

DECLARATION OF CONFLICT OF INTEREST

New antithrombotic therapies: revisiting stroke prevention in atrial fibrillation

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Disclosures for Lars Wallentin

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Pfizer	Research grant
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Merck - Schering-Plough	Research grant
Eli Lilly & Co.	Research grant
Regado Biosciences	Consultancy
Athera Biotechnologies	Consultancy
Portola	Consultancy
Evolva	Consultancy
GE Health Care	Consultancy

Atrial fibrillation

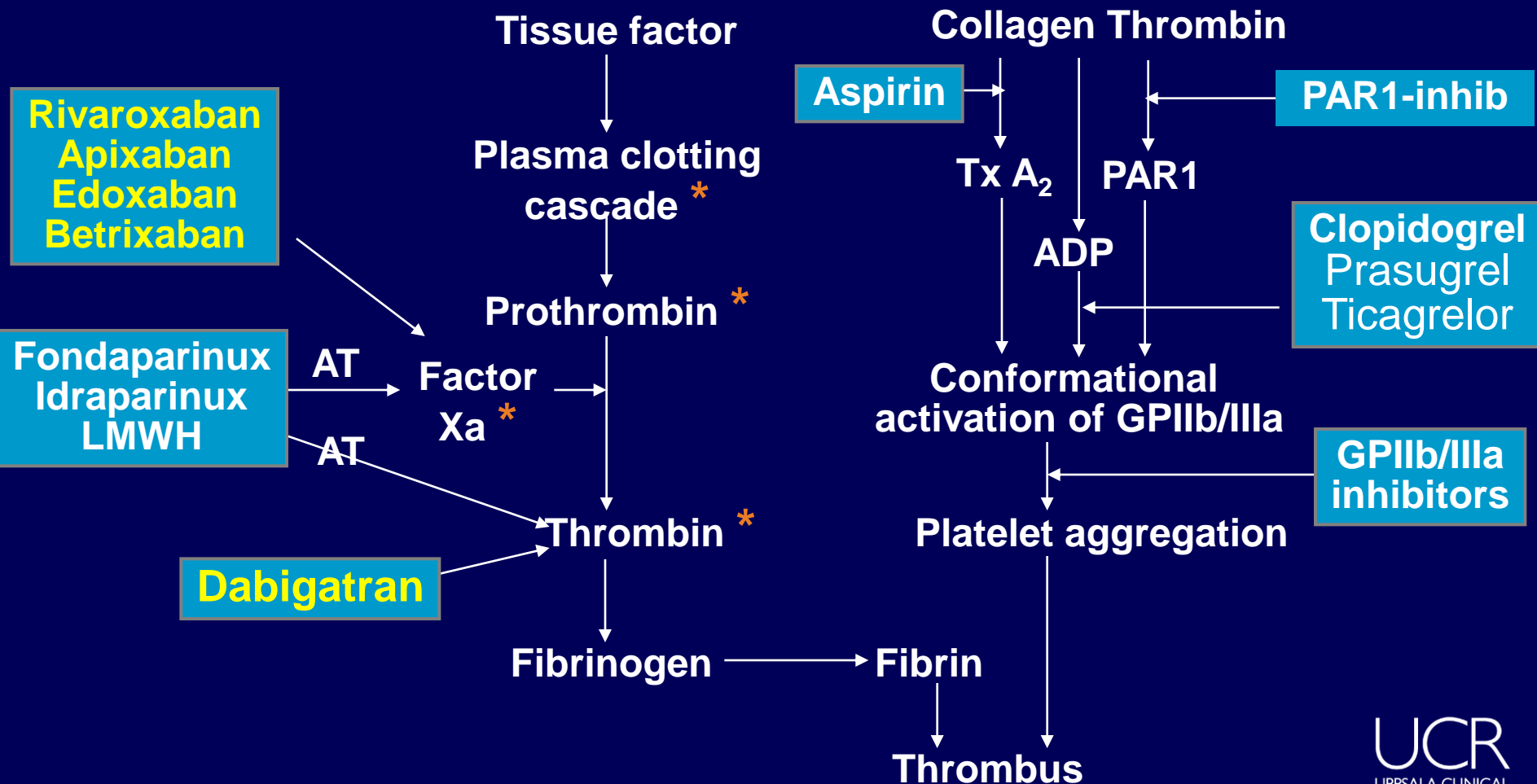
- Most common arrhythmia
- 1.5% of the population
- Increases with age

Stroke risk

- Five fold increase at AF
- Risk related to risk factors
- Congestive heart failure
- Hypertension
- Age > 75
- Diabetes
- S₂troke
- Reduced with antithrombotics
- Aspirin (– 19%)
- Warfarin (– 64%)

Targets for long-term antithrombotic treatment

Warfarin*



Alternatives to warfarin

- At least same anti-thrombotic effect
- Lower risk of bleeding – especially intracranial bleeding
- Few other side-effects
- Oral bioavailability – once or twice daily
- No food or drug interactions
- Broad therapeutic window at standard dosing
- Stable anticoagulation without frequent laboratory monitoring
- Good patient acceptability and long-term tolerance

Pharmacology of novel anticoagulants

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Mechanism of action	Selective direct FIIa inhibitor	Selective direct FXa inhibitor	Selective direct FXa inhibitor	Competitive inhibitor of FXa
Bioavailability	Oral prodrug with poor oral bioavailability	Good oral bioavailability	Good oral bioavailability	Good oral bioavailability
T_{1/2}	12 - 17 hours (80% renal excretion)	6 - 9 hours	12 hours	9 -11 hours
Dosing	Twice daily	Once daily	Twice daily	Once daily
Time to max effect	1 - 4 h	1 - 4 h	1 - 4 h	1 - 4 hr

