ORAL ANTICOAGULATION USE IN PATIENTS WITH ATRIAL FIBRILLATION AND CHRONIC KIDNEY DISEASE

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Introduction:

Prevalence

AF mechanisms

Stroke risk

Bleeding risk

PREVALENCE

- Atrial fibrillation (AF) and chronic kidney disease (CKD) share common risk factors and are increasingly prevalent globally.
- The two conditions often co-exist: 20% of patients with CKD have symptomatic AF, whereas around 50% of patients with AF will have some degree of renal impairment.
- Patients with both conditions have a higher risk of stroke, cardiovascular morbidity, and all-cause mortality compared with patients who only have either AF or CKD.

1. Potpara TS, et al. Nat Rev Nephrol 2018;14:337–51.
2. Boriani G, et al. Europace 2015;17: 1169–96

SCREENING FOR AF

ESC AF guidelines 2020

Recommendation	Class	Level
Opportunistic screening for AF by pulse taking or ECG rhythm strip is recommended in patients ≥65 years of age.	I	B
Systematic ECG screening should be considered to detect AF in individuals aged ≥75 years, or those at high risk of stroke.	IIa	B

Hindricks G, et al. Eur Heart J 2021;42:373-498.

AF PATHOPHYSIOLOGY IN CKD

Factor	Mechanism
Hypertension	Left ventricular hypertrophy, frequently due to hypertension, can cause heart failure and myocardial fibrosis, each predisposing to AF.
Heart failure	This is a substrate for the development of AF through atrial dilatation, fibrosis, and electromechanical remodeling.
Vascular disease	Peripheral, cerebral, and coronary artery disease are associated with an increased risk of AF.
Diabetes mellitus	Often associated with vascular disease, and thus the risk of AF, diabetes mellitus is also associated with autonomic imbalance, and therefore AF.
Urea and electrolyte imbalance	Uremia and hyperparathyroidism are associated with myocardial fibrosis, which is arrhythmogenic. Dialysis induced ischemia and abnormal pre-dialysis potassium are associated with AF. Dysregulation of intracellular calcium flux also predisposes to AF.
Autonomic imbalance	Heightened sympathetic activity is common in CKD which, in turn, predisposes to AF.

CLOTTING AND BLEEDING IN CKD

- Renal dysfunction causes alterations in hemostatic systems that may result in both a prothrombotic state and a bleeding diathesis.
- Patients with AF and CKD have a markedly increased morbidity and mortality especially due to their excessive risk for both thromboembolic and severe bleeding events, making risk stratification and treatment challenging.

1. *Reinecke H, et al. J Am Soc Nephrol 2009;20:705–11.*
2. *Steffel J, et al. Eur Heart J 2012;33:2766–8.*

Factors predisposing to the increased risk of thromboembolism in coexistent CKD and AF

Virchow's triad

Blood viscosity

Hypercoagulability

- ↑ Thrombin-antithrombin complex
- ↑ Fibrinogen
- ↑ D-dimer
- ↑ Plasma tissue factor
- ↑ Prothrombin 1 & 2
- ↑ Plasminogen activator inhibitor 1
- ↑ von Willebrand factor
- Inhibition of tissue plasminogen activator
- Inhibition of urokinase

Endothelial microparticles

- ↑ Soluble tissue factor release
- ↑ Surface tissue factor

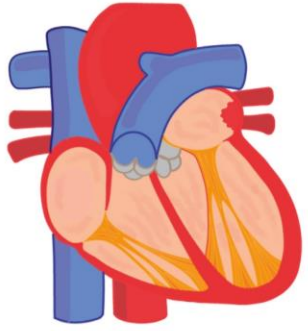
Platelet dysfunction

- ↑ Platelet production
- ↑ Platelet reactivity
- ↑ Platelet aggregation

Blood flow

Atrium

- Atrial dilatation
- Atrial asystole
- Left atrial appendage characteristics



Vessel/Tissue wall

Myocardial tissue

Atrial fibrosis

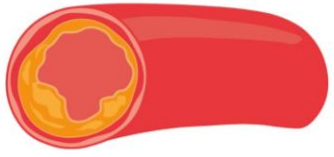
- Myocyte hypertrophy
- Fibroelastosis
- Endocardial fibrosis and infiltration

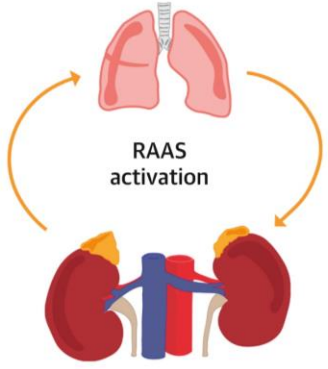
Ventricular hypertrophy

- Myocardial fibrosis

Vascular factors

- Arteriosclerosis
- Accelerated atherosclerosis
- Arterial wall calcification
- ↑ arterial wall stiffness





