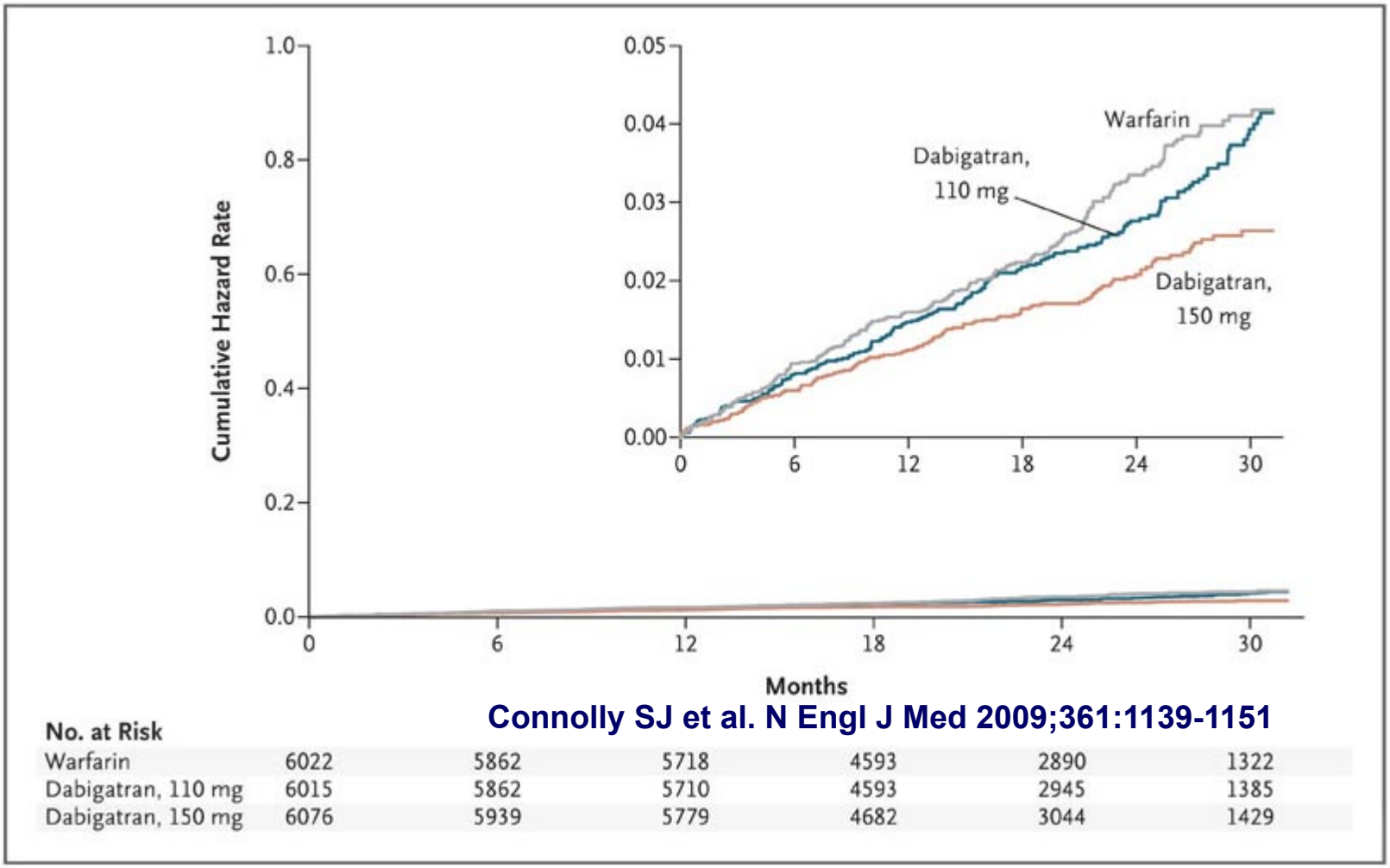
The New Anticoagulants are Here!
Do you know how to use them?
Arrhythmia Winter School February 11th, 2012

Jeff Healey

RELY: A New Era in AF

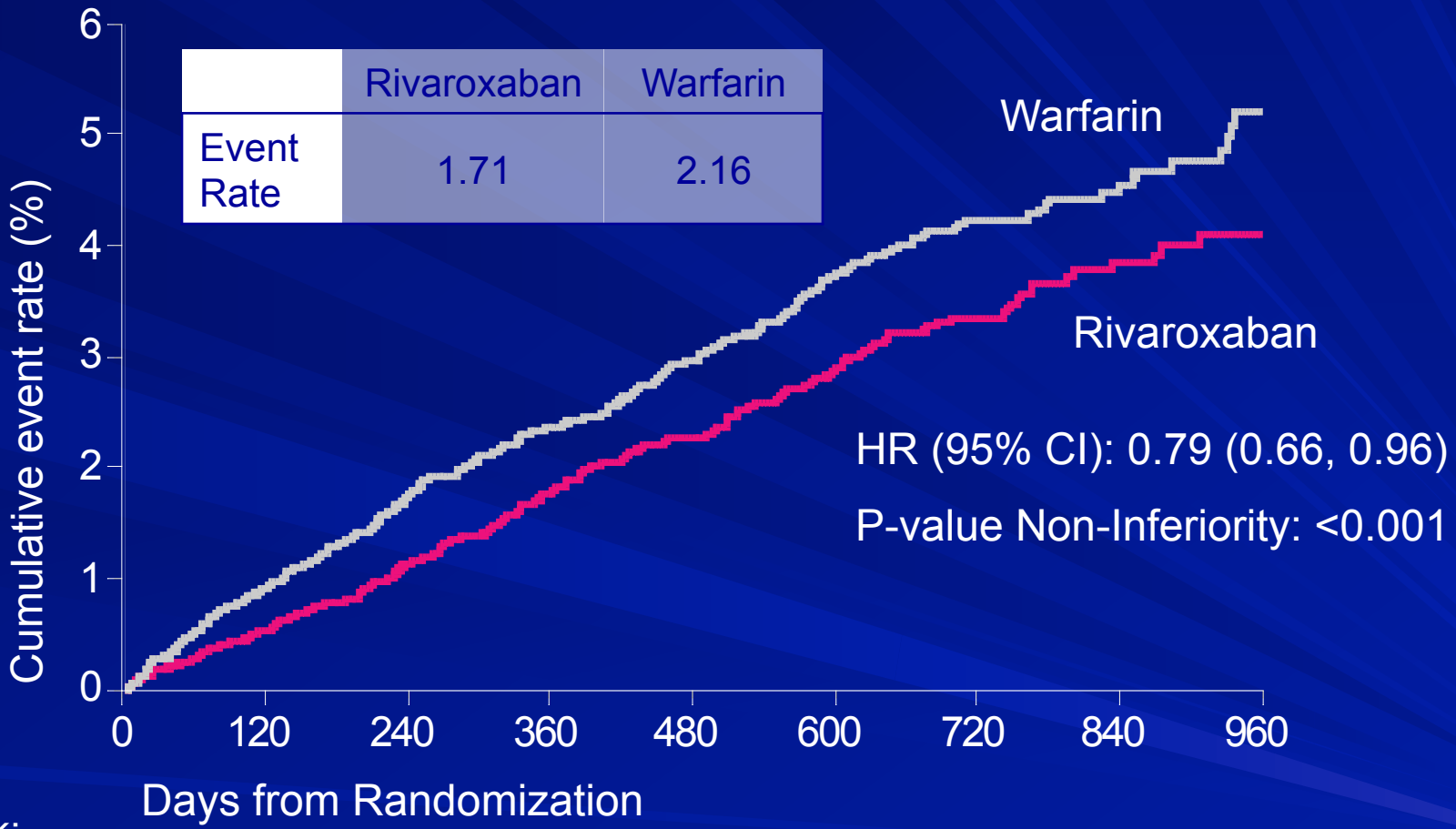


Connolly SJ et al. N Engl J Med 2009;361:1139-1151

No. at Risk						
Warfarin	6022	5862	5718	4593	2890	1322
Dabigatran, 110 mg	6015	5862	5710	4593	2945	1385
Dabigatran, 150 mg	6076	5939	5779	4682	3044	1429

