



AMERICAN
COLLEGE of
CARDIOLOGY
FOUNDATION

ACC Special Fellows' Session II

Oral Anticoagulation 2012

*New Oral Anticoagulants for Stroke Prevention
in Patients with Atrial Fibrillation*

October 25, 2012

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MEDICINE



Disclosure

Relationships with Industry

Consulting fees from the following companies involved in development of anticoagulant drugs and device-base thromboembolism prevention strategies:

- Bayer HealthCare
- Biotronik, Inc.
- Boehringer Ingelheim
- Daiichi Sankyo Pharma
- Janssen Pharmaceuticals
- Johnson & Johnson
- Medtronic
- Sanofi-Aventis

Atrial Fibrillation

An Opportunity for Stroke Prevention

Affects ~1% of the population, ~10% of elderly

The number is rising.

4-5%/year stroke rate

The risk may be falling.

12%/year for those with prior stroke

An important opportunity for stroke prevention.

AF-related strokes have worse outcomes

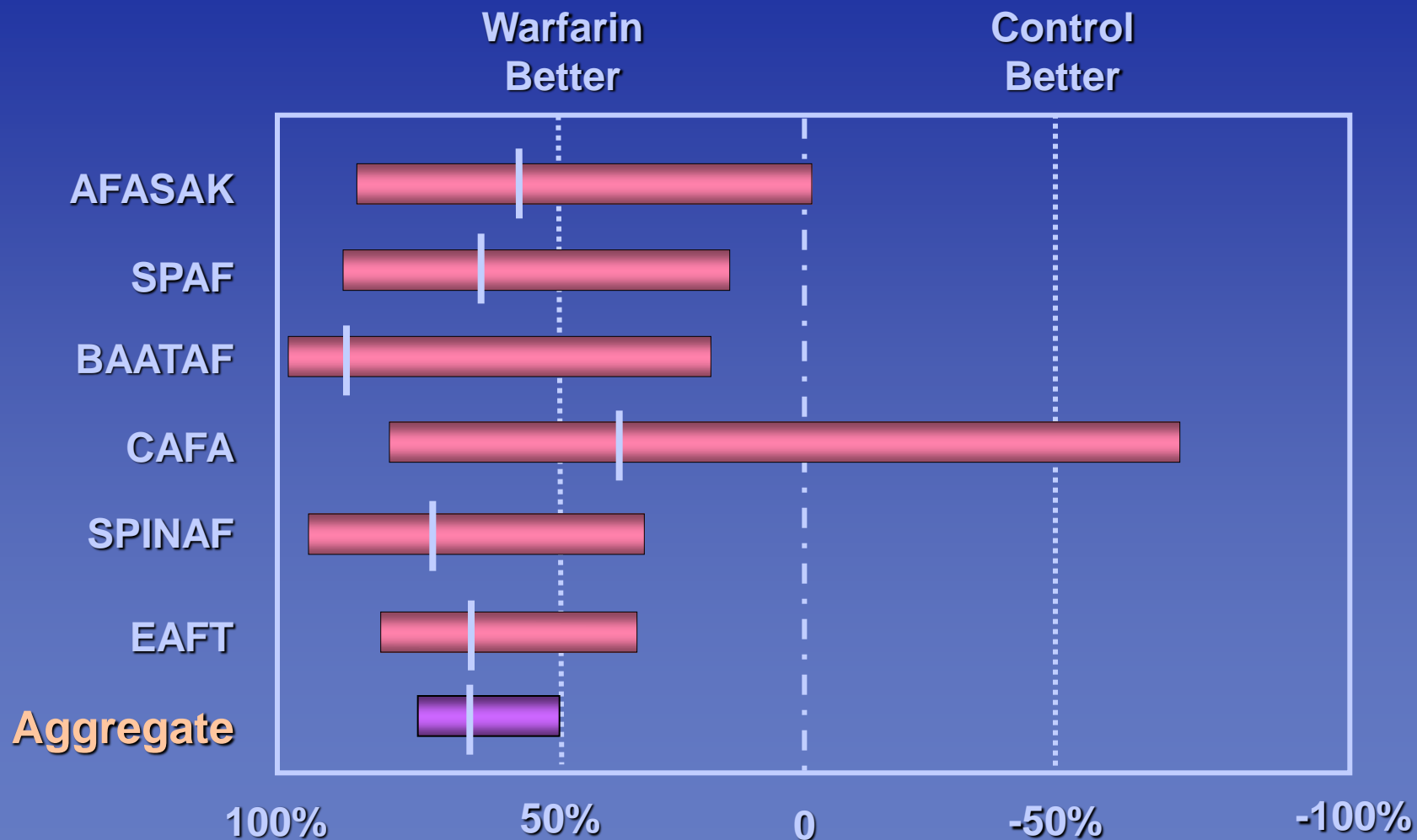
More often fatal or permanently disabling.

\$ billions annual cost for stroke care

Prevention means savings.

