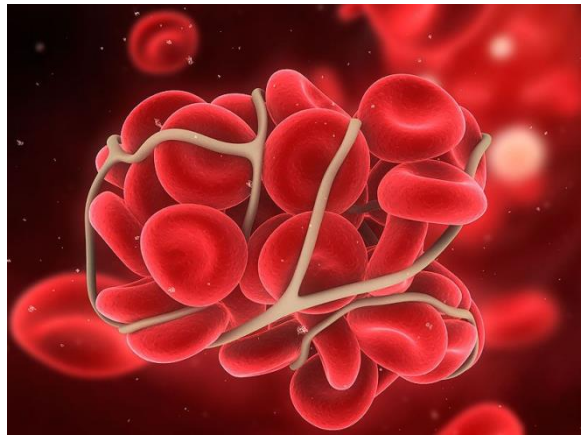

Practical Points on DOACs in Patients with CKD

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Tehran Heart Center

TEHRAN HEART CENTER

DOAC Pharmacologic Properties

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Mechanism of action	Direct IIa inhibitor	Direct Xa inhibitor	Direct Xa inhibitor	Direct Xa inhibitor
Bioavailability	3%–7%	66% without food, 80%–100% with food	50%	62%
Onset of anticoagulant activity	1.5 hr	2–4 hr	2–3 hr	1–2 hr
Half-life[a]	12–17 hr	9–13 hr	12 hr	9–10 hr
Renal clearance	80%	36%	27%	50%
Protein binding	35%	90%	87%	55%
Removed by dialysis	Yes	No	No	No
P-gp transport	Yes	Yes	Yes	Yes
Hepatic metabolism	None	CYP 3A4/5 and 2J2	CYP3A4/5	Minimal (4% CYP3A4/5)
Antidote for reversal	Yes	Yes	Yes	Yes?

[a]Half-life can be increased in patients with severe illness with renal and/or hepatic failure.

Patient assessment in each visit

	Interval	Comments
1. Adherence	Each visit	• Instruct patient to bring NOAC card and complete list of medication: make note and assess average adherence • Re-educate on importance of strict intake schedule • Inform about adherence aids (special boxes; smartphone applications; . . .). Consider specific adherence measuring interventions (review of pharmacy refill data; electronic monitoring[51]; special education session; . . .)
2. Thromboembolism	Each visit	• Systemic circulation (TIA, stroke, peripheral) • Pulmonary circulation
3. Bleeding	Each visit	• 'Nuisance' bleeding: preventive measures possible? Motivate patient to diligently continue anticoagulation • Bleeding with impact on quality-of-life or with risk: prevention possible? Need for revision of anticoagulation indication, dose or timing?
4. Other side effects	Each visit	Carefully assess relation with NOAC: decide for continuation (and motivate), temporary cessation, or change of anticoagulant drug
5. Co-medications	Each visit	• Prescription drugs; over-the-counter drugs (Pharmacokinetics and drug–drug interactions of non-vitamin K antagonist oral anticoagulants section). • Careful interval history: also temporary use can be risky
6. Blood sampling (incl. hemoglobin, renal and liver function)	Yearly	Patients other than those specified below
	6-monthly	≥75 years (especially if on dabigatran) or frail (see **chapter 2**)
	x-monthly	If renal function CrCl ≤60 mL/min: recheck interval = CrCl/10
	If needed	If intercurrent condition that may impact renal or hepatic function
7. Assessing and minimizing modifiable risk factors for bleeding	Each visit	• As recommended by current guidelines[3] • Particularly: uncontrolled hypertension (systolic >160 mmHg), medication predisposing for bleeding (e.g. aspirin, NSAIDs), labile INR (if on VKA), excessive alcohol intake)
8. Assess for optimal NOAC and correct dosing	Each visit	Especially based on the above, re-assess whether a. The chosen NOAC is the best for the patient b. The chosen dose is correct

EHRA 2018

Monitoring

	Dabigatran[229,230]	Apixaban[231], SmPc	Edoxaban[184,232]	Rivaroxaban[131,186]
Expected plasma levels of NOACs in patients treated for AF (based on dTT/ECA for dabigatran and anti-FXa activity for Xa inhibitors)				
Expected range of plasma levels *at peak* for standard dose (ng/mL)[a]	6		91–321	184–343
Expected range of plasma levels *at trough* for standard dose (ng/mL)[a]	3		31–230	12–137
Expected impact of NOACs on routine coagulat				
PT	↑		↑(↑)	↑↑ (↑)
aPTT	↑↑(↑)	(↑)	↑	↑
ACT	↑(↑)	↑	↑	↑
TT	↑↑↑↑	—	—	—

PT

INR

PTT

EHRA 2018

Contraindications

- Mechanical Valves
- Severe MS
- AKI
- Severe hepatic impairment (Cirrhotic, Child Pugh C)
- Pregnancy/ Lactation
- APS

Child-Turcotte-Pugh Classification of Severity of Liver Disease

	Score[a]		
	1 Point	2 Points	3 Points
Bilirubin (mg/dL)	<2	2–3	>3
Albumin (mg/dL)	>3.5	2.8–3.5	<2.8
INR	<1.7	1.7–2.3	>2.3
Ascites	None	Mild to moderate	Severe
Encephalopathy (grade)	None	Mild to moderate (1 and 2)	Severe (3 and 4)

[a]Class A, 5–6 points; class B, 7–9 points; class C, 10–15 points.
INR, international normalized ratio.

EHRA 2018
ESC 2019

APS

- EMA recommendation against the use of DOACs, especially in patients who have APS with triple positivity for aPL.
- EULAR: Rivaroxaban should not be used in patients with triple aPL positivity because of the high risk for recurrent events, whereas DOACs could be considered in patients not able to achieve a target INR despite good adherence to VKA or those with contraindications to VKA (eg, allergy or intolerance to VKA)
- EULAR: switching patients from VKA to DOAC treatment owing to poor adherence to VKA treatment or INR monitoring should be avoided.

