
بسم الله الرحمن الرحیم

Acute treatment and secondary prevention of cardioembolic stroke

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Sources of cardioembolic stroke:

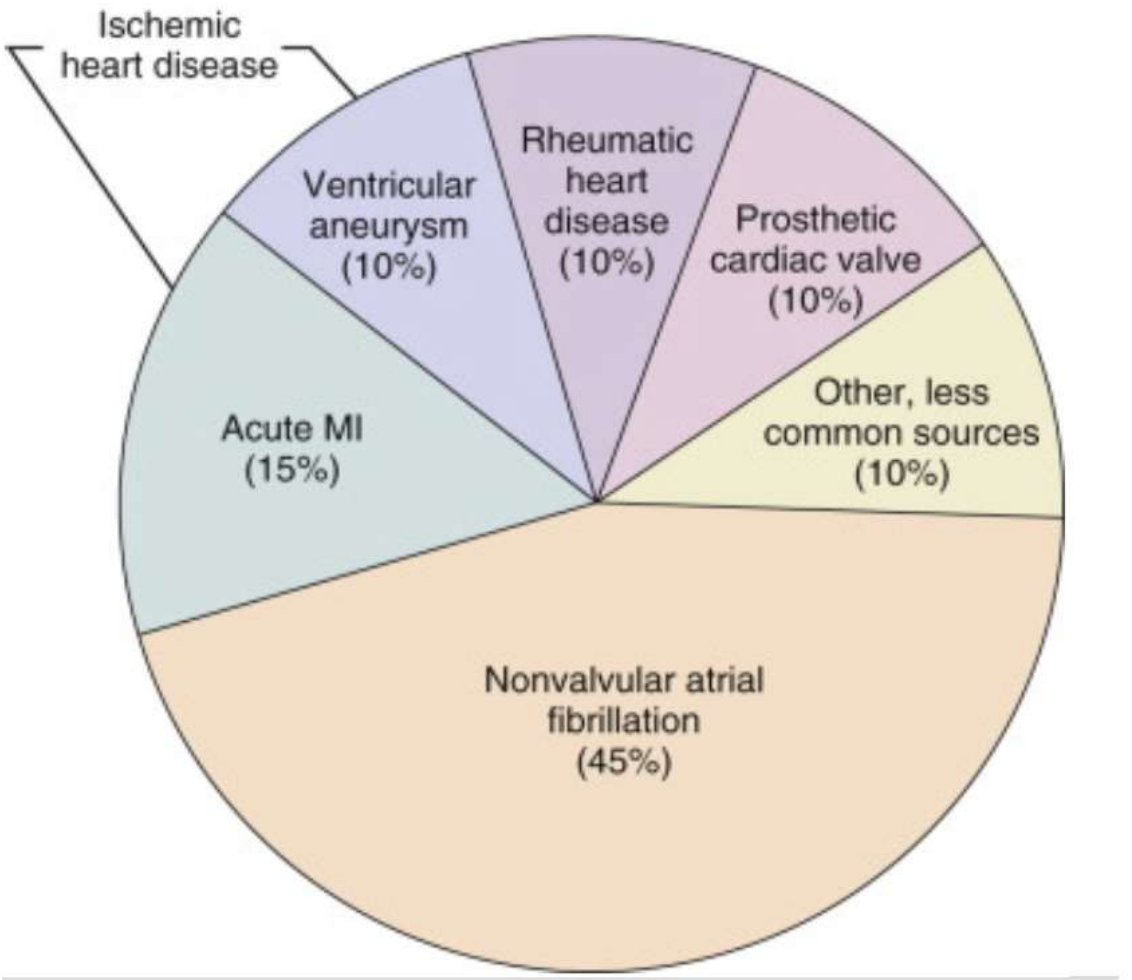

Table 7. Treatment of AIS: IV Administration of Alteplase

Infuse 0.9 mg/kg (maximum dose 90 mg) over 60 min, with 10% of the dose given as a bolus over 1 min.
Admit the patient to an intensive care or stroke unit for monitoring.
If the patient develops severe headache, acute hypertension, nausea, or vomiting or has a worsening neurological examination, discontinue the infusion (if IV alteplase is being administered) and obtain emergency head CT scan.
Measure BP and perform neurological assessments every 15 min during and after IV alteplase infusion for 2 h, then every 30 min for 6 h, then hourly until 24 h after IV alteplase treatment.
Increase the frequency of BP measurements if SBP is >180 mm Hg or if DBP is >105 mm Hg; administer antihypertensive medications to maintain BP at or below these levels (Table 5).
Delay placement of nasogastric tubes, indwelling bladder catheters, or intra-arterial pressure catheters if the patient can be safely managed without them.
Obtain a follow-up CT or MRI scan at 24 h after IV alteplase before starting anticoagulants or antiplatelet agents.

Some of the indications currently proposed by many experts for early full-dose IV heparin after stroke or transient ischemic attack (TIA) include the following:

•Conditions with potential high risk of early cardiogenic reembolization, such as atrial fibrillation with proven intracardial thrombus on echocardiography, artificial valves, left atrial or ventricular thrombi, or MI during the last 4 weeks

•Symptomatic dissection of the arteries supplying the brain (after exclusion of subarachnoid hemorrhage on CT scan)

•Symptomatic extracranial or intracranial arteriosclerotic stenosis with crescendo TIAs or early progressive stroke

•Basilar artery occlusion before or after intra-arterial pharmacological or mechanical thrombolysis.

•Known hypercoagulable states (eg, protein C and S deficiencies, activated protein C [APC] resistance, antithrombin deficiency, relevant titer of antiphospholipid antibodies)

•Cerebral venous sinus thrombosis

3.9. Antiplatelet Treatment (Continued)	COR	LOE	New, Revised, or Unchanged
2. In patients presenting with minor noncardioembolic ischemic stroke (NIHSS score ≤3) who did not receive IV alteplase, treatment with dual antiplatelet therapy (aspirin and clopidogrel) started within 24 hours after symptom onset and continued for 21 days is effective in reducing recurrent ischemic stroke for a period of up to 90 days from symptom onset.	**I**	**A**	New recommendation.

ESC European Society of Cardiology

Europace (2021) **00**, 1–65
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POSITION PAPER
EHRA PRACTICAL GUIDE

2021 European Heart Rhythm Association Practical Guide on the Use of Non-Vitamin K Antagonist Oral Anticoagulants in Patients with Atrial Fibrillation

A 75 y/o male presented with left hemiparesis and LCHFW. At Brain imaging he has acute ischemic lesion at right fronto-parietal lobe. There was no significant stenosis at cervical and Brian vessels, echo was unremarkable for cardiac source of stroke and ECG showed AF rhythm. What is the best medication for secondary prevention of stroke (at long term)?

1. ASA 80:OD
2. Ticagrelor 90:BID
3. Warfarin (INR 2-3)
4. NOACs

Non-vitamin K antagonist oral anticoagulants (NOACs) are considered by atrial fibrillation (AF) guidelines world-wide as the preferred choice of anticoagulants to prevent stroke in patients with AF.[1–4]

References

1. Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomstrom-Lundqvist C *et al.* 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J* 2021;**42**:373–498.
2. January CT, Wann LS, Calkins H, Chen LY, Cigarroa JE, Cleveland JC Jr *et al.* 2019 AHA/ACC/HRS focused update of the 2014 AHA/ACC/HRS Guideline for the management of patients with atrial fibrillation: report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society in Collaboration With the Society of Thoracic Surgeons. *Circulation* 2019;**140**:e125–51.
3. Andrade JG, Verma A, Mitchell LB, Parkash R, Leblanc K, Atzema C *et al.* 2018 focused update of the Canadian Cardiovascular Society Guidelines for the management of atrial fibrillation. *Can J Cardiol* 2018;**34**:1371–92.
4. Chiang CE, Okumura K, Zhang S, Chao TF, Siu CW, Wei Lim T *et al.* 2017 consensus of the Asia Pacific Heart Rhythm Society on stroke prevention in atrial fibrillation. *J Arrhythm* 2017;**33**:345–67.

