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Anticoagulant Therapy in ACS

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ESC European Society of Cardiology

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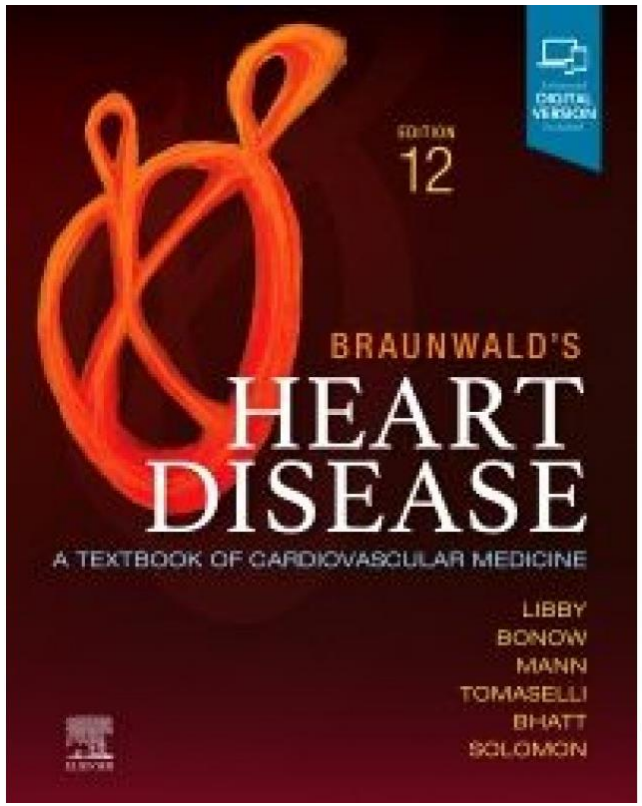
ESC GUIDELINES

2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation

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



UpToDate®

Coronary artery disease patients requiring combined anticoagulant and antiplatelet therapy

CASE # 1

Case Profile

- 50 yrs./o man with acute chest pain and inferior STEMI
- RF: C/S, dyslipidemia
- Hypertension: + controlled
- Family history: +

CASE # 1

Case Scenario

- After successful Primary PCI of RCA with DES (3.5 * 36 mm)
- Episodes of Transient AF in CCU

- **What is your plan for ACT?**

1. No need for ACT
2. Apixaban 5 BD
3. Rivaroxaban 20 Daily
4. Warfarin

CASE # 1

Guideline Recommendations

ESC European Society of Cardiology

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ESC GUIDELINES

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Table 7 Stroke risk factors in patients with AF

Most commonly studied clinical risk factors (a systematic review)[324]	Positive studies/All studies	Other clinical risk factors[325]	Imaging biomarkers[291,326–328]	Blood/urine biomarkers[329–332]
Stroke/TIA/systemic embolism	15/16	Impaired renal function/ CKD	*Echocardiography*	Cardiac troponin T and I Natriuretic peptides Cystatin C Proteinuria CrCl/eGFR CRP IL-6 GDF-15 von Willebrand factor D-dimer
Hypertension	11/20	OSA	LA dilatation Spontaneous contrast or thrombus in LA Low LAA velocities Complex aortic plaque	
Ageing (per decade)	9/13	HCM		
Structural heart disease	9/13	Amyloidosis in degenerative cerebral and heart diseases		
Diabetes mellitus	9/14	Hyperlipidaemia		
Vascular disease	6/17	Smoking	*Cerebral imaging*	
CHF/LV dysfunction	7/18	Metabolic syndrome[333]	Small-vessel disease	
Sex category (female)	8/22	Malignancy		

CHF = congestive heart failure; CKD = chronic kidney disease; CrCl = creatinine clearance; CRP = C-reactive protein; eGFR = estimated glomerular filtration rate; GDF-15 = growth differentiation factor-15; IL-6 = interleukin 6; LA = left atrium; LAA = left atrial appendage; LV = left ventricular; OSA = obstructive sleep apnoea; TIA = transient ischaemic attack.

Table 8 CHA_2DS_2-VASc score[334]

CHA_2DS_2-VASc score Risk factors and definitions		Points awarded	Comment
C	**Congestive heart failure** Clinical HF, or objective evidence of moderate to severe LV dysfunction, or HCM	1	Recent decompensated HF irrespective of LVEF (thus incorporating HFrEF or HFpEF), or the presence (even if asymptomatic) of moderate-severe LV systolic impairment on cardiac imaging[335]; HCM confers a high stroke risk[336] and OAC is beneficial for stroke reduction.[337]
H	**Hypertension** or on antihypertensive therapy	1	History of hypertension may result in vascular changes that predispose to stroke, and a well-controlled BP today may not be well-controlled over time.[324] Uncontrolled BP - the optimal BP target associated with the lowest risk of ischaemic stroke, death, and other cardiovascular outcomes is 120 - 129/<80 mmHg.[338]
A	**Age 75 years or older**	2	Age is a powerful driver of stroke risk, and most population cohorts show that the risk rises from age 65 years upwards.[339] Age-related risk is a continuum, but for reasons of simplicity and practicality, 1 point is given for age 65 - 74 years and 2 points for age ≥75 years.
D	**Diabetes mellitus** Treatment with oral hypoglycaemic drugs and/or insulin or fasting blood glucose >125 mg/dL (7 mmol/L)	1	Diabetes mellitus is a well-established risk factor for stroke, and more recently stroke risk has been related to duration of diabetes mellitus (the longer the duration of diabetes mellitus, the higher the risk of thromboembolism[340]) and presence of diabetic target organ damage, e.g. retinopathy.[341] Both type 1 and type 2 diabetes mellitus confer broadly similar thromboembolic risk in AF, although the risk may be slightly higher in patients aged <65 years with type 2 diabetes mellitus compared to patients with type 1 diabetes mellitus.[342]
S	**Stroke**Previous stroke, TIA, or thromboembolism	2	Previous stroke, systemic embolism, or TIA confers a particularly high risk of ischaemic stroke, hence weighted 2 points. Although excluded from RCTs, AF patients with ICH (including haemorrhagic stroke) are at very high risk of subsequent ischaemic stroke, and recent observational studies suggest that such patients would benefit from oral anticoagulation.[343–345]
V	**Vascular disease** Angiographically significant CAD, previous myocardial infarction, PAD, or aortic plaque	1	Vascular disease (PAD or myocardial infarction) confers a 17 - 22% excess risk, particularly in Asian patients.[346–348] Angiographically significant CAD is also an independent risk factor for ischaemic stroke among AF patients (adjusted incidence rate ratio 1.29, 95% CI 1.08 - 1.53).[349] Complex aortic plaque on the descending aorta, as an indicator of significant vascular disease, is also a strong predictor of ischaemic stroke.[350]
A	**Age 65 – 74 years**	1	See above. Recent data from Asia suggest that the risk of stroke may rise from age 50 - 55 years upwards and that a modified CHA_2DS_2-VASc score may be used in Asian patients.[351,352]
Sc	**Sex category (female)**	1	A stroke risk modifier rather than a risk factor.[353]
Maximum score		**9**	