NOACs are not recommended in patients with severe renal impairment,[d] during pregnancy and lactation, and in patients with antiphospholipid antibody syndrome.[260,261,312–314]	III	C

EHRA 2018

Drug-Drug Interactions

JACC REVIEW TOPIC OF THE WEEK

Select Drug-Drug Interactions With Direct Oral Anticoagulants

JACC Review Topic of the Week

EHRA 2018: RIF, Azoles, Antiretrovirals, St John`s Worth

Amiodarone	Apixaban	Combination is considered safe
	Betrixaban	Reduce dose of betrixaban to 80 mg once then 40 mg daily; avoid use if CrCl <30 ml/min
	Dabigatran	Combination considered safe if CrCl >50 ml/min Avoid combination if CrCl <50 ml/min for VTE and <30 ml/min for NVAF
	Edoxaban	Combination is considered safe
	Rivaroxaban	Avoid use if CrCl <80 ml/min
Calcium-Channel Blockers		
Verapamil	Apixaban	Combination is considered safe
	Betrixaban	Reduce dose of betrixaban to 80 mg once then 40 mg daily; avoid use if CrCl <30 ml/min
	Dabigatran	Avoid use if CrCl <30 ml/min for NVAF and <50 ml/min for VTE
	Edoxaban	Combination is considered safe
	Rivaroxaban	Avoid combination when CrCl is <80 ml/min
Diltiazem	Apixaban	Combination is considered safe
	Betrixaban	Reduce dose of betrixaban to 80 mg once, then 40 mg daily; avoid use if CrCl <30 ml/min
	Dabigatran	Combination is considered safe
	Edoxaban	Combination is considered safe
	Rivaroxaban	Avoid use if CrCl <80 ml/min
Enzyme Inducers		
Phenytoin, carbamazepine, primidone, rifampin, phenobarbital, St. John's wart	Apixaban Betrixaban Edoxaban Dabigatran Rivaroxaban	Avoid combination; consider warfarin

EHRA Guideline 2018

	Via[142,145,146]	Dabigatran etexilate	Apixaban[130]	Edoxaban	Rivaroxaban
Drug					
Carbamazepine	Strong CYP3A4/P-gp induction; CYP3A4 competition	SmPC	−50%[SmPC]	−35%[SmPC]	SmPC, Ref.[147]
Ethosuximide	CYP3A4 competition; No relevant interaction known/assumed				
Gabapentin	No relevant interaction known/assumed				
Lamotrigine	P-gp competition; No relevant interaction known/assumed				
Levetiracetam	P-gp induction; P-gp competition				
Oxcarbazepine	CYP3A4 induction; P-gp competition				
Phenobarbital	Strong CYP3A4/P-gp induction; P-gp competition		SmPC	SmPC	SmPC
Phenytoin	Strong CYP3A4/P-gp induction; P-gp competition	SmPC, Ref.[148]	SmPC	SmPC	SmPC
Pregabalin	No relevant interaction known/assumed				
Topiramate	CYP3A4 induction; CYP3A4 competition				
Valproic acid	CYP3A4/P-gp induction				Ref.[149]
Zonisamide	CYP3A4 competition; No relevant interaction known/assumed				

DOACs in Renal Transplant

- Interactions with dabigatran occur primarily at the absorption level where P-gp efflux in the intestines predominates.
- Direct FXa inhibitors have interactions occurring at the absorption and elimination phase. This may further enhance exposure and increase the probability of a bleeding event during which metabolism or excretion is inhibited (e.g. CsA).
- Presence of renal dysfunction, CNI, additional P-gp or CYP3A4 inhibitors (e.g. antifungals or antibiotics) or other covariates (e.g. extremes in body weight) may contribute to a higher likelihood of bleeding.

DOACs in Renal Transplant

(1) dosage adjustments should be made to reflect renal function and CNI coadministration, (ClCr<80 ml/min)

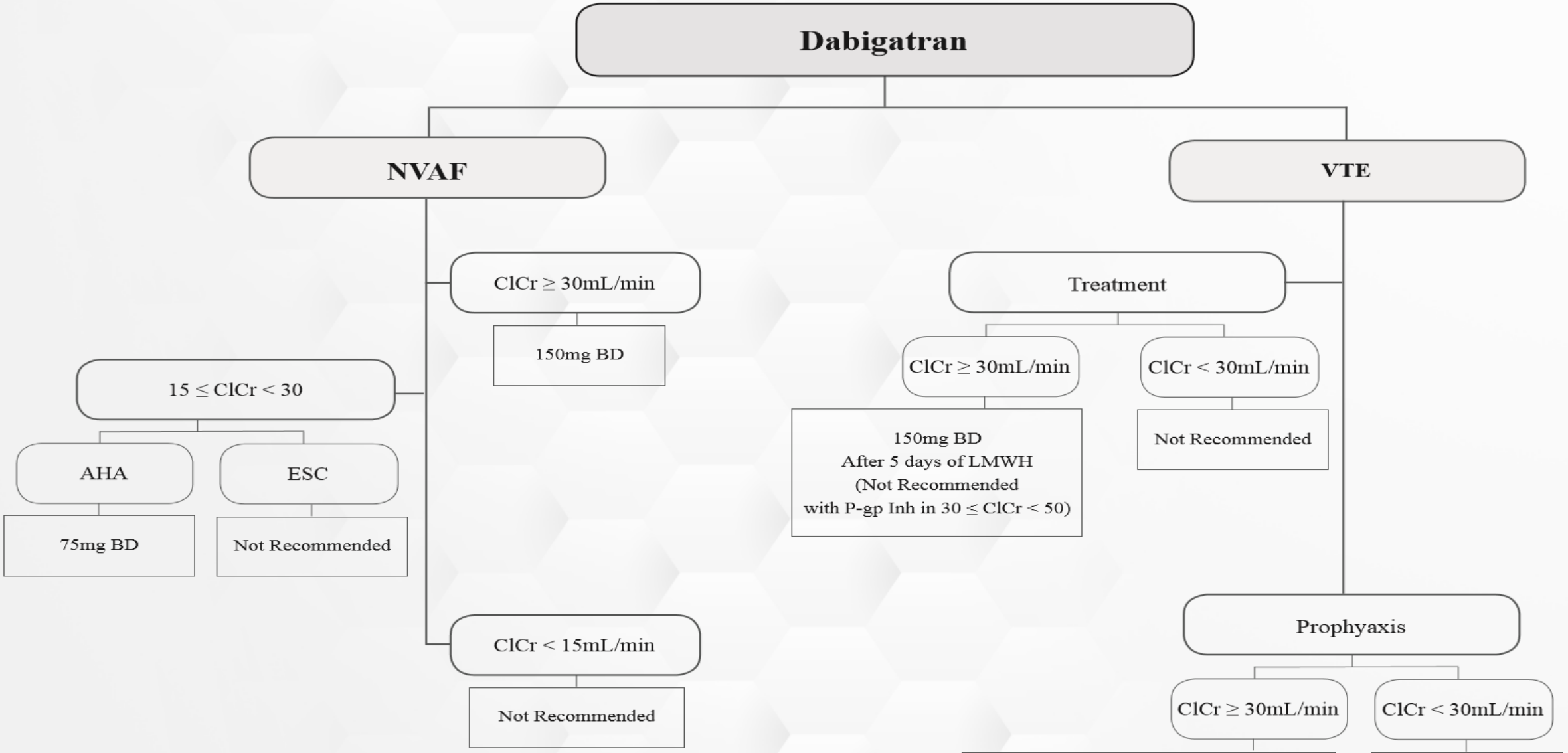
(2) although the use of anti-FXa activity as a correlate to plasma drug levels is appropriate, calibration specificity of antiFxa activity for the Fxa inhibitor is critical to make an accurate determination and

(3) lastly, the choice of tacrolimus for immunosuppression may be favorable compared to CsA.

