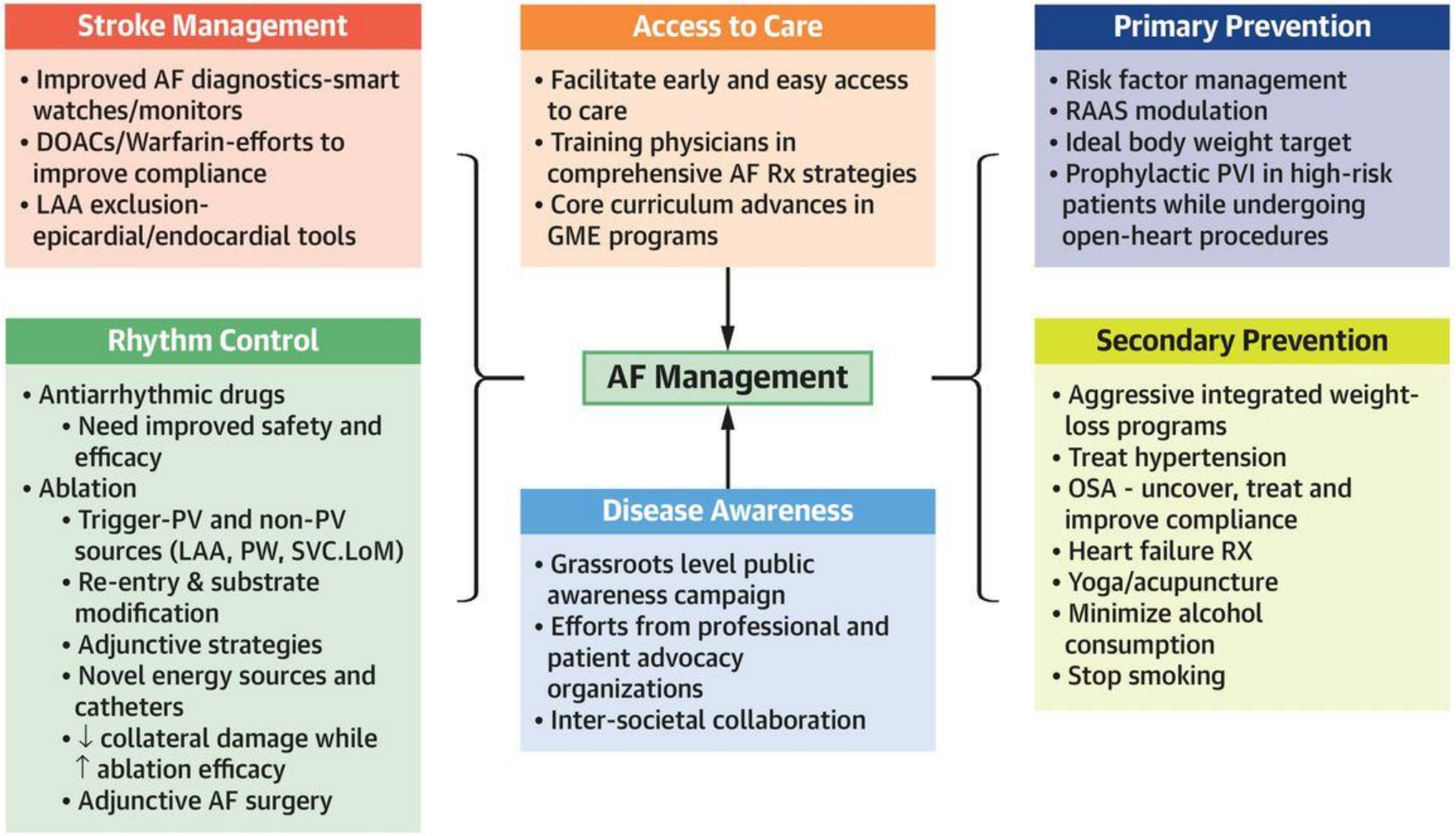
Stroke Prevention in Atrial Fibrillation

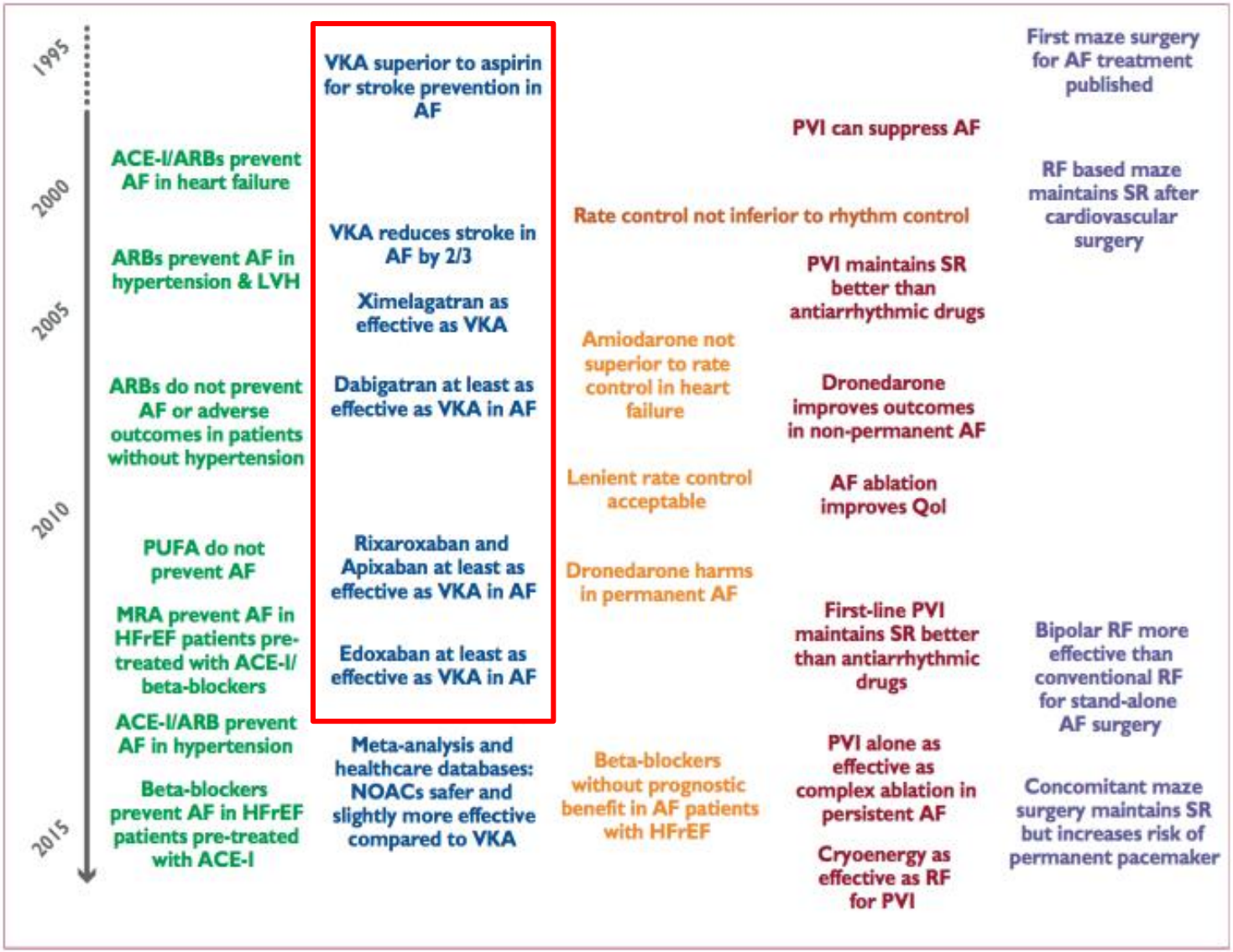
The simplified treatment strategy for general physicians

臺大醫院心臟科 賀立婷醫師

CENTRAL ILLUSTRATION: Management of AF



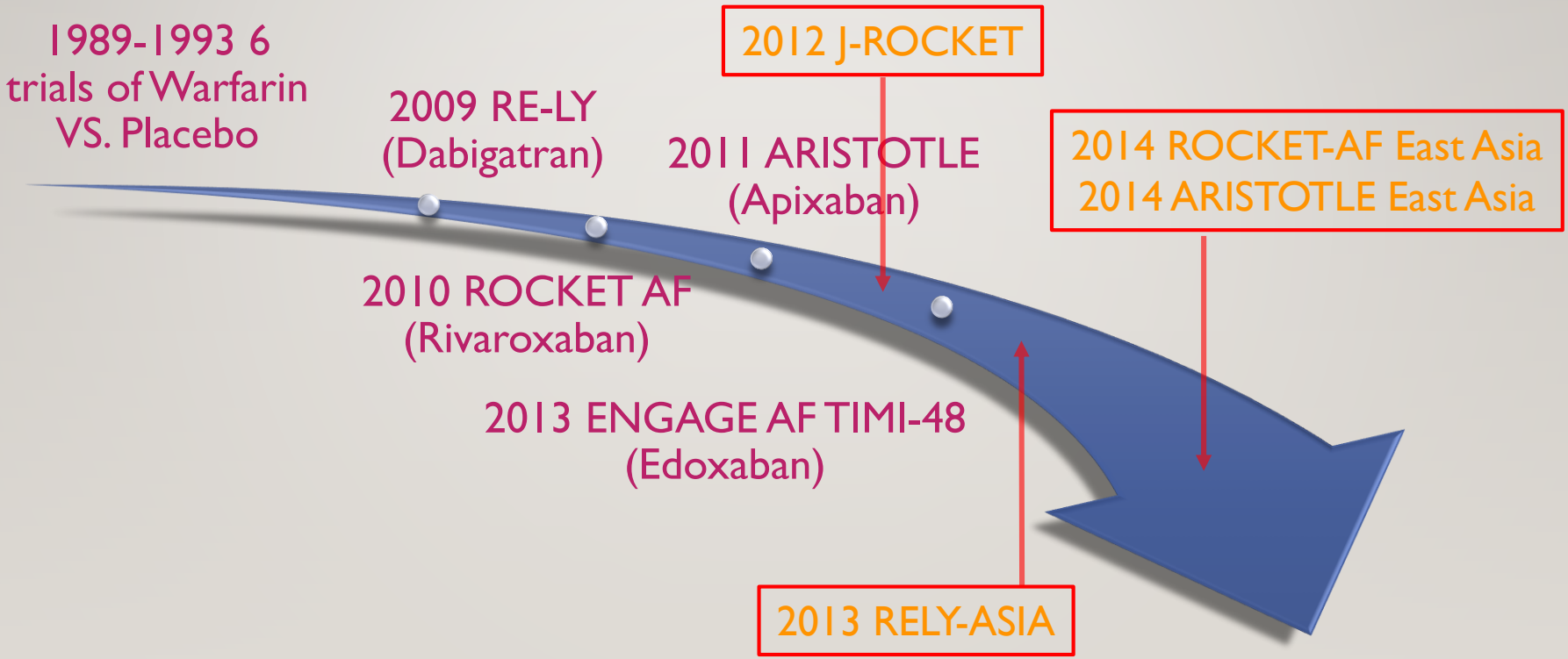
Chung, M.K. et al. J Am Coll Cardiol. 2020;75(14):1689-713.