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

Class[a]	Level[b]	
I	A	2. NOACs (dabigatran, rivaroxaban, apixaban, and edoxaban) are recommended over warfarin in NOAC-eligible patients with AF (except with moderate-to-severe mitral stenosis or a mechanical heart valve).[S4.1.1-8–S4.1.1-11] **NEW:** Exclusion criteria are now defined as moderate-to-severe mitral stenosis or a mechanical heart valve. When the NOAC trials are considered as a group, the direct thrombin inhibitor and factor Xa inhibitors were at least noninferior and, in some trials, superior to warfarin for preventing stroke and systemic embolism and were associated with lower risks of serious bleeding.

ESC European Society of Cardiology

European Heart Journal (2020) **00**, 1–125
doi:10.1093/eurheartj/ehaa612

2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association of Cardio-Thoracic Surgery (EACTS)

Recommendations for the prevention of thrombo-embolic events in AF

Recommendations	Class[a]	Level[b]
For stroke prevention in AF patients who are eligible for OAC, NOACs are recommended in preference to VKAs (excluding patients with mechanical heart valves or moderate-to-severe mitral stenosis).[423,424]	I	A

Why NOACs?

2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association of Cardio-Thoracic Surgery (EACTS)

- NOACs were associated with similar ischemic stroke risk reduction compared with VKAs but a 51% reduction in hemorrhagic stroke and a significant 10% reduction in all-cause mortality.

Dosing

Table 2 OACs and approved/studied doses across indications

Stroke prevention in atrial fibrillation (SPAF)		
	Standard dose	**Comments/dose reduction**
Apixaban[47]	5 mg BID	2.5 mg BID if two out of three fulfilled: weight ≤60 kg, age ≥80 years, serum creatinine ≥133 µmol/L (1.5 mg/dL) (*or* single criterion: if CrCl 15–29 mL/min) (Cockcroft–Gault)
Dabigatran[48]	150 mg BID/110 mg BID	No pre-specified dose-reduction criteria in phase III trial[a]
Edoxaban[49]	60 mg QD	30 mg QD if: weight ≤60 kg *or* CrCl 15–49 mL/min *or* concomitant therapy with strong P-Gp inhibitor (see 'Pharmacokinetics and drug-drug interactions of NOACs' section)
Rivaroxaban[46]	20 mg QD	15 mg QD if CrCl ≤15–49 mL/min

'SmPc' refers to European SmPc.
BID, twice daily; CrCl, creatinine clearance; GI, gastrointestinal; NOAC, non-vitamin K antagonist oral anticoagulant; QD, once daily.
[a]SmPC: 110 mg BID if age ≥80 years, concomitant verapamil, increased risk of GI bleeding.

For the presented gentleman, if he has cardiac valve diseases, for which of these conditions we are not allowed to use NOACs?

1. Prosthetic (mechanical) Mitral valve replacement
2. Prosthetic (mechanical) Aortic valve replacement
3. Moderate to severe rheumatic mitral stenosis
4. All of above

In patients with Bio-prosthetic valve replacement and AF, are allowed to use NOACs?

1. Not at all
2. Yes, 3 months after operation
3. Yes, 6 months after operation
4. Yes, 12 months after operation

Table I Selected indications and contraindications for NOAC therapy in AF patients

Condition	Eligibility for NOAC	Comment
Mechanical prosthetic valve	Contraindicated	Excluded from pivotal RCTs Data indicating worse outcome[15,16]
Moderate to severe mitral stenosis (usually rheumatic)	Contraindicated	Excluded from pivotal RCTs Little rationale for less efficacy and safety vs. VKA
Other mild to moderate valvular disease (e.g. degenerative aortic stenosis, mitral regurgitation etc.)	Included in NOAC trials	Data regarding efficacy and safety overall consistent with patients without valvular heart disease[12,17–22]
Bioprosthetic valve/valve repair (after >3 months postoperative)	Acceptable	Some data from NOAC RCTs Single RCT indicating non-inferiority to VKA[24] Patients without AF usually on ASA after 3–6 months post-surgery, hence NOAC therapy acceptable for stroke prevention if diagnosed with AF
Severe aortic stenosis	Limited data (excluded in RE-LY)	No pathophysiological rationale for less efficacy and safety Most will undergo intervention
Transcatheter aortic valve implantation	Acceptable	Single RCT + observational data May require combination with APT[25,26]
Percutaneous transluminal aortic valvuloplasty	With caution	No prospective data May require combination with APT
Hypertrophic cardiomyopathy	Acceptable	No rational for less efficacy and safety vs. VKA Observational data positive for NOACs[33–36]

Hatched, limited data; See text for details.

AF, atrial fibrillation; NOAC, non-vitamin K antagonist oral anticoagulant; RCT, randomized clinical trial; VKA, vitamin K antagonist.

NOACS in Pregnancy and breastfeeding

- NOACs are contraindicated in pregnancy (A test to R/O pregnancy in women of reproductive age).
- NOACs are contraindicated in breast feeding.

NOACs in Children

- Pediatric patients have been excluded from the pivotal stroke prevention RCTs and AF with need for OAC is rare in this population.
- NOAC therapy should be discouraged in children but can be considered in fully grown adolescents with body weight > 50 kg.

Our patient on Apixaban (9-21), calls on 13:00 and ask “I forgot to take my pill at the morning”, what should I do now?

1. Take up a 5 mg Apixaban and next dose at the scheduled time (21:00).
2. Take up a 2.5 mg Apixaban and next dose at the scheduled time (21:00).
3. skipped the dose and take next dose at the scheduled time (21:00).
4. skipped the dose and take a 7.5 mg Apixaban at next scheduled time (21:00).

Missed dose

- A forgotten dose may be taken until half of the dosing interval has passed.
- Hence, for NOACs with a twice daily (BID) dosing regimen (i.e., intake every 12 h), a forgotten full dose can be taken up until 6 h after the scheduled intake
- For NOACs with a once daily (QD) dosing regimen, a forgotten dose can be taken up until 12 h after the scheduled intake.
- After these time points, the dose should be skipped, and the next scheduled dose should be taken.

Double dose:

- For NOACs with a BID dosing regimen, the next planned dose (i.e. after 12 h) may be skipped, with the regular BID dosing regimen restarted 24 h after the double dose intake.

- For NOACs with a QD dosing regimen, the patient should continue the normal dosing regimen, i.e. without skipping the next daily dose.

Uncertainty about dose intake:

- For NOACs with a BID dosing regimen, it is generally advisable to not take another tablet/capsule, but to continue with the regular dose regimen, i.e. starting with the next dose at the 12 h interval.

- For NOACs with a QD dosing regimen, when thromboembolic risk is high (CHA2DS2-VASc >_3), it may generally be advisable to take another tablet 6–8 h after the original (uncertain) intake and then continue the planned dose regimen.
In case the thromboembolic risk is low (CHA2DS2-VASc <_2) we advise to wait until the next scheduled dose.

AF Anticoag Guideline Comparison

CHEST 2018 vs AHA/ACC/HRS 2019

CHA_2DS_2-VASc Score	
CHF (heart failure)	1
Hypertension	1
Age ≥ 75	2
Diabetes	1
Stroke	2
Vascular Disease	1
Age 65-74	1
Sex Category (female)	*1*

First-Line (for both):
DOAC therapy over warfarin

Anticoagulate based on CHA_2DS_2-VASc score

CHEST 2018
≥1 for males or
≥2 for females
(i.e. at least 1 non-sex risk factor)

AHA/ACC/HRS 2019
≥2 for males
or ≥3 for females
(i.e. at least 2 non-sex risk factors)

CHA2DS2-VASc Score for Risk Stratification of Stroke

CHADS $_2$ Score * (svbfile:///var/mobile/Containers/Data/Application/DCCA1459-30AF-4175-B23F-53E1D87AB417/Documents/3-s2.0-C20120027561/base/hl0000205)	Risk	Stroke Rate (%/year)
0	Low	0
1	Low	1.3
2	Moderate	2.2
3	Moderate	3.2
4	High	4
5	High	6.7
6	Very High	9.8
7	Very High	9.6
8	High	6.7
9	Very High	15.2

