Improving the Odds Against Stroke

Improving the Odds Against Stroke

Learning Objectives

- Identify factors that put patients at risk for stroke
- Individualize treatment strategies based on clinical trial data and pharmacologic properties of novel oral anticoagulants and warfarin
- Discuss emerging data on novel oral anticoagulants (NOACs) for secondary prevention of thromboembolic stroke
- Review the importance of long-term monitoring to detect asymptomatic atrial fibrillation and/or the cause of cryptogenic stroke

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Facing a Stacked Deck

Identifying Patients With AF at High Risk for Stroke

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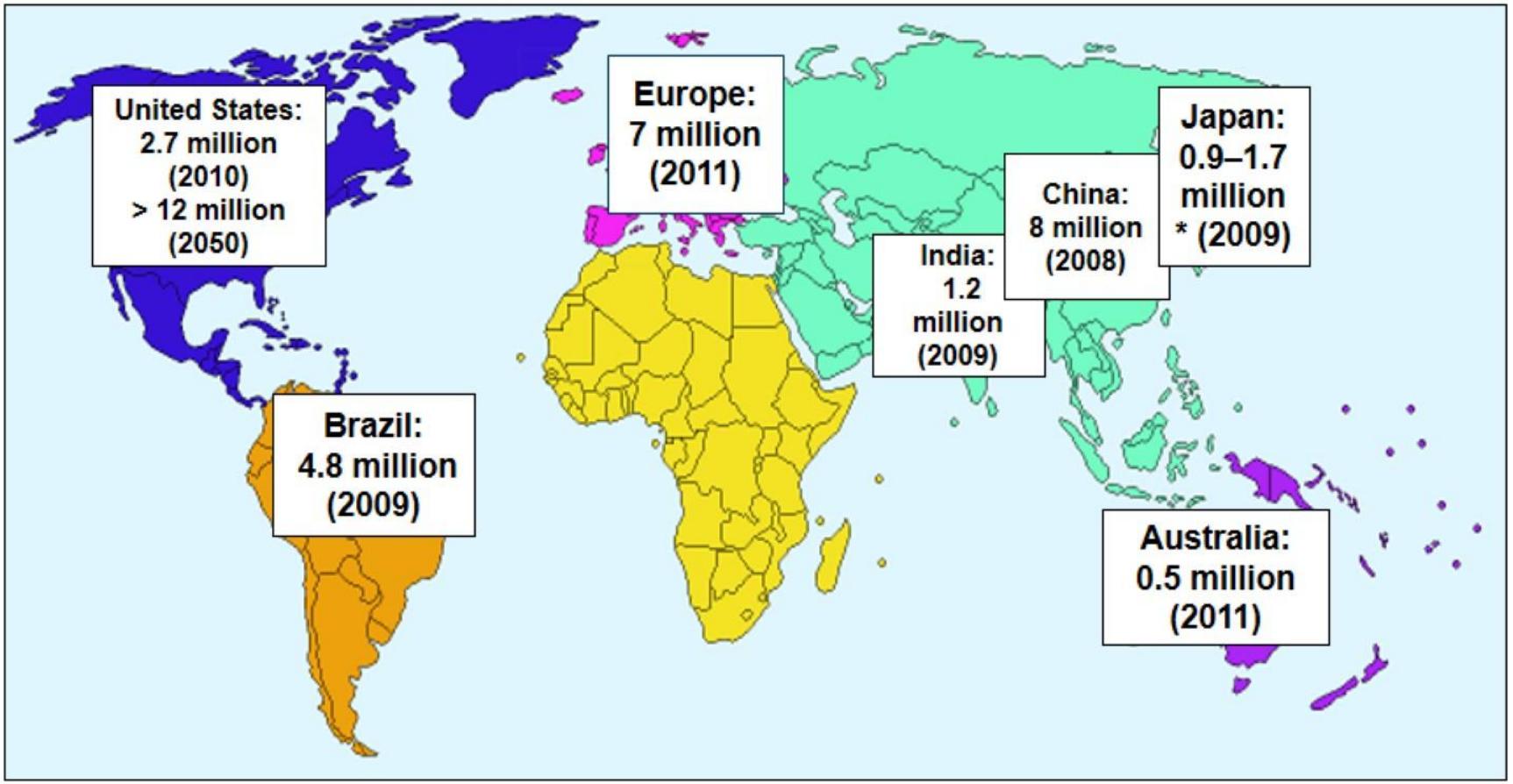
Impact of Atrial Fibrillation

- Most common arrhythmia in clinical practice; accounts for one-third of hospitalizations for cardiac rhythm disturbances
- 1 of 6 strokes is due to AF (1 of 3 strokes in octogenarians)
- Recent data suggest that a proportion of cryptogenic stroke also due to AF

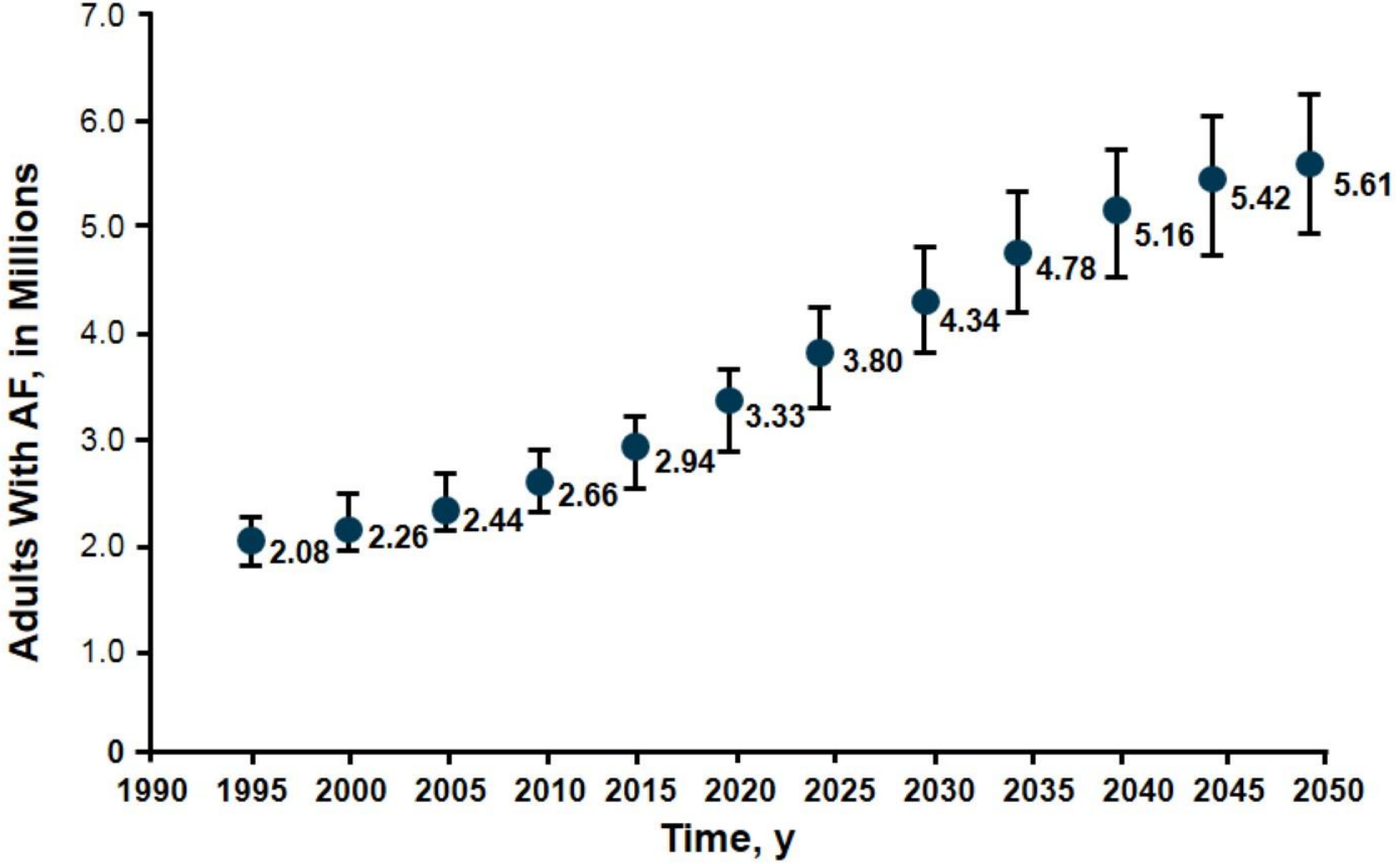
Fuster V, et al. *Circulation.* 2011;123:e269-e367.[1]

Prevalence of Atrial Fibrillation
A Global Disease



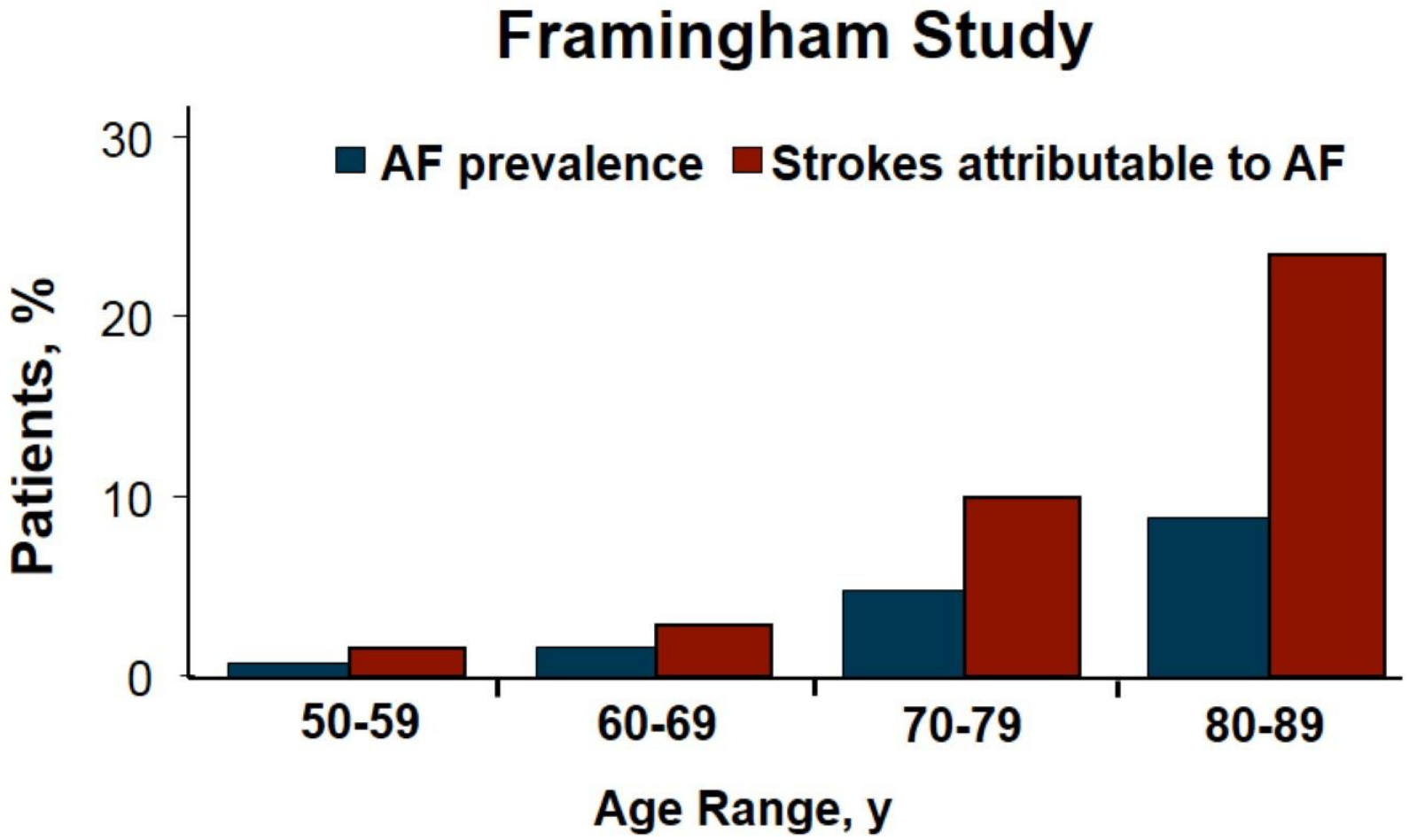
Fegin VL, et al. *Lancet*. 2014;383:245-254.[2]

Projected Number of US Adults With AF Between 1995 and 2050



Go AS, et al. *JAMA*. 2001;285:2370-2375.[3]

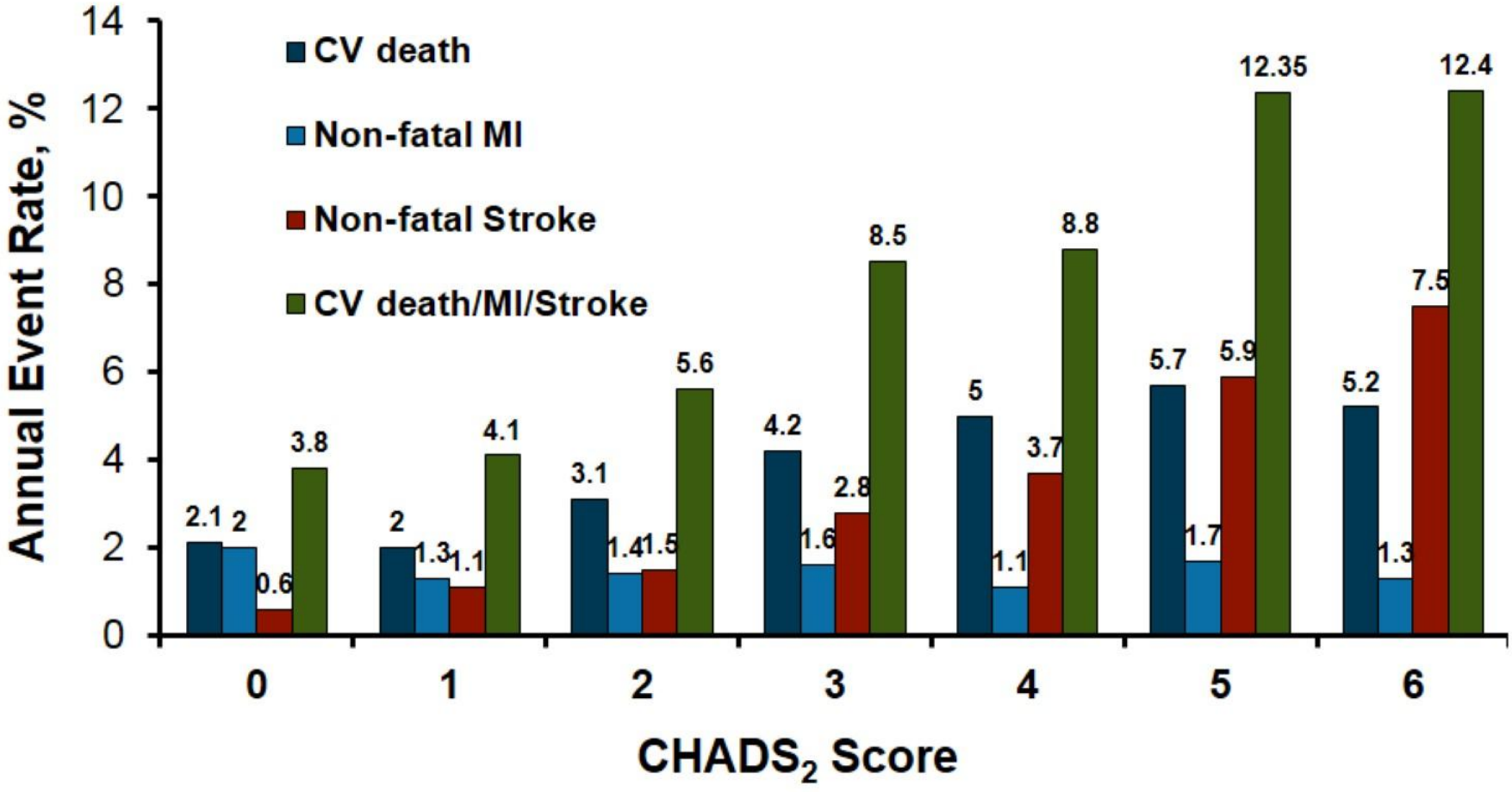
The Percentage of Strokes Attributable to AF Increases With Age



Wolf PA, et al. *Stroke* 1991;22:983-988.[4]

CV Event Rates in Patients With AF Related to $CHADS_2$ Score

REACH Registry



Reprinted from Goto S, et al. *Am Heart J.* 2008;156:855,[5] with permission from Elsevier.

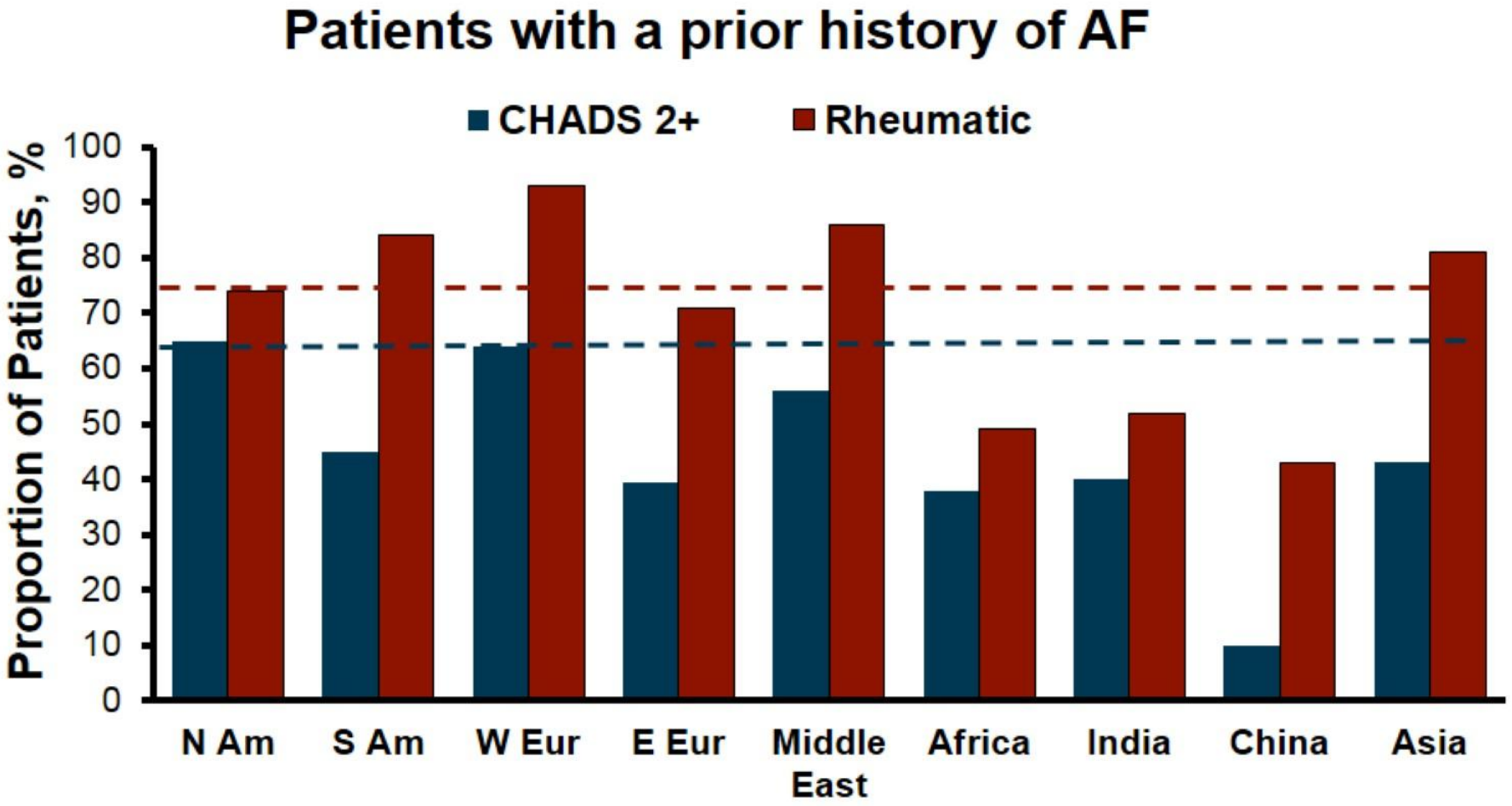
Global Atrial Fibrillation Registry

- 15,400 patients, 164 sites, 46 countries
  - Permanent 50.5%, persistent 22.6%, paroxysmal 26.9%, first onset 27.7%
- Objectives
  - Describe variations between regions in conditions predisposing to AF
  - Identify differences in treatment for AF with a focus on BP management and anticoagulation

Region	Sites	Patients
N America	19	1817
S America	23	1134
W Europe	19	1983
E Europe	22	2542
Middle East	8	887
Africa	20	1137
India	22	2536
China	20	2023
Southeast Asia	11	1341

Oldgren J, et al. *Circulation*. 2014;129:1568-1576.[6]

Global Atrial Fibrillation Registry: Differences in Oral Anticoagulant Use



Oldgren J, et al. *Circulation*. 2014;129:1568-1576.[6]

Global Atrial Fibrillation Registry
INR Control by Region

Region	Mean TTR, %
North America	50.9
South America	46.8
Western Europe	62.4
Eastern Europe	56.0
India	33.7
China	35.5
Southeast Asia	36.0
Middle East	42.2
Africa	32.7

Oldgren J, et al. *Circulation*. 2014;129:1568-1576.[6]

ORBIT-AF
Outcome Registry for Better Informed Treatment of Atrial Fibrillation

- ORBIT-AF -- national, prospective registry
- Eligible pts: ≥ 18 years, able to consent
- Consecutive enrollment
- 10,130 patients from 176 sites nationwide
- Providers: cardiologists, EPs, and primary care
- Longitudinal information -- 6-monthly for 2 years
- Objectives
  - Describe a large representative AF population including demographics, comorbidities, and risk profiles
  - Define current practice patterns for the treatment, particularly stroke prevention
  - Identify patterns of care and subsequent outcomes by risk (ie, low vs high risk)
  - Assess adherence and resource use associated with anticoagulant prophylaxis
  - Assess the adoption and impact of emerging antithrombotic and antiarrhythmic therapies on outcomes in AF and healthcare resource use

Piccini JP, et al. *Am Heart J.* 2011;162:606-612.[7]

Comparison of Physician-Assigned vs Empirical Risk Assessments

Risk Stroke, % patients

	Low (< 3%)	Intermediate (3-6%)	High (> 6%)
$CHADS_2$ Score	6	22	72
Physician-Assigned Stroke Risk	41	43	16