ACE-I = angiotensin-converting enzyme inhibitor; AF = atrial fibrillation; ARB = angiotensin receptor blocker; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; LVH = left ventricular hypertrophy; NOAC = non-vitamin K antagonist oral anticoagulant; PUFA = polyunsaturated fatty acid; PVI = pulmonary vein isolation; QoL = quality of life; RF = radiofrequency; SR = sinus rhythm; VKA = vitamin K antagonist.

Figure 1 Timeline of findings from landmark trials in atrial fibrillation management, including treatment of concomitant conditions and prevention (green), anticoagulation (blue), rate control therapy (orange), rhythm control therapy (red), and atrial fibrillation surgery (purple).

Clinical Trials For Stroke Prevention in AF



Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials

Christian T Ruff, Robert P Giugliano, Eugene Braunwald, Elaine B Hoffman, Naveen Deenadayalu, Michael D Ezekowitz, A John Camm, Jeffrey I Weitz, Basil S Lewis, Alexander Parkhomenko, Takeshi Yamashita, Elliott M Antman

Lancet. 2014 Mar 15;383(9921):955-62.

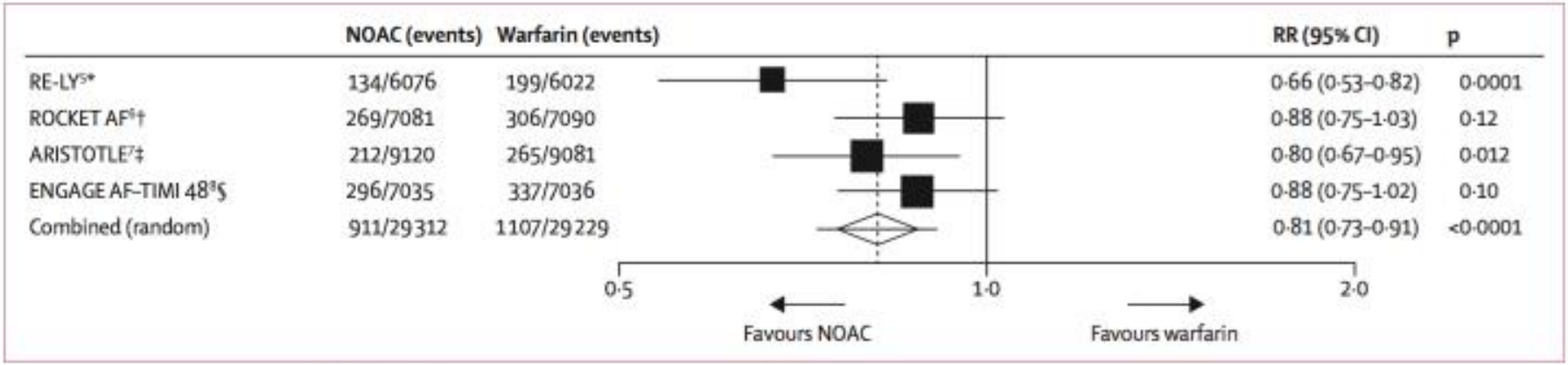


***Figure 1*: Stroke or systemic embolic events**

Data are n/N, unless otherwise indicated. Heterogeneity: I^2=47%; p=0·13. NOAC=new oral anticoagulant. RR=risk ratio. *Dabigatran 150 mg twice daily. †Rivaroxaban 20 mg once daily. ‡Apixaban 5 mg twice daily. §Edoxaban 60 mg once daily.

ACE-I = angiotensin-converting enzyme inhibitor; AF = atrial fibrillation; ARB = angiotensin receptor blocker; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; LVH = left ventricular hypertrophy; NOAC = non-vitamin K antagonist oral anticoagulant; PUFA = polyunsaturated fatty acid; PVI = pulmonary vein isolation; QoL = quality of life; RF = radiofrequency; SR = sinus rhythm; VKA = vitamin K antagonist.

European Heart Journal (2016) 37, 2893–2962

Figure 1 Timeline of findings from landmark trials in atrial fibrillation management, including treatment of concomitant conditions and prevention (green), anticoagulation (blue), rate control therapy (orange), rhythm control therapy (red), and atrial fibrillation surgery (purple).

CLASS IA	NOACs (dabigatran, rivaroxaban, apixaban, and edoxaban) are recommended over warfarin in NOAC-eligible patients with AF (except with moderate-to-severe mitral stenosis or a mechanical heart valve).

2019 AHA/ACC/HRS Focused Update

Who Needs Anti-coagulation?

CLASS IA	For patients with AF and an elevated CHA_2DS_2-VASc score of 2 or greater in men or 3 or greater in women, oral anticoagulants are recommended.

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Table 3 **Definitions and points in the CHA_2DS_2-VA score.**

Score	Points	Definition
C	1	**C**ongestive heart failure—recent signs, symptoms or admission for decompensated heart failure; this includes both HFrEF and HFpEF, or moderately to severely reduced systolic left ventricular function, whether or not there is a history of heart failure
H	1	History of **H**ypertension, whether or not BP is currently elevated
A_2	2	**A**ge ≥75 years
D	1	**D**iabetes
S_2	2	History of prior **S**troke or TIA or systemic thromboembolism
V	1	**V**ascular disease, defined as prior myocardial infarction or peripheral arterial disease or complex aortic atheroma or plaque on imaging (if performed)
A	1	**A**ge 65–74 years

AF, atrial fibrillation; BP, blood pressure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; TIA, transient ischaemic attack.

Heart, Lung and Circulation (2018) 27, 1209–1266

Who Needs Anti-coagulation?

CLASS IIA	For patients with AF (except with moderate- to-severe mitral stenosis or a mechanical heart valve) and a CHA_2DS_2-VASc score of 0 in men or 1 in women, it is reasonable to omit anticoagulant therapy

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Who Needs Anti-coagulation?

CLASS IIB	For patients with AF (except with moderate- to-severe mitral stenosis or a mechanical heart valve) and a CHA_2DS_2-VASc score of 1 in men and 2 in women, prescribing an oral anticoagulant to reduce thromboembolic stroke risk may be considered.

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Which Anti-coagulant?

CLASS IA	NOACs (dabigatran, rivaroxaban, apixaban, and edoxaban) are recommended over warfarin in NOAC-eligible patients with AF (except with moderate-to-severe mitral stenosis or a mechanical heart valve).

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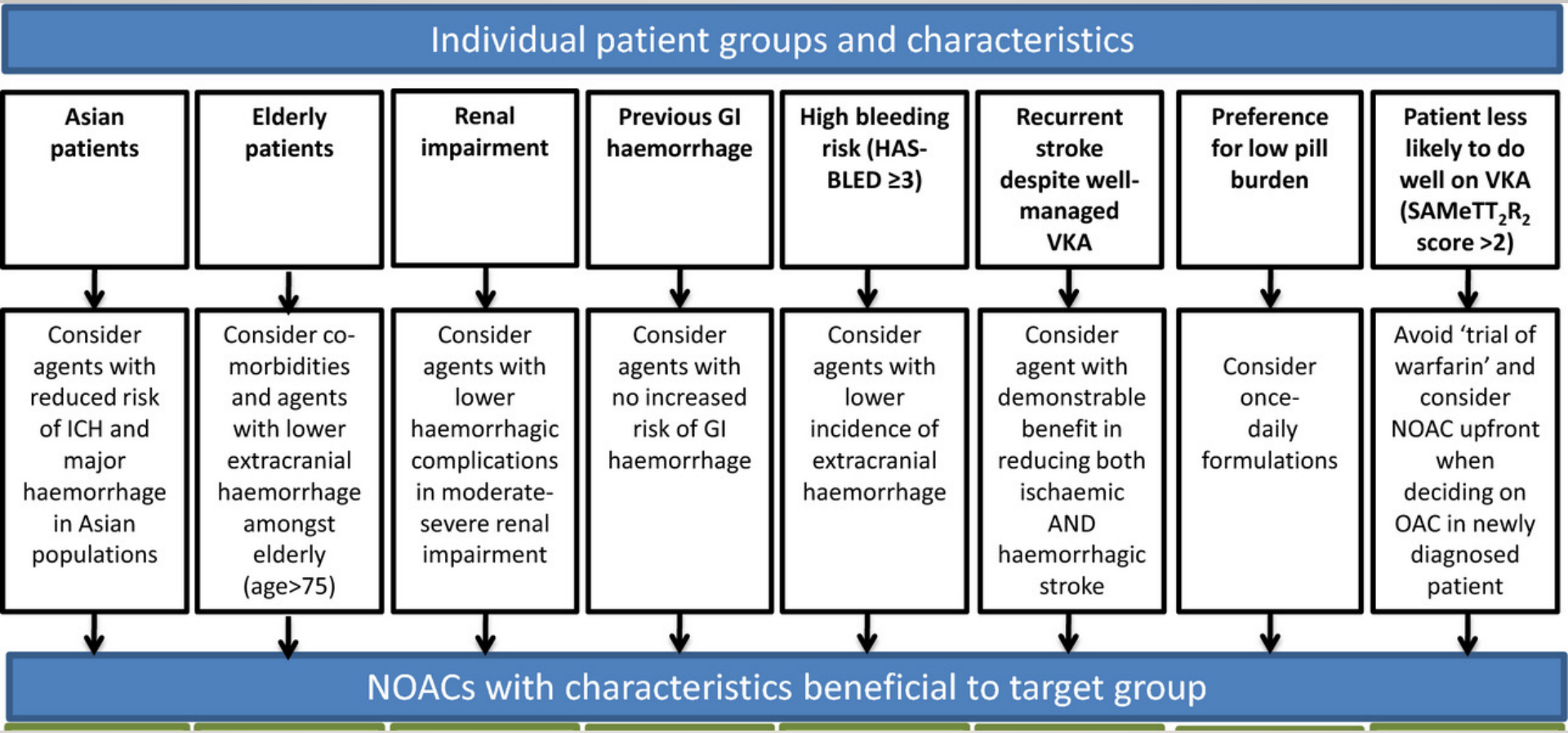
Summary 1

For patients with AF (except with moderate- to-severe mitral stenosis or a mechanical heart valve), CHA_2DS_2-VASc score of 2 or greater in men or 3 or greater in women, NOACs are recommended for stroke prevention.

