64° CONGRESSO NAZIONALE SIGG

Continuità di affetti, continuità di cure

ROMA, 27/30 NOVEMBRE 2019 - AUDITORIUM DELLA TECNICA

LA GESTIONE DELLA TAO NELL'INSUFFICIENZA RENALE CRONICA MODERATA

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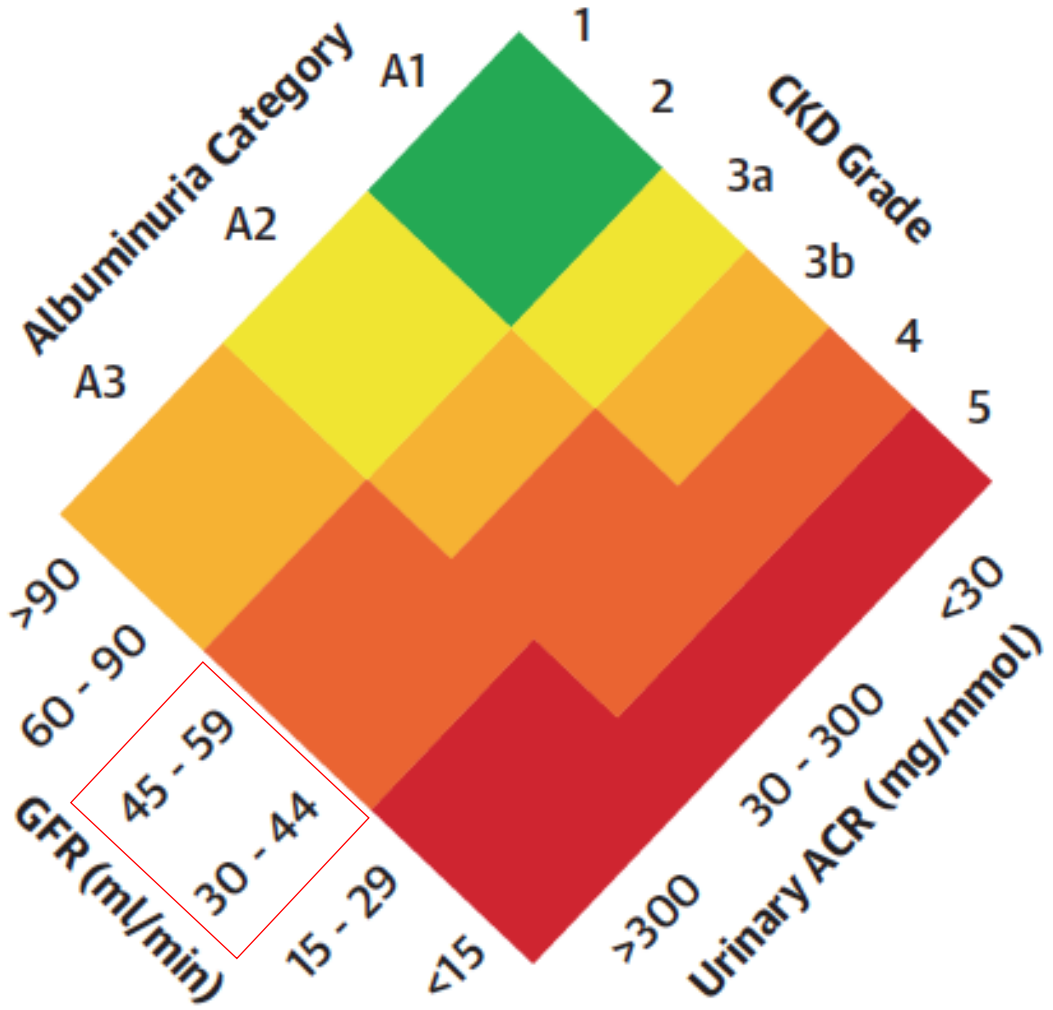
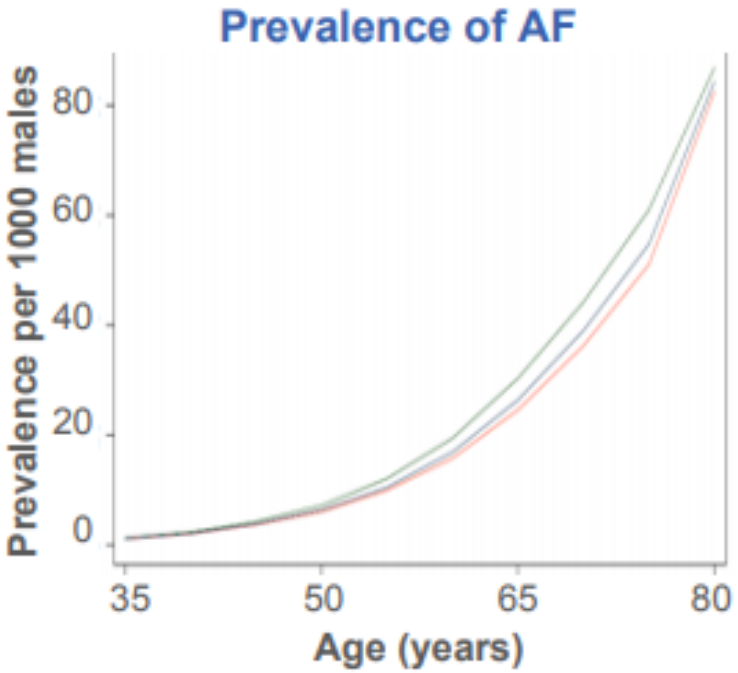
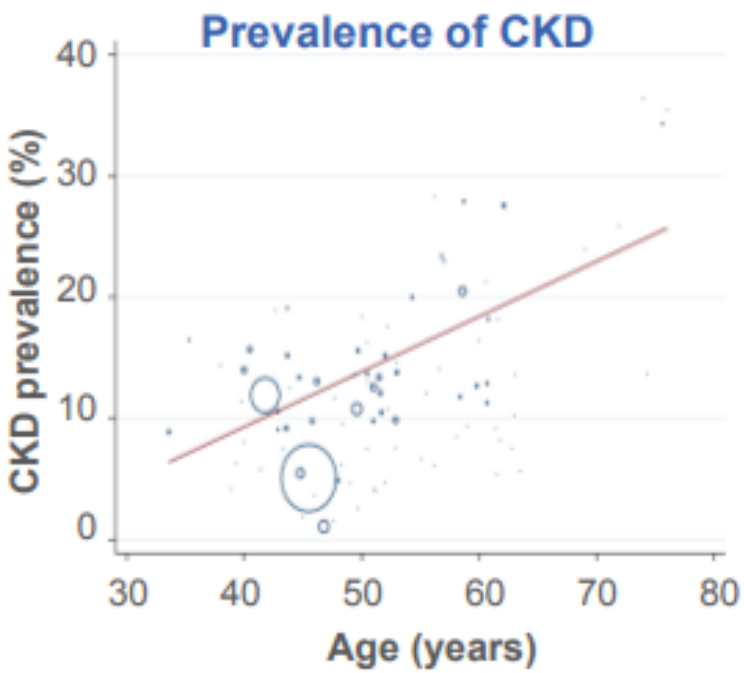
Stages of chronic kidney disease