ROCKET-AF: Primary Efficacy Outcome

Stroke and non-CNS Embolism



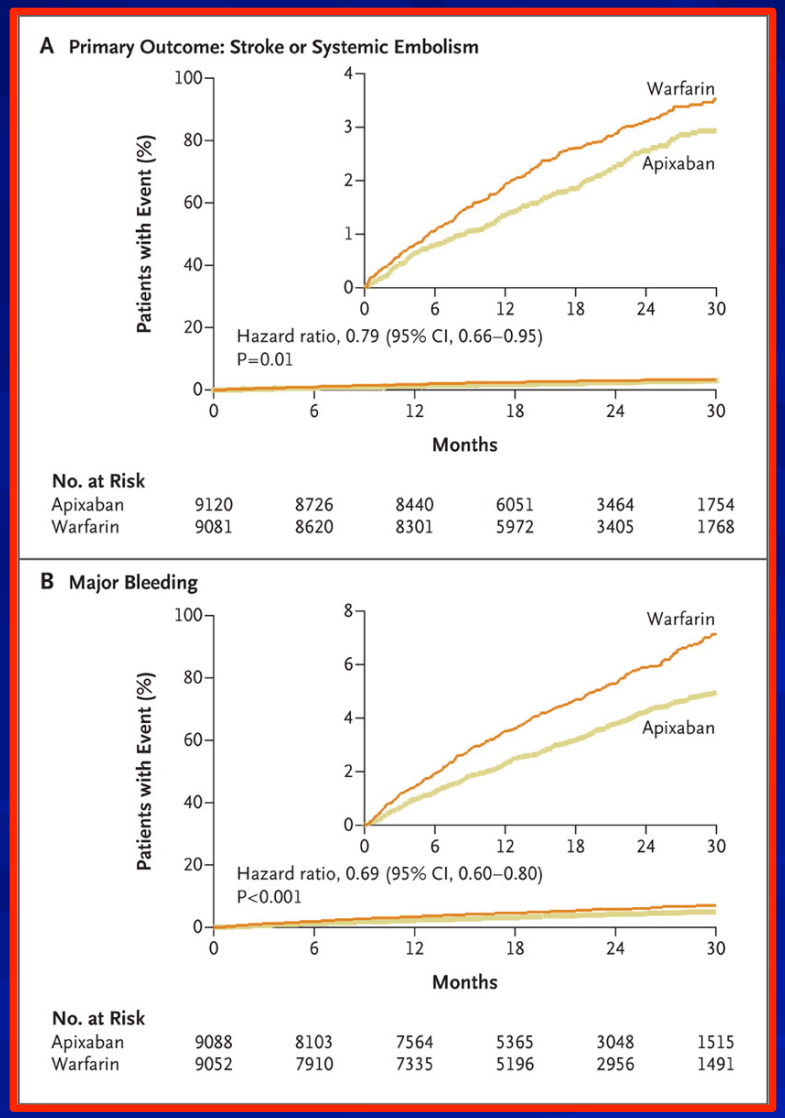
	Rivaroxaban	Warfarin
Event Rate	1.71	2.16

No. at risk:

Rivaroxaban	6958	6211	5786	5468	4406	3407	2472	1496	634
Warfarin	7004	6327	5911	5542	4461	3478	2539	1538	655

Event Rates are per 100 patient-years
Based on Protocol Compliant on Treatment Population

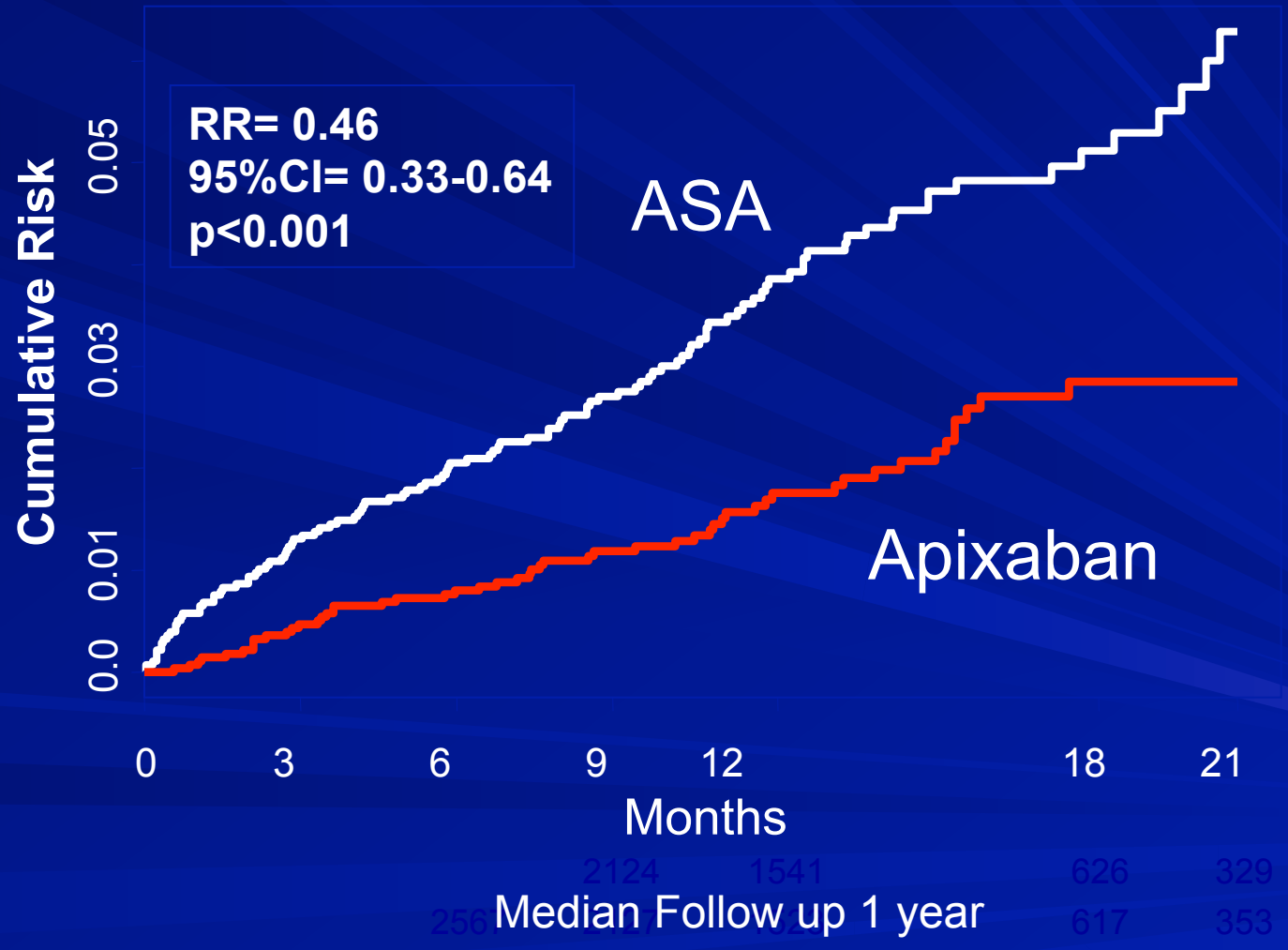
ARISTOTLE: Outcomes



Granger CB. N Engl J Med 2011; 365(11)

