CSHP-NB Branch Education, NB Pharmacy Conference, May 29, 2010

Can we RE-LY on new oral anticoagulants to prevent cardioembolic stroke?

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Objectives

- To review results of a recently released clinical trial in anticoagulation
  - Dabigatran versus warfarin in patients with atrial fibrillation. RE-LY Study.
- And…to do so without showing a slide of the coagulation cascade!

Disclosure

- I have received lecturer honoraria from AstraZeneca, MerckFrosst, NovoNordisk, Pfizer; and research funds from MedBuy Inc.

Atrial Fibrillation & Stroke: What We Already Know

- Atrial fibrillation (AF) is the most common arrhythmia in Canada affecting 200,000 to 250,000 persons[1]
- AF causes up to 15% of all strokes usually by formation of an atrial thrombus which can embolize & occlude a cerebral artery causing a stroke[1]
- AF-related strokes are more severe, cause greater disability & have worse prognosis than strokes in patients without AF[1]

- Warfarin:
  - Decreases stroke risk in patients with AF by 60-70%[2]
  - Is recommended for AF patients at stroke risk >4% ($CHADS_2$ score ≥ 2)[3]
    - **C**ongestive Heart Failure, **H**ypertension, **A**ge 75 or more, **D**iabetes (1 pt each); Prior **S**troke/ TIA (2 pts)
  - Is superior to ASA or ASA/clopidogrel[2,4,5]

1. CADTH Issue 116, Mar 2010; 2. Arch Intern Med 1994; 3. Circulation 2006; 4. Lancet 2006; 5. Stroke 2008

Atrial Fibrillation & Stroke: What We Already Know

Warfarin

- Is inexpensive
- Has slow onset & long duration of activity
- Requires loading & individualized maintenance dosing for optimal effect
- Is prescribed for only 50-65% of appropriate candidates
- When used, is maintained at therapeutic INR levels for approx 69% of time (range 46-78%).

- Underuse of warfarin in clinical practice is related to fear of nuisance &/or serious bleeding, need for INR testing, & numerous interactions with drugs, NHPs, food, etc.

- An effective yet safer, more convenient therapy is needed!

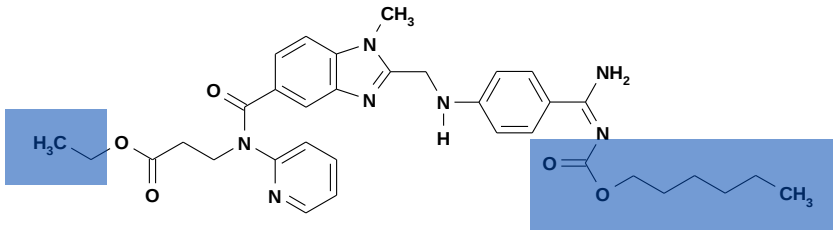
Dabigatran etexilate

- Oral direct thrombin (factor II) inhibitor
  - Reversibly, competitively inhibits free and fibrin-bound IIa activity
- Approved in Canada for VTE prevention post TKR/THR[1]
- Predictable ph'kinetics with fixed dosing – no coag monitoring required

1. Pradax™ product monograph, Boehringer-Ingelheim website

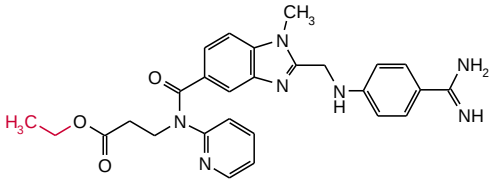
Dabigatran: Prodrug concept

Dabigatran etexilate



Plasma esterases

Intermediates



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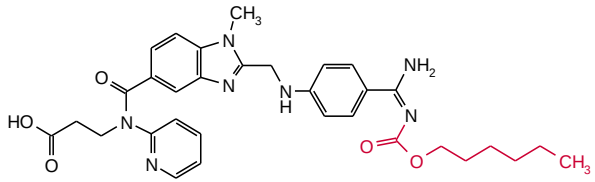