RAAS Activation

- ↑ D-dimer
- ↑ Plasminogen activator inhibitor 1
- ↑ Angiotensin II

Inflammation

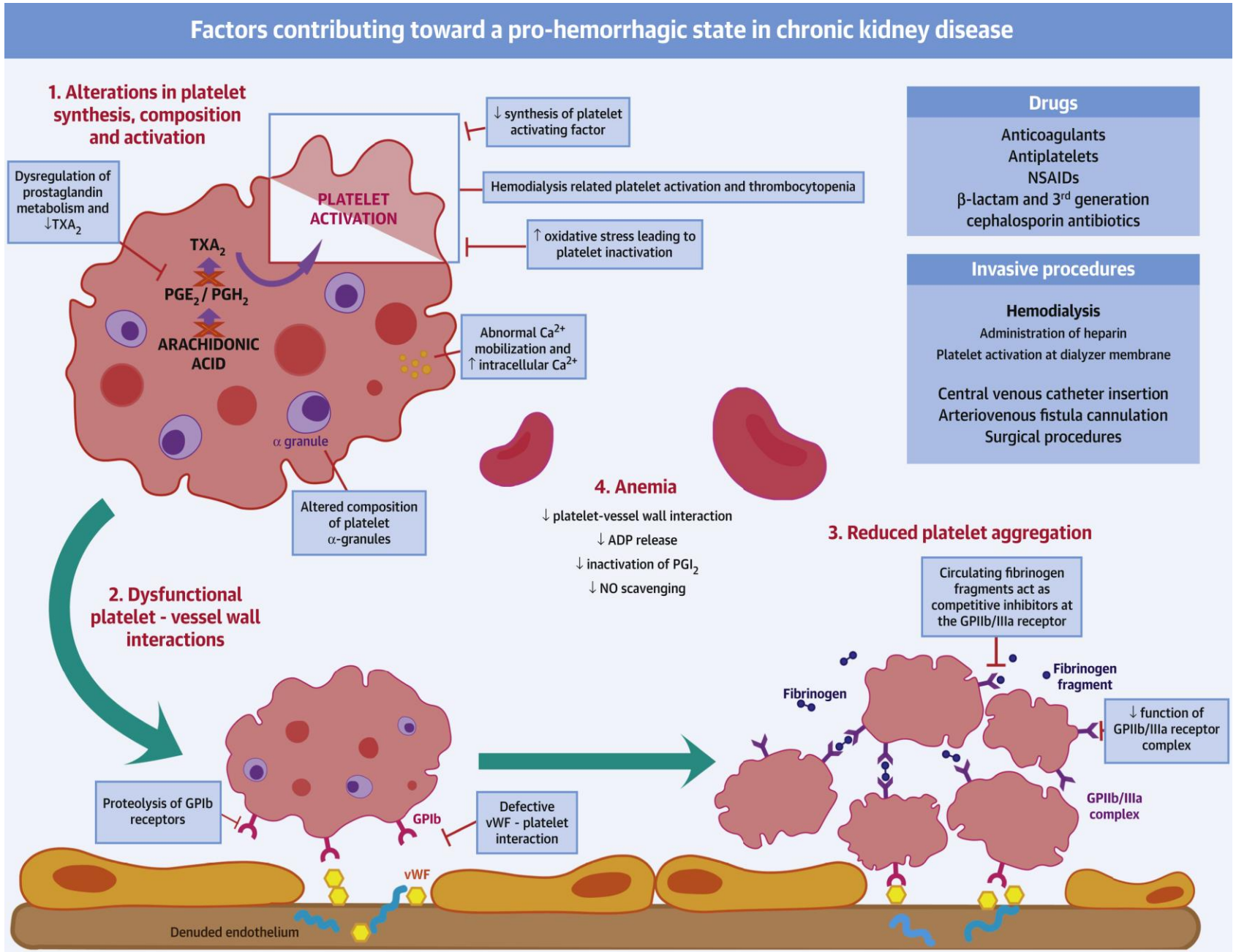
- ↑ IL-6
- ↑ Fibrinogen
- ↑ IL-1 B
- ↑ Tumor necrosis factor
- ↑ C-reactive protein
- ↑ von Willebrand factor

Vascular remodeling

- Tissue fibrosis

Endothelial dysfunction

- Impaired arterial vasodilatation


Factors contributing toward a pro-hemorrhagic state in chronic kidney disease
1. Alterations in platelet synthesis, composition and activation
↓ synthesis of platelet activating factor
Hemodialysis related platelet activation and thrombocytopenia
↑ oxidative stress leading to platelet inactivation
Dysregulation of prostaglandin metabolism and ↓TXA2
PLATELET ACTIVATION
TXA2
PGE2 / PGH2
ARACHIDONIC ACID
Abnormal Ca2+ mobilization and ↑ intracellular Ca2+
α granule
Altered composition of platelet α-granules
Drugs
Anticoagulants
Antiplatelets
NSAIDs
β-lactam and 3rd generation cephalosporin antibiotics
Invasive procedures
Hemodialysis
Administration of heparin
Platelet activation at dialyzer membrane
Central venous catheter insertion
Arteriovenous fistula cannulation
Surgical procedures
4. Anemia
↓ platelet-vessel wall interaction
↓ ADP release
↓ inactivation of PGI2
↓ NO scavenging
2. Dysfunctional platelet - vessel wall interactions
3. Reduced platelet aggregation
Circulating fibrinogen fragments act as competitive inhibitors at the GPIIb/IIIa receptor
Fibrinogen
Fibrinogen fragment
↓ function of GPIIb/IIIa receptor complex
GPIIb/IIIa complex
Proteolysis of GPIb receptors
GPIb
Defective vWF - platelet interaction
vWF
Denuded endothelium

CHALLENGES OF QUANTIFYING LOSS OF RENAL FUNCTION

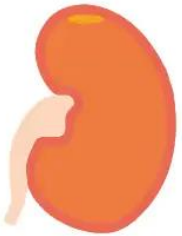
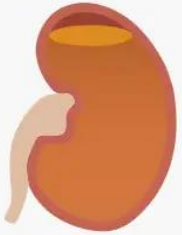
Used for NOAC dose choice

Used for CKD diagnosis and classification

	Equation	Additional Variables
Cockroft and Gault	$\text{GFR (ml/min)} = \frac{(140 - \text{age}) \times \text{weight (kg)}}{7.2 \times \text{SCr (mg/dl)}}$	× 0.085 if female
MDRD 4-Variable study equation	$\text{GFR (ml/min/1.73 m}^2\text{)} = 186 \times \text{SCr (mg/dl)}^{-1.154} \times \text{age}^{-0.203} \times 0.742 \text{ (if female)}$	× 1.21 if Black-American × 0.763 if Japanese × 1.233 if Chinese
MDRD 4-Variable study equation (IDMS tra	$\text{GFR (ml/min/1.73 m}^2\text{)} = 175 \times \text{SCr (mg/dl)}^{-1.154} \times \text{age}^{-0.203} \times 0.742 \text{ (if female)}$	× 1.21 if Black-American × 0.763 if Japanese × 1.233 if Chinese
CKD - EPI creatinine equation	$\text{GFR} = 141 \times \min\left(\frac{\text{SCr}}{\kappa}, 1\right)^{\alpha} \times \max\left(\frac{\text{SCr}}{\kappa}, 1\right)^{-1.209} \times 0.993^{\text{age}}$ $\alpha = -0.329$ if female, -0.411 if male $\kappa = 0.7$ if female, 0.9 if male $\min$ = the minimum of $\frac{\text{SCr}}{\kappa}$ or 1 $\max$ = the maximum of $\frac{\text{SCr}}{\kappa}$ or 1	× 1.018 if female × 1.159 if Black

STAGES OF CKD

Abnormal GFR: < 60 mL/min

Stage of CKD	STAGE 1	STAGE 2	STAGE 3A	STAGE 3B	STAGE 4	STAGE 5
eGFR	90 or greater	Between 60 and 89	Between 45 and 59	Between 30 and 44	Between 15 and 29	Less than 15
Level of kidney damage	 Mild kidney damage	 Mild kidney damage	 Mild to moderate kidney damage	 Mild to moderate kidney damage	 Moderate to severe kidney damage	 End-stage kidney disease. Kidneys are close to failure or have completely failed. You will need to start dialysis or have a kidney transplant.

