ACC Middle East Conference 2018

In partnership with:

جمعية القلب السعودية
Saudi Heart Association

OAC in Special Population (CKD, VHD , Pregnancy)

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Disclosers

- Proctorship fees: Boehringer Ingeheim, Pfizer, Bayer

NOAC in AF-Valvular Heart Diseases (VHD)

- Current definitions of “valvular” and“nonvalvular” AF are misleading
- VHD (other than moderate/ severe mitral stenosis or mechanical heart valves)
- VHD does not affect the overall relative efficacy or safety of NOACs
- Recently proposed term “MARM-AF,” standing for “MechanicalAnd Rheumatic Mitral valvular AF” could be useful

DOAC in Valvular Heart Diseases (VHD)

Frequency of Valvular Heart Disease Subtypes

RE-LY, ROCKET AF, ARISTOTLE, and ENGAGE AF Trials

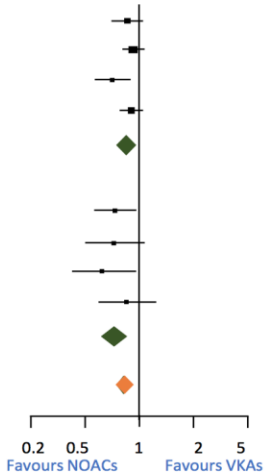
VHD Subtype	RE-LY (n=3950)	ROCKET AF (n=2003)	ARISTOTLE (n=4808)	ENGAGE AF-TIMI 48 (n=2824)
Moderate/severe mitral regurgitation	3101 (78.5)	1756 (87.7)	3526 (73.3)	2250 (79.6)
Mild mitral stenosis	193 (4.9)	NR	131 (2.7)	254 (9.0)
Moderate/severe aortic regurgitation	817 (20.7)	486 (24.3)	887 (18.4)	369 (13.0)
Moderate/severe aortic stenosis	471 (11.9)	215 (10.7)	384 (8.0)	165 (5.8)
Moderate/severe tricuspid regurgitation	1179 (29.8)	NR	2124 (44.0)	NR
Valve surgery (other than mechanical prosthetic heart valve)	NR	106 (5.3)	251 (5.2)	516 (18.2)

Renda G, et al. J Am Coll Cardiol 2017;69:1363–71

SSEE and Major Bleeding in Patients Without and With VHD Treated With Higher-Dose NOACs or Warfarin

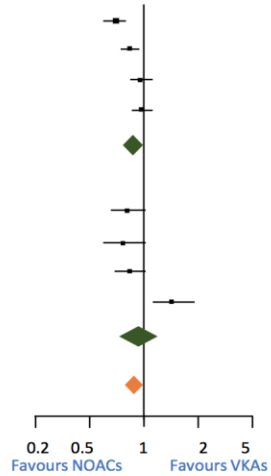
Stroke/SEE

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)	



Major Bleeding

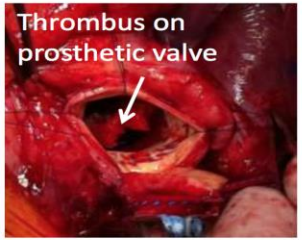
Study or Subgroup	Risk Ratio IV, Random, 95% CI
No VHD	
ARISTOTLE	
ENGAGE AF-TIMI 48 (Higher Dose)	
RE-LY (Higher Dose)	
ROCKET AF	
Subtotal RR (95% CI)=0.85 (0.70-1.02)	
VHD	
ARISTOTLE	
ENGAGE AF-TIMI 48 (Higher Dose)	
RE-LY (Higher Dose)	
ROCKET AF	
Subtotal RR (95% CI)=0.93 (0.68-1.27)	
Total (95% CI) RR=0.88 (0.75-1.02)	



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

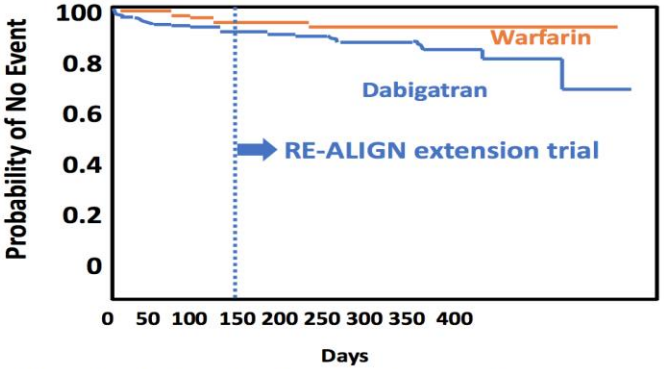
RE-ALIGN

Warfarin vs. Dabigatran with Mechanical Heart Valves

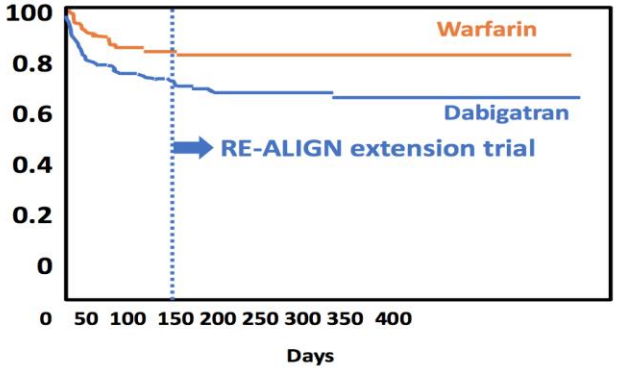


RE-ALIGN - ph2 dose-finding trial of dabigatran in pts with mechanical valves, 150-330 mg bid, adjusted based on renal function and results of Hemoclot

First Thromboembolic Event



First Bleeding Event



Trial **terminated early** after enrolment of 252 pts

Eikelboom JW, et al. N Engl J Med 2013;369:1206-1214

OAC in Pregnancy

Balance the maternal risk of thromboembolism and hemorrhage

Warfarin continued throughout pregnancy offers the best thromboembolic protection to the mother

