

Where Do We Stand with NOAC in AF?

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Disclosure

- Boeringer Ingelheim : lecturer
- St Jude Medical Inc. : consultant
- J&J Biosense-Webster Inc. : CTR of Excellence
- Boston Scientific Inc. : WATCHMAN proctor

Patterns of Atrial Fibrillation

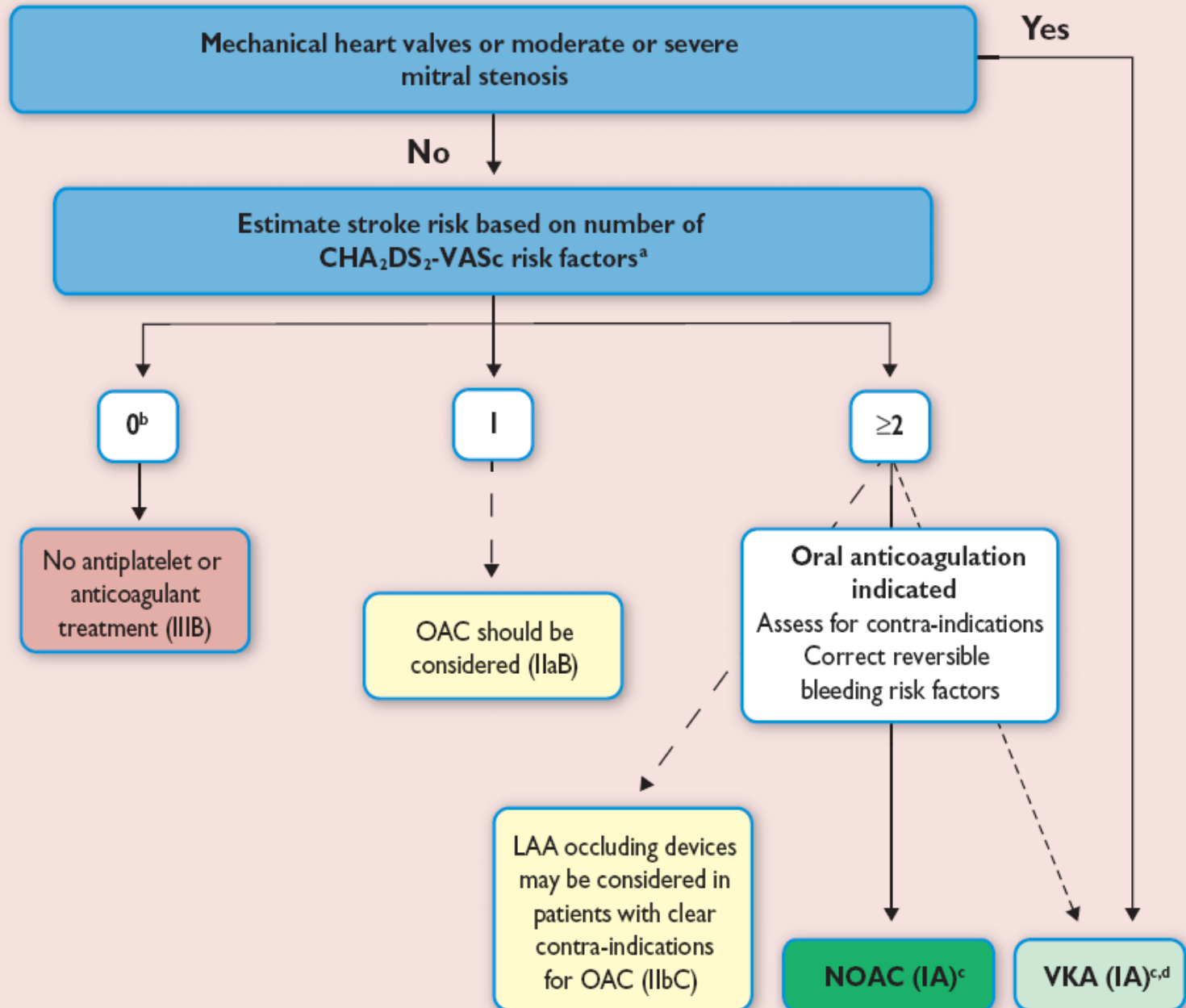
2016 ESC guidelines for AF Managements

Krchof et al. Eur Heart J. 2016;37(38):2893-2962.

AF pattern	Definition
First diagnosed AF	AF that has not been diagnosed before, irrespective of the duration of the arrhythmia or the presence and severity of AF-related symptoms.
Paroxysmal AF	Self-terminating, in most cases within 48 hours. Some AF paroxysms may continue for up to 7 days. ^a AF episodes that are cardioverted within 7 days should be considered paroxysmal. ^a
Persistent AF	AF that lasts longer than 7 days, including episodes that are terminated by cardioversion, either with drugs or by direct current cardioversion, after 7 days or more.
Long-standing persistent AF	Continuous AF lasting for ≥ 1 year when it is decided to adopt a rhythm control strategy.
Permanent AF	AF that is accepted by the patient (and physician). Hence, rhythm control interventions are, by definition, not pursued in patients with permanent AF. Should a rhythm control strategy be adopted, the arrhythmia would be re-classified as 'long-standing persistent AF'.

Antithrombotic Therapy for NV AF

2016 ESC guidelines for AF Managements

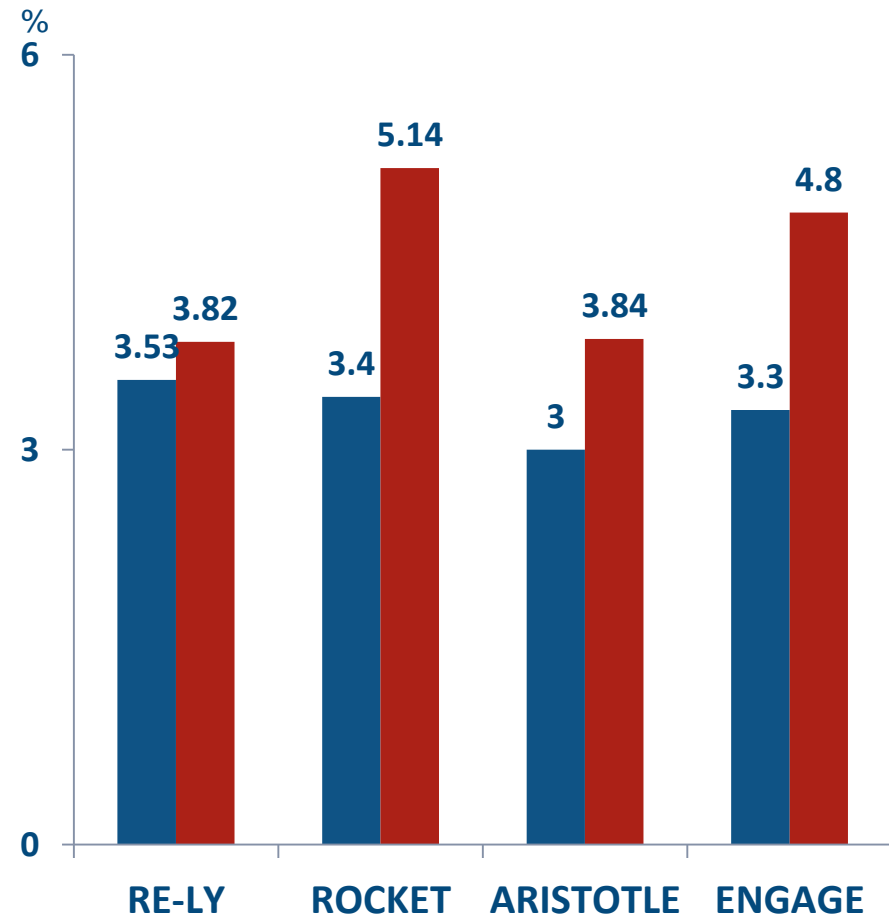
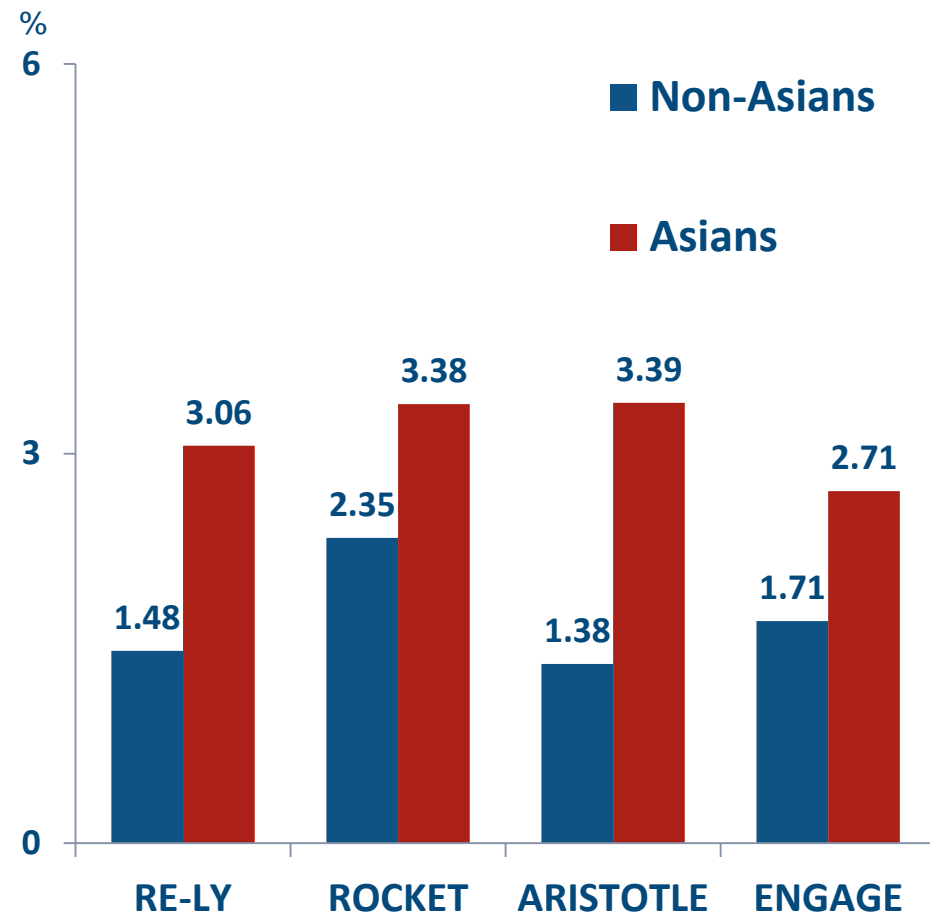


STE & Maj. Bleeding on Warfarin in Asian

Lip GY et al. Int J Cardiol. 2015;180:246

Stroke and systemic embolism on warfarin

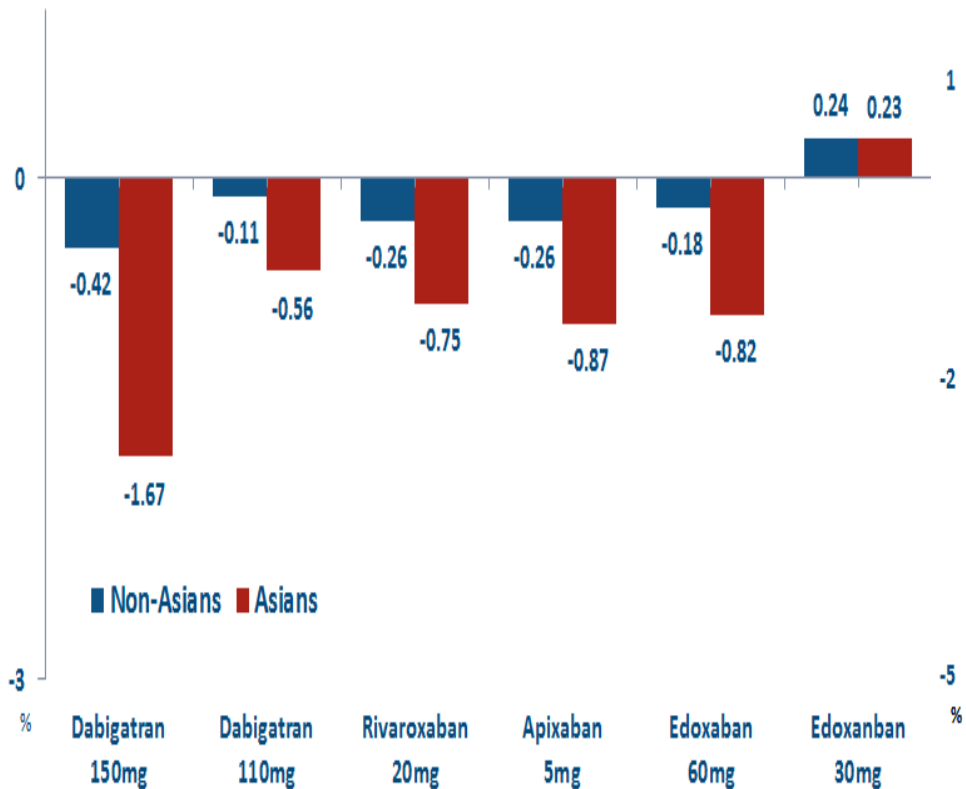
Major bleeding on warfarin



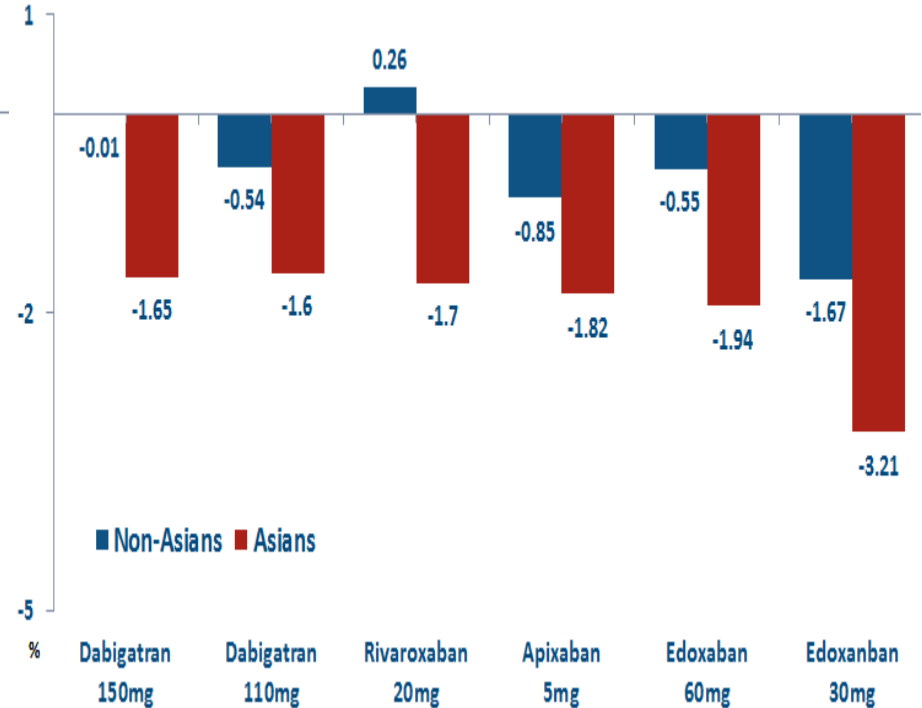
Absolute Risk Reduction by NOACs in Asian