BLEEDING AND CLOTTING SCORING SCHEMES IN CKD

- In the general population with AF, OAT is supported by guidelines that mandate the use of scoring systems to estimate thromboembolic and bleeding risk, most commonly through the CHA2DS2-VASc and HAS-BLED scores, respectively.
- Other scores include CHADS2, R2CHADS2 (renal dysfunction+ CHADS2), ABC, GARFIELD, ATRIA, ORBIT, and HEMORR2HAGES.
- Although these scoring systems have been studied in a range of populations, their transferability to the setting of CKD is largely untested.
- The most commonly used score for predicting stroke risk, CHA2DS2-VASc, was superior to CHADS2 in predicting the risk of ischemic stroke in a Taiwanese cohort of patients with ESRD requiring dialysis.
- While the commonly used scores to estimate bleeding (HAS-BLED, ATRIA, ORBIT, and HEMORR2HAGES) attempt to reflect kidney function, they do not utilize eGFR thresholds and they fail to differentiate between patients receiving different forms of renal replacement therapy. Current bleeding scoring systems are unreliable when applied to dialysis patients

THROMBOEMBOLIC RISK ASSESSMENT

CHA2DS2-VASc		Definition	Point
C	Congestive heart failure	Clinical HF, or moderate to severe LV dysfunction on cardiac imaging, or HCM	1
H	Hypertension	History of hypertension or on antihypertensive therapy	1
A2	Advanced age	Age 75 years or older	2
D	Diabetes mellitus	Treatment with oral hypoglycemic drugs and/or insulin or FBS>125 mg/dL	1
S2	Stroke	Previous stroke, TIA, or thromboembolism	2
V	Vascular disease	CAD, PAD, or aortic plaque	1
A	Age	65-74 years	1
S	Sex category	Female	1
Maximum score			9