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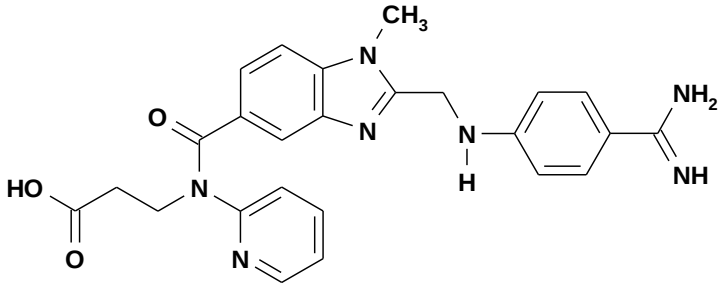
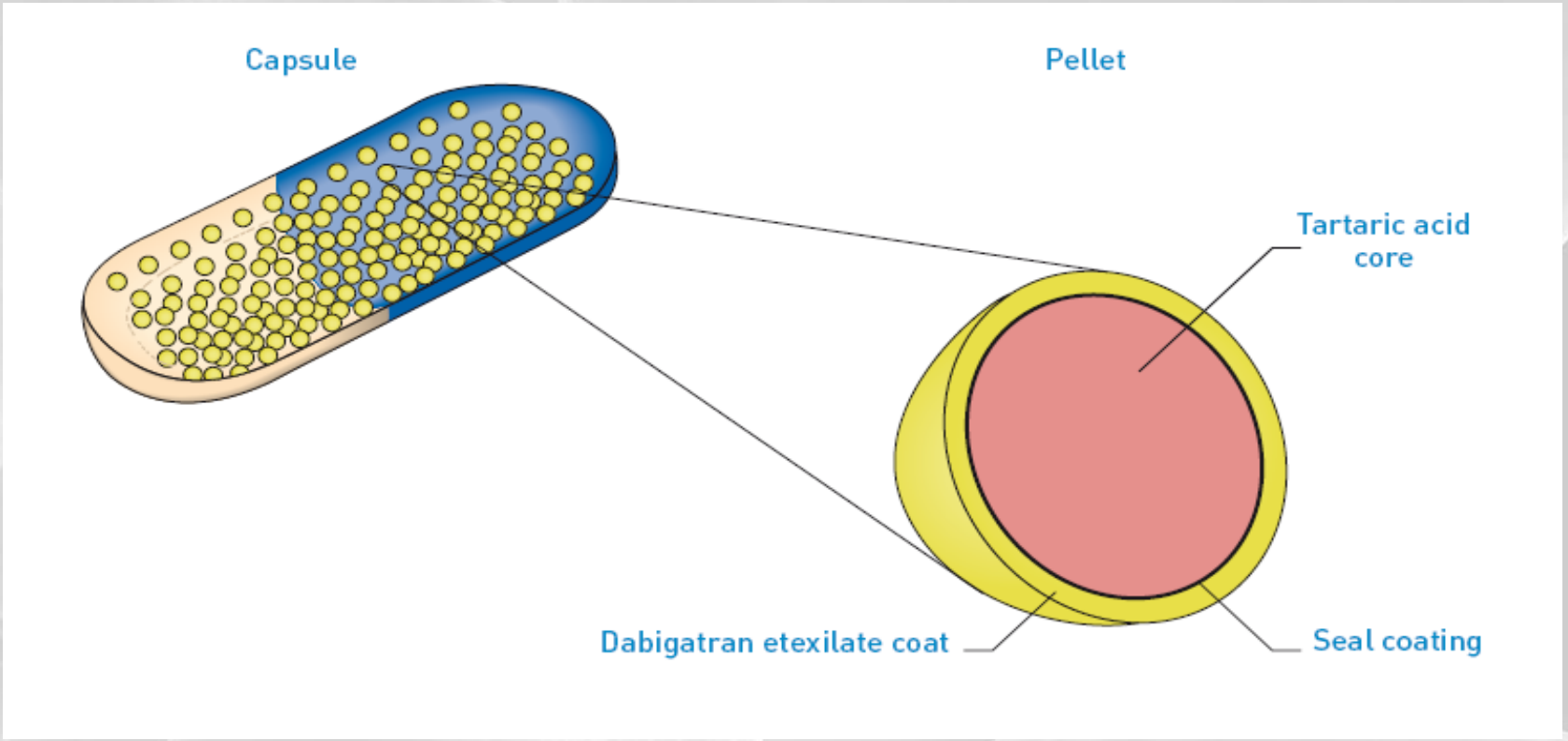
Plasma esterases