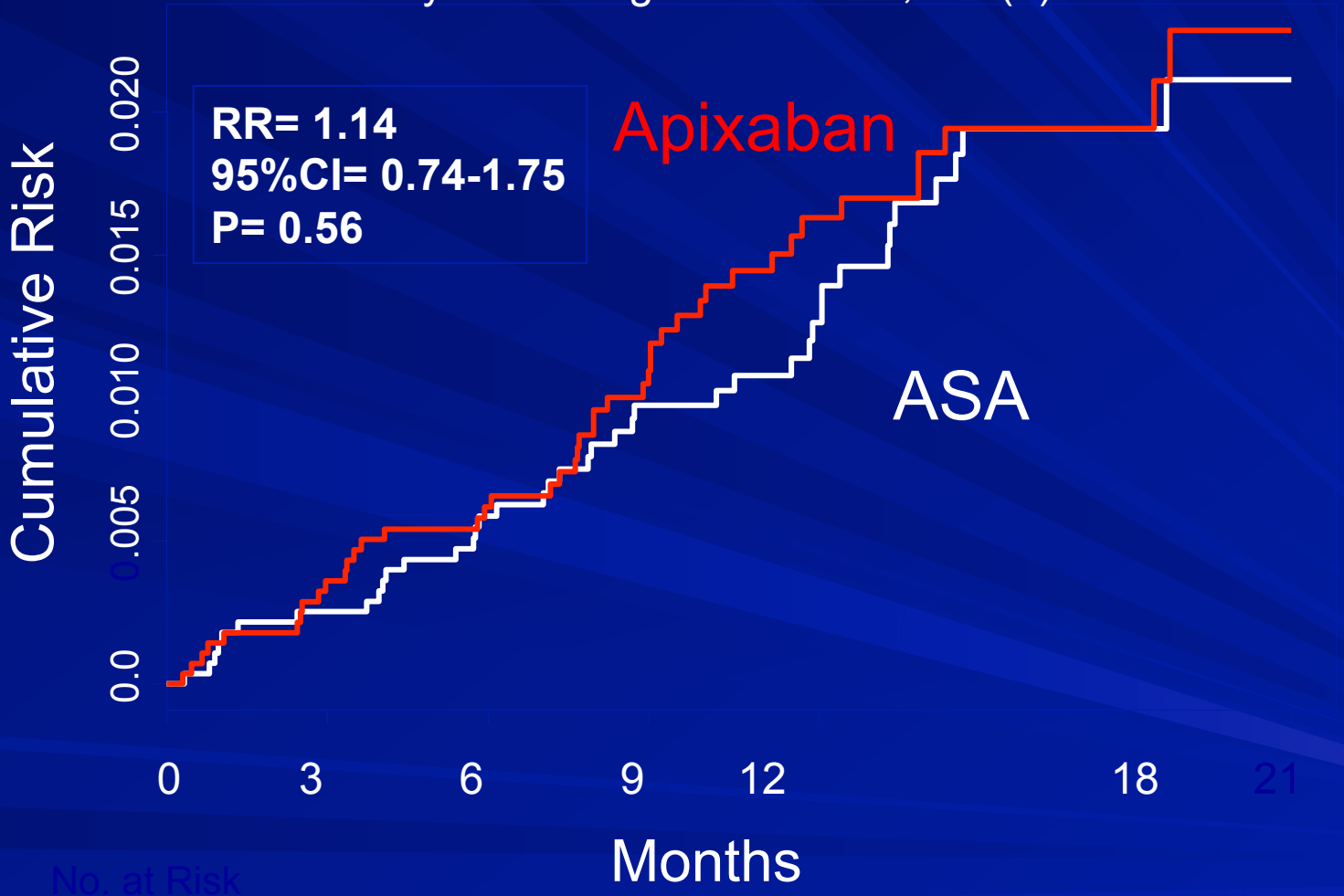
AVERROES: Stroke or Systemic Embolism

Connolly SJ. N Engl J Med 2011; 364(9)

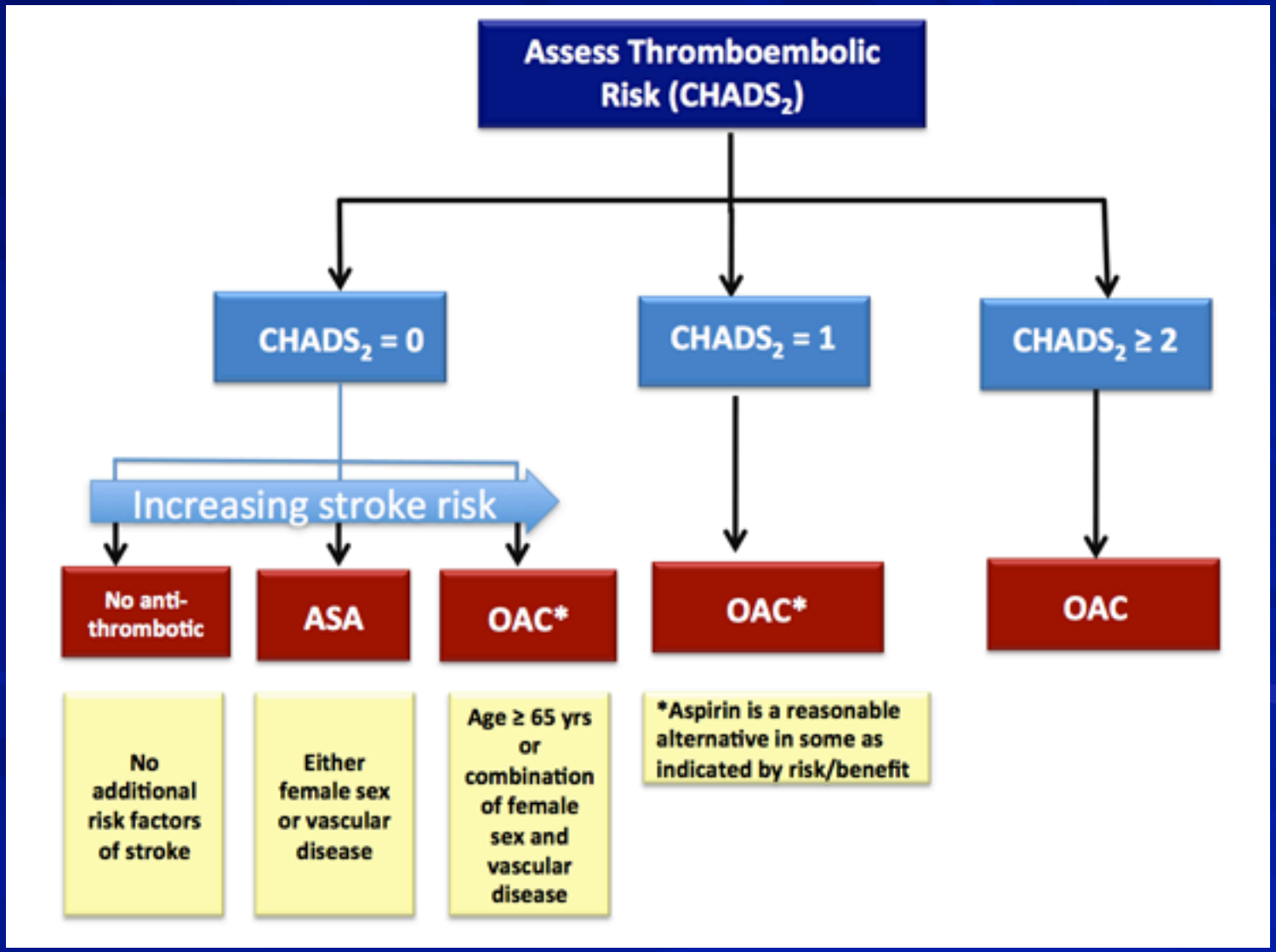


AVERROES: Major Bleeding

Connolly SJ. N Engl J Med 2011; 364(9)



CCS AF Guidelines 2012 Update



CCS AF Guidelines: 2012 Update

- 1. We recommend that all patients with AF or atrial flutter (paroxysmal, persistent or permanent), should be stratified using a predictive index for stroke (e.g. $CHADS_2$) and for the risk of bleeding (e.g. HAS-BLED), and that most patients should receive either an oral anticoagulant or aspirin. (Strong recommendation, High Quality Evidence)
- 2. We suggest, that when OAC-therapy is indicated, most patients should receive dabigatran, rivaroxaban or apixaban* in preference to warfarin. (Conditional recommendation. High Quality Evidence).
- *Once approved by Health Canada.