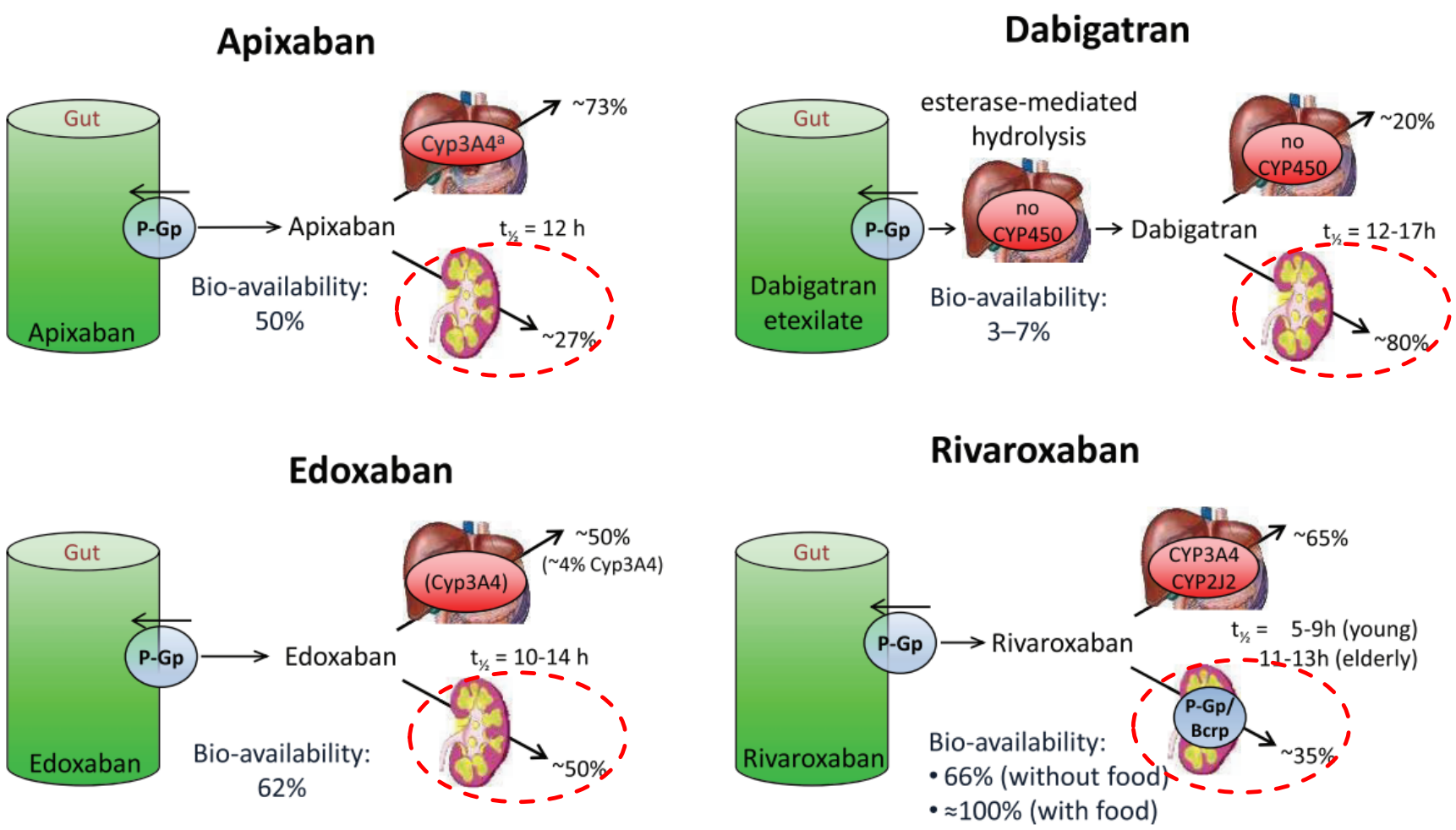
BLEEDING RISK ASSESSMENT

HASBLED		Definition	Point
H	Uncontrolled hypertension	SBP >160 mmHg	1
A	Abnormal renal and/or hepatic function	Dialysis, transplant, serum creatinine >2.6 mg/dL Cirrhosis, bilirubin > 2 upper limit of normal, AST/ALT/ALP >3 upper limit of normal	1 point for each
S	Stroke	Previous ischemic or hemorrhagic stroke	1
B	Bleeding history or predisposition	Previous major hemorrhage or anemia or severe thrombocytopenia	1
L	Labile INR	TTR <60% in patients receiving VKAs	1
E	Elderly	Aged >65 years or extreme frailty	1
D	Drugs	Concomitant use of antiplatelet or NSAID; and/or excessive (≥8) alcohol per week	1 point for each
Maximum score			9

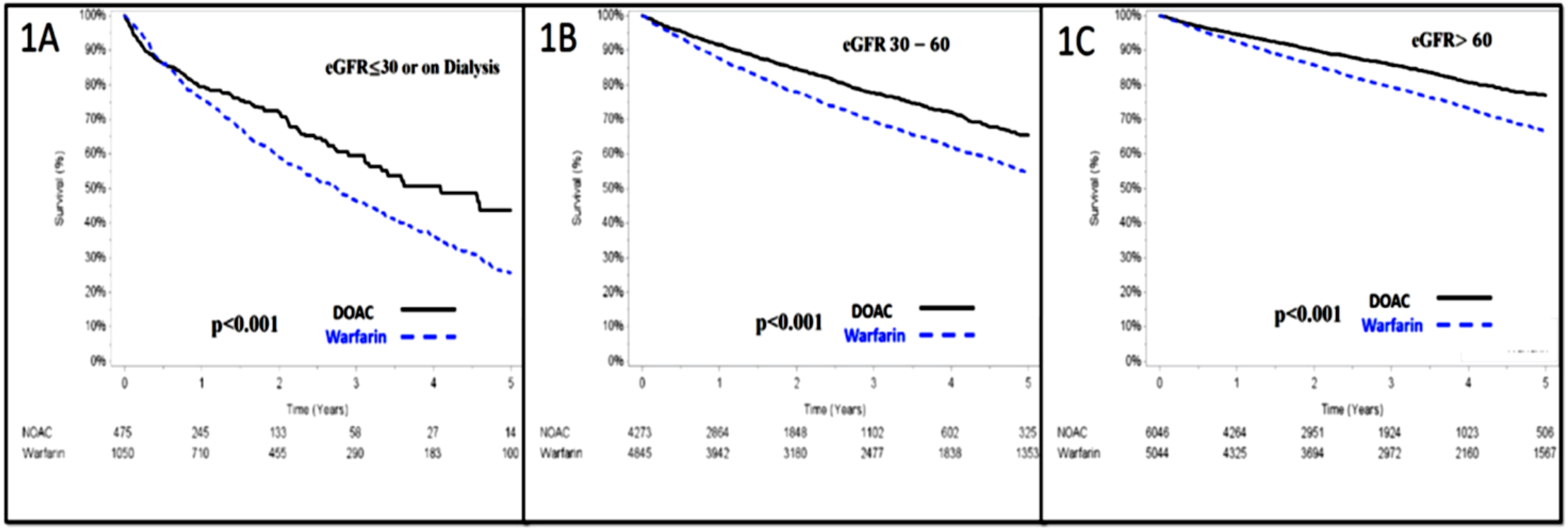
OAC in Patients with CKD and AF

VKAs vs NOAC (DOAC)

RENAL CLEARANCE OF NOACS

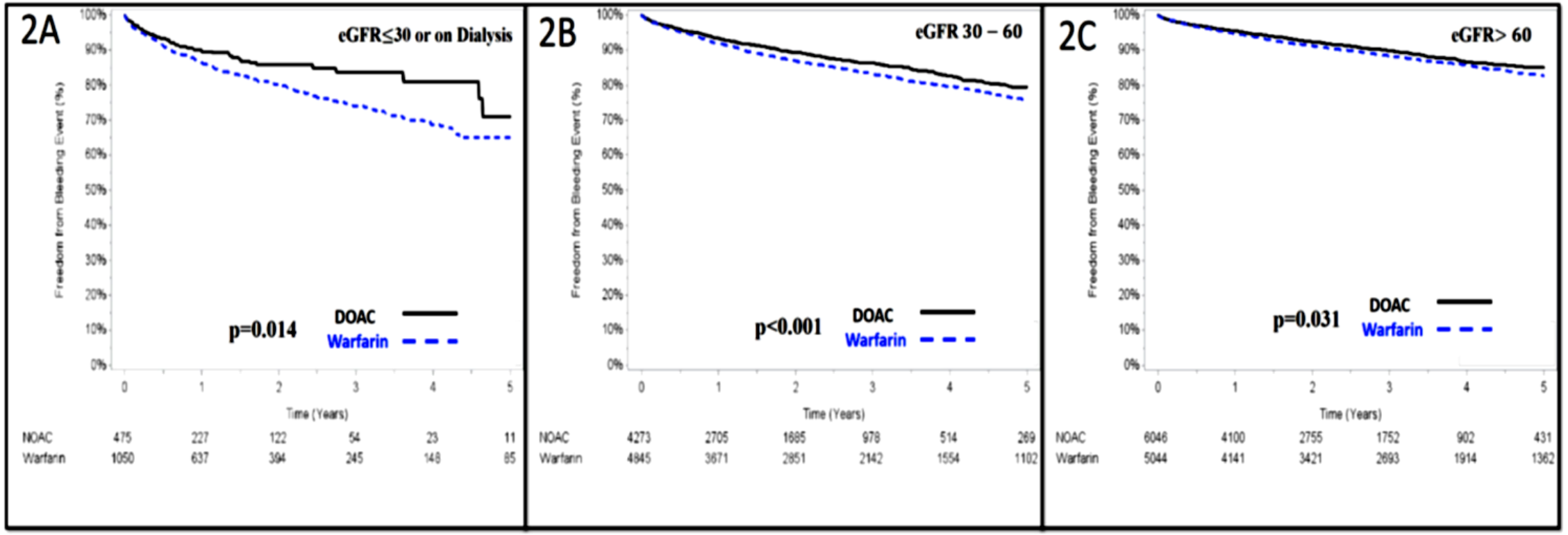


MORTALITY RISK ACCORDING THE eGFR: NOACs VS WARFARIN



Makani A, et al. Am J Cardiol 2020;125:210–214.

