DOACs (Direct Oral Anticoagulants) and reversal. Considerations for vascular surgeons.

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No conflict of interest… « unfortunately »

DOACs in clinical practice in 2022

- DOACS (first approval in 2010) :attractive alternatives to vitamin K antagonist.
- More immediate drug onset and offset effects and fewer drug and food interactions
- Indicated for prevention and treatment of several cardiovascular conditions.
- Emerged as leading therapeutic alternatives that provide both clinicians and patients satisfaction (PO and no monitoring in usual clinical situation)
- Follow-up kidney function (creatinine clearance with CG equation)
- Every year, 10% of treated patients scheduled for invasive procedure
- **Recently published trial probably announced enlarged indications in postoperative of vascular surgery and for high cardiovascular risks patient**

Clinical indications

Actually

- Stroke prevention in NVAF (80%)
- Prevention and treatment of deep vein thrombosis and pulmonary embolism
- Prevention of thromboembolism after total knee or hip replacement
- Prevention of thromboembolism after PCI with NVAF
- Prevention of atherothrombotic events after an acute coronary syndrome (ACS)

Near future

- Prevention and treatment of deep vein thrombosis for oncologic patients
- **Prevention of major cardiovascular events in patients with peripheral artery disease or after limb revascularization**

Pharmacokinetics characteristics

TABLE 1 | Summary of main pharmacokinetic characteristics of DOACs.

Characteristic	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Prodrug	Yes	No	No	No
Bioavailability (%)	3–7 (due to its high polarity)	70 (without food) 100 (with food)	50	62
Time to maximum effect [T_{max} (h)]	1.5–2 h	2–4 h	1–3 h	1–2 h
Volume of distribution [VD (L)]	50–70	50	23	107
Plasma protein binding (%)	35	>90	87	55
Half-life (h)	12–14	5–9 (young adults) 11–13 (elderly)	~12	10–14
Metabolism	No (20% glucuronic acid conjugation)	(65%) CYP3A4, CYP2J2	(73%) CYP3A4/5, 1A2, 2C8, 2C9, 2C19, 2J2	(50%) CYP3A4/5 (<10%)
Substrate for CYP3A4	No	Yes	Yes	Yes
Substrate for P-gp	Yes, dabigatran etexilate	Yes	Yes	Yes
Substrate for other transporters	Unknown	BCRP	BCRP	Unknown
Elimination	80% renal (unchanged) 20% liver	33% renal 66% liver	25% renal 75% liver	50% renal 50% liver
Drug–drug interactions	P-gp	P-gp, CYP3A4	P-gp, CYP3A4	P-gp, CYP3A4
Food–drug interactions	Prolongs T_{max} to 2 h (intake with food discouraged)	Mean AUC increases to ~40% (Intake with food mandatory)	No effect (Intake with food discouraged)	No effect (Intake with food: no official recommendation)
Daily doses required	Twice daily	Once daily	Twice daily	Once daily

BCRP: breast cancer–resistant gene protein, CYP: cytochromes P450, P-gp: P-glycoprotein.

