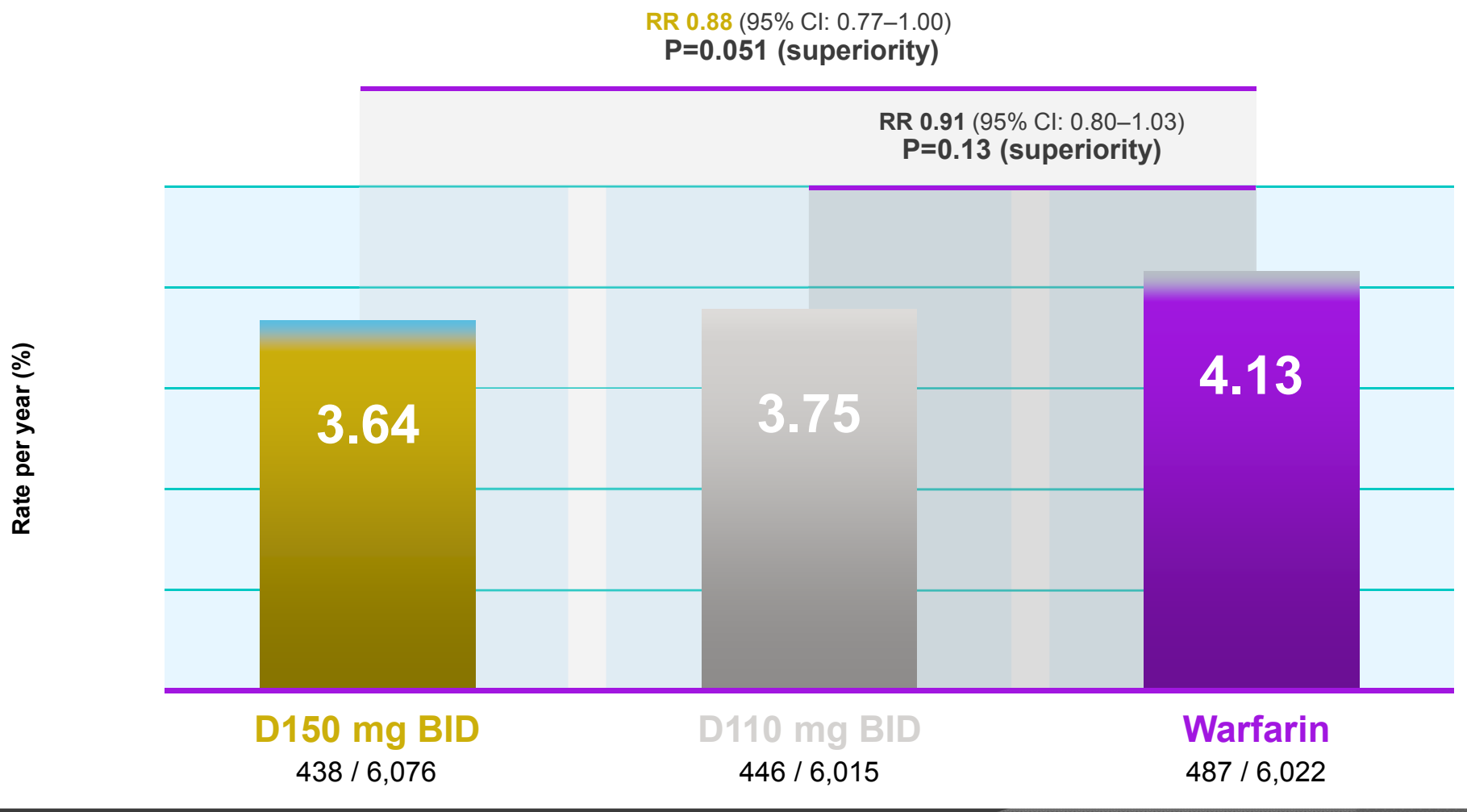
ALL-CAUSE MORTALITY

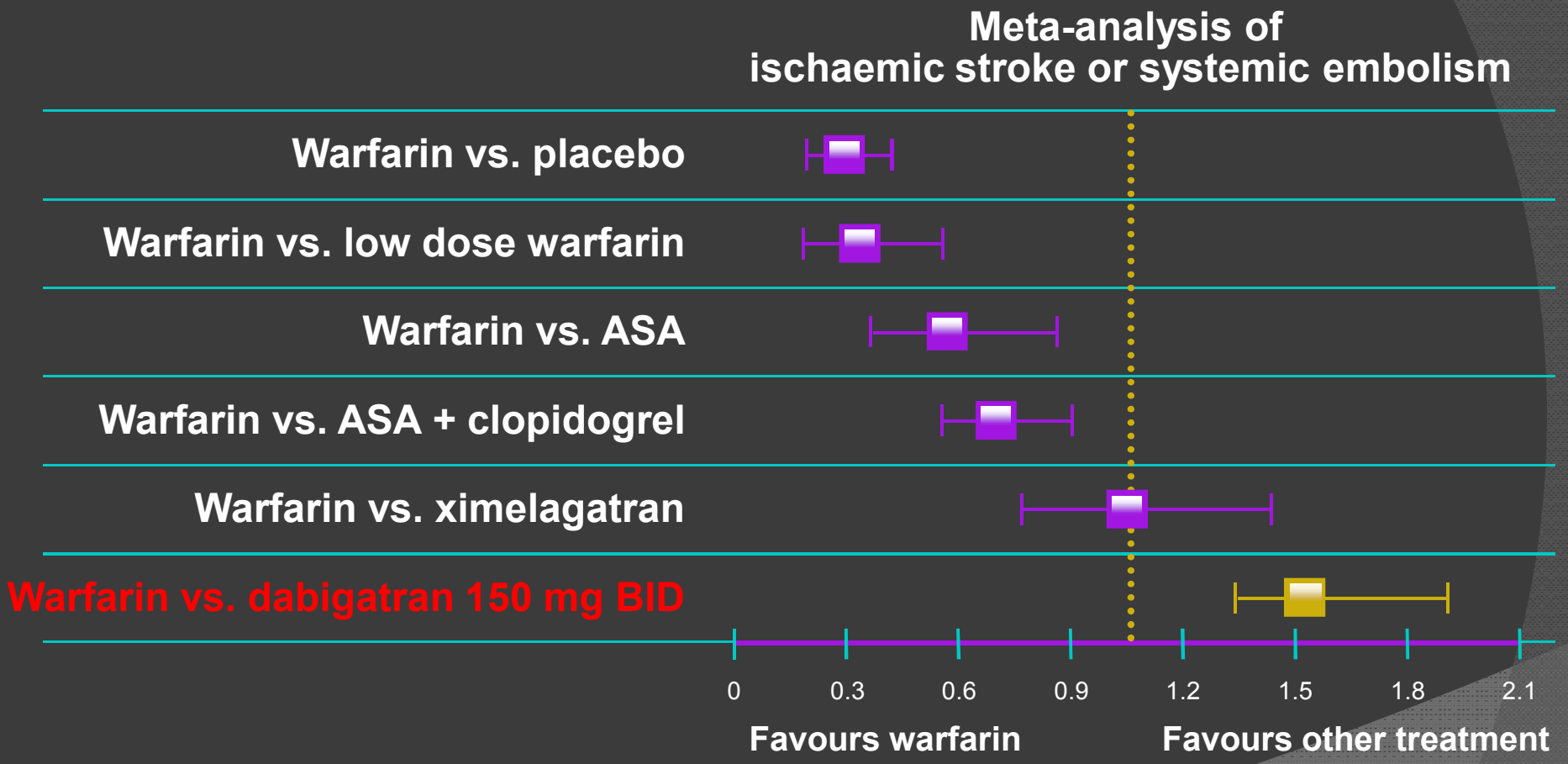


D = dabigatran; RR = relative risk; RRR = relative risk reduction.

Dabigatran etexilate is not approved for clinical use in stroke prevention in atrial fibrillation outside the US and Canada.

