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Old and New Anticoagulants For Stroke Prevention

Benefits and Risks

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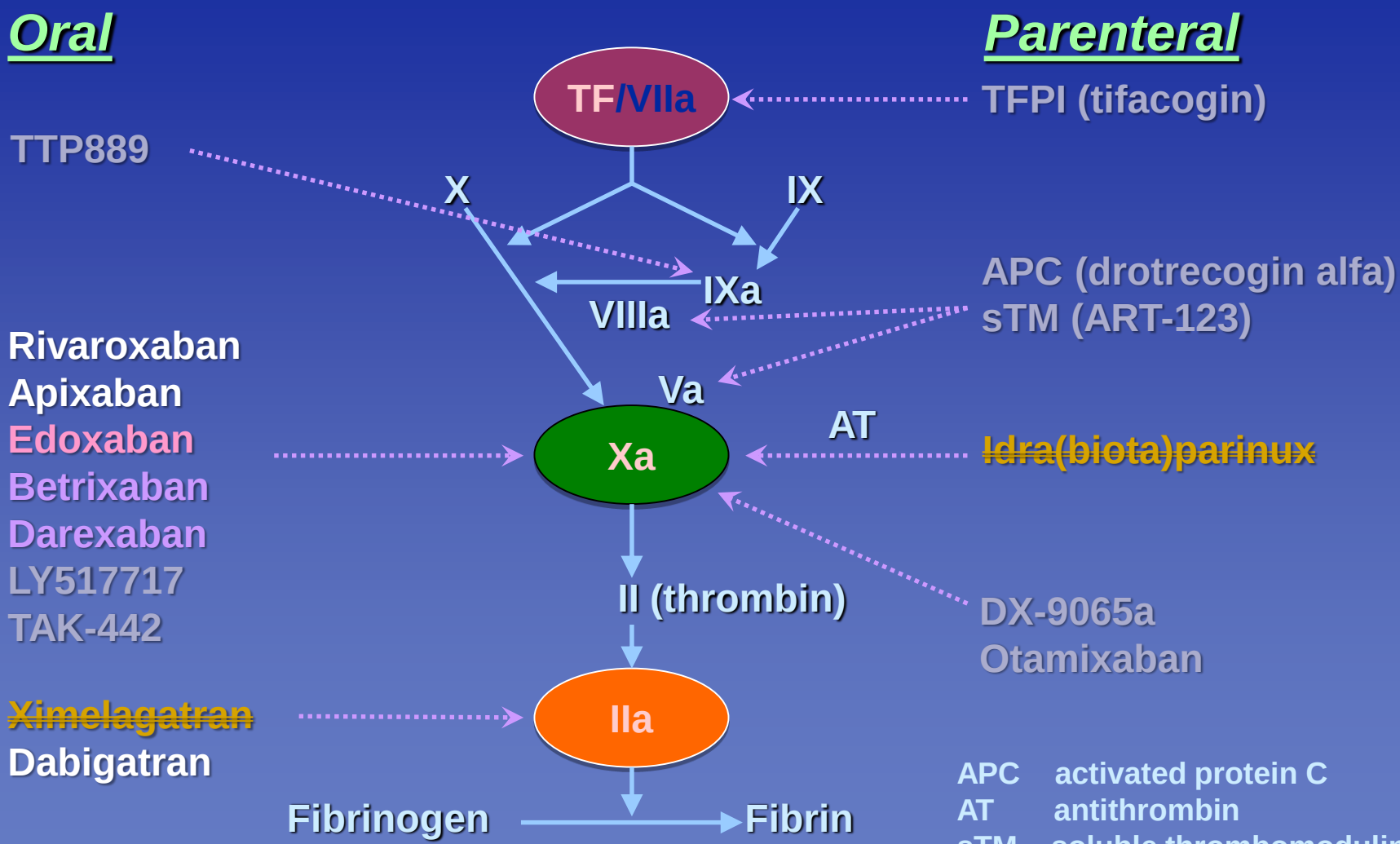
Disclosure

Relationships with Industry

Consulting fees from the following companies involved in developing anticoagulant drugs and device-based strategies for thromboembolism prevention:

- **Bayer HealthCare**
- **Biotronik**
- **Boehringer Ingelheim**
- **Boston Scientific**
- **Daiichi Sankyo**
- **Janssen**
- **Johnson & Johnson**
- **Medtronic**
- **Sanofi-Aventis**

Targets for New Anticoagulants



APC activated protein C
AT antithrombin
sTM soluble thrombomodulin
TF tissue factor
FPI tissue factor pathway inhibitor

Adapted from Weitz JI, Bates SM. *J Thromb Haemost* 2005; 3:1843
Turpie AGG. *Eur Heart J* 2007; 29,155
Guertin KR, Choi YM. *Curr Med Chem* 2007; 14:2471

"New" Oral Anticoagulants

Phase III Trials for Stroke Prevention in Patients with AF

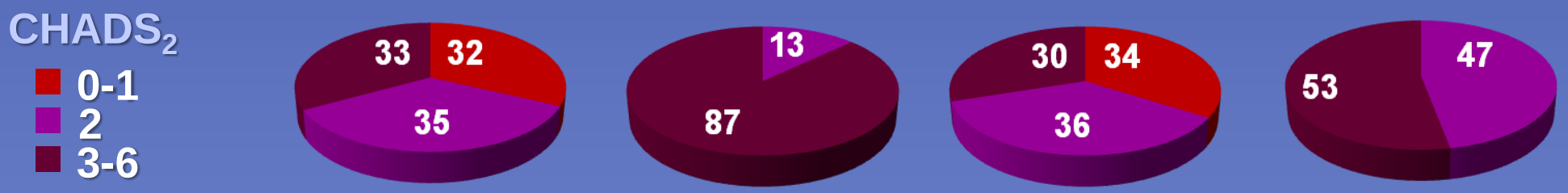
Trial Acronym	Drug	Dose (mg)	Design	n	Risk Factors (#)	Dose adjustment
RE-LY	Dabigatran	150 bid 110 bid	PROBE	18,113	1	None
ROCKET-AF	Rivaroxaban	20 qd 15 qd*	Blinded	14,264	≥ 2	21% at baseline
ARISTOTLE	Apixaban	5 bid 2.5 bid*	Blinded	18,206	≥ 1	5% at baseline
ENGAGE-AF	Edoxaban	60 qd 30 qd*	Blinded	21,105	≥ 2	25% at baseline >9% after

* Adjusted based on renal function or other factors associated with reduced drug clearance

Trials of NOACs for AF

Clinical Characteristics and Stroke Risk Factors

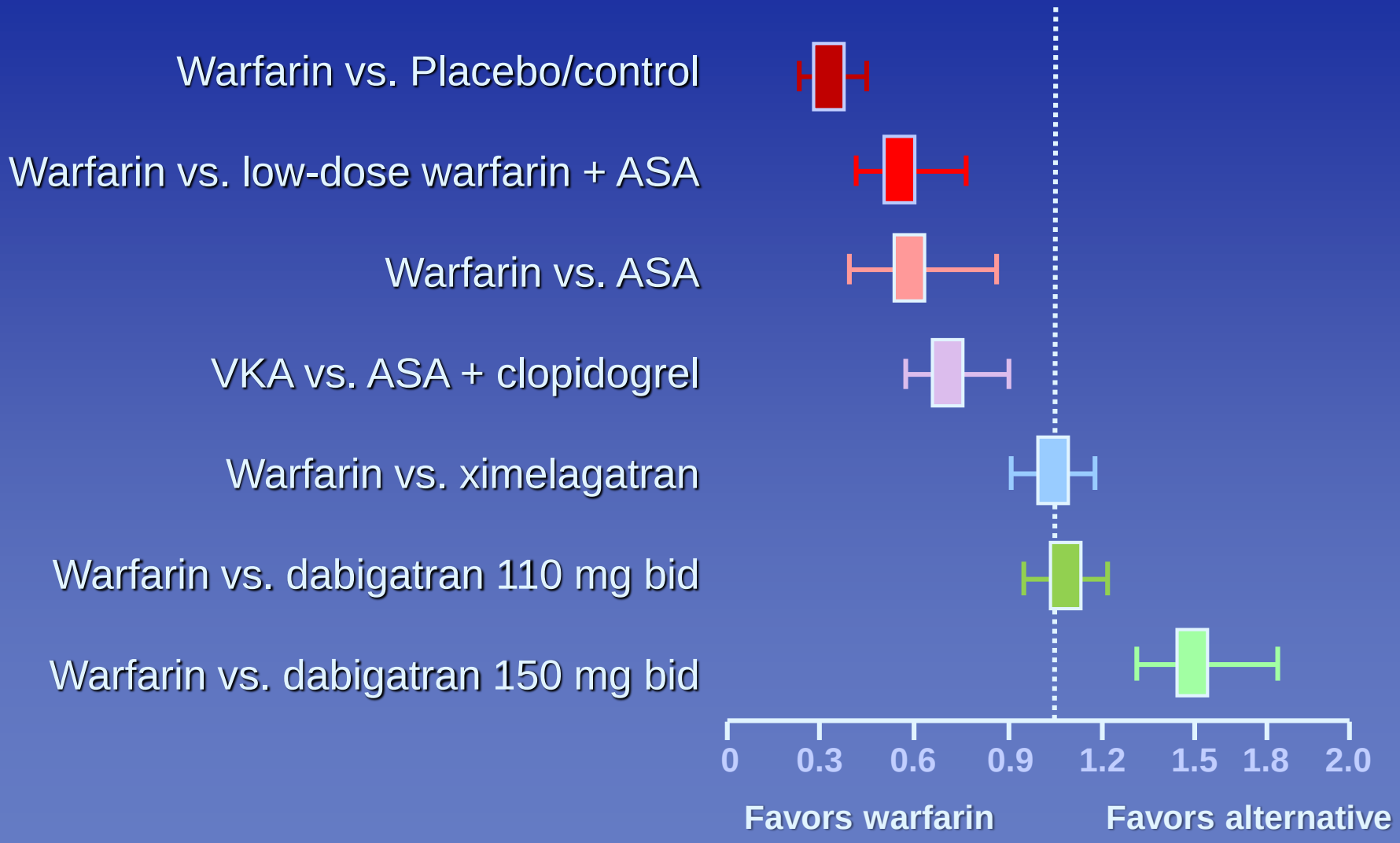
	RE-LY (Dabigatran)	ROCKET-AF (Rivaroxaban)	ARISTOTLE (Apixaban)	ENGAGE AF (Edoxaban)
# Randomized	18,113	14,264	18,206	21,105
Age, years	72 ± 9	73 [65-78]	70 [63-76]	72 [64-78]
Female, %	37	40	35	38
Paroxysmal AF	32	18	15	25
VKA naive	50	38	43	41
Aspirin use	40	36	31	29