BLEEDING RISK ACCORDING THE eGFR: NOACs VS WARFARIN



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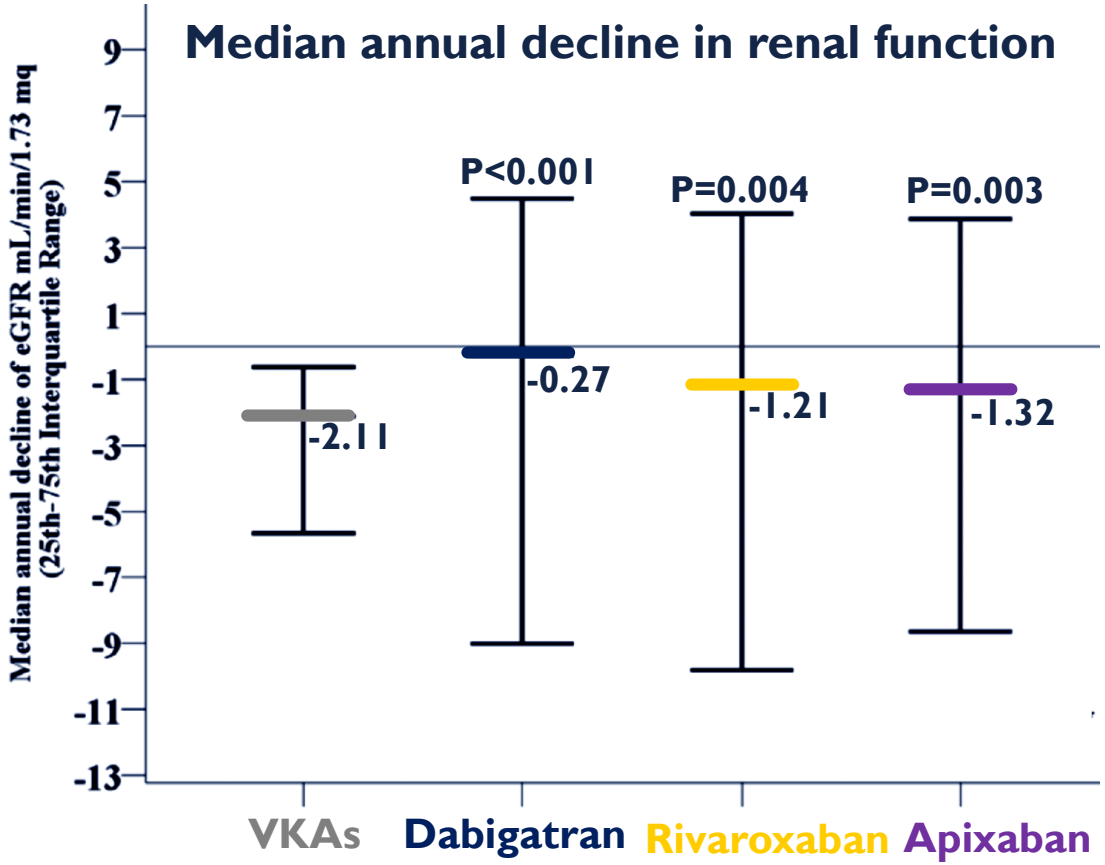
CLINICAL OUTCOMES BASED ON RENAL FUNCTION AND ANTICOAGULATION STRATEGY

	EGFR <=30 ml/min or on dialysis			EGFR >30-60 ml/min			EGFR >60 ml/min		
	Events/ Incidence*	Adjusted HR (95%CI)	p Value	Events/ Incidence*	Adjusted HR (95%CI)	p Value	Events/ Incidence*	Adjusted HR (95% CI)	p Value
All-cause mortality									
DOAC	133/19.3	0.76 (0.63-0.92)	0.005	748/8.4	0.74 (0.68, 0.81)	<0.001	726/5.3	0.76 (0.70, 0.84)	<0.001
Warfarin	613/26.3	REF	REF	2,041/12.3	REF	REF	1,540/8.1	REF	REF
Bleeding event									
DOAC	51/7.9	0.69 (0.50, 0.93)	0.017	439/5.3	0.83 (0.74, 0.94)	0.003	485/3.8	0.93 (0.82, 1.04)	0.209
Warfarin	216/10.5	REF	REF	871/5.9	REF	REF	699/4.0	REF	REF
Embolic stroke									
DOAC	14/2.1	0.60 (0.34, 1.09)	0.092	204/2.4	0.87 (0.73, 1.04)	0.117	239/1.8	0.86 (0.73, 1.02)	0.087
Warfarin	66/2.9	REF	REF	400/2.5	REF	REF	380/2.1	REF	REF
Hemorrhagic stroke									
DOAC	4/0.6	0.55 (0.19, 1.61)	0.276	30/0.3	0.41 (0.27, 0.61)	<0.001	46/0.3	0.58 (0.40, 0.82)	0.002
Warfarin	23/1.0	REF	REF	127/0.8	REF	REF	114/0.6	REF	REF

Makani A, et al. Am J Cardiol 2020;125:210–214.

ATHERO-AF: AN ITALIAN MULTICENTER COHORT STUDY EVALUATED RENAL FUNCTION IN PATIENTS WITH AF TREATED WITH VKA OR DOAC



ATHERO-AF cohort was composed of 1667 AF patients. Of these, 743 were on VKAs (590 on warfarin and 153 on acenocumarol) and 924 were on NOACs. Of these, 280 were on dabigatran, 299 on rivaroxaban and 345 on apixaban.