Key Features of New Oral Agents

	Dabigatran[1,2,3,7]	Rivaroxaban[3,4,7]	Apixaban[3,5,7]	Edoxaban[3,6,7]
Mechanism of action	Direct thrombin inhibitor	Direct Xa inhibitor	Direct Xa inhibitor	Direct Xa inhibitor
Current Indications (Canada)	• Stroke prevention in AF (Oct/2010) • VTE prophylaxis post orthopaedic surgery (Mar/2009)	• VTE prophylaxis post orthopaedic surgery (Sep/2008)	None	None
Prodrug	Prodrug	No	No	No
Bioavailability	6 %	> 80 %	66 %	>50 %
Tmax	2 hrs	2-4 hrs	3 hrs	1-2 hrs
Half-life	14-17 hours	7-11 hours	8-15 hours	9-11 hours
Dosing Frequency	QD (orthopaedic) BID (AF)	QD (orthopaedic & AF)	BID (orthopaedic & AF)	QD (AF)
Excretion	80% renal, 20% fecal	66% renal (33% unchanged, 33% inactive metabolites); 33% fecal	70% fecal; 25% renal	Predominantly renal
Food Interactions	None	None	None	None
Drug Interactions	P-glycoprotein	CYP3A4 and P-glycoprotein	CYP3A4 and P-glycoprotein	Potentially P-glycoprotein

Practical Considerations for New Agents (Dabigatran)

- Initiation and follow-up
- Drug interactions
- Monitoring
  - Effect and Adherence
- Managing bleeding
- Reversal
  - Surgery and Trauma
- Myocardial infarction
- Choice between agents, doses

Practical Considerations: Starting/Stopping Dabigatran

- **Assess renal function prior to starting dabigatran**
- **Switching from warfarin to dabigatran:**
  - Stop warfarin, initiate dabigatran once INR <2.0
- **Switching from parenteral anticoagulants to dabigatran**
  - Start 0-2 hours prior to the time that the next dose of the alternate therapy would be due (or at the time of discontinuation in the case of IV UFH)
- **Switching from dabigatran to parenteral anticoagulants**
  - Wait 12 hours after the last dose of dabigatran

Drug Interactions

- Most relevant involve strong interactions and combination of > 1 moderate
- P-Glycoprotein
  - Rifampin, Quinidine, ketoconazole
  - Combinations (verapamil, amiodarone)
- CYP-3A4
  - Rifampin, clarithromycin, azoles, protease inhibitors, nefazodone

Monitoring Effect of Dabigatran

- Not routinely needed, not done in trials
- Dabigatran will prolong PTT
  - Typically > 40 for patients on drug (compliance)
- TCT and Hemoclot tests
  - Hemoclot uses standard amount of thrombin
- "therapeutic range" for dabigatran 50-320
- Low/moderate risk surgery can be done with value ≤ 50
  - Efficacy of drug to prevent stroke decreases at this level as well

(How) Should I monitor levels?

- Specific test may not be routinely available
- aPTT, TCT is semi-quantitative
  - Drug is present/absent (e.g., adherence, safe to proceed with surgery)
- Hemoclot is quantitative
  - Mechanism of an event (stroke, bleeding)
  - Timing of high risk surgery
  - Response to dialysis

The Truths about Bleeding

- All effective antithrombotic drugs cause bleeding
- Most antithrombotic drugs lack a specific antidote
- Patients who took the drug with the antidote in RE-LY (open design) did worse than those that took the drug without the antidote
- Prevention is better than treatment

How do I manage bleeding?

- Stop the drug (time)
- Evaluate severity and need for surgery
- Local measures
- Fluid and blood product support
- Maintain diuresis
- General hemostatic agents
- Hemodialysis
- Consider potential harm of reversal

Managing Mild Bleeding

- Hold one dose
- If bleeding continues:
  - Stop any concomitant antiplatelet drugs, if possible
  - Investigate for a local cause
- If bleeding continues, check for drug accumulation
  - Measure aPTT: if prolonged, dabigatran is on board
  - Determine creatinine clearance rate
- Consider reducing dose or stopping drug if appropriate

Based on best available information, expert recommendations and *Pradax Product Monograph*, 13 Jun 2011

Managing Moderate/Severe Bleeding

- Stop treatment and investigate the source of bleeding
- Verify the time of the last dose of dabigatran; if within 2 hours, consider oral activated charcoal
- A prolonged aPTT (>80 sec when next dose is due) indicates an excess of anticoagulant effect
- As dabigatran excretion is predominantly renal, maintain adequate diuresis and consider hemodialysis or hemofiltration
- Control bleeding with pressure or surgical hemostasis

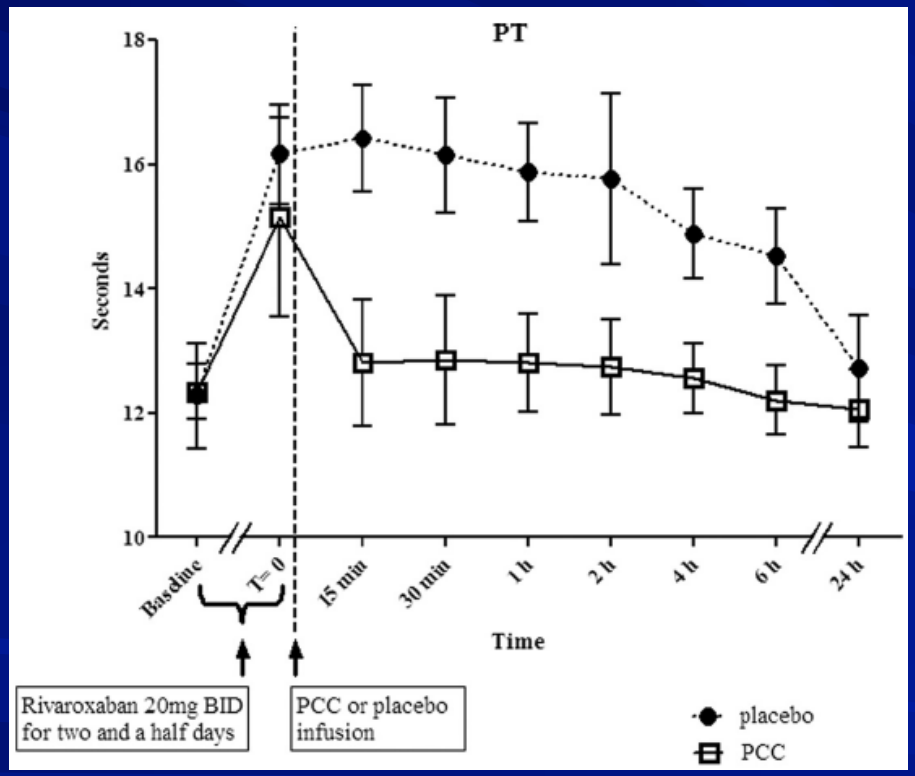
Based on best available information, expert recommendations and *Pradax Product Monograph*, 13 Jun 2011

(How) Can I reverse the new oral anticoagulants?

