2024 EACTS Guidelines on perioperative medication in adult cardiac surgery

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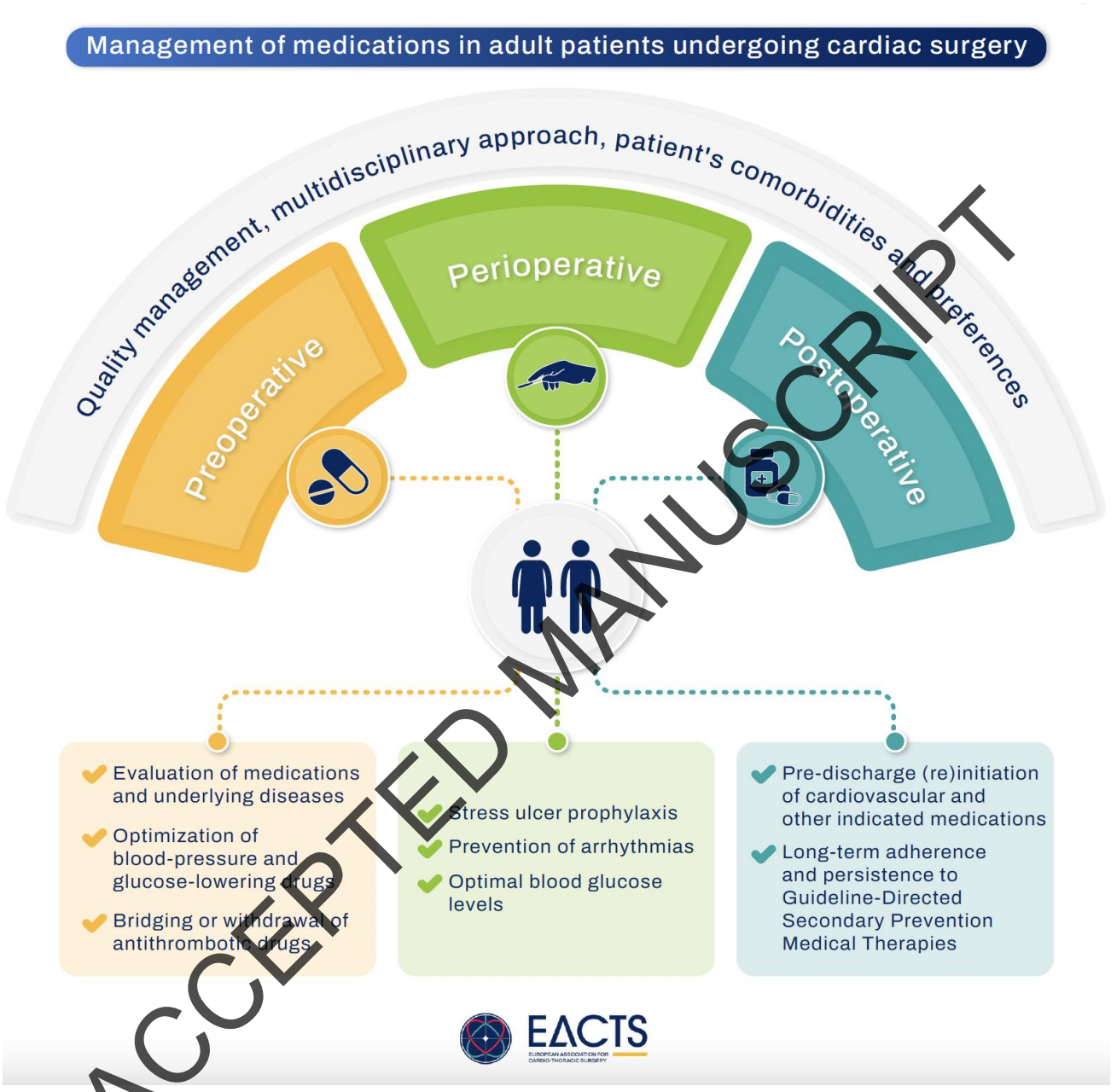
Disclaimer: A clinical guideline aims to apply to all patients with a specific condition. However, there will inevitably be situations where its recommendations aren't suitable for a particular patient. While healthcare professionals and others are encouraged to consider these guidelines in their professional judgment, they don't override the responsibility of healthcare professionals to make decisions tailored to each patient's unique circumstances. Such decisions should be aligned with the latest official recommendations, guidelines from relevant public health authorities, and applicable rules and regulations. It's important that these decisions are made in collaboration with, and agreed upon by, the patient and/or their guardian or carer.

Graphical Abstract



Central Illustration. Multidisciplinary approach in perioperative medication management.

Key words: Guidelines, cardiac surgery, perioperative medication, guideline directed medical therapy, GDMT, evidence based practice, risk reduction, secondary prevention, coronary artery bypass grafting, CABG, valve replacement, transcatheter aortic valve implantation, TAVI, antiplatelet, antithrombotic, beta-blockers, statins, glucose management, pain, steroids, antibiotics, atrial fibrillation.

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Preamble

These guidelines are dedicated to the memory of Professor Jean-Philippe Collet, the initial co-chair of the task force, who sadly passed away during the development of the document.

Clinical practice guidelines synthesize and appraise all available evidence on a specific topic at the time of their creation, helping physicians determine the most effective management strategies for patients. These guidelines evaluate the impact of various drug classes on patient outcomes across perioperative and long-term postoperative periods, weighing the risk–benefit balance of different treatments. Although not substitutes for textbooks, they offer additional and updated information pertinent to contemporary clinical practice and serve as crucial tools supporting physicians' decision making.

It is important to recognize that these recommendations are designed to guide—not dictate—clinical practice and should be tailored to the unique needs of the individual patient. Clinical scenarios vary widely, presenting different variables, comorbidities, medications and settings. Thus, the guidelines are intended to inform, not replace, the clinical judgement of physicians, which is based on their professional knowledge, experience and understanding of the individual patients. Furthermore, these guidelines are not legally binding; the legal obligations of healthcare professionals are determined by local existing laws and regulations, and adherence to these guidelines should not alter such duties.

The European Association for Cardio-Thoracic Surgery (EACTS) established a multidisciplinary task force of experts involved in perioperative and long-term care of patients undergoing cardiac surgery for different indications. To ensure transparency and integrity, all task force members declared their conflicts of interest, which were compiled into a document accessible on the EACTS website (https://www.eacts.org/resources/clinical-guidelines). Any changes to these declarations during the development process were promptly reported to the EACTS Clinical Practice Guidelines Committee. The task force was funded solely by the EACTS, without involvement from the healthcare industry or other entities.

The EACTS governing bodies supervised the development, refinement and approval of these extensively revised guidelines. Endorsed by the EACTS Council, these guidelines represent their official position on this subject, demonstrating a commitment to ongoing improvement. Regular updates are planned to ensure that the guidelines stay relevant and beneficial in the rapidly evolving field of clinical practice.

Abbreviations and Acronyms

ACEI:	Angiotensin-converting enzyme inhibitor
ACS:	Acute coronary syndrome
AF:	Atrial fibrillation
AKI:	Acute kidney injury
ARB:	Angiotensin II receptor blocker
ARNI:	Angiotensin receptor neprilysin inhibitor
ASA:	Acetylsalicylic acid
BB:	Beta-blocker
CABG:	Coronary artery bypass grafting
CCB:	Calcium channel blocker
CI:	Confidence interval
CKD:	Chronic kidney disease
CPB:	Cardiopulmonary bypass
DAPT:	Dual antiplatelet therapy
DM:	Diabetes mellitus
DOAC:	Direct oral anticoagulant
DSWI:	Deep sternal wound infection
EACTS:	European Association for Cardio-Thoracic Surgery
eGFR:	Estimated glomerular filtration rate
F:	Factor
FXa:	Activated coagulation factor X
GDMT:	Guideline-directed medical therapy
GI:	gastrointestinal
GLP-1RA:	Glucagon-like peptide-1 receptor agonists
HbA1c:	Haemoglobin A1c
HFrEF:	Heart failure with reduced ejection fraction
HTA:	Arterial hypertension
H2RB:	Histamine-2 receptor blockers

ICU:	Intensive care unit
INR:	International normalized ratio
LDL-C:	Low-density lipoprotein cholesterol
LMWH:	Low-molecular-weight heparin
LVEF:	Left ventricular ejection fraction
MACE:	Major adverse cardiovascular events
MHV:	Mechanical heart valves
Min:	Minute
MI:	Myocardial infarction
MRA:	Mineralocorticoid receptor antagonist
NSAID:	Non-steroidal anti-inflammatory drugs
OAC:	Oral anticoagulation
OR:	Odds ratio
PCC:	Prothrombin complex concentrate
PCI:	Percutaneous coronary intervention
PE:	Pulmonary embolism
POAF:	Postoperative atrial fibrillation
RAS	Renin-angiotensin system
RAAS:	Renin-angiotensin-aldosterone system
RCT:	Randomized controlled trial
RR:	Risk ratio
SAPT:	Single antiplatelet therapy
SAVR:	Surgical aortic valve replacement
SGLT2:	Sodium-glucose cotransporter-2
SNRI:	Serotonin and noradrenaline reuptake inhibitor
SSI:	Surgical site infection
SSRI:	Selective serotonin reuptake inhibitor
TAVI:	Transcatheter aortic valve implantation
TTR:	Time in therapeutic range
UFH:	Unfractionated heparin

VKA: Vitamin K antagonist

VTE: Venous thromboembolism

1 Introduction

Adult cardiac surgery is an essential therapeutic approach to reduce short- and long-term mortality and morbidity in patients with acute or chronic cardiac diseases. The outcomes after cardiac surgery rely not only on patient selection and surgical expertise, but also on the management of underlying conditions as well as on the pharmacological prevention and treatment of complications. Therefore, perioperative medical treatment and prophylaxis are key factors in ensuring the perioperative and long-term success of cardiac surgery and in impacting a patient's quality of life and healthcare costs.

Pharmacological therapy affects outcome(s) after adult cardiac surgery across 3 distinct stages: preoperative, intraoperative and postoperative (1). Preoperatively, the medical/surgical team may need to initiate, interrupt or maintain medications to mitigate the risk for intra- and immediate postoperative complications. Intraoperatively, managing blood glucose levels and administering prophylactic antibiotics in a timely and effective manner are essential to reduce infectious complications and ensure the best possible surgical outcomes. Postoperatively, restarting or initiating new medications in a timely fashion is essential for preventing ischaemic events, controlling arrhythmias, managing cardiovascular risk factors and treating heart failure (HF) and reducing mortality, all of which contribute to optimal long-term prognoses.

For patients, cardiac surgery is always a major and challenging experience in their lives, is associated with increased disease awareness and represents a unique opportunity to optimize medical therapy and improve their quality of life. It serves as a teachable opportunity to emphasize the importance of medication adherence, lifelong follow-up and lifestyle modifications. Patients undergoing cardiac operations frequently receive suboptimal treatment, despite the well-established benefits of intensive, patient-centred medication therapy both perioperatively and in the long term (2-5).