Lip GY et al. Int J Cardiol. 2015;180:246

Absolute Risk Reduction of STE with NOAC

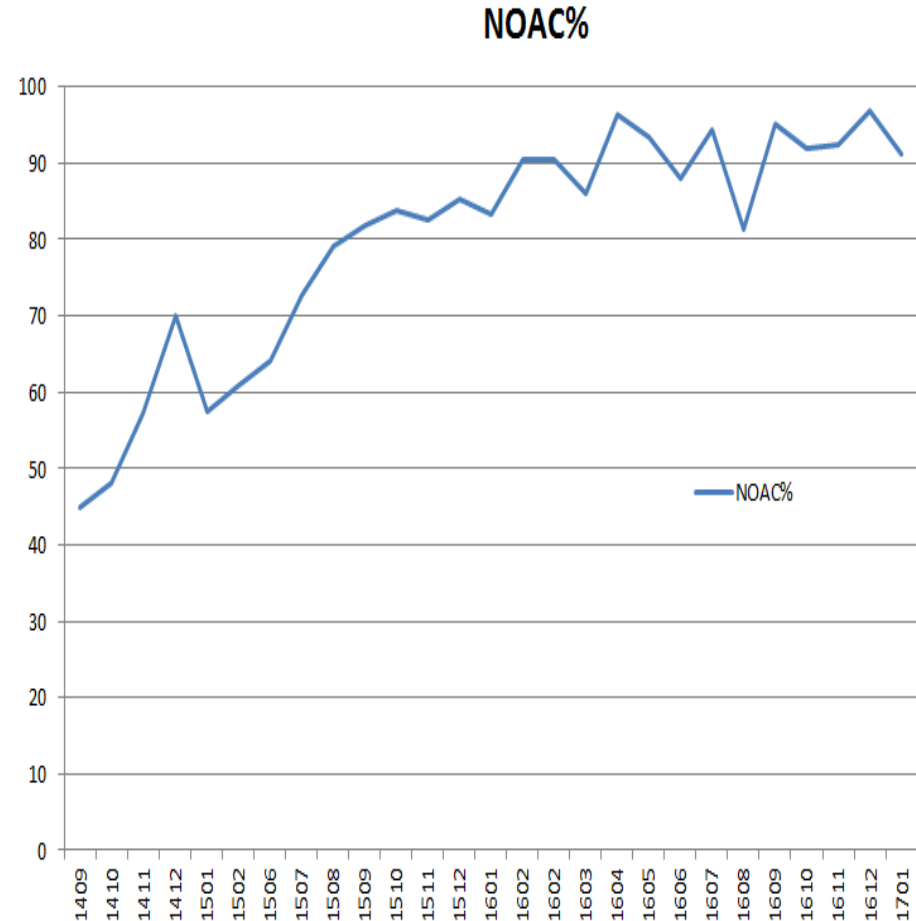
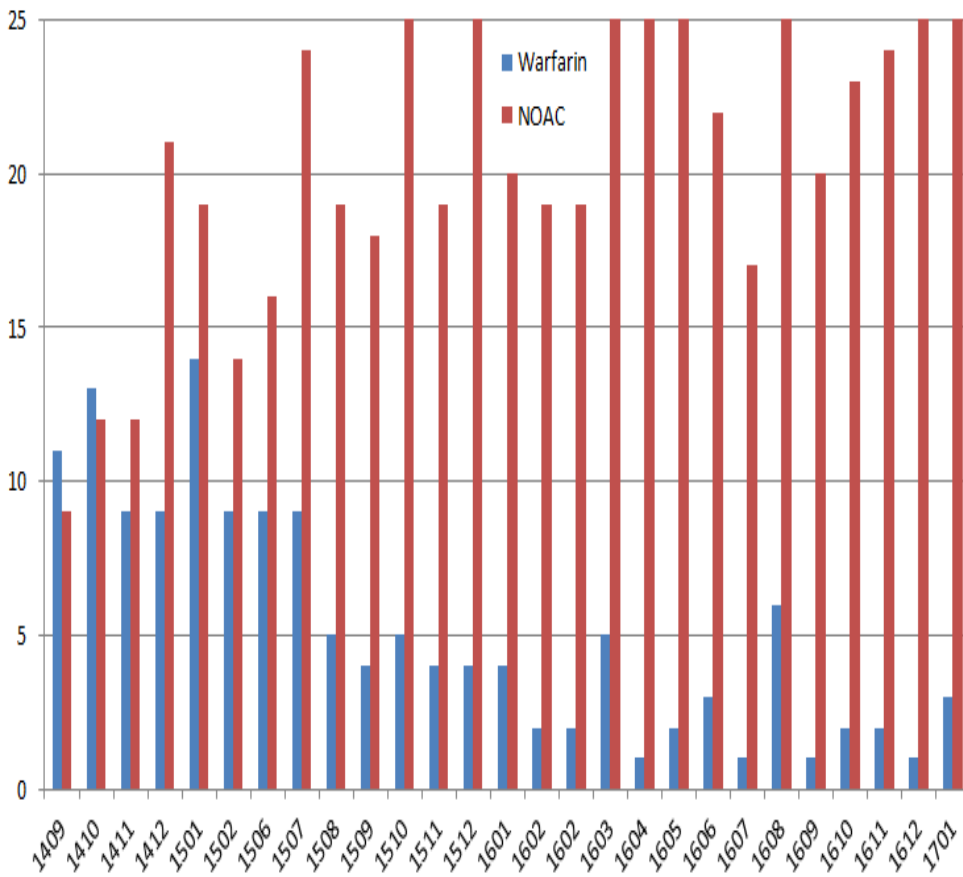


Absolute Risk Reduction of Major Bleeding with NOAC



NOAC in AF Ablation

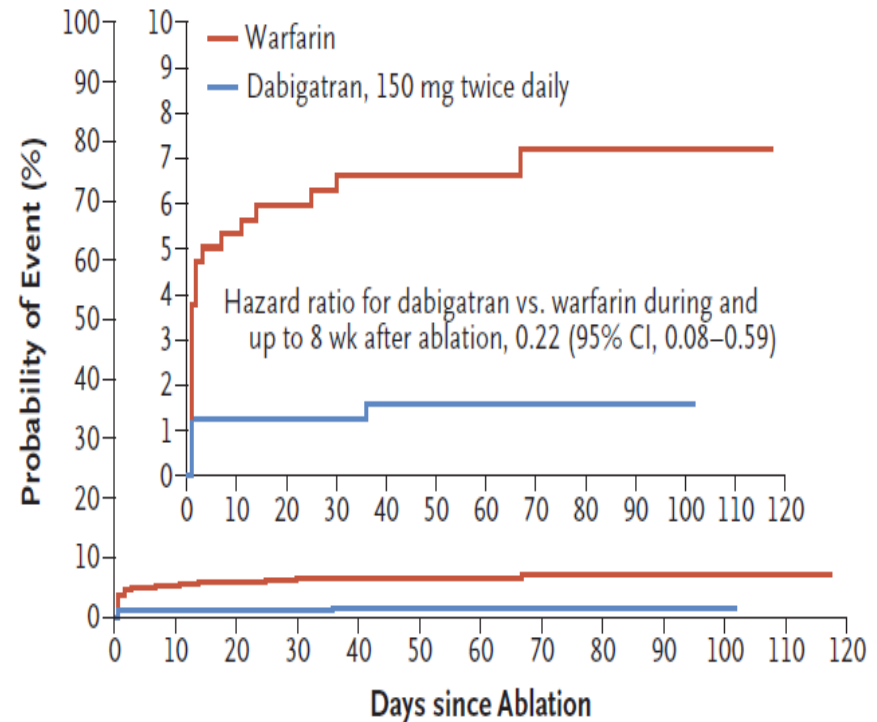
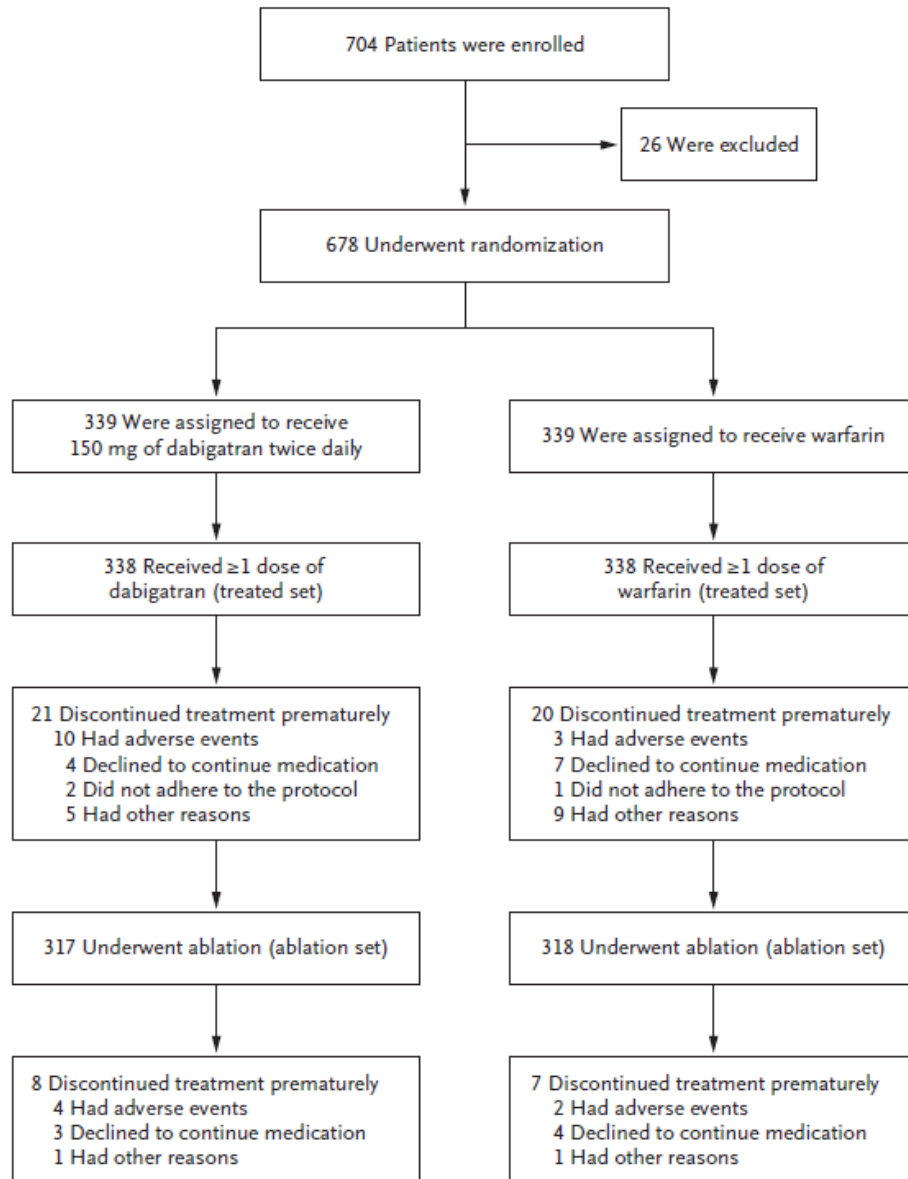
Yonsei Experience (n=727, 28mo, Sep 2014~Jan 2017)



RE-CIRCUIT

RCT: Uninterrupted Dabigatran vs. Warfarin in AF Ablation (n=704)

Calkins et al. New Eng J Med. 2017; E-Pub.



No. at Risk

Dabigatran	317	313	311	311	306	305	297	83	4	2	1	0	0
Warfarin	318	301	297	296	295	295	278	85	13	5	3	1	0

Adverse Events: RE-CIRCUIT

RCT: Uninterrupted Dabigatran vs. Warfarin in AF Ablation (n=704)

Calkins et al. New Eng J Med. 2017; E-Pub.

