

Điều trị chống đông cho bệnh nhân rung nhĩ lớn tuổi

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Sơ lược về dịch tễ học rung nhĩ

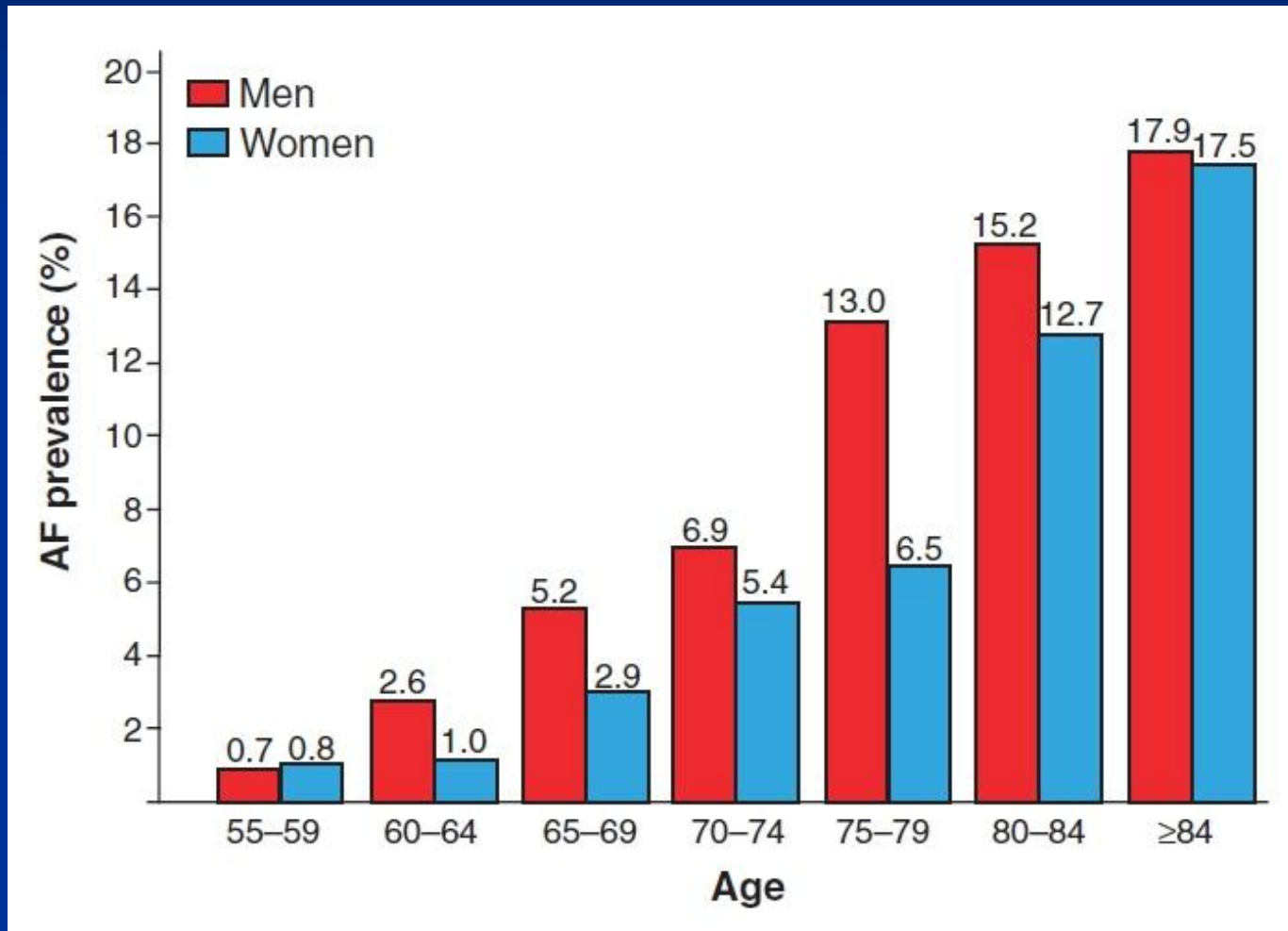
- Rung nhĩ chiếm 1/3 các trường hợp nhập viện vì rối loạn nhịp tim¹
- Số bệnh nhân rung nhĩ ước tính hiện nay:
 - Châu Âu: 4.5 triệu¹
 - Hoa Kỳ: 5.1 triệu²
- Tần suất lưu hành rung nhĩ ngày càng tăng vì các nguyên nhân sau:
 - Dân số thế giới ngày càng già đi
 - Tần suất lưu hành các bệnh tim mạch mạn ngày càng tăng
 - Tần suất lưu hành các YTNC của rung nhĩ ngày càng tăng

1. ACC/AHA/ESC guidelines: Fuster V et al. Circulation 2006;114:e257–354 & Eur Heart J 2006;27:1979–2030;

2. Miyasaka Y et al. Circulation 2006;114:119–25;

3. Heeringa J et al. Eur Heart J 2006;27:949–53

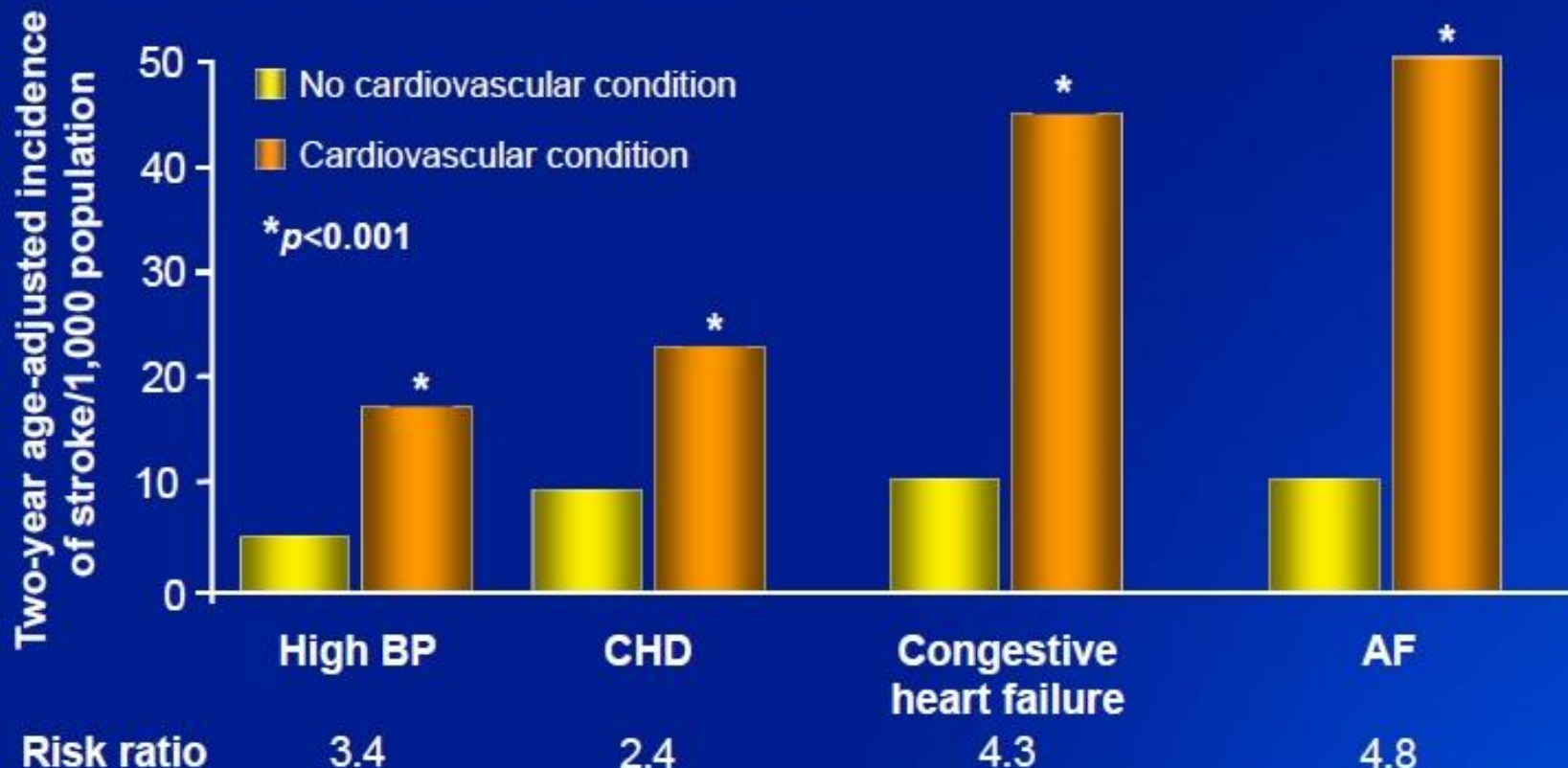
Tần suất lưu hành rung nhĩ tùy theo lứa tuổi



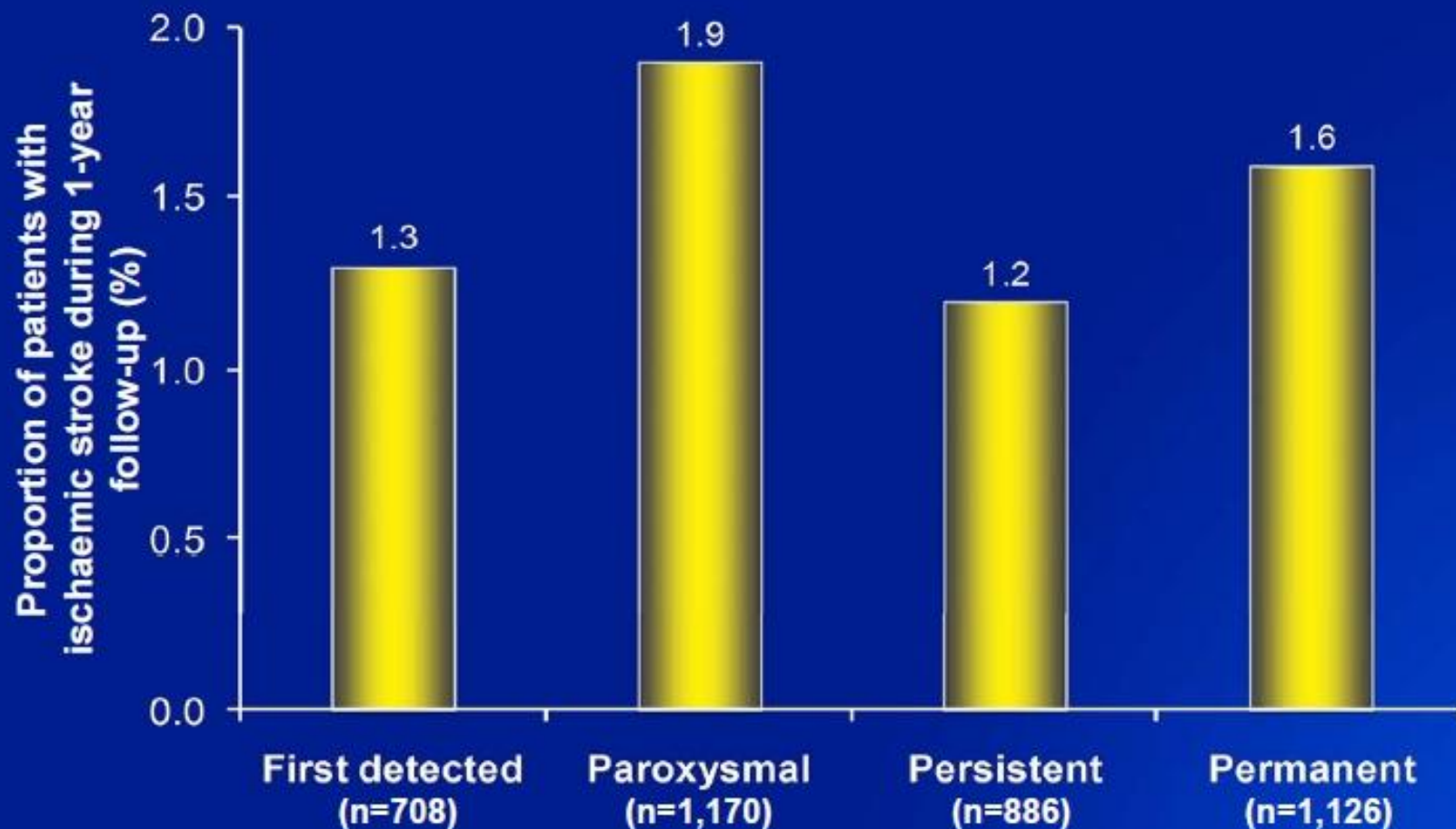
(Heeringa J, et al. *Eur Heart J* 2006;27:949-953)