Trial design comparing new agents in patients with AF

- Single, large trial (N = 14000 to 18000)
- Event driven – 450 primary events
- Randomized vs warfarin
- Double blind, double dummy or PROBE
- Non-inferiority (or superiority) - on and off treatment
- CHADS2 score ≥ 1 or ≥ 2
- Median TTR 2-3 for warfarin treated pts - aim = 65%
- Complete follow-up of all patients

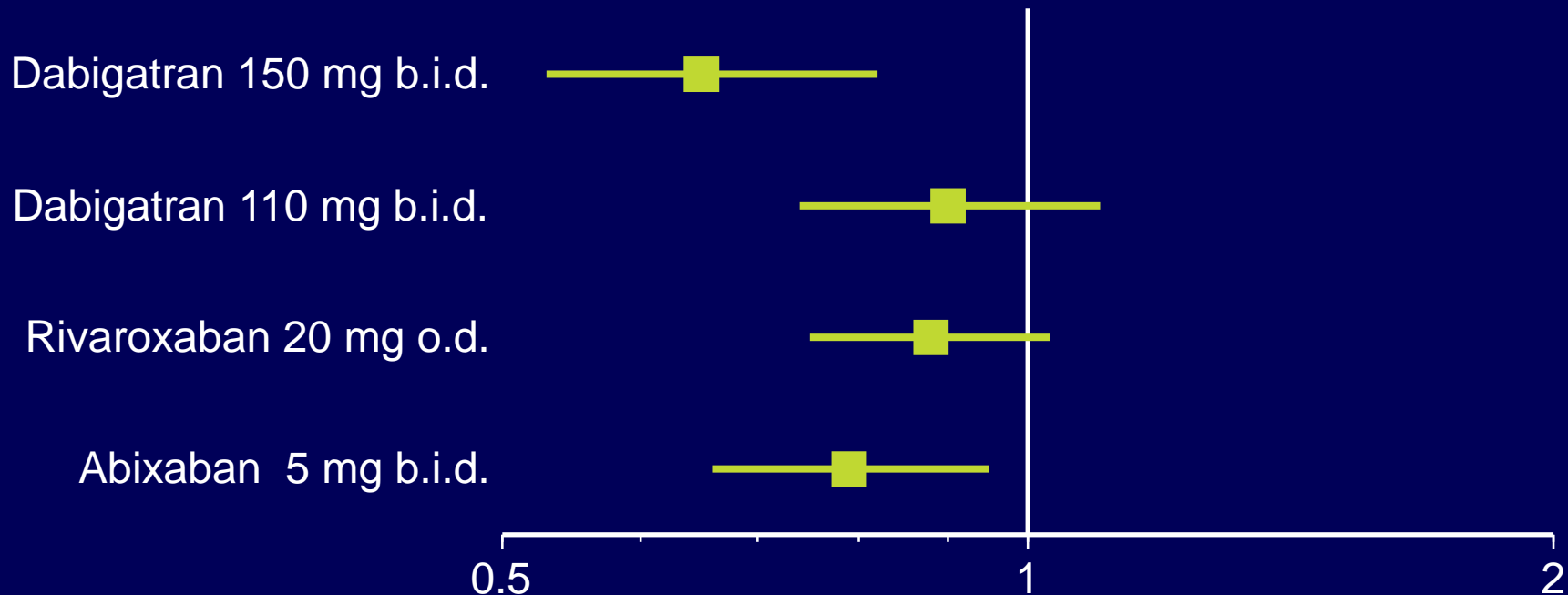
Trials with new agents vs warfarin (aim INR 2.0-3.0) in AF

	RELY	ROCKET	ARISTOTLE	ENGAGE-AF
Sample size	18,113	14,266	18,201	20,500
New treatment	Dabigatran 110mg BID & 150mg BID	Rivaroxaban 20mg QD	Apixaban 5mg BID	Edoxaban 30mg QD & 60mg QD
Design	Non-inferiority PROBE	Non-inferiority Double-blind	Non-inferiority Double-blind	Non-inferiority Double-blind
CHADS2	≥ 1	≥ 2	≥ 1	≥ 2
Primary outcome	Stroke or systemic embolism	Stroke or systemic embolism	Stroke or systemic embolism	Stroke or systemic embolism
Safety outcome	Primary: Major Bleeding	Primary: Major Bleeding	Primary: Major Bleeding	Primary: Major Bleeding

Connolly S et al NEJM 2009; Patel M et al NEJM 2011; Granger C et al NEJM 2011; ENGAGE- AF Study Investigators. AHJ 2010

