How to deal with antiplatelet before non cardiac surgery

M.Hajikarimi

Interventional cardiologist

Assistant professor of QUMS

Algorithm for dual antiplatelet therapy (DAPT) in patients treated with percutaneous coronary intervention

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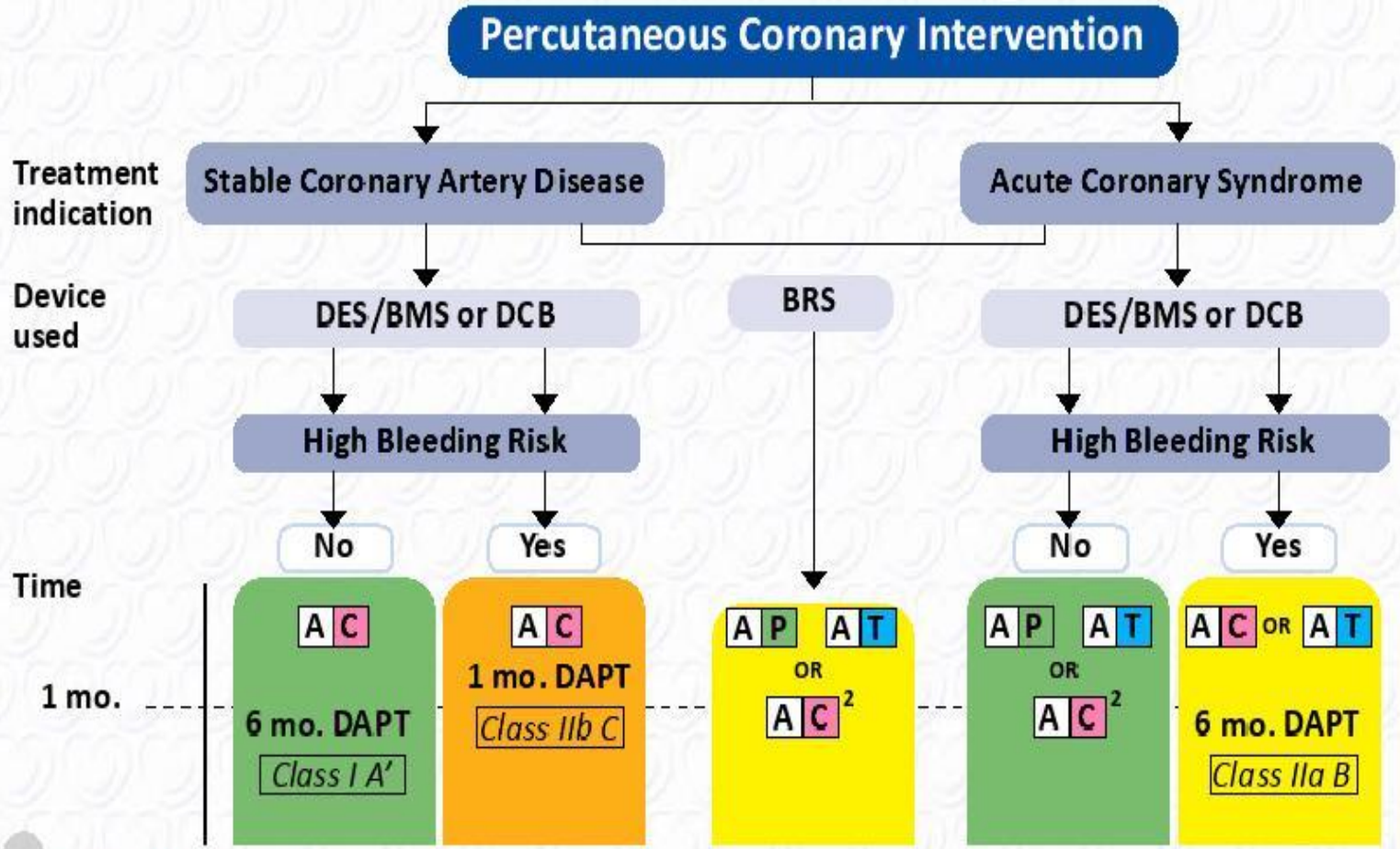

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Algorithm for dual antiplatelet therapy (DAPT) in patients treated with percutaneous coronary intervention

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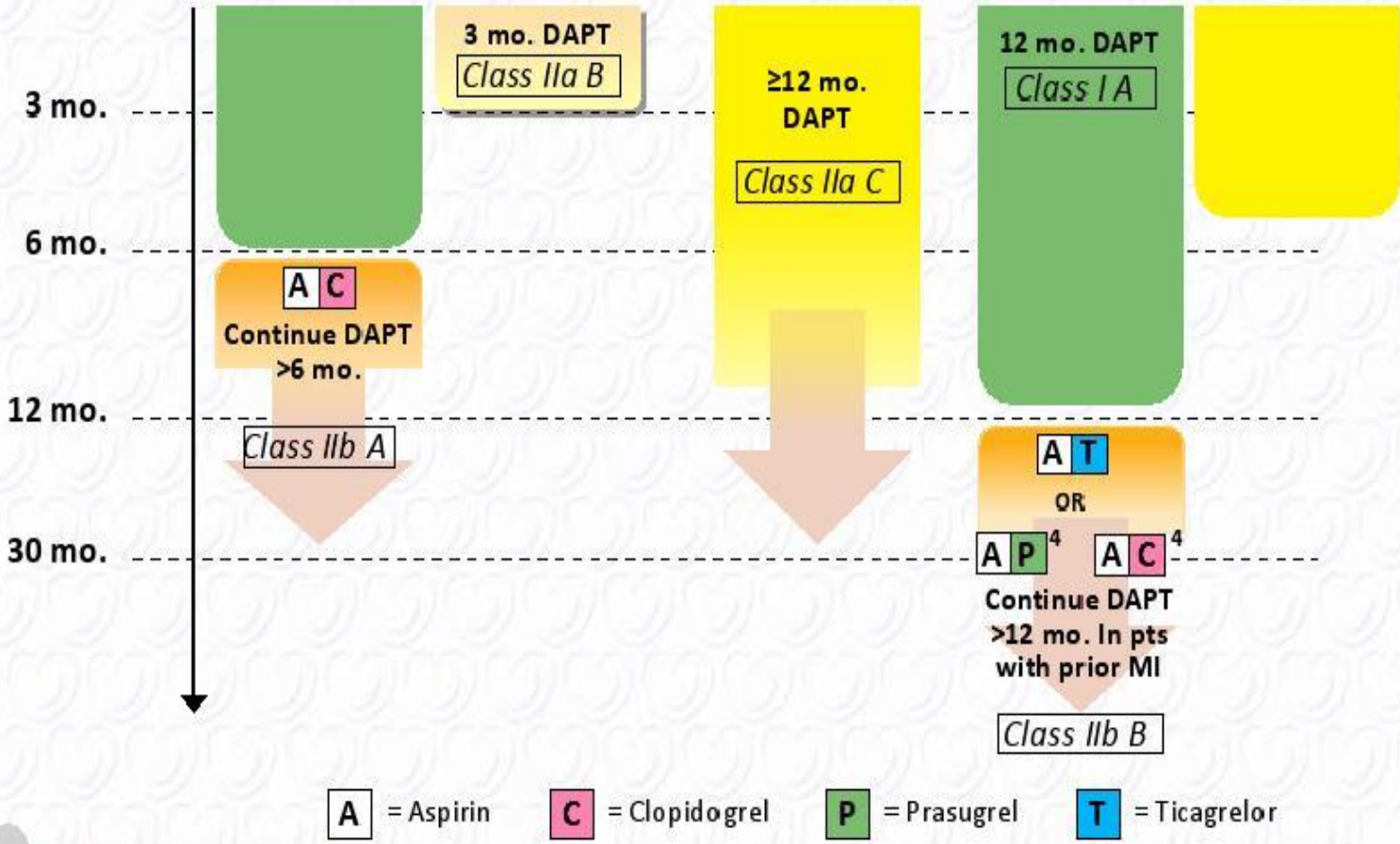