AF: an important independent risk factor for stroke

Framingham Heart Study: risk of stroke with AF is greater than with other known risk factors

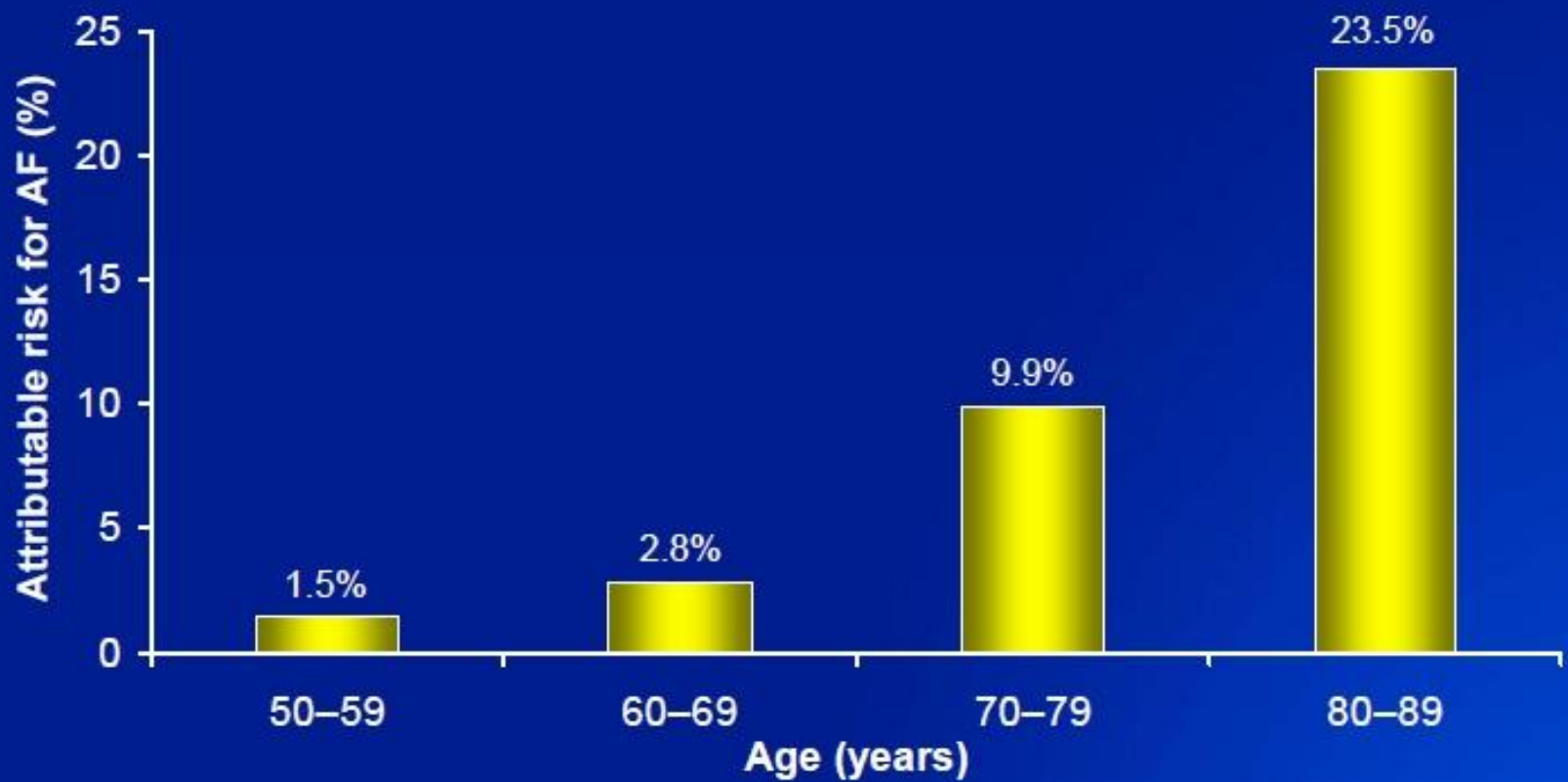


Ischaemic stroke risk is independent of the type of AF



Proportion of strokes attributable to AF increases with age

Framingham Heart Study (N=5,070)



Significant increase in AF-attributable stroke risk with age (p -value for trend <0.01)

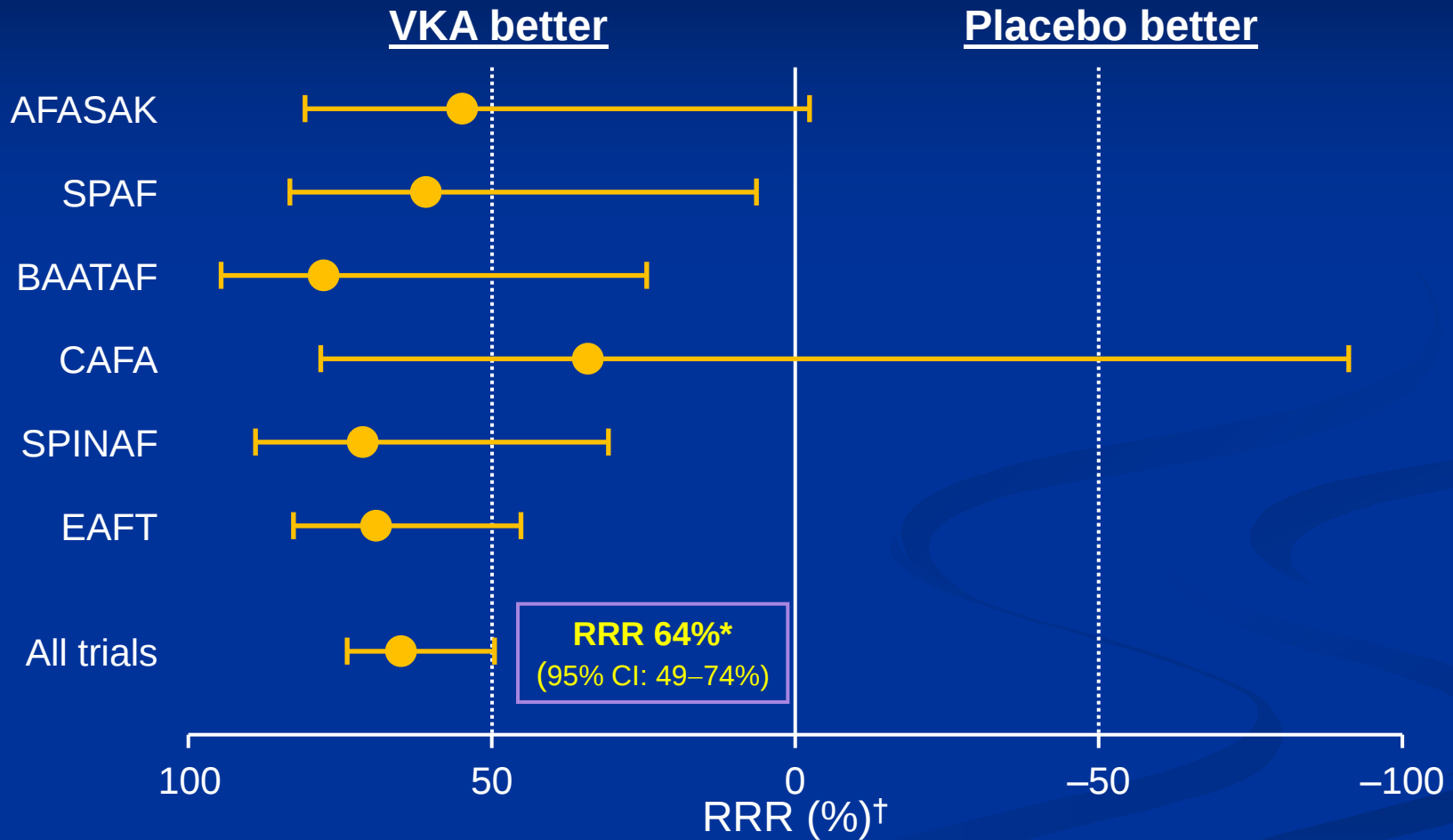
Wolf PA et al. *Stroke* 1991;22:983-988

CHA₂DS₂-VASc score and stroke risk in patients with AF

Item	Points		CHA ₂ DS ₂ -VASc	1-year stroke rate
Previous stroke TIA or systemic embolism	2	Add points together →	9	23.64%
Age ≥75 years	2		8	22.38%
Congestive heart failure*	1		7	21.50%
Hypertension	1		6	19.74%
Diabetes mellitus	1		5	15.26%
Age 65–74 years	1		4	9.27%
Female gender	1		3	5.92%
Vascular disease	1		2	3.71%
			1	2.01%
			0	0.78%

*Or moderate-to-severe left ventricular systolic dysfunction (left ventricular ejection fraction ≤40%)