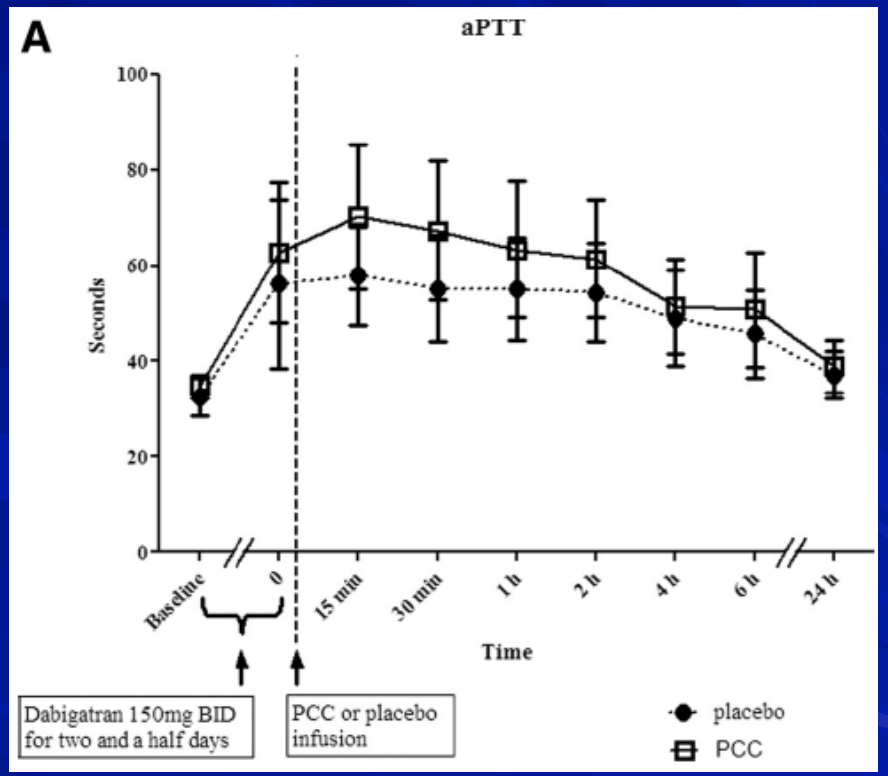
- Recombinant factor VIIa (rVIIa)
- Prothrombin complex concentrates (PCC)
  - II, VII, IX, X, C, S, small amounts of heparin
  - 25-50 units per kg
  - Octaplex
- Activated prothrombin complex concentrates (aPCC): FEIBA
- Antifibrinolytic agents (e.g., tranexamic acid)

PCC (Humans)

Rivaroxaban (PT)



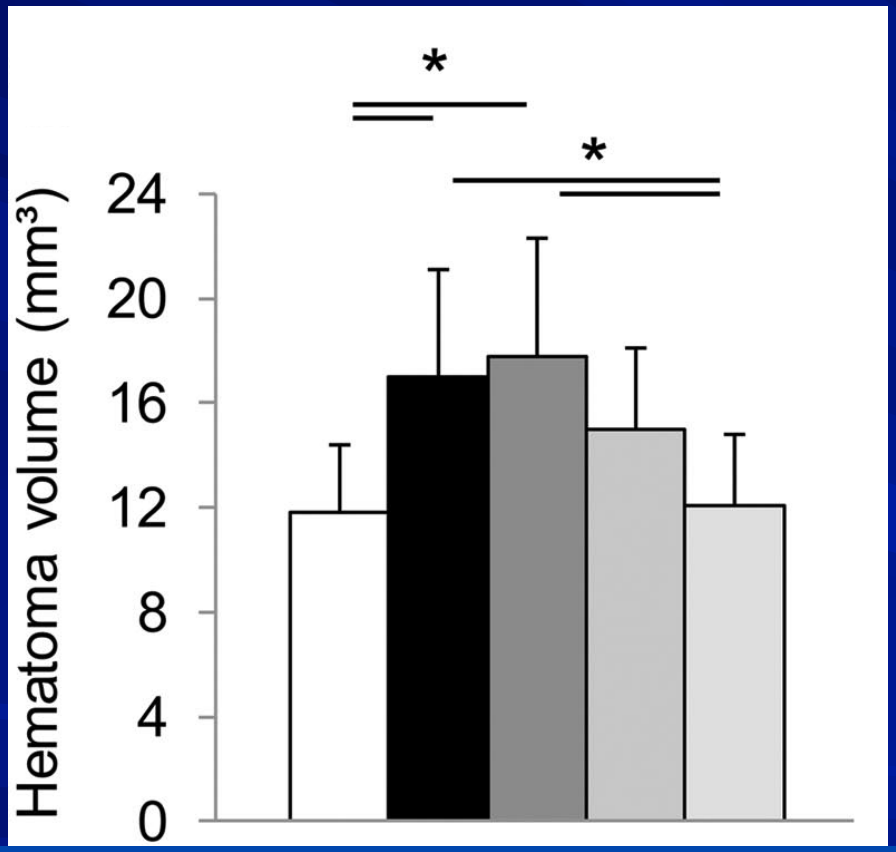
Dabigatran (aPTT)



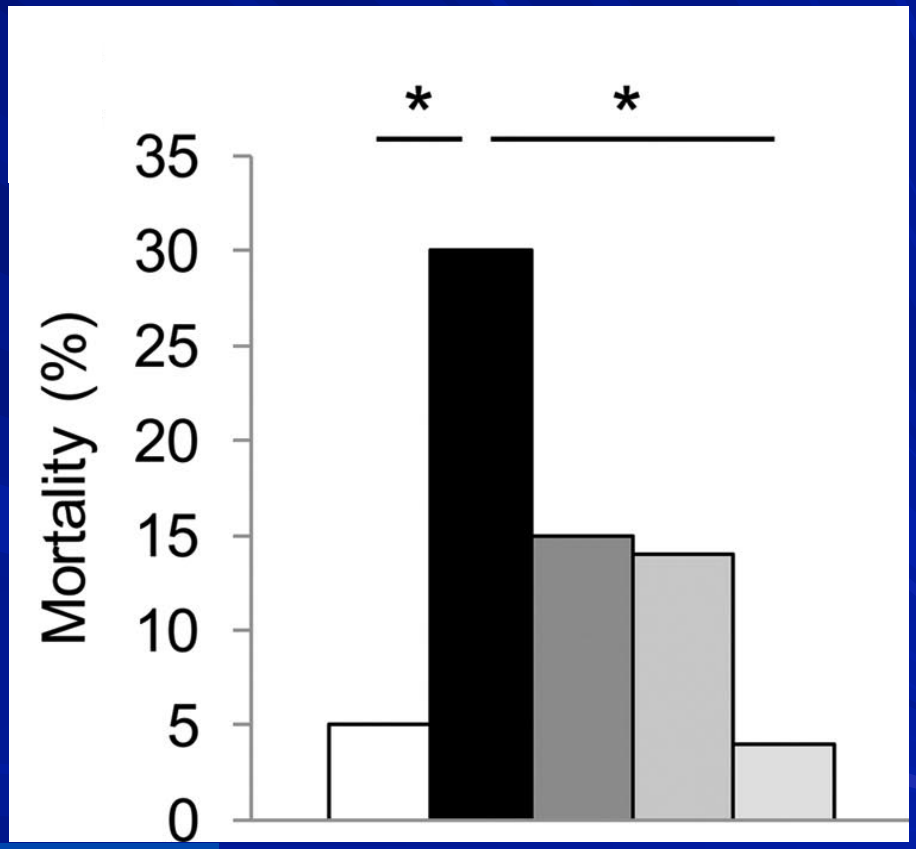
Eerenberg E, et al. Circulation 2011

General Hemostatic Agents (Mouse-Dabigatran ICH Model)