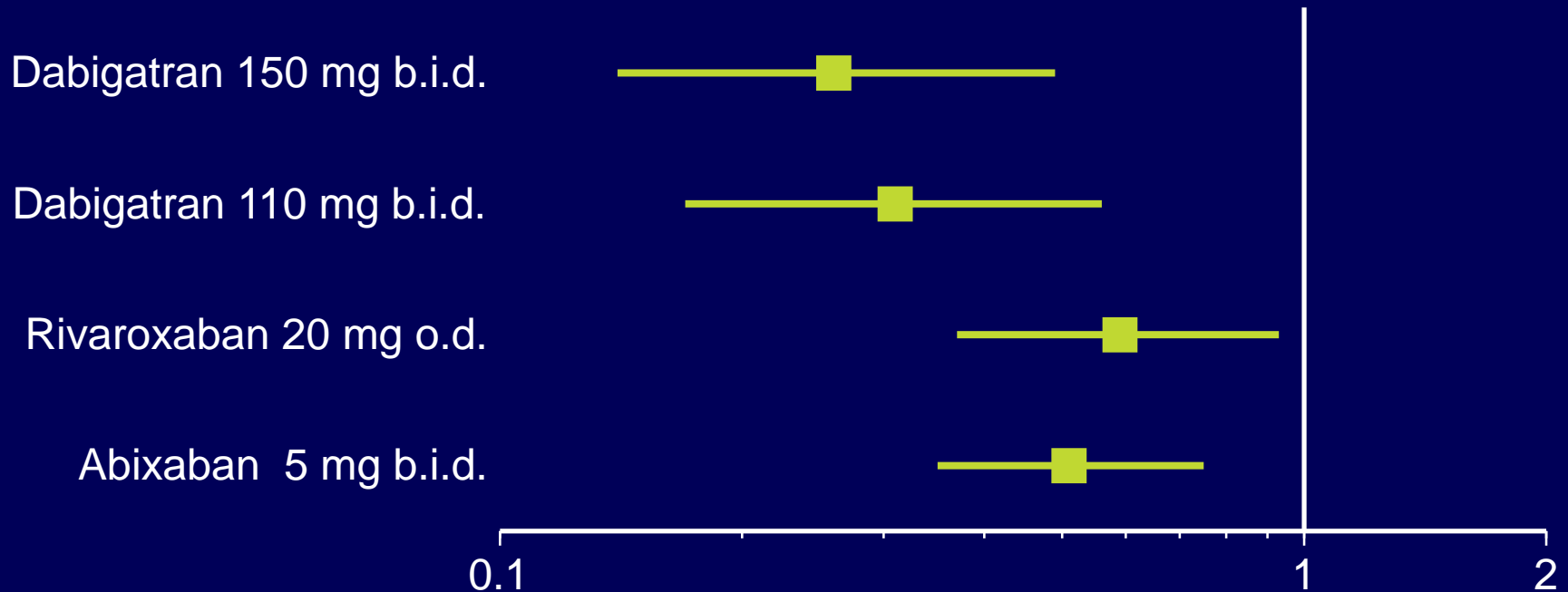
New antithrombotic therapies compared to warfarin

Stroke or systemic embolism



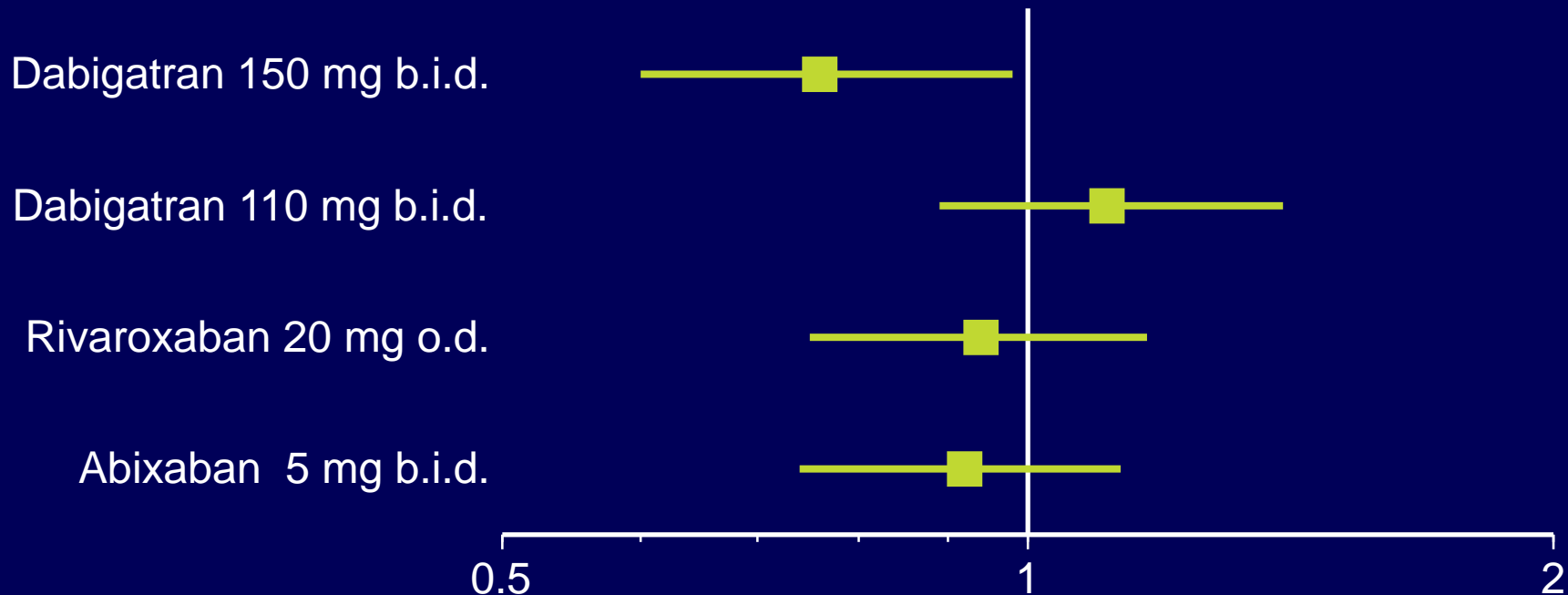
New antithrombotic therapies compared to warfarin