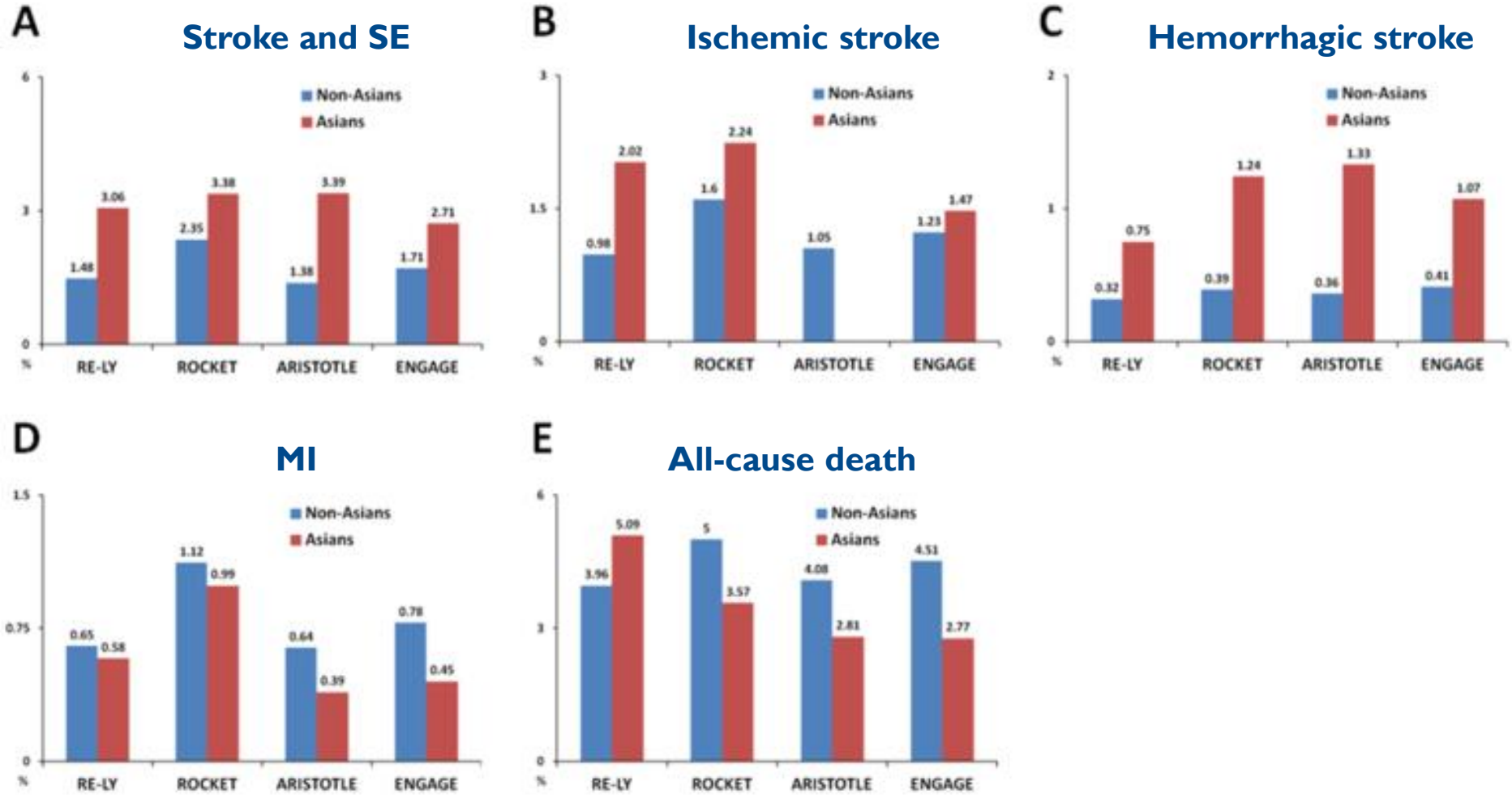
Table 13 Characteristics of approved non-vitamin K antagonist oral anticoagulants compared

	Dabigatran (RE-LY)			Rivaroxaban (ROCKET-AF)		Apixaban (ARISTOTLE)		Edoxaban (ENGAGE AF-TIMI 48)		
Mechanism	Oral direct thrombin inhibitor			Oral direct factor Xa inhibitor		Oral direct factor Xa inhibitor		Oral direct factor Xa inhibitor		
Bioavailability, %	6			66 fasting, 80–100 with food		50		62		
Time to peak levels, hours	3			2–4		3		1–2		
Half-life, hours	12–17			5–13		9–14		10–14		
Excretion	80% renal			66% liver, 33% renal		27% renal		50% renal		
Dose	150 mg twice daily or 110 mg twice daily			20 mg once daily		5 mg twice daily		60 mg once daily or 30 mg once daily		
Dose reduction in selected patients				Rivaroxaban 15 mg once daily if CrCl 30–49 mL/min		Apixaban 2.5 mg twice daily if at least 2 of age ≥80 years, body weight ≤60 kg or serum creatinine level ≥1.5 mg/dL (133 μmol/L)		Edoxaban 60 mg reduced to 30 mg once daily, and edoxaban 30 mg reduced to 15 mg once daily, if any of the following: creatinine clearance of 30–50 mL/min, body weight ≤60 kg, concomitant use of verapamil or quinidine or dronedarone		
Study design	Randomized, open-label			Randomized, double-blind		Randomized, double-blind		Randomized, double-blind		
Number of patients	18 113			14 264		18 201		21 105		
Follow-up period, years	2			1.9		1.8		2.8		
Randomized groups	Dose-adjusted warfarin vs. blinded doses of dabigatran (150 mg twice daily, 110 mg twice daily)			Dose-adjusted warfarin vs. rivaroxaban 20 mg once daily		Dose-adjusted warfarin vs. apixaban 5 mg twice daily		Dose-adjusted warfarin vs. edoxaban (60 mg once daily, 30 mg once daily)		
Age, years	71.5 ± 8.7 (mean ± SD)			73 (65–78) [median (interquartile range)]		70 (63–76) [median (interquartile range)]		72 (64–78) [median (interquartile range)]		
Male sex, %	63.6			60.3		64.5		61.9		
$CHADS_2$ score (mean)	2.1			3.5		2.1		2.8		
	Warfarin	Dabigatran 150	Dabigatran 110	Warfarin	Rivaroxaban	Warfarin	Apixaban	Warfarin	Edoxaban 60	Edoxaban 30
	n = 6022	n = 6076	n = 6015	n = 7133	n = 7131	n = 9081	n = 9120	n = 7036	n = 7035	n = 7034
	Event rate, %/year	Event rate, %/year (RR vs. warfarin)	Event rate, %/year (RR vs. warfarin)	Event rate, %/year	Event rate, %/year (HR vs. warfarin)	Event rate, %/year	Event rate, %/year (HR vs. warfarin)	Event rate, %/year	Event rate, %/year (HR vs. warfarin)	Event rate, %/year (HR vs. warfarin)
Stroke/systemic embolism	1.72	1.12 (0.65, 0.52–0.81; *P* for non-inferiority and superiority <0.001)	1.54 (0.89, 0.73–1.09; *P* for non-inferiority <0.001)	2.4	2.1 (0.88, 0.75–1.03; *P* for non-inferiority <0.001, *P* for superiority = 0.12)	1.60	1.27 (0.79, 0.66–0.95; *P* <0.001 for non-inferiority, *P* = 0.01 for superiority)	1.80	1.57 (0.87, 0.73–1.04; *P* <0.001 for non-inferiority, *P* = 0.08 for superiority)	2.04 (1.13, 0.96–1.34; *P* = 0.005 for non-inferiority, *P* = 0.10 for superiority)
Ischaemic stroke	1.22	0.93 (0.76, 0.59–0.97; *P* = 0.03)	1.34 (1.10, 0.88–1.37; *P* = 0.42)	1.42	1.34 (0.94; 0.75–1.17; *P* = 0.581)	1.05	0.97 (0.92, 0.74–1.13; *P* = 0.42)	1.25	1.25 (1.00, 0.83–1.19; *P* = 0.97)	1.77 (1.41, 1.19–1.67; *P* <0.001)
Haemorrhagic stroke	0.38	0.10 (0.26, 0.14–0.49; *P* <0.001)	0.12 (0.31, 0.17–0.56; *P* <0.001)	0.44	0.26 (0.59; 0.37–0.93; *P* = 0.024)	0.47	0.24 (0.51, 0.35–0.75; *P* <0.001)	0.47	0.26 (0.54, 0.38–0.77; *P* <0.001)	0.16 (0.33, 0.22–0.50; *P* <0.001)
Major bleeding	3.61	3.40 (0.94, 0.82–1.08; *P* = 0.41)	2.92 (0.80, 0.70–0.93; *P* = 0.003)	3.45	3.60 (1.04; 0.90–2.30; *P* = 0.58)	3.09	2.13 (0.69, 0.60–0.80; *P* <0.001)	3.43	2.75 (0.80, 0.71–0.91; *P* <0.001)	1.61 (0.47, 0.41–0.55; *P* <0.001)
Intracranial bleeding	0.77	0.32 (0.42, 0.29–0.61; *P* <0.001)	0.23 (0.29 0.19–0.45; *P* <0.001)	0.74	0.49 (0.67; 0.47–0.93; *P* = 0.02)	0.80	0.33 (0.42, 0.30–0.58; *P* <0.001)	0.85	0.39 (0.47, 0.34–0.63; *P* <0.001)	0.26 (0.30, 0.21–0.43; *P* <0.001)
Gastrointestinal major bleeding	1.09	1.60 (1.48, 1.19–1.86; *P* <0.001)	1.13 (1.04, 0.82–1.33; *P* = 0.74)	1.24	2.00 (1.61; 1.30–1.99; *P* < 0.001)	0.86	0.76 (0.89, 0.70–1.15; *P* = 0.37)	1.23	1.51 (1.23, 1.02–1.50; *P* = 0.03)	0.82 (0.67, 0.53–0.83; *P* <0.001)
Myocardial infarction	0.64	0.81 (1.27, 0.94–1.71; *P* = 0.12)	0.82 (1.29, 0.96–1.75; *P* = 0.09)	1.12	0.91 (0.81; 0.63–1.06; *P* = 0.12)	0.61	0.53 (0.88, 0.66–1.17; *P* = 0.37)	0.75	0.70 (0.94, 0.74–1.19; *P* = 0.60)	0.89 (1.19, 0.95–1.49; *P* = 0.13)
Death from any cause	4.13	3.64 (0.88, 0.77–1.00; *P* = 0.051)	3.75 (0.91, 0.80–1.03; *P* = 0.13)	2.21	1.87 (0.85; 0.70–1.02; *P* = 0.07)	3.94	3.52 (0.89, 0.80–0.99; *P* = 0.047)	4.35	3.99 (0.92, 0.83–1.01; *P* = 0.08)	3.80 (0.87, 0.79–0.96; *P* = 0.006)