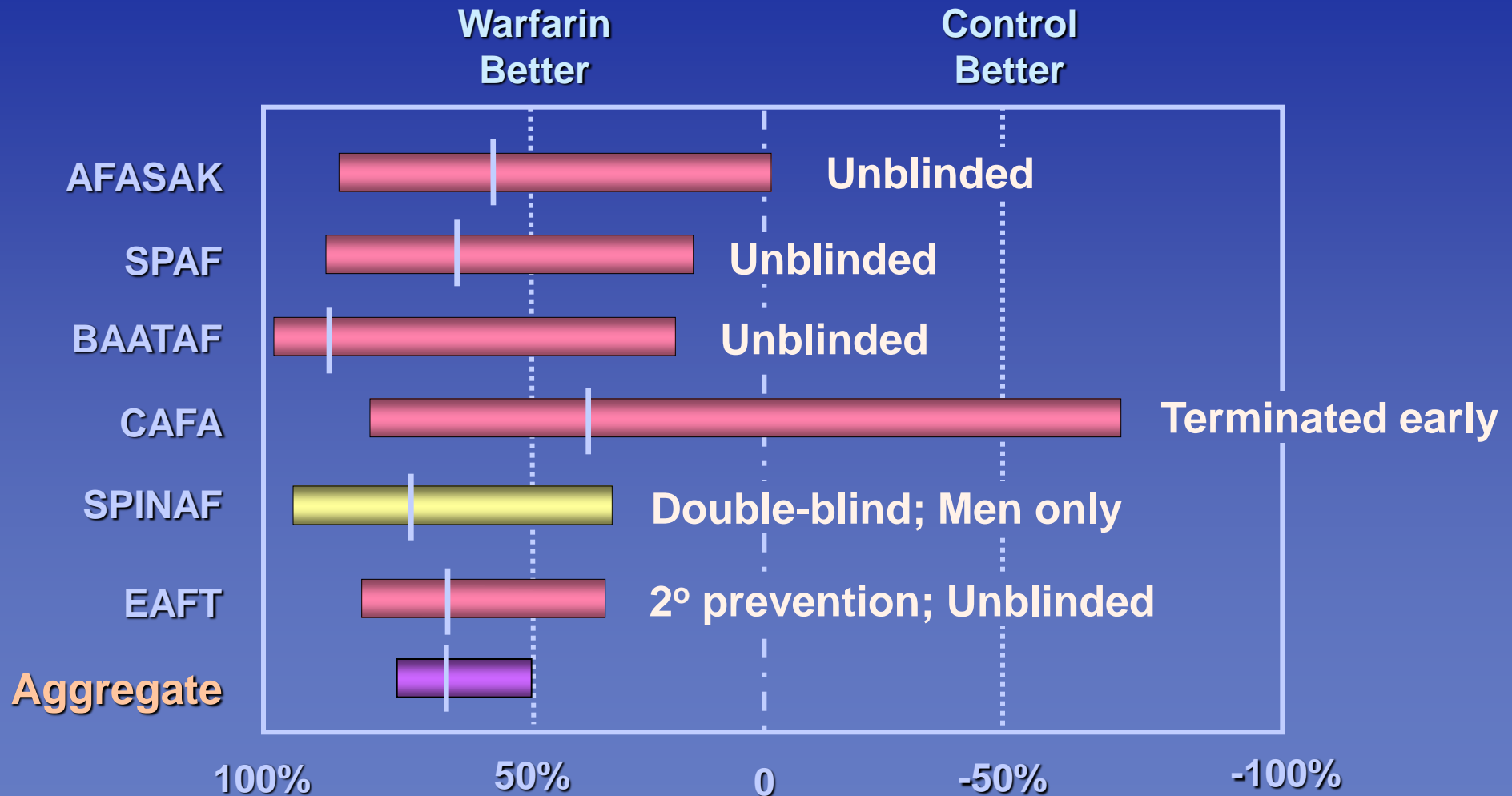
Anticoagulation in Atrial Fibrillation

Stroke Risk Reductions



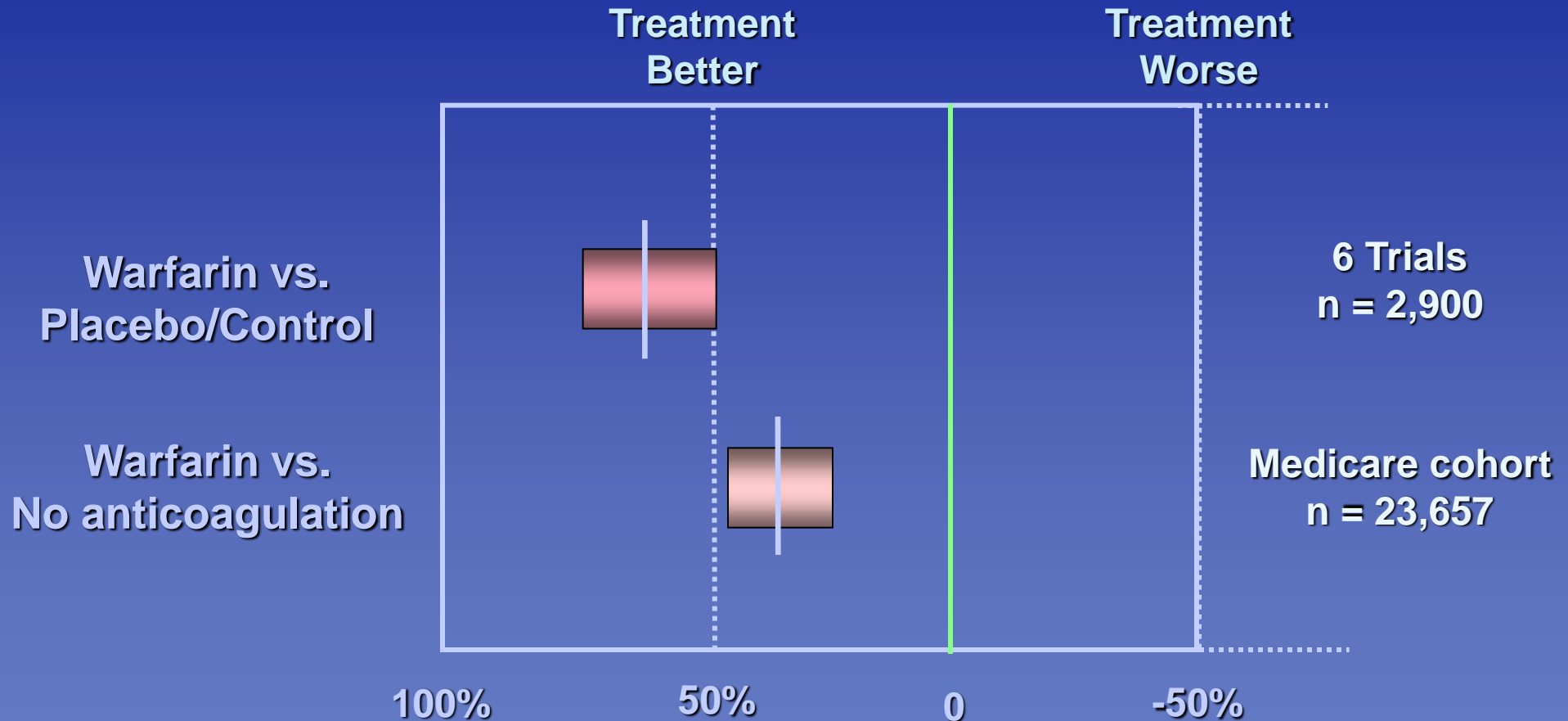
Anticoagulation in Atrial Fibrillation

The Standard of Care for Stroke Prevention

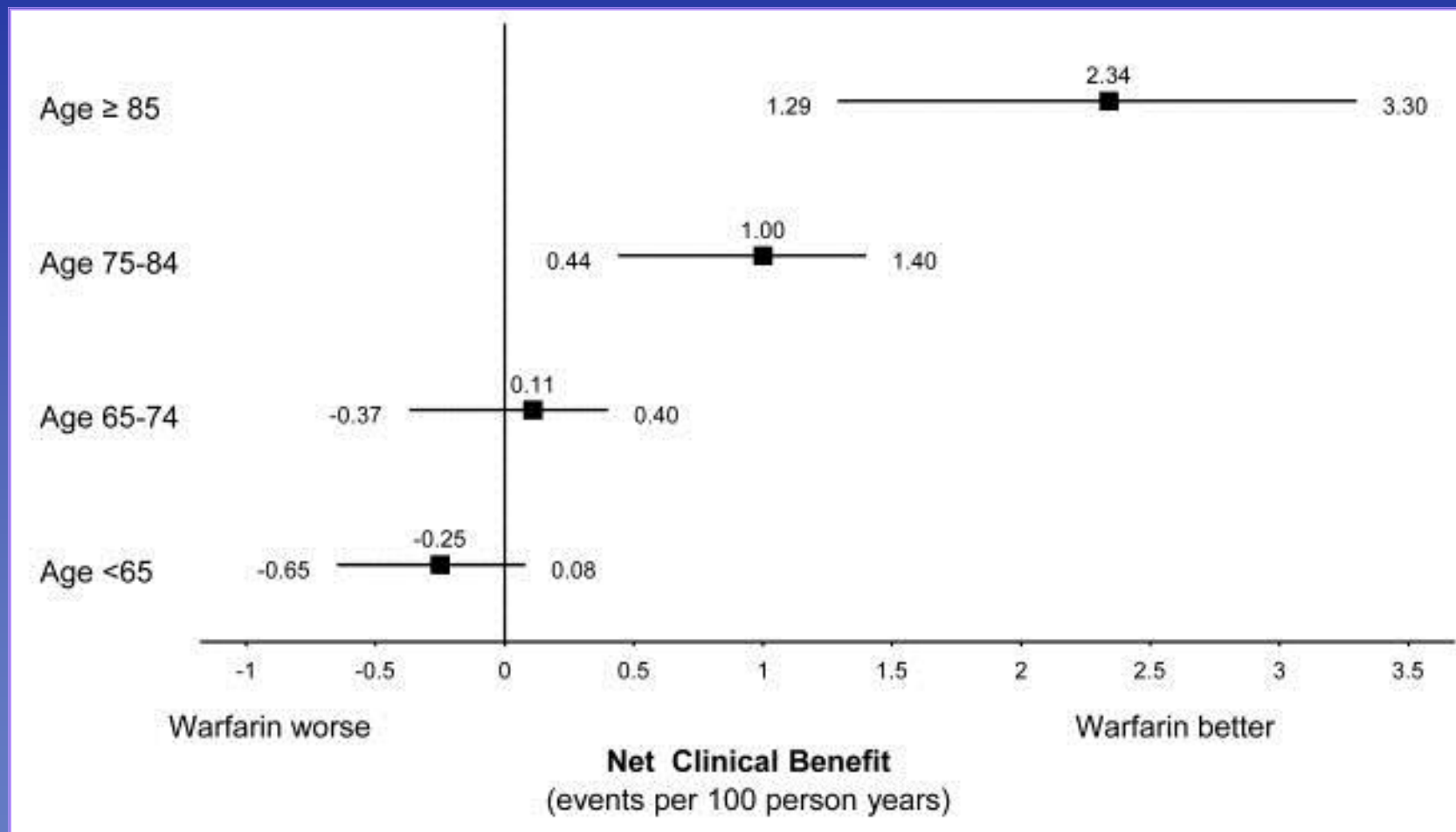


Efficacy of Warfarin in Trials vs. Practice

Stroke Risk Reductions

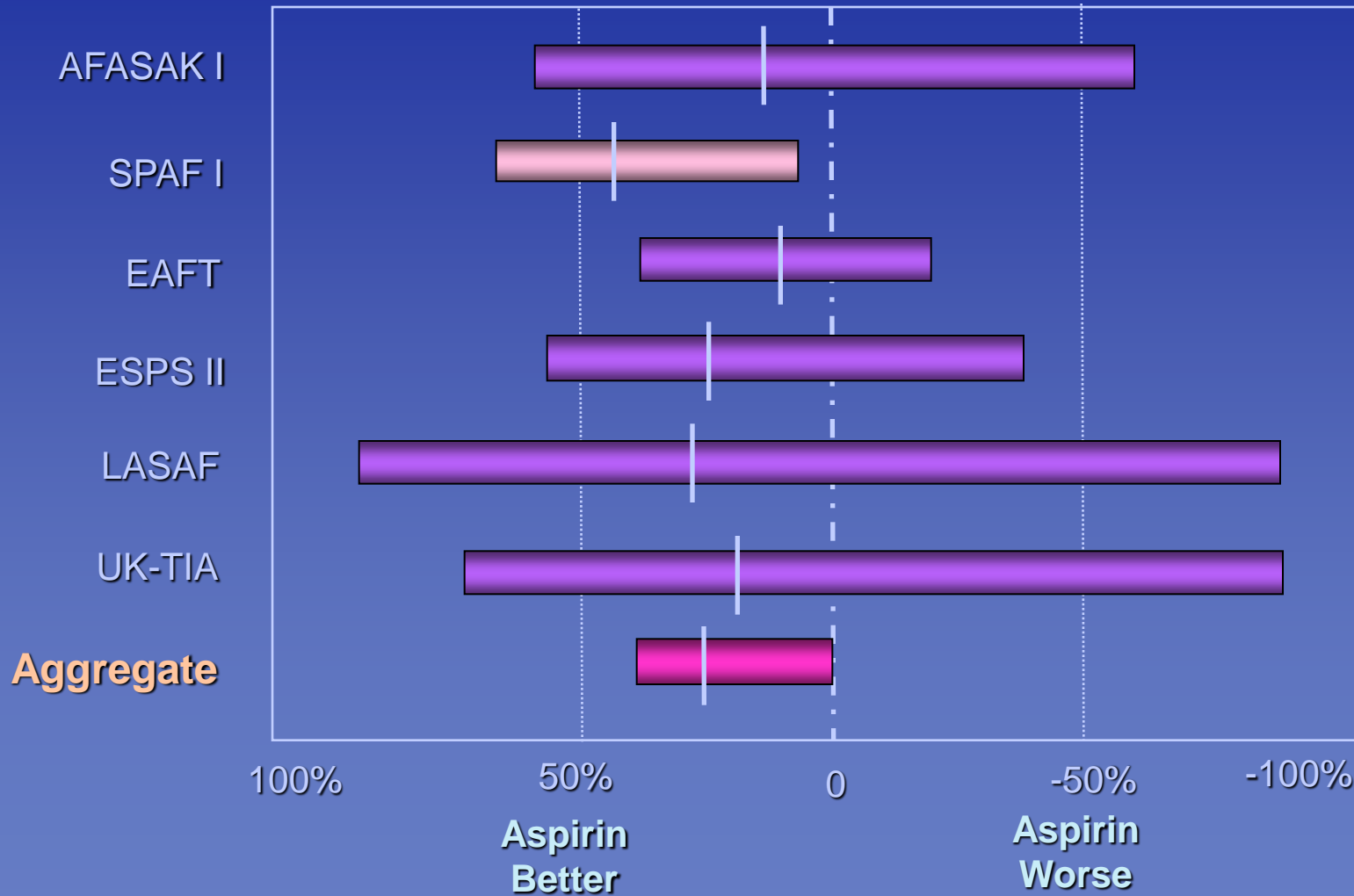


Net Clinical Benefit of Warfarin *Related to Patient Age*



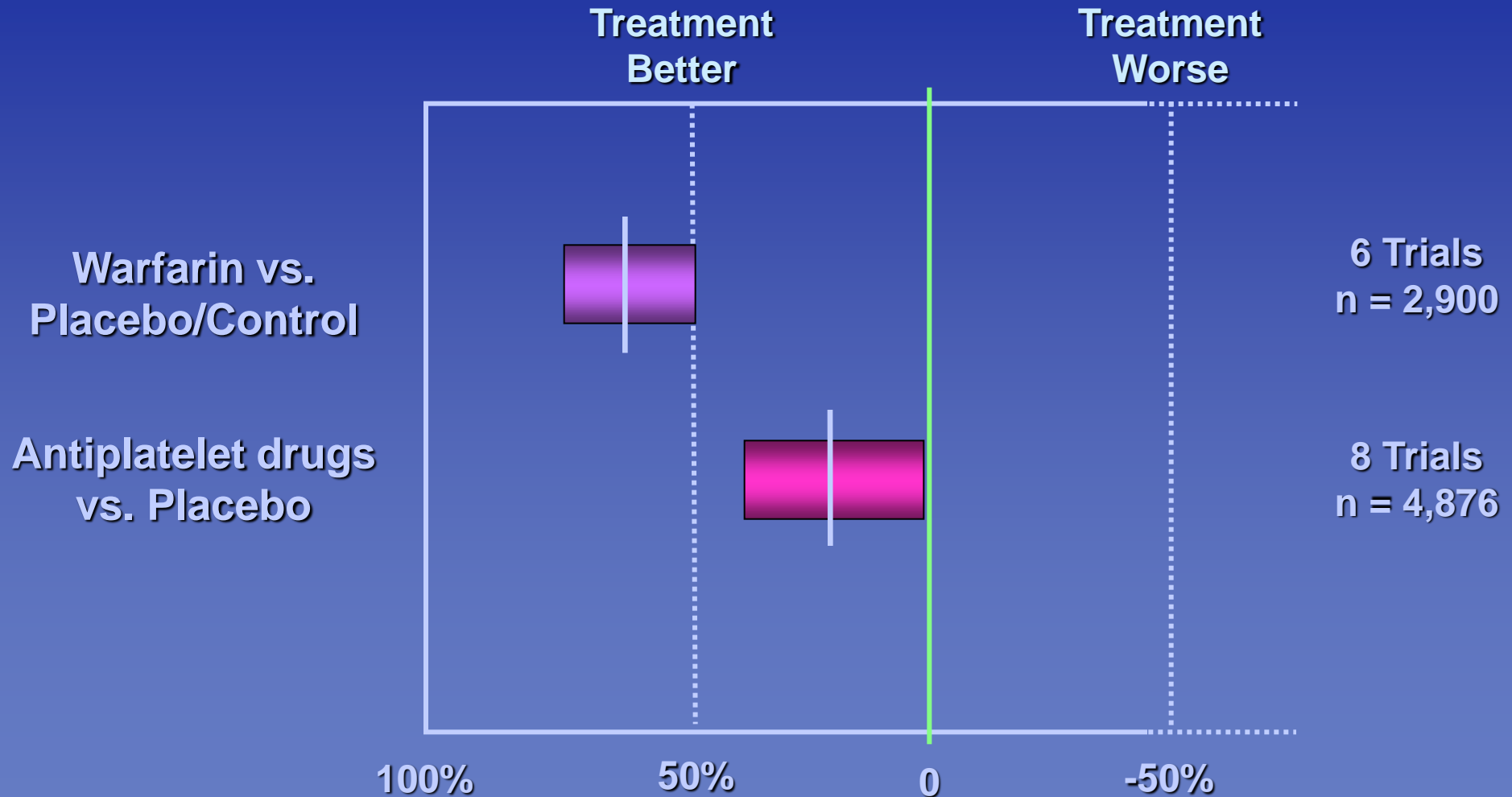
Aspirin for Atrial Fibrillation

Stroke Risk Reductions



Antithrombotic Therapy for Atrial Fibrillation

Stroke Risk Reductions



Atrial Fibrillation



Effective.

Atrial Fibrillation



Who Needs It?

Risk Stratification in AF

Stroke Risk Factors

High-Risk Factors

- Mitral stenosis
- Prosthetic heart valve
- History of stroke or TIA

Less Validated Risk Factors

- Age 65–75 years
- Coronary artery disease
- Female gender
- Thyrotoxicosis

Moderate-Risk Factors

- Age >75 years
- Hypertension
- Diabetes mellitus
- Heart failure or ↓ LV function

Dubious Factors

- Duration of AF
- Pattern of AF
(persistent vs. paroxysmal)
- Left atrial diameter

The CHADS₂ Index

Stroke Risk Score for Atrial Fibrillation

	<u>Score (points)</u>	<u>Prevalence (%)*</u>
Congestive Heart failure	1	32
Hypertension	1	65
Age >75 years	1	28
Diabetes mellitus	1	18
Stroke or TIA	2 (should be 3?)	10
Moderate-High risk	≥2	50-60
Low risk	0-1	40-50

VanWalraven C, et al. *Arch Intern Med* 2003; 163:936.

* Nieuwlaat R, et al. (EuroHeart survey) *Eur Heart J* 2006 (E-published).

The CHADS₂ Index

Stroke Risk in Patients with Atrial Fibrillation

	<u>Score (points)</u>	<u>Risk of Stroke (%/year)</u>	
	0	1.9	
Approximate Risk threshold for Anticoagulation	1	2.8	3%/year
	2	4.0	
	3	5.9	
	4	8.5	
	5	12.5	
	6	18.2	

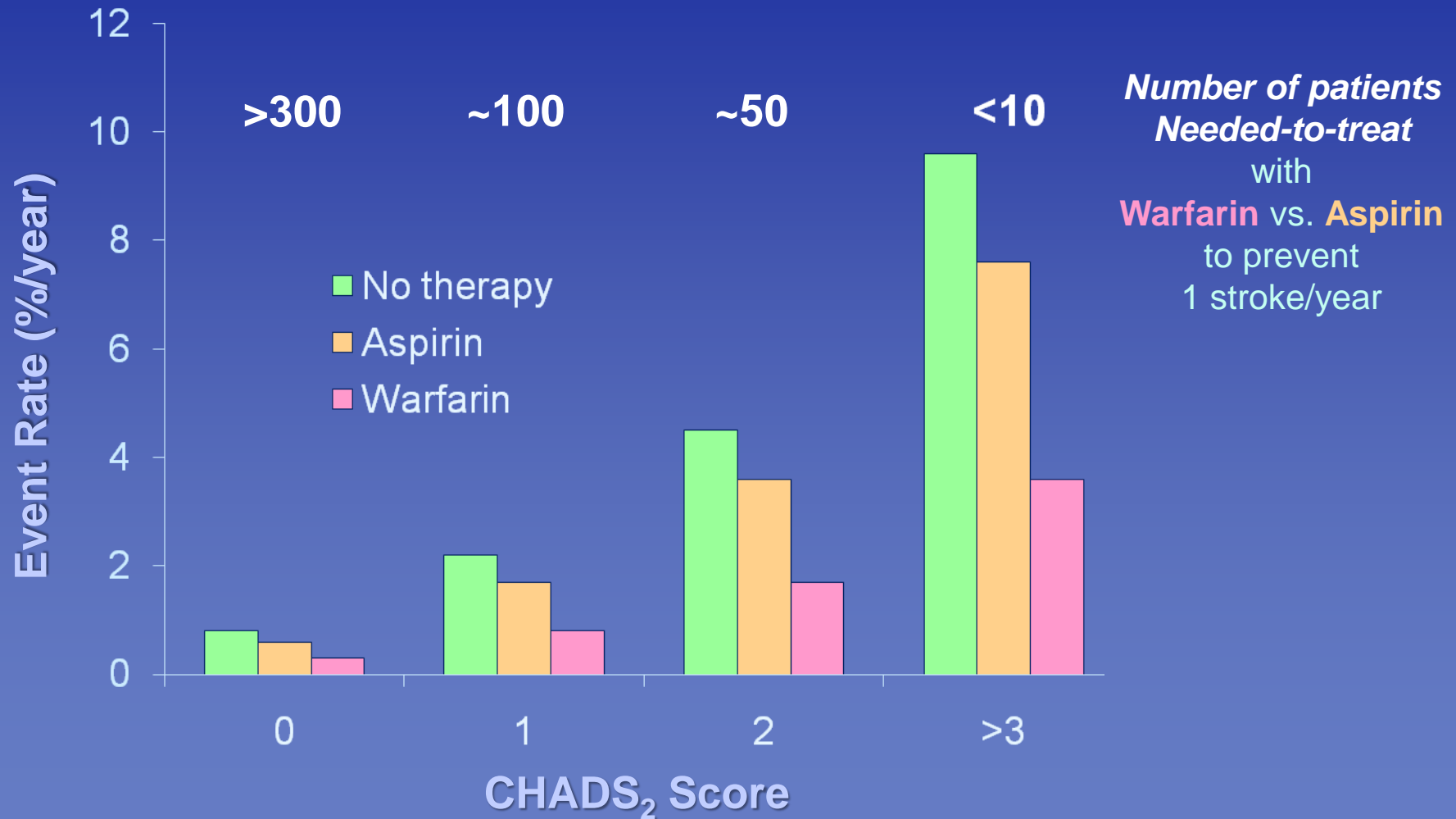
Van Walraven C, et al. *Arch Intern Med* 2003; 163:936.

Go A, et al. *JAMA* 2003; 290: 2685.

Gage BF, et al. *Circulation* 2004; 110: 2287.

Risk Stratification and Anticoagulation

Stroke Reduction with Warfarin Instead of Aspirin



Antithrombotic Therapy for Atrial Fibrillation

ACC/AHA/HRS Guidelines, Updated 2011

Risk Category	Recommended Therapy
No risk factors CHADS₂ = 0	Aspirin, 81-325 mg qd or No therapy
One moderate risk factor CHADS₂ = 1	Aspirin, 81-325 mg/d or Warfarin (INR 2.0-3.0, target 2.5) or Factor IIa/Xa inhibitor*
Any high risk factor or >1 moderate risk factor CHADS₂ ≥ 2	Warfarin (INR 2.0-3.0, target 2.5) or Factor IIa/Xa inhibitor*
Mitral stenosis or prosthetic valve	Warfarin (INR 2.0-3.0 or higher)

Wann S, et al. *J Am Coll Cardiol* 2011; 57:223.

*Furie KL, et al. *Stroke* 2012; 43: (published online August 2)



"Actually, it's more of a guideline than a rule."

- Bill Murray in Ghostbusters[©] (1984),
relaxing his rule "never to get involved with possessed people" in response to Sigourney Weaver's seductive advances.

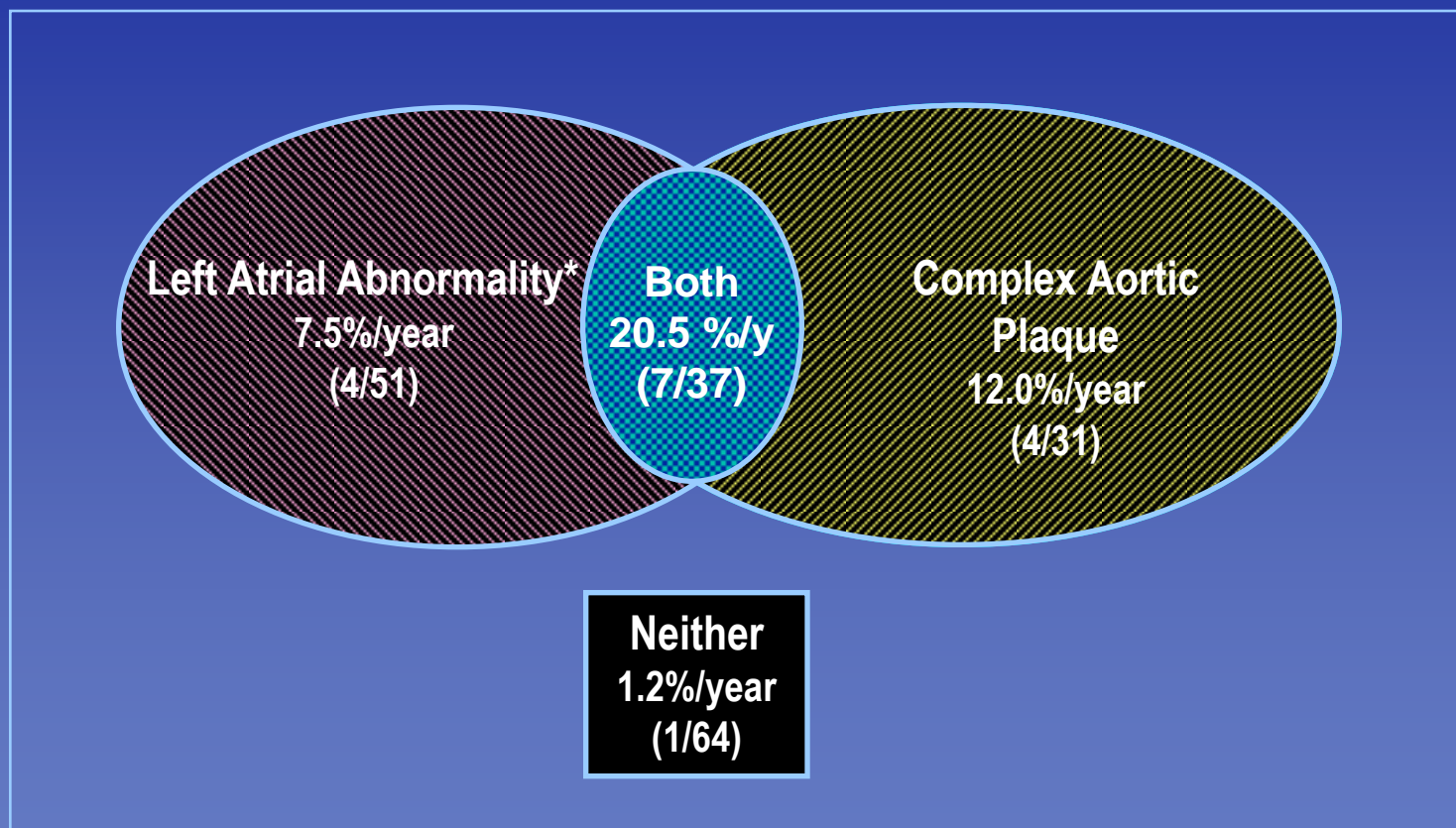
Patient Selection for Anticoagulation

Additional Considerations

- Risk of bleeding
- Newly anticoagulated vs. established therapy
- Availability of high-quality anticoagulation management program
- Patient preferences

TEE-Defined Patient Subsets

Event Rates During Combination Therapy



* left atrial appendage thrombus (13%)
dense spontaneous echo-contrast (19%)
peak appendage emptying velocity ≤ 20 cm/sec

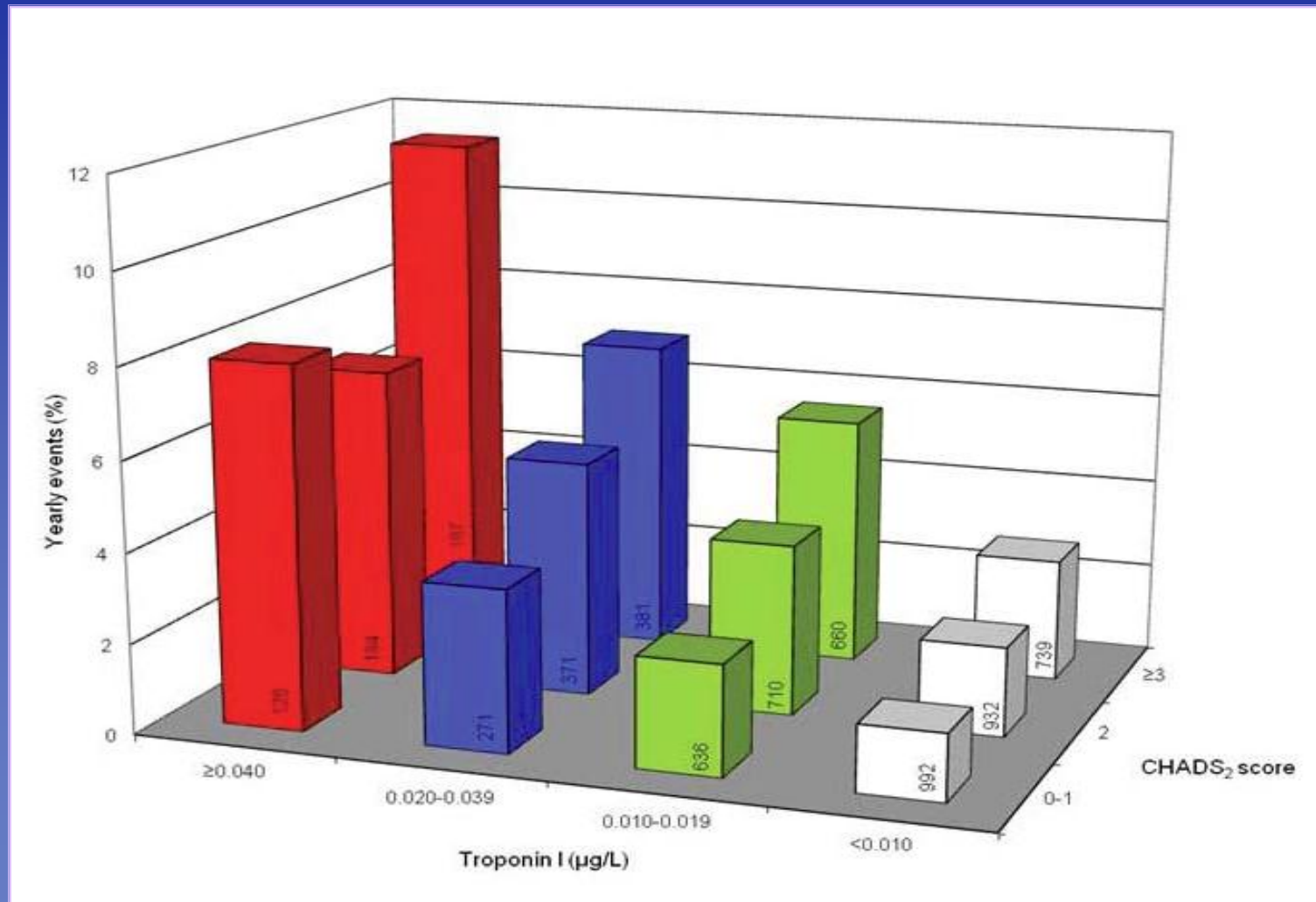
The CHA₂DS₂VASc Index

Stroke Risk Score for Atrial Fibrillation

	<u>Weight (points)</u>
C ongestive heart failure or LVEF \leq 35%	1
H ypertension	1
A ge >75 years	2
D iabetes mellitus	1
S troke/TIA/systemic embolism	2
V ascular Disease (MI/PAD/Aortic plaque)	1
A ge 65-74 years	1
S ex category (female)	1
Moderate-High risk	≥ 2
Low risk	0-1