Assessment of Bleeding Risk

Letter	Clinical characteristic[a]	Points awarded
H	Hypertension	1
A	Abnormal renal and liver function (1 point each)	1 or 2
S	Stroke	1
B	Bleeding	1
L	Labile INRs	1
E	Elderly (e.g. age >65 years)	1
D	Drugs or alcohol (1 point each)	1 or 2
		Maximum 9 points

BP >160 systolic
Dialysis or Cr > 200
LFT – bil x2, ALT/AST x 3
Labile INR (TTR<60%)
NSAIDS, antiplatelets

- Score:
  - 0 = 1%
  - 1 = 1%
  - 2 = 1.8%
  - 3 = 3.74%
  - >4 = > 8%
- Score 3 or more – caution and **careful monitoring** with OAC/aspirin
- NOT CONTRAINDICATION

HAS-BLED Score for Bleeding Risk on Anticoagulation [36]

HAS-BLED Score * (svbfile:///var/mobile/Containers/Data/Application/DCCA1459-30AF-4175-B23F-53E1D87AB417/Documents/3-s2.0-C20120027561/base/hl0000242)	Bleeding Risk (% per 100 patient-years
0	1.2
1	2.8
2	3.6
3	6.0
4	9.5
5	7.4

Clinical characteristics	Definition	Score
Hypertension	SBP > 160 mmHg	1
Abnormal renal and liver function (1 score each)	Renal: dialysis, transplantation, or creatinine ≥ 2.3 mg/dL Liver: chronic hepatitis, cirrhosis, bilirubin > 2 ULN, with ALT > 3 ULN	1 or 2
Stroke	Previous history, particularly lacunar	1
Bleeding tendency or predisposition	Recent bleed, anemia, etc.	1
Labile INRs	Unstable/high INR, or TTR < 60%	1
Elderly	Age > 65 y, extreme frailty	1
Drugs or alcohol (1 score each)	Drugs: concomitant antiplatelet, or NSAID use	1 or 2

Table 1: Stroke and bleeding risk stratification with the CHA_2DS_2-VASc and HAS-BLED schemas

CHA_2DS_2-VASc	Score	HAS-BLED	Score
Congestive heart failure/LV dysfunction	1	Hypertension i.e. uncontrolled BP	1
Hypertension	1	Abnormal renal/liver function	1 or 2
Aged ≥75 years	2	Stroke	1
Diabetes mellitus	1	Bleeding tendency or predisposition	1
Stroke/TIA/TE	2	Labile INR	1
Vascular disease [prior MI, PAD, or aortic plaque]	1	Age (e.g. >65)	1
Aged 65-74 years	1	Drugs (e.g. concomitant aspirin or NSAIDSs) or alcohol	1
Sex category [i.e. female gender]	1		
Maximum score	**9**		**9**

- Bleeding risk, as estimated using the HAS-BLED score, is not in itself a reason to deny OAC to AF patients at risk of stroke or reduce the dose of the NOAC. Instead, particularly patients at high bleeding risk (e.g. HAS-BLED >_3) should have their modifiable bleeding risk factors identified and addressed, and should be scheduled for an earlier and more frequent clinical follow-up.

2019 (COVID-19) pandemic

In addition to the general preference of NOACs over VKA for stroke prevention in AF due to efficacy and safety, NOAC therapy comes with some potentially important practical advantages over VKA based anticoagulation during the coronavirus disease of *2019 (COVID-19) pandemic*, including the lack of necessity for frequent clinic/office visits for INR monitoring. As a result, both the individual's risk for contracting the virus as well as the workload on the healthcare system would be reduced.

Covid-19 vaccines are usually administered by intramuscular (i.m.) injection. In patients on NOACs it is advisable to follow the scheme for ‘minor risk’ interventions:

- Leave out the morning dose of the NOAC prior to i.m. injection;
- Use a fine-gauge needle for injection;
- Apply firm pressure for 2–5 min after the injection;
- In QD NOACs: take the left-out morning dose 3 h after the injection and
- In BID NOACs: re-start NOAC with the next scheduled dose.

Which one the drugs listed below, do not have interaction with NOACs?

1. Lacosamide, Lamotrigin, Zonisamide
2. Na Valproate, Carbamazepine, Phenytoin
3. Levetiracetam, Oxcarbazepine, Topiramate
4. Phenobarbital, Phenytoin, Na Valproate

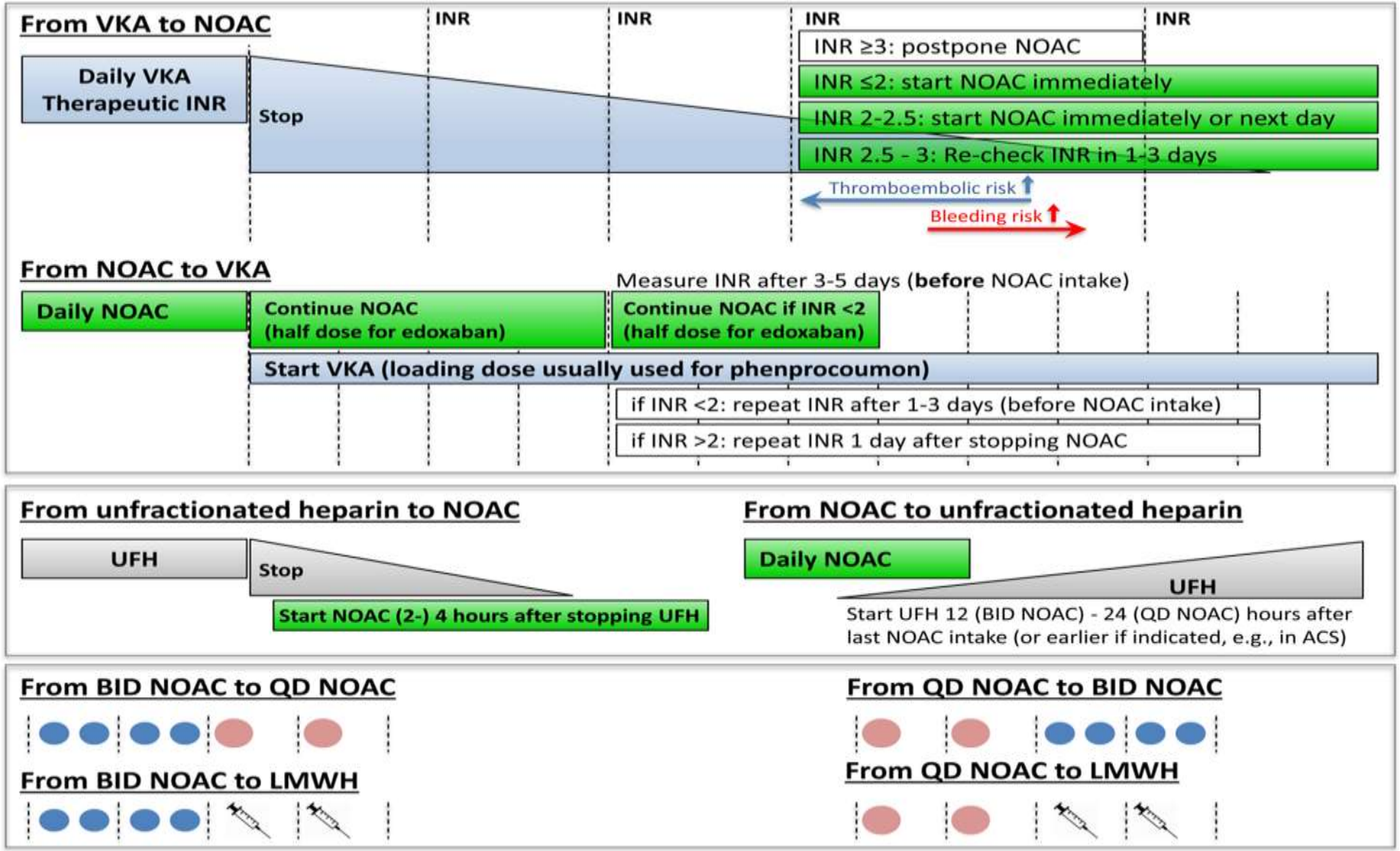
Anticipated effects of common antiepileptic drugs on non-vitamin K antagonist oral anticoagulants plasma levels:

	Via [426, 539-541]	Dabigatran etexilate	Apixaban	Rivaroxaban
Carbamazepine	Strong CYP3A4/P-gp induction; CYP3A4 competition	-29% [542]	-50% (SmPC)	SmPC
Lacosamide	–	No relevant interac		
Lamotrigine	P-gp competition	No relevant interac		
Levetiracetam	P-gp induction; P-gp competition			
Oxcarbazepine	CYP3A4 induction; P-gp competition			
Phenobarbital	Strong CYP3A4/possible P-gp induction		SmPC	SmPC
Phenytoin	Strong CYP3A4/P-gp induction; P-gp competition	SmPC [543]	SmPC	SmPC
Topiramate	CYP3A4 induction; CYP3A4 competition			
Valproic acid	CYP3A4/P-gp induction/inhibition			Ref 544
Zonisamide	CYP3A4 competition; weak P-gp inhibition	No relevant interaction(PC)		

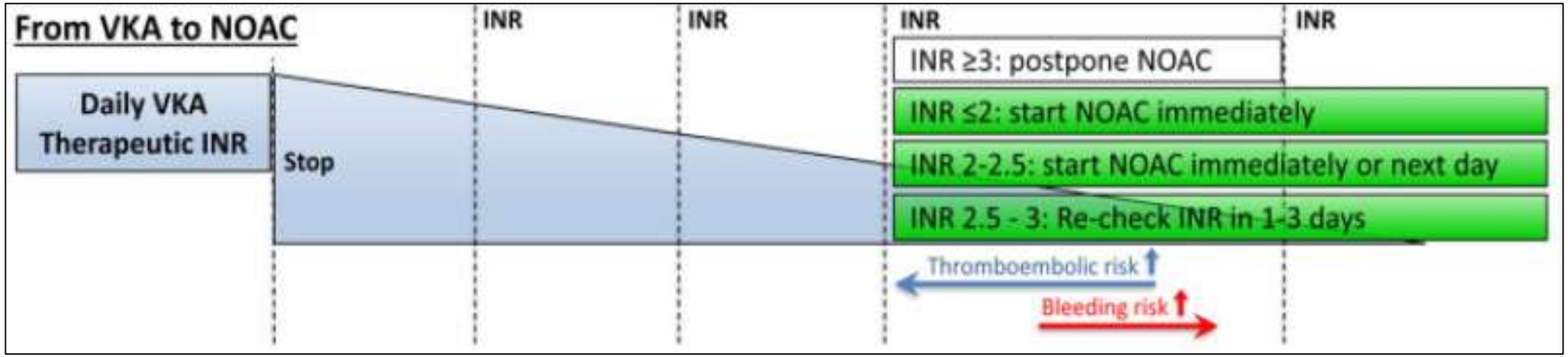
White: No relevant drug–drug interaction anticipated.
Blue (dark): Contraindicated due to reduced NOAC plasma levels.
Blue (light): Caution required, especially in case of polypharmacy or in the presence of ≥2 light blue interactions due to *reduced* NOAC plasma levels.

Table 8 Anticipated effects of common herbal medicines on non-vitamin K antagonist oral anticoagulants plasma levels

	Via [545, 546, 547]	Dabigatran etexilate	Apixaban	Edoxaban	Rivaroxaban
Garlic	Mild CYP3A4 inhibition; anticoagulation / antiplatelet effect				
Ginger	Anticoagulation / antiplatelet effect				
Ginkgo biloba	P-gp inhibition; anticoagulation / antiplatelet effect				
Ginseng	Anticoagulation / antiplatelet effect				
Green Tea	P-gp inhibition; anticoagulation / antiplatelet effect				

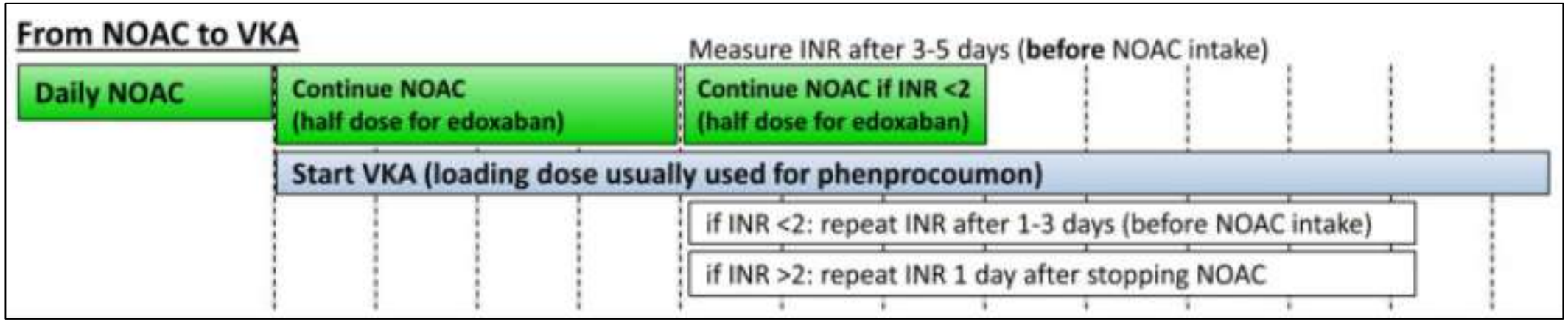

From VKA to NOAC
INR
INR
INR
INR
Daily VKA Therapeutic INR
Stop
INR ≥3: postpone NOAC
INR ≤2: start NOAC immediately
INR 2-2.5: start NOAC immediately or next day
INR 2.5 - 3: Re-check INR in 1-3 days
Thromboembolic risk
Bleeding risk
From NOAC to VKA
Measure INR after 3-5 days (before NOAC intake)
Daily NOAC
Continue NOAC (half dose for edoxaban)
Continue NOAC if INR <2 (half dose for edoxaban)
Start VKA (loading dose usually used for phenprocoumon)
if INR <2: repeat INR after 1-3 days (before NOAC intake)
if INR >2: repeat INR 1 day after stopping NOAC
From unfractionated heparin to NOAC
UFH
Stop
Start NOAC (2-) 4 hours after stopping UFH
From NOAC to unfractionated heparin
Daily NOAC
UFH
Start UFH 12 (BID NOAC) - 24 (QD NOAC) hours after last NOAC intake (or earlier if indicated, e.g., in ACS)
From BID NOAC to QD NOAC
From BID NOAC to LMWH
From QD NOAC to BID NOAC
From QD NOAC to LMWH

From Warfarin to NOACs



SmPC: the NOAC can be started when INR is <3 for rivaroxaban and <2.0 for apixaban and dabigatran

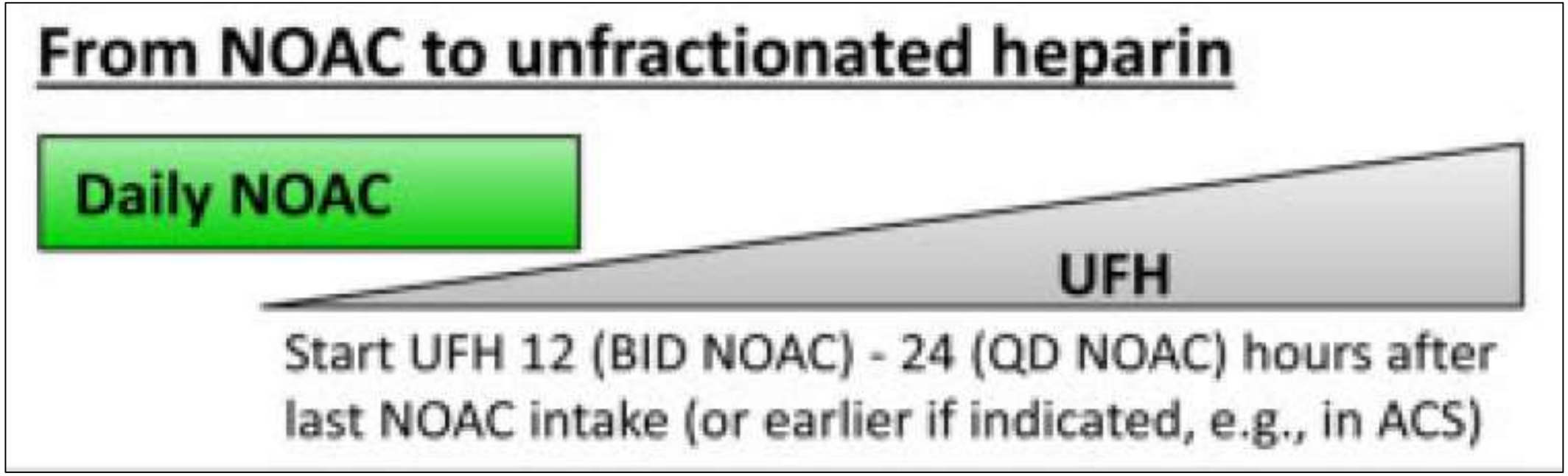
From NOACs to Warfarin



From NOACs to Warfarin

- As NOACs may have an impact on INR measurements it is important that the INR is measured just before the next intake of the NOAC during concomitant administration, and is re-measured 2-3 days after stopping the NOAC (i.e. reflecting solely VKA therapy) to ensure adequate anticoagulation.