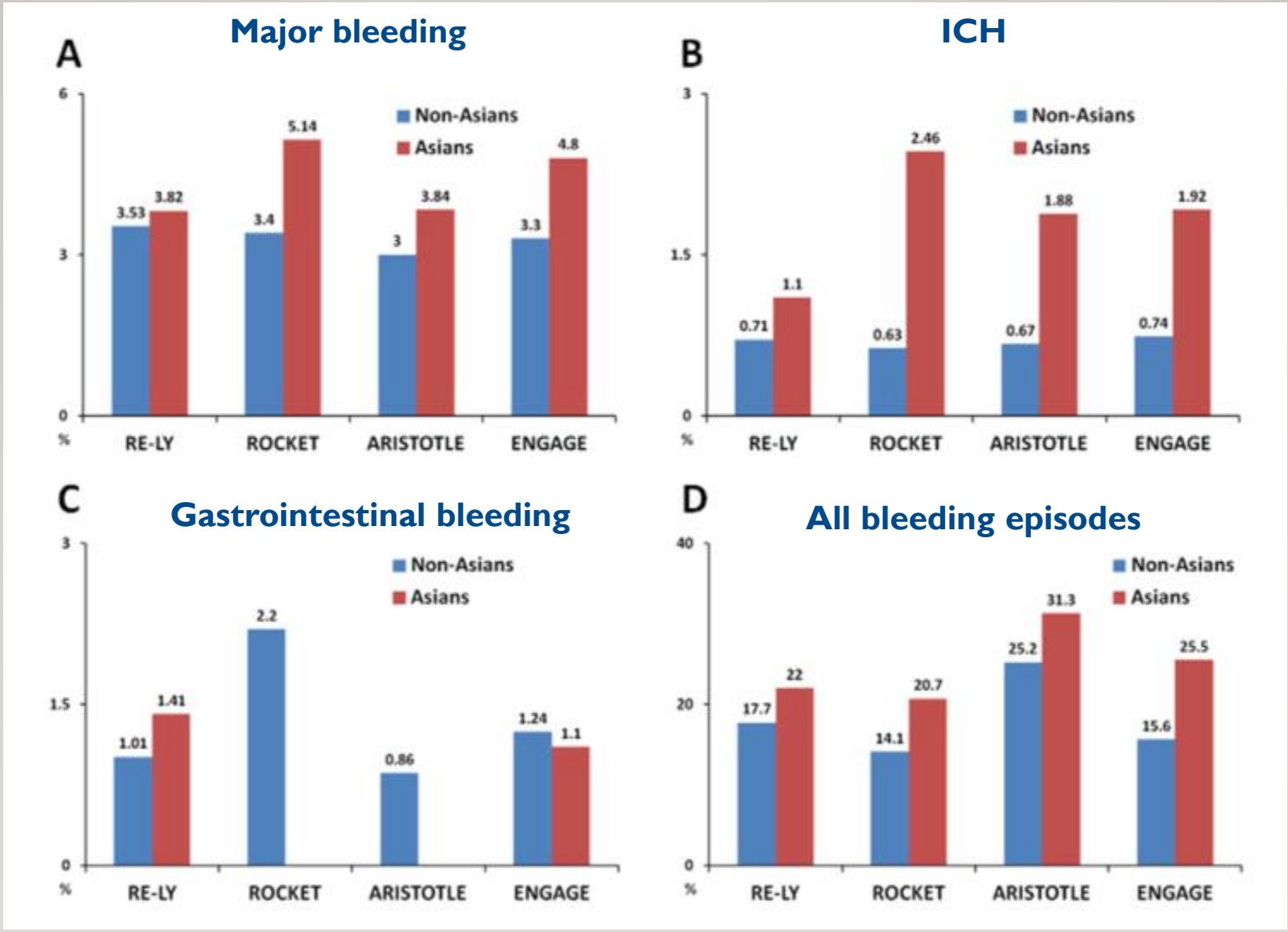


J Intern Med. 2015 Jul;278(1):1-18.

1) ASIAN

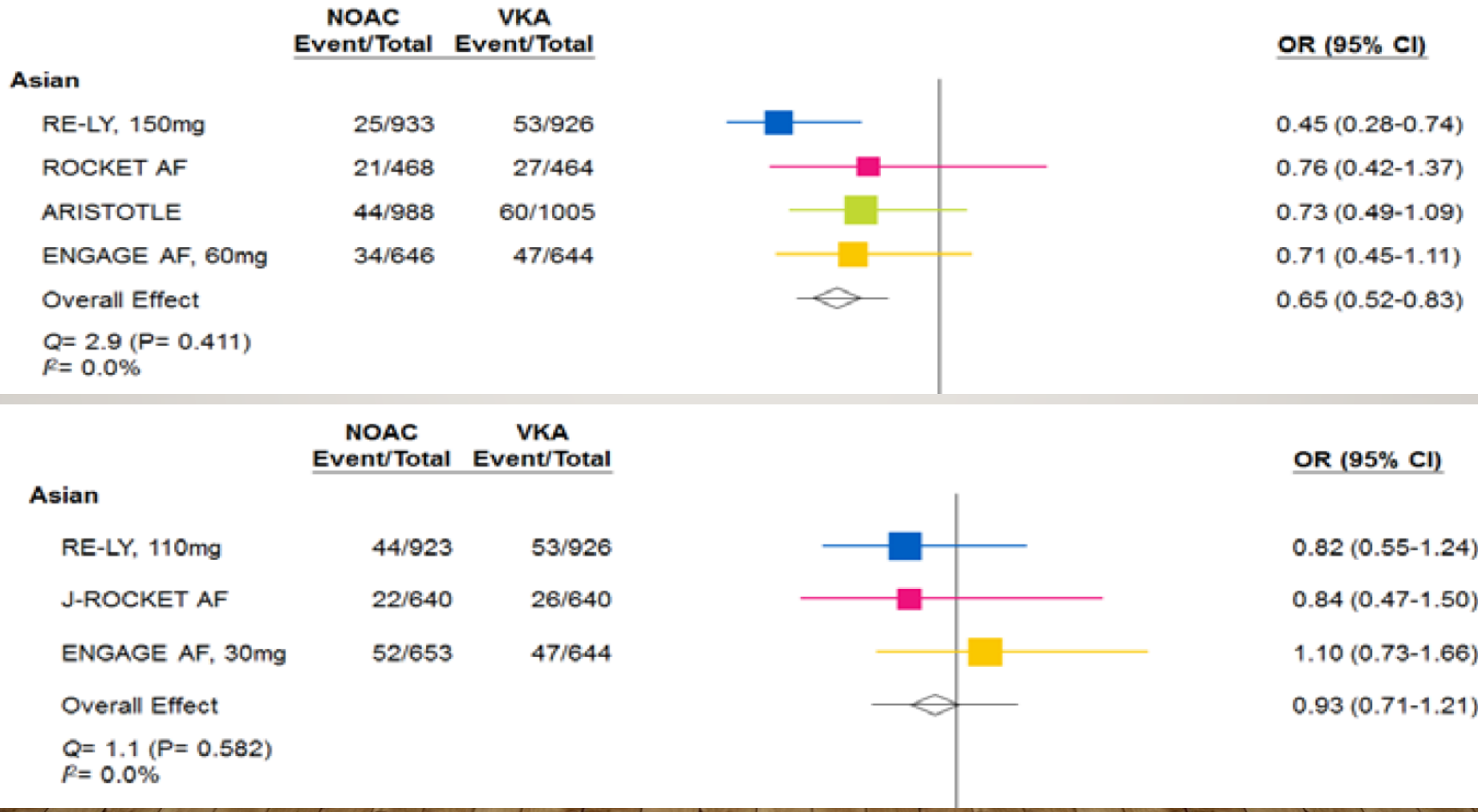


Int J Cardiol. 2015 Feb 1;180:246-54



Int J Cardiol. 2015 Feb 1;180:246-54

Stroke and SEE



Stroke 2015 Sep;46(9):2555-61

Major Bleeding

Stroke 2015 Sep;46(9):2555-61

Individual patient groups and characteristics

Asian patients

↓

Consider agents with reduced risk of ICH and major haemorrhage in Asian populations

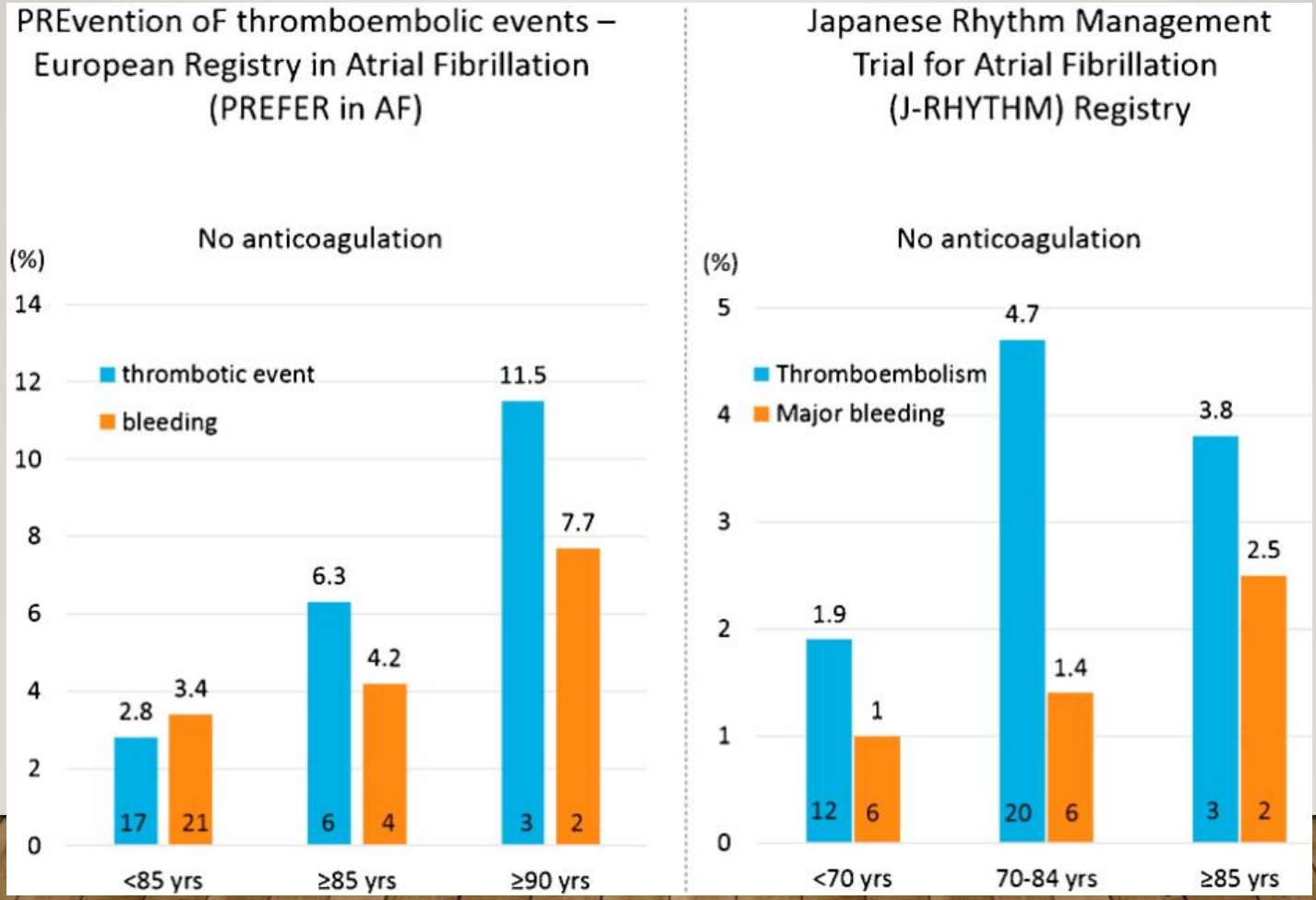
↓

Apixaban
Dabigatran
Edoxaban

2) ELDERLY

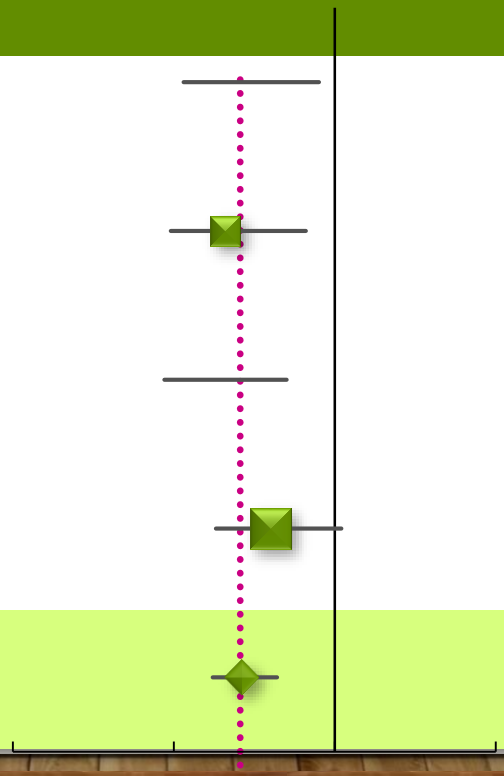
Elderly Patients

Ageing Res Rev. 2019 Jan;49:115-124.