In 2017, EACTS published its first guidelines on perioperative medication, targeting the treatment and prevention of adverse events in patients undergoing elective or emergency adult cardiac surgery (1). Since then, substantial new and practice-changing evidence has emerged, pressuring the EACTS Clinical Guideline Committee for a comprehensive update. Consistent with the 2017 EACTS guideline, the current version does not address medications used for procedure-related complications, such as graft

vasospasm, vasoplegic syndrome, perioperative ischaemia, perioperative myocardial infarction (MI), low cardiac output syndrome, acute kidney injury (AKI), neurological complications, pneumonia and wound infections and comprehensive patient blood management. These topics are comprehensively covered in other relevant EACTS guidelines and expert consensus documents, and readers are referred to them (6-12). Moreover, supplements are beyond the scope of the present document (13, 14). Finally, the governing bodies have decided that the management of drugs for anaesthesia and postoperative pain control should be covered in a specific document with the involvement of relevant representative organizations. The central illustration summarizes what is new in this edition compared with the 2017 edition, emphasizing what is crucial according to the class of recommendation.

The main objective of this guideline is to provide accessible and essential information not only to clinicians and surgeons but also to other professionals involved in the care of patients undergoing cardiac surgery, ensuring streamlined critical appraisal of evidence in a productive and interactive multi-expertise environment. Additionally, it provides evidence-based recommendations and identifies gaps in evidence, thereby paving the way to and offering the rationale for future research.

2 Methodology

To ensure that evidence-based best-practice guidelines remain contemporary, the EACTS governing bodies regularly review new evidence and revise these guidelines based on established standards for developing and implementing clinical practice documents (15). Given the significant advances in the field of perioperative and long-term pharmacological therapies since the first publication (1) and the fact that most guidelines become outdated 5 years after their last revision (16), a comprehensive update of the Perioperative Medication Guidelines in Adult Cardiac Surgery was deemed necessary.

A multidisciplinary task force was established to represent a wide range of expertise involved in the care of cardiac surgery patients, selecting specialists from various fields, regions and clinical and research settings. The scope of the guidelines was agreed upon by the governing bodies of the societies, while the task force members determined the final table of contents. To systematically review the latest evidence, the task force conducted a systematic literature review using the standardized Population, Intervention, Comparison, Outcome and Time (PICOT) questions format, with the help of a medical informatics specialist. The literature search included all study types, such as randomized controlled trials (RCTs), systematic reviews and meta-analyses, registries, observational comparative and descriptive studies, case series, cohort studies and expert opinions. An initial systematic literature review, focused on human research published in English from January 2016 and indexed in MEDLINE, EMBASE and the Cochrane Library, was conducted from September to December 2023 (see search strings for each section in the supplementary material). Additional studies published after December 2023, during the guideline writing and external validation processes, were also considered and included when relevant. The references in this document are representative but not exhaustive. The recommendations in the guidelines are, whenever possible, evidence-based and derived primarily from RCTs and meta-analyses.

To ensure that the document's development remained unbiased and impartial, task force members were required to declare any interests before starting the project and to inform the EACTS Clinical Practice Guidelines Committee of any changes until the publication of the guideline. Members could only work on recommendations and supporting text if they had no relevant conflicts of interest. All

sections were collaboratively written by the members. The development of each recommendation was based on the entirety of current scientific, pharmacological and medical knowledge, assessing the risks and benefits of the intervention using validated methodologies (Tables 1 and 2) (15). In areas lacking strong evidence, expert consensus was used to address important daily practice issues. Preliminary consensus was reached through conference calls and in-person meetings, with a minimum of 75% agreement among present members necessary to move the draft recommendations forward. An anonymous electronic survey then gathered votes on each recommendation, along with the corresponding Class of Recommendation and Level of Evidence. A consensus was achieved with an 80% response rate and at least 75% affirmative votes on each recommendation. EACTS appointed a peer review committee, adhering to strictly multidisciplinary patterns, to examine the document. Following a comprehensive review process, the document was endorsed for publication by the EACTS Clinical Practice Guidelines Committee and Council, resulting in its publication in the *European Journal of Cardio-Thoracic Surgery.*

Table 1: Levels of evidence	
Level of evidence A	**Data derived from multiple randomized clinical trials or meta-analyses.**
Level of evidence B	**Data derived from a single randomized clinical trial or from large non-randomized studies.**
Level of evidence C	**The consensus of expert opinion and/or small studies, retrospective studies and registries.**

Table 2: Classes of recommendations		
Class of recommendations	**Definition**	**Suggested wording**

Class I	**Evidence and/or general agreement that a given treatment or procedure is beneficial, useful and effective.**	**Is recommended/is indicated**
Class II	**Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure.**	
Class IIa	**Weight of evidence/opinion is in favour of usefulness/efficacy.**	**Should be considered**
Class IIb	**Usefulness/efficacy is less well established by evidence/opinion.**	**May be considered**
Class III	**Evidence/general agreement that the given treatment/procedure is not useful/effective and may sometimes be harmful.**	**Is not recommended**

3 Preoperative management

In patients electively admitted for cardiac surgery, up to 80% are on medication(s) that require specific attention during the preoperative period such as antiplatelets, anticoagulants, blood-pressure and/or glucose-lowering drugs, among others (17). However, it was recently reported that 70–90% of drugs with a recommended interruption before the operation are not managed correctly (17). This overlook in preoperative medication management calls for a more systematic management of medication review and adjustment in the preoperative setting to ensure optimal patient safety and better surgical effectiveness. Therefore, a medication review 7 to 14 days prior to the elective operation, using institutionally developed checklists and action plans, is highly advised. Such an approach would involve careful evaluation of each patient's medication regimen and implementation of guidelines for medication management, the goal being to optimize the risk/benefit balance of either continuing or discontinuing medications prior to surgery [for anticoagulant and/or antiplatelet drugs see section 4; for glucose-lowering drugs see section 11; for sodium-glucose cotransporter-2 (SGLT2) inhibitors see sections 6.2 (heart failure) and 11 (blood glucose management); and for antidepressant drugs see section 12].

Because obesity is on the rise (18), an increasing fraction of patients with obesity is expected to undergo cardiac surgery. Among individuals with obesity, those with higher degrees of obesity (WHO classes ≥ 2) appear to have the highest risk of peri- and postoperative complications and death and have high pharmacological complexity (19, 20). Preoperative management of body weight is beyond the scope of this guideline, because it may require long-term preoperative strategies to reach an optimal body size for surgery. However, we acknowledge that morbid and severe obesity may require new specific and complex management requirements and encourage a multidisciplinary approach in addressing these complex patients to allow surgery under the best possible conditions.

3.1 Preoperative hypertension

Pre-existing essential arterial hypertension (HTA) is reported in approximately 75% of patients undergoing coronary artery bypass grafting (CABG) and in more than 80% of those undergoing surgical

aortic valve replacement (SAVR) (21, 22). HTA is associated with prolonged intensive care unit (ICU) stays and increased perioperative deaths among cardiac surgery patients (23, 24). Patients with uncontrolled HTA often experience unstable blood pressure during the entire perioperative period. In case of treatment-refractory or new-onset, non-'white coat' HTA, the potential benefits of delaying surgery for optimization must be carefully weighed against the risks associated with postponement. It is important that both the anaesthetist and the cardiac surgeon are made aware of new-onset HTA in a patient (25). If the blood pressure is over 180 mmHg systolic and 110 mmHg diastolic, elective cardiac surgery should generally be postponed until the situation is resolved, considering the relative cardiovascular risk and the potential harm from delaying the operation (26). Several blood-pressure-lowering drugs are available and should be carefully assessed and managed during the preoperative period in patients undergoing cardiac surgery (25, 27) (Table 3). It is crucial to recognize that, although antihypertensive medications may reach peak plasma levels within hours, their clinical onset of action can take weeks. This fact necessitates particular attention when managing these drugs preoperatively.

Table 3: Pharmacokinetics of antihypertensive medications

Drug	Initial dose	Maintenance dose	Maximum dose	Onset of action	Peak concentration	Half-life	Metabolism
Angiotensin-converting enzyme inhibitors							
Fosinopril	10 mg od	10–40 mg od	40 mg od	1 h	3 h	12 h	Hepatic (non-CYP450) into active metabolites (mainly fosinoprilat)
Captopril	25 mg bid	25–150 mg bid	450 mg bid or tid	15–30 min	60–90 min	2 h	Hepatic (50%, non-CYP450) into inactive metabolite
Enalapril	2.5 mg od	10–40 mg od	40 mg od	0.5–1 h	4-6 h	11 h	Hepatic (70%, non-CYP450) into active metabolites (mainly enalaprilat)
Lisinopril	10 mg od	10–40 mg od	80 mg od	1 h	6–8 h	12 h	Not metabolized, excreted unchanged in urine
Ramipril	2.5 mg od	2.5–10 mg od	10 mg od	1–2 h	2–4 h	13–17 h	Hepatic (non-CYP450) into active metabolites (mainly ramiprilat)
Trandolapril	0.5 mg od	2–4 mg od or bid	4mg od	0.5 h	3–6 h	15–23 h	Hepatic (non-CYP450) into active metabolite (trandolaprilat)
Angiotensin II receptor antagonists							

Candesartan cilexetil	8 mg od	8–32 mg od	32 mg od	2–3 h	2–4 h	9 h	Hepatic (non-CYP450) into active metabolites (candesartan)
Valsartan	80 mg od	80–320 mg od	320 mg od	2 h	2–4 h	6 h	Hepatic 20%, non-CYP450
Losartan	50 mg od	50–100 mg od	100 mg od	1–2 h	1 h, 3–4 h metabolite	6–9 h	Hepatic metabolism (CYP2C9 and 3A4); inactive and active metabolites
Olmesartan	20 mg od	20–40 mg od	40 mg od	1–2 h	1–2 h	10–15 h	Prodrug converted into olmesartan, the intestinal wall
Irbesartan	150 mg od	150–300 mg od	300 mg od	1–2 h	1.5–2 h	11–15 h	Hepatic (non CYP450) into inactive metabolite
Beta-blockers							
Atenolol	25 mg od	25–100 mg od	100 mg od	3 h	2–4 h	6–7 h	Hepatic (non-CYP450) inactive metabolite
Bisoprolol	2.5 mg od	2.5–10 mg od	20 mg od	1–2 h	2–4 h	9–12 h	Hepatic (CYP 3A4 and 2D6) into inactive metabolite
Carvedilol	12.5 mg od	12.5–25 mg od	25 mg od	1 h	5 h	7–10 h	Hepatic (several CYP450s) active metabolite
Metoprolol†	25 mg od	25–100 mg od	400 mg od	1–2 h	1.5–2 h	3–4 h	Hepatic (CYP2D6) inactive metabolite
Nebivolol	5 mg od	5–40 mg od	40 mg od	1–2 h	1.5–4 h	10–32 h	Hepatic (CYP2D6 and UDP-GT) into active metabolite
Calcium channel blockers							
Nifedipine†	30 mg od	30–90 mg od	90 mg od	30 min	2.5–5 h	2–5 h	Hepatic (CYP3A4) into inactive metabolite
Amlodipine	5 mg od	5–10 mg od	10 mg od	2–3 h	6–12 h	30–50 h	Hepatic (CYP3A4 and UDP-GT) into inactive metabolite
Diltiazem†	180 mg od	180–420 mg od	480 mg od	30–60 min	2–4 h	3–4.5 h	Hepatic (CYP3A4) into active and inactive metabolite
Verapamil†	80 mg od	120–360 mg dd or bid	480 mg od or bid	1–2 h	7–11 h	3–7 h	Hepatic (CYP3A4) into active metabolite
Felodipine	2.5 mg od	2.5–10 mg od	20 mg od	2–5 h	2–5 h	10–16 h	Hepatic (CYP3A4) into inactive metabolite
Diuretics							
Hydrochlorothiazide	12.5 mg od	12.5–50 mg od or bid	50 mg od or bid	3–4 d	1–2.5 h	5.6–14.8 h	Not metabolized
Furosemide	20 mg od	20–80 mg od or bid	80 mg od or bid	30–60 min	1–2 h	1–1.5 h	Hepatic 20% (non-CYP3A4) activity of metabolite unknown

†Extended release.
bid: twice daily; CYP450: cytochrome P450; od: once daily; tid: three-times a day.