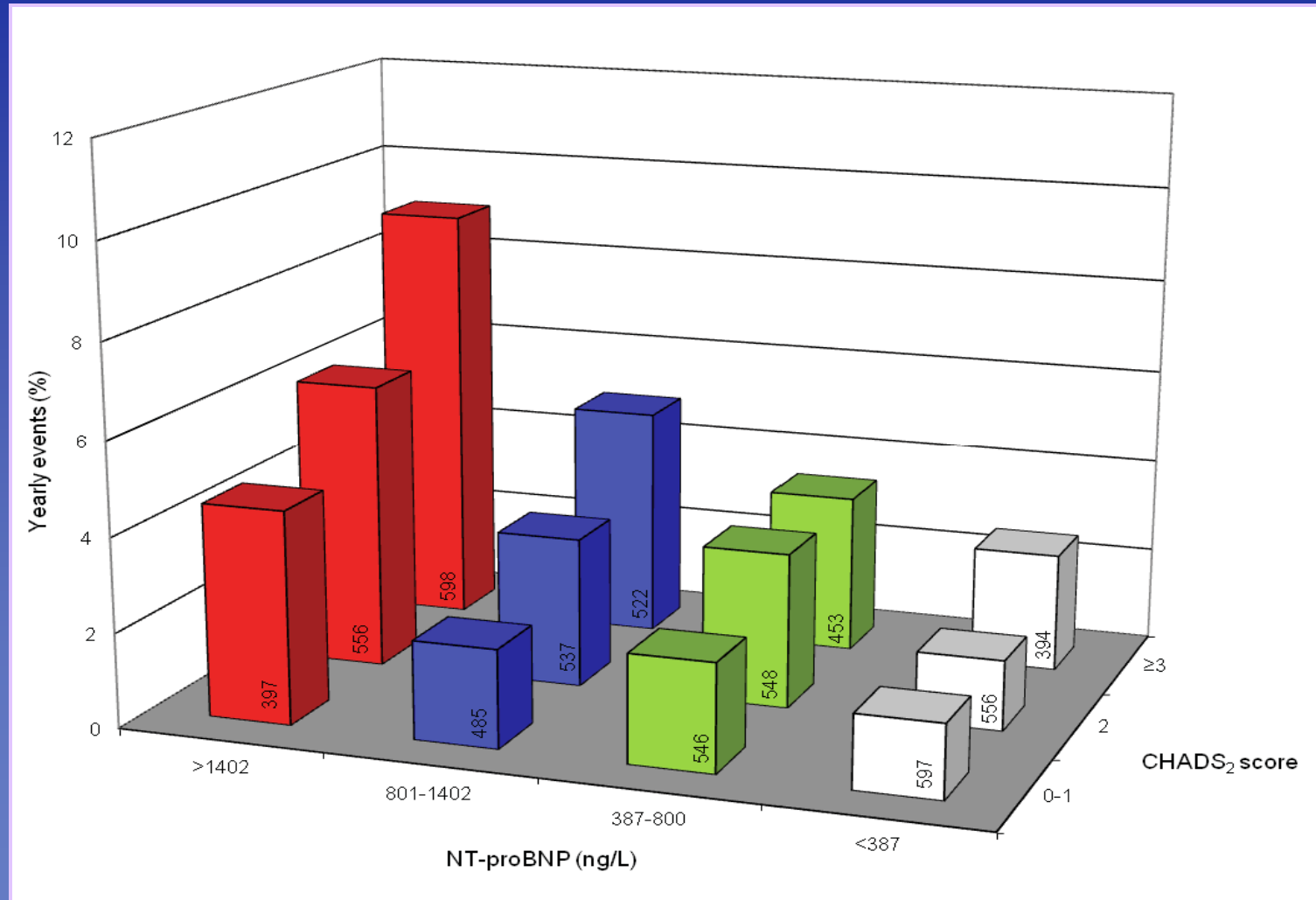
Risk of Stroke or Systemic Embolism Related to Troponin-I Levels at Entry

Hazard Ratios in the RE-LY Trial



Risk of Stroke or Systemic Embolism Related to NT-proBNP Levels at Entry

Hazard Ratios in the RE-LY Trial



The HAS-BLED Score

Risk Score for Predicting Bleeding in Anticoagulated Patients with Atrial Fibrillation

	<u>Weight (points)</u>
Hypertension (>160 mmHg systolic)	1
Abnormal renal or hepatic function	1-2
Stroke	1
Bleeding history or anemia	1
Labile INR (TTR <60%)	1
Elderly (age >75 years)	1
Drugs (antiplatelets, NSAIDs) & alcohol	1-2
High risk (>4%/year)	≥ 4
Moderate risk (2-4%/year)	2-3
Low risk (<2%.year)	0-1

Intracerebral Hemorrhage

The Worst Complication of Antithrombotic Therapy

- >10% of intracerebral hemorrhages (ICH) occur in patients on antithrombotic therapy
- Aspirin increases the risk by ~40%
- Warfarin (INR 2–3) doubles the risk to 0.3–0.6%/year
- ICH during anticoagulation is catastrophic

Risk Factors for ICH

During Anticoagulation

Established or likely factors

- Age >75 years
- Hypertension (systolic BP >160 mmHg)
- Cerebrovascular disease (prior stroke)
- Intensity of anticoagulation
- Initial period of anticoagulation
- Concomitant antiplatelet therapy
- Amyloid cerebral angiopathy
- Leukoaraiosis
- Ethnicity
- Tobacco and alcohol

Hart RG, et al. *Stroke* 1995;26:1471.

Sjöblom L, et al. *Stroke* 2001; 32: 2567

Shen AY, et al. *J Am Coll Cardiol* 2007; 50: 309.

The ACTIVE Trial

Clopidogrel + Aspirin

Atrial Fibrillation + Risk Factors

ACTIVE - W

ACTIVE - A

Anticoagulation-eligible

VKA
(INR 2-3)

Clopidogrel
+ Aspirin

Open-label
Non-inferiority
n = 6,706

OAC Contraindications or Unwilling

Aspirin
+ Placebo

Clopidogrel
+ Aspirin

Double-blind
Superiority
n = 7,554

Irbesartan, 300 mg/d vs. Placebo
n = 9,016

ACTIVE - I

Risk Factors:

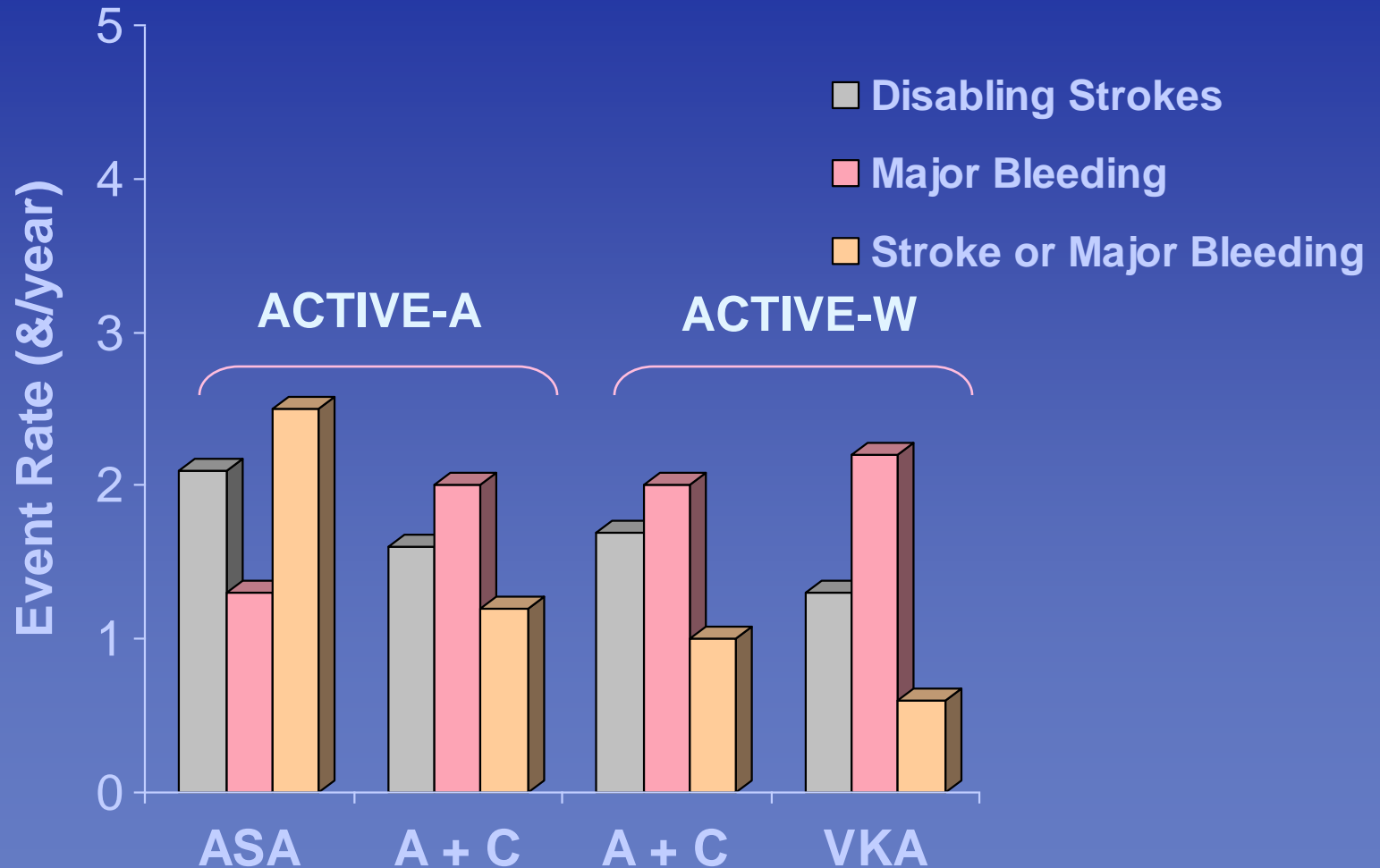
Age ≥ 75 , hypertension, prior stroke/TIA, LVEF $< 45\%$, PAD, age 55-74 + CAD or diabetes

Primary outcome: Stroke, systemic embolism, MI or cardiovascular death

The ACTIVE Trials

Rates of Disabling Stroke and Major Bleeding

Mean CHADS₂ Score = 2.1

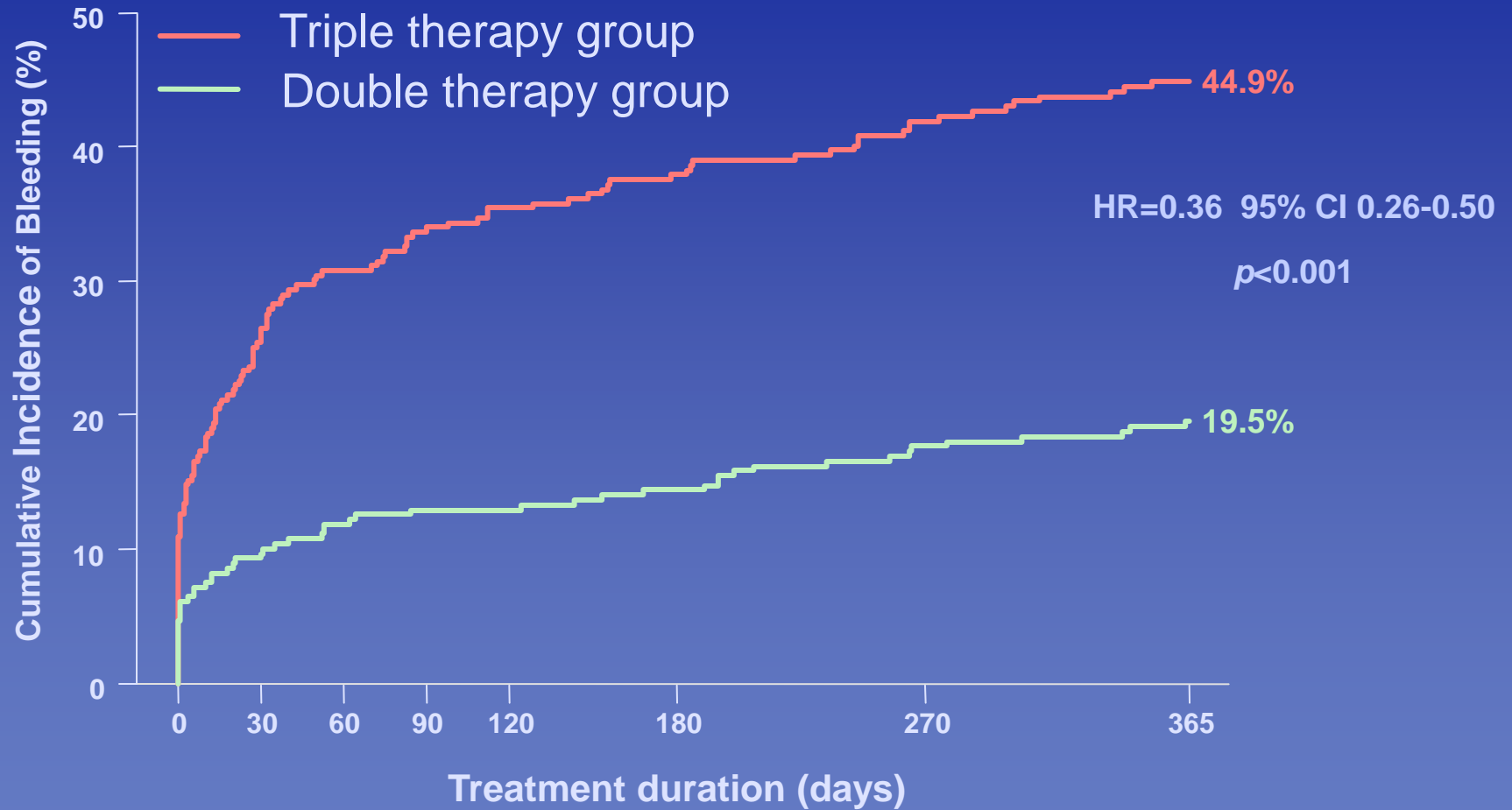


Connolly SJ, et al. *Lancet* 2006; 367:1903.

Connolly SJ, et al. *N Engl J Med* 2009; 360:2066.

WOEST Study Primary Endpoint

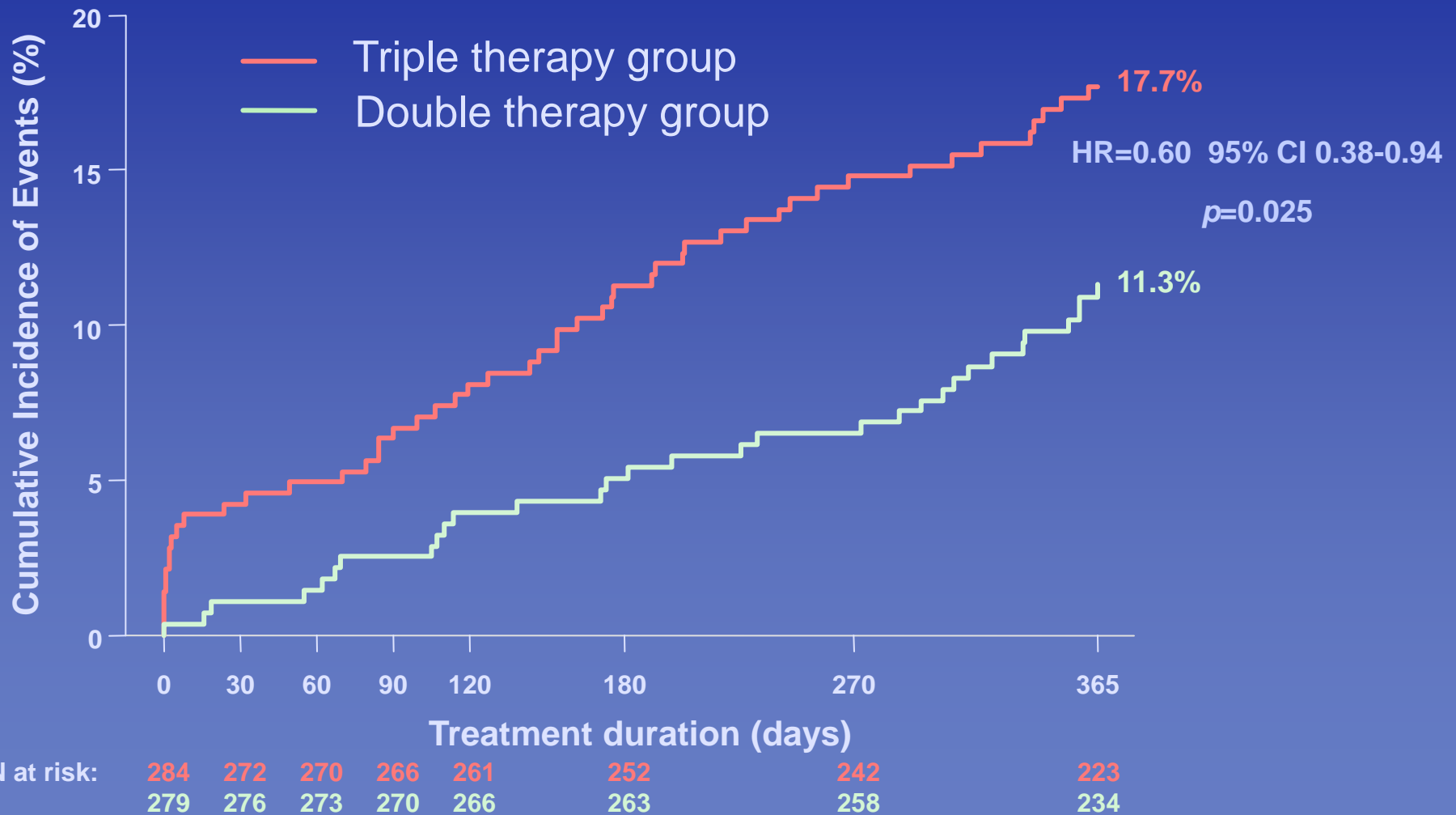
Incidence of TIMI Bleeding Events



N at risk:	284	210	194	186	181	173	159	140
	279	253	244	241	241	236	226	208

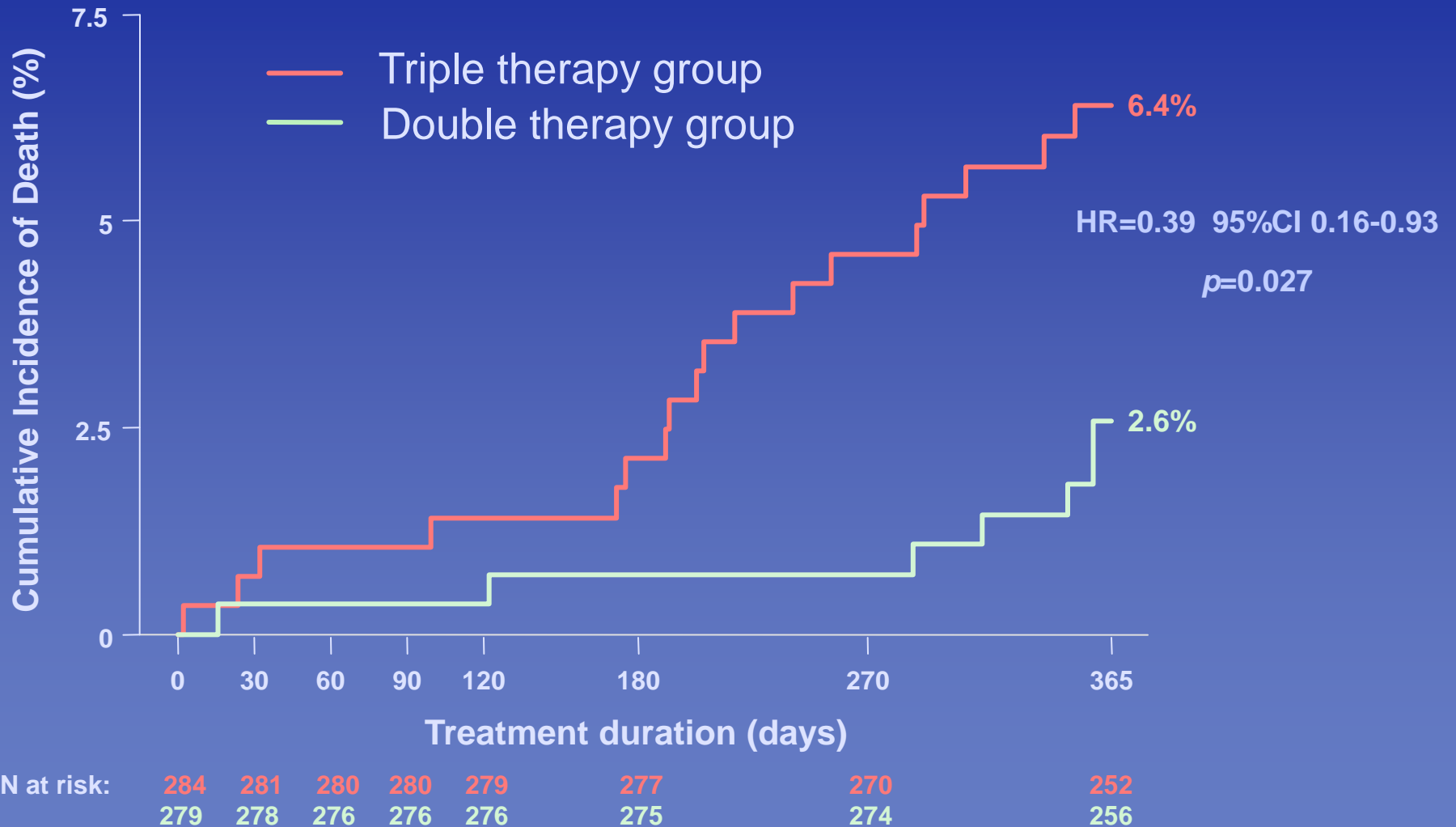
WOEST Study Secondary Endpoint

*Incidence of Death, MI, Stroke,
Stent Thrombosis & Target Vessel Revascularization*