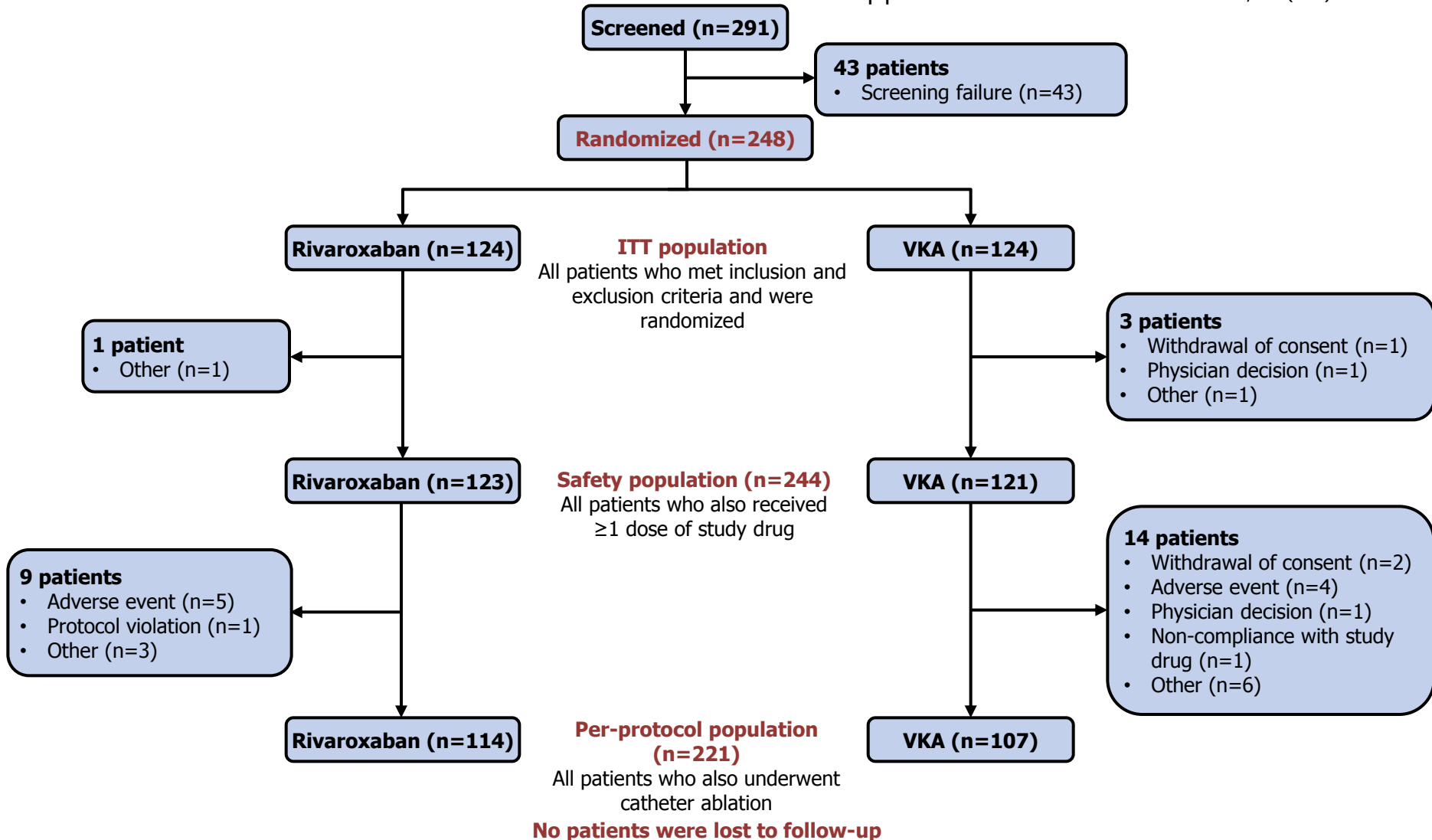
Table 2. Adverse Events during the Treatment Period (Treated Set).*

Event	Dabigatran, 150 mg twice daily (N = 338)	Warfarin (N = 338)	Total (N = 676)
	<i>number (percent)</i>		
Any adverse event	225 (66.6)	242 (71.6)	467 (69.1)
Severe adverse event†	11 (3.3)	21 (6.2)	32 (4.7)
Adverse event leading to treatment discontinuation	19 (5.6)	8 (2.4)	27 (4.0)
Serious adverse event	63 (18.6)	75 (22.2)	138 (20.4)
Fatal adverse event	0	0	0
Immediately life-threatening event	1 (0.3)	2 (0.6)	3 (0.4)
Event that resulted in clinically significant or persistent disability or incapacity	0	1 (0.3)	1 (0.1)
Event that required hospitalization	26 (7.7)	34 (10.1)	60 (8.9)
Event that prolonged hospitalization	13 (3.8)	22 (6.5)	35 (5.2)
Other‡	29 (8.6)	27 (8.0)	56 (8.3)

VENTURE AF

RCT: NOAC vs. Warfarin in AF Ablation (n=248)

Cappato et al. Eur Heart J. 2015;36(28):1805-11.



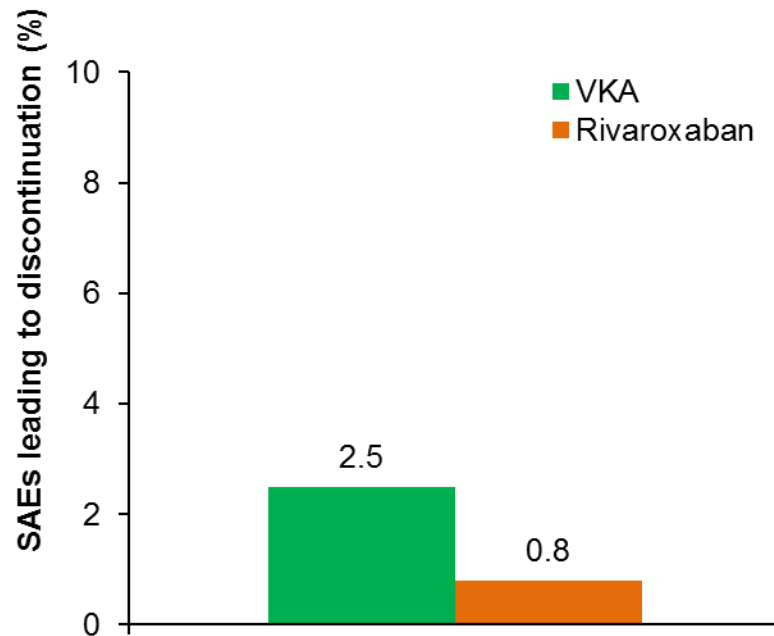
VENTURE AF: Complications

	Rivaroxaban	VKA	Total
Any adjudicated event	26	25	51
	n=123	n=121	N=244
Any bleeding event*	21	18	39
Major bleeding event	0	1	1
Vascular pseudoaneurysm	0	1	1
Non-major bleeding event	21	17	38
Most relevant:			
Arteriovenous fistula	0	1	1
Catheter/puncture site haemorrhage	1	1	2
Haematoma/vessel puncture site haematoma	8	10	18
Vascular pseudoaneurysm	3	1	4
	n=124	n=124	N=248
Any thromboembolic events (composite)#	0	2	2
Ischaemic stroke	0	1	1
Vascular death	0	1	1
	n=114	n=107	N=221
Any other procedure-attributable event†	5	5	10
Pericardial effusion without tamponade	0	1	1

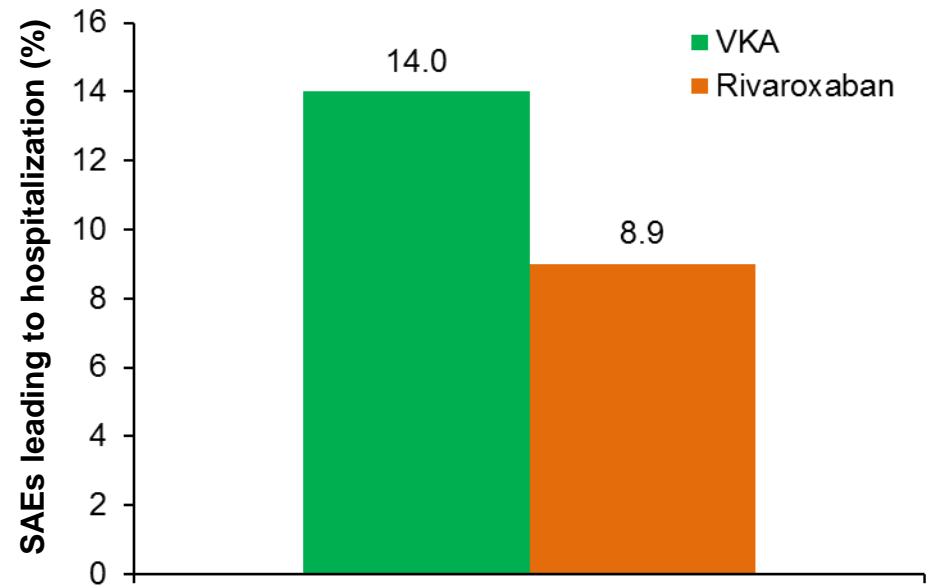
Serious Adverse Events

Cappato et al. Eur Heart J. 2015;36(28):1805-11.

...drug discontinuation



...hospitalization



The number of SAEs leading to drug discontinuation or hospitalization were very low and similar across the treatment groups

Summary 1. NOAC in Asian or AF Ablation

- ✚ NOAC showed better efficacy and safety in Asian patients with AF compared to non-Asian.
- ✚ Peri-procedural uninterrupted Dabigatran and Rivaroxaban are validated in patients who underwent AF ablation.

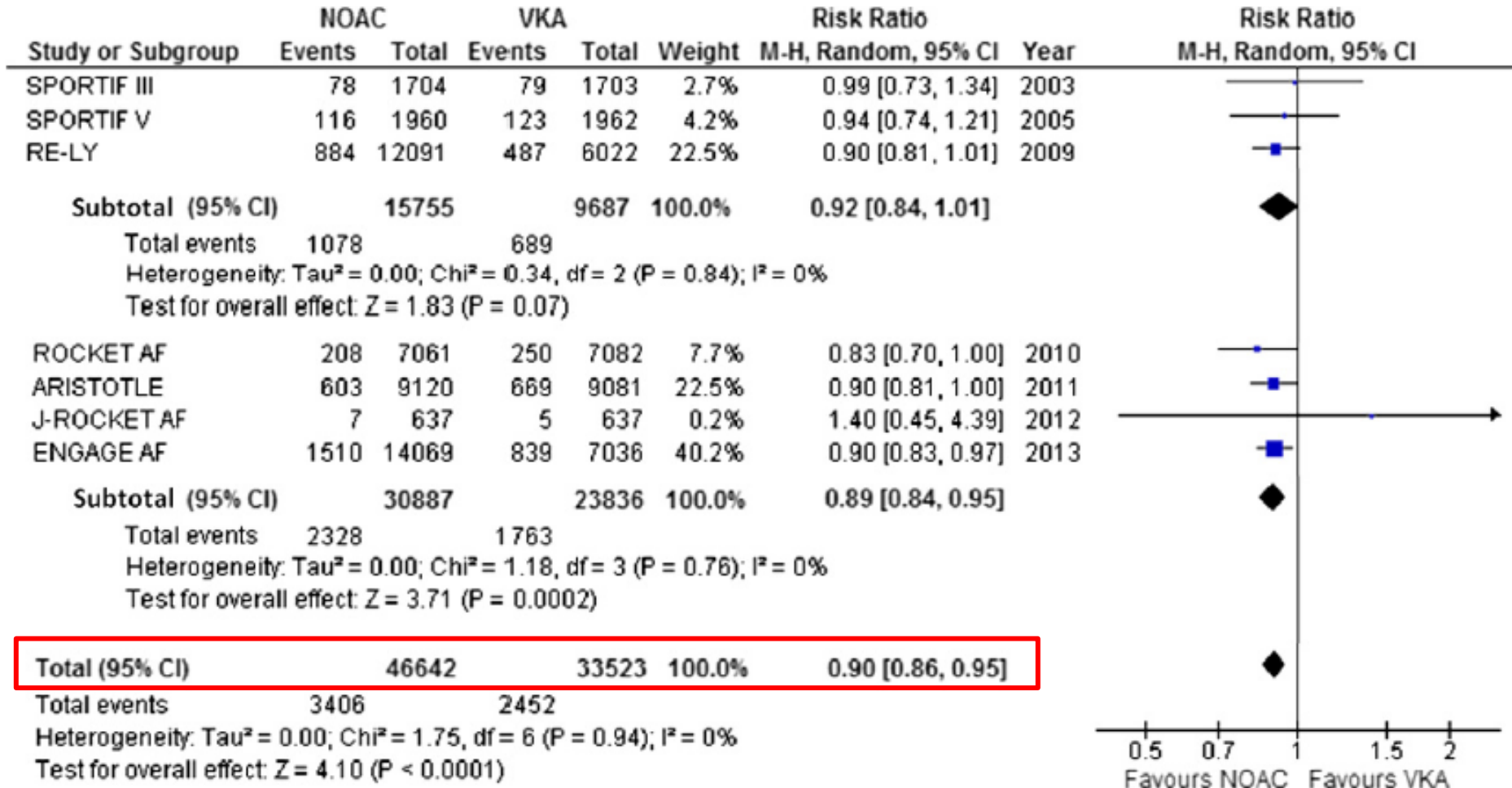
Meta-analyses for NOACs

Mortality Benefits of NOAC

Meta-analysis (7 RCTs, n=80,290)

Providencia et al. Thrombosis Res. 2014;134:1253-64.

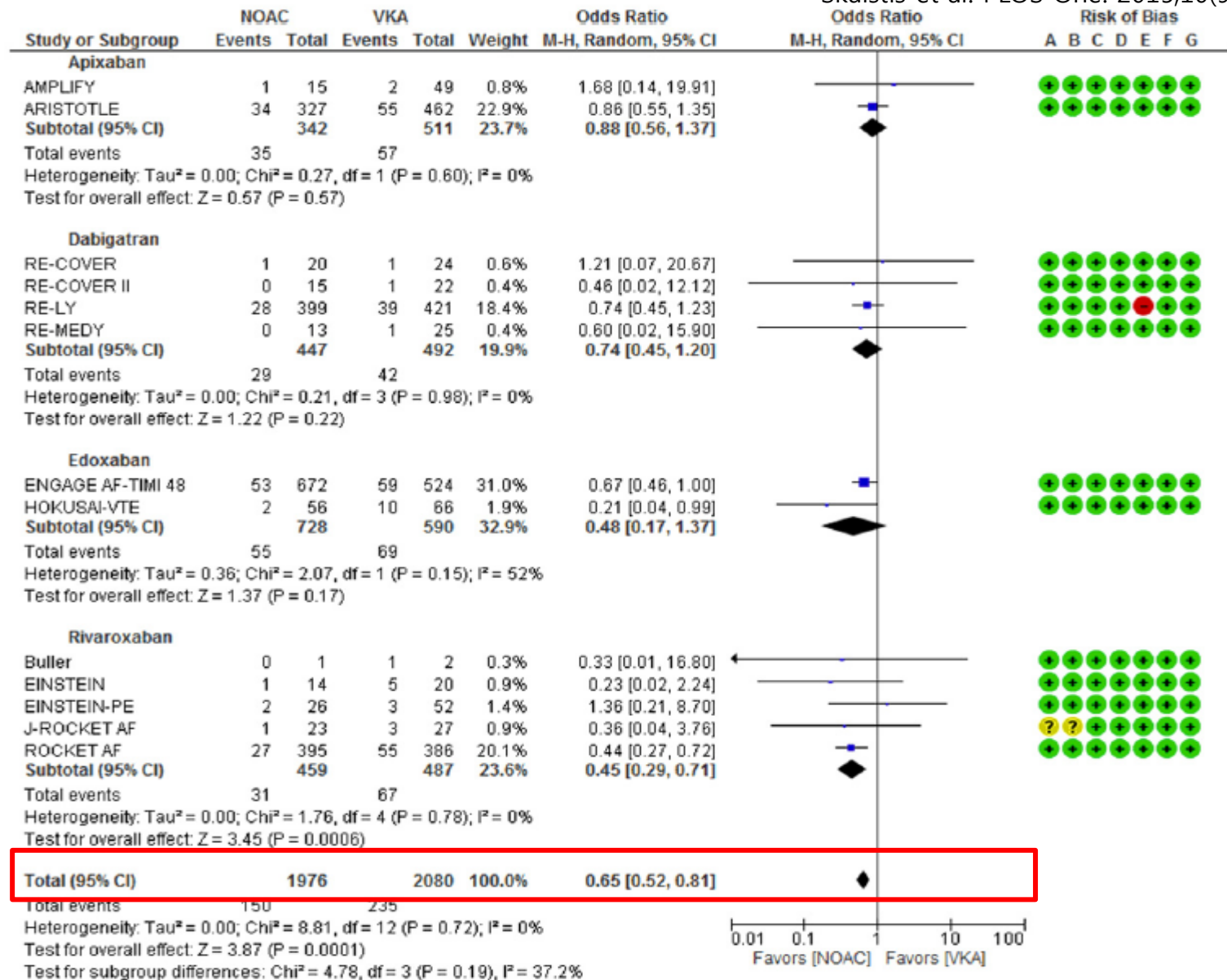
A) Total Mortality



Reduction of Fatal Bleeding

Meta-analysis (20 Trials)