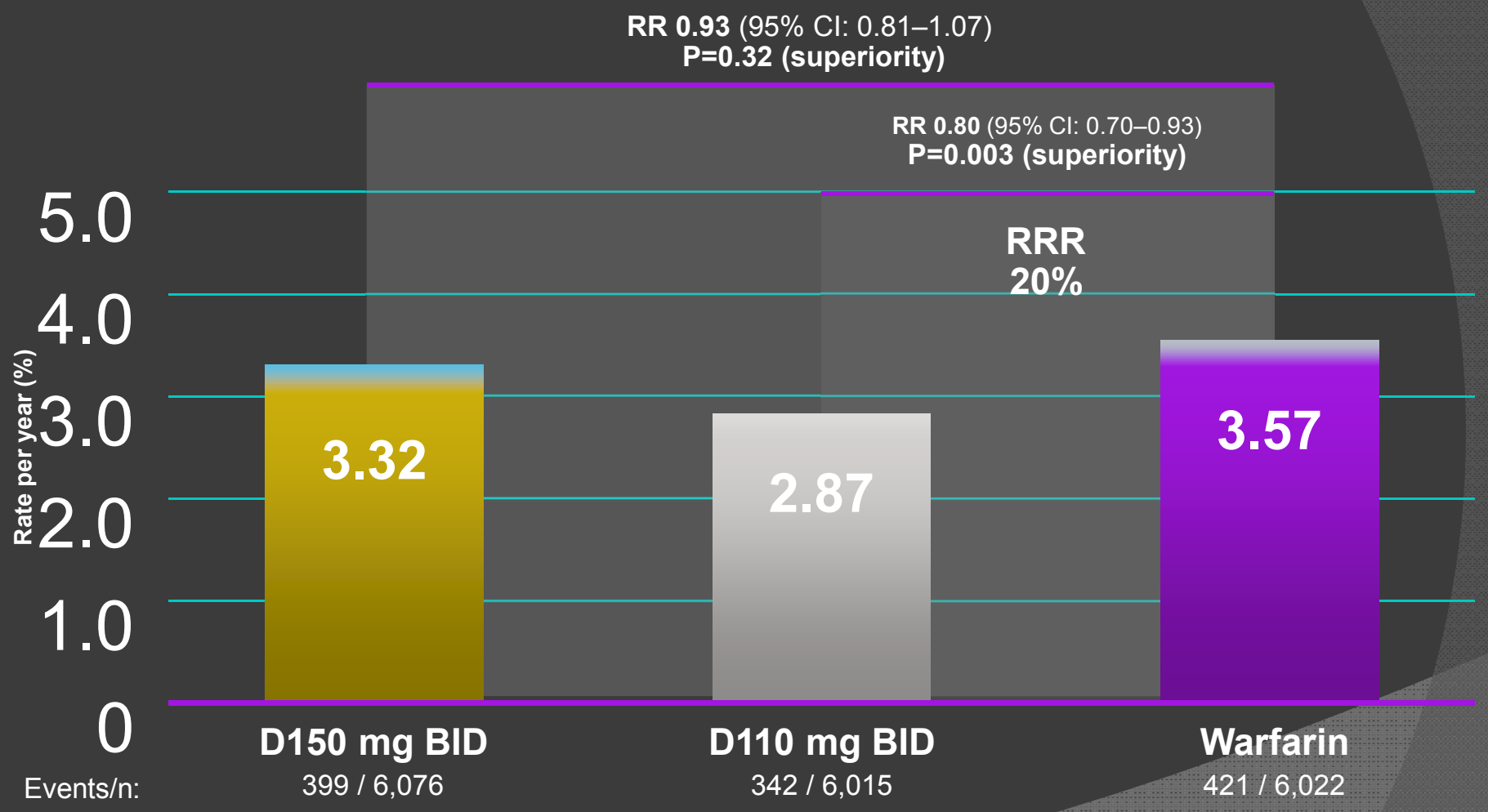
Connolly SJ, et al. *N Engl J Med* 2009;361:1139-1151.

RE-LY® IN PERSPECTIVE



ASA = acetylsalicylic acid.
Dabigatran etexilate is not approved for clinical use in stroke prevention in atrial fibrillation outside the US and Canada.
Camm J. Oral presentation at ESC on 30 Aug 2009 http://www.escardio.org/congresses/esc-2009/webcasts/pages/sunday.aspx

MAJOR BLEEDING RATES