Beta-blockers: Many patients undergoing cardiac surgery are already taking beta-blockers (BBs) (28, 29). Studies suggest maintaining BBs for both elective and emergency cardiac procedures to decrease mortality (30, 31) and dysrhythmias after surgery (32-35). However, continuing BBs in chronic users

until the day of the operation may impair the effectiveness of catecholamines and increase the risk of bradycardia and hypotension in the early postoperative period (36, 37), although this practice has not been associated with an increased length of hospitalization (34). Thus, for patients on long-acting preoperative BBs, a switch to short-acting agents could minimize haemodynamic complications. Nonetheless, the favourable risk–benefit profile of continuing perioperative BB therapy is particularly evident in the marked reduction of new-onset postoperative atrial fibrillation (POAF) (33, 34, 38). Given these findings, continuing BBs through the perioperative period is recommended.

Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers: The risks and benefits of continuing angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) in the perioperative period are still debated (39, 40). Previous studies suggest that ACEIs/ARBs reduce systemic vascular resistance (41), leading to increased risk of perioperative hypotension (42), vasodilatory shock (43), prolonged time on a ventilator and prolonged stay in the ICU (44). Recent clinical trials (45, 46) and large-scale observational studies (47, 48) suggest that perioperative continuation of ACEI/ARB does not adversely affect outcomes and may potentially enhance survival in the early postoperative period (47, 48). If interrupted, the timing should be based on the drug's half-life and on the individual characteristics of patients with hypertension: Long-acting inhibitors may be discontinued 24 h before open-heart surgery, whereas short-acting inhibitors may be interrupted on the day of the operation. Patients on long-acting ACEIs and ARBs may be switched to short-acting ACEIs or ARBs to better handle the timing of discontinuation and reduce the risk of perioperative hyper- and hypotension. ACEIs/ARBs should be carefully (re)introduced in the early postoperative period, guided by haemodynamic parameters.

Calcium channel blockers: Older studies suggest that abrupt cessation of calcium channel blockers (CCBs), especially in cases of coronary revascularization, may lead to severe vasospasm (49) or an increased risk of bleeding (50, 51). More recent studies have reported that continuing short-acting diltiazem could result in more stable haemodynamics and a reduction in mortality for cardiac surgery patients without excess bleeding (52, 53). Therefore, preoperative continuation of CCBs is generally considered safe. In patients with poor haemodynamic control, those on long-acting CCBs may be switched to short-acting CCBs. Caution is advised if CCBs are used with BB on the morning of the

operation, because this combination can enhance the negative inotropic and chronotropic effects of β-blockade. Existing research on the effectiveness of preoperative CCBs for cardioprotection, the prevention of perioperative coronary vasospasm (54, 55) and the improvement of short-term outcomes (53, 56) remain inconclusive. This issue requires further investigation, particularly because multiple arterial grafts, which are prone to vasospasm, are being used and recommended with increasing frequency in CABG surgery (57).

α-Blockers: There are no data on the risk/benefit balance associated with continuing or discontinuing α-blockers preoperatively. It is general practice to maintain these drugs on the day of surgery, because abrupt withdrawal can lead to extreme hypertension and myocardial ischaemia. A Cochrane Review found that administering low-dose α-blockers [clonidine (21 RCTs), dexmedetomidine (24 RCTs) and mivazerol (2 RCTs)] compared with placebo in patients undergoing cardiac surgery did not reduce the rate of death or of MI (58); however, it doubled the risk of clinically significant bradycardia (58, 59). Therefore, prophylactic α-blockers should not be initiated preoperatively to reduce the risk of ischaemic complications in patients who are not treated with clonidine.

Diuretic agents: A large observational study with over 22,000 open-heart surgery patients, included in the Veterans Health Administration Database, reported a 22% relative risk increase of postoperative AKI associated with chronic use of thiazide or loop diuretics, while postoperative AKI was associated with increased mortality and major morbidity (60). However, the effect of preoperative interruption of chronic diuretic therapy on AKI remains unexplored. A single-centre underpowered trial found that, compared with placebo, spironolactone did not protect against AKI in cardiac surgery and even suggested a trend towards increased risk [odds ratio (OR) 1.48; 95% confidence interval (95% CI) 0.82–2.66], although this result was mostly driven by AKI stage 1 (61). Although continuing diuretic agents may lead to hypovolaemia and hypotension, electrolyte imbalances are typically manageable during cardiopulmonary bypass (CPB). Despite limited and somewhat conflicting data, the task force consensus is to continue diuretics until the day of the operation, switching to parenteral agents postoperatively if necessary.

The continuation of mineralocorticoid receptor antagonists (MRAs) throughout the perioperative period has not been associated with increased rates of AKI requiring dialysis, mortality or major morbidities (cardiovascular, neurological and infectious) in observational settings (62). Nonetheless, their role in this clinical context still warrants further investigation through prospective studies, especially given the higher reported incidence of postoperative low cardiac output state (62).

Recommendation Table 1. Recommendations for preoperative hypertension medications

Recommendations	Class[a]	Level[b]	Ref[c]
It is recommended to continue BBs until open-heart surgery.	**I**	**A**	**(32-35)**
Continuing ACEIs and ARBs should be considered until open-heart surgery, taking into account each drug's half-life and the characteristics of the individual patient.	**IIa**	**B**	**(45-48)**
It is recommended to continue CCBs and diuretics until open-heart surgery.	**I**	**C**	**-**

ACEI: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blocker; BBs: beta-blockers; CCB: calcium channel blocker.
[a]Class of recommendation.
[b]Level of evidence.
[c]References.

3.2 Prophylaxis for perioperative arrhythmias

The most common arrhythmia following cardiac surgery is POAF, with an incidence ranging from 15% to 40% in different patient groups (38). Approximately 90% of POAF cases occur within the first 6 days after the operation (63). New-onset POAF is associated with an increased incidence of major short-term complications, including stroke (64, 65). It is also associated with an increased long-term risk of death and thromboembolic complications (33, 65-69). Furthermore, POAF predicts the likelihood of developing atrial fibrillation (AF) in the months following discharge from the index hospitalization (66,

70, 71). Early recurrence of AF is associated with an increased risk of future hospitalization with HF, but no association was observed between early AF recurrence and all-cause mortality (71).

Robust research has established the significant effectiveness of BBs in reducing the new-onset POAF across various cardiac surgery procedures (32-35, 38). Therefore, patients currently taking BBs are recommended to continue their treatment both before and after surgery.

However, the decision to initiate BBs immediately before surgery solely to prevent arrhythmias requires careful consideration. Since 2007, the National Quality Forum in the United States has endorsed the administration of BBs at least 24 h before isolated CABG surgery as one of the quality metrics. However, conclusive evidence supporting the benefits of initiating BBs shortly before the operation is still lacking (72). If BBs are to be administered preoperatively in naïve patients, a gradual adjustment of the dose is recommended, using short-acting drugs and formulations based on the patient's blood pressure and heart rate and starting several days before the operation.

Amiodarone for arrhythmia prophylaxis is more effective than BBs but carries a higher risk of acute and long-term complications (33, 73-77). Still, it could be an option for patients who are intolerant to BBs. Although magnesium, fish oil and omega-3 fatty acids are thought to prevent POAF, RCTs provide conflicting evidence, preventing a definitive recommendation (78-80). The recent TIGHT K non-inferiority, open label, RCT randomized 1690 post-CABG patients in sinus rhythm and no kidney disease to potassium supplementation when serum concentration fell <4.5 mEq/L (tight group) or <3.6 mEq/L (relaxed group). There was no difference in new-onset POAF, flutter, or tachyarrhythmia both clinically detected and electrocardiographically confirmed up to 120 hours postoperatively or at hospital discharge (81). Currently, no data from large RCTs support using steroids (82) or statins (83-85) to prevent POAF in cardiac surgery (86).

Recommendation Table 2. Recommendations for prophylaxis of perioperative arrhythmias

Recommendations	Class[a]	Level[b]	Ref[c]

It is recommended to continue BBs throughout the perioperative period to prevent postoperative arrhythmias.	**I**	**A**	**(32-35, 87)**
Short–term, low–dose BBs may be considered in BB–naïve patients to prevent arrhythmias following open–heart surgery.	**IIb**	**B**	**(72)**
Amiodarone may be considered to prevent POAF in open–heart surgery.	**IIb**	**A**	**(33, 73, 75, 88)**
It is not recommended to initiate steroids and statins early before open-heart surgery to prevent POAF.	**III**	**A**	**(82-85)**

BBs: beta-blockers; POAF: postoperative atrial fibrillation.
[a]Class of recommendation.
[b]Level of evidence.
[c]References.

3.3 Stress ulcer prophylaxis

The incidence of upper gastrointestinal (GI) bleeding following cardiac surgery is estimated to be around 0.5% to 1%, with associated mortality rates of up to 30% to 40% (89, 90). Thus, the administration of gastroprotectant drugs is indicated immediately before cardiac surgery and in the early postoperative phase to reduce GI complications after surgery.

There is comprehensive support in the literature for proton pump inhibitors (PPIs) over histamine-2 receptor blockers (H2RBs) for reducing GI complications in cardiac surgery patients (91-93). Evidence from a pivotal trial involving 210 participants revealed a lower incidence of active ulcers in patients treated with the PPI rabeprazole (4.3%) compared with those receiving ranitidine, an H2RB (21.4%), and teprenone, a mucosal protector (28.6%) (94). However, secondary analysis from the PEPTIC trial (Effect of Stress Ulcer Prophylaxis With Proton Pump Inhibitors vs Histamine-2 Receptor Blockers on In-Hospital Mortality Among ICU Patients Receiving Invasive Mechanical Ventilation) showed no significant differences in efficacy or safety between PPIs and H2RBs (95), yet the findings must be cautiously interpreted due to a 20% medication crossover (96). Furthermore, studies suggest a link

between the use of a PPI and AKI dialysis (97) or pneumonia in patients in the ICU (98) but may be influenced by confounding factors (93, 99). Considering current evidence, it is recommended to use PPIs for stress ulcer prophylaxis in cardiac surgery, with H2RBs as a viable alternative.