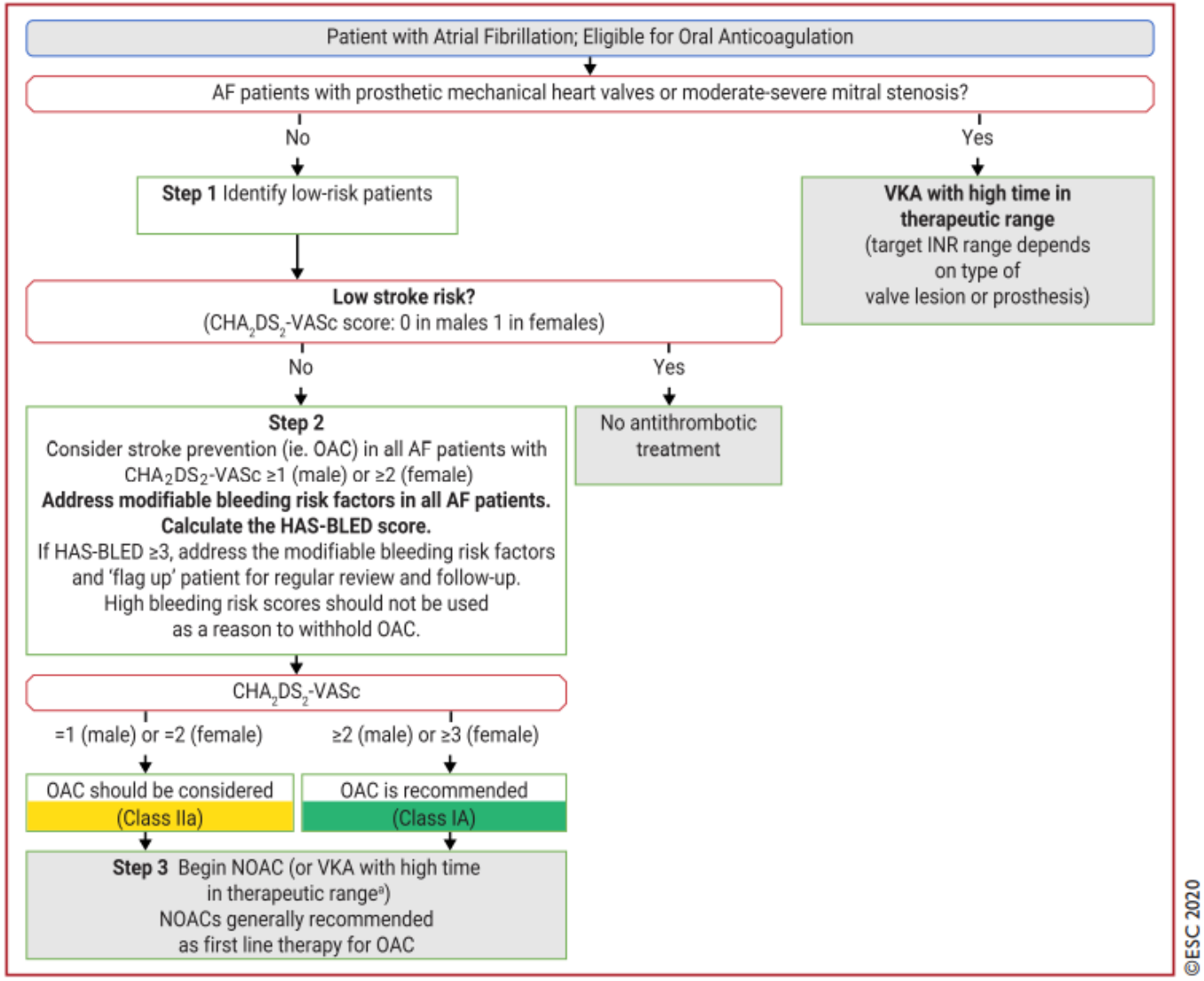


Figure 12 'A' - Anticoagulation/Avoid stroke: The 'AF 3-step' pathway. AF = atrial fibrillation; CHA_2DS_2-VASc = Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, Stroke, Vascular disease, Age 65 - 74 years, Sex category (female); HAS-BLED = Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile INR, Elderly (>65 years), Drugs/alcohol concomitantly; INR = international normalized ratio; NOAC = non-vitamin K antagonist oral anticoagulant; OAC = oral anticoagulant; SAMe-TT_2R_2 = Sex (female), Age (<60 years), Medical history, Treatment (interacting drug(s)), Tobacco use, Race (non-Caucasian) (score); TTR = time in therapeutic range; VKA = vitamin K antagonist.
[a]If a VKA being considered, calculate SAMe-TT_2R_2 score: if score 0–2, may consider VKA treatment (e.g. warfarin) or NOAC; if score >2, should arrange regular review/frequent INR checks/ counselling for VKA users to help good anticoagulation control, or reconsider the use of NOAC instead; TTR ideally >70%.

Patient Risks

Thrombotic Risk

Bleeding Risk

Table 10 Clinical risk factors in the HAS-BLED score[395]

Risk factors and definitions		Points awarded
H	**Uncontrolled hypertension** SBP >160 mmHg	1
A	**Abnormal renal and/or hepatic function** Dialysis, transplant, serum creatinine >200 µmol/L, cirrhosis, bilirubin > × 2 upper limit of normal, AST/ALT/ALP >3 × upper limit of normal	1 point for each
S	**Stroke** Previous ischaemic or haemorrhagic[a] stroke	1
B	**Bleeding history or predisposition** Previous major haemorrhage or anaemia or severe thrombocytopenia	1
L	**Labile INR[b]** TTR <60% in patient receiving VKA	1
E	**Elderly** Aged >65 years or extreme frailty	1
D	**Drugs or excessive alcohol drinking** Concomitant use of antiplatelet or NSAID; and/or excessive[c] alcohol per week	1 point for each
Maximum score		**9**

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; SBP = systolic blood pressure; INR = international normalized ratio; NSAID = Non-steroidal anti-inflammatory drug; TTR = time in therapeutic range; VKA = vitamin K antagonist.

[a]Haemorrhagic stroke would also score 1 point under the 'B' criterion.

[b]Only relevant if patient receiving a VKA.

[c]Alcohol excess or abuse refers to a high intake (e.g. >14 units per week), where the clinician assesses there would be an impact on health or bleeding risk.

Table 9 Risk factors for bleeding with OAC and antiplatelet therapy

Non-modifiable	Potentially modifiable	Modifiable	Biomarkers
Age >65 years	Extreme frailty ± excessive risk of falls[a]	Hypertension/elevated SBP	GDF-15
Previous major bleeding	Anaemia	Concomitant antiplatelet/NSAID	Cystatin C/CKD-EPI
Severe renal impairment (on dialysis or renal transplant)	Reduced platelet count or function	Excessive alcohol intake	cTnT-hs
Severe hepatic dysfunction (cirrhosis)	Renal impairment with CrCl <60 mL/min	Non-adherence to OAC	von Willebrand factor (+ other coagulation markers)
Malignancy	VKA management strategy[b]	Hazardous hobbies/occupations	
Genetic factors (e.g. CYP 2C9 polymorphisms)		Bridging therapy with heparin	
Previous stroke, small-vessel disease, etc.		INR control (target 2.0 - 3.0), target TTR >70%[c]	
Diabetes mellitus		Appropriate choice of OAC and correct dosing[d]	
Cognitive impairment/dementia			

CKD-EPI= Chronic Kidney Disease Epidemiology Collaboration; CrCl = creatinine clearance; cTnT-hs = high-sensitivity troponin T; CYP = cytochrome P; GDF-15 = growth differentiation factor-15; INR = international normalized ratio; NSAID = non-steroidal anti-inflammatory drug; OAC = oral anticoagulant; SBP = systolic blood pressure; TTR = time in therapeutic range; VKA = vitamin K antagonist.

[a]Walking aids; appropriate footwear; home review to remove trip hazards; neurological assessment where appropriate.

[b]Increased INR monitoring, dedicated OAC clinicals, self-monitoring/self-management, educational/behavioural interventions.

[c]For patients receiving VKA treatment.

[d]Dose adaptation based on patient's age, body weight, and serum creatinine level.

Bleeding Risk

- **A high bleeding risk score should not lead to withholding OAC**
  - the net clinical benefit of OAC is even greater amongst such patients.

- **Focusing attention on modifiable bleeding risk factors** that should be managed and (re)assessed at every patient contact

- **Identifying high-risk patients with non-modifiable** bleeding risk factors who should be reviewed earlier (for instance in 4 weeks rather than 4 - 6 months) and more frequently.

Bleeding Risk

- This is related to the fact that practitioners mostly worry about the risk of bleeding (as an **iatrogenic event**)
- whereas the risk of a stroke is often viewed as a possible **'natural course of the disease'.**
  - However, various large trials and observational series indicate that high-risk patients derive a particularly pronounced benefit from anticoagulation.
- **for patients -in contrast to physicians- the risk of stroke usually outweighs the risk of a bleed.**

Bleeding Risk

- **Bleeding risk is dynamic:**
  - Attention to **the change in bleeding risk** profile is a stronger predictor of major bleeding events compared with simply relying on baseline bleeding risk.
  - 3.5-fold higher risk of major bleeding in the **first 3 months** amongst patients who had a **change** in their bleeding risk profile.
  - A history of falls is not an independent predictor of bleeding on OAC
- A modelling study estimated that a patient would need to fall **295 times per year** for the benefits of ischemic stroke reduction with OAC to be outweighed by the potential for serious bleeding.

Consideration

Absolute contraindications to OAC

- Active serious bleeding (where the source should be identified and treated),
- Associated comorbidities:
  - severe thrombocytopenia <50 platelets/lL,
  - severe anemia under investigation
- Recent high-risk bleeding event such as intracranial hemorrhage (ICH).
- Non-drug options may be considered in such cases

Anticoagulant specifics

We choose a NOAC rather than warfarin

- More stroke prevention
- Decreased the rates of major bleeding and intracranial hemorrhage

NOAC dosing in AF patients post-ACS/PCI (see 'Patients with atrial fibrillation and coronary artery disease' section)

	Standard dose	Comments/dose reduction
Apixaban[244]	5 mg BID	Dose reduction as for SPAF
Dabigatran[247]	150 mg BID or 110 mg BID	110mg as for SPAF[403]
Edoxaban[245]	60 mg QD	Dose reduction as for SPAF
Rivaroxaban[246]	15 mg QD	Dose reduction to 10 mg QD if CrCl 30–49 mL/min

In addition to single/dual antiplatelet therapy, where applicable. See 'Patients with atrial fibrillation and coronary artery disease' section for details.
BID, twice daily; CrCl, creatinine clearance; QD, once daily; SPAF, stroke prevention in atrial fibrillation.