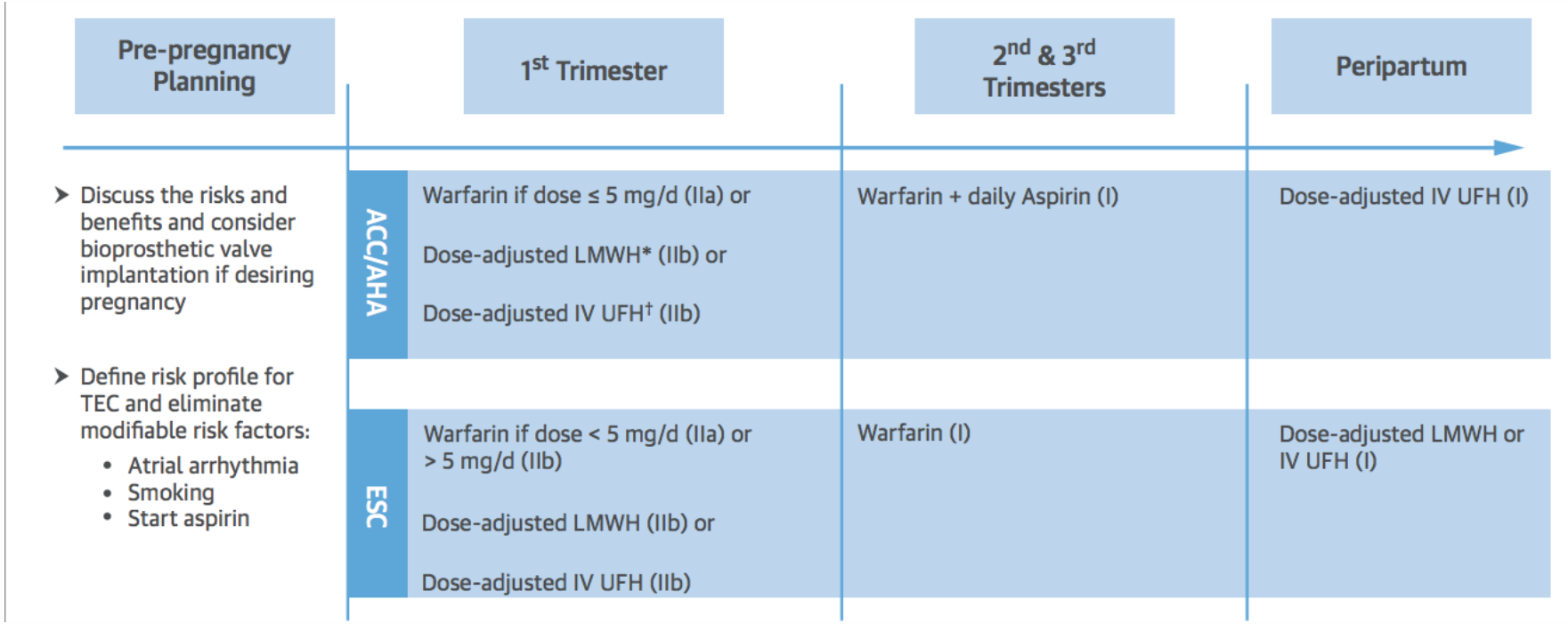
(ACC/AHA) valvular heart disease guidelines support use of warfarin at doses = 5 mg/day throughout pregnancy

a systematic review and meta-analysis. Can J Cardiol 2015 Nov 12

OAC in Pregnancy

>5mg (LMUH/ UH):

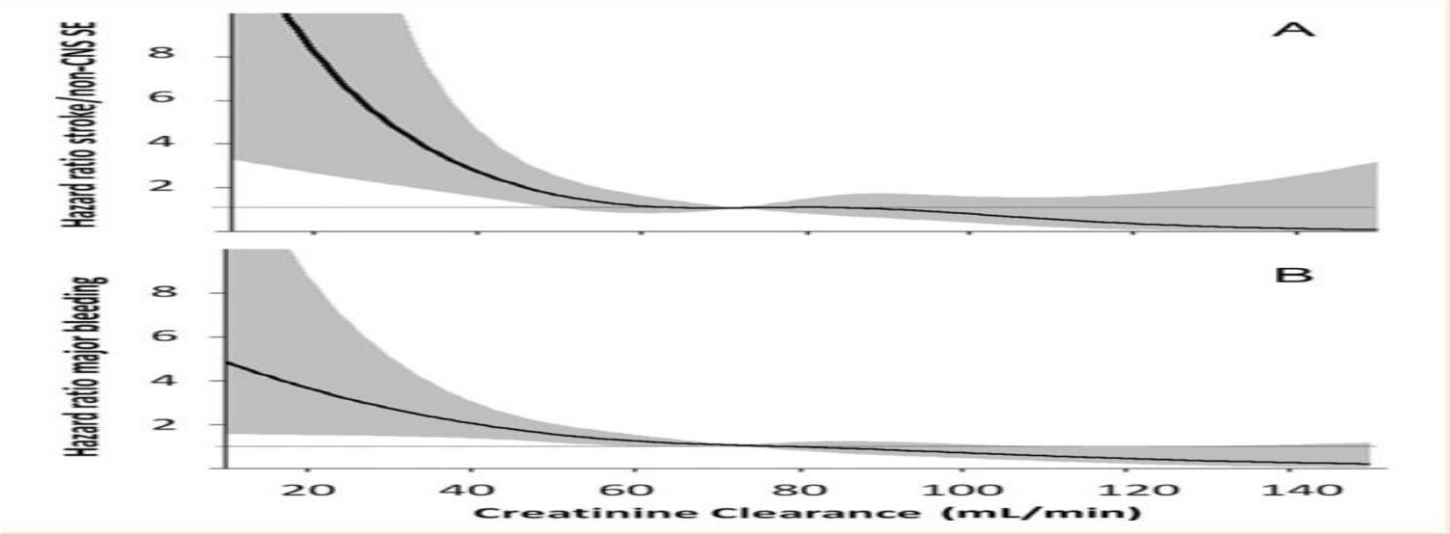
- Weight based LMWH
- Peak anti-Xa level (1.0 to 1.2 U/ml) should be checked 4 to 6 h post-dose, trough>0.6 U/ml


