Stroke Prevention in Atrial Fibrillation

The simplified treatment strategy for general physicians

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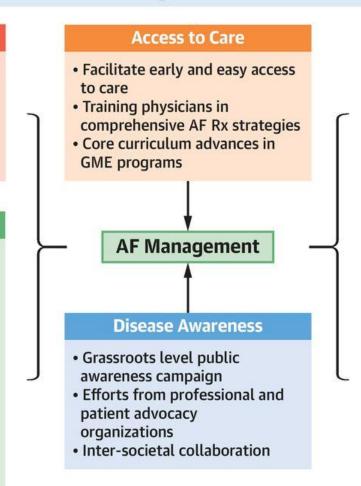
CENTRAL ILLUSTRATION: Management of AF

Stroke Management

- Improved AF diagnostics-smart watches/monitors
- DOACs/Warfarin-efforts to improve compliance
- LAA exclusionepicardial/endocardial tools

Rhythm Control

- · Antiarrhythmic drugs
 - Need improved safety and efficacy
- Ablation
 - Trigger-PV and non-PV sources (LAA, PW, SVC.LoM)
 - Re-entry & substrate modification
 - Adjunctive strategies
 - Novel energy sources and catheters
 - ↓ collateral damage while
 ↑ ablation efficacy
 - · Adjunctive AF surgery



Primary Prevention

- Risk factor management
- RAAS modulation
- · Ideal body weight target
- Prophylactic PVI in high-risk patients while undergoing open-heart procedures

Secondary Prevention

- Aggressive integrated weightloss programs
- Treat hypertension
- OSA uncover, treat and improve compliance
- · Heart failure RX
- Yoga/acupuncture
- Minimize alcohol consumption
- Stop smoking

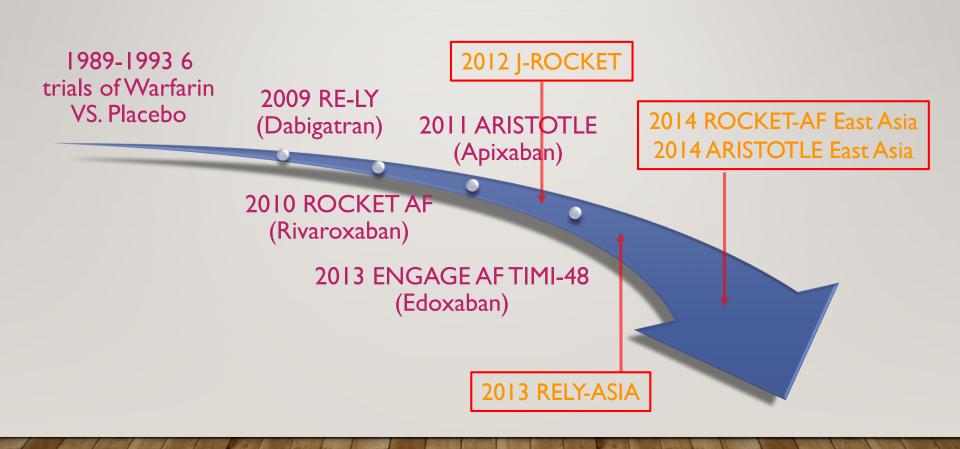
Chung, M.K. et al. J Am Coll Cardiol. 2020;75(14):1689-713.

والم		VKA superior to aspirin for stroke prevention in			First maze surgery for AF treatment published
	104014	AF		PVI can suppress AF	
,000	ACE-I/ARBs prevent AF in heart failure				RF based maze maintains SR after
		VKA reduces stroke in	Rate control not infer	ior to rhythm control	cardiovascular surgery
	ARBs prevent AF in hypertension & LVH	AF by 2/3		PVI maintains SR	
5	hypertension & LVH	Ximelagatran as		better than antiarrhythmic drugs	
ò		effective as VKA	Amiodarone not	and any anima of age	
	App. J	Dabigatran at least as	superior to rate	Dronedarone	
	ARBs do not prevent AF or adverse	effective as VKA in AF	control in heart failure	improves outcomes	
	outcomes in patients			in non-permanent AF	
	without hypertension		Lenient rate control	AF ablation	
1010			acceptable	improves Qol	
۲	PUFA do not	Rixaroxaban and	- 10 MM		
	prevent AF	Apixaban at least as effective as VKA in AF	Dronedarone harms in permanent AF		
	MRA prevent AF in		in permanent ru	First-line PVI maintains SR better	Bipolar RF more
	HFrEF patients pre- treated with ACE-I/	Edoxaban at least as		than antiarrhythmic	effective than
- 1	beta-blockers	effective as VKA in AF		drugs	conventional RF for stand-alone
	ACE-I/ARB prevent			PM/II - I	AF surgery
	AF in hypertension	Meta-analysis and healthcare databases:	Beta-blockers	PVI alone as effective as	
, 4	Beta-blockers prevent AF in HFrEF	NOACs safer and slightly more effective	without prognostic benefit in AF patients with HFrEF	complex ablation in persistent AF	Concomitant maze surgery maintains SR but increases risk of
Pols	patients pre-treated with ACE-I	compared to VKA	WIGH FIFTEF	Cryoenergy as effective as RF for PVI	permanent pacemake

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.