Hemorrhagic stroke



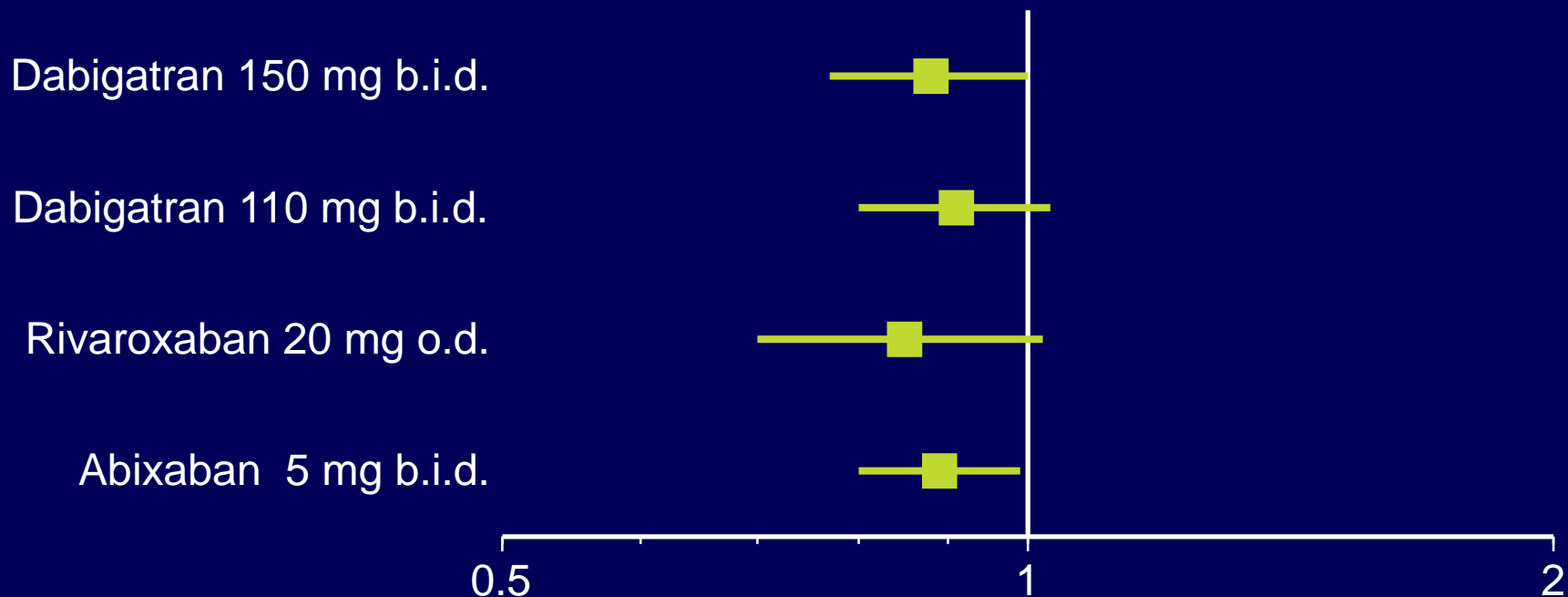
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Stroke of ischemic or unknown origin



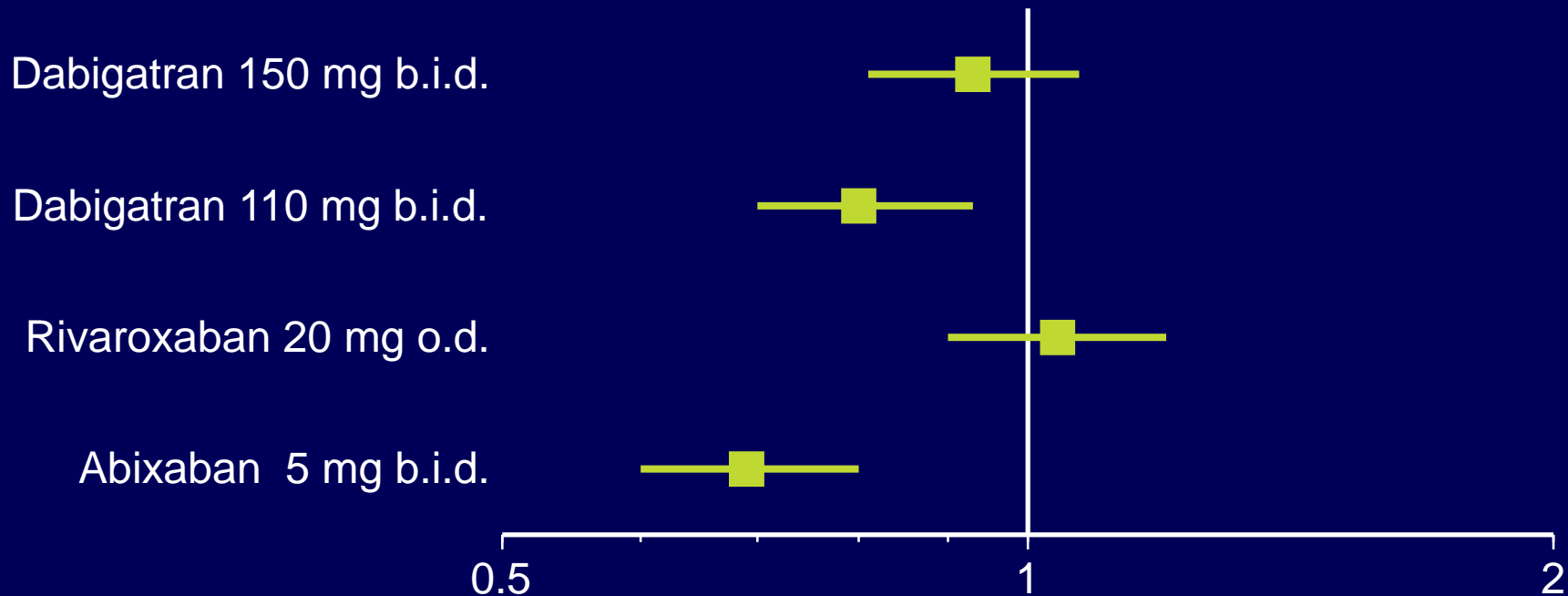
New antithrombotic therapies compared to warfarin

