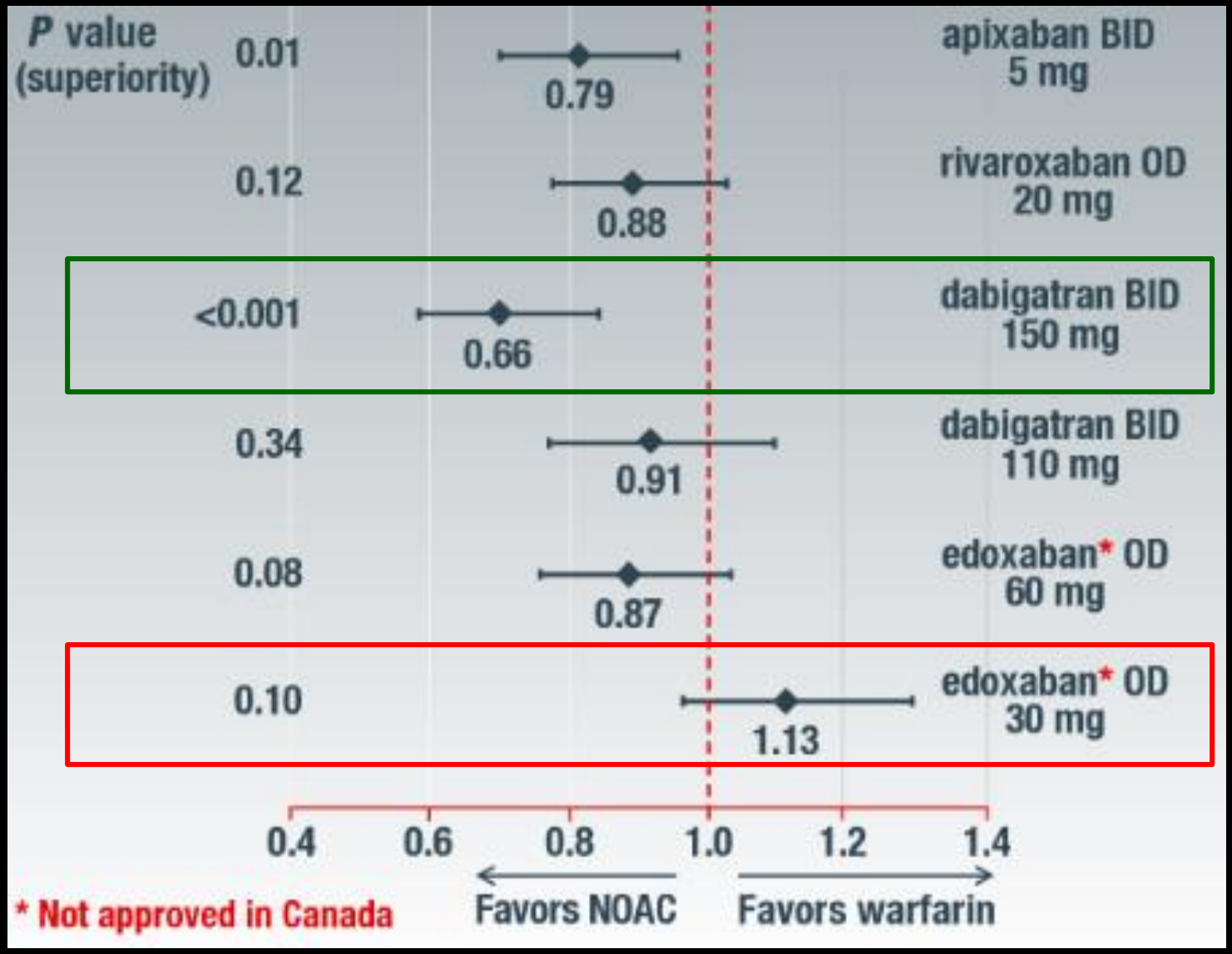
Higher NOAC Dose = Less Emboli

1. RELY
2. ROCKET AF
3. ARISTOTLE
4. ENGAGE

   AF

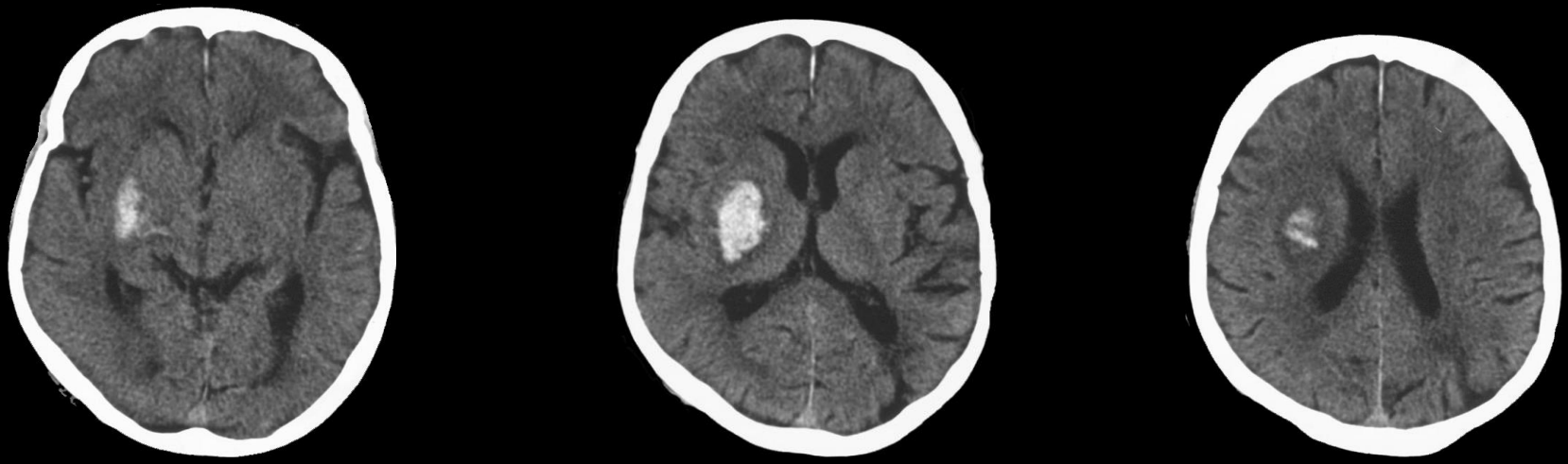
70 000 patients