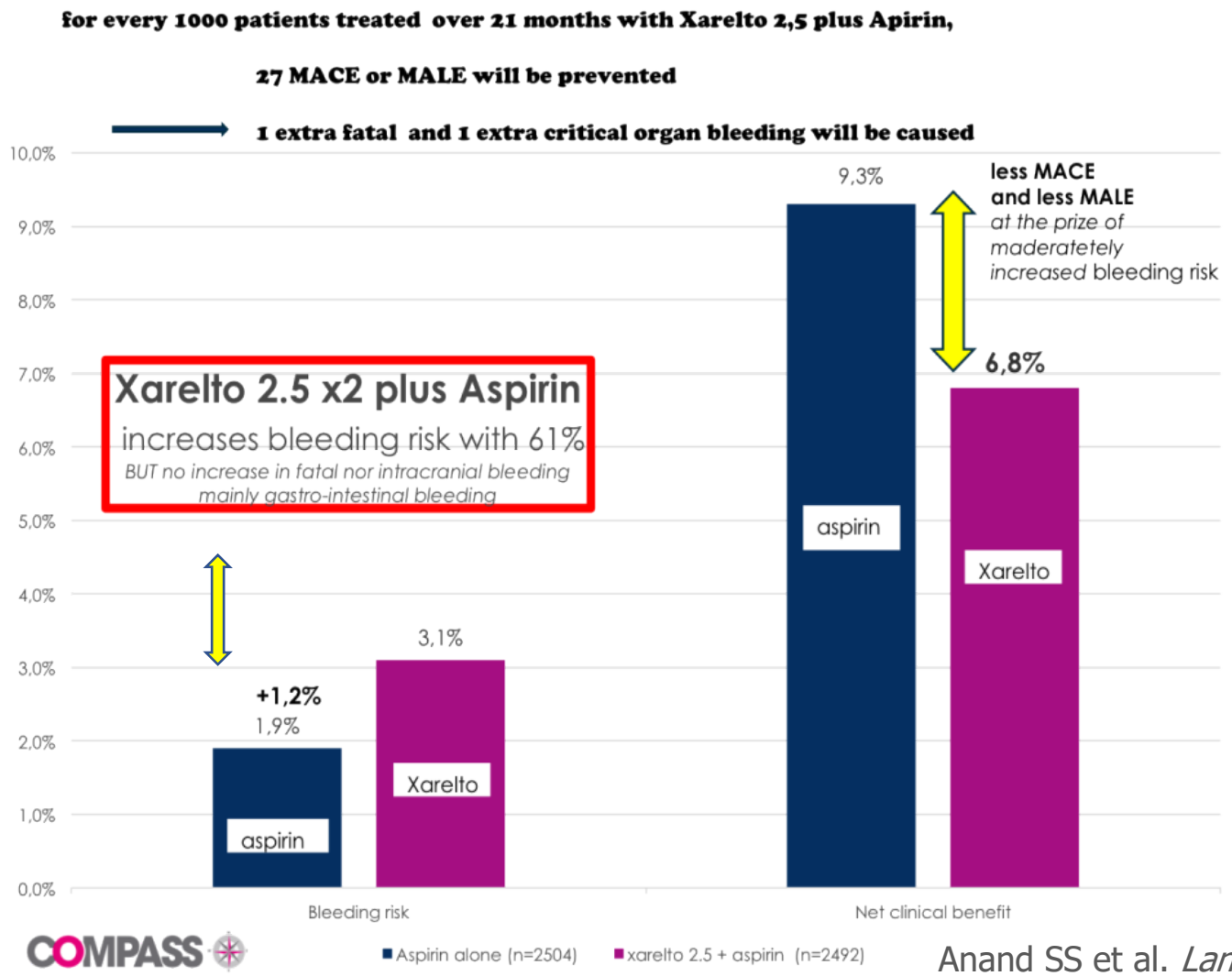
Posology

	Rivaroxaban	Apixaban	Edoxaban	Dabigatran
Venous thromboembolism prophylaxis after major orthopaedic surgery (hip or knee replacement surgery) → *low doses*				
Dosage	10 mg daily	2.5 mg BID	NA	220 mg x1 daily
Dosage adjustments	No	No		150 mg x1 daily if: CrCl 30 to 50 ml min^{-1}; or age≥75; or concomitant use of verapamil, amiodarone, or quinidine
Stroke prevention in nonvalvular atrial fibrillation → *high doses*				
Dosage	20 mg daily	5 mg BID	60 mg daily	150 mg BID
Dosage adjustments	15 mg daily if CrCl 15 to 50 ml min^{-1}	2.5 mg BID if two of three criteria met: age ≥80; body weight ≤60 kg; Creatinine ≥133 micromol l^{-1} If CrCl 15 to 29 ml min^{-1}: 2.5 mg BID	30 mg daily if: CrCl 15 to 50 ml min^{-1}; or body weight ≤60 kg; or concomitant use of ciclosporin, dronedarone, erythromycin or ketoconazole	110 mg BID if age ≥80 or concomitant use of verapamil 110 or 150 BID if CrCl 30 to 50 ml min^{-1} or age 75 to 80
Acute venous thromboembolism treatment → *high doses*				
Dosage	15 mg BID x 21 days, then 20 mg once daily	10 mg BID x 7 days, then 5 mg BID	60 mg daily	150 mg BID
Dosage adjustments	15 mg BID x 21 days, then 15 mg once daily if CrCl 15 to 50 ml min^{-1}	No dose adjustment	30 mg daily if: CrCl 15 to 50 ml min^{-1}; or body weight ≤ 60 kg; or concomitant use of ciclosporin, dronedarone, erythromycin, or ketoconazole	110 mg BID if age≥80 or concomitant use of verapamil 110 or 150 BID if CrCl 30 to 50 ml min^{-1} or age 75 to 80
Extended prevention of recurrent DVT and PE → *low doses*				
Dosage	10 mg once daily or 20 mg once daily	2.5 mg BID		
Dosage adjustments	If CrCl 15 to 50 ml min^{-1}: for 10 mg, no adjustment; but consider 15 mg once daily instead of 20 mg once daily	No		
Acute coronary syndrome → *low doses*				
Dosage	2.5 mg BID	NA	NA	NA
Prevention of atherothrombotic events in symptomatic peripheral artery disease → *low doses*				
Dosage	2.5 mg BID	NA	NA	NA