Blood Sampling interval

- **Including:**
  - **Hemoglobin**
  - **Renal function**
  - **liver function**

Time interval	patients
Yearly	In all patients except those below
4-monthly	• ≥75 years (especially if on dabigatran) • or frail

If renal function CrCl ≤60 mL/min:
CrCl/10= minimum recheck interval (in months).

Stroke prevention in atrial fibrillation (SPAF)

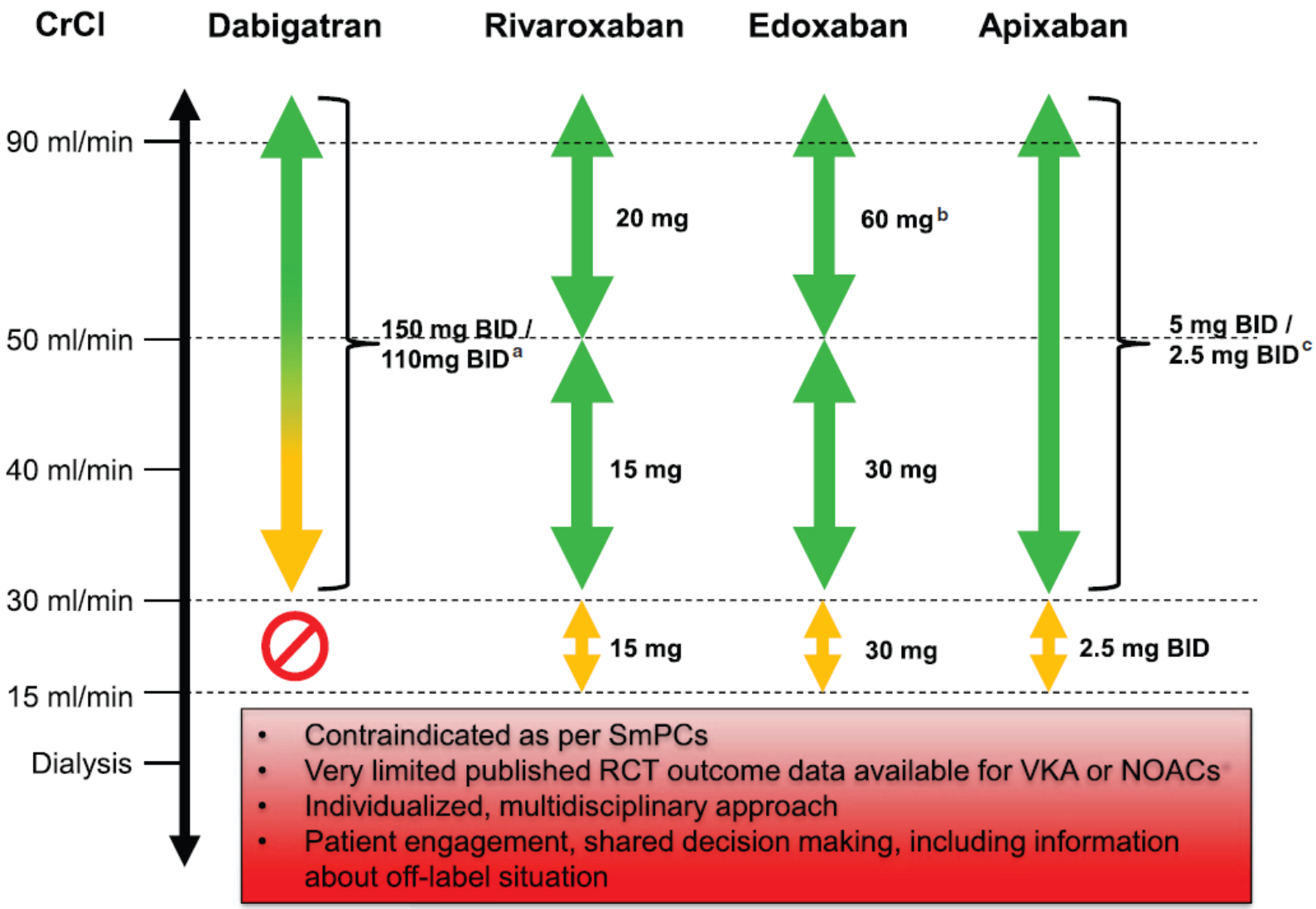
	Standard dose	Comments/dose reduction
Apixaban[47]	5 mg BID	2.5 mg BID if two out of three fulfilled: weight ≤60 kg, age ≥80 years, serum creatinine ≥133 µmol/L (1.5 mg/dL) (*or* single criterion: if CrCl 15–29 mL/min)
Dabigatran[48]	150 mg BID/110 mg BID	No pre-specified dose-reduction criteria in phase 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.

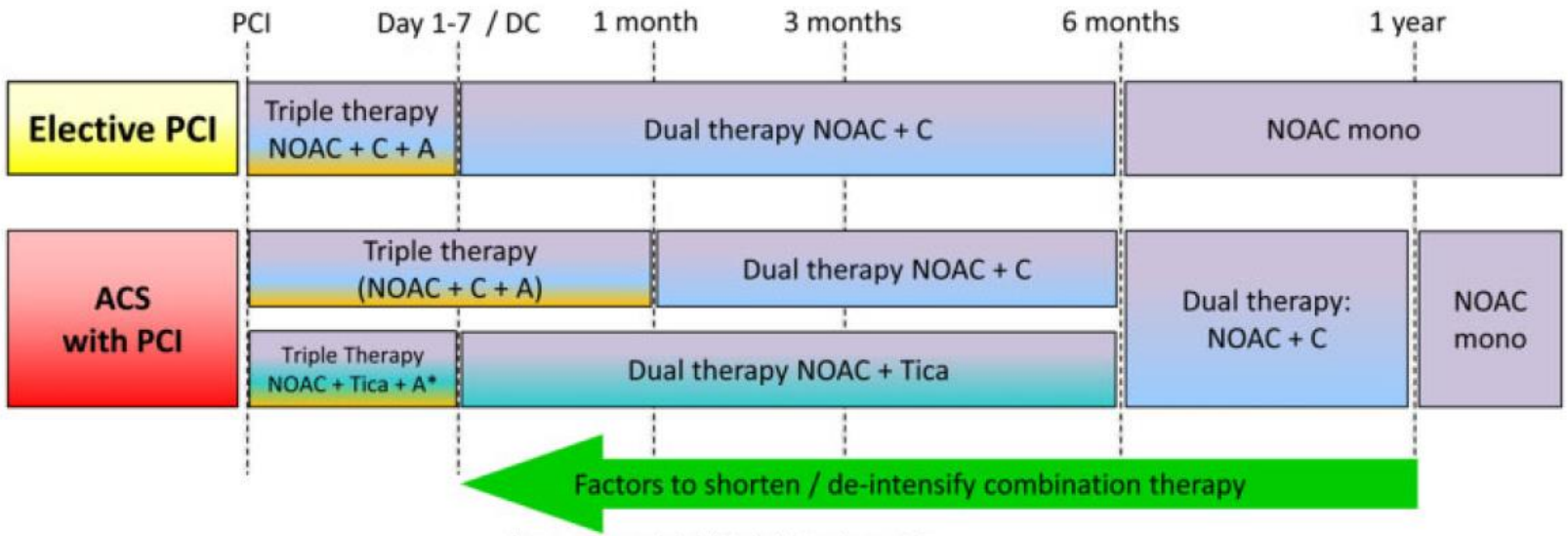
BID, twice daily; CrCl, creatinine clearance; GI, gastrointestinal; NOAC, non-vitamin K antagonist oral anticoagulant; QD, once daily.

[a]SmPC: 110 mg BID if age ≥80 years, concomitant verapamil, increased risk of GI bleeding.

Use of NOACs according to renal function



Anticoagulation therapy after elective PCI or ACS in patients with AF



In all patients:

- Avoid use of BMS / first generation DES
- Use PPI if on triple / dual therapy
- Minimize bleeding risk by assessing and treating modifiable bleeding risk factors (e.g., hypertension, etc.)
- Close follow-up; check for signs of (occult) bleeding

'Shorten/de-intensify':
e.g. discontinuing Aspirin or P_2Y_{12} inhibitor at an earlier stage.