All NOACs showed a lower decline in renal function over time compared to those on VKAs.

Dabigatran showing the most favorable profile for renal outcomes.[2]

Pastori D, et al. Br J Clin Pharmacol. 2020;1–9.

G TO RENAL FUNCTION

*** Dabigatran 110 mg bid**

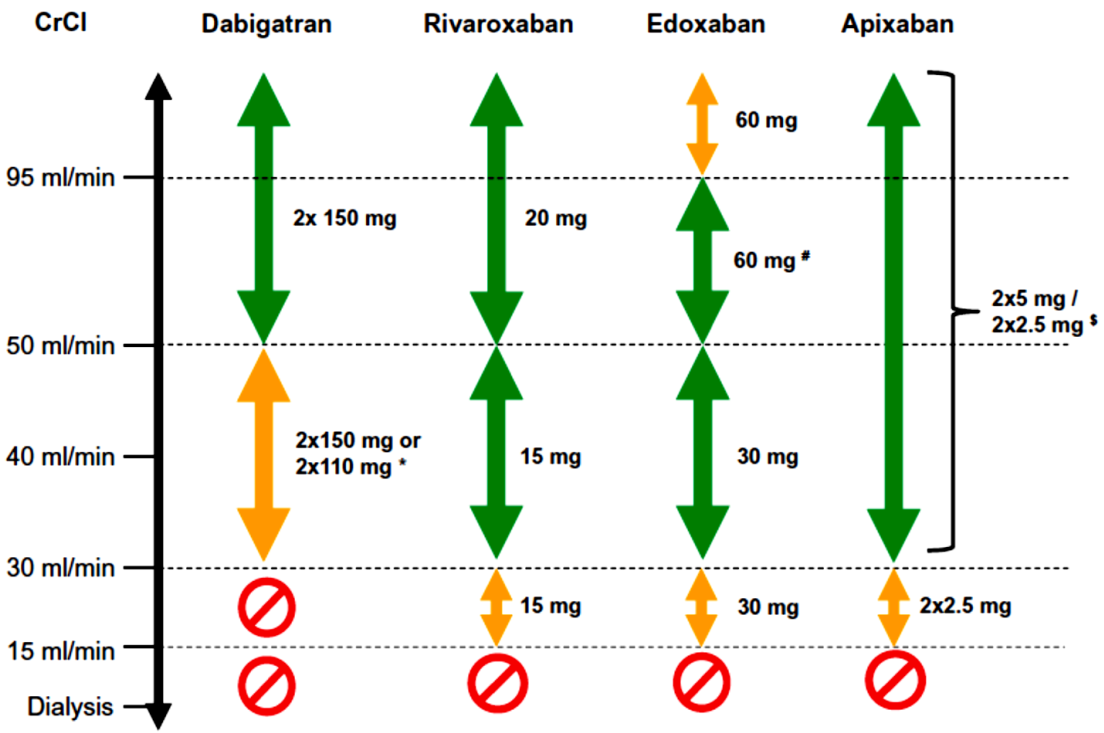
- Age ≥80 years
- Concomitant use of verapamil, or
- Increased bleeding risk

$ Apixaban 2.5 mg bid

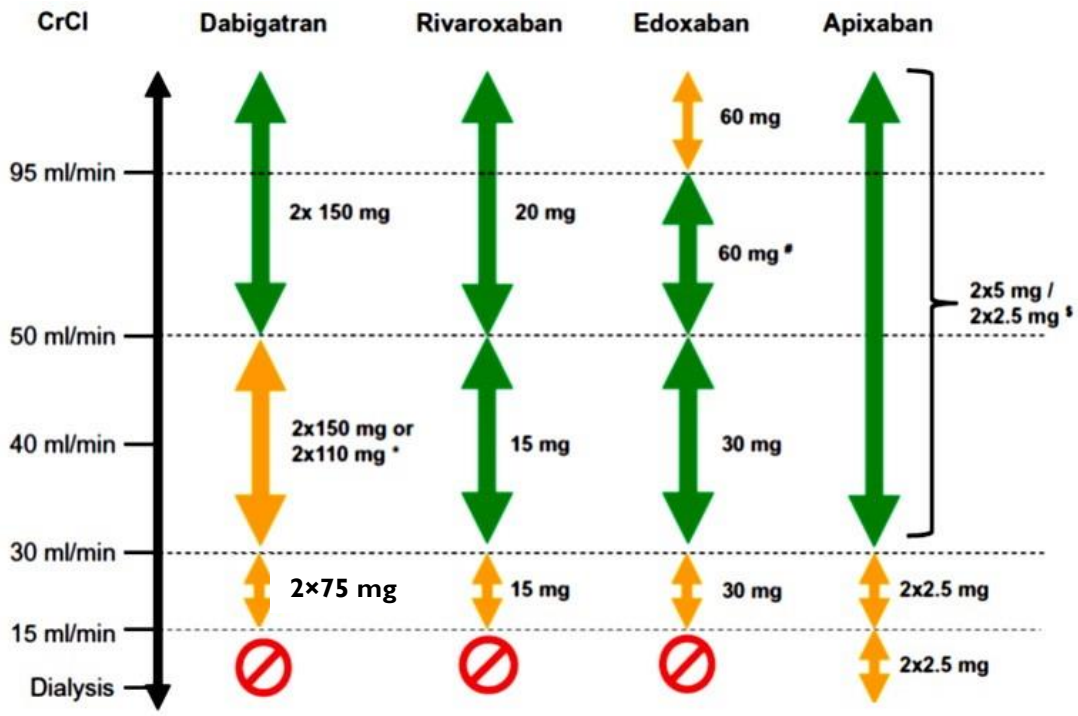
At least 2 of 3 criteria:

- Age ≥80 years,
- Body weight ≤60 kg, or
- Serum creatinine ≥1.5 mg/dL (133 µmol/L)

2020 ESC guideline recommendation



2019 AHA/ACC/HRS guideline recommendation



OAC CHOICE IN SEVERE CKD (CRCL: 15-29 ML/MIN)