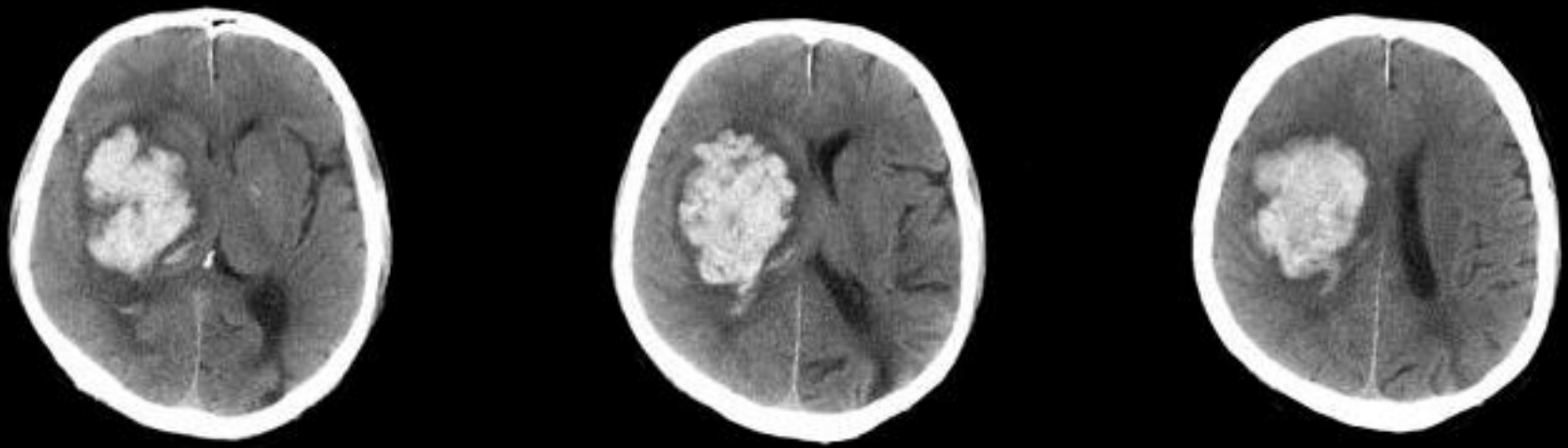
Anticoagulant *Associated* ICH

3 h

INR =2.4



6 h

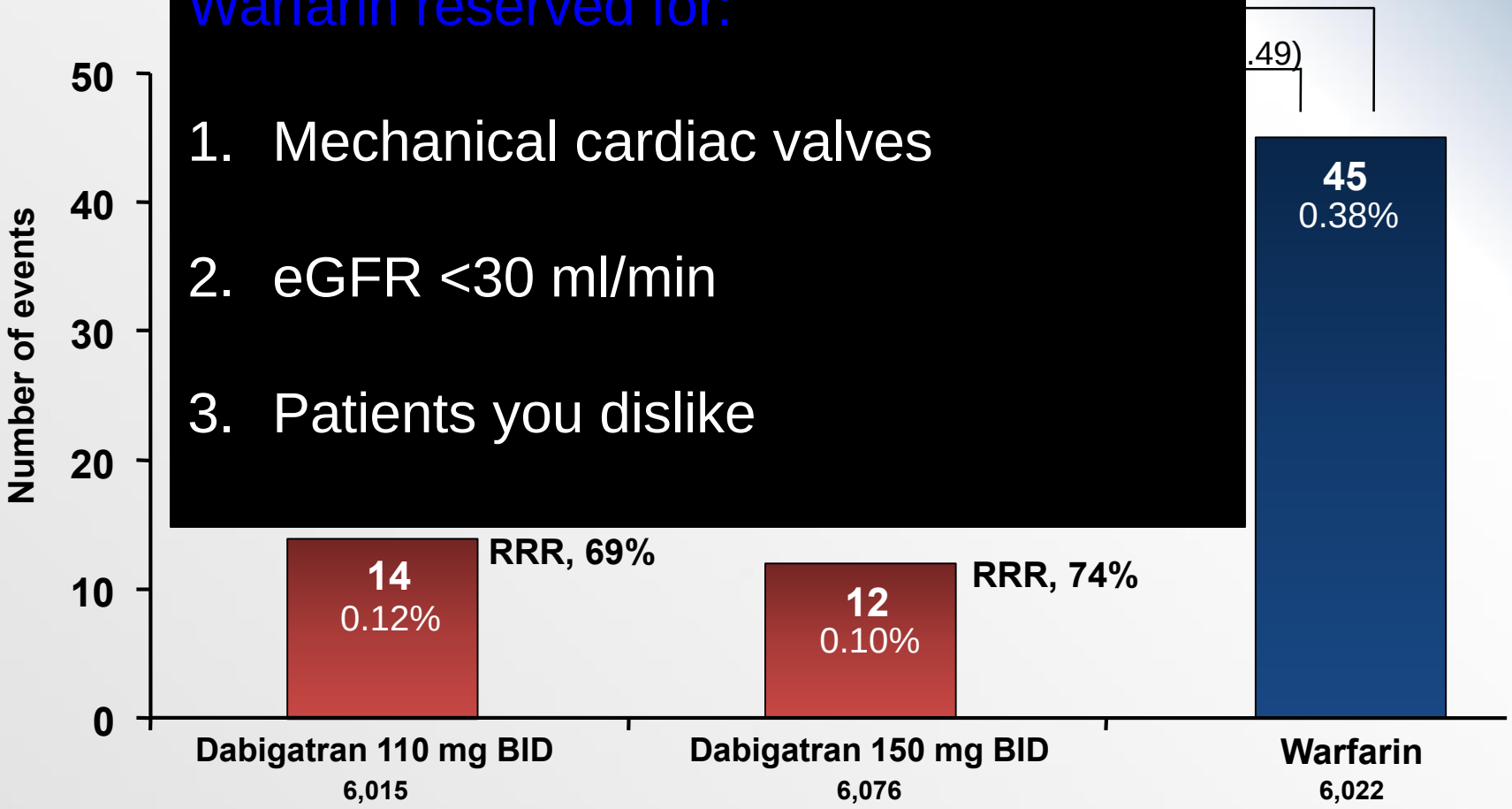


Hematoma growth is 8 x more likely in warfarin patients

ICH Rates = Those of ASA!