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APIXABAN VERSUS WARFARIN IN PATIENTS WITH ATRIAL FIBRILLATION

RESULTS OF THE ARISTOTLE TRIAL

Atrial Fibrillation with at Least One Additional Risk Factor for Stroke

Inclusion risk factors
- Age ≥ 75 years
- Prior stroke, TIA, or SE
- HF or LVEF ≤ 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)

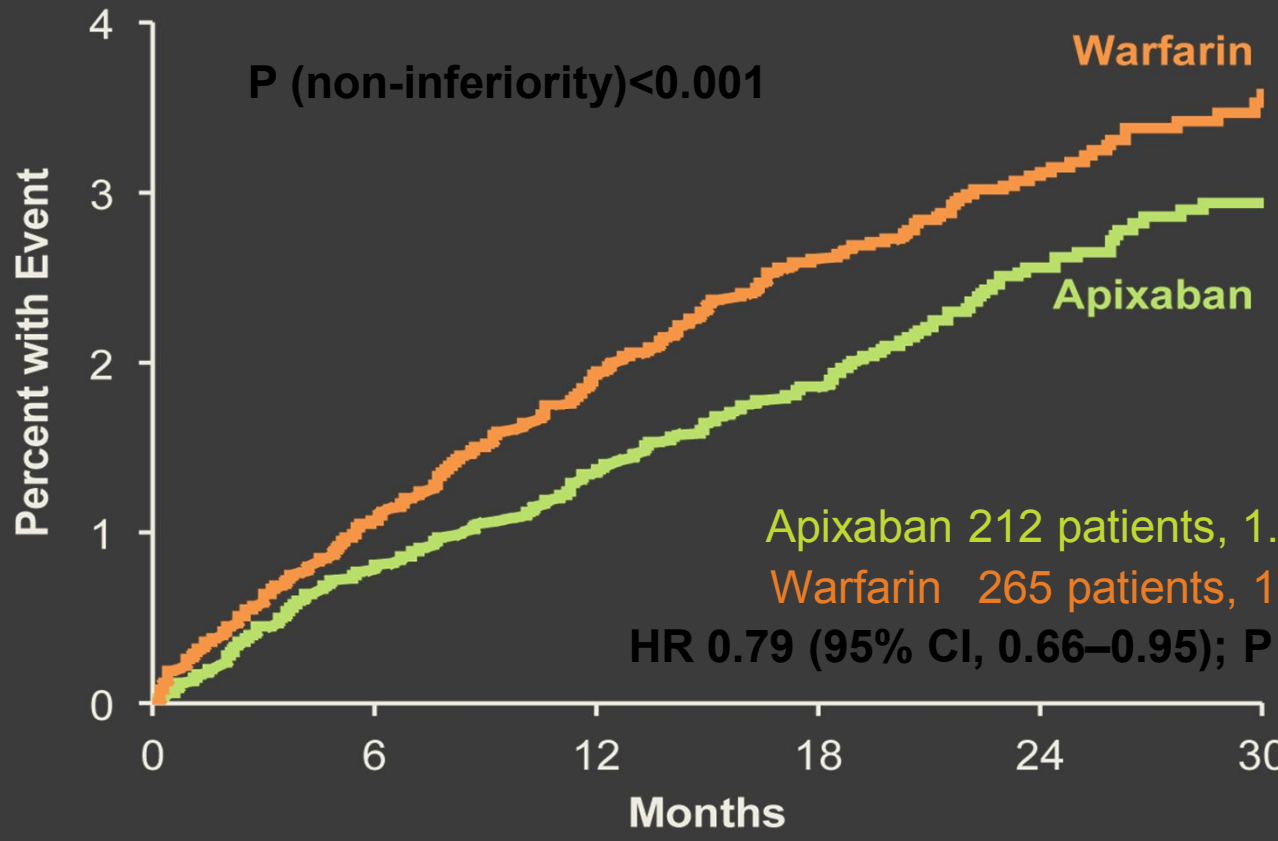
Warfarin/warfarin placebo adjusted by INR/sham INR based on encrypted point-of-care testing device