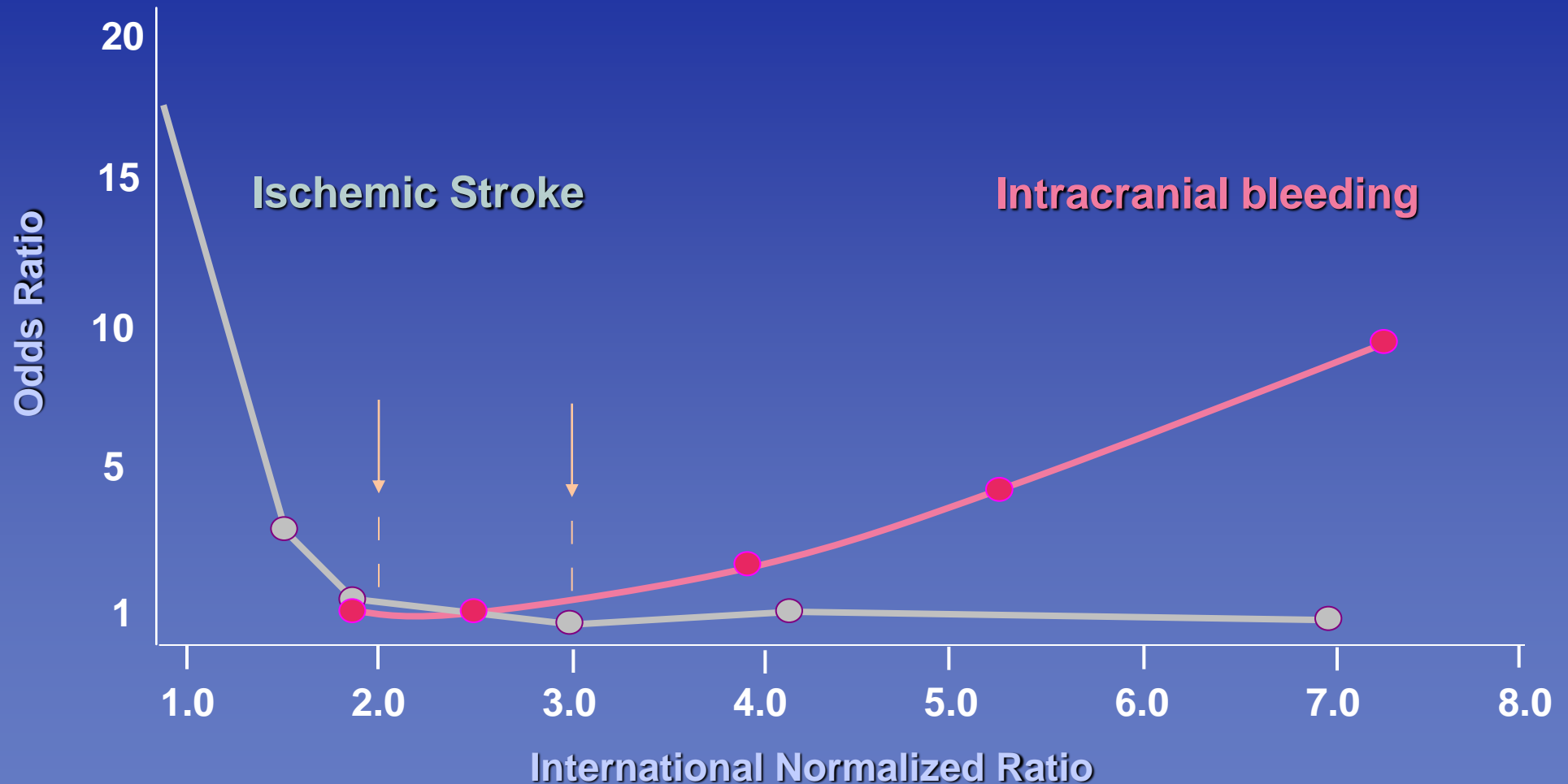
WOEST Study

All-cause Mortality



INR at the Time of Stroke or Bleeding

Efficacy and Safety of Warfarin



Fang MC, et al. *Ann Intern Med* 2004; 141:745.

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

The Ideal Anticoagulant

Essential Properties

- Wide therapeutic margin
- Infrequent oral dosing
- Lack of food/drug interactions
- No need for laboratory monitoring
- Readily reversible effect
- Affordability

Investigational Anticoagulant Targets

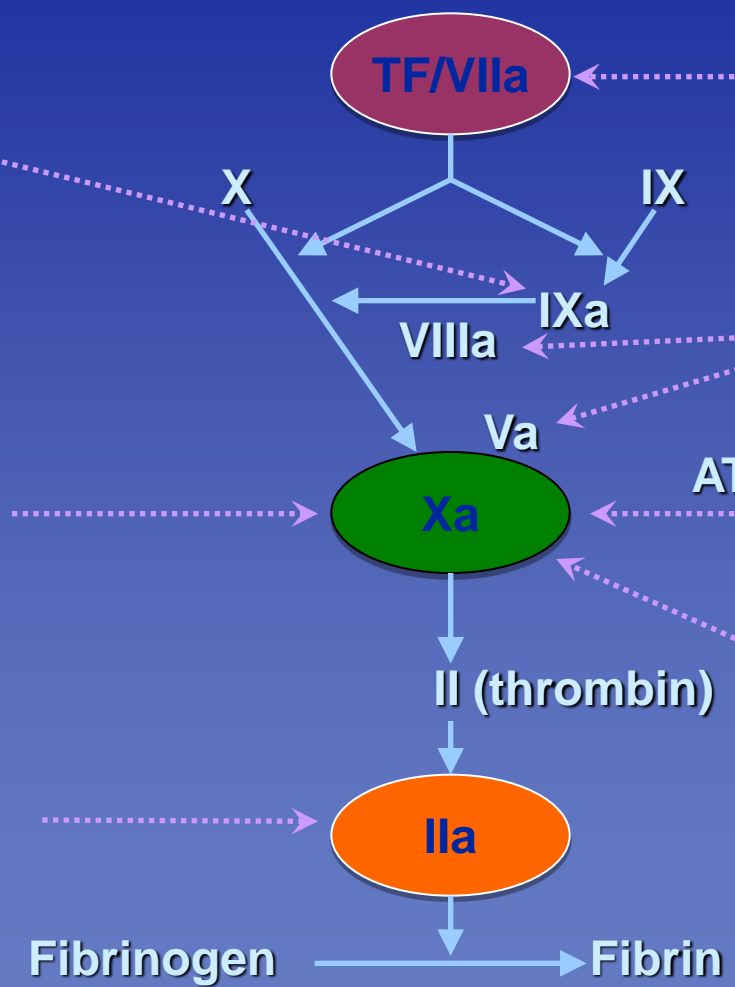
ORAL

PARENTERAL

TTP889

Rivaroxaban
Apixaban
Edoxaban
Betrixaban
Darexaban
LY517717
TAK-442

Dabigatran



TFPI (tifacogin)

APC (drotrecogin alfa)
sTM (ART-123)

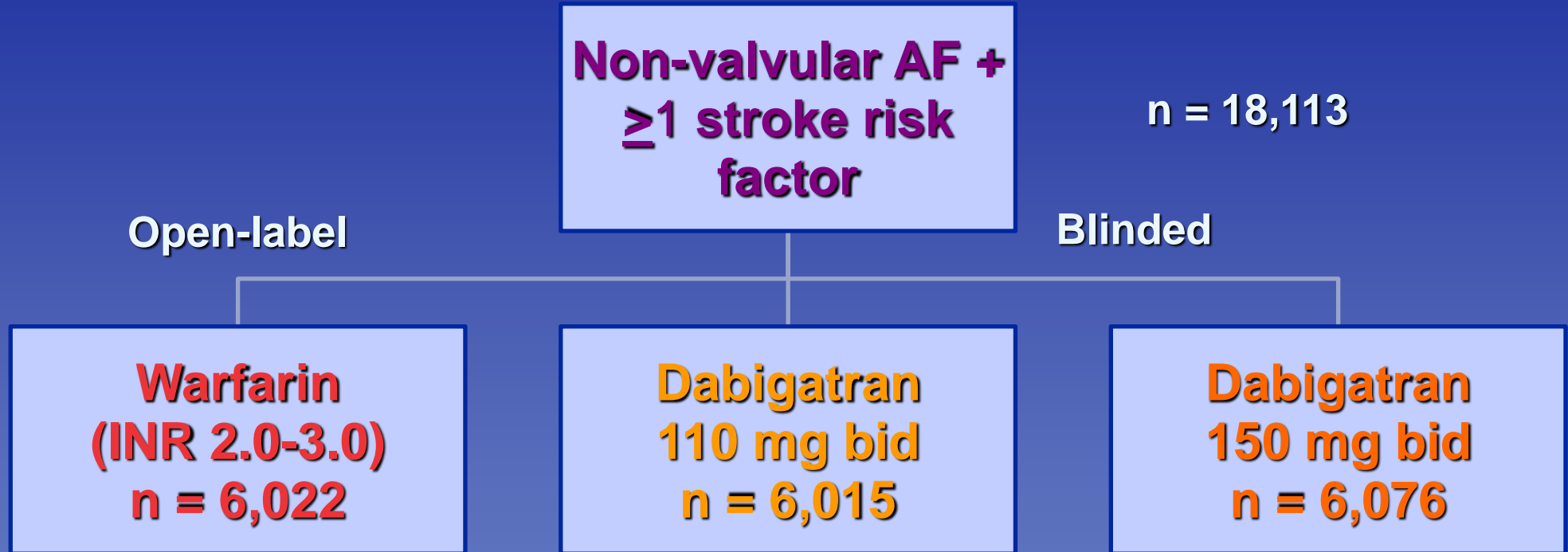
Idraparinux

DX-9065a
Otamixaban

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

RE-LY Trial

Randomized Evaluation of Long-term Anticoagulant Therapy with Dabigatran Etexilate



Primary objective: noninferiority vs. warfarin

Observation period: minimum 1, mean 2, maximum 3 years

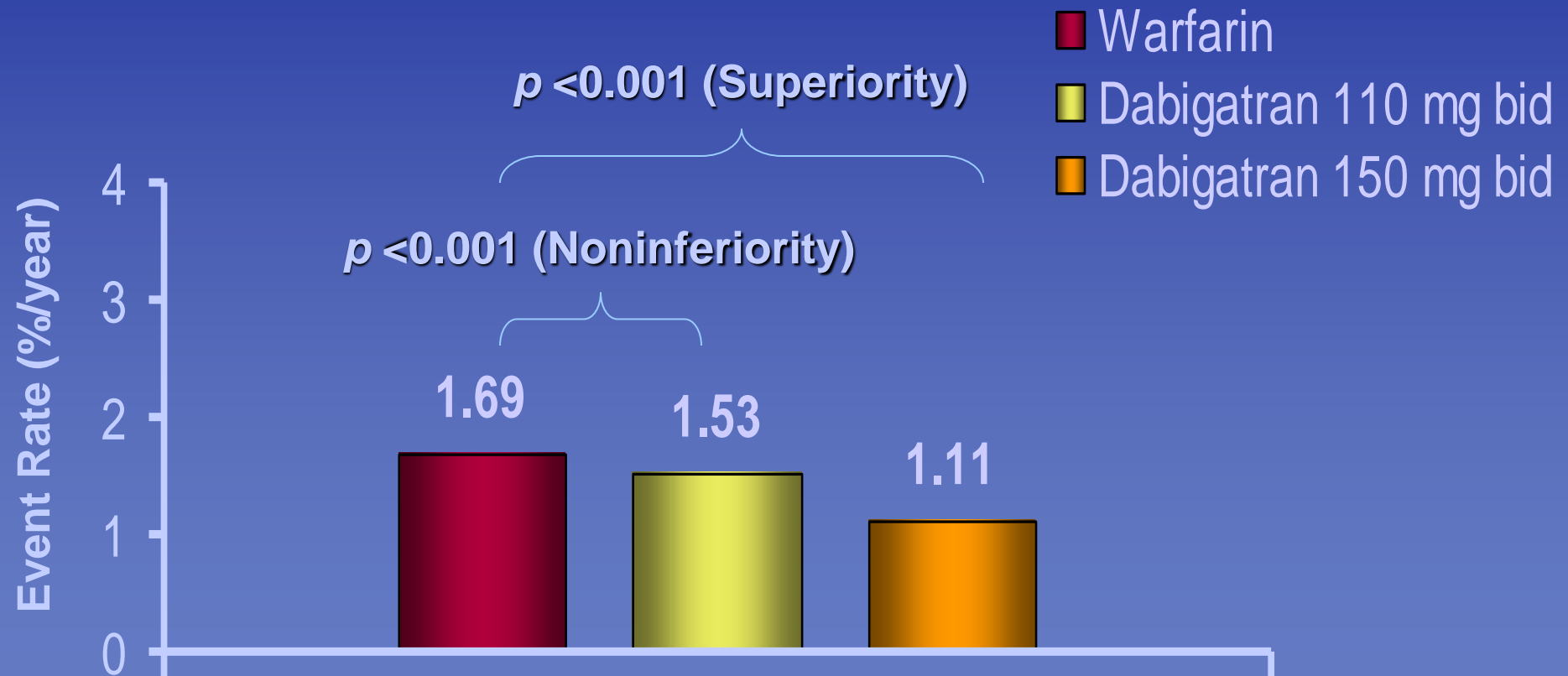
Primary endpoint: all stroke + systemic embolism

Safety measure: bleeding during treatment

RE-LY Trial

Primary Events

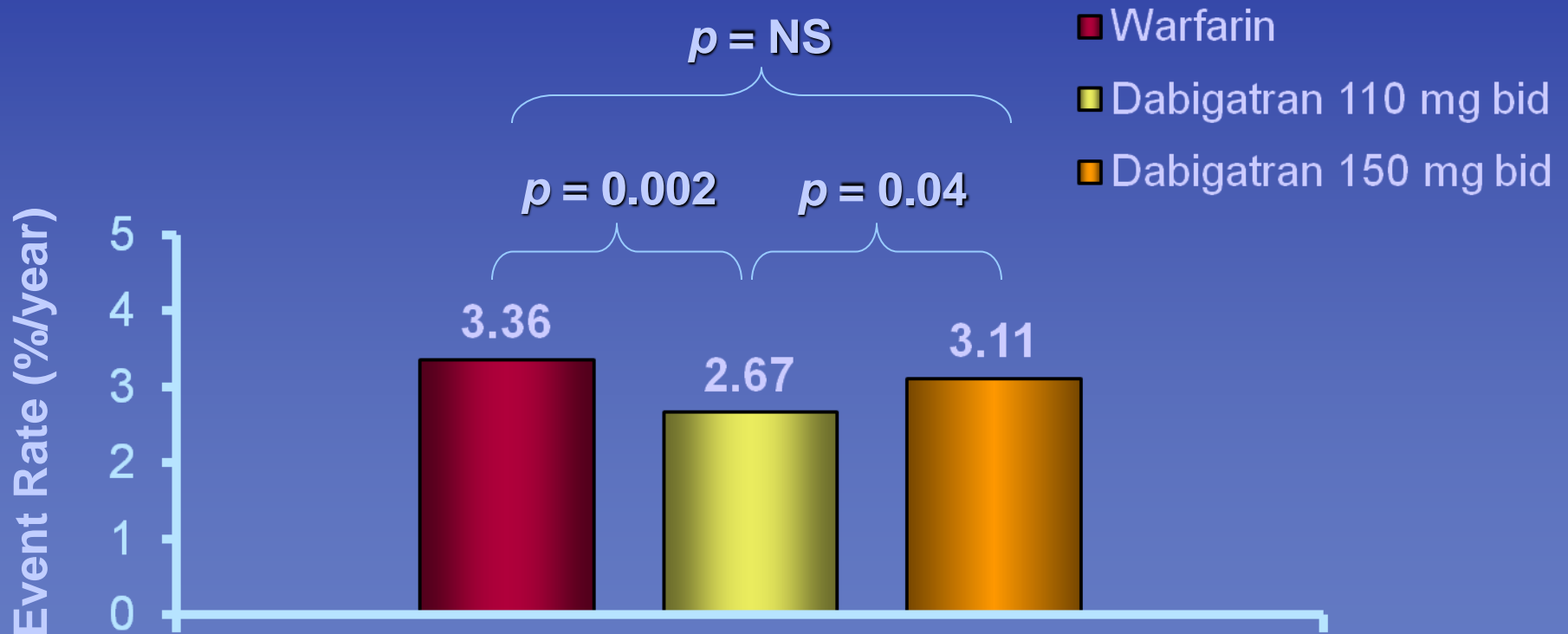
All Strokes and Systemic Embolic Events



RE-LY Trial

All Major Bleeding

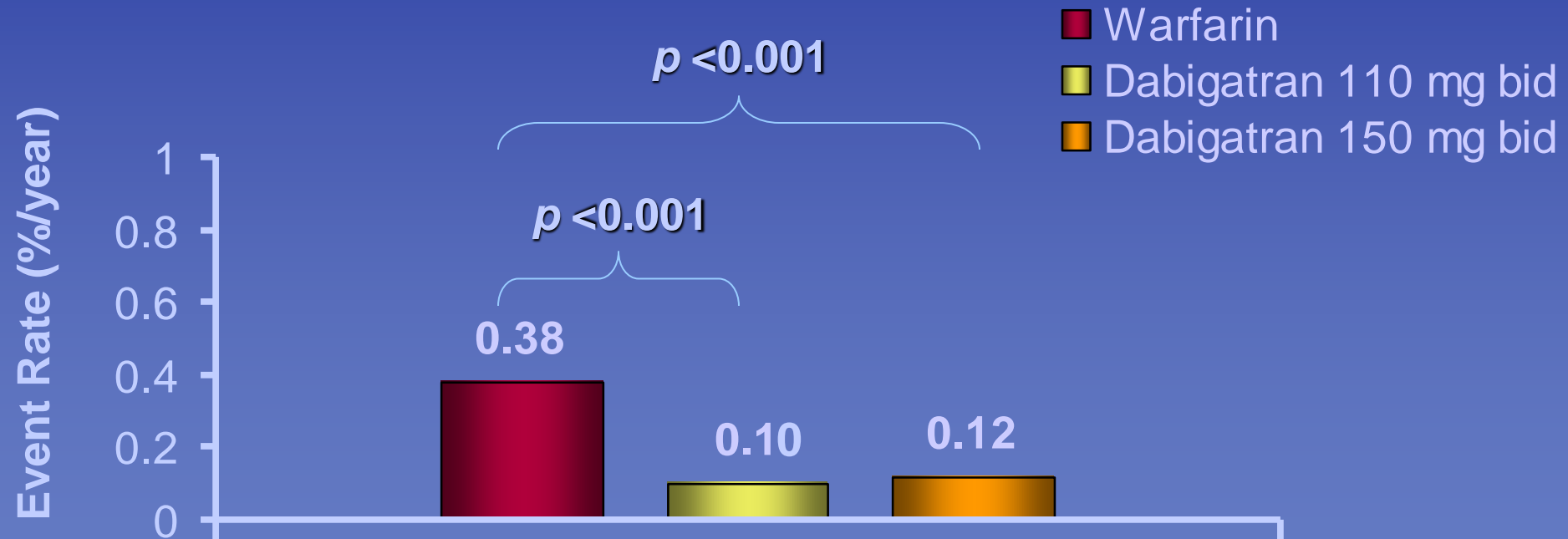
Hgb \downarrow ≥ 2 g/dl or Transfusion ≥ 2 units or Critical Site