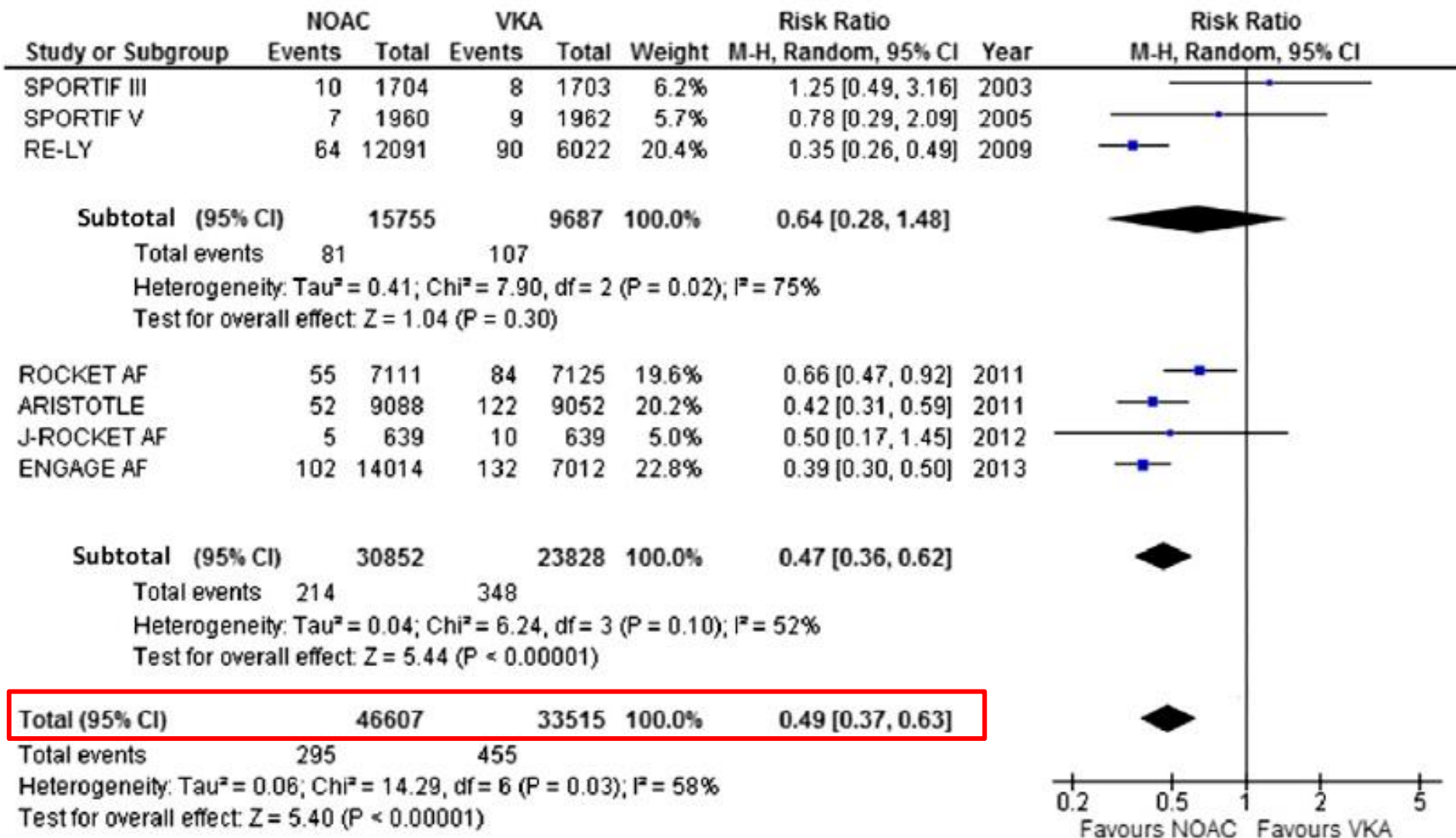
Skaistis et al. PLOS One. 2015;10(9):e0137444.



Reduction of Intracranial Bleeding

Meta-analysis (7 RCTs, n=80,290)

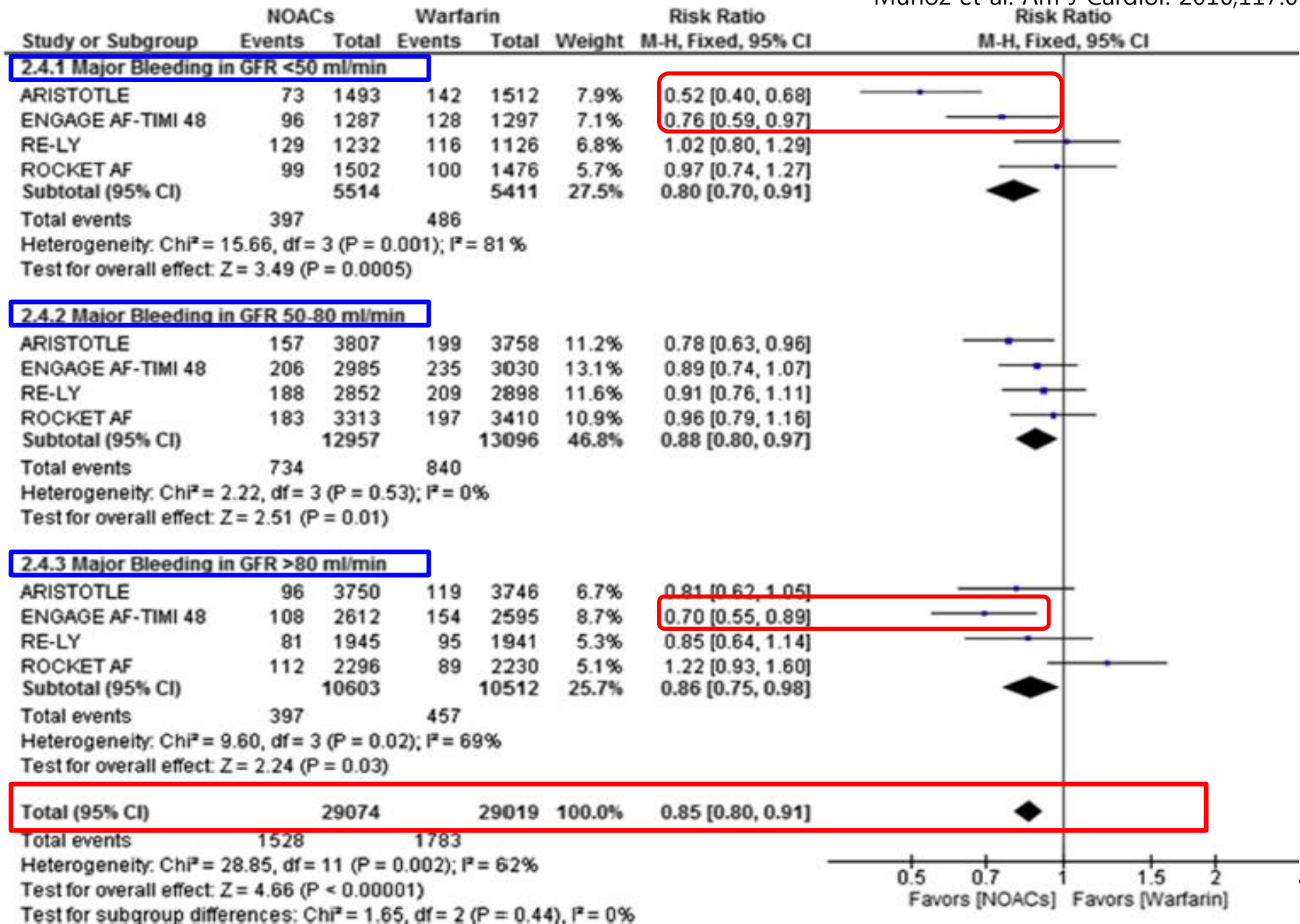
Providencia et al. Thrombosis Res. 2014;134:1253-64.



Risk of Major Bleeding in Relation to GFR

Meta-analysis (4 RCTs, n=58,338)

Munoz et al. Am J Cardiol. 2016;117:69-75.

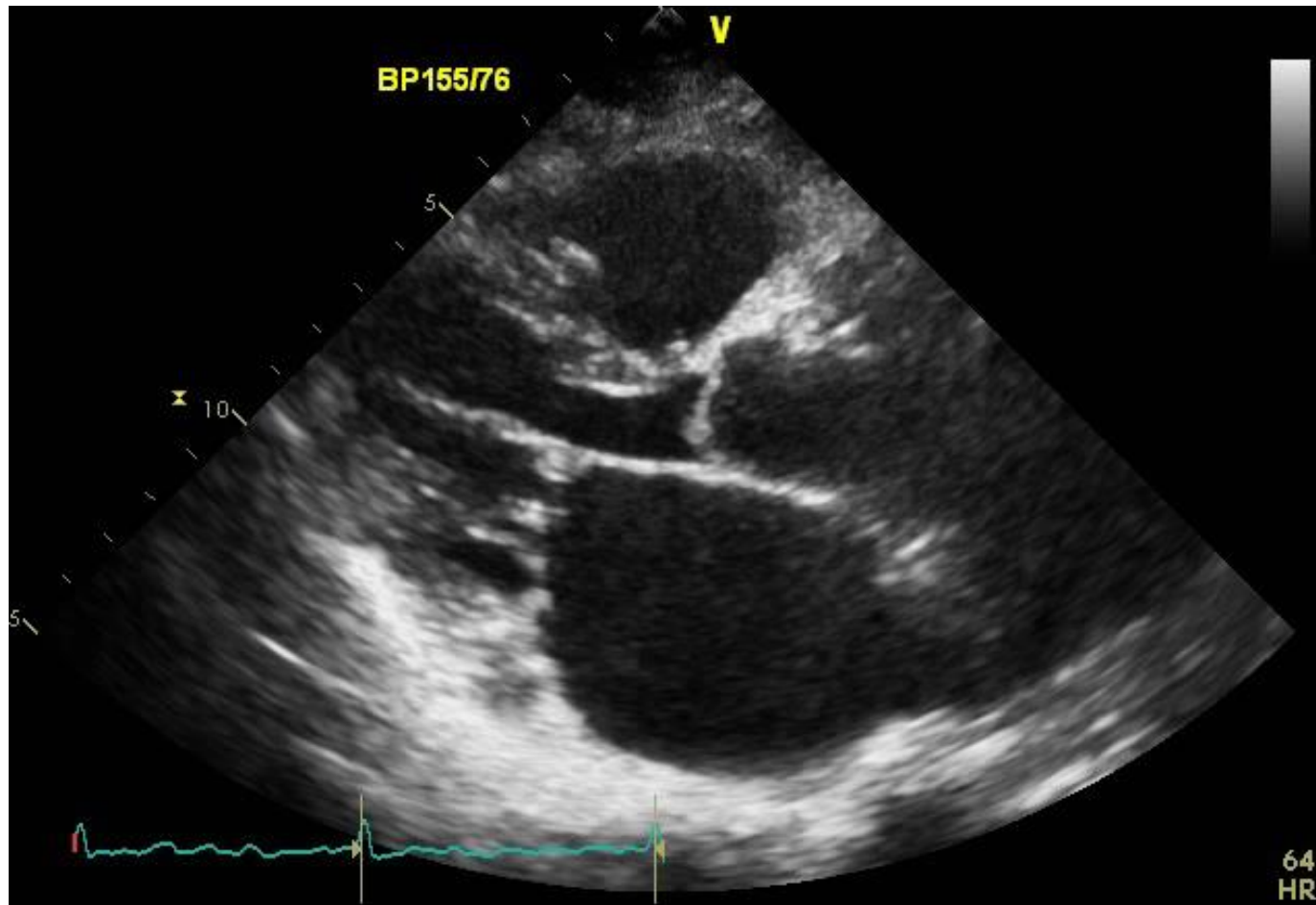


Summary 2. NOAC has Mortality Benefit

- ✚ NOAC reduced major hemorrhage including ICH, resulting in mortality benefit compared to warfarin in patients with NVAF.

NOACs in VHD

M/67. CHA₂DS₂-VASc score 1 Longstanding persistent AF, Moderate MS



Non-valvular AF

2015 Updated EHRA Practical Guide for NOAC

Heidbuchel et al. Europace. 2015;17(10):1467-507.