Connolly SJ, et al. *N Engl J Med* 2009;361:1139.
Patel MR, et al. *N Engl J Med* 2011; 365:883.
Granger CB et al. *N Eng J Med* 2011; 365.
Giugliano RP, et al. *N Engl J Med* 2013; 369: 2093.

Relative Risks of Stroke and Systemic Embolism

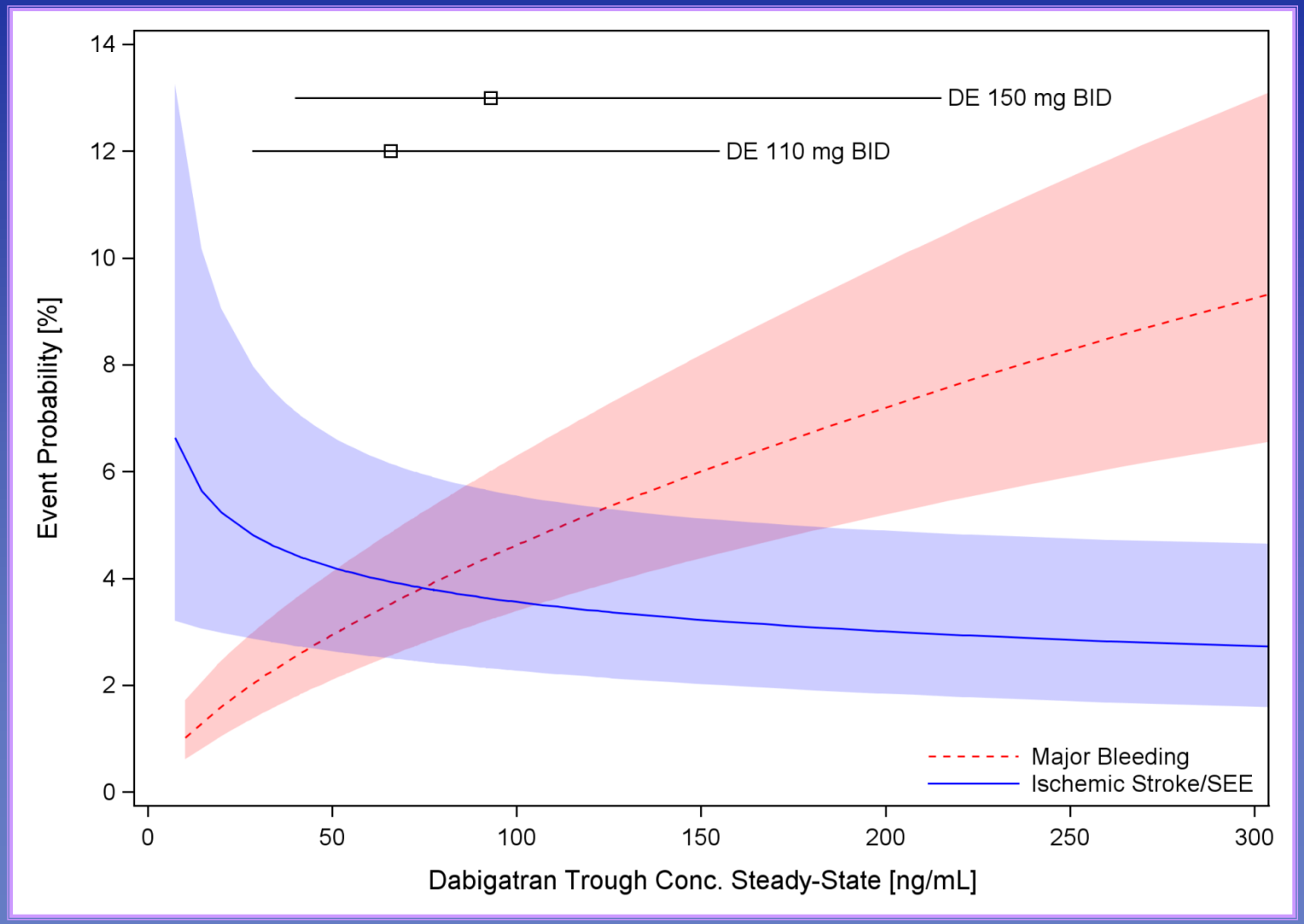
Meta-Analysis



Camm AJ. European Society of Cardiology, Barcelona, August 30 2009.

Ischemic Stroke and Major Bleeding In Relation to Dabigatran Plasma Concentrations

