亞東紀念醫院
Far Eastern Memorial Hospital

Tailored anticoagulant strategy for your NVAF patients with co-morbidities

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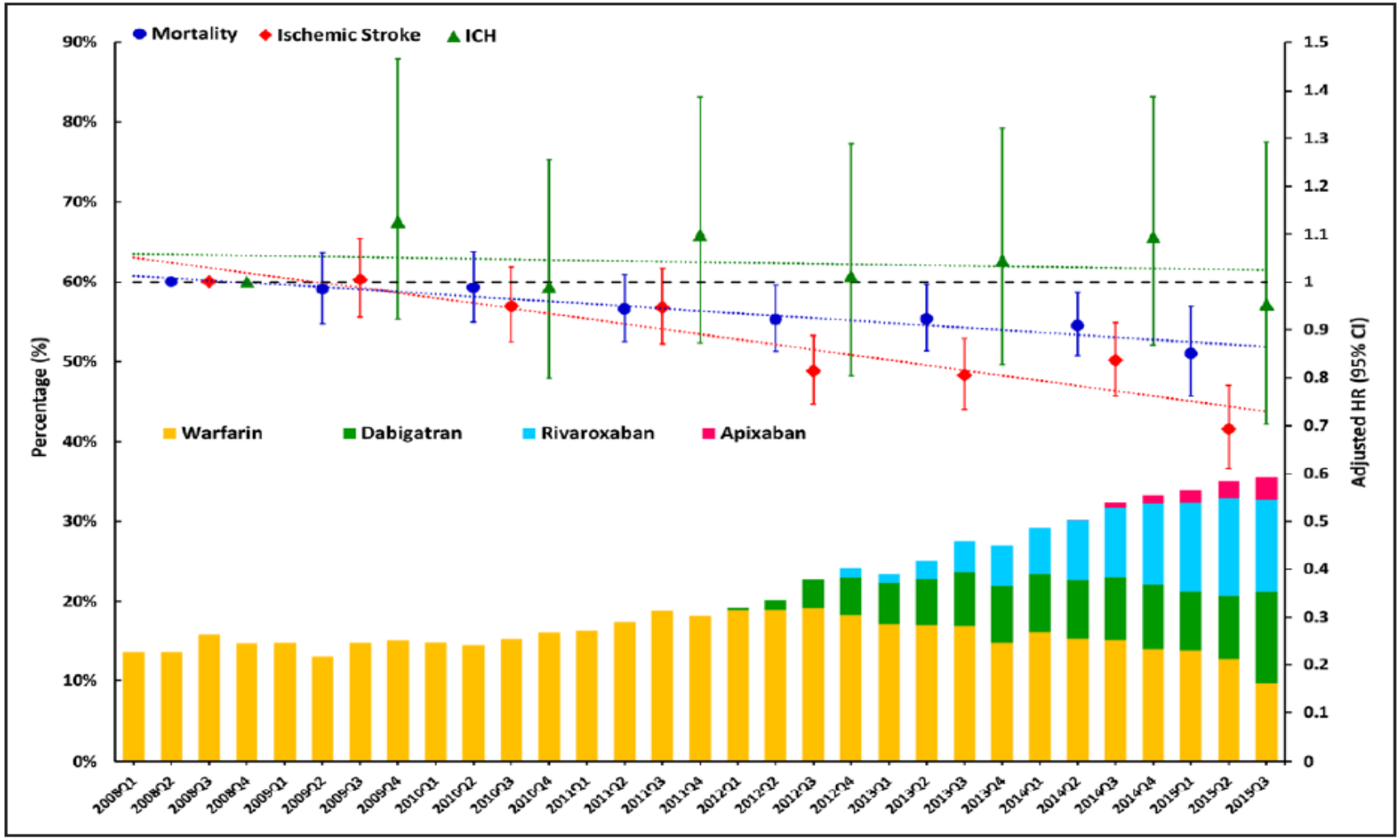
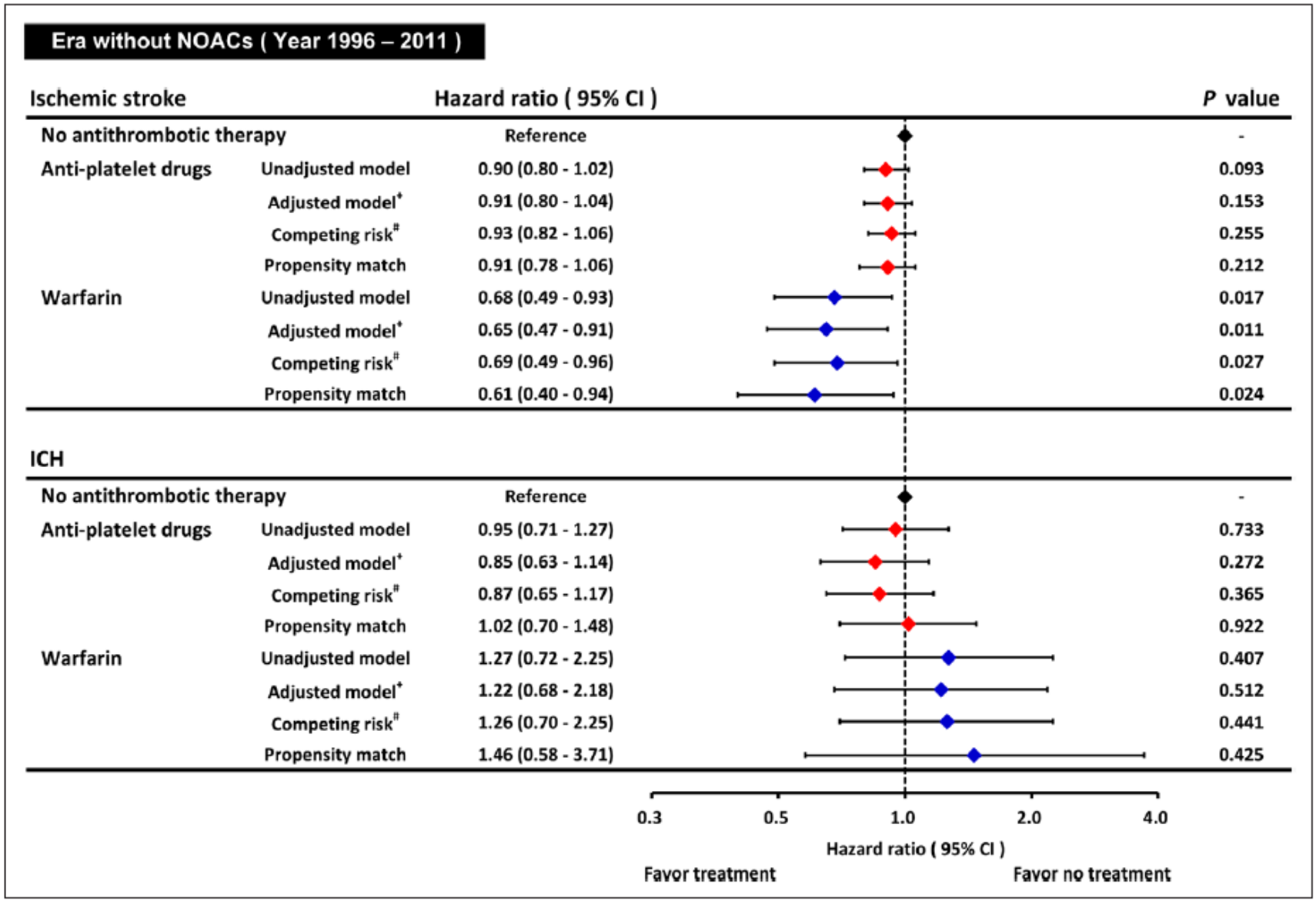
Cardiovascular center,
Far Eastern Memorial Hospital,
New Taipei City, Taiwan

