ANTICOAGULATION IN CKD

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INTRODUCTION

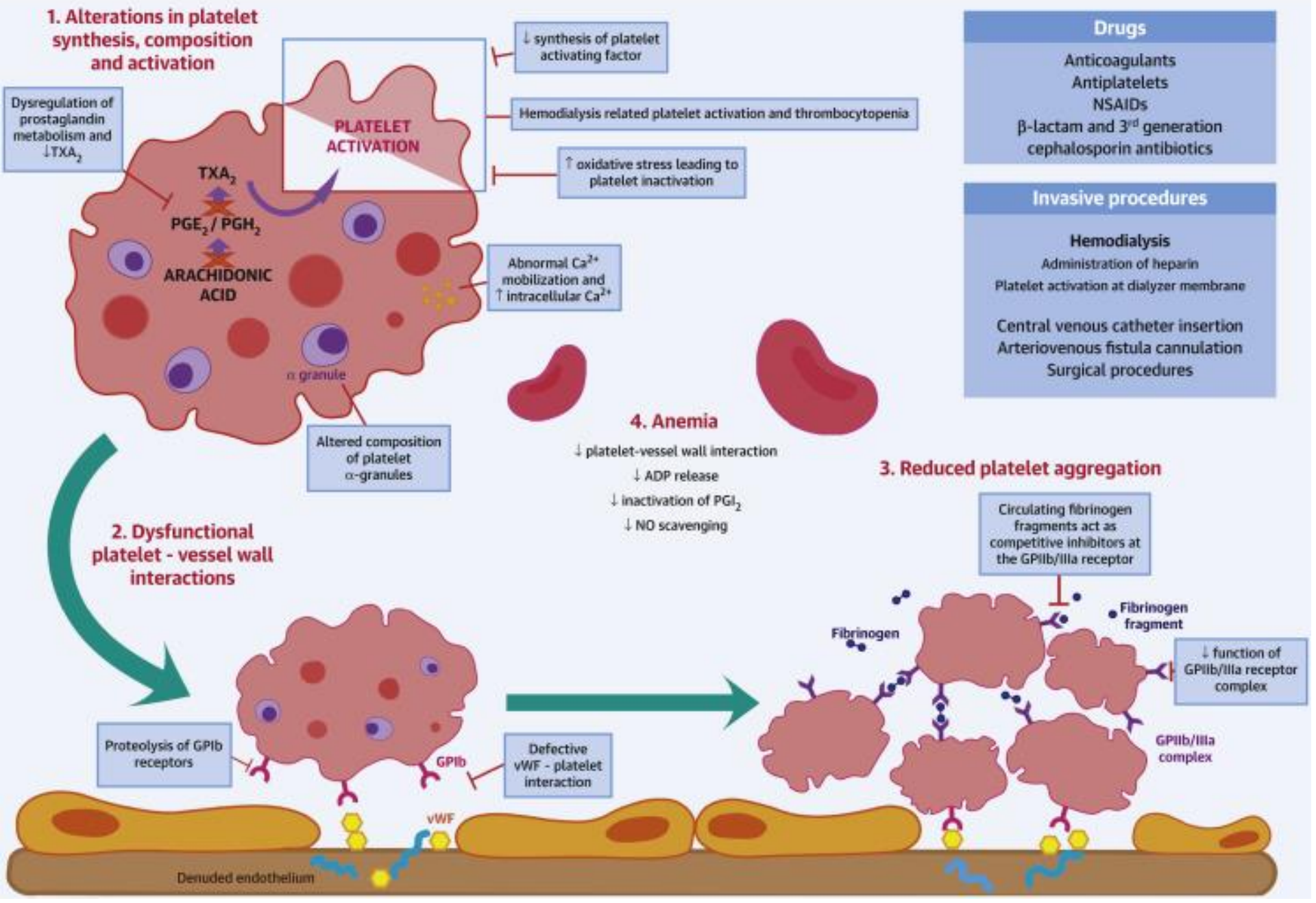
- The risk for venous thromboembolism (VTE) is two to three times greater in patients with CKD.