Pre-pregnancy Planning
1st Trimester
2nd & 3rd Trimesters
Peripartum
Discuss the risks and benefits and consider bioprosthetic valve implantation if desiring pregnancy
Define risk profile for TEC and eliminate modifiable risk factors:
Atrial arrhythmia
Smoking
Start aspirin
ACC/AHA
Warfarin if dose ≤ 5 mg/d (IIa) or
Dose-adjusted LMWH* (IIb) or
Dose-adjusted IV UFH† (IIb)
Warfarin + daily Aspirin (I)
Dose-adjusted IV UFH (I)
ESC
Warfarin if dose < 5 mg/d (IIa) or > 5 mg/d (IIb)
Dose-adjusted LMWH (IIb) or
Dose-adjusted IV UFH (IIb)
Warfarin (I)
Dose-adjusted LMWH or IV UFH (I)

OAC in CKD

- Bidirectional interaction between AF & CKD
- Patients with AF & CKD are at increased risk of morbidity & mortality due to
  - Higher risk of thromboembolic events
  - Higher risk of severe bleeding episodes
- All the NOACs are at least partially excreted by the kidneys

Risk of Stroke and systemic embolism and major bleeding according to creatinine clearance



Apostolakis Euro. H. Journal (2013)34, 3572–3579

The 2018 European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation

	Dabigatran[158,182]	Apixaban[183]	Edoxaban[184]	Rivaroxaban[185,186]
Bioavailability	3–7%	50%	62%	15 mg/20 mg: 66% without food, 80–100% with food
Prodrug	Yes	No	No	No
Clearance non-renal/renal of absorbed dose	20%/80%	73%/27%	50%/50%	65%/35%
Plasma protein binding	35%	87%	55%	95%
Dialysability	50–60% (in part dialysable)	14% (in part dialysable)	n.a. (in part dialysable)	n.a. (in part dialysable)

Case 1

70 Year old, M with HTN, ISCH.CM (EF25%), New onset AF, NYHA class 2, CKD (crcl 40ml/min), CHADS-VASc :4, Wt: 85 kg.

What is the best stroke prevention strategy?

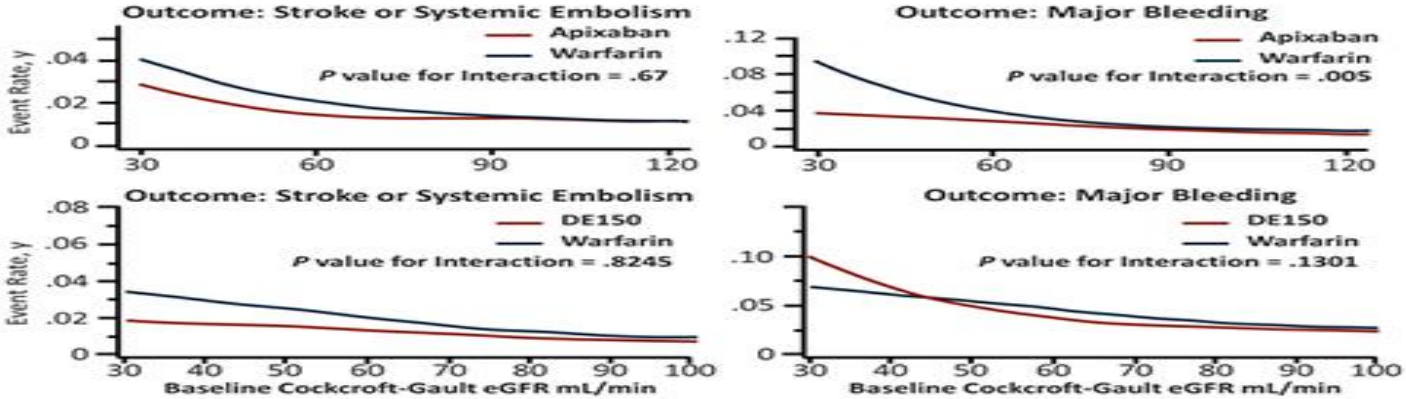
A) Warfarin
B) Dabigatran 110 mg bid
C) Rivaroxaban 15 mg od
D) Apixaban 2.5 mg bid

Evidence

DOAC in Chronic Kidney disease with CrCl > 30 ml per min

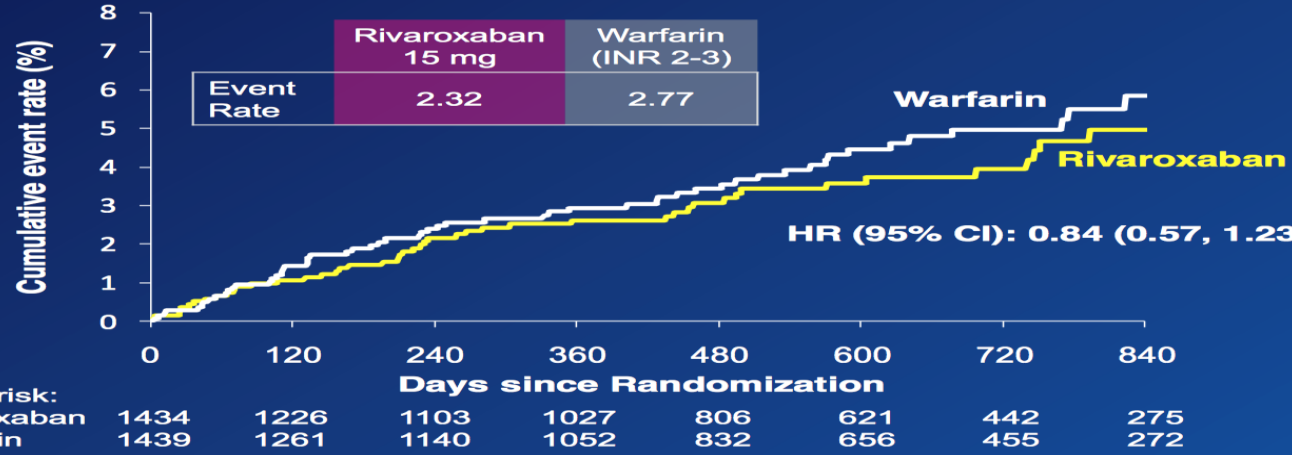
Renal Dysfunction

Efficacy and Safety of Apixaban[a] and Dabigatran[b] With Continuous Analysis of Renal Function



a. Hohnloser SH, et al. *Eur Heart J*. 2012;33:2821-2830[13]; b. Hijazi Z, et al. *Circulation*. 2014;129:961-970.[19]