Warfarin reserved for:

1. Mechanical cardiac valves
2. eGFR <30 ml/min
3. Patients you dislike



RR=relative risk; RRR=relative risk reduction
Dabigatran etexilate is in clinical development and not licensed for clinical use in stroke prevention for patients with atrial fibrillation

Connolly SJ, et al. N Engl J Med 2009;361:1139-1151

SHIFT
New Strategies to Help In SPAF Treatment

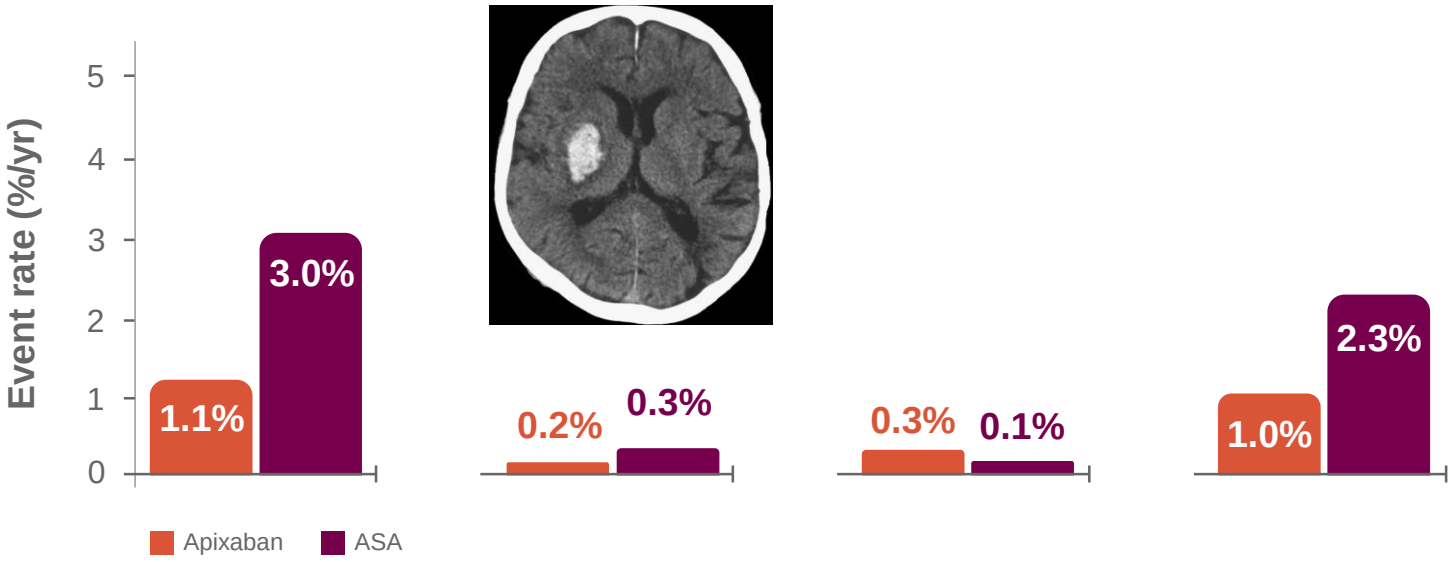
AVERROES: Type of stroke

Ischaemic stroke
HR: 0.37
95% CI: 0.25; 0.55
p<0.001

Haemorrhagic stroke
HR: 0.67
95% CI: 0.24; 1.88
p=0.45

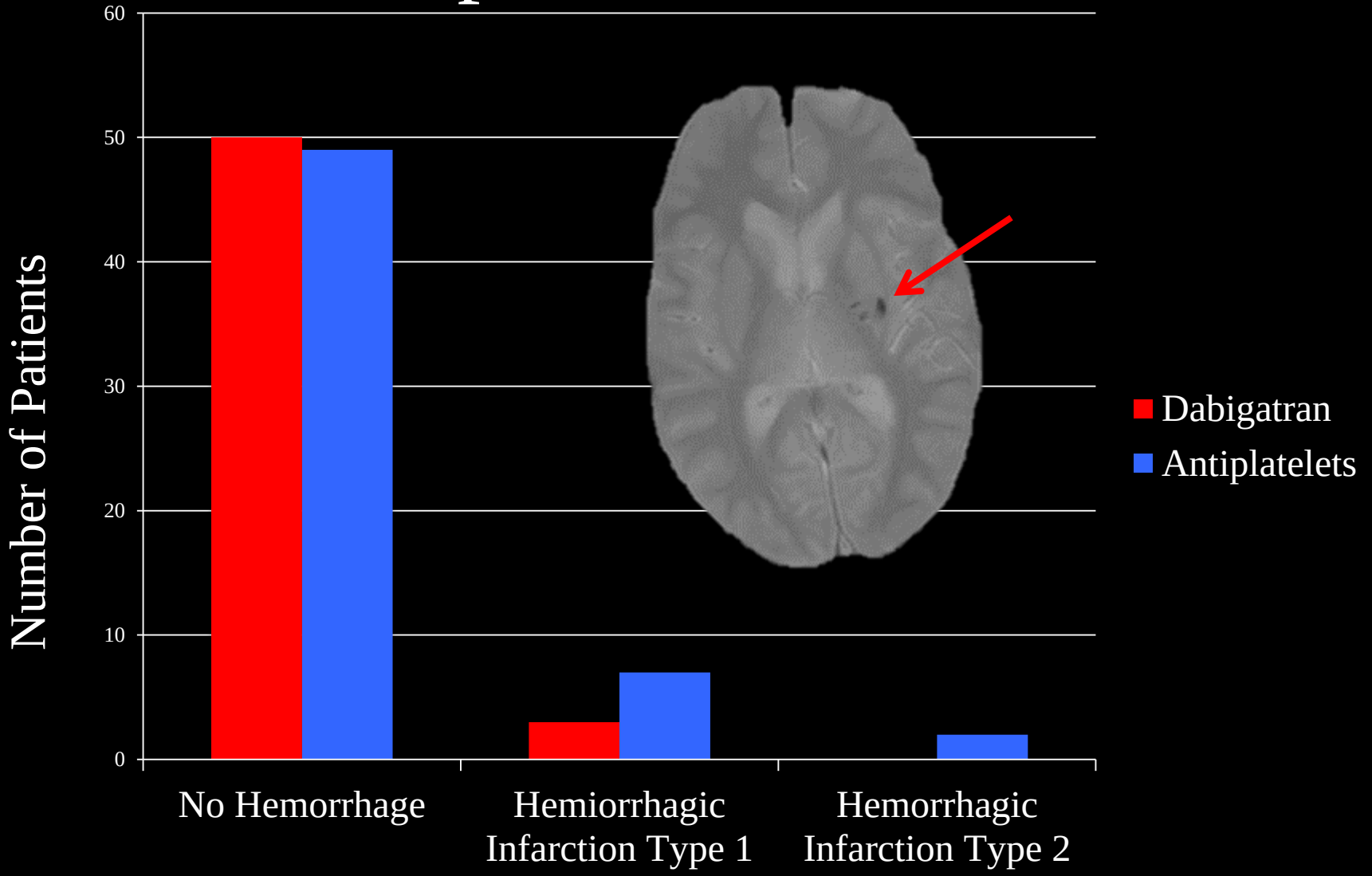
Unspecified stroke
HR: 2.24
95% CI: 0.69; 7.27
p=0.18

