Why do we Still Use Warfarin in 2020?

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Disclosures

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Other	NHLBI Atrial Fibrillation Working Group; Steering Committee American College of Cardiology/Medscape Center of Excellence on Atrial Fibrillation; HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation

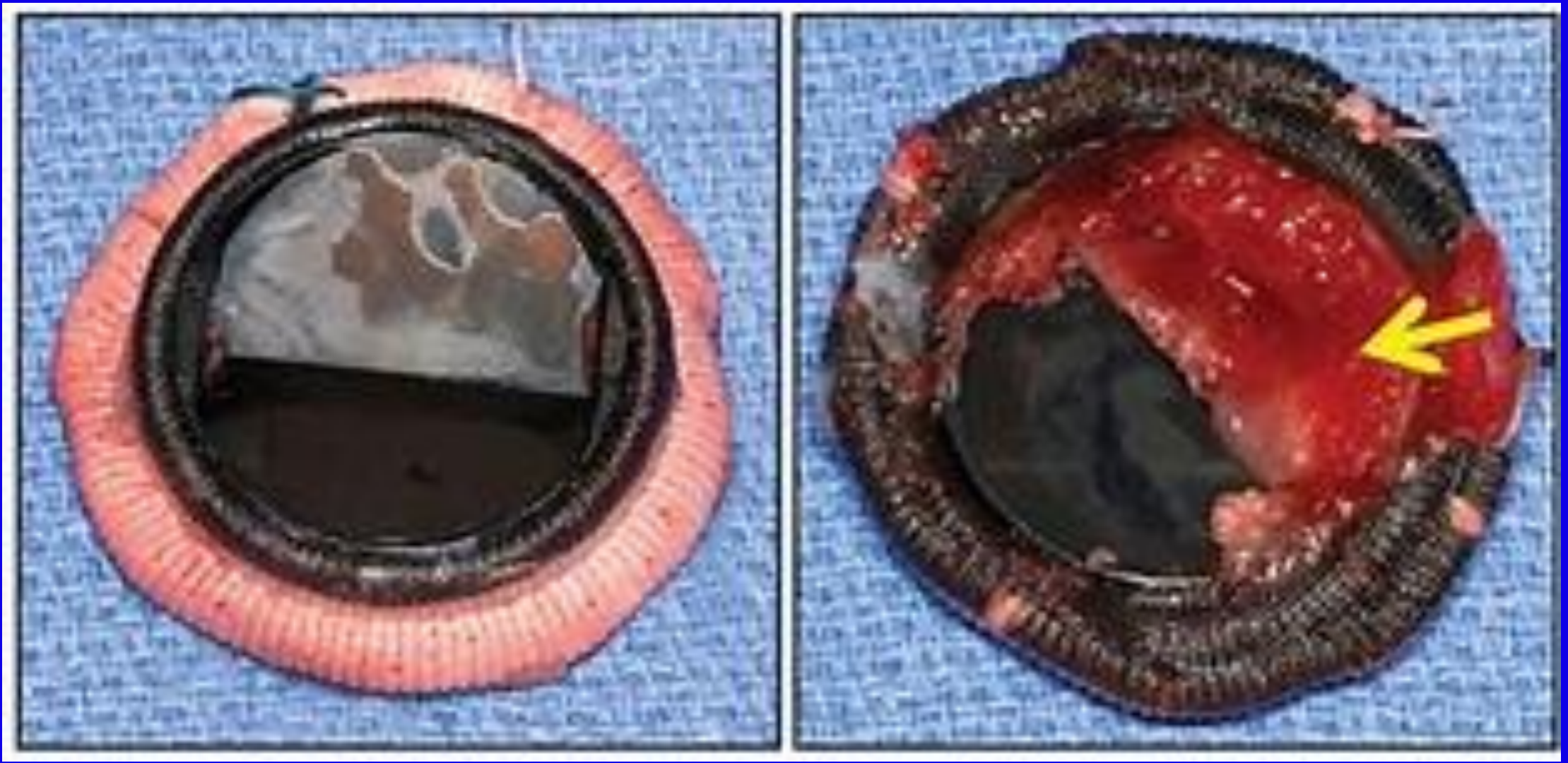
2019 AHA/ACC/HRS Focused Update of the 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation

Developed in Collaboration With the Society of Thoracic Surgeons

Anticoagulation Regimen – Balancing Risks and Benefits

Recommendations for Selecting an Anticoagulant Regimen—Balancing Risks and Benefits		
COR	**LOE**	**Recommendations**
I	**C-EO**	**For patients with AF (except with moderate-to-severe mitral stenosis or a mechanical heart valve) who are unable to maintain a therapeutic INR level with warfarin, use of a NOAC is recommended.** **MODIFIED**: Exclusion criteria are now defined as moderate-to-severe mitral stenosis or a mechanical heart valve, and this recommendation has been changed in response to the approval of edoxaban. (Section 4.1. in the 2014 AF Guideline)

PROSTHETIC VALVE THROMBOSIS



Healthcare | Heart Disease | Latest News

FDA approves CryoLife's request for PROACT Xa Clinical Trial to determine if Apixaban is a good alternative for Warfarin

Mariyam Tanveer • December 24, 2019 0

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Outcomes of Direct Oral Anticoagulants in Patients With Mitral Stenosis

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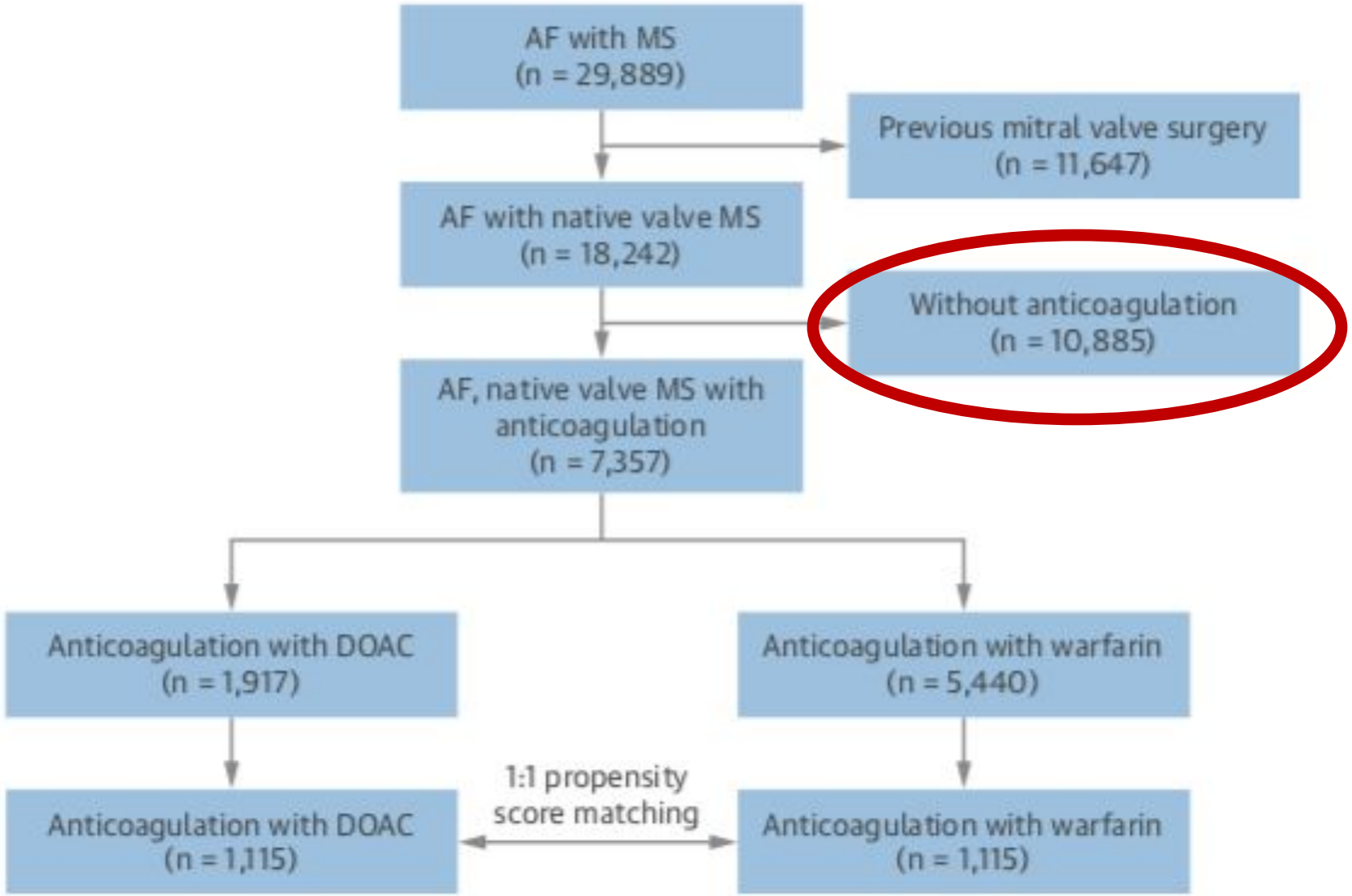
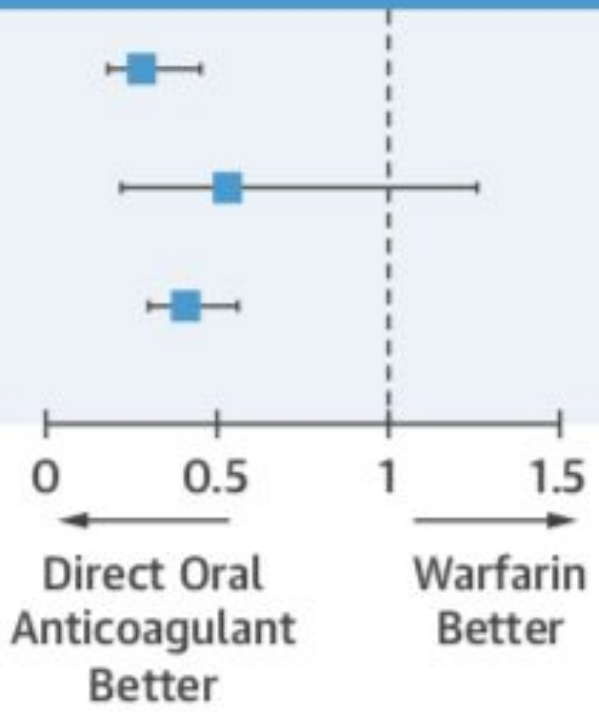
OFF LABEL USE. HYPOTHESIS GENERATING. NEED MORE STUDIES