Thuốc KVK giảm có ý nghĩa nguy cơ đột quĩ ở bệnh nhân rung nhĩ



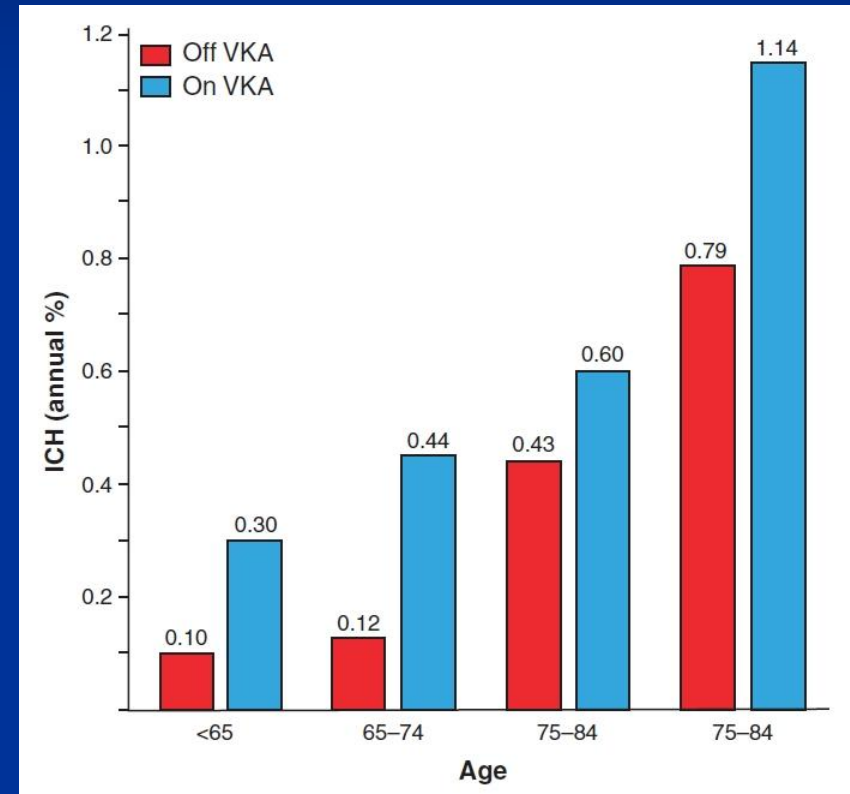
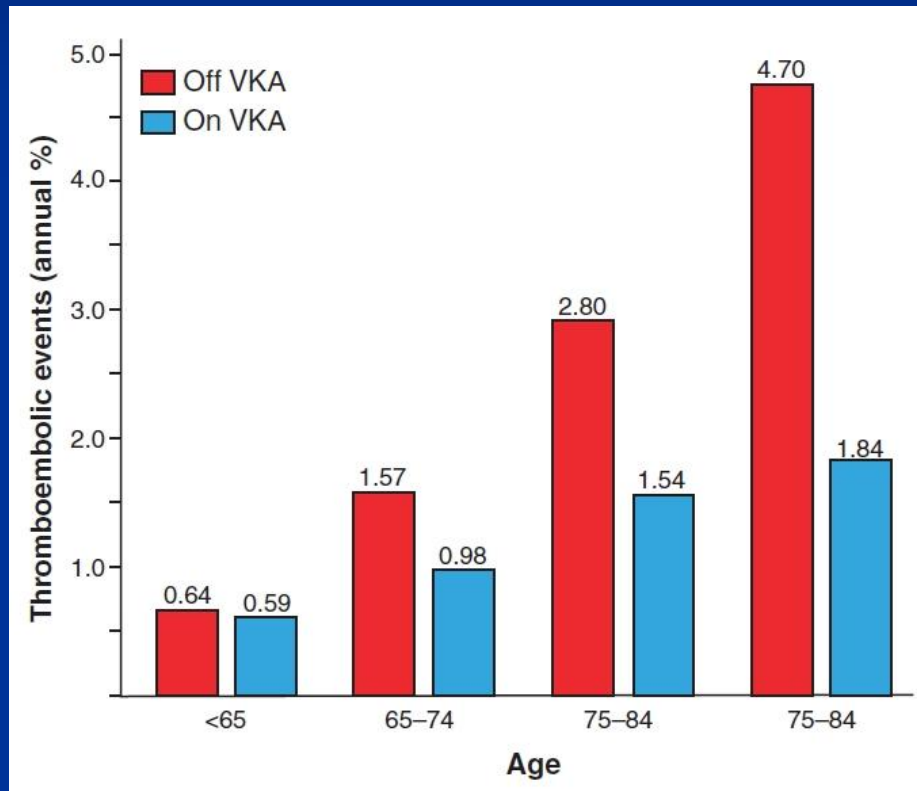
VKA = vitamin K antagonist; AF = atrial fibrillation; Random effects model; Error bars = 95% CI; *P>0.2 for homogeneity; †Relative risk reduction (RRR) for all strokes (ischaemic and haemorrhagic) for ischaemic stroke only the RRR was 67% (95%CI: 54–77%)

Hart RG et al. Ann Intern Med 2007;146:857–67

Phòng ngừa đột quỵ / thuyên tắc mạch hệ thống trong rung nhĩ không do bệnh van tim (ESC 2012)

- **$CHA_2DS_2-VASc = 0$** : Không cần dùng thuốc chống huyết khối (I–B)
- **$CHA_2DS_2-VASc \geq 2$** : Dùng thuốc chống đông uống, trừ khi có chống chỉ định (I–A)
- **$CHA_2DS_2-VASc = 1$** : Xem xét dùng thuốc chống đông uống sau khi đánh giá nguy cơ chảy máu và hỏi ý kiến của bệnh nhân (IIa–A)
 - * Bệnh nhân nữ < 65 tuổi, không có YTNC khác: không dùng thuốc (IIa–B)
- **Nếu bệnh nhân từ chối dùng thuốc chống đông**: Xem xét dùng thuốc chống tiểu cầu với phối hợp ASA 75-100 mg + clopidogrel 75 mg (nguy cơ chảy máu thấp) hoặc - hiệu quả kém hơn - ASA 75-325 mg (IIa–B)

Điều trị chống đông bằng KVK giảm nguy cơ thuyên tắc do huyết khối nhưng tăng nguy cơ chảy máu trong hộp sọ

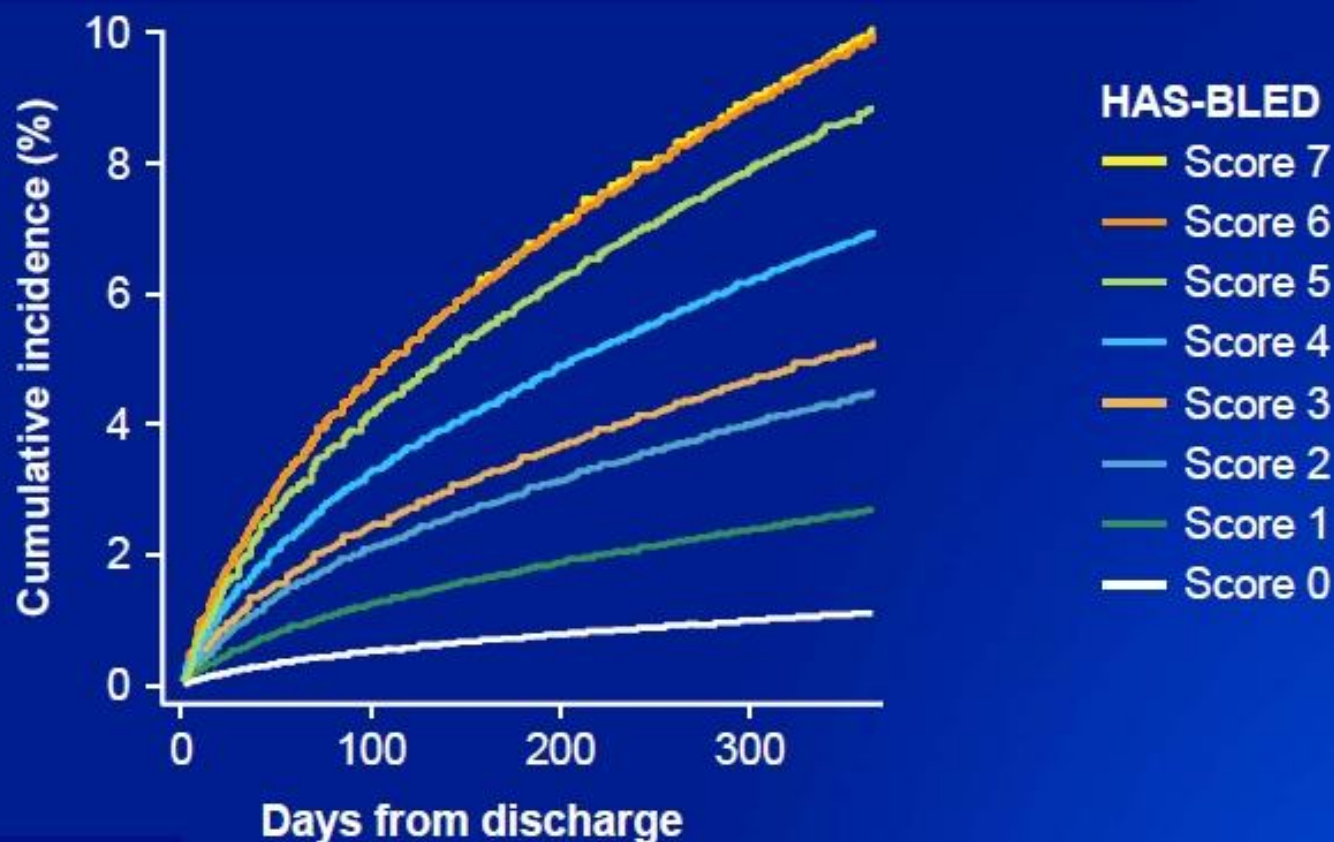


HAS-BLED bleeding risk score

Clinical characteristic	Points
Hypertension (systolic BP >160 mm Hg)	1
Abnormal renal or liver function	1 + 1
Stroke	1
Bleeding	1
Labile INRs	1
Elderly (age >65 years)	1
Drugs or alcohol	1 + 1
Cumulative score	Range 0–9

Higher bleeding rates seen with high HAS-BLED score (p -value for trend <0.001)

Cumulative incidence of bleeding* by HAS-BLED score



*Non-OAC cohort

Tolerability of Warfarin During First Year of Therapy: US Elderly Patients

(N = 472; Age $\geq$ 65 years)

CHADS ₂ Score	Major Bleed	Off Therapy
	Rate (Per 100 Person-Years)	Rate (Per 100 Person-Years)
0	3.1	15.6
1	4.3	17.1
2	2.0	12.9
3	19.5	32.6
≥ 4	23.4	32.1

- TTR = 58%
- Major hemorrhage 7.2%, ICH 2.5%
 - Rates 2.75 times higher in patients $\geq$ 80 years
- 28% patients discontinued warfarin at 1 year

Các biện pháp cải thiện liệu pháp kháng vitamin K ở bệnh nhân rung nhĩ lớn tuổi

■ Tăng cường huấn luyện bác sĩ:

- Nắm vững thang điểm phân tầng nguy cơ đột quỵ (CHADS_2 , $\text{CHA}_2\text{DS}_2\text{-VASc}$)
- Nắm vững thang điểm phân tầng nguy cơ chảy máu (HASBLED)