RE-LY Trial

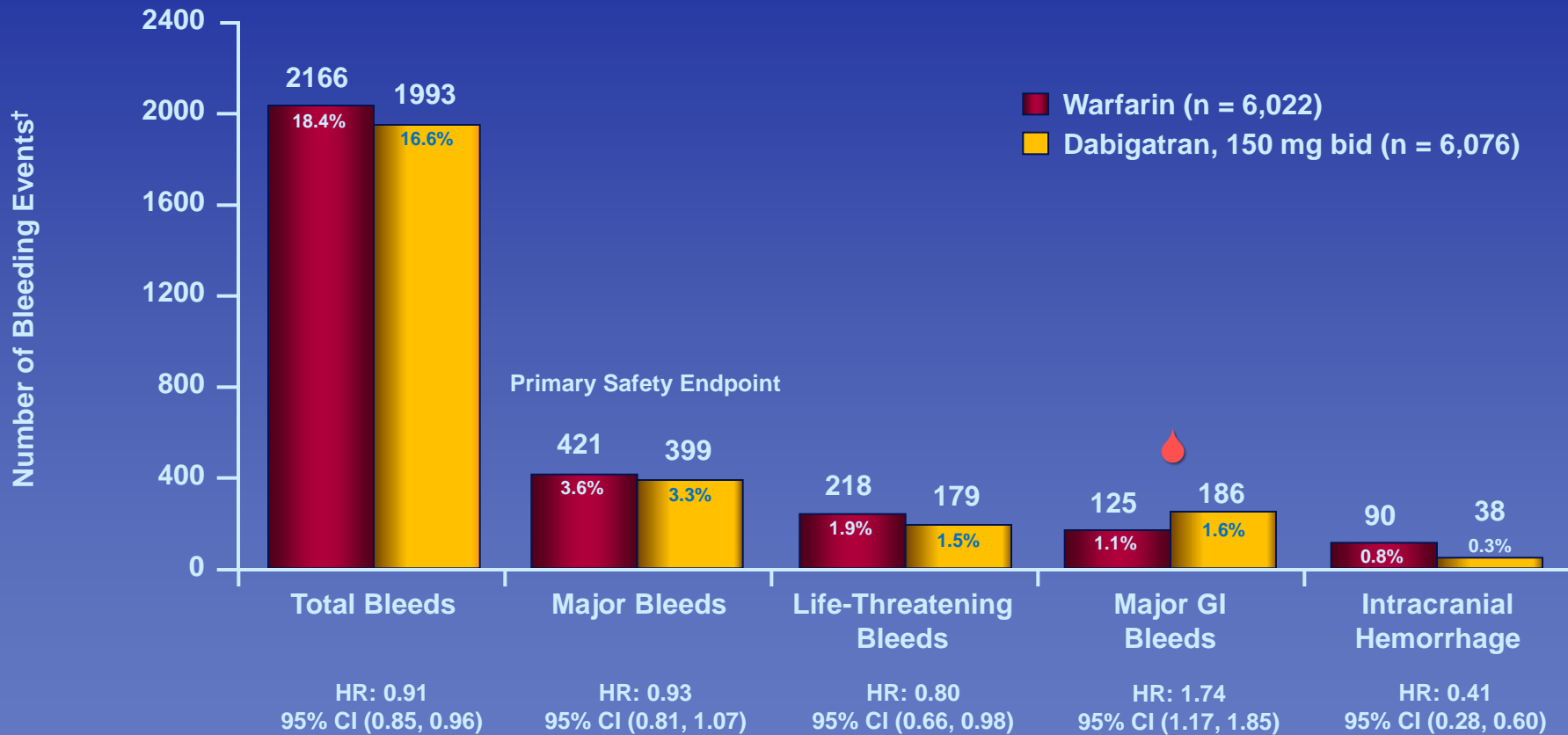
Hemorrhagic Stroke Events

Intracerebral hemorrhages



Analysis of Bleeding Events

RE-LY Trial



% refers to event rate per 100 patient years.

*The risk of major bleeding with dabigatran etexilate, 150 mg bid was similar to warfarin across major subgroups except age.

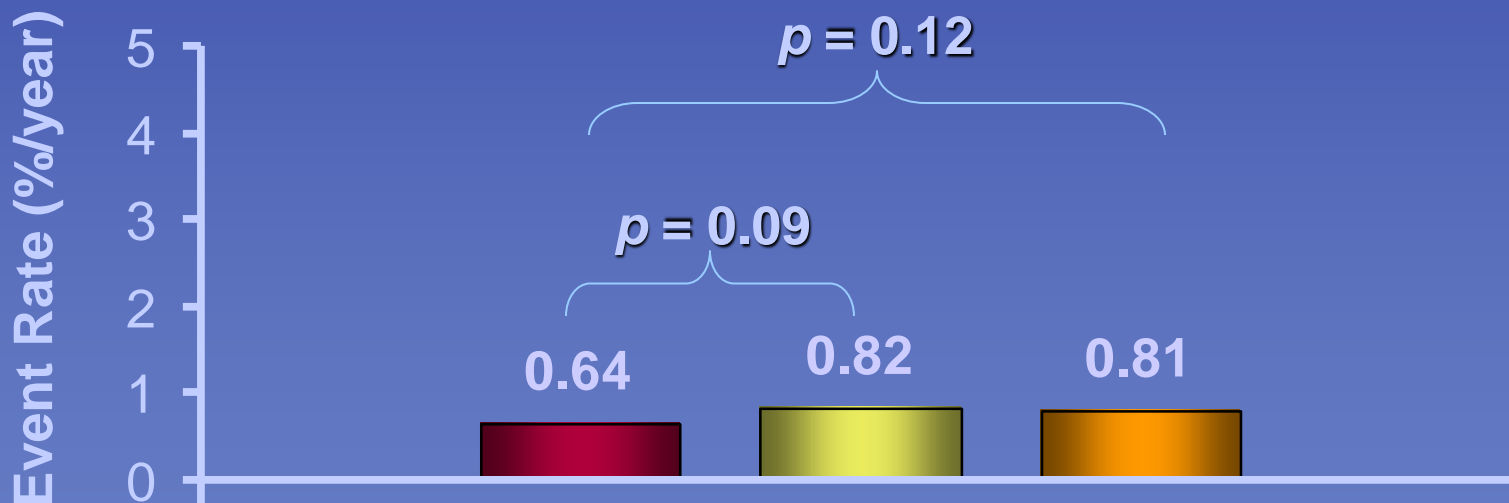
†Patients contributed multiple events and events were counted in multiple categories.

RE-LY Trial

*Acute Myocardial Infarction**

* Includes asymptomatic events identified during FDA review

- Warfarin
- Dabigatran 110 mg bid
- Dabigatran 150 mg bid



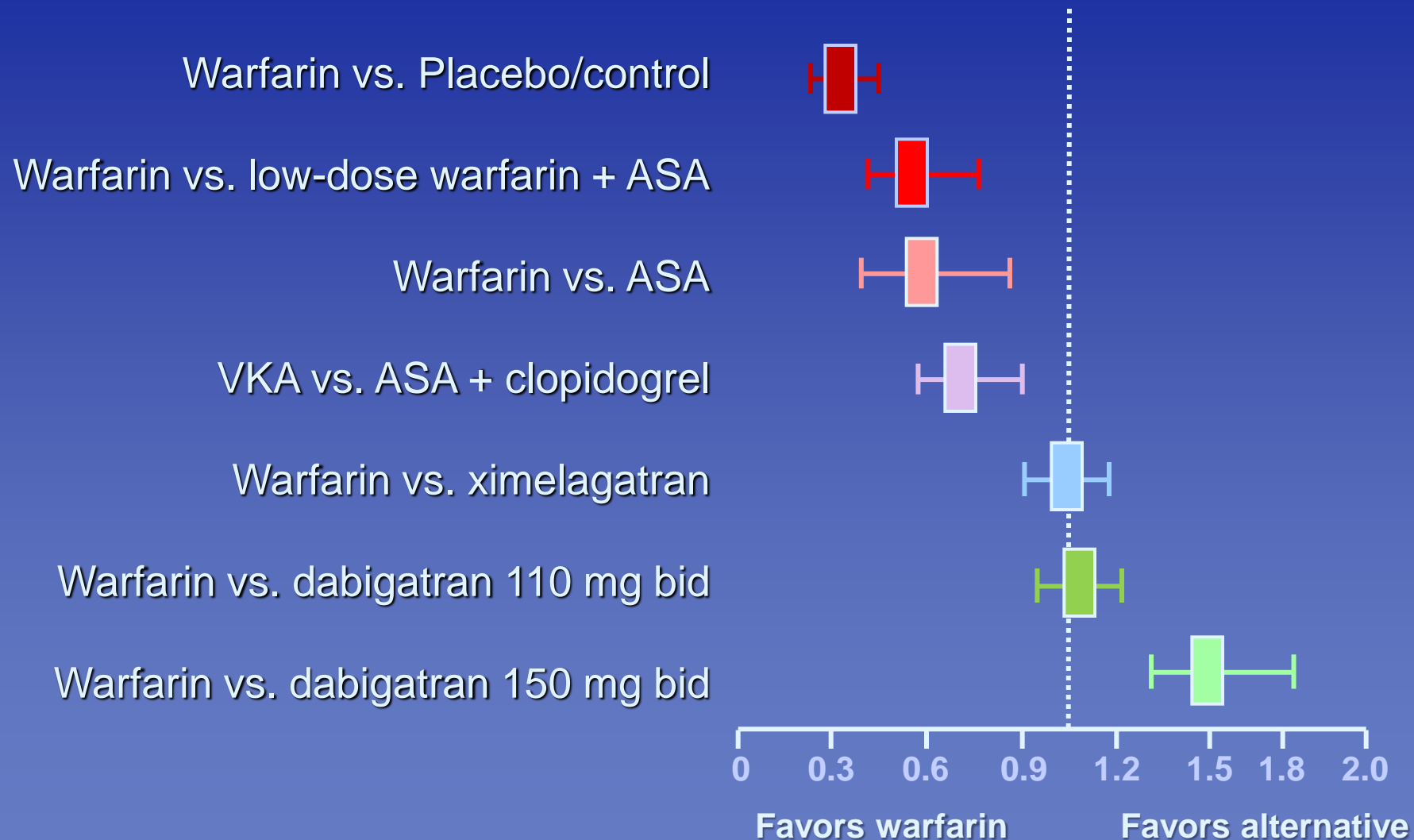
Dabigatran Etexilate (Pradaxa[®])

Adverse Reactions

- **Dyspepsia (11.3) [5.8]**
- **Fatigue (6.6) [6.2]**
- **Dizziness (8.3) [9.4]**
- **Dyspnea (9.5) [9.7]**
- **Peripheral edema (7.9) [7.8]**
- **Diarrhea (6.5) [5.7]**

Relative Risks of Stroke and Systemic Embolism

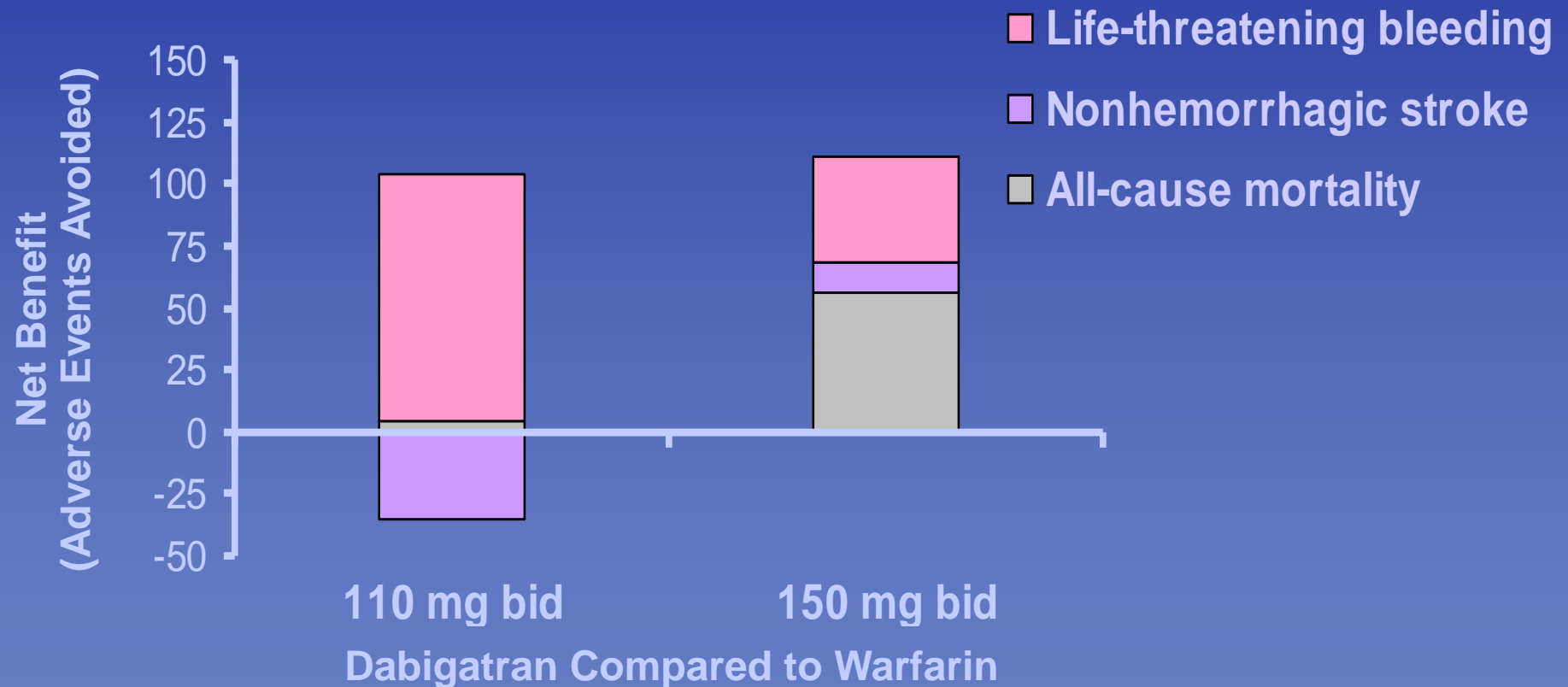
Meta-Analysis



RE-LY Trial

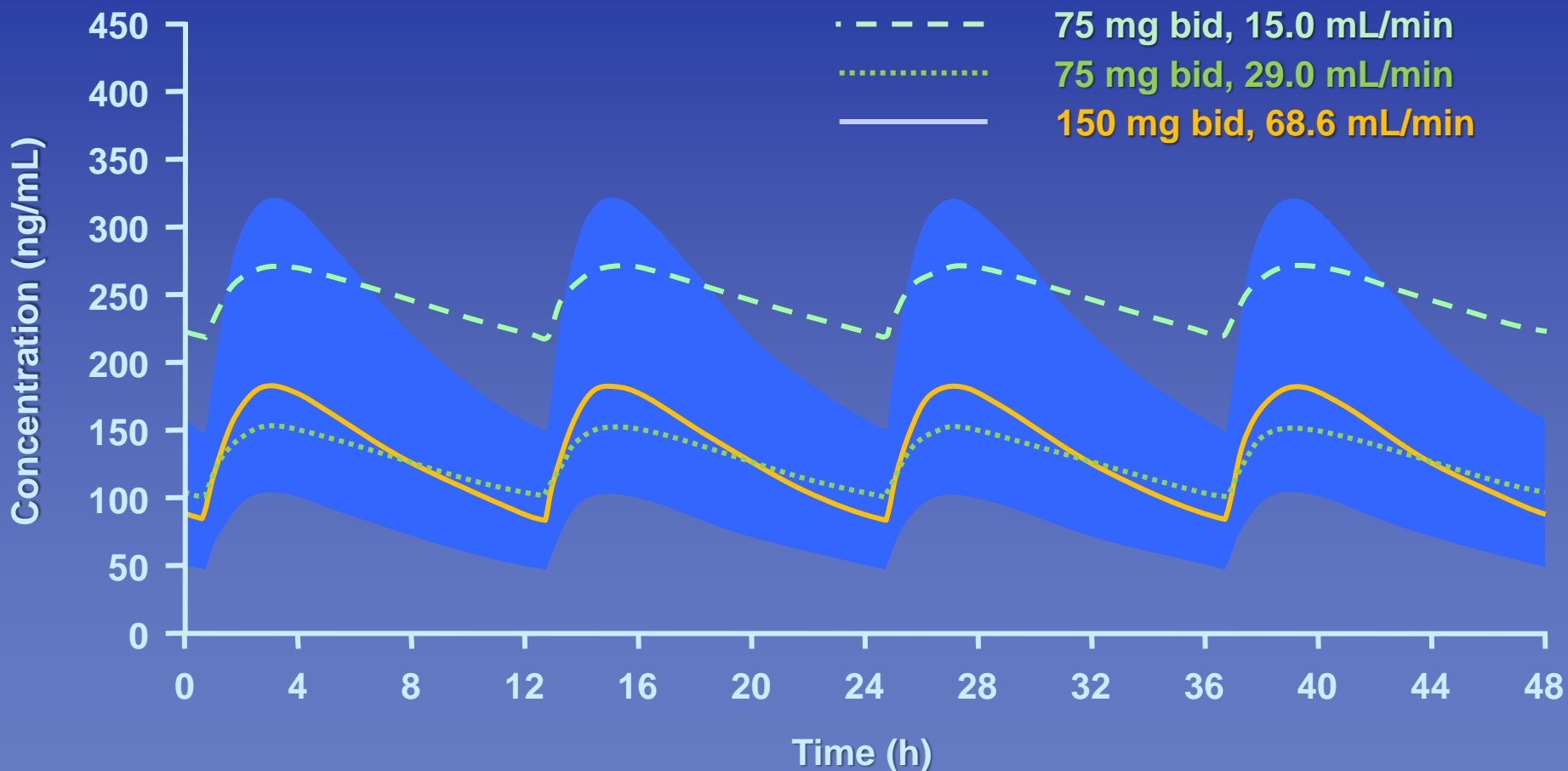
Net Clinical Benefit

Nonhemorrhagic strokes + Life-threatening bleeds + Deaths



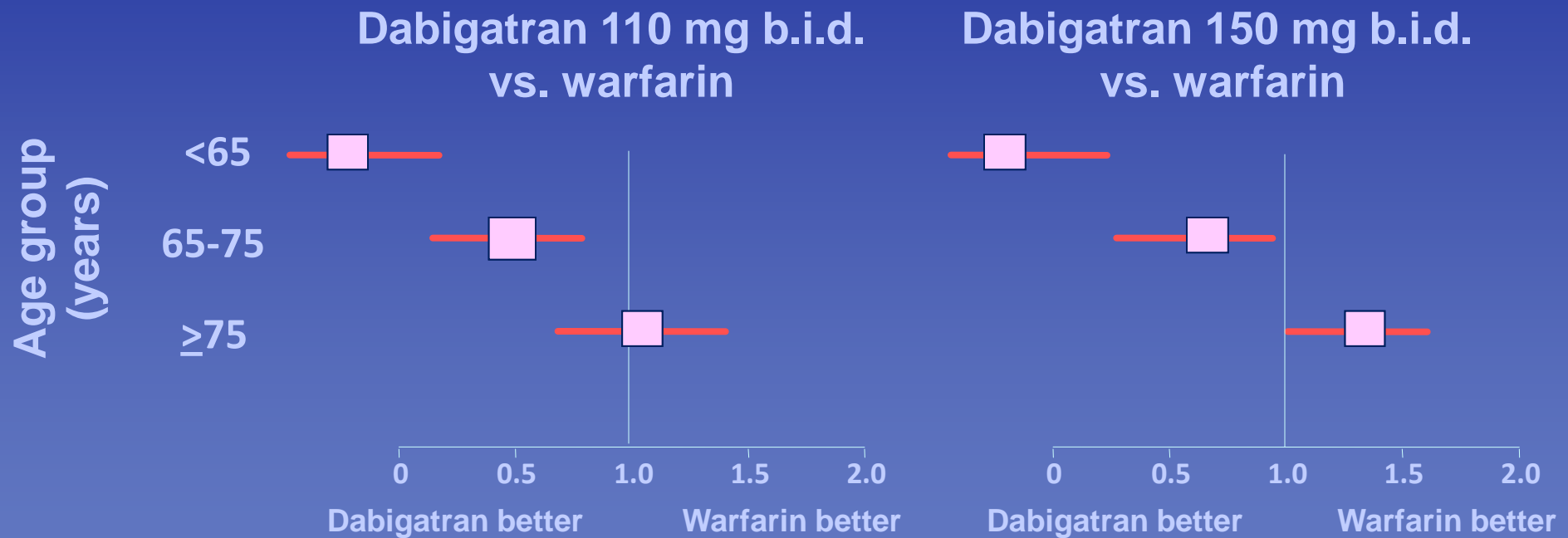
Dabigatran Dosing in Patients With Renal Impairment