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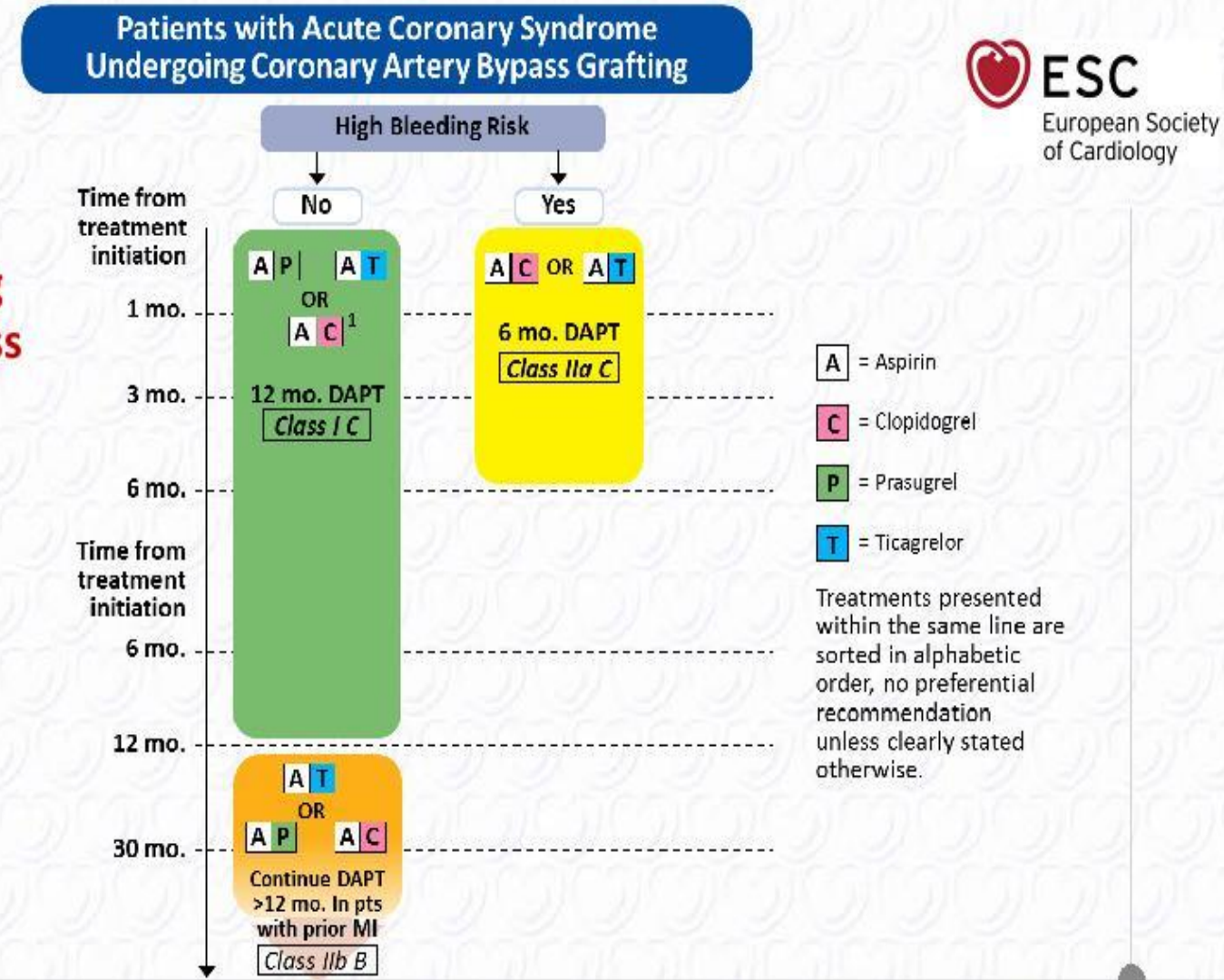
Algorithm for dual antiplatelet therapy (DAPT) in patients with acute coronary syndrome undergoing coronary artery bypass grafting



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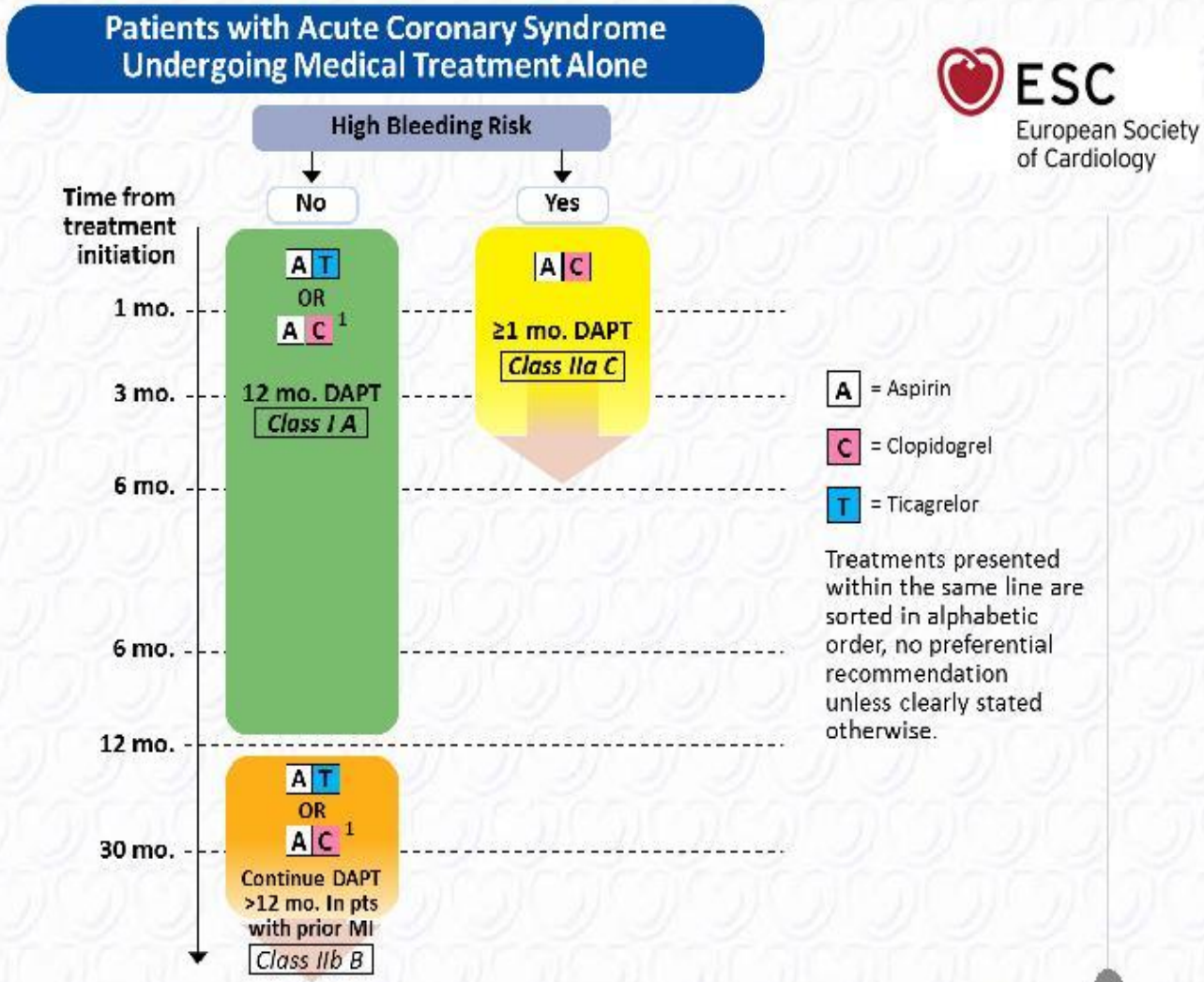
Algorithm for dual antiplatelet therapy (DAPT) in patients with acute coronary syndrome undergoing medical management



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Dual antiplatelet therapy in patients undergoing elective non-cardiac surgery

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Recommendations	Class	Level
It is recommended to continue aspirin perioperatively if the bleeding risk allows, and to resume the recommended antiplatelet therapy as soon as possible post-operatively.	I	B
After coronary stent implantation, elective surgery requiring discontinuation of the $P2Y_{12}$ inhibitor should be considered after 1 month, irrespective of the stent type, if aspirin can be maintained throughout the peri-operative period.	IIa	B
Discontinuation of $P2Y_{12}$ inhibitors should be considered at least 3 days before surgery for ticagrelor, at least 5 days for clopidogrel and at least 7 days for prasugrel.	IIa	B
A multidisciplinary expert team should be considered for pre-operative evaluation of patients with an indication for DAPT before elective surgery.	IIa	C

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Dual antiplatelet therapy in patients undergoing elective non-cardiac surgery *(continued)*

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Recommendations	Class	Level
In patients with recent MI or other high ischaemic risk features requiring DAPT, elective surgery may be postponed for up 6 to months.	IIb	C
If both oral antiplatelet agents have to be discontinued perioperatively, a bridging strategy with intravenous antiplatelet agents may be considered, especially if surgery has to be performed within 1 month after stent implantation.	IIb	C
It is not recommended to discontinue DAPT within the first month of treatment in patients undergoing elective non cardiac surgery.	III	B

Timing for elective non-cardiac surgery in patients treated with dual antiplatelet therapy (DAPT) after percutaneous coronary intervention (PCI)