Disabling or fatal stroke
HR: 0.43
95% CI: 0.28; 0.65
p<0.001



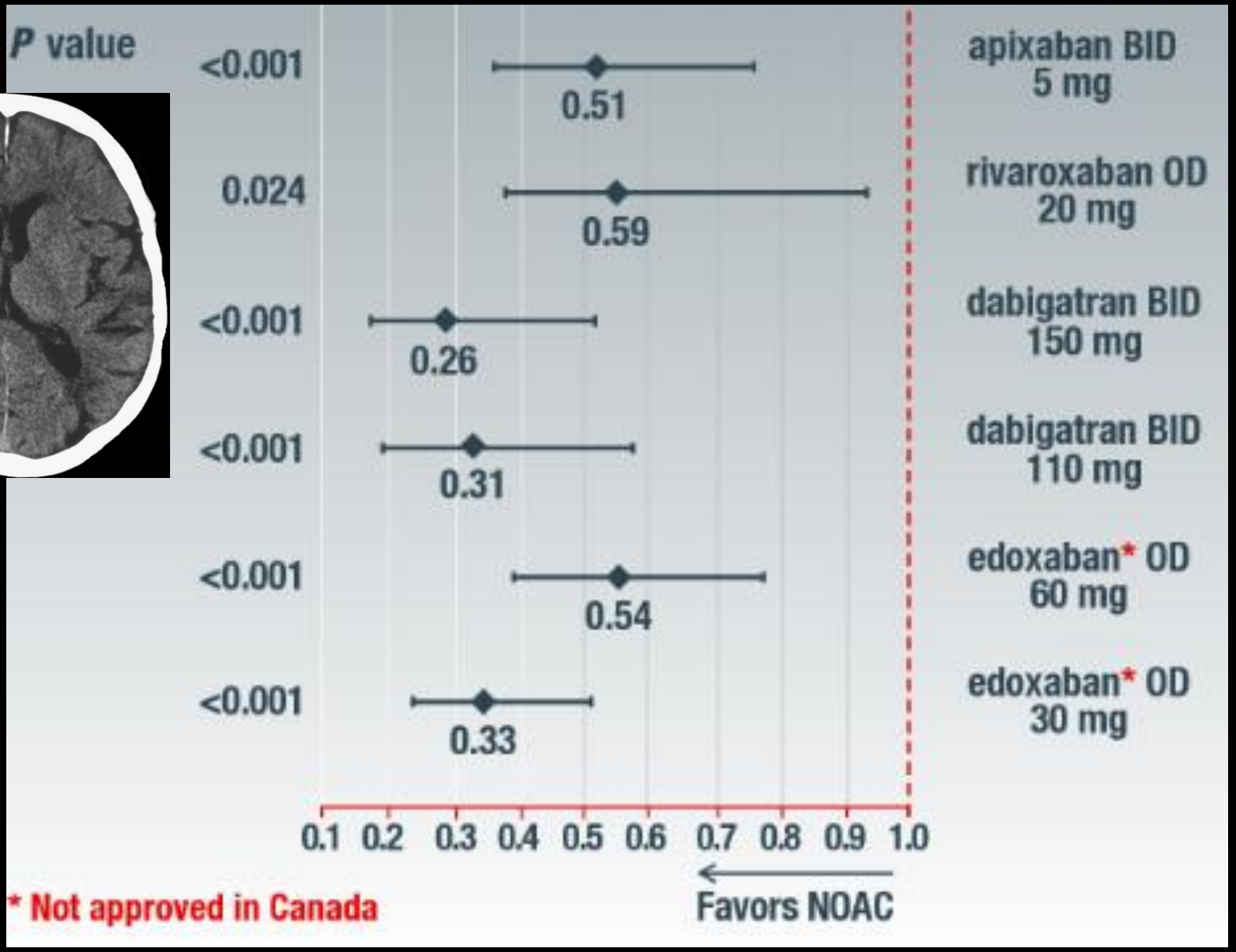
Adapted from Connolly et al. N Engl J Med 2011;364:806-17.

Case Control Study: Dabigatran is as Safe as Antiplatelets in Acute Stroke

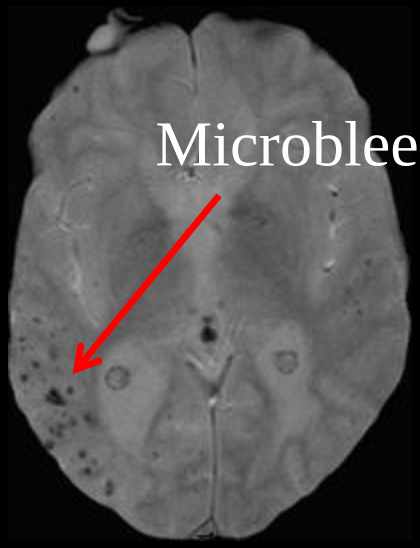


ICH: Warfarin is Bad For the Brain

70 000 patients



Why are NOACs Better for the Brain?