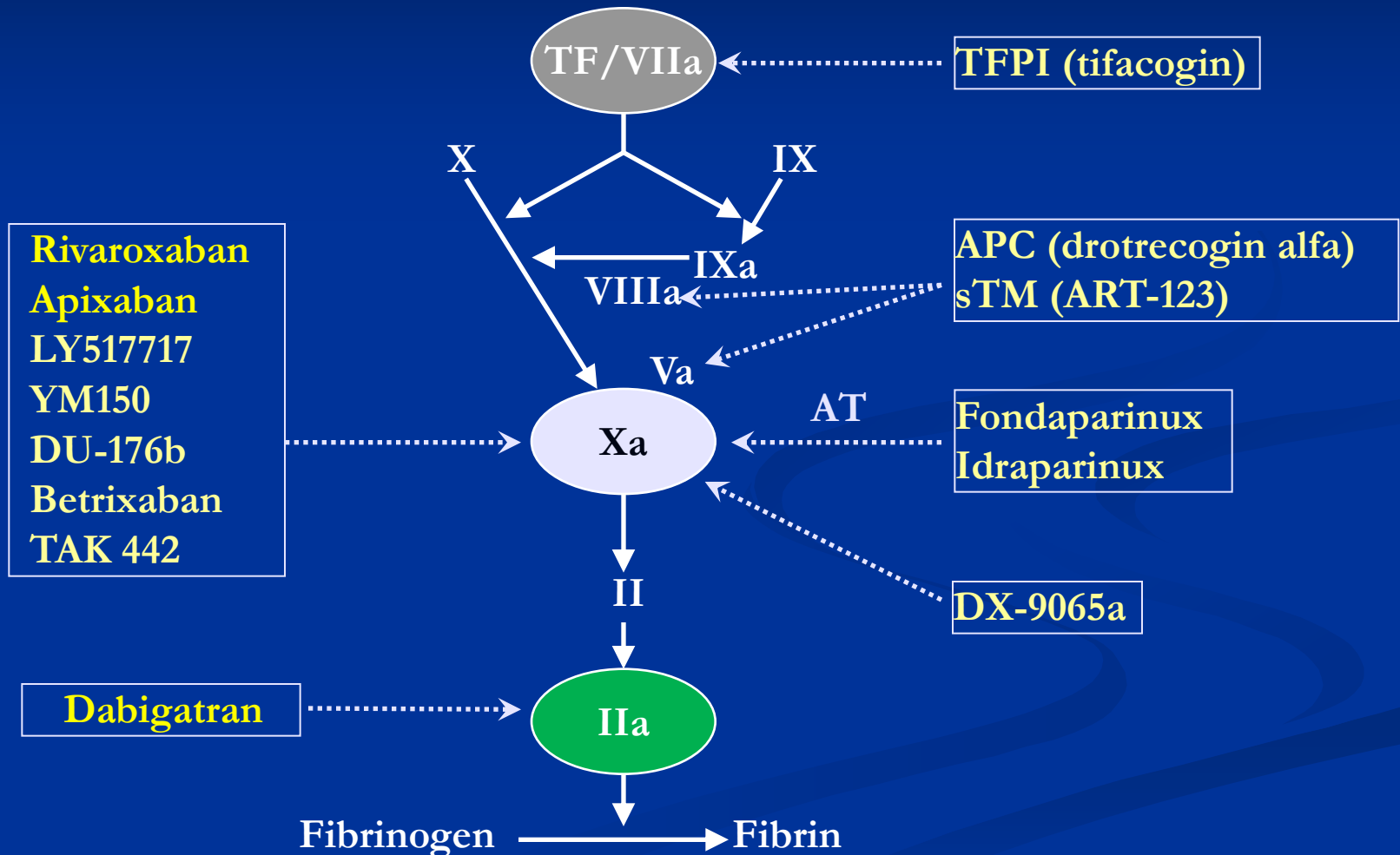
■ Cải thiện theo dõi INR và tuân trị:

- Hướng dẫn cách uống thuốc rõ ràng, dễ hiểu
- Cơ sở hạ tầng y tế phù hợp ($\rightarrow$ xét nghiệm INR dễ dàng)
- Tăng cường giáo dục, hướng dẫn cho bệnh nhân

Các thuốc chống đông mới

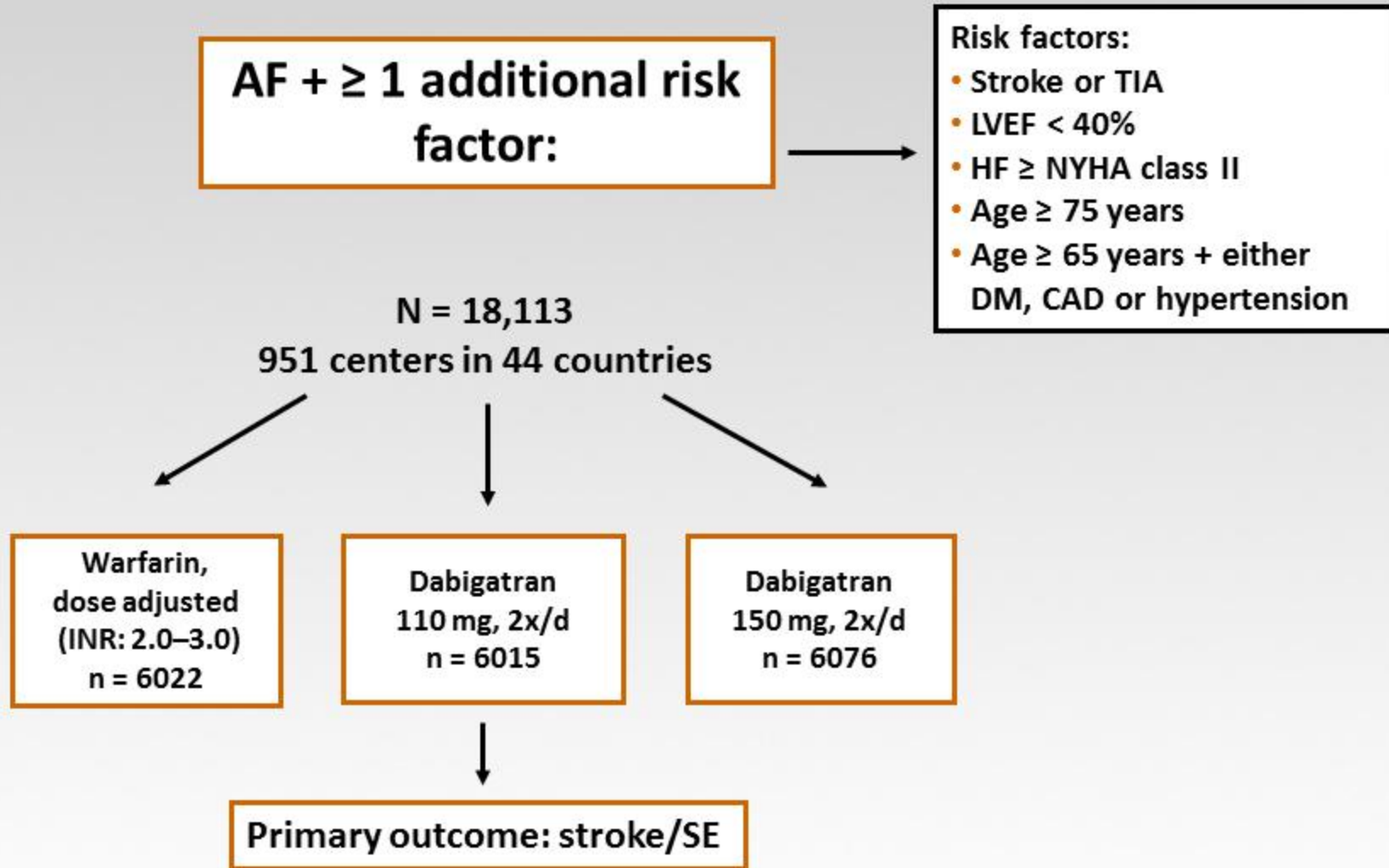
ĐƯỜNG UỐNG

ĐƯỜNG TIÊM

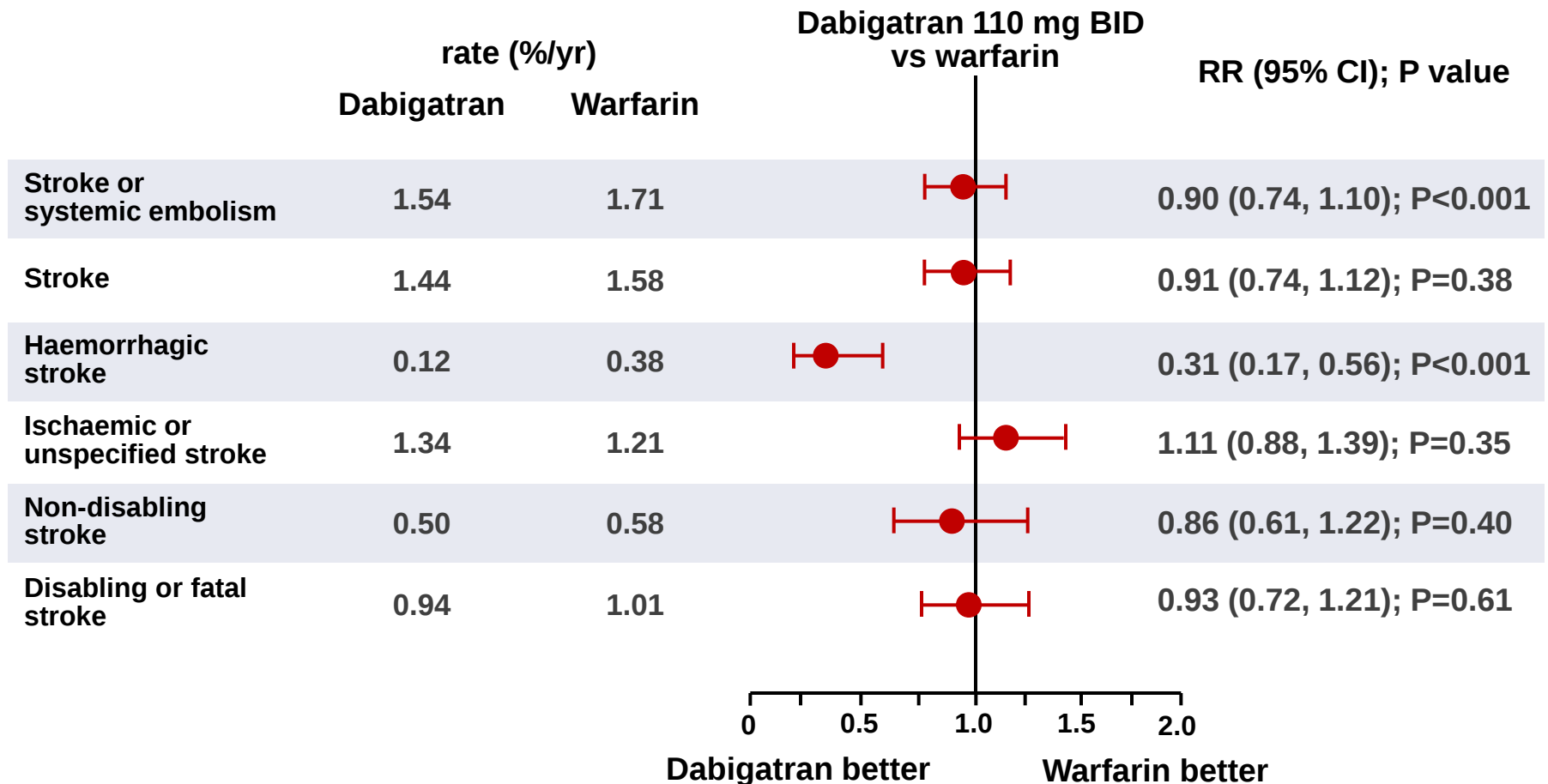


RELY

(Randomized Evaluation of Long-term Anticoagulation Therapy)