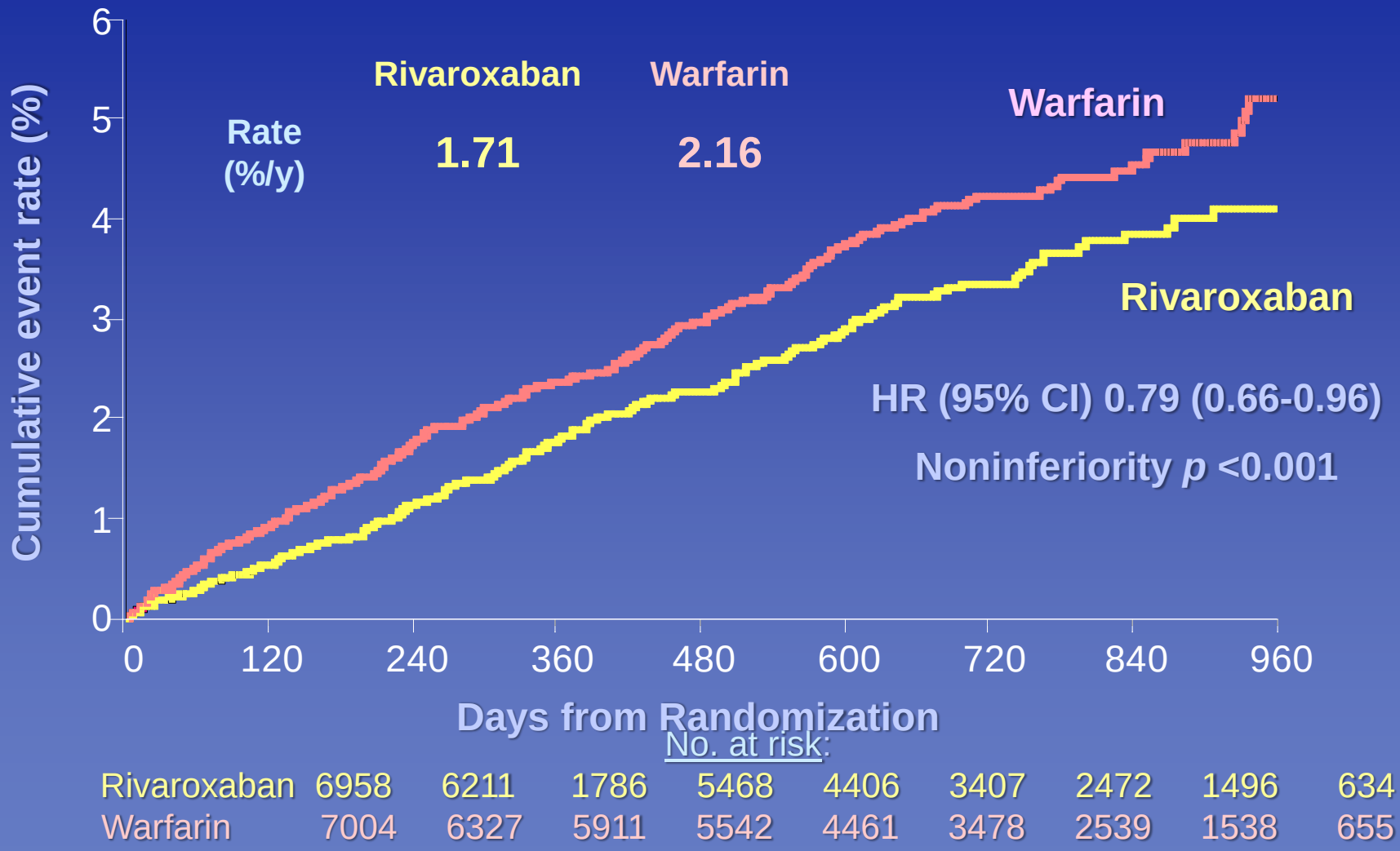
RE-LY Trial



Reilly, P, et al. *J Am Coll Cardiol* 2014; 63: 321.

ROCKET-AF Trial

Stroke and Systemic Embolism



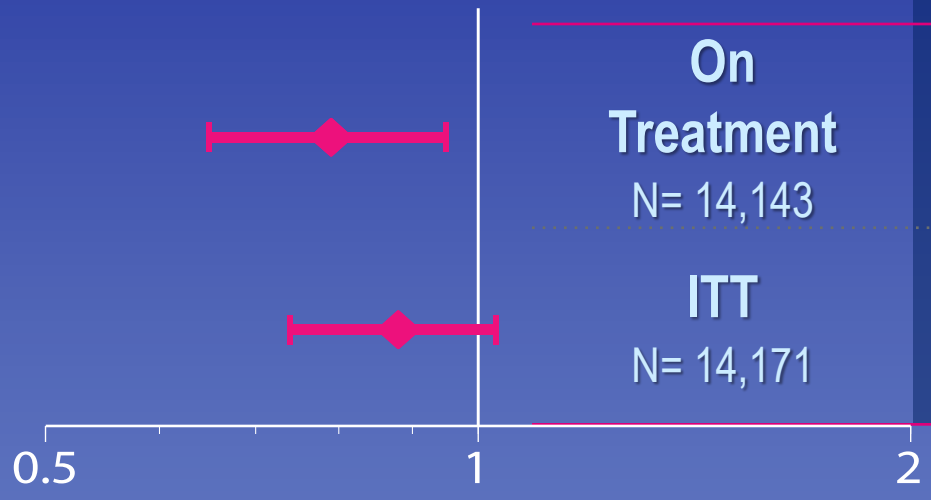
No. at risk:

Rivaroxaban	6958	6211	1786	5468	4406	3407	2472	1496	634
Warfarin	7004	6327	5911	5542	4461	3478	2539	1538	655

Patel MR, et al. *N Engl J Med* 2011; 365:883.

ROCKET-AF Trial

Stroke and Systemic Embolism



	Rivaroxaban	Warfarin	HR (95% CI)	*p**
	Event Rates (%/year)			
On Treatment N= 14,143	1.7	2.2	0.79 (0.65,0.95)	0.015
ITT N= 14,171	2.1	2.4	0.88 (0.74,1.03)	0.117

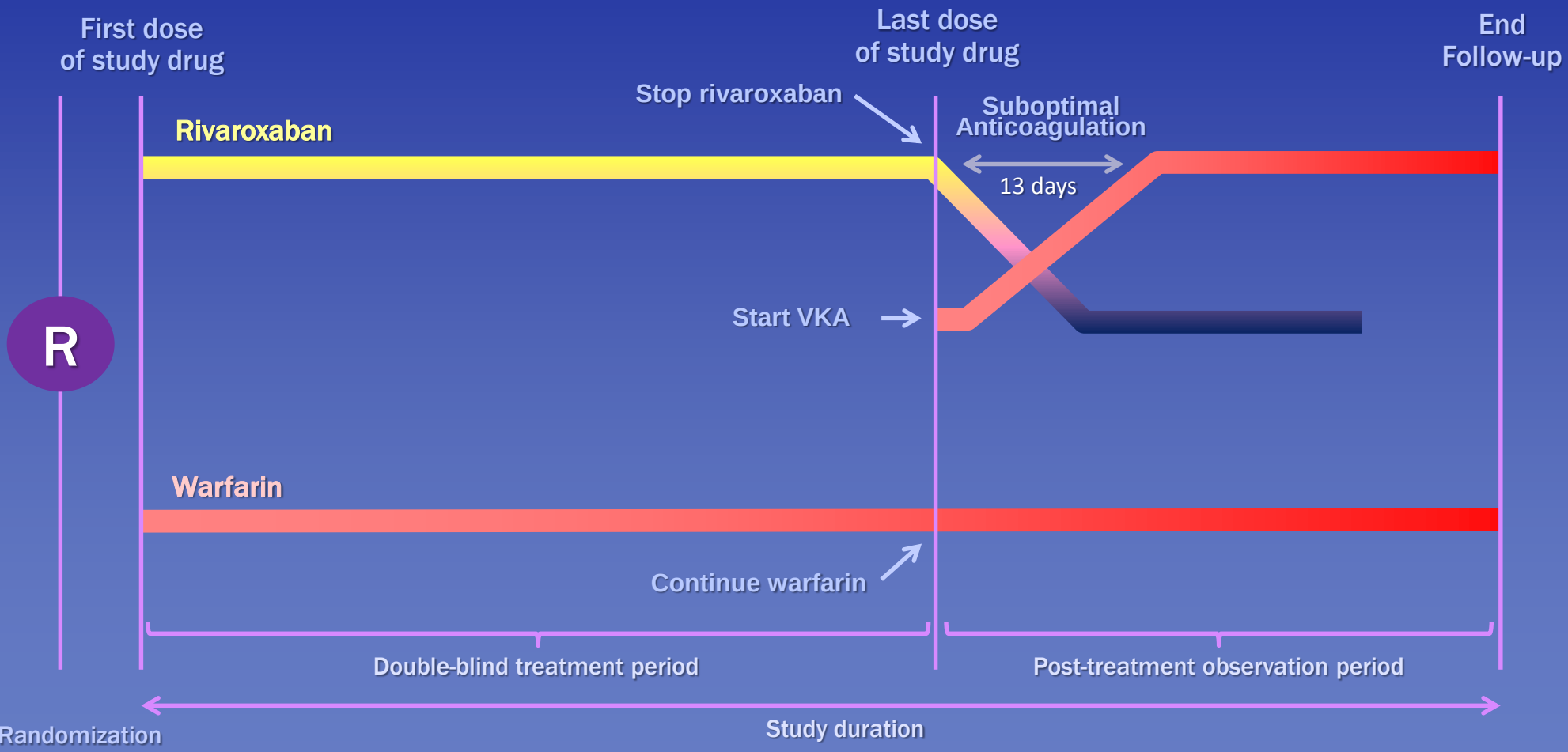
* *p*-values for superiority

Patel MR, et al. *N Engl J Med* 2011; 365:883.