NOAC Meta-analysis in Elderly Patients – Efficacy
Patients Age Above 75 Years Old

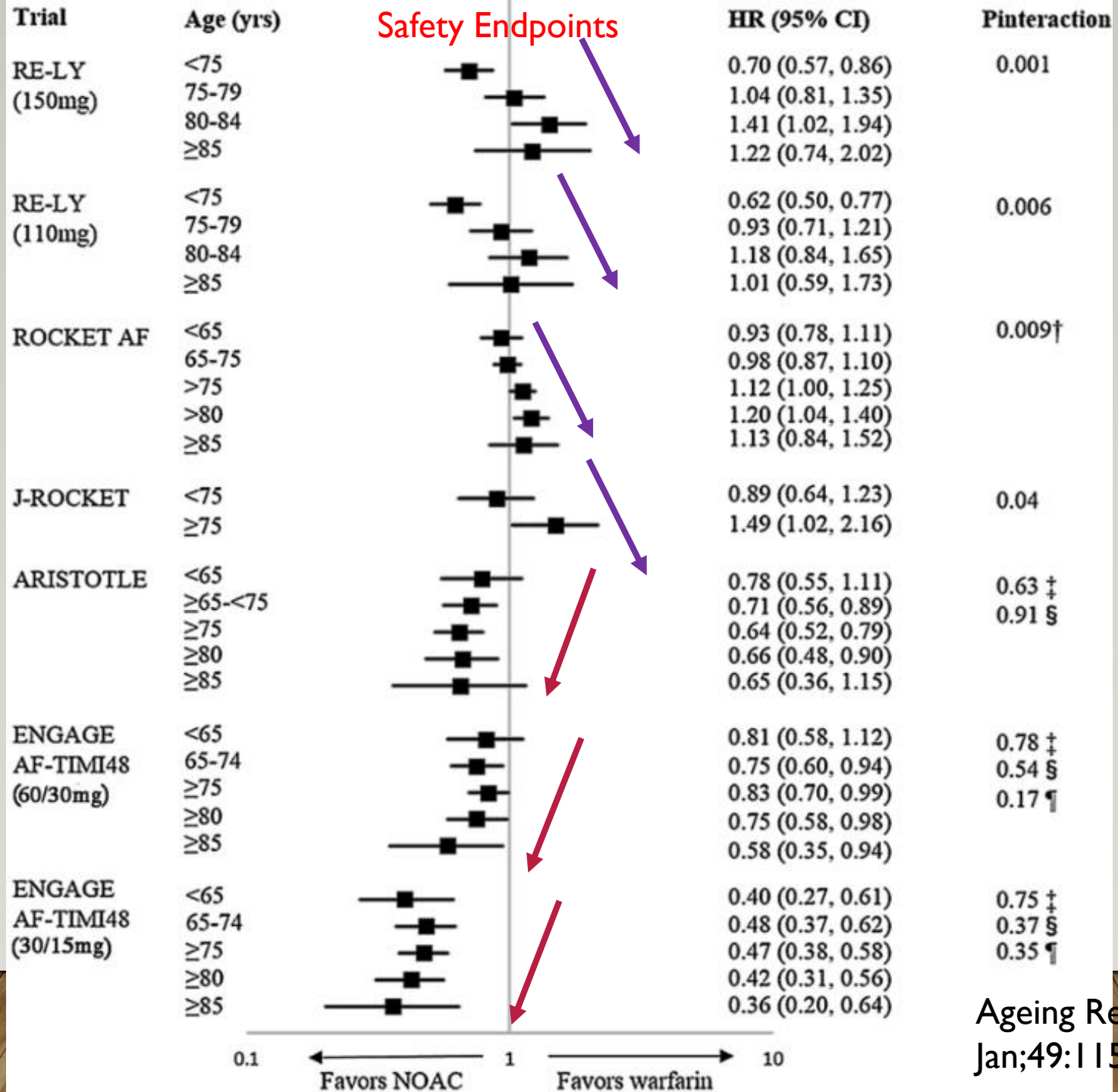
Stroke or TEE	DOAC Arm	Control Arm	Odd ratio	95%CI	weight
Apixaban (ARISTOTLE)	79/2,850	109/2,828	**0.71**	0.53–0.95	22.9%
Dabigatran 150mg (RE-LY)	69/2,466	101/2,430	**0.66**	0.49–0.91	20.4%
Edoxaban 60mg (ENGAGE AF-TIMI 48)	75/2,838	115/2,805	**0.63**	0.47–0.85	22.7%
Rivaroxaban (ROCKET AF)	125/3,082	154/3,082	**0.80**	0.63–1.02	34.0%
Fixed Effect Model	348/11,236	479/11,145	**0.71**	0.62–0.82	100%



Heterogeneity ：I^2 =0%、τ^2 =0、p=0.6283
Test for overall effect：p<0.0001

Swiss Med Wkly. 2016; 146: w14356.

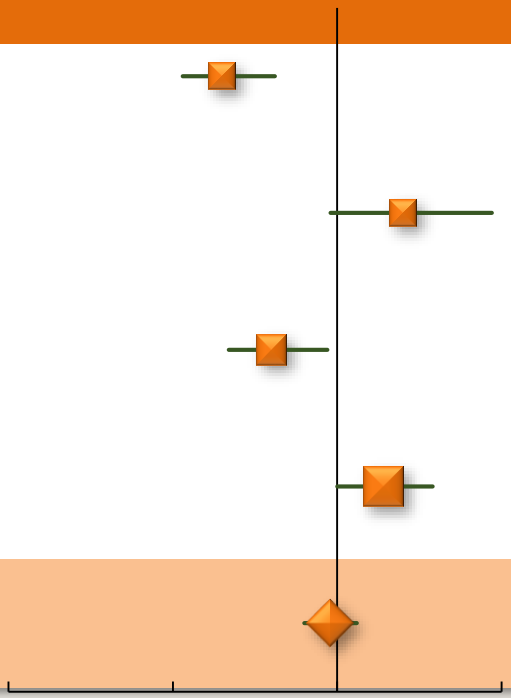
Safety Endpoints



Ageing Res Rev. 2019 Jan;49:115-124.

NOAC Meta-analysis in Elderly Patients – Safety
Patients Age Above 75 Years Old

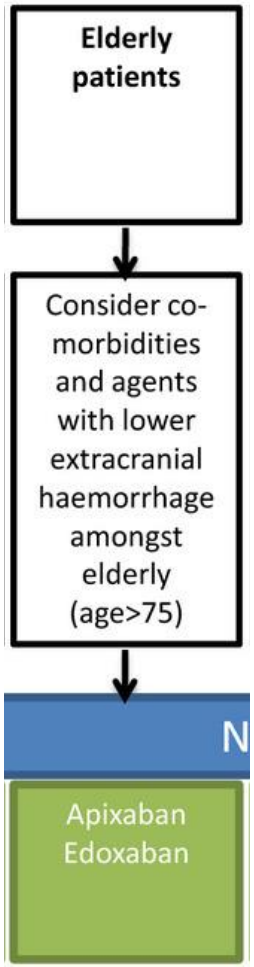
Major bleeding or NMCR bleeding	DOAC Arm	Control Arm	Odd ratio	95% CI	weight
Apixaban (ARISTOTLE)	151/2,836	224/2,819	**0.65**	0.53–0.81	15.7%
Dabigtran 150mg (RE-LY)	227/2,145	188/2,088	**1.20**	0.98–1.47	17.2%
Edoxaban 60mg (ENGAGE AF-TIMI 48)	224/2,838	270/2,805	**0.80**	0.67–0.97	20.8%
Rivaroxaban (ROCKET AF)	693/2,688	633/2,702	**1.14**	1.00–1.29	46.3%
Fixed Effect Model	1,295/10,507	1,315/10,414	**0.98**	0.90–1.06	100%



Heterogeneity：I^2 =89.1%、τ^2 =0.0662、p<0.0001
Test for over all effect：p = 0.5999

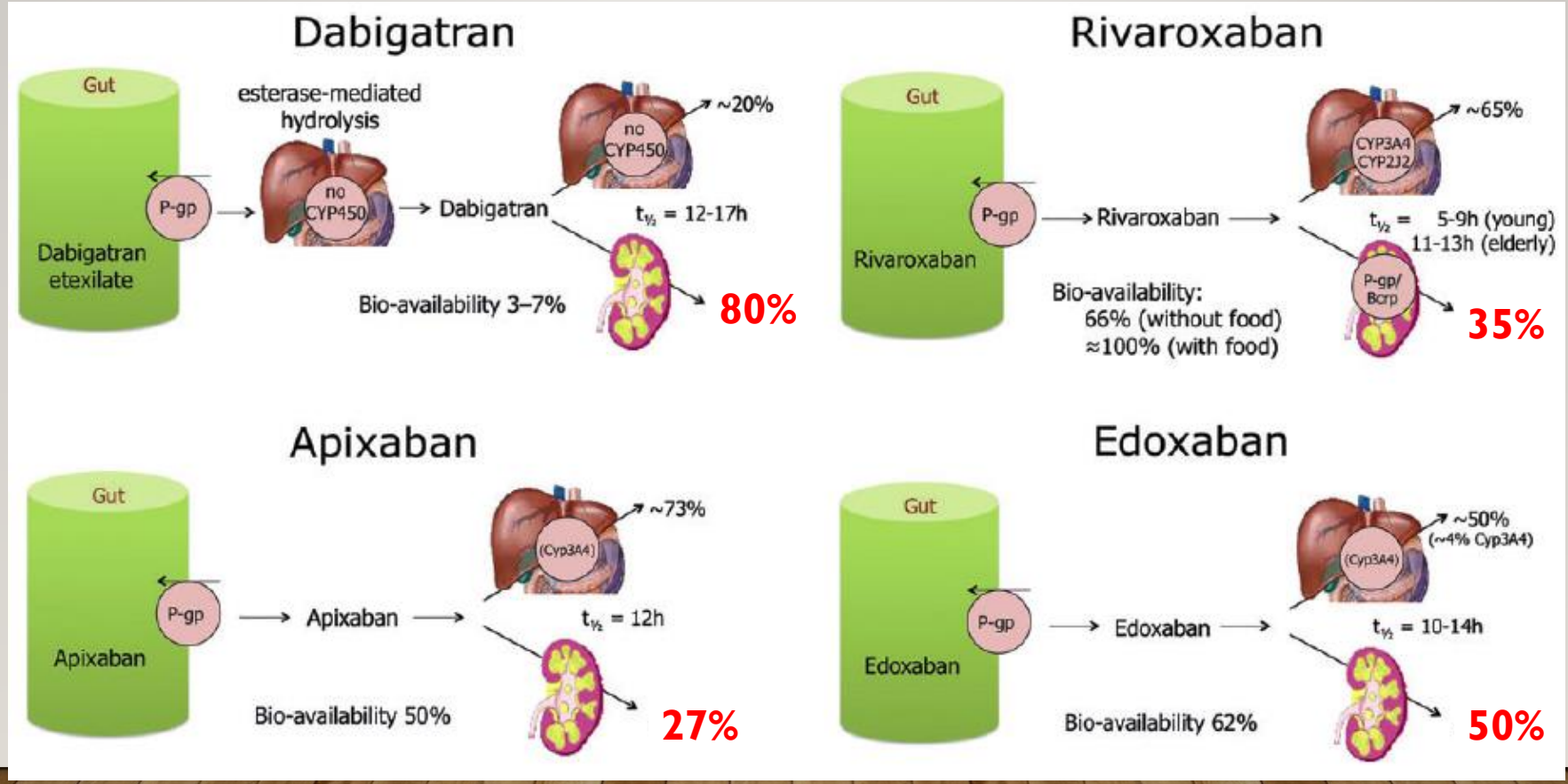
Swiss Med Wkly. 2016; 146: w14356.