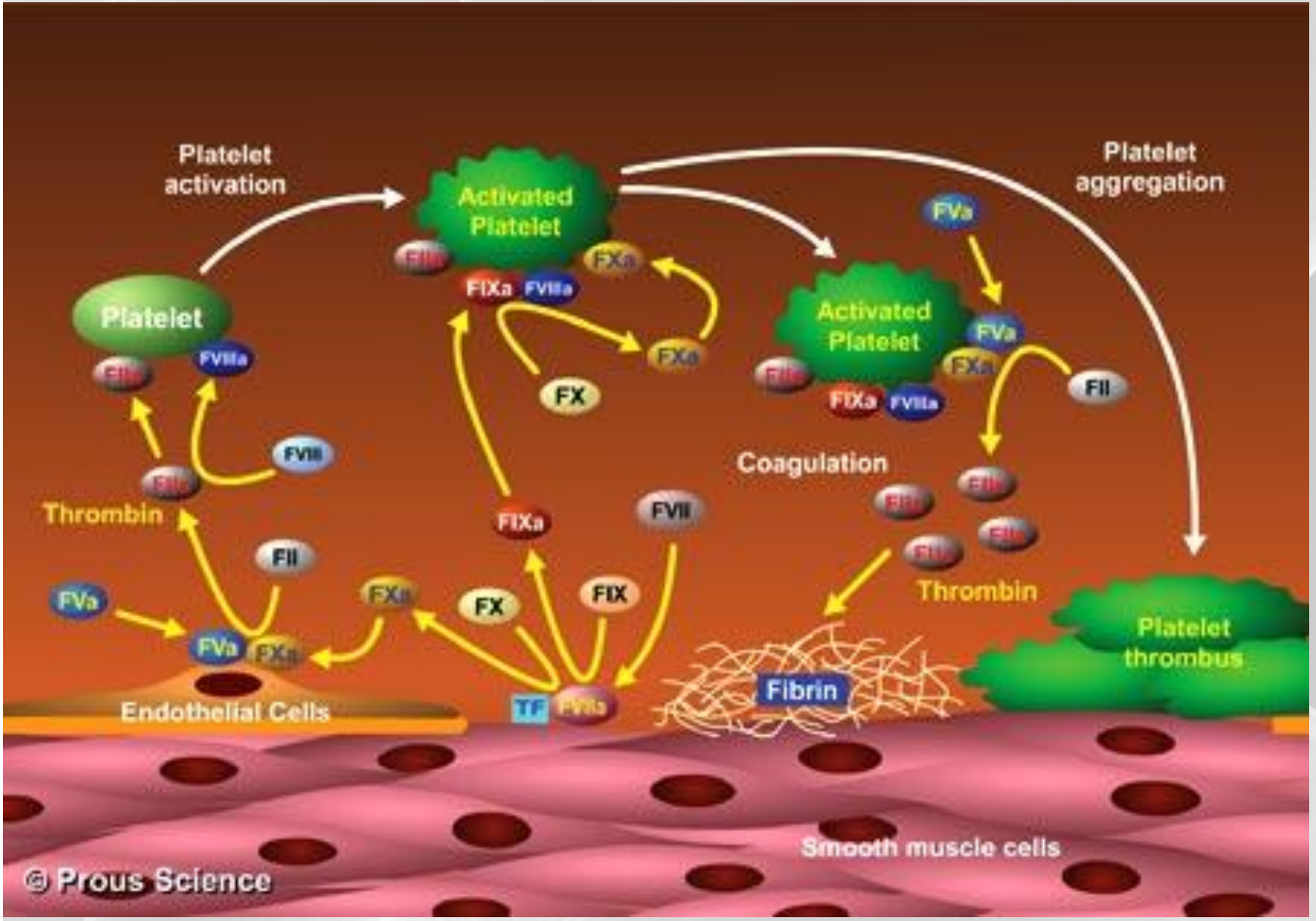
Dabigatran in systemic circulation



Dabigatran etexilate: Capsule formulation



Generation of acidic microenvironment by tartaric acid core
→ increase of drug dissolution and absorption
→ ensures that absorption is less affected by variations in gastric pH


Platelet activation
Activated Platelet
Platelet aggregation
Platelet
FVIIIa
FIXa FVIIIa
FXa
FX
FVa
Activated Platelet
FVa
FXa
FII
FIXa FVIIIa
Coagulation
FVIII
Thrombin
FIXa
FVII
FII
FVa
FXa
FX
FIX
Thrombin
Platelet thrombus
Fibrin
Endothelial Cells
TF
FVIIa
Smooth muscle cells
© Prous Science

Dabigatran etexilate

PK/PD:

- Bioavailability 6.5% - non-medicinal tartaric acid
- Prodrug – rapid biotransformation to active drug
  - Esterase-catalysed hydrolysis in plasma & liver
- Rapid onset: max inhibition of IIa after 1–4 h

- Short half-life: 12–17 h
- Renal excretion: 80% (avoid if CrCl <30 ml/min)

- Drug interactions with P-glycoprotein:
  - Increased effect with inhibitors: quinidine, amiodarone, verapamil, clarithromycin
  - Decreased effect with inducers: rifampin, St.John's wort
  - No interaction with CYP450 system

1. Pradax™ product monograph, Boehringer-Ingelheim website

Randomized **E**valuation of **L**ong-term Anticoagulant Therap**Y**

The NEW ENGLAND JOURNAL of MEDICINE

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Dabigatran versus Warfarin in Patients with Atrial Fibrillation