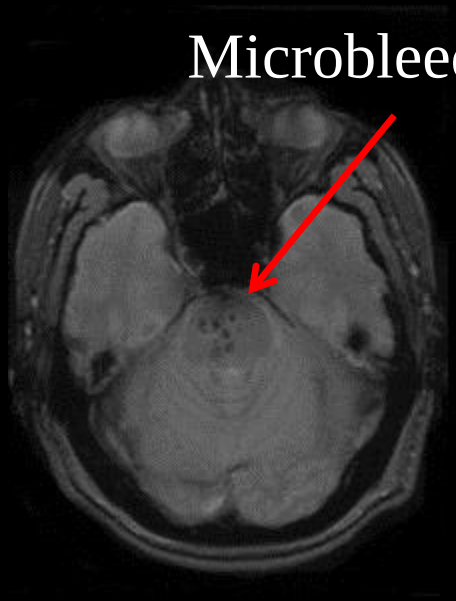


Microbleeds

VKA (warfarin)

II

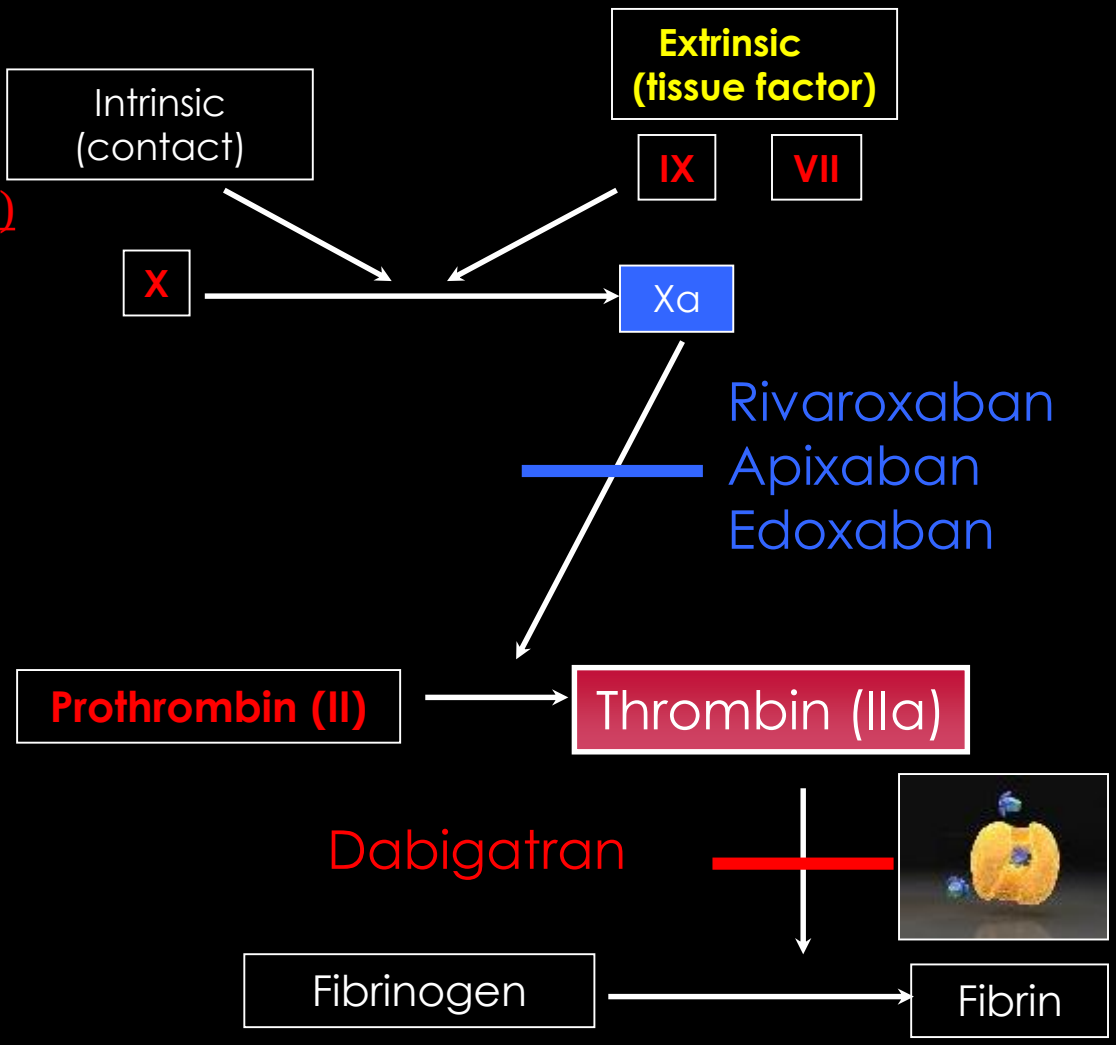
VII



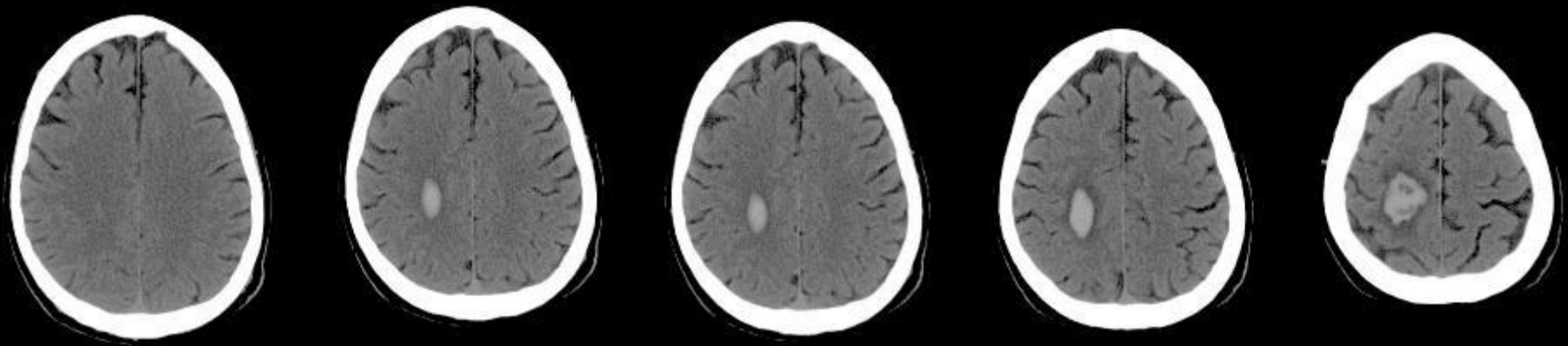
Microbleeds

IX

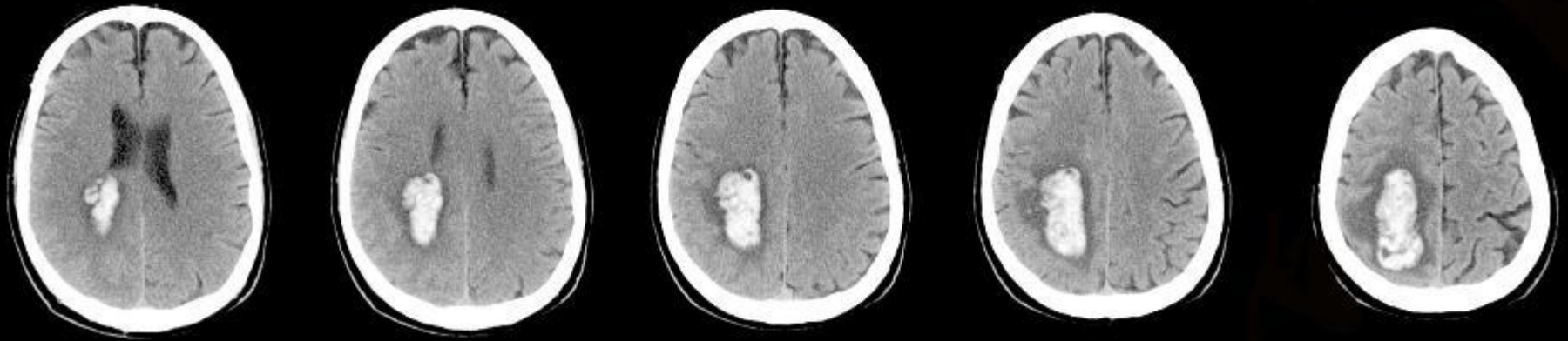
X



INR 3.1: Management Options?



1. Vitamin K 5 mg PO
2. FFP 1 unit IV – INR not re-checked