All-cause mortality



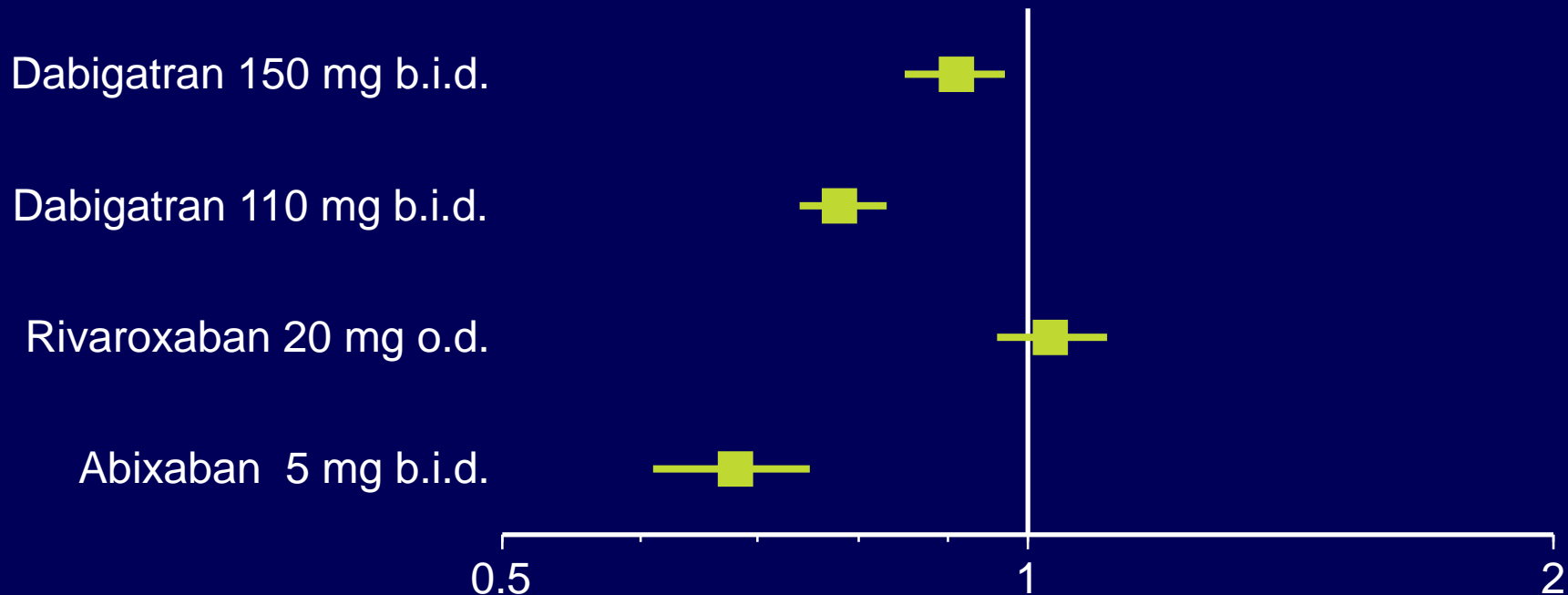
New antithrombotic therapies compared to warfarin

Major bleeding



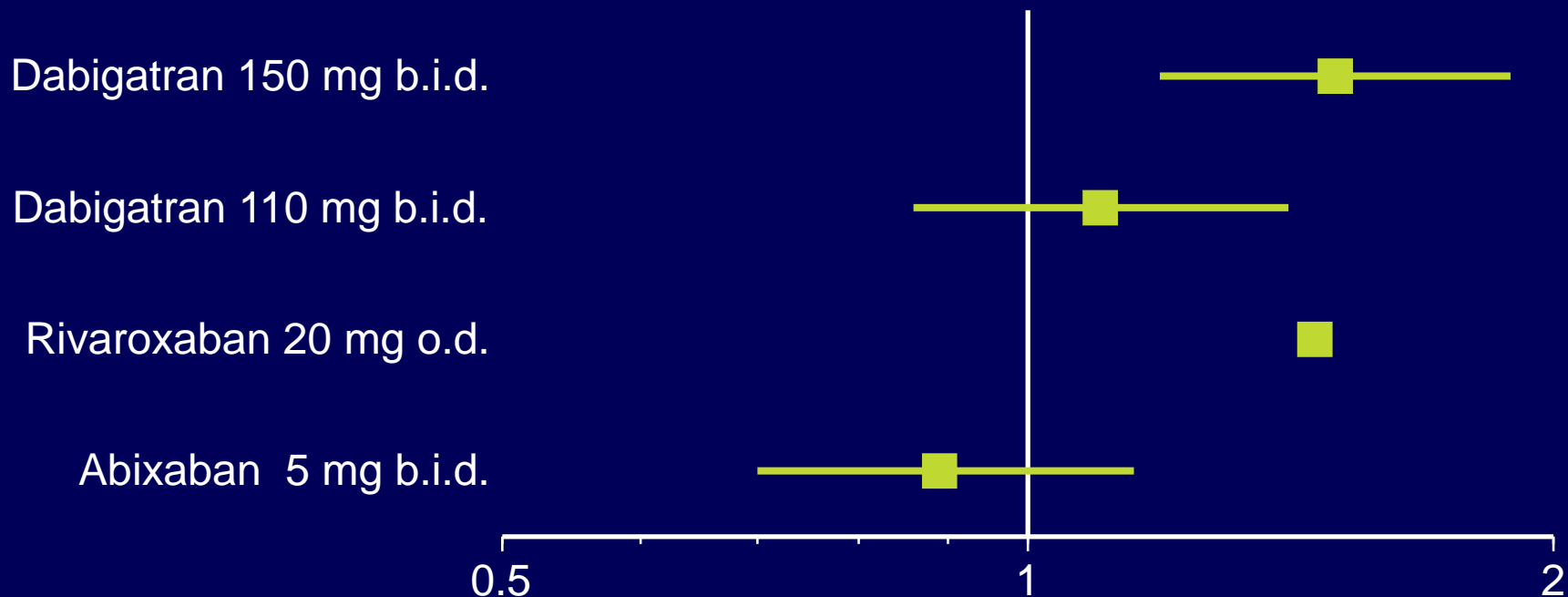
New antithrombotic therapies compared to warfarin