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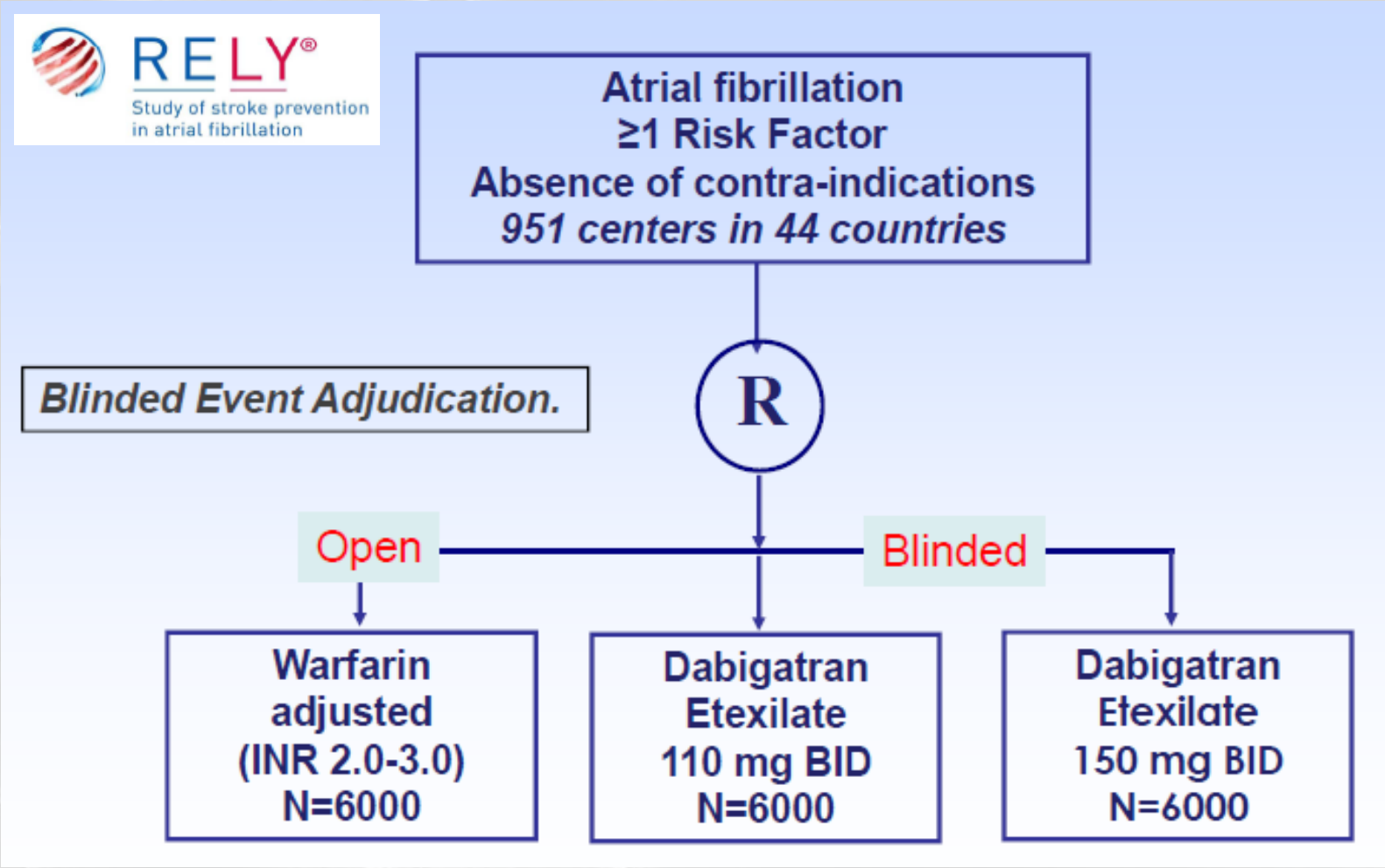
Phase 2 studies determined 110 mg BID (PETRO) and 150 mg BID (previous VTE prevention trials) to be viable doses

RE-LY: A non-inferiority trial

- Design: Phase III, multicentre, prospective randomized trial (funded by B-I)
  - Largest AF stroke prevention trial to date
- Subjects: Patients with AF and ≥1 risk factor randomized to warfarin or dabigatran

RE-LY: A non-inferiority trial



RE-LY Outcomes

- Primary study outcome: stroke or systemic embolism
- Primary safety outcome: major hemorrhage
- Secondary: stroke, systemic embolism, death
- Analysed by ITT