Recommendation Table 3. Recommendations for stress ulcer prophylaxis

Recommendations	Class[a]	Level[b]	Ref[c]
The perioperative administration of gastroprotection, preferably with a PPI rather than histamine-2 receptor blockers, is recommended to prevent gastrointestinal bleeding in patients having open-heart surgery.	I	B	(94, 95)

PPI: proton pump inhibitor.
[a]Class of recommendation.
[b]Level of evidence.
[c]References.

4 Antithrombotic management

Antithrombotic drugs, including antiplatelet and anticoagulant agents, are essential in the management of cardiovascular diseases for reducing new ischaemic complications and recurrence. However, antithrombotic drugs invariably increase the risk of bleeding that, while generally lower than their benefits in cardiovascular patients, must be carefully considered in the perioperative setting of cardiac surgery. The complexity of maximizing the ischaemic prevention while minimizing the risk of bleeding necessitates a careful multidisciplinary approach to achieve optimal short- and long-term patient outcomes.

There is no universally defined optimal timing for all cardiac operations. However, in preparation for their introduction into clinical practice, the present guideline classifies surgical indications as emergency, i.e. to be performed within 24 hours (h), urgent i.e. to be performed during the same hospitalization and elective, i.e. deferrable to allow optimal preparation for the operation.

4.1 Acetylsalicylic acid

4.1.1 Preoperative period

Most patients with established coronary artery disease who are referred for CABG have already been treated with low-dose acetylsalicylic acid (ASA) for secondary prevention. Although earlier aggregate data meta-analyses of RCTs and observational studies examining a strategy of continuing ASA until the time of CABG versus discontinuation of ASA have yielded mixed results (100-103), the sum of the evidence points to a benefit of continuing ASA until the operation with regard to a risk reduction for perioperative MI, but not for death. In a meta-analysis of 13 RCTs including 2,399 patients, continuing ASA was associated with a lower risk of MI versus discontinuation of ASA (OR, 0.56; 95% CI, 0.33–0.96; *P* = 0.03), without a significant difference in the risk of operative mortality (OR, 1.16; 95% CI, 0.42–3.22; *P* = 0.77) (102). Continuing ASA was associated with higher perioperative blood loss and transfusions but not with an increased risk of surgical re-exploration. The risk of bleeding appears dose-dependent, with an increased risk found for patients taking ASA >100 mg/day (101, 104, 105). Of note, the limitations of these studies include considerable heterogeneity with regard to duration and timing of

preoperative ASA administration, concomitant use of antifibrinolytics, outcomes definition and ascertainment.

In patients undergoing CABG who are ASA-naïve or in whom ASA has been discontinued, there is no clear evidence for a benefit of the preoperative initiation of ASA. In the ATACAS (Aspirin and Tranexamic Acid for Coronary Artery Surgery) trial, patients who received 100 mg ASA 1 to 2 h before CABG had a similar risk of the composite outcome of death or thrombotic complications at 30 days and a similar risk of bleeding compared to those who received placebo (106). In another RCT, patients who were randomized to preoperatively receive a higher dose, 300 mg, ASA had increased postoperative bleeding and transfusion rates, without significant differences in major cardiovascular events compared to placebo (107).

Discontinuation of antiplatelet therapy places patients at risk of perioperative ischaemic events (108), especially those with high-risk coronary artery disease or recent acute coronary syndrome (ACS), and must be balanced against an increased risk of surgical bleeding. Discontinuation of ASA preoperatively should therefore be considered in patients at a high risk of bleeding (e.g. redo operations, stage 4 or 5 kidney disease, haemostatic disorders), although limited evidence exists.

In patients with a preoperative indication for ASA who are undergoing non-coronary cardiac surgery, ASA may be discontinued 3 days before the day of the operation based on pharmacodynamic data reporting an adequate recovery of the cyclooxygenase-dependent platelet function (109-111). The ASA should be restarted postoperatively as soon as it is considered safe.

4.1.2 Postoperative period

The early initiation of low-dose ASA after CABG is associated with a reduced risk of death and ischaemic complications (4, 112) and should be continued indefinitely in patients who do not have contraindications to ASA. The routine use of ASA to prevent the occurrence of saphenous vein graft occlusion is based on early placebo-controlled RCTs demonstrating the benefit of ASA compared with placebo (113, 114). A meta-analysis of 17 RCTs (1,443 patients) showed that ASA significantly reduced graft occlusion (ASA with or without dipyridamole vs placebo: OR 0.60, 95% CI 0.51–0.71, $P < 0.0001$)

(115). A low- (100 mg) to-medium (325 mg) daily dose of ASA initiated within 6 h of CABG was associated with improved graft patency, without an increase in bleeding (115, 116). However, it is important to consider that more extensive evidence from larger and longer trials based on dose comparisons indicate that higher ASA dosing can increase the risk of GI bleeding (117-119).

Recommendation Table 4. Recommendations for acetylsalicylic acid

Recommendations	Class[a]	Level[b]	Ref[c]
Preoperative period			
In patients undergoing CABG who are on low-dose ASA preoperatively, continuing ASA throughout the perioperative period is recommended to reduce ischaemic events.	**I**	**B**	**(102, 104)**
Postoperative period			
In patients undergoing CABG, it is recommended to (re)start low-dose ASA within 24 h (ideally <6 h) postoperatively to reduce ischaemic events and graft occlusion.	**I**	**B**	**(112, 116)**

ASA: acetylsalicylic acid; CABG: coronary artery bypass grafting; SVG: saphenous vein graft.
[a]Class of recommendation.
[b]Level of evidence.
[c]References.

4.2 $P2Y_{12}$-receptor inhibitors

Dual antiplatelet therapy (DAPT) with ASA and $P2Y_{12}$-receptor inhibitors (clopidogrel, ticagrelor and prasugrel) is currently recommended after percutaneous coronary intervention (PCI) and ACS, irrespective of treatment strategy, because it reduces the risk of thrombotic complications and clinical events compared with ASA monotherapy (120-122). DAPT is associated with an increased risk of major spontaneous and surgical bleeding complications; however, the absolute benefit outweighs the absolute risk. More effective $P2Y_{12}$-receptor inhibitors (ticagrelor or prasugrel) are generally

recommended over clopidogrel due to the reduced risk of major vascular events, but at the expense of increased spontaneous and surgical bleeding complications (123-125). Clopidogrel is characterized by lower and more variable platelet inhibition and should only be used in patients considered at high risk of bleeding. The choice of antiplatelet regimen and the duration of therapy should balance the bleeding versus the thrombotic risks of the patient.

4.2.1 Preoperative management

Continuing DAPT until the day of the operation increases the risk of bleeding, transfusions and re-exploration for bleeding, as shown in RCTs (126-128), observational studies (129, 130) and meta-analyses (131, 132). Consequently, it is recommended that the $P2Y_{12}$-receptor inhibitors be discontinued before elective surgery in a timely manner whenever feasible (6). Elective operations may be postponed until the recommended DAPT treatment period is completed. In emergency or urgent cases, often in patients with ACS with or without mechanical complications, the risk for thrombotic complications (stent thrombosis and MI) while waiting for clearance of the $P2Y_{12}$-receptor inhibitor must be weighed against the risk for perioperative bleeding complications. Thus, in patients at very high risk for thrombotic events, emergency or urgent surgery may be performed without discontinuation of $P2Y_{12}$-receptor inhibitors. Bridging with cangrelor, a reversible intravenous effective $P2Y_{12}$ inhibitor with an ultrashort half-life, may be considered (133, 134) (Fig. 1).

Recommended discontinuation intervals differ according to the pharmacodynamic profile of each $P2Y_{12}$-receptor inhibitor. When $P2Y_{12}$-receptor inhibitors are discontinued, ASA therapy should be continued until the operation. Discontinuation of clopidogrel at least 5 days before CABG did not increase the risk of bleeding complications (132). A longer time interval (7 days) is recommended for prasugrel due to the higher degree of platelet inhibition (124) and a higher incidence of CABG-related bleeding complications compared with clopidogrel (124, 128, 135). Discontinuation of ticagrelor at least 3 days before the CABG procedure does not increase bleeding complications (123, 129), likely due to its reversible mechanism of action, as reported in multiple studies (127, 129, 136).

4.2.2 Preoperative platelet function testing

There is a significant interindividual variability in the magnitude and duration of the antiplatelet effect between different $P2Y_{12}$-receptor inhibitors (135-137) due not only to pharmacodynamics, but also from pharmacokinetics. Platelet function testing to assess the degree of residual platelet inhibition and the haemostatic recovery may guide the timing for surgical procedures to ensure the degree of platelet function recovery and therefore to reduce the bleeding risk, in patients who have received oral $P2Y_{12}$-receptor inhibitors close to open heart surgery or if the time since discontinuation is unclear or the optimal discontinuation is not feasible (135-138). However, this recommendation is supported by the haemostatic plausibility rather than by RCTs or observational studies assessing perioperative bleeding complications. Moreover, validated cut-ofs of $P2Y_{12}$-dependent aggregation able to predict perioperative bleeding remain currently unknown across different methods and devices.

Preoperative adenosine diphosphate-induced platelet aggregation predicts CABG-related bleeding complications in both clopidogrel- (138-141) and ticagrelor- (142, 143) treated patients with ACS. A strategy based on preoperative platelet function testing to determine the timing of CABG in clopidogrel-treated patients led to a 50% shorter waiting time compared with an arbitrary time-based discontinuation strategy (144). Platelet function testing in patients with ACS eligible for CABG appears to be a valuable approach to refine the timing and safety of the operation. The preoperative management of antiplatelet drugs, provided that the clinical presentation of a particular patient allows, is summarized in Fig. 1.