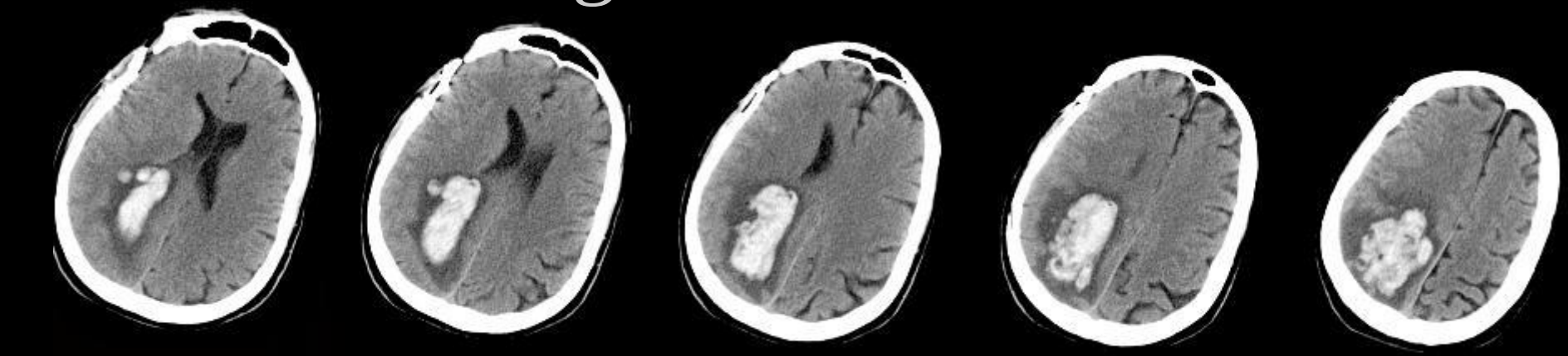
3 hours later: patient now hemiplegic, GCS 15

Management Continued

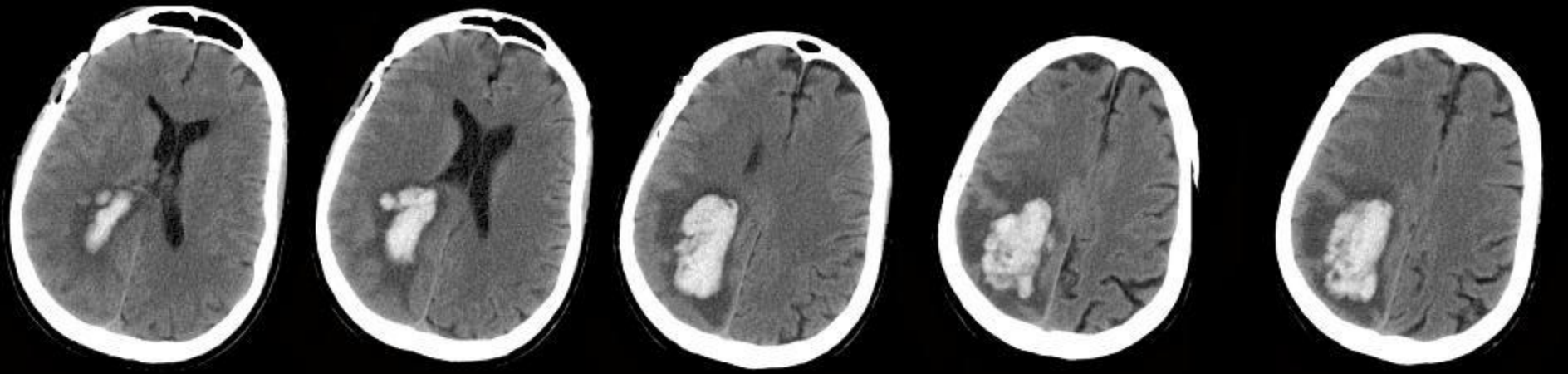
FFP 2 units IV -- INR 2.8

4 hours later

Management Continued



Transfer to tertiary centre
FFP 4 units IV -- INR 1.0



Treating ICH with PCC (Octaplex)