Individual patient groups and characteristics



3) RENAL FAILURE

Renal Clearance Rate of 4 NOACs



2015 ESC Updated European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist anticoagulants in patients with non-valvular atrial fibrillation

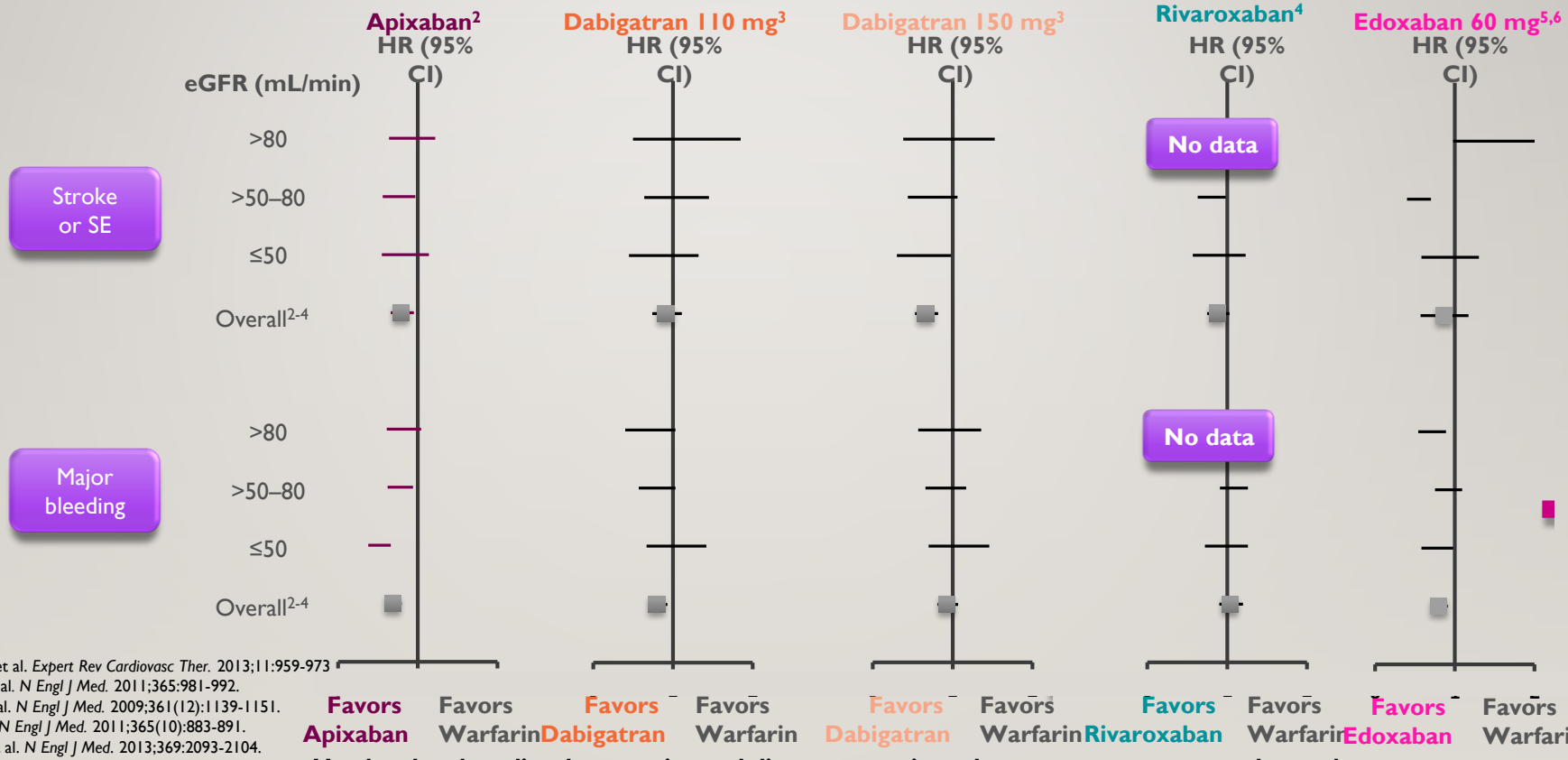
Phase III Trials for DOACs v.s Warfarin[1-5]

	Apixaban	Dabigatran	Edoxaban	Rivaroxaban
Study (N)	ARISTOTLE (18,201)	RE-LY (18,113)	ENGAGE AF (21,105)	ROCKET-AF (14,264)
Renal Exclusion	CrCl <25 mL/min	CrCl <30 mL/min	CrCl <30 mL/min	CrC <30 mL/min
Patients with CKD (%)	**15%** with CrCl 30-50 mL/min	**20%** with CrCl 30-49 mL/min	**19%** with CrCl <50 mL/min	**21%** with CrCl 30-49 mL/min

FXa=factor Xa; PK=pharmacokinetic; T_{max}=time to maximum concentration.

1. Hart RG et al. *Nat Rev Nephrol.* 2012;8(10):569-578; 2. Kirchhof P et al. *Eur Heart J*. 2016; [Epub ahead of print]. doi:10.1093/eurheartj/ehw210., 3. Ansell J. *Am Soc Hematol*. 2010:221-228; 4. Heidbuchel H et al. *Europace*. 2015;17(10):1467-1507., 5. Warfarin SmPC. 2013.

Overall, DOACs Maintain Similar Efficacy and Safety Profiles in Patients with or without Renal Impairment[1-6]



1. Capranzano P et al. *Expert Rev Cardiovasc Ther.* 2013;11:959-973
2. Granger CB et al. *N Engl J Med.* 2011;365:981-992.
3. Connolly SJ et al. *N Engl J Med.* 2009;361(12):1139-1151.
4. Patel MR et al. *N Engl J Med.* 2011;365(10):883-891.
5. Giugliano RP et al. *N Engl J Med.* 2013;369:2093-2104.
6. Edoxaban Prescribing Information. 2015.

Head-to-head studies do not exist, and direct comparisons between agents may not be made.

CLASS IIB	For patients with AF (except with moderate- to-severe mitral stenosis or a mechanical heart valve) and moderate-to-severe CKD with an elevated CHA_2DS_2-VASc score, treatment with reduced doses of direct thrombin or factor Xa inhibitors may be considered.

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CLASS IIB	For patients with AF who have a CHA_2DS_2-VASc score of 2 or greater in men or 3 or greater in women and who have end-stage chronic kidney disease or are on dialysis, it might be reasonable to prescribe warfarin (INR 2.0 to 3.0) or apixaban for oral anticoagulation.
CLASS III (No benefit)	In patients with AF and end-stage CKD or on dialysis, the direct thrombin inhibitor dabigatran or the factor Xa inhibitors rivaroxaban or edoxaban are not recommended because of the lack of evidence from clinical trials that benefit exceeds risk.

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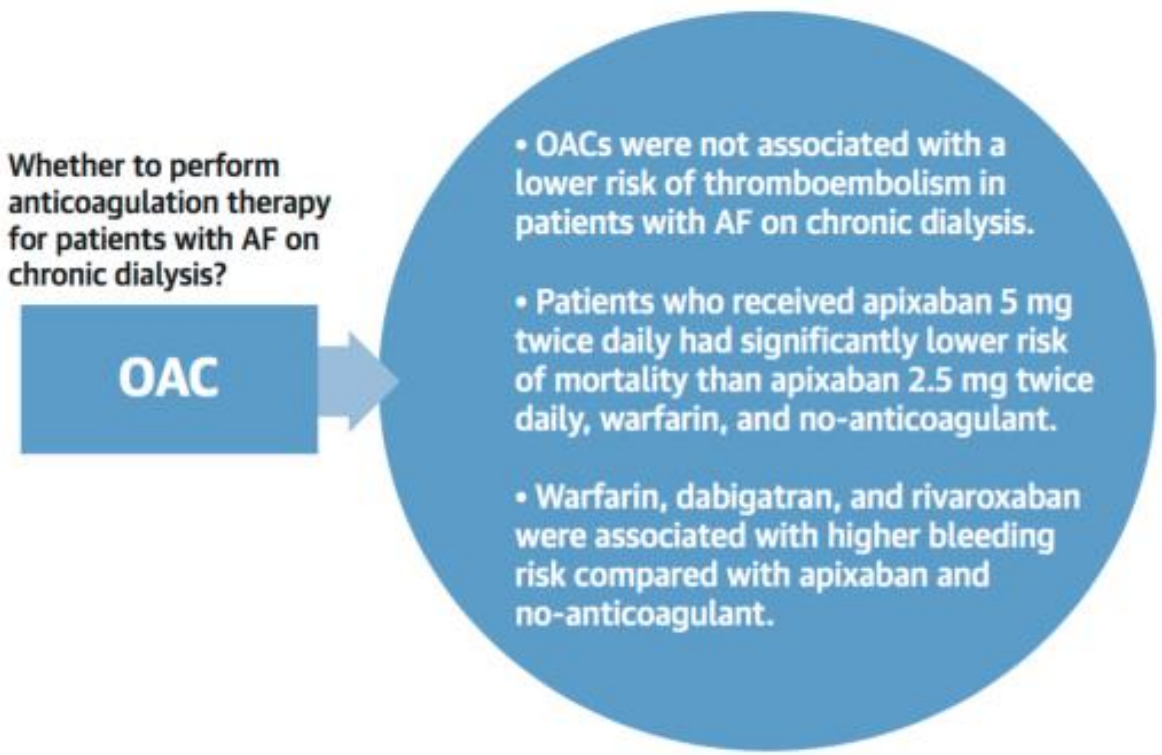
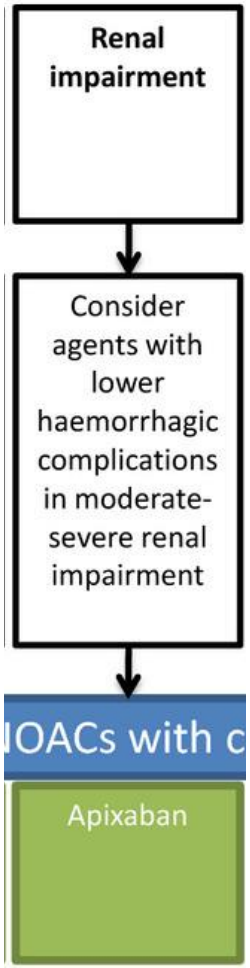
CENTRAL ILLUSTRATION Patients With Oral Anticoagulation Management



Kuno, T. et al. J Am Coll Cardiol. 2020;75(3):273-85.