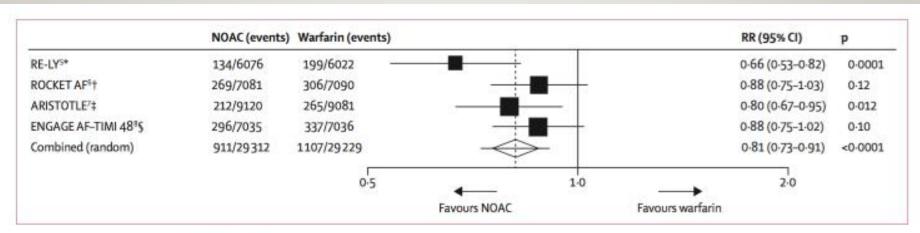


Figure 1: Stroke or systemic embolic events

Data are n/N, unless otherwise indicated. Heterogeneity: I²=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.

?		VKA superior to aspirin for stroke prevention in AF		DVI	First maze surgery for AF treatment published
ACE-I/	ARBs prevent			PVI can suppress AF	RF based maze
		VKA reduces stroke in AF by 2/3	Rate control not infer	ior to rhythm control	maintains SR after cardiovascular surgery
	prevent AF in ension & LVH	Ximelagatran as effective as VKA	Amiodarone not	PVI maintains SR better than antiarrhythmic drugs	
ARBs o	io not prevent or adverse nes in patients t hypertension	Dabigatran at least as effective as VKA in AF	superior to rate control in heart failure	Dronedarone improves outcomes in non-permanent AF	
2			Lenient rate control acceptable	AF ablation improves Qol	
pr	FA do not event AF	Rixaroxaban and Apixaban at least as effective as VKA in AF	Dronedarone harms in permanent AF	First-line PVI	
HFrEF	prevent AF in patients pre- d with ACE-I/ a-blockers	Edoxaban at least as effective as VKA in AF		maintains SR better than antiarrhythmic drugs	Bipolar RF more effective than conventional RF for stand-alone
AF in	ARB prevent hypertension a-blockers	Meta-analysis and healthcare databases: NOACs safer and	Beta-blockers without prognostic	PVI alone as effective as complex ablation in	AF surgery Concomitant maze
patien	t AF in HFrEF ts pre-treated th ACE-I	slightly more effective compared to VKA	benefit in AF patients with HFrEF	persistent AF Cryoenergy as	surgery maintains SR but increases risk of permanent pacemake

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).

Who Needs Anti-coagulation?

CLASS IA

For patients with AF and an elevated CHA₂DS₂-VASc score of 2 or greater in men or 3 or greater in women, oral anticoagulants are recommended.

Table 3 Definitions and points in the CHA₂DS₂-VA score.

Score	Points	Definition
С	1	Congestive 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
Н	1	History of Hypertension, whether or not BP is currently elevated
A ₂	2	A ge ≥75 years
D	1	Diabetes
S ₂	2	History of prior Stroke or TIA or systemic thromboembolism
V	1	Vascular disease, defined as prior myocardial infarction or peripheral arterial disease or complex aortic atheroma or plaque on imaging (if performed)
Α	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 CHA₂DS₂-VASc score of 0 in men or I in women, it is reasonable to omit anticoagulant therapy

Who Needs Anti-coagulation?

CLASS IIB

For patients with AF (except with moderate- to-severe mitral stenosis or a mechanical heart valve) and a CHA₂DS₂-VASc score of I in men and 2 in women, prescribing an oral anticoagulant to reduce thromboembolic stroke risk may be considered.

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).