Primary outcome: stroke or systemic embolism

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

Primary Outcome

Stroke (ischemic or hemorrhagic) or systemic embolism



21% RRR

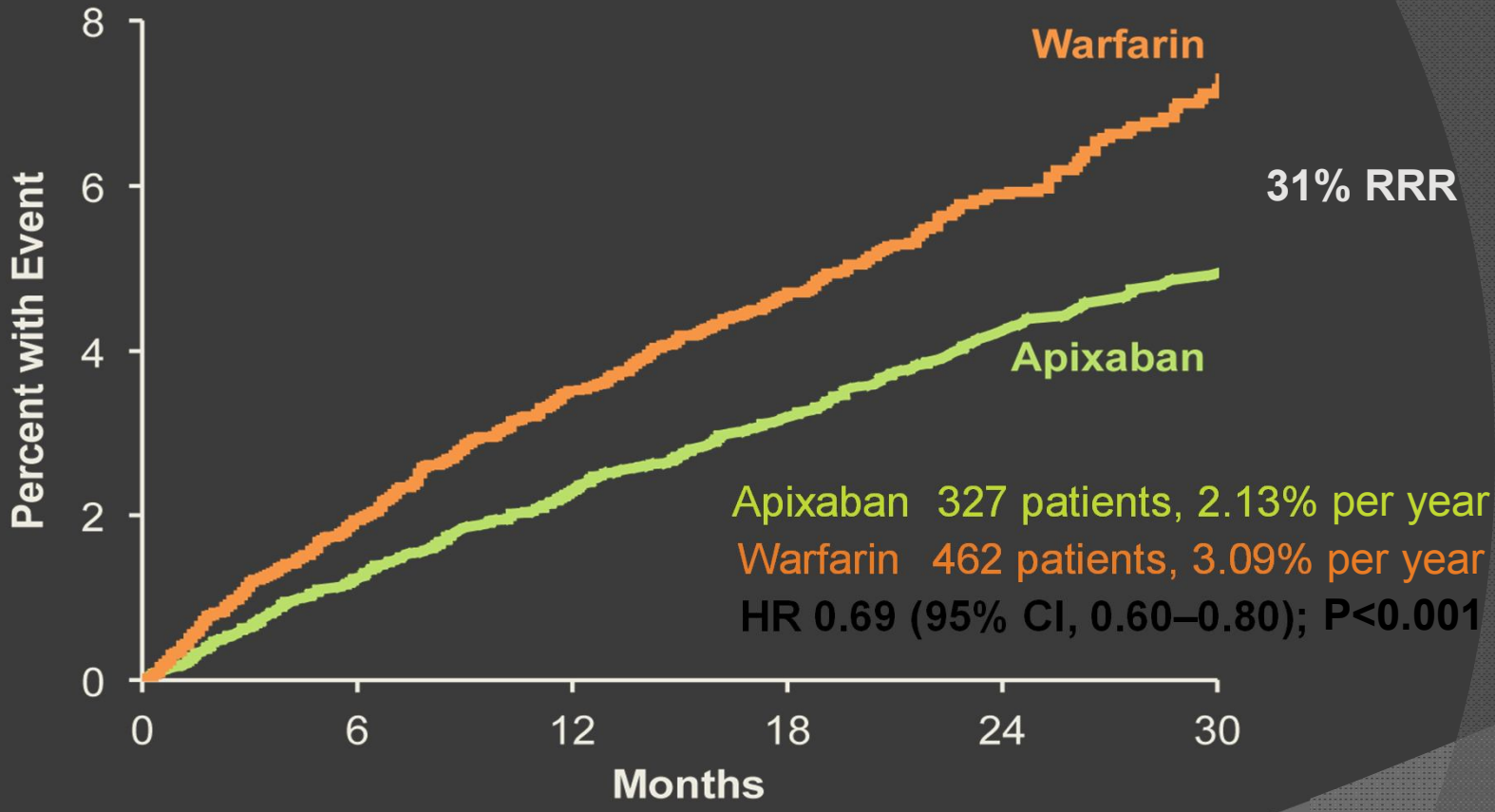
Apixaban 212 patients, 1.27% per year