Pharmacokinetic Modeling



Relative Risks of Major Bleeding

Each of Two Doses of Dabigatran vs. Warfarin



ROCKET-AF Trial

Study Design

Risk Factors

- CHF
- Hypertension
- Age \geq 75
- Diabetes

At least 2 or 3 required*

or

- Stroke, TIA or systemic embolism

Atrial Fibrillation

Rivaroxaban

20 mg daily
15 mg for Cr Cl 30-49 ml/min

Randomize
Double Blind /
Double Dummy
(n ~ 14,264)

Warfarin

INR target - 2.5
(2.0-3.0 inclusive)

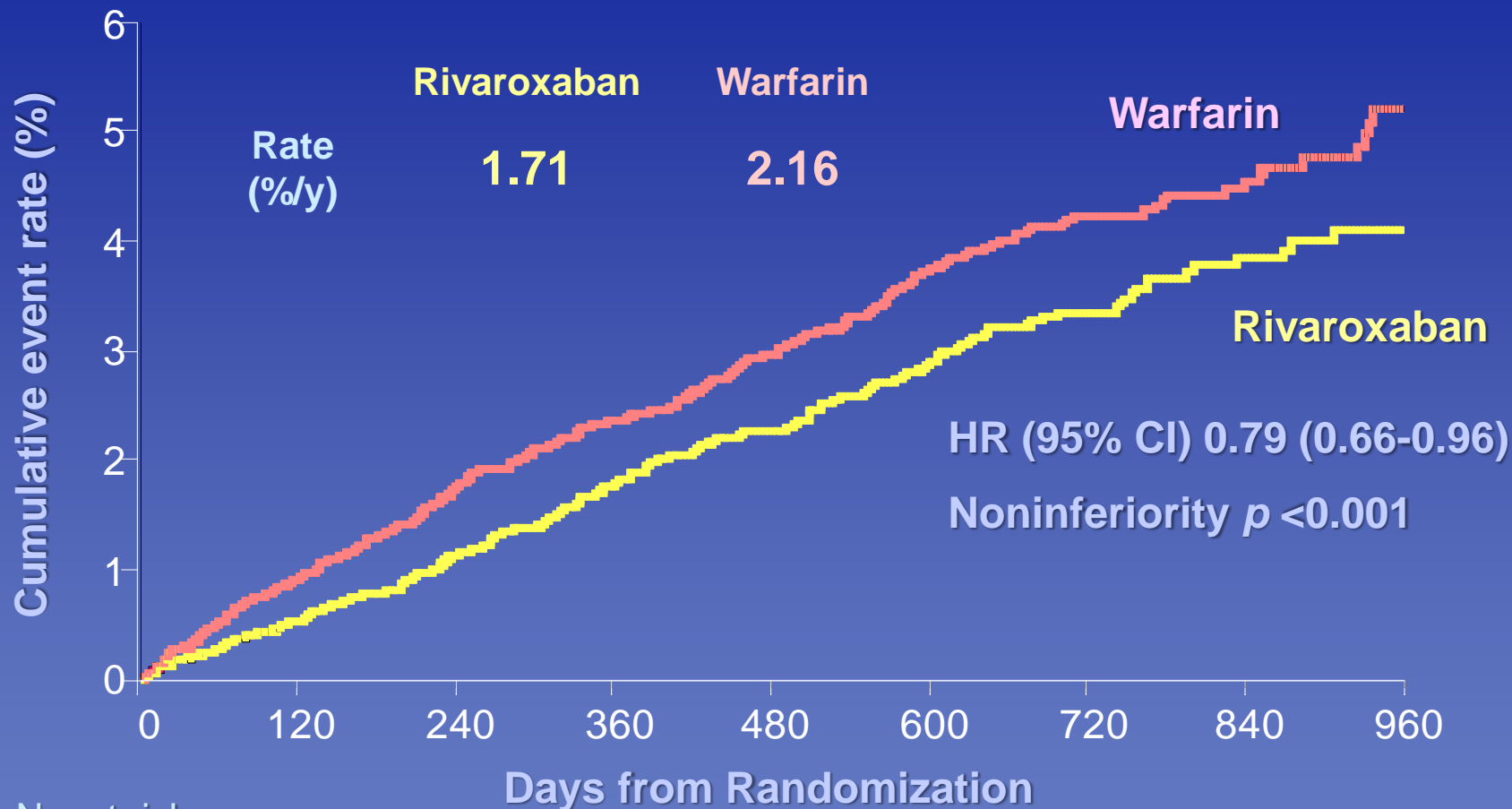
Monthly Monitoring
Adherence to standard of care guidelines

Primary Endpoint: Stroke or non-CNS Systemic Embolism

* Enrollment of patients without prior stroke, TIA or systemic embolism and only 2 factors limited to 10%

ROCKET-AF Trial

Stroke and Systemic Embolism

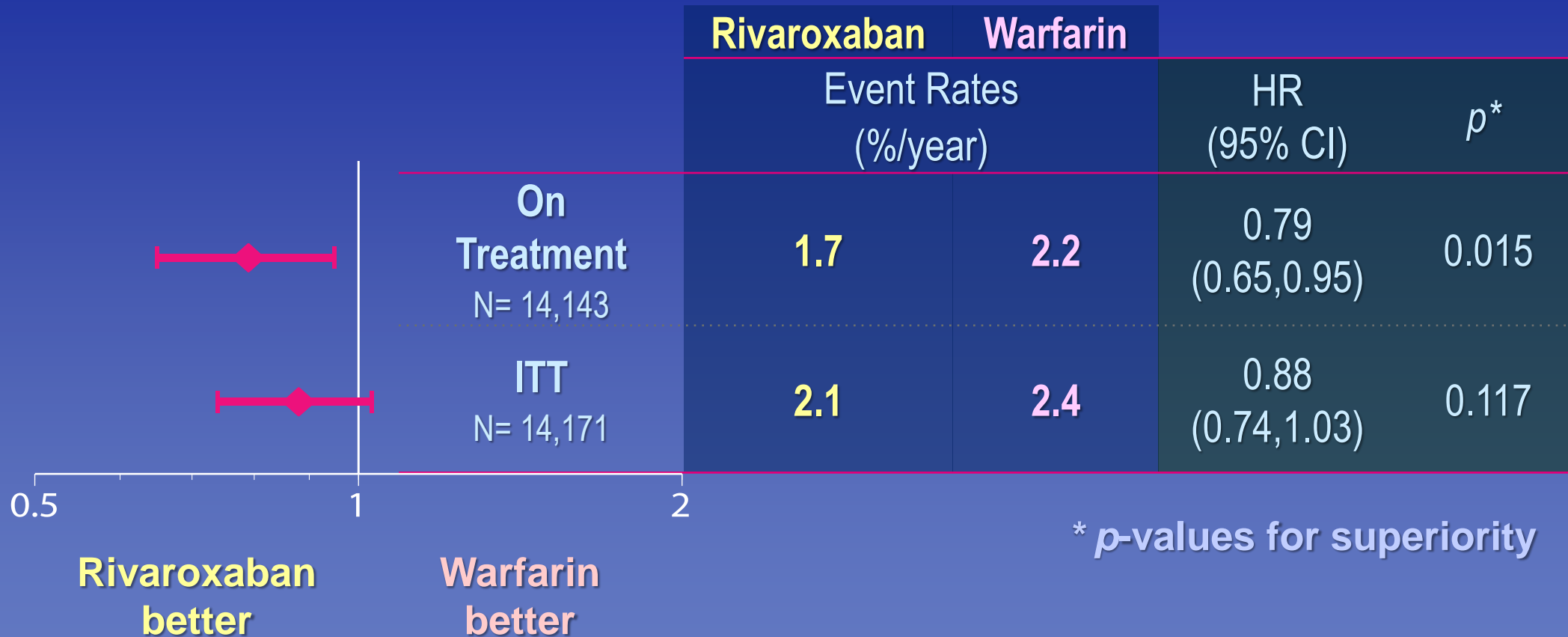


No. at risk:

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

ROCKET-AF Trial

Stroke and Systemic Embolism

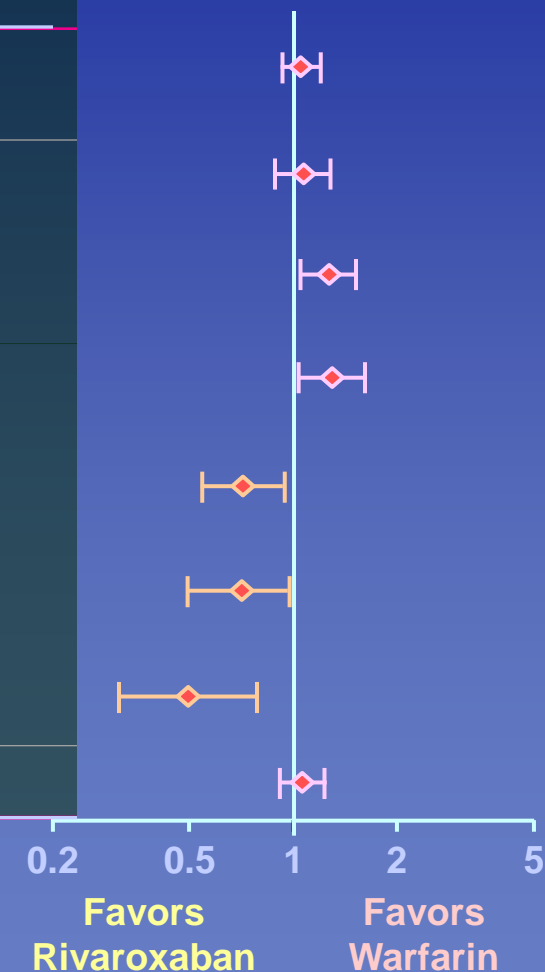


ROCKET-AF Trial

Hemorrhagic Events

Outcome	Rivaroxaban (n=7,111)	Warfarin (n=7,125)	Hazard ratio (95% CI)
All bleeding	14.9	14.5	1.03 (0.96, 1.11)
Major bleeding	3.6	3.4	1.04 (0.90, 1.20)
Hemoglobin ↓ (≥2 g/dL)	2.8	2.3	1.22 (1.03, 1.44)*
Transfusion 2 u RBC	1.6	1.3	1.25 (1.01, 1.55)*
Critical site	0.8	1.2	0.69 (0.53, 0.91)*
Intracranial	0.5	0.7	0.67 (0.47, 0.93)*
Fatal	0.2	0.5	0.50 (0.31, 0.79)*
Other clinically relevant	11.8	11.4	1.04 (0.96, 1.13)

Hazard ratio and 95% CIs

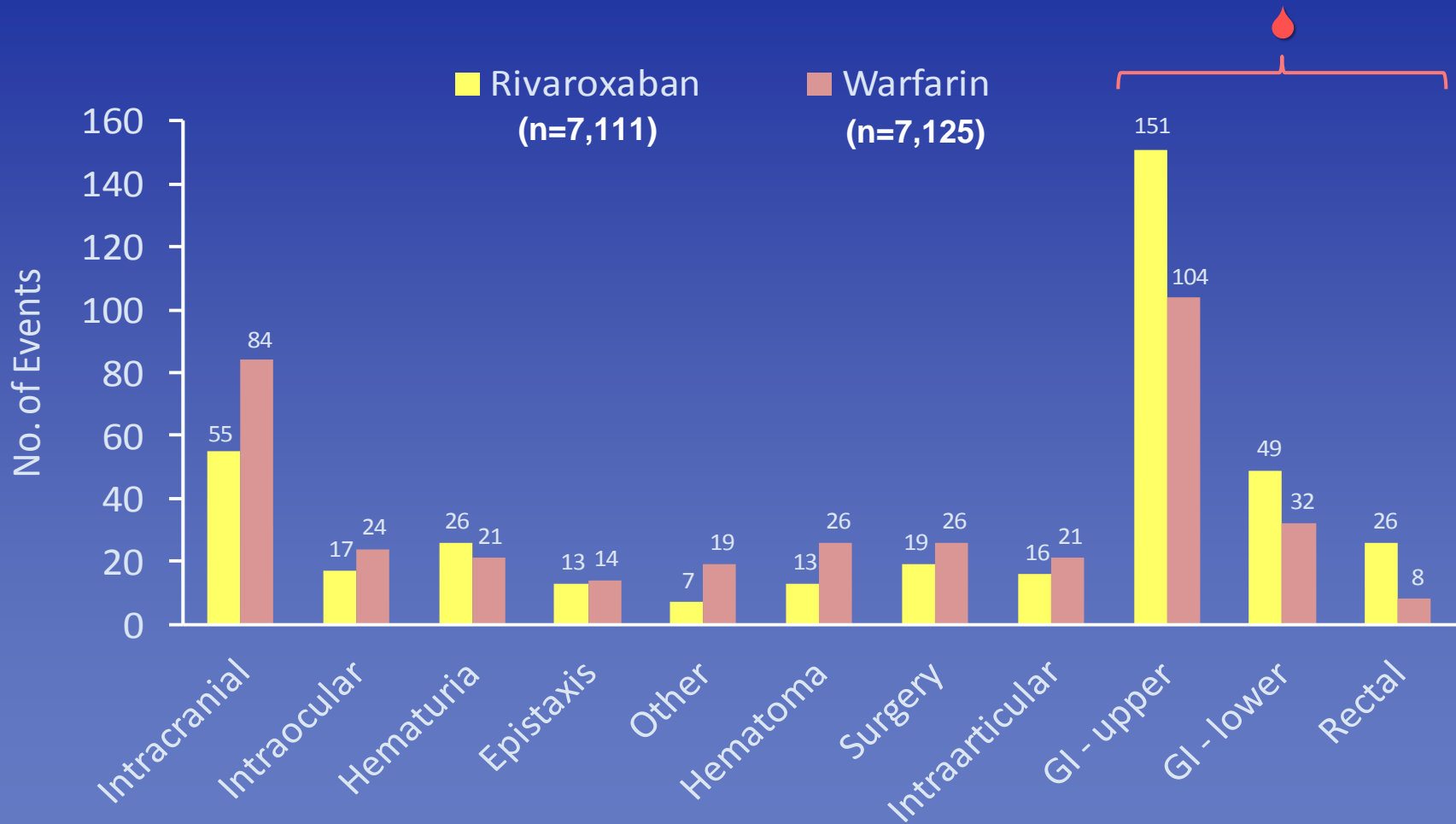


Event rates %/y in the on-treatment population

* statistically significant 2-sided *p*-value for superiority

Analysis of Bleeding Events

ROCKET-AF Trial



*Safety population on-treatment; incidence $\geq 0.2\%$ in either group.