'Lengthen/intensify':
e.g. continuing triple combinations longer, or continuing P_2Y_{12} inhibitor longer.

***A**: aspirin 75–100 mg QD;*
***C**: clopidogrel 75 mg QD;*
***Tica**: Ticagrelor 90 mg BID.*

If triple therapy needs to be continued after discharge clopidogrel is preferred over ticagrelor (due to lack of data).

Anticoagulant specifics

For patients taking warfarin

Whose **INR** has been relatively **easy to maintain** and who **prefer** to continue warfarin after having heard an explanation of the potential benefits of DOACs, it is reasonable to continue taking warfarin.

In these patients, consideration should be given to home monitoring of INR to reduce variability in INR.

Preferred INR: 2.0 to 2.5

CASE # 1

Our plan:

- Loading: ASA 300mg + ticagrelor 180mg
- Maintenance: ASA 80mg QD + ticagrelor 90mg BD
- After AF: + Apixaban 5mg BD
  - We had no extra plan for more intervention.
- On discharge: Ticagrelor 90mg BD +ASA 80mg Apixaban 5mg BD for1w then DC ASA

Time periods

Discharge to 12 months

After 12 months

Time periods

Discharge to 12 months

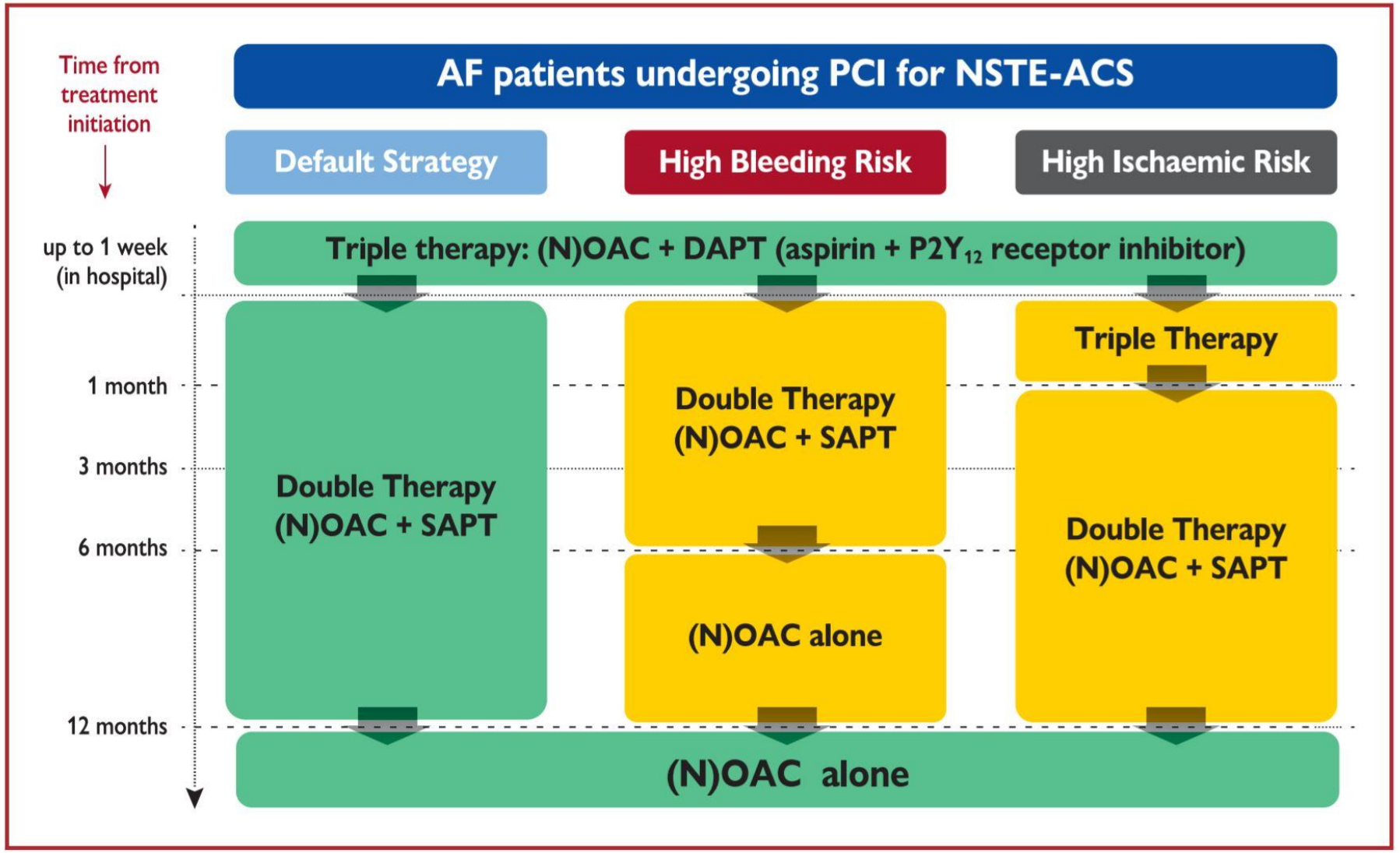
- We discharge patients on a direct-acting oral anticoagulant (DOAC) plus a P2Y12 inhibitor plus aspirin.
  - In most patients, we continue aspirin for **up to one week** based on how the randomized trials discussed below were carried out.
- During the 12 months, reevaluation:
  - **any new ischemic or bleeding episode**
  - **or change in bleeding risk**
- **At 12 months**, antithrombotic therapy should be reevaluated

Extended Therapy

After 12 months

- **NOAC monotherapy**
- **NOAC plus a single antiplatelet agent** (either aspirin or clopidogrel)
- In patients at the end of the spectrum where bleeding risk is high and ischemic risk is low, long-term NOAC monotherapy is reasonable.
- On the other hand, for patients at high ischemic risk and low bleeding risk, NOAC plus a single antiplatelet agent makes sense.

Acute management of elective PCI or ACS in AF patients treated with NOAC



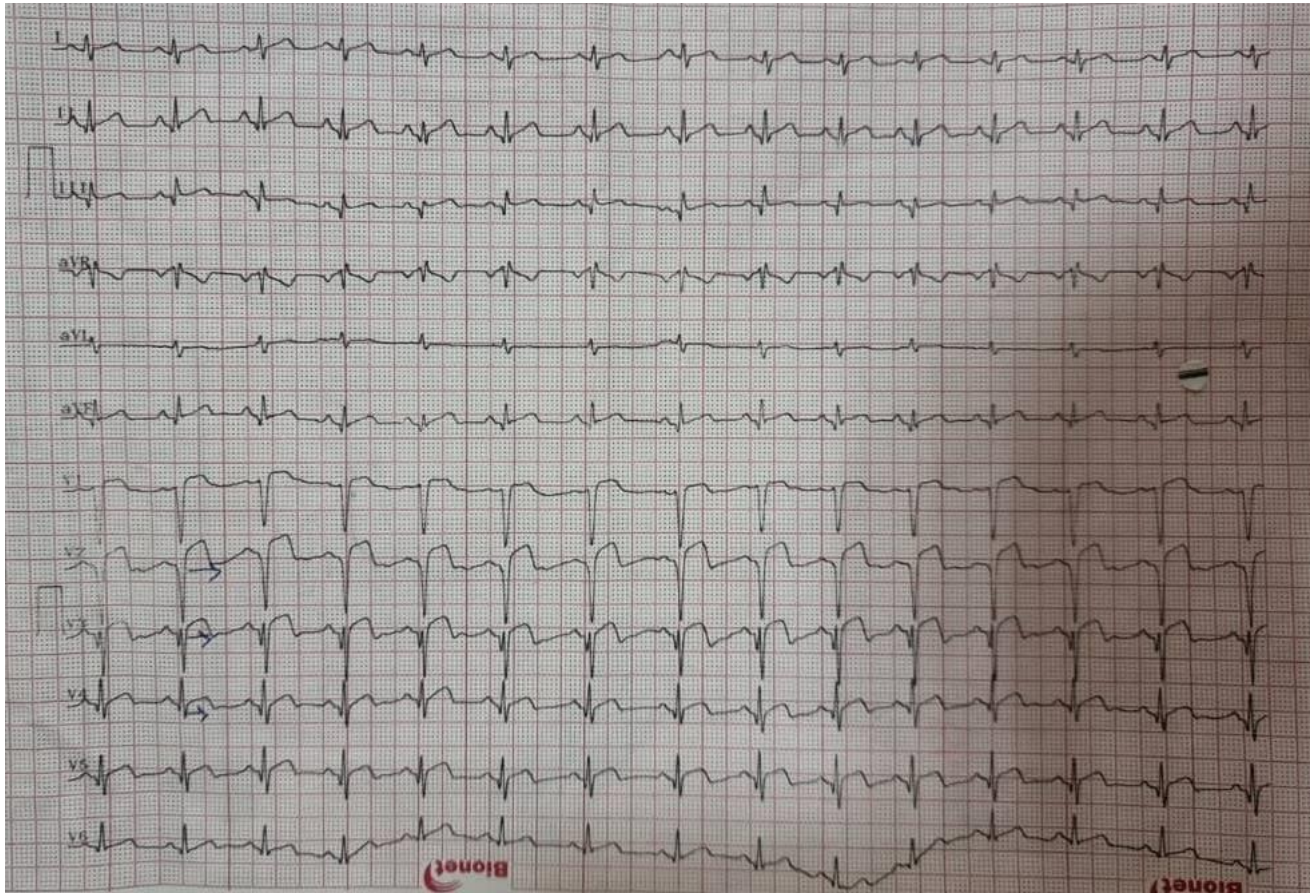
CASE # 2

Case Profile

- 42 yr./o man with intermittent chest pain in last three days.
- Acute ongoing CP from 8 hrs. ago
- RF: C/S
- ECG : ST elevation in precordial leads
- He was transferred to Cath Lab for Primary PCI.

