2024 EACTS guidelines on perioperative medication in adult cardiac surgery: embracing precision medicine driven by strong evidence-based methodology

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Guidelines are pivotal for optimal patient management and should be grounded by evidence-based medicine with accurate methodology.[1] The European Association of Cardio-Thoracic Surgery has recently released the "2024 EACTS Guidelines on Perioperative Medication in Adult Cardiac Surgery",[2] which address significant novel advancements in the pharmacological management of adult patients undergoing various types of cardiac surgery, including open-heart surgery (coronary and non-coronary) and transcatheter aortic valve implantation. These guidelines comprise several drug classes and provide recommendations on their use, discontinuation and/or (re)introduction at the different phases surrounding elective, urgent or emergent cardiac interventions: early before, during, and after the operation, both short- and long-term. A substantial portion of the document focuses on antithrombotic agents, and several novel aspects and approaches warrant attention.

Regarding antiplatelet drugs, low-dose aspirin remains the reference drug for patients undergoing coronary artery bypass grafting (CABG). It holds Class of Recommendation (CoR) for perioperative continuation unless the patient is at a very high bleeding risk (e.g., complex and redo operations, severe renal insufficiency, congenital or acquired bleeding disorders) in which case aspirin should be suspended for 3 days if possible. For patients already on dual antiplatelet treatment (DAPT) with aspirin plus a $P2Y_{12}$ inhibitor (clopidogrel, prasugrel or ticagrelor), stopping the $P2Y_{12}$ inhibitor is recommended before surgery, within a time frame aligned with its pharmacokinetics and pharmacodynamics, while continuing aspirin (Figure 1).

A new CoR II (Level of Evidence [LoE] B) recommendation suggests using the intravenous $P2Y_{12}$ inhibitor cangrelor, rather than a glycoprotein IIb/IIIa inhibitor, as bridging therapy while the oral $P2Y_{12}$ inhibitor is being cleared, but only in patients at high thrombotic risk such as those with a recent stent implant, recent thromboembolic event and angiographic results raising concern. The present document reaffirms the option of testing for the residual platelet function in patients who have received an oral $P2Y_{12}$-receptor inhibitor within the 6 days before the open-heart surgery to help in guiding the optimal timing of the operation and reduce bleeding risks. Importantly, the Task Force makes clear that platelet function testing in this setting has the sole scope of evaluating whether platelet function has fully recovered. There is no attempt to interpret results over his purpose, identify drug-response thresholds predictive of clinical outcomes, or recommend one particular assay to test platelet function over another, as strong evidence and consensus in this respect remain lacking.

With respect of oral anticoagulant drugs, the guidelines comprehensively address the management of patients on direct oral anticoagulants (DOACs: apixaban, dabigatran, edoxaban, rivaroxaban), taking into account each drug's major pharmacokinetic and pharmacodynamic characteristics (Table 1). The guidelines underline that the traditional concept of 'bridging' does not apply to DOACs, based on their PK and reversible PD characteristics, with a low-grade recommendation (CoR II LoE B) to use heparins before surgery once DOACs are cleared, only for individuals at very high risk of thrombosis. The guide-

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Key words: cardiac surgery; guidelines; antiplatelet therapy; anticoagulant therapy; surgery; evidence-based medicine; personalized medicine.