NOAC Eligible

NOAC Contraindicated

Mechanical Prosthetic Valve

✓

Moderate to Severe MS

✓

Mild to Moderate Other Valve Ds ✓

Severe AS ✓ (limited data)

Bioprosthetic Valve ✓ (except for post-OP 3mo)

Mitral Valve Repair ✓ (except for post-OP 3~6mo)

TAVR ✓ (with anti-PLT agent)

HCM ✓ (no prospective data)

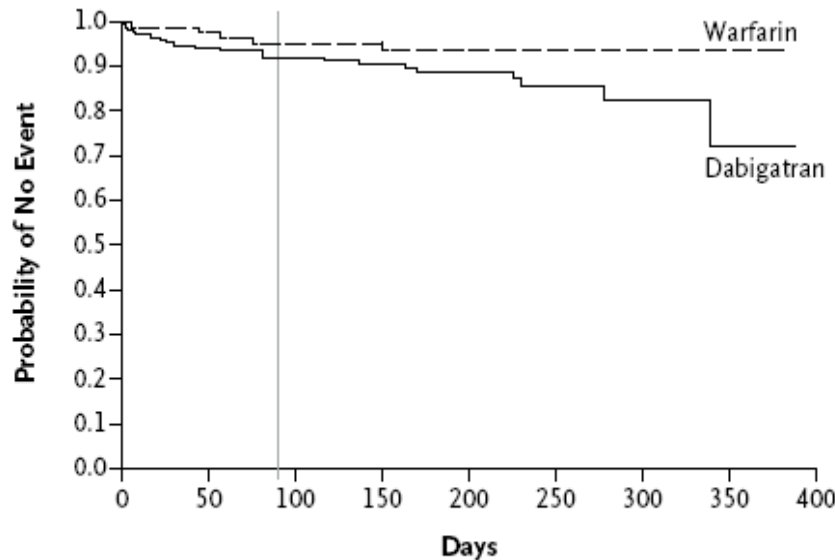
NOAC in Mechanical Valve

RE-ALIGN Trials

Eikelboom et al. N Eng J Med. 2013;369:1206-14

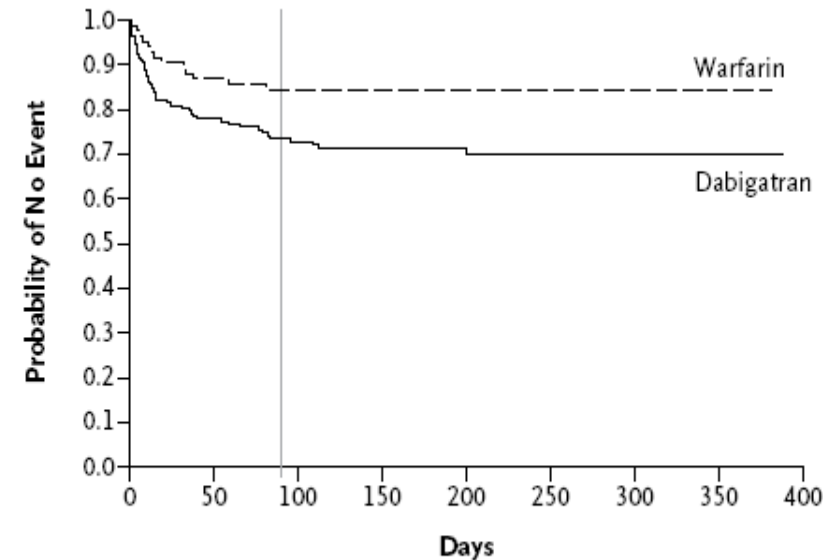
Dabigatran 150~300bid vs. Warfarin INR 2.0~3.5

A First Thromboembolic Event



No. at Risk		0	50	100	150	200	250	300	350	400
Dabigatran		168	156	126	108	73	44	15	7	
Warfarin		84	82	66	55	40	22	9	4	

B First Bleeding Event



No. at Risk		0	50	100	150	200	250	300	350	400
Dabigatran		168	129	103	86	58	32	11	6	
Warfarin		84	73	56	50	38	22	11	4	

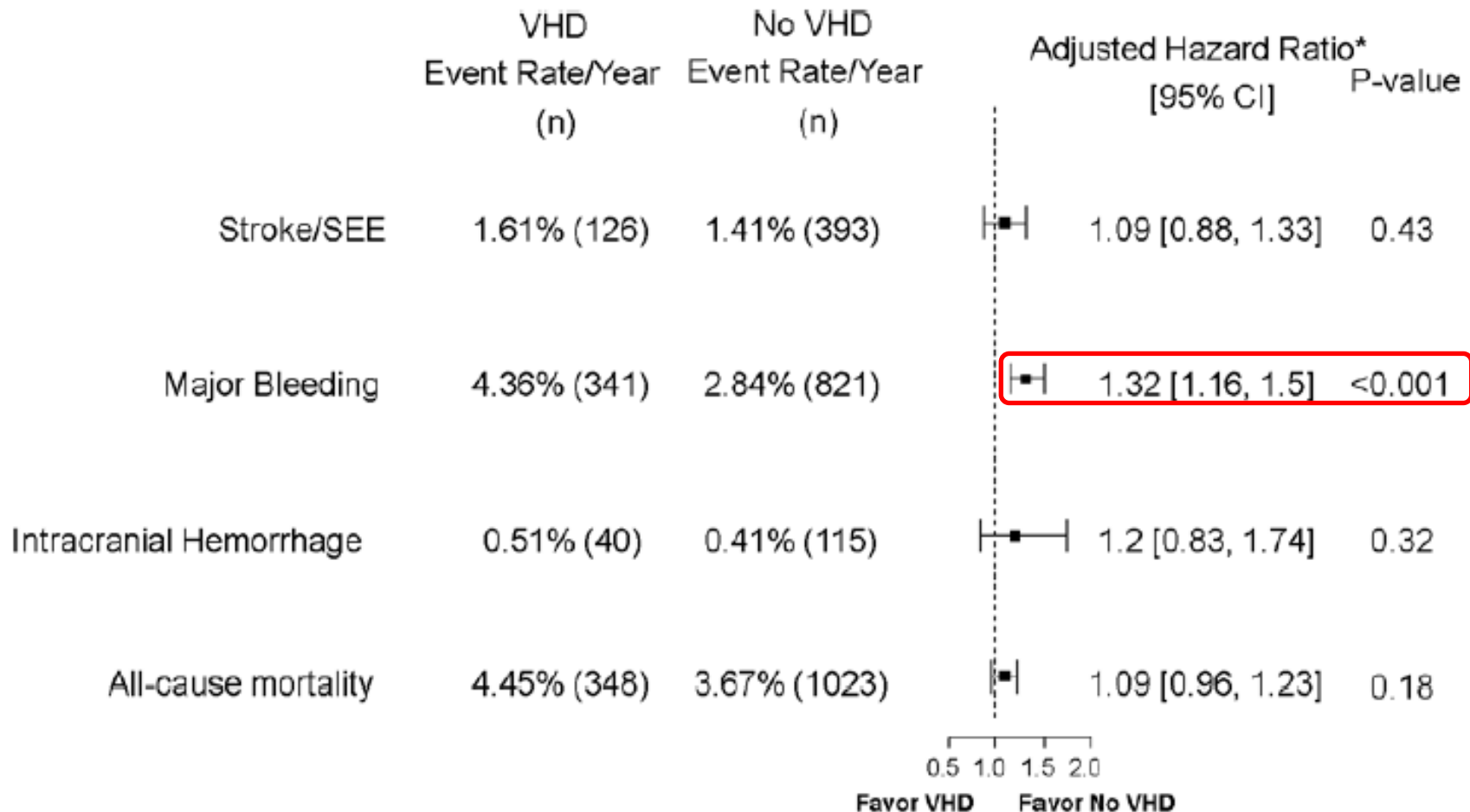
However, **AF with VHD** does not mean **Valvular AF**.
Ongoing studies TAVR and other populations.

NOAC in VHD, not Valvular AF

Post-hoc Analysis of RE-LY Trial

Ezekowitz et al. Circulation. 2016;134:589-598.

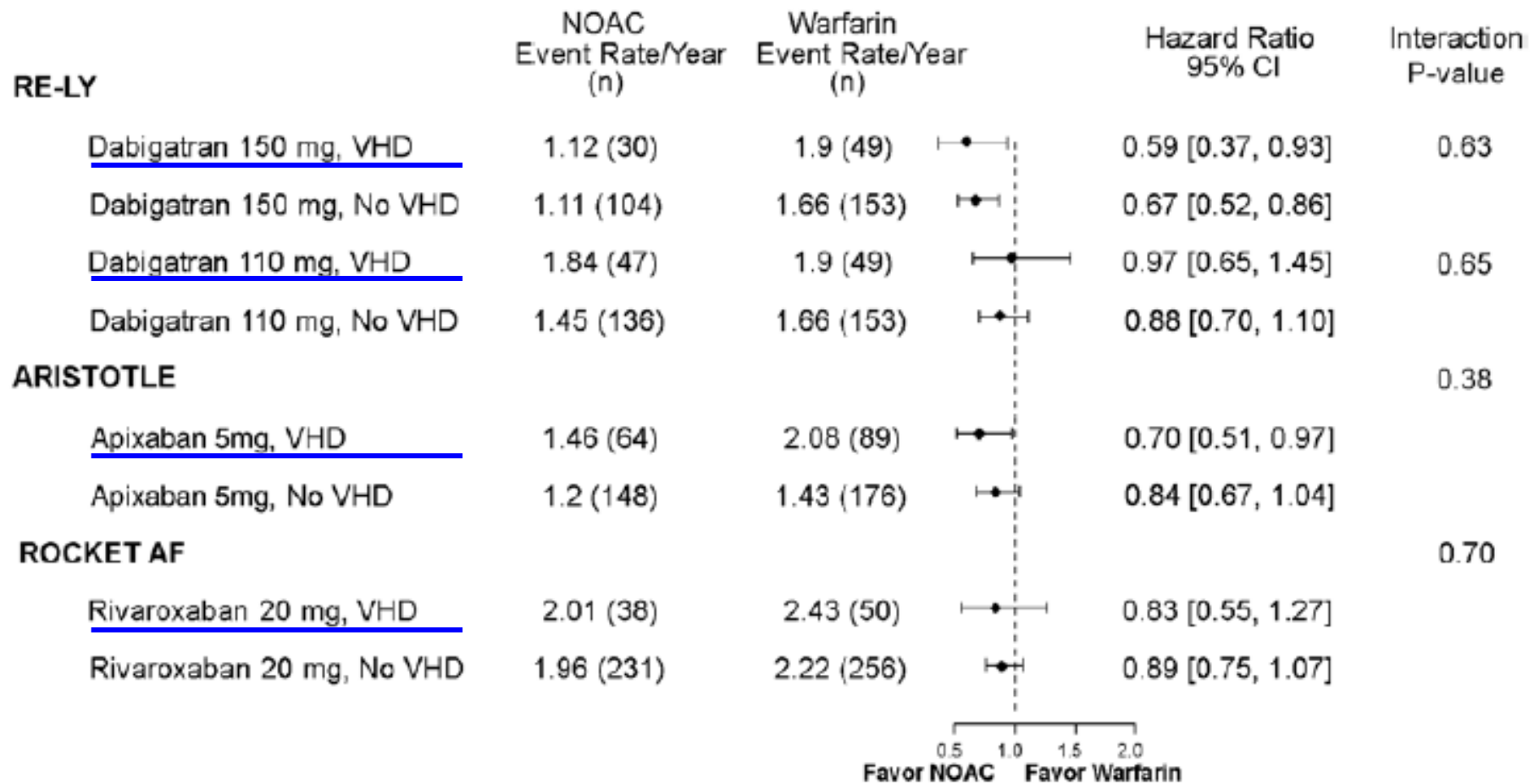
In RE-LY, 21% had VHD (MR 17%, AR 4.5%, AS 2.6%, TR 6.5%, mild MS 4.9%)
With VHD: older, female, CAD, GFR<50



Stroke & STE in VHD (not Valvular AF)

Post-hoc Analyses

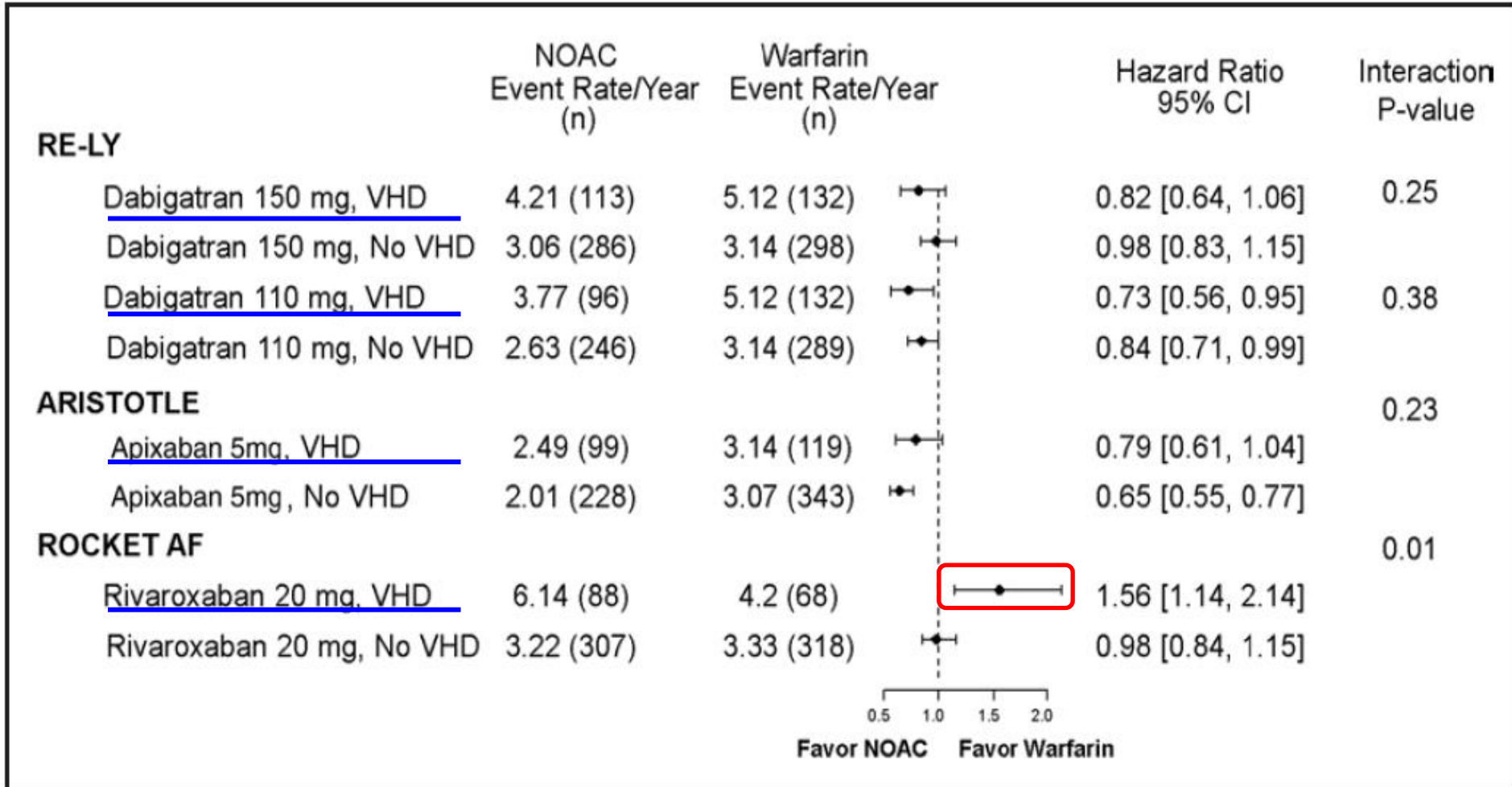
Ezekowitz et al. Circulation. 2016;134:589-598.