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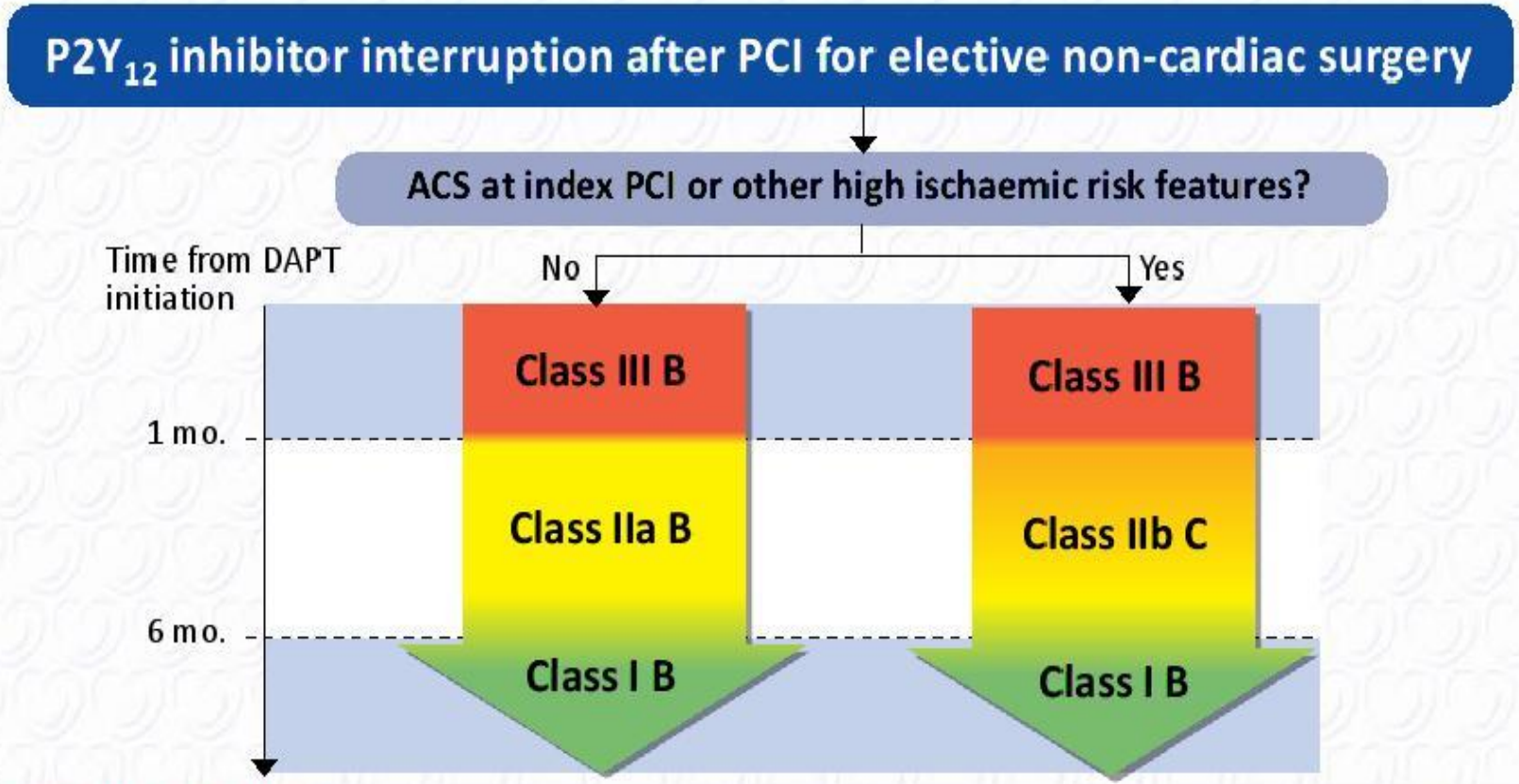

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Minimal discontinuation and re-implementation time frames of dual antiplatelet therapy (DAPT) for patients undergoing elective surgery

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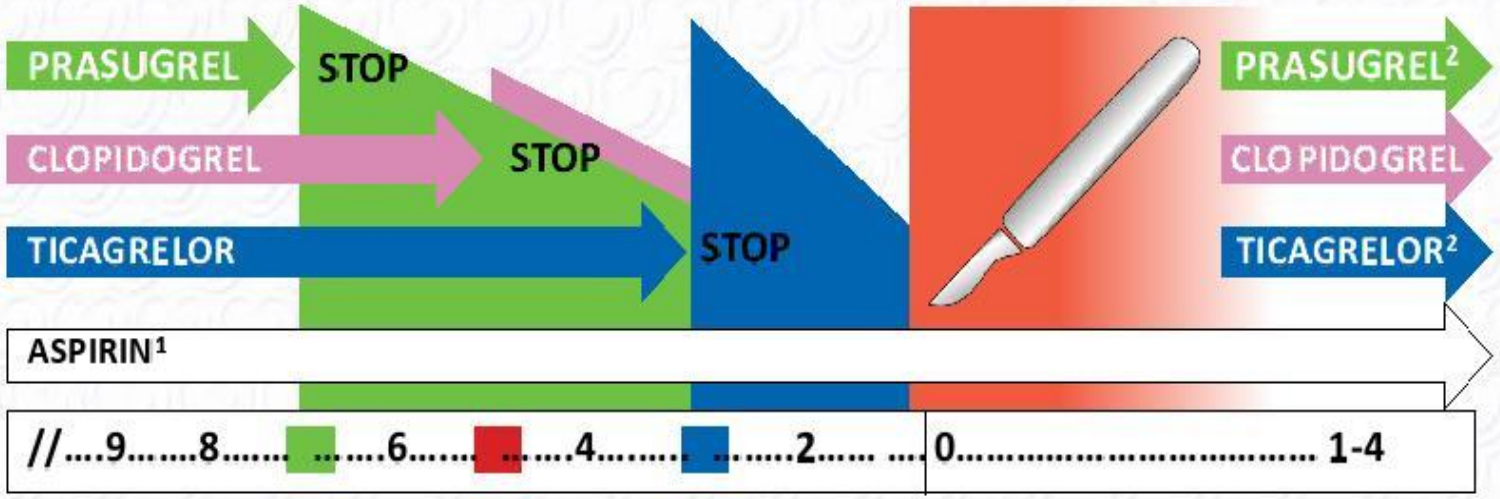

= Expected average platelet function recovery

[1] Decision to stop aspirin throughout surgery should be made on a single case basis taking into account the surgical bleeding risk.

[2] In patients not requiring OAC.

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Patients scheduled for both PCI and non cardiac surgery

- PCI should be base on evidence of clinically significant ischemia and size of the territory at risk
- In case where PCI can not be deferred and non cardiac surgery is urgent (< 30 days) POBA is reasonable
- When stenting is required new generation of DES is recommended

Non emergency non cardiac surgery during 12 months after PCI

- Defer planned non urgent surgery until at least 6 months after PCI
- When the risk of delaying surgery out weight the benefits minimal duration of DAPT was 4 weeks
- P2Y12 receptor blocker should be discountinued for as brief a period as possible
- ASA should be continued through the perioperative period
- Minor surgery and dental procedures usually donot require cession of antiplatelet drugs

Urgent or emergent non cardiac surgery

- We should consider the relative risks and benefits of continuing DAPT
- While platelet transfusion may be necessary for excessive bleeding after surgery , the role of prophylactic transfusion has not been well studied

Alternative to DAPT

- GP IIB/IIIA receptor blocker -> high risk of bleeding
- Parental anti coagulation don’t decrease the risk of stent thrombosis

Changing antiplatelet

Indication

- Post MI pericarditis
- Patients with ACS who expose with clopidogrel previously
- Change antiplatelet strategy base on HBR and ischemic score during one years after PCI
- Choice of antiplatelet strategy after 1 year PCI
- Triple therapy (antiplatelet and OAC)
- Antiplatelet co therapy with fibrinolysis

Recommendations for antiplatelet and anticoagulant therapy in acute coronary syndrome (2)

Recommendations	Class	Level
Antiplatelet therapy (continued)		
Clopidogrel (300–600 mg LD, 75 mg o.d. MD) is recommended when prasugrel or ticagrelor are not available, cannot be tolerated, or are contraindicated.	I	C
If patients presenting with ACS stop DAPT to undergo CABG, it is recommended they resume DAPT after surgery for at least 12 months.	I	C
Prasugrel should be considered in preference to ticagrelor for ACS patients who proceed to PCI.	IIa	B
GP IIb/IIIa receptor antagonists should be considered if there is evidence of no-reflow or a thrombotic complication during PCI.	IIa	C
In $P2Y_{12}$ receptor inhibitor-naïve patients undergoing PCI, cangrelor may be considered.	IIb	A
In older ACS patients, especially if HBR, clopidogrel as the $P2Y_{12}$ receptor inhibitor may be considered.	IIb	B

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Switching between oral $P2Y_{12}$ inhibitors