ROCKET-AF Trial

Events During Transition to Open-Label VKA

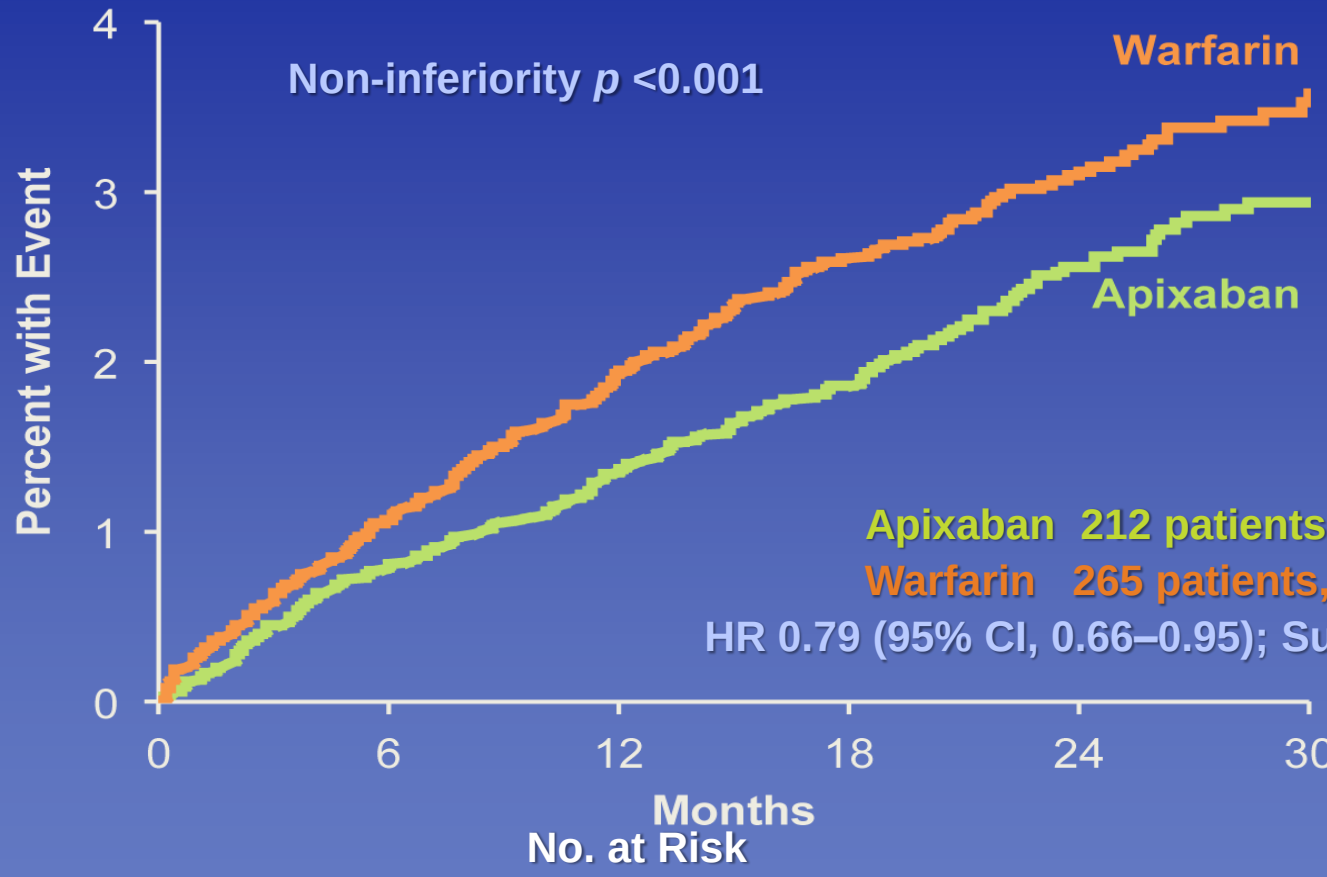
Patients Completing the Study on Treatment



Patel MR, et al. *J Am Coll Cardiol* 2013; 61: 651.