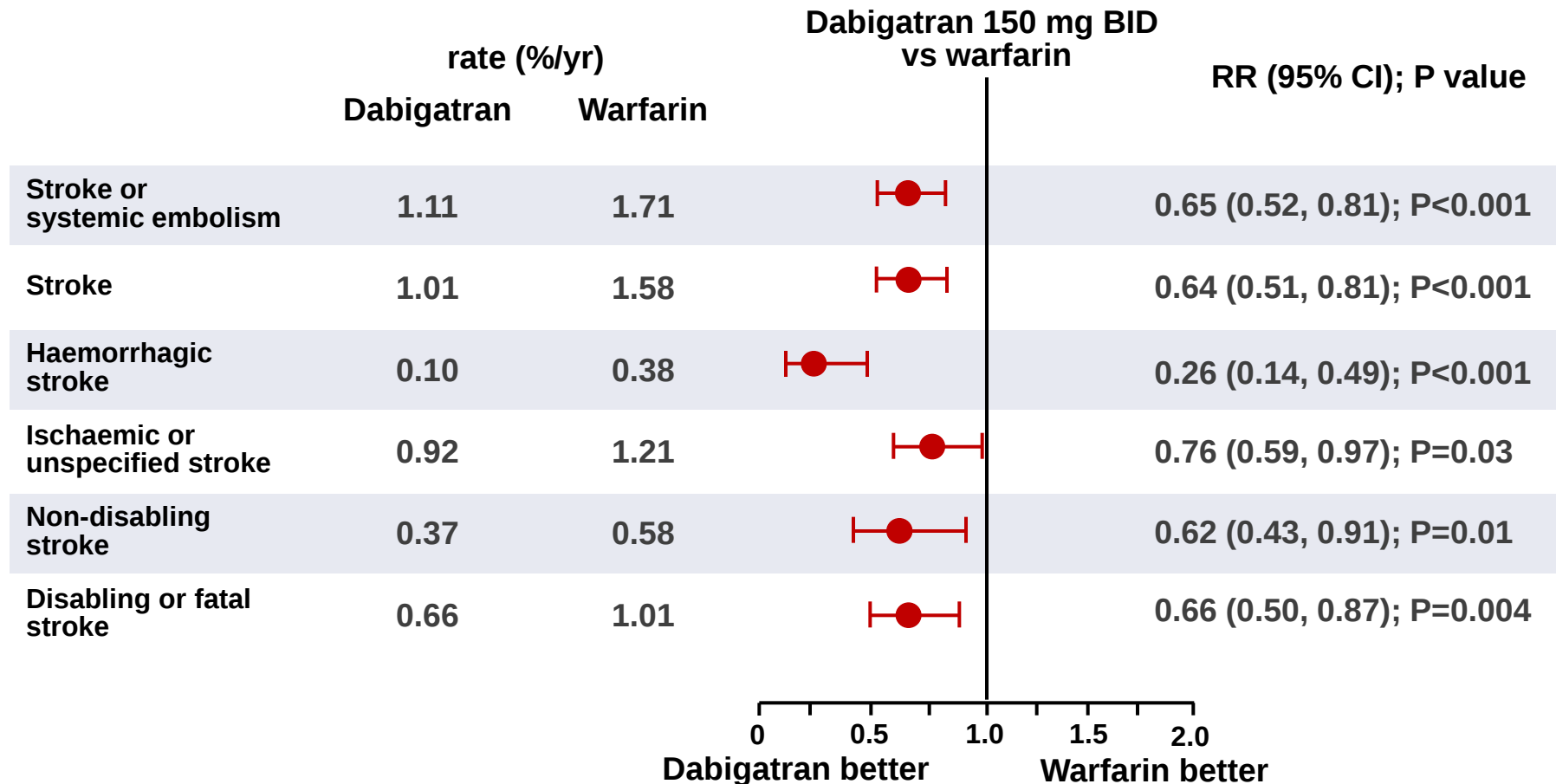
RE-LY: dabigatran etexilate 110 mg BID was found to be non-inferior to warfarin for stroke or systemic embolism



Error bars = 95% confidence intervals; BID = twice daily; RR = relative risk

Connolly SJ et al. N Engl J Med 2009;361:1139–51; Connolly SJ et al. N Engl J Med 2010;363:1875–6

RE-LY: dabigatran etexilate 150 mg BID was found to be superior to warfarin for stroke or systemic embolism



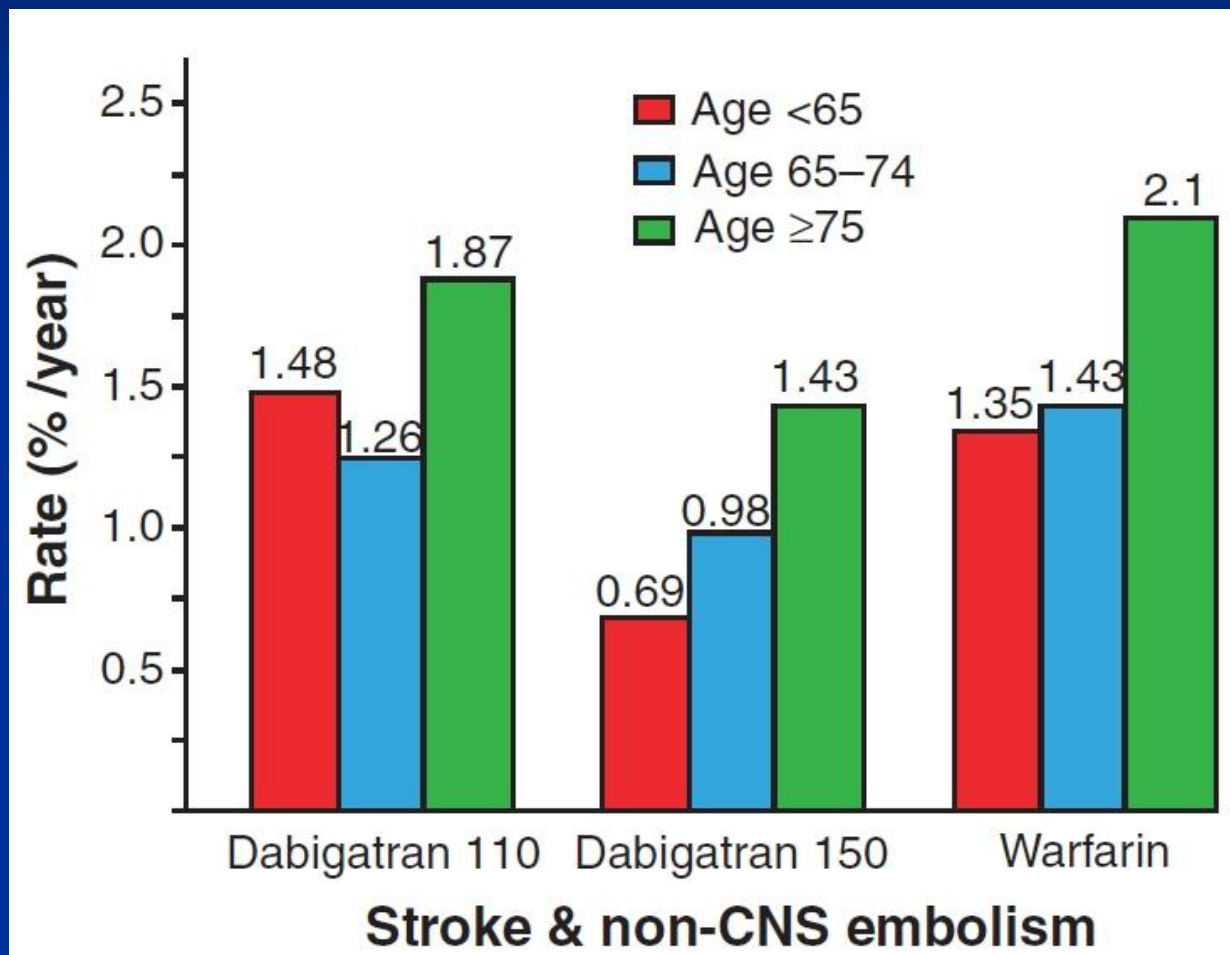
Error bars = 95% confidence intervals; BID = twice daily; RR = relative risk

Connolly SJ et al. N Engl J Med 2009;361:1139–51; Connolly SJ et al. N Engl J Med 2010;363:1875–6