Data for DOAC indications from the respective Summary of Product Characteristics (SmPC). BID, twice a day; CrCl, creatinine clearance; DOAC, direct oral anticoagulant; NA, not applicable.

Compass trial

N ENGL J MED 377;14 NEJM.ORG OCTOBER 5, 2017



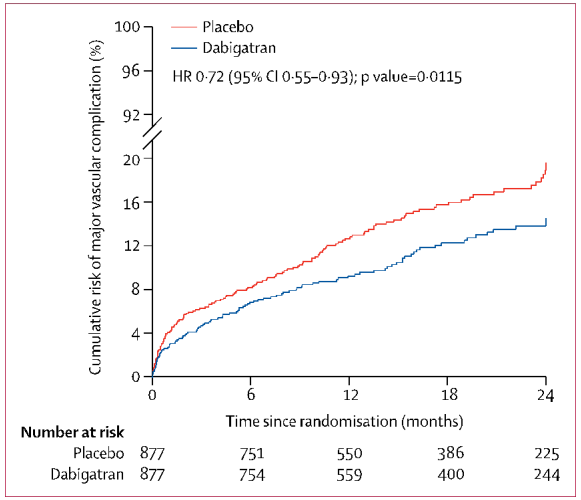
Anand SS et al. *Lancet* 2018;391;219–229;

Manage trial

Devereaux PJ et al

www.thelancet.com **Vol 391 June 9, 2018**

- 1754 patients with MINS after non cardiac surgery
- Dabigatran 110mgX2+ AAS vs AAS
- Reduced MACE (1 month to 2 years) without increase of critical bleeding



	Dabigatran (n=877)	Placebo (n=877)	Hazard ratio (95% CI)	p value
Primary safety outcome				
Composite of life-threatening, major, and critical organ bleeding	29 (3%)	31 (4%)	0·92 (0·55–1·53)	0·78
Secondary safety outcomes				
Life-threatening bleeding	9 (1%)	8 (1%)	1·11 (0·43–2·88)	..
Major bleeding	21 (2%)	25 (3%)	0·83 (0·46–1·48)	..
Critical organ bleeding	5 (1%)	10 (1%)	0·49 (0·17–1·43)	..
Intracranial bleeding	4 (<1%)	3 (<1%)	1·32 (0·30–5·90)	..
Haemorrhagic stroke	2 (<1%)	2 (<1%)	0·98 (0·14–6·96)	..
Clinically significant lower gastrointestinal bleeding	15 (2%)	6 (1%)	2·50 (0·97–6·44)	..
Clinically non-significant lower gastrointestinal bleeding	33 (4%)	7 (1%)	4·77 (2·11–10·80)	..
Minor bleeding	134 (15%)	84 (10%)	1·64 (1·25–2·15)	..
Fracture	39 (4%)	28 (3%)	1·38 (0·85–2·24)	..
Dyspepsia	129 (15%)	98 (11%)	1·33 (1·02–1·73)	..

Data are n (%) unless otherwise indicated.