Stroke or non-CNS embolism among those with CrCl 30–49 mL/min

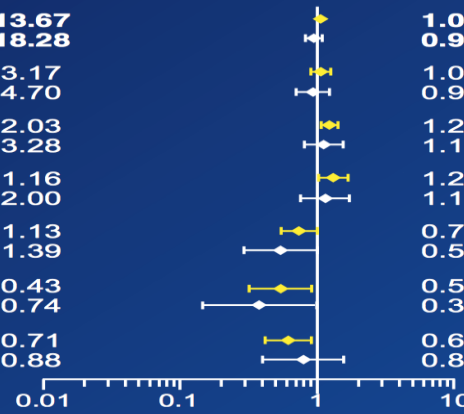


Event rates are % per year
Based on Protocol Compliant on Treatment Population

ROCKET AF

Safety outcomes

Clinical endpoint (% per year)	Rivaroxaban (N=7111)	Warfarin (N=7116)	HR (95% CI) Rivaroxaban vs warfarin	*P* (interaction)
Principal safety outcome*	14.24 17.82	13.67 18.28	**1.04 (0.96–1.13)** **0.98 (0.84–1.14)**	**0.45**
Major bleeding	3.39 4.49	3.17 4.70	1.07 (0.91–1.26) 0.95 (0.72–1.26)	0.48
Hct or Hb drop	2.54 3.76	2.03 3.28	1.25 (1.03–1.52) 1.14 (0.83–1.58)	0.65
Transfusion	1.49 2.34	1.16 2.00	1.28 (0.99–1.65) 1.17 (0.77–1.76)	0.71
Critical organ	0.83 0.76	1.13 1.39	0.74 (0.55–0.99) 0.55 (0.30–1.00)	0.39
Fatal bleeding	0.23 0.28	0.43 0.74	0.55 (0.32–0.93) 0.39 (0.15–0.99)	0.53
Intracranial haemorrhage	0.44 0.71	0.71 0.88	0.62 (0.42–0.92) 0.81 (0.41–1.60)	0.51



Based on safety population on treatment
*Composite of major plus non-major clinically relevant bleeding.
†Rivaroxaban 20 mg od. ‡Rivaroxaban 15 mg od

ROCKET AF

The 2018 European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation

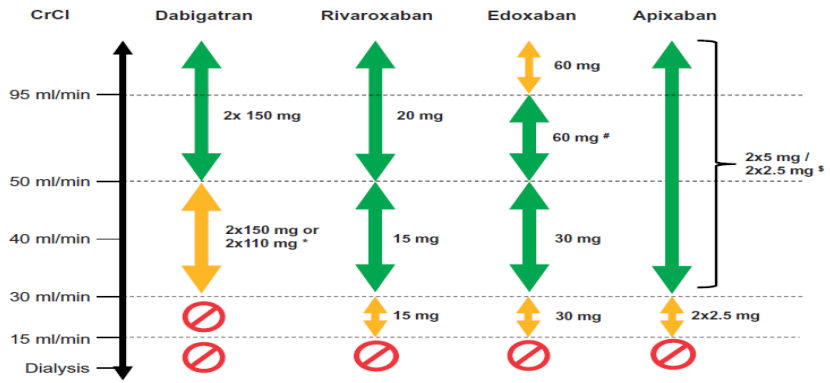


Figure 4 Use of non-vitamin K antagonist oral anticoagulants according to renal function. *2 × 110 mg in patients at high risk of bleeding (per SmPc). #Other dose reduction criteria may apply (weight ≤60 kg, concomitant potent P-Gp inhibitor therapy). $2 × 2.5 mg only if at least two out of three fulfilled: age ≥80 years, body weight ≤60 kg, creatinine ≥1.5 mg/dL (133 µmol/L). Orange arrows indicate cautionary use (dabigatran in moderate renal insufficiency, FXa inhibitors in severe renal insufficiency, edoxaban in 'supranormal' renal function); see text for details.

Back to Case 1

70 Year old, M with HTN, ISCH.CM (EF25%), New onset AF ,

NYHA class 2, CKD (crcl 40ml/min), CHADS-VASc : 4, Wt: 85 kg

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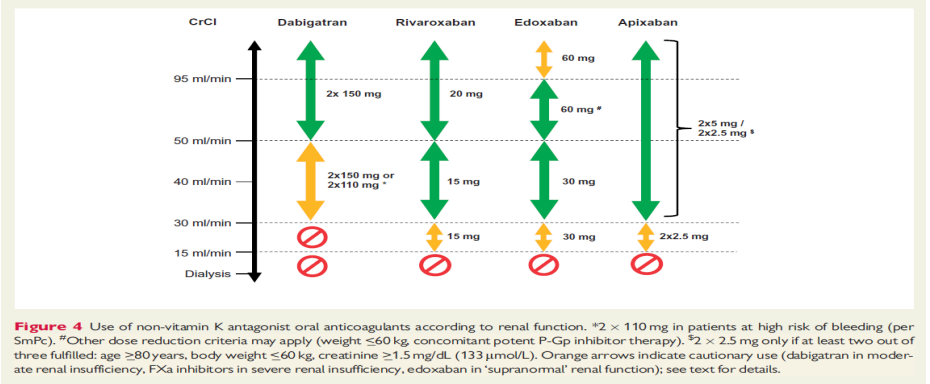


Figure 4 Use of non-vitamin K antagonist oral anticoagulants according to renal function. *2 × 110 mg in patients at high risk of bleeding (per SmPc). #Other dose reduction criteria may apply (weight ≤60 kg, concomitant potent P-Gp inhibitor therapy). $2 × 2.5 mg only if at least two out of three fulfilled: age ≥80 years, body weight ≤60 kg, creatinine ≥1.5 mg/dL (133 µmol/L). Orange arrows indicate cautionary use (dabigatran in moderate renal insufficiency, FXa inhibitors in severe renal insufficiency, edoxaban in 'supranormal' renal function); see text for details.