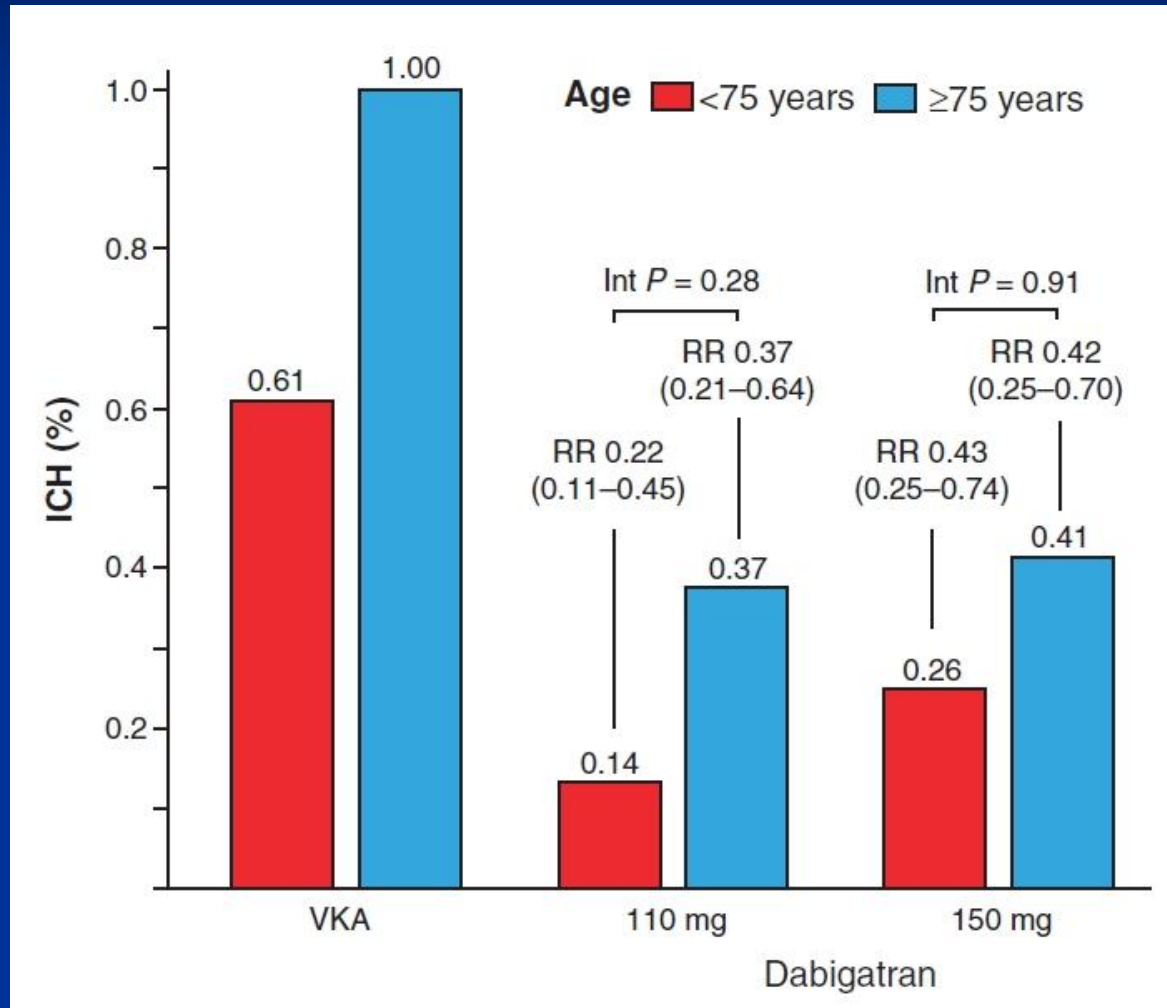
RE-LY: Major Bleeding and ICH

	<u>Dabigatran</u>		Warfarin	Dabigatran 110 mg vs Warfarin		Dabigatran 150 mg vs Warfarin		Dabigatran 150 mg vs 110 mg	
	110 mg	150 mg							
	Rate/ Year	Rate/ Year		RR (95% CI)	P	RR (95% CI)	P	RR (95% CI)	P
Major Bleeding	2.71 %	3.11 %	3.36 %	0.80 (0.69-0.93)	.003	0.93 (0.81-1.07)	.31	1.16 (1.00-1.34)	.052
All ICH	0.23 %	0.30 %	0.74 %	0.31 (0.20-0.47)	< .001	0.40 (0.27-0.60)	< .001	1.32 (0.82-2.17)	.28

RE-LY: Đột quỵ / thuyên tắc hệ thống theo lứa tuổi



RE-LY: Chảy máu trong hộp sọ theo lứa tuổi



ROCKET AF

(Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation)

**AF + risk for future stroke
(history of stroke/TIA/SE) or
≥ 2 additional risk factors**

Risk factors:

- CHF or LVEF ≤ 35%
- Hypertension
- Age ≥ 75 years
- DM

N = 14,264

1178 centers in 45 countries

**Oral rivaroxaban 20 mg
+ placebo***

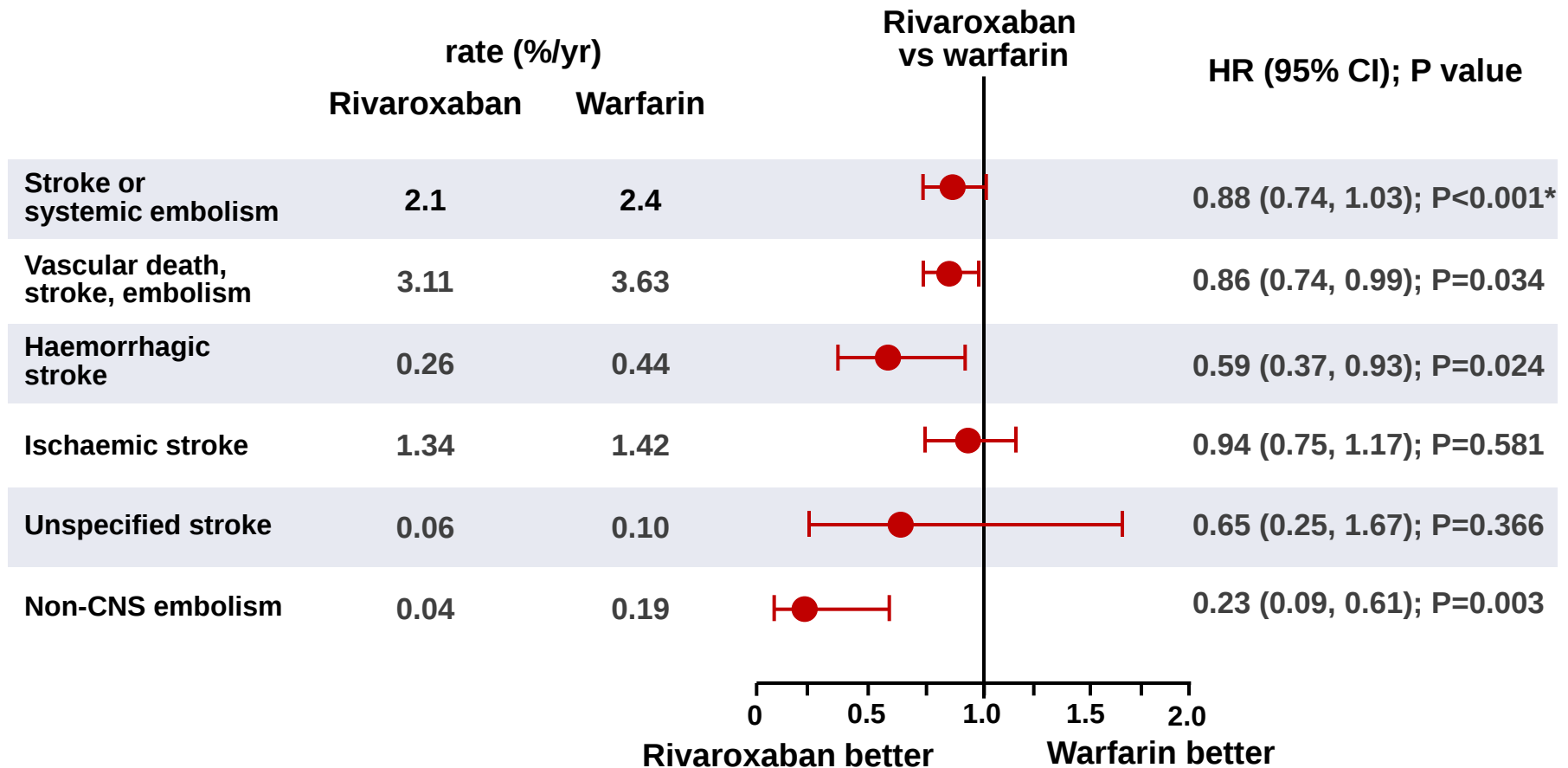
**Warfarin*
+ placebo**

*Titrated by INR/sham INR
to INR: 2.5 (range: 2.0-3.0).

Primary outcome: stroke/SE

ROCKET AF Study Investigators. *Am Heart J.* 2010;159:340-347.
Patel MR, et al. *N Engl J Med.* 2011;365:883-891.

ROCKET-AF: rivaroxaban was non-inferior to warfarin for the primary outcome of stroke and systemic embolism



*P value for non-inferiority, intention-to-treat population, all other results based on safety on-treatment population

Error bars = 95% confidence intervals; BID = twice daily; CNS = central nervous system; HR = hazard ratio

Patel MR et al. N Engl J Med 2011;365:883–91

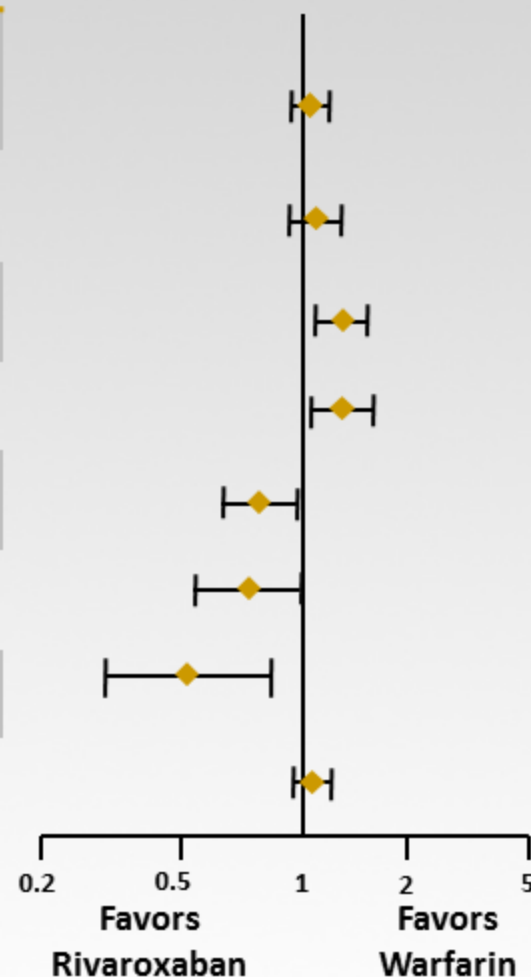
ROCKET AF: Bleeding Analysis

Parameter	Rivaroxaban (N = 7111) (% per year)	Warfarin (N = 7125) (% per year)	Hazard Ratio (95% CI)
Primary safety endpoint: major and CRNB	14.9	14.5	1.03 (0.96,1.11)
Major bleeding	3.6	3.5	1.04 (0.90,1.20)
Hemoglobin drop (≥ 2 g/dL)	2.8	2.3	1.22 (1.03,1.44)*
Transfusion	1.7	1.3	1.25 (1.01,1.55)*
Critical organ bleeding	0.8	1.2	0.69 (0.53,0.91)*
Intracranial bleeding	0.5	0.7	0.67 (0.47,0.93)*
Fatal bleeding	0.2	0.5	0.50 (0.31,0.79)*
Nonmajor clinical relevant bleeding	11.8	11.4	1.04 (0.96,1.13)

- Major bleeding from gastrointestinal site (upper, lower, and rectal): rivaroxaban = 224 events (3.2%); warfarin = 154 events (2.25%); $P < .001$ *
- Safety population, on-treatment analysis

*Statistically significant.