FIGURE 1 Flow Chart of Atrial Fibrillation With Mitral Stenosis Patients



CENTRAL ILLUSTRATION Mitral Stenosis and Atrial Fibrillation for Direct Oral Anticoagulant Versus Warfarin: Hazard Ratios

Direct Oral Anticoagulant Versus Warfarin	HR (95% CI)
Ischemic Stroke and Systemic Embolism	0.28 (0.18-0.45)
Intracranial Hemorrhage	0.53 (0.22-1.26)
All-Cause Death	0.41 (0.30-0.56)



Highlights ineffectiveness of Warfarin in clinical practice

Kim, J.Y. et al. J Am Coll Cardiol. 2019;73(10):1123-31.

Strokes or systemic embolisms and all-cause death rates were significantly lower in the direct oral anticoagulant group compared with the warfarin group. There was a nonsignificant difference in the rate of the incidence of intracranial hemorrhages between the direct oral anticoagulant group and the warfarin group. CI = confidence interval; HR = hazard ratio.

ANTIPHOSPHOLIPID SYNDROME

Direct-acting oral anticoagulants (DOACs): increased risk of recurrent thrombotic events in patients with antiphospholipid syndrome

A clinical trial has shown an increased risk of recurrent thrombotic events associated with rivaroxaban compared with warfarin, in patients with antiphospholipid syndrome and a history of thrombosis. Other direct-acting oral anticoagulants (DOACs) may be associated with a similarly increased risk.

5.6 Increased Risk of Thrombosis in Patients with Triple Positive Antiphospholipid Syndrome

Direct-acting oral anticoagulants (DOACs), including ELIQUIS, are not recommended for use in patients with triple-positive antiphospholipid syndrome (APS). For patients with APS (especially those who are triple positive [positive for lupus anticoagulant, anticardiolipin, and anti–beta 2-glycoprotein I antibodies]), treatment with DOACs has been associated with increased rates of recurrent thrombotic events compared with vitamin K antagonist therapy.