Warfarin 265 patients, 1.60% per year

HR 0.79 (95% CI, 0.66–0.95); P (superiority)=0.011

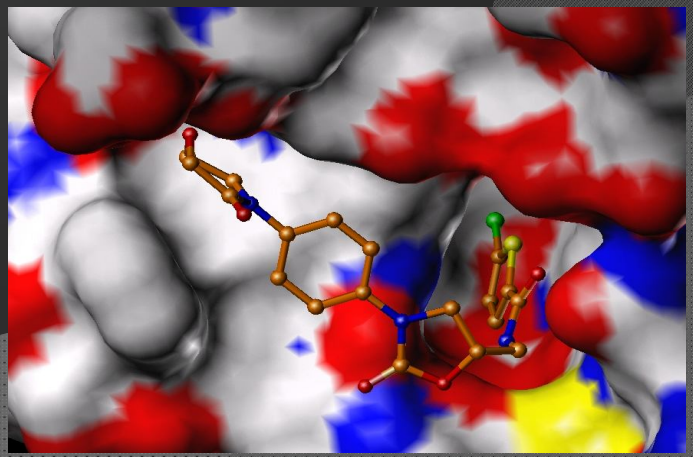
Major Bleeding

ISTH definition

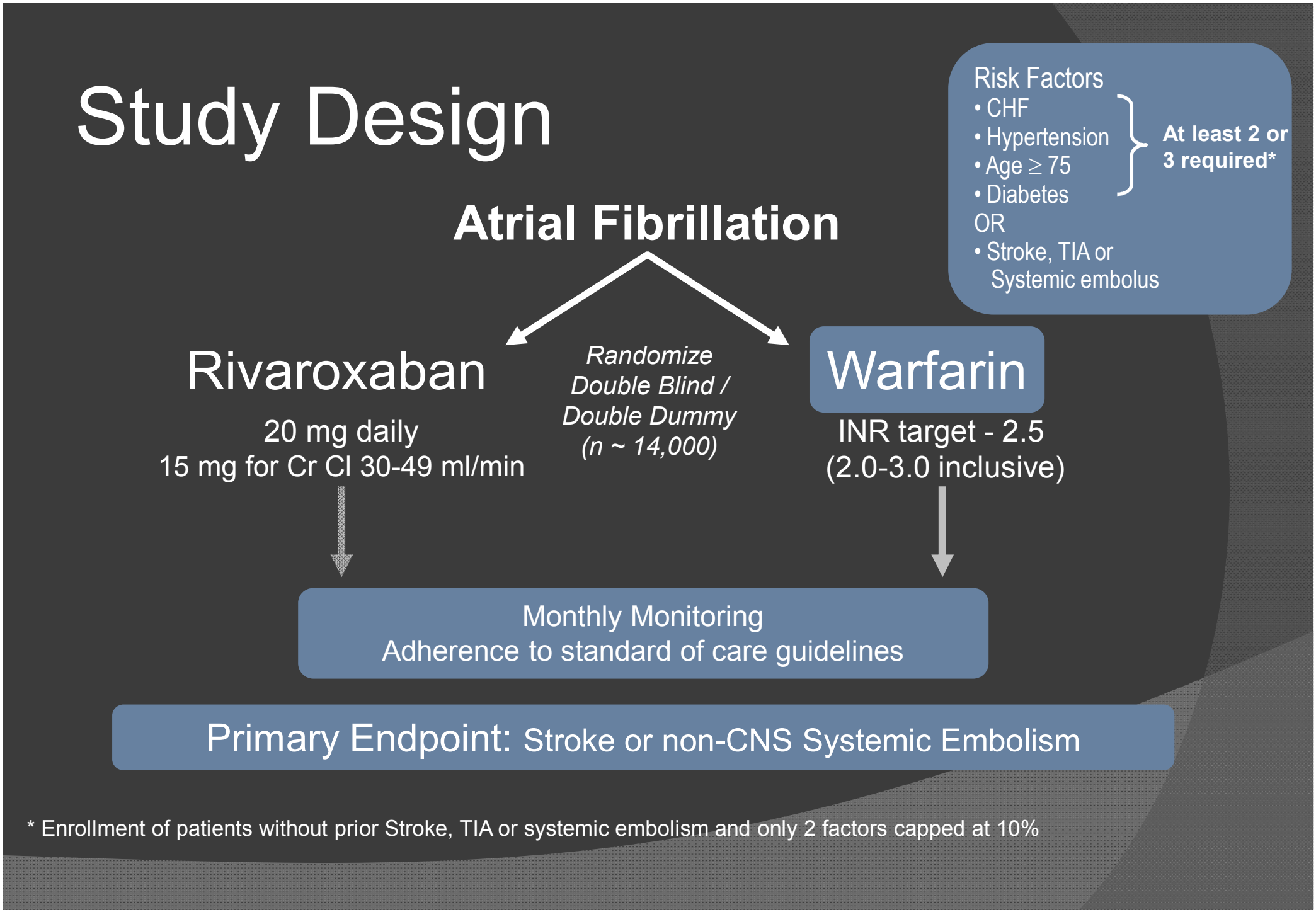


Rivaroxaban Once-daily oral direct factor