Hematoma size

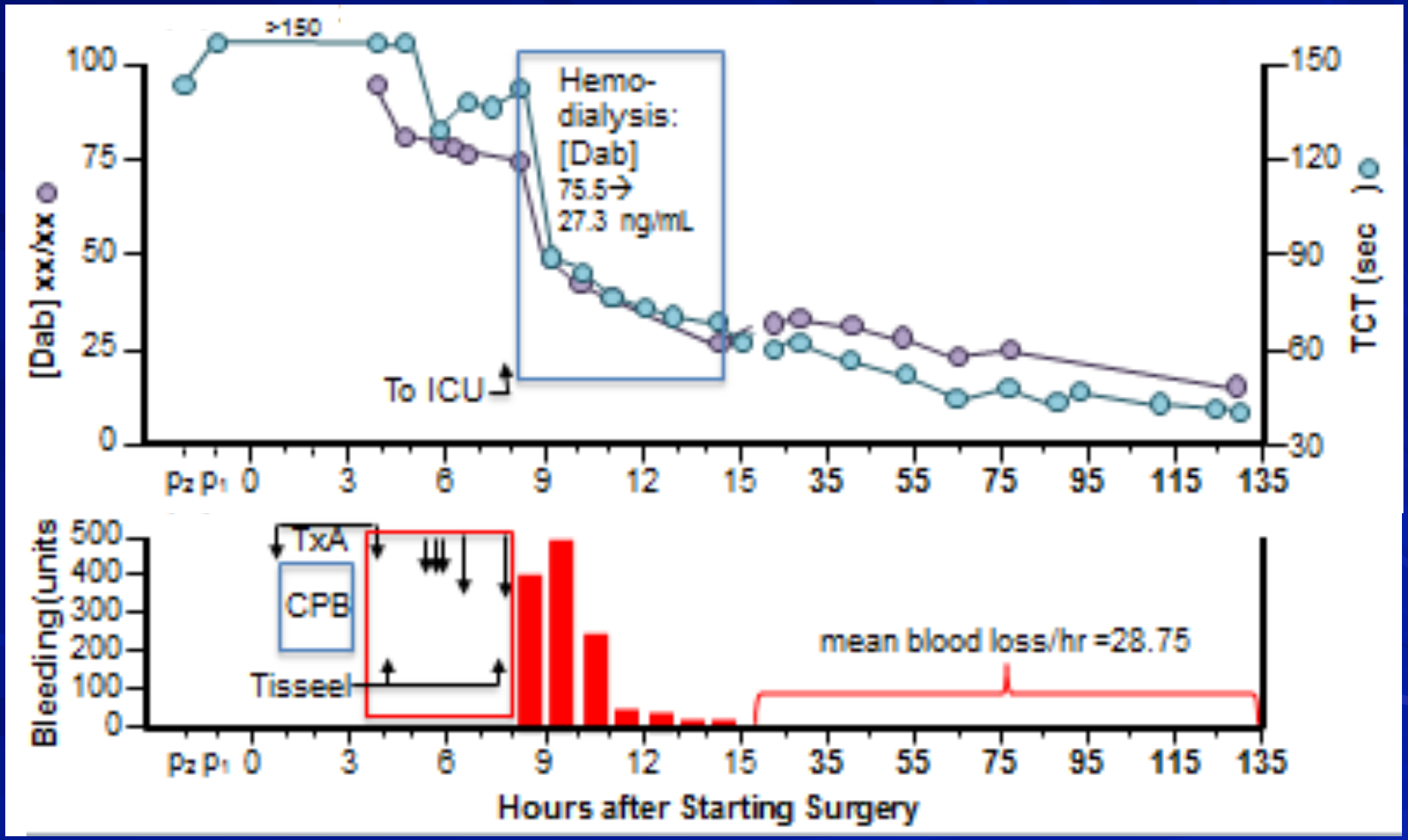


Mortality



Zhou W, et al. Stroke 2011

Dabigatran, rVIIa & Hemodialysis



Warkentin T (unpublished)

How Do I Manage Interruption?

Renal Function Impairment (CrCl, mL/min)	Estimated Half-life (hrs)	Stopping Dabigatran before Surgery/Procedure	
		High risk for Bleeding	Standard Risk for Bleeding
mild: ≥50 to 80	15 (12-18)	*2-3 days**	*24 hrs (2 doses)**
moderate: ≥30 to <50	18 (18-24)	4 days	at least 2 days (48 hrs)
severe: <30	27 (>24)	>5 days	2-4 days

Healey JS. AHA 2011

Perioperative Outcomes in RE-LY

	Dab110 N=1487 % (n)	Dab150 N=1546 % (n)	Warfarin N=1558 % (n)	D110 vs. Warfarin RR (95% CI, P-value)	D150 vs. Warfarin RR (95% CI, P-value)
Patients					
Bleeding Events					
Minor Bleed	8.1 (120)	9.0 (139)	7.8 (122)	1.03 (0.81-1.31, p=0.81)	1.15 (0.91-1.45, p=0.24)
Major Bleed	3.8 (57)	5.1 (78)	4.6 (72)	0.83 (0.59-1.17, p=0.28)	1.09 (0.80-1.49, p=0.58)
Fatal Bleed	0.2 (3)	0.1 (2)	0.1 (2)	1.57 (0.26-9.39, p=0.62)	1.01 (0.14-7.15, p=0.99)
Requiring Re-Operation	0.6 (9)	1.4 (22)	1.0 (16)	0.59 (0.26-1.33, p=0.20)	1.39 (0.73-2.63, p=0.32)
Requiring RBC Transfusion	3.3 (49)	3.5 (54)	4.0 (64)	0.81 (0.56-1.18, p=0.27)	0.86 (0.60-1.23, p=0.42)
Thrombotic Events					
CV Death	0.6 (9)	0.5 (7)	0.5 (7)	1.35 (0.50-3.61, p=0.55)	1.01 (0.35-2.96, p=0.99)
Stroke (all-cause)	0.5 (7)	0.5 (7)	0.6 (10)	0.73 (0.28-1.92, p=0.53)	0.71 (0.27-1.85, p=0.48)
Systemic Embolism	0.1 (1)	0.1 (1)	0.1 (1)	1.05 (0.07-16.7, p=0.97)	1.01 (0.06-16.1, p=1.0)
Ischemic Stroke or Systemic Embolism	0.5 (7)	0.5 (7)	0.5 (7)	1.05 (0.55-2.01, p=0.89)	1.01 (0.35-2.87, p=0.99)
Myocardial Infarction	0.1 (2)	0.5 (8)	0.3 (5)	0.42 (0.08-2.16, p=0.28)	1.61 (0.53-4.92, p=0.40)
Pulmonary Embolism	0.1 (1)	0.1 (2)	0.2 (3)	0.35 (0.04-3.35, p=0.34)	0.67 (0.11-4.02, p=0.66)
Composite of CV Death, Ischemic Stroke, Non-CNS and Pulmonary Embolism	1.2 (18)	1.5 (23)	1.2 (18)	1.05 (0.55-2.01, P=0.89)	1.29 (0.70-2.38, P=0.42)

Healey JS. AHA 2011

Perioperative Outcomes in RE-LY

	Dab110 % (n/N)	Dab150 % (n/N)	Warfarin % (n/N)	D110 vs. Warfarin RR (95% CI, P-value)	P-Inter	D150 vs. Warfarin RR (95% CI, P-value)	P-Inter
Urgent Surgery	17.8% (19/107)	17.7% (25/141)	21.6% (24/111)	0.82 (0.48-1.41, 0.47)		0.82 (0.50-1.35, 0.43)	
Elective Surgery	2.8% (38/1380)	3.8% (53/1405)	3.3% (48/1447)	0.83 (0.55-1.26, 0.38)	0.90	1.14 (0.77-1.67, 0.51)	0.31
Major Surgery	6.1% (29/473)	6.5% (33/511)	7.8% (39/498)	0.78 (0.49-1.24, 0.30)		0.82 (0.53-1.29, 0.40)	
Minor Surgery	1.9% (8/424)	3.2% (14/435)	1.8% (8/436)	1.03 (0.39-2.71, 0.96)	0.61	1.75 (0.74-4.14, 0.19)	0.13
Original Dab Protocol	3.8% (47/1234)	4.9% (66/1346)	4.6% (60/1319)	0.84 (0.58-1.22, 0.35)		1.08 (0.77-1.52, 0.67)	
Amended Dab Protocol	4.0% (10/253)	6.0% (12/200)	5.0% (12/239)	0.79 (0.35-1.79, 0.57)	0.81	1.20 (0.55-2.60, 0.65)	0.81