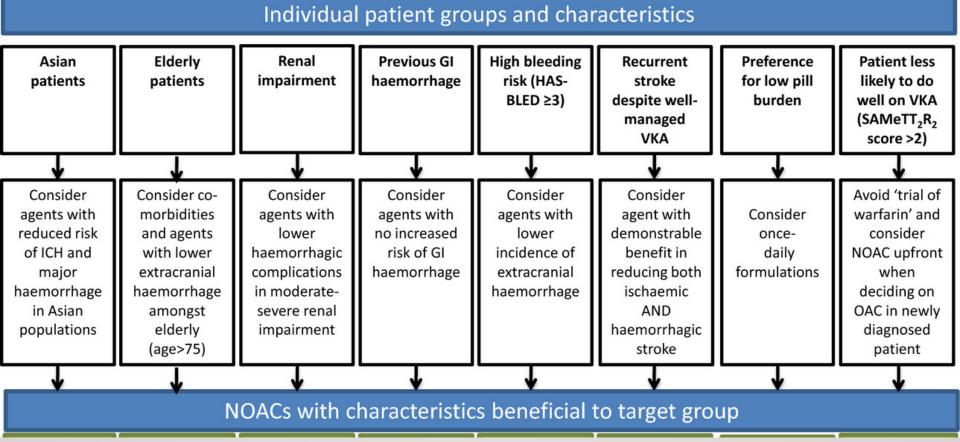
Summary I

For patients with AF (except with moderate- to-severe mitral stenosis or a mechanical heart valve), CHA₂DS₂-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

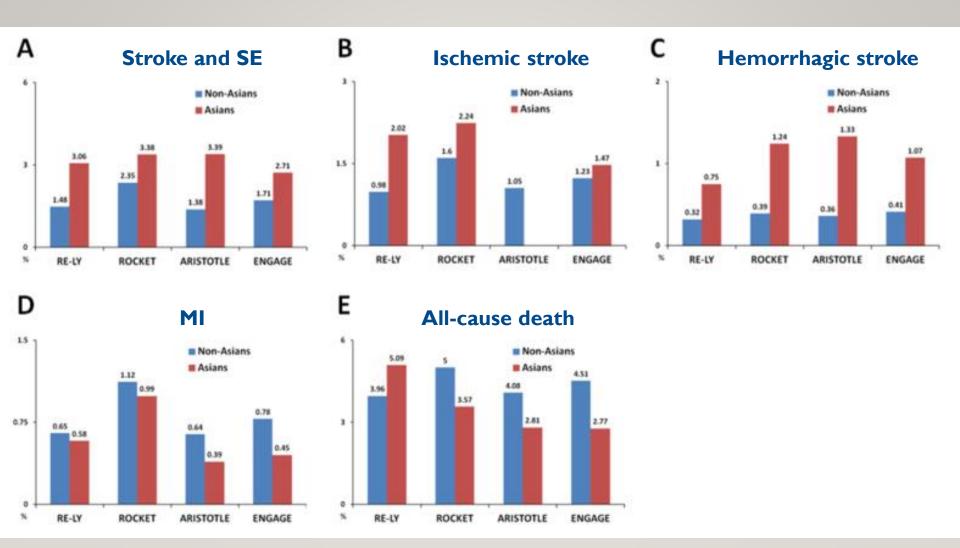
		Dahigatran (RE-LY)			Rivaroxaban (ROCKET-AF)		Aptraban (ARISTOTLE)		Edoxaban (ENGAGE AF-TIMI 48)		
Mechanism	Oral direct t	hrombin inhibitor		Oral direct factor Xa inhibitor		Oral direct factor Xa inhibitor		Oral direct factor Xa inhibitor			
Bioavallability, %	6		1	66 fasting 80-100 with food		50		62			
Time to peak levels, hours	3			2-4	2-4			1-2			
Half-life, hours	12-17		3	5-13		9-14		10-14			
Excretion	80% renal			66% liver, 33% renal		27% renal		50% renal			
Dose	150 mg twice	e daily or 110 mg twice d	tuly	20 mg once daily		5 mg twice	dally	60 mg once	daily or 30 mg once dai	ly	
Dose reduction in selected padients				Rivaroxaban 15 mg mL/min	Rivarosaban 15 mg once daily if CrCl 30-49 mL/min		5 mg twice daily if at least years, body weight 560 kg eatinine level 21.5 mg/dl.)	edosaban 3 the followin	0 mg reduced to 30 mg 0 mg reduced to 15 mg g; creatinine clearance o kg, concomitant use of v rone	once daily, if any of f 30-50 mL/min, bod	
Study design	Randomized	Randomized open-label		Randomized, double	blind	Randomized	. double-blind	Randomize	d, double-blind		
Number of patients	18 113			14 264		18 201		21 105	dis-		
Follow-up period, years	2	ET-CIT.		1.9		1.8		2.8			
Randomized groups	Dose-adjusto	Dose-adjusted warfarin vs. blinded doses		Dose-adjusted work	arin vs. riveroxeben	Dose-adjust	ed warfarin vs. apicaban 5	Dose-adjus	ted warfarin vs. edoxaba		
Age, years	-	of dabigatran (150 mg twice daily, 110 mg twice daily) 71.5 ± 8.7 (mean ± 5D)		73 (65-78) [median (interquartile range)]		-	70 (63-76) [median (interquartile		(60 mg once daily, 30 mg once daily) 72 (64-78) [median (interquantile range)]		
Male sex. %	63.6			100000		64.5		61.9			
CHADS: score (mean)	2.1			500		2.1		2.8			
Crared acore (mean)	Warfarin	Dubigatran 150	Dabigatran I 10	Warterin	Rivarovaban	Warfarin	Apixaban	Warfarin	Edovaban 60	Edovation 30	
	n = 6022	n = 6076	n = 6015	n = 7133	n=7131	n = 9081	n = 9120	n = 7036	n = 7035	n = 7034	
	Event rate, Wyear	Event rate, Nyear (RR vs. warfarin)	Event rate, %/ year (RR vs. warfarin)	Event rate, %/year	Event rate, Wyear (HR. vs. warfarin)	Event rate, Wyear	Event rate, %/year (HR, vs. warfarin)	Event rate, Wyear	Event rate, Nyear (HR vs. warfarin)	Event rate, Wyear (HR vs. warfarin)	
Strokelsystenic 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)	24	2.1 (0.86, 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 som- inferiority, P = 0.01 for superiority)	1.90	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; 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. P <0.001)	
Haemorrhagic stroke	0.30	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. 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)	I.61 (0.47, 0.41-0. 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. 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)	124	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) P <0.001)	
Myocardal 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/ 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)	221	1.87 (0.85; 0.70-1.02; P = 0.07)	3.94	3.52 (0.89, 0.80-0.99; P = 0.047)	435	3.99 (0.92,0.83-1.01; P = 0.08)	3.80 (0.87, 0.79-0: P = 0.006)	