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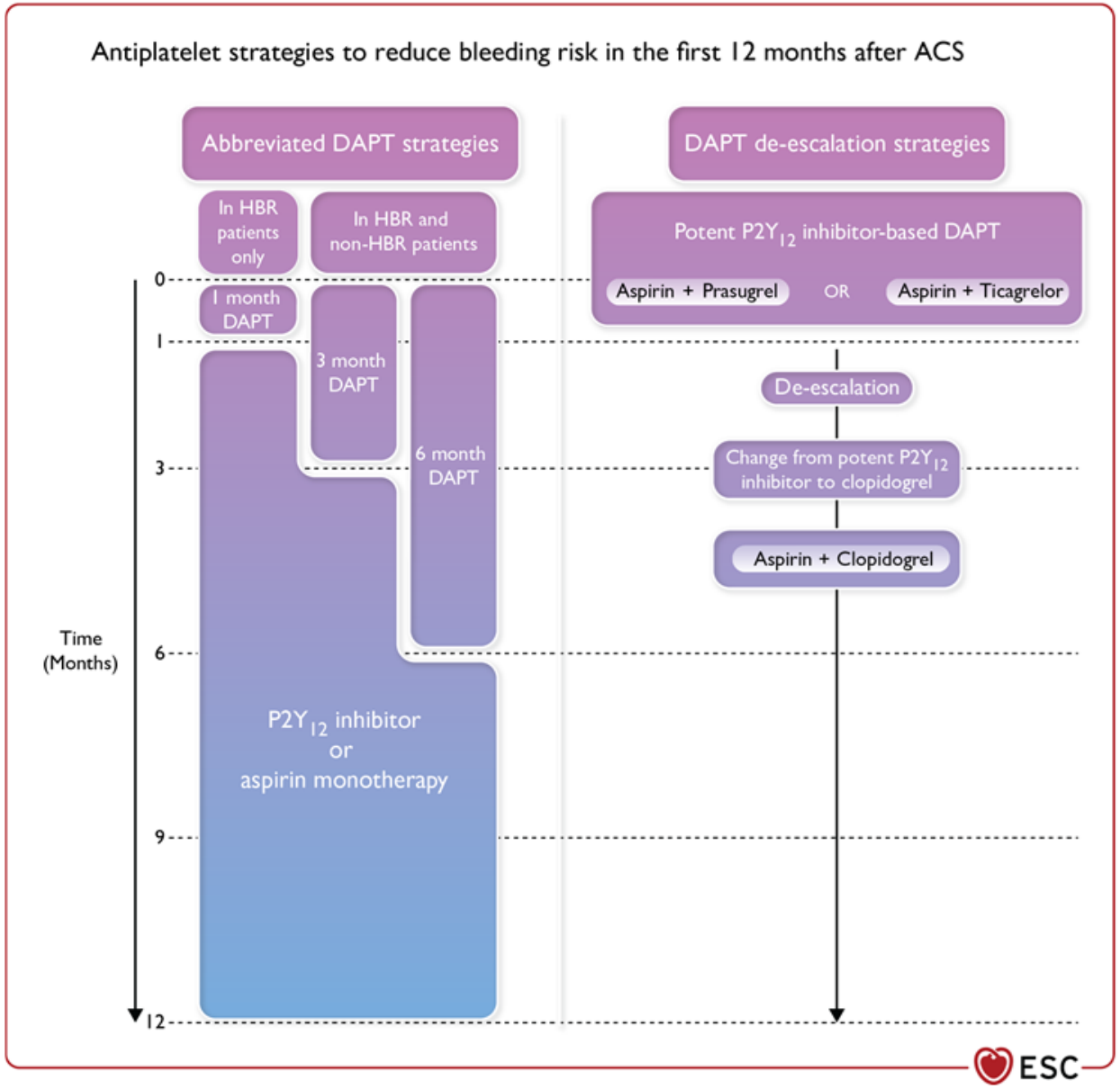
Recommendations	Class	Level
In patients with ACS who were previously exposed to clopidogrel, switching from clopidogrel to ticagrelor is recommended early after hospital admission at a loading dose of 180 mg irrespective of timing and loading dose of clopidogrel, unless contra-indications to ticagrelor exist.	I	B
Additional switching between oral $P2Y_{12}$ inhibitors may be considered in cases of side effects/drug intolerance according to the proposed algorithms.	IIb	C

Figure 11

Alternative antiplatelet strategies to reduce bleeding risk in the first 12 months after an ACS



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Recommendations for alternative antithrombotic therapy regimens (1)

Recommendations	Class	Level
Shortening/de-escalation of antithrombotic therapy		
In patients who are event-free after 3–6 months of DAPT and who are not high ischaemic risk, single antiplatelet therapy (preferably with a $P2Y_{12}$ receptor inhibitor) should be considered.	IIa	A
De-escalation of $P2Y_{12}$ receptor inhibitor treatment (e.g. with a switch from prasugrel/ticagrelor to clopidogrel) may be considered as an alternative DAPT strategy to reduce bleeding risk.	IIb	A
In HBR patients, aspirin or $P2Y_{12}$ receptor inhibitor monotherapy after 1 month of DAPT may be considered.	IIb	B
De-escalation of antiplatelet therapy in the first 30 days after an ACS event is not recommended.	III	B

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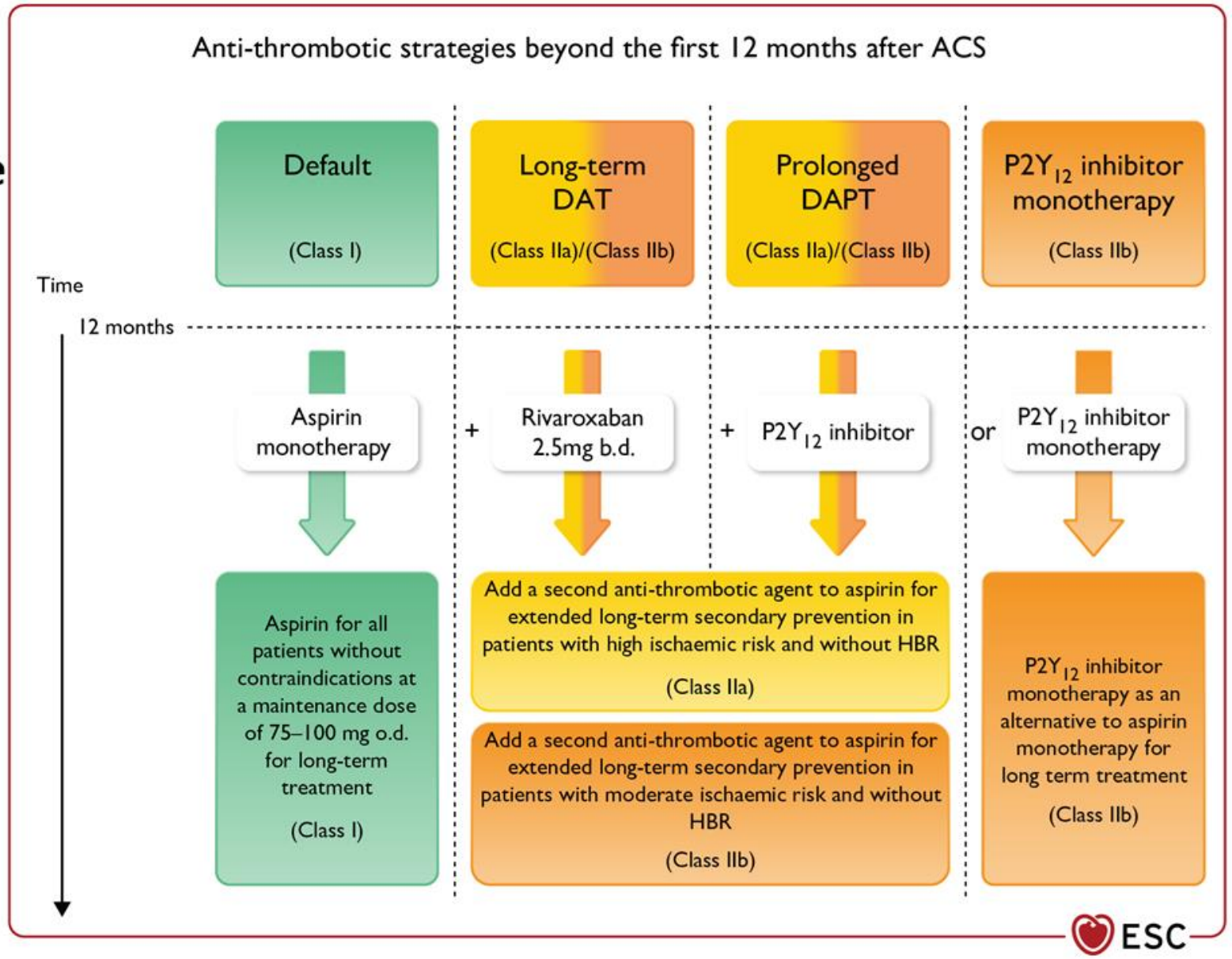
Figure S4

Antithrombotic strategies beyond the first 12 months after ACS



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Recommendations for alternative antithrombotic therapy regimens (2)

Recommendations	Class	Level
Prolonging antithrombotic therapy		
Discontinuation of antiplatelet treatment in patients treated with an OAC is recommended after 12 months.	I	B
Adding a second antithrombotic agent to aspirin for extended long-term secondary prevention should be considered in patients with high ischaemic risk and without HBR.	IIa	A
Adding a second antithrombotic agent to aspirin for extended long-term secondary prevention may be considered in patients with moderate ischaemic risk and without HBR.	IIb	A
$P2Y_{12}$ inhibitor monotherapy may be considered as an alternative to aspirin monotherapy for long-term treatment.	IIb	A

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Recommendations for antiplatelet and anticoagulant therapy in acute coronary syndrome (6)

Recommendations	Class	Level
Combining antiplatelets and OAC		
As the default strategy for patients with atrial fibrillation and CHA_2DS_2-VASc score ≥1 in men and ≥2 in women, after up to 1 week of triple antithrombotic therapy following the ACS event, dual antithrombotic therapy using a NOAC at the recommended dose for stroke prevention and a single oral antiplatelet agent (preferably clopidogrel) for up to 12 months is recommended.	I	A
During PCI, a UFH bolus is recommended in any of the following circumstances: - if the patient is on a NOAC - if the INR is <2.5 in VKA-treated patients.	I	C
In patients with an indication for OAC with VKA in combination with aspirin and/or clopidogrel, careful regulation of the dose intensity of VKA with a target INR of 2.0–2.5 and a time in the therapeutic range >70% should be considered.	IIa	B