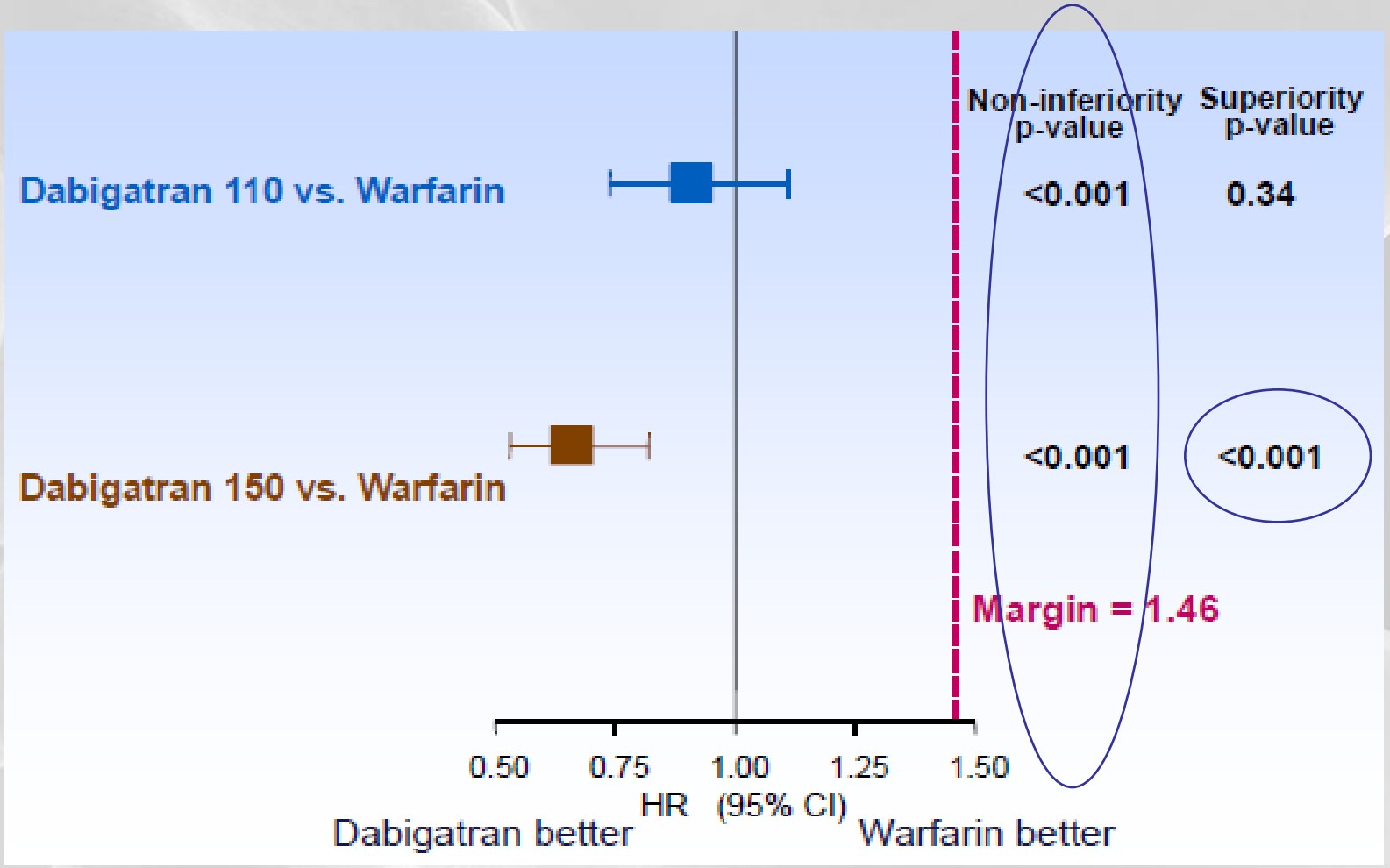
RE-LY Execution

- Enrolment Dec 2005-Dec 2007
- Follow up Dec 2008-Mar 2009
- Median F/U 2.0 years
- 20 patients lost to F/U (99.9% complete!)
- Warfarin group: mean TTR 64%

RE-LY Baseline Characteristics

Characteristic	Dabigatran 110 mg	Dabigatran 150 mg	Warfarin
Randomized	6015	6076	6022
Mean age (years)	71.4	71.5	71.6