Major Bleeding in VHD

Post-hoc Analyses

Ezekowitz et al. Circulation. 2016;134:589-598.



Proportions of VHD in Major Trials

Meta-analyses (4 RCTs, n=13,585)

Renda et al. J Am Coll Cardiol. 2017;69:1363-71.

VHD Subtype	RE-LY (n = 3,950)	ROCKET-AF (n = 2,003)	ARISTOTLE (n = 4,808)	ENGAGE AF-TIMI 48 (n = 2,824)
Moderate/severe mitral regurgitation	3,101 (78.5)	1,756 (87.7)	3,526 (73.3)	2,250 (79.6)
Mild mitral stenosis*	193 (4.9)	NR	131 (2.7)	254 (9.0)
Moderate/severe aortic regurgitation	817 (20.7)	486 (24.3)	887 (18.4)	369 (13.0)
Moderate/severe aortic stenosis	471 (11.9)	215 (10.7)	384 (8.0)	165 (5.8)
Moderate/severe tricuspid regurgitation	1,179 (29.8)	NR	2,124 (44.0)	NR
Valve surgery (other than mechanical prosthetic heart valve)	NR	106 (5.3)†	251 (5.2)	516 (18.2)

Values are n (%). *These patients were analyzed with the No-VHD group because the VHD definition adopted always included at least "moderate" VHD. †Biologic prosthetic valves also excluded.

NR = not reported; other abbreviations as in [Table 1](#).

Efficacy & Safety of NOAC in VHD

Meta-analyses (4 RCTs, n=13,585)

Renda et al. J Am Coll Cardiol. 2017;69:1363-71.

Stroke/SEE

Major Bleeding

Study or Subgroup

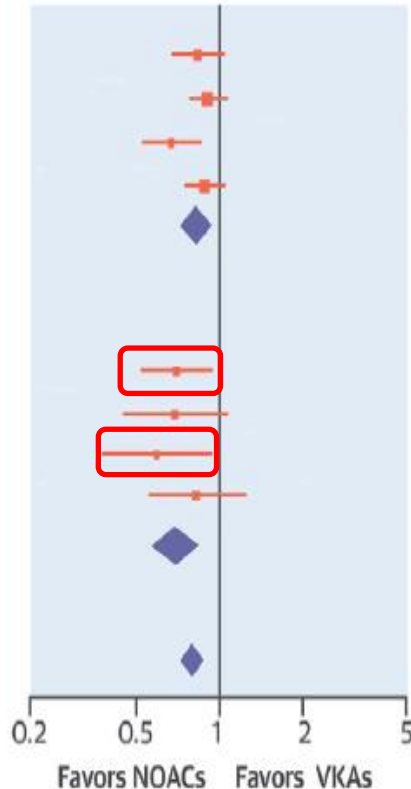
Risk Ratio
IV, Random, 95% CI

Study or Subgroup

Risk Ratio
IV, Random, 95% CI

NO VHD

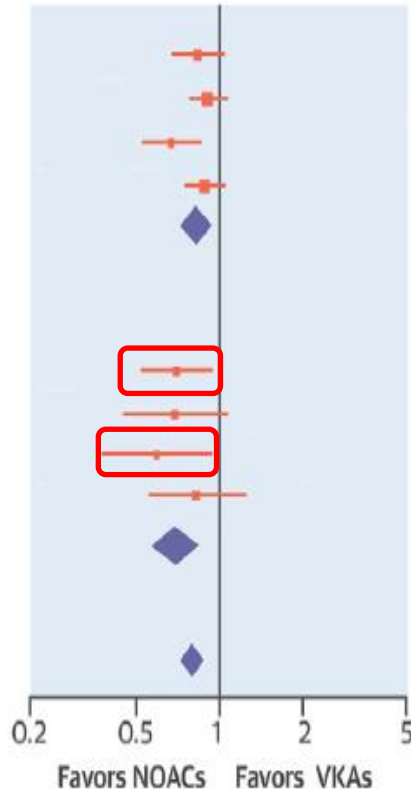
ARISTOTLE
ENGAGE AF-TIMI 48 (Higher Dose)
RE-LY (Higher Dose)
ROCKET AF
Subtotal RR (95% CI)=0.84 (0.75-0.95)



VHD

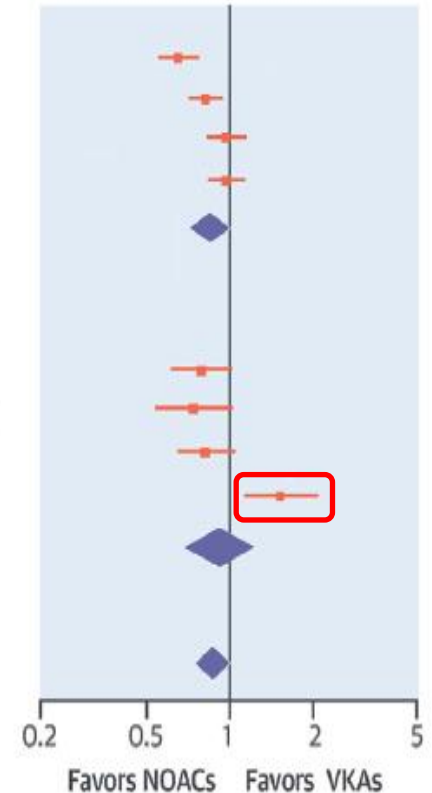
ARISTOTLE
ENGAGE AF-TIMI 48 (Higher Dose)
RE-LY (Higher Dose)
ROCKET AF
Subtotal RR (95% CI)=0.70 (0.58-0.86)

Total (95% CI) RR=0.81 (0.73-0.89)



NO VHD

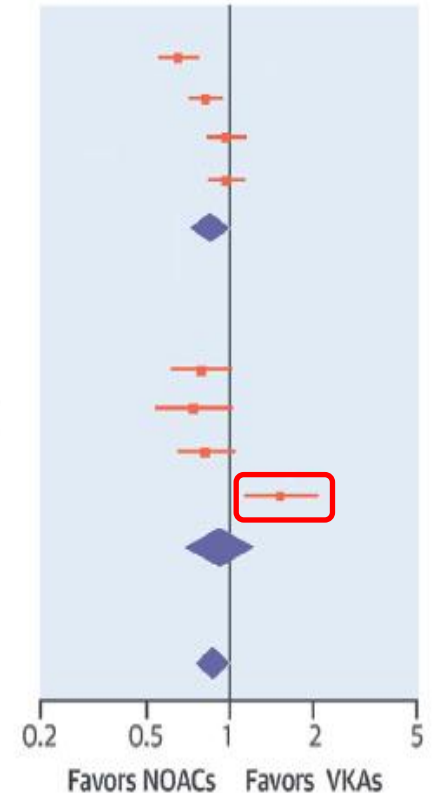
ARISTOTLE
ENGAGE AF-TIMI 48 (Higher Dose)
RE-LY (Higher Dose)
ROCKET AF
Subtotal RR (95% CI)=0.85 (0.70-1.02)



VHD

ARISTOTLE
ENGAGE AF-TIMI 48 (Higher Dose)
RE-LY (Higher Dose)
ROCKET AF
Subtotal RR (95% CI)=0.93 (0.68-1.27)

Total (95% CI) RR=0.88 (0.75-1.02)

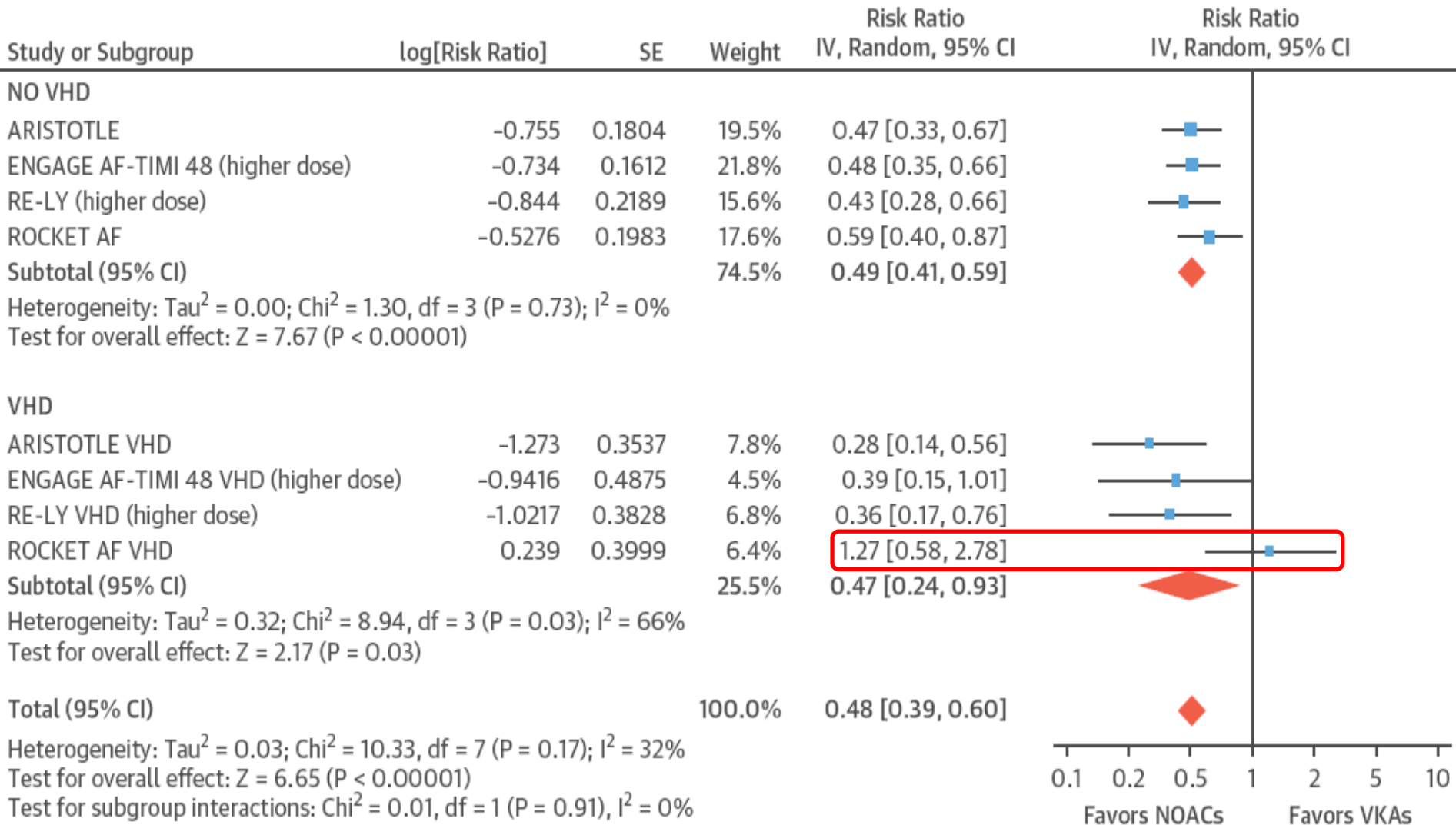


Intracranial Hemorrhage in VHD

Meta-analyses (4 RCTs, n=13,585)

Renda et al. J Am Coll Cardiol. 2017;69:1363-71.

Intracranial hemorrhage

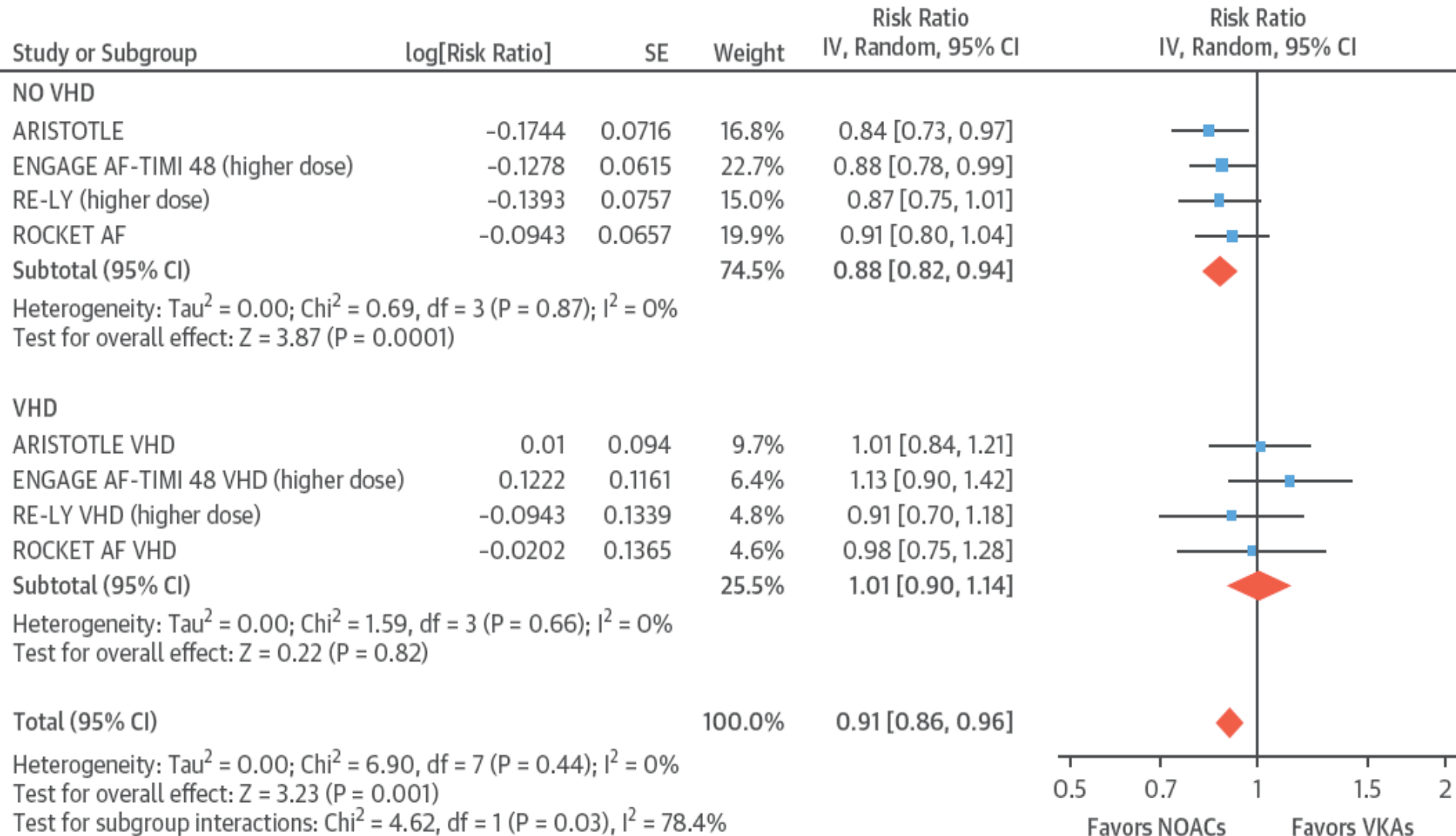


All Cause Mortality in VHD

Meta-analyses (4 RCTs, n=13,585)

Renda et al. J Am Coll Cardiol. 2017;69:1363-71.