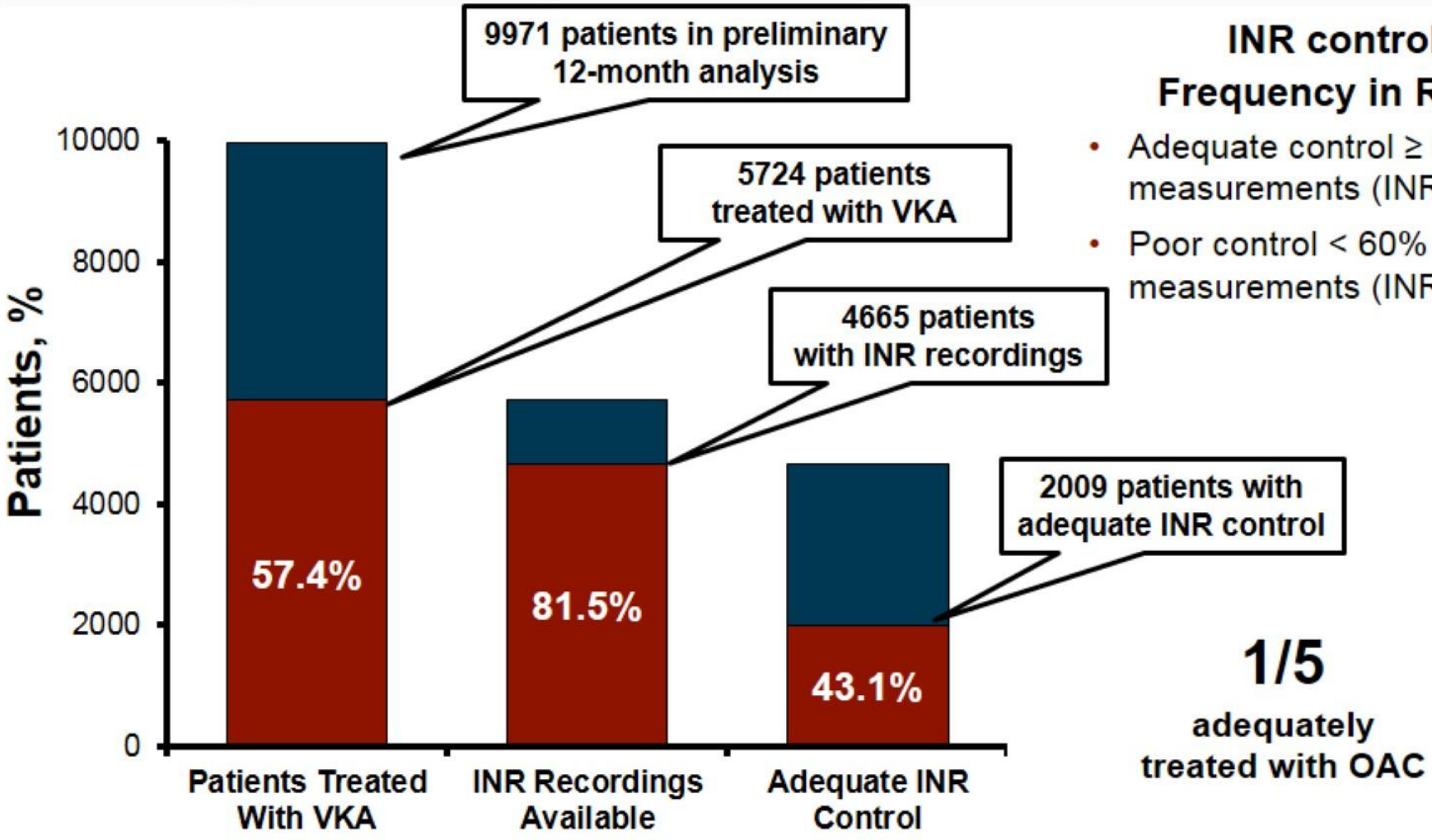
Bleeding Risk, % patients

	Low (< 3%)	Intermediate (3-6%)	High (> 6%)
ATRIA Bleeding Score	74	9	17
Physician-Assigned Stroke Risk	59	34	7

Steinberg BA, et al. *Circulation*. 2014;129:2005-2012.[8]

GARFIELD

VKA Treatment - Inadequate INR Control



INR control: Frequency in Range

- Adequate control ≥ 60% of measurements (INR 2-3)
- Poor control < 60% of measurements (INR 2-3)

1/5

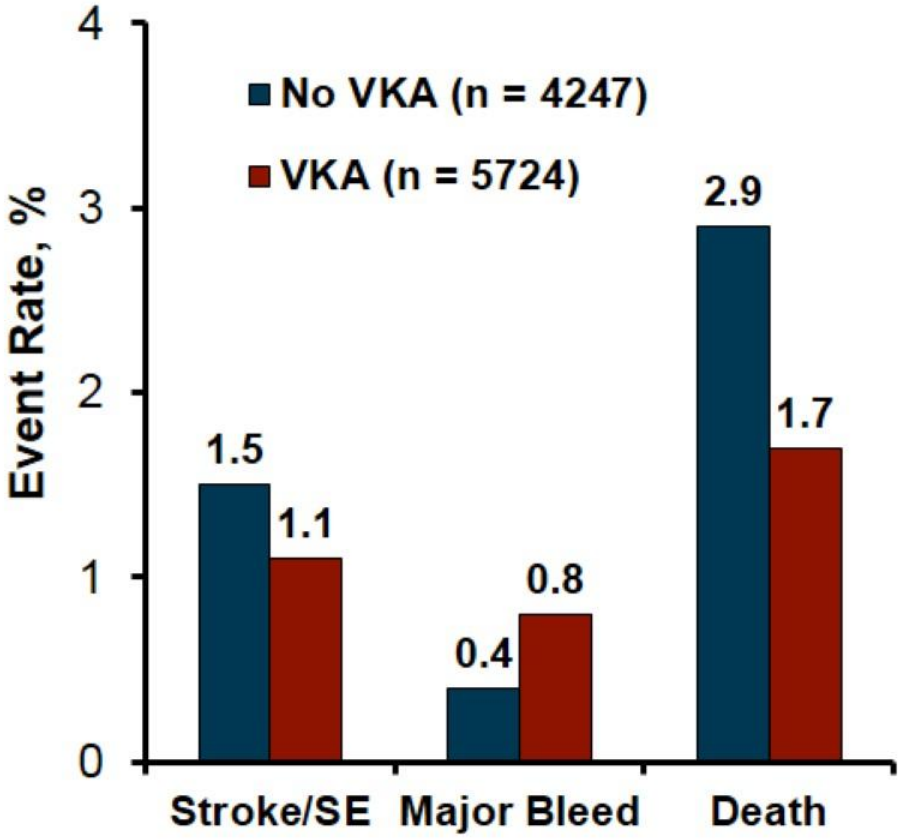
adequately treated with OAC

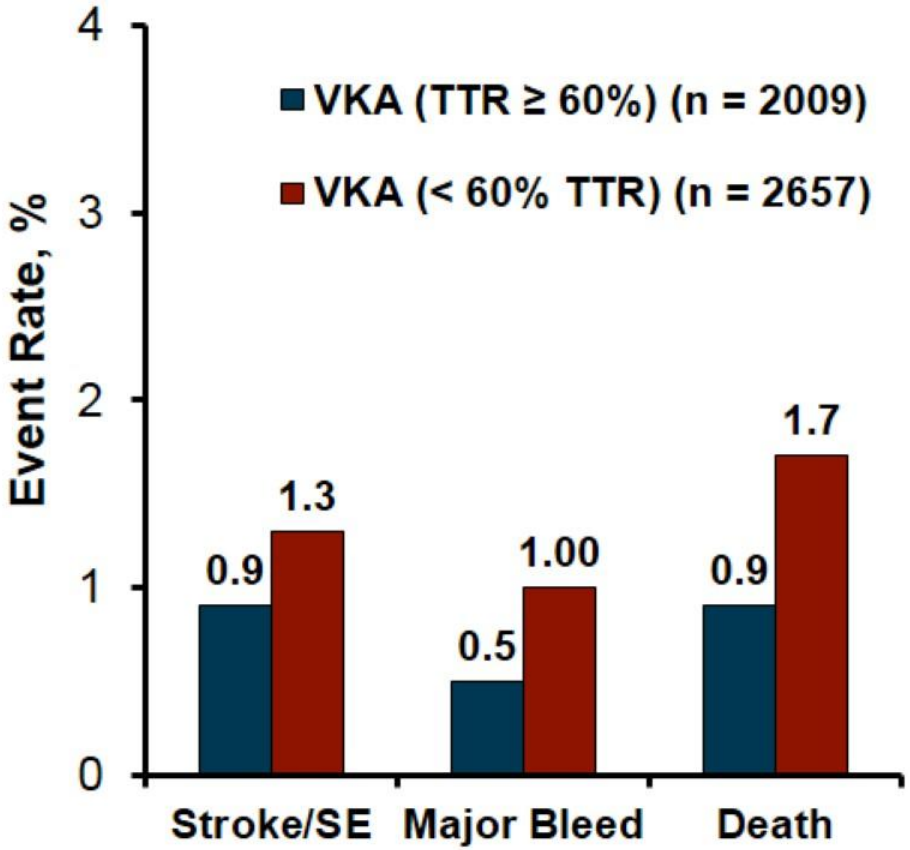
INR = international normalized ratio.

Kakkar AK. *Circulation*. 2012;126:2792-2793.[9]

GARFIELD

Preliminary First Year Event Rates by Treatment and VKA Control



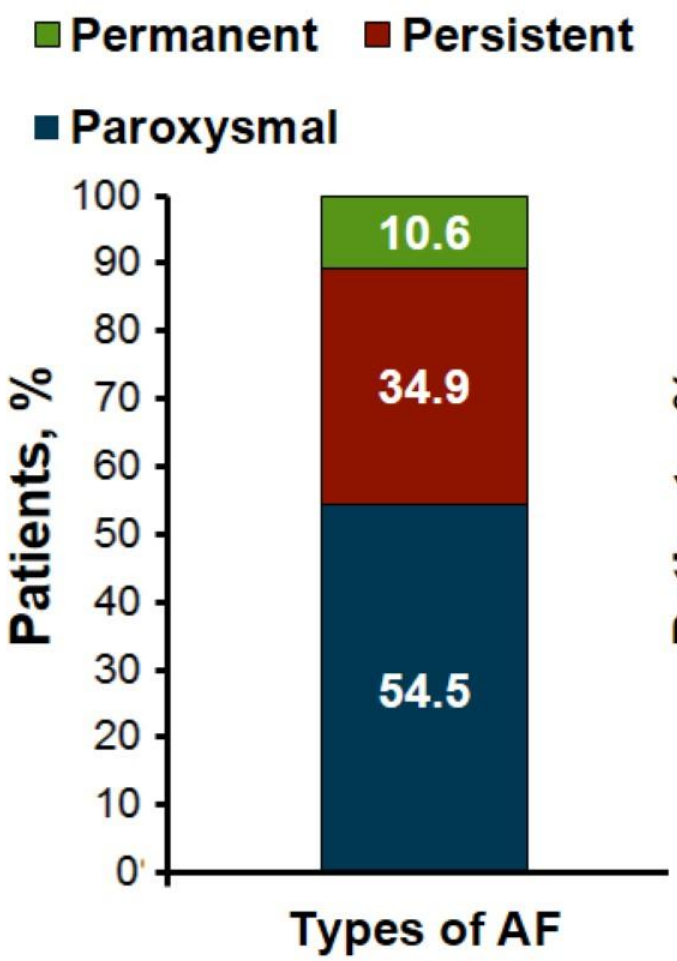


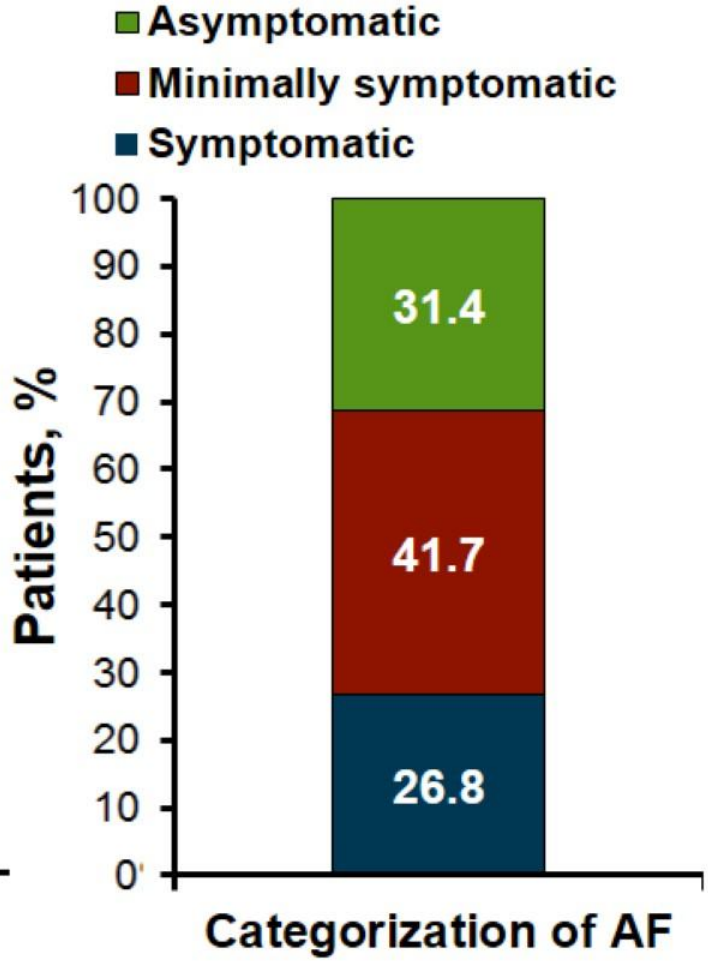
Kakkar AK. *Circulation*. 2012;126:2792-2793.[9]

GLORIA

Global Registry on Long-term Oral Antithrombotic Treatment in Patients With Atrial Fibrillation

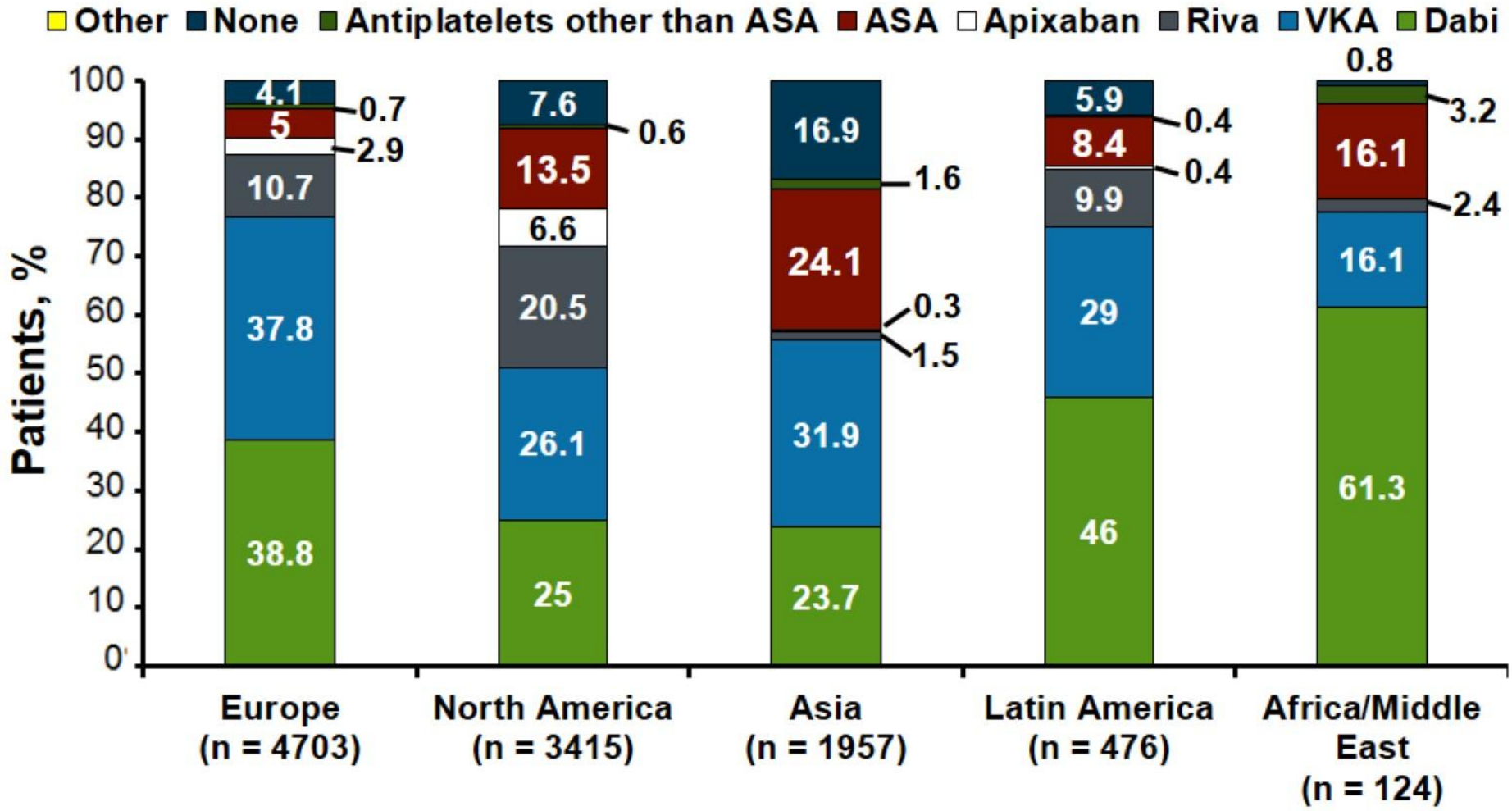
- Large, international, observational registry involving patients with newly diagnosed nonvalvular AF at risk for stroke
- Enrolling up to 56,000 patients in nearly 50 countries





Huisman MV, et al. ESC 2014. FP 896.[10]

GLORIA
Antithrombotic Treatment at Baseline

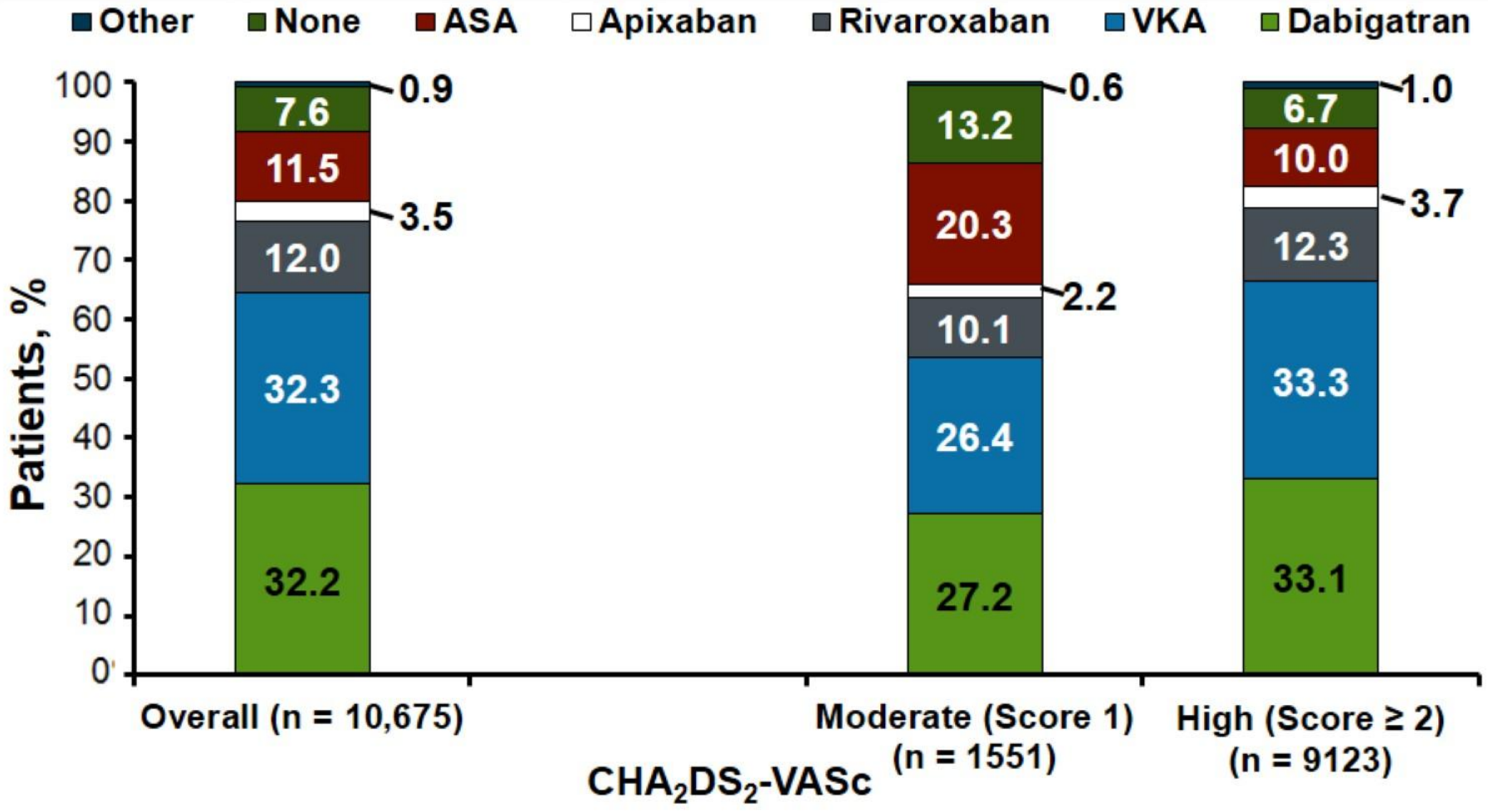


"Other" includes combination or oral anticoagulants.

Huisman MV, et al. ESC 2014. FP 896.[10]

GLORIA -- Cohort 2

Antithrombotic Treatment by Stroke Risk



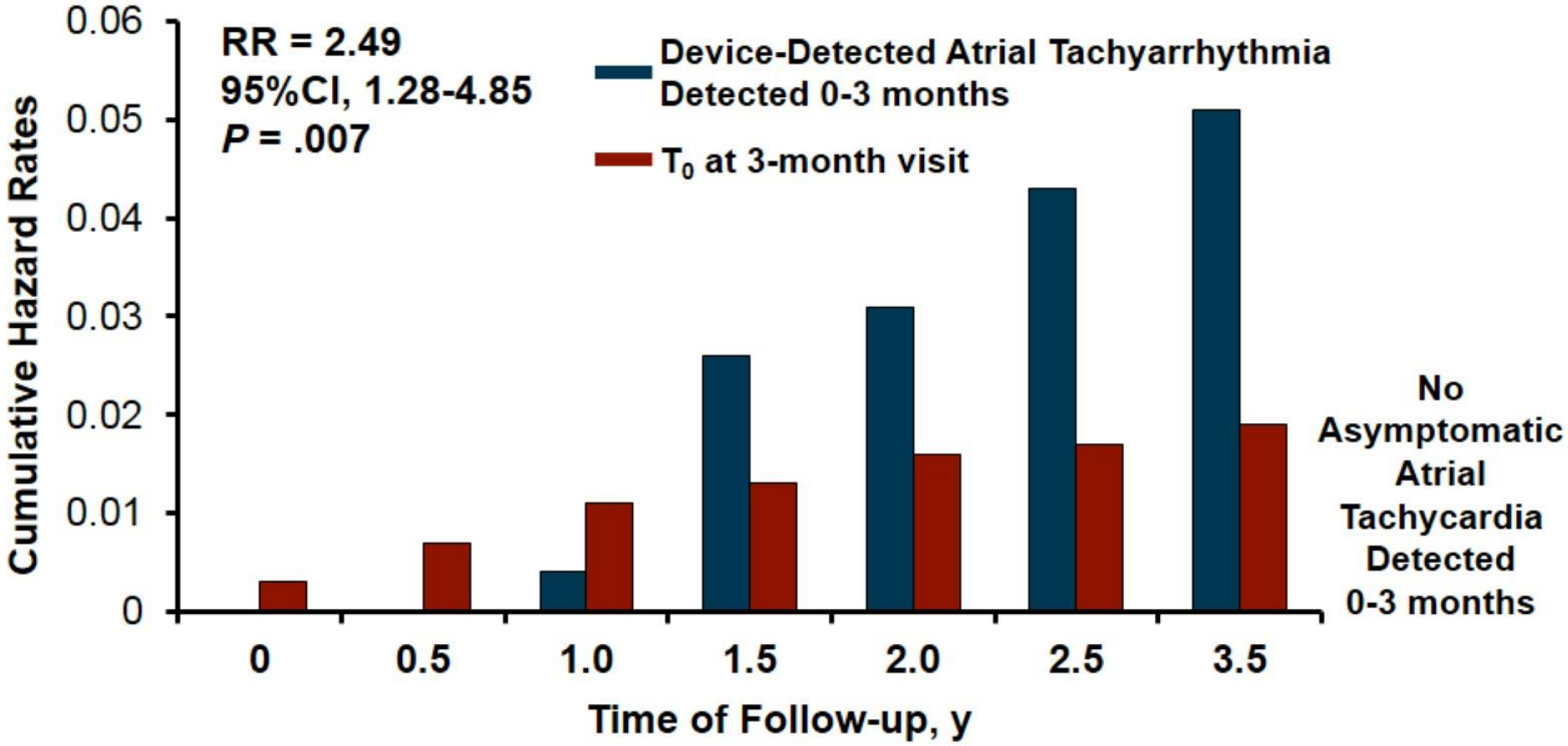
CHA_2DS_2-VASc score missing for 1 patient.