Table 3: Safety outcomes

Voyager Pad trial

N ENGL J MED 382;21 NEJM.ORG MAY 21, 2020

- Bonaca MP et al
- PRM study/ 6564 patients **after lower limb revascularization**
- Xarelto 2,5mgX2+ASA vs ASA
- Reduction of cardiovascular risk (MALE+MACE) but increase bleeding (5,94 vs 4,06%)

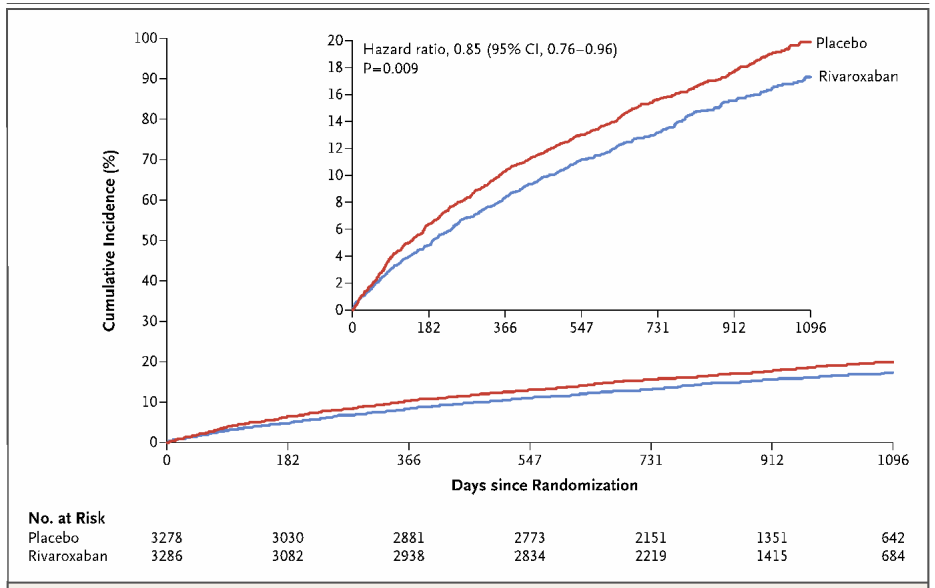


Figure 2. Kaplan–Meier Analysis of the Primary Composite Efficacy Outcome.
The primary efficacy outcome was a composite of acute limb ischemia, major amputation for vascular causes, myocardial infarction, ischemic stroke, or cardiovascular death. The inset shows the same data on an expanded y axis.

Table 3. Safety Outcomes.*

Outcome	Rivaroxaban (N=3256)		Placebo (N=3248)		Hazard Ratio (95% CI)	P Value
	Patients with Event	K–M Estimate at 3 Yr	Patients with Event	K-M Estimate at 3 Yr		
	no. (%)	%	*no. (%)*	%		
Principal safety outcome: TIMI major bleeding	62 (1.90)	2.65	44 (1.35)	1.87	1.43 (0.97–2.10)	0.07
Intracranial hemorrhage	13 (0.40)	0.60	17 (0.52)	0.90	0.78 (0.38–1.61)	
Fatal bleeding	6 (0.18)	0.21	6 (0.18)	0.21	1.02 (0.33–3.15)	
Intracranial or fatal bleeding	17 (0.52)	0.74	19 (0.58)	0.97	0.91 (0.47–1.76)	
Secondary safety outcomes						
ISTH major bleeding	140 (4.30)	5.94	100 (3.08)	4.06	1.42 (1.10–1.84)	0.007
BARC major bleeding†	93 (2.86)	3.86	73 (2.25)	2.92	1.29 (0.95–1.76)	0.10