Hazard Ratio and 95% CI



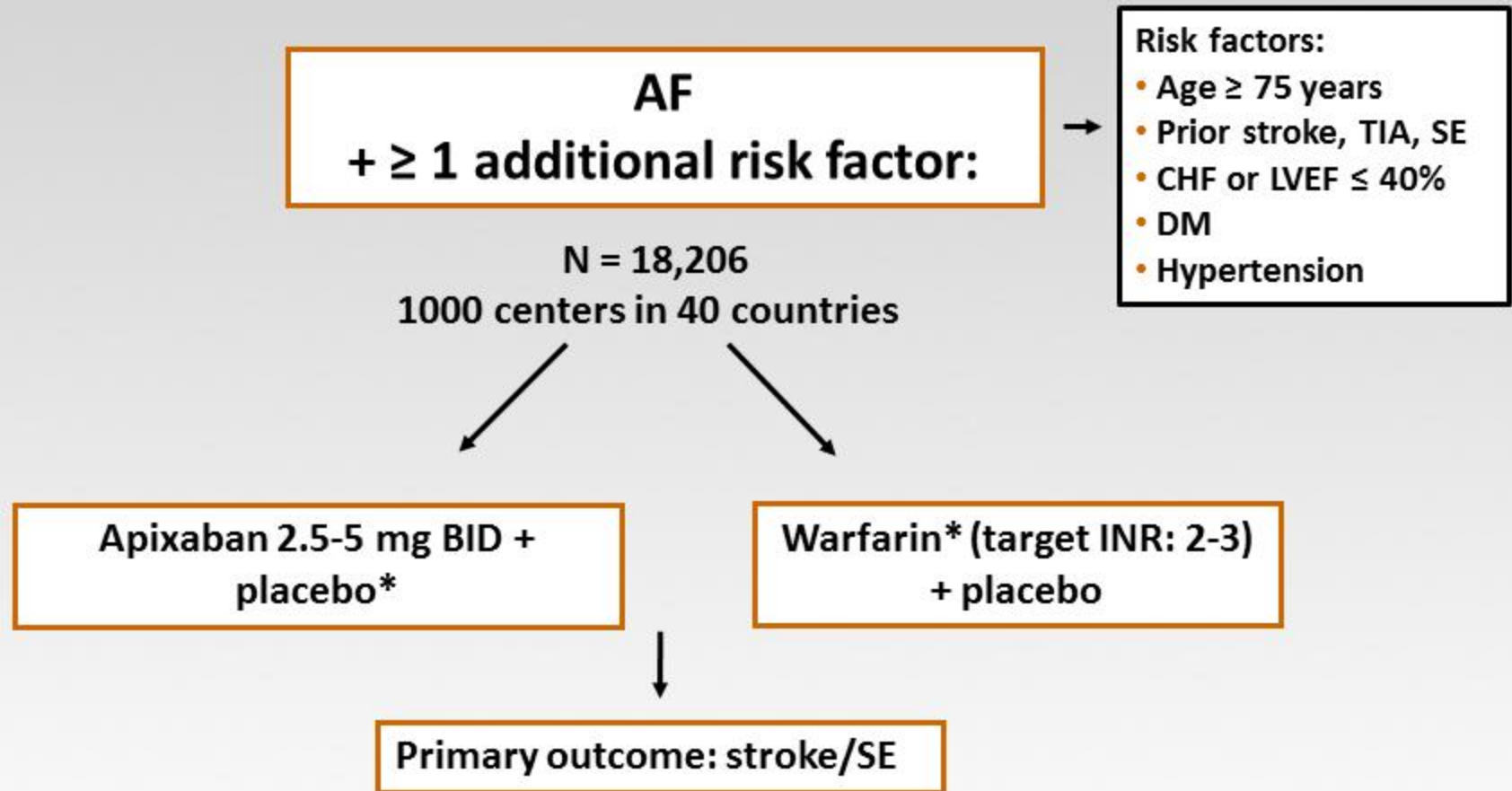
ROCKET AF: Rivaroxaban vs warfarin among elderly patients with NVAF

Endpoint	Age $\geq$ 75 year			Age < 75 years			Interaction P value
	R (n=3082)	W (n=3082)	HR (95%CI) R vs W	R (n=3999)	W (n=4008)	HR (95%CI) R vs W	
Stroke or systemic embolism	2,29	2,85	0,80 (0,63-1,02)	2,00	2,10	0,95 (0,76-1,19)	0,31
Intracerebral bleeding	0,66	0,83	0,80 (0,49-1,28)	0,37	0,68	0,54 (0,33-0,89)	0,27

(Halperin JL, et al. Stroke 2012;43:A148)

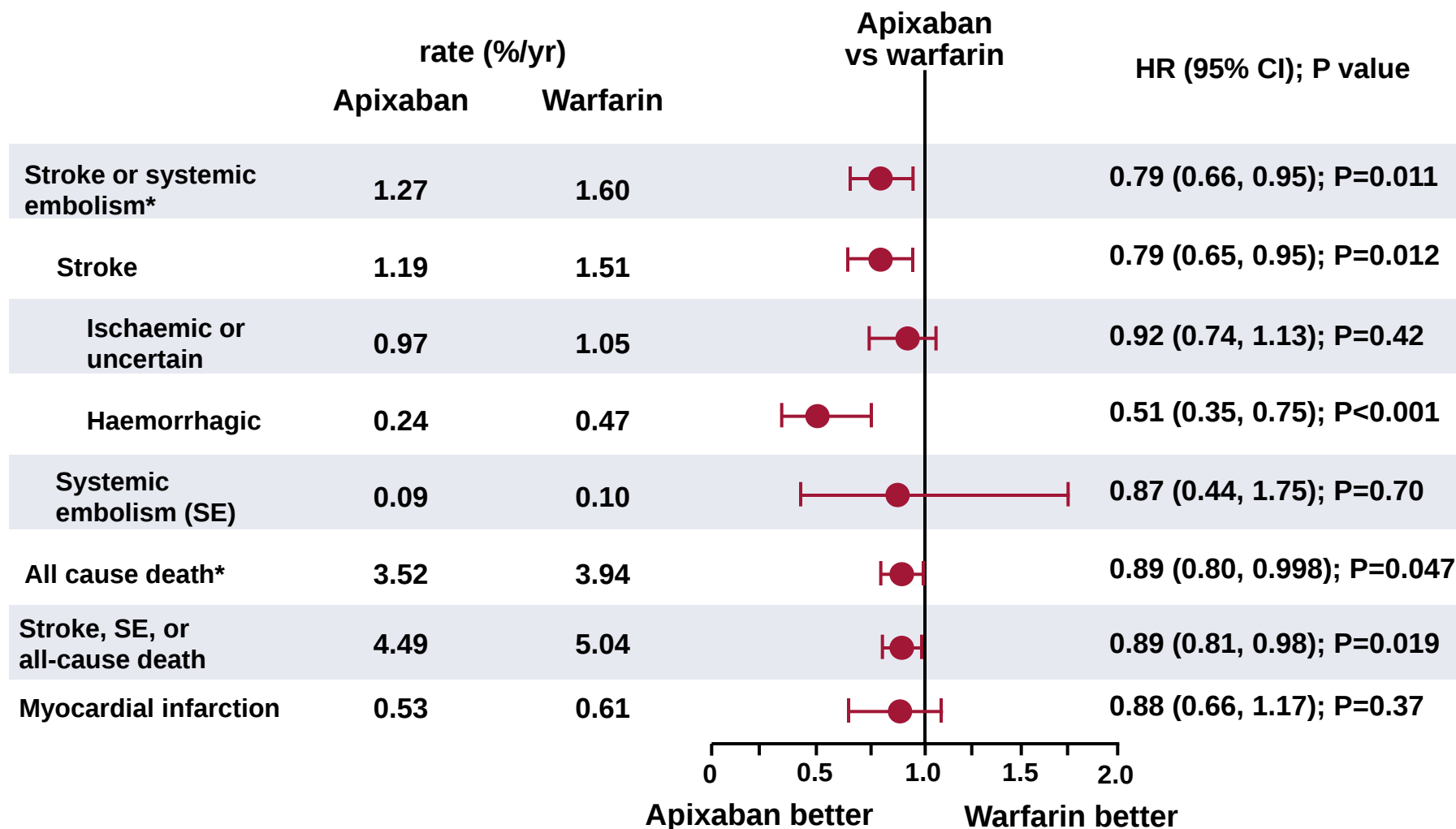
ARISTOTLE

(Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation)



* Adjusted by INR/sham INR at encrypted point-of-care testing device.

ARISTOTLE: apixaban was found to be superior to warfarin for the primary outcome of stroke or systemic embolism



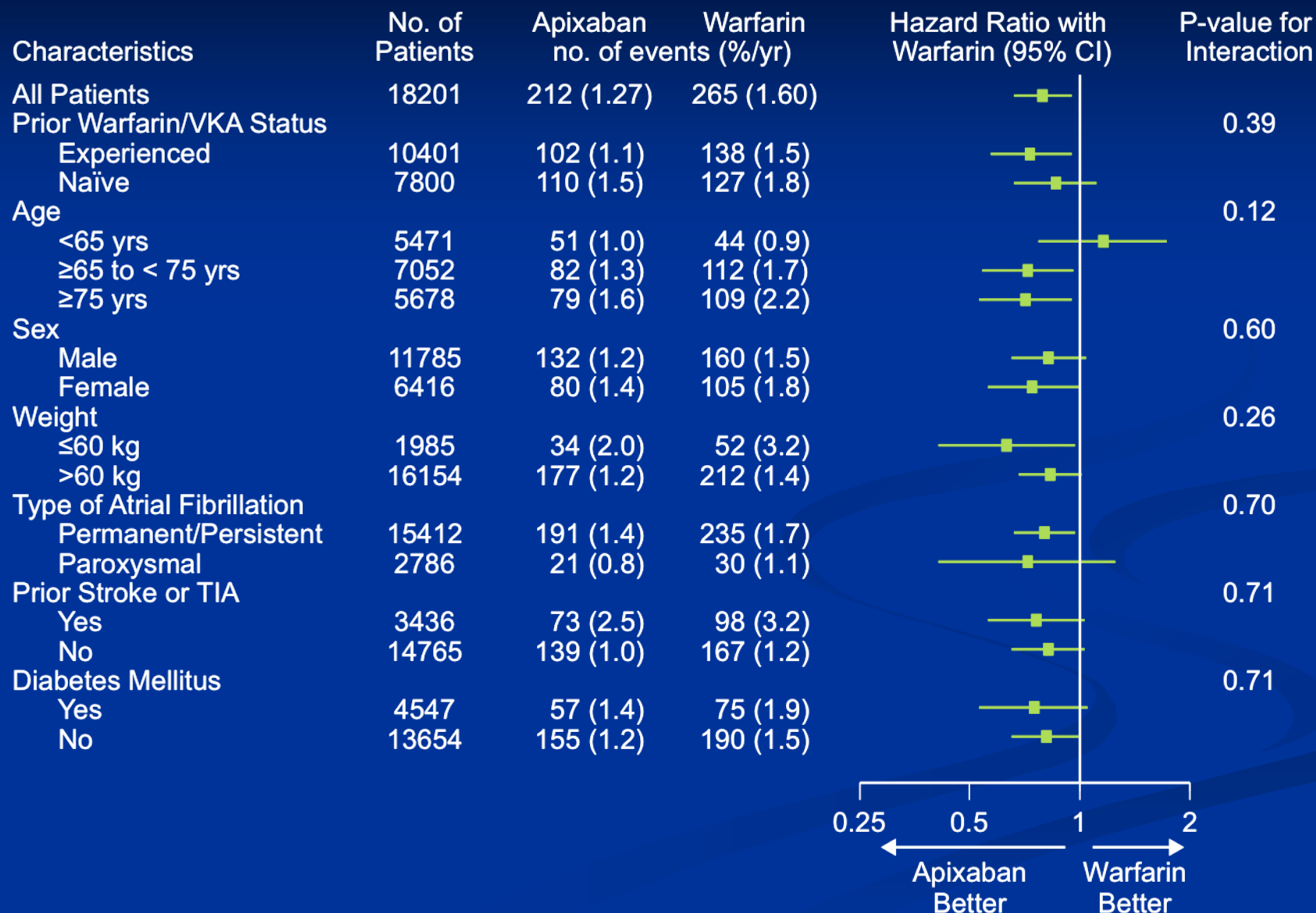
*Part of sequential testing sequence preserving the overall type I error; CI = confidence interval; HR = hazard ratio