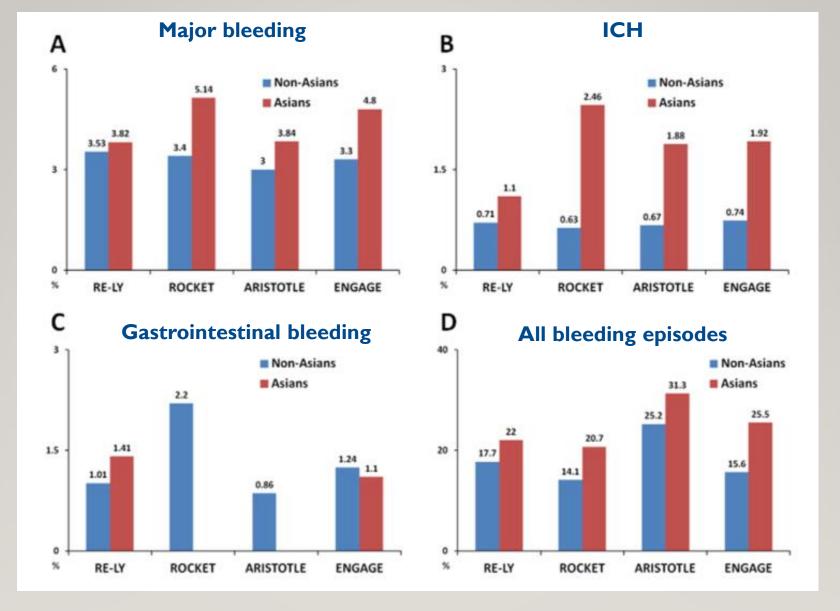


J Intern Med. 2015 Jul;278(1):1-18.

I) ASIAN



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



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

Stroke and SEE

Asian RE-LY, 150mg 25/933 53/926 ROCKET AF 21/468 27/464 ARISTOTLE 44/988 60/1005 ENGAGE AF, 60mg 34/646 47/644 Overall Effect		NOAC Event/Total	VKA Event/Total
ROCKET AF 21/468 27/464 ARISTOTLE 44/988 60/1005 ENGAGE AF, 60mg 34/646 47/644	Asian		
ARISTOTLE 44/988 60/1005 ENGAGE AF, 60mg 34/646 47/644	RE-LY, 150mg	25/933	53/926
ENGAGE AF, 60mg 34/646 47/644	ROCKET AF	21/468	27/464
	ARISTOTLE	44/988	60/1005
Overall Effect	ENGAGE AF, 60mg	34/646	47/644
	Overall Effect		
Q= 2.9 (P= 0.411) P= 0.0%			