"Other" includes antiplatelets other than ASA and combination of oral anticoagulants.

Huisman MV, et al. ESC 2014. FP 896.[10]

ASSERT

Ischemic Stroke or Systemic Embolism



# At Risk						
+	261	249	238	218	178	122
-	2319	2145	2070	1922	1556	1197

Healey J, et al. *N Engl J Med*. 2012;366:120-129.[11]

Arrhythmia Alliance
"Know your Pulse"

Clinic	Pulse Checks	All AF	Unknown AF
Neurology	324	33	8
Hypertension	250	21	5
Diabetes	301	30	10
Nephrology	290	18	2

A. John Camm. Unpublished data.

Conclusions

- AF common and growing in prevalence
- An important cause of stroke, especially in older people
- Underuse of anticoagulation remains a problem
- Disconnect between actual risk and perceived risk
- Suboptimal INR control in a proportion of patients
- Silent AF associated with increased risk of stroke
  - Likely will be increasing detection in future

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An Ace Up Your Sleeve

New Evidence for Managing Patients at High Risk for Stroke

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Senior Investigator
TIMI Study Group
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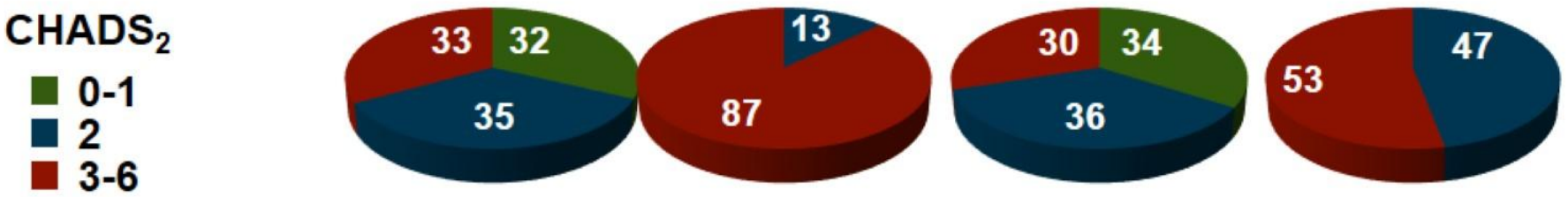
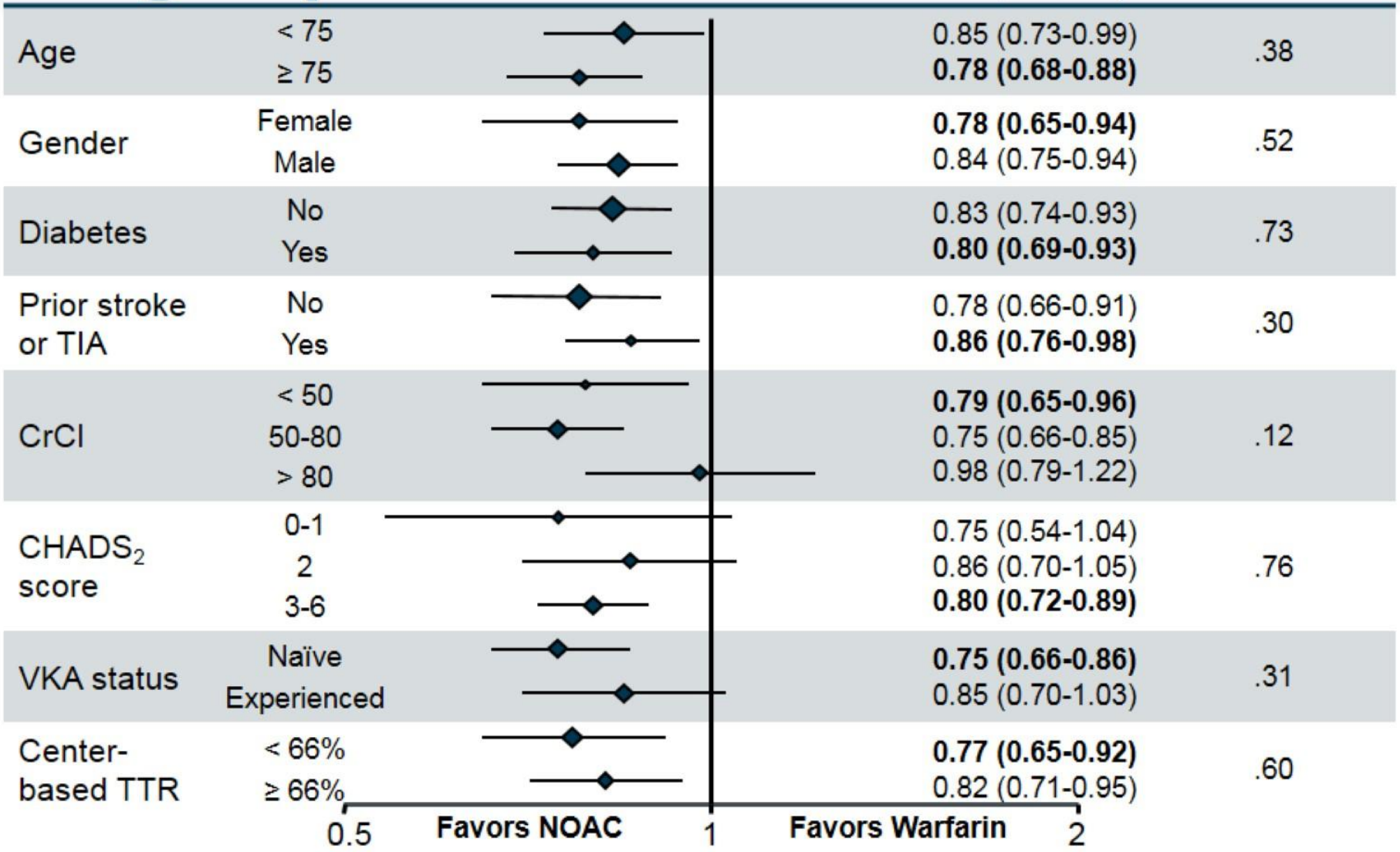
NOAC Trials in AF
Baseline Characteristics

	RE-LY[a] (Dabigatran)	ROCKET AF[b] (Rivaroxaban)	ARISTOTLE[c] (Apixaban)	ENGAGE AF-TIMI 48[d] (Edoxaban)
# Randomized	18,113	14,264	18,201	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 naïve, %	50	38	43	41
Aspirin use,%	40	36	31	29



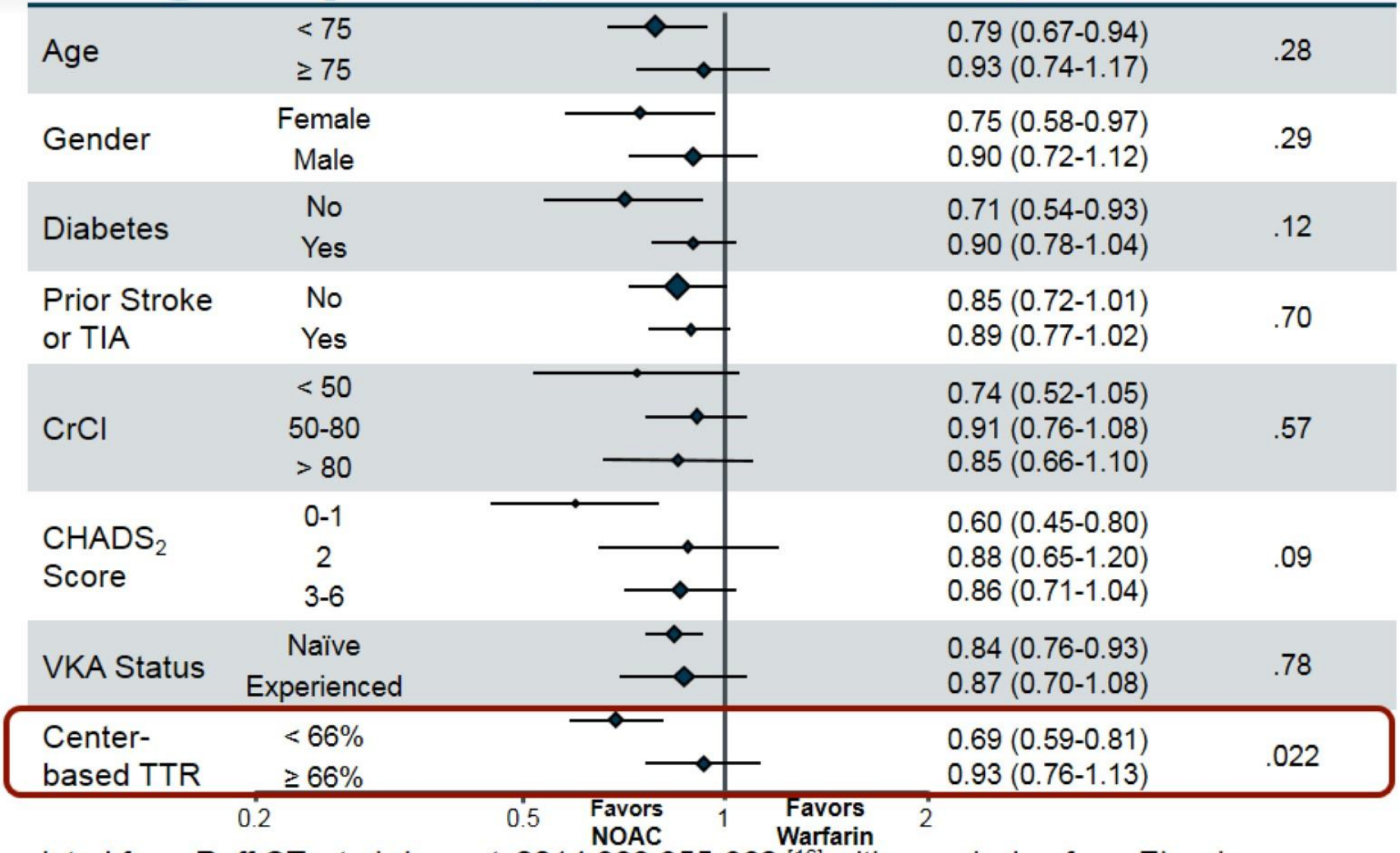
a. Connolly SJ, et al. *N Engl J Med.* 2009;361:1139-1151.[12]
b. Patel MR, et al. *N Engl J Med.* 2011;365:883-891.[13]
c. Granger CB, et al. *N Engl J Med.* 2011;365:981-992.[14]
d. Giugliano RP, et al. *N Engl J Med.* 2013; 369:2093-2104.[15]

Metanalysis of 4 NOAC Trials Subgroups: *Stroke or SEE*



Reprinted from Ruff CT, et al. *Lancet.* 2014;383:955-962,[16] with permission from Elsevier.

Metanalysis of 4 NOAC Trials
Subgroups: *Major Bleeding*



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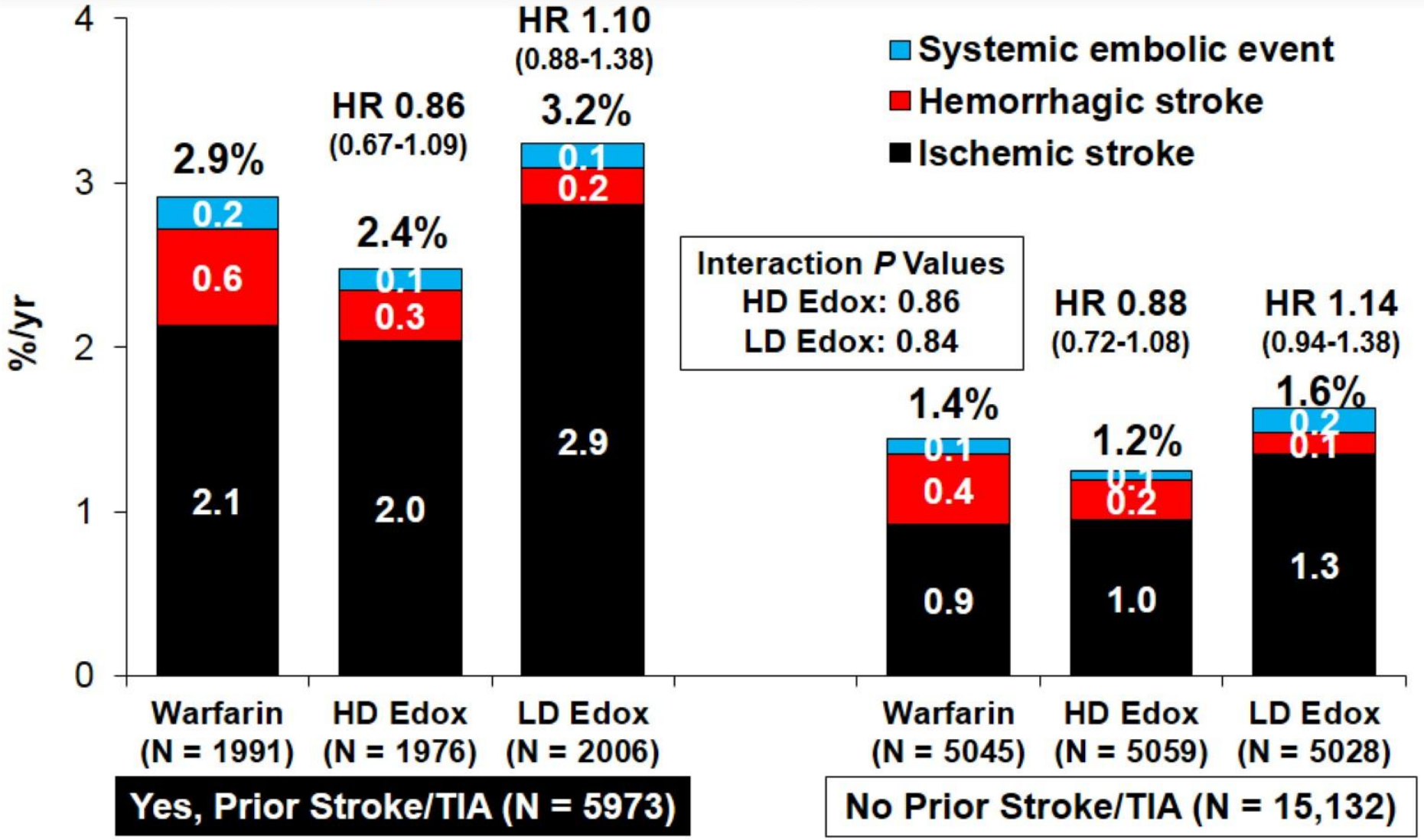
Primary Efficacy Events Stratified by History of Stroke/TIA



Data provided by Dr. Giugliano

Other Efficacy Events by Treatment Group

Patients With History of Prior Stroke/TIA (N = 5973)

Outcome	Warfarin, %/y	HDE, %/y	HR Adj (HDE vs W)	*P*	LDE, %/y	HR adj, (LDE vs W)	*P*
All stroke	2.67	2.30	0.86	.24	3.09	1.14	.26
Fatal stroke	0.67	0.57	0.86	.54	0.65	0.96	.88
Disabl stroke	0.58	0.42	0.73	.26	0.70	1.17	.51
Isch stroke	2.13	2.04	0.96	.76	2.87	**1.33**	**.02**
Hem stroke	0.59	0.31	**0.52**	**.03**	0.22	**0.37**	**.004**
CV death	3.76	2.96	**0.79**	**.03**	2.82	**0.74**	**.005**
Death, stroke, SEE	7.12	5.89	**0.83**	**.02**	6.23	0.86	.051

No *P*-int were < .05 for treatment * prior stroke/TIA subgroups

Data provided by Dr. Giugliano

Safety and Net Outcomes by Treatment Group
Patients With History of Prior Stroke/TIA (N = 5973)

Outcome	Warfarin, %/y	HDE, %/y	HR Adj (HDE vs W)	*P*	LDE, %/y	HR adj, (LDE vs W)	*P*
Major bleed	3.86	3.25	0.84	.14	2.01	**0.52**	**< .001**
Fatal bleed	0.41	0.16	**0.40**	**.04**	0.20	0.49	.08
ICH	1.09	0.62	**0.57**	**.02**	0.40	**0.37**	**< .001**
Life-threatening bleed	1.09	0.66	**0.61**	**.04**	0.31	**0.29**	**< .001**
Death, stroke SEE, Major bleed	9.74	8.24	**0.84**	**.01**	7.88	**0.80**	**< .001**
Death, disabling stroke, LT bleed	6.50	5.11	**0.79**	**.003**	4.82	**0.73***	**< .001**
Death, stroke, ICH	7.42	5.95	**0.80**	**.004**	6.19	**0.82**	**.01**

**P*-int .044; all other treatment*subgroup *P*-int > .05

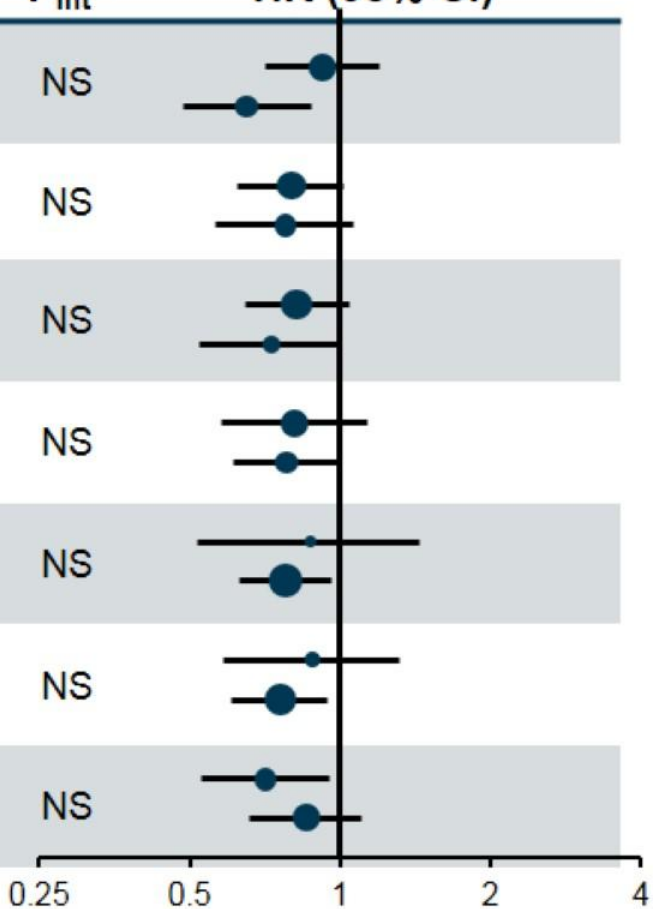
Data provided by Dr. Giugliano

Prespecified Subgroups in ENGAGE AF-TIMI 48

Efficacy (Stroke or SEE)

mITT Population, On-Treatment

			Event Rate, %/y			← Edoxaban 60/30 mg better / Warfarin better →
		Pts	Edox 60/30 mg	Warfarin	P_{int}[a]	HR (95% CI)
Subgroup age, y	< 75	8381	1.10	1.19	NS	
	≥ 75	5643	1.31	2.02		
Sex	Female	8736	1.16	1.46	NS	
	Male	5288	1.21	1.55		
$CHADS_2$ score	≤ 3	10,833	0.98	1.20	NS	
	4-6	3191	1.91	2.62		
Dose adjusted	Yes	3556	1.79	2.21	NS	
	No	10,468	1.00	1.29		
Weight, kg	≤ 60	1379	2.06	2.41	NS	
	> 60	12,465	1.10	1.41		
CrCL; mL/min	30-50	2607	1.72	1.97	NS	
	> 50	11,296	1.06	1.40		
Prior VKA	Naive	5767	1.26	1.77	NS	
	Exp	8257	1.13	1.32		

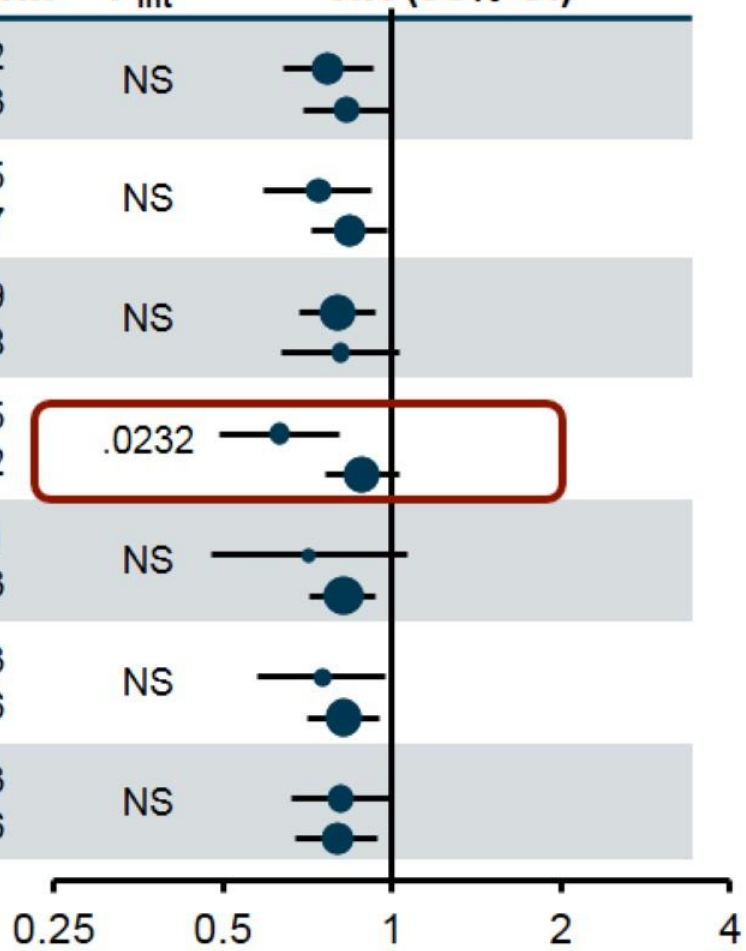


Data provided by Dr Giugliano

Prespecified Subgroups in ENGAGE AF-TIMI 48

Safety (Major Bleeding), Safety Population, On-treatment Period

		Pts	Event Rate, %/y Edox 60/30 mg	Warfarin	P_{int}[a]	HR (95% CI)
						← Edoxaban 60 mg better Warfarin better →
Subgroup age, y	< 75	8381	2.02	2.62	NS	
	≥ 75	5643	4.01	4.83		
Sex	Female	8736	2.48	3.35	NS	
	Male	5288	2.90	3.47		
$CHADS_2$ Score	≤ 3	10,833	2.47	3.09	NS	
	4-6	3191	3.79	4.68		
Dose adjusted	Yes	3556	3.05	4.85	.0232	
	No	10,468	2.66	3.02		
Weight, kg	≤ 60	1379	3.18	4.51	NS	
	> 60	12,465	2.71	3.33		
CrCL; mL/min	30-50	2607	3.91	5.23	NS	
	> 50	11,296	2.51	3.06		
VKA use	Naïve	5767	2.86	3.53	NS	
	Exp.	8257	2.67	3.36		



Data provided by Dr. Giugliano

Transitioning Between OACs
FDA Black Box Warnings

Rivaroxaban[a]

WARNING: (A) PREMATURE DISCONTINUATION OF XARELTO INCREASES THE RISK OF THROMBOTIC EVENTS, and (B) SPINAL/EPIDURAL HEMATOMA

See full prescribing information for complete boxed warning

PREMATURE DISCONTINUATION OF XARELTO INCREASES THE RISK OF THROMBOTIC EVENTS

Premature discontinuation of any anticoagulant, including XARELTO, increases the risk of thrombotic events. To reduce this risk, consider coverage with another anticoagulant if XARELTO is discontinued for a reason other than pathological bleeding or completion of a course of therapy (2.2, 2.6, 5.1, 14.1).