Xa inhibition Compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation

ROCKET AF



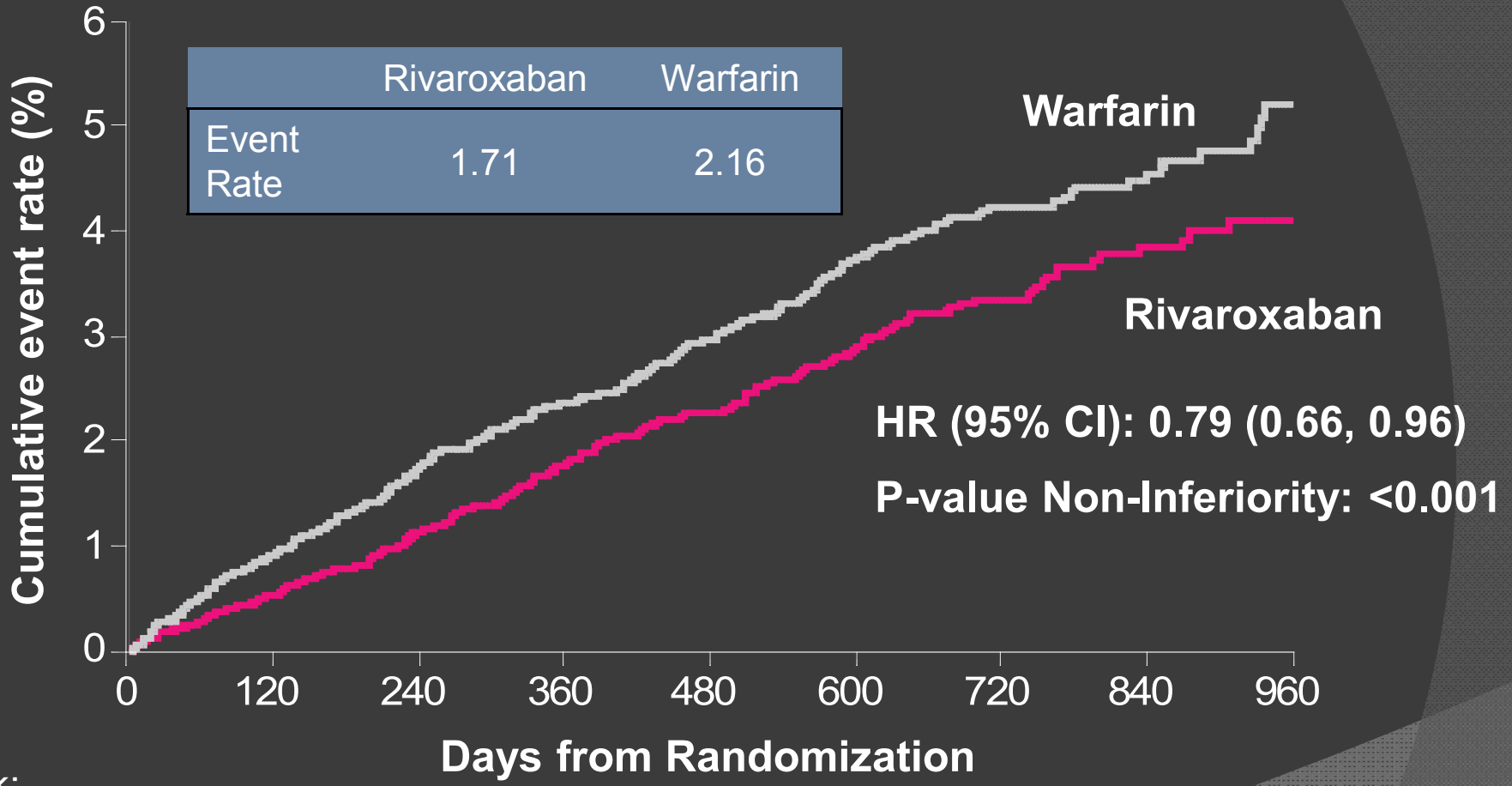
Study Design



* Enrollment of patients without prior Stroke, TIA or systemic embolism and only 2 factors capped at 10%