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Recommendations for fibrinolytic therapy (1)

Recommendations	Class	Level
Fibrinolytic therapy		
When fibrinolysis is the reperfusion strategy, it is recommended to initiate this treatment as soon as possible after diagnosis in the pre-hospital setting (aim for target of <10 min to lytic bolus).	I	A
A fibrin-specific agent (i.e. tenecteplase, alteplase, or reteplase) is recommended.	I	B
A half-dose of tenecteplase should be considered in patients >75 years of age.	IIa	B
Antiplatelet co-therapy with fibrinolysis		
Aspirin and clopidogrel are recommended.	I	A

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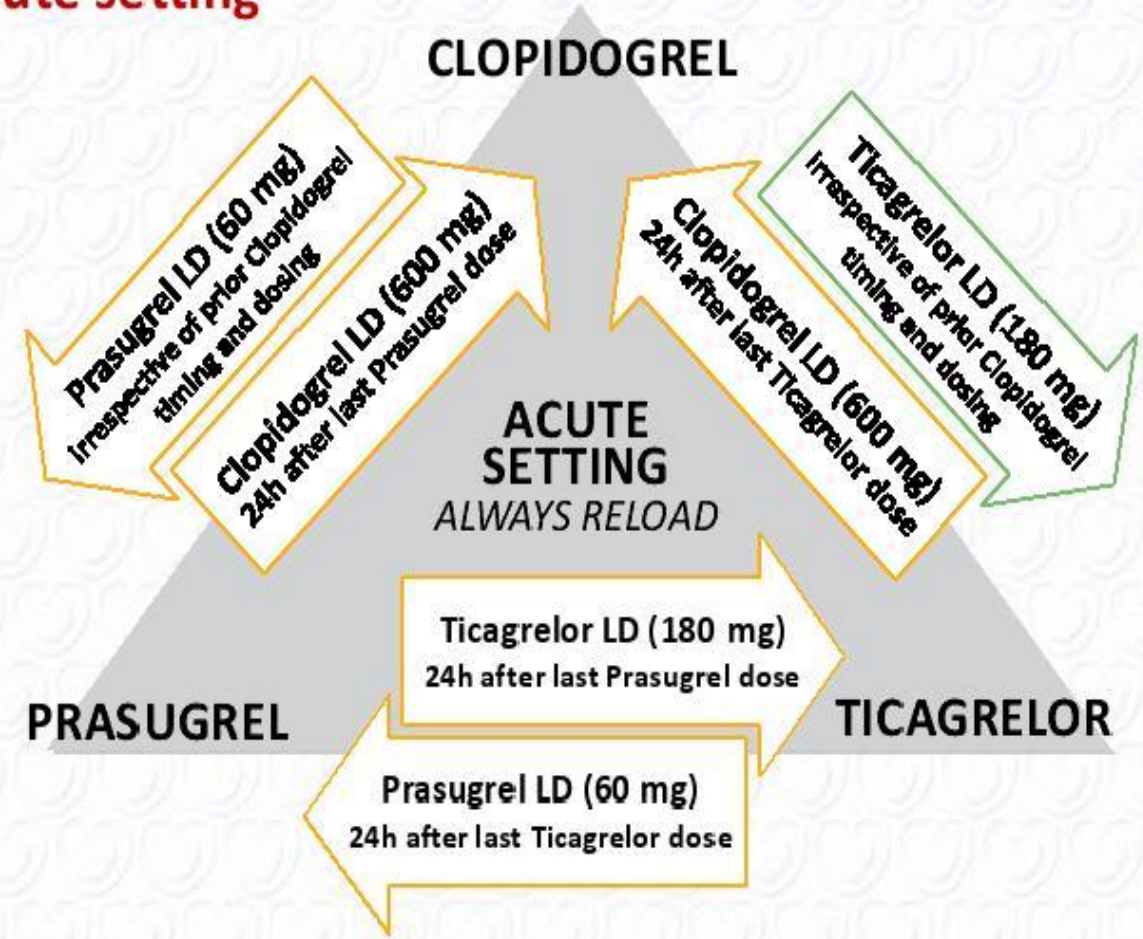
Algorithm for switching between oral $P2Y_{12}$ inhibitors in the acute setting



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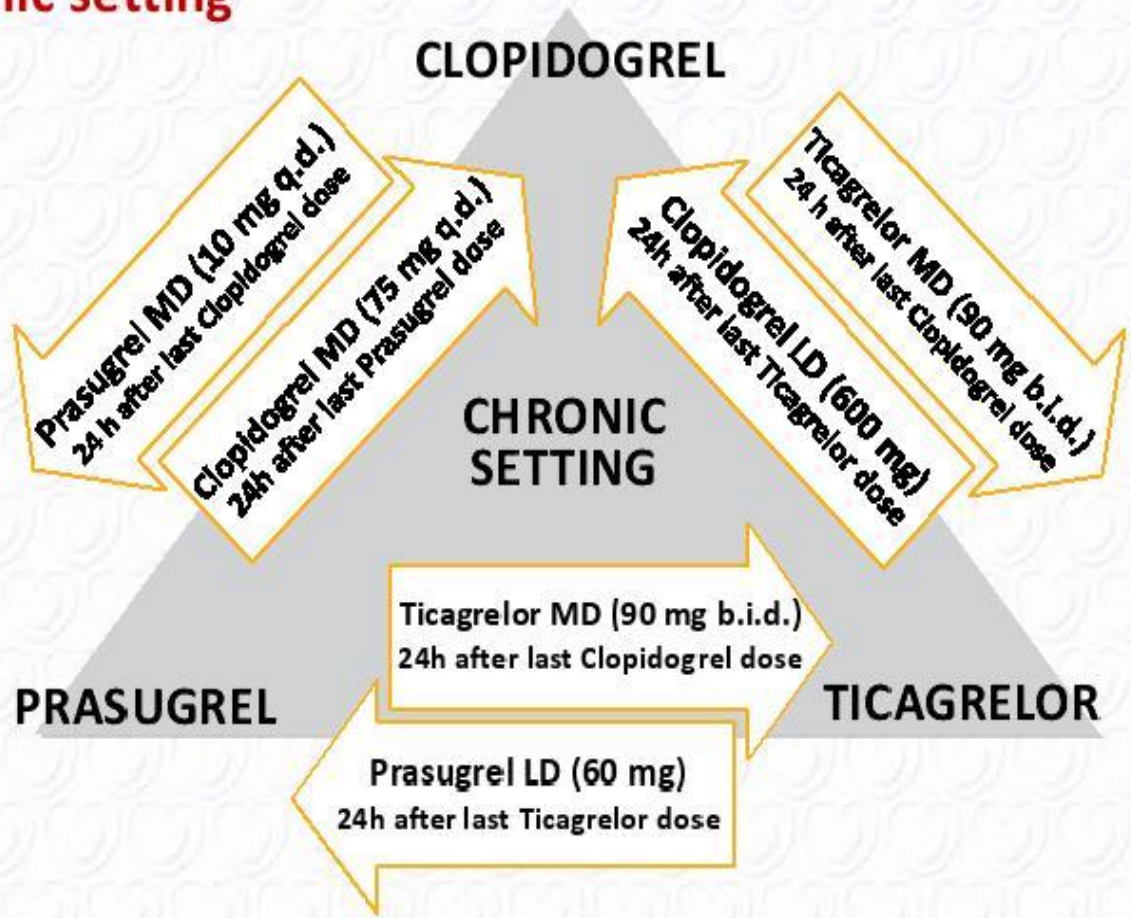
Algorithm for switching between oral $P2Y_{12}$ inhibitors in the chronic setting



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Transitioning between anticoagulants