Baseline CT
INR 3.6
Total hematoma volume 15.3 mL

INR 1.2 (42 minutes later)
Total hematoma volume 67.6 mL

Poor Prognosis in Warfarin-Associated Intracranial Hemorrhage Despite Anticoagulation Reversal

Dar Dowlatshahi, MD, PhD; Kenneth S. Butcher, MD, PhD; Negar Asdaghi, MD, MSc; Susan Nahirniak, MD; Manya L. Bernbaum, BSc; Antonio Giulivi, MD; Jason K. Wasserman, PhD; Man-Chiu Poon, MD; Shelagh B. Coutts, MD; on behalf of the Canadian PCC Registry (CanPro) Investigators*

Background and Purpose—Anticoagulant-associated intracranial hemorrhage (aaICH) presents with larger hematoma volumes, higher risk of hematoma expansion, and worse outcome than spontaneous intracranial hemorrhage. Prothrombin complex concentrates (PCCs) are indicated for urgent reversal of anticoagulation after aaICH. Given the lack of randomized controlled trial evidence of efficacy, and the potential for thrombotic complications, we aimed to determine outcomes in patients with aaICH treated with PCC.

Methods—We conducted a prospective multicenter registry of patients treated with PCC for aaICH in Canada. Patients were identified by local blood banks after the release of PCC. A chart review abstracted clinical, imaging, and laboratory data, including thrombotic events after therapy. Hematoma volumes were measured on brain CT scans and primary outcomes were modified Rankin Scale at discharge and in-hospital mortality.

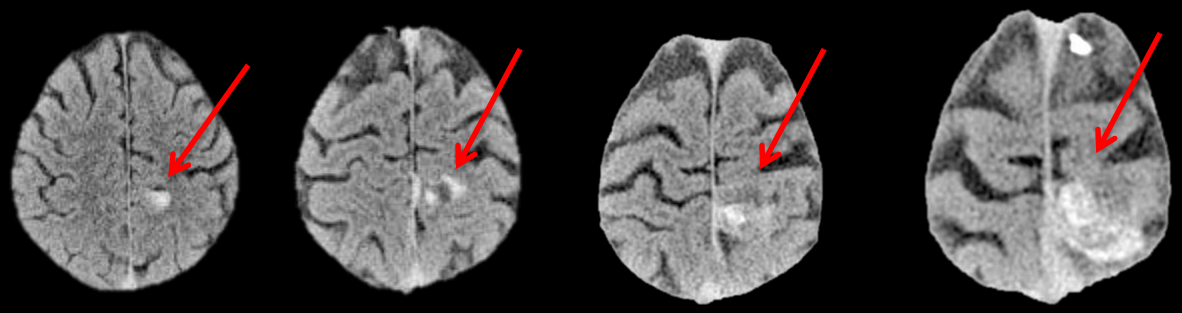
Results—Between 2008 and 2010, 141 patients received PCC for aaICH (71 intraparenchymal hemorrhages). The median age was 78 years (interquartile range, 14), 59.6% were male, and median Glasgow Coma Scale was 14. Median international normalized ratio was 2.6 (interquartile range, 2.0) and median parenchymal hematoma volume was 15.8 mL (interquartile range, 31.8). Median post-PCC therapy international normalized ratio was 1.4: 79.5% of patients had international normalized ratio correction (<1.5) within 1 hour of PCC therapy. Patients with intraparenchymal hemorrhage had an in-hospital mortality rate of 42.3% with median modified Rankin Scale of 5. Significant hematoma expansion occurred in 45.5%. There were 3 confirmed thrombotic complications within 7 days of PCC therapy.

Conclusions—PCC therapy rapidly corrected international normalized ratio in the majority of patients, yet mortality and morbidity rates remained high. Rapid international normalized ratio correction alone may not be sufficient to alter prognosis after aaICH. (***Stroke*. 2012;43:00-00.**)

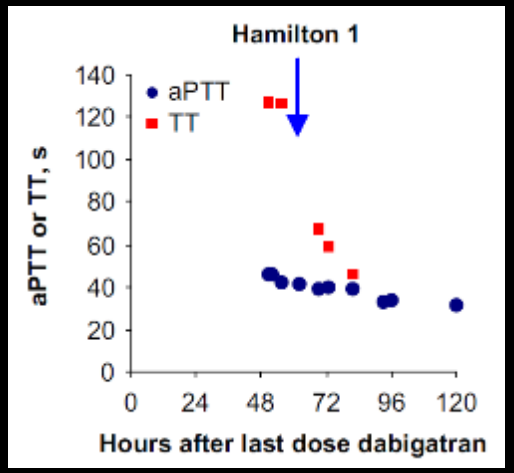
Key Words: acute care ■ acute Rx ■ anticoagulation ■ emergency medicine ■ hemorrah ■ intrac. ■ intracerebral hemorrhage