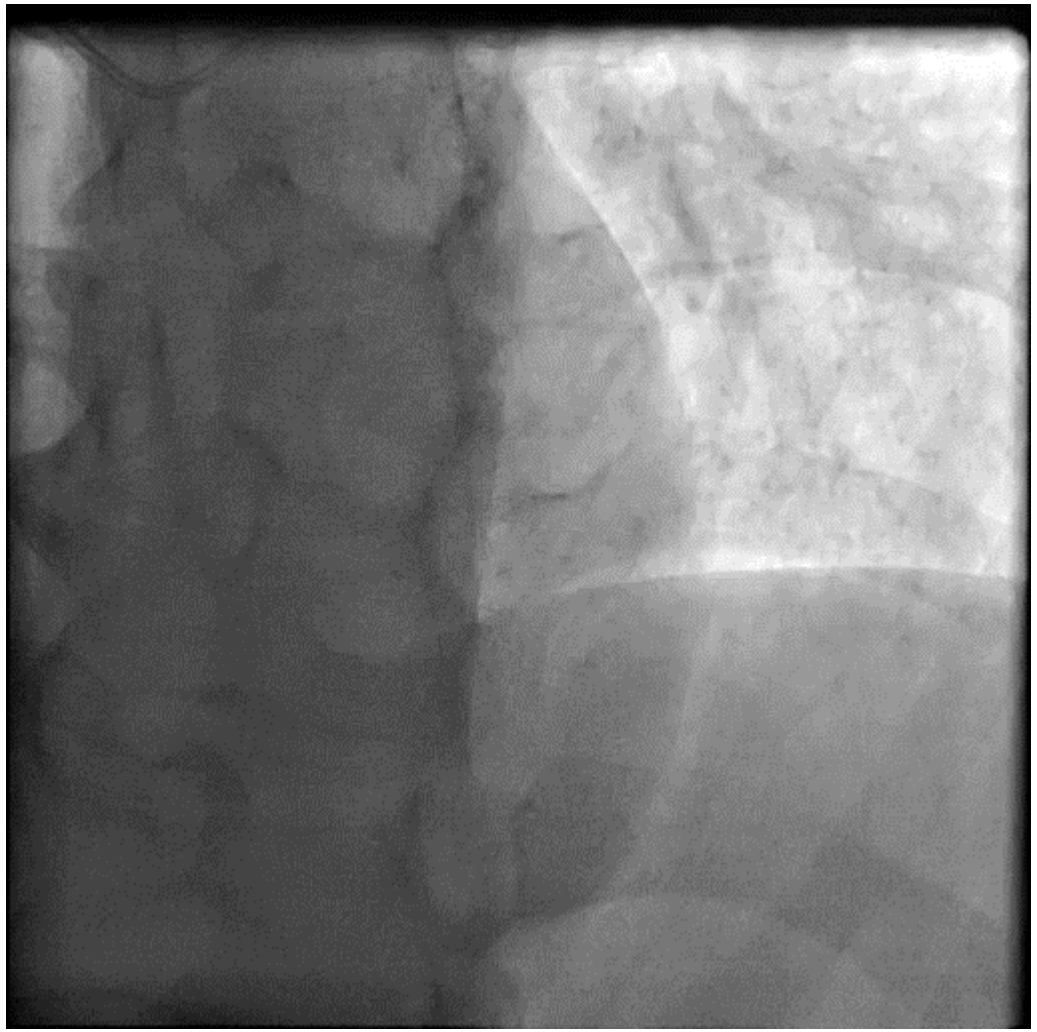
CASE # 2

ECG



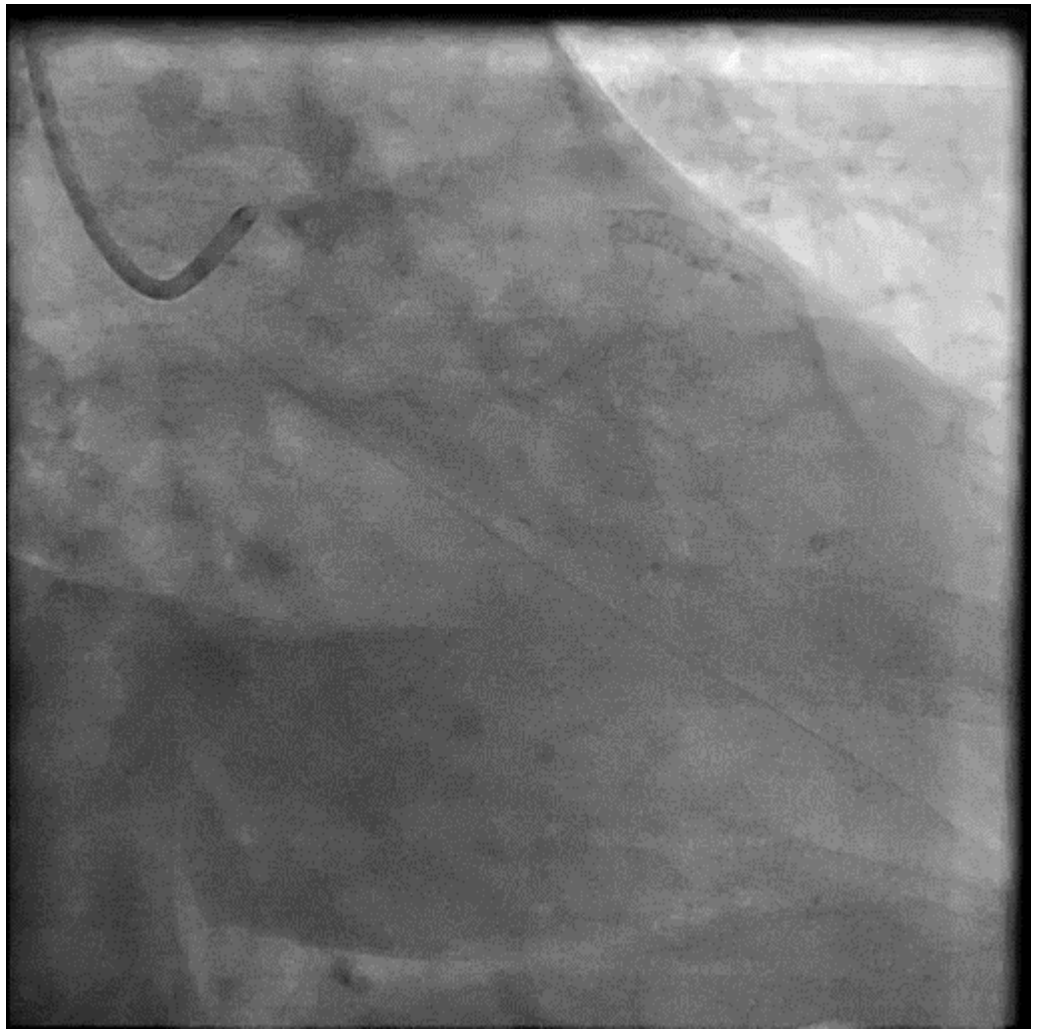
CASE # 2

Angiography



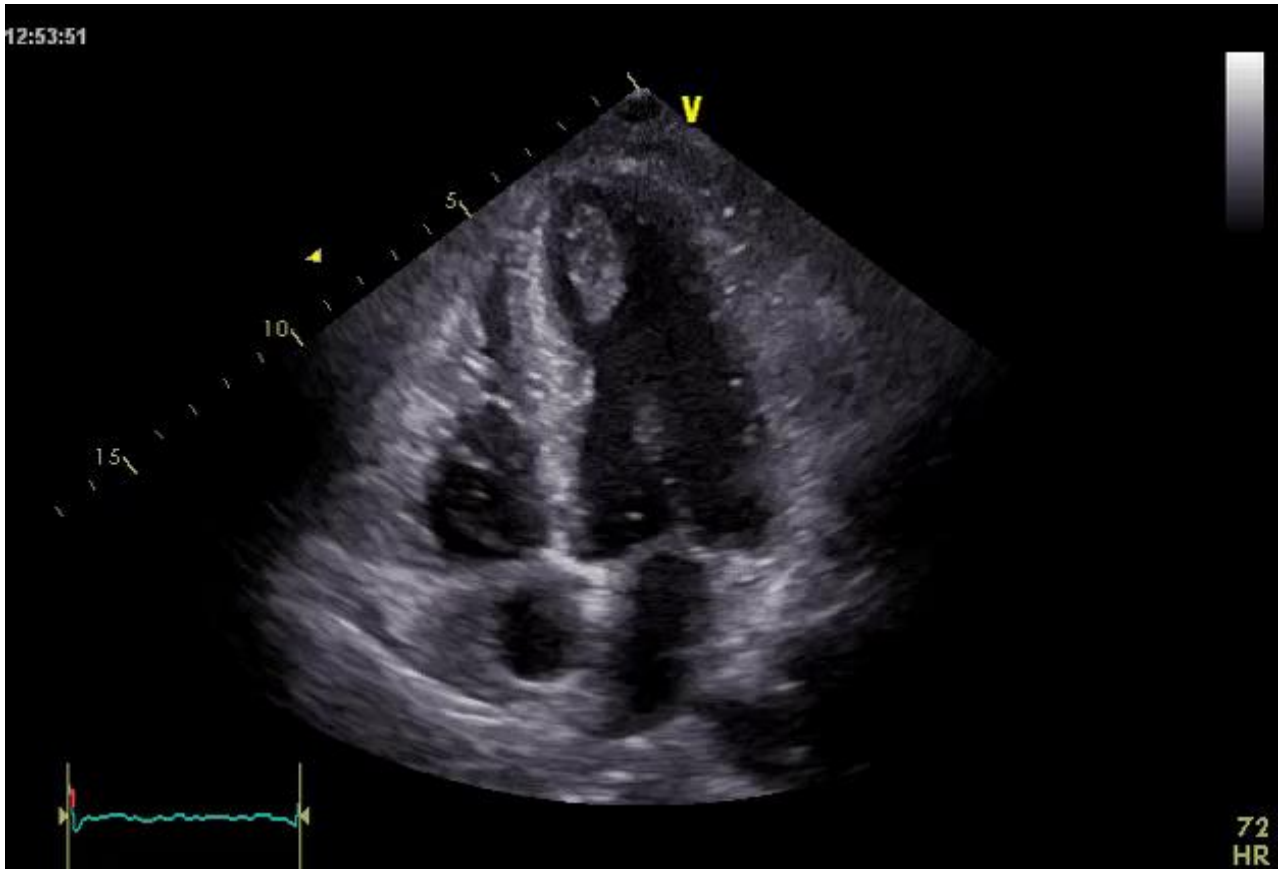
CASE # 2

PCI result



CASE # 2

Echocardiography on the third day:



CASE # 2

What is the best choice for antiplatelet?

1. ASA 300 mg + Clopidogrel 600 mg
2. ASA 300 mg + Ticagrelor 180 mg
3. ASA 80 mg + Ticagrelor 180 mg
4. Wait until we see the angiography

CASE # 2

What is your plan for anticoagulation?

Anticoagulant:

1. Heparin and warfarin
2. Heparin and apixaban
3. Just NOAC:

Antiplatelet :

1. Continue ASA + Ticagrelor
2. Ticagrelor
3. ASA + Clopidogrel
4. Clopidogrel

INCIDENCE

— Over the past 30 years, the incidence of LV thrombus has decreased as the frequency of early reperfusion therapies has increased. The likely mechanism is that early reperfusion, compared with no or late reperfusion, leads to smaller infarction [1-12]. Its impact may be greatest in patients with anterior infarctions, which tend to be larger than infarcts at other locations. (See 'Pathophysiology' above.)

The incidence of LV thrombi in the prereperfusion era was reported to be as high as 40 percent in patients with anterior infarction [4,7]. Most thrombi developed within the first two weeks (median five to six days) after MI [3,4,7,10,11]. In a series of 30 patients with LV thrombus after an acute anterior MI, 27 percent were present at less than 24 hours, 57 percent at 48 to 72 hours, 75 percent at one week, and 96 percent at two weeks [5].

Data are more limited on the incidence of LV thrombus in the reperfusion era. In two series of ST-elevation MI (STEMI) patients treated with primary percutaneous coronary intervention, the incidence of LV thrombus was about 4 percent [13,14].

However, the true incidence of LV thrombus in the current reperfusion era may be higher than in the above studies, as reported incidence depends on the sensitivity of the diagnostic test used. Cardiovascular magnetic resonance (CMR) imaging with late gadolinium enhancement (LGE) has been shown to be considerably more sensitive than transthoracic echocardiography (TTE) with or without an intravenous endocardial border definition contrast agent. In a study of 201 STEMI patients, of whom 199 were treated with reperfusion, who were evaluated with LGE-CMR, the incidence of LV thrombus was 8 percent [1].

Finally, some of these studies may have underestimated the true incidence, as patients at high risk for LV thrombus (severe heart failure and systolic blood pressure below 100 mmHg) were excluded. (See 'Diagnosis' below.)

SUMMARY AND RECOMMENDATIONS

- Left ventricular (LV) thrombus is a major cause of embolic stroke after acute myocardial infarction (MI). Patients with large anterior MI are at the highest risk for the development of LV thrombi; these patients usually have an LV ejection fraction (LVEF) less than 30 percent and a severe anteroapical or basal inferolateral wall motion abnormality with aneurysm on an imaging study. (See 'Pathophysiology' above.)