OACs decrease the risk of adverse events in AF patient

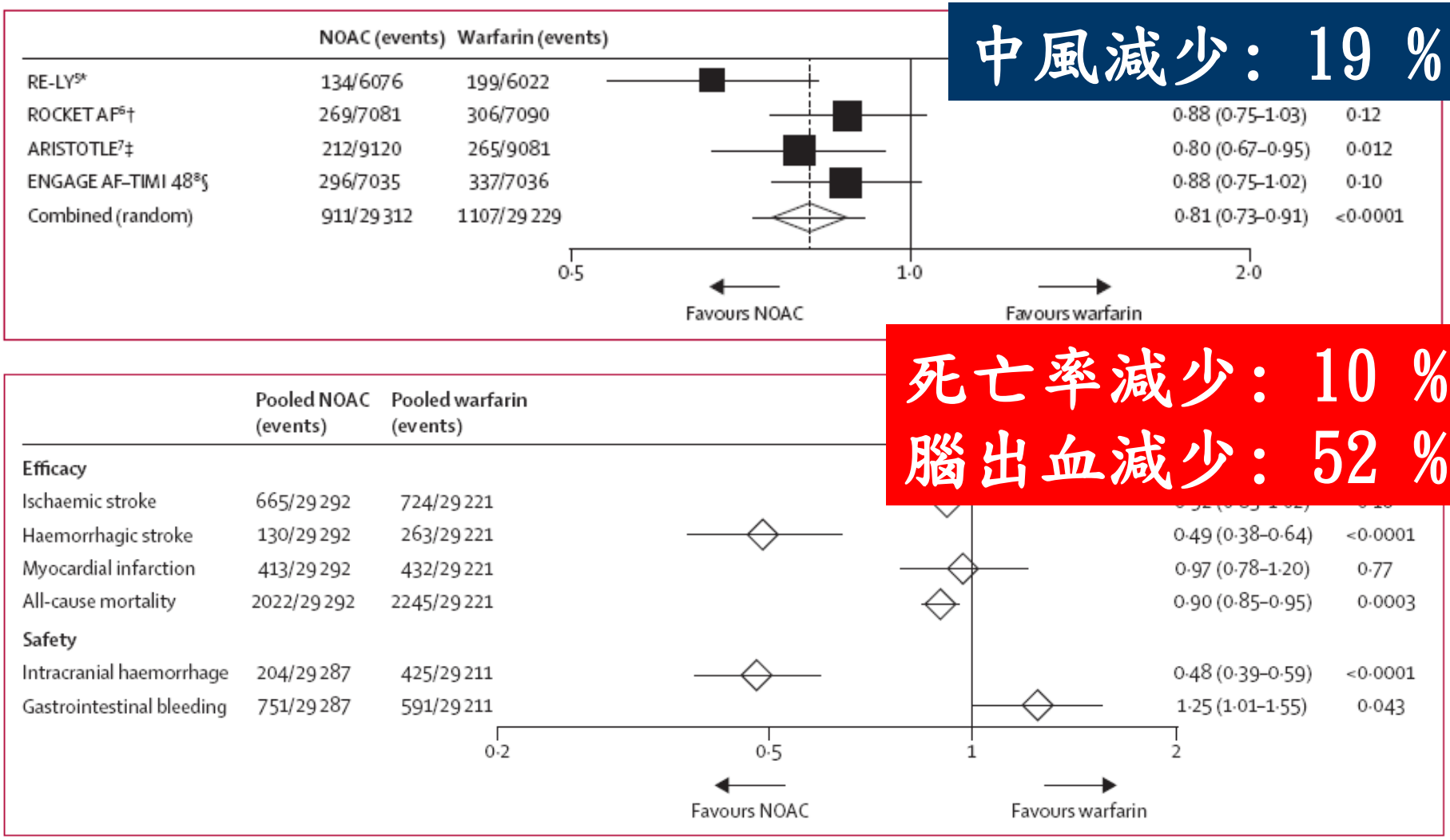


Circulation. 2018;138:1485–1487



Circulation. 2018;138:37

NOAC had better performance than Warfarin



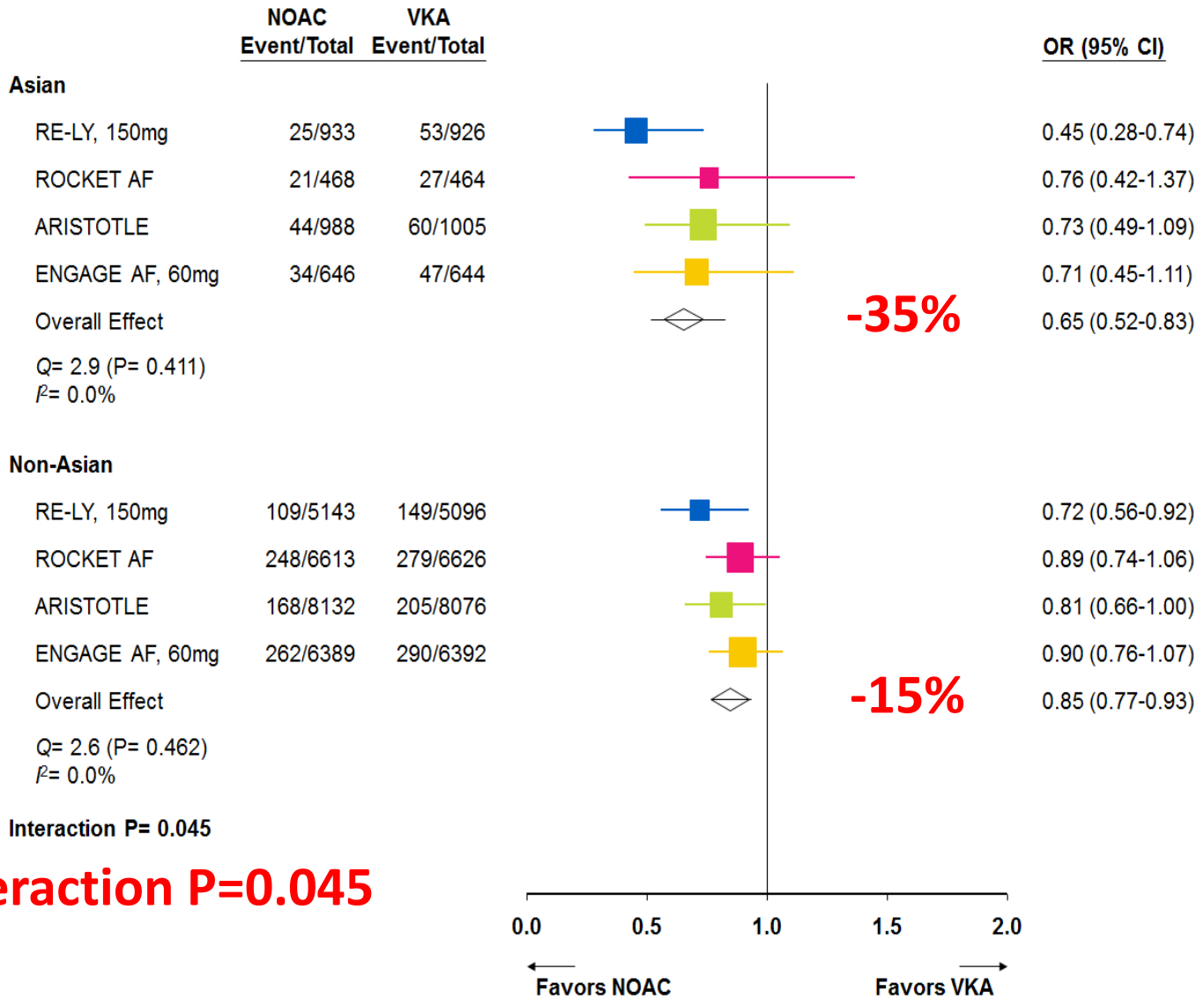
中風減少：19 %

死亡率減少：10 %

腦出血減少：52 %

Lancet 2014; 383: 955–62

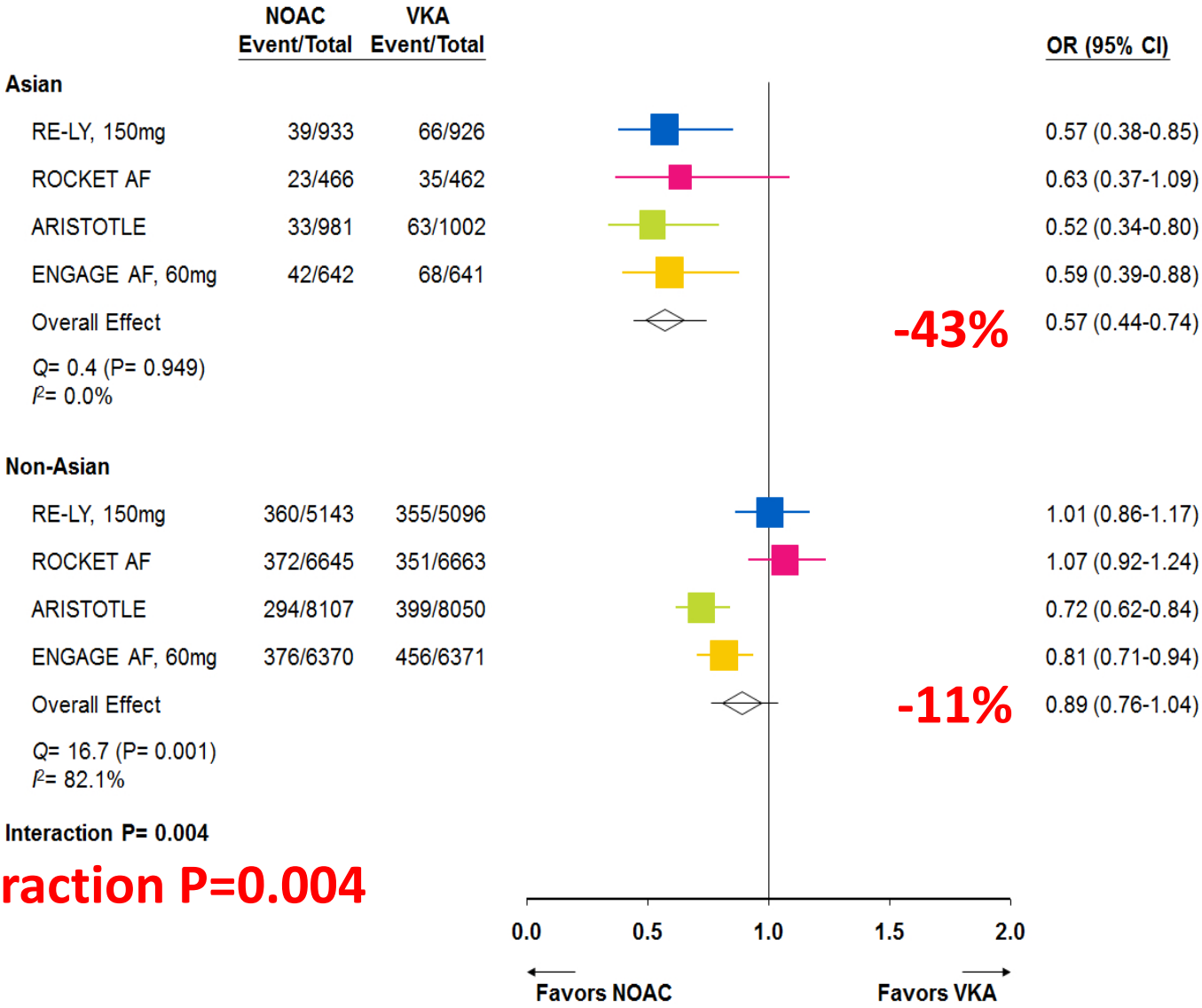
Stroke and systemic embolism



Interaction P=0.045

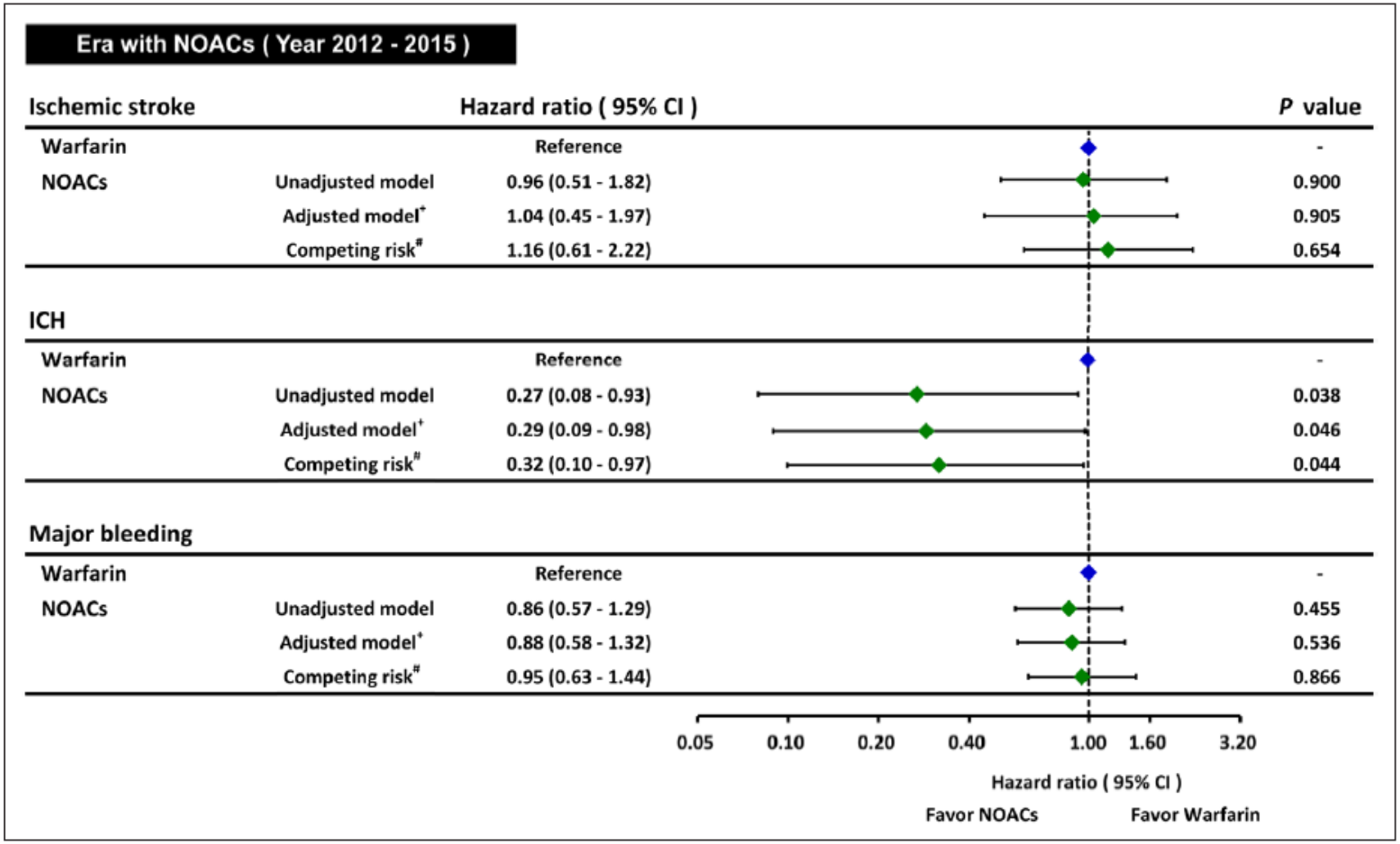
Wang, Lip, Lin, and Chiang, Stroke. 2015 Sep;46(9):2555-61

Major bleeding



Interaction P=0.004

Wang, Lip, Lin, and Chiang, Stroke. 2015 Sep;46(9):2555-61



Circulation. 2018;138:37

Efficacy and Safety Endpoints of NOACs in Asians

	Stroke/ SEE	Ischemic stroke	Hemorrhage stroke	MI	All-cause death	CV death	Major bleeding	Intracranial hemorrhage	GI bleeding	Bleeding of any cause
Dabigatran[a] 150 mg	V	V	V			NR	V	V		V
Dabigatran[a] 110 mg			V			NR	V	V		V
Rivaroxaban								V	NR	
Apixaban			V			NR	V	V	NR	V
Edoxaban 60 mg			V		V	V	V	V		V
Edoxaban 30 mg		X	V				V	V		V

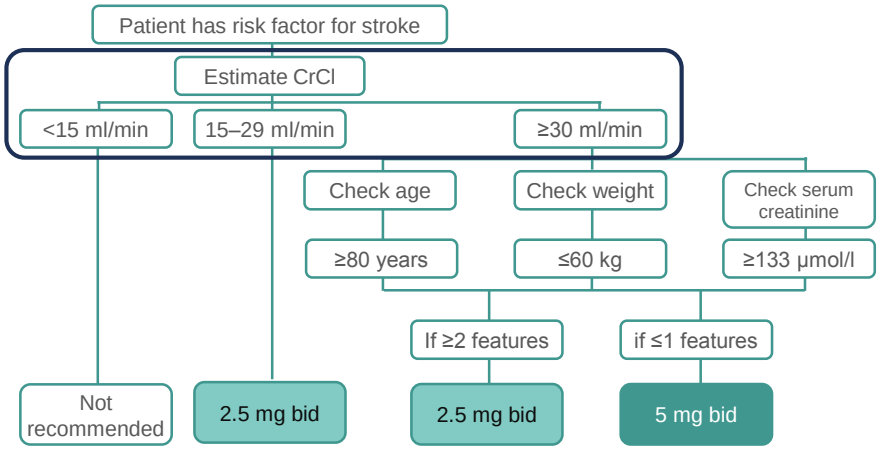
GI = gastrointestinal; NOACs = non-vitamin K antagonist oral anticoagulants; NR = not reported; SEE = systemic embolization events;
V = p value less than 0.05 when compared with warfarin.
[a] China, Japan, South Korea, Taiwan, Hong Kong, Philippines, Singapore, Malaysia, Thailand, India.

1. **Standard-dose NOACs** should be recommended as first choice for the stroke prevention in Asians.
2. **Low-dose NOACs** should be recommended as therapeutic choice when standard-dose NOACs are not appropriate, such as in patients with age 75 years or in those patients with moderate to severe chronic kidney disease.

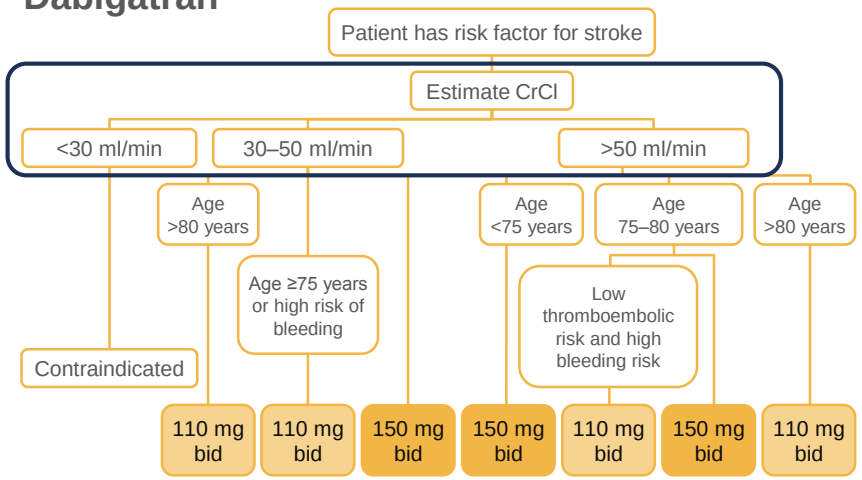
Chiang et al. J Formos Med Assoc. **2016** Nov;115(11):893-952

Dose Adjustments in NVAF Patients with ≥1 Risk Factors for Stroke/Systemic Embolism

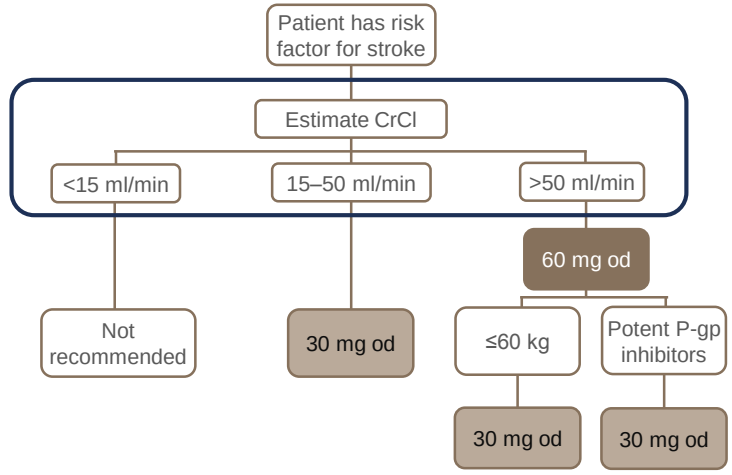
Apixaban[1]



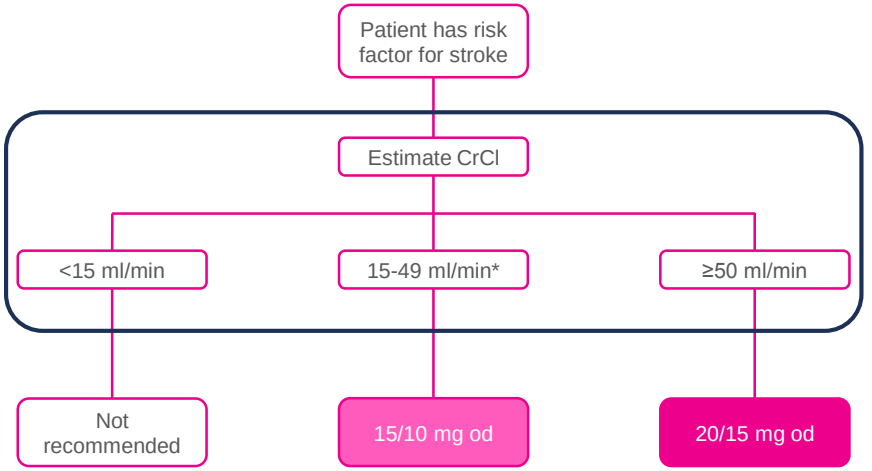
Dabigatran[2]



Edoxaban[3]



Rivaroxaban[4]



1. Apixaban SmPC; 2. Dabigatran SmPC; 3. Edoxaban SmPC; 4. Rivaroxaban SmPC

	ROCKET AF				ARISTOTLE				ENGAGE AF-TIMI 48			
	Eligible for reduced-dose NOAC		Eligible for full-dose NOAC		Eligible for reduced-dose NOAC		Eligible for full-dose NOAC		Eligible for reduced-dose NOAC		Eligible for full-dose NOAC	
	Rivaroxaban 15 mg (*n* = 1474)	Warfarin (*n* = 1476)	Rivaroxaban 20 mg (*n* = 5637)	Warfarin (*n* = 5640)	Apixaban 2.5 mg (*n* = 428)	Warfarin (*n* = 403)	Apixaban 5 mg (*n* = 8692)	Warfarin (*n* = 8678)	Edoxaban 30 mg (*n* = 1784)	Warfarin (*n* = 1787)	Edoxaban 60 mg (*n* = 5251)	Warfarin (*n* = 5249)
Age (years)	79	79	71	71	83	83	70	69	77	77	70	70
Female sex	55	56	36	35	51	56	35	34	55	55	32	32
Body weight (kg)	NR	NR	NR	NR	58	58	83	83	65	65	86	86
CrCl (mL/min)	42	42	75	74	37	38	76	76	46	46	79	79
CHADS2 score	3.7	3.7	3.4	3.4	2.8	2.8	2.1	2.1	3.0	3.0	2.8	2.8
Prior stroke or systemic embolism	50	49	56	56	19	16	12	13	32	32	27	27
Heart failure	66	65	62	62	38	34	35	35	56	56	59	58
Hypertension	92	92	90	90	85	85	87	88	90	91	95	95
Diabetes mellitus	32	33	43	41	18	16	25	25	25	27	39	39
Median TTR	NA	58	NA	58	NA	65	NA	66	NA	66	NA	69