ARISTOTLE Trial

Primary Outcome: All Stroke or Systemic Embolism



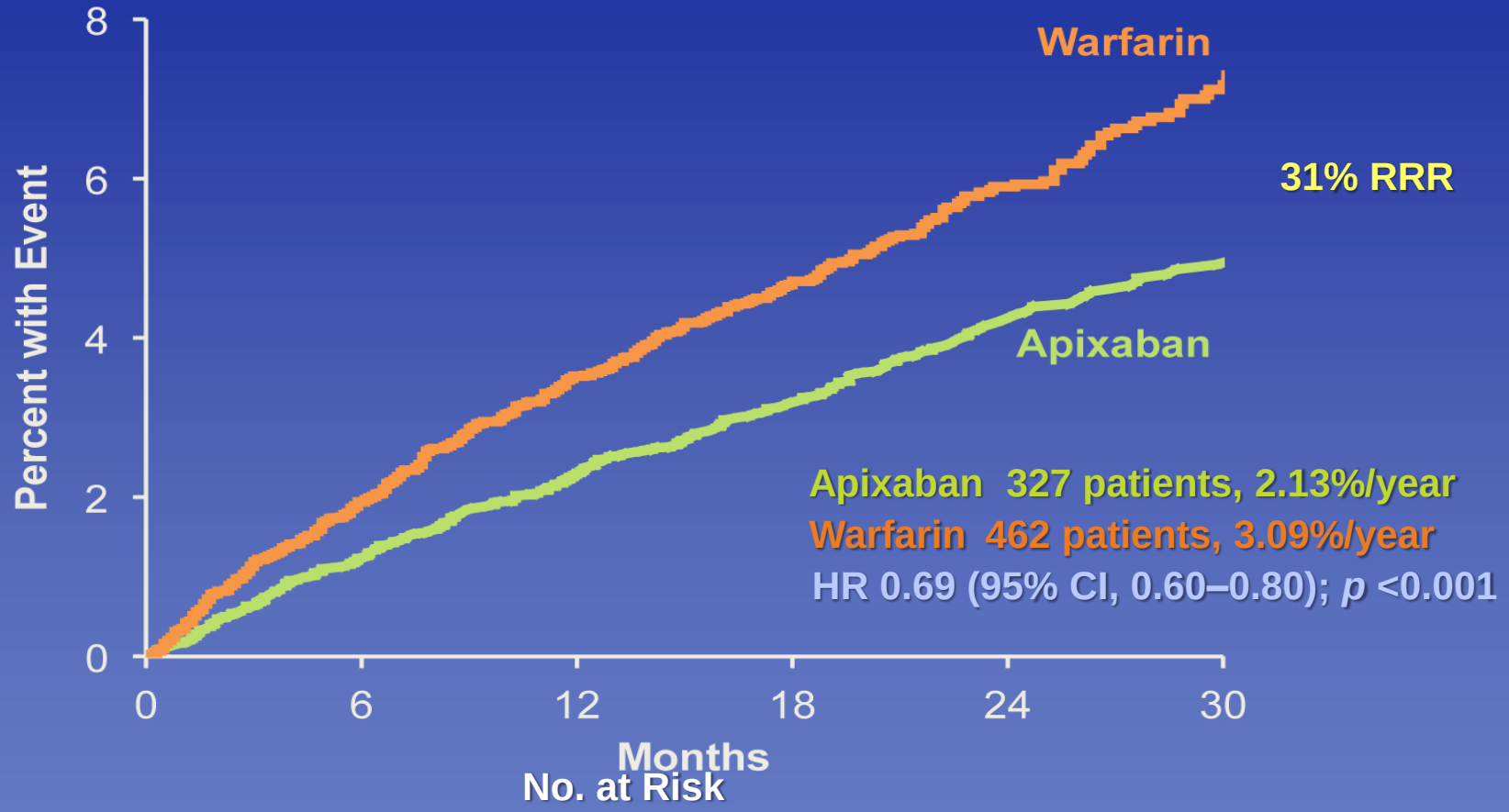
No. at Risk

Warfarin	9081	8620	8301	5972	3405	1768
Apixaban	9120	8726	8440	6051	3464	1754

Granger CB et al. *N Engl J Med* 2011; 365

ARISTOTLE Trial

Major Bleeding Events



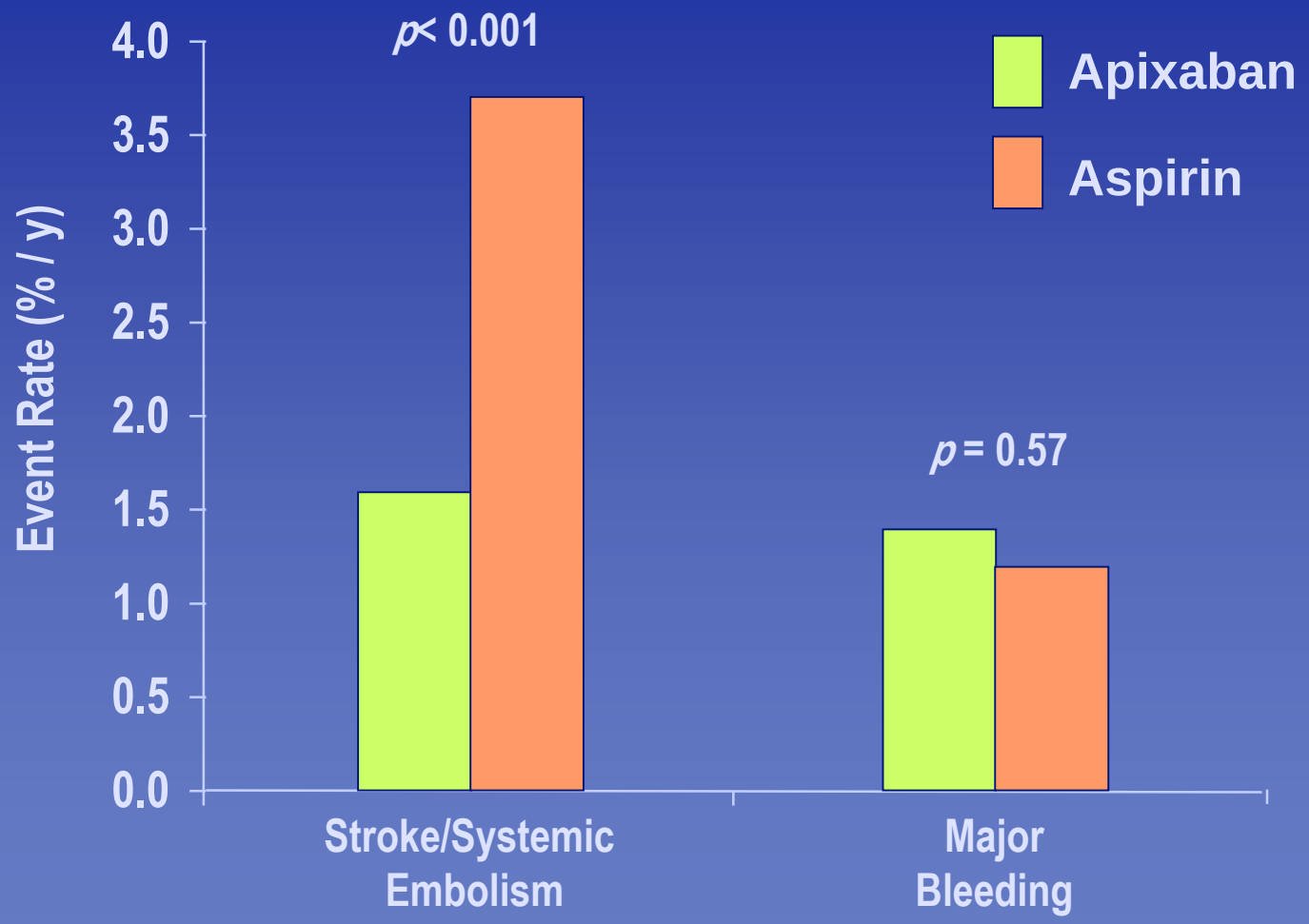
No. at Risk

Warfarin	9052	7910	7335	5196	2956	1491
Apixaban	9088	8103	7564	5365	3048	1515

Granger CB et al. *N Engl J Med* 2011; 365

Apixaban vs. Aspirin: The AVERROES Trial

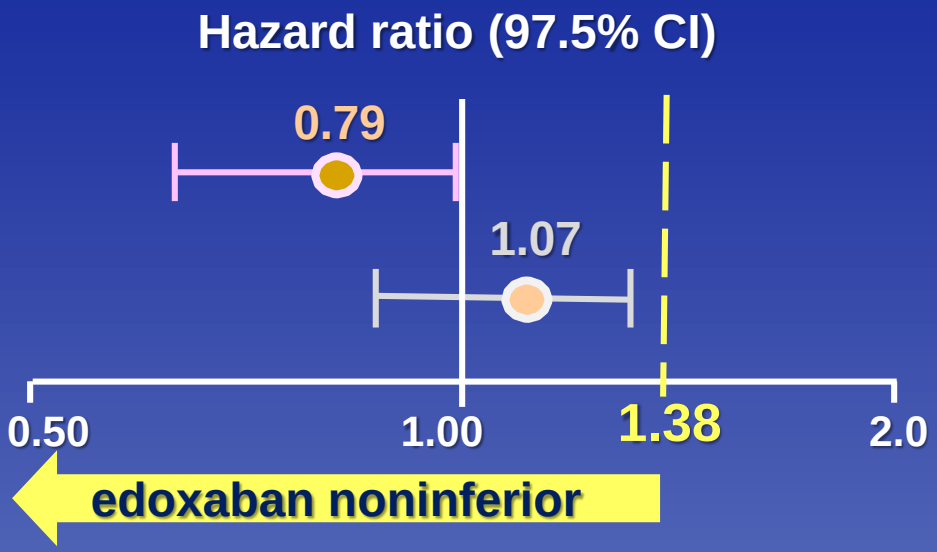
Efficacy and Safety Event Rates



Connolly S. *N Engl J Med* 2011; 364: 806.

ENGAGE AF TIMI-48 Trial

Primary Endpoint Stroke + Systemic Embolism



Edoxaban 60* mg QD vs warfarin

Edoxaban 30* mg QD vs warfarin

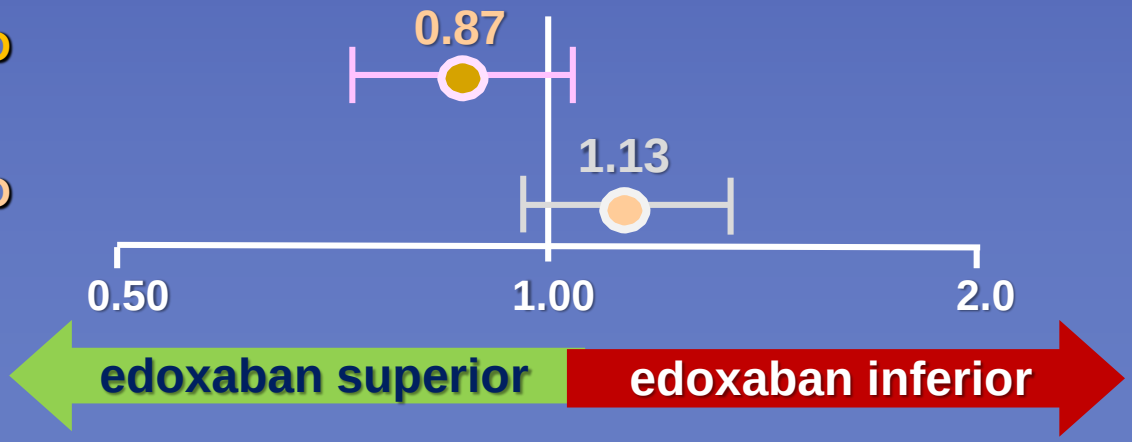
Warfarin TTR 68.4%

Non-inferiority

(mITT, on-treatment)

***p* <0.0001**

***p* = 0.005**



Edoxaban 60* mg QD vs warfarin

Edoxaban 30* mg QD vs warfarin

Superiority

(ITT, Overall)

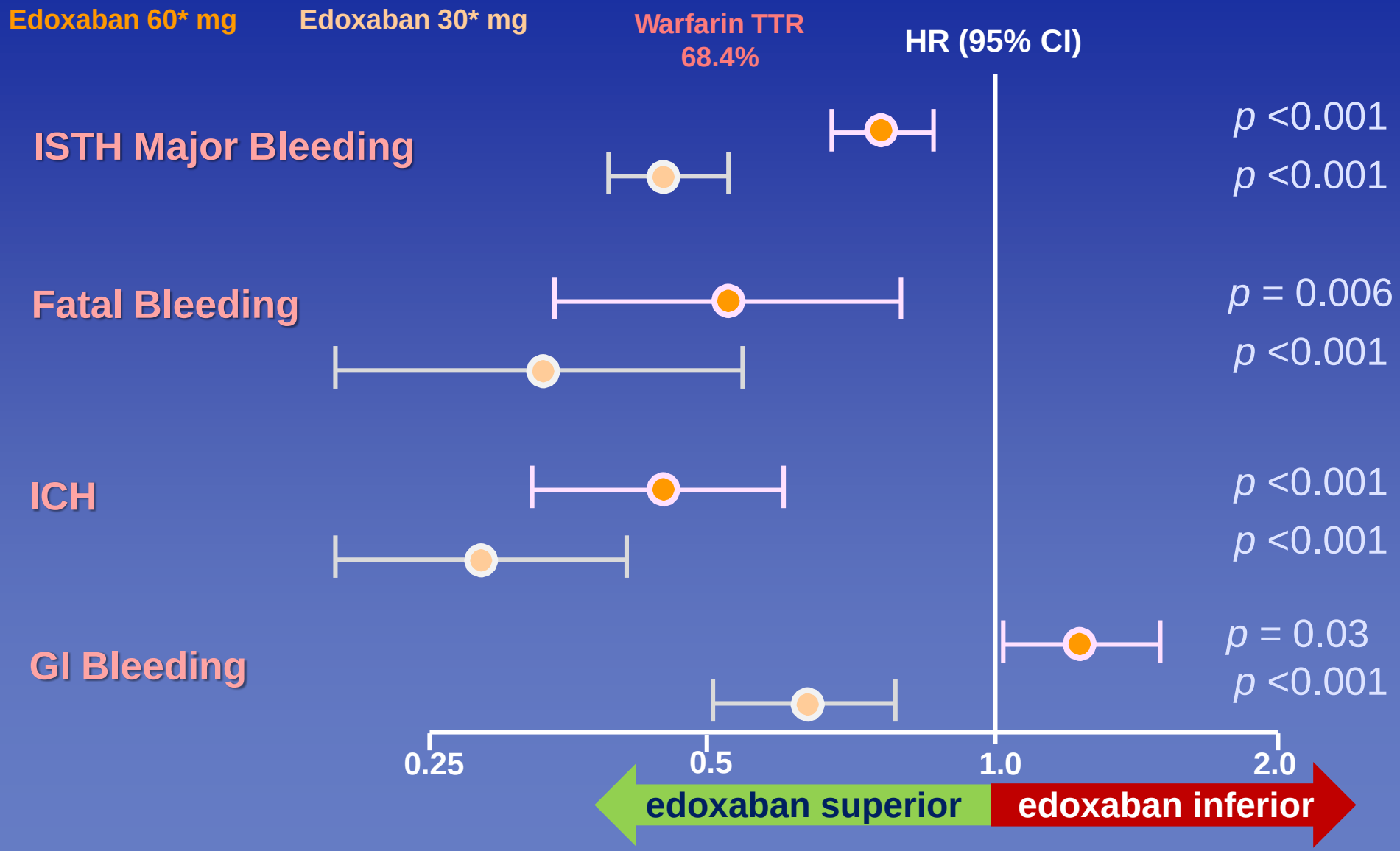
***p* = 0.08**

***p* = 0.10**

Giugliano RP, et al. *N Engl J Med* 2113; 369: 2093.