All-cause death



Summary 3. NOAC in VHD

- ✚ NOAC showed similar efficacy and safety compared to warfarin in patients with VHD without mortality benefit.
- ✚ However, rivaroxaban increased major bleeding rate compared to warfarin in patients with VHD.

Efficacy & Safety of NOACs in Elderly Patients

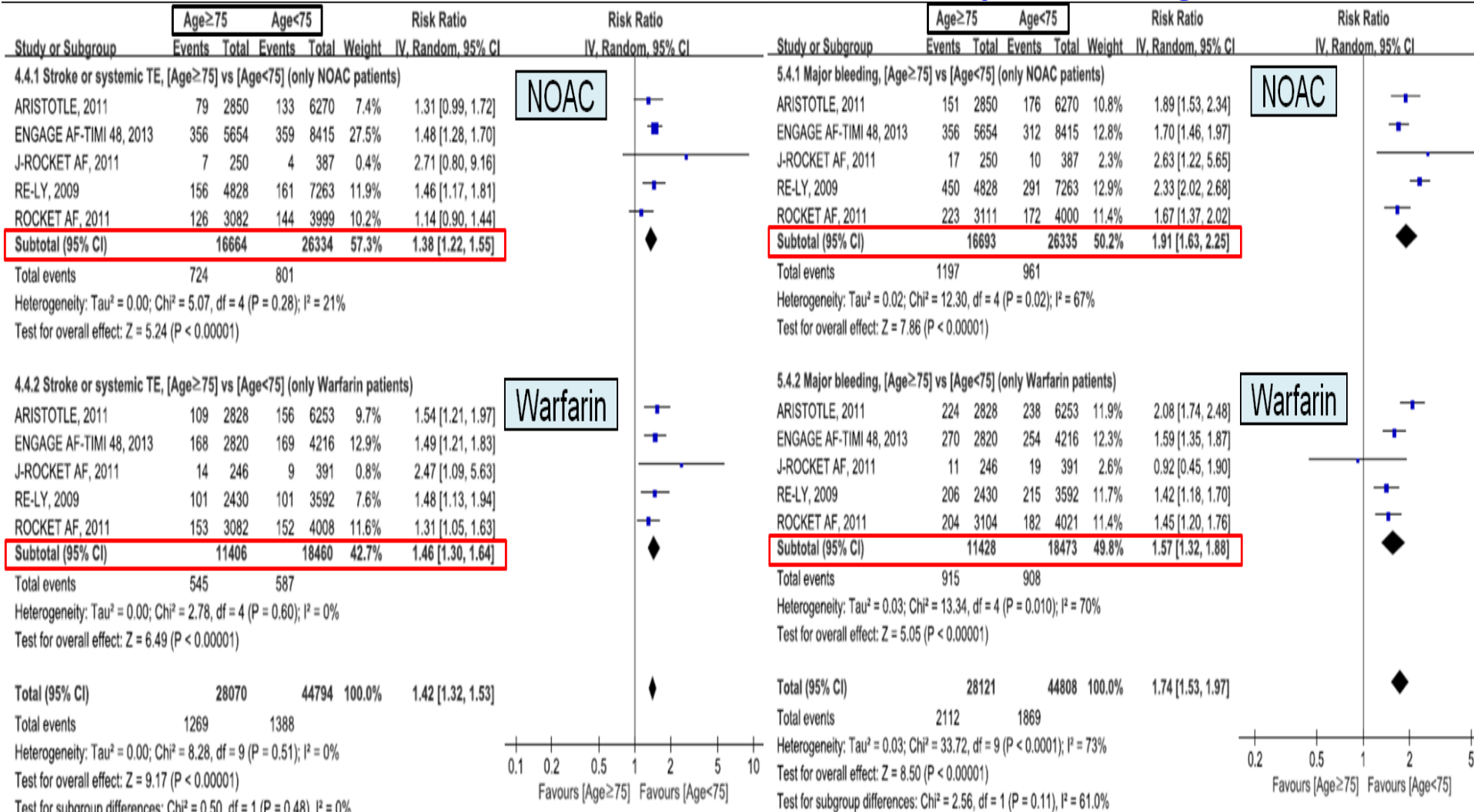
NOAC in Elderly Patients Over 75

Meta-analysis (5 RCTs, n=62,961)

Kim IS et al. [Unpublished data]

STE

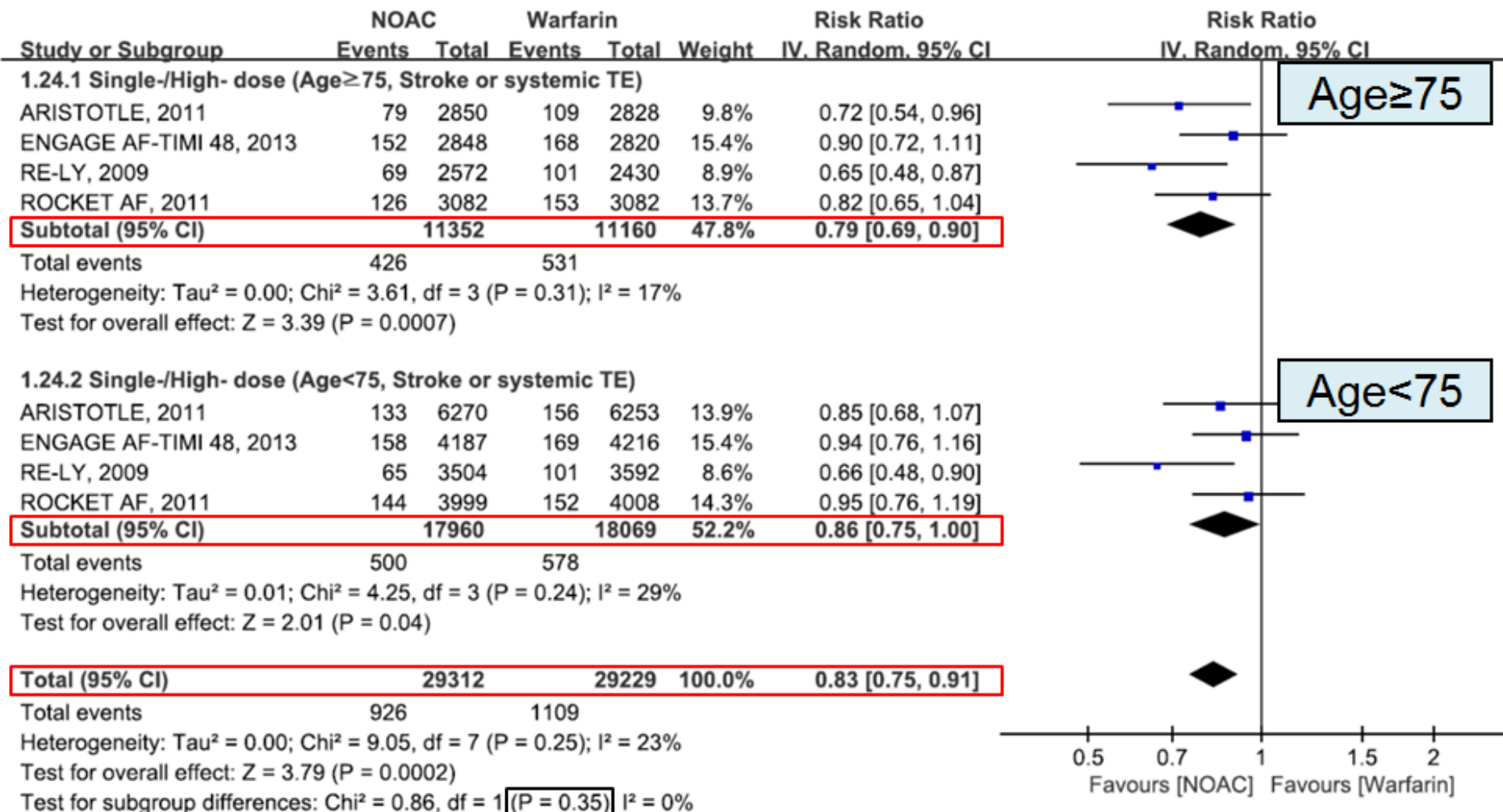
Major Bleeding



Stroke & STE Under Standard Dose NOAC

Meta-analysis (5 RCTs, n=62,961)

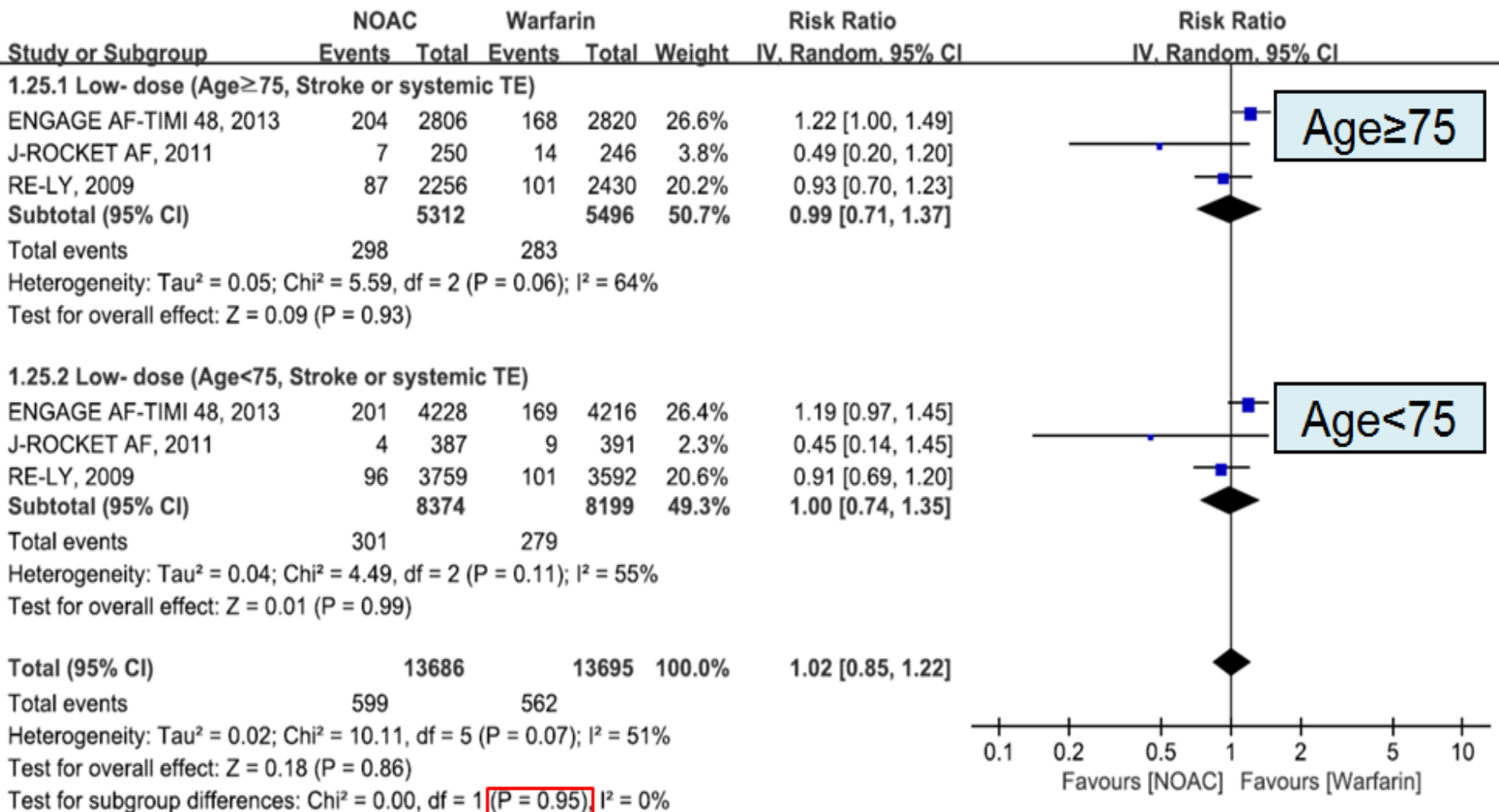
Kim IS et al. [Unpublished data]



Stroke & STE in Low Dose NOAC

Meta-analysis (5 RCTs, n=62,961)