Drug-drug Interactions With NOACs

	Mechanism of Action	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Dronedarone	P-gp inhibitor		No specific recommendations	No specific recommendations	
Clarithromycin	Strong inhibition of CYP3A4 and P-gp				No specific recommendations
Itraconazole	Strong inhibition of CYP3A4 and P-gp		Avoid use		No specific recommendations
Ketoconazole	Strong inhibition of CYP3A4 and P-gp	With CrCl 30-50 ml/min reduce dose to 75 mg twice daily	Avoid use		No specific recommendations
Ritonavir	Strong inhibition of CYP3A4 and P-gp		Avoid use		No specific recommendations
Carbamazepine	Strong *inducer* of CYP3A4 and P-gp	Avoid use	Avoid use	Avoid use	No specific recommendations
Phenytoin	Strong *inducer* of CYP3A4 and P-gp	Avoid use	Avoid use	Avoid use	No specific recommendations
Rifampin	Strong *inducer* of CYP3A4 and P-gp	Avoid use	Avoid use	Avoid use	Avoid use
St. John's wort	Strong *inducer* of CYP3A4 and P-gp	Avoid use	Avoid use	Avoid use	No specific recommendations

Red: Avoid Yellow: Reduced Dose Green: OK to use

Kovacs RJ, et al. *J Am Coll Cardiol*. 2015.

Oncology Drugs with Strong CYP3A4 and P-gp interactions (rivaroxaban, apixaban)

- Antimitotic agents: PACLITAXEL
- Tyrosine Kinase Inhibitors: IMATINIB, CRIZOTINIB, VEMURAFENIB
- Hormonal agents: BICALUTAMIDE, ENZALUTAMIDE, ABIRATERONE
- Immune modulating agents: CYCLOSPORIN, DEXAMETHASONE

J Thromb Thrombolysis. 2020 Jan 10. doi: 10.1007/s11239-020-02037-3. [Epub ahead of print]

The real world use of combined P-glycoprotein and moderate CYP3A4 inhibitors with rivaroxaban or apixaban increases bleeding.

Hanigan S[1,2], Das J[3], Pogue K[4,5], Barnes GD[6,7], Dorsch MP[5].

⊕ Author information

Abstract

The use of direct oral anticoagulants for stroke prevention in atrial fibrillation continues to rise. Certain populations may be at higher risk for increased drug exposure and adverse events. Pharmacokinetic studies suggest increased exposure of rivaroxaban and apixaban with combined P-gp and moderate CYP3A4 inhibitors but the clinical relevance of this is unknown. This retrospective cohort study included patients receiving rivaroxaban or apixaban from January 1, 2012 to December 31, 2016 with a moderate inhibitor (amiodarone, dronedarone, diltiazem, verapamil) for at least 3 months in the drug-drug interaction (DDI) group. Propensity matching was used to identify similar control patients without the presence of the DDI. The primary outcome was a time to event analysis of any bleeding episode as defined by the International Society of Thrombosis and Hemostasis. After propensity matching, 213 patients with similar baseline characteristics were included in each group. The mean CHA2DS2-VASc score was 3.0 and median duration of follow-up was 1.45 years. The primary outcome occurred in 26.4% of patients in the DDI group and 18.4% in the control group (hazard ratio 1.8, 95% confidence interval [CI] 1.19 to 2.73; p-value = 0.006). There was no difference in bleeding rates based on type of inhibitor. Use of a combined P-gp and moderate CYP3A4 inhibitor with rivaroxaban or apixaban increased bleeding risk compared to patients without the DDI in this real world, retrospective study. Analysis in a larger patient population is needed to confirm these findings.