NOAC to IV anticoagulants



- In a patient with Nasogastric tube, we are allowed to use all except?

1. Apixaban
2. Edoxaban
3. Dabigatran
4. Rivaroxaban

- Which of the NOACs must be taken with food?

1. Apixaban
2. Edoxaban
3. Dabigatran
4. Rivaroxaban

Food intake, antacids, and nasogastric tube administration

- **Nasogastric tube:** Data have shown that administration in crushed form, e.g. via a nasogastric tube, does not alter the bioavailability for Apixaban and rivaroxaban. In contrast, dabigatran capsules must not be opened as it results in a substantial increase in drug bioavailability (75% per SmPC).
- **Food intake:** Rivaroxaban needs to be taken with food since plasma concentration increases by 39% to a very high bioavailability of almost 100%
- **Antacids:** The concomitant use of PPIs and H2-blockers: *without effect* on clinical efficacy.

Indication for anticoagulation and choice between VKA and NOAC

- After the indication for OAC is established, NOACs are preferred over VKAs in all NOAC-eligible AF patients.
- When starting a NOAC, knowledge of current kidney and liver function is required as all NOACs are eliminated to some extent via the kidneys, and renal function affects NOAC dosing. Importantly, kidney function should be assessed using the Cockcroft–Gault formula.

Calculation of estimated clearance according to the Cockcroft-Gault formula*:

$$\frac{[140 - \text{age (years)}] \times \text{ideal weight (kg)}}{([\text{creatinine (mg/dl)}] \times 72)}$$

* For women, multiply by 0.85

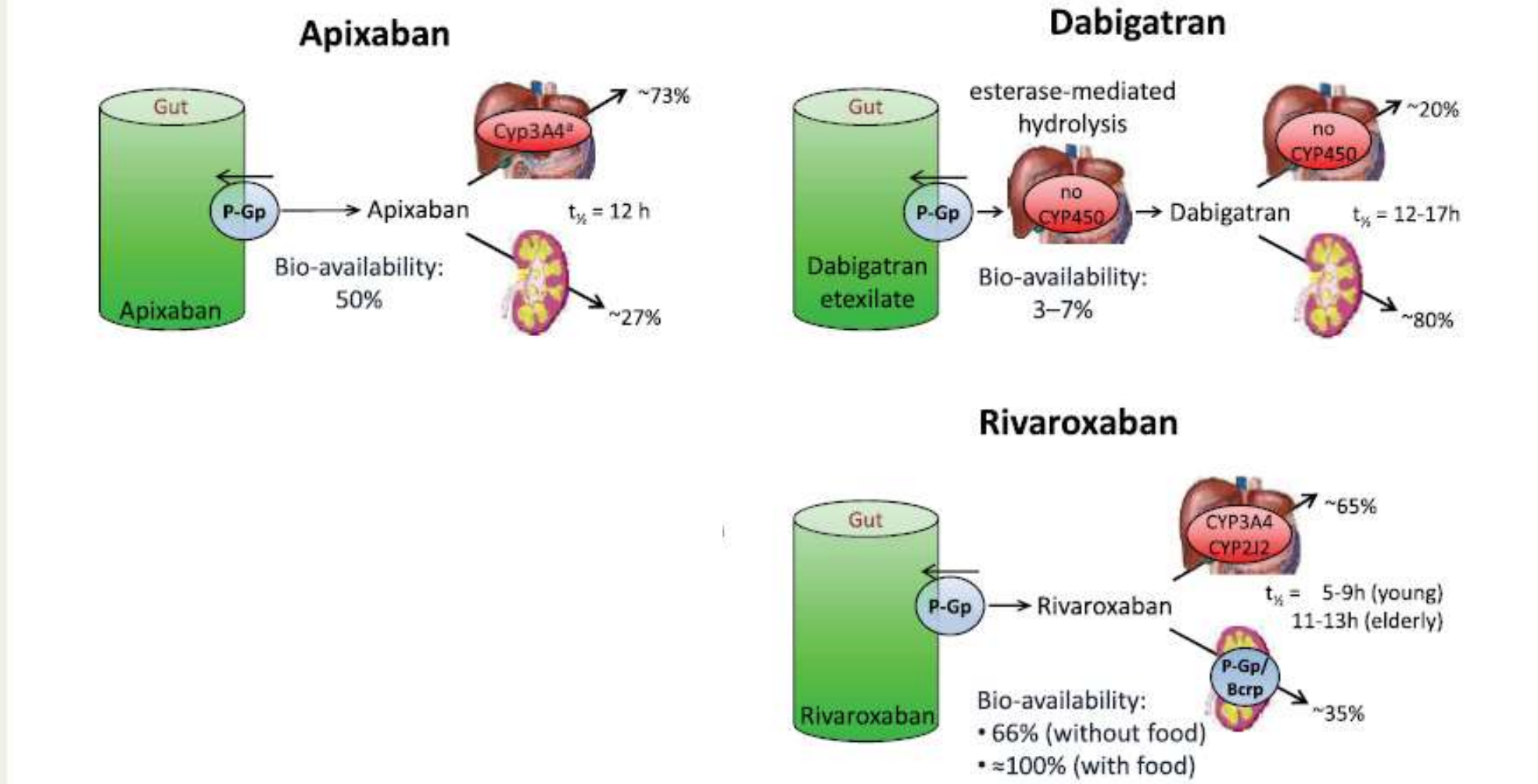


Figure 5 Absorption and metabolism of the different NOACs. There are interaction possibilities at the level of absorption or first transformation, and at the level of metabolization and excretion. [a]Also via CYP1A2, CYP2J2, CYP2C8, CYP2C9, and CYP2C19. NOAC, non-vitamin K antagonist oral anticoagulant.