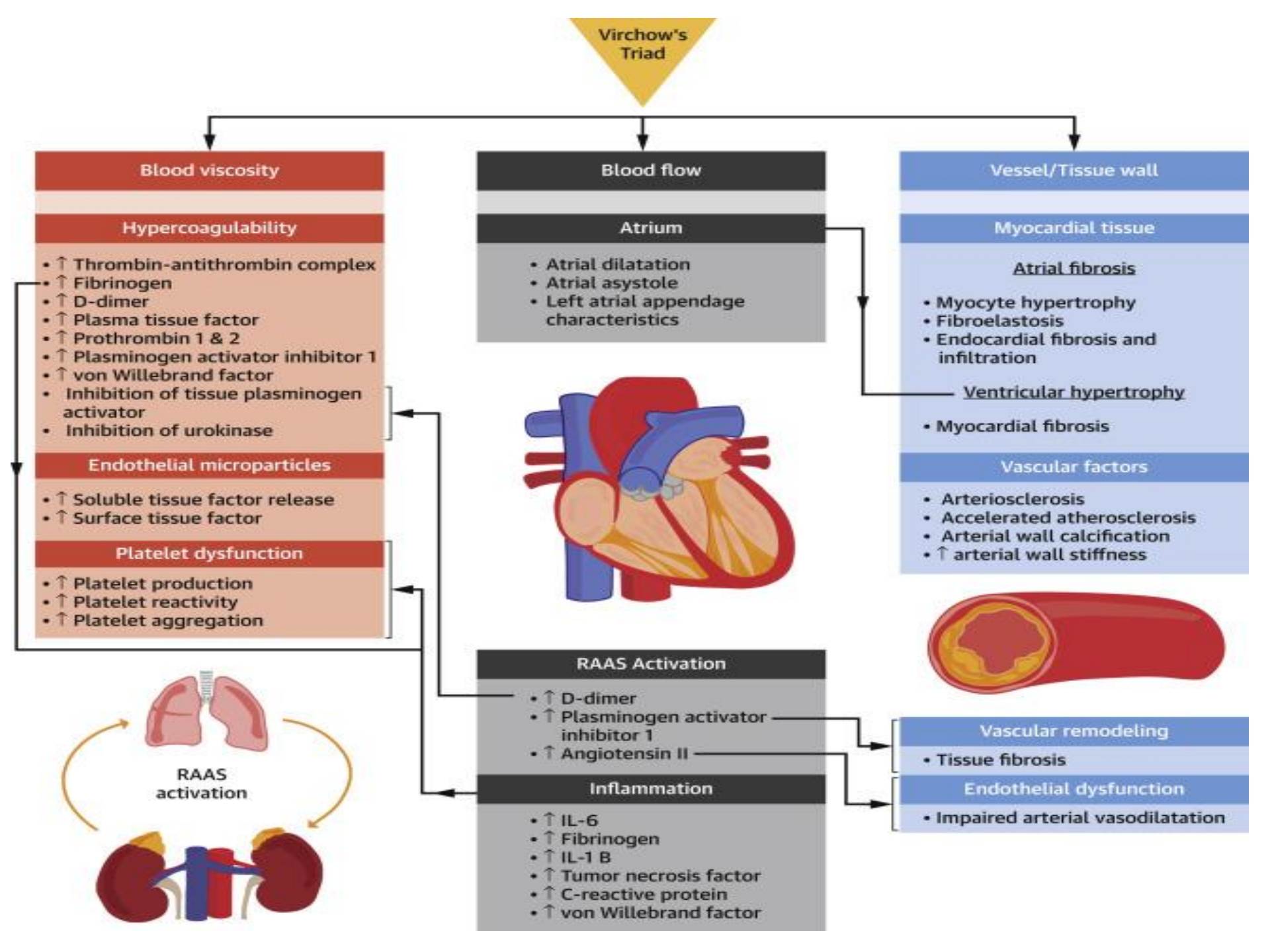
- The risk for atrial fibrillation (AF) is also 10 to 20 times greater in patients with CKD and ESKD.

- Paradoxically, patients with CKD, and especially those with ESKD are not only at a higher risk of thrombosis, they are also at increased risk of bleeding even without anticoagulant treatment.

- The pathophysiological mechanisms of the increased bleeding risk associated with uremia are diverse and include increased vascular prostaglandin I_2, decreased von Willebrand factor, hyperparathyroidism, chronic inflammation, decreased nitric oxide bioavailability, anaemia and platelet abnormalities leading to abnormal adhesion and aggregation.

Factors contributing toward a pro-hemorrhagic state in chronic kidney disease




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
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