	NOAC Event/Total	VKA Event/Total	OR (95% CI)
Asian			
RE-LY, 110mg	44/923	53/926	0.82 (0.55-1.2
J-ROCKET AF	22/640	26/640	 0.84 (0.47-1.5
ENGAGE AF, 30mg	52/653	47/644	1.10 (0.73-1.6
Overall Effect			 0.93 (0.71-1.2
Q= 1.1 (P= 0.582) P= 0.0%			

Major Bleeding

	NOAC Event/Total	VKA Event/Total		OR (95% CI)
Asian			I	
RE-LY, 150mg	39/933	66/926		0.57 (0.38-0.85)
ROCKET AF	23/466	35/462		0.63 (0.37-1.09)
ARISTOTLE	33/981	63/1002		0.52 (0.34-0.80)
ENGAGE AF, 60mg	42/642	68/641		0.59 (0.39-0.88)
Overall Effect			→	0.57 (0.44-0.74)
Q= 0.4 (P= 0.949) P= 0.0%				

	NOAC Event/Total	VKA Event/Total	OR (95% CI)
Asian			
RE-LY, 110mg	39/923	66/926	 0.57 (0.38-0.86
J-ROCKET AF	26/639	33/639	 0.78 (0.46-1.32
ENGAGE AF, 30mg	24/652	68/641	 0.32 (0.20-0.52
Overall Effect			 0.52 (0.32-0.86
Q= 6.3 (P= 0.042) P= 68.5%			

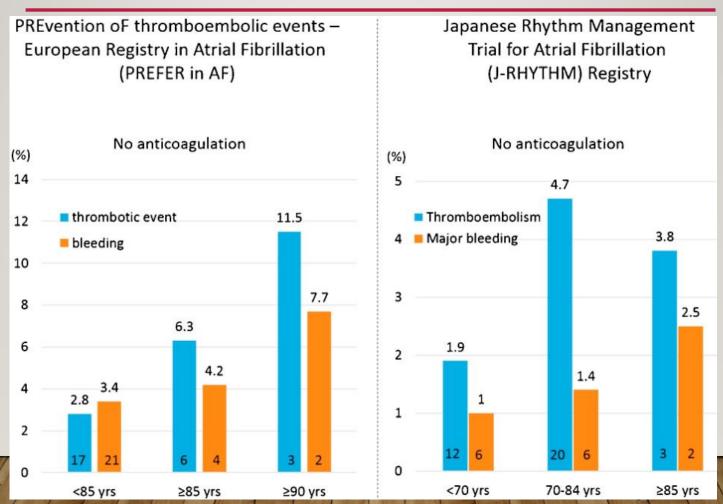
Individual patient groups and characteristics



2) ELDERLY

Elderly Patients

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

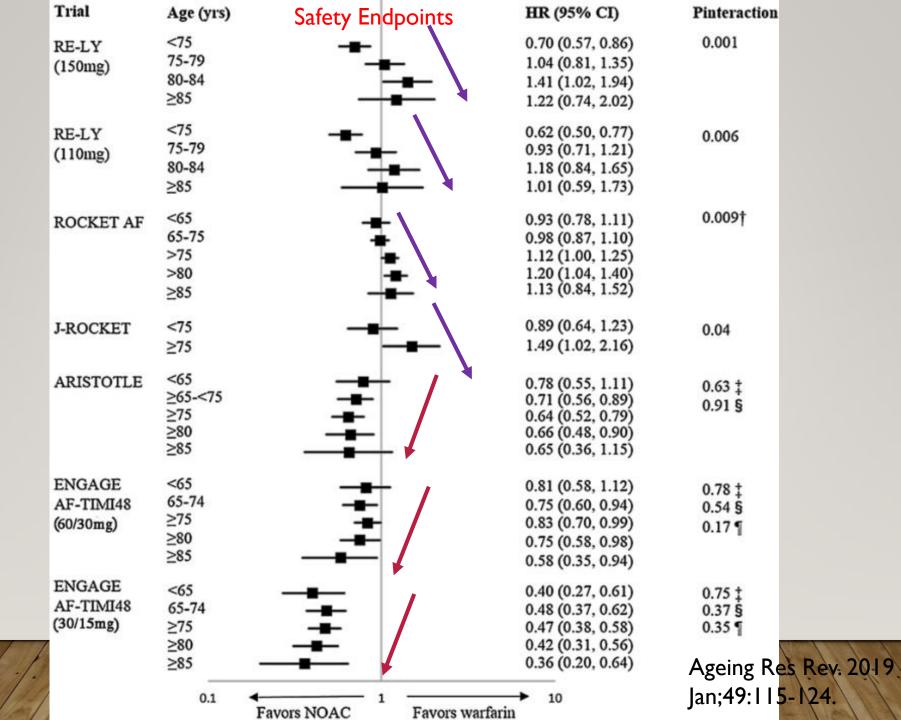


NOAC Meta-analysis in Elderly Patients – Efficacy Patients Age Above 75 Years Old