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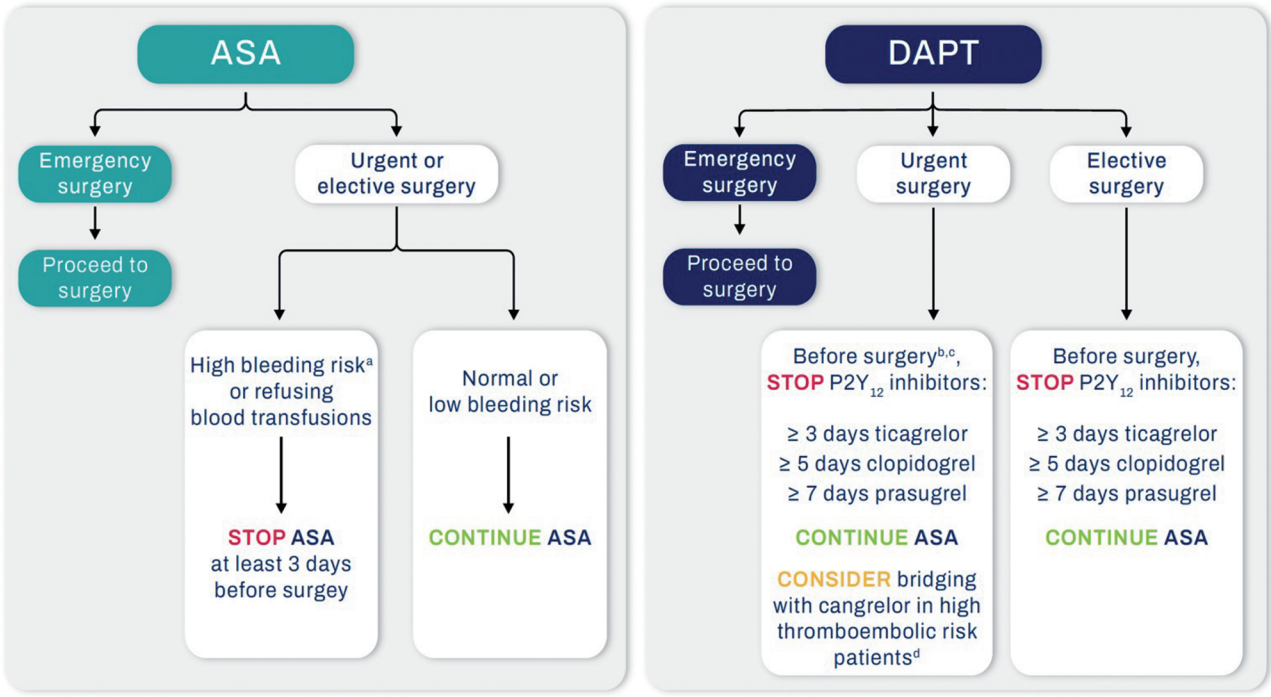
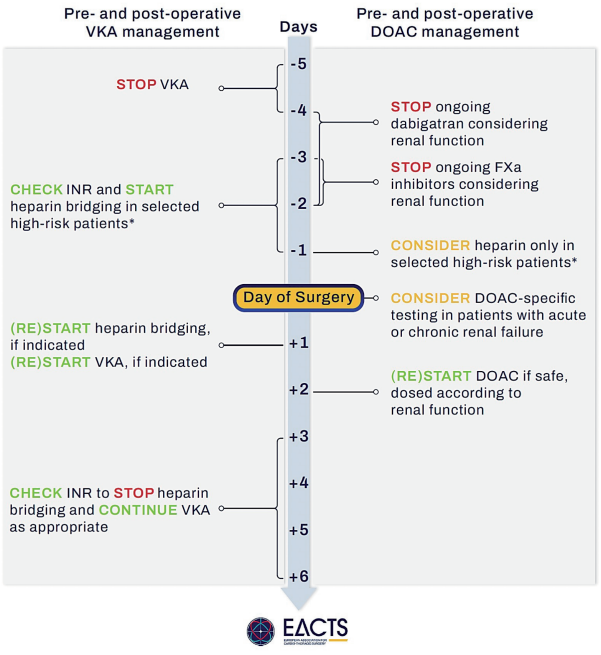


Figure 1. Management of single or dual antiplatelet drugs in patients undergoing cardiac surgery. [a]Complex and redo operations, severe renal insufficiency, congenital or acquired bleeding disorders. [b]If clinical condition allows the optimal time for interruption. [c]Platelet function testing in patients needing urgent surgery may be considered to refine the timing and safety of the operation. [d]Recent stent implant, recent thromboembolic event and angiographic results raising concern. ASA, acetylsalicylic acid; d, days; DAPT, dual antiplatelet therapy. Reproduced from Jeppsson A *et al.* Eur J Cardiothorac Surg 2024;67:ezae355; with permission.



lines also suggest using calibrated assays to measure drug levels in selected situations, such as severe renal impairment, since significant evidence indicates that some DOAC concentrations can remain within the therapeutic levels even 48 h after discontinuation (Figure 2). Additionally, the authors also propose a threshold for residual DOAC's levels that might be safe before elective cardiac surgery, though further clinical validation in

Figure 2. Perioperative management of VKA and DOACs. Postoperative bridging for vitamin K antagonists, with unfractionated heparin or low-molecular-weight heparin, should be discontinued once the international normalized ratio reaches the adequate target range, confirmed by two consecutive tests. *Patients with a mechanical prosthetic heart valve, atrial fibrillation with rheumatic valvular disease, an acute thrombotic event within the prior 12 weeks, acquired or congenital prothrombotic defects, left ventricular apex thrombus. Of note, direct oral anticoagulants are contraindicated in patients with mechanical prosthetic heart valves. DOAC, direct oral anticoagulants; FXa, activated coagulation factor X; INR, international normalized ratio; VKA, vitamin K antagonists. Reproduced from Jeppsson A *et al.* Eur J Cardiothorac Surg 2024;67:ezae355; with permission.

Table 1. Characteristics of the different types of direct oral anticoagulants.