- For patients at risk of LV thrombus, we obtain a transthoracic echocardiogram with echo contrast to screen for LV thrombus in those with an aneurysm. (See 'Diagnosis' above.)

- Our recommendations for the use of anticoagulation are as follows (see 'Prevention of embolic events' above):

    - For patients with MI and documented LV thrombus, we recommend anticoagulation (**Grade 1B**). Most of our contributors prefer direct-acting oral anticoagulants (DOAC; also referred to as non-vitamin K antagonist oral anticoagulants) to warfarin for prophylaxis for LV thrombus.

    - In patients treated with warfarin, parenteral anticoagulation with unfractionated heparin or low molecular weight heparin should be started as soon as possible and continued until effective oral anticoagulation has been achieved. Warfarin should be started soon after initiation of parenteral anticoagulation; the goal of therapy is an international normalized ratio of 2 to 3.

    - For patients with MI and no clear thrombus but an LVEF less than 30 with anteroapical or basal inferior/inferolateral wall akinesis/dyskinesis and aneurysm, we suggest prophylactic anticoagulation (**Grade 2C**).

      For patients with MI and an LVEF between 30 and 40 percent with a severe anteroapical hypokinesis on imaging but no dyskinesis or aneurysm or thrombus on imaging, we suggest not treating with prophylactic anticoagulation (**Grade 2C**).

      The relative benefits and risks of anticoagulation need to be weighed carefully in these two groups.

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Thrombosis Journal

RESEARCH Open Access

Warfarin versus direct oral anticoagulants for treating left ventricular thrombus: a systematic review and meta-analysis

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Abstract

Background: Left ventricular thrombus (LVT) is not uncommon and pose a risk of systemic embolism, which can be mitigated by adequate anticoagulation. Direct oral anticoagulants (DOACs) are increasingly being used as alternatives to warfarin for anticoagulation, but their efficacy and safety profile has been debated. We aim to compare the therapeutic efficacy and safety of DOACs versus warfarin for the treatment of LVT.

Methodology: We systematically searched PubMed/Medline, Google Scholar, Cochrane library, and LILCAS databases from inception to 14th August 2020 to identify relevant studies comparing warfarin and DOACs for LVT treatment and used the pooled data extracted from retrieved studies to perform a meta-analysis.

Results: We report pooled data on 1955 patients from 8 studies, with a mean age of 61 years and 59.7 years in warfarin and DOACs group, respectively. The pooled odds ratio for thrombus resolution was 1.11 (95% CI 0.51–2.39) on comparing warfarin to DOAC, but it did not reach a statistical significance ($p = 0.76$). The pooled risk ratio (RR) of stroke or systemic embolization and bleeding in patients treated with warfarin vs DOACs was 1.04 (95% CI 0.64–1.68; $p = 0.85$), and 1.15 (95% CI 0.62–2.13; $p = 0.57$), respectively; with an overall RR of 1.09 (95% CI 0.70–1.70; $p = 0.48$) for mortality.