Apixaban[b]

WARNING: DISCONTINUING ELIQUIS IN PATIENTS WITHOUT ADEQUATE CONTINUOUS ANTICOAGULATION INCREASES RISK OF STROKE

See full prescribing information for complete boxed warning.

Discontinuing ELIQUIS places patients at an increased risk of thrombotic events. An increased rate of stroke was observed following discontinuation of ELIQUIS in clinical trials in patients with nonvalvular atrial fibrillation. If anticoagulation with ELIQUIS must be discontinued for a reason other than pathological bleeding, coverage with another anticoagulant should be strongly considered. (2.4, 5.1)

Dabigatran[c]

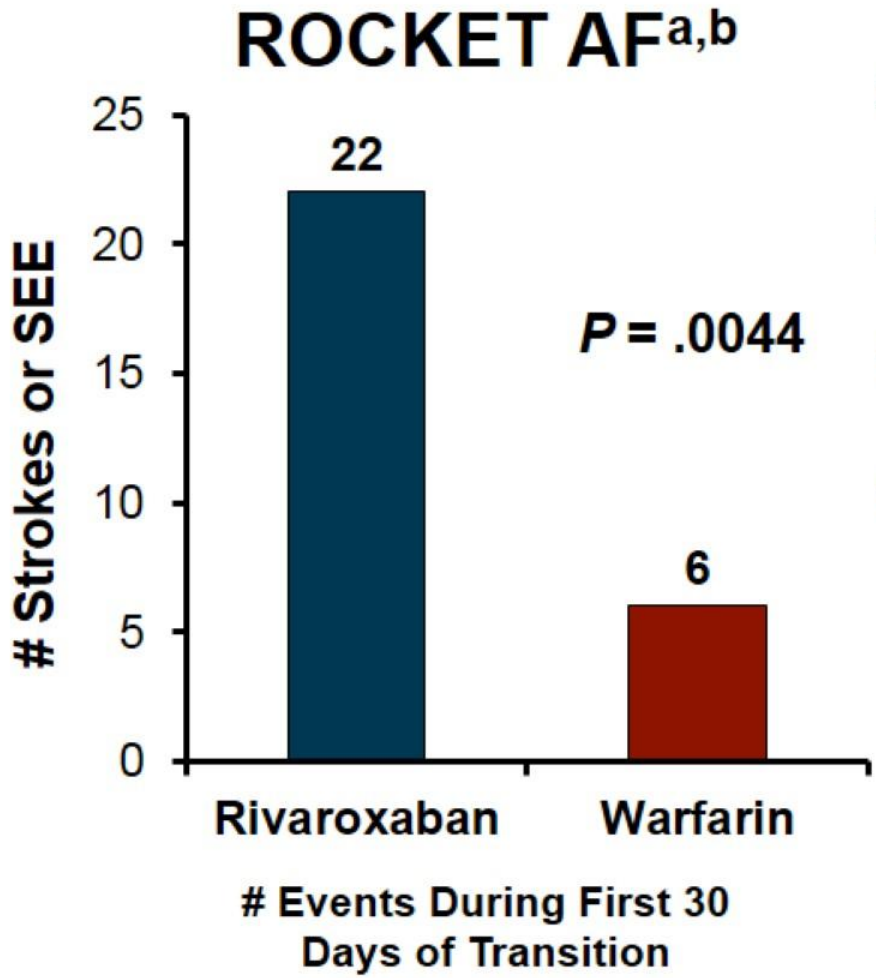
WARNING: DISCONTINUING PRADAXA IN PATIENTS WITHOUT ADEQUATE CONTINUOUS ANTICOAGULATION INCREASES RISK OF STROKE

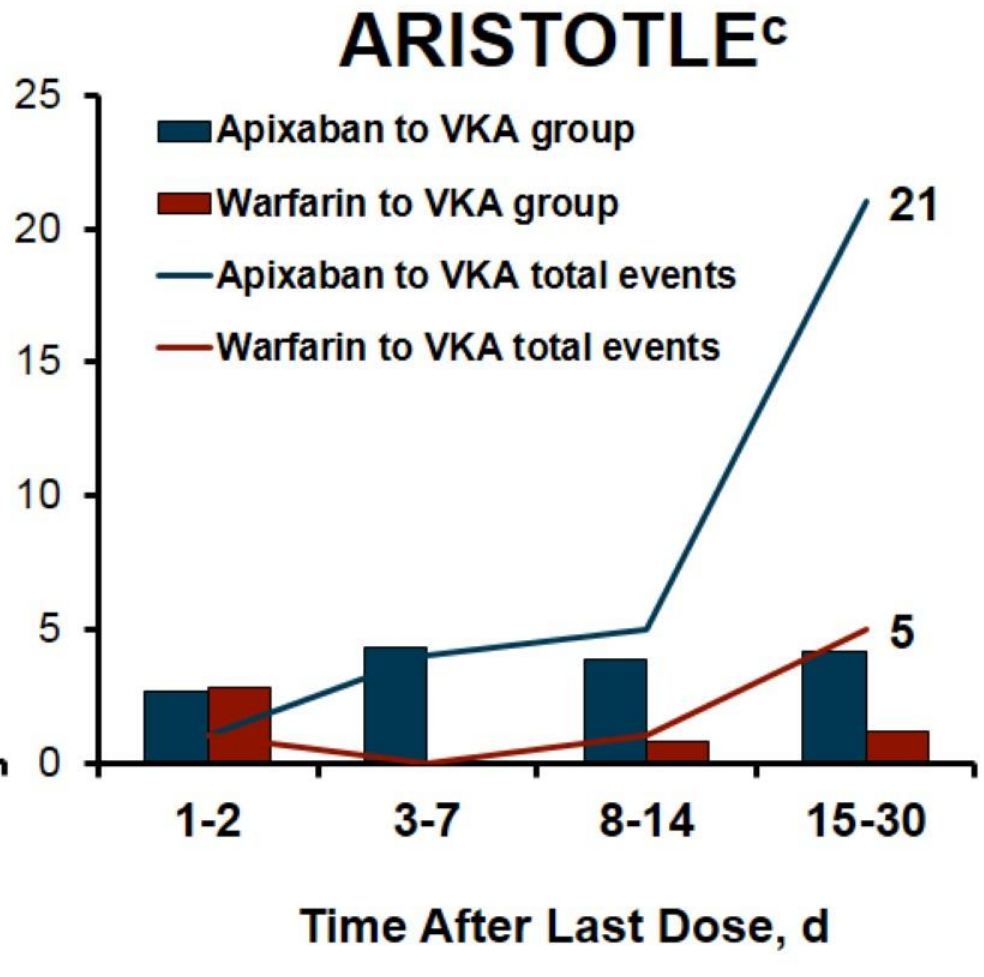
See full prescribing information for complete boxed warning.

Discontinuing PRADAXA places patients at an increased risk of thrombotic events. If anticoagulation with PRADAXA must be discontinued for a reason other than pathological bleeding, consider coverage with another anticoagulant. (2.6, 5.1)

a. Xarelto® PI 2014.[17]
b. Eliquis® PI 2014.[18]
c. Pradaxa® PI 2014.[19]

Rivaroxaban and Apixaban Transition
Increased Risk of Stroke or SEE

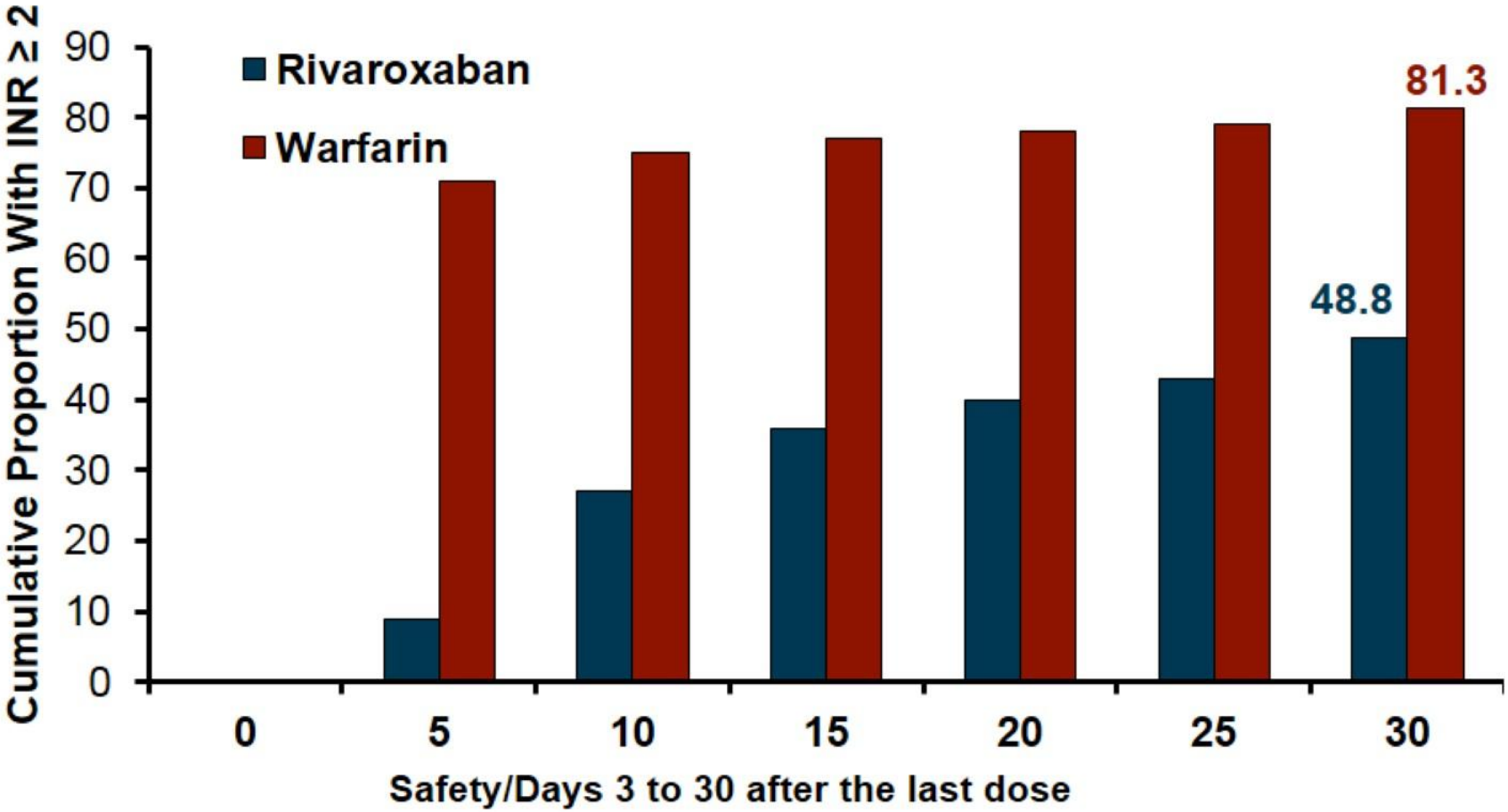




a. Patel MR, et al. *N Engl J Med*. 2011;365:883-891[13]; b. Patel MR, et al. *J Am Coll Cardiol*. 2013;61:651-658[20]; c. Granger CB, et al. *Eur Heart J*. 2012;33:685-686.[21]

Explanation?

Delay in Achieving Therapeutic INR in ROCKET AF



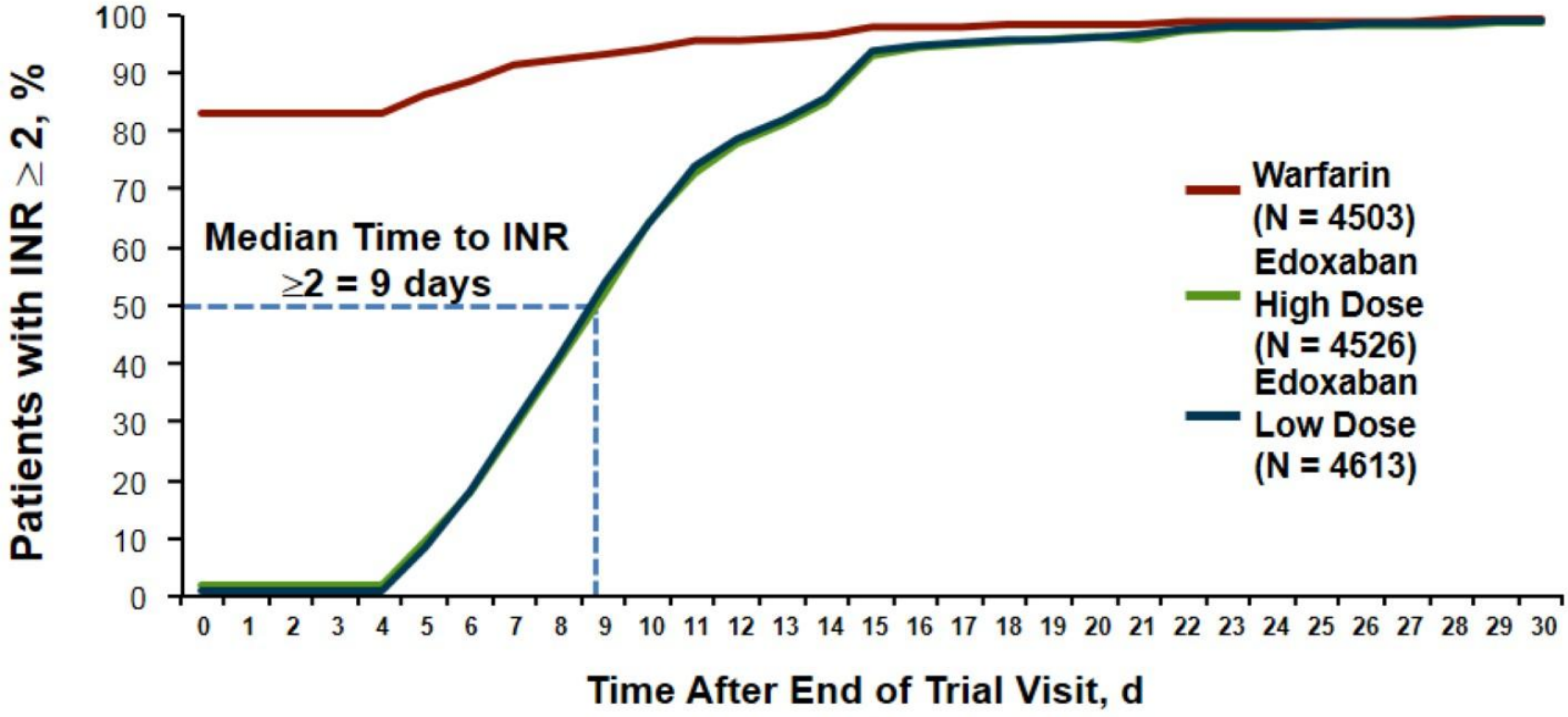
Patel MR, et al. *J Am Coll Cardiol.* 2013;61:651-658[20]

Transition Strategy
Part 1

In patients transitioning to oral VKA:

1. **At least 3 INRs measured days 4-14**
2. **Mandatory use of VKA dose algorithm**

	Patients With INR ≥ 2	
	Day 14, %	Day 30, %
Warfarin	96.6	99.4
Edoxaban HD	84.9	98.7
Edoxaban LD	85.8	98.9



Reprinted from Ruff CT, et al. *J Am Coll Cardiol.* 2014; 64:576-584,[22] with permission from the American College of Cardiology Foundation.

Transition Strategy
Part 2

Bridging edoxaban if starting an oral VKA: Overlap of edoxaban/placebo until the INR was > 2.0 (14 days maximum)

Randomization Arm	Study Drug During Double Blind Phase of Trial	Edoxaban / Placebo Transition Kit
Edoxaban high exposure	60 mg	30 mg
	30 mg (dose reduced)	15 mg
Edoxaban low exposure	30 mg	30 mg
	15 mg (dose reduced)	15 mg
Warfarin	Warfarin	Placebo

Ruff CT, et al. *J Am Cardiol Coll.* 2014;64:576-584.[22]

Transition Period Outcomes

- All pts transitioned → VKA or NOAC
- If VKA: Frequent INRs, overlapped VKA + edox (30 or 15 mg) for ≤ 2 wk until INR ≥ 2.0
- If NOAC: start when INR < 2.0

Events After Transition to Open-label Anticoagulant	Warfarin (n = 4503)	High-dose Edoxaban (n = 4526)	Low-dose Edoxaban (n = 4613)
Stroke or SEE* through 30 d	7 (0.16%)	7 (0.15%)	7 (0.15%)
Major Bleeds through 14 d	6 (0.13%)	4 (0.09%)	5 (0.11%)

Data shown include all patients on blinded study drug at the end of the treatment period

SEE = systemic embolic event. No SEEs occurred during the 30-day transition period.

Ruff CT, et al. *J Am Cardiol Coll.* 2014;64:576-584.[22]

Summary

- NOACs decrease stroke/SEE in AF patients at high risk for thromboembolism compared with warfarin
- NOACs decrease bleeding compared with warfarin in these same high-risk patients
- Patients transitioning between anticoagulants are at high risk for stroke
- ENGAGE AF-TIMI 48 trial established a safe way to transition from edoxaban to another OAC

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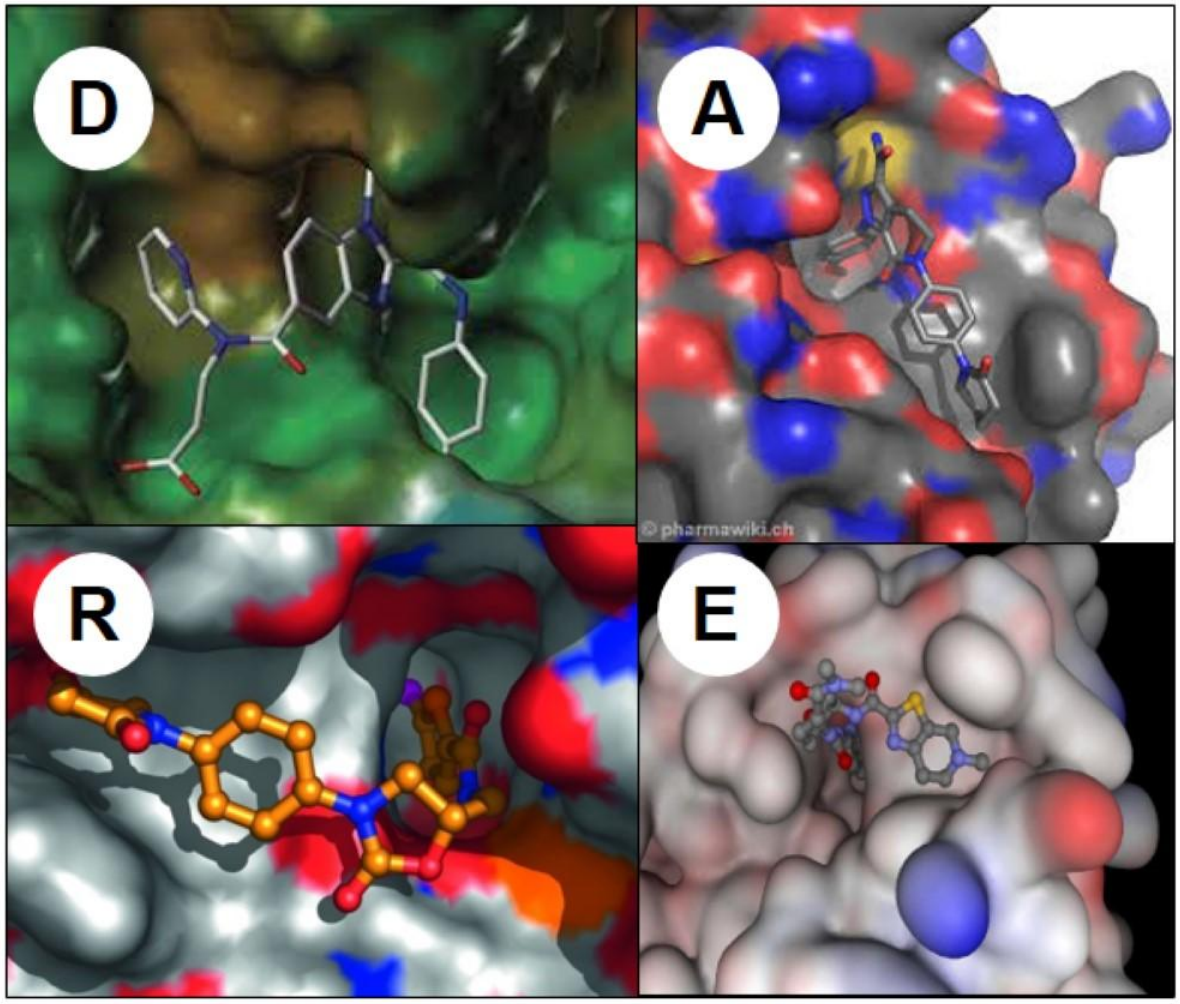
A Safe Bet

Pearls to Improve Outcomes in Stroke

A. John Camm, MD
Professor of Clinical Cardiology
St George's University of London
London, United Kingdom

Molecular Structure of NOACs



Alternatives to VK-Antagonists

NOACs	**Novel Oral Anticoagulants**
DOACs	**D**irect **O**ral **A**nticoagulants
TSOACs	**T**arget **S**pecific **O**ral **A**nticoagulants
NOACs	**N**on-VKA **O**ral **A**nticoagulants