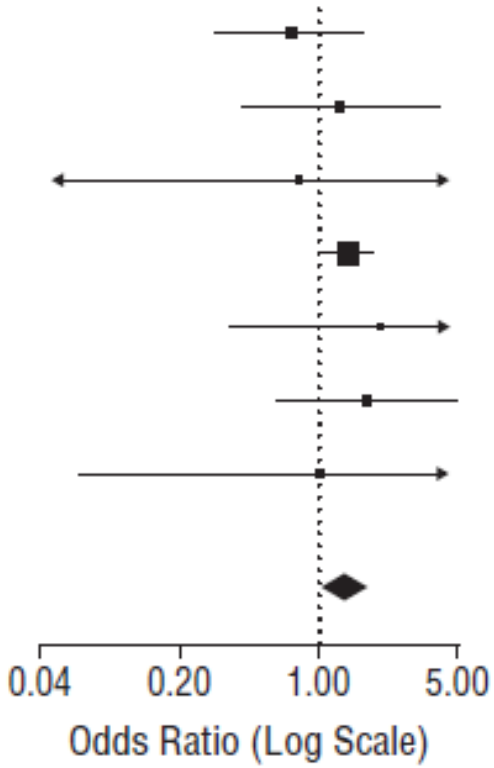
Cardioversion / Ablation

- Patients can be maintained on dabigatran while being cardioverted
- It is reasonable to believe that dabigatran can be safely given the day after AF ablation (although this has not been studied)

Based on best available information, expert recommendations and *Pradax Product Monograph*, 13 Jun 2011
Eitel et al., Dabigatran in patients undergoing catheter ablation for atrial fibrillation. *Europace Journal* 2011 ; 13 (3), Abstract P1051

Dabigatran and MI

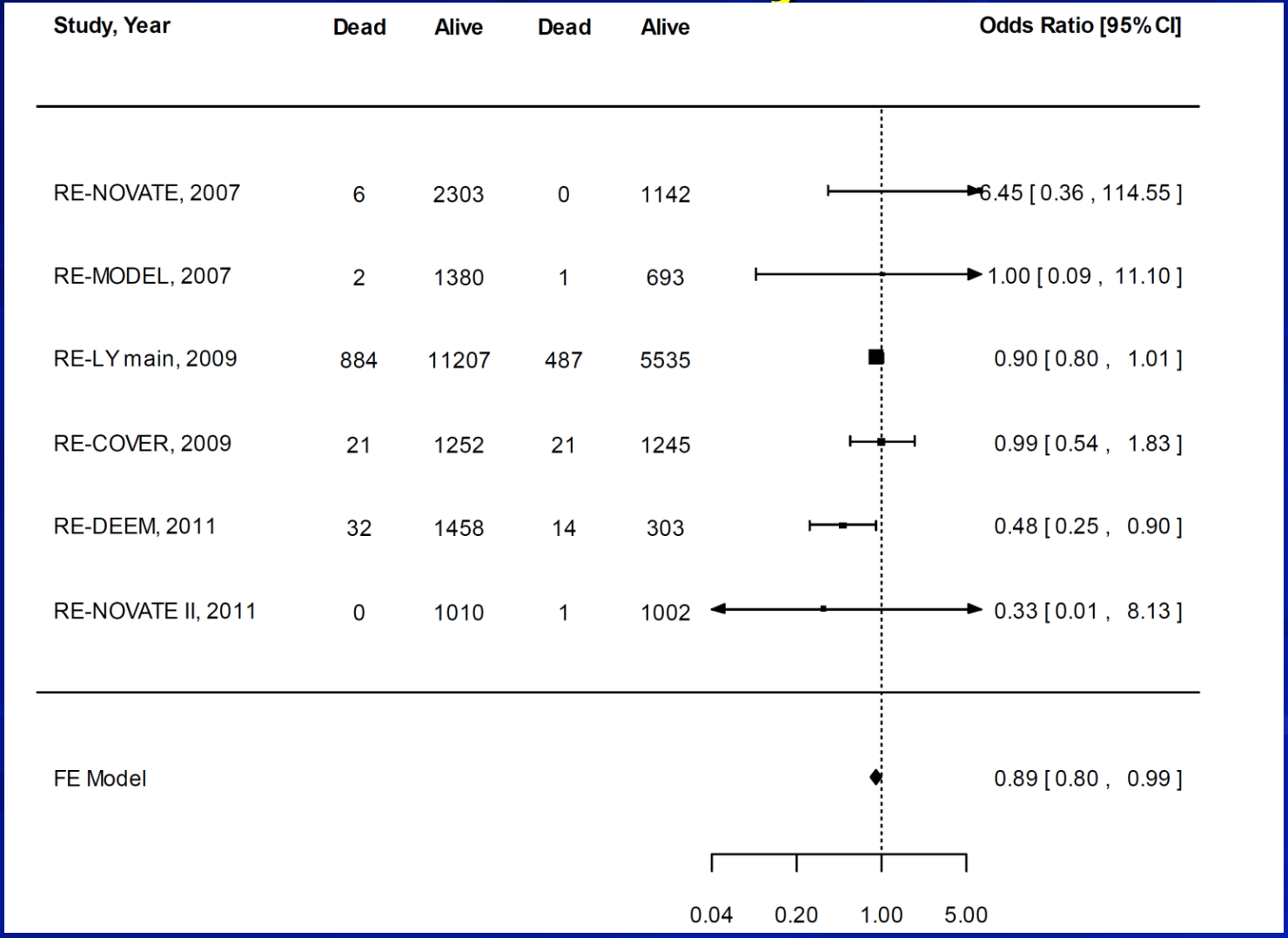
Study, y	Dabigatran, No. ACEv	Dabigatran, No. No Event	Control, No. ACEv	Control, No. No Event	Odds Ratio (95% CI)
RE-NOVATE,[10] 2007	13	2296	9	1133	0.71 (0.30-1.67)
RE-MODEL,[11] 2007	10	1372	4	690	1.26 (0.39-4.02)
PETRO,[12] 2007	2	443	0	70	0.79 (0.04-16.73)
RE-LY original,[2,3] 2009	175	11 916	63	5959	1.39 (1.04-1.86)
RE-COVER,[13] 2009	4	1269	2	1264	1.99 (0.36-10.90)
RE-DEEM,[14] 2011	32	1458	4	313	1.72 (0.60-4.89)
RE-NOVATE II,[15] 2011	1	1009	1	1002	0.99 (0.06-15.90)
FE model					1.33 (1.03-1.71)



Mortality OR 0.89; 95% CI: 0.80-0.99

Uchino K, et al. Arch Intern Med 2012

Dabigatran Trials Meta-analysis mortality



Uchino, K. et al. Arch Intern Med 2012;0:archinternmed.2011.1666v1-6.