Male (%)	64.3	63.2	63.3
CHADS2 score (mean)	2.1	2.2	2.1
0-1 (%)	32.6	32.2	30.9
2 (%)	34.7	35.2	37.0
3+ (%)	32.7	32.6	32.1
Prior stroke/TIA (%)	19.9	20.3	19.8
Prior MI (%)	16.8	16.9	16.1
CHF (%)	32.2	31.8	31.9
Baseline ASA (%)	40.0	38.7	40.6
Warfarin Naïve (%)	49.9	49.8	51.4

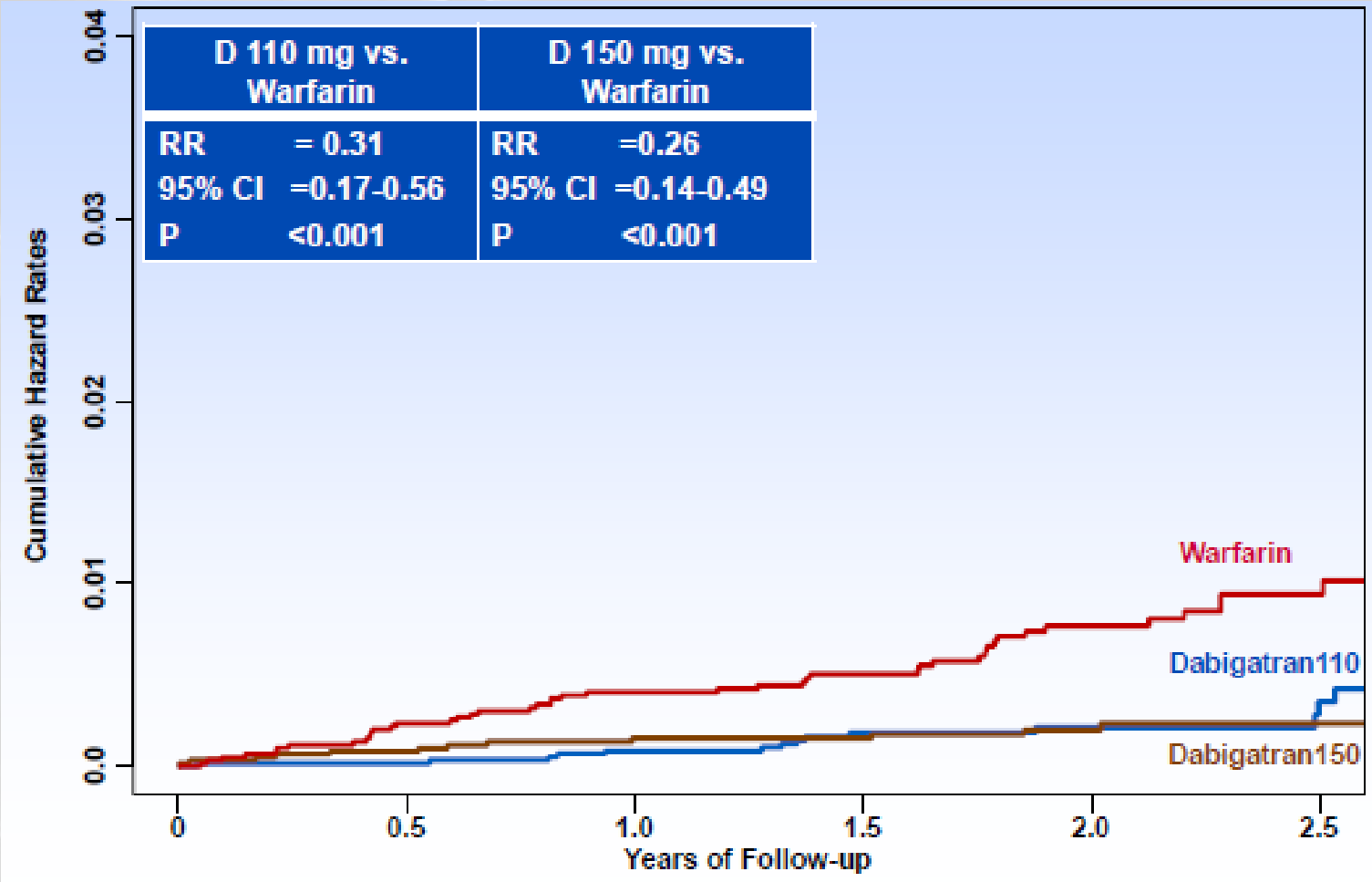
RE-LY Primary Outcome: Stroke or Systemic Embolism