European Heart Journal (2019) 40, 1492–1500

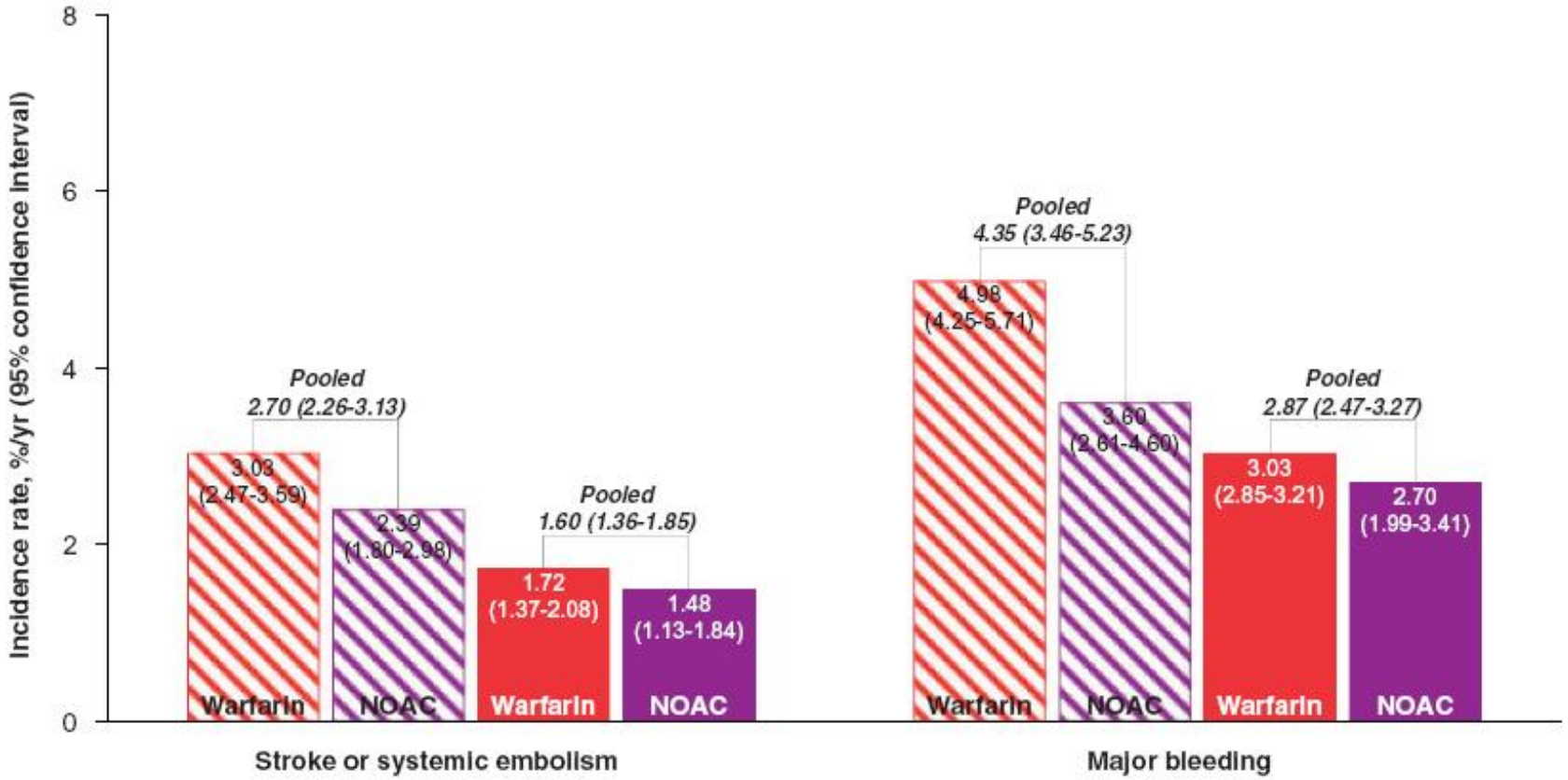
	ROCKET AF				ARISTOTLE				ENGAGE AF-TIMI 48			
	Eligible for reduced-dose NOAC		Eligible for full-dose NOAC		Eligible for reduced-dose NOAC		Eligible for full-dose NOAC		Eligible for reduced-dose NOAC		Eligible for full-dose NOAC	
	Rivaroxaban 15 mg (*n* = 1474)										Edoxaban 60 mg (*n* = 5251)	Warfarin (*n* = 5249)
Age (years)	79										70	70
Female sex	55										32	32
Body weight (kg)	NR										86	86
CrCl (mL/min)	42										79	79
CHADS2 score	3.7										2.8	2.8
Prior stroke or systemic embolism	50										27	27
Heart failure	66	65	62	62	38	34	35	35	56	56	59	58
Hypertension	92	92	90	90	85	85	87	88	90	91	95	95
Diabetes mellitus	32	33	43	41	18	16	25	25	25	27	39	39
Median TTR	NA	58	NA	58	NA	65	NA	66	NA	66	NA	69

Dose Adjustment Group

Older
More CKD
Higher CHADS2 score

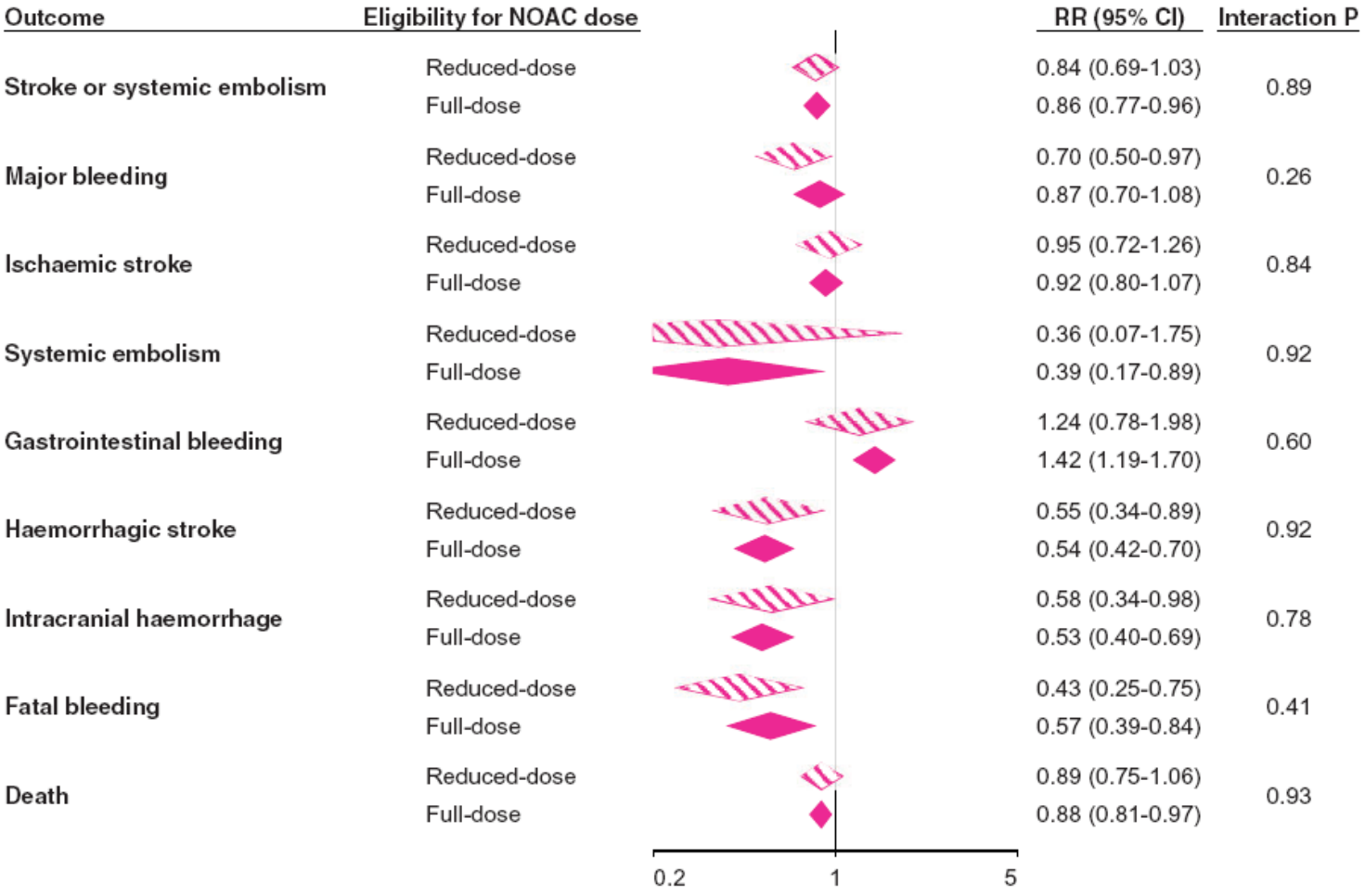
European Heart Journal (2019) 40, 1492–1500

Higher stroke and major bleeding rate in dose reduction group



European Heart Journal (2019) 40, 1492–1500

Comparative performance between reduced-dose and full-dose NOAC relative to warfarin



European Heart Journal (2019) 40, 1492–1500

Factors influencing NOAC dosing regimens

ON-LABEL dosing regimens

Appropriate dose/reduced dose of NOAC depending on one or several factors:

- Renal function

- Age

- Body weight

- Concomitant therapy with strong P-Gp inhibitors

OFF-LABEL dosing regimens

Reasons for giving reduced dose of NOAC when criteria indicate standard dose:

- Physicians perception of frailty in a patient without specific criteria utilized

- Patients with borderline criteria for dose-reduction; physicians more worried about major bleeding than thromboembolic events

- Estimated increased bleeding risk (using bleeding scores)

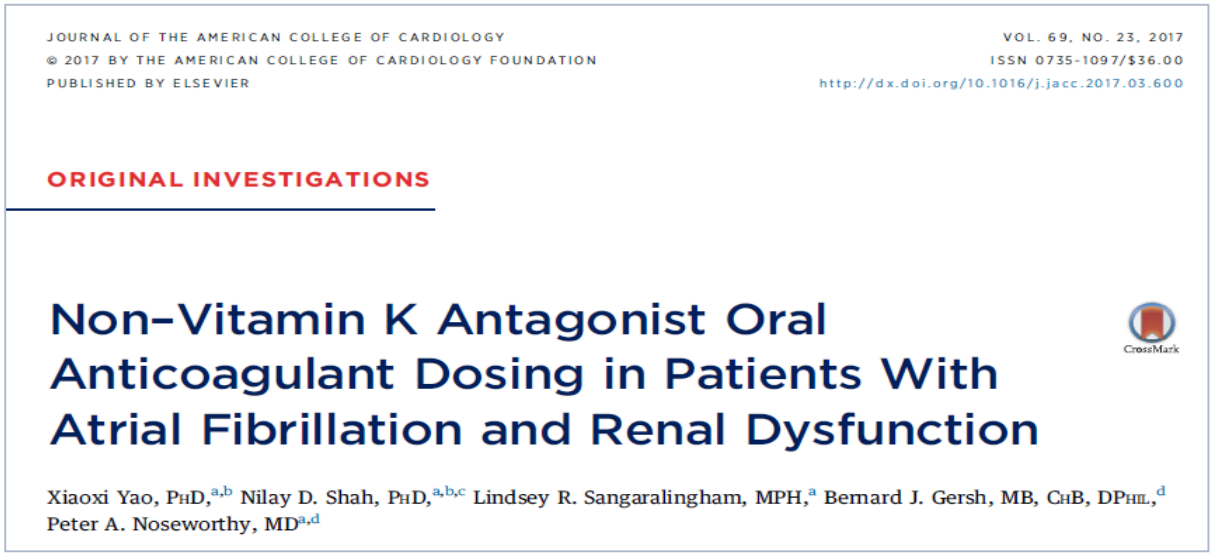
Reasons for giving standard dose of NOAC when criteria indicate reduced dose:

- Progression of renal failure or weight loss (intercurrent diseases)

- Prescription of new drugs/reduced awareness of drug interactions

European Heart Journal (2019) 40, 1501

Inappropriate low dose use of NOAC in real world might not lead to improved outcomes but may be hazardous



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http://dx.doi.org/10.1016/j.jacc.2017.03.600

ORIGINAL INVESTIGATIONS

Non–Vitamin K Antagonist Oral Anticoagulant Dosing in Patients With Atrial Fibrillation and Renal Dysfunction

Xiaoxi Yao, PhD,[a,b] Nilay D. Shah, PhD,[a,b,c] Lindsey R. Sangaralingham, MPH,[a] Bernard J. Gersh, MB, ChB, DPhil,[d] Peter A. Noseworthy, MD[a,d]

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EDITORIAL COMMENT

When Less Is Not More*

Sean D. Pokorney, MD, MBA, Eric D. Peterson, MD, MPH, Jonathan P. Piccini, MD, MHS

MAYO CLINIC

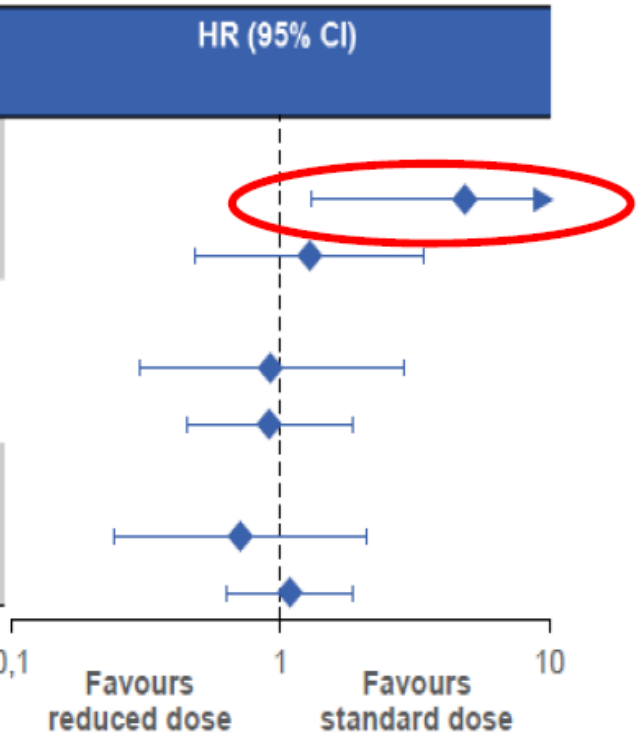
- IF=19.896
- independent funding by Mayo Clinic
- No industry funding

J Am Coll Cardiol 2017;69:2779–90, J Am Coll Cardiol 2017;69:2791–93

Inappropriate Reduced Dose of Apixaban Might Significantly Increase the Risk of Stroke/SE

- Retrospective claims database analysis 13,392 patients without renal indication for dose reduction
- Median follow-up: 4.0 months (IQR 1.0–9.6 months)

	Reduced dose	Standard dose	HR (95% CI)	*p*-value
	Event rate per 100 person-years			
Apixaban	N=550	N=550		
Stroke/SE	2.57	0.54	4.87 (1.30–18.26)	0.02
Major bleeding	6.01	4.64	1.29 (0.48–3.42)	0.61
Dabigatran	N=412	N=412		
Stroke/SE	1.64	1.75	0.92 (0.30–2.87)	0.89
Major bleeding	4.99	5.54	0.91 (0.45–1.85)	0.80
Rivaroxaban	N=815	N=815		
Stroke/SE	1.23	1.65	0.71 (0.24–2.09)	0.54
Major bleeding	5.42	4.90	1.09 (0.63–1.87)	0.76