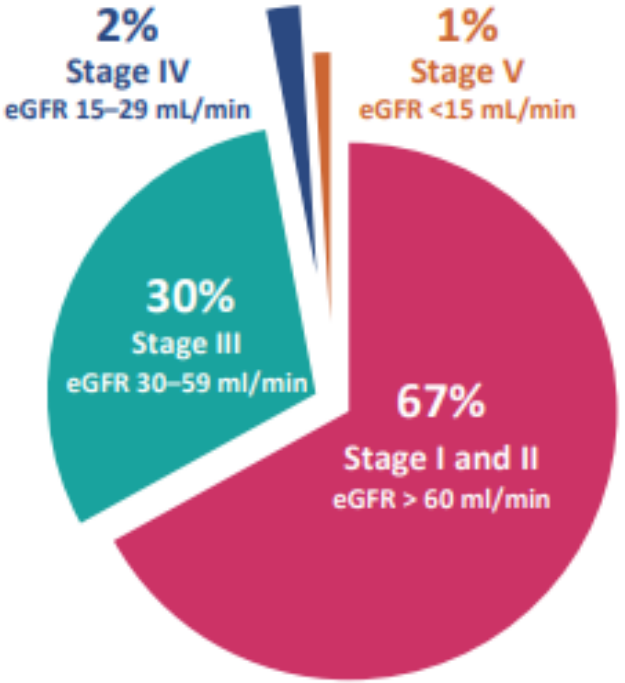


Kumar S et al. JACC 2019;74:2204-15

Patients with AF have frequently renal dysfunction







Prevalence of AF and CKD increases with age

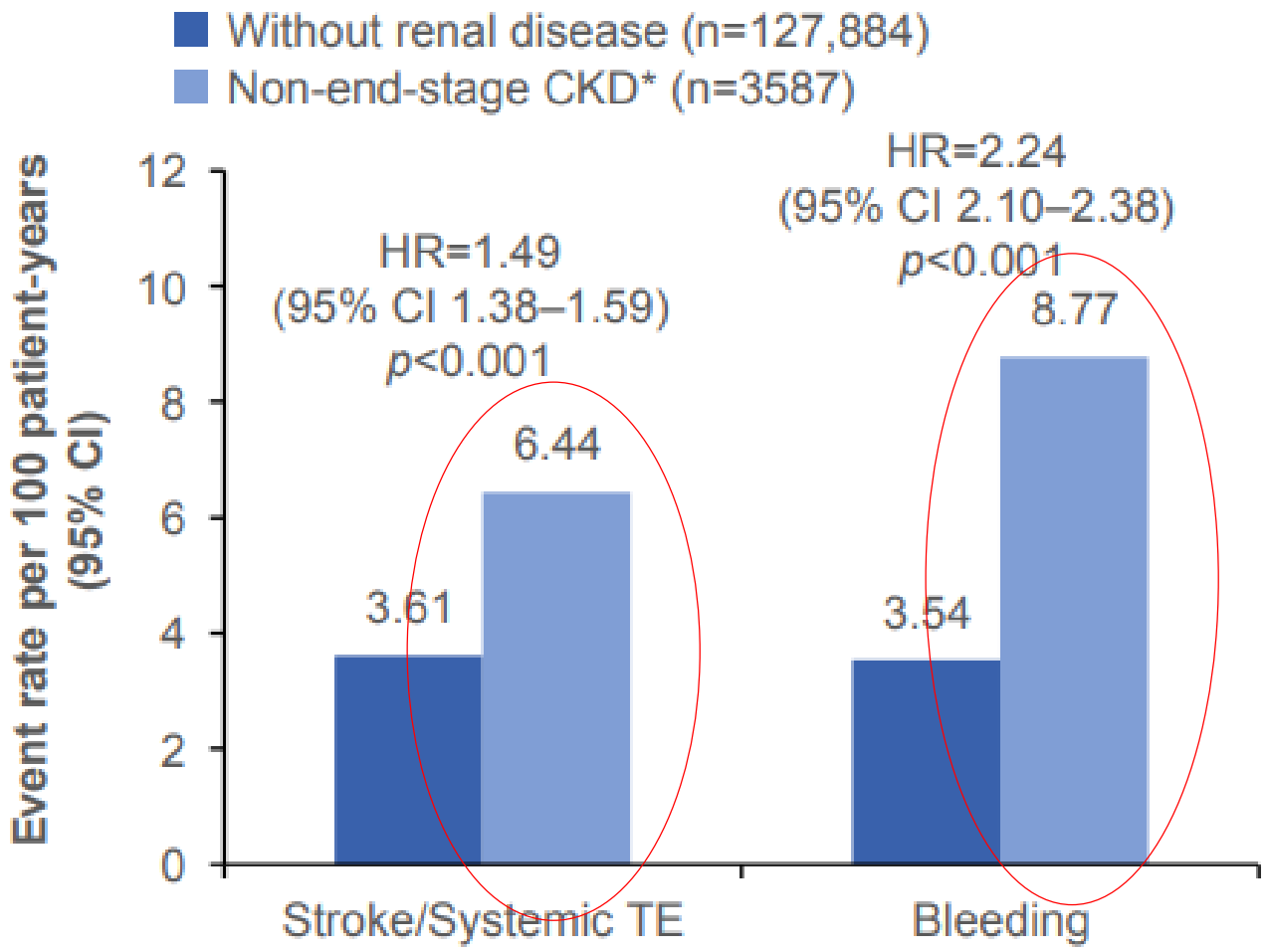
1/3 of patients with atrial fibrillation have CKD and 15%-20% of CKD patients have atrial fibrillation. Atrial fibrillation is nearly 3 times as frequent in stage III CKD patients as in age and sex-matched patients without stage III CKD.

Chugh S et al. Circulation 2014

Hill Rn et al. Plos One 2016

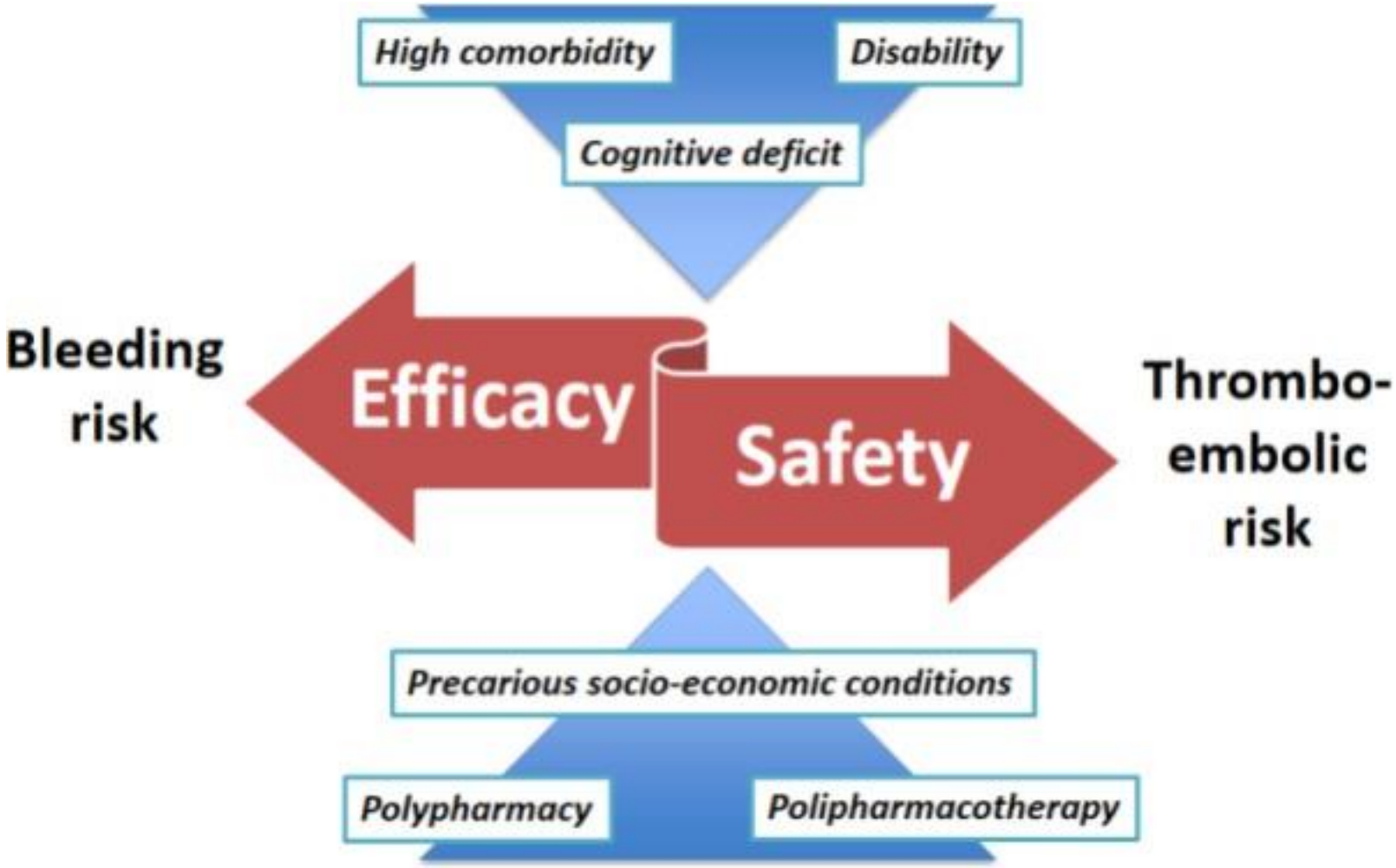
Hart RG et al. Can J Cardiol 2013

Patients with NVAF and CKD are at higher risk of stroke and bleeding: Danish cohort study (132372 pts)



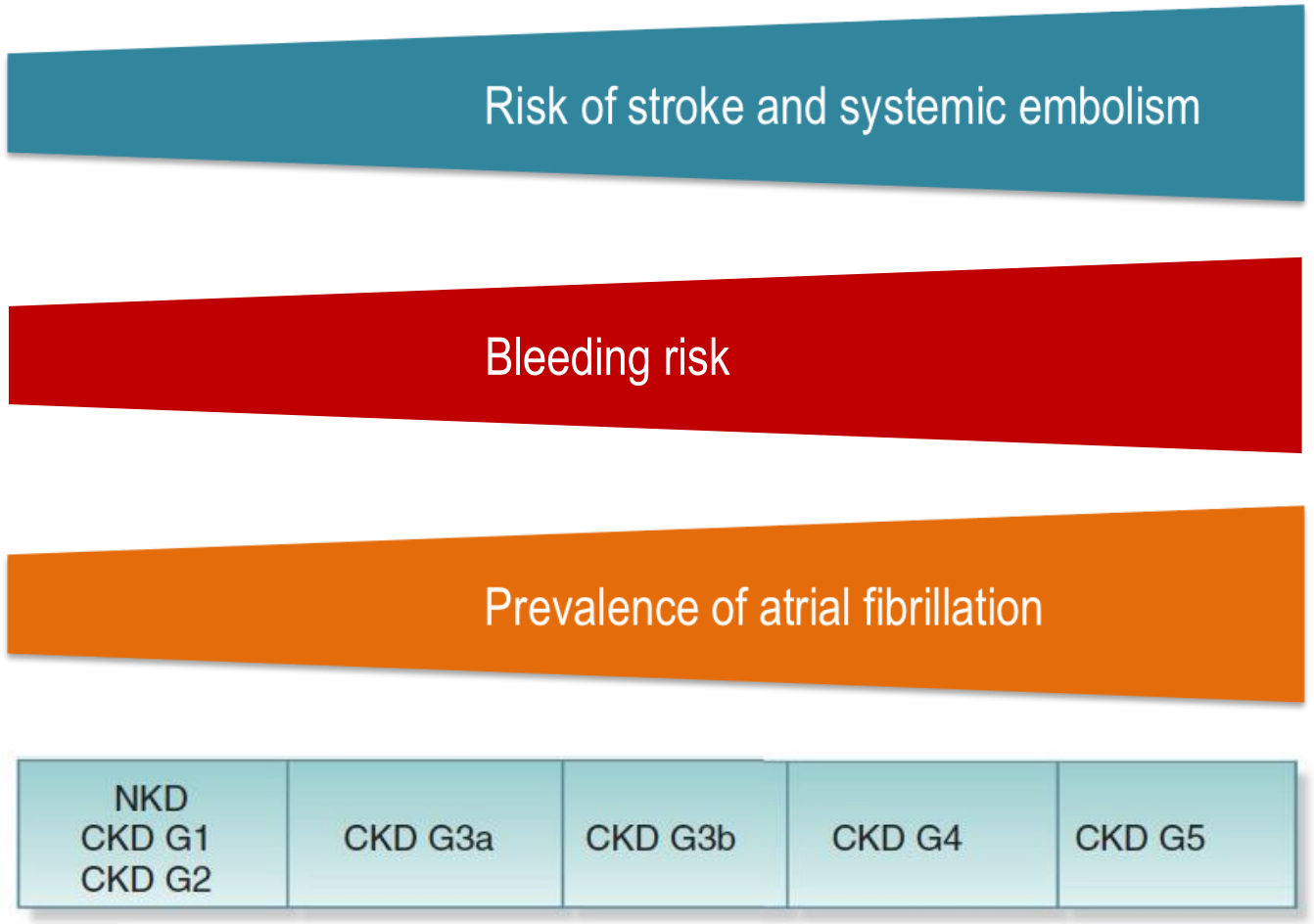
Olesen JB et al. N Engl J Med 2012;367:625-35

The impact of frailty on the critical balance between efficacy and safety in the management of antithrombotic therapy in the elderly.