- In the case of those requiring CsA, which is a P-gp, BCRP, OATP and moderate CYP3A4 inhibitor, dabigatran may be appropriate based on its predominate P-gp transport in the GI tract.

Take Home Message

- DOACs should be avoided in the immediate post-operative period and considered only after there is stability of renal and hepatic function and when bleeding risk has stabilized.
- The Cockcroft-Gault formula using ideal body weight is used for dosing adjustments for apixaban and edoxaban while actual body weight is used to adjust dabigatran and rivaroxaban.



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Rivaroxaban

NVAF

- ClCr ≥ 50mL/min
  - 20mg Daily
- ClCr < 15mL/min
  - Not Recommended
- 15 ≤ ClCr < 50
  - 15mg Daily

(10 mg Daily can be used with DAPT [PIONEER - AF])

VTE

Treatment

- ClCr ≥ 30mL/min
  - -15mg BD for 21 days then 20mg Daily.
  - -After 6mo 10mg Daily.
- ClCr < 30mL/min
  - Not Recommended

Prophylaxis

- ClCr ≥ 30mL/min
  - 10mg Daily
- ClCr < 30mL/min
  - Not Recommended

Vascular Dose

ACS

- ClCr ≥ 30mL/min
  - 2.5mg BD
- ClCr < 30mL/min
  - Not Recommended

CCS

- ClCr ≥ 15mL/min
  - 2.5mg BD
- ClCr < 15 mL/min
  - Not Recommended

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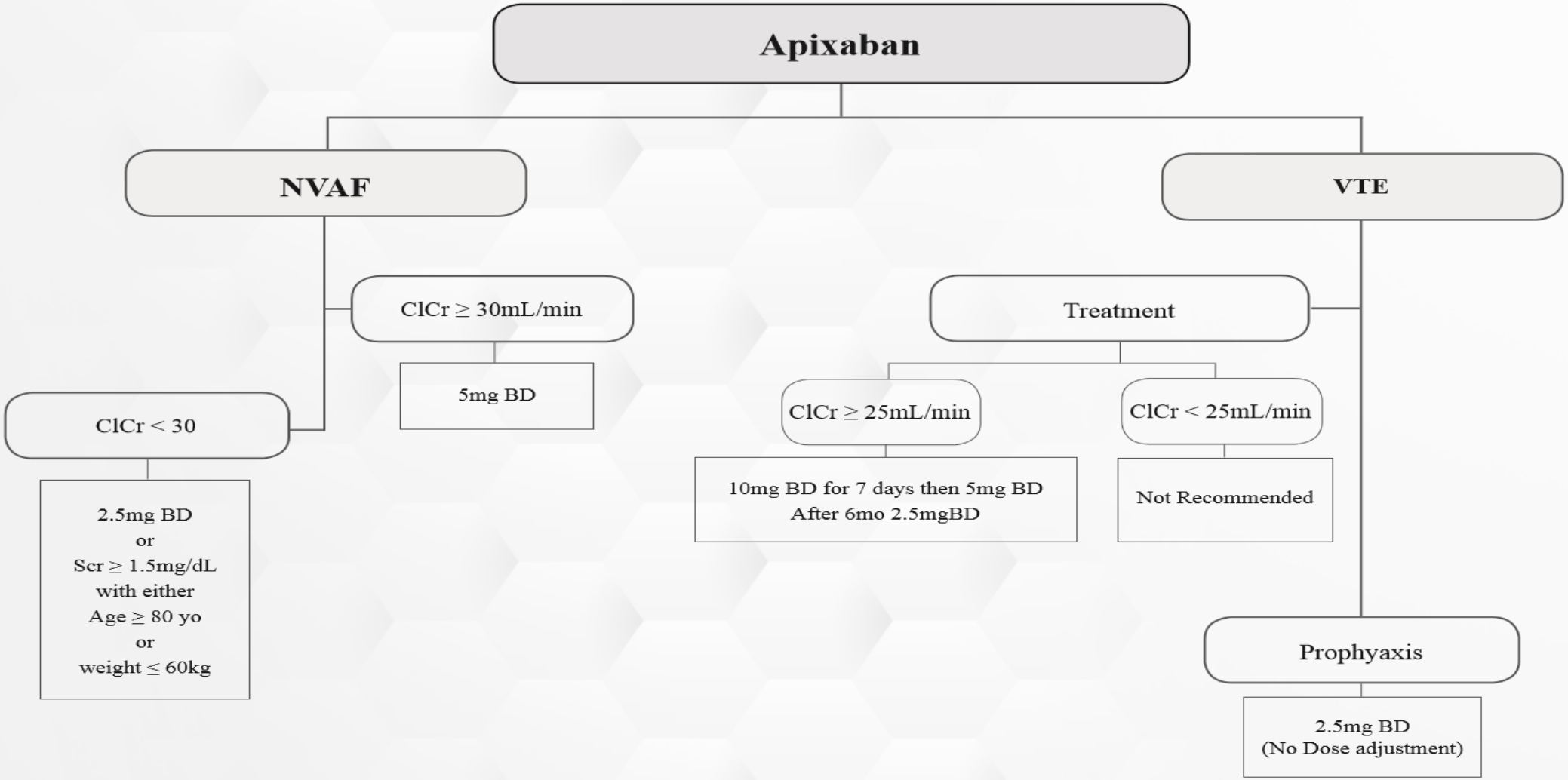