ENGAGE AF TIMI-48 Trial

Safety Outcome: Bleeding On Treatment



Giugliano RP, et al. *N Engl J Med* 2113; 369: 2093.

Nonvalvular Atrial Fibrillation
A Moving Target?

Original warfarin trials excluded:

- Rheumatic heart disease (mitral stenosis)
- Prosthetic heart valves (mechanical or biological)
- Valve repair (rare, not considered)
- Thyrotoxicosis
- Self-limited AF due to acute illness or surgery

Identifying Patients with Nonvalvular AF

Valvular Disease Exclusion Criteria in Trials of NOACS

Trial	Excluded Valvular Diseases
SPORTIF III & V	Mitral stenosis or previous valvular heart surgery
RE-LY	Hemodynamically relevant valve disease or prosthetic valve
ROCKET AF	Mitral stenosis or prosthetic heart valve
AVERROES	Valvular disease requiring surgery or mechanical prosthetic heart valve
ARISTOTLE	Moderate or severe mitral stenosis or prosthetic heart valve requiring anticoagulation
ENGAGE AF	Moderate or severe mitral stenosis or mechanical heart valve. (Patients with bioprosthetic heart valves or valve repair could be included.)

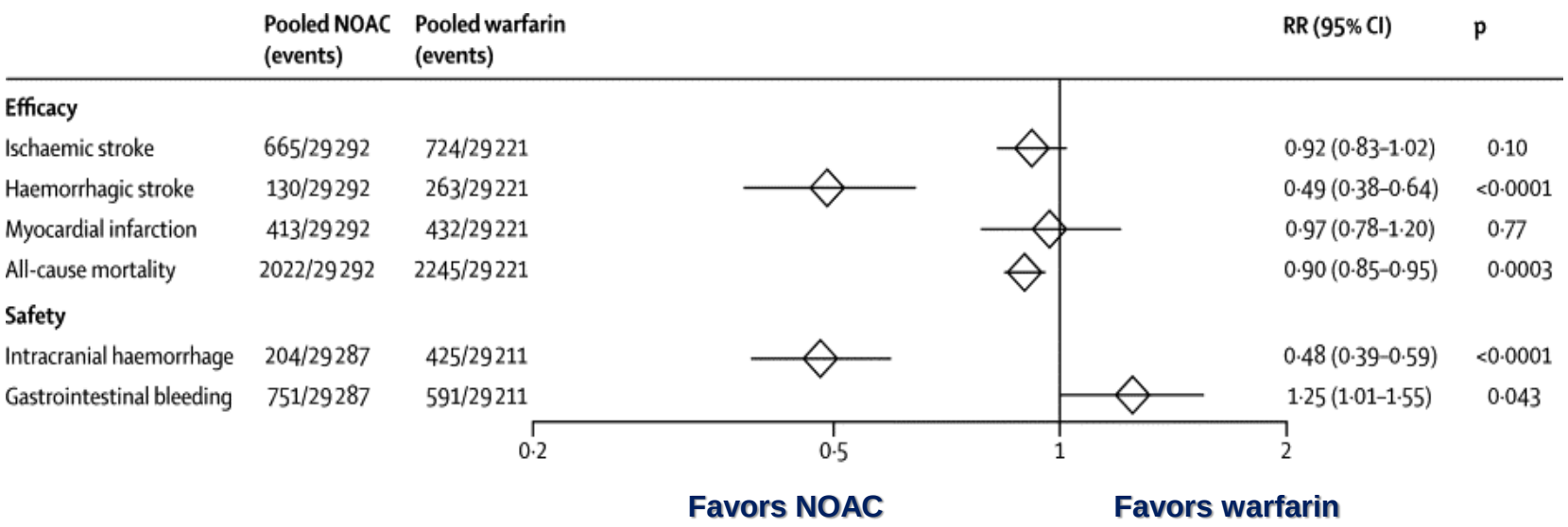
Newer Oral Anticoagulants for AF

Key Similarities

- All are noninferior to warfarin for prevention of total stroke and systemic embolism
- All reduce the risk of intracerebral hemorrhage
- Outcomes of major bleeding are generally better than with warfarin
- Reductions in mortality are comparable, ~10%/year, mainly related to lower rates of cardiovascular death and fatal bleeding.

Meta-analysis of NOACs vs. Warfarin in Non-valvular AF

Secondary Efficacy and Safety Outcomes



Ruff CT, et al. *Lancet* 2014; 383; 955.

Newer Anticoagulants for AF
Inferences from the Pivotal Trials

- Differences in outcomes may be due to variations in study design, sample size, intrinsic risk, concurrent treatment and other factors, rather than the drugs themselves.
- In the doses approved for use in the U.S., factor Xa inhibitors may have less efficacy against ischemic stroke than dabigatran but also less toxicity.
- Factor Xa inhibitors are less dependent on renal elimination and have fewer GI side effects than dabigatran.

Target-Specific Oral Anticoagulants for AF

Areas of Uncertainty Requiring Further Study

- Patients with AF undergoing PCI or CABG
- Cardioversion of AF
- Catheter ablation, Maze or intra-operative cryoablation
- Device-detected AF
- Bioprosthetic heart valves
- Valve repair
- Prior hemorrhagic stroke