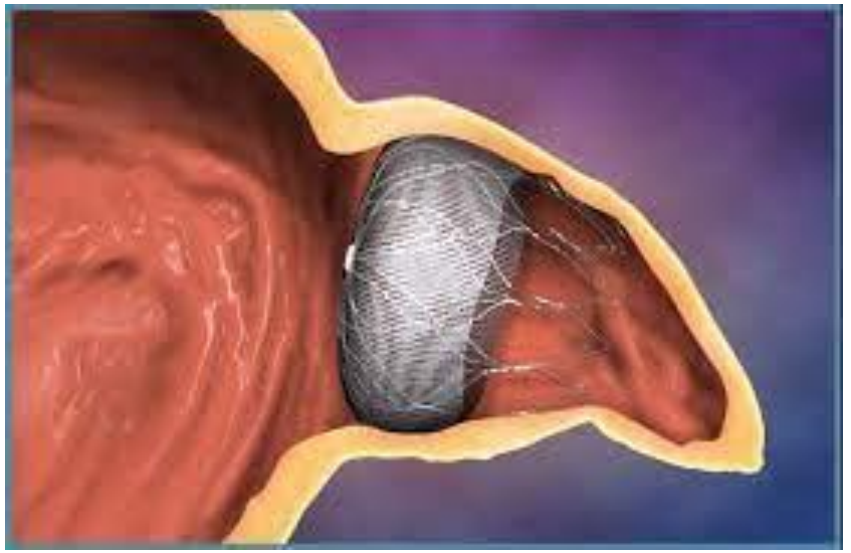
- There are no RCT data on the use of VKAs for stroke prevention in AF patients with severe CKD or on dialysis. Similarly, all phase III NOAC trial exclude the patients with CrCL <30mL/min (Except for few patients on apixaban with CrCL 25-30 mL/min).
- Observational data indicate a favourable efficacy and safety profile of all three Fxa inhibitors compared with VKA in patients with severe CKD.
- In view of the individual NOAC pharmacokinetics (27% renal clearance for apixaban), dose reduction criteria (50% reduction for apixaban and edoxaban), and available evidence form RCTs, the use of either *apixaban or edoxaban may be preferable in these patients*, but direct head-to-head comparisons are missing.

OAC IN PATIENTS WITH ESRD (CRCL ≤15 ML/MIN) OR ON DIALYSIS

- Given the lack of strong evidence, the decision to anticoagulate and (if so) whether to use a NOAC or VKA in patients with end-stage renal failure or on dialysis requires a high degree of individualization.
- Measurements of NOAC plasma levels, although intuitively appealing for this situation, has never been prospectively investigated for hard clinical endpoints.
- Patients need to be informed of the lack of data as well as the "off-label" character of whichever drug is chosen including the uncertain benefit and the increased risk of complications.

ALTERNATE STROKE PREVENTION STRATEGIES IN END-STAGE CKD PATIENTS

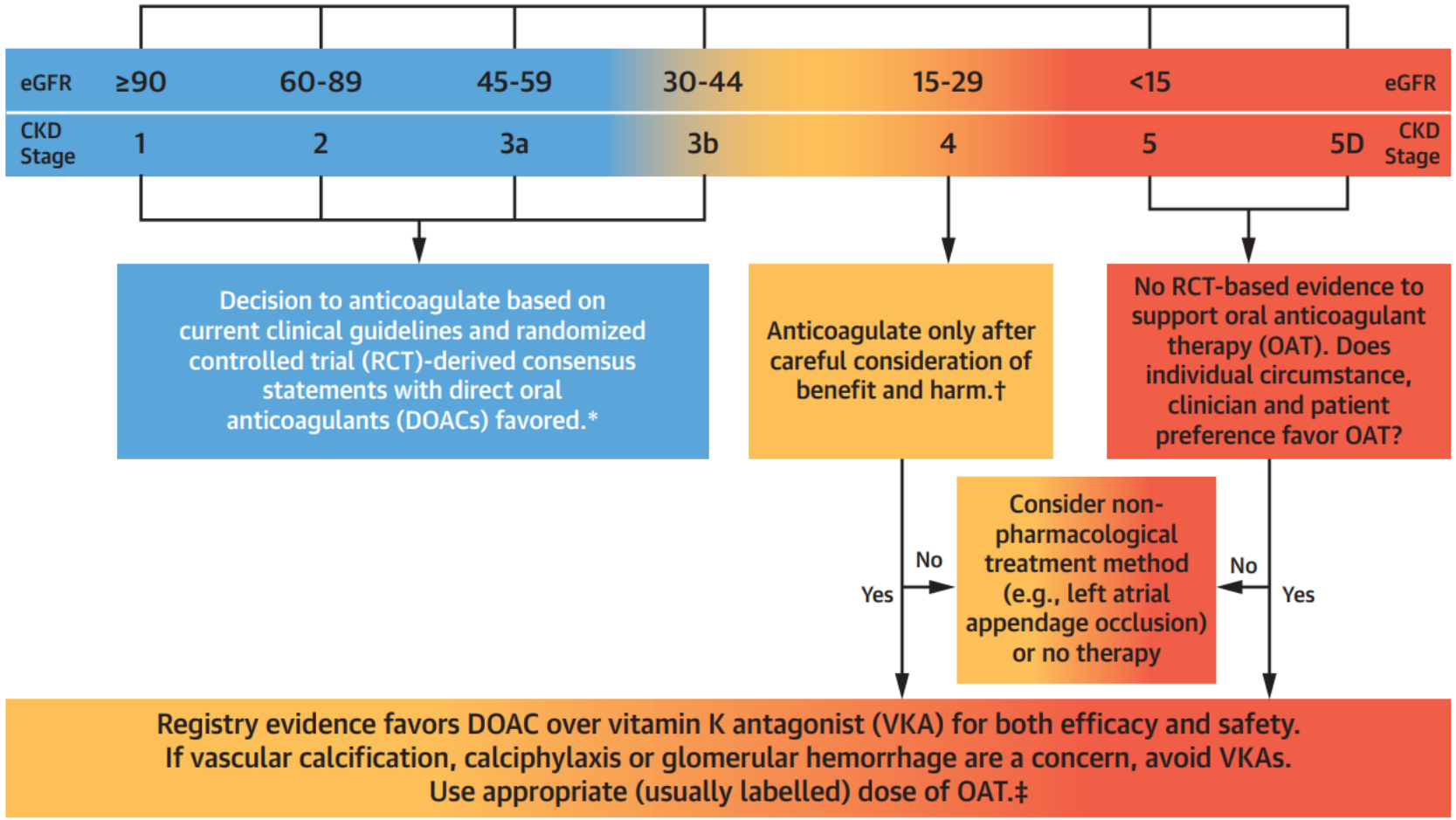
- Of note, there are also no RCT data for the use of alternative stroke prevention strategies such as left atrial appendage (LAA) occluder implantation for these individuals.