Bencivenga L et al. Frontiers Physiol 2018;9:876

CKD: risk of stroke and bleeding



Adapted from Heine GH et al. Kidney Int. 2017;91:778-780

Risk Factors	Score
Congestive Heart Failure/LV dysfunction	1
Hypertension	1
Age ≥ 75 years	2
Diabetes Mellitus	1
Stroke/TIA/Thromboembolism	2
Vascular Disease	1
Age 65 – 74	1
Female	1
Total	**9**

CHA2DS2-VASc score	Stroke Risk per Year
0	0%
1	1.3%
2	2.2%
3	3.2%
4	4.0%
5	6.7%
6	9.8%
7	9.6%
8	6.7%
9	15.2%

NO RENAL DISFUNCTION

HAS-BLED

Letter	Clinical Characteristic	Points
H	Hypertension	1
A	Abnormal Liver or Renal Function	1 or 2
S	Stroke	1
B	Bleeding	1
L	Labile INR	1
E	Elderly (age > 65)	1
D	Drugs or Alcohol	1 or 2
Maximum Score		9

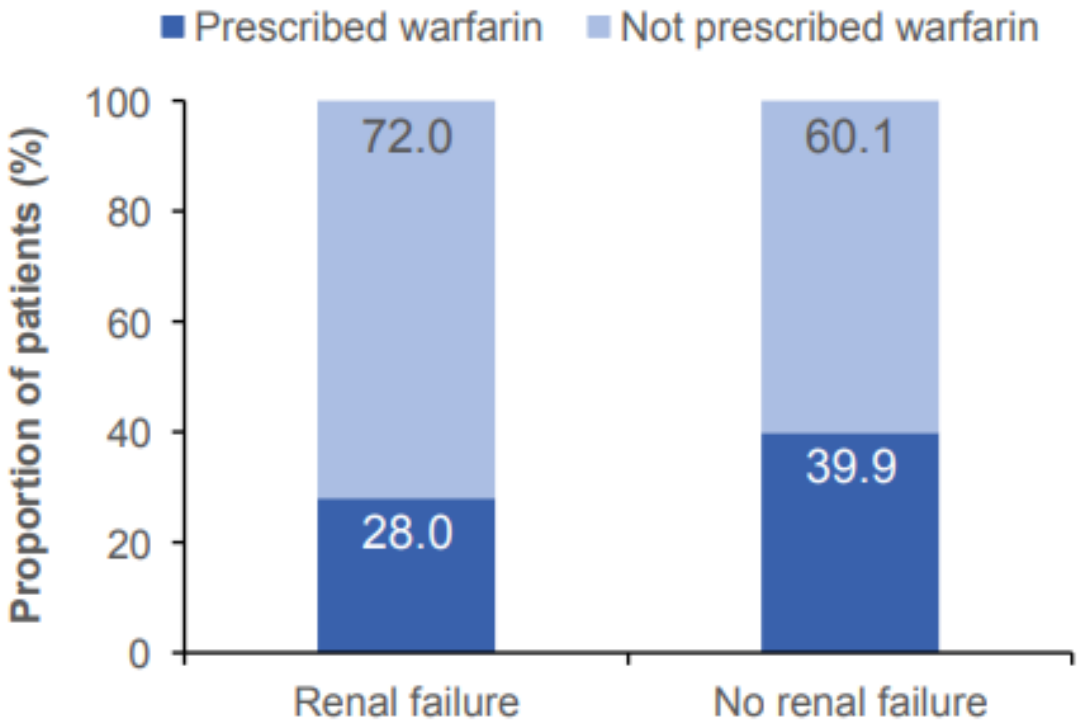
NO SEVERITY

Patients with AF and renal dysfunction are often not anticoagulated

Retrospective non-randomized study of Swedish health registers comprising 307 351 patients with AF, of whom 13 435 had a previous diagnosis of renal failure.

Patients with AF and renal dysfunction are more often undertreated with warfarin than those with normal renal function

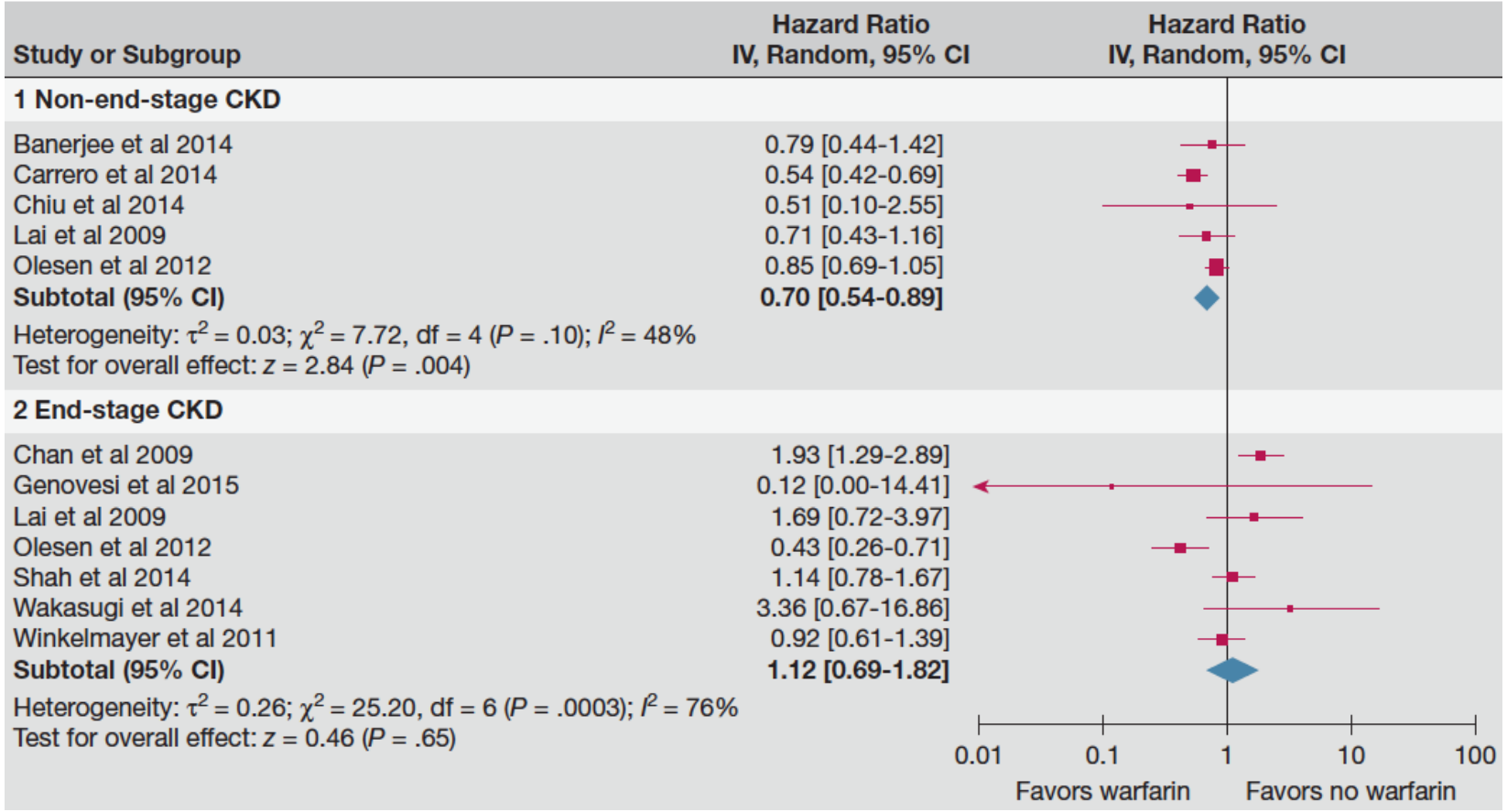
Proportion of pts with AF prescribed warfarin



Friberg L et al. Eur Heart J 2015;36:296-306

Stroke, Major Bleeding, and Mortality Outcomes in Warfarin Users With Atrial Fibrillation and Chronic Kidney Disease

Stroke/embolism



Warfarin was beneficial in patients with AF and non-end-stage chronic kidney disease (CKD), reducing stroke risk and mortality without increasing the risk of major bleeding. In contrast, in patients with AF and end-stage CKD, warfarin had no effect on stroke and mortality but led to a higher risk of major bleeding