Target	Apixaban Factor Xa	Edoxaban Factor Xa	Rivaroxaban Factor Xa	Dabigatran Factor IIa (active metabolite)
Daily dosing for approved indications:				
Non-valvular AF	5 (or 2.5) mg bid	60 (or 30) mg od	20 (or 15) mg od	150 (or 110) mg bid
Acute VTE	10 mg bid (7 days)	60 mg od	15 mg bid (21 days)	150 mg bid
Chronic VTE	2.5 mg bid	30 mg	10 mg od	220 mg od
CCS/PVD	—	—	2.5 mg bid (+ASA)	—
Bioavailability (%)	50–60	60	80	<10
Half-life (h)	8–14	10–14	7–11	12–17
Plasma protein binding (%)	87	55	92–95	35
T_{max} (h)	3–4	1–2	2–4	1–2
Renal clearance (%)	27–30	50	60	85–90
Biotransformation	50% excreted unchanged ~30% CYP3A4P-gp and BCRP substrate	60% excreted unchanged ~10% CYP3A4 Strong P-Gp substrate	35% excreted unchanged ~20% CYP3A4 P-gp and BCRP substrate	Strong P-gp substrate
Clinically relevant drug–drug interactions increasing anticoagulant effect	Caution with combined strong inhibitors of 3A4 and P-gp	Reduced dose with combined strong inhibitors of 3A4 and P-gp	Caution with combined strong inhibitors of 3A4 and P-gp	DDIs on the P-gp with verapamil, dronedarone, amiodarone
Discontinuation time before surgery in relation to CrCl	CrCl> 50 ml/min: 48 h CrCl 30–50 ml/min: 72 h	CrCl> 50 ml/min: 48 h CrCl 30–50 ml/min: 72 h	CrCl> 50 ml/min: 48 h CrCl 30–50 ml/min: 72 h	CrCl ≥ 50 ml/min: 48 h CrCl 30–49‡ ml/min: 96 h, possibly assess drug concentration
	CrCl 15–30 ml/min :96 h possibly assess drug concentration CrCl <15 not recommended	CrCl 15–30 ml/min: 96 h possibly assess drug concentration CrCl <15 not recommended	CrCl 15–30 ml/min: 96 h possibly assess drug concentration CrCl <15 not recommended	CrCl <30 contraindicated
Reference threshold associated with surgical bleeding risk	Anti-Xa† ≥30 ng/ml	Anti-Xa† ≥30 ng/ml	Anti-Xa† ≥30 ng/ml	Diluted thrombin time >21 s
Antidotes	Andexanet alfa	Andexanet alfa¶	Andexanet alfa	Idarucizumab
Non-specific, haemostatic reversal agents	4 factor-PCC	4 factor-PCC	4 factor-PCC	(Activated) PCC, activated (recombinant) FVII; haemodialysis, ultrafiltration

†Anti-FXa activity tests calibrated for the specific agent. BCRP, breast cancer resistance protein; bid, twice-daily; CrCl, creatinine clearance; DDI, drug-drug interactions; DOAC, direct oral anticoagulant; F, factor; od, once daily; P-gp, P-glycoprotein. ‡Dabigatran is contraindicated if CrCL <30 mL/min in adult patients and <50 mL/min/1.73 m^2 in paediatric patients. ¶Not yet approved, but data from the ANNEXA-4 (andexanet alfa, a novel antidote to the anticoagulation effects of factor Xa Inhibitors) trial on reversal of edoxaban have been published.[3] Reproduced from Jeppsson A *et al.* Eur J Cardiothorac Surg 2024;67:ezae355; with permission.

both cardiac and non-cardiac surgery settings is needed. Overall, these recommendations for measuring platelet function or DOAC concentrations in selected, complex situations are noteworthy examples of cardiovascular precision pharmacology and medicine, setting an evidence-based foundation in a guideline document.

A great attention is devoted to preventing gastrointestinal bleeding from stress ulcers, an often-overlooked issue that can be potentially catastrophic in patients undergoing cardiac surgery with cardiopulmonary bypass (CPB). Accordingly, there is CoR I to use perioperative gastroprotection in patients undergoing cardiac surgery. This is especially relevant for patients on antithrombotic drugs for underlying cardiovascular disease or surgery-related complications as in the case of de novo postoperative atrial fibrillation. Moreover, gastroprotective drugs are recommended in patients on selective serotonin reuptake inhibitors (SSRIs), while the concomitant use of SSRIs and non-steroidal anti-inflammatory drugs is not recommended since it enhances the risk of gastrointestinal bleeding complications.

Emergency cardiac surgery is particularly challenging in patients on anti-Xa DOACs when there is no sufficient time to discontinue the drug prior to surgery. Andexanet alfa, an anti-factor Xa drug's antidote, has not been tested in non-bleeding patients undergoing emergency cardiac surgery in phase 3 ANNEXA-4 (andexanet alfa, a novel antidote to the anticoagulation effects of factor Xa inhibitors) registrative trial. Thus, its use for emergency surgery is off-label. Furthermore, the preoperative use of andexanet alpha in cardiac surgery is associated with an acquired, transient heparin resistance during CPB, increasing the risk of clot formation in the bypass circuit. The European Medicines Agency warns against using andexanet alpha preoperatively in cardiac surgery if heparin is needed during the intervention. Alternatively,

antithrombin concentrate and higher doses of heparin may be used to overcome resistance and achieve the required anticoagulation levels. Bivalirudin or argatroban can be also used as an alternative anticoagulation for CPB.

With the goal of optimizing the risk/benefit ratio in an inherently high-risk population requiring cardiac surgery, where antithrombotic therapy is frequently indicated for primary and secondary prevention, these guidelines provide a targeted set of recommendations to minimize bleeding risks without increasing patients' vulnerability to thromboembolic events. Thus, they pay special attention to different pharmacodynamic or pharmacokinetic drug interactions with a precision medicine framework, grounded in sound evidence. Finally, the document highlights numerous knowledge gaps, serving as a platform for future research that should further refine clinical practice and advance patient care.

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