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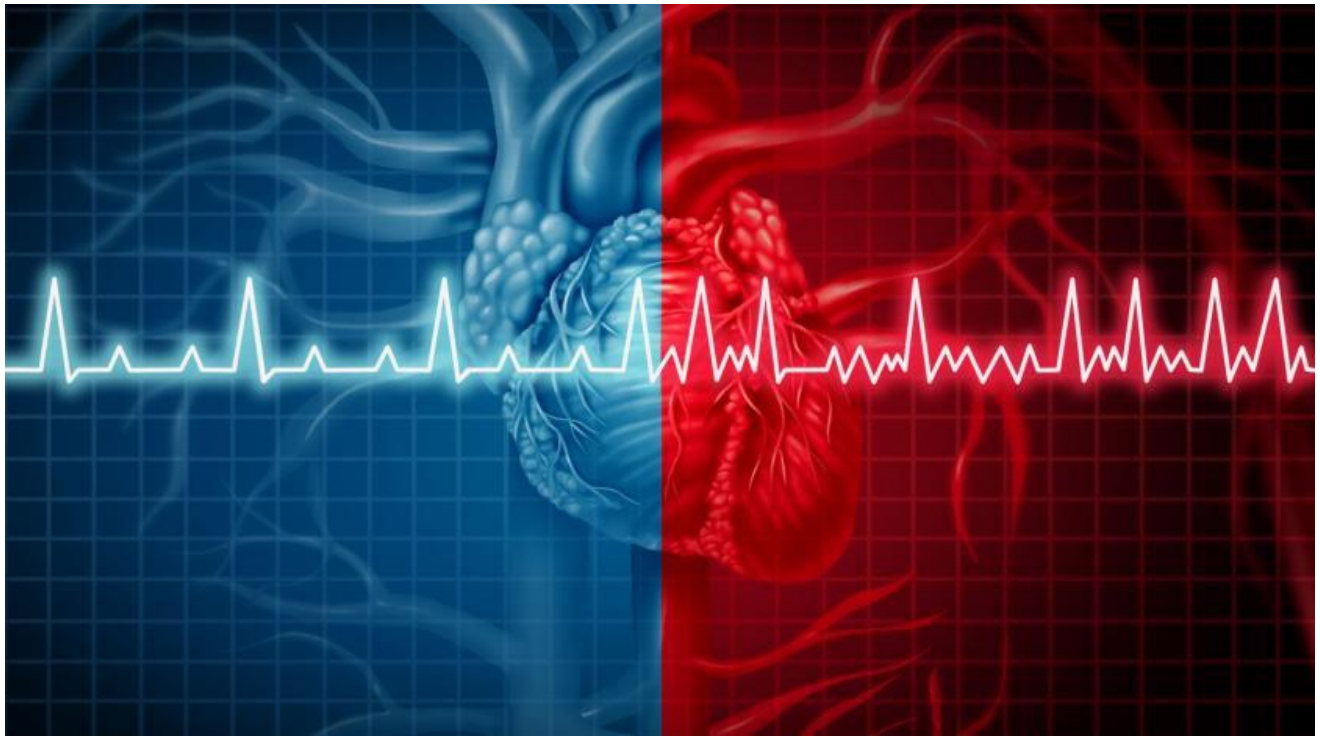


Atrial Fibrillation

Apixaban Role

Thrombotic Risk Assessment
$CHADS_2$ Score and CHA_2DS_2-VASc Score

$CHADS_2$ Score

Risk Factors	Score
C = CHF	1
H = Hypertension	1
A = Age ≥ 75 years	1
D= Diabetes mellitus	1
S_2 = Stroke/TIA/TE	2

CHA_2DS_2-VASc Score

Risk Factors	Score
C = CHF/LVD	1
H = Hypertension	1
A_2 = Age ≥ 75 years	2
D = Diabetes mellitus	1
S_2 = Stoke/TIA/TE	2
V = Vascular disease)MI, PAD, aortic plaque(	1
A = Age 65-74 years	1
Sc = Sex category (female(	1

Gage BF, et al. *JAMA* 2001;.285:2₈ 64-2870
Lip GY, et al. *Chest* 2010;.137:263-272

Assessment of Bleeding Risk

HAS-BLED Score

- H = Hypertension (Systolic blood pressure > 160 mm Hg (1
- A = Abnormal renal and liver function (1 point each(1 or 2
  - Renal = chronic dialysis, renal transplant, or SCr ≥ 200 μmol/L (2.26 mg/dL(
  - Liver = chronic hepatic disease, bilirubin > 2X ULN, in association with AST/ALT/Alk Phos > 3X ULN
- S = Stroke 1
- B = Bleeding (history of bleeding or predisposition to bleeding such as a bleeding diathesis or anemia(1
- L = Labile INRs (Unstable/high INRs or time in therapeuticrang > (%60 1
- E = Elderly (> 65 years old(1
- D = Drugs or alcohol excess (1 point each(1or 2
  - Drugs = antiplatelet or nonsteroidal anti-inflammatory drugs

Pisters R, et al. *Chest* 2010;.138:1093-1100

Guideline Recommendations

Antithrombotic Therapy in Patients with NVAF Based on CHA_2DS_2-VASc Score

CHA_2DS_2-VASc	CHA_2DS_2-VASc	CHA_2DS_2-VASc
0 in M/1 in F	1 in M/2 in F	≥1 in M/≥2 in F
Reasonable to omit antithrombotic therapy or consider aspirin	Consider no antithrombotic therapy, oral anticoagulation, or aspirin	Oral anticoagulant therapy is indicated

Guidelines recommend DOAC over warfarin

ACCP 2018: OAC for **≥1 in M/≥2 in F**

January CT, et al. *J Am Coll Cardiol* 2019.

AF

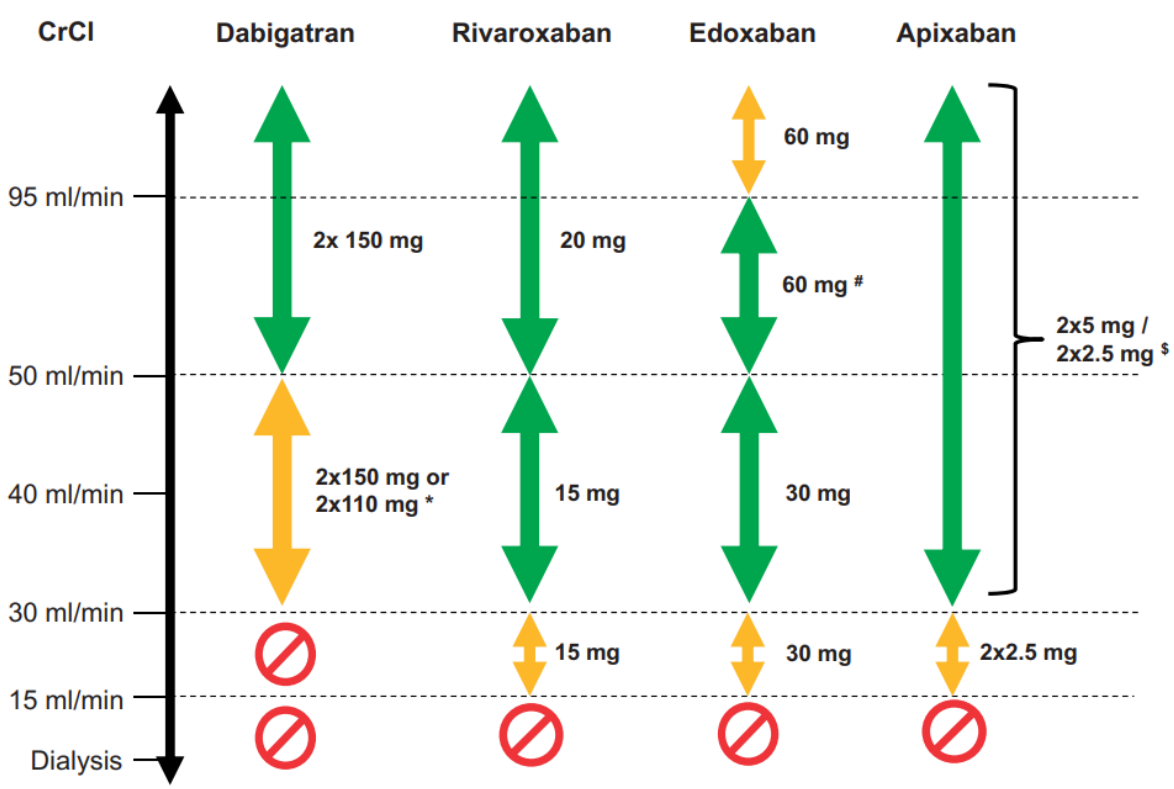
The apixaban label suggests 5 mg BD in ESRD If younger than 80 and weigh > 60 kg.