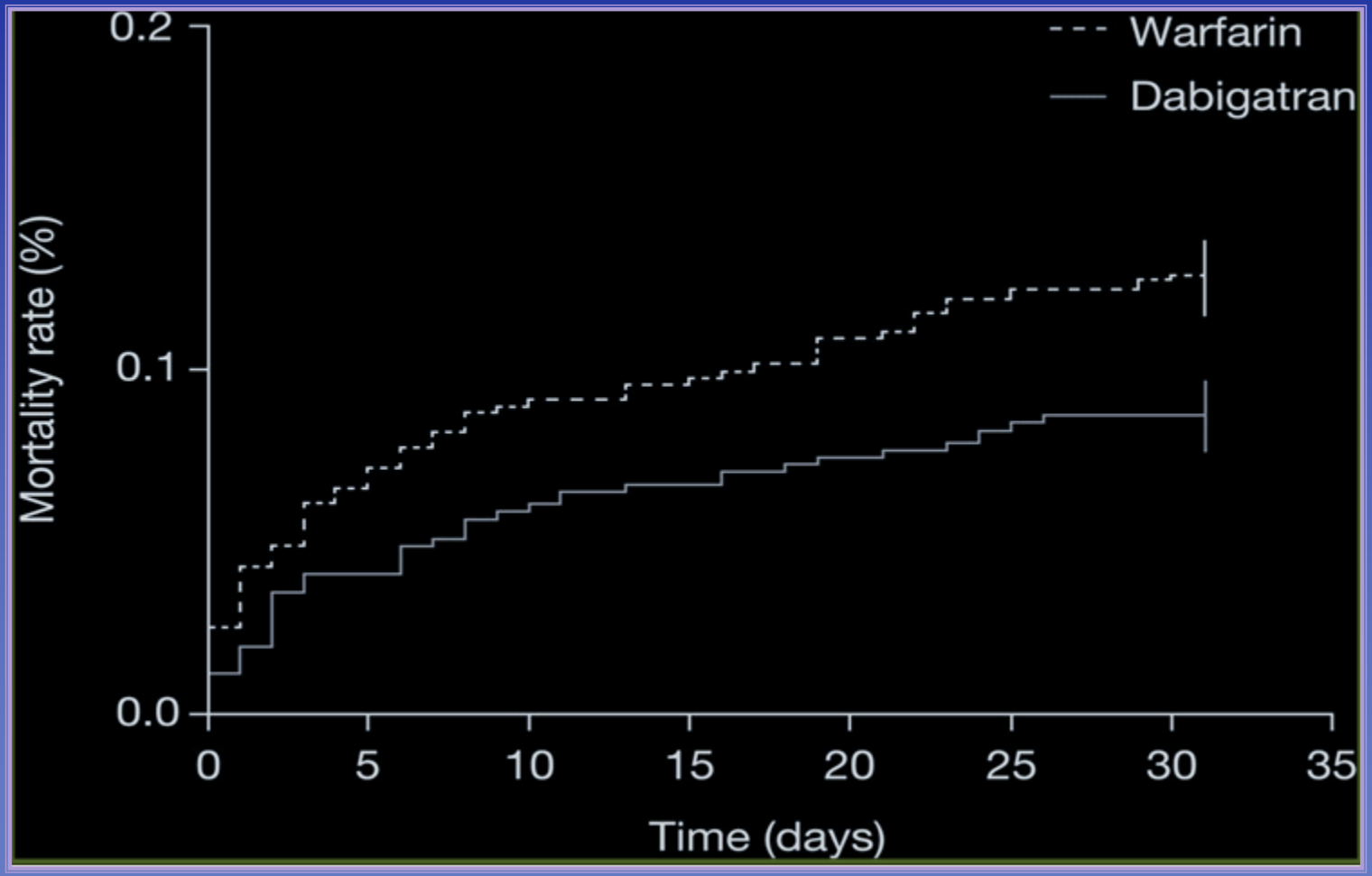
Common Concerns about the NOACs

- How to choose between VKA and NOAC – which NOAC to select?
- Lack of monitoring – insecurity about dosing and adherence
- No simple spot-checks – “need-to-know” occasions
- Short half-lives – concern about missed doses
- No antidotes yet – how to manage major bleeding?
- Drug-drug interactions – under- and over-dosing
- Clinical development incomplete – *e.g.,* cardioversion, ablation, PCI
- Contraindications – valvular AF
- Need to monitor renal and hepatic function
- Expense for health care systems and patients

Modified from Camm AJ, American Heart Association Scientific Sessions, Dallas, TX, November 2013

Outcomes of Major Bleeding During Treatment with Dabigatran or Warfarin

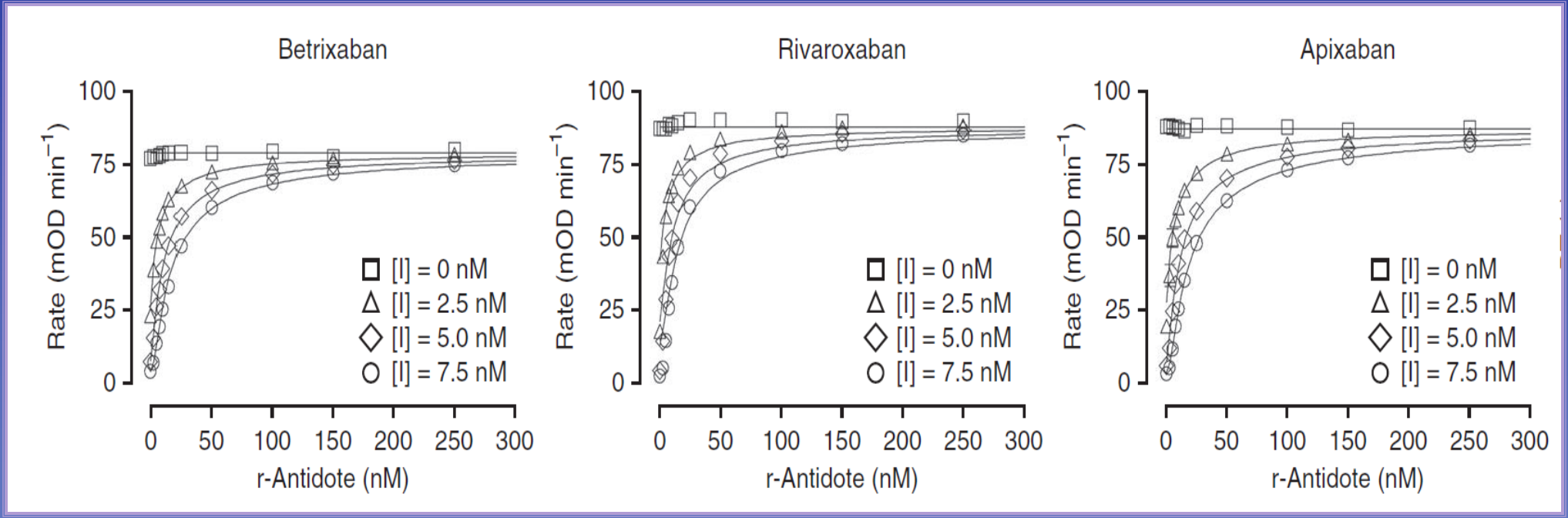
1,034 Patients, 1,121 Major Bleeds in 5 Phase III Trials



Majeed A, et al. *Circulation* 2013; 128: 2325.

Reversal of the Anticoagulant Effect of Factor Xa Inhibitors

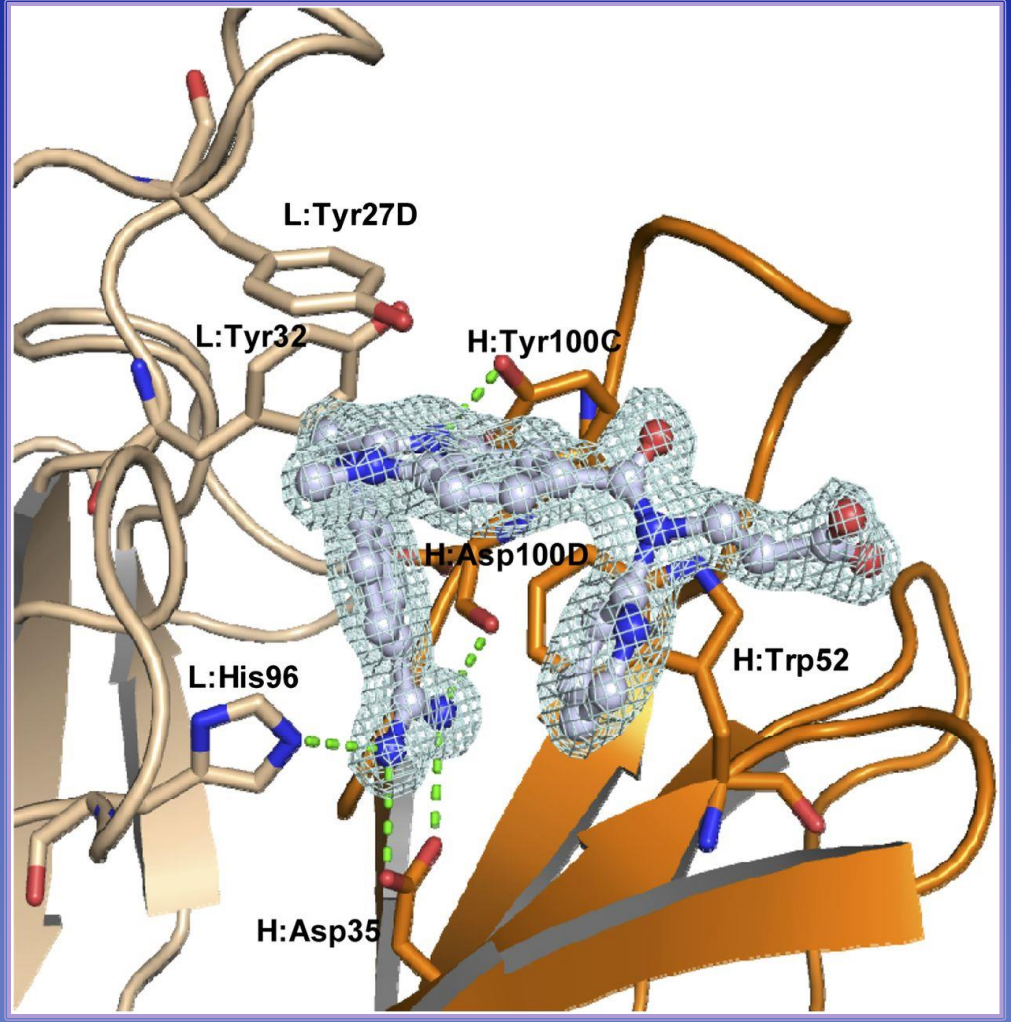
Dose-Dependent Action of Recombinant Andexanet alfa (PRT064445) On fXa Suppression by Betrixaban, Rivaroxaban or Apixaban