Dahal K et al. Chest 2016;149:951-9

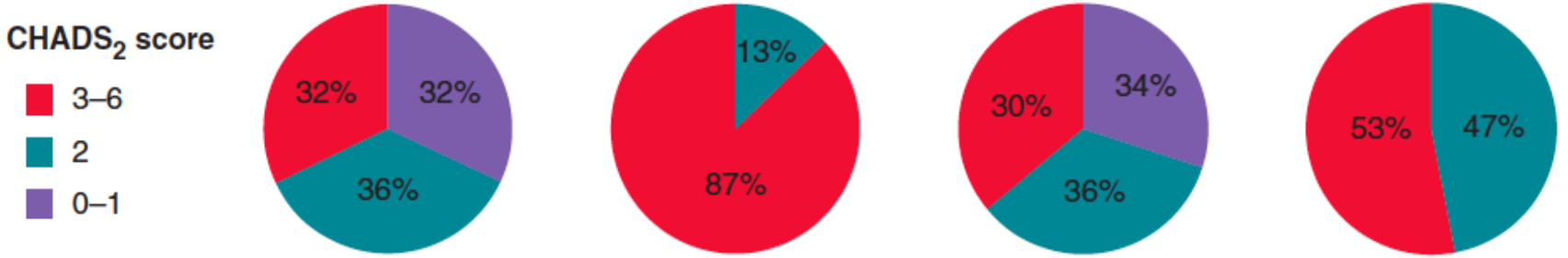
Absorption and metabolism of NOACs

Management with VKAs is challenging due to their narrow therapeutic range, unpredictable dose-response, and interactions with drugs and food, which necessitate close monitoring of the INR

	Dabigatran	Apixaban	Edoxaban *	Rivaroxaban
Bioavailability	3-7%	50%	62%	66% (w/o food) ~100% with food
Prodrug	yes	no	no	no
Clearance: non-renal/renal of adsorbed dose if normal renal function	20%/80%	73%/27%	50%/50%	65%/35%

Steffel J et al. Eur Heart J 2018;39:1330-92

RCTs on NOACs in pts with AF

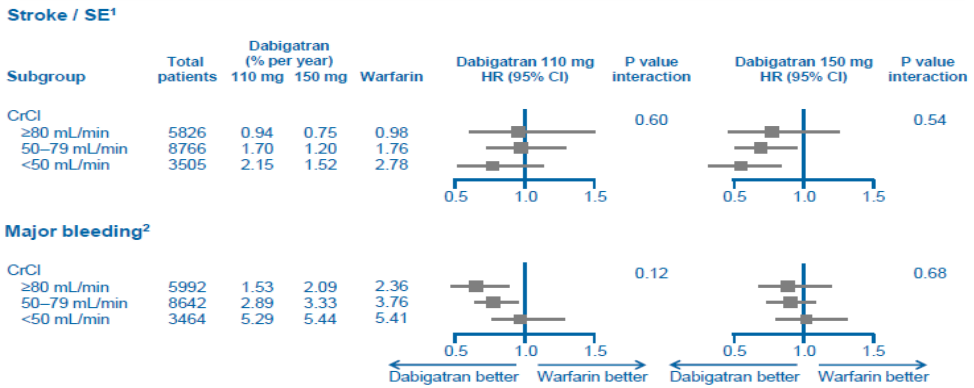


	RE-LY	ROCKET AF	ARISTOTLE	ENGAGE AF
	Mean $CHADS_2$ score – 2.1	**Mean $CHADS_2$ score – 3.5**	**Mean $CHADS_2$ score – 2.1**	**Mean $CHADS_2$ score – 2.8**
Dose reduction	No dose reduction–patients randomized between two doses of dabigatran (110 or 150 mg bid)	At randomization: Rivaroxaban 15 mg od for patients with CrCl 30–49 mL/min	At randomization: Apixaban 2.5 mg bid for patients with ≥2 of the following criteria: • Age ≥80 years • Body weight ≤60 kg • Serum creatinine level ≥1.5 mg/dL	Throughout the study period: Edoxaban 30 mg od for patients with ≥1 of the following criteria: • CrCl 30–50 mL/min • Body weight ≤60 kg • Concomitant use of verapamil or quinidine
Patients taking reduced	50.0%	20.7%[12]	4.7%	25.3%

Camm et al. Europace 2017

Compared with warfarin, all four NOACs showed consistent efficacy and safety in patients with mild to moderate CKD vs. non-CKD pts

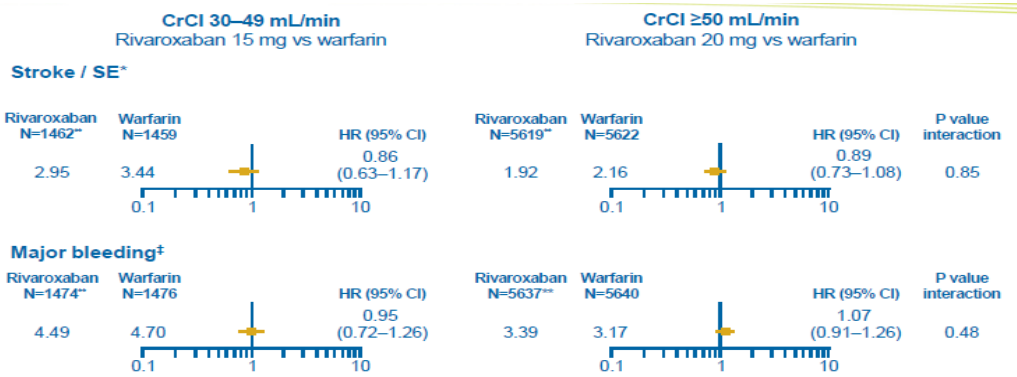
Dabigatran vs. warfarin in CKD



Patients with CrCl <30 mL/min were excluded from the RE-LY trial. CrCl was calculated according to the Cockcroft-Gault method¹

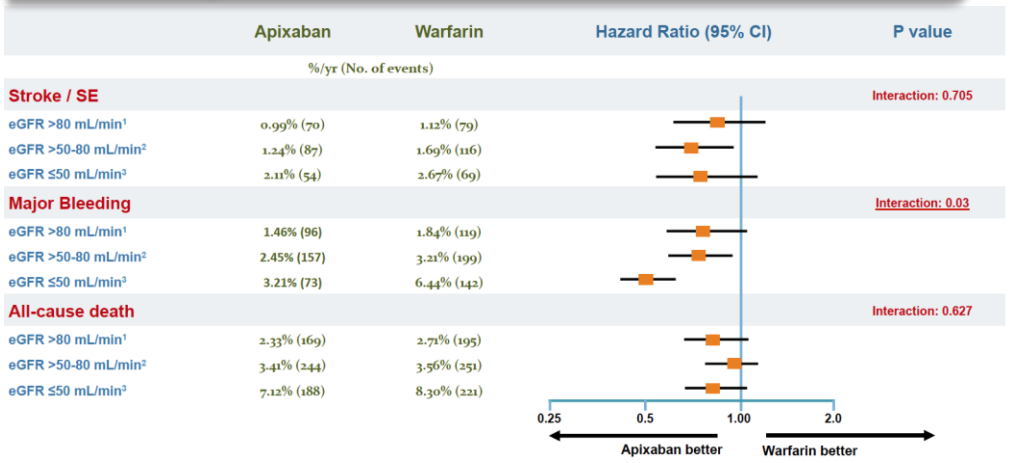
Eikelboom JW et al. Circulation 2011

Rivaroxabanvs. warfarin in CKD



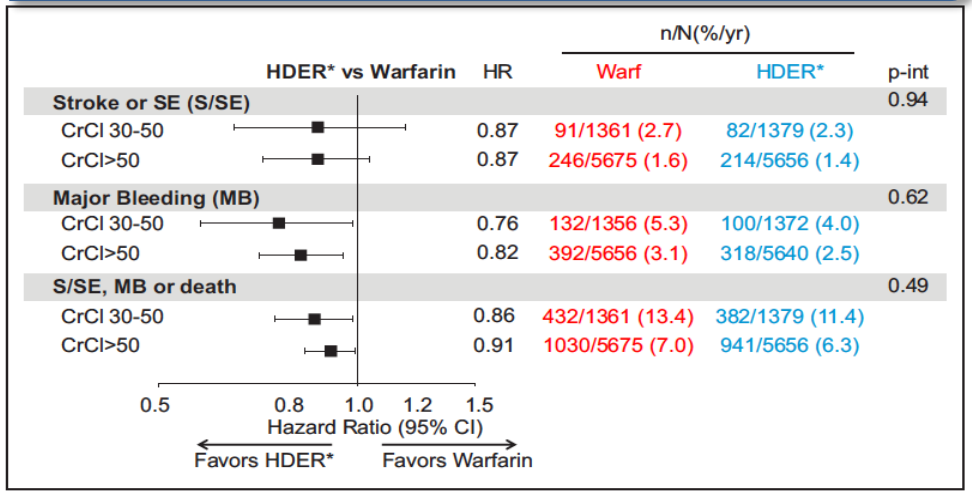
Fox KAA et al. Eur Heart J 2011

Apixaban vs. warfarin in CKD



Hohnsoloser et al. Eur Heart J 2012

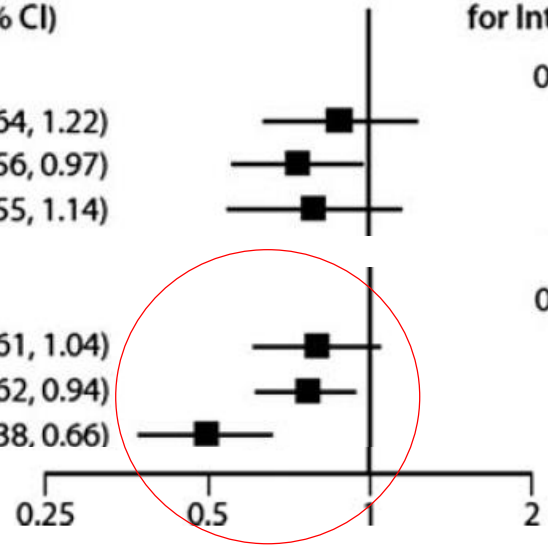
Edoxaban vs. warfarin in CKD



Bohula EA et al. Circulation 2016

Bleeding benefit with Apixaban compared to warfarin becomes more provident at lower GFR, while stroke reduction benefit is maintained