A recent study showed a 2-fold increase in Cmax and AUC using 5 mg BD daily and suggests that the 2.5-mg BD can be considered.

Agent	Standard Dosing	Dose Adjustment[a]	Avoid Use[a]
Dabigatran	150 mg twice daily	75 mg twice daily • CrCl 15–30 mL/min/1.73 m^2 • CrCl 30–50 mL/min/1.73 m^2 with ketoconazole or dronedarone	• CrCl < 15 mL/min /1.73 m^2 • Dialysis • CrCl 15–30 mL/min/1.73 m^2 with amiodarone, verapamil, ketoconazole, dronedarone, diltiazem, and clarithromycin • Rifampin
Rivaroxaban	20 mg once daily with meals	15 mg once daily with meals • CrCl 15–50 mL/min/1.73 m^2 • Dialysis[b]	• Strong CYP3A4 and P-gp inducers (e.g., rifampin, phenytoin, carbamazepine, St. John's wort) • Strong CYP3A4 and P-gp inhibitors (e.g., protease inhibitors, itraconazole, ketoconazole, conivaptan)
Apixaban	5 mg twice daily	2.5 mg twice daily • Two of three criteria (age ≥ 80 yr, weight ≤ 60 kg, or SCr ≥ 1.5 mg/dL) • Use with strong CYP3A4 and P-gp inhibitors (e.g., protease inhibitors, itraconazole, ketoconazole, conivaptan) • Dialysis?[b,c]	• Strong CYP3A4 and P-gp inducers (e.g., rifampin, phenytoin, carbamazepine, St. John's wort) • If on 2.5 mg twice daily – Strong CYP3A4 and P-gp inhibitors (e.g., protease inhibitors, itraconazole, ketoconazole, conivaptan)
Edoxaban	60 mg once daily	30 mg once daily • CrCl 15–50 mL/min/1.73 m^2	• CrCl > 95 mL/min/1.73 m^2 • CrCl < 15 mL/min/1.73 m^2 • Dialysis • Rifampin

ASHP/ACCP Anticoagulation 2020

Dosing in CKD



In AF patients with a CHA_2DS_2-VASc score ≥2 in M or ≥3 in F and a ClCr <15 ml/min or on dialysis, it is reasonable to use warfarin or apixaban as OAC (COR IIb, LOE B-NR).

EHRA 2018
AHA 2019

Reduced dose

- Reduced dose of 2.5 mg BD was used in about 5% of the patients in the ARISTOTLE trial.
- Reduced dose is being used in many patients (up to 30%),with most not meeting the trial criteria for the reduced dose.
- *One study suggests this is associated with a 20% increased risk of ischemic stroke and with no difference in major bleeding.*

JACC 2017;69:2779-90

Atrial Fibrillation

Stroke Prevention Summary

- Primary Efficacy – Stroke or Systemic Embolism
  - All agents non-inferior to warfarin
  - Dabigatran and apixaban demonstrated superiority
  - Rivaroxaban and edoxaban only demonstrated superiority in per - protocol analysis – primary efficacy outcome
- Hemorrhagic Stroke
  - All agents significantly better than warfarin
- Ischemic Stroke
  - Only dabigatran significantly better than warfarin
- Major Bleeding
  - Only apixaban and edoxaban significantly safer than warfarin
  - No difference with dabigatran and rivaroxaban
- All Cause Mortality
  - Only apixaban significantly lower than warfarin (p=(0.01
  - All agents provide an approximate 10% reduction in all cause mortality