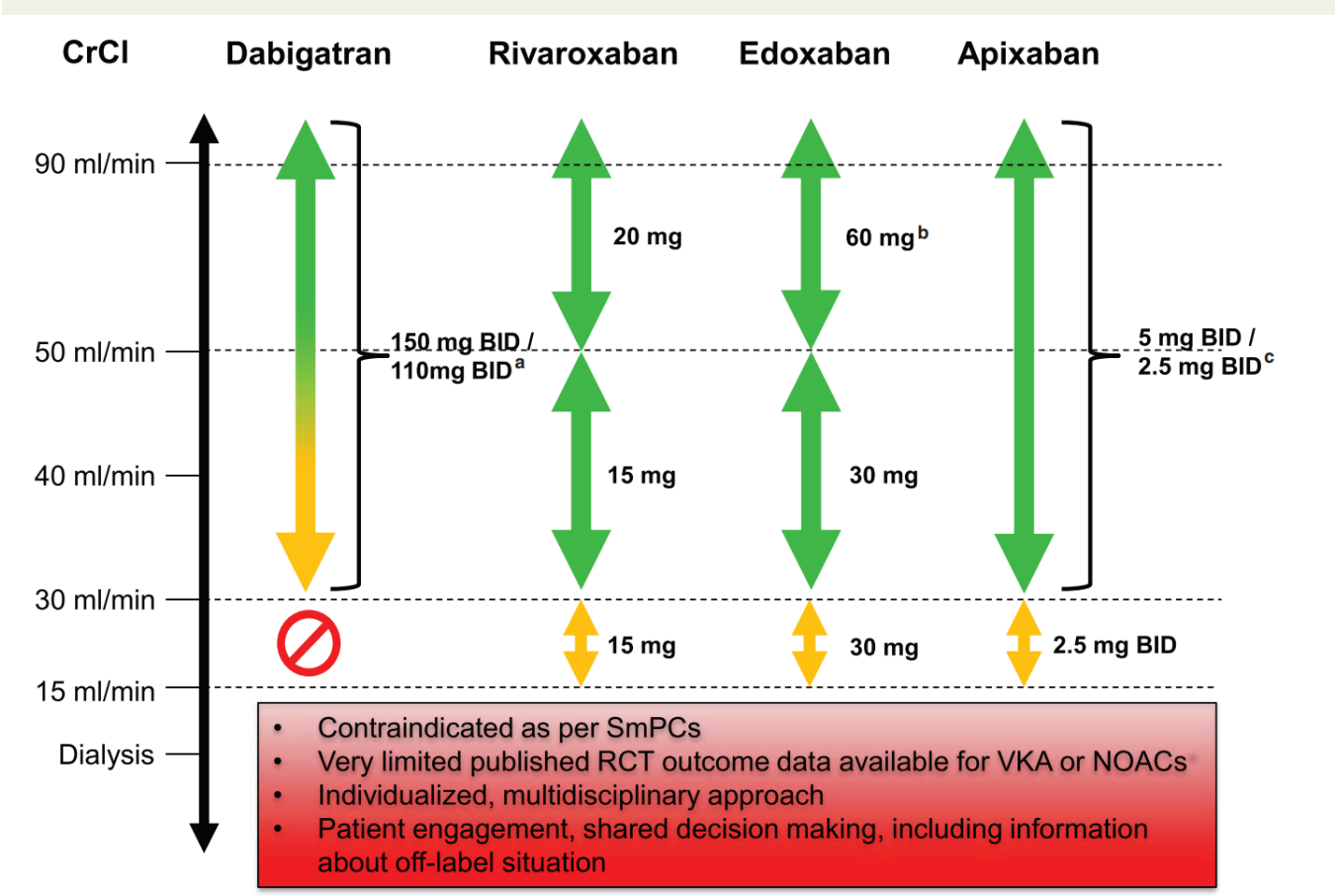
Indication

- Patient preference in suitable cases
- Availability
- Drug interaction
- pre pregnancy consult
- Acute coronary events
- Patient on dialysis or GFR <15
- Altered gastrointestinal anatomy
- Overweight or underweight

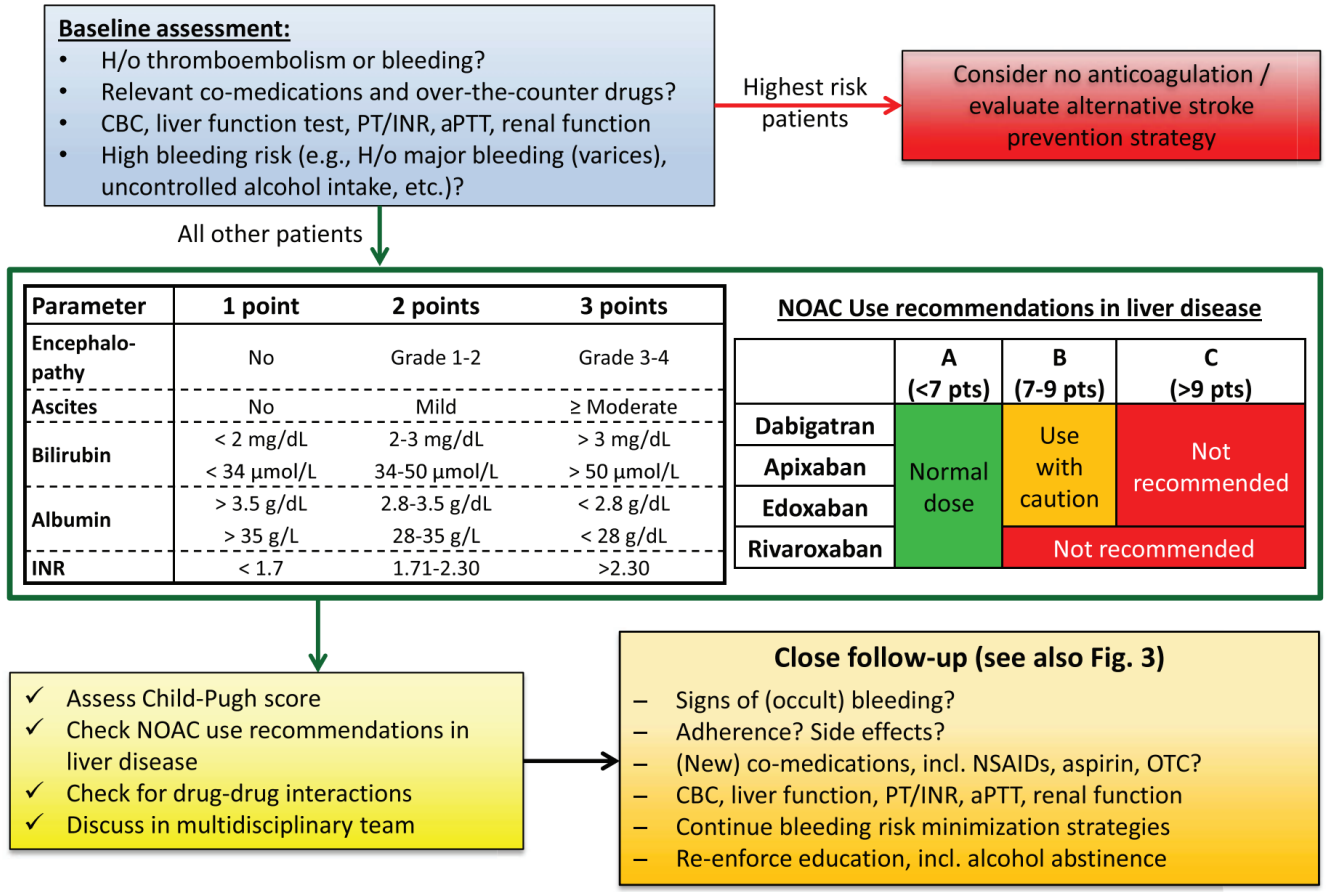
NOAC are not used in individuals with:

- Mechanical prosthetic heart valve
- Pregnancy
- Antiphospholipid syndrome
- Mitral stenosis(MVA less than 1.5) and AF