Dabigatran Associated ICH Treatment

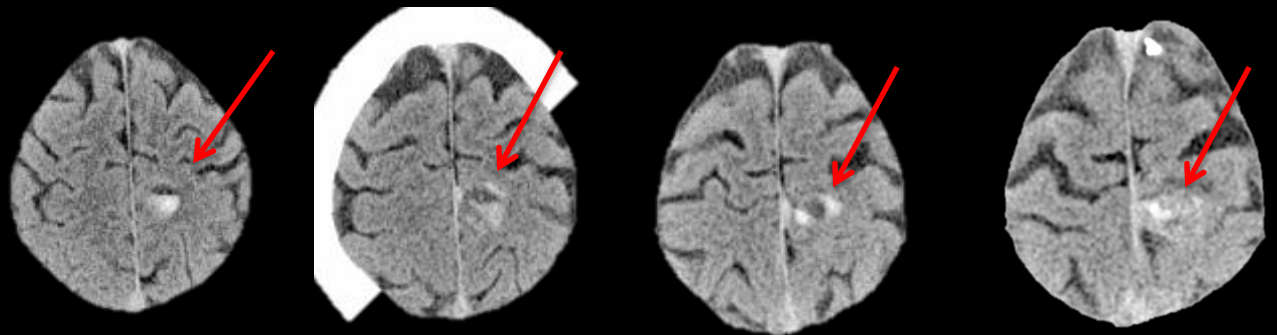
4 hours
Thrombin Time (TT)
= 32.5 (prolonged)



FEIBA
Dose =100 IU/kg

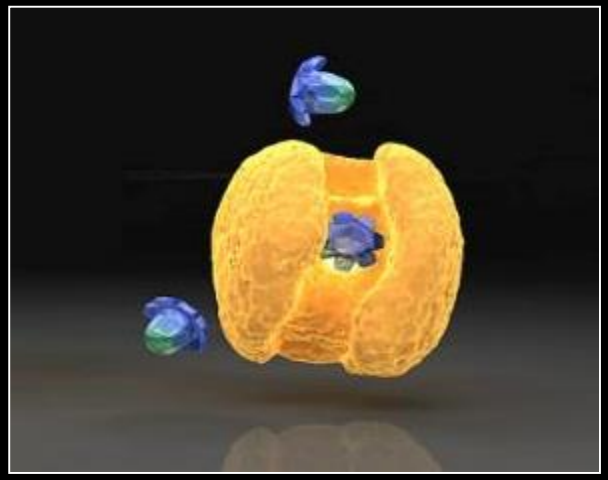


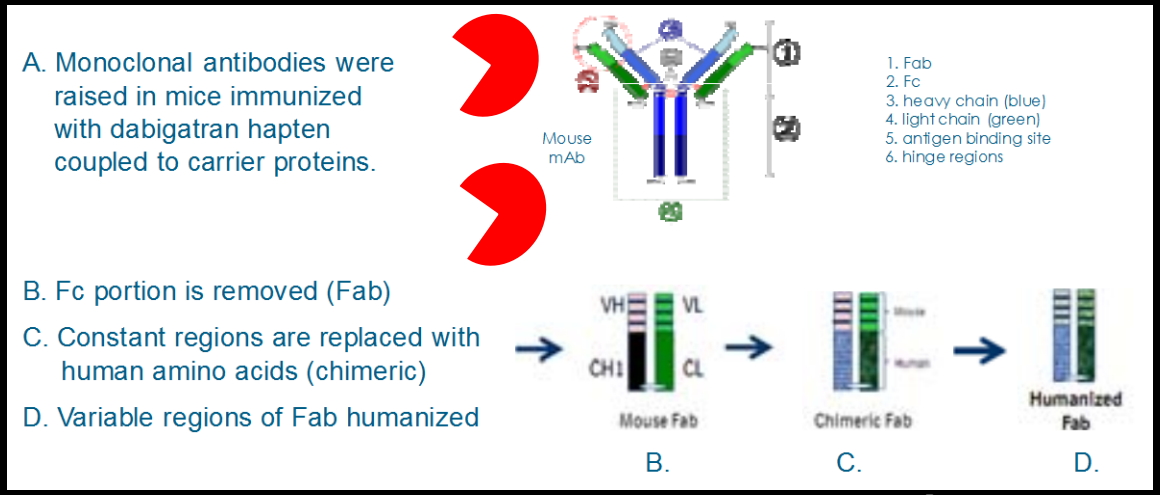
6 hours
TT = 21.9
(normal)



NOAC Reversal: (Near) Future

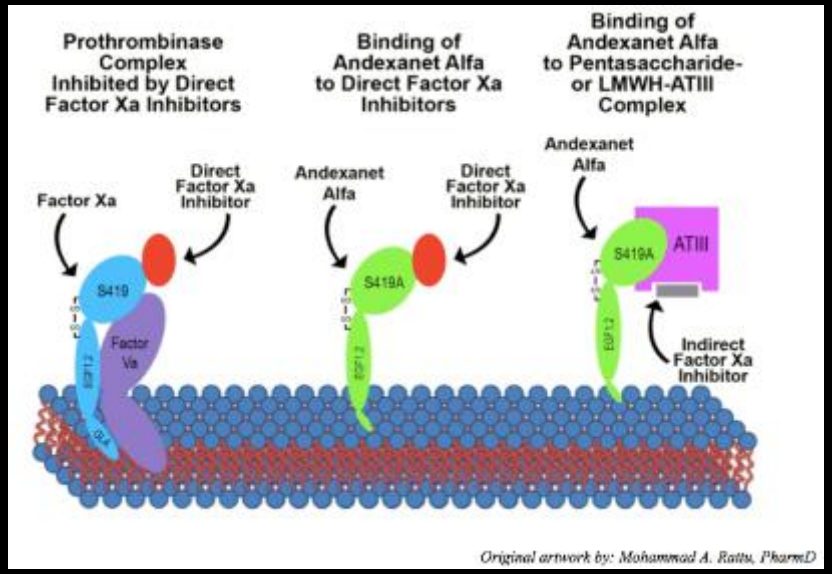
Dabigatran





Van Ryn et al, ACC, 2011

Rivaroxaban
Apixaban
Edoxaban



Agent/Dose: Rational Pharmacology

Dabigatran 150 bid

- **Patients < 80 y.o. with normal renal function**

Rivaroxaban / Apixaban /Dabigatran 110 bid

- GFR 30-50
- Age >80
- Previous bleeding

ASA 81 mg/day: Only for active CAD/stent patients

The Right Tool for the Right Job

Patients with ↑ ICH Risk

Patients with ↑ Systemic Bleed Risk

Retroperitoneal Bleed

Diverticulitis

Peptic Ulcer

When Does the NOAC Early Adoption Phase End?