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

Primary Safety Outcomes

	Rivaroxaban	Warfarin		
	Event Rate	Event Rate	HR (95% CI)	P-value
Major and non-major Clinically Relevant	14.91	14.52	1.03 (0.96, 1.11)	0.442
Major	3.60	3.45	1.04 (0.90, 1.20)	0.576
Non-major Clinically Relevant	11.80	11.37	1.04 (0.96, 1.13)	0.345

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

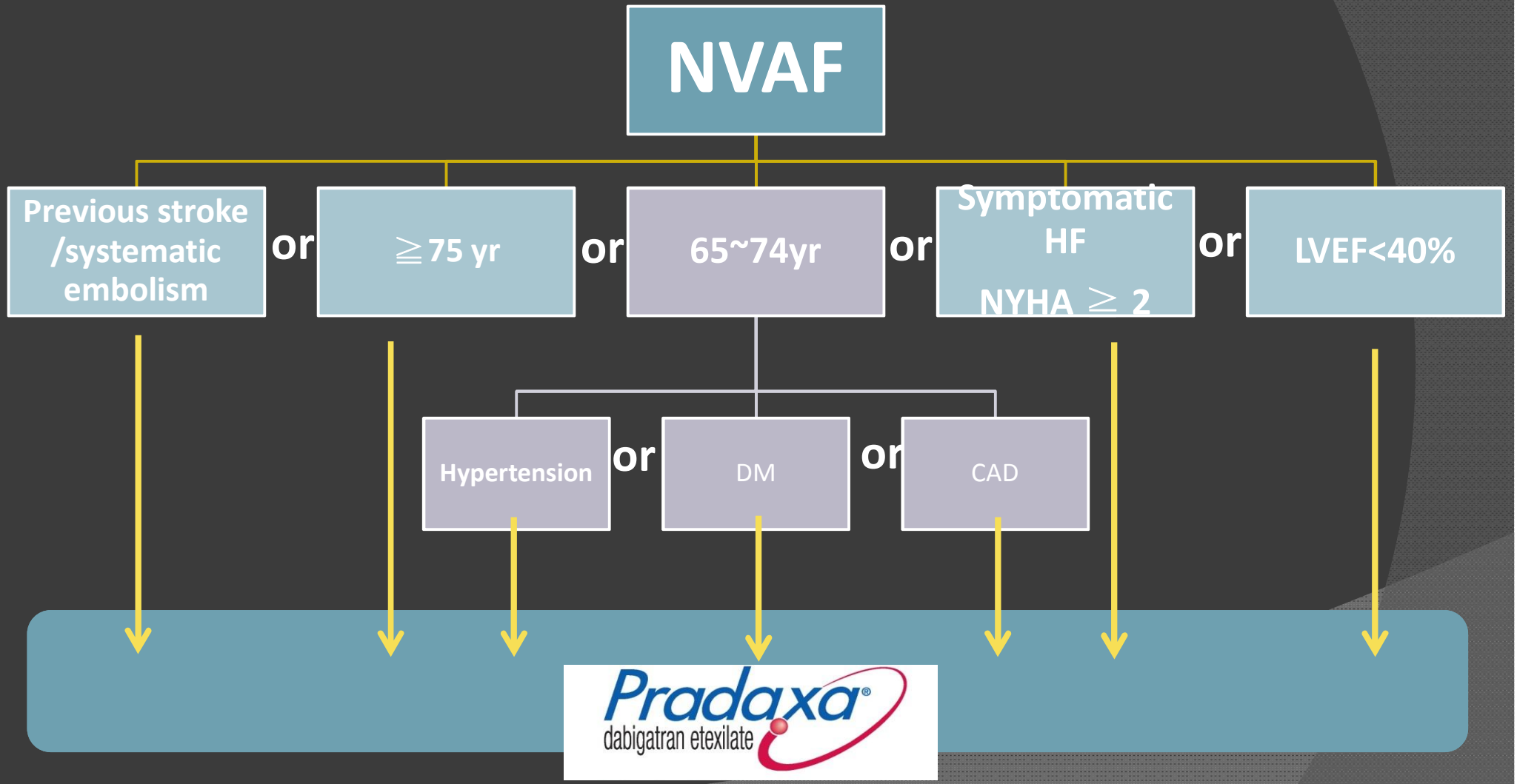
Global Study to Assess the Safety and Effectiveness of DU-176b(Edoxaban) vs Standard Practice of Dosing With Warfarin in Patients With Atrial Fibrillation (EngageAFTIMI48)

STILL ONGOING

Limitation of current oral anticoagulant

- No monitoring
- Unable to titrate dose
- Failure of therapy vs. poor compliance
- Short $t_{1/2}$
- Poor compliance may affect efficacy more than VKA
- No antidote
- Renal/hepatic dose adjustments likely required
- Cost

Pradaxa BNHI Reimbursement Criteria



Novel anticoagulant in ACS

Table 3 Phase II Double-Blind, Placebo-Controlled, Dose-Escalation Trials of New Anticoagulants in Acute Coronary Syndromes