CKD with Creatinine clearance > 30

- All DOAC are reasonable

- Preference for Rivaroxaban (15 mg), Apixaban (5mg X2)

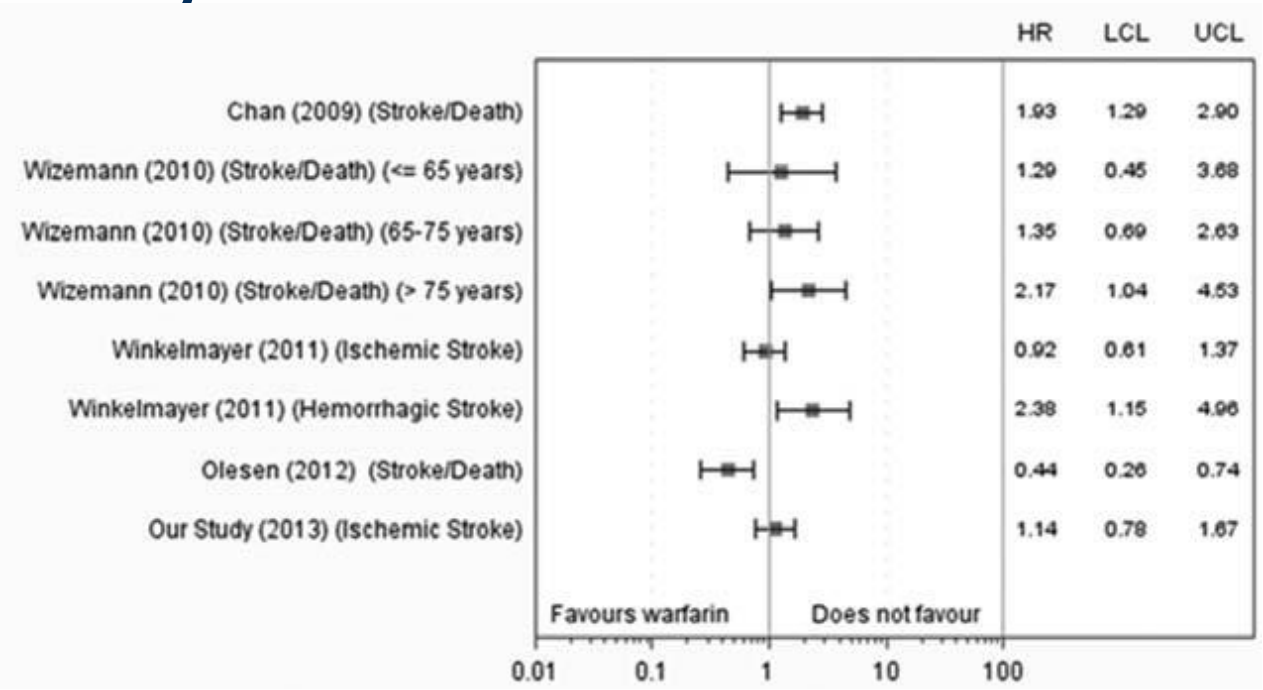
Case 2

66 year old, F,HTN, DM, EF 50%, ESRD on HD , Pers. AF, CHADS-VASc : 4

What is the best stroke prevention strategy?

A) ASA
B) Warfarin
C) Apixaban
D) I don't Know

Warfarin use and stroke in patients with AF undergoing dialysis

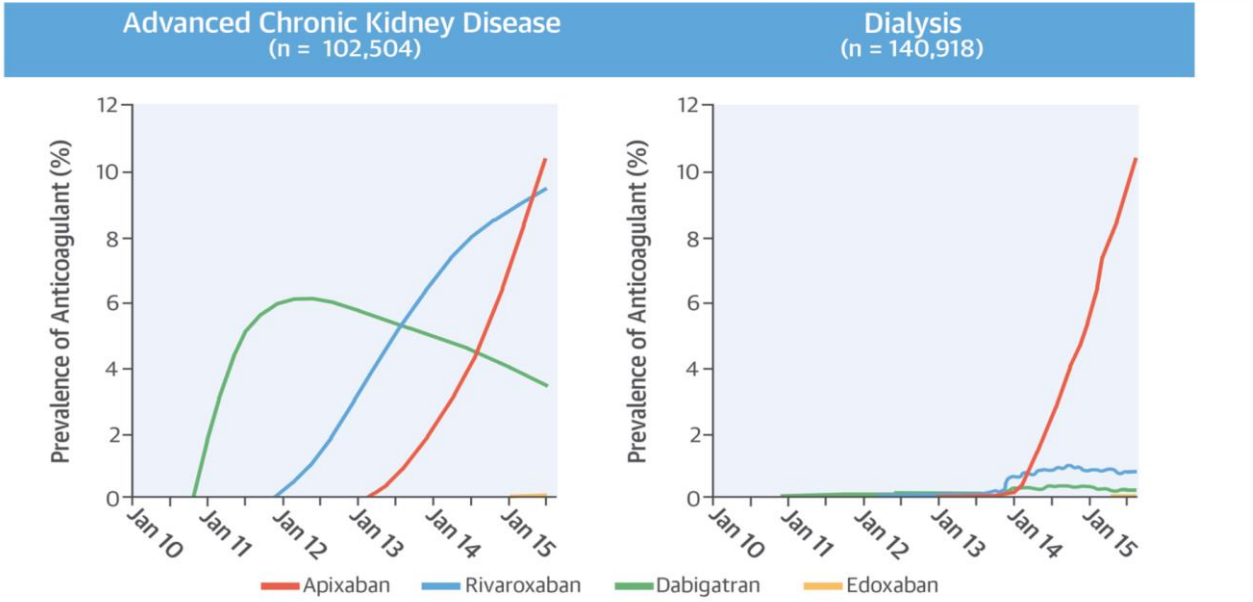


Shah M. circulation 2014;129:1196-1203

Fact

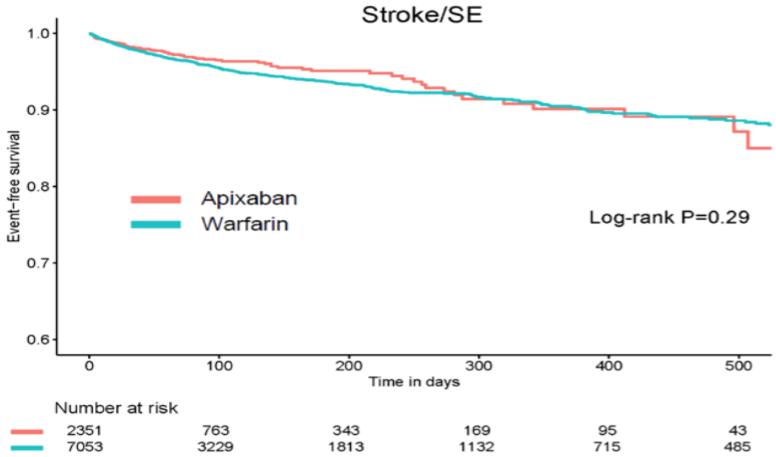
None of the Randomized trials of DOACs included patients with CrCl< 25-30 mL/min