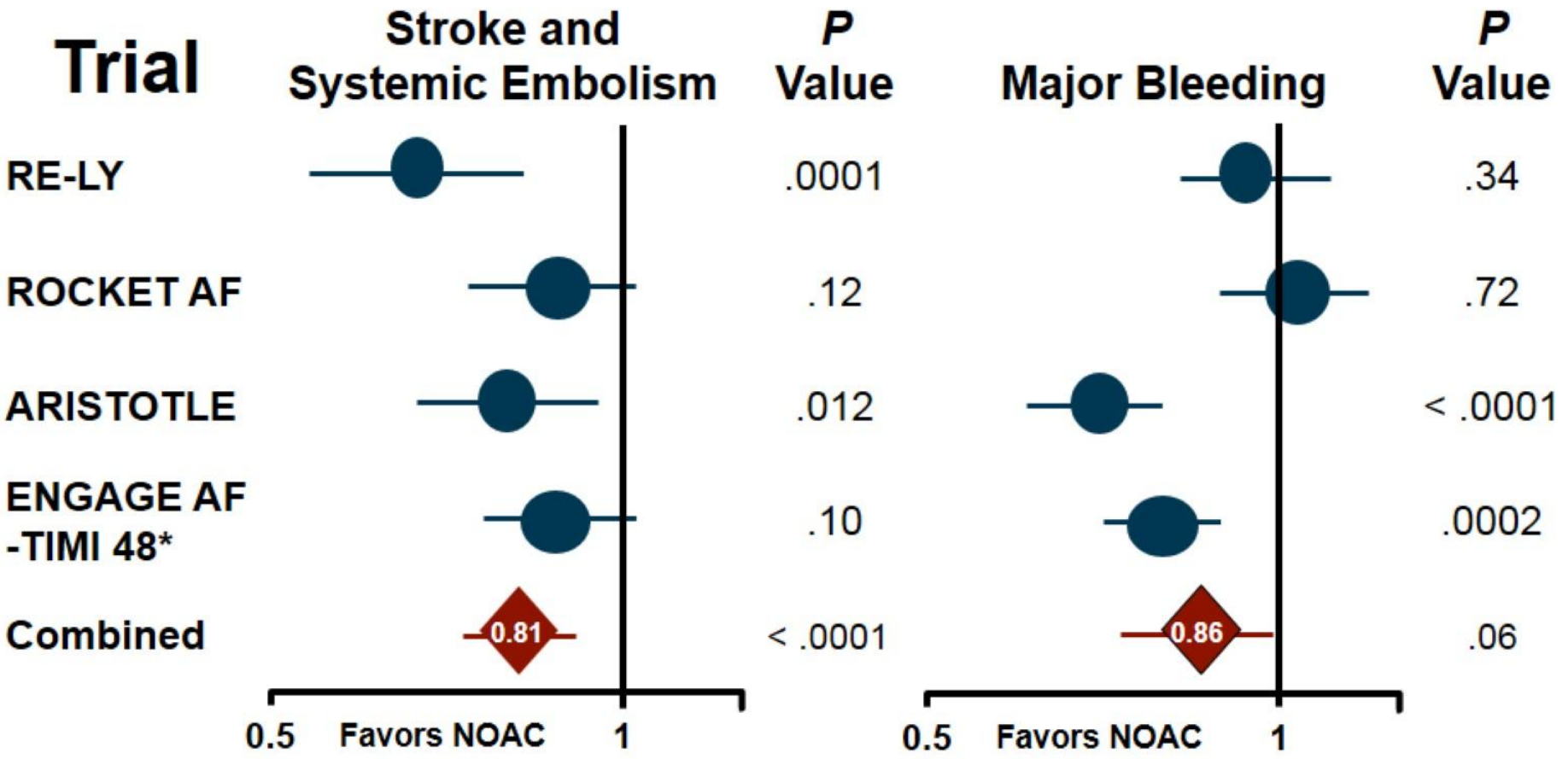
Properties of NOAC Drugs

	Dabigatran	Apixaban	Rivaroxaban	Edoxaban
Bio-availability	3–7%	50%	66% without food Almost 100% with food	62%
Prodrug	Yes	No	No	No
Clearance non-renal/renal of absorbed dose	20%/80%	73%/27%	65%/35%	50%/50%
Liver metabolism: CYP3A4 involved	No	Yes (elimination; minor CYP3A4)	Yes (elimination)	Minimal (< 4% of elimination)
Absorption with food	No effect	No effect	+ 39% more	6-22% more
Intake with food recommended?	No	No	Mandatory	No official recommendation yet
Absorption with H2B/PPI	−12-30%	No effect	No effect	No Effect
Asian ethnicity	+25%	No effect	? reduced dose (Japan)	No effect
GI tolerability	Dyspepsia 5-10%	No problem	No problem	No effect
Elimination half-life	12-17 h	12 h	5-9 h (young) 11-13 h (elderly)	9-11 h

Heidbuchel H, et al. *Europace* 2013;15:625-651,[23]
by permission of the European Society of Cardiology.

NOAC 4-trial Meta-analysis Full Dose

Pre-specified Meta-analysis of all 71,683 Patients



*Edoxaban is not approved for clinical use in AF

Reprinted from Ruff CT, et al. *Lancet*. 2014;383:955-962,[16] with permission from Elsevier.

Efficacy vs Safety
NOAC 4-trial Meta-analysis Full Dose

Result	Risk Ratio	95% CI	*P* Value
Efficacy			
Ischemic stroke	0.92	0.83-1.02	.10
Hemorrhagic stroke	0.49	0.38-0.64	< .0001
Myocardial infarction	0.97	0.78-1.20	.77
All-Cause mortality	0.90	0.85-0.95	.0003
Safety			
Intracranial hemorrhage	0.48	0.39-0.59	< .0001
Gastrointestinal bleeding	1.25	1.01-1.55	.043

Ruff C, et al. *Lancet.* 2014;383:955-962.[16]

Results of NOAC vs Warfarin Phase 3

Outcomes vs Warfarin	Dabigatran 110 mg	Dabigatran 150 mg	Rivarox-aban	Apixaban	Edoxaban* 30 mg	Edoxaban* 60 mg
↓ stroke/systemic embolism	Non-inferiority	Superiority	Non-inferiority	Superiority	(UT) Non-inferiority	(FT) Non-inferiority
↓ stroke	No	Yes	No	Yes	No	No
↓ ischaemic/ unspecified stroke	No	Yes	No	No	No	No
↓ hemorrhagic stroke	Yes	Yes	Yes	Yes	Yes	Yes
↓ disabling/fatal stroke	No	Yes	No	Yes	No	No
↓ vascular death	No	Yes	No	No	Yes	Yes
↓ all-cause death	No	No	No	Yes	Yes	Yes
↓ Major bleeding	Yes	No	No	Yes	Yes	Yes
↓ ICH	Yes	Yes	Yes	Yes	Yes	Yes
↑ GI bleeding	No	Yes	Yes	No	No	Yes
↓ treatment discontinuation	No	No	No	Yes	Yes	Same

*Edoxaban is not approved for clinical use in AF.

UT = unfavourable trend; FT = favorable trend

a. Connolly SJ, et al. *N Engl J Med.* 2009;361:1139-1151[12]; b. Patel MR, et al. *N Engl J Med.* 2011;365:883-891[13]; c. Granger CB, et al. *N Engl J Med* 2011;365:981-992[14]; d. Giugliano RP, et al. *N Engl J Med* 2013;369:2093-2104.[15]

NOAC AF Studies

	RE-LY[a]	ROCKET-AF[b]	ARISTOTLE[c]	ENGAGE AF[d]
Drug	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
N	18,113	14,264	18,201	21,105
Dose, mg	150, 110	20	5	60, 30
Frequency	BID	OD	BID	OD
Initial dose reduction	No	20→15 mg	5→2.5 mg	60→30 mg 30→15 mg
Dose reduction at baseline, %	0	21	5	25
Mean $CHADS_2$ score	2.1	3.5	2.1	2.8
VKA naïve, %	50	38	43	41
Paroxysmal AF, %	32	18	15	25
Prior stroke, TIA %	20	55	19	28
Design	PROBE	2x blind	2x blind	2x blind
Follow-up time, y	2.0	1.9	1.8	2.8

PROBE = prospective, randomized, open-label, blinded end-point evaluation

a. Connolly SJ, et al. *N Engl J Med.* 2009;361:1139-1151[12]; b. Patel MR, et al. *N Engl J Med.* 2011;365:883-91[13]; c. Granger CB, et al. *N Engl J Med.* 2011;365:981-992[14]; d. Giugliano RP, et al. *N Engl J Med.* 2013; 369:2093-104 [15]

Indirect Treatment Analysis

	Apixaban vs Dabigatran 110		Apixaban vs Dabigatran 150		Apixaban vs Rivaroxaban		Dabigatran 110 vs Rivaroxaban		Dabigatran 150 vs Rivaroxaban	
	HR	**95% CI**	**HR**	**95% CI**	**HR**	**95% CI**	**HR**	**95% CI**	**HR**	**95% CI**
Efficacy endpoints										
Stroke or systemic embolism	0.88	(0.67-1.15)	1.22	(0.91-1.62)	0.9	(0.71-1.13)	1.02	(0.79-1.32)	**0.74**	**(0.56-0.97)**
Stroke	0.86	(0.65-1.14)	1.23	(0.92-1.66)	0.93	(0.71-1.22)	1.08	(0.81-1.44)	0.75	(0.56 -1.02)
Ischemic/uncertain type of stroke	0.83	(0.61-1.13)	1.21	(0.88-1.67)	0.98	(0.72-1.33)	1.18	(0.86-1.62)	0.81	(0.58-1.13)
Hemorrhagic stroke	1.65	(0.81-3.34)	1.96	(0.94-4.08)	0.86	(0.48-1.57)	0.53	(0.25-1.12)	**0.44**	**(0.20-0.96)**
Systemic embolism	NA		NA		**3.78**	**(1.16-12.31)**	NA		NA	
Non-disabling stroke	NA		NA		NA		0.83	(0.53-1.32)	**0.60**	**(0.37-0.97)**
Mortality endpoints										
Death from any cause	0.98	(0.83-1.16)	1.01	(0.85-1.20)	1.05	(0.84-1.30)	1.07	(0.85-1.34)	1.04	(0.82-1.30)
Death from vascular causes	NA		NA		NA		1.01	(0.78-1.31)	0.96	(0.74-1.24)
Other endpoints										
Myocardial infarction	0.68	(0.45-1.03)	0.69	(0.46-1.05)	1.09	(0.74-1.60)	**1.59**	**(1.07-2.37)**	**1.57**	**(1.05-2.33)**
Pulmonary embolism	0.62	(0.17-2.20)	0.48	(0.14-1.68)	NA		NA		NA	
Bleeding endpoints										
Major bleeding	0.86	(0.7-1.06)	**0.74**	**(0.61-0.91)**	**0.66**	**(0.54-0.81)**	**0.77**	**(0.63-0.94)**	0.89	(0.73-1.09)
Major CRNM bleeding	NA		NA		**0.66**	**(0.58-0.75)**	NA		NA	
Life-threatening bleeding	NA		NA		NA		1.36	(0.82-2.27)	1.62	(0.97-2.70)
Intracranial bleeding	1.35	(0.79-2.32)	1.05	(0.63-1.76)	0.63	(0.39-1.01)	**0.46**	**(0.27-0.80)**	0.60	(0.35-1.01)
Gastrointestinal bleeding	0.81	(0.57-1.15)	**0.59**	**(0.42-0.83)**	NA		NA		NA	
Extracranial/unclassified bleeding	0.84	(0.67-1.05)	**0.74**	**(0.59-0.92)**	NA		NA		NA	

Lip GY, et al. *J Am Coll Cardiol.* 2012;60:738-746,[24]
with permission from The American College of Cardiology Foundation.

Indirect Treatment Analysis (cont)

	Apixaban vs Dabigatran 110		Apixaban vs Dabigatran 150		Apixaban vs Rivaroxaban		Dabigatran 110 vs Rivaroxaban		Dabigatran 150 vs Rivaroxaban	
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Efficacy endpoints										
Stroke or systemic embolism	0.88	(0.67-1.15)	1.22	(0.91-1.62)	0.9	(0.71-1.13)	1.02	(0.79-1.32)		
Hemorrhagic stroke	1.65	(0.81-3.34)	1.96	(0.94-4.08)	0.86	(0.48-1.57)	0.53	(0.25-1.12)		
Systemic embolism	NA		NA				NA			
Non-disabling stroke	NA		NA		NA		0.83	(0.53-1.32)		
Mortality endpoints										
Other endpoints										
Myocardial infarction	0.68	(0.45-1.03)	0.69	(0.46-1.05)	1.09	(0.74-1.60)				
Bleeding endpoints										
Major bleeding	0.86	(0.7-1.06)							0.89	(0.73-1.09)
Major CRNM bleeding	NA								NA	
Intracranial bleeding	1.35	(0.79-2.32)							0.6	(0.35-1.01)
Gastrointestinal bleeding	0.81	(0.57-1.15)							NA	
Extracranial/unclassified bleeding	0.84	(0.67-1.05)					NA		NA	

Less SE Riva

Less stroke with D'gatran 150

More MI with Dabigatran

Less bleeding with Apixaban

Less bleeding with D'gatran 110

Lip GY, et al. *J Am Coll Cardiol.* 2012;60:738-746.[24]

Dose Reduction for Patient Characteristics in NOAC Studies

RE-LY[a] Dabigatran	ROCKET AF[b] Rivaroxaban	ARISTOTLE[c] Apixaban	ENGAGE-AF[d] Edoxaban *
• None – US Regulators • CrCl 15-30 mL/min: 75 mg BID • Age > 80 years • CrCl 30-50 mL/min + P-gp inhibitor dronedarone or ketoconazole	• 20 → 15 mg OD for: – Creatinine clearance < 30–49 mL/min	• 5 → 2.5 mg BID for ANY TWO of: – Age ≥ 80 years – body weight ≤ 60 kg – Serum creatinine ≥ 1.5 mg/dL • US Regulators – strong dual inhibitors of CYP3A4 and P-gp	• 60 → 30 mg OD or 30 → 15 mg OD for: – Creatinine clearance 30–50 mL/min – body weight ≤ 60 kg – Use of quinidine, verapamil or dronedarone

BID = twice daily; OD = once daily

* not approved as of November 2014

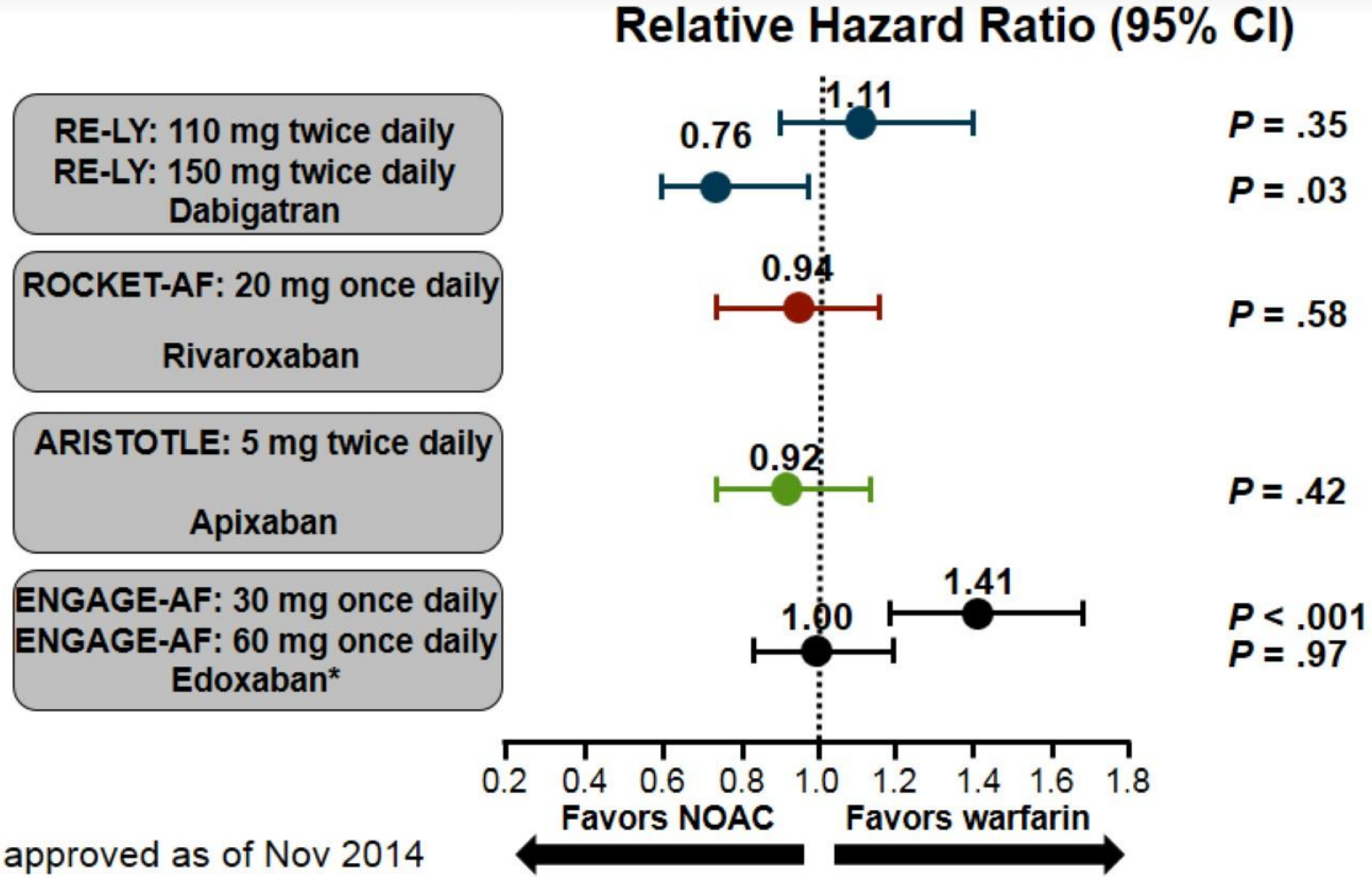
a. Connolly SJ, et al. *N Engl J Med*. 2009;361:1139-1151.[12]

b. Patel MR, et al. *N Engl J Med*. 2011;365:883-891.[13]

c. Granger CB, et al. *N Engl J Med*. 2011;365:981-992.[14]

d. Giugliano RP, et al. *N Engl J Med*. 2013;369:2093-2104.[15]

Phase 3 AF Trials
Ischemic Stroke



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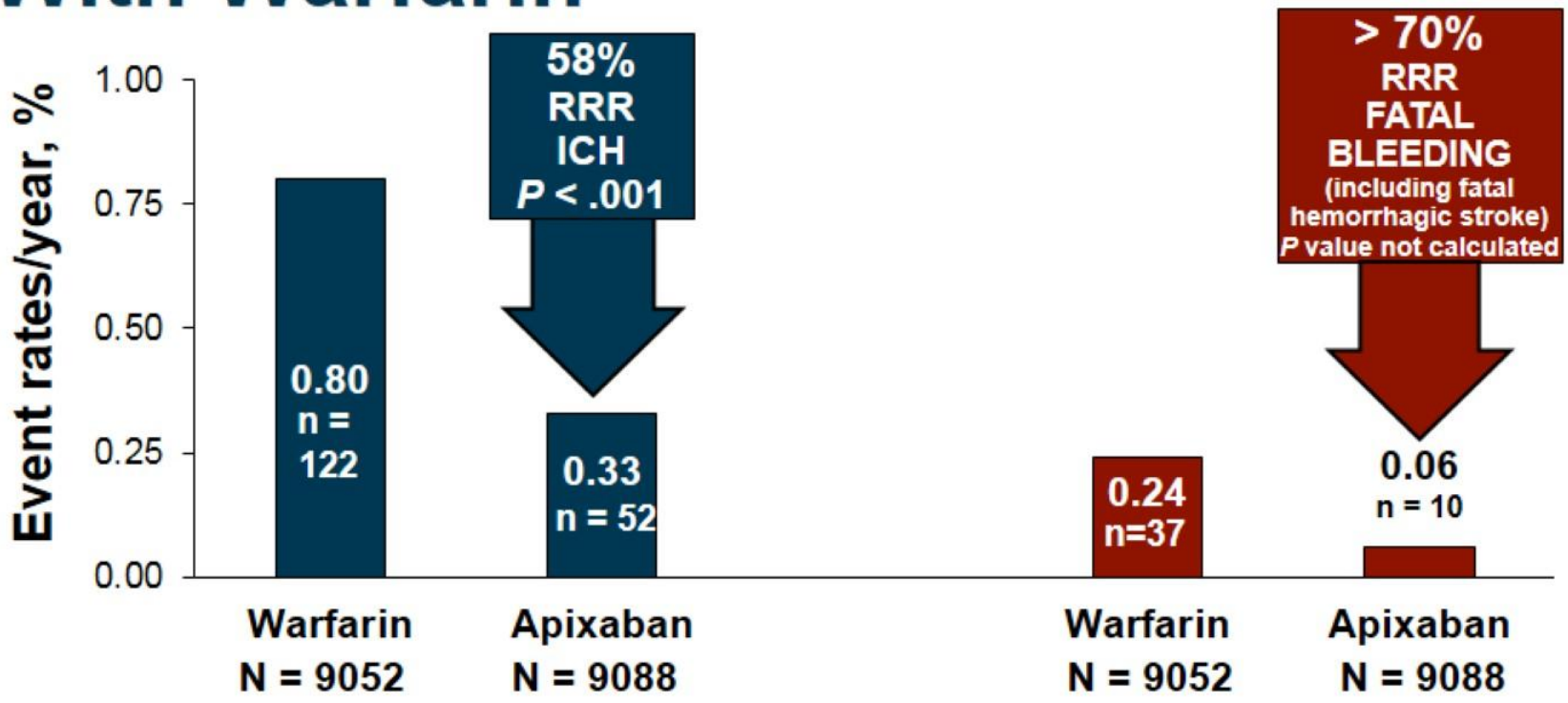
a. Connolly SJ, et al. *N Engl J Med*. 2009;361:1139-1151[12]; b. Patel MR, et al. *N Engl J Med*. 2011;365:883-891[13]; c. Granger CB, et al. *N Engl J Med*. 2011;365:981-992[14]; d. Giugliano RP, et al. *N Engl J Med*. 2013;369:2093-2104.[15]

Apixaban -- Reduced ICH and Lowered Fatal Bleeding Compared With Warfarin



- Apixaban had a lower numerical incidence of major GI bleeding compared with warfarin
  - (0.76% vs 0.86% per year; HR = 0.89; 95% CI, 0.70-1.15; *P* = .37)

ICH = intracranial hemorrhage

Granger CB, et al. *N Engl J Med*. 2011;365:981-992.[14]