RENAL FUNCTION

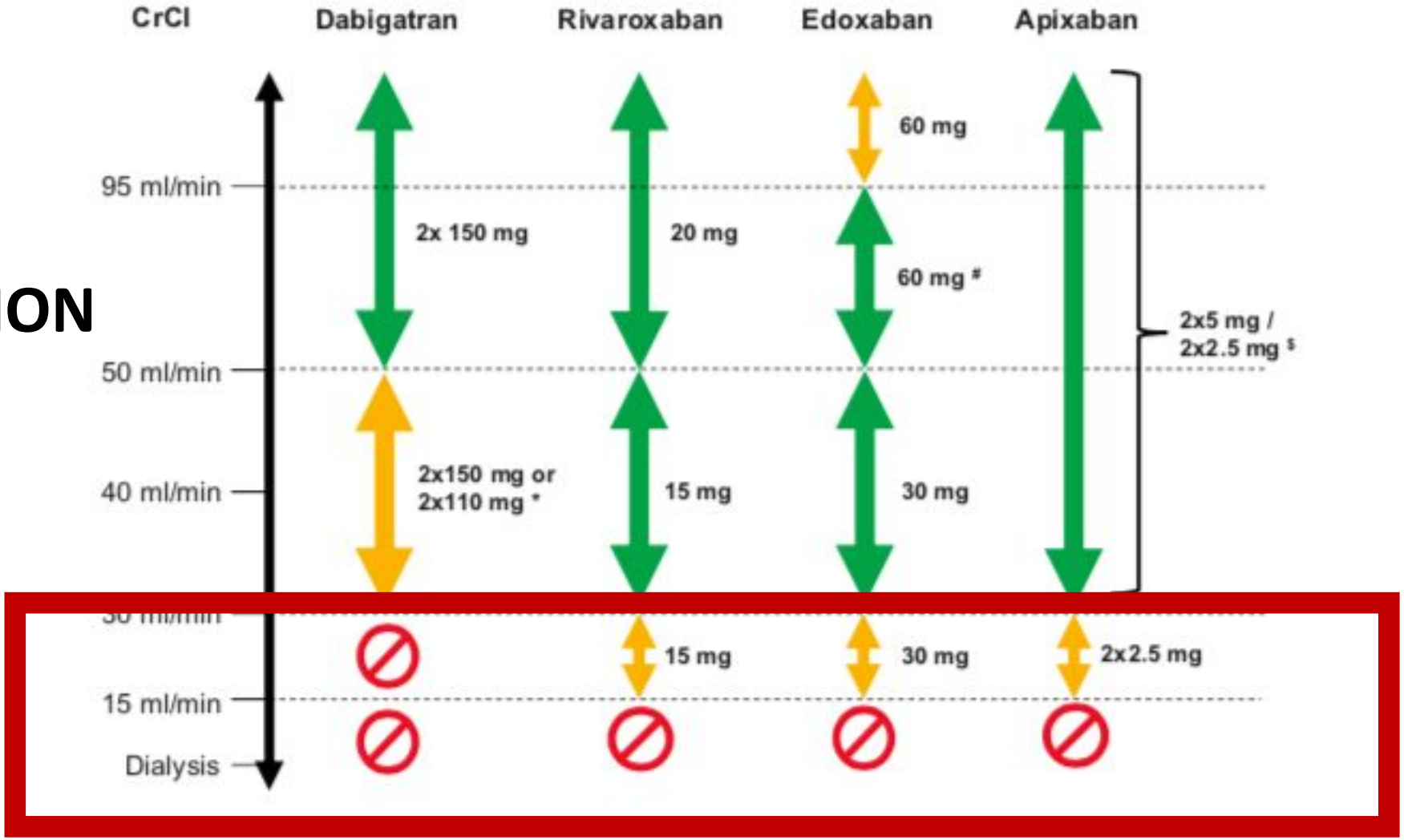


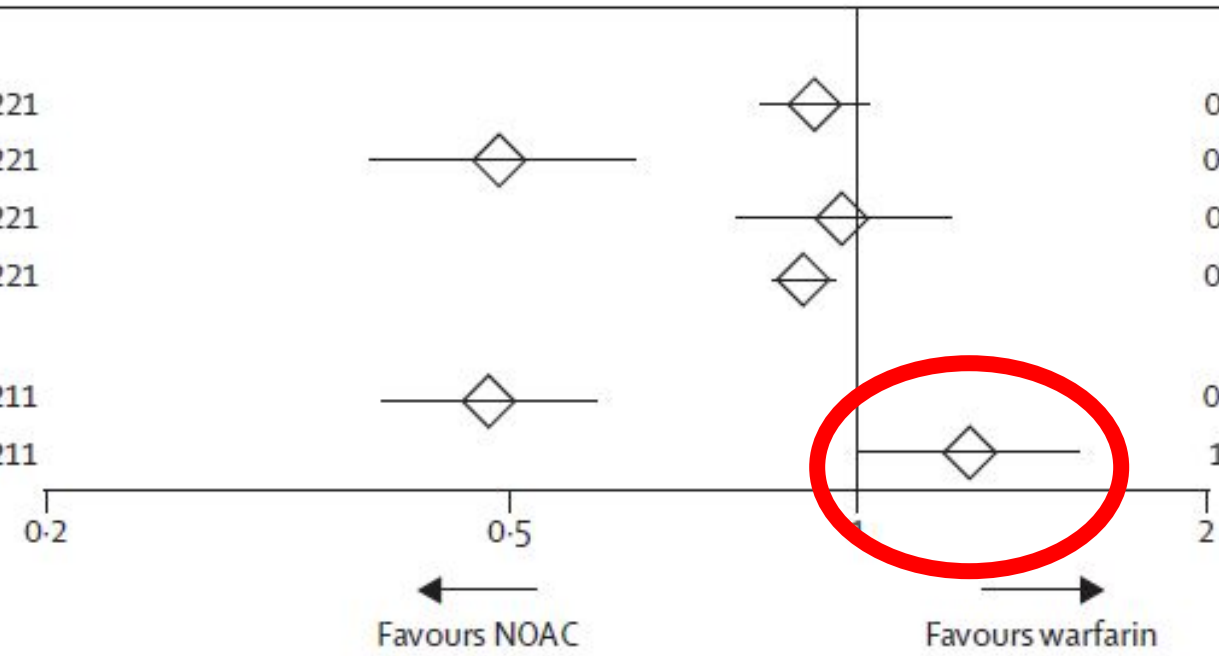
Figure 4 Use of non-vitamin K antagonist oral anticoagulants according to renal function. *2 × 110 mg in patients at high risk of bleeding (per SmPc). #Other dose reduction criteria may apply (weight ≤60 kg, concomitant potent P-Gp inhibitor therapy). $2 × 2.5 mg only if at least two out of three fulfilled: 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.

AVERAGE CO-PAY FOR 30-DAY SUPPLY OF APIXABAN 5 MG SAMPLE OF MEDICARE DRUG PLANS

Anthem MediBlue Essential (HMO)		$4	$42
Cigna-HealthSpring Preferred (HMO)	WARFARIN 30-DAY SUPPLY	$2	$194
EnvisionRxPlus (PDP)		$4	$56
Express Scripts Medicare - Choice (PDP)		$2	$42
Express Scripts Medicare - Value (PDP)		$1	$27
Humana Enhanced (PDP)		$6	$467

Meta-Analysis: Secondary Endpoints