	Normal renal function or stage 1–2 CKD (eGFR ≥60 mL/min/1.73 m²)	Stage 3 (eGFR 30–59 mL/min/ 1.73 m²)	Stage 4 (eGFR 15–29 mL/min/ 1.73 m²)	Stage 5 (eGFR <15 mL/min/ 1.73 m² OR dialysis)
$P2Y_{12}$ inhibitors				
Clopidogrel	300–600 mg orally, then 75 mg a day	No dose adjustment	No dose adjustment	Use only for selected indications (e.g. stent thrombosis prevention)
Prasugrel	60 mg orally then 10 mg a day	No dose adjustment	No dose adjustment	NOT recommended
Ticagrelor	180 mg orally then 90 mg twice a day	No dose adjustment	No dose adjustment	NOT recommended
Cangrelor	30 μg/kg bolus and 4 μg/kg/min infusion	No dose adjustment	No dose adjustment	No dose adjustment
Anticoagulants				
Unfractionated heparin	Prior to coronary angiography: 60–70 IU/kg iv (max 5000 IU) and infusion (12–15 IU/kg/ hour) (max 1000 IU/hour), target aPTT 1.5–2.5× control During PCI: 70–100 IU/kg iv (50–70 IU/kg if concomitant with GPI)	No dose adjustment	No dose adjustment	No dose adjustment
Enoxaparin	1 mg/kg sc twice a day	No dose adjustment	1 mg/kg sc once a day	NOT recommended
Bivalirudin	Bolus 0.75 mg/kg iv, infusion 1.75 mg/kg/hour		No adjustment of bolus, reduce infusion rate to 1 mg/kg/hour	On dialysis, no adjustment of bolus, reduce infusion rate to 0.25 mg/kg/hour
Fondaparinux	2.5 mg sc daily	No dose adjustment	NOT recommended if eGFR <20 mL/min/1.73 m²	NOT recommended
Glycoprotein IIB/IIIA inhibitors				
Eptifibatide	Bolus 180 μg/kg iv, infusion 2 μg/kg/min	No adjustment of bolus, reduce infusion rate to 1 μg/kg/min if eGFR <50 mL/min/1.73 m²	NOT recommended	NOT recommended
Tirofiban	Bolus 25 μg/kg or 10 μg/kg iv, infusion 0.15 μg/kg/min	No dose adjustment	No adjustment of bolus, reduce infusion to 0.05 μg/ kg/min	NOT recommended
Abciximab	Bolus 0.25 mg/kg iv, infusion 0.125 μg/kg/min (max 10 μg/ min)	No specific recommendations for the use of abciximab or for dose adjustment in the case of renal failure. Careful evaluation of haemorrhagic risk is needed		

	Warfarin	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
Routine dose	Adjusted to INR	150 mg, 2×/d	5 mg, 1×/d	60 mg, 1×/d	20 mg, 1×/d
CKD dose adjustment	Adjusted to INR	None	2.5 mg, 2×/d, if Scr > 1.5 mg/dL + age ≥ 80 y or weight < 60 kg	30 mg, 1×/d, if CL_{cr} 15-50 mL/min	15 mg, 1×/d, if CL_{cr} 15-50 mL/min
Mechanisms of action	Inhibits synthesis of vitamin K–dependent clotting factors (II, VII, IX, X)	Direct thrombin inhibitor	Direct factor Xa inhibitor	Direct factor Xa inhibitor	Direct factor Xa inhibitor
4-h dialysis removal	<1%	50%-60%	7%	9%	<1%
Volume of distribution, L	8	50-70	21	107	50
Excretion	Nonrenal	50%-60% renal	CYP3A4/5 (P-glycoprotein liver enzyme); 27% renal	CVP3A4 (liver enzyme); 50% renal; 40% bile	CYP3A4/5 and CYP2J2 (liver enzymes); 36% renal
Reversal agents	Vitamin K, fresh frozen plasma, 4-factor prothrombin complexes	Idarucizumab	4-factor prothrombin complexes	4-factor prothrombin complexes	4-factor prothrombin complexes
FDA approved for CKD-5D	Yes	No	Yes	No	No
Concerns for use in CKD-5D[a]	Requires frequent monitoring, high interindividual variability in drug response, may increase risk for calciphylaxis and vascular calcification	Reversal agent may not be readily available, lack of data for safe dosing in CKD-5D	Reversal agent may not be readily available, dosing in CKD-5D based on pharmacokinetic data only	Reversal agent may not be readily available, lack of data for safe dosing in CKD-5D	Reversal agent may not be readily available, dosing recommendations in CKD-5D based on pharmacokinetic data only

Note: Data in table based on references 89-91, 93-95, 97, 98.