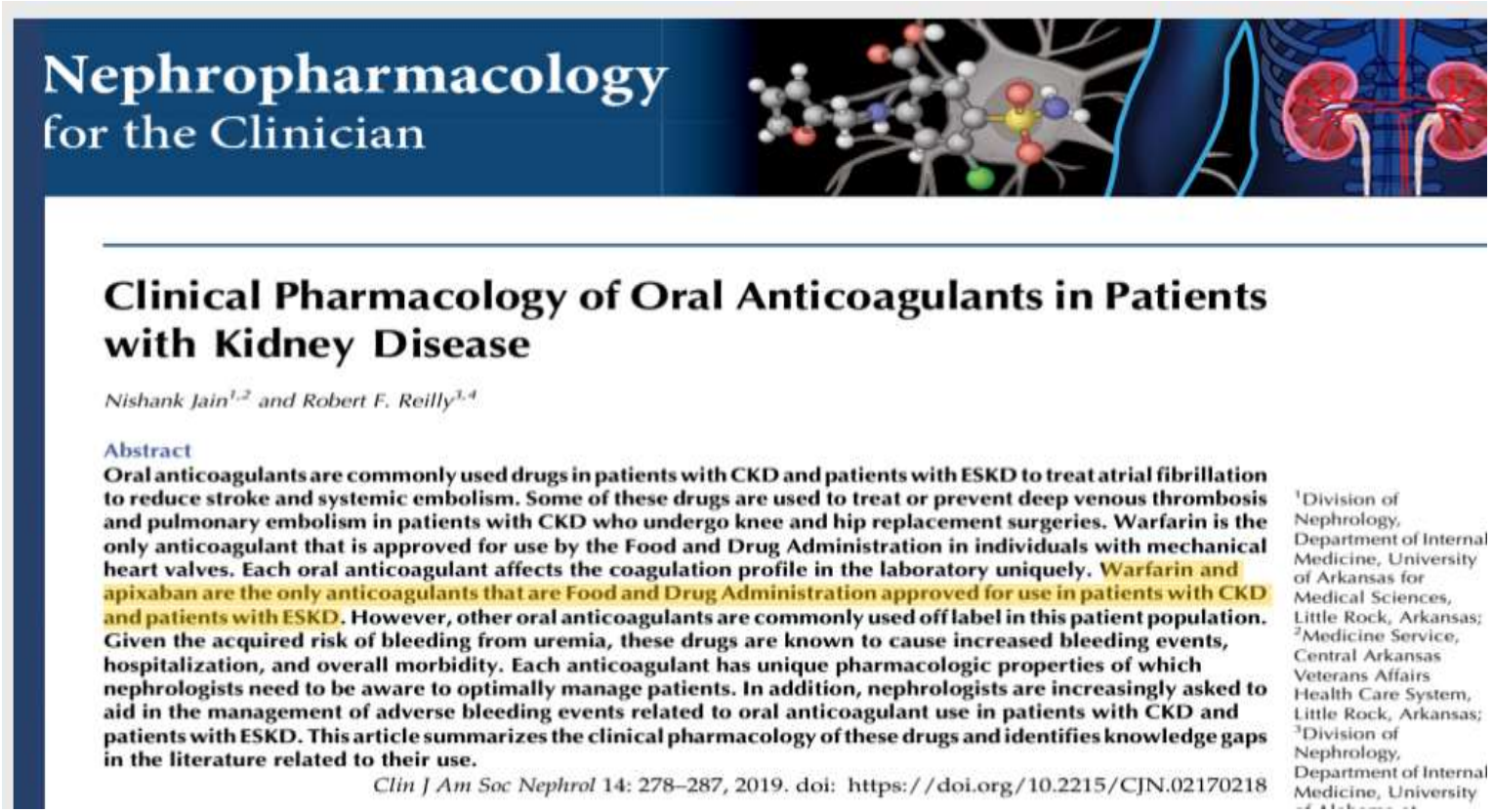
Oral anticoagulant therapy in patients with severe CKD (CrCl of 15–29 mL/min):

There are no RCT data on the use of warfarin for thromboprophylaxis in AF patients with severe CKD or on dialysis, and all landmark trials with NOACs essentially excluded patients with a creatinine clearance (CrCl) of <30mL/min (apart from few patients on apixaban
with CrCl 25–30mL/min).

- In the US (but not in Europe), a low dose dabigatran 75mg BID has been approved for patients with severe CKD (a CrCl of 15–29mL/min), based on pharmacokinetic simulations.

- Rivaroxaban, apixaban, and edoxaban (but not dabigatran) are approved in Europe for the use in patients with severe CKD (stage 4, i.e. a CrCl of 15–29mL/min), with a reduced dose regimen.

In view of the individual NOAC pharmacokinetics (27% renal clearance for apixaban), dose-reduction criteria (50% reduction for apixaban and edoxaban), and available evidence from RCTs, the use of either apixaban or edoxaban may be preferable in these patients.



Nephropharmacology
for the Clinician

Clinical Pharmacology of Oral Anticoagulants in Patients with Kidney Disease

Nishank Jain[1,2] *and Robert F. Reilly*[3,4]

Abstract

Oral anticoagulants are commonly used drugs in patients with CKD and patients with ESKD to treat atrial fibrillation to reduce stroke and systemic embolism. Some of these drugs are used to treat or prevent deep venous thrombosis and pulmonary embolism in patients with CKD who undergo knee and hip replacement surgeries. Warfarin is the only anticoagulant that is approved for use by the Food and Drug Administration in individuals with mechanical heart valves. Each oral anticoagulant affects the coagulation profile in the laboratory uniquely. Warfarin and apixaban are the only anticoagulants that are Food and Drug Administration approved for use in patients with CKD and patients with ESKD. However, other oral anticoagulants are commonly used off label in this patient population. Given the acquired risk of bleeding from uremia, these drugs are known to cause increased bleeding events, hospitalization, and overall morbidity. Each anticoagulant has unique pharmacologic properties of which nephrologists need to be aware to optimally manage patients. In addition, nephrologists are increasingly asked to aid in the management of adverse bleeding events related to oral anticoagulant use in patients with CKD and patients with ESKD. This article summarizes the clinical pharmacology of these drugs and identifies knowledge gaps in the literature related to their use.

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Warfarin and apixaban are the only anticoagulants that are Food and Drug Administration approved for use in patients with CKD and patients with ESKD.

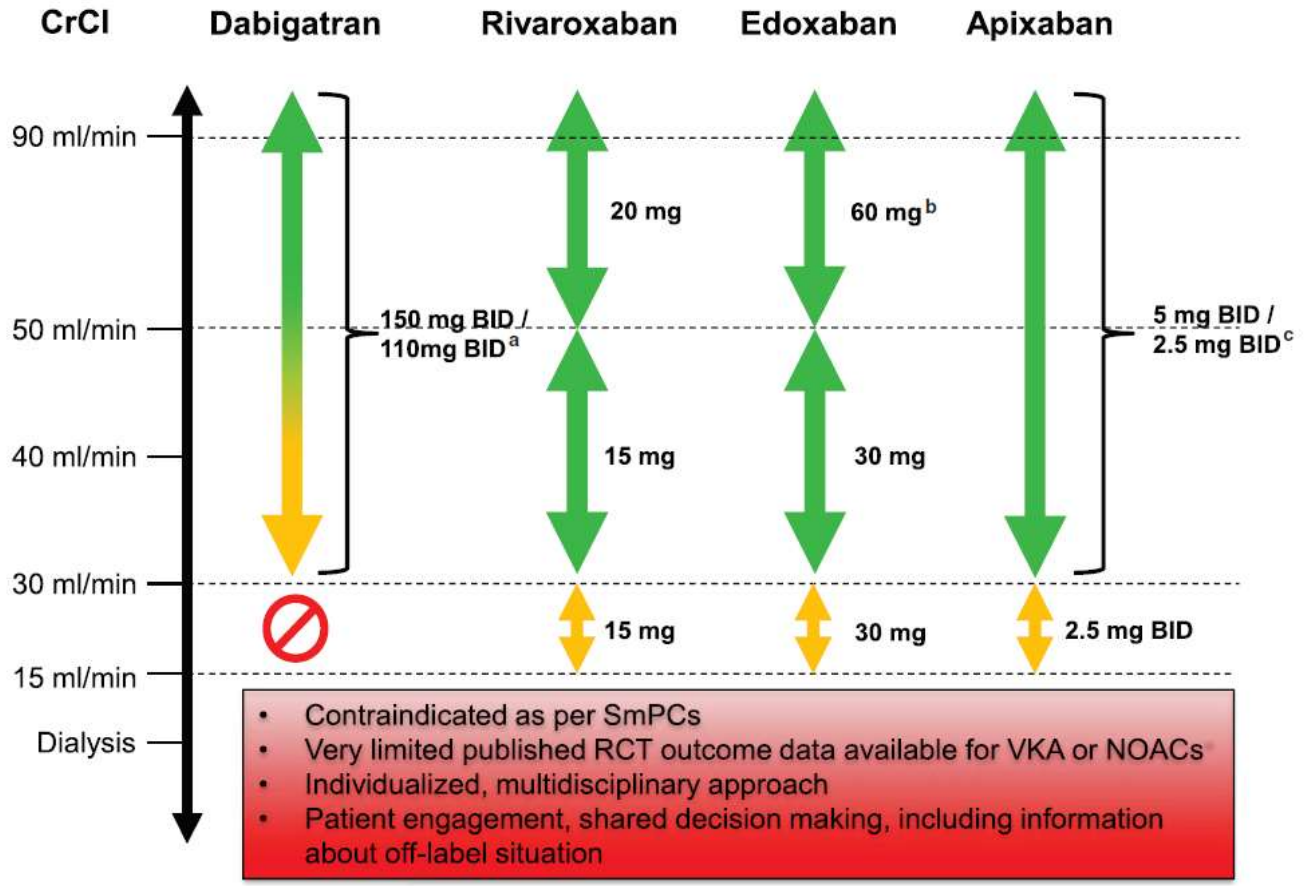

Figure 7 Use of NOACs according to renal function. [a]110 mg BID in patients at high risk of bleeding (per SmPc). [b]Other dose reduction criteria may apply (weight ≤ 60 kg, concomitant potent P-Gp inhibitor therapy). According to EMA, SmPc edoxaban should be used in 'high CrCl only after a careful evaluation of the individual thromboembolic and bleeding risk'.[473] See text for details. [c]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; see text for details. BID, twice daily; CrCl, creatinine clearance; EMA, European Medicines Agency; NOAC, non-vitamin K antagonist oral anticoagulant; RCT, randomized clinical trial; VKA, vitamin K antagonist.