Duration of DOACs discontinuation and plasmatic concentrations

European Heart Journal (2017) **38**, 2431–2439

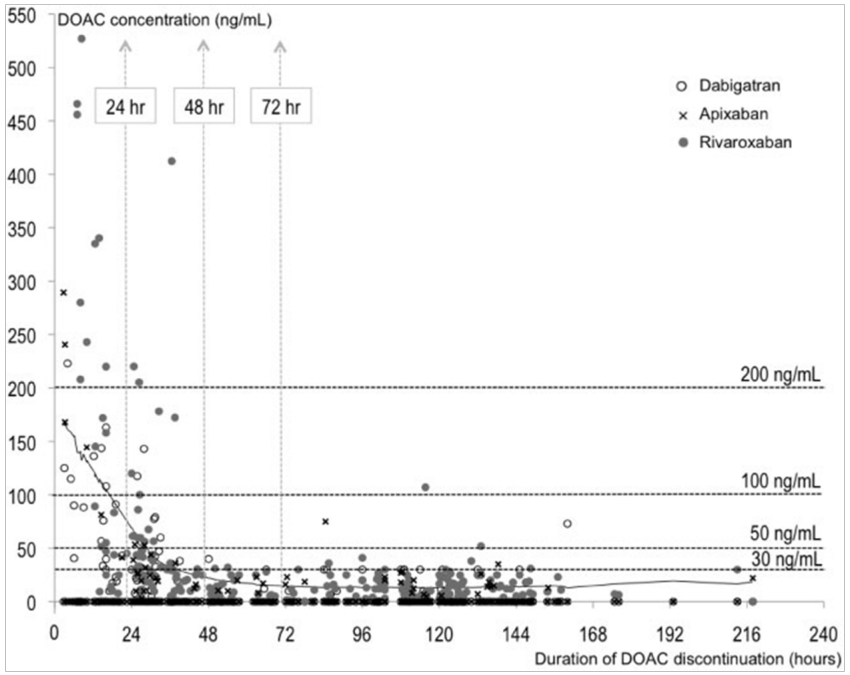


Figure 1 Fit plot of DOAC concentrations measured at the time of invasive procedure according to the duration of DOAC discontinuation. DOAC, direct oral anticoagulant.

Threshold= 30-50ng/mL for no bleeding increase

Before elective surgery: **No bridging**

GIHP	Low bleeding risk	High bleeding risk
Before procedure	No drug at D-1 evening and at D0 morning	Rivaroxaban Apixaban Edoxaban: Last dose at D-3 Dabigatran GFR>50mL/mn= Last dose D-4 GFR<50mL/mn= Last dose D-5
After procedure	First dose H+6 after surgery	First dose>6h with low dose LMWH Plain dose at 48-72h (if no more bleeding risk)

GIHP 2015

- **Stop 2 T1/2 for low dose and 5 T1/2 for curative treatment**
- Neurosurgery (or perineuraxial punction); stop 120h (french task force)
- No dosage and no bridging

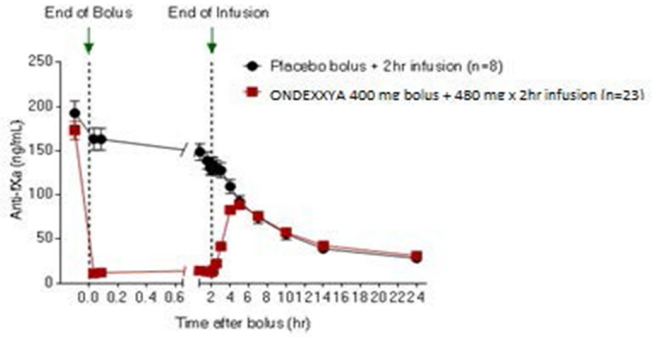
Antagonists and NS prohemostatic agents

1/ **Idarucizumab (Praxbind®): specific antagonist for dabigatran**

- High efficacy, high cost (3750 us $)
- 2,5gX2 in 10 mn with immediate reversion. No prothrombotic effect

2/ **For Xabans: Andexanet alpha (ondexxya®)**: specific antagonist

- Cost: low dose=29700 $ X 2 for High Dose
- Prothrombotic risk not excluded (↓ TFPI)
- EMA authorized but unavailable in Belgium



3/ Novo7, aPCC discussed. **4f PCConcentrate** widely used: unspecific but indicated if no andexanet: 25-50ui/kg

4/ Aripazine: « universal antagonist »
but actually unavailable

Andexanet regimen

	Initial intravenous bolus	Continuous intravenous infusion	Total number of 200 mg vials needed
Low dose	400 mg at a target rate of 30 mg/min	4 mg/min for 120 minutes (480 mg)	5
High dose	800 mg at a target rate of 30 mg/min	8 mg/min for 120 minutes (960 mg)	9