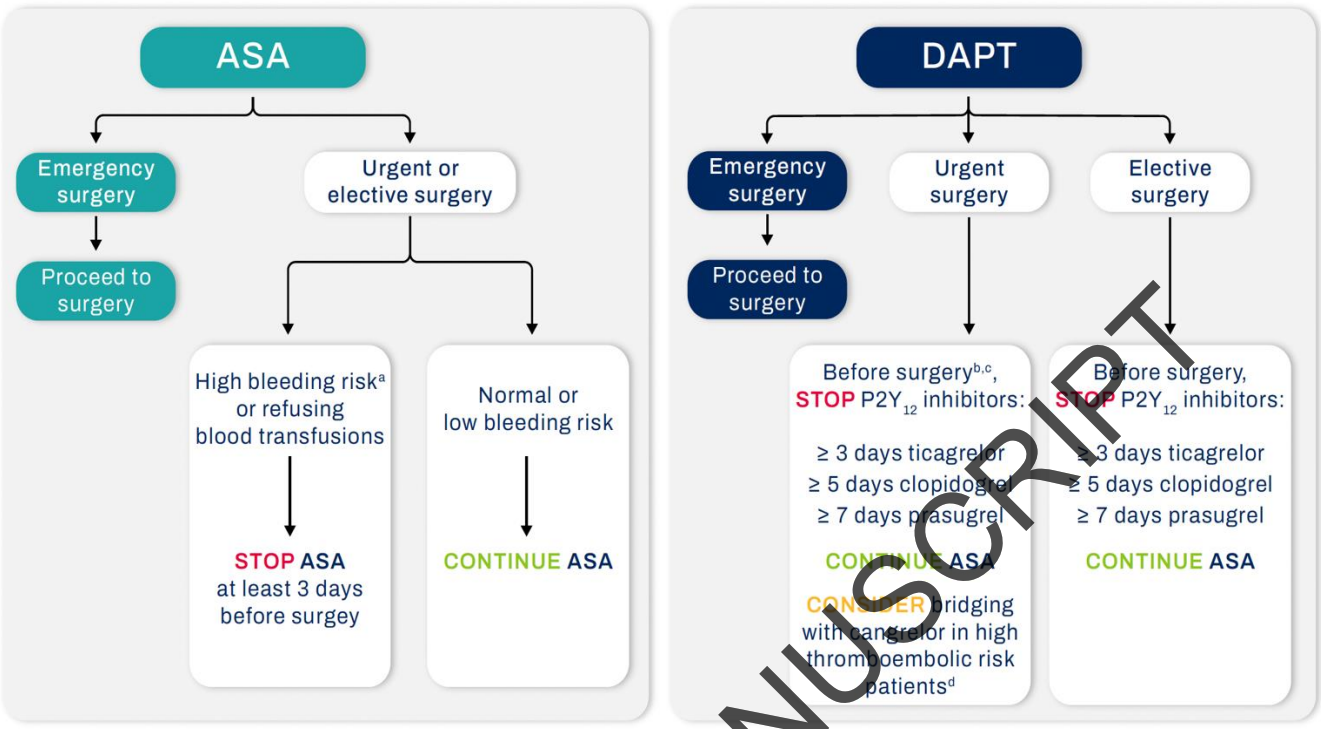

Figure 1: Management of single or dual antiplatelet drugs in patients undergoing cardiac surgery.

[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.

4.2.3 Postoperative management

Current guidelines recommend DAPT for all patients with ACS independently of revascularization (123), including patients undergoing CABG or other non-coronary cardiac procedures. DAPT has been associated with reduced risk of graft failure (145, 146), reduced all-cause mortality and ischaemic events after CABG in patients with ACS (126, 127). The potential benefits of DAPT after CABG are offset

by an increased risk of bleeding complications, but evidence is conflicting. The magnitude of the benefit appears to be more pronounced in patients with ACS than in those with chronic coronary syndromes and has been more consistently shown with ticagrelor than with clopidogrel for patients having CABG after ACS (145, 146). Overall, the evidence for a benefit of DAPT after CABG is heterogeneous and large RCTs are needed. The decision to use DAPT should be individualized based on patient characteristics and indication for surgery and by weighing the potential antithrombotic benefits against the risks of bleeding. DAPT after CABG should be restarted as soon as it is considered safe in patients with ACS and/or PCI with the indicated dose and duration (123). There are no data regarding the timing for restarting DAPT, although studies comparing different antiplatelet strategies following CABG often restart DAPT 48 h postoperatively (146).

Recommendation Table 5. Recommendations for $P2Y_{12}$ inhibitors

Recommendations	Class[a]	Level[b]	Ref[c]
Preoperative period			
In patients on DAPT who need non-emergency open-heart surgery, it should be considered to postpone surgery at least 3 days after discontinuation of ticagrelor, 5 days after clopidogrel and 7 days after prasugrel, to reduce bleeding.	**IIa**	**B**	**(127-129, 137)**
Testing for residual platelet function may be considered in patients who have received an oral $P2Y_{12}$-receptor inhibitor <7 days before open-heart surgery, to guide the timing of the operation and reduce bleeding.	**IIb**	**B**	**(138, 140, 143)**
Bridging $P2Y_{12}$-receptor inhibitors with a reduced intravenous dose of cangrelor until open-heart surgery may be considered in patients at high thromboembolic risk, to reduce major cardiovascular events.	**IIb**	**C**	**(133, 134)**
Postoperative period			

In patients with recent ACS or PCI, resuming or starting DAPT after open-heart surgery for the indicated duration is recommended as soon as it is considered safe to reduce the risk of stent thrombosis and major cardiovascular events.	**I**	**B**	**(126-128)**
In patients with CCS undergoing CABG, DAPT after surgery may be considered to reduce graft failure.	**IIb**	**B**	**(145, 146)**

ACS: acute coronary syndrome; CABG: coronary artery bypass surgery; CCS: chronic coronary syndrome; DAPT: dual antiplatelet therapy; PCI: percutaneous coronary intervention.
[a]Class of recommendation.
[b]Level of evidence.
[c]References.

4.3 Glycoprotein IIb/IIIa receptor antagonists

The use of GPIIb/IIIa-receptor antagonists (eptifibatide, tirofiban) in patients with ACS treated with PCI has become limited since the availability of effective oral and intravenous $P2Y_{12}$-receptor inhibitors (123). Recovery of platelet function with eptifibatide and tirofiban occurs approximately 4 h after discontinuation of treatment (147). Earlier discontinuation prior to surgery may further reduce bleeding risk in patients with stage 4 and stage 5 chronic kidney disease (CKD).

Recommendation Table 6. Recommendation for GPIIb/IIIa inhibitors

Recommendation	Class[a]	Level[b]	Ref[c]
In patients undergoing CABG, it is recommended to discontinue eptifibatide or tirofiban at least 4 h before open-heart surgery, to reduce bleeding.	**I**	**C**	**-**

CABG: coronary artery bypass surgery.
[a]Class of recommendation.
[b]Level of evidence.
[c]References.

4.4 Preoperative anticoagulation and bridging

Oral anticoagulation (OAC) is crucial in preventing and treating thromboembolic complications in different conditions. Elective cardiac surgery requires careful planning and decision-making, particularly for OAC, to minimize bleeding risk while protecting the patient from thrombotic complications. The development of strategies that decrease the risks of thrombosis and minimize major or clinically relevant bleeding remains a crucial field of research, despite the significant improvement in safety/efficacy balance associated with direct oral anticoagulants (DOACs) versus vitamin K antagonists (VKA).

4.4.1 Preoperative anticoagulation interruption in nonemergency cardiac patients

In patients on VKAs (Table 4) and with no indications for bridging (see section 4.4.3), it is recommended to discontinue VKA at least 4 days prior to any scheduled elective cardiac operation and monitor the international normalized ratio (INR) daily (123). The target INR for surgery should be <1.5 measured at least twice, including the day of the operation, a level deemed safe for these procedures (148). For patients who have an INR > 1.8 the day before the operation, either low-dose intravenous or low-dose oral vitamin K can be used, i.e. between 1 and 2.5 mg to avoid residual effects and rebound of thrombotic risk, given the high underlying thrombotic risk of the patients (149-151). Vitamin K given intravenously (IV) corrects the INR approximately 4 h earlier than oral administration (150, 151); however, there are no differences at 24 h, and the clinical relevance of a slightly earlier INR correction is unknown. Body weight- and INR-adjusted 4-factor prothrombin complex concentrate (PCC) can also be used, alone or in combination with vitamin K, for a fast (6–8 h preoperative administration) and complete reversal of VKA, using a relatively low starting dose (12.5 IU/kg), given the patient's high thrombotic risk (152).

DOACs are currently the recommended first-line treatment for venous thromboembolism (VTE) prevention and treatment as well as for non-valvular AF (153-155). DOACs brought new challenges in cardiac surgery, particularly in determining the timing for safe drug interruption before elective

procedures (156, 157) to minimize major and life-threatening bleeding (157-159). Given their reversible pharmacodynamics, 'bridging' is not applicable to this drug class. The specific discontinuation time frame varies based on drug's type, half-life, posology, indication and on patient's liver and renal function [estimated as creatinine clearance (CrCl)], usually using the Cockcroft-Gault equation. This is especially important for dabigatran etexilate, because dabigatran's active metabolite is almost exclusively dependent on renal clearance and this agent is contraindicated in patients with CrCl < 30 ml/min (Table 5). DOACs should be interrupted between 36 and 48 h before surgery (160-162) in patients with normal renal function (CrCl >80 ml/min), depending on their reversible pharmacodynamics and half-life. Because dabigatran has almost-exclusive renal clearance, patients with CrCl between 50 and 80 ml/min should have dabigatran discontinued 48 hours before surgery (162, 163). For patients with CrCl between 30 and 50 ml/min, an additional 24 hours (approximately 2 half-lives of the drug) is required (163).

Table 4: Vitamin K antagonists

Generic name	Bio-availability (%)	Protein binding (%)	Metabolism	Half-life (h)	Elimination
Warfarin	>95	>99	S-enantiomer (more potent): CYP2C9 (and CYP2C19) R-enantiomer: CYP3A4, CYP2C19 and CYP1A2	S-enantiomer ~31 R-enantiomer: 48	Renal and intestinal (inactive metabolites)
Acenocoumarol	>60	>98	CYP2C9 Minor CYP2C9/19 and 1A2	8–11	Mostly renal (inactive metabolites)
Phenprocoumon	95–100	>99	CYP2C9 and 3A4	110–130	Mostly renal
Phenindione	>90	88	CYP2C9 and 3A4	5–10	Mostly renal

Table 5: Characteristics of the different direct oral anticoagulant drugs

	Apixaban	Edoxaban	Rivaroxaban	Dabigatran
Target	FXa	FXa	FXa	FIIa (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% CYP3A4 P-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> 50 ml/min: 48 h	CrCl> 50 ml/min: 48 h	CrCl ≥ 50 ml/min: 48 h
	CrCl 30–50 ml/min: 72 h	CrCl 30–50 ml/min: 72 h	CrCl 30–50 ml/min: 72 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-FXa† ≥30 ng/ml	anti-FXa† ≥30 ng/ml	anti-FXa† ≥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) RCT on reversal of edoxaban have been published (164)

In urgent situations, when possible, delaying surgery ideally for 48 h to allow clearance of DOACs is the preferable option. In selected, complex patients with polypharmacy and comorbidities, measuring DOACs may be useful, although the validation of specific laboratory test results in the clinical outcome for each DOAC is still lacking (165-169).

For anti-FXa DOACs, prothrombin time within the normal range suggests minimal residual blood anticoagulation (170-172), whereas calibrated activated partial thromboplastin time within the normal range suggests minimal dabigatran blood concentrations (172). However, data regarding the clinical impact of minimal anti-FXa or anti-FIIa activity that is not detectable by many routine assays remain conflicting, especially in cardiac surgery.