Granger CB et al. N Engl J Med 2011;365:981-92

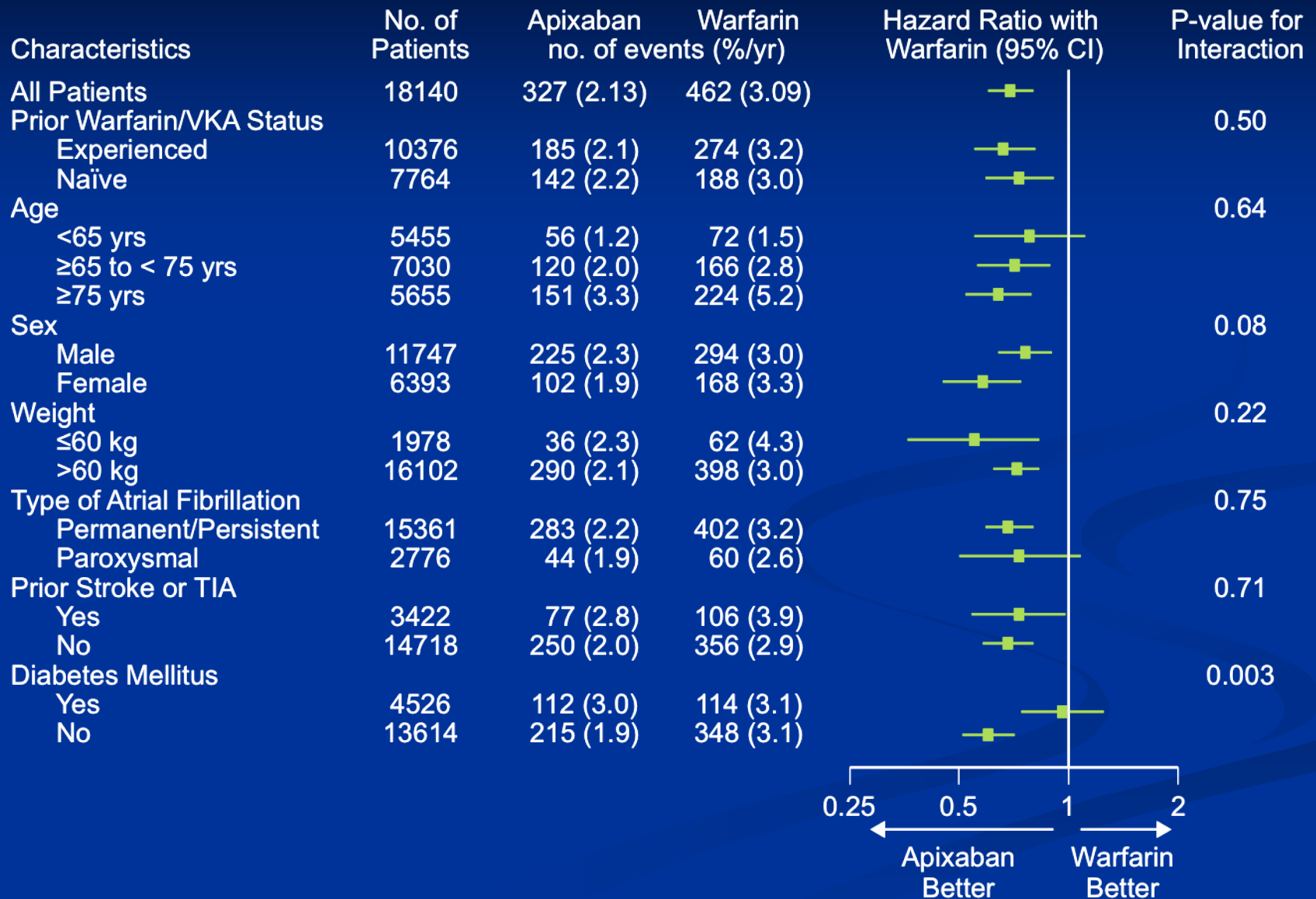
ARISTOTLE: Bleeding Outcomes

Outcome	Apixaban n = 9088 %/yr	Warfarin n = 9052 %/yr	HR (95% CI)	P
Primary outcome: ISTH major bleeding	2.13	3.09	0.69 (0.60-0.80)	< .001
• Intracranial	0.33	0.80	0.42 (0.30-0.58)	< .001
• Gastrointestinal	0.76	8.86	0.89 (0.70-1.15)	.37
Major/CRNM bleeding	4.07	6.01	0.68 (0.61-0.75)	< .001
• GUSTO severe	0.52	1.13	0.46 (0.35-0.60)	< .001
• TIMI major	0.96	1.69	0.57 (0.46-0.70)	< .001
• Any bleeding	18.1	25.8	0.71 (0.68-0.75)	< .001

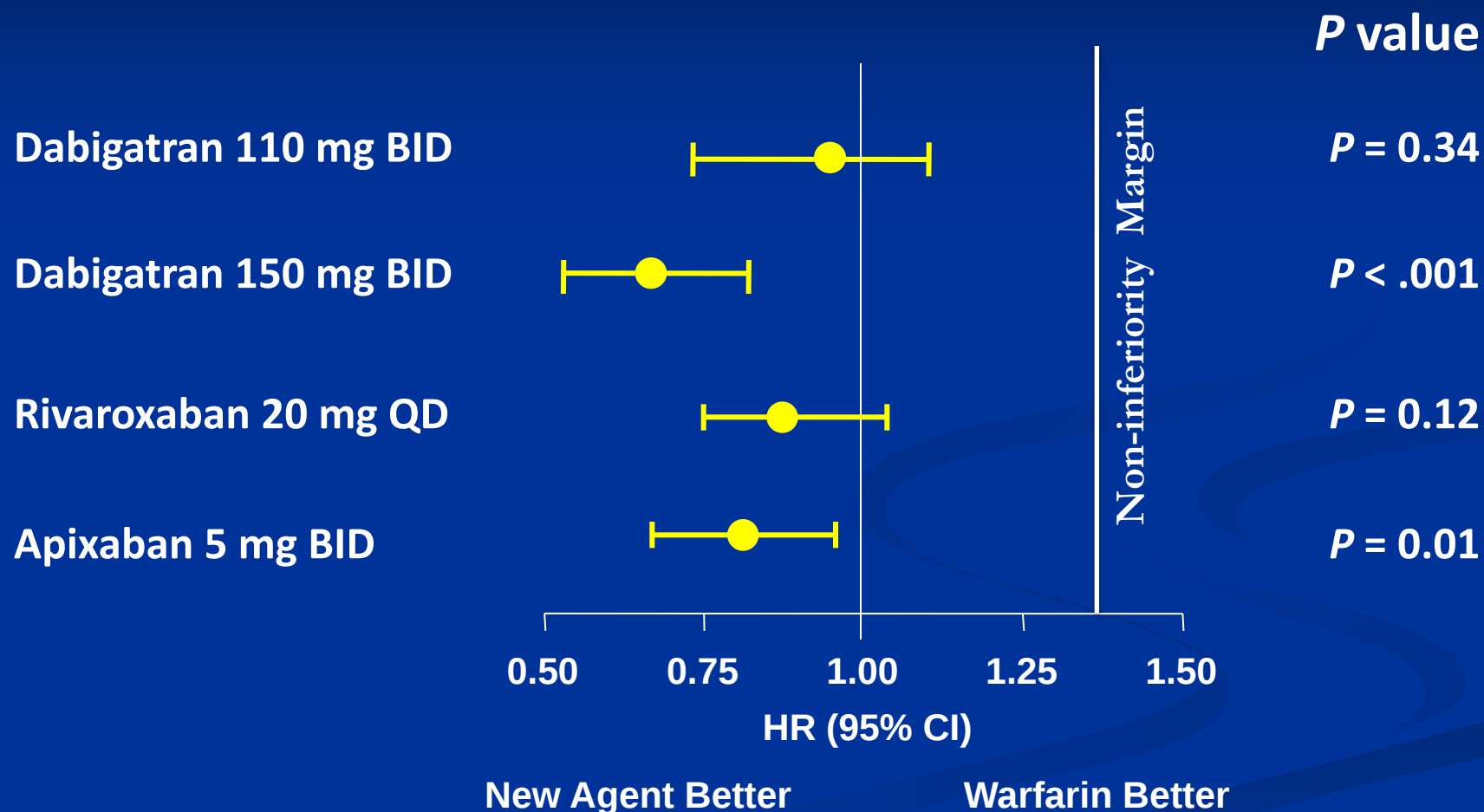
ARISTOTLE: Subgroups for Stroke and Systemic Embolism



ARISTOTLE: Subgroups for Major Bleeding



Primary endpoint (stroke or systemic embolism) in RCT comparing novel oral anticoagulants with warfarin



Not head to head comparison – For illustrative purposes only

Connolly SJ, et al. N Engl J Med 2009;361:1139–51; Connolly SJ et al. N Engl J Med 2010;363:1875–6; Patel MR, et al. N Engl J Med 2011;365:883–91; Granger C, et al. N Eng J Med 2011;365:981–92.

Rates of intracranial bleeding (%/yr)

RELY	Dabigatran 110 mg (n = 6015)	Dabigatran 150 mg (n = 6076)	Warfarin (n = 6022)	P value
	0.23	0.30	0.74	< 0.001
ROCKET AF	Rivaroxaban (n = 7111)		Warfarin (n = 7125)	
	0.50		0.70	0.02
ARISTOTLE	Apixaban (n = 9088)		Warfarin (n = 9052)	
	0.33		0.80	< 0.001

ESC 2012 Recommendations for Novel Agents in the Presence of Renal Impairment

Recommendations	Class	Level
Baseline and subsequent regular assessment of renal function (by CrCl) is recommended in patients following initiation of any novel OAC, which should be done annually but more frequently in those with moderate renal impairment where CrCl should be assessed 2-3 times per year.	IIa	B
Novel OACs (dabigatran, rivaroxaban, and apixaban) are not recommended in patients with severe renal impairment (CrCl < 30 mL/min).	III	A

CrCl = creatinine clearance

KẾT LUẬN

- Bệnh nhân rung nhĩ lớn tuổi có nguy cơ cao bị đột quỵ /thuyên tắc hệ thống → cần được điều trị chống đông.
- Điều trị chống đông làm tăng nguy cơ chảy máu trong hộp sọ, đặc biệt ở người lớn tuổi.
- Nếu dùng thuốc kháng vitamin K: cần có tiếp cận thích hợp để cải thiện việc theo dõi INR và tuân trị.
- Thuốc kháng đông uống mới (dabigatran, rivaroxaban, apixaban):
 - Không phải theo dõi đông máu
 - Hiệu quả không thua kém warfarin
 - Ít gây chảy máu trong hộp sọ hơn
 - Không dùng nếu $Cl_{cr} < 30$ ml/phút