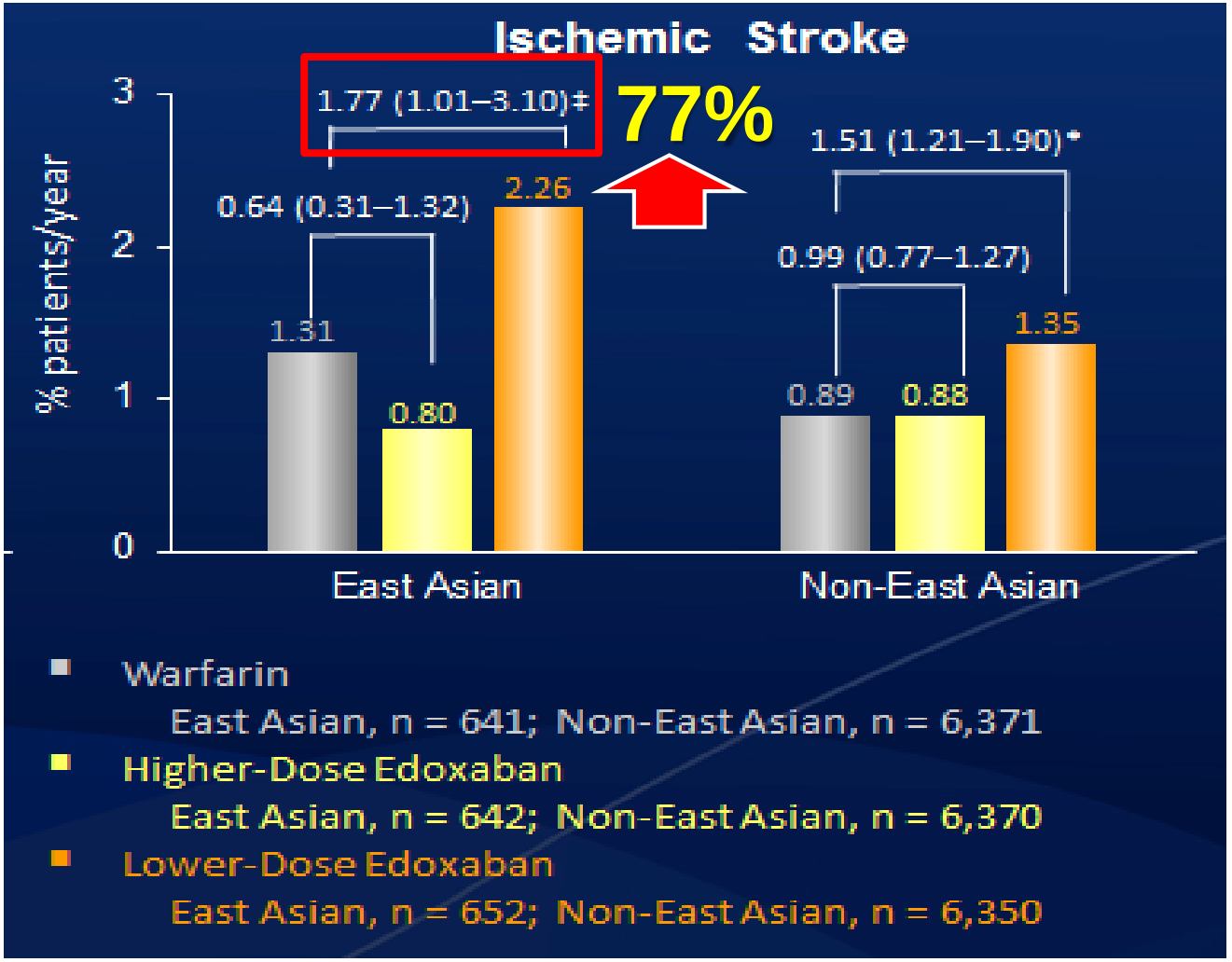
Results are not intended for direct comparison between NOACs

Inappropriate reduced dose of apixaban lead to dramatic stroke/SE increase

Propensity score matching used to account for differences in baseline characteristics between patients receiving reduced and standard doses

Yao X *et al, J Am Coll Cardiol* 2017;69:2779–2790

Lower dose Edoxaban significantly increases 77% ischemic stroke in east Asian population



Text indicates hazard ratio for edoxaban dose vs warfarin and 95% confidence intervals. mITT = modified intent-to-treat. *$P < 0.001$, †$P \leq 0.01$, #$P = 0.03$; ‡$P = 0.05$.

Yamashita T, et al. *Circ J*. 2016; 80(4):860-9.

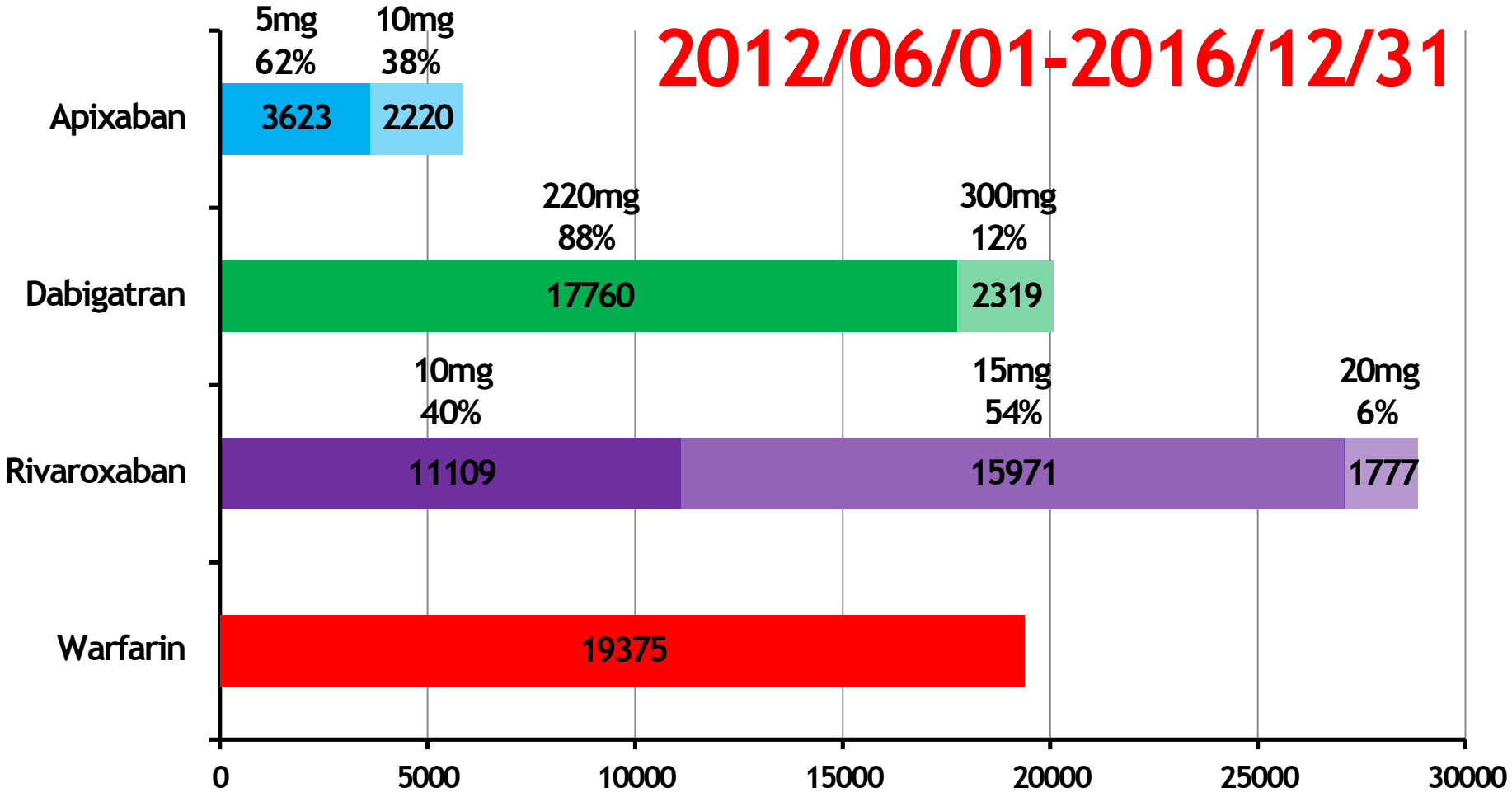
Consistent protection between Japanese clinical trials and the real world in elderly & renal impaired patients

	XAPASS		J-ROCKET AF	
	Major bleeding	ICH	Major bleeding	ICH
Overall (%/patient-years, n/N)	1.02 (141/9,762)	0.43 (60/9,762)	3.00 (26/639)	0.65 (5/639)
Elderly (Age ≥75) (%/patient-years, n/N)	1.34 (88/4,749)	0.56 (37/4,749)	5.01 (16/252)	1.47 (4/252)
Renal impairment (CrCl 30-49mL/min) (%/patient-years, n/N)	1.78 (49/2,038)	0.65 (18/2,038)	5.09 (8/141)	1.32 (2/141)
Prior ischemic stroke/TIA/SE (%/patient-years, n/N)	1.76 (51/2,204)	0.83 (24/2,204)	2.40 (13/408)	0.62 (3/408)

Hori M. et al: Circ J 2012;76:2104–2111, Hori M. et al: Circ J 2014;78:1349-1356, Hori M. et al: Circ J 2013; 77:632-638, Tanahashi N. et al: JSCD 2013; 22:1317-1325

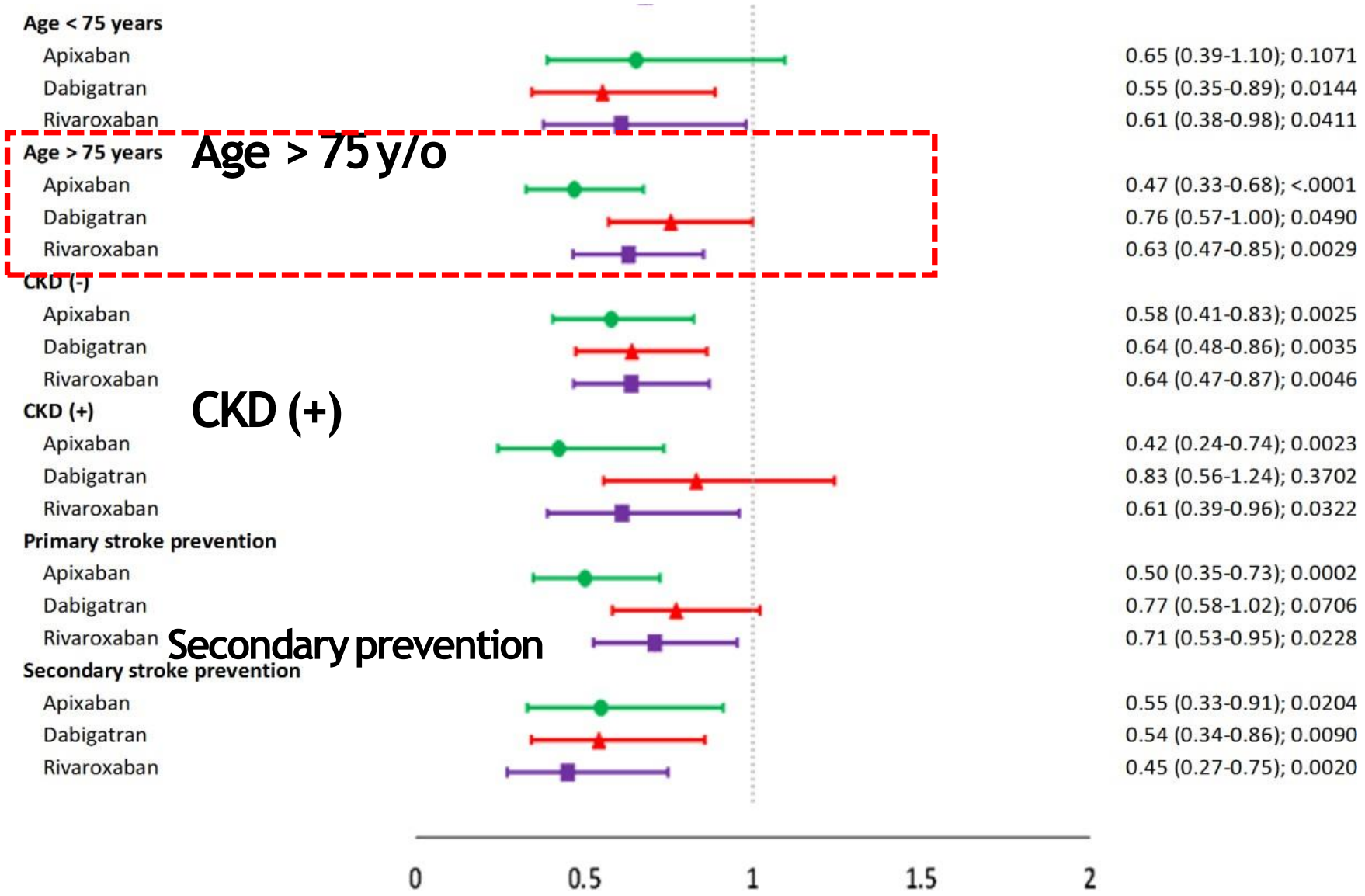
NOAC used in Taiwan

The largest Asian-specific NOAC Cohort



Yi-Hsin Chan, Lai-Chu See and Chi-Tai Kuo. JAHA. 2018;7:e008150

The safety (all major bleeding) of NOACs persisted among high-risk subgroups in Taiwan's real world practice

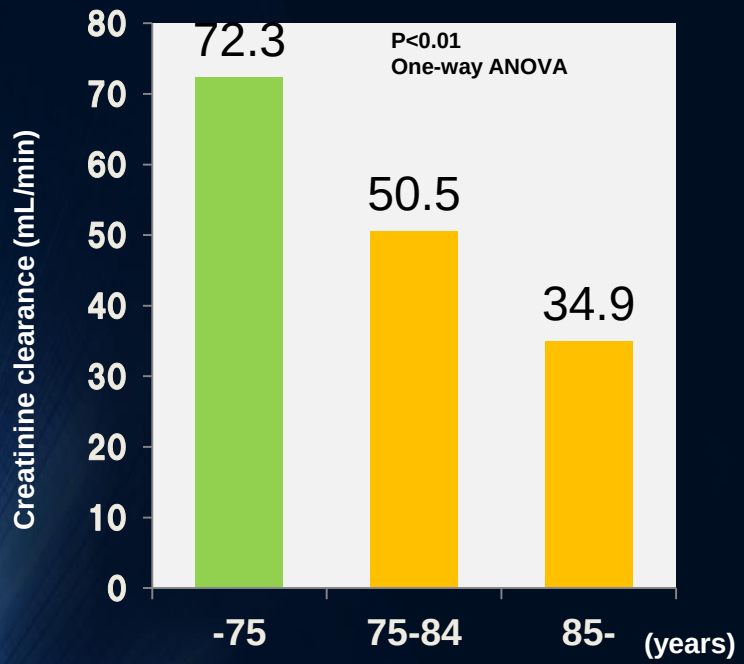


Yi-Hsin Chan, Lai-Chu See and Chi-Tai Kuo. JAHA. 2018;7:e008150

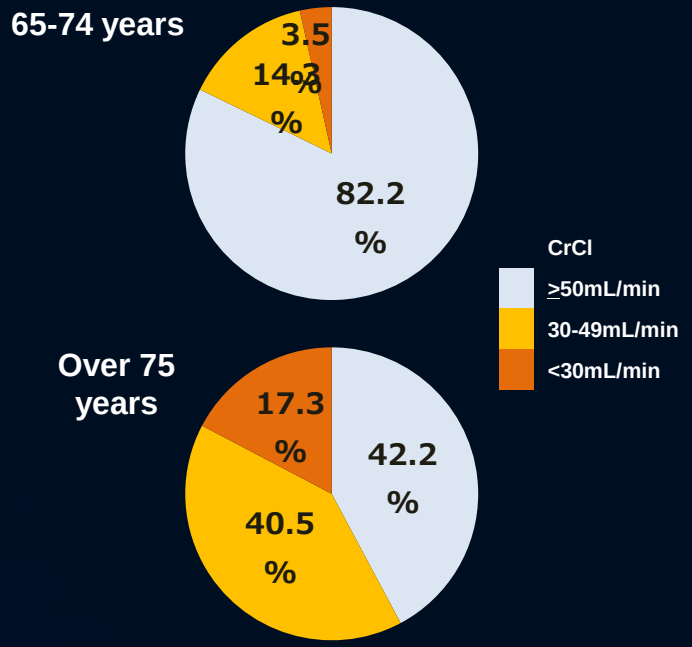
Relationship Between Age and Renal Function in AF Patients

Fushimi AF Registry

Relation between Age Category and Mean CrCl[1)]



Distribution of Age Category and CrCl[2)]



➢In AF patients, with aging, renal function is getting worse.