Diluted thrombin time is linearly correlated with dabigatran concentrations (with a safety value below 21 s) (173). Calibrated anti- FXa assays are linearly correlated with DOAC levels. Generally, anti-FXa levels <30 ng/ml are considered safe for performing major surgery(174), thus for higher residual concentrations, surgery should be delayed by 12 h (for concentrations of 30-200 ng/ml) or 24 h (for concentrations of 200–400 ng/ml) (175).

4.4.2 Management of vitamin K antagonist in patients with indications for bridging

The decision to bridge VKA with unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH) depends on the underlying thrombotic risk of the patient. Preoperative bridging of VKA may be associated with increased intra- and postoperative bleeding. Therefore not all patients on VKAs undergoing cardiac surgery should be bridged (176). In the BRIDGE (Perioperative Bridging Anticoagulation in Patients with Atrial Fibrillation) trial, 1884 patients with AF who were taking VKA were randomized to LMWH (dalteparin) or placebo after warfarin interruption; thromboembolic events were similar between the groups (0.3% vs 0.4%), but major bleeding was significantly higher in the dalteparin group (3.2% vs 1.3%, *P*=0.005) (177). However, the trial excluded high thrombotic risk patients due to mechanical heart valves (MHV), recent stroke (within 12 weeks), embolism, transient ischaemic attack or valvular AF (177). Similarly, a recent meta-analysis of 6 RCTs and 12 observational studies showed a similar risk of thromboembolism between bridging and non-bridging, but bridging was associated with an increased risk of major bleeding (178). Consequently, bridging VKA is recommended only for patients at high risk of thrombotic events, such as those with MHVs; AF with rheumatic valvular disease; a recent acute thrombotic event within the past 12 weeks, defined as an ischaemic stroke; or pulmonary embolism (PE); and patients with acquired or congenital severe prothrombotic defects and with thrombus in the left ventricular apex.

Bridging does not generally apply to DOACs, because their rapid and reversible pharmacodynamics (Table 6), make them easier to discontinue and resume postoperatively, thus not necessitating conventional heparin bridging. After preoperative DOAC interruption (Table 6 and Fig. 2), in patients

deemed at very high thrombotic risk, heparin may be used on the day before the intervention, but with no clinical data in support.

OAC discontinuation and heparin use are summarized in Fig. 2. Some studies suggest a reduction in postoperative major bleeding, including re-exploration for bleeding, in patients who received preoperative UFH compared with LMWH (179, 180). Conversely, other studies indicate that overall adverse events, encompassing thromboembolism and bleeding, are comparable or even lower in patients treated with LMWH than in those treated with UFH (181-183). UFH usually requires in-hospital continuous IV infusion and monitoring, unlike LMWH. Thus, LMWH is an easier option for bridging VKA, though its effectiveness and safety can vary depending on body weight and renal function, respectively. Moreover, in case of major bleeding, at variance with UFH, LMWHs are not fully reversible with protamine sulphate, which should be considered. Finally, the optimal dose regimen of LMWH for bridging of VKA-treated patients is unknown. LMWH used as a bridging strategy in VKA-treated patients is usually administered until the day before the operation, depending on the type and posology. Bridging with fondaparinux is generally not recommended due to its long half-life (17–21 h) and the lack of an antidote (184).

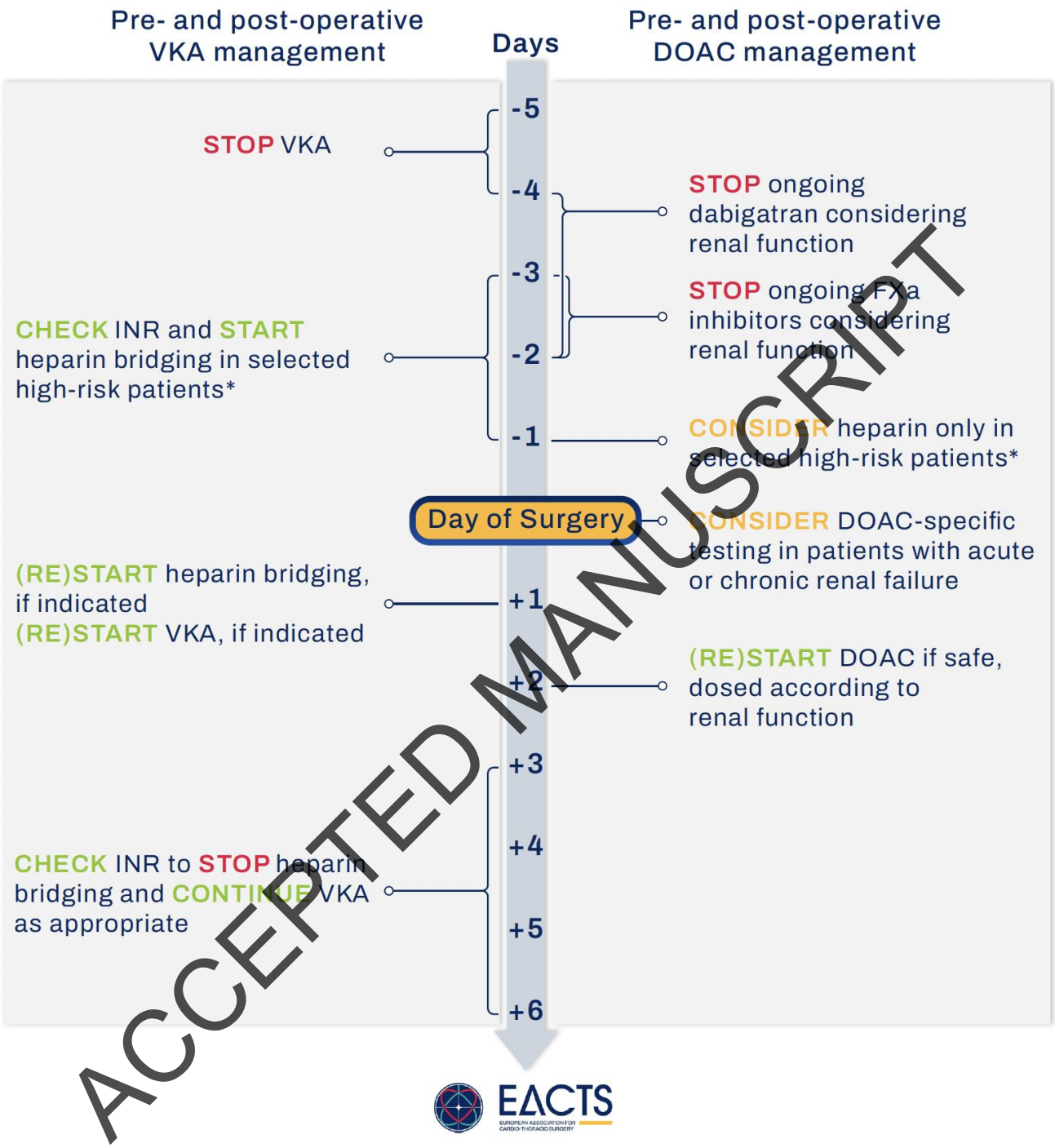

Figure 2: Perioperative management of VKA and DOACs.

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.

At present, there is no definitive evidence specifying the best timing for discontinuing preoperative UFH and LMWH. Based on the half-life of the different heparins, it is recommended to discontinue IV UFH 2–4 h before the start of the operation and check the activated partial thromboplastic time levels (185) and LMWHs no later than 12 h before the operation, considering the LMWH type (because LMWHs have different half-lives) and dosages (185, 186). When the last dose of a twice-daily LMWH regimen, e.g. enoxaparin, is administered about 14 h (usually the evening) prior to the operation, relatively high anti-Xa activity may still be present at the time of surgery (187) and a longer discontinuation period may be warranted, especially in patients with reduced renal function.

4.4.3 Management of preoperative anticoagulation in emergency operations

For emergency operations in non-bleeding patients under OAC, the benefits of performing the procedure as soon as possible must be weighed against the risk of major bleeding. When it is not feasible to interrupt VKAs within the suitable time interval, 4-factor PCC at a fixed or body-weight adjusted dose, and in relation to the patient's INR, is recommended as first-line therapy for fast reversal, along with vitamin K1 (intravenous or oral) (188, 189). For emergency, non-bleeding patients on anti-FXa DOACs (Table 5), using drug-specific tests is advised. If plasma concentrations are above a reference interval and the operation cannot be postponed, the off-label use of 4-factor PCC (typically 50 U/kg) has been suggested to be safe and effective (188, 190-192). Activated PCC or recombinant activated FVII may also be considered for non-bleeding patients on dabigatran, but must be balanced against a heightened risk of arterial thrombosis, including MI, associated with these reversal agents (190, 193, 194). Idarucizumab can be used for the specific, rapid and safe reversal of dabigatran in

emergency bleeding and in non-bleeding situations requiring major invasive procedures (Table 6). The efficacy of 5 g of IV idarucizumab in reversing the anticoagulant effects of dabigatran was tested in the RE-VERSE AD (Reversal Effects of Idarucizumab on Active Dabigatran) trial in patients with uncontrolled, life-threatening bleeding or requiring major urgent procedures, with diluted thrombin time normalization as the primary trial outcome (195). Idarucizumab completely reversed diluted thrombin time in over 98% of patients (196). In emergency cardiac surgery, including heart transplants, the use of idarucizumab has shown its effectiveness, but the number of studies is small, and the number of cardiac surgery patients in the RE-VERSE AD (Reversal of Dabigatran Anticoagulant Effect With Idarucizumab) trial is extremely limited (156, 197). Patients treated with idarucizumab experienced no complications related to heparinization for the initiation of CPB, because the antidote binds the drug rather than FIIa. However, given the small number of exposed patients, careful haemostatic surveillance is needed because 7.5% of patients treated with idarucizumab required surgical re-exploration for bleeding, and 66% were given perioperative transfusions (156). Further studies on safety and clinical efficacy are needed. Following the administration of idarucizumab, dabigatran can be resumed 24 h later if the patient is clinically stable and has achieved adequate haemostasis based on the REVERSE-AD trial, but the experience after cardiac surgery is limited (198). Moreover, antithrombotic therapies can be initiated after idarucizumab, providing the patient is stable and reaches adequate haemostasis (198).