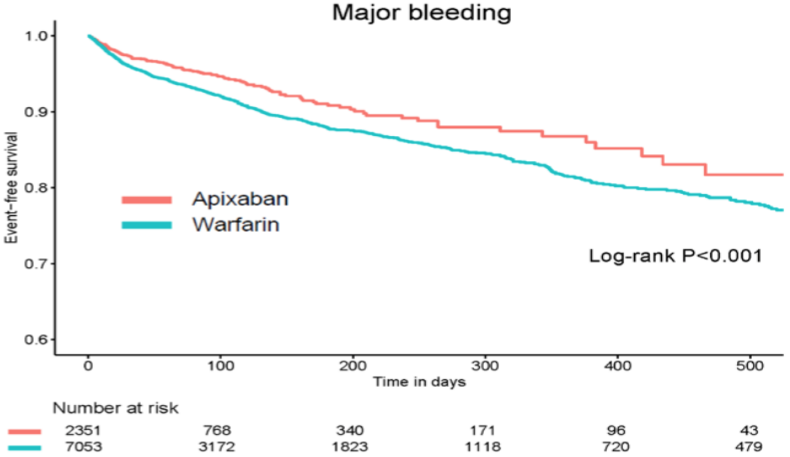
Trends in DOAC use in patients with CKD



Chan, K.E. et al. J Am Coll Cardiol. 2016;67(24):2888-99.

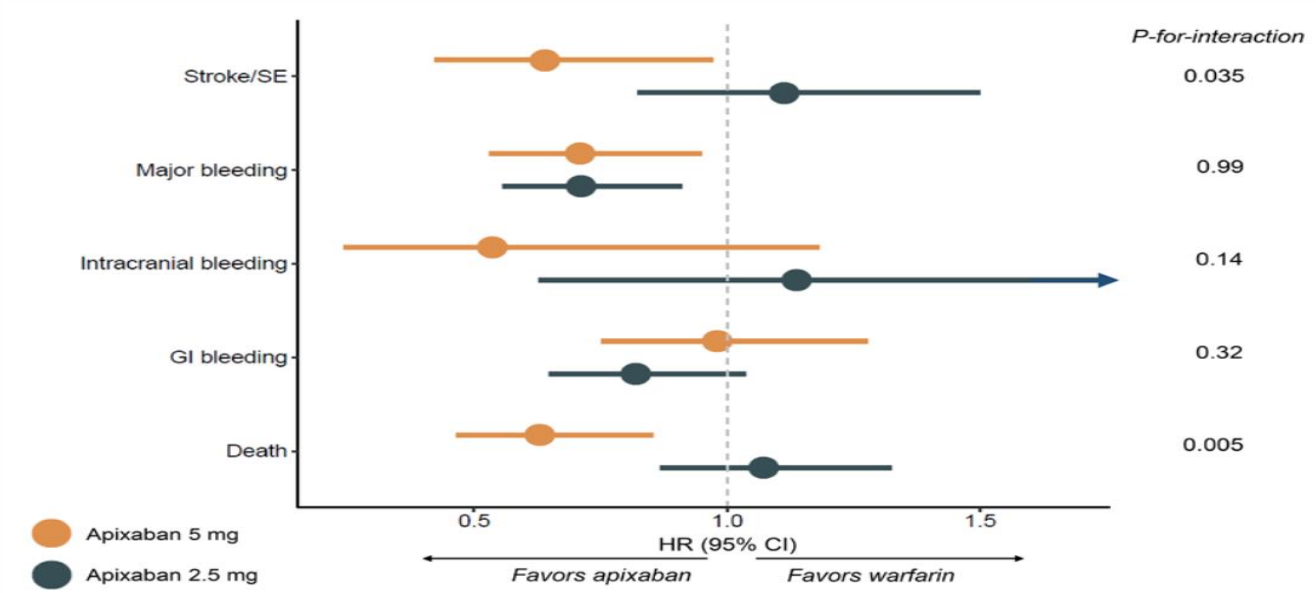
Abixaban vs Warfarin in patients with AF and ESRD in the US





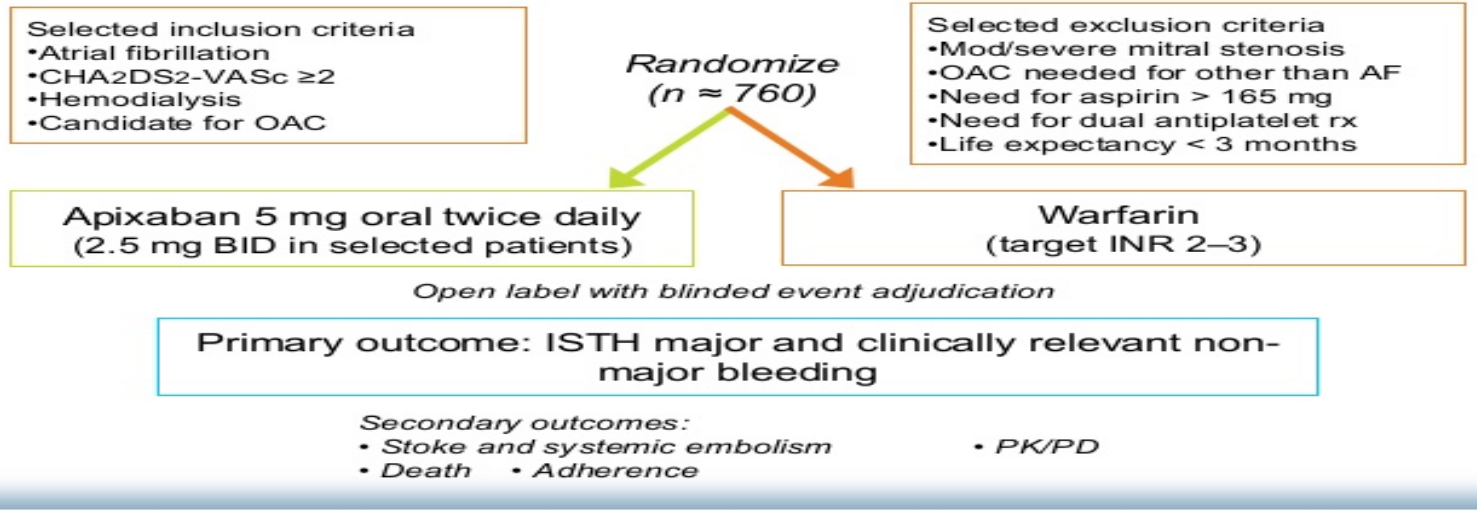
Siontis k. Circulation.2018;138:1519–1529.