NOAC IN AF PATIENTS AFTER KIDNEY TRANSPLANTATION

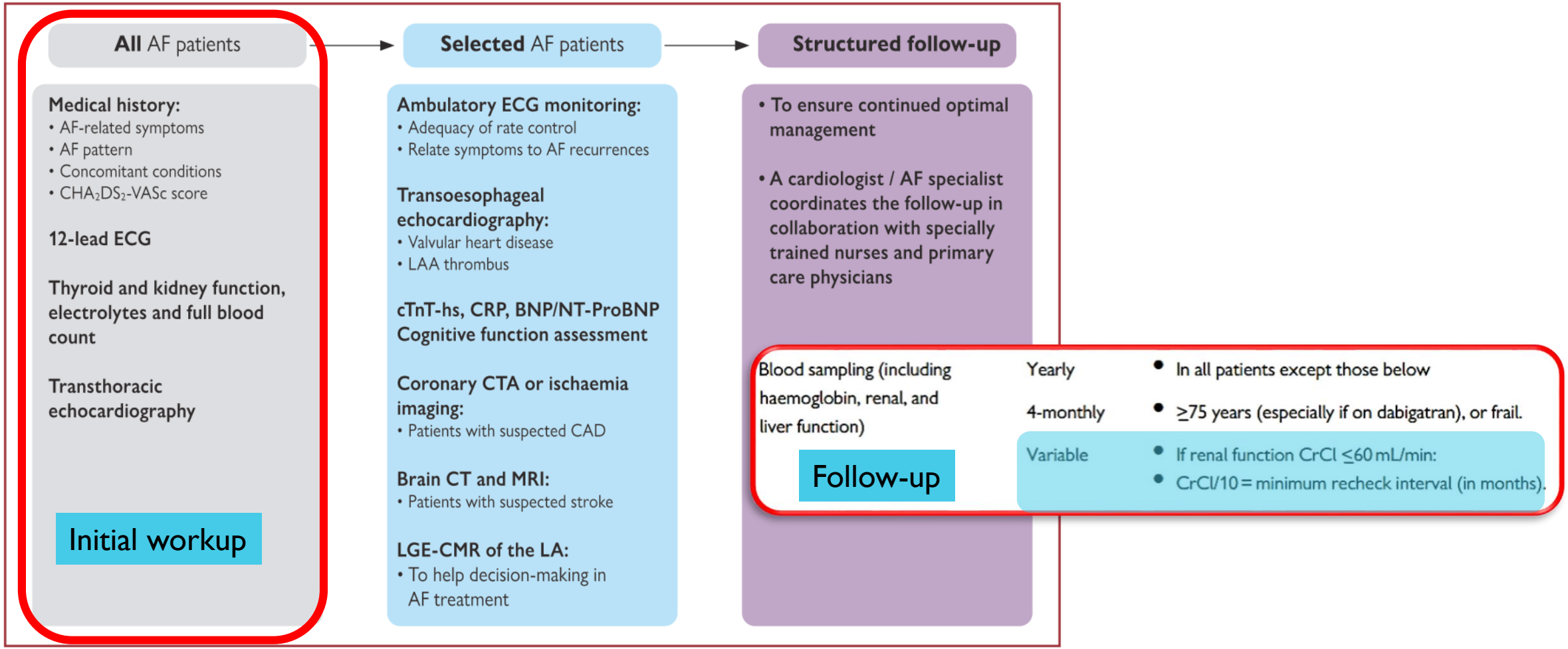
- There are no data on the use of NOACs in AF patients after kidney transplantation.
- If NOACs are used in such patients, the dosing regimen should be selected according to the estimated renal function, and caution is needed concerning possible DDIs between the NOAC and concomitant immunosuppressive therapies

PROPOSED APPROACH TO STROKE PREVENTION IN A PATIENT WITH CONCOMITANT CKD AND AF



Kumar, S. et al. J Am Coll Cardiol. 2019;74(17):2204-15.

DIAGNOSTIC WORK-UP AND FOLLOW-UP IN AF PATIENTS



TAKE HOME MESSAGE

- Clinical trial and real-world clinical data from the non-CKD setting cannot be reliably and safely extrapolated into clinical practice for patients with significant/dialysis-requiring CKD. Initiating OAT in CKD patients is contentious due to their increased propensity to both thrombosis and bleeding.
- Furthermore, conventional scoring systems for estimating bleeding and clotting risk are not validated in CKD patients and cannot be relied upon alone for clinical decision-making.
- Until dedicated RCTs are undertaken, the decision of whether and how to initiate OAT in patients with concomitant CKD and AF requires an individualized approach with physician-patient collaboration.

TAKE HOME MESSAGE

- In mild-to-moderate CKD (eGFR 30-49 mL/min or higher), the evidence suggests that NOACs are preferred options over VKAs for both efficacy and safety (apixaban, rivaroxaban, edoxaban, and dabigatran).
- In severe CKD (eGFR 15-29 mL/min), there is limited RCT evidence to predict how NOACs may compare VKAs, although observational evidence for superior efficacy and safety of NOAC over warfarin continues to accumulate (apixaban and rivaroxaban>rivaroxaban).
- There is no RCT based evidence to support anticoagulation therapy in ESRD (GFR ≤ 15 mL/min). OAC should only be initiated after careful consideration of benefit and harm (warfarin or apixaban).
- In AF patients that had a history of major bleeding and contraindications to OAC, catheter-based occlusion of the left atrial appendage could be considered.