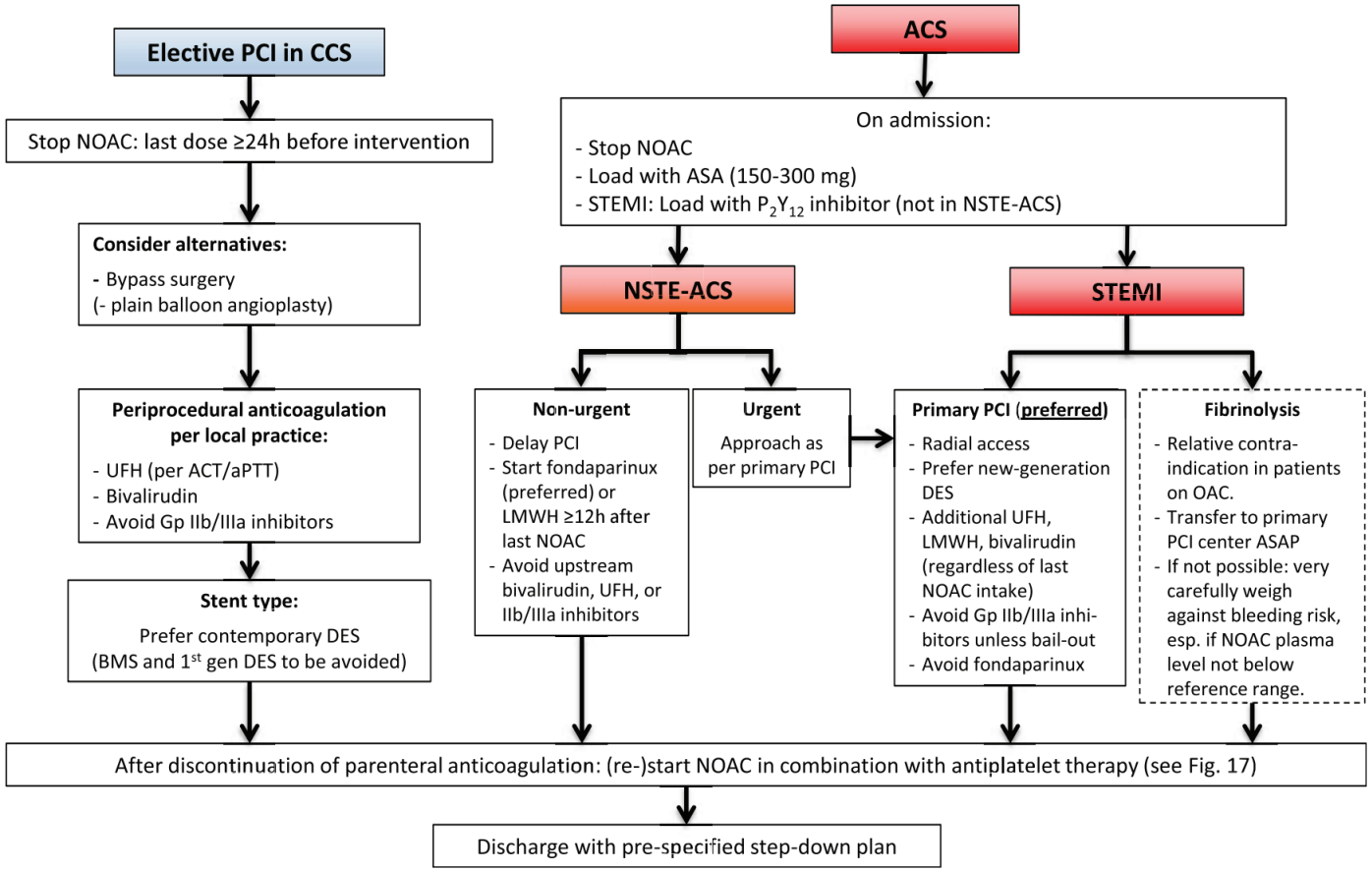
CKD and NOAC


CrCl
Dabigatran
Rivaroxaban
Edoxaban
Apixaban
90 ml/min
50 ml/min
40 ml/min
30 ml/min
15 ml/min
Dialysis
20 mg
60 mg[b]
150 mg BID / 110mg BID[a]
15 mg
30 mg
5 mg BID / 2.5 mg BID[c]
15 mg
30 mg
2.5 mg BID
• Contraindicated as per SmPCs
• Very limited published RCT outcome data available for VKA or NOACs
• Individualized, multidisciplinary approach
• Patient engagement, shared decision making, including information about off-label situation

Liver dysfunction and NOAC



NOAC and ACS


Elective PCI in CCS
Stop NOAC: last dose ≥24h before intervention
Consider alternatives:
- Bypass surgery
(- plain balloon angioplasty)
Periprocedural anticoagulation per local practice:
- UFH (per ACT/aPTT)
- Bivalirudin
- Avoid Gp IIb/IIIa inhibitors
Stent type:
Prefer contemporary DES
(BMS and 1st gen DES to be avoided)
ACS
On admission:
- Stop NOAC
- Load with ASA (150-300 mg)
- STEMI: Load with P_2Y_{12} inhibitor (not in NSTE-ACS)
NSTE-ACS
STEMI
Non-urgent
- Delay PCI
- Start fondaparinux (preferred) or LMWH ≥12h after last NOAC
- Avoid upstream bivalirudin, UFH, or IIb/IIIa inhibitors
Urgent
Approach as per primary PCI
Primary PCI (preferred)
- Radial access
- Prefer new-generation DES
- Additional UFH, LMWH, bivalirudin (regardless of last NOAC intake)
- Avoid Gp IIb/IIIa inhibitors unless bail-out
- Avoid fondaparinux
Fibrinolysis
- Relative contra-indication in patients on OAC.
- Transfer to primary PCI center ASAP
- If not possible: very carefully weigh against bleeding risk, esp. if NOAC plasma level not below reference range.
After discontinuation of parenteral anticoagulation: (re-)start NOAC in combination with antiplatelet therapy (see Fig. 17)
Discharge with pre-specified step-down plan

Suggested strategies to reduce bleeding risk related to percutaneous coronary intervention (2)

Strategies (continued)

- In patients on OAC:
  a. PCI performed without interruption of VKAs or NOACs
  b. In patients on VKAs, do not administer UFH if INR >2.5
  c. In patients on NOACs, regardless of the timing of the last administration of NOACs, add low-dose parenteral anticoagulation (e.g. enoxaparin 0.5 mg/kg i.v. or UFH 60 IU/kg)
- Aspirin is indicated but avoid pretreatment with $P2Y_{12}$ receptor inhibitors
- GP IIb/IIIa receptor inhibitors only for bailout or peri-procedural complications

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Drugs interaction

Table 7 **Anticipated effects of common antiepileptic drugs on non-vitamin K antagonist oral anticoagulants plasma levels**

	Via[426, 539-541]	Dabigatran etexilate	Apixaban	Edoxaban	Rivaroxaban
P-gp substrate		Yes	Yes	Yes	Yes
CYP3A4 substrate		No	Yes (≈25%)	No (<4%)	Yes (≈18%)
Drug					
Brivaracetam	–	No relevant interaction known/assumed			
Carbamazepine	Strong CYP3A4/P-gp induction; CYP3A4 competition	-29% [542]	-50% (SmPC)	SmPC	SmPC
Ethosuximide	CYP3A4 competition	No relevant interaction known/assumed			
Gabapentin	–	No relevant interaction known/assumed			
Lacosamide	–	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/possible P-gp induction		SmPC	SmPC	SmPC
Phenytoin	Strong CYP3A4/P-gp induction; P-gp competition	SmPC [543]	SmPC	SmPC	SmPC
Pregabalin	–	No relevant interaction known/assumed			
Topiramate	CYP3A4 induction; CYP3A4 competition				
Valproic acid	CYP3A4/P-gp induction/inhibition				Ref 544
Zonisamide	CYP3A4 competition; weak P-gp inhibition	No relevant interaction known/assumed (SmPC)			

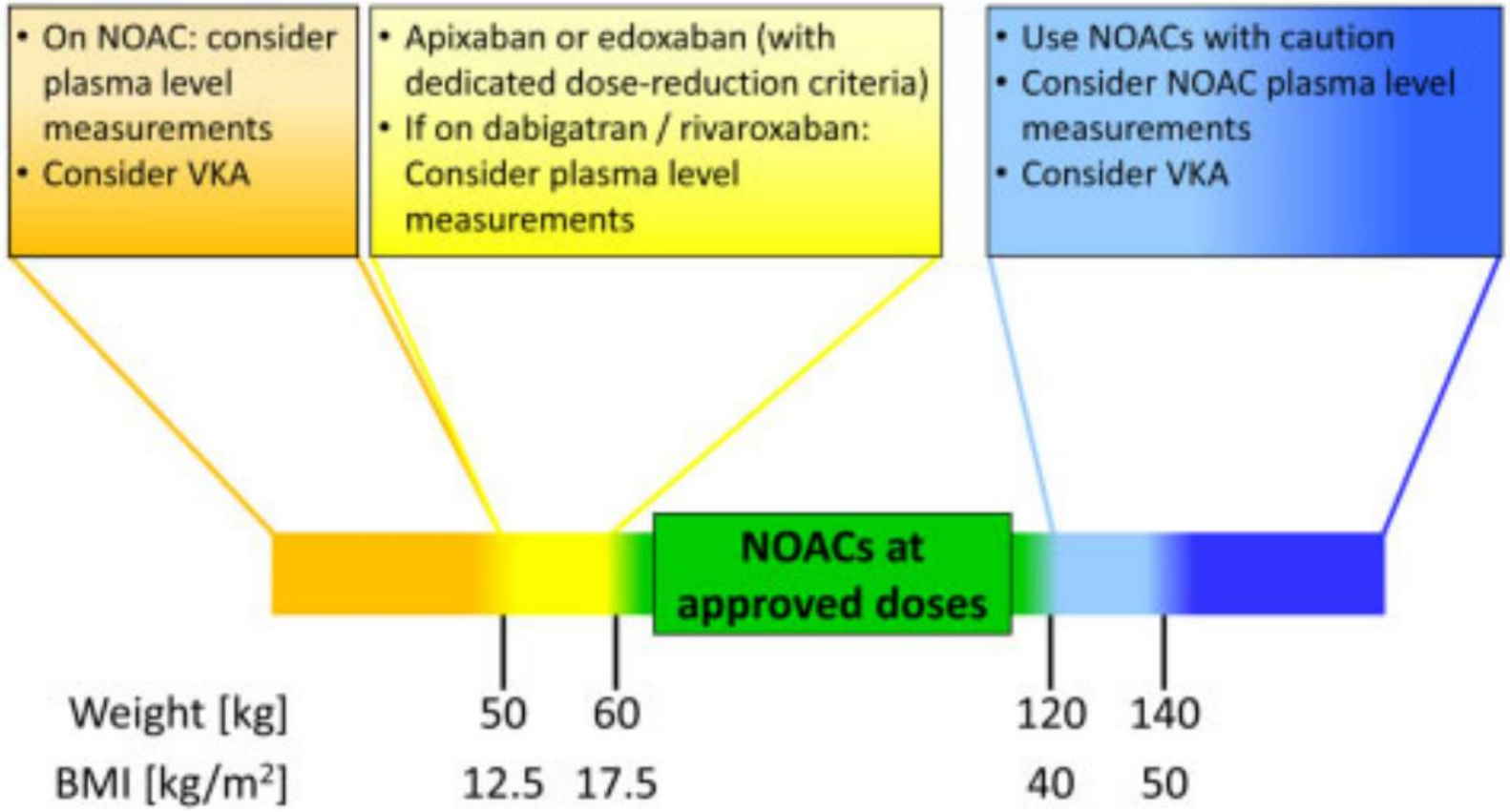
Table 5 Effect of drug-drug interactions and clinical factors on NOAC plasma levels and anticoagulant effects