The safety and efficacy of andexanet alfa in reversing the anticoagulant effects of rivaroxaban and apixaban in emergency cardiac surgery was not tested in the phase 3 ANNEXA-4 (Andexanet Alfa, a Novel Antidote to the Anticoagulation Effects of Factor Xa Inhibitors) RCT. Therefore, it has no approval for reversal during major invasive procedures in non-bleeding patients (Table 6). Thus, use of andexanet alfa for emergency surgery in patients taking anti-FXa DOACs is off-label, reflecting the ANNEXA-4 trial design (199). Whereas andexanet alfa effectively reduces anti-FXa activity and improves clinical haemostasis in patients with major bleeding on anti-FXa DOACs and enoxaparin (164), its preoperative use in cardiac surgery has been linked to a possible transient heparin resistance during CPB (156, 200), resulting in clot formation in the CPB circuit that adversely affects patient outcomes. Consequently, the European Medicines Agency cautions against the preoperative use of andexanet alfa in cardiac surgery

due to the possibility of developing transient, acquired heparin resistance when heparin is required for surgery (201). Thus, andexanet alfa warrants careful consideration and routine avoidance in patients undergoing cardiac surgery with CPB. However, in specific emergency when risks associated with possible heparin resistance are minimal, such as post-transcatheter intervention tamponade or persistent bleeding after weaning from CPB, andexanet alfa may be an option to attenuate the anticoagulation effects, if circulating DOAC levels are detectable. In the case of andexanet alfa used before cardiac interventions requiring heparinization, antithrombin concentrate and higher heparin doses may be attempted to overcome resistance and achieve the required anticoagulation levels (202). Alternatively, bivalirudin or argatroban can be used instead of heparin to overcome transient heparin resistance (200). The diagnosis and treatment of heparin-induced thrombocytopenia are comprehensively addressed in EACTS guideline on patient blood management (12).

The data on haemadsorption devices able to adsorb the anti-FXa DOACs or ticagrelor in cardiac surgery patients are very limited. Thus, recommendations cannot be made yet for this type of approach.

Table 6: Direct reversal agents for direct oral anticoagulants

	Andexanet alfa	**Idarucizumab**
Specific reversed drug	Rivaroxaban Apixaban Edoxaban† (Enoxaparin†)	Dabigatran
Drug target	Decoy protein sequestering all FXa inhibitors	Monoclonal antibody fragment binding only dabigatran
Dosing	i. Last DOAC administration ≥ 8 h: low dose ii. Last DOAC administration < 8 h: a. Low-dose, if rivaroxaban dosage is ≤ 10 mg, or apixaban ≤ 5 mg or edoxaban < 30 mg† b. High-dose, if rivaroxaban dosage > 10 mg, or apixaban > 5 mg, or edoxaban ≥ 30 mg†	5 g (2 vials of 2.5 g/50 mL)

Administration	Low-dose: 400 mg bolus, followed by 2-h infusion, 4 mg/min High-dose: 800 mg bolus, followed by 2-h infusion, 8 mg/min	Two intravenous doses administered within 5–10 min (infusion or bolus)
Onset	Within minutes	Within minutes
Half-life	5–7 h	Biphasic: 45 min (initial), terminal 4–8 h

†Not yet approved for edoxaban or enoxaparin, but the extension of the phase 3 RCT (203) reported similar efficacy in reducing anti-Xa activity compared to rivaroxaban and apixaban (164).

‡

DOAC: direct oral anticoagulants; FXa: activated coagulation factor X.

Recommendation Table 7. Recommendations for management of preoperative anticoagulation

Recommendations	Class[a]	Level[b]	Ref[c]
Preoperative period			
It is recommended to discontinue VKAs at least 4 days before elective, open-heart surgery to aim for an INR ≤ 1.5 on the day of surgery.	**I**	**B**	**(176)**
It is recommended to discontinue DOAC therapy between 48 and 96 h before elective, open-heart surgery, depending on the drug's half-life and renal function, with no need for routine heparin bridging.	**I**	**B**	**(157-159, 161)**
In emergency, open-heart surgery, idarucizumab should be considered to reverse dabigatran, if needed.	**IIa**	**B**	**(197)**

In an emergency, open-heart operation involving CPB, andexanet alfa is not recommended in patients on FXa inhibiting DOACs before weaning from CPB.	**III**	**C**	**(156)**
Bridging for VKA is recommended in patients at high thrombotic risk due to: • mechanical prosthetic heart valve • AF with rheumatic valvular disease • acute thrombotic event within the prior 12 weeks • acquired or congenital prothrombotic defects[d] • left ventricular apex thrombus.	**I**	**C**	**-**
Bridging VKA with UFH or LMWH is recommended, if indicated[e].	**I**	**B**	**(176, 179-183)**
In patients on preoperative UFH, it is recommended to stop UFH 2–4 h before surgery and to measure aPTT, to avoid bleeding.	**I**	**C**	**-**
In patients on preoperative bridging with LMWH, it is recommended to administer the last dose 12 to 24 h before surgery, depending on the type of LMWH.	**I**	**B**	**(186, 187)**

AF: atrial fibrillation; aPTT: activated partial thromboplastin time; CPB: cardiopulmonary bypass; DOAC: direct oral anticoagulant; FXa: activated coagulation factor X; INR: international normalized ratio; LMWH: low-molecular-weight heparin; UFH: unfractionated heparin; VKAs: vitamin K antagonists.

[a]Class of recommendation.

[b]Level of evidence.

[c]References.

[d]Defects of antithrombin, protein C, protein S, factor V Leiden mutation, antiphospholipid syndrome.

[e]According to the indications provided in the current recommendation table.

4.5 Postoperative bridging and long-term antithrombotic drug management

The implantation of artificial heart valves and prosthetic materials in cardiac surgery significantly increases the risk of thromboembolic events. Consequently, antithrombotic prophylaxis becomes an essential component of postoperative care, depending on the type and anatomic site of the intervention.

4.5.1 Mechanical heart valves

Patients with MHVs require lifelong VKA therapy, with routine INR monitoring, unless major bleeding occurs requiring temporary discontinuation (Fig. 3) (204-206). Treatment with VKA should be started, possibly on the first postoperative day and, as soon as it is considered safe, in combination with heparin bridging therapy (Fig. 2). Bridging with either a therapeutic dose of UFH or LMWH is initiated as soon as postsurgical bleeding is deemed minimal, usually within the first 24 h of admission to the postoperative ICU. Bridging after open-heart surgery appears associated with a reduced rate of thromboembolic events compared to no bridging (207). Although IV UFH infusion has been the usual choice for bridging, LMWH has gained use due to its subcutaneous dosing, which facilitates dosing and early mobilization of patients. Evidence from earlier studies (208-211) and a recent single-centre observational study in Chinese patients (212) provides similar safety and efficacy outcomes between different heparins. Nevertheless, randomized data are needed to determine the timing and dosage for UFH and LMWH bridging strategies. Bridging should be discontinued once the INR reaches the adequate therapeutic range in 2 consecutive tests.

The postoperative risk of thromboembolism peaks around 1 month after MHV implantation and continues to be elevated in the first 6 months (213). The target INR for patients with MHV is determined by the type and site (e.g. aortic, mitral or tricuspid) of the prosthesis and the underlying characteristics and comorbidities of the patient (e.g. recent thrombosis, age, kidney function). For patients with congenital or acquired hypercoagulable states, increased risk for thromboembolic events and a left ventricular ejection fraction (LVEF) below 35% or for those with mitral and tricuspid prostheses, a higher INR therapeutic range is recommended (target INR 3, range 2.5–3.5). Adequate time in the therapeutic

range (TTR), i.e. ≥70%, indicates stability of VKA response, high quality of the treatment and improved safety (214), whereas a low TTR is an independent predictor of adverse outcomes following MHV replacement (7, 215). Some studies indicate that a lower INR range with the addition of low-dose ASA might be safer and equally effective. In addition, for some of the newer generations of aortic MHVs, lower INR ranges can be used in patients without additional risk factors and at a high risk of bleeding (216, 217); however they should not be used in patients with mitral MHVs (218). Still, more evidence is needed concerning the possibility of scaling down VKA intensity in newer generation valves.

Given the complexity of VKA therapy, its high variability due to interactions with drugs and food, genetics and patient characteristics and comorbidities (219), patient education is crucial to significantly improve adherence, TTR and quality of VKA (220). In RCTs, INR self-monitoring was safer than non-monitoring (221, 222) in patients who were well-trained and motivated. DOACs have also been tested in RCTs following MHV implantation. The phase 2, RE-ALIGN (Randomized, Phase II Study to Evaluate the Safety and Pharmacokinetics of Oral Dabigatran Etexilate in Patients after Heart Valve Replacement) RCT investigated the safety and efficacy of different doses of dabigatran versus VKA in patients with an aortic or mitral MHV (223). However, this trial was stopped prematurely due to an elevated risk of thromboembolic complications and major bleeding associated with dabigatran. Similarly, the recent PROACT (Prospective Randomized On-X Anticoagulation Clinical Trial) Xa RCT assessed the safety and efficacy of apixaban versus VKA among patients with newer-generation mechanical bileaflet aortic valves and was terminated due to higher thromboembolic events in the apixaban arm (224). As a result, DOACs are currently contraindicated for patients with MHV (Fig. 3).

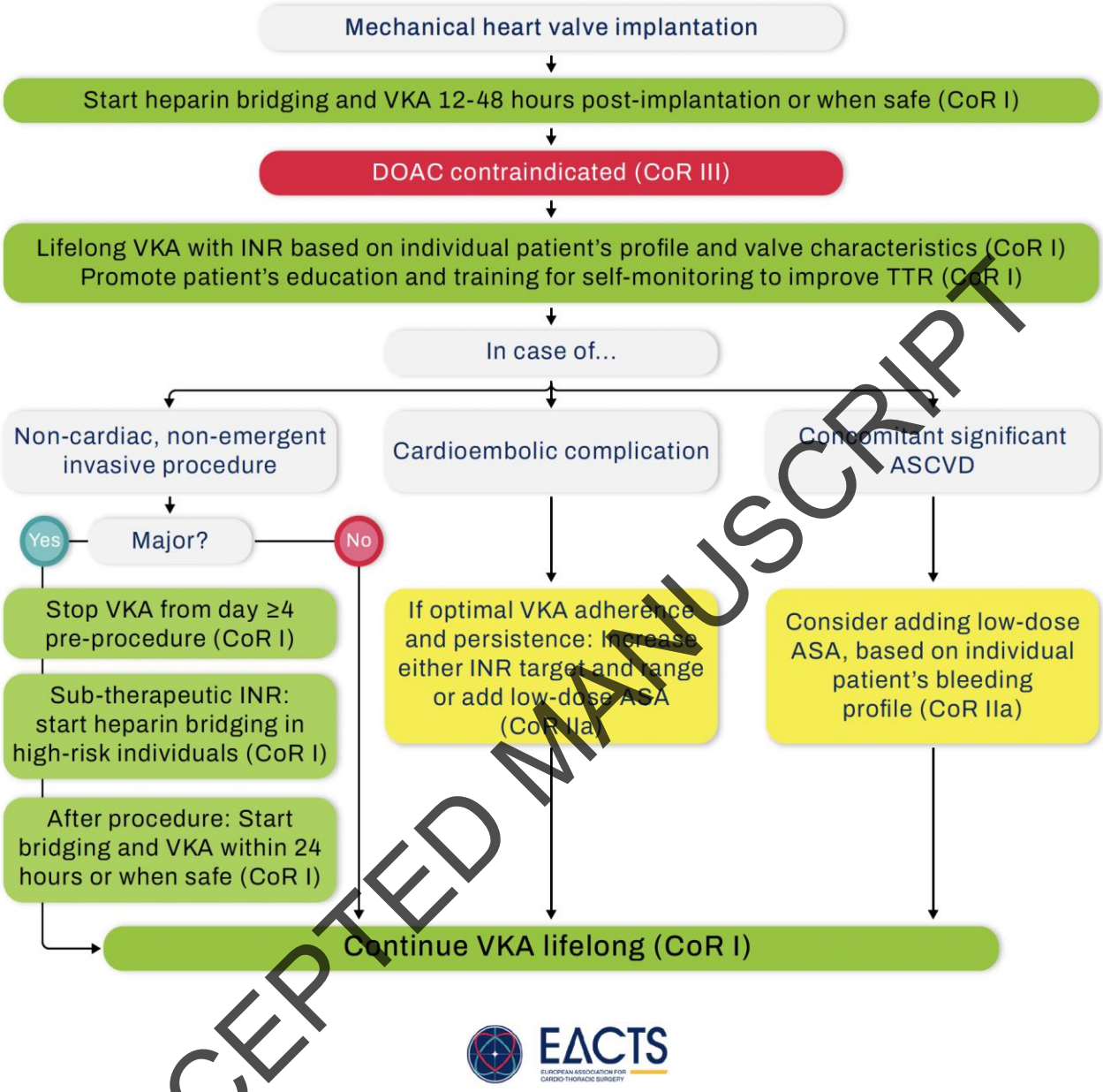

Figure 3: Management of patients with prosthetic heart valves. ASA: acetylsalicylic acid; ASCVD: atherosclerotic cardiovascular disease; CoR: class of recommendation; DOAC: direct oral anticoagulant; INR: international normalized ratio; TTR: time in therapeutic range; VKA: vitamin K antagonist.