ATRIAL FIBRILLATION

Assess CHA_2DS_2-VASc score
Anticoagulation recommended if score is 1+ (males) or 2+ (females)

	CrCl 80+ mls/min	CrCl 50-79 mls/min	CrCl 30-49 mls/min	CrCl 15-29 mls/min	CrCl <15 mls/min, or dialysis-dependent **
Apixaban	5mg BD	5mg BD	5mg BD	Consider 2.5mg BD	Consider
Rivaroxaban	20mg OD	20mg OD	15mg OD	15mg OD	Contraindicated
Edoxaban	60mg OD	60mg OD	30mg OD	30mg OD	Contraindicated
Dabigatran	150mg BD	150mg BD	110mg BD***	Consider 75mg BD	Contraindicated
VKA *	INR 2-3	INR 2-3	INR 2-3	INR 2-3	Consider

* Data favours the use of DOACs over VKA regarding bleeding risk. VKA should be used in patients with metallic heart valves or other CI to DOACs

** consider alternative options eg. LAA closure, anti-platelets, or no anti-thrombotic agent

*** 110mg BD dabigatran used in Europe; 75mg BD for CrCl 15-30 ml/min approved in US

VENOUS THROMBOEMBOLISM

	CrCl 80+ mls/min	CrCl 50-79 mls/min	CrCl 30-49 mls/min	CrCl 15-29 mls/min	CrCl <15 mls/min, or dialysis-dependent **
Apixaban	Loading then 5mg BD	Loading then 5mg BD	Loading then 5mg BD	Loading then 5mg BD	Consider
Rivaroxaban	Loading then 20mg OD	Loading then 20mg OD	Loading then 20mg OD	Loading then 20mg OD	Contraindicated
Edoxaban*	60mg OD	60mg OD	30mg OD	30mg OD	Contraindicated
Dabigatran*	150mg BD	150mg BD	150mg or 110mg BD	Contraindicated	Contraindicated
VKA *	INR 2-3	INR 2-3	INR 2-3	INR 2-3	Consider

* At least 5 days of parenteral anticoagulation required prior to commencement of Dabigatran and Edoxaban in VTE; When commencing VKA, parenteral anticoagulation is required until the INR is >2 for 2 consecutive days, or for 5 days, whichever is longer.

** Data favours the use of DOACs over VKA regarding bleeding risk. Very limited data in ESRD

Future considerations may include FXI inhibitors

	RE-LY	ROCKET AF	ARISTOTLE	ENGAGE AF-TIMI 48
Trial Characteristics				
Drug	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Year of publication	2009	2011	2011	2013
Study doses	110 mg, 2×/d; 150 mg, 2×/d	20 mg daily (15 mg daily for eCL_{cr} 30-49 mL/min)	5 mg, 2×/d[a]	60 mg daily (30 mg daily for $eCL_{cr} \leq 50$ mL/min)
N	18,113	14,264	18,201	21,105
Patients With CKD				
No. with moderate CKD	3,554 (20%)	2,950 (21%)	3,017 (17%)	2,740 (19.5%)
Definition/cutoff for moderate CKD	eCL_{cr} 31-49 mL/min	eCL_{cr} 30-49 mL/min	eCL_{cr} 25-50 mL/min	eCL_{cr} 30-50 mL/min
Age, y	76 (median)	79 (median)	78 (mean)	79 (median)
Female sex	47%	55%	53%	54%
$CHADS_2$ score[b]	45% had score ≥ 3	3.7 ± 1.0	2.6 ± 1.2	3.1 ± 1.1
Primary Outcome Measure: Stroke and Systemic Embolism				
Study arm	110 mg: 2.3%/y; 150 mg: 1.5%/y	2.3%/100 pt-y	2.1%/y	2.3%/y
Control arm	2.7%/y	2.8%/100 pt-y	2.7%/y	2.7%/y
HR (95% CI)	110 mg: 0.85 (0.59-1.24); 150 mg: 0.56 (0.37-0.85)	0.84 (0.57-1.23)	0.79 (0.55-1.14)	0.87 (0.64-1.19)
Primary Safety Outcome: Major Bleeding				
Study arm	110 mg: 5.5%/y; 150 mg: 5.5%/y	4.5%/100 pt-y	3.2%/y	4%/y
Control arm	5.5%	4.7%/100 pt-y	6.4%/y	5.3%/y
HR (95% CI)	110 mg: 0.99 (0.77-1.28); 150 mg: 1.02 (0.79-1.30)	0.95 (0.72-1.26)	0.50 (0.38-0.66)	0.76 (0.58-0.98)

Abbreviations: ARTISTOTLE, Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation; CI, confidence interval; CKD, chronic kidney disease; eCL_{cr}, estimated creatinine clearance (calculated by Cockcroft-Gault formula); ENGAGE AF-TIMI 48, Effective Anticoagulation With Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis in Myocardial Infarction; HR, hazard ratio; NOAC, non–vitamin K–dependent oral anticoagulant; pt-y, patient-years; RE-LY, Randomized Evaluation of Long Term Anticoagulant Therapy; ROCKET AF, Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation.

[a]Dose adjustment for apixaban occurred if 2 of 3 factors were met: serum creatinine ≥1.5 mg/dL, age ≥80 years, or weight ≤ 60 kg.

[b]Mean ± standard deviation unless indicated otherwise.