1) Yamashita Y et al, Chest 2016; 149: 401-12, 2) Abe M et al, Am J Cardiol 2017; 119: 1229-37

Patients with AF and CKD: stroke & bleeding risk

- Danish national registries data, 1997–2008
  - 132,372 patients included, 3587 patients (2.7%) with non-end-stage CKD*

Risk comparison for AF patients with non-end-stage CKD vs without CKD

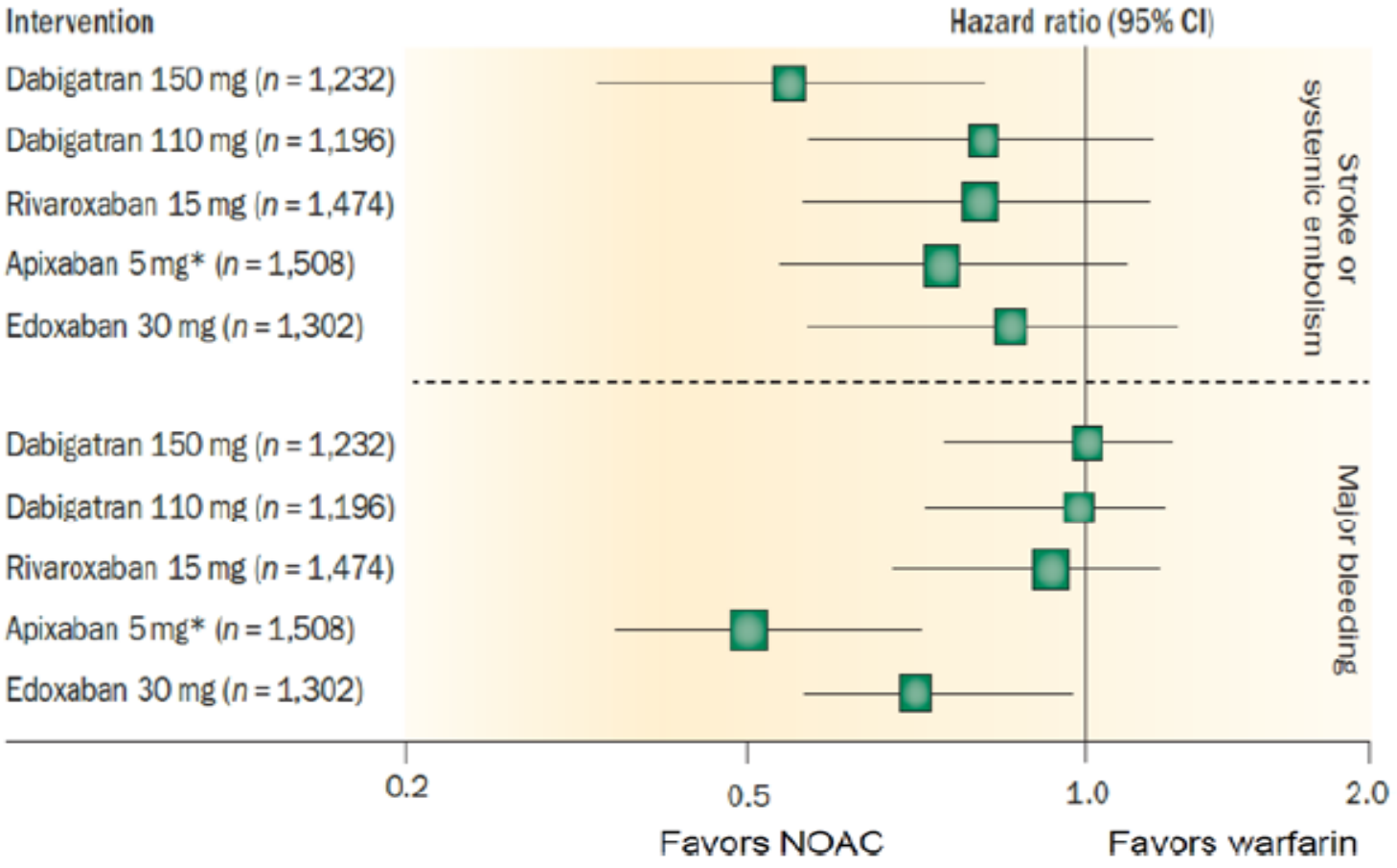
Stroke risk:	1.49 (CI: 1.38–1.59; $p<0.001$)
Bleeding risk:[#]	2.24 (CI 2.10–2.38; $p<0.001$)

AF patients with CKD have significantly higher bleeding and stroke rate

*Of the patients with non-end-stage CKD, 1778/3587 (50%) received antithrombotic medication at baseline
[#]Bleeding risk was assessed using the HAS-BLED score, which reflects the risk of major bleeding among patients with AF who are receiving anticoagulant therapy
AF=Atrial fibrillation; CI=Confidence interval; CKD=Chronic kidney disease.

Olesen JB *et al, N Engl J Med* 2012;367:625–35.

Similar benefit of NOAC in CKD group



Circulation. **2016;133:1512**

Pharmacokinetic Characteristics of NOACs

	Apixaban	Dabigatran	Edoxaban	Rivaroxaban
Target	Factor Xa	Thrombin	Factor Xa	Factor Xa
Bioavailability, %	66	6.5	50	80
Prodrug	No	Yes	No	No
Half-life, h	8–13	12–14	9–11	7–13
Renal clearance, %	25	80	35	66; half as inactive drug

NOAC indicates novel oral anticoagulant.

Circulation. **2016;133:1512**

US FDA Dose Recommendations of NOACs for Nonvalvular AF and CKD

eCrCl, mL/min*	Apixaban†	Dabigatran	Edoxaban‡	Rivaroxaban
>90	5 or 2.5 mg twice daily	150 mg twice daily	60 mg once daily	20 mg once daily with evening meal
51–90	5 or 2.5 mg twice daily	150 mg twice daily	60 mg once daily	20 mg once daily with evening meal
31–50	5 or 2.5 mg twice daily	150 mg twice daily	30 mg once daily	15 mg once daily with evening meal
15–30	5 or 2.5 mg twice daily	75 mg twice daily	30 mg once daily	15 mg once daily with evening meal
<15 not on dialysis	5 or 2.5 mg twice daily	Not recommended	Not recommended	Not recommended
<15 on dialysis	5 or 2.5 mg twice daily	Not recommended	Not recommended	Not recommended

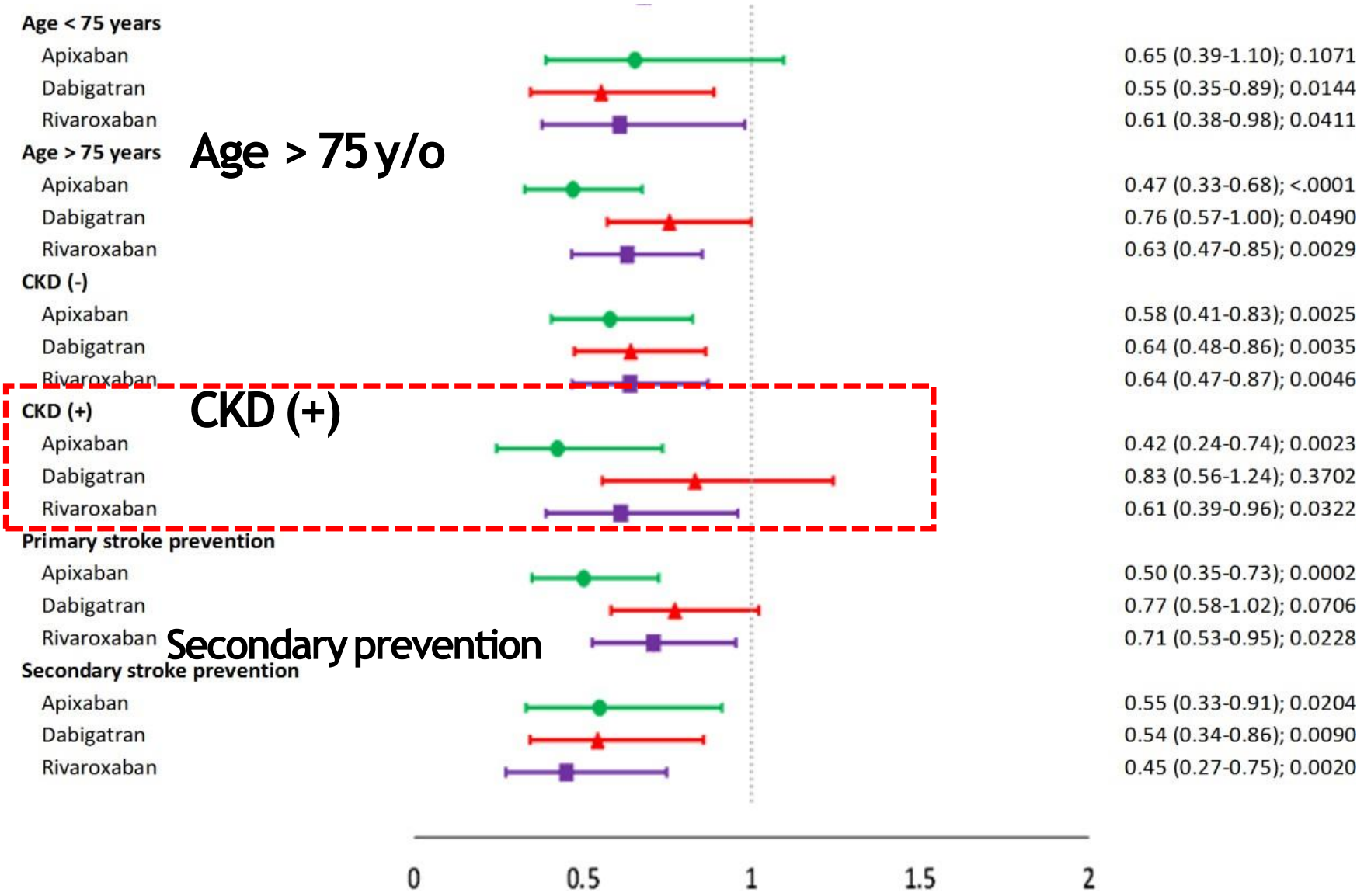
Circulation. **2016;133:1512**

Apixaban vs Warfarin in ESRD

Outcome	Overall	Apixaban	Warfarin	Hazard Ratio (95% CI)	*P* Value
Stroke/systemic embolism					
No. of patients	9404	2351	7053	0.88 (0.69–1.12)	0.29
No. of events	454	81	373		
Event rate per 100 PY	11.9	12.4	11.8		
Major bleeding					
No. of patients	9404	2351	7053	0.72 (0.59–0.87)	<0.001
No. of events	844	129	715		
Event rate per 100 PY	22.3	19.7	22.9		
Gastrointestinal bleeding					
No. of patients	9404	2351	7053	0.86 (0.72–1.02)	0.09
No. of events	865	155	710		
Event rate per 100 PY	23.4	23.8	23.4		
Intracranial bleeding					
No. of patients	9400	2350	7050	0.79 (0.49–1.26)	0.32
No. of events	132	21	111		
Event rate per 100 PY	3.4	3.1	3.5		
Death					
No. of patients	9404	2351	7053	0.85 (0.71–1.01)	0.06
No. of events	912	159	753		
Event rate per 100 PY	24.7	23.7	24.9		

Circulation. 2018;138:1519

The safety (all major bleeding) of NOACs persisted among high–risk subgroups in Taiwan's real world practice



Yi-Hsin Chan, Lai-Chu See and Chi-Tai Kuo. JAHA. 2018;7:e008150

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Prior ischemic stroke/TIA/SE (%/patient-years, n/N)	1.76 (51/2,204)	0.83 (24/2,204)	2.40 (13/408)	0.62 (3/408)

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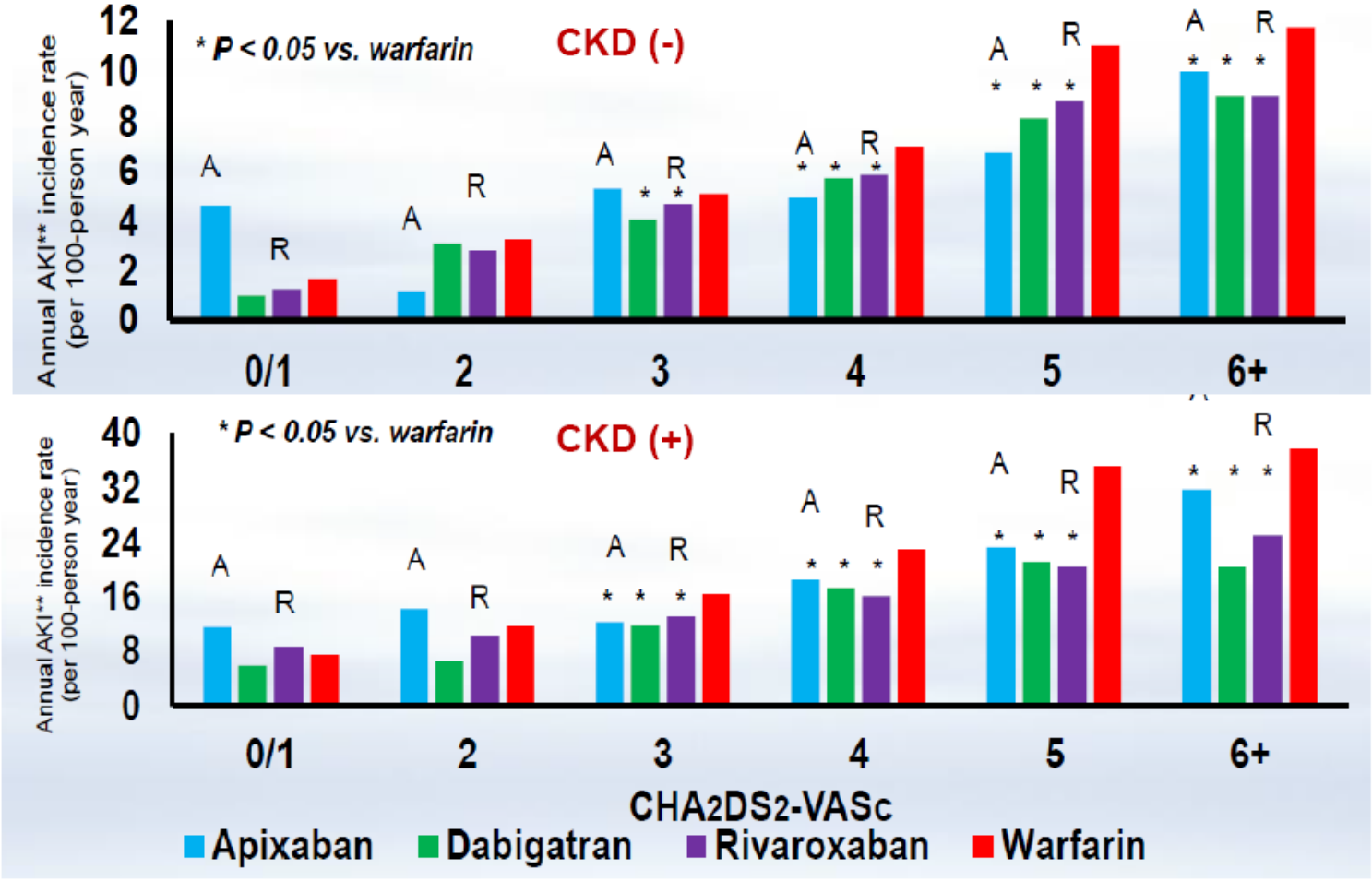
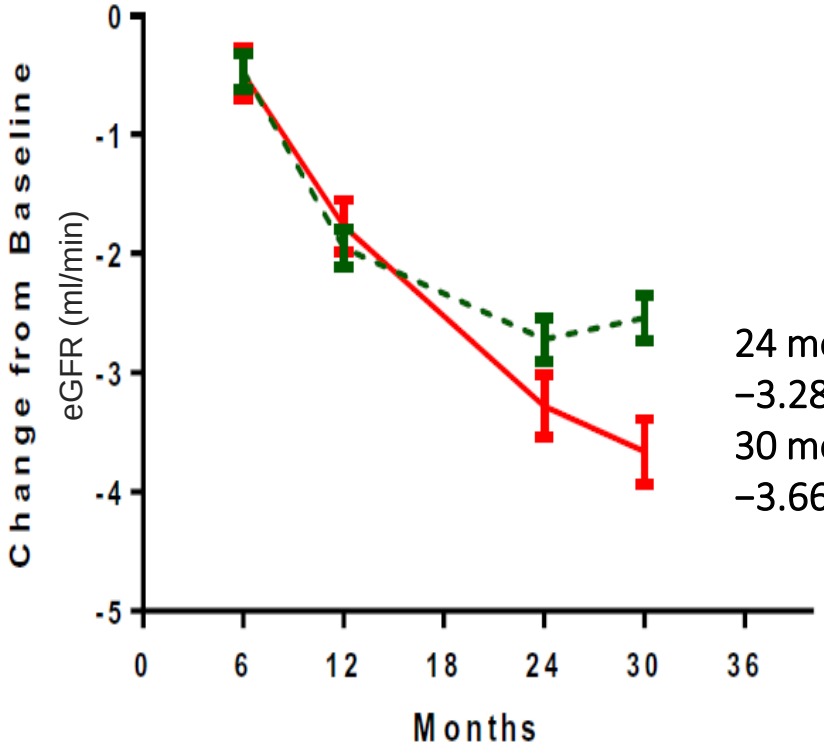
Less AKI in NOAC treatment Group



IJC. 2018;261:78

Changes in Renal function in NOACs

- Patients treated with DOACs were at lower risk for worsening renal function than were those treated with warfarin, especially after 24 and 30 months.