		Apixaban %/year (n)	Warfarin %/year (n)	Hazard Ratio (95% CI)	P– value for Interaction
Primary efficacy outcome (Stroke/Systemic embolism)	Cockcroft–Gault *eGFR mL/min*				0.705
	>80	0.99 (70)	1.12 (79)	0.88 (0.64, 1.22)	
	>50–80	1.24 (87)	1.69 (116)	0.74 (0.56, 0.97)	
	≤50	2.11 (54)	2.67 (69)	0.79 (0.55, 1.14)	
Major bleeding	Cockcroft-Gault *eGFR mL/min*				0.030
	>80	1.46 (96)	1.84 (119)	0.80 (0.61, 1.04)	
	>50–80	2.45 (157)	3.21 (199)	0.77 (0.62, 0.94)	
	≤50	3.21 (73)	6.44 (142)	0.50 (0.38. 0.66)	



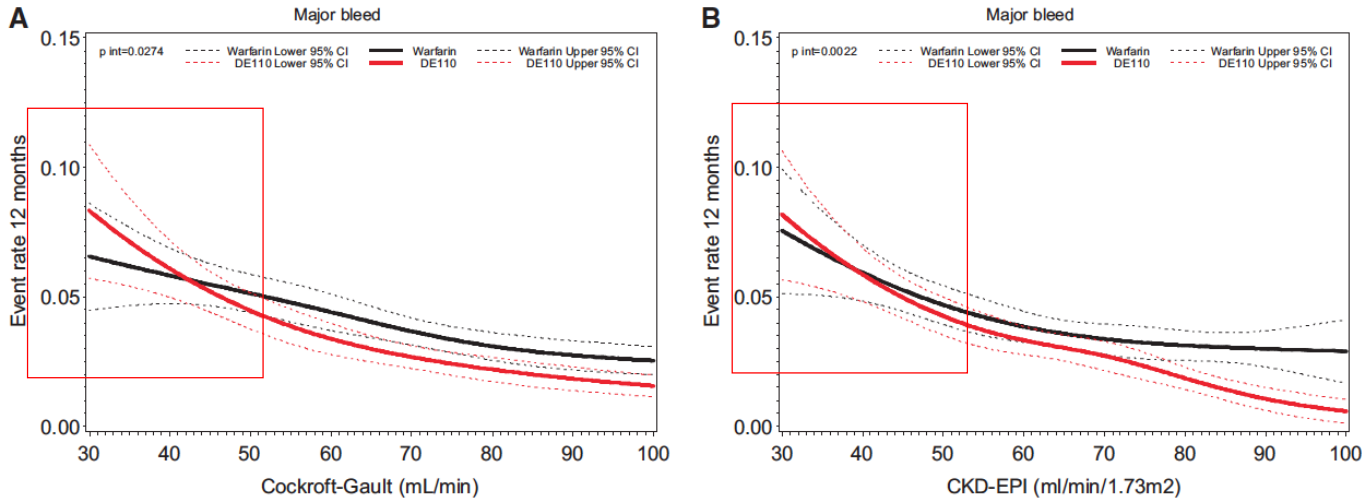
EHRA practical guide: NOAC in HF

trials.[190,195–199] In addition, the ARISTOTLE trial data analysis suggests that the bleeding benefit with apixaban compared with warfarin becomes significantly more prominent at lower CrCl values, while the stroke reduction benefit is maintained.[181,197] In contrast, the bleeding benefit of 110 mg dabigatran over warfarin is lost in patients with CrCl <50 mL/min while maintaining a similar stroke risk reduction compared with VKA.[195]

Steffel J et al. Eur Heart J 2018;39:1330-92

Hohnloser SH et al. Eur Heart J 2012;33:2821-30

Bleeding benefit of 110 mg dabigatran over warfarin is lost in pts with GFR <50 mL/min, maintaining a similar stroke risk reduction



EHRA practical guide: NOAC in HF

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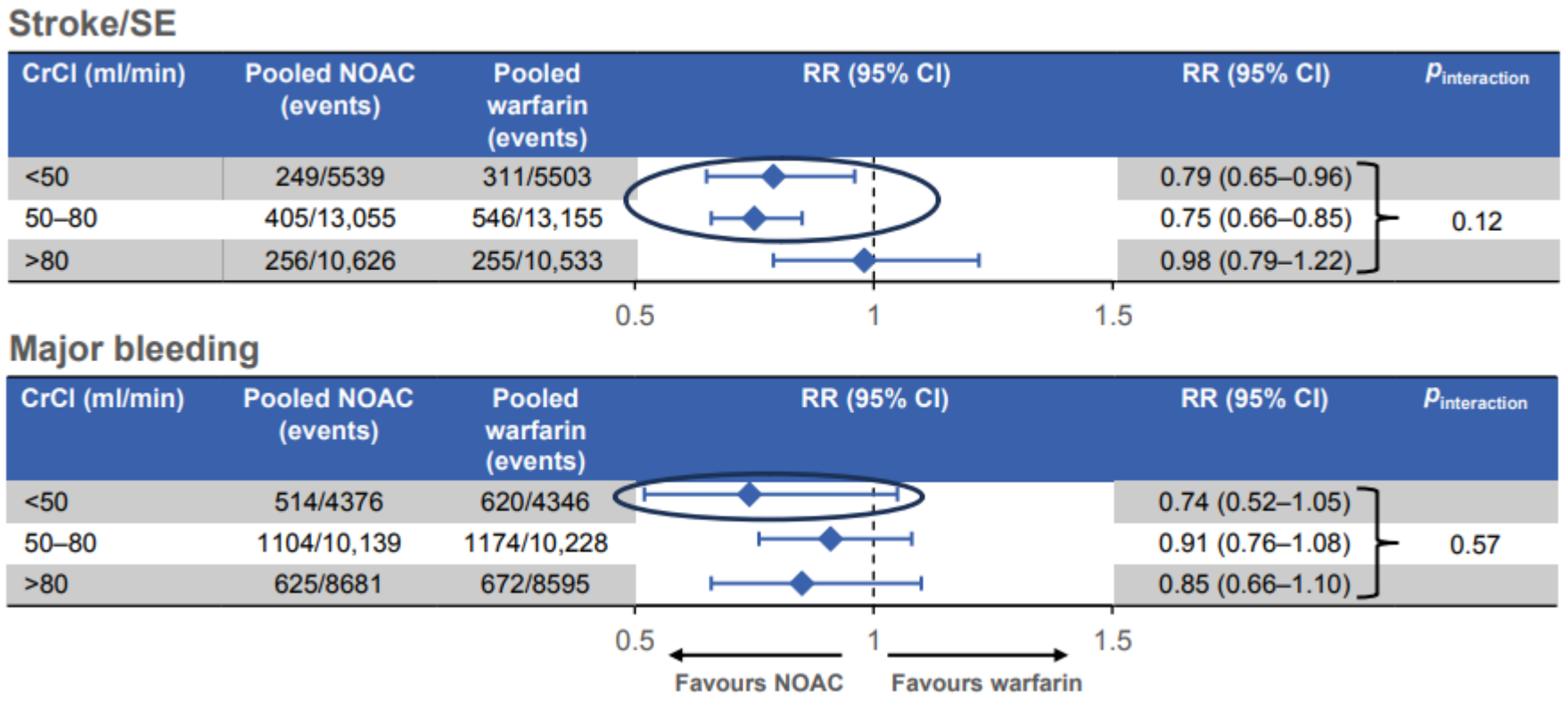
Steffel J et al. Eur Heart J 2019;39:1330-92

Hijazi Z et al. Circulation 2014;129:961-70

Comparison of the efficacy and safety of new oral anticoagulants with warfarin

Prespecified meta-analysis of all 71 683 participants included in the RE-LY, ROCKET AF, ARISTOTLE, and ENGAGE AF–TIMI 48 trials.



Ruff TC et al. Lancet 2014;383:955-62

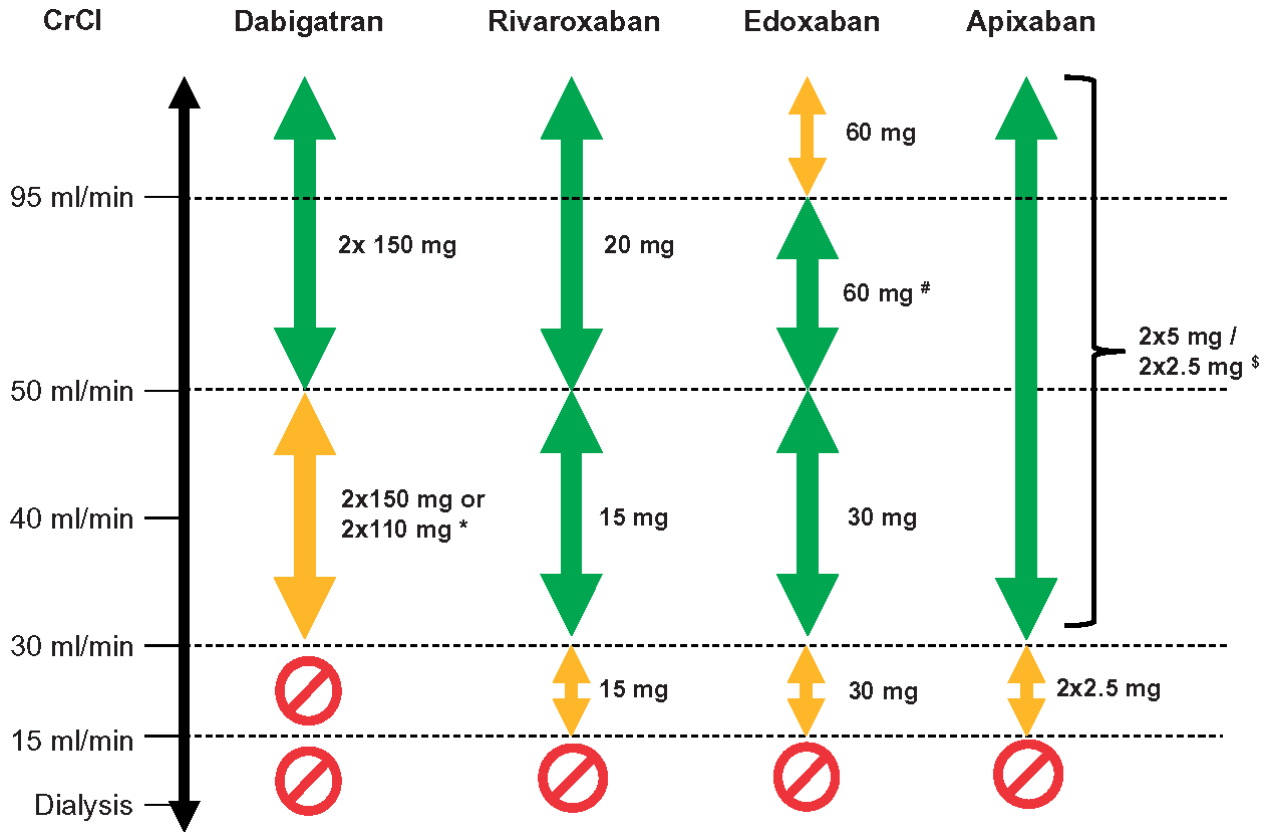
International guidelines

TABLE 4 DOAC Dosing and Oral Anticoagulation Medical Guidelines (2016 Onwards) for AF in CKD