Before emergent procedure: 1/ Dabigatran treated patient

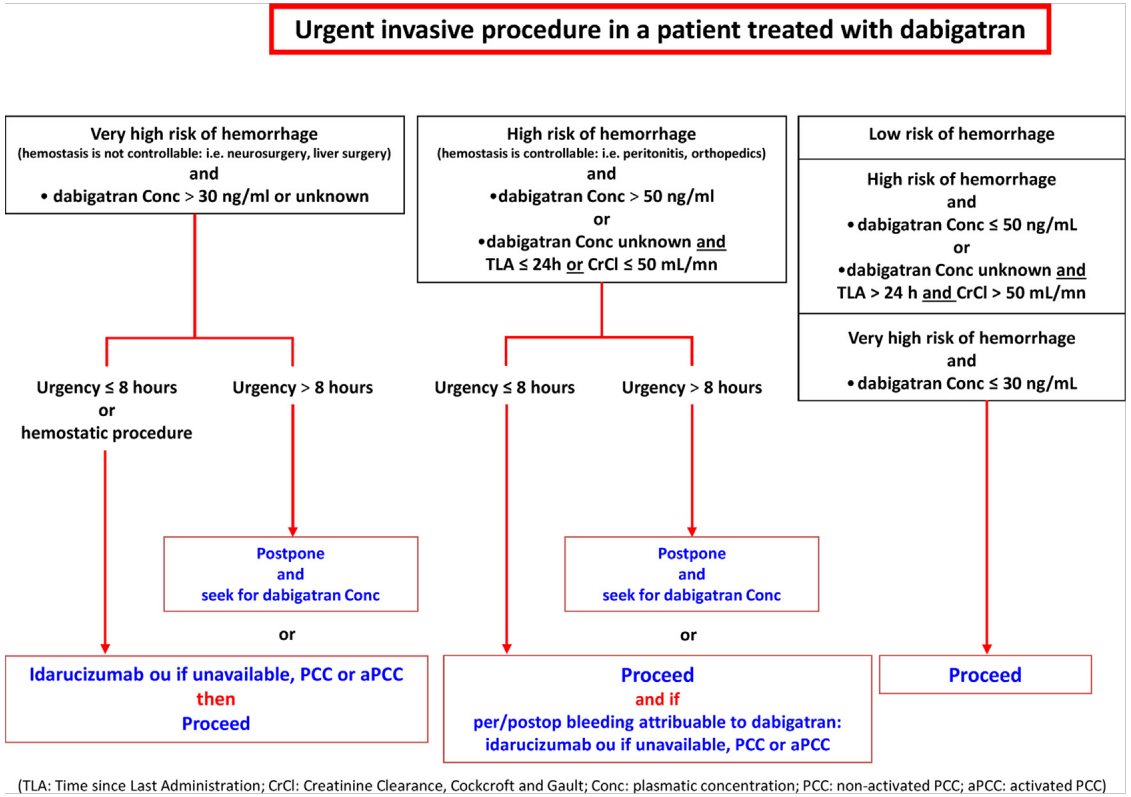


Fig. 2. Urgent invasive procedure in a patient treated with dabigatran.

2 messages:

- Dosage usefull
- defer if possible 1 to 2 T1/2

Before emergent procedure
2/ Xaban treated patient

- **Preoperative specific dosage usefull**
- Safety if LMWH calibrated assay<0,1ui/mL
- No excessive bleeding if dosage<30(50) ng/mL
- Very high risk if>400ng/mL
- **Defer if possible 1 to 2 T1/2 (12 to 24h)**
- If impossible, proceed to surgery and antagonise if persistant bleeding and dosage>50ng/mL
- Antagonise first if
  - Very high risk hemorrhage
  - If no **andexanet** available, use **4 factors PCC 25- 50ui/kg**

Before locoregional anaesthesia

Table 3 Management in high bleeding risk blocks (neuraxial and deep nerve blocks)