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 : $I^2 = 0\%$, $\tau^2 = 0$, p=0.6283

Swiss Med Wkly. 2016; 146: w14356. Test for overall effect: p<0.0001

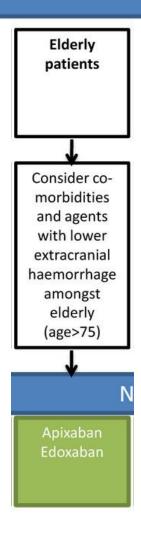


NOAC Meta-analysis in Elderly Patients – Safety Patients Age Above 75 Years Old

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	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%

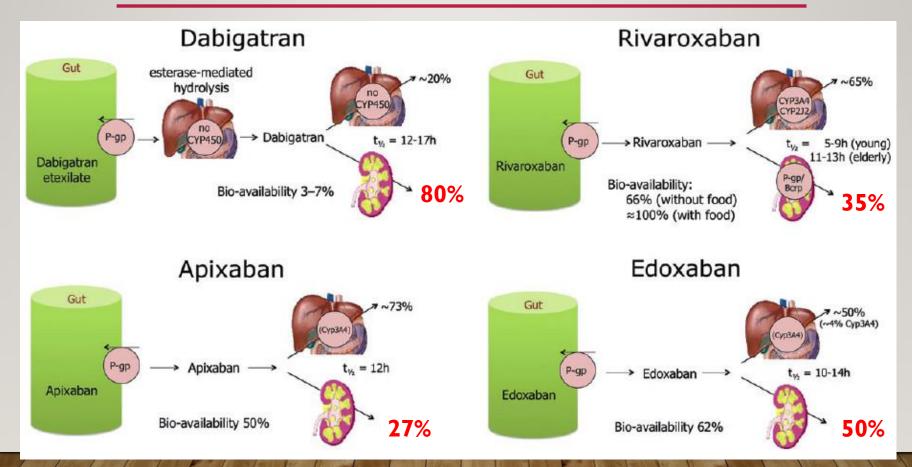
Heterogeneity: $I^2 = 89.1\%$, $\tau^2 = 0.0662$, p<0.... Test for over all effect: p = 0.5999

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

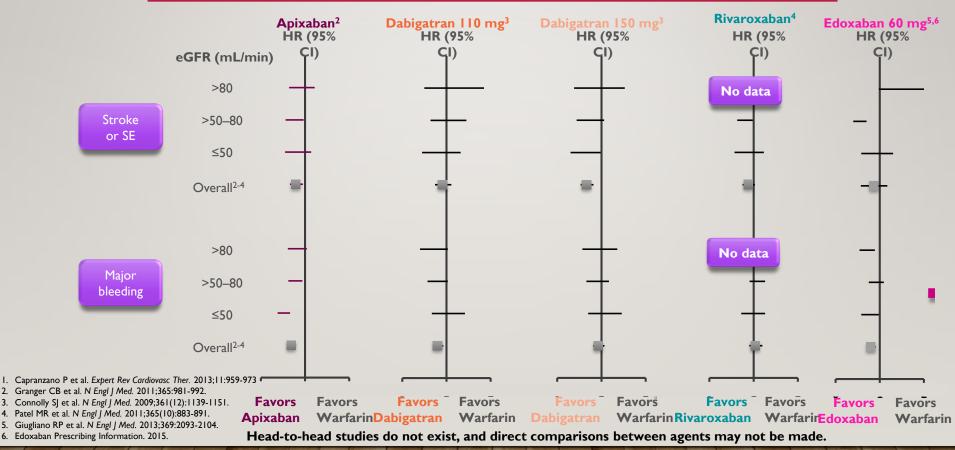
Phase III Trials for DOACs v.s Warfarin 1-5

	A pixaban	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	<u>19%</u> 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



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 CHA₂DS₂- VASc score, treatment with reduced doses of direct thrombin or factor Xa inhibitors may be considered.