RE-LY Primary Outcome: Superiority Analysis

	D 110mg	D 150mg	warfarin	D 110mg vs. Warfarin		D 150mg vs. Warfarin	
	Annual rate	Annual rate	Annual rate	RR 95% CI	P*	RR 95% CI	P
Stroke or systemic Embolism	1.5 %	1.1 %	1.7 %	0.91 0.74 1.11	0.34	0.66 0.53 0.82	<0.001
Stroke	1.4 %	1.0 %	1.6 %	0.92 0.74-1.13	0.41	0.64 0.51-0.81	<0.001

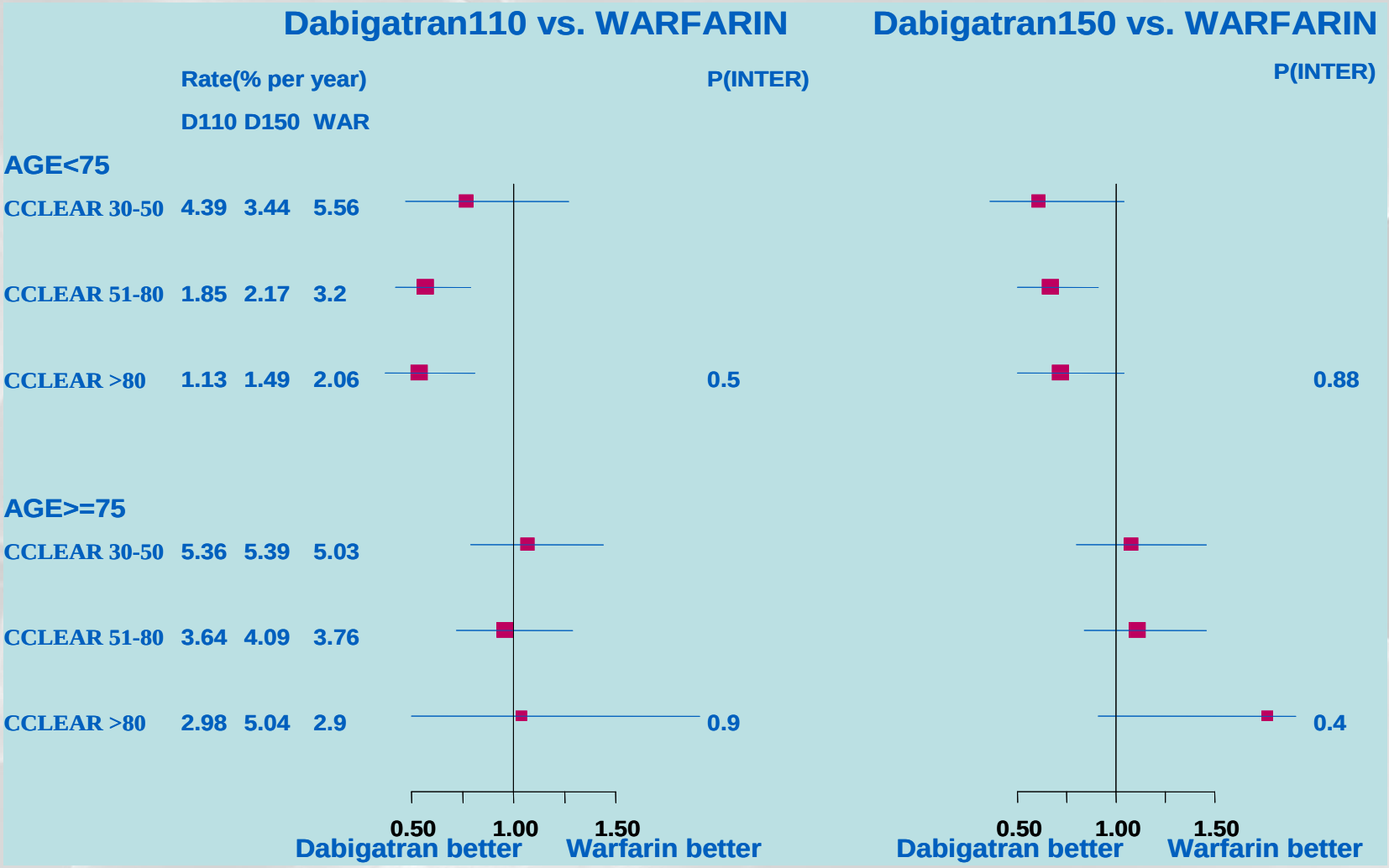
Hemorrhagic Stroke



RE-LY Primary Outcome by Subgroup

- No significant interaction seen with treatment effect of dabigatran:
  - At either dose,
  - With or without long-term warfarin, or
  - Across levels of baseline CrCl

Major Bleeding: Effect of Renal Function by Age



RE-LY Bleeding

	D 110mg	D 150mg	warfarin	D 110mg vs. Warfarin		D 150mg vs. Warfarin	
	Annual rate	Annual rate	Annual rate	RR 95% CI	p	RR 95% CI	p
Total	14.6%	16.4%	18.2%	0.78 0.74-0.83	<0.001	0.91 0.86-0.97	0.002
Major	2.7 %	3.1 %	3.4 %	0.80 0.69-0.93	0.003	0.93 0.81-1.07	0.31
Life-Threatening major	1.2 %	1.5 %	1.8 %	0.68 0.55-0.83	<0.001	0.81 0.66-0.99	0.04
Gastro-intestinal Major	1.1 %	1.5 %	1.0 %	1.10 0.86-1.41	0.43	1.50 1.19-1.89	<0.001

RE-LY Net Clinical Benefit

	D 110mg	D 150mg	warfarin	D 110mg vs. Warfarin		D 150mg vs. Warfarin	
	Annual rate	Annual rate	Annual rate	RR 95% CI	p	RR 95% CI	p
MI	0.7%	0.7 %	0.5 %	1.35 0.98-1.87	0.07	1.38 1.00-1.91	0.048
Death	3.8 %	3.6 %	4.1 %	0.91 0.80-1.03	0.13	0.88 0.77-1.00	0.05
Net Clinical Benefit	7.1 %	6.9 %	7.6 %	0.92 0.84-1.02	0.10	0.91 0.82-1.00	0.04

Net Clinical Benefit includes vascular events, death and major bleed

Dabigatran 110 vs 150mg: Net Clinical Benefit

	Dabigatran 110mg	Dabigatran 150mg	D 150mg vs. D 110 mg	
	Number rate/yr	Number rate/yr	Relative Risk 95% CI	p
Stroke and systemic embolism	1.5%	1.1 %	0.73 0.58-0.91	0.005
Hemorrhagic stroke	0.1%	0.1 %	0.85 0.39-1.83	0.67
Major Hemorrhage	2.7 %	3.1 %	1.16 1.00-1.34	0.05
Net Clinical Benefit	7.1 %	6.9 %	0.98 0.89-1.08	0.66

RE-LY Other Outcomes

- Less hospitalization for pts on dabigatran
- AEs: Dyspepsia was significantly more common with dabi (110mg=11.3%, 150mg=11.8%) than warf (5.8%)
- LFT: No difference in frequency of ALT or AST >3x ULN (approx 2%)
- D/C drug
  - @1 yr: D110=15%; D150=16%; W=10%
  - @2 yr: D110=21%; D150=21%; W=17%
  - GI Sx: D110=2.2%; D150=2.1%; W=0.6%

RE-LY Limitations

- Reporting bias
  - Warfarin (open-label) – regular F/U for INR may have improved detection of outcome events
  - Blinded adjudication by 2 independent investigators unaware of assigned treatment
- Overall, RE-LY was very well designed & executed with extremely low loss to F/U

RE-LY Conclusions

- Compared to adjusted-dose warfarin,
  - Dabigatran 110 mg BID had a similar rate of stroke & systemic embolism with lower rates of major bleeding,
  - Dabigatran 150 mg BID significantly decreased stroke & systemic embolism rates but with a similar rate of major hemorrhage
  - Dabigatran increased dyspepsia & GI bleed

RE-LY Conclusions (cont.)