Major + clinically relevant bleeding



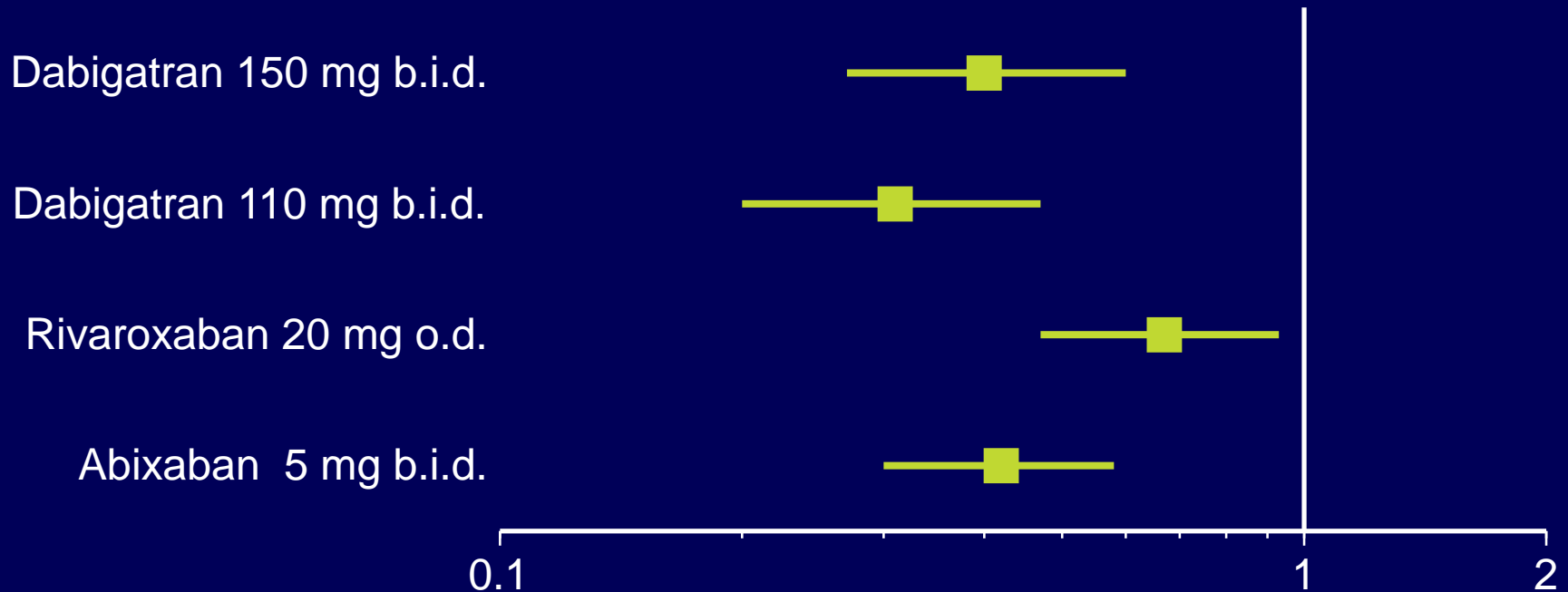
New antithrombotic therapies compared to warfarin