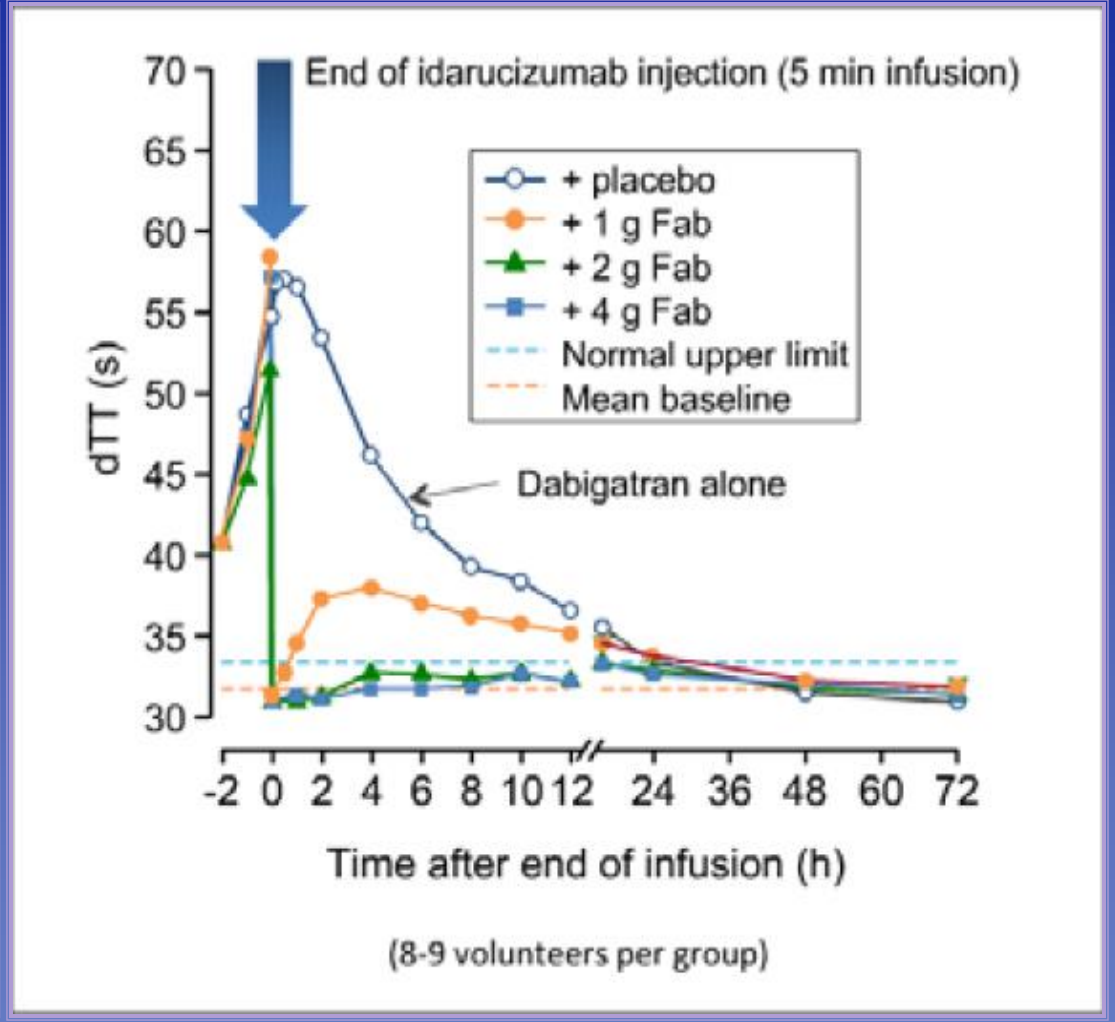


Lu G, et al. *Nature Med* 2013: 19: 446.

Development of a Specific Dabigatran Antidote

aDabi-Fab Binding and Reversal of the Anticoagulant Effect





Millar CM, Lane DA. *Blood* 2013; *121*:3543.
Schiele F, et al. *Blood* 2013; *121*:3554.

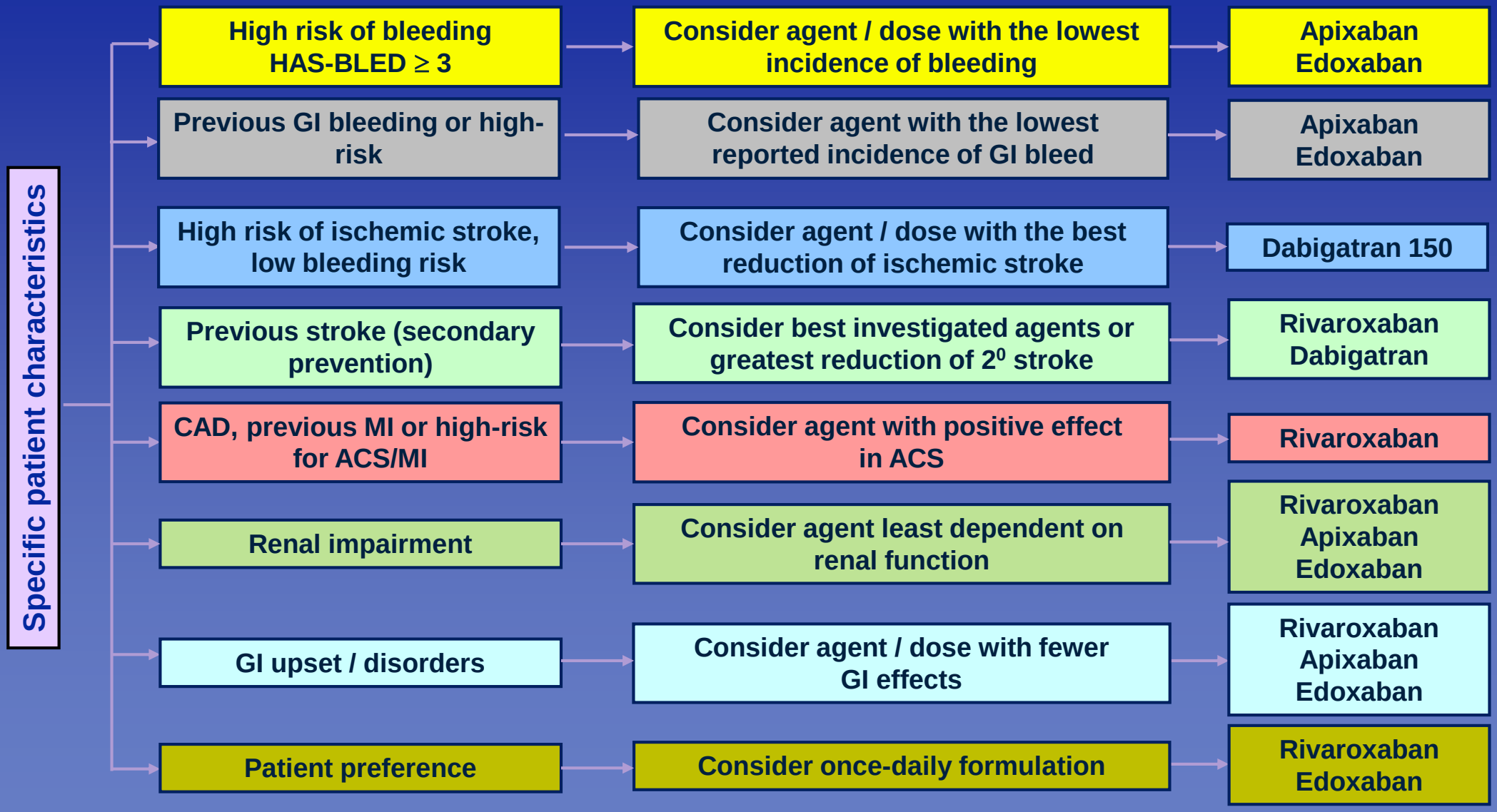
van Ryn J, et al. *Circulation* 2013 Suppl A-17765.

Summary of Phase III NOAC Trial Results

Outcomes *vs.* warfarin		Dabigatran 150 mg bid	Rivaroxaban	Apixaban	Edoxaban 60 mg qd
↓	Stroke/systemic embolism	Superiority	Non-inferiority	Superiority	Non-inferiority
↓	Stroke	Yes	No	Yes	Yes
↓	Ischemic or unspecified Stroke	Yes	No	No	No
↓	Hemorrhagic stroke	Yes	Yes	Yes	Yes
↓	Disabling or fatal stroke	Yes	No	Yes	Yes
↓	Vascular death	Yes	No	No	Yes
↓	All-cause mortality	No	No	Yes	No
↓	Major bleeding	No	No	Yes	Yes
↓	ICH	Yes	Yes	Yes	Yes
↑	GI bleeding	Yes	Yes	No	No
↓	Treatment discontinuation	No	No	Yes	Yes

Modified after Savalieva I, Camm AJ. *Clin Cardiol* 2014; 37: 32

Considerations in NOAC Selection for AF



Modified after Savalieva I, Camm AJ. *Clin Cardiol* 2014; 37: 32


Thank you !