24 months: DOACs, −2.72; warfarin, −3.28; P = 0.07;
30 months: DOACs, −2.54; warfarin, −3.66; P < 0.01

Thromb Res. 2017 Dec;160:41-50

JACC Journals

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Renal Outcomes in Anticoagulated Patients With Atrial Fibrillation

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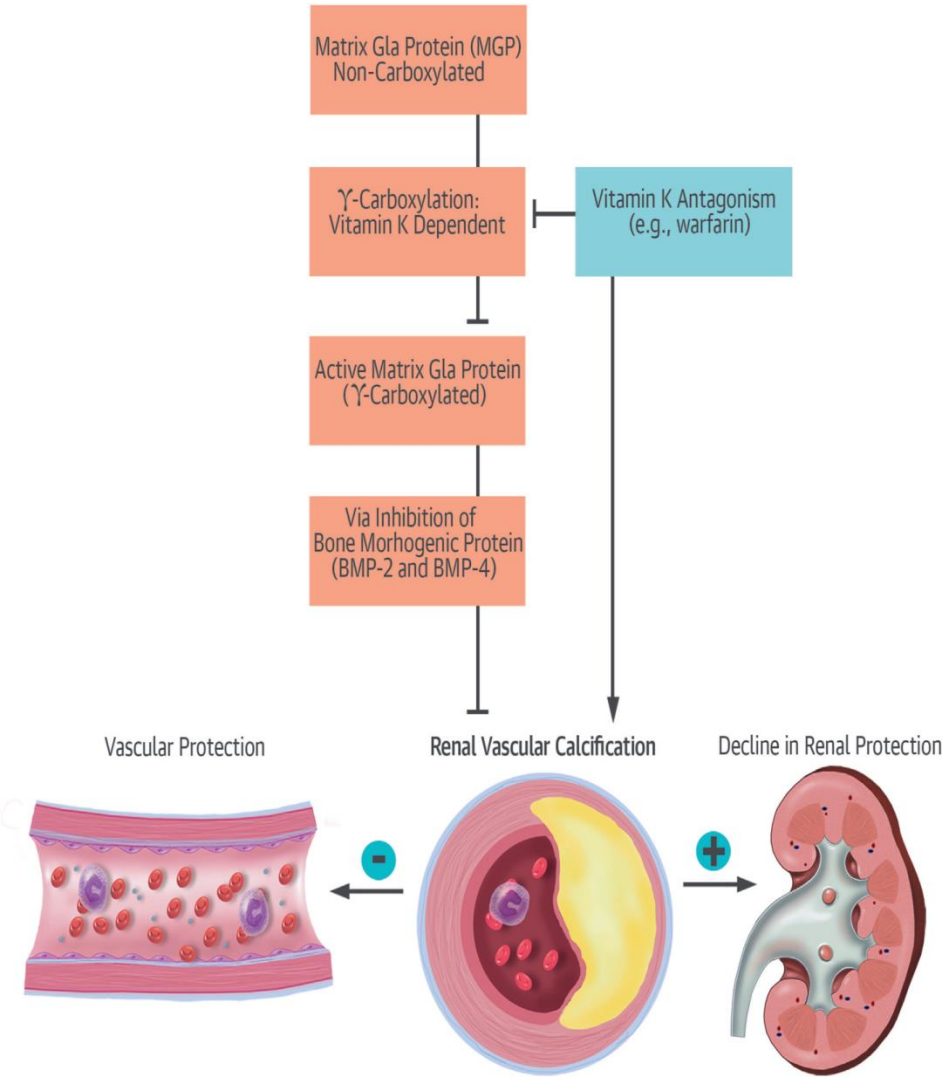
TABLE 3 Number of Events, Event Rates per 100 Person-Years, and Hazard Ratios With 95% CIs

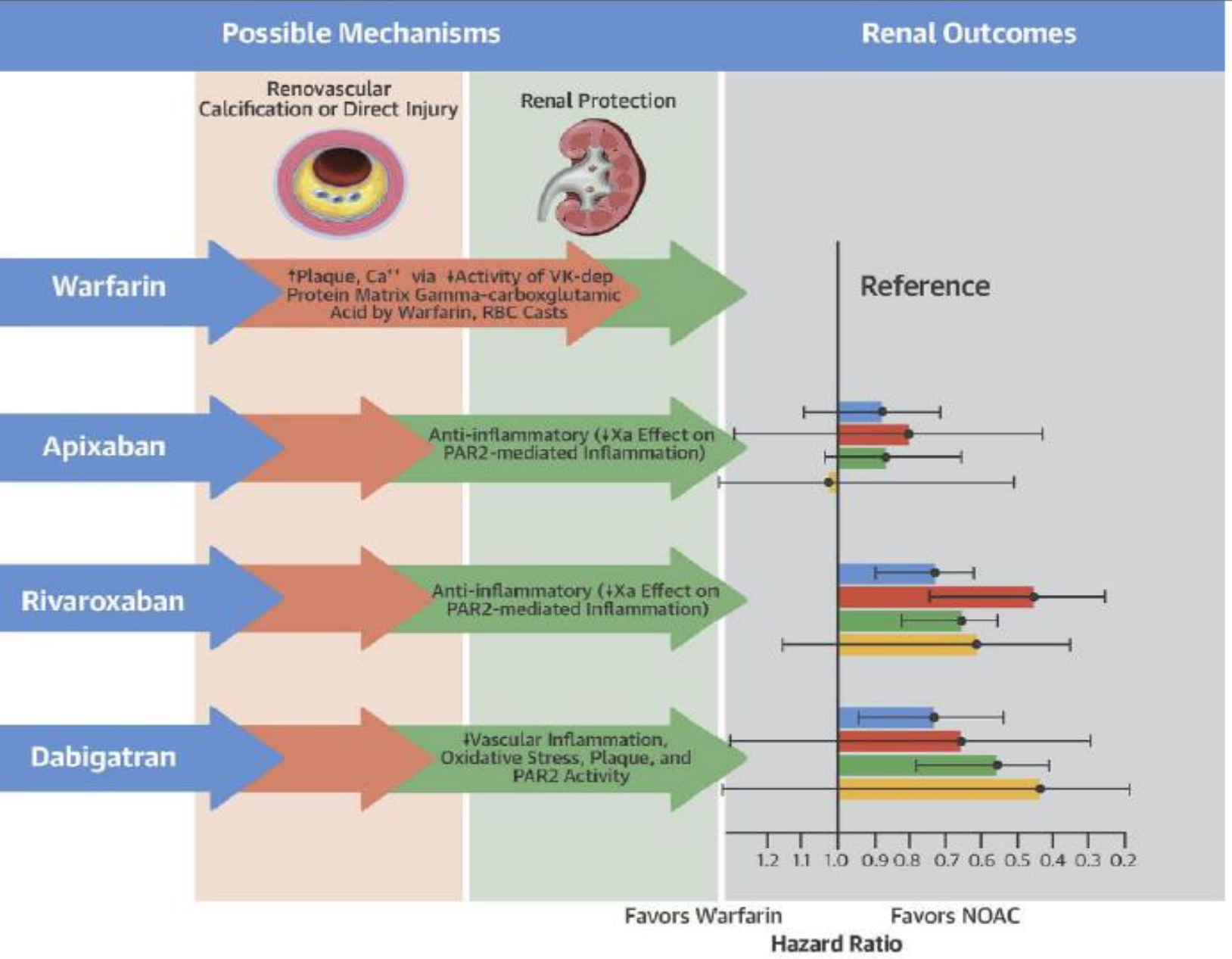
	No. of Events	Crude Event Rate (95% CI)	Weighted Event Rate (95% CI)	Hazard Ratio (95% CI)	p Value for Hazard Ratio
30% decline in eGFR					
Apixaban	166	19.40 (16.66-22.59)	18.31 (14.97-22.60)	0.88 (0.70-1.10)	0.25
Dabigatran	103	10.94 (9.02-13.28)	14.29 (11.24-18.43)	0.72 (0.56-0.93)	0.01
Rivaroxaban	208	14.63 (12.77-16.75)	15.10 (13.06-17.53)	0.73 (0.62-0.87)	<0.001
Warfarin	546	22.61 (20.79-24.59)	20.64 (18.79-22.71)	Reference	Reference
Doubling of creatinine					
Apixaban	20	2.23 (1.44-3.45)	2.54 (1.39-5.14)	0.80 (0.41-1.56)	0.51
Dabigatran	12	1.23 (0.70-2.16)	2.05 (1.03-4.70)	0.64 (0.30-1.34)	0.24
Rivaroxaban	21	1.40 (0.91-2.15)	1.47 (0.96-2.38)	0.46 (0.28-0.75)	<0.01
Warfarin	89	3.43 (2.78-4.22)	3.26 (2.62-4.12)	Reference	Reference
AKI					
Apixaban	131	9.87 (8.32-11.72)	9.38 (7.56-11.77)	0.84 (0.66-1.07)	0.16
Dabigatran	63	4.86 (3.80-6.22)	5.93 (4.36-8.26)	0.55 (0.40-0.77)	<0.001
Rivaroxaban	145	6.87 (5.84-8.09)	7.63 (6.44-9.09)	0.69 (0.57-0.84)	<0.001
Warfarin	441	12.63 (11.51-13.87)	11.15 (10.05-12.39)	Reference	Reference
Kidney failure					
Apixaban	13	0.96 (0.56-1.65)	1.33 (0.61-3.50)	1.02 (0.45-2.31)	0.95
Dabigatran	4	0.30 (0.11-0.80)	0.55 (0.14-3.77)	0.45 (0.13-1.59)	0.21
Rivaroxaban	14	0.64 (0.38-1.09)	0.80 (0.48-1.47)	0.63 (0.35-1.15)	0.13
Warfarin	58	1.58 (1.22-2.04)	1.28 (0.98-1.69)	Reference	Reference

Yao et al. JAm Coll Cardiol 2017;70:2621–32

Warfarin-Related Nephropathy (WRN)



J Am Coll Cardiol. 2015; 65(23)：2481-93



Yao, X. et al. J Am Coll Cardiol. 2017;70(21):2621-32.

2019 AHA/ACC/HRS Guidelines

4.2. Anticoagulant Options (Modified From Section 4.2., "Antithrombotic Options," in the 2014 AF Guideline)

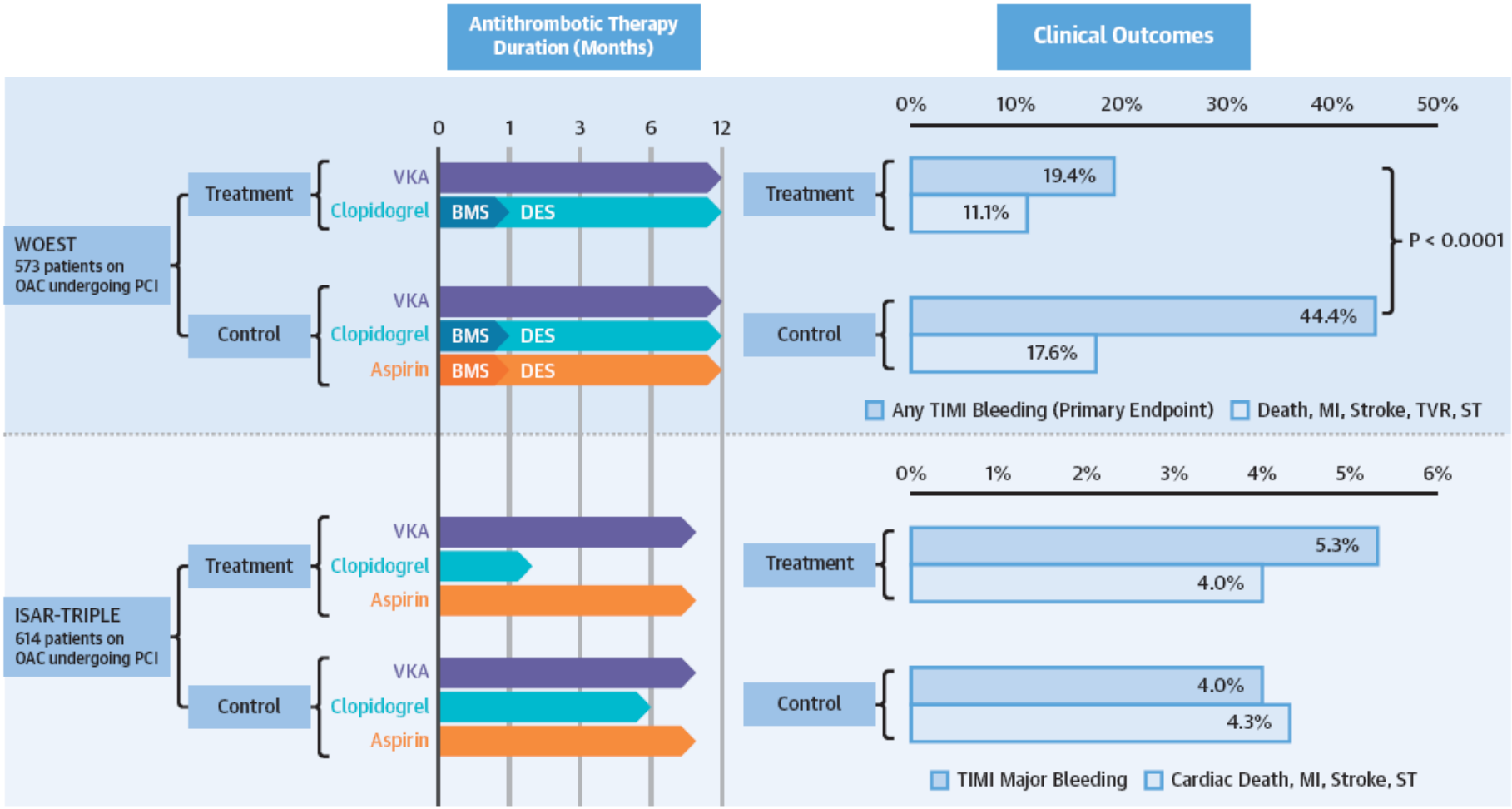
4.2.2.2. Non–Vitamin K Oral Anticoagulants (Modified From Section 4.2.2.2., "New Target-Specific Oral Anticoagulants," in the 2014 AF Guideline)

Over time, NOACs (particularly dabigatran and **rivaroxaban**) may be associated with lower risks of adverse renal outcomes than warfarin in patients with AF (S4.2.2.2-16) .

- Yao. J Am Coll Cardiol. 2017;70:2621-32

J Am Coll Cardiol. 2019 Jan 21. pii: S0735-1097(19)30209-8. doi: 10.1016/j.jacc.2019.01.011.