Conclusions: DOACs appears to be non-inferior or at least as effective as warfarin in the treatment of left ventricular thrombus without any statistical difference in stroke or bleeding complications.

Keywords: Left ventricular thrombus, Warfarin, Anticoagulation, DOAC/NOAC, Relative risk

Apixaban vs. warfarin in patients with left ventricular thrombus: a prospective multicentre randomized clinical trial‡

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Aims Current guidelines recommend anticoagulation with a vitamin K antagonist to treat left ventricular (LV) thrombus after myocardial infarction (MI). Data on the use of direct oral anticoagulants (DOACs) in this setting are limited. The aim of the study was to assess the efficacy of apixaban vs. warfarin in treating LV thrombus after MI.

Methods and results We conducted a prospective, randomized, multicentre open-label clinical trial including patients with LV thrombus detected by 2D transthoracic echocardiography 1–14 days after acute MI. Thirty-five patients were enrolled in three medical centres; 17 patients were randomized to warfarin and 18 patients to apixaban. The primary outcome was the presence and size of LV thrombus 3 months after initiation of anticoagulation. Secondary outcomes were major bleeding, stroke or systemic embolism, re-hospitalization, and all-cause mortality. Mean LV thrombus size at enrolment was 18.5 mm × 12.3 mm in the warfarin group and 19.9 mm × 12.4 mm in the apixaban group (P = NS). Thirty-two patients completed 3 months follow-up. In the warfarin group, two patients withdrew, and in the apixaban group one patient died. Thrombus completely resolved in 14 of 15 patients in the warfarin group and in 16 of 17 patients in the apixaban group (P = NS and $P = 0.026$ for non-inferiority). Two patients had major bleeding in the warfarin group, while no major bleeding events were recorded in the apixaban group. There was one stroke in the warfarin group and one death in the apixaban group.

Conclusion Our results suggest that apixaban is non-inferior to warfarin for treatment of patients with LV thrombus after acute MI with a 20% non-inferiority margin.

CASE # 2

Our plan:

- Loading: ASA 300mg + ticagrelor 180mg
  - Maintenance: ASA 80mg QD + ticagrelor 90mg BD
- After LV clot:
  - Apixaban for 2-4 weeks
    - If resolved we continue therapy
    - If not we switch to warfarin
  - De-escalation of Ticagrelor

Some points in NOACs

Treatment of DVT/PE

	Initial therapy	Remainder of treatment phase
Apixaban[498]	10 mg BID, 7 days	5 mg BID, no dose reduction
Dabigatran[499]	Heparin/LMWH	150 mg BID, no dose reduction[a]
Edoxaban[500]	Heparin/LMWH	60 mg QD, same dose reduction as for SPAF (see above)
Rivaroxaban[501,502]	15 mg BID, 21 days	20 mg QD, no dose reduction[b]

BID, twice daily; GI, gastrointestinal; LMWH, low molecular weight heparin; QD, once daily; SPAF, stroke prevention in atrial fibrillation.

[a]Per SmPC: 110 mg BID if age ≥80 years, concomitant verapamil, increased risk of GI bleeding [based on pharmacokinetic/pharmacodynamic (PK/PD) analyses; not studied in this setting].

[b]Per SmPc: 15 mg if risk of bleeding outweighs risk for recurrent DVT and PE (based on PK/PD analyses; not studied in this setting).

Long-term prevention of recurrent DVT/PE

	Standard dose	Comments/dose adjustment
Apixaban[503]	2.5 mg BID	
Dabigatran[504]	150 mg BID	No pre-specified dose-reduction criteria in clinical trial[a]
Edoxaban[473,500,505]	60 mg QD[b]	
Rivaroxaban[506]	10 mg QD	[c]

BID, twice daily; QD, once daily.

[a]SmPC: 110 mg BID if age ≥80 years, concomitant verapamil (both based on pharmacokinetics/pharmacodynamics analyses; not studied in this setting).

[b]Not specifically studied, follow-up data available up to 12 months in phase III trial.

[c]SmPc: 20 mg QD in patients at high risk of recurrence.

NOACs after coronary artery bypass grafting

- In patients **without AF**, dual antiplatelet therapy (**DAPT**) is frequently administered to patients following coronary artery bypass grafting (CABG), as it has been associated with:
  - improved vein graft patency
  - reduced mortality (weak level of evidence).
- In patients with concomitant AF, the combination of a single antiplatelet agent (aspirin or clopidogrel) with a NOAC appears reasonable
  - But in contrast to patients after percutaneous coronary intervention (PCI)/acute coronary syndrome (ACS) randomized trial evidence is not available.
- One year post-CABG, NOACs may be continued as monotherapy, similar to other patients with chronic coronary syndrome (CCS).

NOAC use in post-operative AF

- Post-operative AF is common following cardiac surgery, with incidences reported as high as 20–50%.
- The 2020 ESC AF guidelines indicate that long-term OAC therapy may be considered in patients at risk for stroke with (newly developed) postoperative AF after cardiac surgery (**Class IIb**, level of evidence B),
  - since both the short- and long-term risk of stroke may be substantially elevated in such patients

Covid-19 vaccination

- 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 (esp. in case of high stroke risk and QDNOAC);
  - In **BID** NOACs: re-start NOAC with the next scheduled dose.

APS

Patients with ‘non-valvular’ AF and antiphospholipid syndrome should be treated with **VKA** rather than NOACs, as a higher rate of thromboembolic events and major bleeding was observed with rivaroxaban vs. warfarin in these patients

Missed Dose

- A forgotten dose may be taken until **half** of the dosing interval has passed.
- 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.

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)
  - in the presence of factors potentially prolonging the anticoagulant effect such as CKD.

Surgical Interventions

Table 12 Classification of elective surgical interventions according to bleeding risk

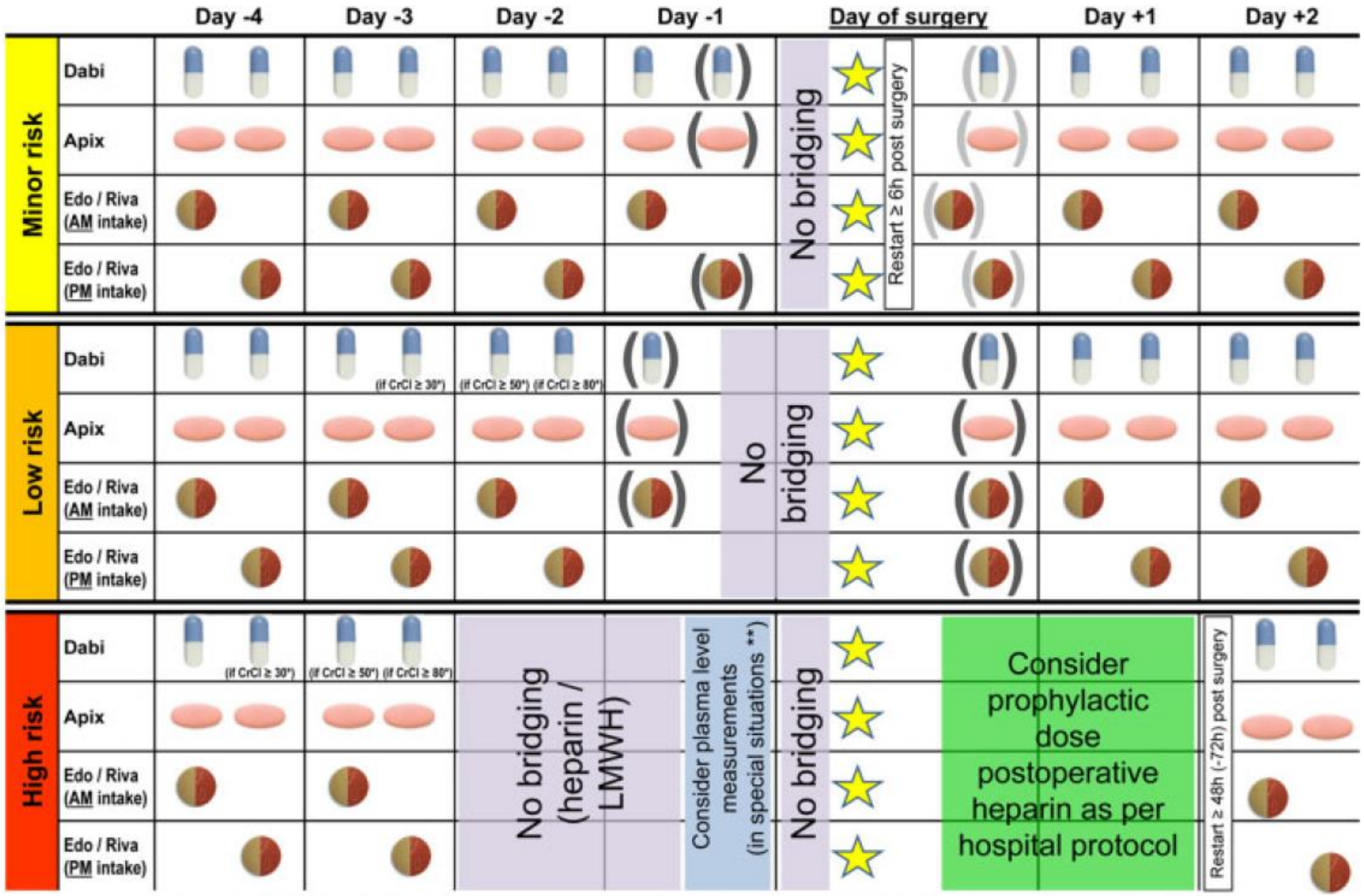
Minor risk interventions (i.e. infrequent bleeding and with low clinical impact)
Dental extractions (1–3 teeth), paradontal surgery, implant positioning, subgingival scalling/cleaning
Cataract or glaucoma intervention
Endoscopy without biopsy or resection
Superficial surgery (e.g. abscess incision; small dermatologic excisions, skin biopsy)
Pacemaker or ICD implantation (except complex procedures)
Electrophysiological study or catheter ablation (except complex procedures)
Routine elective coronary/peripheral artery intervention (except complex procedures)
Intramuscular injection (e.g. vaccination)
Low-risk interventions (i.e. infrequent bleeding or with non-severe clinical impact)
Complex dental procedures
Endoscopy with simple biopsy
Small orthopaedic surgery (foot, hand, arthroscopy, . . .)
High-risk interventions (i.e. frequent bleeding and/or with important clinical impact)
Cardiac surgery
Peripheral arterial revascularization surgery (e.g. aortic aneurysm repair, vascular bypass)
Complex invasive cardiological interventions, including lead extraction, (epicardial) VT ablation, chronic total occlusion PCI etc.
Neurosurgery
Spinal or epidural anaesthesia; lumbar diagnostic puncture
Complex endoscopy (e.g. multiple/large polypectomy, ERCP with sphincterotomy etc.)
Abdominal surgery (incl. liver biopsy)
Thoracic surgery
Major urologic surgery/biopsy (incl. kidney)
Extracorporeal shockwave lithotripsy
Major orthopaedic surgery