Abixaban vs Warfarin in patients with AF and ESRD in the US



Siontis k. Circulation.2018;138:1519–1529.

RENAL-AF Trial: Study Overview



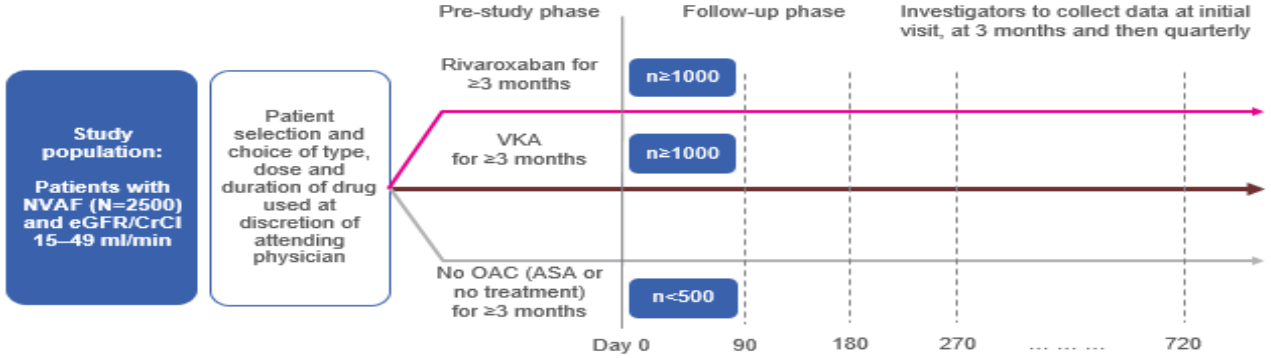
RENAL-AF

Investigator initiated
ClinicalTrials.gov Identifier: NCT02942407

XARENO – An Ongoing Real-World Study of Rivaroxaban in Renally Impaired Patients

Official study title: Factor XA – inhibition in RENal patients with non-valvular atrial fibrillation Observational registry

Objective: To assess CKD progression and safety of anticoagulation strategies in NVAF patients with eGFR 15–49 ml/min /1.73 m² in routine clinical practice



Short design: Observational, open-label, active-controlled, multicentre study (N=2500)

www.clinicaltrials.gov/ct2/show/NCT02663076

◄ Slide Index

Back to Case 2

66 year old, F,HTN, DM, EF 50%, ESRD on HD, Pers. AF, CHADS-VASc : 4
What is the best stroke prevention strategy?

A) ASA (X)
B) Warfarin (?)
C) Apixaban (?)
D) I don't Know ()

Conclusion

- Moderate CKD (CrCl30-50) : DOAC therapy is preferred
- Apixaban, Rivaroxaban > Dabigatran
- Optimal therapy in advance CKD and ESRD is not clear
- ? Warfarin for now
- DOAC vs LA occlude in the future ?

Thanks

Non–Vitamin K Antagonist Oral Anticoagulants in Patients With Atrial Fibrillation and Valvular Heart Disease

Giulia Renda, MD, PhD,[a] Fabrizio Ricci, MD,[a] Robert P. Giugliano, MD, SM,[b] Raffaele De Caterina, MD, PhD[a]

ABSTRACT

BACKGROUND Valvular heart disease (VHD) and atrial fibrillation (AF) often coexist. Phase III trials comparing non–vitamin K antagonist oral anticoagulants (NOACs) with warfarin excluded patients with moderate/severe mitral stenosis or mechanical heart valves, but variably included patients with other VHD and valve surgeries.

OBJECTIVES This study aimed to determine relative safety and efficacy of NOACs in patients with VHD.

METHODS We performed a meta-analysis of the 4 phase III AF trials of the currently available NOACs versus warfarin in patients with coexisting VHD to assess pooled estimates of relative risk (RR) and 95% confidence intervals (CIs) for stroke/systemic embolic events (SSEE), major bleeding, intracranial hemorrhage (ICH), and all-cause death.

RESULTS Compared with warfarin, the rate of SSEE in patients treated with higher-dose NOACs was lower and consistent among 13,585 patients with (RR: 0.70; 95% CI: 0.58 to 0.86) or 58,098 without VHD (RR: 0.84; 95% CI: 0.75 to 0.95; interaction p = 0.13). Major bleeding in patients on higher-dose NOACs versus warfarin was similar and consistent among patients with (RR: 0.93; 95% CI: 0.68 to 1.27) or without VHD (RR: 0.85; 95% CI: 0.70 to 1.02; interaction p = 0.63 for VHD/no-VHD difference). Intracranial hemorrhage was lower with higher-dose NOACs than with warfarin irrespective of VHD (RR: 0.47; 95% CI: 0.24 to 0.93, and 0.49; 95% CI: 0.41 to 059, respectively; interaction p = 0.91). No protective effect of higher-dose NOACs in preventing all-cause death seemed to be present in patients with VHD versus without VHD (RR:1.01; 95% CI: 0.90 to 1.14 vs. RR: 0.88; 95% CI: 0.82 to 0.94, respectively; interaction p = 0.03).

CONCLUSIONS High-dose NOACs provide overall efficacy and safety similar in AF patients with or without VHD.