NVAF and PCI with Stenting

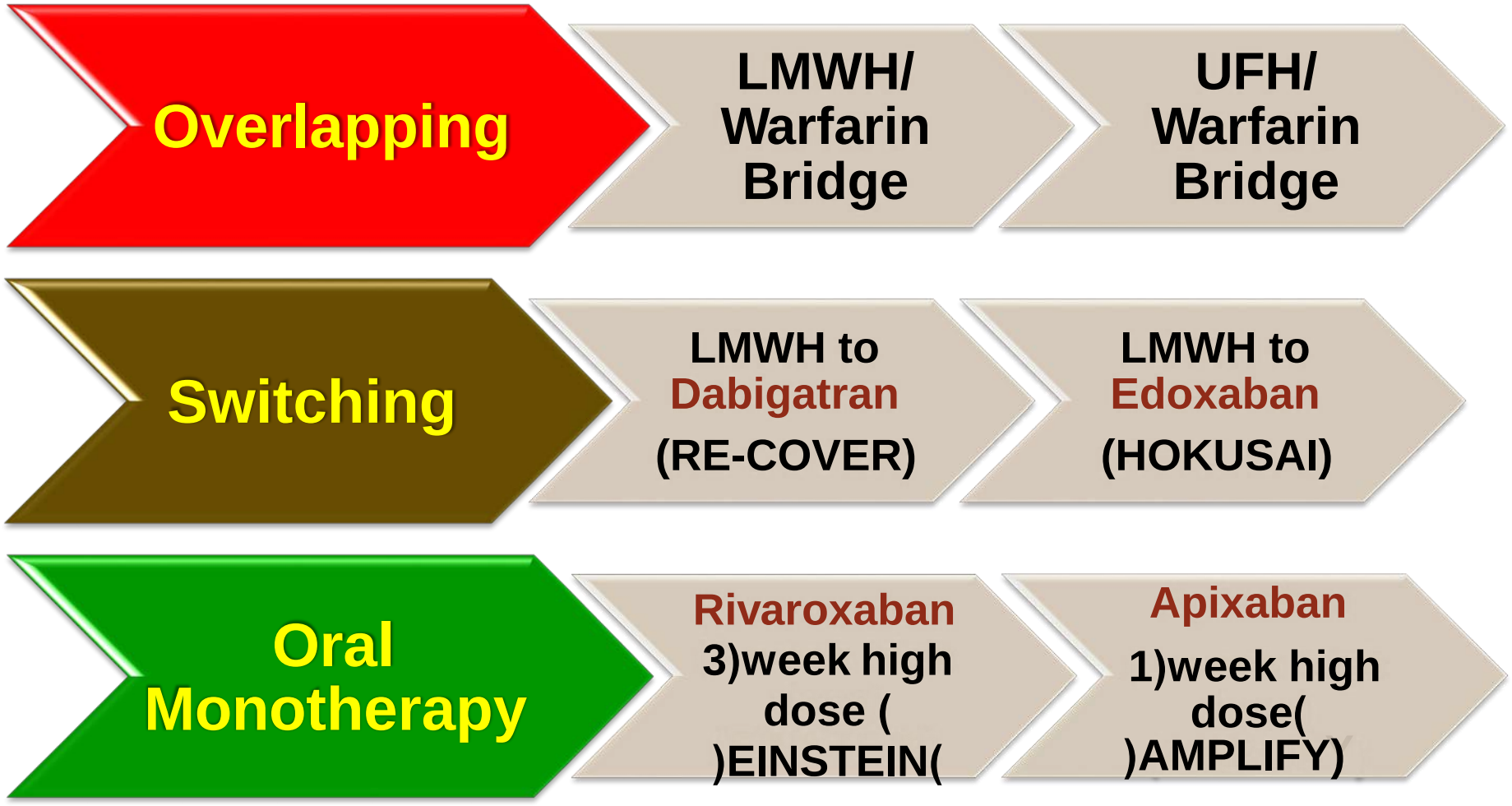
- **PIONEER-AF PCI trial (n=2124)**
  - Rivaroxaban 15 mg Daily with clopidogrel
  - Less bleeding compared to warfarin triple therapy
  - Less hospitalization for bleeding and ischemic events
- **RE-DUAL PCI trial (n=2725)**
  - Dabigatran 150 mg BD with clopidogrel
  - Less bleeding compared to warfarin triple therapy
  - Also dabigatran 110 mg with clopidogrel arm
- **AUGUSTUS trial (n=4614)**
  - Apixaban 5 mg BD with clopidogrel
  - Less bleeding compared to warfarin triple therapy
  - Also less hospitalization
- **ENTRUST-AF PCI trial (n=1506)**
  - Edoxaban 60 mg daily with clopidogrel
  - Non-inferior bleeding compared to warfarin triple therapy

Gibson CM, et al. NEJM 2016
Cannon CP, et al. NEJM 2017
Lopes RD, et al. NEJM 2019
Vranckx P, et al. Lancet 2019

Triple therapy

a. Use of a DOAC over warfarin makes sense, given the lower bleeding with DOACs.
b. Current evidence using rivaroxaban 15 mg daily with clopidogrel, apixaban 5 mg BD with clopidogrel, or dabigatran 150 mg BD with clopidogrel (except in older adult patients) is the best evidence to date for reducing bleeding risk in these patients.
c. Results of the ENTRUST-AF PCI trial do not suggest a significant safety benefit over traditional triple therapy.
d. No trials large enough to evaluate ischemic or thrombotic outcomes are planned and would likely take longer to complete than the patent life of the current DOACs.

Approaches to the Treatment of VTE



Goldhaber SZ, et al. *Lancet* 2012;.379:835-1846
Kearon C et al. *Chest* 2016;.149:315-352

Treatment Strategy	Anticoagulant Choices
Bridging therapy	Injectable anticoagulant (UFH, LMWH, or fondaparinux) initiated with warfarin and overlapped for at least 5 days and until a therapeutic INR is achieved. Then discontinue injectable anticoagulant and continue warfarin for the appropriate duration
Switching therapy	Injectable anticoagulant (UFH, LMWH, or fondaparinux) for at least 5 days; then stop injectable anticoagulant therapy and initiate dabigatran or edoxaban for the appropriate duration
Monotherapy	Initiate rivaroxaban or apixaban at higher initial dose and then convert patient to lower dose for the appropriate duration

The 2016 ACCP guidelines prefer DOACs to warfarin for patients with VTE without cancer because of less bleeding and greater convenience.

Patients with CKD: For all DOACs if CrCl<30 mL/minute
For Apixaban if CrCl< 25 mL/minute

ACCP 2016
EHRA 2018
ESC 2019
ASHP/ACCP Anticoagulation 2020

NCCN Guidelines

Apixaban, dabigatran, edoxaban, and rivaroxaban	Contraindications: • Stage IV/V chronic ki ▸ Apixaban[f]: CrCl <2 ▸ Dabigatran, edoxab • Active/clinically sign ▸ Apixaban or edoxal ▸ Dabigatran or rivar • Strong dual inhibitor apixaban[17] • Inducers/inhibitors o Relative contraindicat • DOACs have been as should be used with • Use with caution in p • For patients receivin testing. • Consider drug-drug

DOACs (preferred for patients without gastric or gastroesophageal lesions)[a]

- Apixaban (category 1)
  - 10 mg PO BID for 7 days followed by 5 mg PO BID[12-15]
- Edoxaban (category 1)
  - Initial therapy with LMWH[b,3,4] or UFH[c,5] for at least 5 days followed by edoxaban 60 mg PO daily (or 30 mg PO daily in patients with Cockcroft-Gault estimated CrCl 30–50 mL/min or weight <60 kg or concomitant potent p-glycoprotein inhibitors)[d,6,7]
- Rivaroxaban
  - 15 mg PO BID for the first 21 days followed by 20 mg daily[8-11]

LMWH (preferred for patients with gastric or gastroesophageal lesions)

- Dalteparin (category 1)
  - 200 units/kg SC daily for 30 days, then switch to 150 units/kg once daily[e,4,16,17]
- Enoxaparin
  - 1 mg/kg SC every 12 hours (can consider decreasing intensity to 1.5 mg/kg daily after first month)[f,3,18-20]

DOACs (if above regimens not appropriate or unavailable)[a]

- Dabigatran
  - Initial therapy with LMWH[b,3,4] or UFH[c,5] for at least 5 days
    dabigatran 150 mg PO BID[d,21,22]

r rivaroxaban[9] and

act bleeding, and
y, or instrumentation.

closely with laboratory

ESC Guideline

ESC European Society of Cardiology

Recommendations	Class[a]	Level[b]
For patients with PE and cancer, weight-adjusted subcutaneous LMWH should be considered for the first 6 months over VKAs.[360–363]	IIa	A
Edoxaban should be considered as an alternative to weight-adjusted subcutaneous LMWH in patients without gastrointestinal cancer.[366]	IIa	B
Rivaroxaban should be considered as an alternative to weight-adjusted subcutaneous LMWH in patients without gastrointestinal cancer.[367]	IIa	C
For patients with PE and cancer, extended anticoagulation (beyond the first 6 months)[c] should be considered for an indefinite period or until the cancer is cured.[378]	IIa	B