AF = atrial fibrillation; OAC = oral anticoagulant.

Individual patient groups and characteristics



4) HIGH BLEEDING RISK

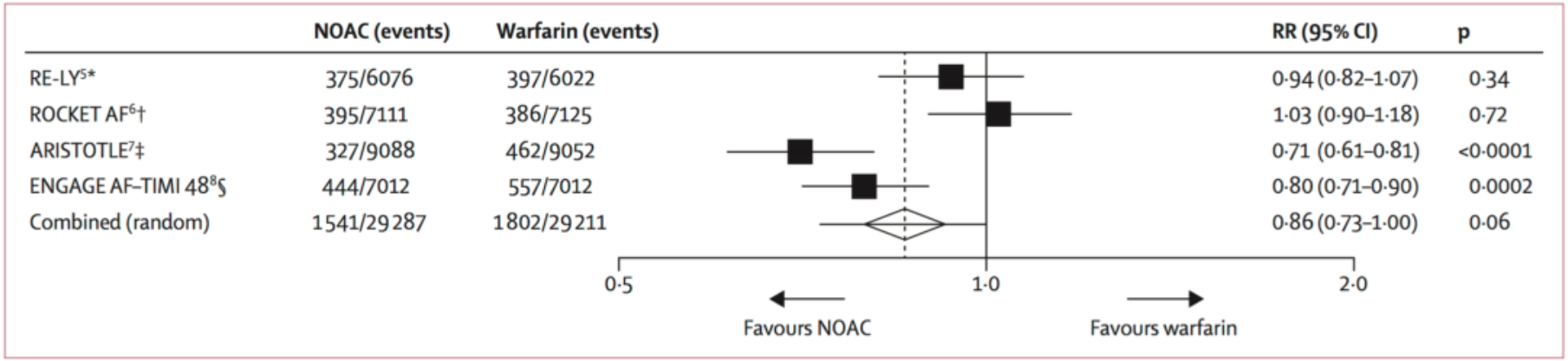


***Figure* 3: Major bleeding**

Data are n/N, unless otherwise indicated. Heterogeneity: I^2=83%; p=0·001. NOAC=new oral anticoagulant. RR=risk ratio. *Dabigatran 150 mg twice daily. †Rivaroxaban 20 mg once daily. ‡Apixaban 5 mg twice daily. §Edoxaban 60 mg once daily.

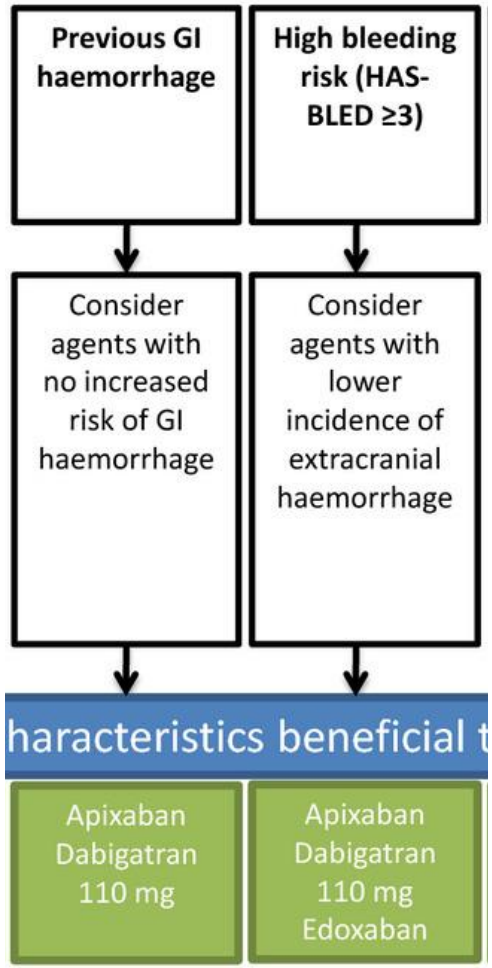
High-dose dabigatran (RR 1.50, 95% CI 1.19–1.89; $P < 0.001$), high-dose edoxaban (RR 1.23, 95% CI 1.02–1.50; $P = 0.03$) and rivaroxaban (3.2% vs. 2.2%, $P < 0.001$) were all associated with a significantly increased risk of gastrointestinal haemorrhage compared to warfarin in their respective trials, but low-dose edoxaban was associated with significantly less gastrointestinal bleeding (RR 0.67, 95% CI 0.53–0.83; $P < 0.001$).

Lancet. 2014 Mar 15;383(9921):955-62

NOAC	Direct Thrombin Inhibitor	Factor Xa inhibitor		
	Dabigatran (Pradaxa®)	Rivaroxaban (Xarelto®)	Apixaban (Eliquis®)	Edoxaban (Lixiana®)
Dialysis Removable	✓	✗	✗	✗
Specific Antidote	Idarucizumab	Andexanet alpha		

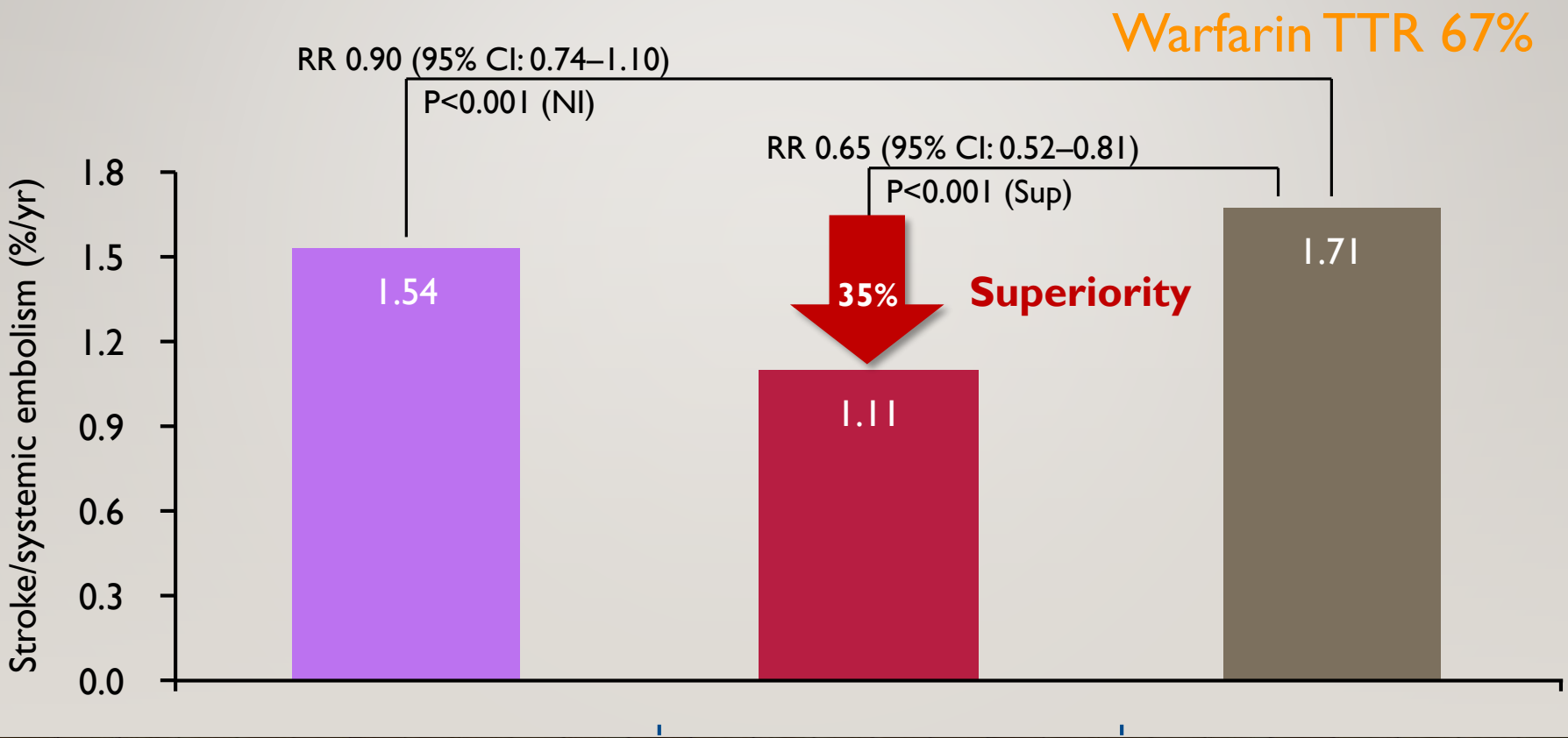
- Idarucizumab & andexanet alpha have been granted breakthrough therapy designation by US FDA.