	Pooled NOAC (events)	Pooled warfarin (events)	RR (95% CI)	p
Efficacy				
Ischaemic stroke	665/29 292	724/29 221	0·92 (0·83–1·02)	0·10
Haemorrhagic stroke	130/29 292	263/29 221	0·49 (0·38–0·64)	<0·0001
Myocardial infarction	413/29 292	432/29 221	0·97 (0·78–1·20)	0·77
All-cause mortality	2022/29 292	2245/29 221	0·90 (0·85–0·95)	0·0003
Safety				
Intracranial haemorrhage	204/29 287	425/29 211	0·48 (0·39–0·59)	<0·0001
Gastrointestinal bleeding	751/29 287	591/29 211	1·25 (1·01–1·55)	0·043



COULD FACTOR XI INHIBITORS REDUCE BLEEDING?

www.thelancet.com Published online December 4, 2013 http://dx.doi.org/10.1016/S0140-6736(13)62343-0

OTHER KNOWLEDGE GAPS

- NOAC “failure”-LAA thrombus, stroke, VTE
- Hepatic dysfunction (Childs-Pugh B and C)
- Short gut syndrome, gastric bypass
- Active malignancy-excess bleeding GI cancer –use LMWH
- Extremes in weight
- Pregnancy-LMWH for high risk

THANK YOU