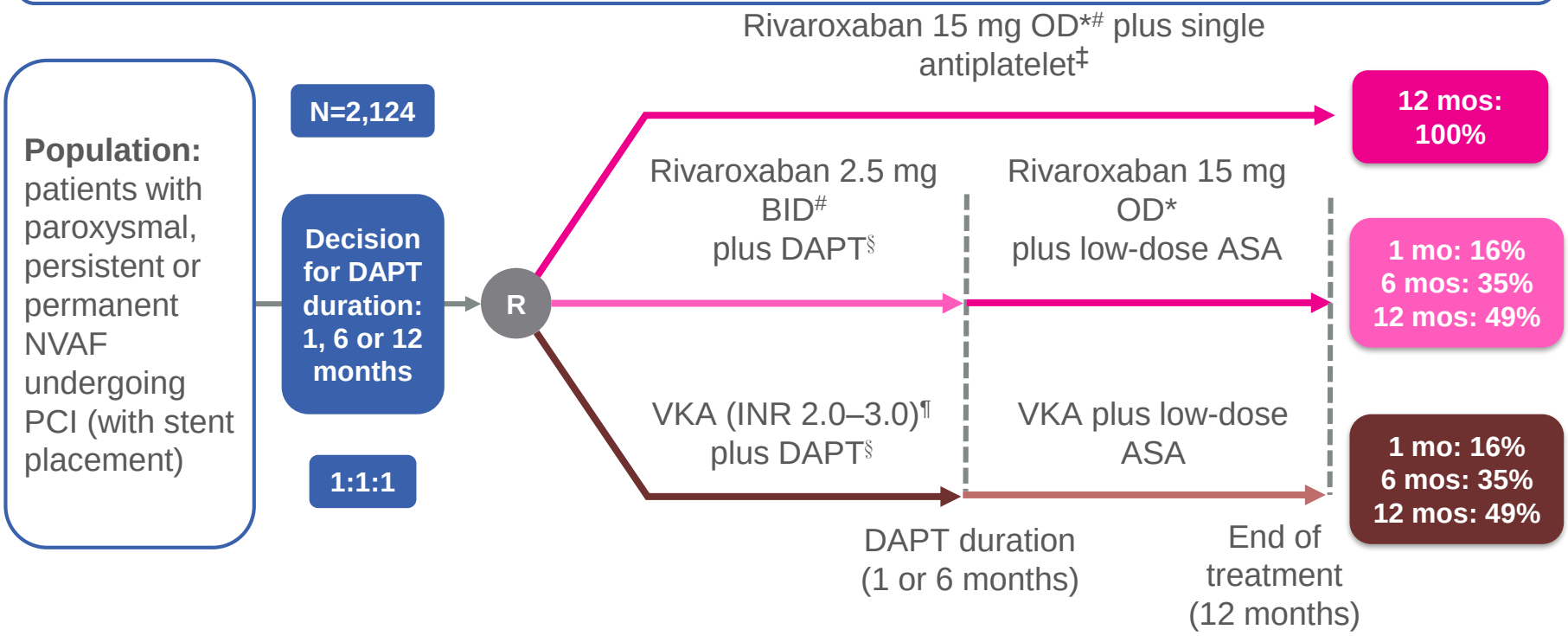
AF with PCI



JACC 2019;74:83

Rivaroxaban is the First & Currently Only NOAC to Provide Data From a Dedicated RCT in AF-PCI

Design: An open-label, randomized, controlled phase IIIb safety study

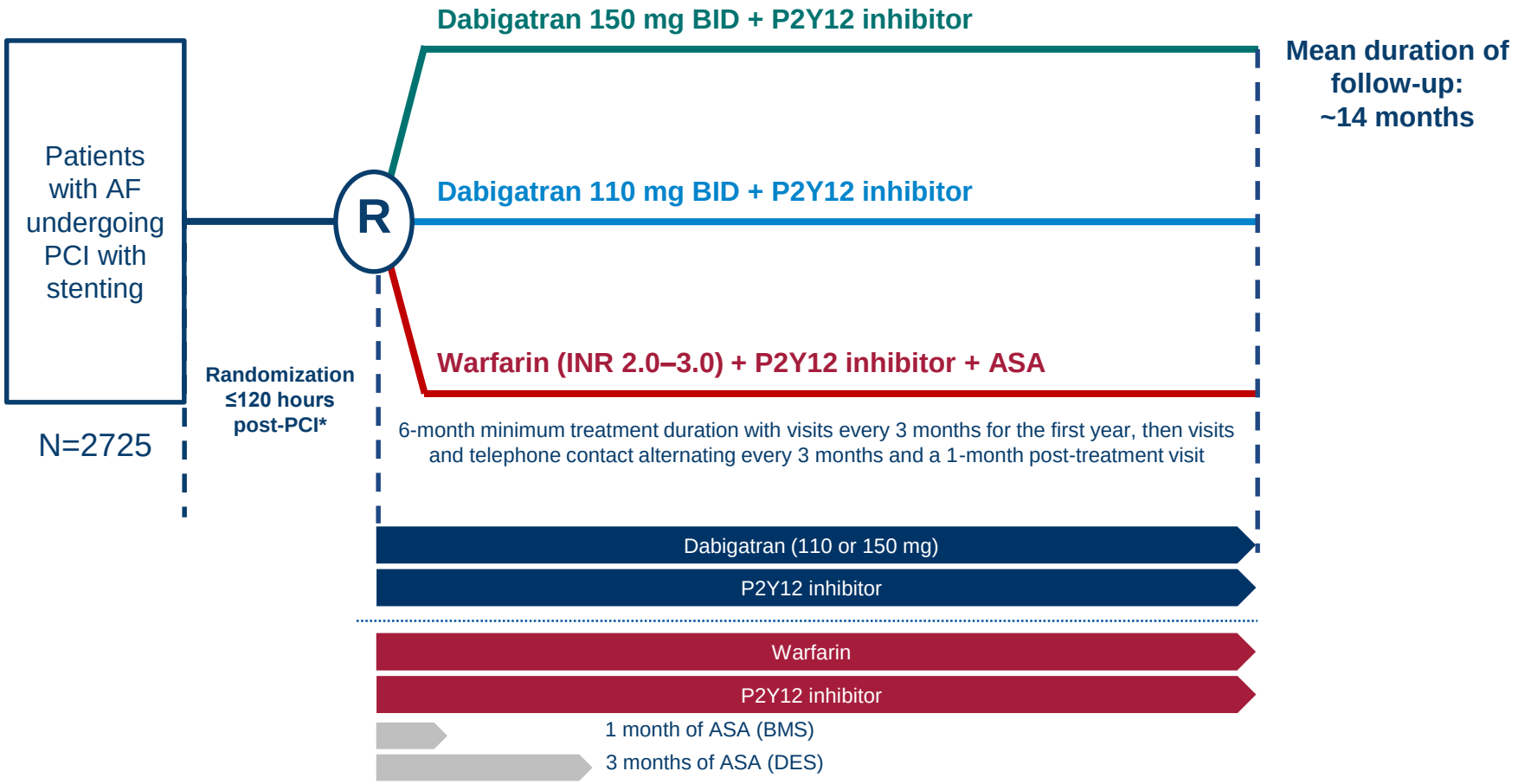


*CrCl 30–49 ml/min: 10 mg OD; #first dose 72–96 hours after sheath removal; ‡clopidogrel (75 mg daily) (alternative use of prasugrel or ticagrelor allowed, but capped at 15%); §ASA (75–100 mg daily) plus clopidogrel (75 mg daily) (alternative use of prasugrel or ticagrelor allowed, but capped at 15%); ¶first dose 12–72 hours after sheath removal

1. Janssen Scientific Affairs, LLC. 2016. https://clinicaltrials.gov/ct2/show/NCT01830543 [accessed 10 Oct 2016];
2. Gibson CM *et al*, *Am Heart J* 2015;169:472–478e5; 3. Gibson CM et al, *New Engl J Med* 2016; doi: 10.1056/NEJMoa1611594

Study Design: Multicenter, randomized, open-label trial following a PROBE design

RE-DUAL PCI
Study in NVAF patients undergoing PCI



***Study drug should be administered 6 hours after sheath removal and no later than ≤120 hrs post-PCI (≤72 hrs is preferable).** PROBE, prospective, randomized, open, blinded end-point; R, randomization; BMS, bare metal stent; DES, drug-eluting stent.

ClinicalTrials.gov: NCT02164864; Cannon et al. Clin Cardiol 2016; Cannon et al. N Engl J Med 2017

Randomization and treatment

Inclusion

- AF (prior, persistent/permanent, paroxysmal)
- Physician decision that oral anticoagulation is indicated
- ACS and/or PCI with planned P2Y12 inhibitor for at least 6 months

Exclusion

- Contraindication to DAPT
- Other reason for warfarin (mechanical valve, moderate/severe mitral stenosis)

Randomize

n = 4,600 patients

Apixaban | **Warfarin**

P2Y12 inhibitor for all patients x 6 months
Aspirin for all on the day of ACS and/or PCI until randomization
Aspirin versus placebo after randomization

Aspirin | **Placebo** | **Aspirin** | **Placebo**

Primary outcome	Key secondary outcome	Other secondary outcomes
Major/CRNM bleeding (through 6 months)	All-cause death, All-cause hospitalization	Death, MI, stroke, stent thrombosis, urgent revascularization, hospitalization

AF, atrial fibrillation; ACS, acute coronary syndrome; PCI, percutaneous coronary intervention; DAPT, dual antiplatelet therapy; CRNM, clinically relevant non-major; MI, myocardial infarction.

Lopes RD, et al. Am Heart J. 2018;200:17-23.

Study Design

PROBE design: Prospective, Randomized, Open label, Blinded endpoint Evaluation in 1500 AF patients with ACS or stable CAD

Inclusion Criteria:
- OAC indication for AF for at least 12 months
- Successful PCI with stent placement (goal of at least 25% ACS)

4 hours – 5 days after sheath removal

RANDOMIZE

- Edoxaban 60 mg/day*
- $P2Y_{12}$ inhibitor** (without aspirin)
- Vitamin K Antagonist***
- $P2Y_{12}$ inhibitor aspirin 1 - 12 months****

12 m.

*Edoxaban dose reduction to 30 mg OD
- if CrCL≤50 ml/min
- BW≤60 kg
- certain P-gp inhibitors

**Clopidogrel 75mg once-daily or if documented need prasugrel 5 or 10mg once-daily or ticagrelor 90mg twice-daily . Predeclared at randomization

*** VKA, target INR 2-3

****aspirin 100mg OD for 1-12 months guided by clinical presentation (ACS or stable CAD), $CHA_2DS\text{-}VASc_2$ and HAS_BLED

Primary outcome:
ISTH major or clinically relevant non-major bleeding

ENTRUST-AFPCI

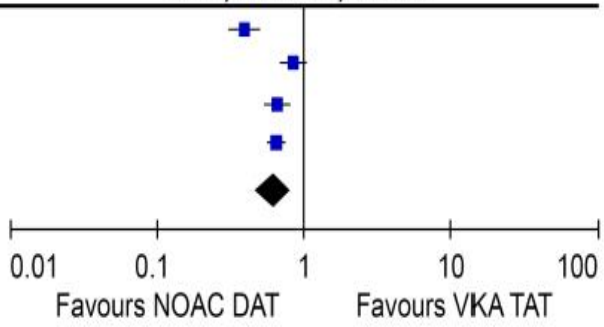
Meta-Analysis:
Comparative NOAC AF PCI trials
ISTH Major or CRNM Bleeding

ISTH Major or Clinically Relevant Non-Major Bleeding

Study or Subgroup	NOAC DAT Events	NOAC DAT Total	VKA TAT Events	VKA TAT Total	Weight	Risk Ratio M–H, Random, 95% CI
AUGUSTUS	84	1143	210	1123	23.7%	0.39 (0.31, 0.50)
ENTRUST AF-PCI	128	751	152	755	24.7%	0.85 (0.68, 1.05)
PIONEER AF-PCI	117	696	178	697	24.8%	0.66 (0.53, 0.81)
RE-DUAL PCI	305	1744	264	981	26.8%	0.65 (0.56, 0.75)
Total (95% CI)		**4334**		**3556**	**100.0%**	**0.62 (0.47, 0.81)**
Total events	634		804			

Heterogeneity: $Tau^2 = 0.07$; $Chi^2 = 22.84$, df = 3 (P <0.0001); $I^2 = 87\%$

Test for overall effect: Z = 3.47 (P = 0.0005)



ENTRUST-AF PCI

Myocardial Infarction and Stent Thrombosis

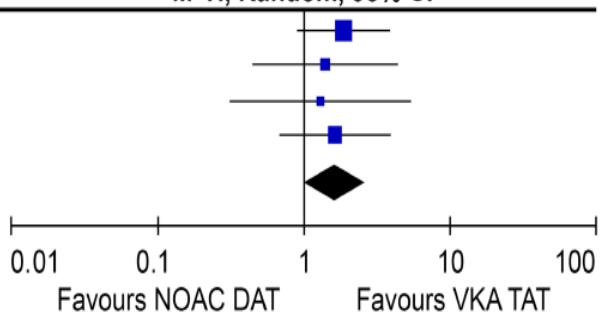
- Endpoints as defined by each of the NOAC AF PCI trials -

Stent Thrombosis

Study or Subgroup	NOAC DAT Events	Total	VKA TAT Events	Total	Weight	Risk Ratio M–H, Random, 95% CI
AUGUSTUS	21	1153	12	1154	40.0%	1.75 (0.87, 3.54)
ENTRUST AF-PCI	8	751	6	755	17.9%	1.34 (0.47, 3.84)
PIONEER AF-PCI	5	694	4	695	11.6%	1.25 (0.34, 4.64)
RE-DUAL PCI	22	1744	8	981	30.6%	1.55 (0.69, 3.46)
Total (95% CI)		**4342**		**3585**	**100.0%**	**1.55 (0.99, 2.41)**
Total events	56		30			

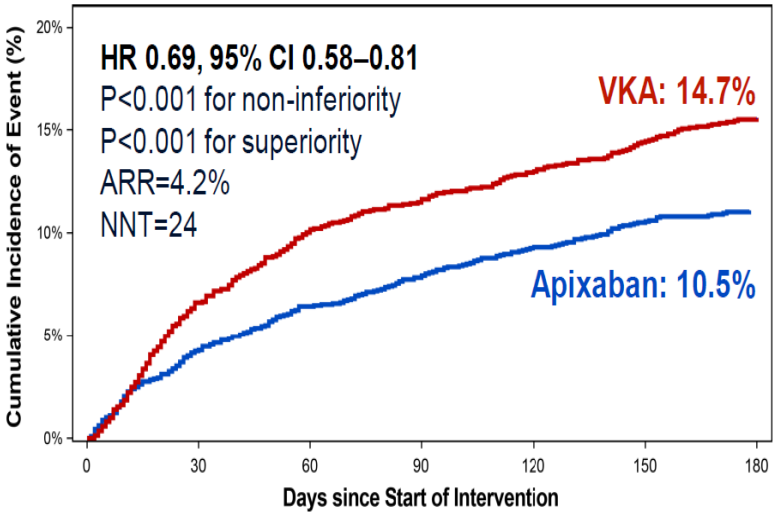
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.29$, df = 3 (P = 0.96); $I^2 = 0\%$

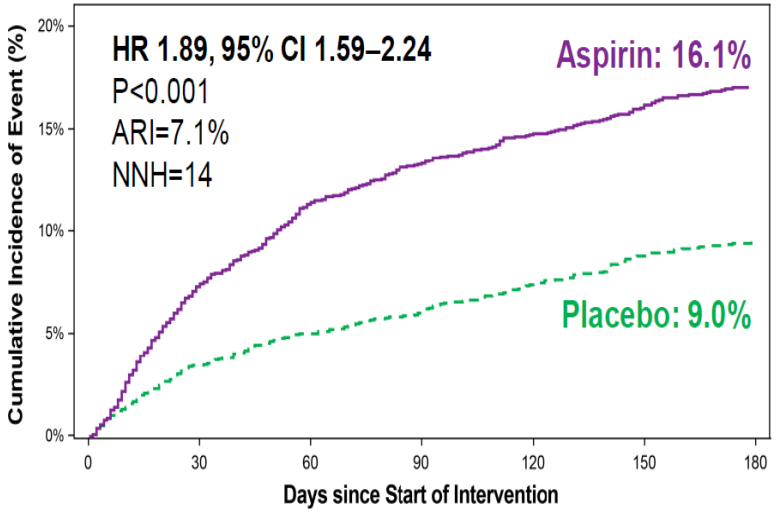
Test for overall effect: Z = 1.92 (P = 0.06)



Major / CRNM Bleeding

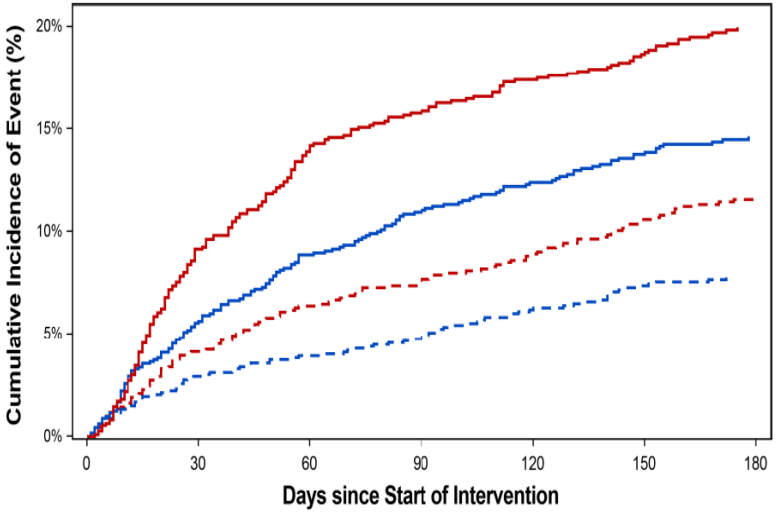
Apixaban vs. VKA and Aspirin vs. Placebo