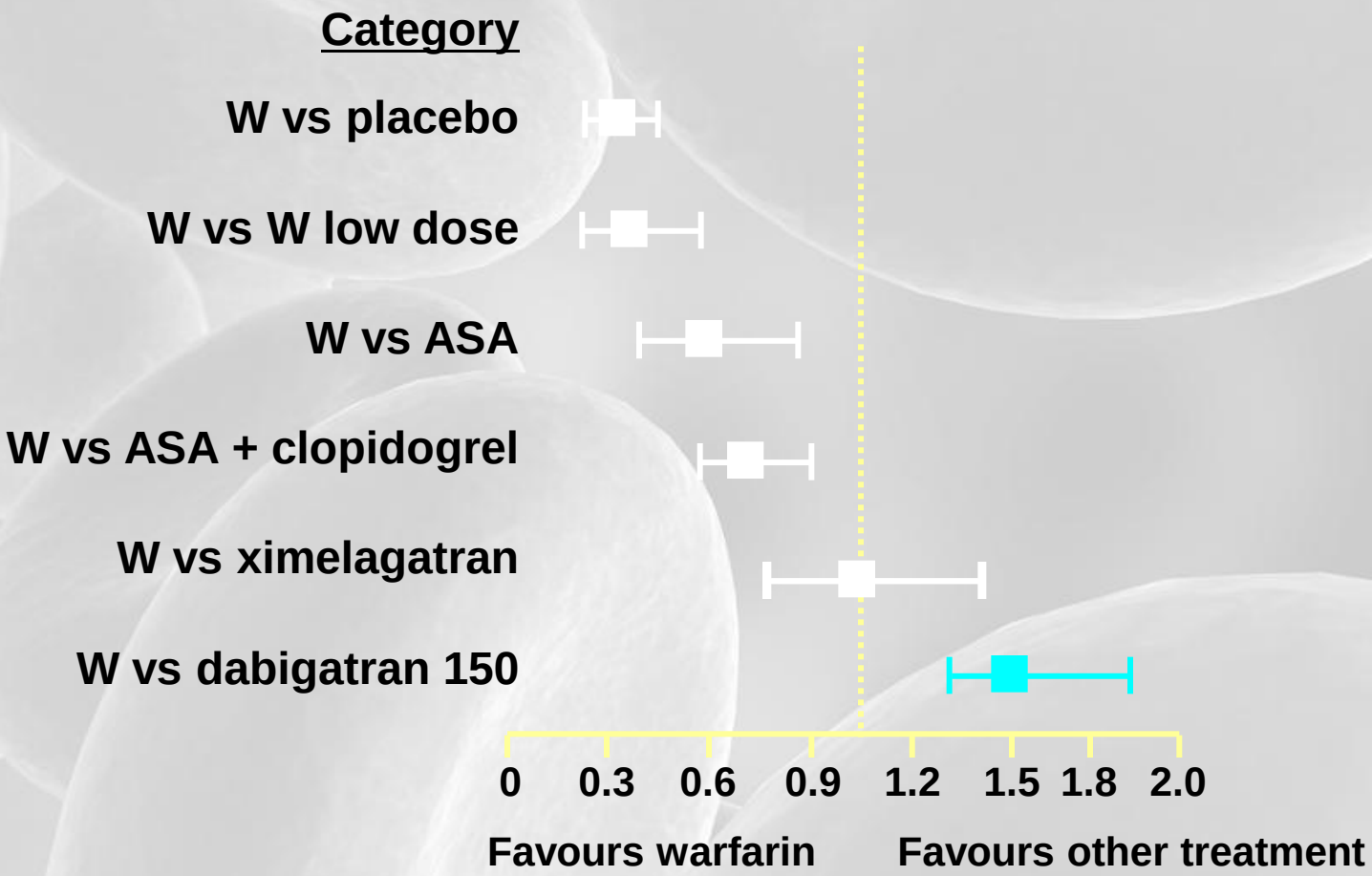
- However, both doses offer advantages over warfarin
  - Dabigatran 150mg BID is more efficacious
  - Dabigatran 110mg BID provides a better safety profile
- There may be potential to tailor therapy to individual patients

Atrial Fibrillation & Stroke: What we **still** don't know

- What is the clinical relevance of drug interactions with dabigatran?
  - Use of amiodarone (10%), PPI (14%) or H2RA (4%) in RE-LY not stratified… wait for substudies & post-marketing reports
- How to use dabigatran in those with hx of dyspepsia and/or GI bleed?
- How to interpret the risk of MI in RE-LY's dabigatran groups?
- What will be the impact in real world practice?
  - Direct costs (drug acquisition) vs warfarin?
    - Dabigatran (Pradax®) $7.85 for 110mg capsule (also available as 75mg cap) vs warfarin $0.40-0.60/day
  - Indirect costs vs warfarin in light of promise for fewer hospitalizations, no INR testing
  - Risk:benefit perspectives & values of individual patients

RE-LY in Perspective

Meta-analysis of ischemic stroke or systemic embolism



Camm J.: Oral presentation at ESC on Aug 30th 2009.

Other drug options for cardioembolic stroke?

- ASA
- ASA + clopidogrel
- Low-dose warfarin + ASA

- Rivaroxaban
  - Direct inhibitor of factor Xa
  - Indicated only for VTE prevention post-THR/TKR
  - CEDAC supported public coverage for rivaroxaban but not dabigatran
  - Daily cost $9.92 for 10mg tablet
  - ROCKET-AF trial in progress
    - 20mg daily vs adjusted-dose warfarin
    - Results expected in late 2010 or 2011

Questions?