Gastrointestinal bleeding



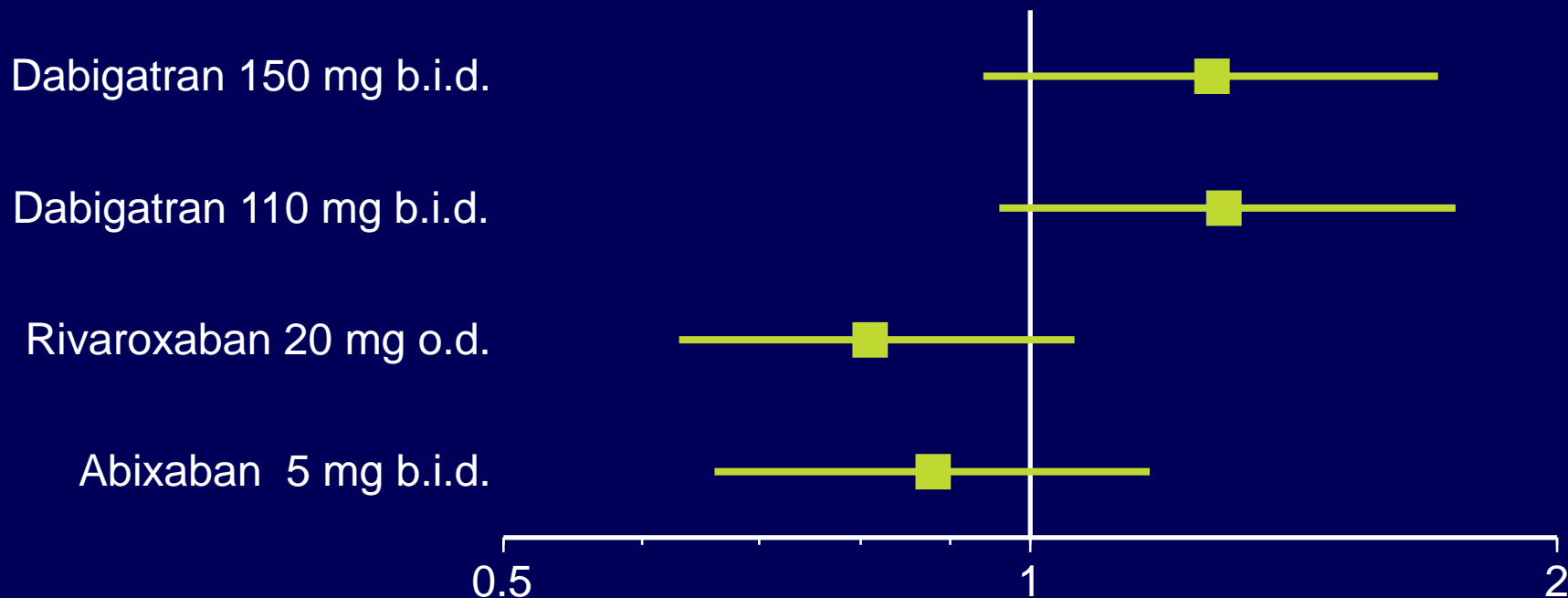
New antithrombotic therapies compared to warfarin

Intracranial hemorrhage



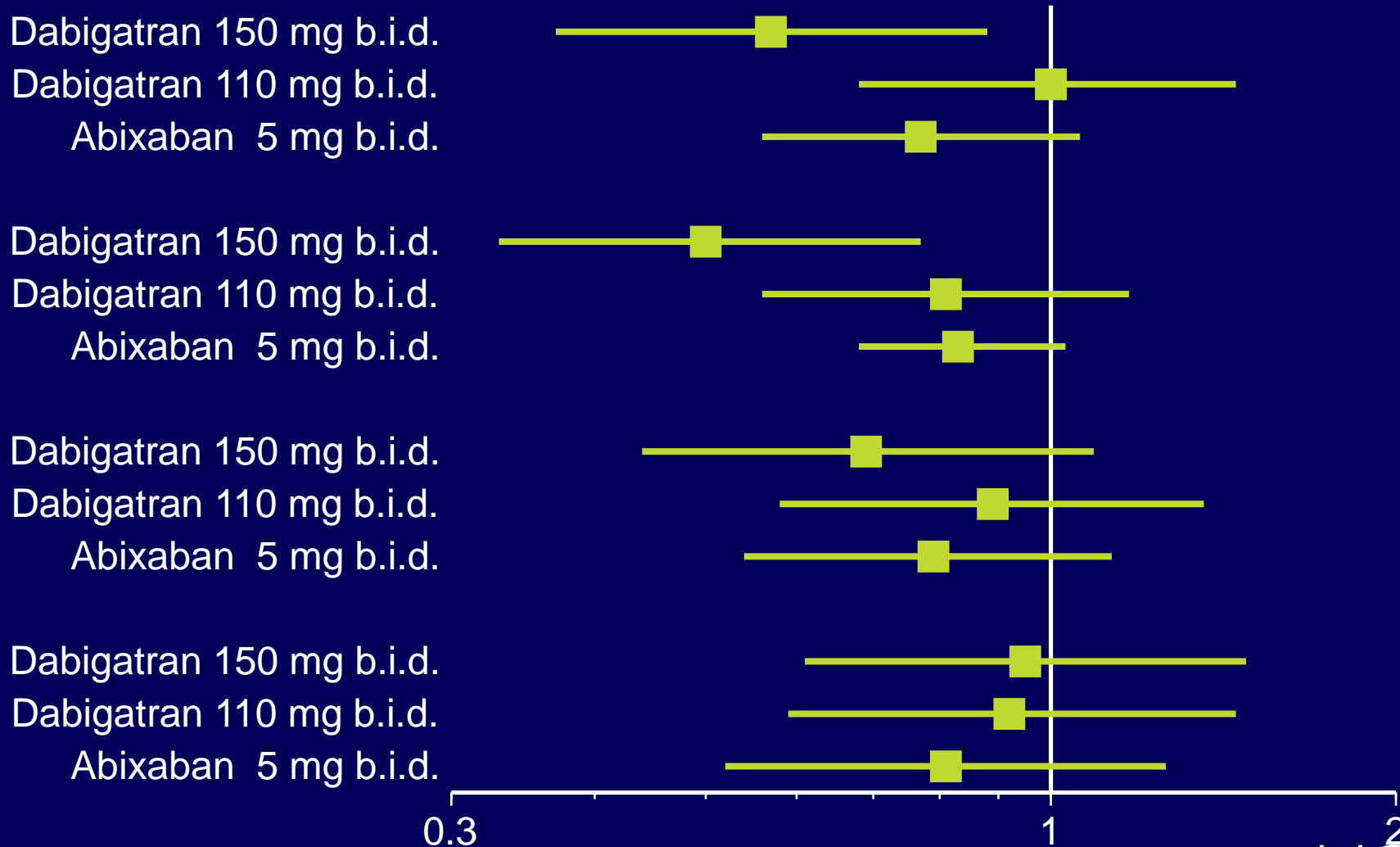
New antithrombotic therapies compared to warfarin