Triple

Dual



VKA + Aspirin: 18.7%

Apixaban + Aspirin: 13.8%

VKA + Placebo: 10.9%

Apixaban + Placebo: 7.3%

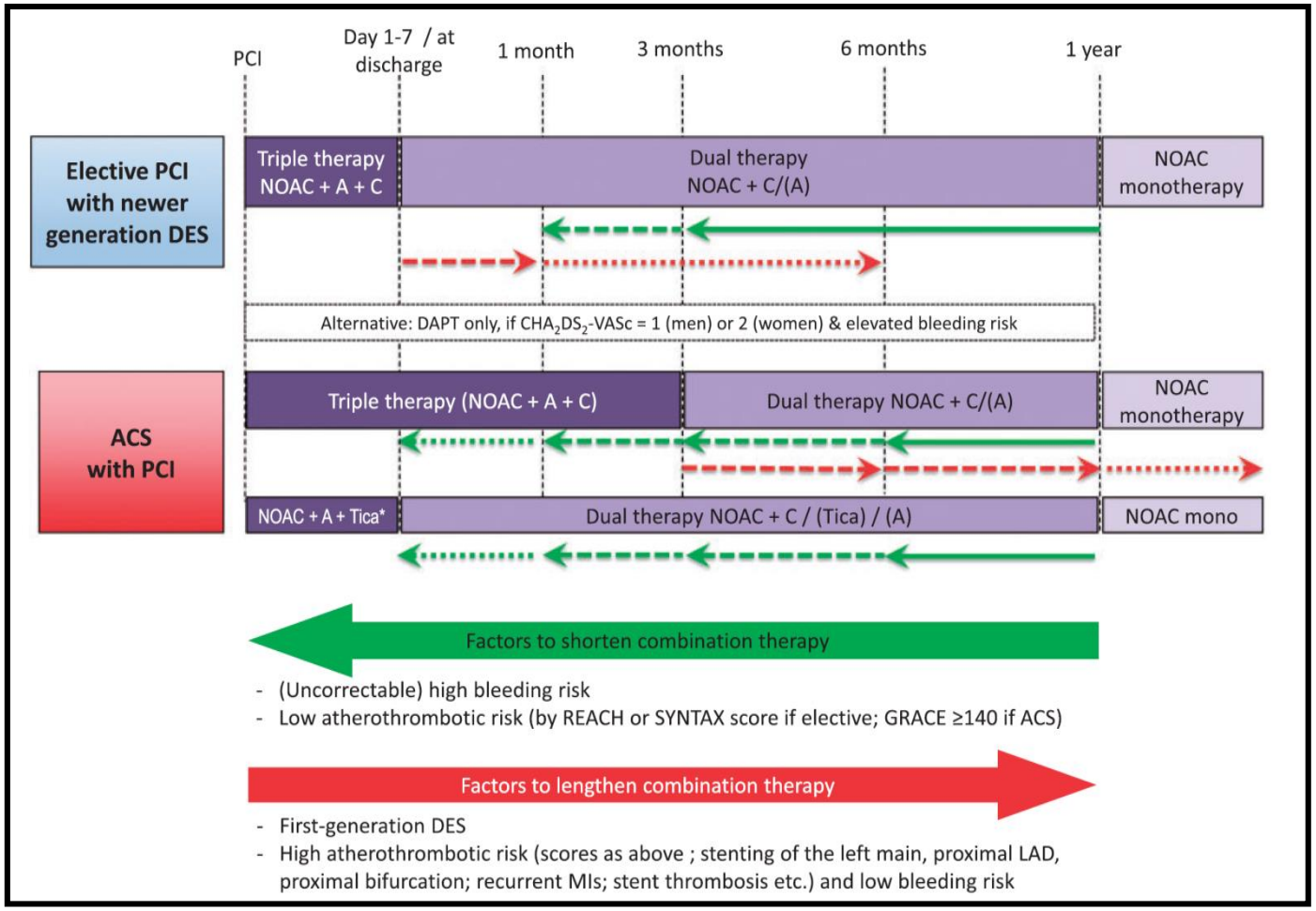
Apixaban + Placebo vs. VKA + Aspirin: ARR=11.4% (NNT=9)

Major / CRNM Bleeding

ARR: absolute risk reduction
NNT: number needed to treat
ARI: absolute risk increase
NNH: number needed to harm

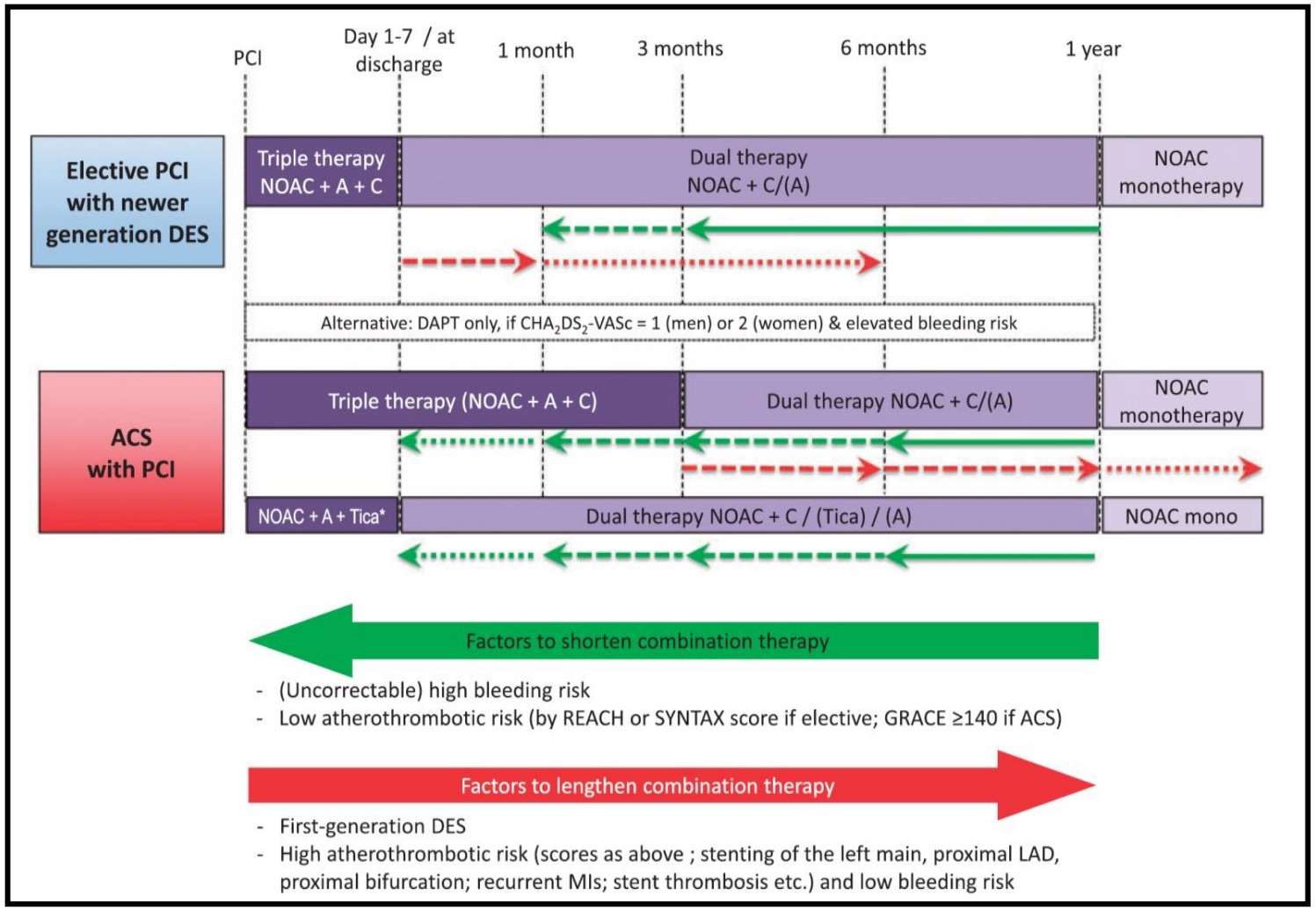
Reference: Antithrombotic Therapy after Acute Coronary Syndrome or PCI in Atrial Fibrillation, Lopes RD, et al, NEJM, March 17, 2019

The 2018 EHRA Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with AF



European Heart Journal (2018) 39, 1330–1393

The 2018 EHRA Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with AF



Dual therapy is acceptable

NOAC rather than warfarin

Standard stroke prevention dose (Rivaroxaban 15/10mg in Asia)

Triple therapy for high risk Apixaban better than warfarin

European Heart Journal (2018) 39, 1330–1393

Atrial Fibrillation and Ischemic events with Rivaroxaban in patiEnts with stable coronary artery disease: AFIRE Study

AFIRE

A multicenter, prospective, randomized, open-label, parallel-group trial [1)]

2200 patients with AF ($CHADS_2 \geq 1$) and stable CAD

Key inclusion criteria

- Underwent PCI or CABG more than 1 year earlier
- Angiographically confirmed CAD (with stenosis of ≥50%) not requiring revascularization

Key exclusion criteria

- A history of stent thrombosis
- Coexisting active tumor
- Poorly controlled hypertension

RANDOMIZE

Rivaroxaban Monotherapy

Rivaroxaban 10 or 15 mg/day [2)*]

*The level of rivaroxaban in blood samples obtained from Japanese patients who were taking rivaroxaban at the 15-mg dose was similar to the level in white patients who were taking the 20-mg dose.

Combination Therapy

Rivaroxaban 10 or 15 mg/day

Single antiplatelet

Aspirin 81 or 100 mg/day,

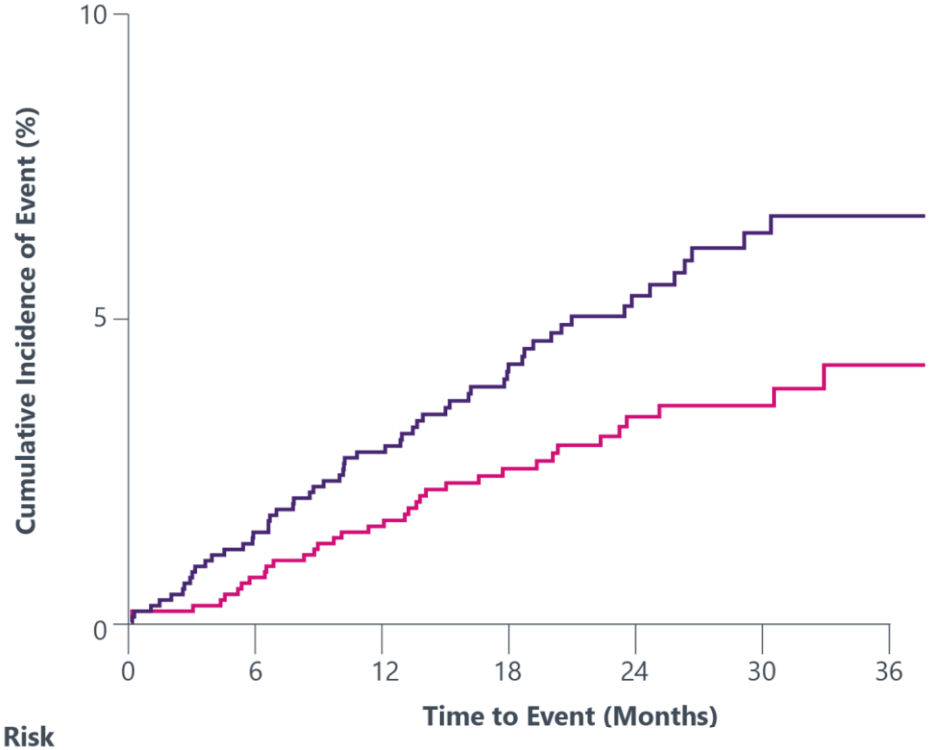
Clopidogrel 50 or 75 mg/day, Prasugrel 2.5 or 3.75 mg/day

UMIN Clinical Trials Registry number, UMIN000016612.
ClinicalTrials.gov number, NCT02642419.

1) Yasuda S, et al. *Int J Cardiol.* 2018. *2*) Tanigawa T, et al. *Drug Metab Pharmacokinet.* 2013.

Kaplan-Meier Estimates of First Occurrence of Primary Safety Events

AFIRE



Combination therapy

2.76% per patient-year

Monotherapy

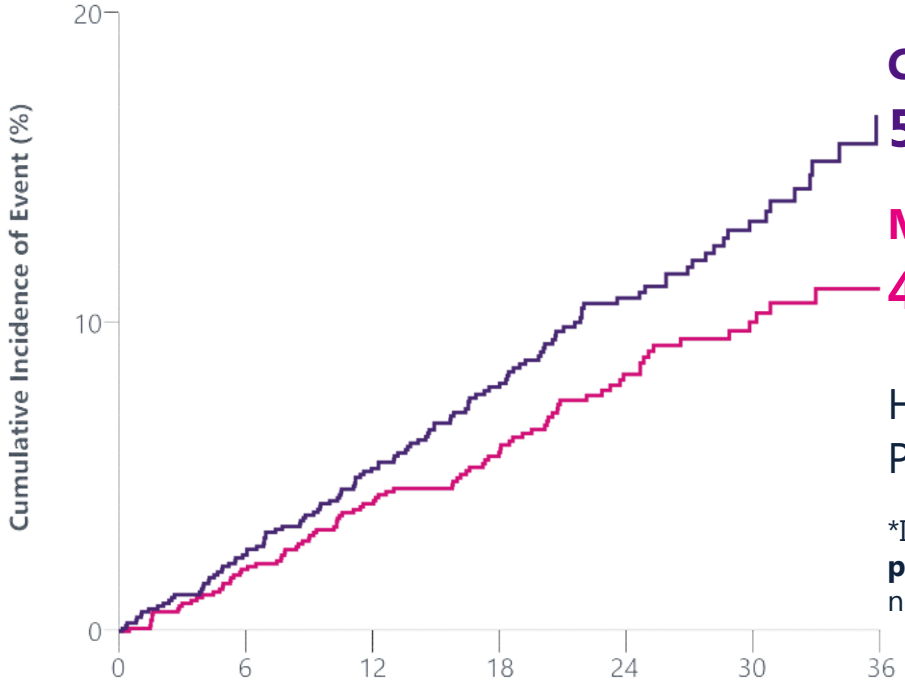
1.62% per patient-year

HR, **0.59** (**0.39** to **0.89**)
P=0.01 (sup.)

No. at Risk							
Rivaroxaban monotherapy	1099	1074	994	786	526	312	89
Combination therapy	1099	1055	962	750	506	294	80

Kaplan-Meier Estimates of First Occurrence of Primary Efficacy Events

AFIRE



No. at Risk							
Rivaroxaban monotherapy	1107	1071	984	774	518	309	89
Combination therapy	1108	1057	962	754	499	292	80

Combination therapy

5.75% per patient-year

Monotherapy

4.14% per patient-year

HR, **0.72** (**0.55** to **0.95**)
P<0.001 (noninf.)

*In the assessment for **superiority for the primary efficacy end point** (that was not prespecified), the **P value was 0.02.**

Summary

- NOACs improve AF patients outcome in Taiwan
- Patients with renal impairment and elderly AF patients have higher risks of bleeding and stroke
- Proper dose adjustment keeps safety and efficacy treatment of patient
- Inappropriate reduced dose might put patients at risk of increased stroke/SE.
- NOACs (particularly dabigatran and rivaroxaban) may be associated with lower risks of adverse renal outcomes than warfarin in patients with AF
- Dual therapy is acceptable for AF patients with PCI. AFIRE results confirm to drop antiplatelet therapy in AF patients with Rivaroxaban monotherapy

Thank You