For each patient, individual factors relating to bleeding and thromboembolic risk need to be taken into account and be discussed with the operating physician and the patient (see *Figure 13*).

	Dabigatran		Apixaban - Edoxaban - Rivaroxaban	
No perioperative bridging with LMWH / UFH				
Minor risk procedures: - Perform procedure at NOAC trough level (i.e., 12 h / 24 h after last intake). - Resume same day or latest next day.				
	Low risk	**High risk**	**Low risk**	**High risk**
CrCl ≥80 ml/min	≥ 24 h	≥ 48 h	≥ 24 h	≥ 48 h
CrCl 50-79 ml/min	**≥ 36 h**	**≥ 72 h**		
CrCl 30-49 ml/min	**≥ 48 h**	**≥ 96 h**		
CrCl 15-29 ml/min	Not indicated	Not indicated	**≥ 36 h**	
CrCl <15 ml/min	No official indication for use			

Important:

- Timing of interruption may require adaptation based on individual patient characteristics (Fig. 13)
- In patients / situations with risk of NOAC accumulation (renal insufficiency, older age, concomitant medication, see Fig. 6) pausing the NOAC 12-24 hours earlier may be considered.[207,208]
- Resume full dose of NOAC 24h after low-risk- and 48 (-72) h after high-risk interventions



Important: Timing of interruption may require adaptation based on individual patient characteristics (Fig. 13)

Bridging

Based on prior experience with VKA, the very few very high-risk situations in which bridging may be discussed include urgent surgery with a high bleeding risk in patients with:

- a recent (<_3months) thromboembolic event (including stroke, systemic embolism or venous thrombosis/pulmonary embolism)
- suffered an event during previous adequate interruption of NOAC therapy

Switching

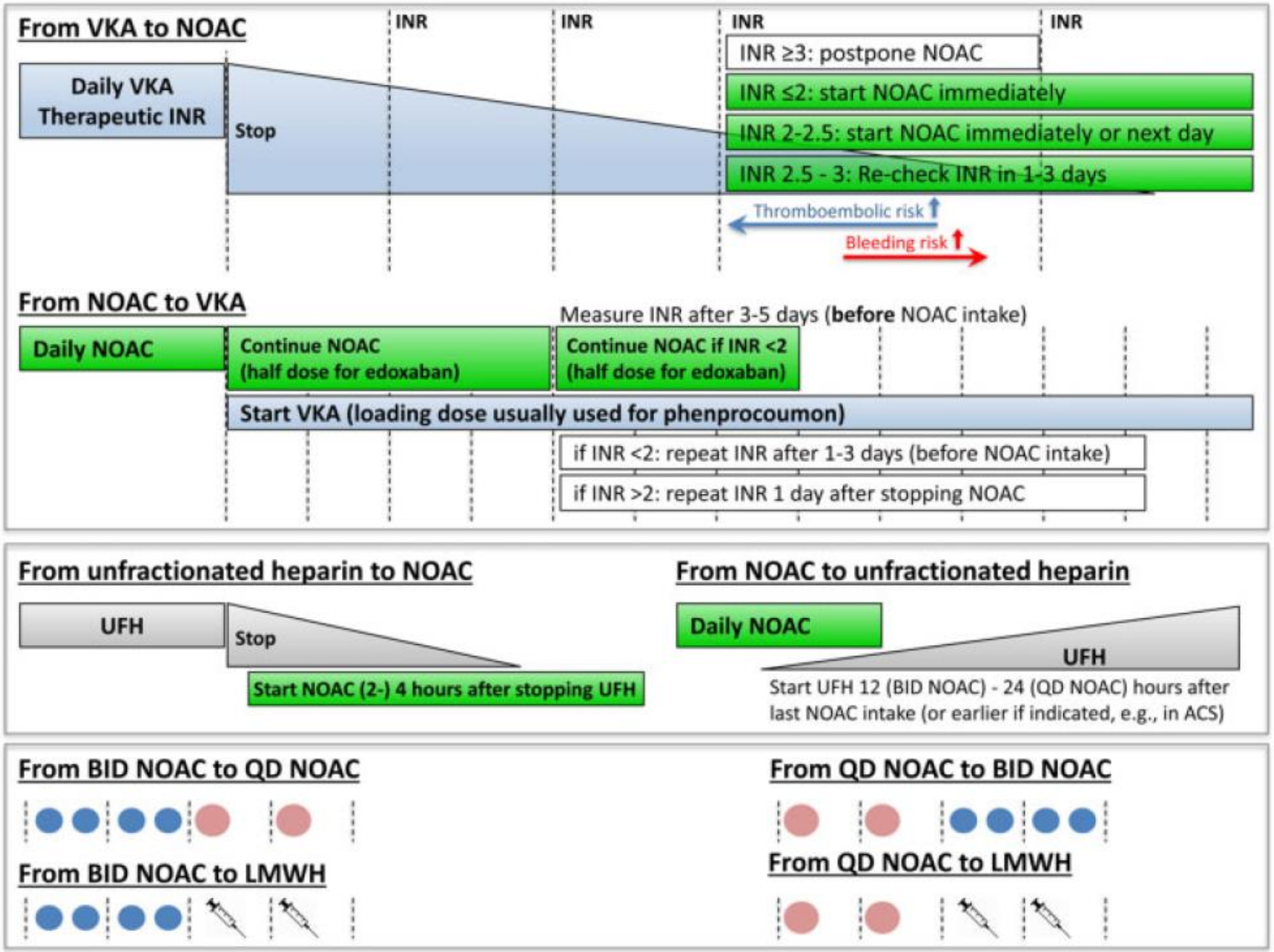

From VKA to NOAC
INR
INR
INR
INR
INR ≥3: postpone NOAC
Daily VKA Therapeutic INR
Stop
INR ≤2: start NOAC immediately
INR 2-2.5: start NOAC immediately or next day
INR 2.5 - 3: Re-check INR in 1-3 days
Thromboembolic risk
Bleeding risk
From NOAC to VKA
Measure INR after 3-5 days (before NOAC intake)
Daily 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

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]

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Thanks for Your Attention

Arvand Pharmed