	Guidelines (Year) (Ref. #)	Warfarin	Dabigatran	Apixaban	Rivaroxaban	Edoxaban
CrCl 30–59 ml/min	AHA/ACC/HRS (2019) (5)	Adjusted dose INR 2–3	150 mg BID	5.0 or 2.5 mg BID*	15 mg QD	30 mg QD
	CHEST guideline (2018) (4)	Adjusted dose TTR >70%	150 or 110 mg BID (non-U.S.)	5.0 or 2.5 mg BID*	15 mg QD	30 mg QD
	KDIGO (2018)† (2)	Adjusted dose INR 2–3	150 or 110 mg BID	5.0 or 2.5 mg BID*	15 mg QD	30 mg QD
	EHRA practical guide (2018) (3)	Adjusted dose INR 2–3	150 mg or 110 mg BID	5.0 or 2.5 mg BID*	20 mg (or 15 mg if CrCl <50)	30 mg QD
	ESC (2016) (1)	Adjusted dose INR 2–3	150 mg or 110 mg BID	5.0 or 2.5 mg BID*	15 mg QD	30 mg (or 15 mg if CrCl <50)
CrCl 15–29 ml/min	AHA/ACC/HRS (2019) (5)	Adjusted dose INR 2–3	75 mg BID	5.0 or 2.5 mg BID*	15 mg QD	Not recommended
	CHEST Guideline (2018) (4)	Adjusted dose TTR >70%	75 mg BID (U.S. only) Not recommended outside U.S.	2.5 mg BID	15 mg QD	30 mg QD
	KDIGO (2018)† (2)	Consider adjusted dose INR 2–3	Unknown (consider 75 mg BID)	Consider 2.5 mg BID	Consider 15 mg QD	Consider 30 mg QID
	EHRA practical guide (2018) (3)	Not discussed	Not recommended	2.5 mg BID	15 mg QD	30 mg QD
	ESC (2016) (1)	Adjusted dose INR 2–3	Not recommended	Not recommended if CrCl <25	Not recommended	Not recommended
CrCl <15 ml/min (Dialysis)	AHA/ACC/HRS (2019) (5)	Adjusted dose INR 2–3	Not recommended	5.0 or 2.5 mg BID*	Not recommended	Not recommended
	CHEST guideline (2018) (4)	Adjusted dose TTR >70%	Not recommended	5 mg BID‡	Not recommended	Not recommended
	KDIGO (2018)† (2)	Equipoise	Not recommended	Consider 2.5 mg BID	Unknown (15 mg QD mentioned)	Not recommended
	EHRA practical guide (2018) (3)	Not discussed	Not recommended	Not recommended	Not recommended	Not recommended
	ESC (2016) (1)	Not discussed	Not recommended	Not recommended	Not recommended	Not discussed

Steffel J et al. Eur Heart J 2018;39:1330-92

European Heart Rhythm Association 2018 Guidelines: Use of NOACs according to renal function

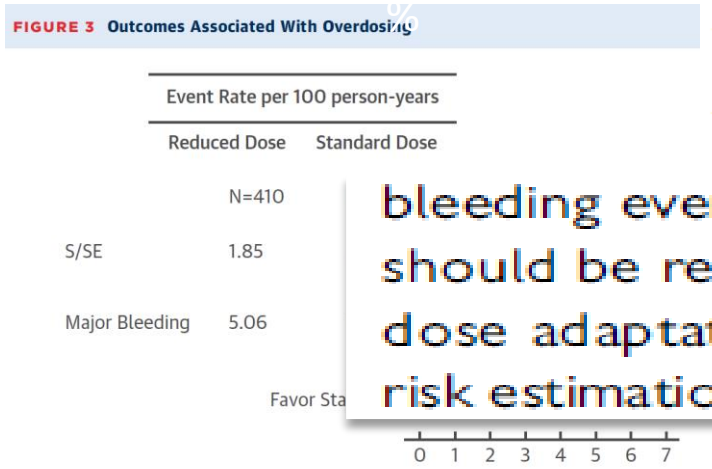


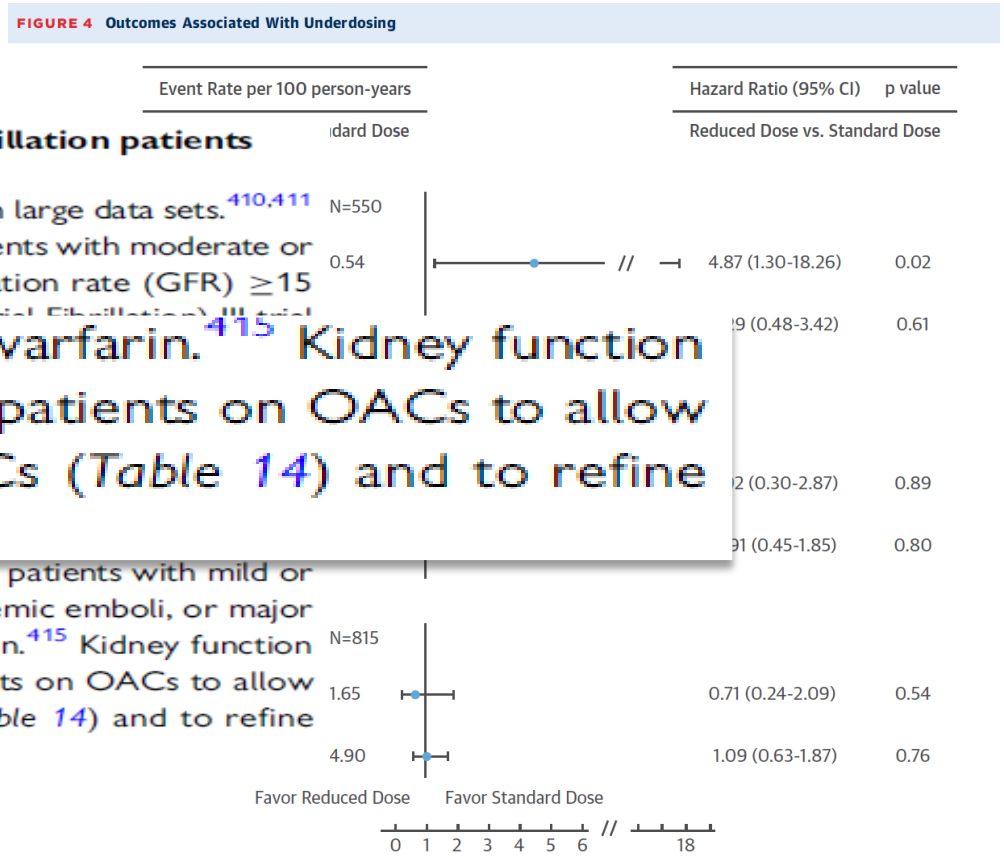
Orange arrows indicate cautionary use (dabigatran in moderate renal insufficiency, FXa inhibitors in severe renal insufficiency, edoxaban in 'supranormal' renal function). *2 × 110 mg in patients at high risk of bleeding. #Other dose reduction criteria may apply (weight ≤60 kg, concomitant potent P-Gp 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).

Steffel J et al. Eur Heart J 2018;39:1330-92

In routine clinical practice, prescribed NOAC doses are often inconsistent with drug labeling.

Large U.S. administrative database, 14,865 AF pts who initiated apixaban, dabigatran, or rivaroxaban. 43% potential overdosing (standard dose in patients with a renal indication for dose reduction) and 13.3% potential underdosing (reduced dose when the renal indication is not present) have been identified.