1. Patel MR et al. *N Engl J Med.* 2011;365(10):883-891. 2. Janssen Pharmaceuticals, Inc. Data on file.

ROCKET-AF Trial

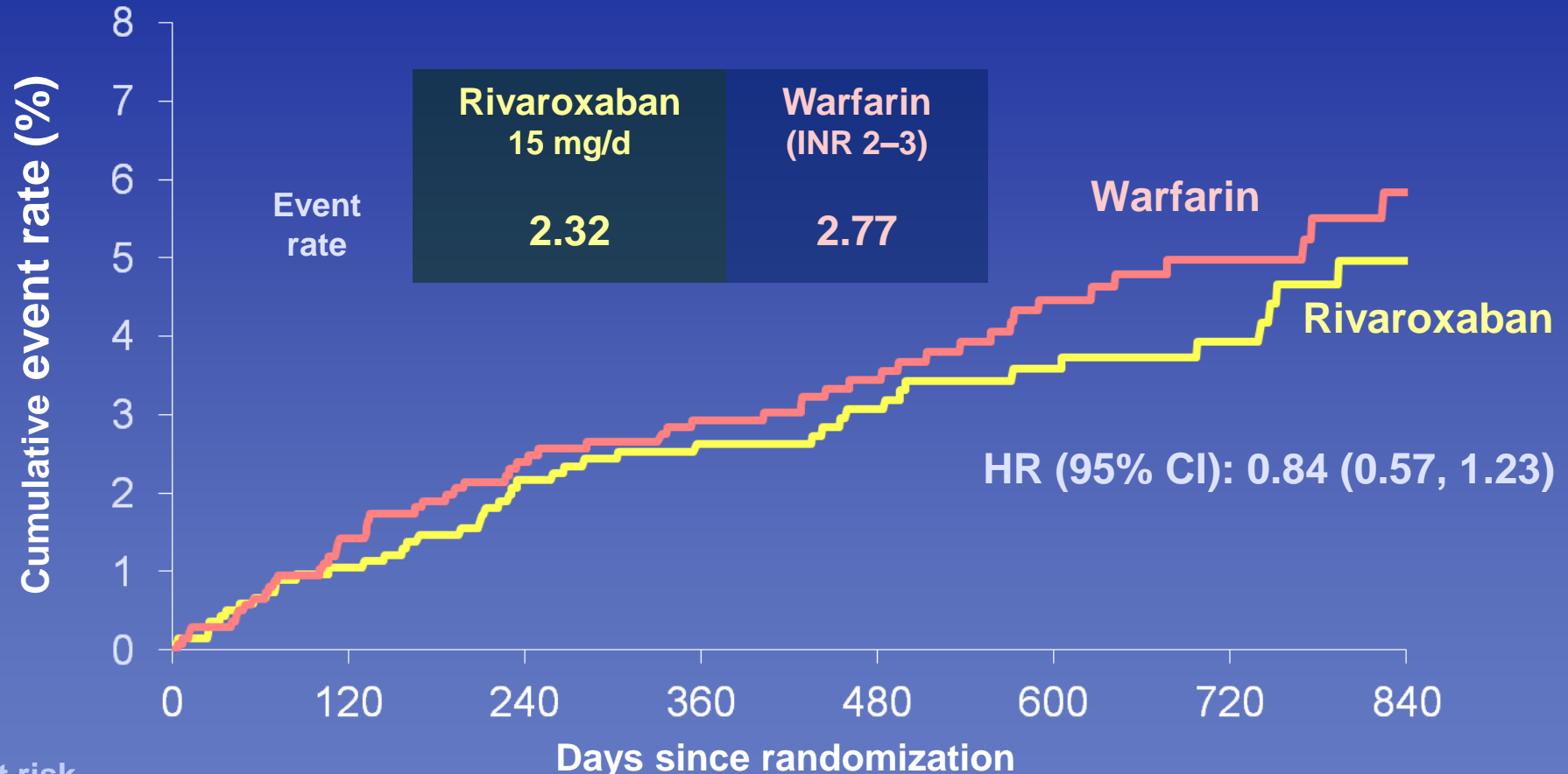
INR Time in Therapeutic Range

Mean = 55%

INR range	Warfarin
	Median (25 th - 75 th %ile)
<1.5	2.7 (0.0 – 9.0)
1.5 to <1.8	7.9 (3.5 – 14.0)
1.8 to <2.0	9.1 (5.3 – 13.6)
2.0 to 3.0	57.8 (43.0 – 70.5)
>3.0 to 3.2	4.0 (1.9 – 6.5)
>3.2 to 5.0	7.9 (3.3 – 13.8)
>5.0	0.0 (0.0 – 0.5)

Primary Events in Patients with Moderately Impaired Renal Function

Creatinine Clearance 30–49 ml/min



Number at risk

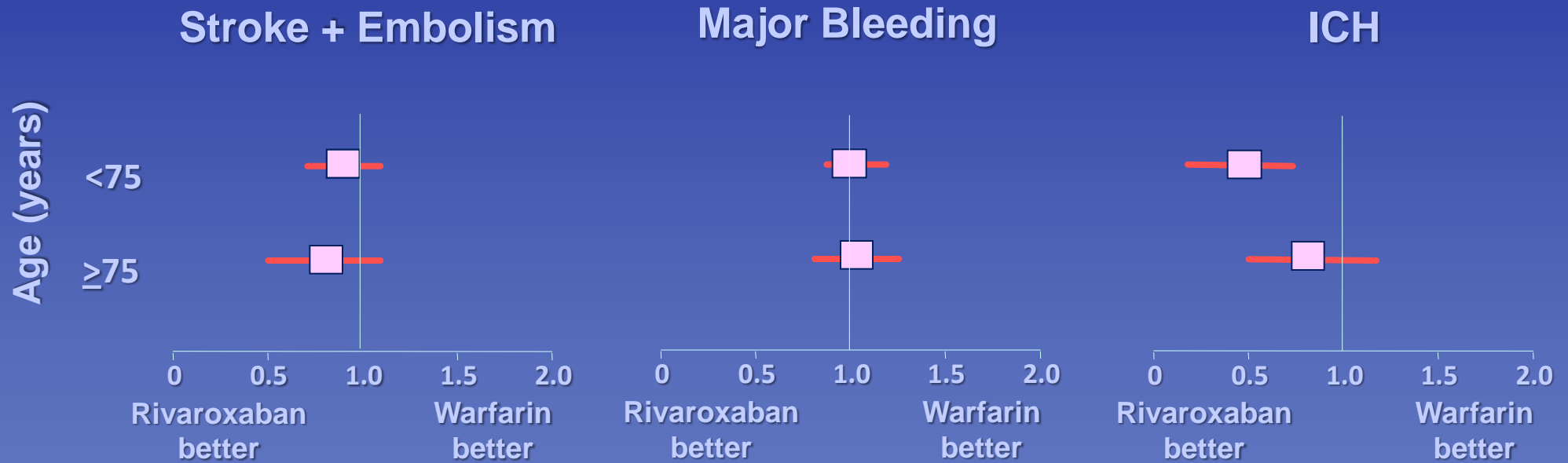
Rivaroxaban	1,434	1,226	1,103	1,027	806	621	442	275
Warfarin	1,439	1,261	1,140	1,052	832	656	455	272

Event rates are % per year

Based on Protocol Compliant on Treatment Population

Relative Risks of Major Events in the Elderly

Rivaroxaban vs. Warfarin



ARISTOTLE Trial

Study Design

Inclusion risk factors

- Age \geq 75 years
- Prior stroke, TIA, or SE
- HF or LVEF \leq 40%
- Diabetes mellitus
- Hypertension

*Randomize
double blind,
double dummy
(n = 18,201)*

Major exclusion criteria

- Mechanical prosthetic valve
- Severe renal insufficiency
- Need for aspirin plus thienopyridine

**Apixaban 5 mg oral twice daily
(2.5 mg bid in selected patients)**

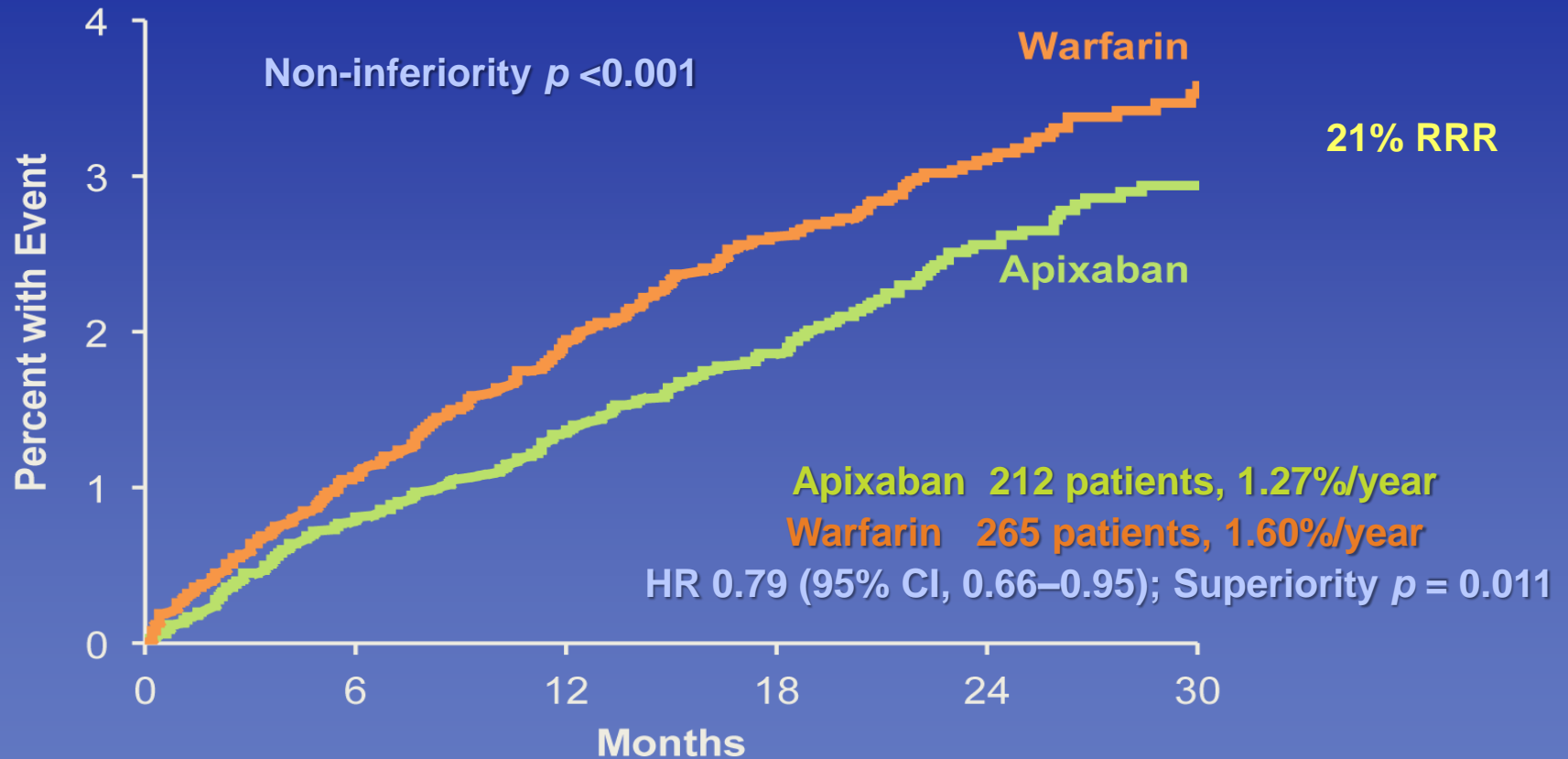
**Warfarin
(target INR 2-3)**

Primary outcome: all stroke or systemic embolism

Hierarchical testing: non-inferiority for primary outcome, superiority for primary outcome, major bleeding, death

ARISTOTLE Trial

Primary Outcome: All Stroke or Systemic Embolism

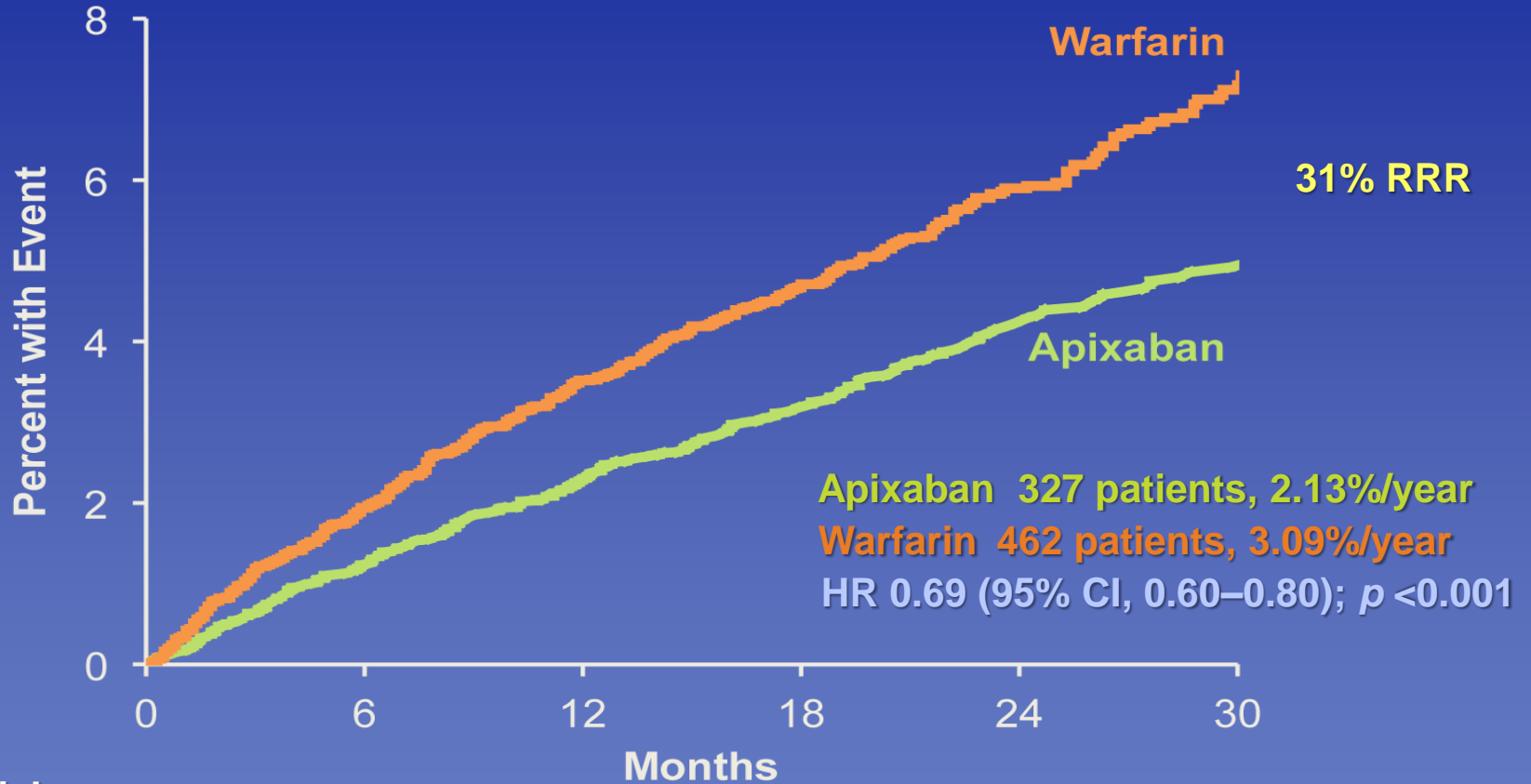


No. at Risk

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

ARISTOTLE Trial

Major Bleeding Events



No. at Risk

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

Novel Oral Anticoagulants in Advanced Development

Pharmacological Properties

Feature	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Target	Ila	Xa	Xa	Xa
Molecular Weight (g/mol)	628	436	460	548
Prodrug	Yes	No	No	No
Bioavailability (%)	6	80	50	45
Time to peak (h)	2	3-6	3	2
Half-life (h)	12-17	9-13	9-14	8-10
Renal excretion (%)	80	65	25	35
Antidote	None	None	None	None

Adapted from

WeitzJI. ACC Scientific Sessions, Atlanta, GA, March 13, 2010.

Gibson M. ESC Scientific Sessions, Paris, France, August 2011.

New Oral Anticoagulants

Phase III Trials for Prevention of Stroke and Systemic Embolism in Patients with AF

Trial Acronym	Drug	Dose (mg)	Design	n	Risk Factors (#)	VKA-naïve (%)
RE-LY	Dabigatran	150 bid 110 bid	PROBE	18,113	1	50
ROCKET-AF	Rivaroxaban	20 qd 15 qd*	Blinded	14,266	≥ 2	38
ARISTOTLE	Apixaban	5 bid 2.5 bid*	Blinded	18,206	≥ 1	43
ENGAGE-AF	Edoxaban	30 qd 60 qd	Blinded	>20,000	≥ 2	~40

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

New Oral Anticoagulants for AF

Variations in Trial Design

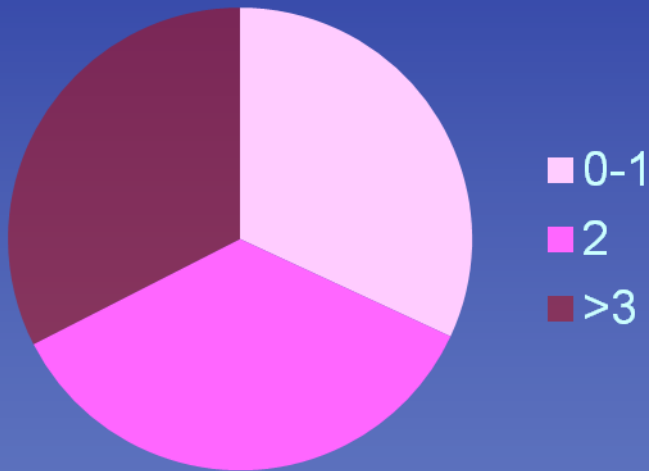
- Blinded vs. open-label
- Intrinsic patient risk
 - CHADS₂ score
 - Prior stroke
 - Age
 - VKA-naïve
- Management of treatment transitions
- Definitions
 - Time in therapeutic range (warfarin)
 - Criteria for major bleeding
- Priority of ITT vs. OT analysis