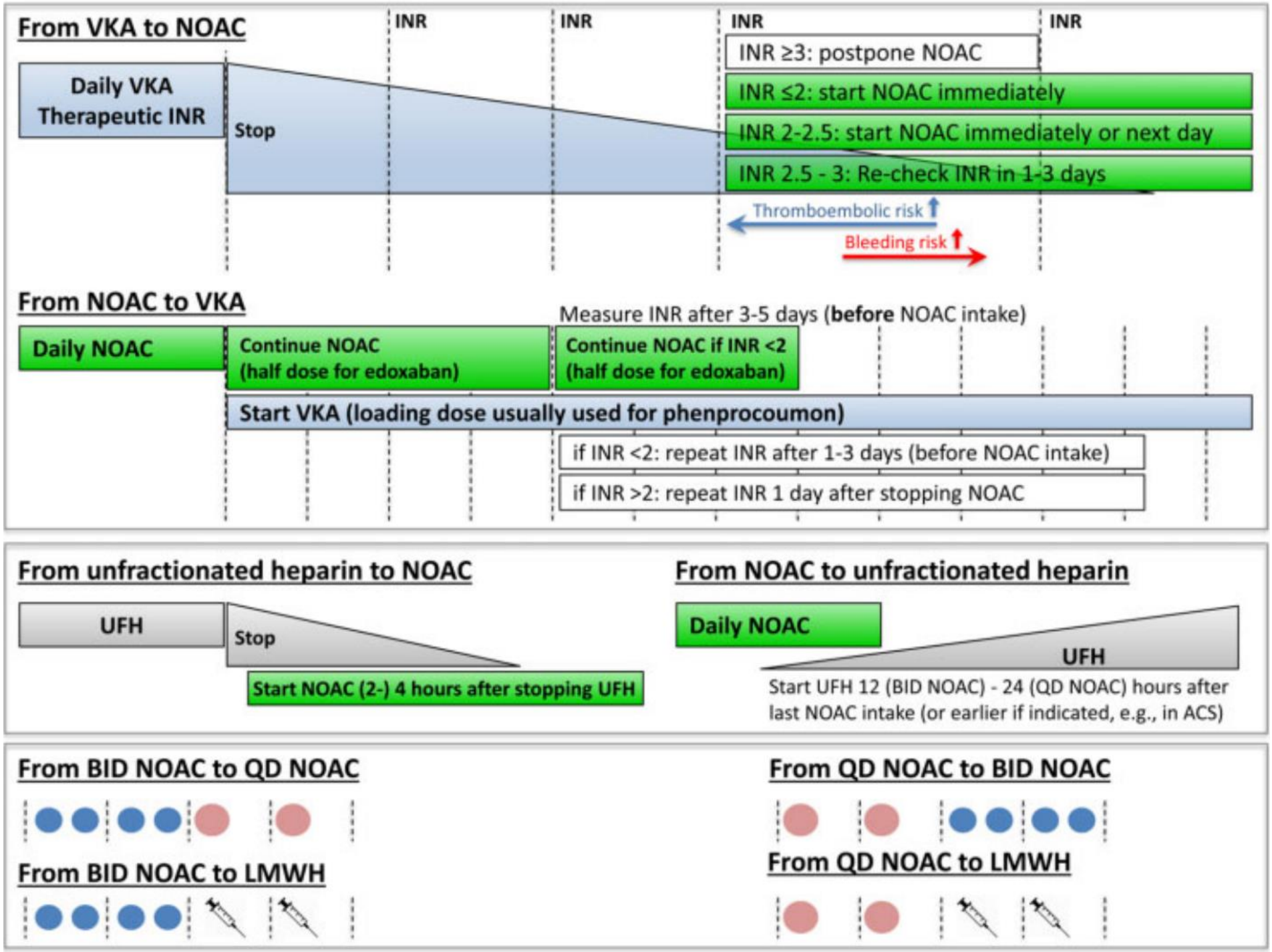
	Via	Dabigatran etexilate	Apixaban	Edoxaban	Rivaroxaban
P-gp substrate		Yes	Yes	Yes	Yes
CYP3A4 substrate		No	Yes (≈25%)	No (<4%)	Yes (≈18%)[519]
Antiarrhythmic drugs					
Amiodarone	Moderate P-gp inhibition	+12% to 60%[SmPC]	No PK data[a]	+40% [521-523]	Minor effect[a]
Digoxin	P-gp competition	No effect[SmPC]	No effect [524]	No effect[523]	No effect [525]
Diltiazem	Weak P-gp and CYP3A4 inhibition	No effect[SmPC]	+40% [526]	No data yet	No effect
Dronedarone	P-gp and CYP3A4 inhibition	+70% to 100%	With caution	+85%[b] [523] (dose reduction to 30 mg once daily by label)	Moderate effect; should be avoided
Quinidine	P-gp inhibition	+53%[SmPC]	No data yet	+77% [523] (No dose reduction required by label)	Extent of increase unknown
Verapamil	P-gp inhibition and weak CYP3A4 inhibition	+12% to 180%[SmPC] (if taken simultaneously) (110 mg BID by label)	No PK data	+53% (SR) [523] (no dose reduction required by label)	+40%[527] (probably not relevant) [528]
Other cardiovascular drugs					
Atorvastatin	P-gp inhibition and CYP3A4 competition	No relevant interaction [529]	No data yet	No effect [523]	No effect [530]
Ticagrelor (see also 'Patients with atrial fibrillation and coronary artery disease' section)	P-gp inhibition	+24% to 65% [SmPC] (give loading dose 2h after dabigatran)[d]	No data – carefully monitor	No data – carefully monitor	No data – carefully monitor
Antibiotics					
Clarithromycin; Erythromycin	P-gp inhibition and strong CYP3A4 inhibition	Clarithromycin: +19% AUC; +15% C_{max} (SmPC)	Clarithromycin: +60% AUC; +30% C_{max} (SmPC)	Erythromycin: +85% AUC; +68% C_{max} [531] (dose reduction to 30 mg once daily by label)	Clarithromycin: +50% AUC; +40% C_{max} Erythromycin: +30% AUC; +30% C_{max} (SmPC)
Rifampicin	P-gp/ BCRP and CYP3A4 induction	– 66% AUC; – 67% Cmax (SmPC)	– 54% AUC; – 42% Cmax (SmPC)	– 35% AUC, (but with compensatory increase of active metabolites) [532]	– 50% AUC; – 22% Cmax (SmPC)

Continued

	via	Dabigatran etexilate	Apixaban	Edoxaban	Rivaroxaban
Antiviral Drugs					
HIV protease inhibitors (e.g., ritonavir)	P-gp and BCRP inhibition or induction; CYP3A4 inhibition	Variable increase / decrease [533, 534]	Strong increase	No data yet	+153% AUC +55% C_{max} (Ritonavir 600 BID) [94]
Fungostatics					
Fluconazole	Moderate CYP3A4 inhibition	No data yet	No data yet	No data yet	+42% AUC; +30% C_{max} (if given systemically) [94]
Itraconazole; Ketoconazole	Potent P-gp and BCRP competition; strong CYP3A4 inhibition	+140 to 150% (ketoconazole) (US: 2 × 75 mg if CrCl 30-50 mL/min)	+100% AUC; +64% C_{max} (ketoconazole) [526]	+87% AUC; +89% C_{max} (dose reduction to 30 mg once daily by label) (ketoconazole) [531]	+160% AUC; +72% C_{max} (ketoconazole, SmPc)
Voriconazole	Strong CYP3A4 inhibition	No data yet	SmPC	No data yet	SmPC
Posaconazole	Mild to moderate P-gp inhibition, strong CYP3A4 inhibition	SmPC	SmPC		SmPC
Other drugs					
Naproxen	P-gp competition; pharmacody-namically (increased bleeding time)	No data yet	+55% AUC; +61% C_{max} [535]	No difference in AUC [536]	No relevant increase o AUC [537]
H_2-blockers; PPI; Al-Mg-hydroxide	GI absorption	Minor effect, not clinically relevant [SmPC]	No effect	Minor effect, not clinically relevant [SmPC]	No effect [105, 538]
SSRIs; SNRIs	Pharmacodynamic effect on platelets	SmPC	SmPC	SmPC	SmPC
St. John's wort	P-gp/ BCRP and CYP3A4 induction				
Other factors					
Age ≥ 80 years	Potential for *increased* plasma levels	110mg BID (SmPC)	b	c	
Age ≥75 years	Potential for *increased* plasma levels			c	
Weight ≤ 60 kg (see 'NOACs in high- and low body weights' section)	Potential for *increased* plasma levels		b	(dose reduction to 30mg according to label) b	
Weight ≥ 120 kg (see 'NOACs in high- and low body weights' section)	Potential for *decreased* plasma levels				
Chronic kidney disease	Potential for *increased* plasma levels				
Other factors with potentially increased bleeding risk		For example : • Concomitant antiplatelet drugs; NSAID; systemic steroid therapy; other anticoagulants • Severe Frailty / falls risk • History of bleeding or predisposition (anemia, thrombocytopenia)			

Overweight and underweight




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
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