9.2.4 Oral anticoagulation in atrial fibrillation patients with chronic kidney disease

CKD is associated with stroke and bleeding in large data sets.[410,411] Anticoagulation can be safely used in AF patients with moderate or moderate-to-severe CKD [glomerular filtration rate (GFR) ≥15

bleeding events on NOACs than on warfarin.[415] Kidney function should be regularly monitored in AF patients on OACs to allow dose adaptation for those on NOACs (*Table 14*) and to refine risk estimation.[416]

In a meta-analysis of the major NOAC trials, patients with mild or moderate CKD suffered fewer strokes, systemic emboli, or major bleeding events on NOACs than on warfarin.[415] Kidney function should be regularly monitored in AF patients on OACs to allow dose adaptation for those on NOACs (*Table 14*) and to refine risk estimation.[416]

Yao X et al JACC 2017;69:2779-90

NOACs and kidney function: equations to gauge renal function EHRA practical guidelines

CKD-EPI
(Chronic Kidney Disease Epidemiology Collaboration)

Recommended by the National Kidney Foundation because it has been shown to be reliable across the range of CKD stages
Comparable to MDRD for GFR<60 ml/min
More accurate for GFR>60 ml/min

Cockroft-Gault

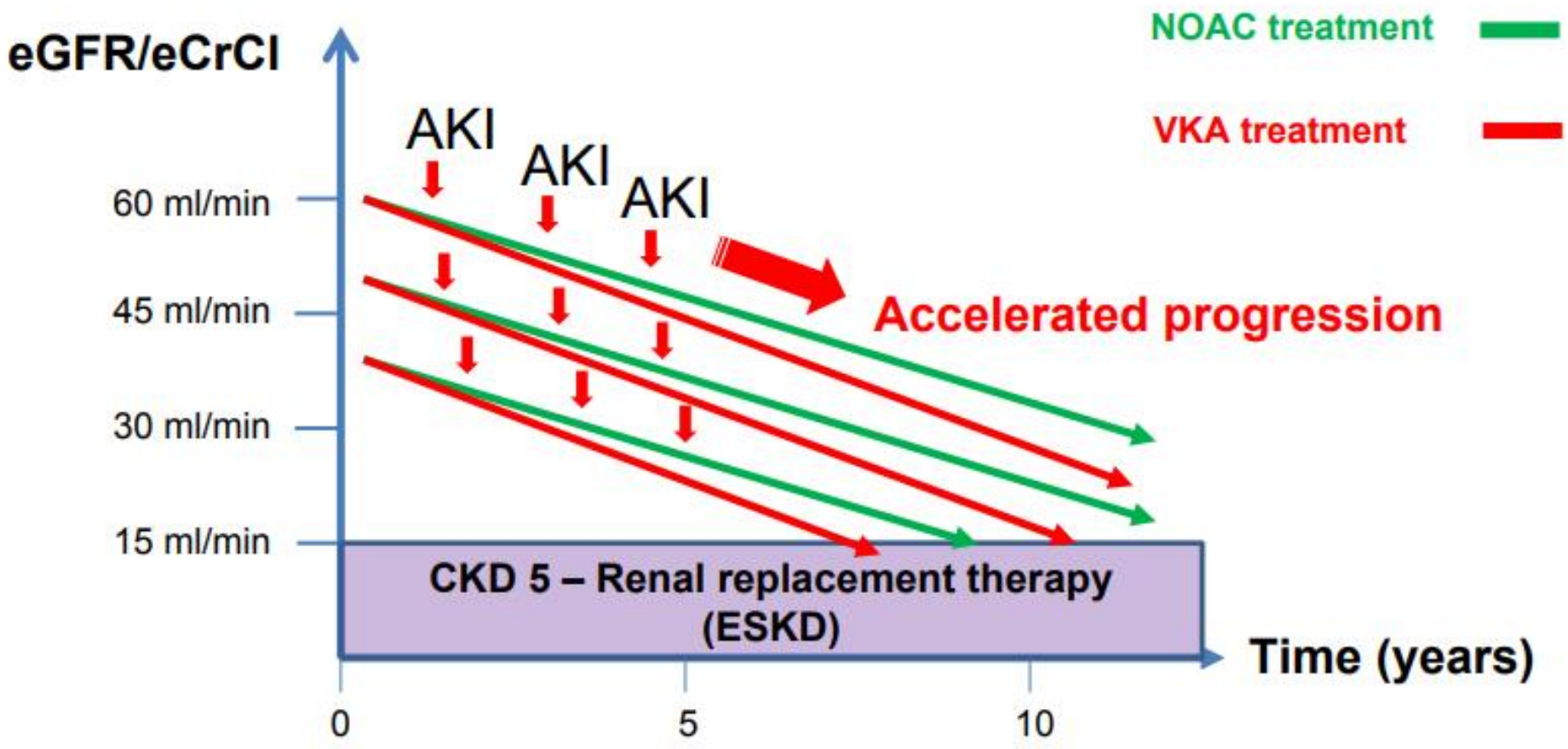
Underestimates GFR<60 ml/min, in obese and pts with oedema
In the context of NOAC treatment, should be preferred since it has been used in most NOAC trials

MDRD
(Modification of Diet in Renal Disease Study)

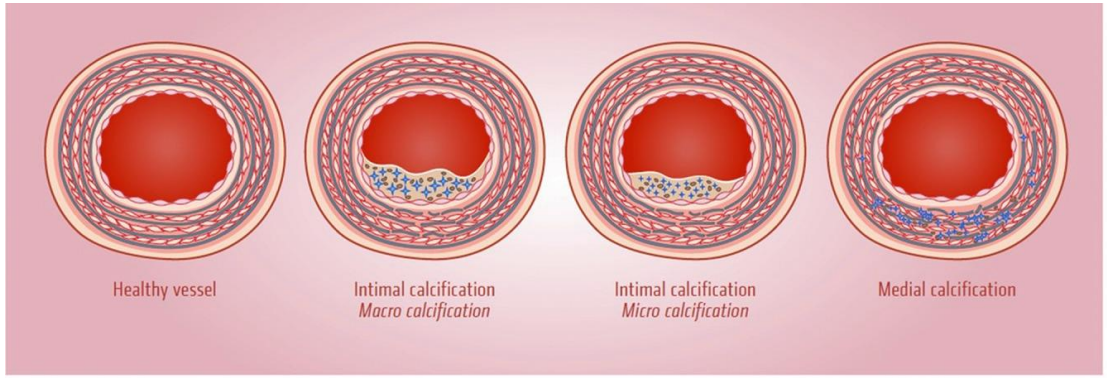
Good performance for GFR<60 ml/min

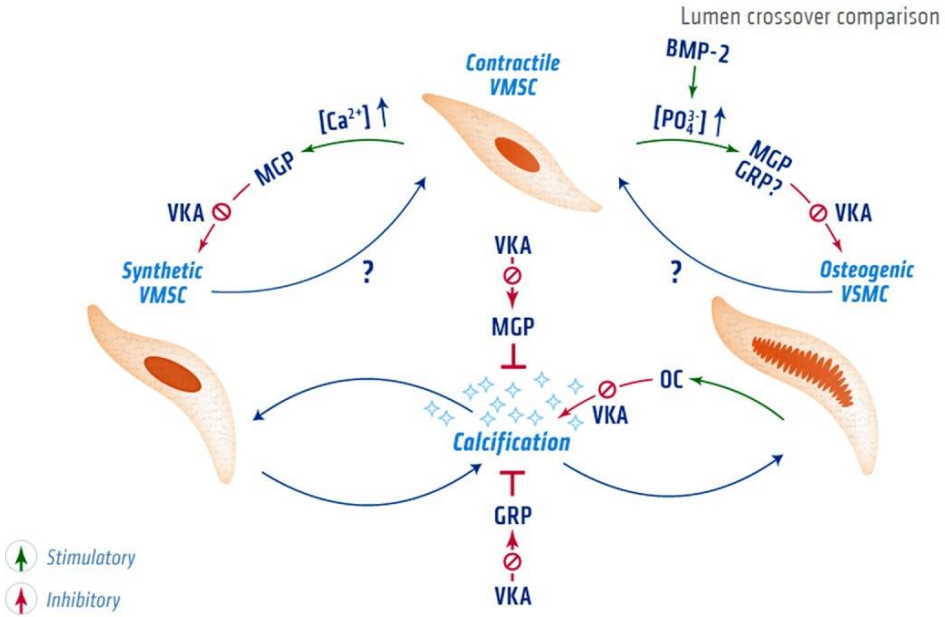
Steffel J et al. Eur Heart J 2018;39:1330-92

Decline in renal function in CKD over time



VKAs promote medial and intimal calcification: Matrix Gla protein

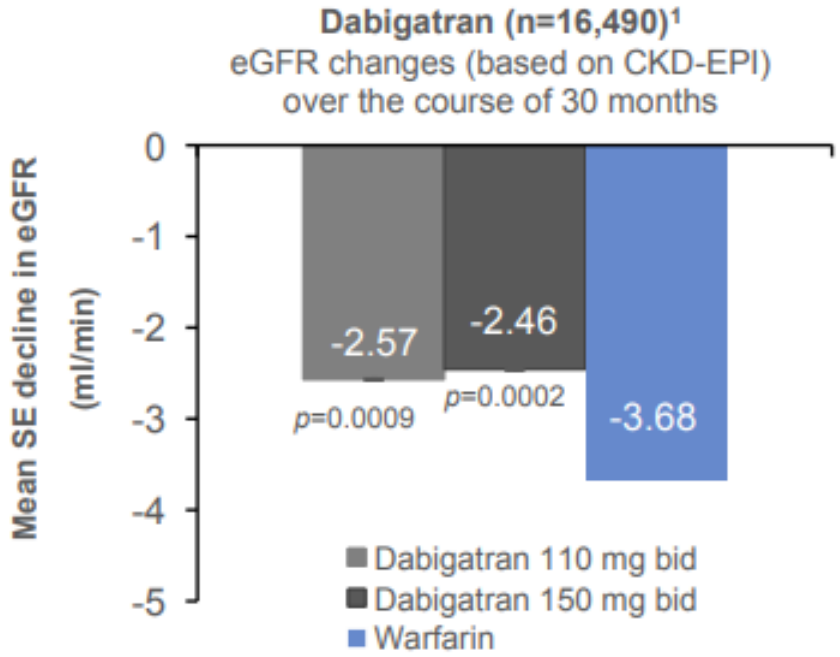


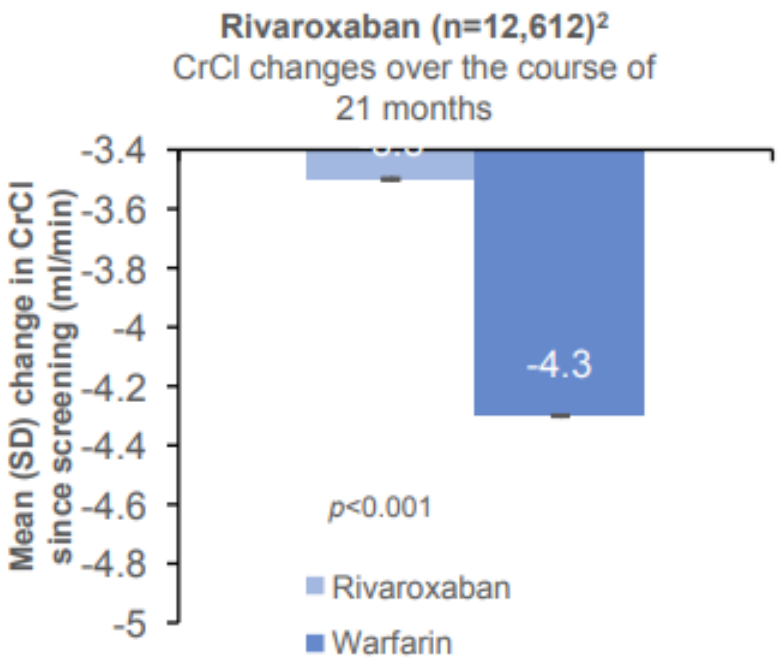


Willerns BA et al. Mol Nutr Food Res 2014;58:1620-35.