Drug and dose	High risk of bleeding block (neuraxial and deep nerve blocks)[a] Time from last drug intake to intervention[c]	Target laboratory value at intervention	Time from intervention to next drug dose
VKA	Until target lab value: (about 3 days acenocoumarol; 5 days warfarin, fluindione; 7 days phenprocoumon)	INR normal	
DXA low[b]	24 h rivaroxaban, edoxaban (30 h if CrCl <30 ml min^{-1}), 36 h apixaban	No testing	
DXA high	72 h or until target laboratory value (until target laboratory value if CrCl <30 ml min^{-1})	DXA level <30 ng ml^{-1} (alternative: anti-Xa $\leq$ 0.1 IU ml^{-1})	Low doses: according to guidelines on postOP VTE prophylaxis[d] (about 8 h – t_{max} = 6 h postop). Consider prolonged time interval after bloody tap[e]
Dabigatran low[b]	48 h	No testing	
Dabigatran high	72 h or until target laboratory value (until target laboratory value if CrCl <50 ml min^{-1})	DTI level $<$ 30 ng ml^{-1} (alternative: thrombin time in normal range of local laboratory)	High doses: according to guidelines on therapeutic anticoagulation[f] (about 24 h postop)
LMWH low $\leq$50 IU anti-Xa kg^{-1} day^{-1} enoxaparin $\leq$40 mg day^{-1}	12 h (24 h if CrCl <30 ml min^{-1})	No testing	
LMWH high	24 h (48 h if CrCl <30 ml min^{-1}) or until target lab value (especially if CrCl <30 ml min^{-1})	anti-Xa $\leq$ 0.1 IU ml^{-1}	VKA, DOAC, LMWH high, UFH high; should not be administered with a catheter in situ
UFH low $\leq$200 IU kg^{-1} day^{-1} SC $\leq$100 IU kg^{-1} day^{-1} i.v.	4 h	No testing	UFH low: 1 h for i.v. in cardiovascular surgery
UFH high	Until target lab value (about 6 h if i.v., 12 h if SC)	aPTT or anti-Xa or ACT in normal range of local laboratory	
Fondaparinux low $\leq$2.5 mg day^{-1}	36 h (72 h if CrCl <50 ml min^{-1})	No testing	
Fondaparinux high	until target lab value (about 4 days)	Calibrated anti-Xa $\leq$ 0.1 IU ml^{-1}	
Aspirin low $\leq$ 200 mg day^{-1}	0	No testing	Routinely prescribed next time point
Aspirin high	3 days (in normal platelet counts) to 7 days	(consider specific platelet function tests in normal range of local laboratory)	6 h
$P2Y_{12}$ inhibitor	5 days ticagrelor 5 to 7 days clopidogrel 7 days prasugrel or until target laboratory value		0-h clopidogrel 75 mg 24 h prasugrel, ticagrelor 2 days clopidogrel 300 mg
Aspirin low + anticoagulant	Aspirin: 0 + time interval of specific anticoagulant	specific laboratory test for combined anticoagulant	Aspirin low: routinely prescribed next time point Combined anticoagulant, antiplatelet drug: according to guidelines on therapeutic anticoagulation, platelet inhibition[f] (about 24 h postOP)
Aspirin low and antiplatelet drug	Aspirin: 0 and time interval of specific antiplatelet drug	(consider specific laboratory test for combined antiplatelet drug)	

1/For GIHP (French taskforce)
stop 120h before perineuraxial anaesthesia or deep nerve block/ 72h for ESAIC
2/For superficial nerve block, more liberal

ESAIC guidelines 2022

Messages

- Potential enlarged indications for DOACs in high vascular risk patients in the next few years. Increased bleeding risk could be the price to pay of improved heart and limb outcome.

Before elective surgery

- No dosage required
- With low doses, (compass), short stop (24-48h) before surgery is safe
- With plain doses (NVAF), stop>48h and great caution with perineuraxial block

Before emergent surgery

- Waiting is blood (life) saving (1 to 2 half life)
- Efficient antagonist available for dabigatran with Praxbind
- For xabans, very high cost, transient effect. If unavailability of andexanet: use 4fPCC if necessary (25-50ui/kg)