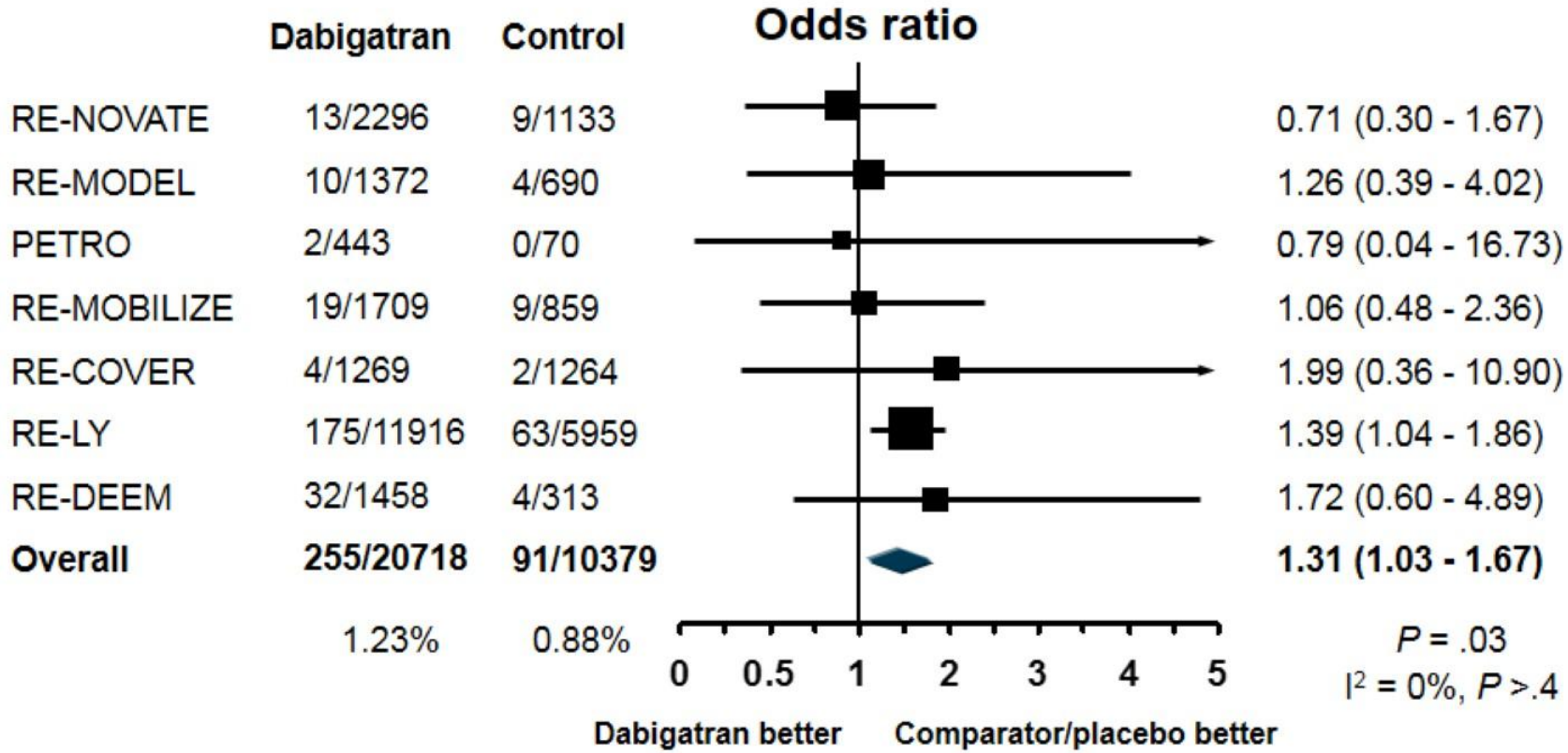
Meta-analysis of GI Bleeding With Dabigatran

Clinical Trial Data

Study Name	GI Bleeding		Total		Risk Ratio (95% CI)
	Dabi	W	Dabi	W	
RE-LY	1281	452	12091	6022	1.41 (1.27-1.56)
RE-COVER	53	35	1274	1265	1.50 (0.99-2.29)
RE-MEDY	5	8	1430	1426	0.62 (0.20-1.90)
RE-COVER II	48	33	1279	1289	1.47 (0.95-2.27)
Meta-analysis	1387	528	16074	10002	1.41 (1.28-1.55)

Sipahi I, et al. *JAMA Intern Med.* 2014;174:150-151.[25]

Dabigatran and MI/ACS Meta-analysis
7 studies, 31,097 Patients



Using RE-LY revised data on MI: OR = 1.25 (1.0 - 1.57), *P* = .05
Excluding short-term trials: OR = 1.33 (1.03 - 1.72), *P* = .03

Uchino K, et al. *Arch Intern Med*. 2012;172:397-402.[26]

Dabigatran
Favorable Benefit-Risk Profile
FDA study of > 134,000 Medicare Patients

Dabigatran was associated with a lower risk of ischemic stroke, intracranial hemorrhage, and death than warfarin

	Incidence rate per 1000 person-years		
	Dabigatran etexilate, %	**Warfarin, %**	**Adjusted HR (95% CI)**
Ischemic stroke	11.3	13.9	0.80 (0.67-0.96)
Intracranial haemorrhage	3.3	9.6	0.34 (0.26-0.46)
Major GI bleeding	34.2	26.5	1.28 (1.14-1.44)
Acute MI	15.7	16.9	0.92 (0.78-1.08)
Mortality	32.6	37.8	0.86 (0.77-0.96)

Comparison of matched new-user cohorts treated with dabigatran etexilate 150 mg or 75 mg* or warfarin for nonvalvular AF based on 2010-2012 Medicare data.
*Primary findings are based on analysis of both doses (no stratification by dose).

Graham DJ, et al. *Circulation*. 2014 Oct 30. [Epub ahead of print][27]

Dabigatran in RE-LY
Most Common Adverse Events

	Dabigatran 110 mg, %	Dabigatran 150 mg, %	Warfarin, %
Dyspepsia*	11.8	11.3	5.8
Dyspnea	9.3	9.5	9.7
Dizziness	8.1	8.3	9.4
Peripheral edema	7.9	7.9	7.8
Fatigue	6.6	6.6	6.2
Cough	5.7	5.7	6.0
Chest pain	5.2	6.2	5.9
Arthralgia	4.5	5.5	5.7
Back pain	5.3	5.2	5.6
Nasopharyngitis	5.6	5.4	5.6
Diarrhea	6.3	6.5	5.7
Urinary tract infection	4.5	4.8	5.6
Upper respiratory tract infection	4.8	4.7	5.2

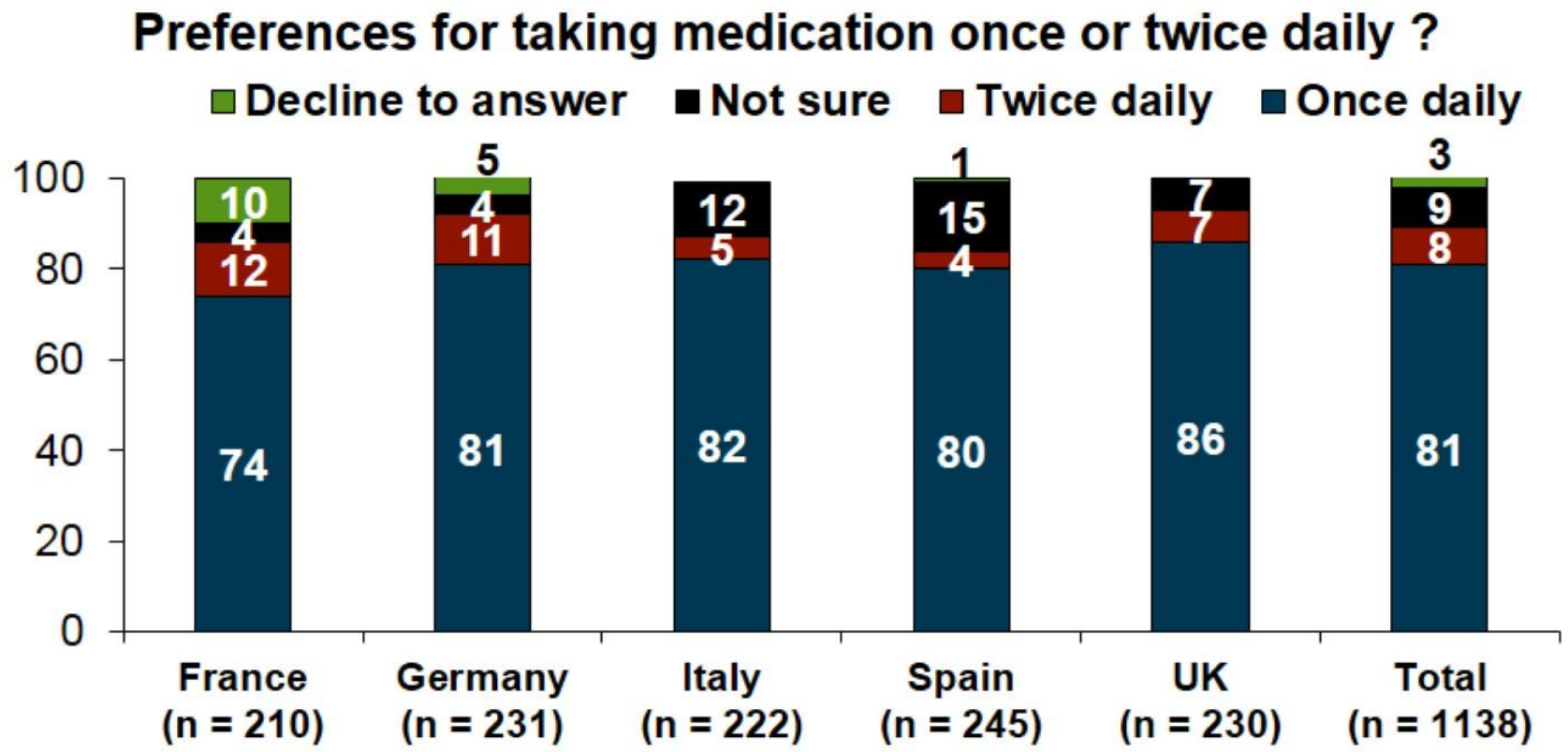
*Occurred more commonly on dabigatran $P < .001$

Connolly SJ, et al. *N Engl J Med*. 2009;361:1139-1151.[12]

Preferences for Anticoagulation Rx

EUropean Patient Survey in Atrial Fibrillation (EUPS-AF)

- 340,476 individuals contacted, 1.08% had AF
  - 1507 respondents, average age 70 y, 50% women



- Overall, 81% preferred OD anticoagulation

Zamorano JL, et al. ESC 2012. Poster P1789.[28]

2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation

Role of Warfarin

Recommendation	Class	Level
Warfarin recommended with mechanical heart valves. Target INR intensity should be based on the type and location of prosthesis	I	B
With prior stroke, TIA, or CHA_2DS_2VASc score ≥ 2, oral anticoagulants are recommended. Options include		
• Warfarin	I	A
• Dabigatran, rivaroxaban, apixaban	I	B
With CHA_2DS_2VASc score ≥ 2 and end-stage CKD (CrCl < 15 mL/min) or on hemodialysis, it is reasonable to prescribe warfarin for oral anticoagulation	IIa	B

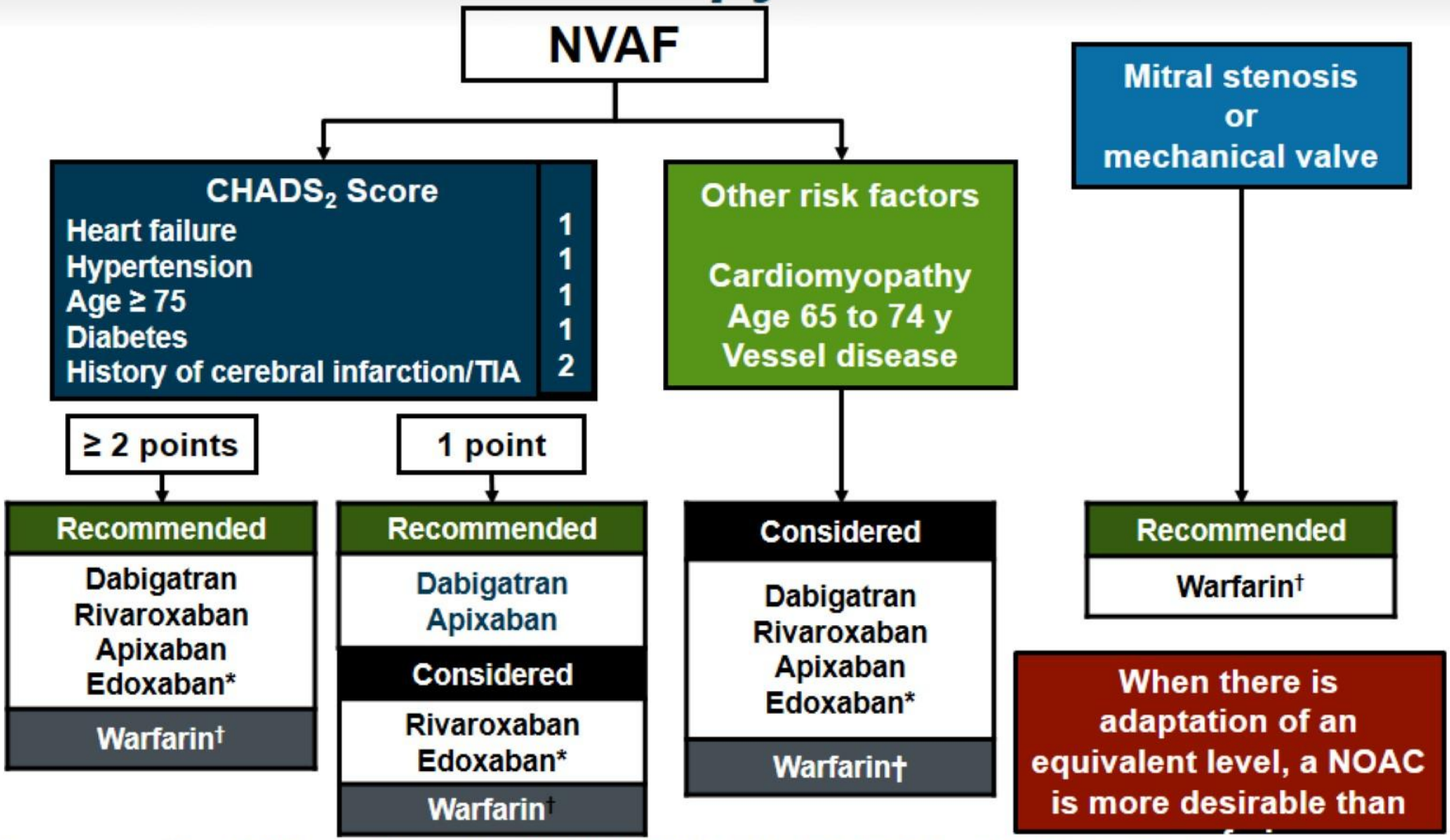
January CT, et al. *J Am Coll Cardiol*. 2014;64:e1-e76.[29]

ESC Guidelines for Anticoagulation

Recommendations	Class	Level
When adjusted-dose VKA (INR 2-3) cannot be used in a patient with AF where an OAC is recommended, due to difficulties in keeping within therapeutic anticoagulation, experiencing side effects of VKAs, or inability to attend or undertake INR monitoring, **one of the NOACs, either:** • **a direct thrombin inhibitor (dabigatran); or** • **an oral factor Xa inhibitor (eg, rivaroxaban, apixaban)** **… is recommended.**	I	B
Where OAC is recommended, one of the NOACs, either: • a direct thrombin inhibitor (dabigatran); or • an oral factor Xa inhibitor (eg, rivaroxaban, apixaban) … **should be considered rather than adjusted-dose VKA** (INR 2-3) for most patients with non-valvular AF, based on their net clinical benefit.	IIa	A

Camm AJ, et al. *Europace*. 2012;14:1385-1413.[30]

JCS 2014 Guidelines
Antithrombotic Therapy of AF



*Not approved for SPAF (as at November 2014); †< 70% TTR: INR 2.0-3.0, ≥ 70% TTR: INR 1.6-2.6

JCS Joint Working Group. *Circ J.* 2014;78:1997-2021.[31]

How to Choose a NOAC?

- Clinical trial results
  - Indirect comparison
    - Adverse event profile
      - Subgroup analyses
        - Non-AF trials
          - Experience
            - Registries
              - Local DTC decisions
                - Single drug choice
                  - Cost-benefit analyses

“Pointers*” Toward Which NOAC to Choose

Image No Longer Available

*All of these “pointers” are debatable

Savelieva I, Camm AJ. *Clin Cardiol*. 2014;37(1):32-47.[32]

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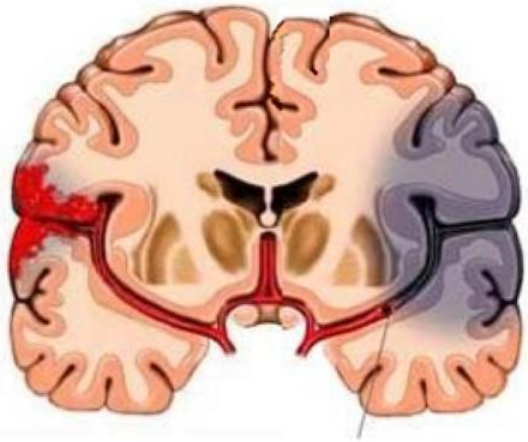
When the Stakes Are High and the Cause of Stroke Is Not Crystal Clear

Rod Passman, MD, MSCE
Professor of Medicine and Preventive Medicine
Director
Center for Atrial Fibrillation
Bluhm Cardiovascular Institute
Northwestern University
Chicago, Illinois

Stroke Etiologies

Vessel Rupture (15%)

Artery Occlusion (85%)



Etiology	%
Atherothrombotic Stenotic artery feeding area of infarction	25-30
Cardioembolic A thrombus or other material dislodges from the heart or aortic arch	20
Lacunar/Small Vessel Small; deep infarct	15-20
Other/Uncommon	5-10
Cryptogenic Unknown cause	25-30

Adams HP Jr, et al. *Stroke*. 1993;24;35-41.[33]
Foulkes MA, et al. *Stroke*. 1988;19:547-554.[34]

Is (Some) Cryptogenic Stroke Really Undetected AF?

- AF major cause of ischemic stroke
- AF can be paroxysmal
- AF can be asymptomatic

Why Is Finding AF Important in a Cryptogenic Stroke Patient?

"For patients with noncardioembolic ischemic stroke or TIA, the use of antiplatelet agents rather than oral anticoagulation is recommended to reduce the risk of recurrent stroke and other cardiovascular events (Class I; Level of Evidence A)"

CHA_2DS_2-VASc Score

Risk Factor	Score
CHF/LV dysfunction	1
Hypertension	1
Age ≥ 75	2
Diabetes	1
Stroke/TIA	2
Vascular disease	1
Age 65-74	1
Female sex	1
Maximum Score	9

Kernan WN, et al. *Stroke.* 2014;45:2160-2236.[35]

Patient Case
RB

- 75-year-old man with a medical history of hyperlipidemia and hypertension
- Transient episode of dizziness followed by dysarthria and confusion lasting < 1 h
- Meds: simvastatin 40 mg, lisinopril 20 mg
- Admission
  - BP 122/69 mm Hg, heart rate 62 bpm
  - no neurologic deficits

RB
Test Results

Evaluation	Results
ECG	NSR at 55 bpm, normal PR
MRI	Multiple punctuate abnormalities adjacent to the right nucleus caudatus and left temporoparietal cortex
Duplex carotid ultrasound	Normal flow
Chest radiograph	Generalized osteopenia
TTE	LA moderately dilated, mild MR, LV function normal
TEE	Normal LA size, no LAA thrombus, normal velocities
48-h telemetry	No AF

RB (cont)
MRI

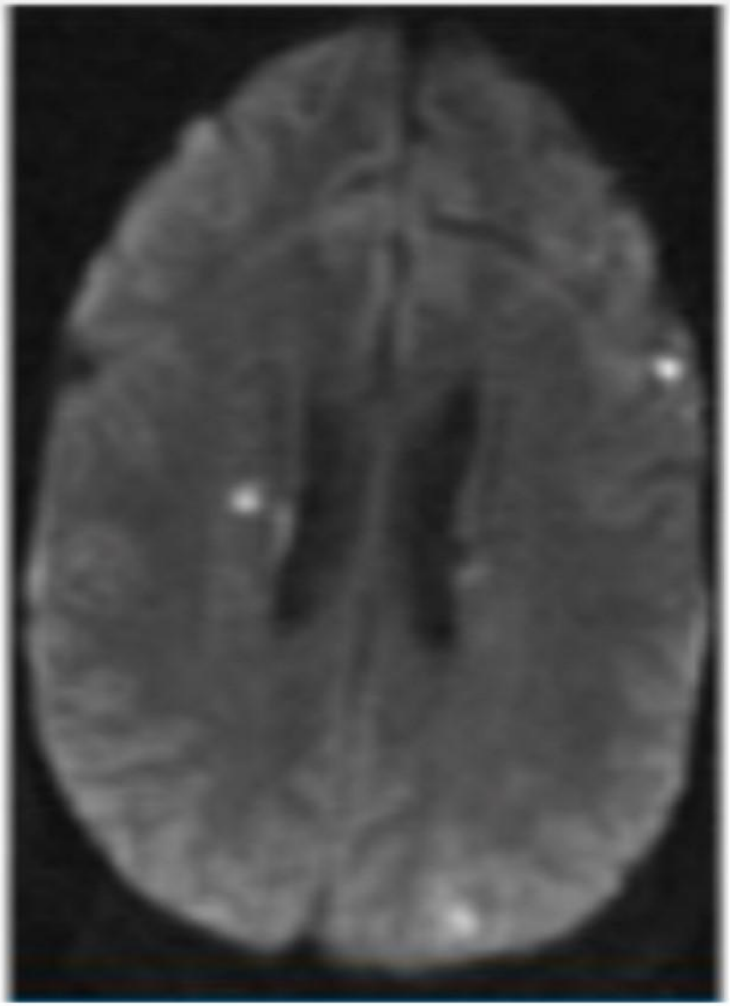


Image courtesy of Rod Passman, MD.

RB (cont): Started on ASA 325 mg

What Is the Next Step?