NOACs vs. Warfarin in RCTs: looking at renal function

In NOAC RCTs, renal function declines over time in overall patient population

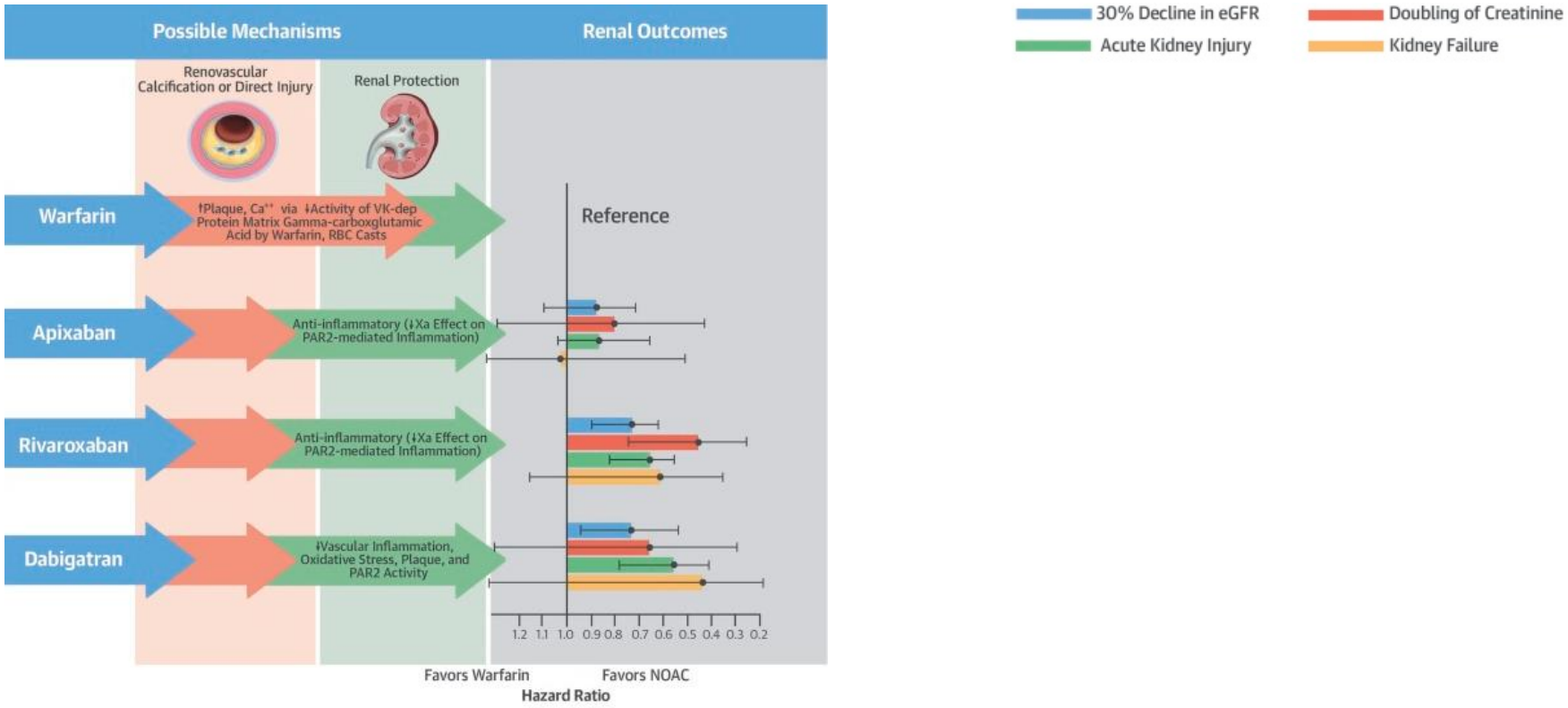




Bohm M et al. JACC 2015;65:2481-93
Fordyce CB et al. Circulation 2016;134:37-47

Renal function with NOAC vs. Warfarin in the Real World

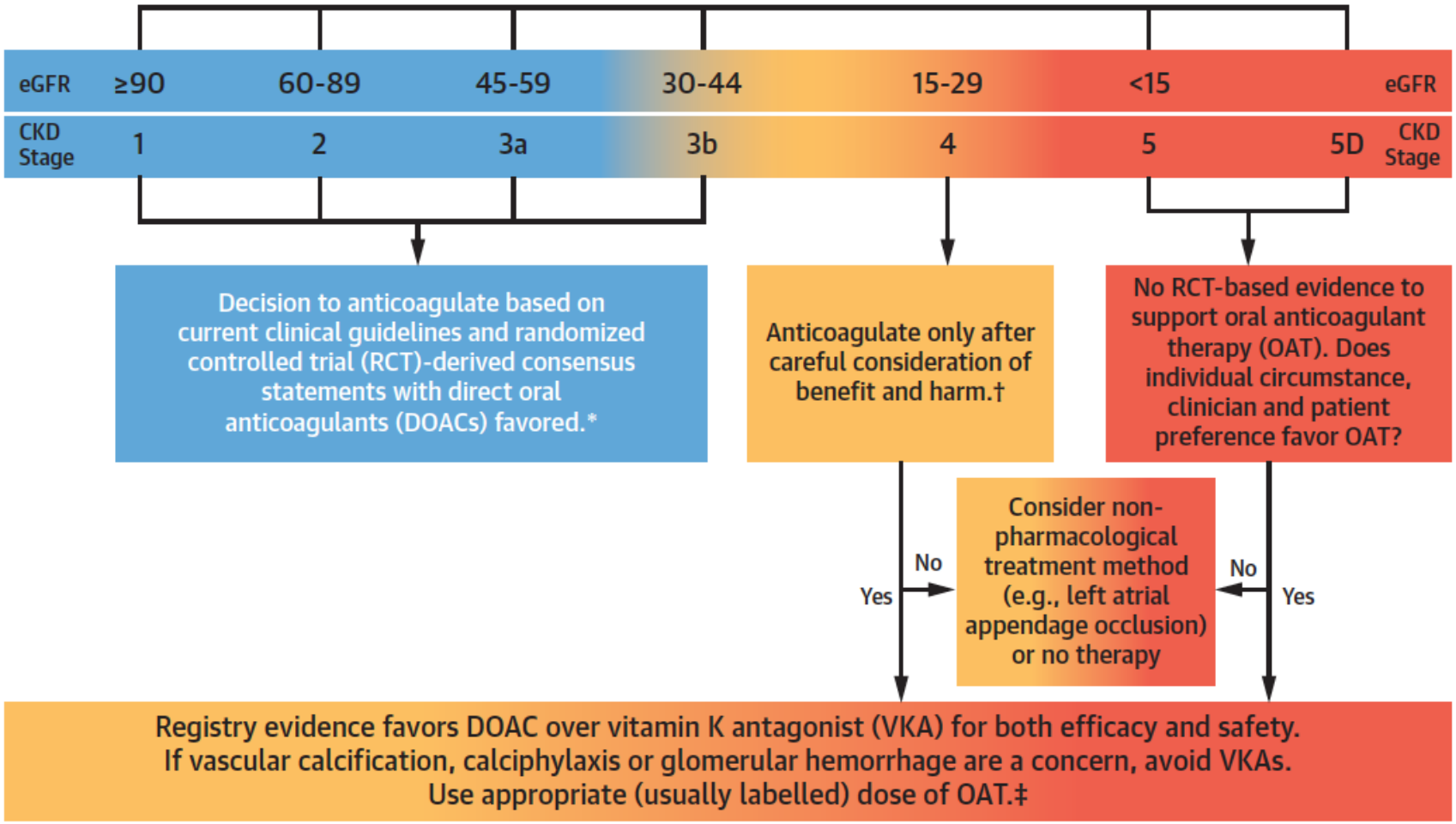
large U.S. administrative database linked to laboratory results, the authors identified 9,769 patients with non-valvular AF who started taking an oral anticoagulant agent between October 1, 2010 and April 30, 2016. Renal function at baseline and at 2 years Follow-up



Renal function decline is common among patients with AF treated with oral anticoagulant agents. NOACs, particularly dabigatran and rivaroxaban, may be associated with lower risks of adverse renal outcomes than warfarin.

Yao X et al. JACC 2017;70:2621-32

Proposed approach to stroke thromboprophylaxis in a patient with concomitant CKD and AF



Kumar S et al. JACC 2019;74:2204-15

SUMMARY

- Renal impairment is not uncommon in patients with AF treated with oral anticoagulants
- Patients with AF and renal impairment are at an increased risk of stroke/SE and major bleedings
- Warfarin reduces the risk of Stroke /SE in patients with AF and CKD
- In patients with moderate renal dysfunction, NOACs are at list not inferior to VKAs
- Patients without renal impairment receiving reduced NOAC doses may be at an increased risk of stroke/SE
- In CKD patients, a renal function worsening is observed overtime, thus renal function has to be periodically monitored