Myocardial infarction



New antithrombotic therapies compared to warfarin

Stroke or SE in relation to centre's TTR



New anticoagulants compared to warfarin in AF 2011

Effet on outcome event	D150	D110	Riva	Apix
Noninferiority stroke	√	√	√	√
Reduction hemorrhagic stroke	√	√	√	√

New anticoagulants compared to warfarin in AF 2011

Effet on outcome event	D150	D110	Riva	Apix
Noninferiority stroke	√	√	√	√
Reduction hemorrhagic stroke	√	√	√	√
Reduction ischemic stroke	√			
Reduction mortality	(√)			√
Reduction major bleeding		√		√

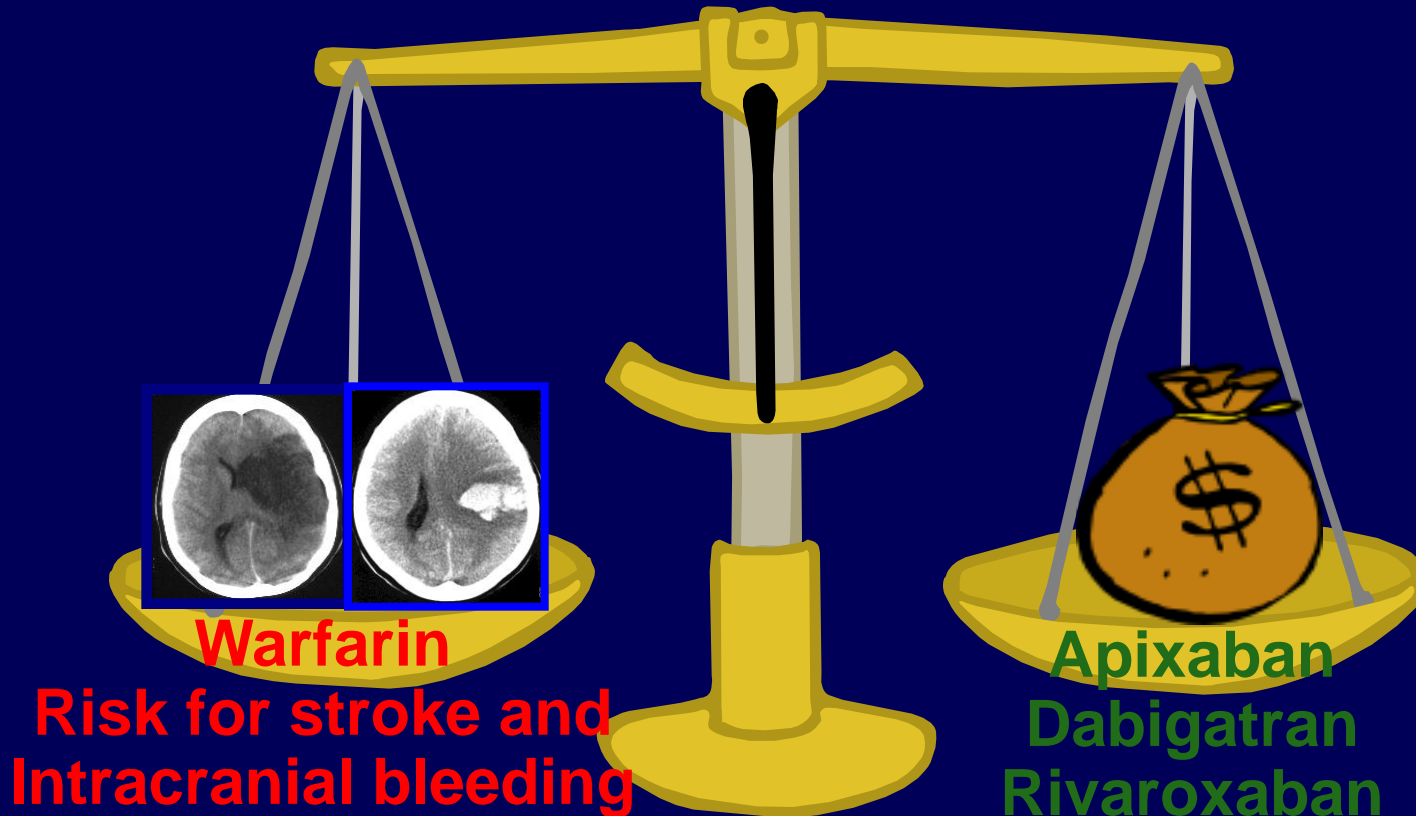
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Noninferiority stroke	√	√	√	√
Reduction hemorrhagic stroke	√	√	√	√
Reduction ischemic stroke	√			
Reduction mortality	(√)			√
Reduction major bleeding		√		√
Increase gastrointestinal bleeding	√		√	
Increase myocardial infarction	(√)	(√)		

New anticoagulants compared to warfarin in AF 2011

Effet on outcome event	D150	D110	Riva	Apix
Noninferiority stroke	√	√	√	√
Reduction hemorrhagic stroke	√	√	√	√
Reduction ischemic stroke	√			
Reduction mortality	(√)			√
Reduction major bleeding		√		√
Increase gastrointestinal bleeding	√		√	
Increase myocardial infarction	(√)	(√)		
Fewer treatment discontinuations				√
Validation in a second randomized trial				√

Three new anticoagulants superior to Warfarin for prevention of stroke and intracranial bleeding in AF available 2011



side effects e.g. other bleedings

Survival

Patient preferences

Health economy