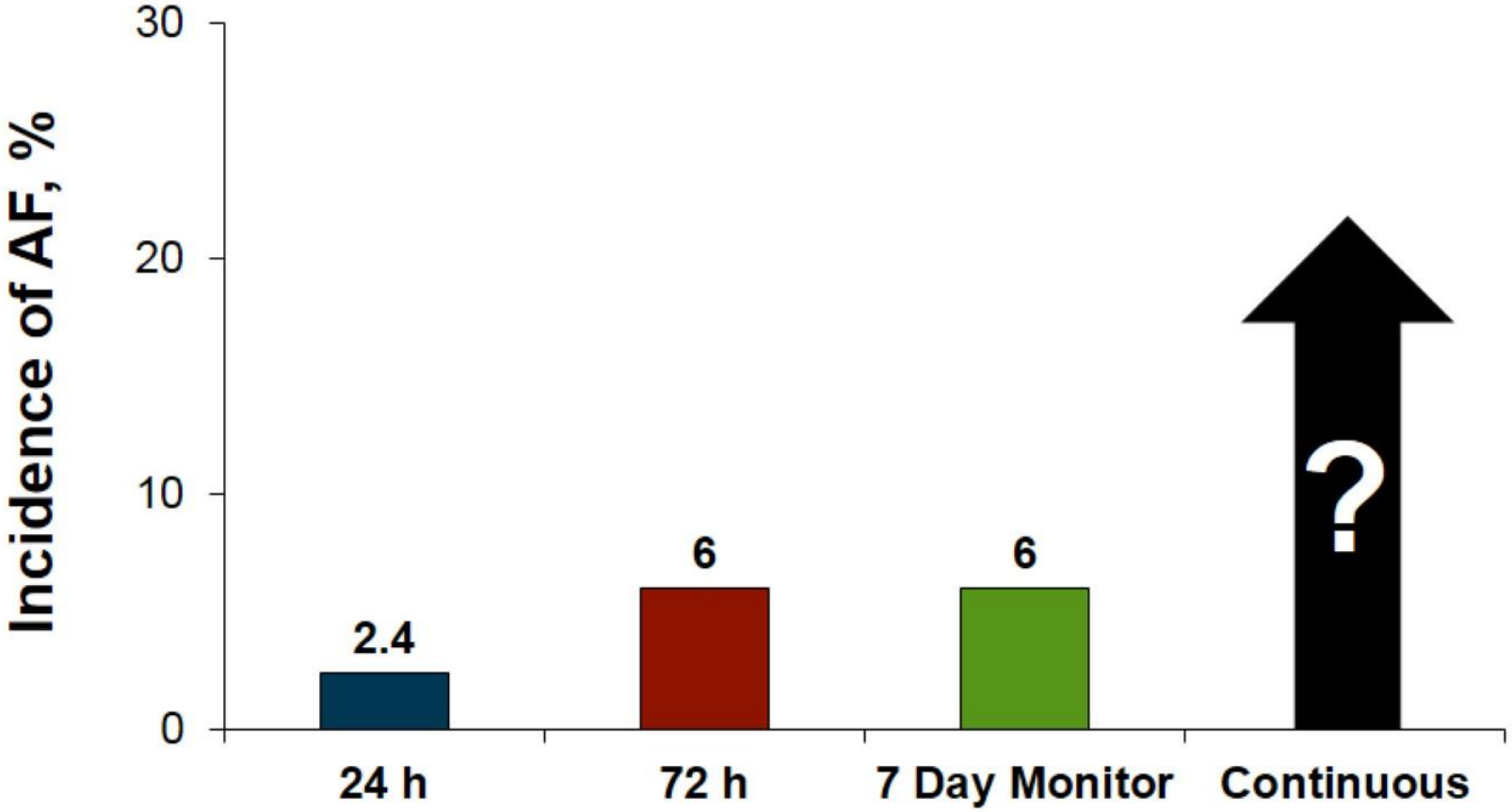
A. Cardiac MRI

B. 30-day cardiac monitor

C. Implantable cardiac monitor

D. Reassurance

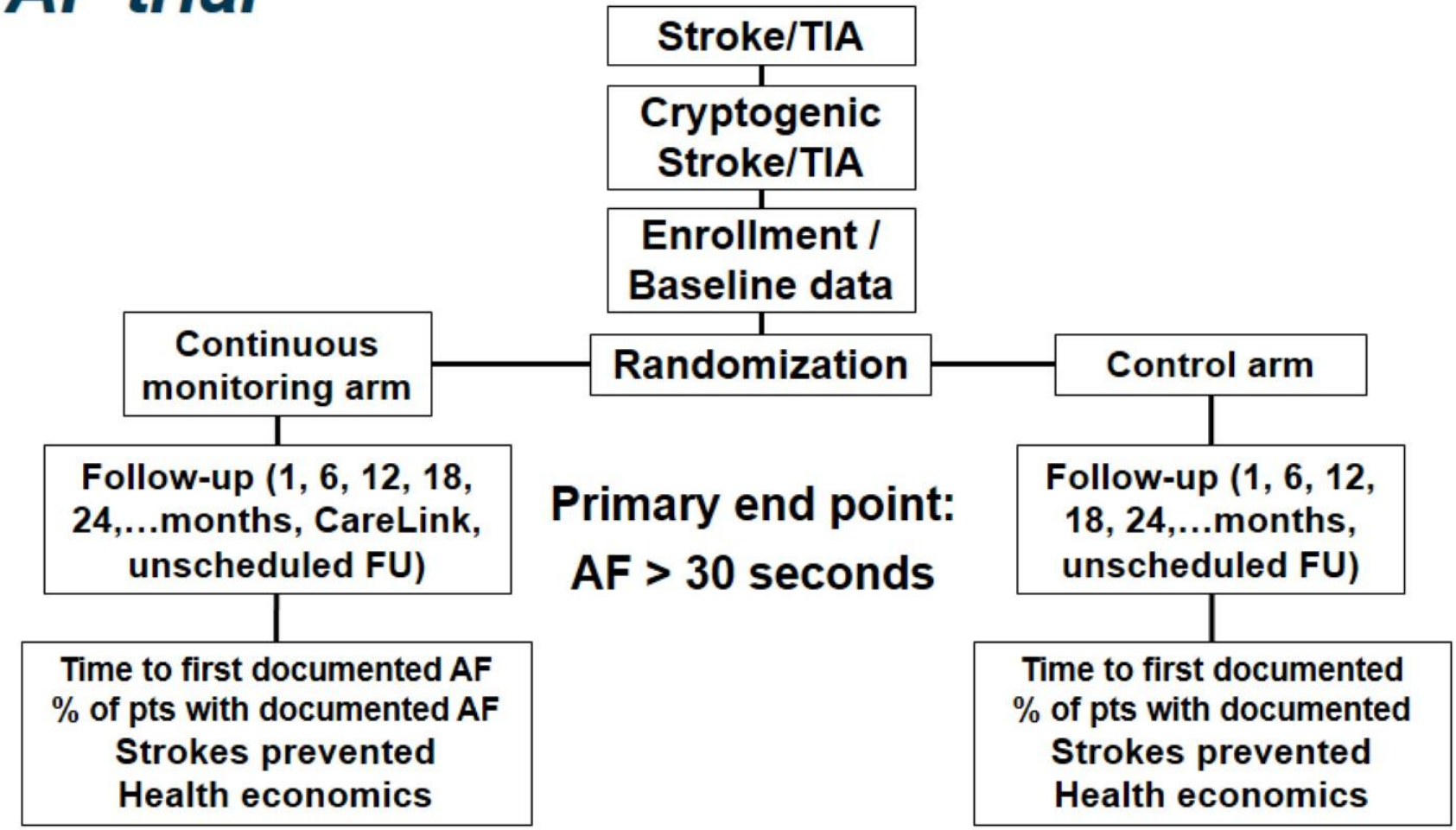
Finding AF in Cryptogenic Stroke
Monitoring Duration



Jabaudon D, et al. *Stroke*. 2004;35:1647-1651.[36]; Shafqat S, et al. *Int Med J*. 2004; 34:305-309.[37]; Schuchert A, et al. *PACE* 1999;22:1082-1084.[38]

CRYSTAL AF

CRYptogenic STroke And underLying AF trial



Sanna T, et al. *N Engl J Med.* 2014;370;2478-2486.[39]

Key Inclusion/Exclusion Criteria

- Inclusion
  - Age ≥ 40 years
  - Cryptogenic stroke (or clinical TIA), with infarct seen on MRI or CT, within the previous 90 days; and no mechanism (including AF) determined after:
    - 12-lead ECG
    - Minimum of 24-hour ECG monitoring (eg, telemetry, Holter)
    - TEE
    - CTA or MRA of head and neck to rule out arterial source
    - Screening for hypercoagulable states in patients > 55 years old
- Exclusion
  - History of AF or atrial flutter
  - Permanent indication or contraindication for anticoagulation
  - Indication for pacemaker or implantable cardioverter defibrillator

Sanna T, et al. *N Engl J Med.* 2014;370;2478-2486.[39]

Comparison of Monitoring Strategies

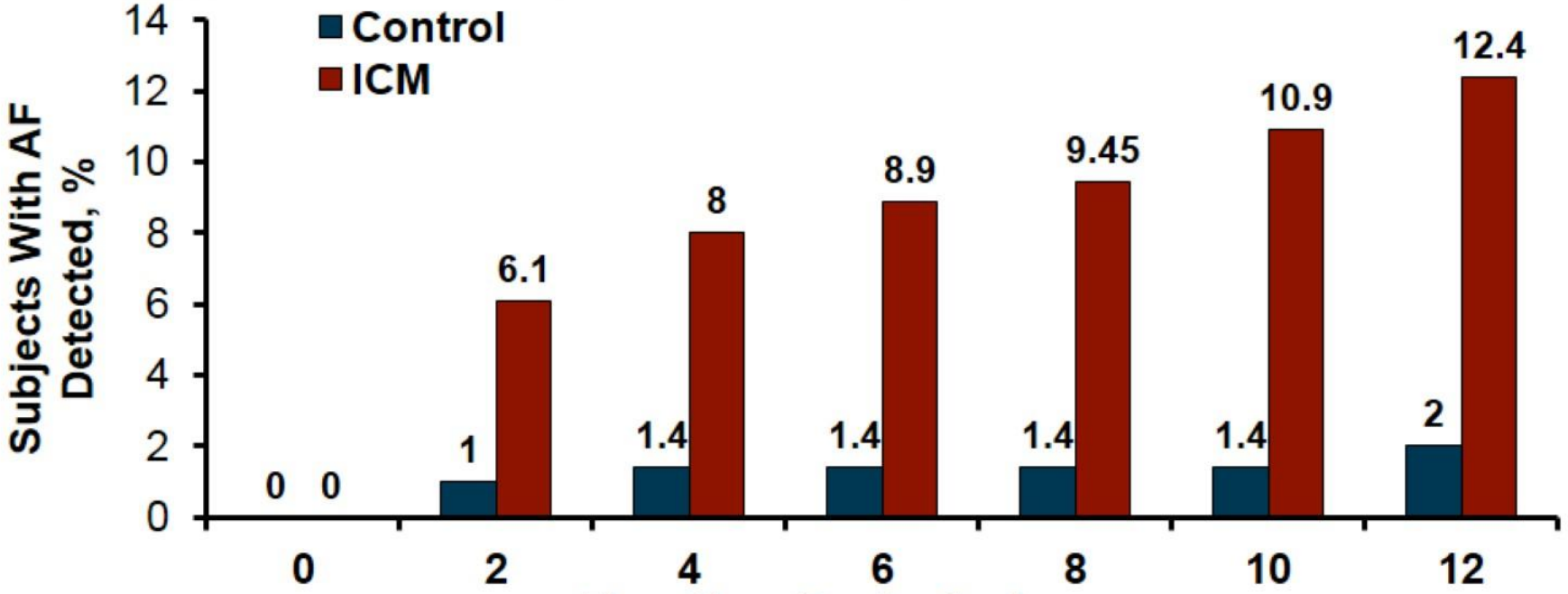
- Continuous Monitoring Arm: Insertion of REVEAL® XT
  - Minimally invasive outpatient procedure
  - Local anesthetic and no leads or fluoroscopy
  - 15- to 30-minute procedure
  - Device can be followed remotely
  - MRI conditional
  - 3-year device longevity
  - Automatic AF detection algorithm
- Standard Monitoring Arm
  - Cardiac monitoring performed according to local standards, after mandated testing completed
  - Symptoms consistent with AF were evaluated by study physicians

Baseline Characteristics

	ICM (N = 221)	Control (N = 220)
Age	61.6 ± 11.4 years	61.4 ± 11.3 years
Male gender	142 (64.3%)	138 (62.7%)
Index event, stroke	200 (90.5%)	201 (91.4%)
Index event, TIA	21 (9.5%)	19 (8.6%)
Time between index event and randomization	36.6 ± 28.2 days	39.6 ± 26.9 days
Time between randomization and device insertion	8.7 ± 27.6 days	n/a

Sanna T, et al. *N Engl J Med.* 2014;370;2478-2486.[39]

Detection Rates
Primary and Secondary End Points

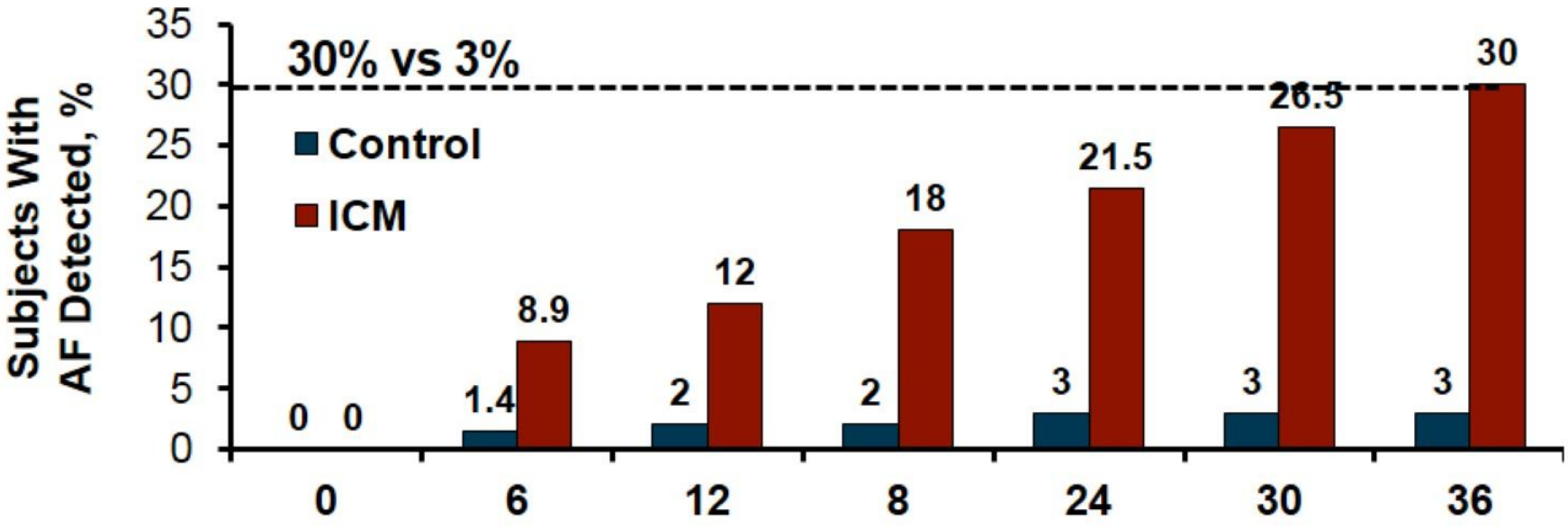


# At Risk							
Control	220	200	197	194	184	184	167
ICM	221	198	194	191	186	182	173

- Primary End Point:
  - Detection of AF at 6 months
  - Hazard Ratio: 6.43 (1.90-21.74); *P* = .0006
- Secondary End Point:
  - Detection of AF at 12 months
  - Hazard Ratio: 7.32 (2.57-20.81); *P* < .0001

Sanna T, et al. *N Engl J Med.* 2014;370;2478-2486.[39]

Detection Rates (cont)
AF at 36 Months



# At Risk							
Control	220	194	167	114	72	36	7
ICM	221	191	173	102	57	29	8

Hazard Ratio: (95% CI) = 8.78 (3.47-22.19)
log-rank
***P* < .0001**

Estimated rate of detection in ICM arm was 30.0% vs 3.0% in control arm

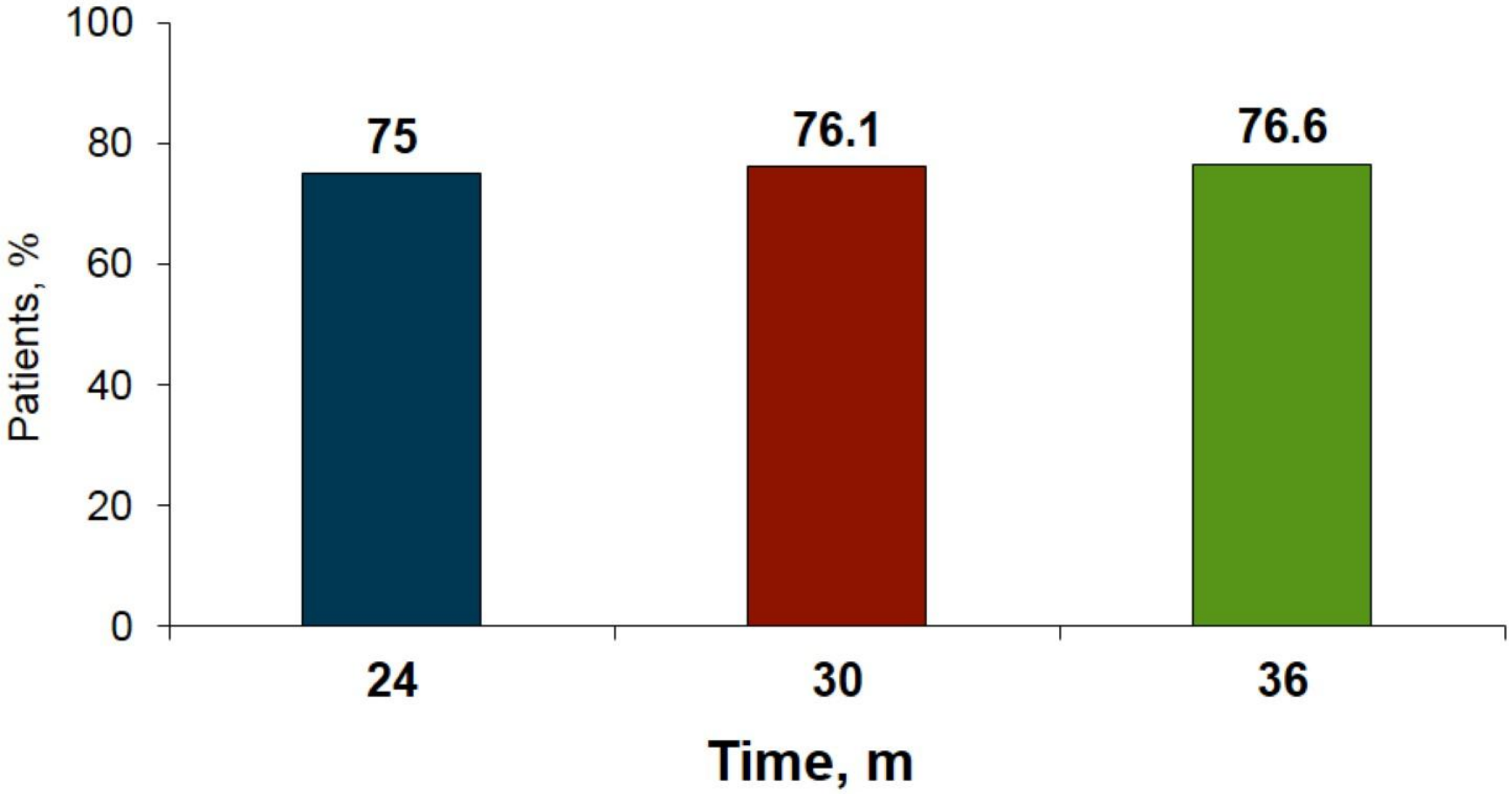
Sanna T, et al. *N Engl J Med.* 2014;370;2478-2486.[39]

Tests Required to Find AF in Control Arm

Follow-up Period	ECGs	Holter Monitors	Event Recorders	Incremental Patients Found with AF
0-6 months	88	20	1	3
6-12 months	33	12	0	1
12-18 months	42	9	0	0
18-24 months	20	5	0	1
24-30 months	16	4	0	0
30-36 months	3	2	0	0
Total	**202**	**52**	**1**	**5**