	Dabigatran Etexilate	Rivaroxaban	Apixaban	Darexaban
Acronym	RE-DEEM	ATLAS	APPRAISE	RUBY-1
n	1,861	3,491	1,715	1,279
STEMI/NSTEMI ACS, %	60/40	52/48	61–67/33–39	71/29
Dual platelet inhibition, %	99	Stratum 1: 0; stratum 2: 100	76	97
Duration of therapy, months	6	6	6	6
Dosage	50–150 B.I.D.	5–20 mg Q.D.	10–20 mg Q.D./2.5–10 mg B.I.D.	10–60 mg Q.D./5–30 mg B.I.D.
Safety outcome, HR (95% CI)	50 mg: 1.82 (0.77–4.29) 75 mg: 2.44 (1.05–5.65) 110 mg: 3.36 (1.60–7.91) 150 mg: 3.88 (1.73–8.74)	Stratum 1: 5 mg: 0.81 (0.09–7.23) 10 mg: 3.40 (0.91–12.65) 20 mg: 6.43 (1.94–21.37) Stratum 2: 5 mg: 2.17 (0.91–5.18) 10 mg: 3.34 (2.15–5.19) 15 mg: 3.41 (1.97–5.89) 20 mg: 4.56 (2.83–7.33)	2.5 mg B.I.D.: 1.78 (0.91–3.48) 10 mg B.I.D.: 2.45 (1.31–4.61) 10-mg B.I.D. and 20-mg Q.D. arms terminated because of a high bleeding* risk	10 mg Q.D.: 1.78 (0.68–4.60) 30 mg Q.D.: 1.83 (0.71–4.75) 60 mg Q.D.: 2.43 (0.98–5.97) 5 mg B.I.D.: 2.05 (0.81–5.15) 15 mg B.I.D.: 2.27 (0.92–5.59) 30 mg B.I.D.: 3.80 (1.66–8.68)

*Bleeding definition: International Society on Thrombosis and Haemostasis major and clinically relevant nonmajor bleeding for dabigatran etexilate, apixaban, and darexaban; Thrombolysis In Myocardial Infarction major, Thrombolysis In Myocardial Infarction minor, or bleeding requiring medical attention for rivaroxaban.

ACS = acute coronary syndrome(s); B.I.D. = twice daily; CI = confidence interval; HR = hazard ratio; NSTEMI = non–ST-segment elevation myocardial infarction; Q.D. = once daily; STEMI = ST-segment elevation myocardial infarction.

Table 5 APPRAISE-2 Versus ATLAS-2: Efficacy and Safety Outcomes

	APPRAISE-2*			ATLAS-2†			HR (95% CI)		
	Apixaban (n = 3,705)	Placebo (n = 3,687)	HR (95% CI)	Rivaroxaban 2.5 mg B.I.D. (n = 5,114)	Rivaroxaban 5 mg B.I.D. (n = 5,115)	Placebo (n = 5,113)	2.5 mg B.I.D. vs. Placebo	5 mg B.I.D. vs. Placebo	Rivaroxaban Combined vs. Placebo
Efficacy outcomes									
CV death	105 (2.8)	109 (3.0)	0.96 (0.73–1.25)	94 (2.7)‡	132 (4.0)	143 (4.1)	0.66 (0.51–0.86)	0.94 (0.75–1.20)	0.80 (0.65–0.99)
Myocardial infarction	182 (4.9)	194 (5.3)	0.93 (0.76–1.14)	205 (6.1)	179 (4.9)	229 (6.6)	0.90 (0.75–1.09)	0.79 (0.65–0.97)	0.85 (0.72–1.00)
Ischemic stroke	23 (0.6)§	34 (0.9)	0.68 (0.40–1.15)	30 (1.0)	35 (0.9)	34 (1.0)	0.89 (0.55–1.45)	1.05 (0.65–1.68)	0.97 (0.66–1.47)
Stent thrombosis	35 (0.9)‖	48 (1.3)	0.73 (0.47–1.17)	47 (2.2)	51 (2.3)#	72 (2.9)	0.65 (0.45–0.94)	0.73 (0.51–1.04)	0.69 (0.51–0.93)
Safety outcomes									
ICH	12 (0.3)**	3 (0.1)	4.06 (1.15–14.38)	14 (0.4)††	18 (0.7)‡‡	5 (0.2)	2.83 (1.02–7.86)	3.74 (1.39–10.07)	3.28 (1.28–8.42)
Fatal bleeding	5 (0.1)	0 (0)	NA	6 (0.1)	15 (0.4)	9 (0.2)	0.67 (0.24–1.89)	1.72 (0.75–3.92)	1.19 (0.54–2.59)

Conclusion

- Great step forward – 3 new alternatives
  - low risk in intracranial bleeding , no definite food interaction, less drug interaction
  - No need for frequent monitor and dosage adjustment
- Still has problem
  - Patient with poor renal function
  - How to manage bleeding ?
  - Cost (cost vs. effectiveness)
  - Af: yes, but ACS or other condition??