Cancer

- DDI: Doxorubicine, Vinblastin, Imatinib, Crizotinib, Vandetinib, Sunitinib, Abiraterone, Enzalutamide

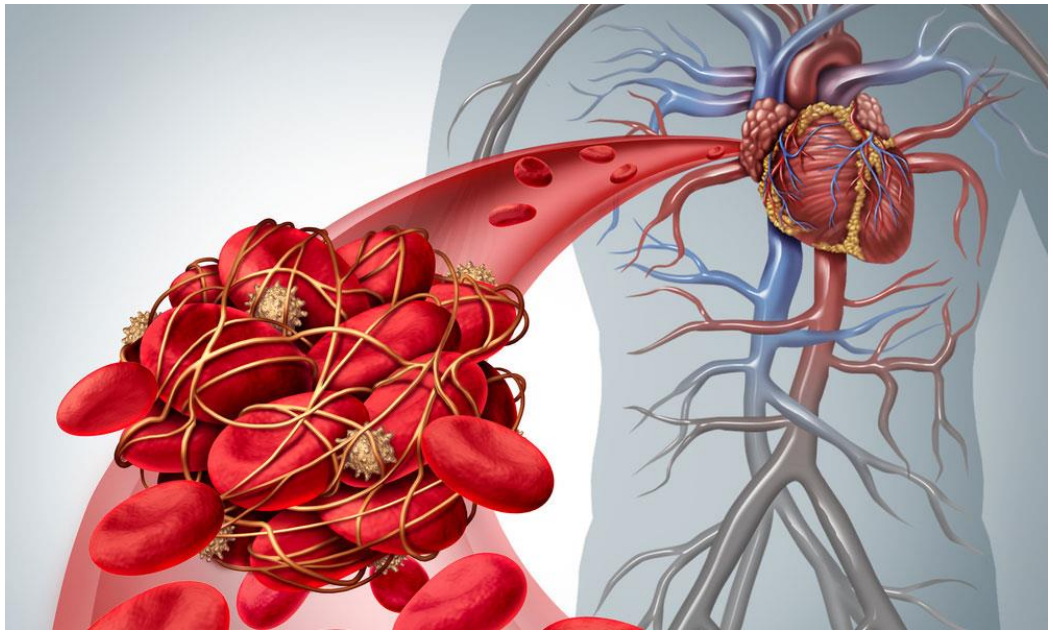
Dosing of DOAC in VTE Treatment

Agent	Standard Dosing	Dose Adjustment[a]	Avoid Use[a]
Dabigatran	150 mg twice daily after 5–10 days of injectable anticoagulation	75 mg twice daily in patients with a CrCl of 30–50 mL/min/1.73 m^2 with ketoconazole or dronedarone	• CrCl ≤ 30 mL/min/1.73 m^2
Rivaroxaban	15 mg twice daily with food for 21 days, followed by 20 mg daily with food. After	None	• CrCl < 15 mL/min/1.73 m^2 • Strong CYP3A4 and P-gp inducers
Apixaban	10 mg twice daily for 7 days, followed by 5 mg twice daily. After 6 months, dose can be reduced to 2.5 mg twice daily	50% dose reduction if receiving 5 or 10 mg twice daily with strong CYP3A4 and P-gp inhibitors (e.g., protease inhibitors, itraconazole, ketoconazole, conivaptan)	• CrCl < 15 mL/min/1.73 m^2 • Strong CYP3A4 and P-gp inducers (e.g., rifampin, phenytoin, carbamazepine, St. John's wort) • If on 2.5 mg twice daily – Strong CYP3A4 and P-gp inhibitors (e.g., protease inhibitors, itraconazole, ketoconazole, conivaptan)
	5–10 days of injectable anticoagulation	• CrCl 15–50 mL/min/ 1.73 m^2 • Potent P-gp inhibitor (verapamil, dronedarone, or quinidine) • Weight ≤ 60 kg	• Rifampin

ASHP/ACCP Anticoagulation 2020

Extended treatment

- AMPLIFY Ext: Apixaban 5 mg and 2.5 mg BD were superior to placebo for efficacy, with similar safety in patients who had already completed 6 months of therapy



VTE Prophylaxis and Treatment

Apixaban Role

VTE Prophylaxis

- Orthopedic surgery;
  - Dabigatran (Hip, inferior to Enoxaparion 30 mg BD in Knee),
  - Rivaroxaban (Hip and Knee)
  - Apixaban (Hip and Knee; superior to Enoxa 40 mg daily, non inferior to enoxa 30 mg BD). No difference in major bleeding.

VTE Prophylaxis in Orthopedic Surgery

Orthopedic Indication	Enoxaparin	Dalteparin	Fondaparinux	Warfarin	Dabigatran	Rivaroxaba	Apixaban
Knee replacement surgery	30 mg SC q12hr initiated 12–24 hr after surgery	2500 IU SC given 6–8 hr after surgery; then 5000 IU SC q24hr[a]	2.5 mg SC q24hr initiated 6–8 hr after surgery	Initiated preoperatively or the evening of the surgical day with adjusted dosing to achieve a target INR of 2.5 ± 0.5	Insufficient evidence	10 mg once daily initiated 6–10 hr aft surgery	2.5 mg twice daily, initiated 12–24 hr after surgery
Hip replacement surgery	30 mg SC q12hr initiated 12–24 hr after surgery OR 40 mg SC q24hr initiated 10–12 hr before surgery	2500 IU SC given 6–8 hr after surgery; then 5000 IU SC q24hr OR 5000 IU SC q24hr initiated the evening before surgery	2.5 mg SC q24hr initiated 6–8 hr after surgery	Initiated preoperatively or the evening of the surgical day with adjusted dosing to achieve a target INR of 2.5 ± 0.5	110 mg initiated 1–4 hr after surgery; then 220 mg once daily	10 mg once daily initiated 6–10 hr aft surgery	2.5 mg twice daily, initiated 12–24 hr after surgery
Hip fracture surgery	30 mg SC q12hr initiated 12–24 hr after surgery[a]	Insufficient evidence	2.5 mg SC q24hr initiated 6–8 hr after surgery	Initiated preoperatively or the evening of the surgical day with adjusted dosing to achieve a target INR of 2.5 ± 0.5	Insufficient evidence	Insufficien evidence	Insufficient evidence
Spine surgery	Pharmacologic prophylaxis is generally not recommended unless patients have additional risk factors of advanced age, malignancy, neurologic deficit, previous VTE, or an anterior surgical approach. Because of the lack of clinical trials, pharmacologic prophylaxis recommendations are general and include SC UFH or an LMWH						

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VTE Prophylaxis in Medically ill Patients

- Apixaban (2.5 mg BD) and rivaroxaban (10 mg once daily) compared with 6–10 days of enoxaparin 40 mg once daily for a month.
- Both trials had significant increases in major bleeding with nominal benefit.