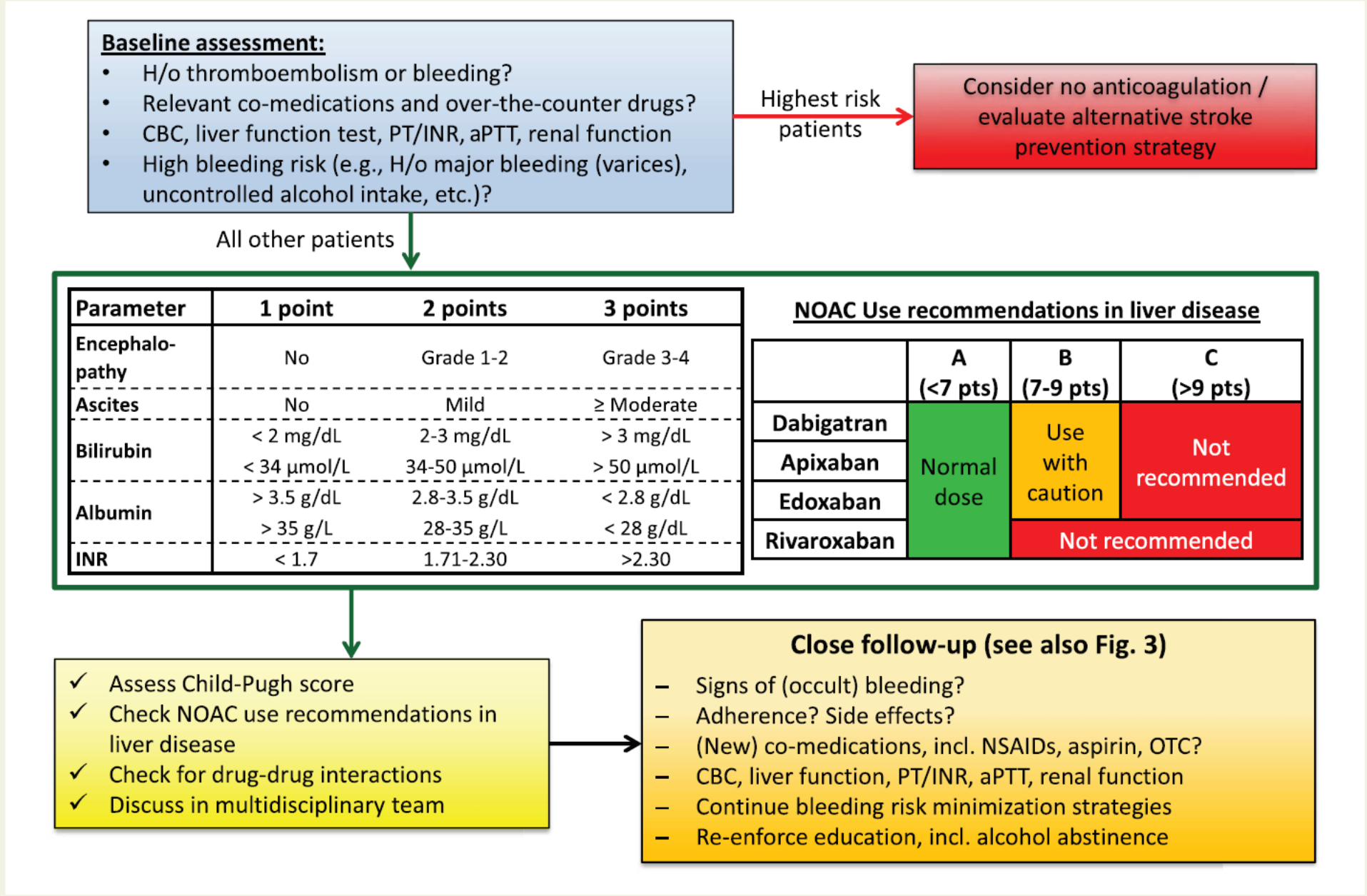

Figure 8 NOACs in patients with liver disease. APTT, activated prothrombin time; INR, international normalized ratio; NOAC, non-vitamin K antagonist oral anticoagulant; NSAID, non-steroidal anti-inflammatory drug; OTC, over-the-counter; PT, prothrombin time.