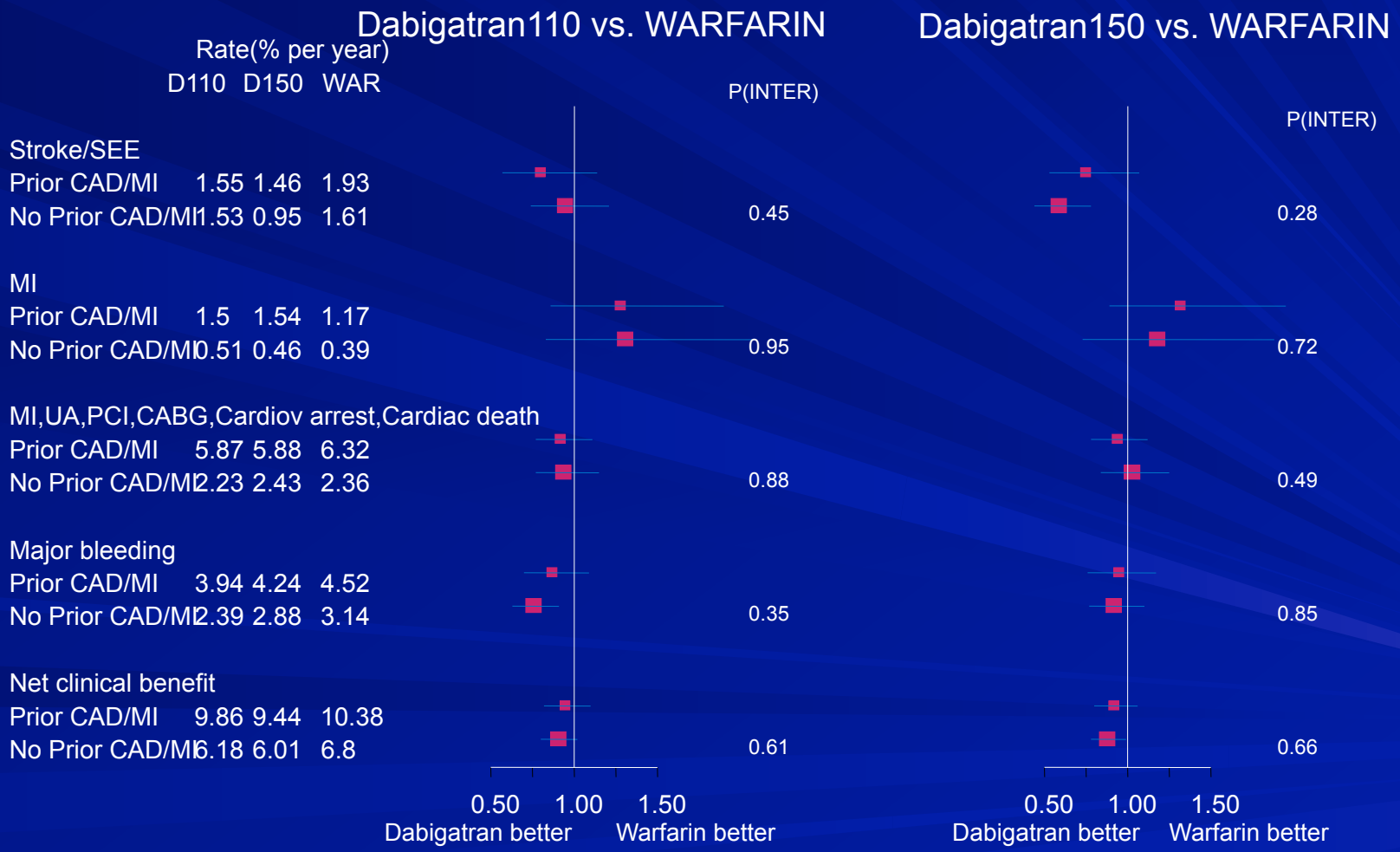
Number of MI, Cardiovascular death and reported hospitalization, randomized set

	DE 110 N (%/yr)	DE150 N (%/yr)	Warfarin N (%/yr)
Randomized	6015	6076	6022
Myocardial infarction	98 0(.82)	97 (0.81)	75 (0.64)
Unstable angina	133 (1.12)	163 (1.35)	166 (1.31)
CABG or PTCA	48 (0.40)	44 (0.37)	46 (0.39)
Cardiac death	177 (1.49)	161 1.34)	174 (1.48)

Circulation. 2012 Jan 3. [Epub ahead of print]

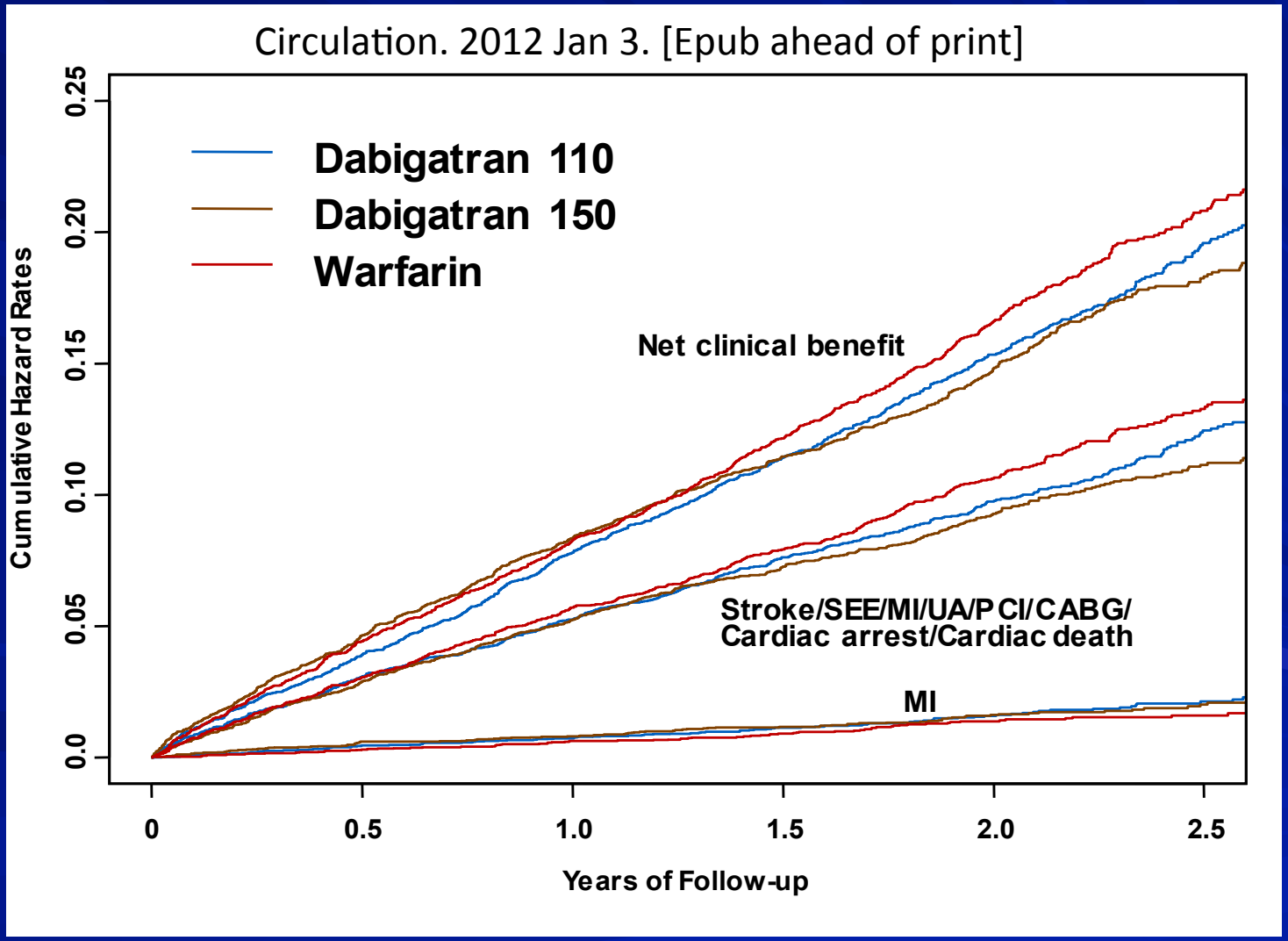
RELY Outcomes According to History of Prior CAD or MI

Circulation. 2012 Jan 3. [Epub ahead of print]



MI, Net Benefit and Composite of Embolic and Ischemic Events

Circulation. 2012 Jan 3. [Epub ahead of print]



Choosing Between New Agents

- Perspective…
  - Use of any anticoagulant much better than ASA/non
  - Use of any of the new anticoagulants offers measurable benefits over warfarin
  - No studies comparing agents
    - Different populations, INR control, study design
    - Results of studies not suited to comparisons
    - Differences likely small
- Patient-tailored therapy
    - Physician judgement