UFH	Enoxaparin	Dalteparin	Fondaparinux	Rivaroxaban	Betrixaban
5000 units SC q8hr or 5000 units SC q12hr	40 mg SC q24hr	5000 IU SC q24hr	2.5 mg SC q24hr[a]	10 mg orally q24hr	160-mg loading dose, followed by 80 mg orally q24hr

Medically ill patients; Betrixaban and rivaroxaban

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Preoperative management of DOAC

Drug	Preprocedural Holding Time
Dabigatran	
CrCl > 50 mL/min/1.73 m^2	1–2 days[a]
CrCl 15–50 mL/min/1.73 m^2	3–5 days[a]
Apixaban, rivaroxaban, and edoxaban	
Minor procedures	1 day
Minor procedures with CrCl < 30 mL/min/1.73 m^2	2 days
Major vascular procedures	2 days

[a]Consider longer times for patients undergoing major surgery, spinal puncture, or placement of spinal or epidural catheter or port.

No Bridge Therapy

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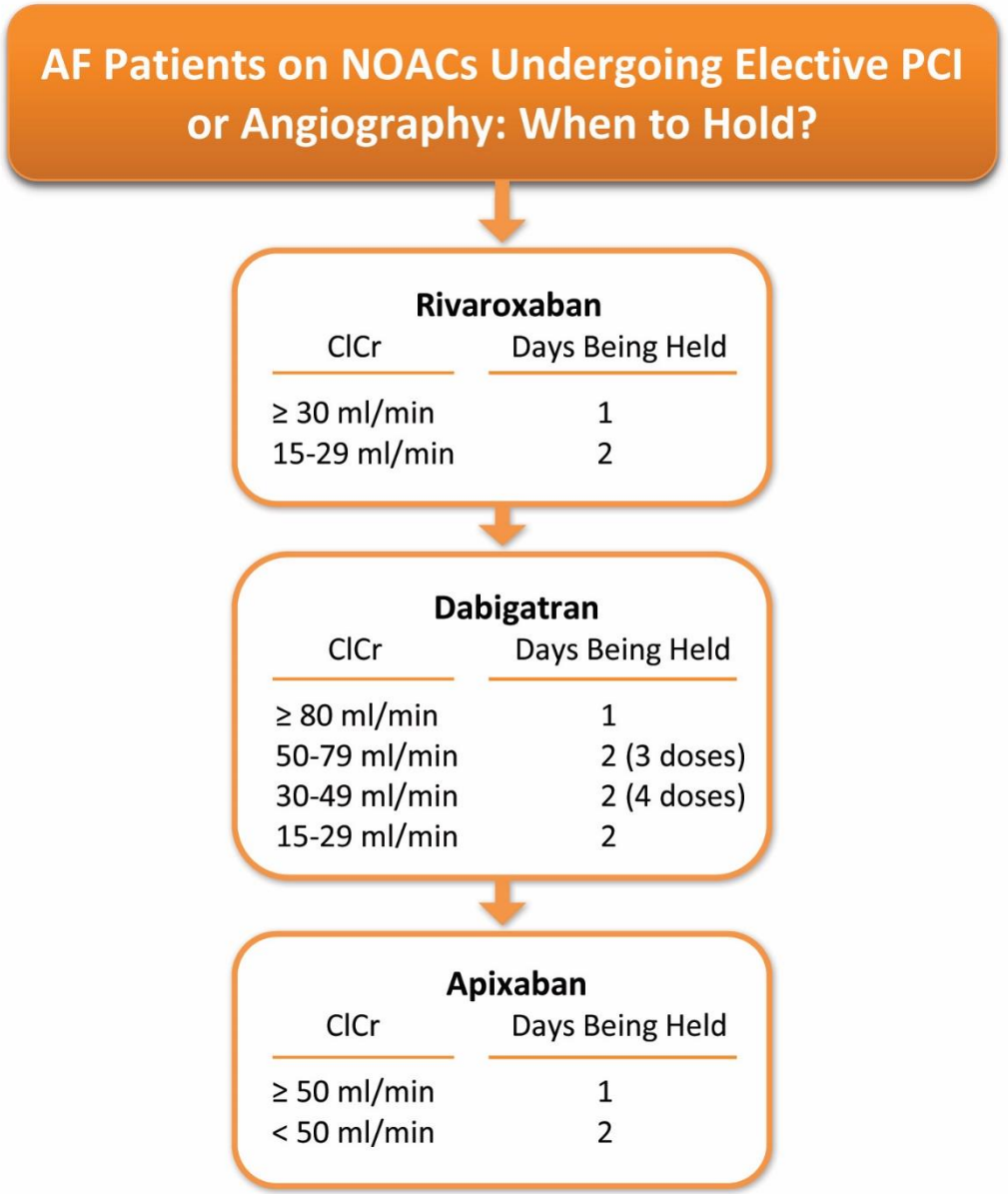
Apixaban before CAG or PCI



Administration

- **With or without food**
- If patient unable to swallow whole tablets, may crush 5 mg or 2.5 mg tablets and suspend in 60 mL of water, D5W, or apple juice or mix with applesauce; administer immediately

Missed Dose

- A forgotten dose can be taken up until **6 hours** after the scheduled dose
- For patients with **high stroke risk** and **low bleeding risk** this can **extend to the next dose**

Double Dose

- The next planned dose may be left out
- Dosing **restart after 24 hours**

Uncertainty about dose intake

- Do not take another tablet
- Start the next dose at the 12h interval

Apixaban conversion to and from other anticoagulants

Converting from Apixaban to Warfarin
Discontinue apixaban, and begin both a parenteral anticoagulant and warfarin at the time the next dose of apixaban would have been taken. Discontinue the parenteral anticoagulant when the INR reaches an acceptable range
Converting from Apixaban to Anticoagulants (with rapid onset) Other than Warfarin
Discontinue apixaban, and begin the new anticoagulant (oral or parenteral; other than warfarin) at the usual time of the next dose of apixaban
Converting from Warfarin to Apixaban
Warfarin should be discontinued and apixaban initiated when INR < 2.0
Converting from Anticoagulants (with rapid onset) Other than Warfarin to Apixaban
Begin apixaban 0–2 hr before the next scheduled administration of the drug (e.g., LMWH or non-warfarin oral anticoagulant), and do not administer the other anticoagulant. For UFH administered by continuous infusion, stop the infusion and start apixaban at the same time