Recently Completed AF Trials

Distribution of Stroke Risk Factors

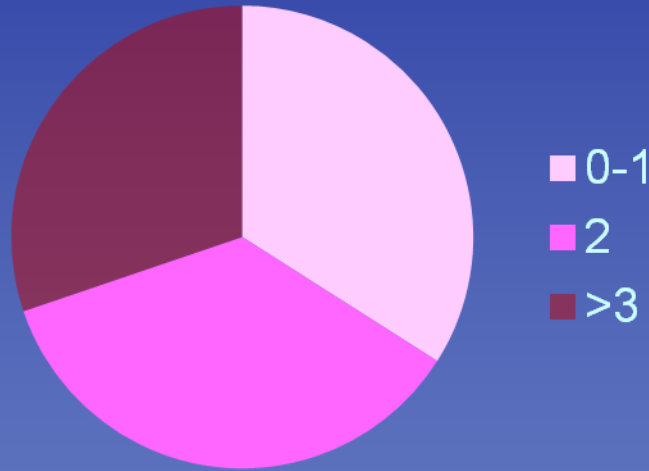
CHADS₂ Scores

RE-LY



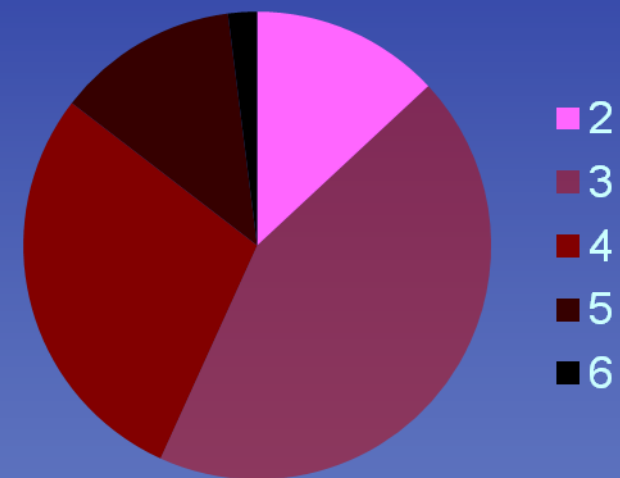
Mean 2.2

ARISTOTLE



Mean 2.1

ROCKET-AF



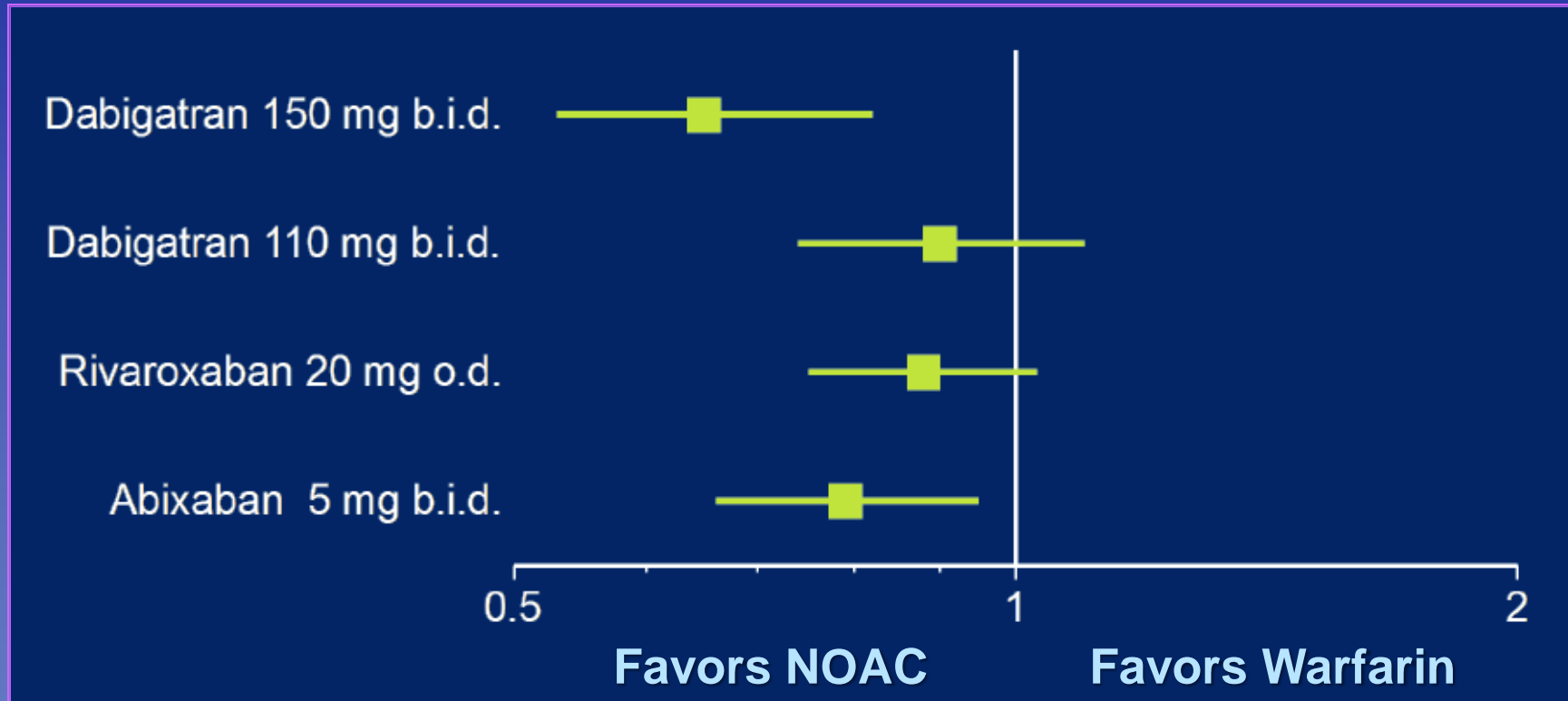
Mean 3.5

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

All Stroke and Systemic Embolism *Comparisons to Warfarin*



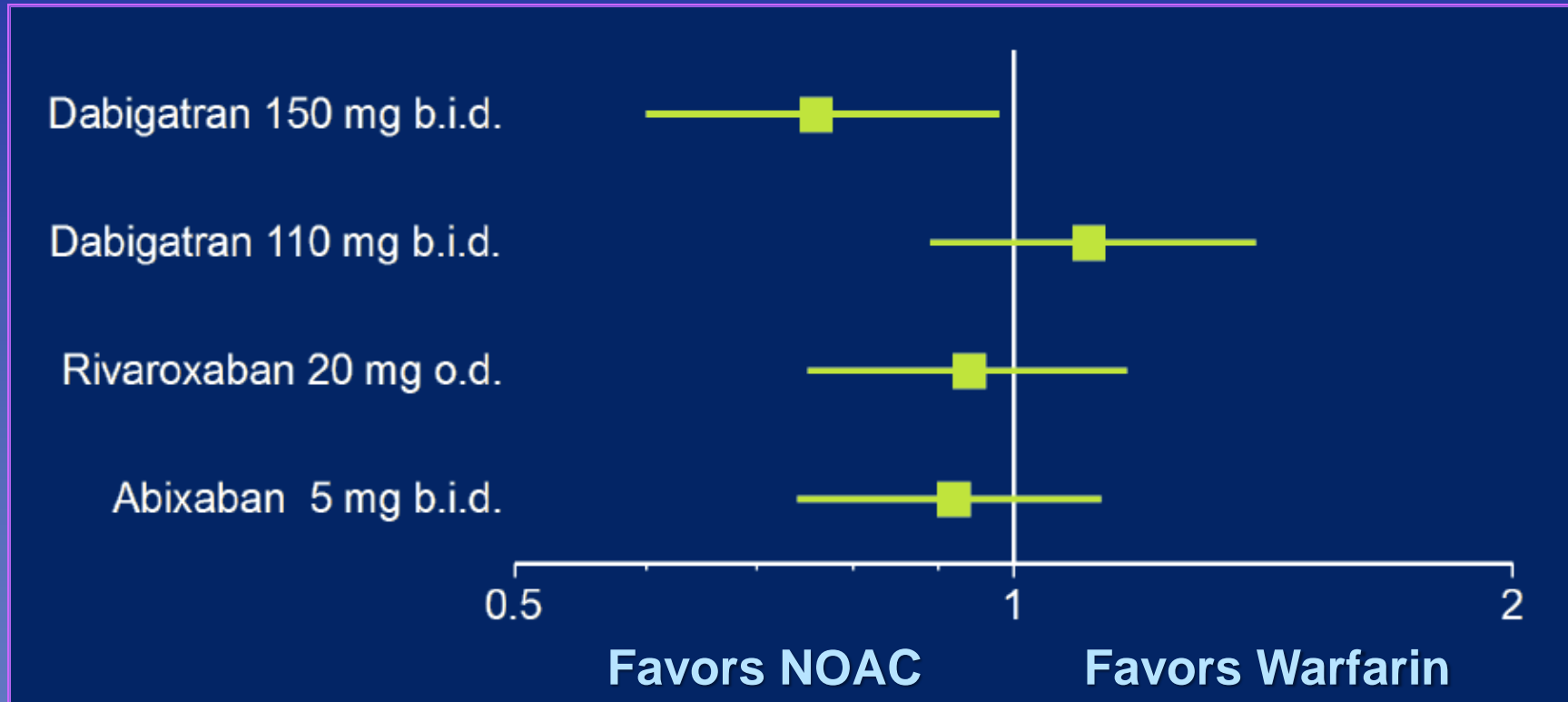
Connolly SJ et al. *N Engl J Med* 2009; 361: 1139.

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

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

Rates of Ischemic Stroke

Comparisons to Warfarin



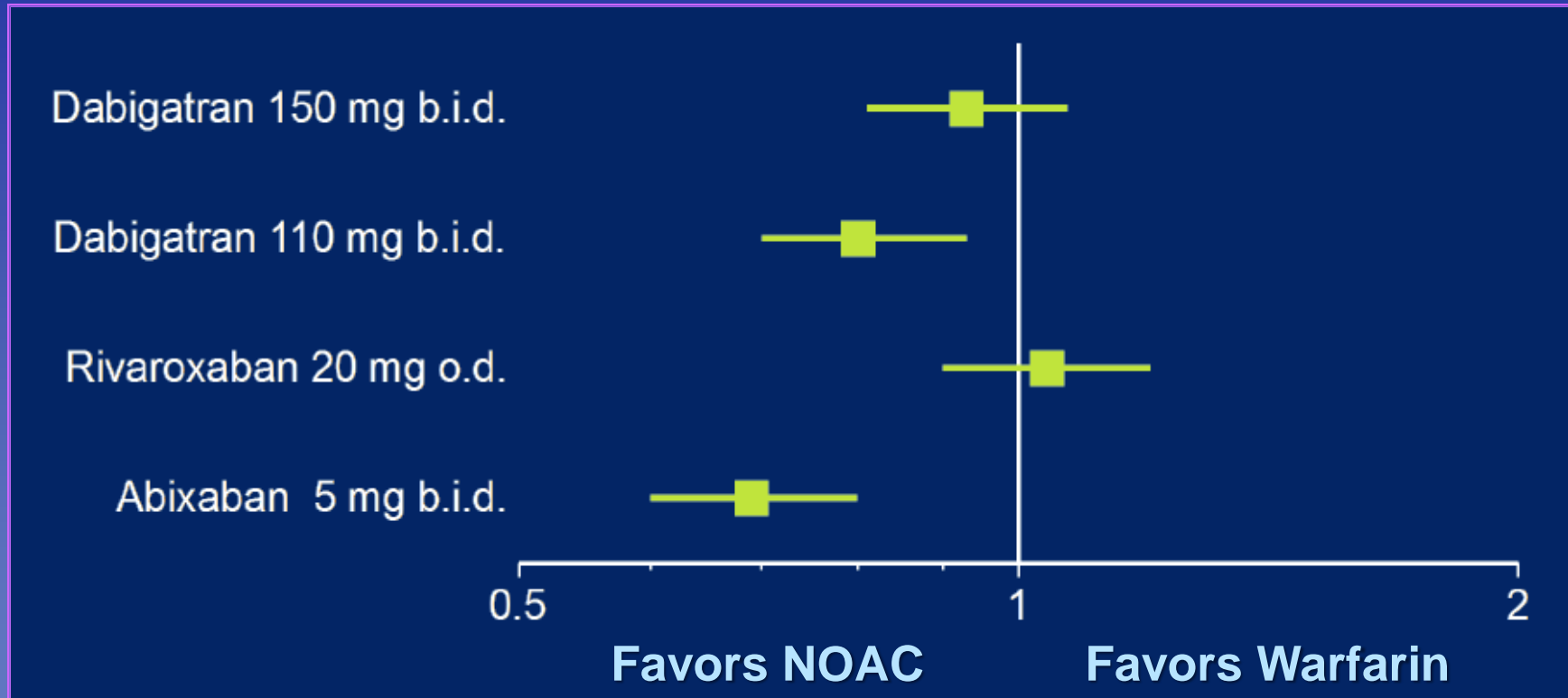
Connolly SJ et al. *N Engl J Med* 2009; 361: 1139.

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

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

Rates of Major Bleeding

Comparisons to Warfarin



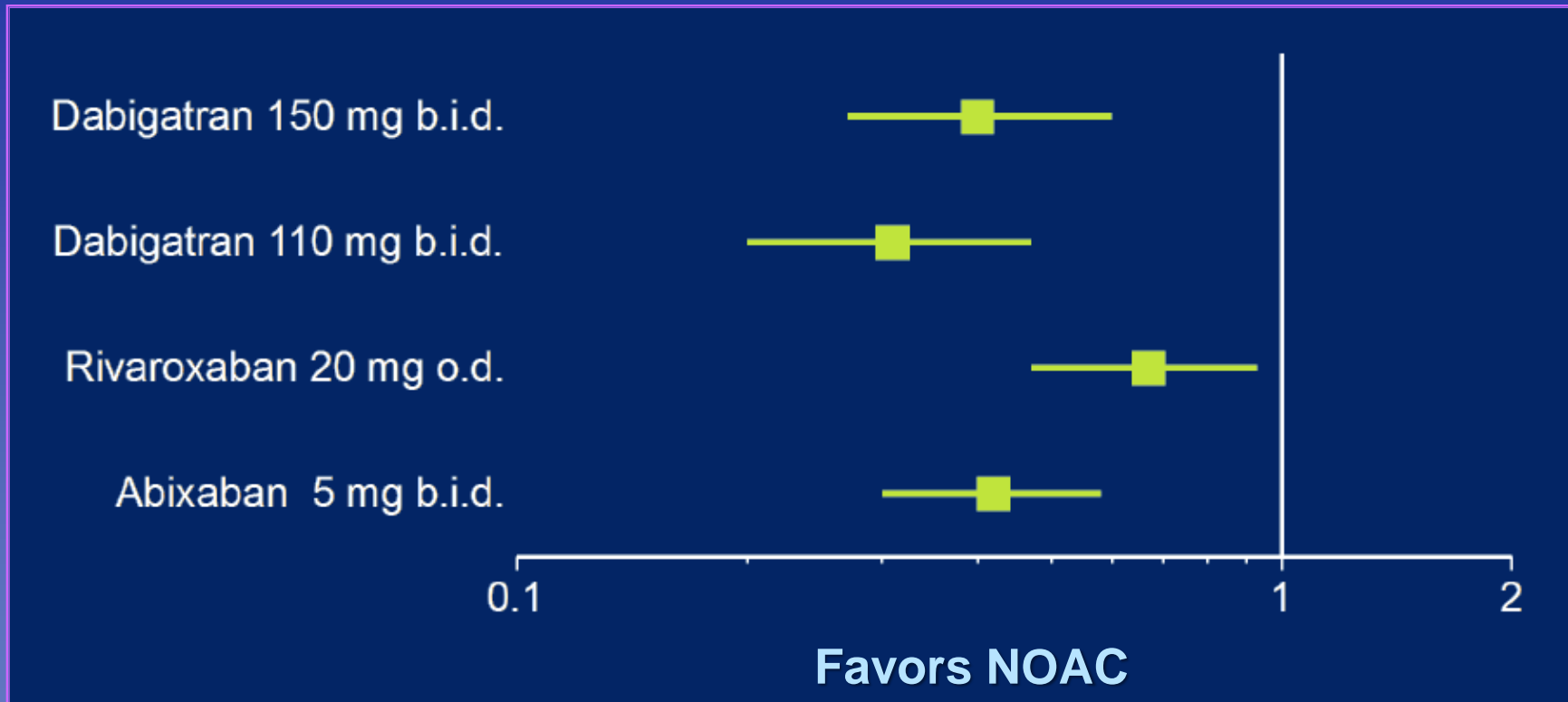
Connolly SJ et al. *N Engl J Med* 2009; 361: 1139.

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

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

Rates of Hemorrhagic Stroke

Comparisons to Warfarin



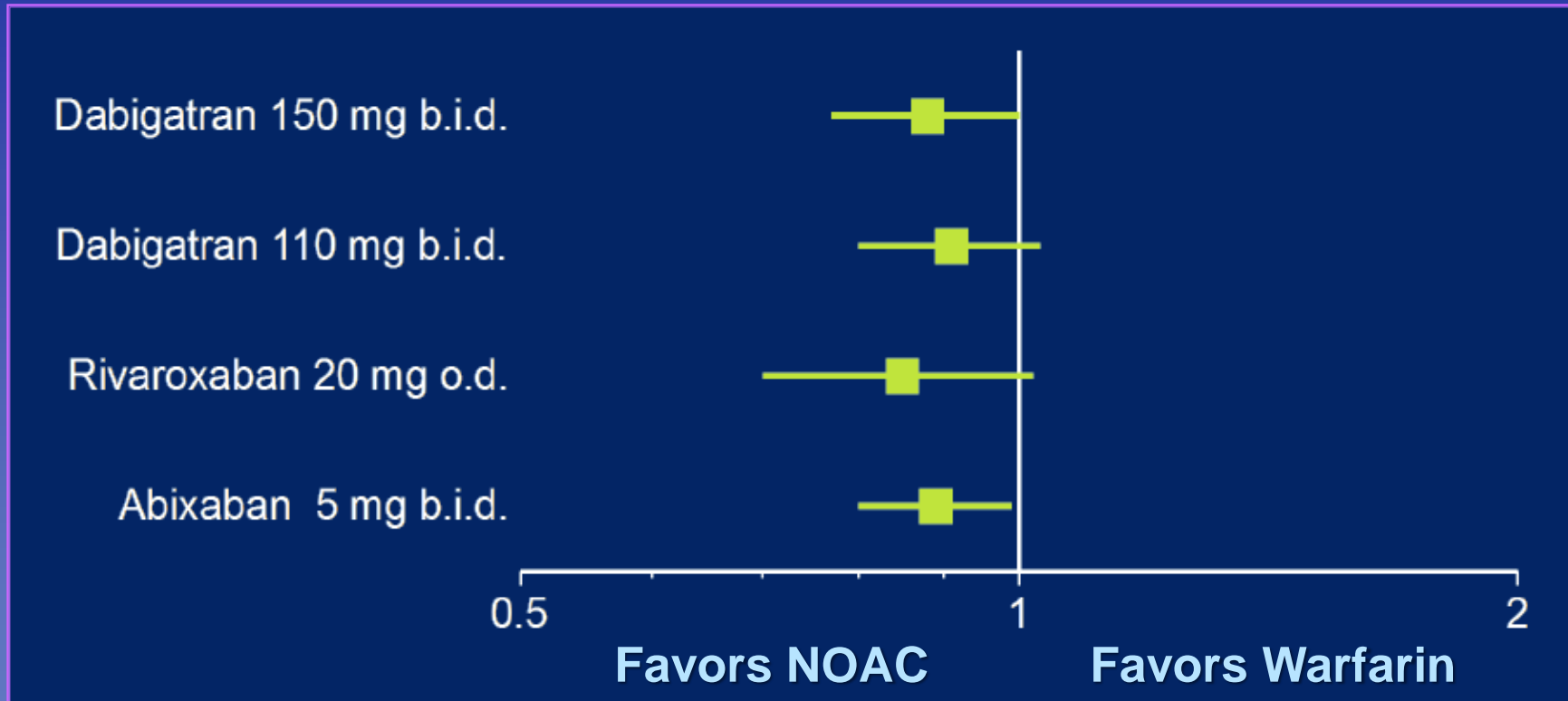
Connolly SJ et al. *N Engl J Med* 2009; 361: 1139.

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

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

All-Cause Mortality Rates

Comparisons to Warfarin



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 Engl J Med* 2011; 365.

Three New 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
- Reductions in mortality are comparable, ~10%/year

Three New Oral Anticoagulants for AF

Several Differences

- Dabigatran (150 mg twice daily) reduced ischemic stroke more than warfarin but caused more extracranial bleeding, especially in the elderly.
- Rivaroxaban (20 mg once daily) reduced fatal bleeding but caused more extracranial bleeding.
- Apixaban (5 mg twice daily) reduced major bleeding and all-cause mortality, but not cardiovascular mortality.

Emerging Anticoagulants

Clinical Uncertainties

- Will a short half-life obviate the need for an antidote or escalate risk related to missed doses?
- How to assess anticoagulant effect in acute situations?
- How to balance benefit and risk for newly anticoagulated patients vs. those stable on warfarin?
- Can better anticoagulants eliminate the need for risk-stratification?
- Will eliminating anticoagulation monitoring adversely impact other aspects of care?

Alternatives to Anticoagulation

Atrial Fibrillation

Current approaches

Restoration and maintenance of sinus rhythm

- Antiarrhythmic drug therapy
- Catheter ablation
- Maze operation

Emerging (investigational) approaches

Obliteration of the left atrial appendage

- Trans-catheter occluding devices
- Thoracoscopic epicardial plication
- Amputation

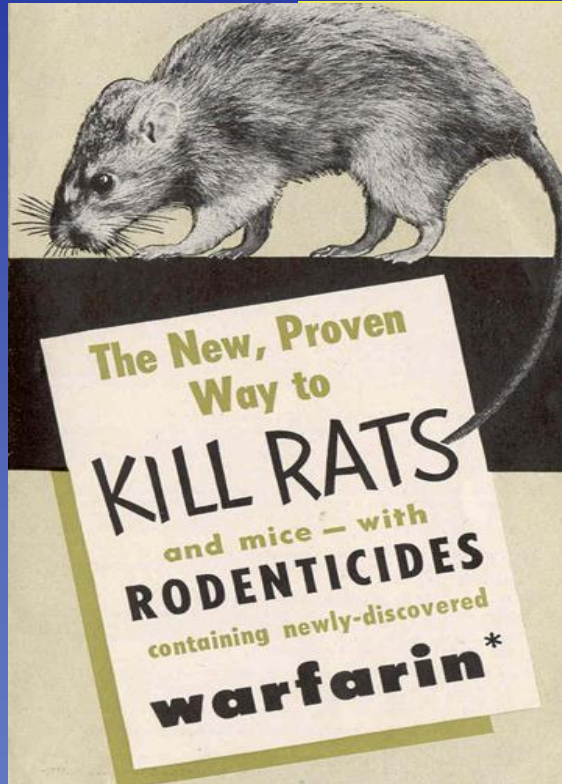
Atrial Fibrillation and Thromboembolism

The Next Challenges

- Integrated risk-stratification schemes that consider both stroke and bleeding and address new anticoagulants
- Accelerating development of reversal agents
- Comparative effectiveness studies
- Targeted upstream AF prevention in susceptible populations

From Fermented Sweet Clover to Molecular Targeting of Thrombosis

The Promise of New Oral Anticoagulants



The Goal:
To bring effective therapy to many more patients and prevent thousands of strokes.

Thank you!