Individual patient groups and characteristics

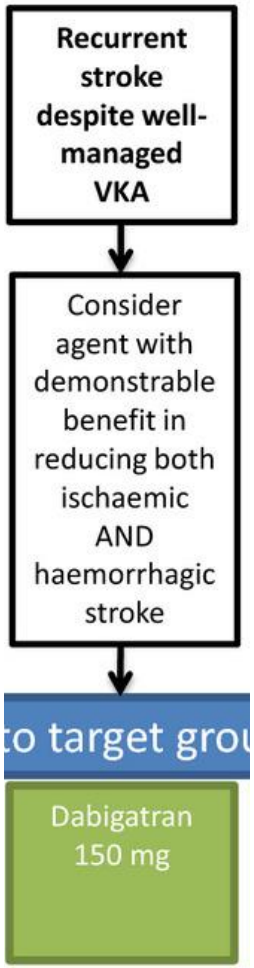


5) HIGH RISK OF STROKE /PREVIOUS TIA/STROKE

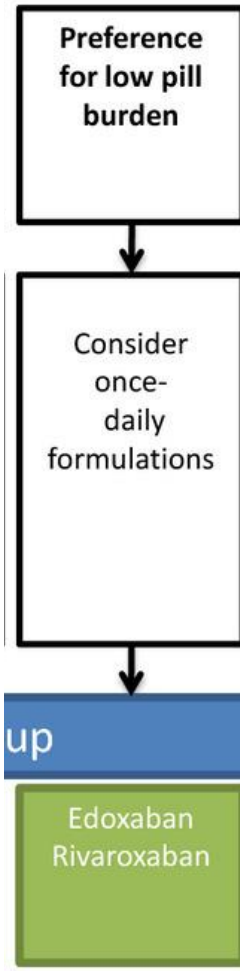
RELY Trial

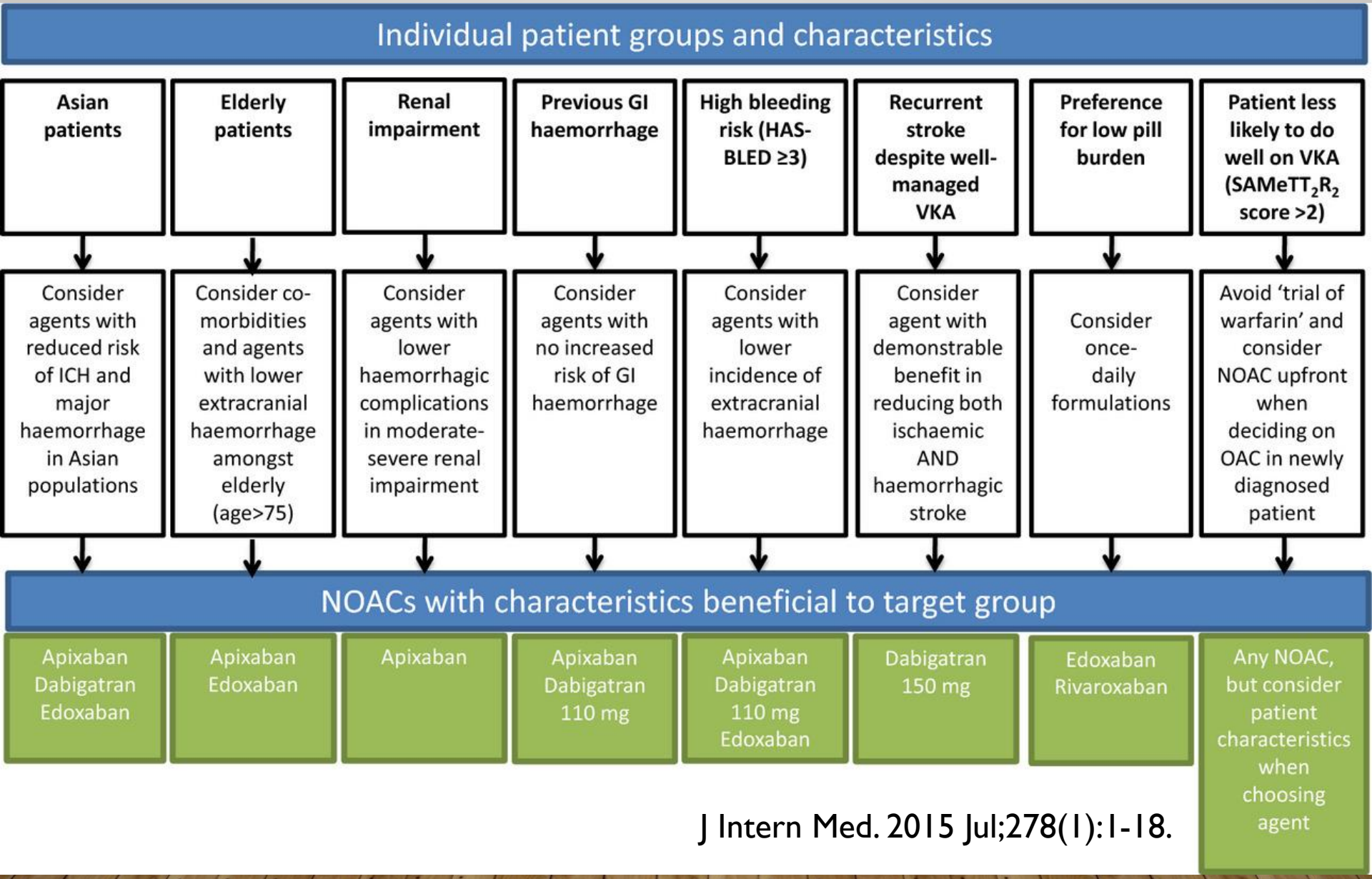

Warfarin TTR 67%
RR 0.90 (95% CI: 0.74–1.10)
P<0.001 (NI)
RR 0.65 (95% CI: 0.52–0.81)
P<0.001 (Sup)
35%
Superiority
Stroke/systemic embolism (%/yr)
1.8
1.5
1.2
0.9
0.6
0.3
0.0
1.54
1.11
1.71
Dabigatran 110 mg BID
Dabigatran 150 mg BID
Warfarin
Events/n:
183/6015
134/6076
202/6022

Individual patient groups and characteristics



Individual patient groups and characteristics

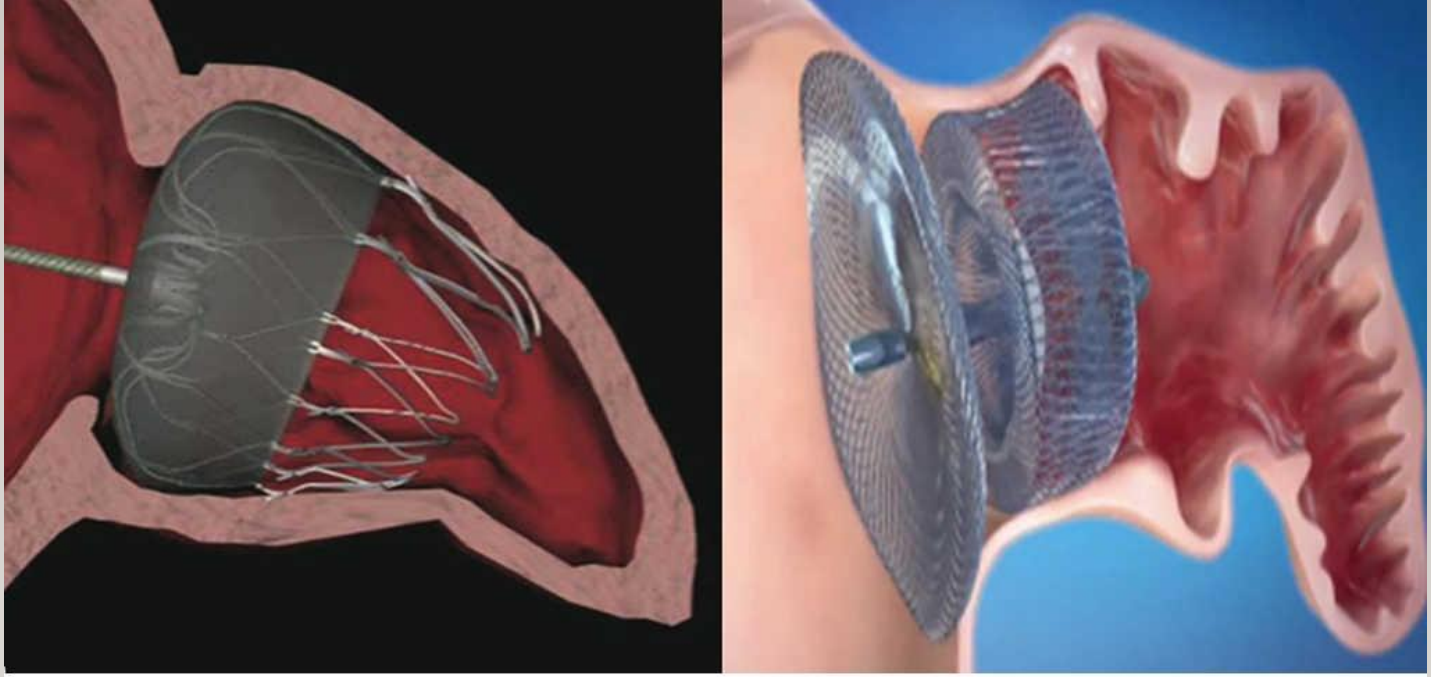




J Intern Med. 2015 Jul;278(1):1-18.

Summary II

Choose the right OAC therapy to fit the individual patient with AF.

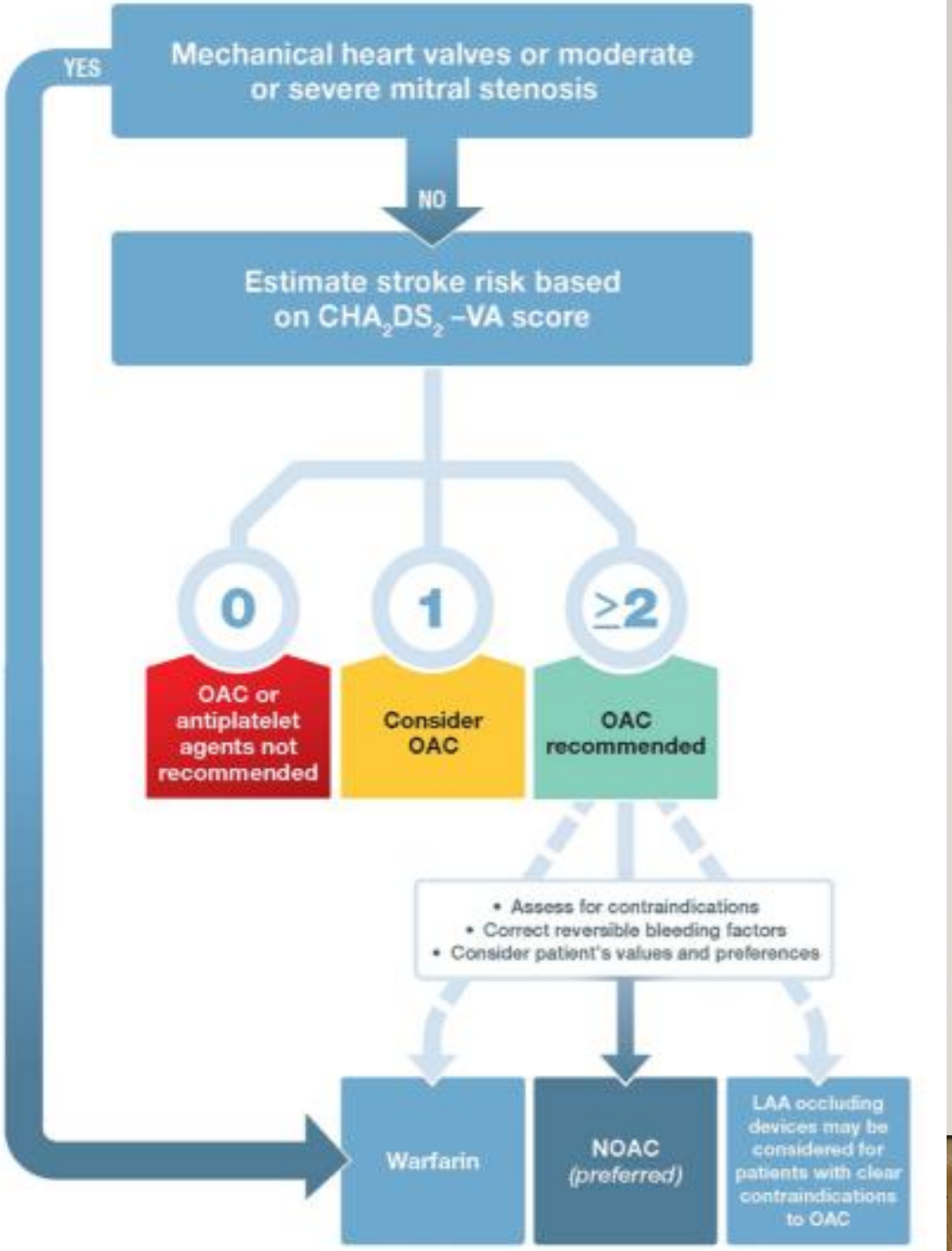


Rev Esp Cardiol. 2013;66:919–22

CLASS IIB	Percutaneous LAA occlusion may be considered in patients with AF at increased risk of stroke who have contraindications to long-term anticoagulation.

Summary III

For patients who are poor candidates for long-term oral anticoagulation, the LAA occluding device provides an alternative.



Heart, Lung and Circulation (2018) 27, 1209–1266