For patients with AF who have a CHA₂DS₂-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 **CLASS IIB** might be reasonable to prescribe warfarin (INR 2.0 to 3.0) or apixaban for oral anticoagulation. In patients with AF and end-stage CKD or on dialysis, the direct thrombin inhibitor dabigatran or the factor Xa **CLASS III** inhibitors rivaroxaban or edoxaban are (No benefit) not recommended because of the lack of evidence from clinical trials that benefit exceeds risk.

CENTRAL ILLUSTRATION Patients With Oral Anticoagulation Management

Whether to perform anticoagulation therapy for patients with AF on chronic dialysis?

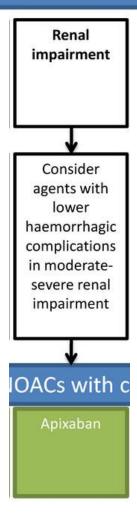
OAC

- OACs were not associated with a lower risk of thromboembolism in patients with AF on chronic dialysis.
- Patients who received apixaban 5 mg twice daily had significantly lower risk of mortality than apixaban 2.5 mg twice daily, warfarin, and no-anticoagulant.
- Warfarin, dabigatran, and rivaroxaban were associated with higher bleeding risk compared with apixaban and no-anticoagulant.

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

	NOAC (events)	Warfarin (events)			RR (95% CI)	р
RE-LY5*	375/6076	397/6022		_	0.94 (0.82-1.07)	0.34
ROCKET AF ⁶ †	395/7111	386/7125	_		1.03 (0.90-1.18)	0.72
ARISTOTLE ⁷ ‡	327/9088	462/9052			0.71 (0.61-0.81)	<0.0001
ENGAGE AF-TIMI 488§	444/7012	557/7012			0.80 (0.71-0.90)	0.0002
Combined (random)	1541/29287	1802/29211			0.86 (0.73–1.00)	0.06
		0.5	1.0		2.0	
			Favours NOAC	Favours warfarin		

Figure 3: Major bleeding

Data are n/N, unless otherwise indicated. Heterogeneity: I²=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.

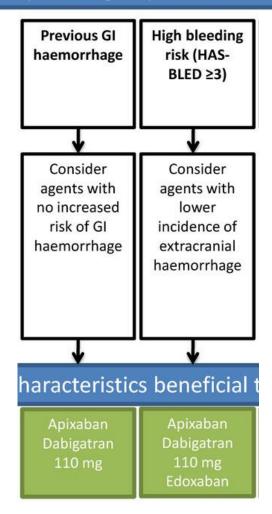
High-dose dabigatran (RR 1.50, 95% CI 1.19–1.89; P < 0.001), high-dose edoxaban (RR 1.23, 95% CI 1.02–1.50; P = 0.03) and rivaroxaban (3.2% vs. 2.2%, P < 0.001) were all associated with a significantly increased risk of gastrointestinal haemorrhage compared to warfarin in their respective trials, but 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		X	X	X		
Specific Antidote	Idarucizumab	Andexanet alpha				

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

Individual patient groups and characteristics



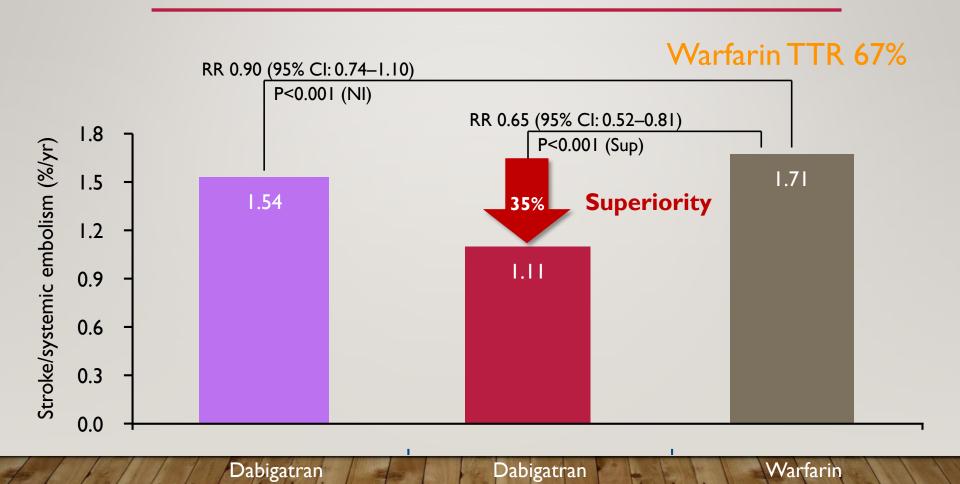
5) HIGH RISK OF STROKE /PREVIOUS TIA/STROKE

RELY Trial

I I 0 mg BID

183/6015

Events/n:

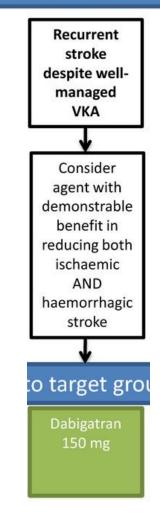


150 mg BID

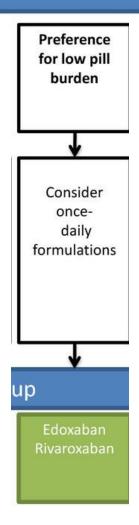
134/6076

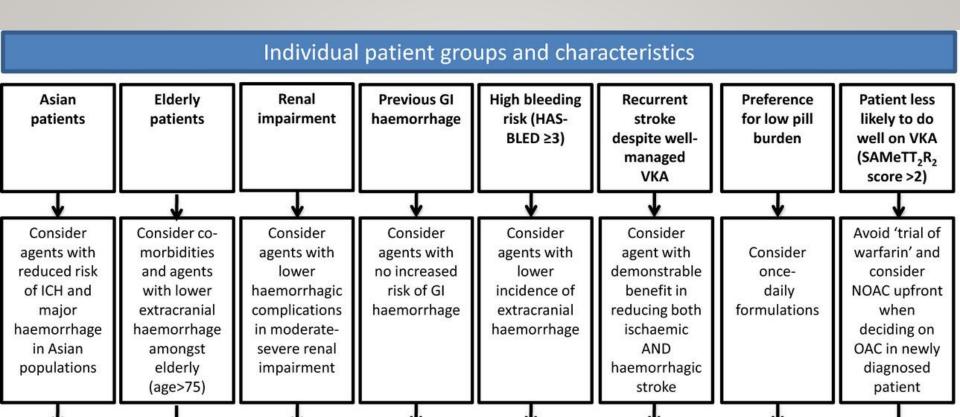
202/6022

Individual patient groups and characteristics



Individual patient groups and characteristics





NOACs with characteristics beneficial to target group

Apixaban Dabigatran Edoxaban

Apixaban Edoxaban Apixabar

Apixaban Dabigatran 110 mg Apixaban Dabigatrar 110 mg

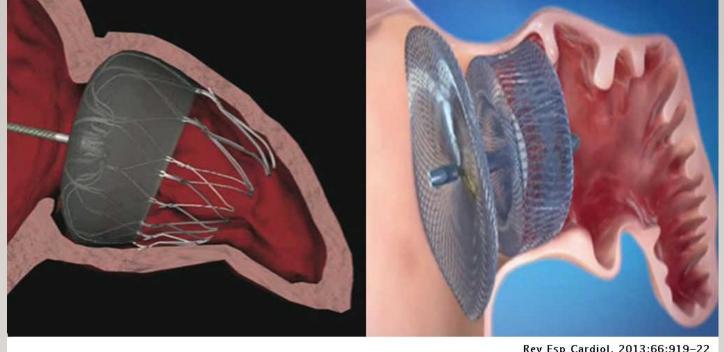
Dabigatran 150 mg

Edoxaban Rivaroxaban Any NOAC, but consider patient characteristics when

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

Summary II

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



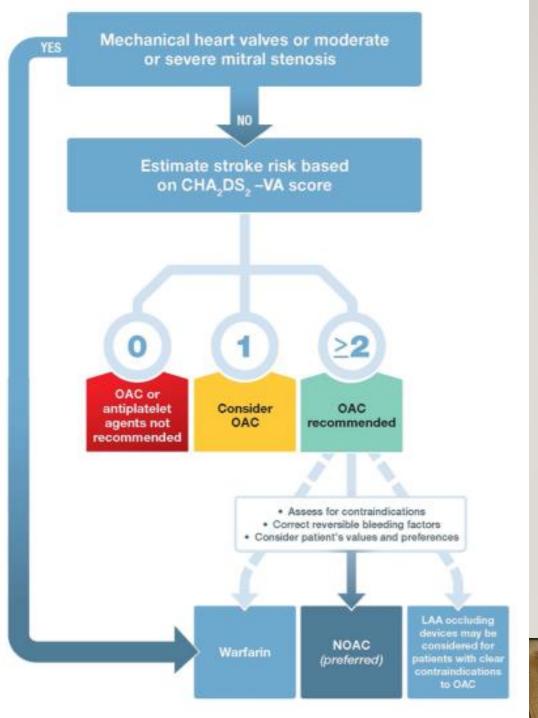
Rev Esp Cardiol. 2013;66:919-22

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