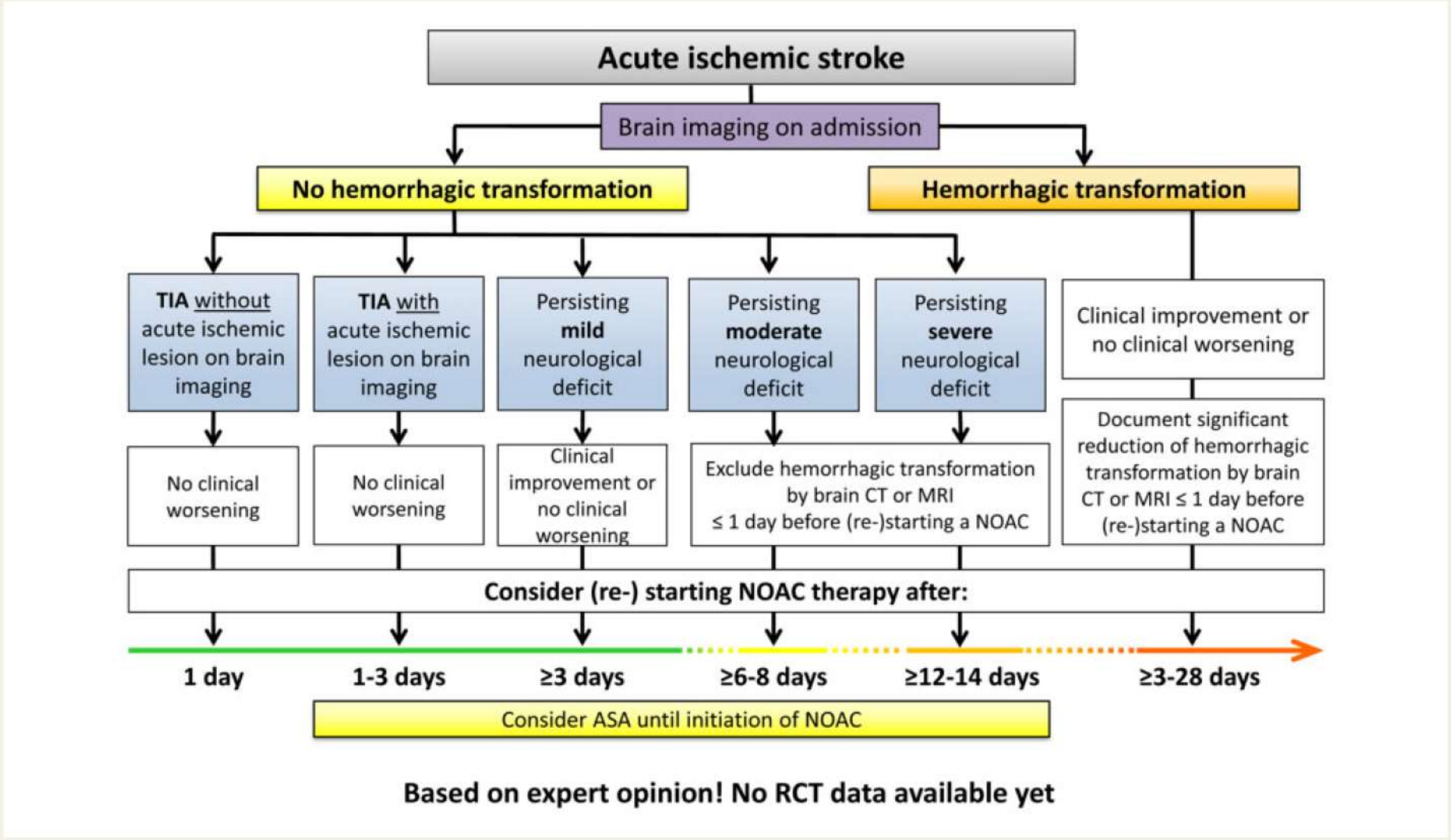

Figure 21 (Re-) initiation of anticoagulation after TIA/stroke. Without proven evidence/RCT data available, based on expert opinion. Consider inclusion of patient in an ongoing trial. (Re-)start only in the absence of contraindications and if stroke size is not expected to substantially increase the risk of secondary haemorrhagic transformation. Consider shorter delays to (re-)start a NOAC in case of a very high risk of stroke recurrence [e.g. LA(A) thrombus] and no haemorrhagic transformation on follow-up brain imaging (using CT or MRI). CT, computed tomography; LA, left atrium; LAA, left atrial appendage; MRI, magnetic resonance imaging; NOAC, non-vitamin K antagonist oral anticoagulant; RCT, randomized clinical trial; TIA, transient ischaemic attack.

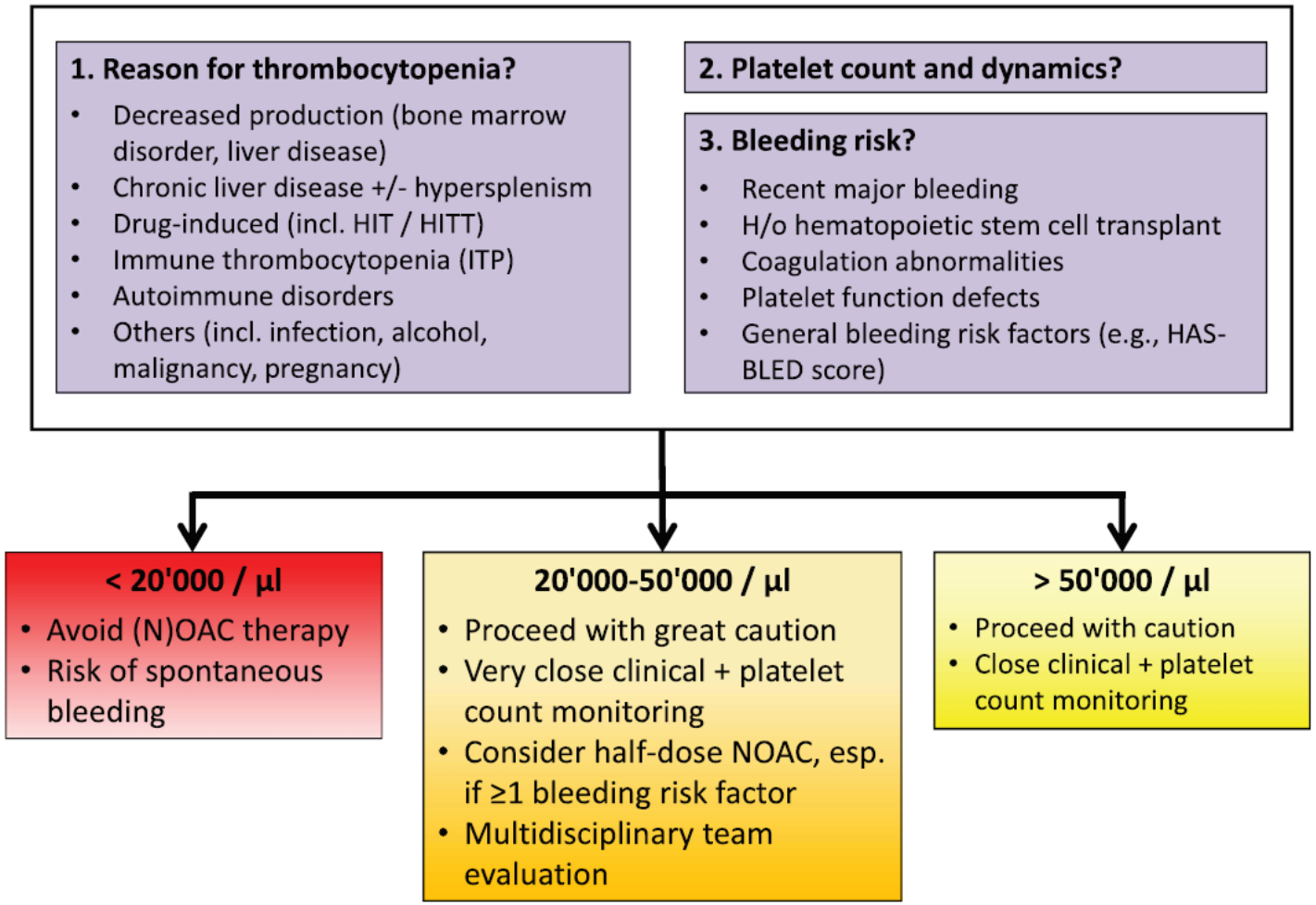

Figure 24 NOACs in patients with thrombocytopenia. NOAC, non-vitamin K antagonist oral anticoagulant.

- Impact of NOACs on thrombophilia testing NOACs interfere with thrombophilia tests and the measurement of coagulation factors. Therefore, leaving a time window of at least 24 h is reasonable between the last intake of a NOAC and blood sampling to confidently assess coagulation parameters.

- This time window may need to be even longer for *lupus anticoagulant* measurements (>_48 h) or in the presence of factors potentially prolonging the anticoagulant effect such as CKD.

Initiator of anticoagulant treatment

- Indication (contraindication?) for anticoagulation
- Baseline blood works, incl. hemoglobin, renal / liver function, full coagulation panel
- Choice of anticoagulant and correct dose
- Education and handover of anticoagulation card
- Organization of follow-up (when, where, by whom, what?)

first FU: 1 month

- **Routine monitoring of anticoagulation level is not required**
- **Yearly:** Hb, renal and liver function
- **If ≥ 75 years or frail:** 4 monthly renal function
- **If CrCl ≤ 60 ml/min:** recheck interval in months = "CrCl:10" (e.g., every 4 months if CrCl = 40)
- **If intercurrent condition that may have impact:** renal and/or liver function

Organization of follow-up and continued care:

6. Blood sampling (including haemoglobin, renal, and liver function)	Yearly	• In all patients except those below
	4-monthly	• ≥75 years (especially if on dabigatran), or frail.
	Variable	• If renal function CrCl ≤60 mL/min: • CrCl/10 = minimum recheck interval (in months).
	If needed	• In case of intercurrent conditions, especially with potential impact on renal or hepatic function (e.g. infection, NSAID use, dehydration etc.).

Interval "quick check" / blood sampling

- 4-monthly: ≥75y (especially if on dabigatran), or frail.
- Every "CrCl/10" months if CrCl ≤60 ml/min
- Immediately in case of intercurrent conditions, esp. with potential impact on renal or hepatic function (e.g., infection, NSAID use, dehydration etc.).

Take home message:

- Cardioembolic stroke is a major etiology accounting for one-fifth of all ischemic strokes.
- Recent advances in technology have enabled us to monitor heart rhythm remotely and detect paroxysmal atrial fibrillation.
- Newer risk stratification scores like CHADS2-Vasc and HAS-BLED have been developed to predict ischemic stroke due to atrial fibrillation as well as bleeding risk on anticoagulation.
- Rheumatic mitral valve disease has the highest risk of ischemic stroke of all native valvular heart disease.
- Newer oral anticoagulants have shown equal or superior efficacy to warfarin in preventing ischemic stroke in non-valvular atrial fibrillation expanding treatment options for this patient population.


Thank You All
for your patience
hearing !!