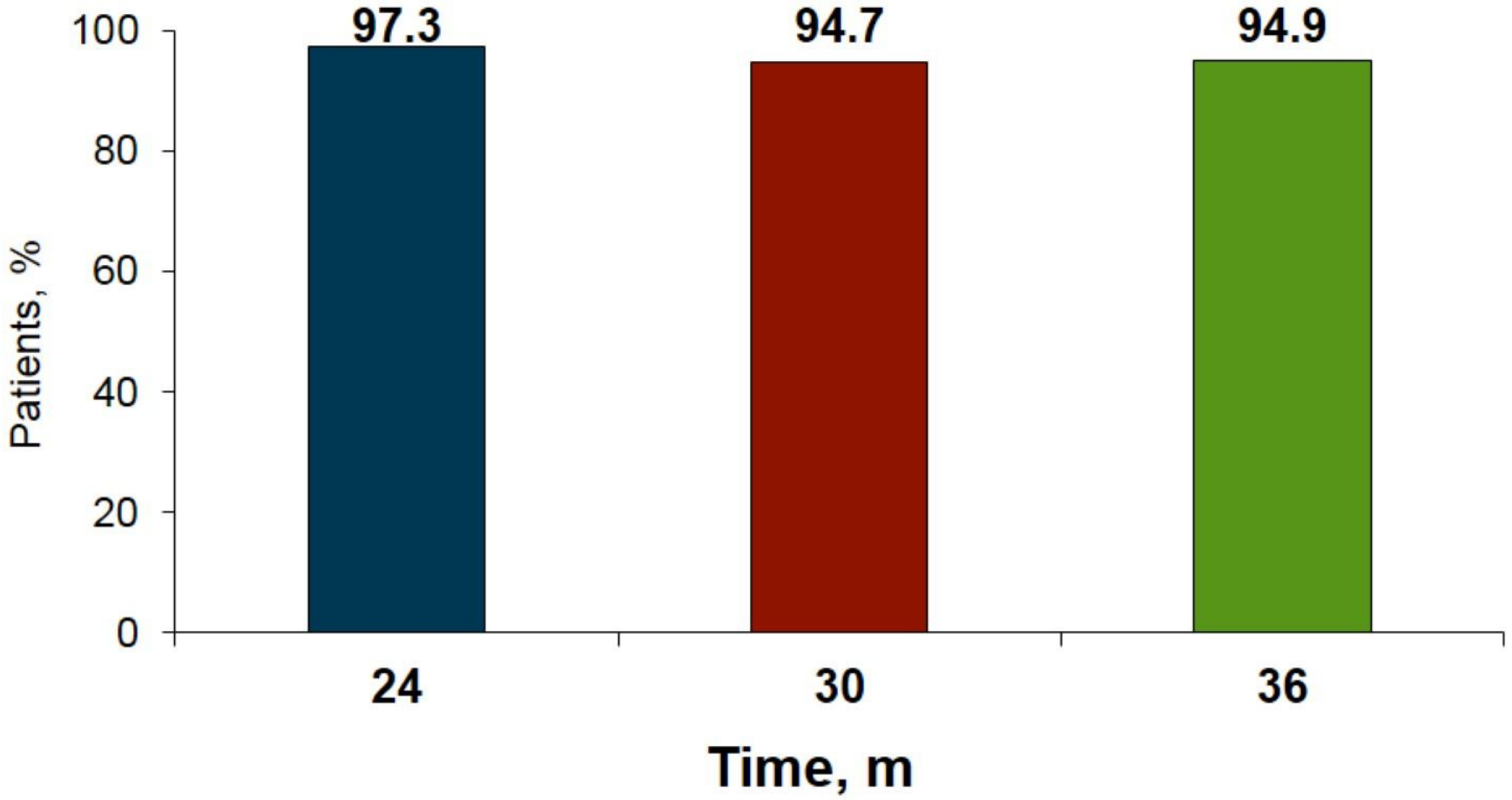
Data provided by Dr. Passman

Asymptomatic AF Episodes
Both Arms



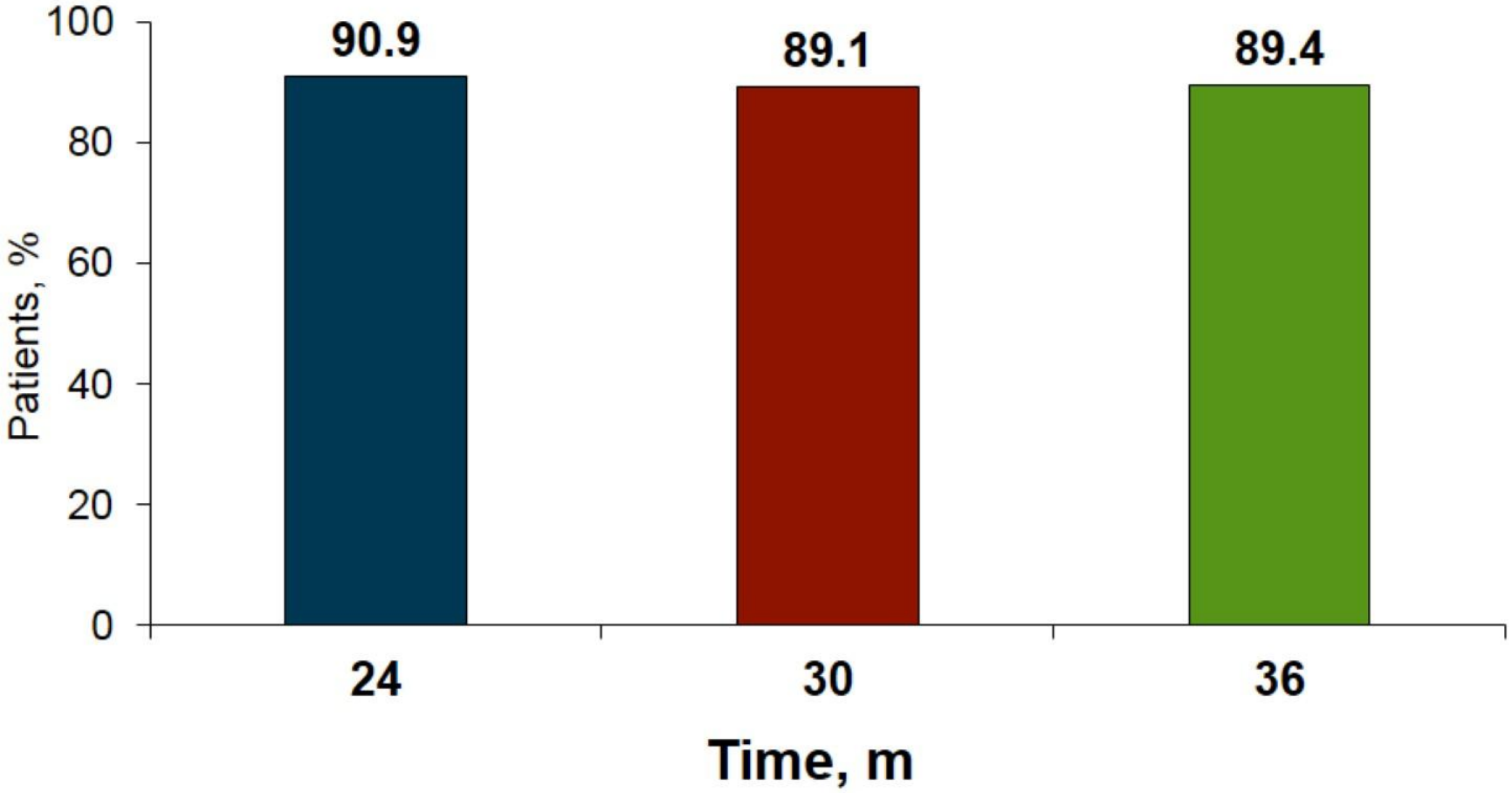
Data provided by Dr. Passman

Proportion of AF Episodes > 6 Minutes



Data provided by Dr. Passman

Clinical Decisions
OAC Use in AF Patients
Both Arms



Data provided by Dr. Passman

CRYSTAL-AF

Time to First AF Detection

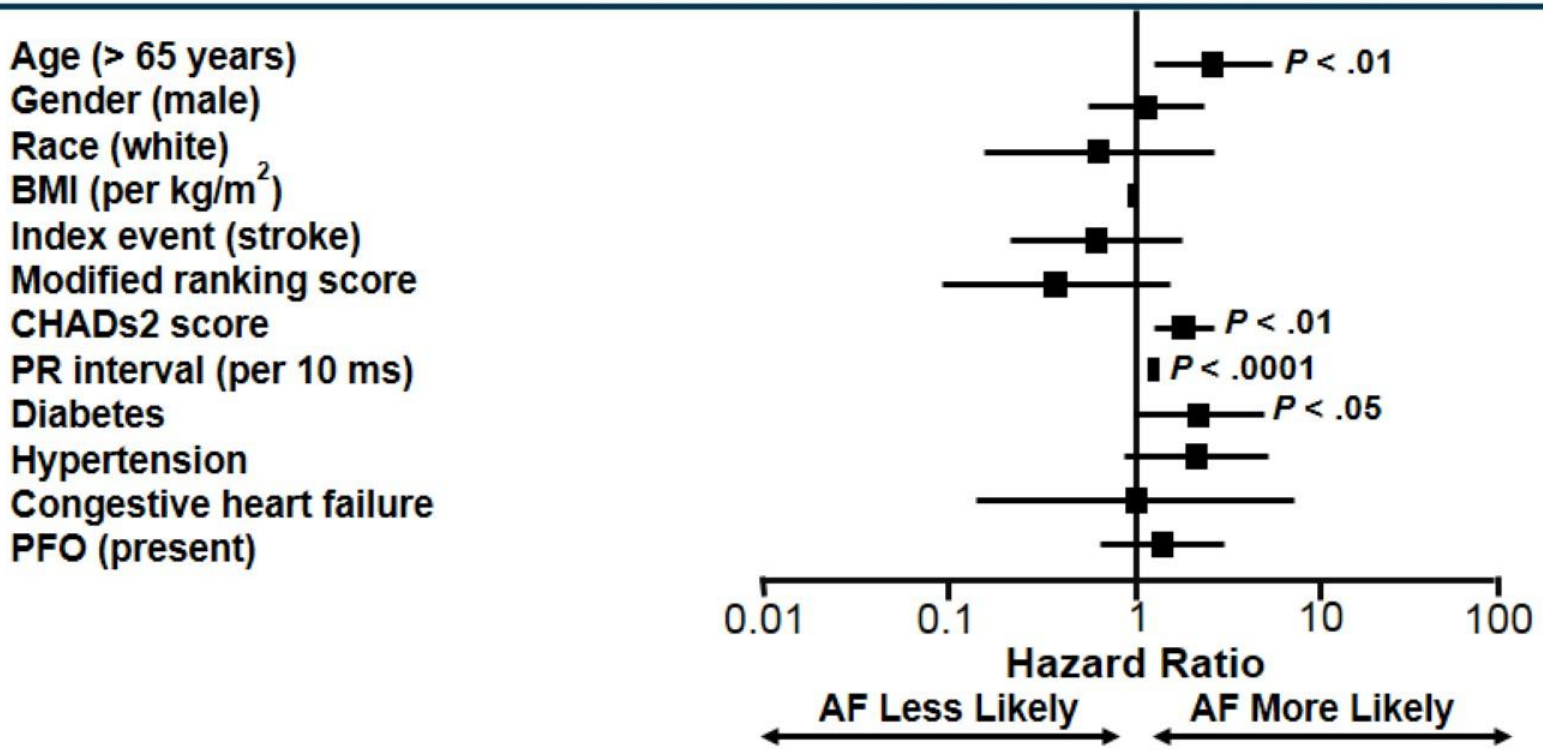
36-Month Data

	ICM (N = 42)	Control (N = 5)
Median time from randomization to AF detection	Median: 8.4 months IQR: 1.4-14.9 months	Median: 2.4 months IQR: 1.1-11.5 months

Sanna T, et al. *N Engl J Med*. 2014;371:1261.[40]

CRYSTAL-AF (cont)
Predictors of AF

Univariate Predictors of Atrial Fibrillation



Variable	HR (95% CI)	*P* Value
Age (per 10 years)	1.91 (1.31-2.80)	.0009
PR interval (per 10 ms)		
On PR-lengthening medication	1.17 (1.02-1.35)	.02
Off PR-lengthening medication	1.58 (1.32-1.90)	< .0001

Assar M, et al. *Eur Heart J.* 2014;35:1109.[41]

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 26, 2014 VOL. 370 NO. 26

Atrial Fibrillation in Patients with Cryptogenic Stroke

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AF Detection	Detection Rate, %
30-day monitor	16.1
Control – 24-h monitor	3.2

Gladstone DJ, et al. *N Engl J Med*. 2014;370:2467-2477.[42]

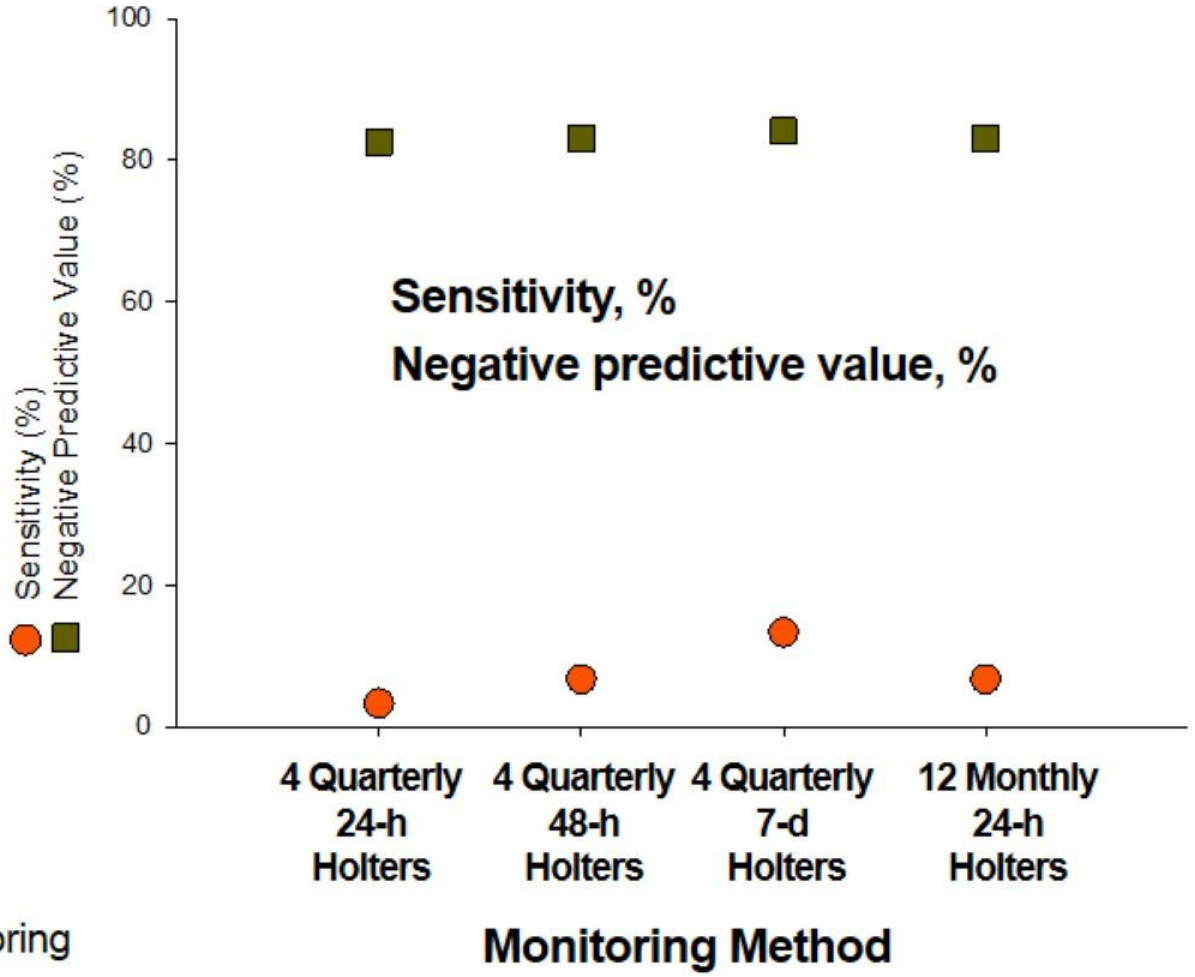
EMBRACE vs CRYSTAL-AF

- Average age was significantly different
  - 73 years in EMBRACE[a] vs 61 years in CRYSTAL-AF[b]
- Stroke Workup in EMBRACE not as rigorous
  - TEE (8%) or intracranial vascular imaging not required
  - Less ECG monitoring prior to study enrollment

a. Gladstone DJ, et al. *N Engl J Med*. 2014;370:2467-2477.[42]
b. Sanna T, et al. *N Engl J Med*. 2014;370;2478-2486.[39]

CRYSTAL-AF Simulation
Periodic Monitoring

- Sensitivity was low, ranging from 3-13%
- NPV ranged from 83-84%

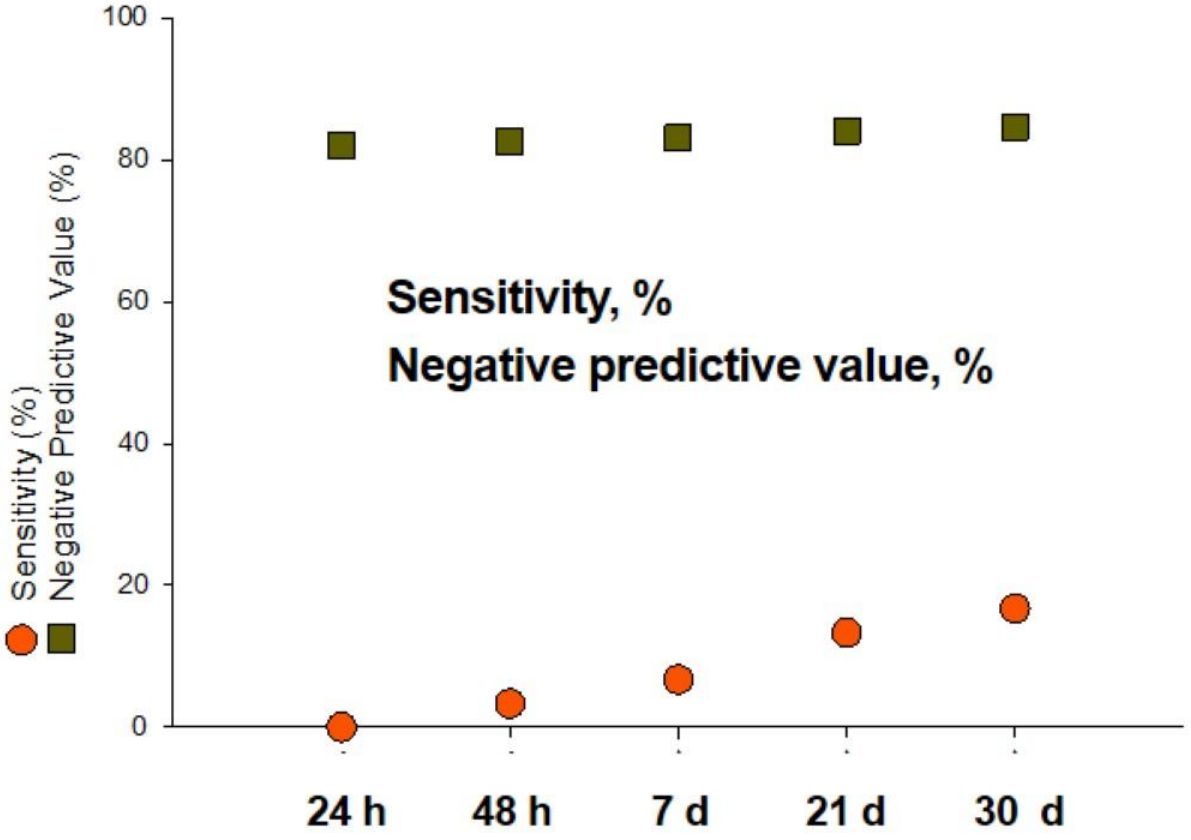


All $P < .001$ vs Continuous Monitoring

Passman RS, et al. HRS 2014. Abstract 07-05.[43]

CRYSTAL-AF Simulation
Short-term Monitoring

- Sensitivity was low, ranging from 0-17%
- NPV ranged from 82-85%



All $P < .001$ vs Continuous Monitoring

Passman RS, et al. HRS 2014. Abstract 07-05.[43]

Patient Case
RB

- 75-year-old man with a medical history of hyperlipidemia and hypertension
- Transient episode of dizziness followed by dysarthria and confusion lasting < 1 h
- Meds: simvastatin 40 mg, lisinopril 20 mg
- Admission:
  - BP 122/69 mm Hg, heart rate 62 bpm
  - no neurologic deficits

RB: ICM Tracing

AF

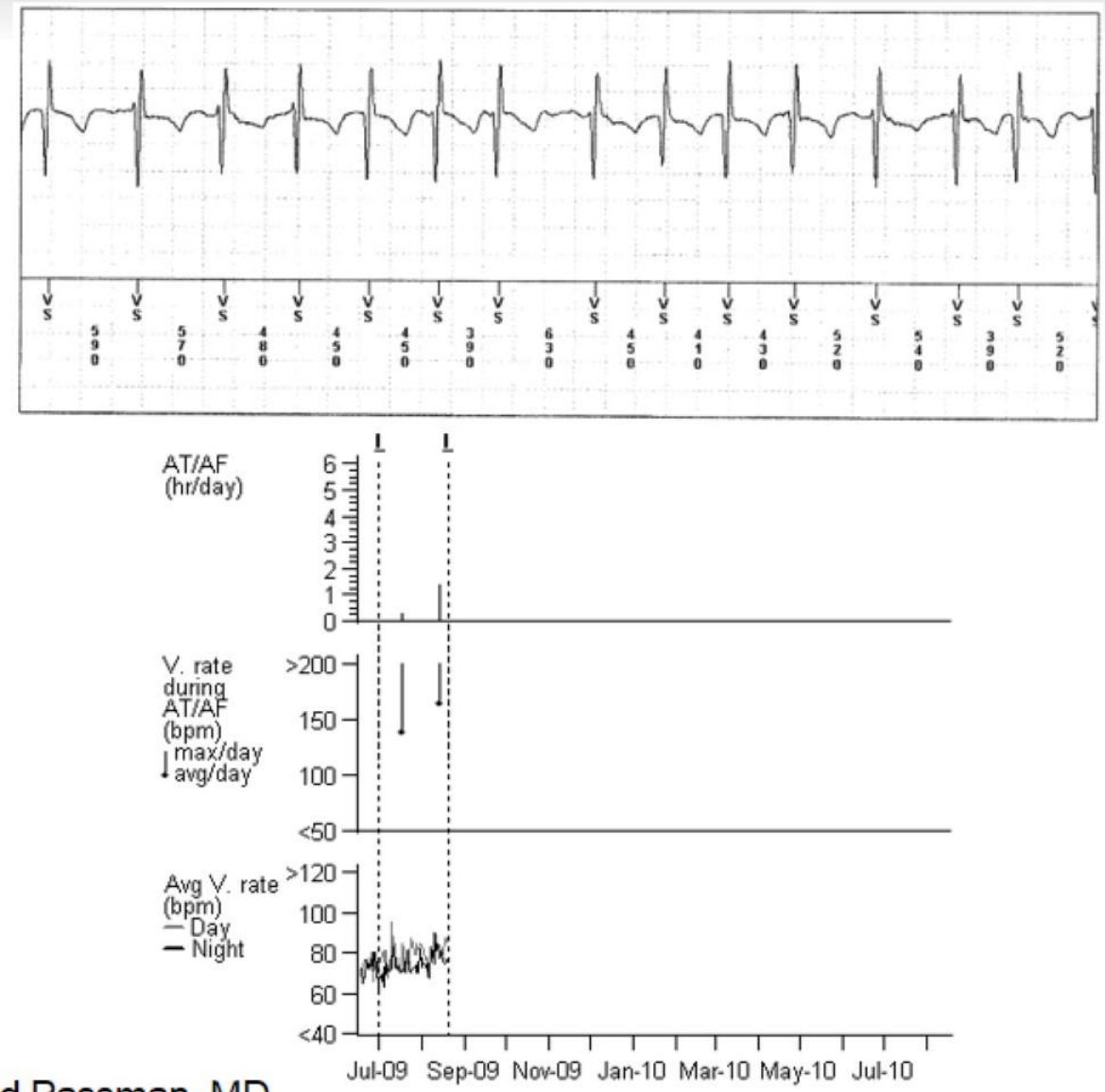


Image courtesy of Rod Passman, MD.

Summary
When the Stakes Are High and the Cause of Stroke Is Not Crystal Clear

- AF in cryptogenic stroke: the more you look, the more you find
- Symptoms and intermittent monitoring are unreliable for AF detection
- ICMs are superior to routine care for AF detection in cryptogenic stroke patients
- Antiplatelet therapy is insufficient to prevent the next event in patients with stroke and AF
- Was AF present before or did it start after stroke -- does it matter?

Abbreviations

ACS = acute coronary syndrome

AF = atrial fibrillation

ASA = acetylsalicylic acid

ARISTOTLE = Apixaban for Reduction in Stroke and Other Thromboembolic Events

ARTESIA = Apixaban for the Reduction of Thrombo-Embolism in Patients With Device-Detected Sub-Clinical Atrial Fibrillation

ASSERT = ASymptomatic atrial fibrillation and Stroke Evaluation in pacemaker patients and the atrial fibrillation Reduction atrial pacing Trial

ATRIA = Anticoagulation and Risk Factors in Atrial Fibrillation

BID = twice daily

BP = blood pressure

bpm = beats per minute

CAD = coronary artery disease

CHA2DS2-VASc = Congestive heart failure/left ventricular dysfunction, Hypertension, Age ≥75 [doubled], Diabetes, Stroke [doubled] -- Vascular disease, Age 65-74, and Sex category [female]

CHADS2 = Congestive heart failure, Hypertension, Age ≥75, Diabetes, Stroke (doubled)

Abbreviations (cont)

CHF = congestive heart failure

CrCl = creatinine clearance

CRYSTAL AF = Cryptogenic Stroke with Underlying Atrial Fibrillation

CTA = computed tomography angiogram

CV = cardiovascular

Dabi = dabigatran

DAP = Dual Antiplatelet

Disabl = disabling

DOAC = direct oral anticoagulant

DTC = direct-to-consumer

ECG = electrocardiogram

Edox = edoxaban

ENGAGE AF-TIMI 48 = Global Study to Assess the Safety and Effectiveness of Edoxaban (DU-176b) vs Standard Practice of Dosing With Warfarin in Patients With Atrial Fibrillation

EP = electrophysiologist

EUPS-AF = European Patient Survey in Atrial Fibrillation

GARFIELD = Global Anticoagulant Registry in the Field

Abbreviations (cont)

GI = gastrointestinal

GLORIA = Global Registry on Long-term Oral Antithrombotic Treatment in Patients With Atrial Fibrillation

HAS-BLED = hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly, drugs/alcohol concomitantly

Hem = hemorrhagic

ICD = implantable cardioverter-defibrillator

ICH = intracranial hemorrhage

ICM = insertable cardiac monitor

INR = international normalized ratio

IQR = interquartile range

Isch = ischemic

LA = left atrium

LAA = left atrial appendage

LT = life-threatening

LV = left ventricular

MI = myocardial infarction

Abbreviations (cont)

mITT = modified intention-to-treat
MR = mitral regurgitation
MRA = magnetic resonance angiogram
MRI = magnetic resonance imaging
NOAC = novel oral anticoagulant
NPV = negative predictive value
NSAID = nonsteroidal anti-inflammatory drug
NSR = normal sinus rhythm
NVAF = nonvalvular atrial fibrillation
OD = once daily
ORBIT-AF = Outcomes Registry for Better Informed Treatment of Atrial Fibrillation
P-gp = P-glycoprotein
PROBE = prospective, randomized, open-label, blinded end-point evaluation
RE-COVER = Efficacy and Safety of Dabigatran Compared to Warfarin for 6 Month Treatment of Acute Symptomatic Venous Thromboembolism
RE-LY = Randomized Evaluation of Long-term Anticoagulant Therapy
RE-MEDY = Secondary Prevention of Venous Thrombo Embolism
Riva = rivaroxaban

Abbreviations (cont)

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

RR = relative risk

SEE = systemic embolic event

TEE = transesophageal echocardiogram

TIA = transient ischemic attack

TIMI = Thrombolysis In Myocardial Infarction

tPA = tissue plasminogen activator

TRENDS = A Prospective Study of the Clinical Significance of Atrial Arrhythmias Detected by Implanted Device Diagnostics

TSOAC = target specific oral anticoagulant

TTE = transthoracic echocardiogram

TTR = time in therapeutic range

VKA = vitamin K antagonist

W = warfarin