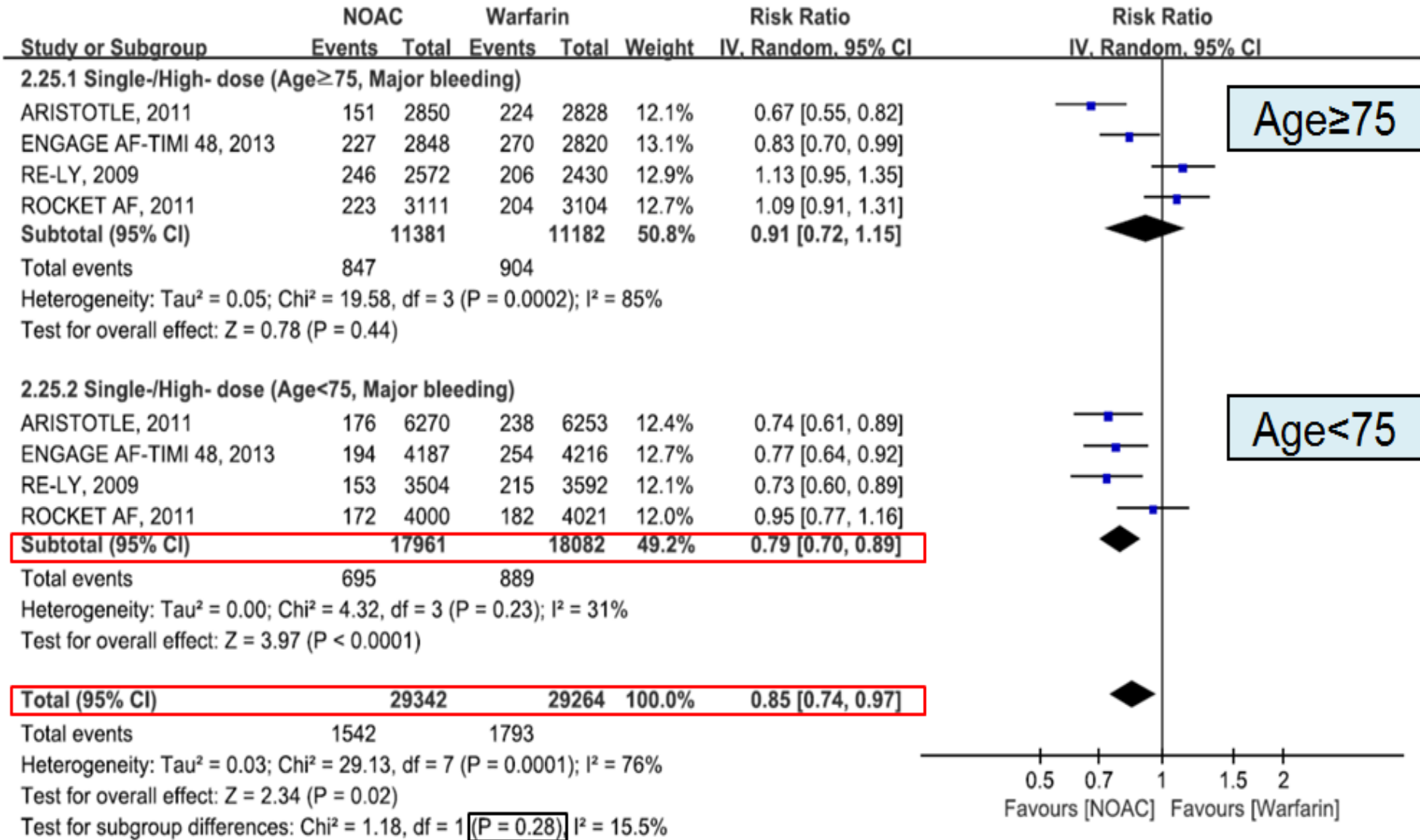
Kim IS et al. [Unpublished data]



Major Bleeding in Standard Dose NOAC

Meta-analysis (5 RCTs, n=62,961)

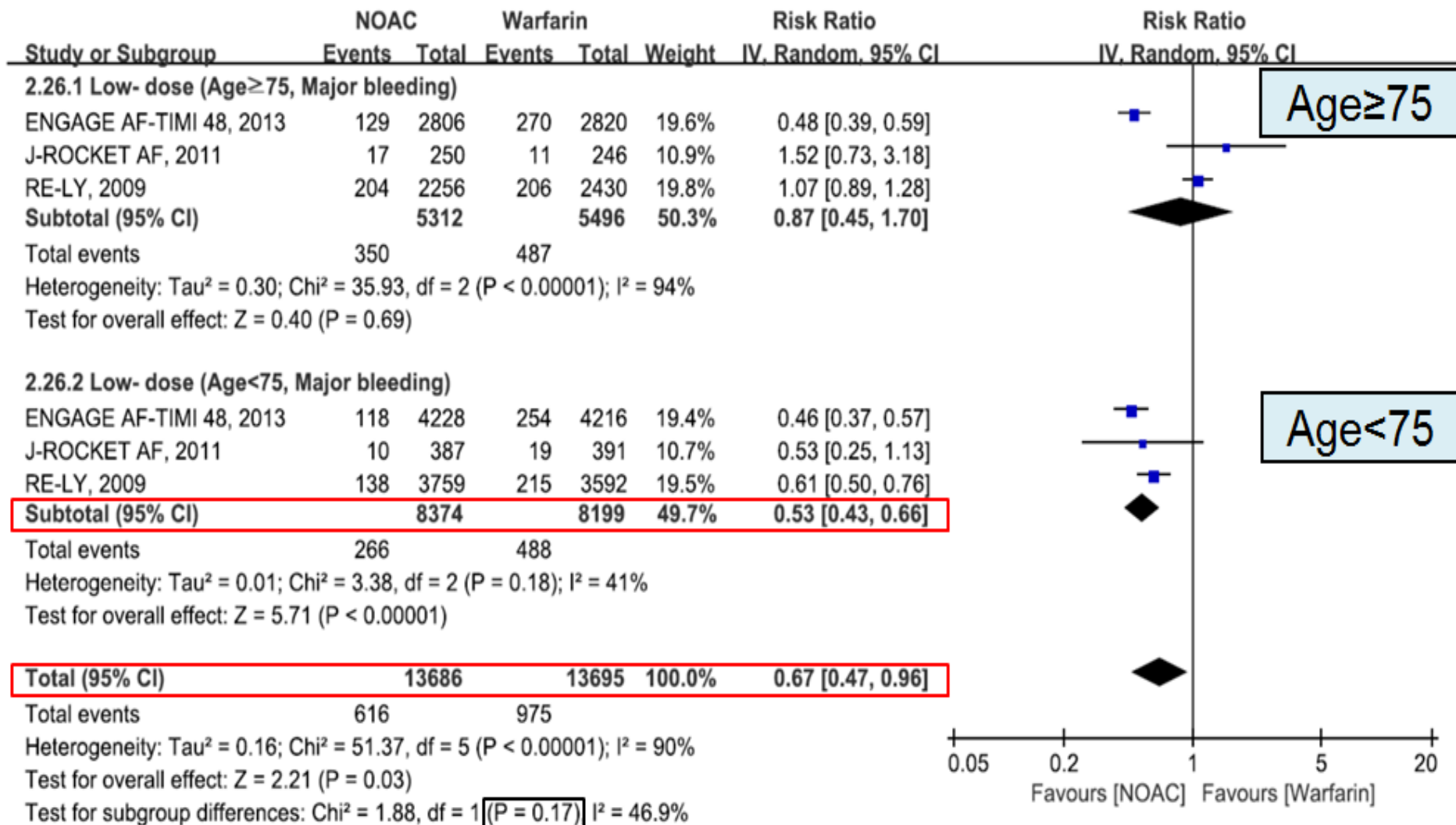
Kim IS et al. [Unpublished data]



Major Bleeding in Low Dose NOAC

Meta-analysis (5 RCTs, n=62,961)

Kim IS et al. [Unpublished data]



Summary 4. NOAC in Elderly Patients

Kim IS et al. [Unpublished data]

- ✚ NOAC showed better efficacy than warfarin in elderly patients.
- ✚ Standard dose NOAC showed better efficacy than warfarin in both elderly and non-elderly patients.
- ✚ NOAC reduced major bleeding risk compared to warfarin in non-elderly patients, and had comparable safety in elderly patients, regardless of dose regimens.

Non-persistence of NOACs

Non-persistence of NOACs

15,857 Dabigatran and 10,119 Rivaroxaban (>14 days gap)

Jackevicius et al. Heart. 2017;[E-Pub]

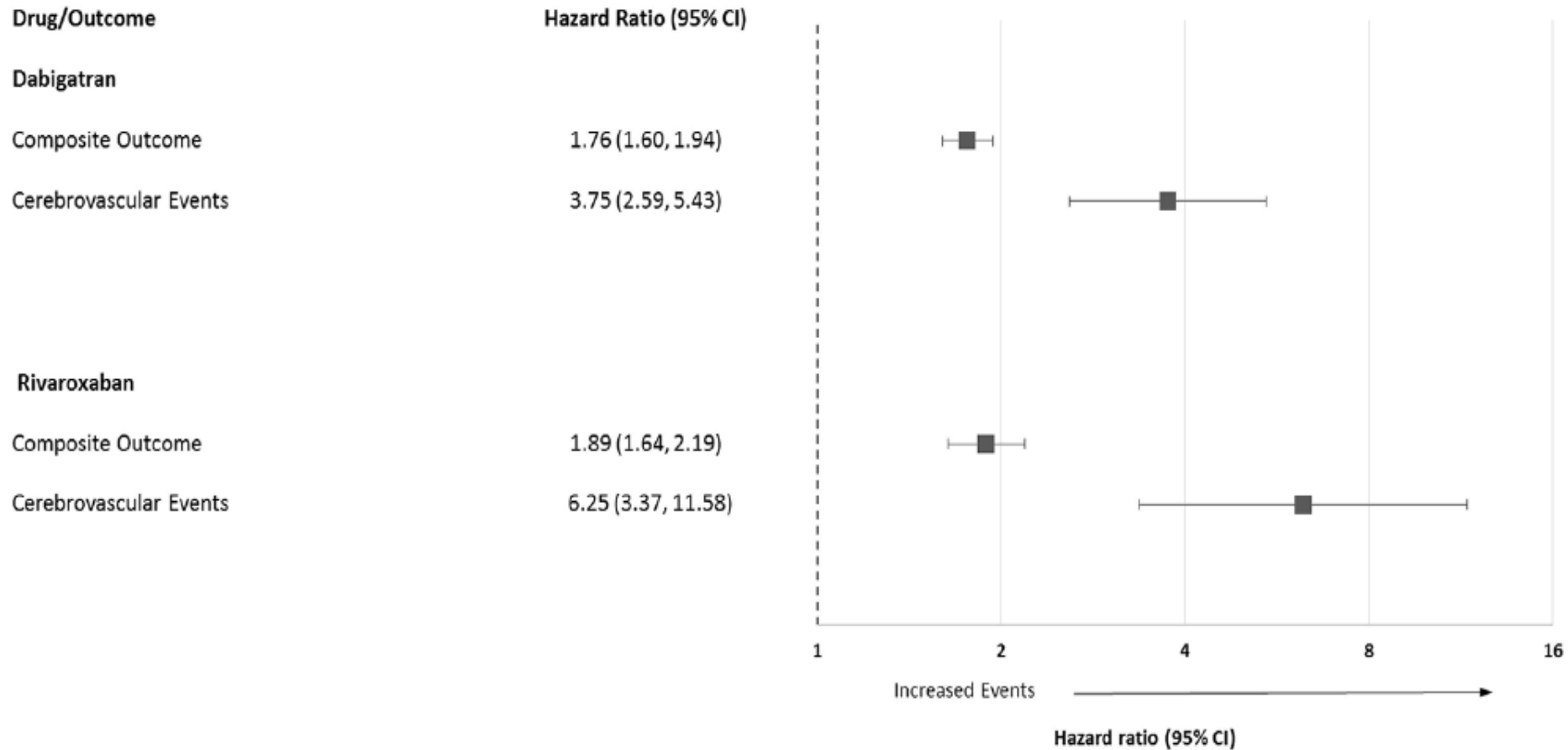
At 6 months, 36.4% were non-persistent to dabigatran and 31.9% were non-persistent to rivaroxaban.

Variable	Dabigatran		Rivaroxaban	
	OR (95% CI)	p Value	OR (95% CI)	p Value
Age (reference >75 years)	0.98 (0.90 to 1.06)	0.61	0.96 (0.85 to 1.08)	0.47
Sex (reference female)	1.08 (1.01 to 1.16)	0.02	1.18 (1.08 to 1.30)	<0.001
Rural residence (vs urban)	0.96 (0.87 to 1.06)	0.39	0.86 (0.75 to 0.99)	0.04
University education	1.09 (0.97 to 1.22)	0.16	0.98 (0.83 to 1.15)	0.80
Prior warfarin use	0.96 (0.90 to 1.03)	0.26	0.86 (0.78 to 0.95)	0.02
High-risk CHADS2 (vs low risk)	0.90 (0.77 to 1.06)	0.21	1.07 (0.85 to 1.35)	0.57
Moderate-risk CHADS2 (vs low risk)	0.98 (0.86 to 1.12)	0.79	1.10 (0.91 to 1.33)	0.35
Hypertension	1.01 (0.93 to 1.10)	0.85	0.98 (0.87 to 1.11)	0.81
Diabetes	0.95 (0.88 to 1.03)	0.24	0.97 (0.86 to 1.09)	0.63
Coronary artery disease	0.96 (0.90 to 1.04)	0.33	0.91 (0.82 to 1.01)	0.07
Chronic kidney disease	1.15 (0.97 to 1.36)	0.11	1.17 (0.95 to 1.44)	0.15
History of bleeding	1.04 (0.95 to 1.15)	0.38	0.94 (0.82 to 1.08)	0.40
Stroke/TIA	1.00 (0.89 to 1.13)	0.94	0.84 (0.70 to 1.00)	0.05
Cardiologist vs generalist	0.98 (0.89 to 1.09)	0.77	1.12 (0.97 to 1.29)	0.13
Internist vs generalist	1.07 (0.98 to 1.17)	0.15	1.17 (1.03 to 1.33)	0.01
Other physician type vs generalist	1.09 (0.98 to 1.20)	0.10	1.11 (0.96 to 1.28)	0.17

CHADS2, congestive heart failure, hypertension, age, diabetes, stroke; TIA: transient ischaemic attack.

Clinical Outcomes Associated with NOAC Non-persistence

Jackevicius et al. Heart. 2017;[E-Pub]



Take-Home Message

- ✚ NOAC showed better efficacy and safety in Asian patients with AF compared to non-Asian.
- ✚ Peri-procedural uninterrupted Dabigatran and Rivaroxaban are validated in patients who underwent AF ablation.
- ✚ NOAC has mortality benefit compared to warfarin in SPAF by reducing the risk of fatal bleeding.
- ✚ NOAC can be considered in AF patients with VHD.
- ✚ NOAC is more effective in elderly, and safer in non-elderly compared to warfarin.
- ✚ However, compliance of NOAC will be a major issue in real-world practice.

Stroke & STE Under NOAC

Meta-analysis (5 RCTs, n=62,961)

Kim IS et al. [Unpublished data]