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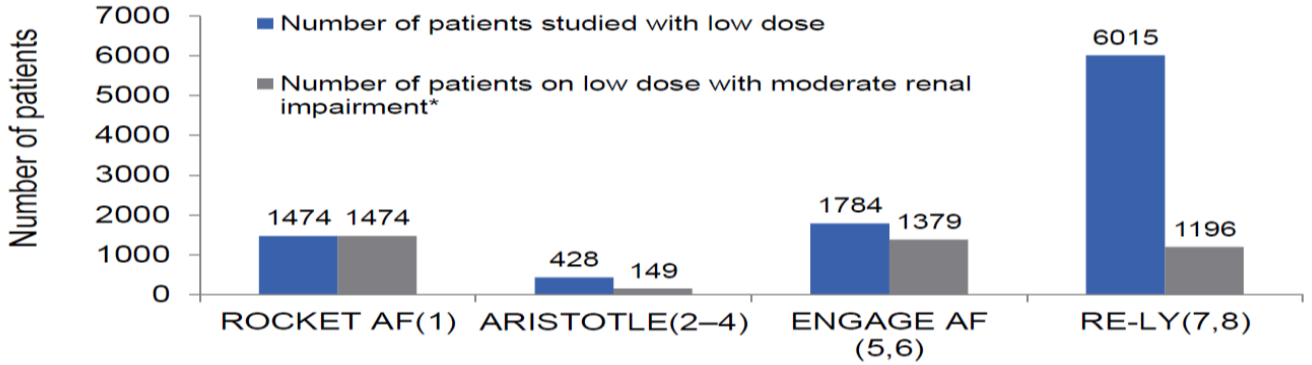
TABLE 1 Select Anticoagulant Agents and Implications in Pregnancy

Drug	Mechanism	Therapeutic Dose	Monitoring	Metabolism/Clearance	Pregnancy Category	Present in Breast Milk	Crosses the Placenta
Warfarin	Vitamin K antagonism	Variable	INR	Hepatic	D	No	Yes
Unfractionated heparin	Antithrombin by potentiating antithrombin III	Variable (IV or SC)	aPTT	Hepatic	C	No	No
Enoxaparin	Inhibits factor Xa and potentiates antithrombin III	1 mg/kg dose every 12 h	Peak anti-Xa level 4-6 h after dose	Hepatic metabolism and renal clearance	B	No	No
Dalteparin	Inhibits factor Xa and thrombin	100 U/kg dose every 12 h	Peak anti-Xa level 4-6 h after dose	Renal	B	No	No
Fondaparinux	Inhibits factor Xa and potentiates antithrombin III	5-10 mg once daily	Peak anti-Xa level 4-6 h after dose	Renal	B	Unknown	No
Dabigatran	Direct thrombin inhibitor	110-150 mg twice daily	NA	Mainly renal excretion	C	Unknown	Likely (57)
Apixaban	Selective Xa inhibitor	2.5-10.0 mg twice daily	NA	Hepatic metabolism and excreted in urine and feces	B	Unknown	Yes (58)
Rivaroxaban	Selective Xa inhibitor	15-20 mg once daily	NA	Hepatic metabolism and excreted in urine and feces	C	Unknown	Likely (59)
Edoxaban	Selective Xa inhibitor	30-60 mg once daily	NA	Hydrolysis and excreted primarily in the urine	C	Unknown	Likely (60)

aPTT = activated partial thromboplastin time; INR = international normalized ratio; IV = intravenous; NA = not applicable; SC = subcutaneous.

Proportion of Patients in Phase III Trials who Received Reduced Dose NOAC

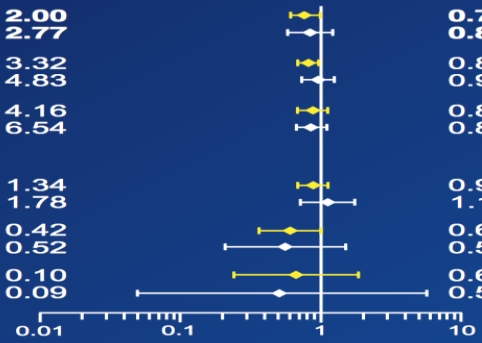


*% of NOAC arm of study; ENGAGE AF: data given for dose adjusted arm of 'high-dose' (60/30) group

1. Fox KAA *et al*, *Eur Heart J* 2011;32:2387–2394; 2. Granger CB *et al*, *N Engl J Med* 2011;365:981–992; 3. Hohnloser SH *et al*, *Eur Heart J* 2012;33:2821–2830; 4. Apixaban FDA medical review; 5. Giugliano RP *et al*, *N Engl J Med* 2013;369:2093–2104; 6. Bohula *et al*, *Circulation* 2016;134:24–36; 7. Connolly SJ *et al*, *N Engl J Med* 2009;361:1139–1151; 8. Hijazi Z *et al*, *Circulation* 2014;129:961–970

Efficacy endpoints on treatment

Clinical endpoint (% per year)	Rivaroxaban (N=7111)	Warfarin (N=7116)	HR (95% CI) Rivaroxaban vs warfarin	*P* (interaction)
Primary efficacy endpoint*	**1.57** **2.32**	**2.00** **2.77**	**0.78 (0.63–0.98)** **0.84 (0.57–1.23)**	**0.76**
PE + vascular death	2.76 4.64	3.32 4.83	0.83 (0.70–0.98) 0.96 (0.73–1.27)	0.38
PE + MI, vascular death	3.55 5.58	4.16 6.54	0.85 (0.73–0.99) 0.85 (0.67–1.09)	0.98
Stroke				
Ischaemic	1.20 1.98	1.34 1.78	0.90 (0.69–1.16) 1.11 (0.71–1.73)	0.41
Haemorrhagic	0.26 0.29	0.42 0.52	0.62 (0.37–1.03) 0.56 (0.21–1.51)	0.88
Undetermined	0.07 0.05	0.10 0.09	0.68 (0.24–1.90) 0.51 (0.05–5.67)	0.84



Based on per-protocol population on treatment
*Stroke and systemic embolism
†Rivaroxaban 20 mg od. ‡Rivaroxaban 15 mg od

ROCKET AF