4.5.1.1 Combined anticoagulation and antiplatelet therapy

Although adding single antiplatelet therapy (SAPT), i.e. low-dose ASA, to VKA reduces the risk of thromboembolic events in patients with an MHV, it significantly increases major bleeding risk compared with VKA alone (213, 225). Consequently, the addition of low-dose ASA (75–100 mg) to VKAs may be considered for patients with coexisting symptomatic atherosclerotic disease or recurrent thromboembolism despite an adequate INR, though evidence supporting this observation is limited (Fig. 3). For patients with an MHV with a definite need for DAPT (e.g. a recent stent implant or ACS), a short term (up to 1 month) of triple therapy with VKA, low-dose ASA and clopidogrel can be considered (123), followed by discontinuation of ASA or clopidogrel (123, 225). Ticagrelor and prasugrel are not recommended in the triple therapy due to safety concerns (123).

4.5.2 Bioprosthetic heart valves

4.5.2.1 Bioprosthetic heart valves in patients with no baseline indications for oral anticoagulation

Recent observations indicate that patients with surgical bioprosthetic aortic valves may develop subclinical leaflet thrombosis in 15–40% of cases, potentially leading to an increased systolic pressure gradient, aortic regurgitation or ischaemic stroke (226, 227). Subclinical valve thrombosis can be detected via computed tomographic imaging or cardiac magnetic resonance imaging as hypo-attenuated leaflet thickening or reduced leaflet motion (228). Whereas these findings are commonly found and are dynamic, the relationship between these imaging-based findings and the worsening of valve haemodynamics or the occurrence of clinical events as well as the prophylactic management (if any) remains unclear (226, 227, 229).

The available data suggest that either VKAs or SAPT with low-dose ASA should be considered during the first 3 months in patients with no previous indications for OAC, although randomized comparisons are lacking. The bleeding risk of the individual patient should be considered, because VKAs are associated with higher bleeding risk than ASA, independently of the indication (230). A large retrospective, observational study from the Society of Thoracic Surgeons Adult Cardiac Surgery Database found comparable rates of death, embolic events and bleeding in patients treated with ASA versus VKAs for 3

months after bioprosthetic SAVR, whereas combined ASA and VKA therapy reduced death and embolic events but significantly increased bleeding (231). A Danish registry study showed a higher incidence of thromboembolic events and cardiovascular deaths in patients having SAVR discontinuing warfarin during the initial 3 months after the operation, also suggesting that extending warfarin for up to 6 months postoperatively may reduce cardiovascular deaths (232). However, another recent observational study of 1,111 patients after SAVR treated with either OAC (VKA or anti-FXa DOACs), OAC plus antiplatelet drug, antiplatelet drug alone or no OAC showed that thrombotic events and death were similar across the groups after 3 and 12 months, whereas bleeding was significantly increased by OAC (233). A small randomized trial of 370 patients who underwent SAVR found that warfarin for 3 months versus ASA significantly increased major bleeding without reducing the number of deaths or thromboembolic events (234). Although it is commonly prescribed, no RCT has assessed the safety and efficacy of the continuation versus the interruption of low-dose ASA beyond 3 months after bioprosthetic SAVR in patients who have no other indications for low-dose ASA. Three months of treatment with VKA should likely be preferred in patients with a bioprosthesis implanted in the mitral or tricuspid position due to the higher risk of dysrhythmias and thromboembolic complications associated with this procedure and site, although RCTs are needed (235-238) (Fig. 4).

4.5.2.2 Bioprosthetic heart valves in patients with previous indications for oral anticoagulation

Long-term use of OAC is recommended in patients following bioprosthetic SAVR who require OAC for pre-existing indications (Fig. 4). Although the quality of the evidence is low, heterogeneous and sometimes conflicting (239-241), there has been a gradual increase in the use of DOACs rather than VKAs in this clinical setting (242, 243). The RIVER (Rivaroxaban for Valvular Heart Disease and Atrial Fibrillation) RCT, which included 1,005 patients with AF and bioprosthetic surgical mitral valve replacement, demonstrated that rivaroxaban was non-inferior to warfarin with respect to the composite primary outcome of death, major adverse cardiovascular events (stroke, transient ischaemic attack, systemic embolism, valve thrombosis or hospitalization for HF) or major bleeding at 12 months (244). However, this RCT had major limitations: only 20% of participants received DOAC before the third

postoperative month, and the primary end point mixing safety and efficacy does not provide clear evidence of the benefit/risk balance. In another small study, the ENAVLE (Explore the Efficacy and Safety of Edoxaban in Patients after Heart Valve Repair or Bioprosthetic Valve Replacement) RCT, which included 220 patients both with and without AF, edoxaban was non-inferior to warfarin in preventing a composite of death from any cause, clinical thromboembolic events, asymptomatic intracardiac thrombosis and major bleeding in the first 3 months following aortic or mitral surgical bioprosthetic valve implant or repair (245). Although these findings suggest that DOACs may be used following bioprosthetic SAVR, large, superiority RCTs assessing benefits and risks are needed.

4.5.3 Valve repair

Currently, the type of antithrombotic prophylaxis following valve repair, balancing benefits and risks, needs to be assessed by adequately powered RCTs. The results of a recent large-scale observational study of 2,216 patients who underwent mitral valve repair without indications for OAC suggest that VKA post mitral valve repair does not reduce the risk of cerebral embolic events but is associated with an increase in major bleeding compared with no VKA. However, it is unclear whether low-dose ASA or no medication was used in the no-VKA group (246). These findings are consistent with those of previous studies indicating a comparable risk of thromboembolism and a significantly increased risk of major bleeding with VKAs compared with SAPT with low-dose ASA following mitral valve repair surgery (247, 248). Considering current data, for patients without indications for OAC, low-dose ASA should be considered over VKA during the first 3 months post-mitral valve repair surgery, although definitive evidence is needed (Fig. 4). Given the similar or even reduced cardioembolic risks associated with valve-sparing aortic root and tricuspid repair surgery, a similar treatment strategy can be considered (249, 250).

4.5.4 Transcatheter aortic valve implantation

A patient-level meta-analysis of 3 RCTs comparing DAPT (low-dose ASA plus clopidogrel) with low-dose ASA alone post-transcatheter aortic valve implantation (TAVI) in patients without an OAC indication

found a significant increase in major or life-threatening bleeding with DAPT over ASA alone at 30 days, without difference in thrombotic outcomes (251). Similarly, the recent POPular-TAVI trial (anticoagulation therapy) in patients who did not have an indication for OAC (cohort A) reported a significant reduction in bleeding and a composite of bleeding or thromboembolic events at 1 year with ASA versus 3 months with DAPT (252). In the GALILEO (Global Study Comparing a rivAroxaban-based Antithrombotic Strategy to an antipLatelet-based Strategy After Transcatheter aortIc vaLve rEplacement to Optimize Clinical Outcomes) RCT, which included patients without indication for OAC following successful TAVI, rivaroxaban plus ASA for the first 3 months was associated with higher risks of death, thromboembolic complications and bleeding versus DAPT (ASA plus clopidogrel) (253). Lastly, data are lacking on antithrombotic management after implanting transcatheter mitral or tricuspid bioprosthetic heart valves (BHV), for which 3 months of VKA is commonly prescribed in the absence of RCT-based evidence (254).

For patients having TAVI who have ongoing indications for OAC due to other medical conditions, continuing OAC alone is advised. The POPular TAVI trial (cohort B) found that patients on OAC having TAVI had significantly fewer major bleeding events within 1 year when treated with OAC alone compared with the combination of OAC and clopidogrel (255). Additionally, VKA-only treatment was non-inferior to VKA and clopidogrel for the composite end point of cardiovascular death, ischaemic stroke or MI. In the ENVISAGE-TAVI AF (Edoxaban Versus Standard of Care and Their Effects on Clinical Outcomes in Patients Having Undergone Transcatheter Aortic Valve Implantation–Atrial Fibrillation) RCT, which involved 1,426 post-TAVI patients with AF and compared edoxaban with VKA, edoxaban was non-inferior on a composite outcome including death from any cause, MI, ischaemic stroke, systemic thromboembolism, valve thrombosis or major bleeding; however, major bleeding was higher in the edoxaban arm, mostly driven by a twofold increase in GI bleeding [5.4 per 100 person-years vs 2.7 per 100 person-years with edoxaban and VKA, respectively; hazard ratio (HR) 2.03; 95% CI, 1.28–3.22] (256). The ATLANTIS (Anti-Thrombotic Strategy to Lower All Cardiovascular and Neurologic Ischemic and Hemorrhagic Events After Trans-Aortic Valve Implantation for Aortic Stenosis) RCT failed to show the superiority of apixaban versus standard care (VKA or SAPT, depending on the underlying indications) in patients undergoing TAVI (257). Although apixaban reduced valve leaflet thrombosis

compared with SAPT in a subgroup analysis, it did not improve major clinical outcomes. In patients without an OAC indication, apixaban increased non-cardiovascular mortality compared with SAPT, similar to the findings in the GALILEO RCT with low-dose rivaroxaban (253). The thrombosis rates between apixaban and VKA were similar, suggesting that apixaban is a potential alternative to VKA post-TAVI when OAC is indicated, even though the trial design and outcome do not allow any firm conclusion (257). Based on recent RCT protocols, there are no data on low-dose ASA efficacy and safety beyond 12 months after TAVI in patients with no indication for OAC (Fig. 4). Data on optimal antithrombotic therapy management following transcatheter mitral or tricuspid valve implantation remain limited and based on individualized patient-based decision making.

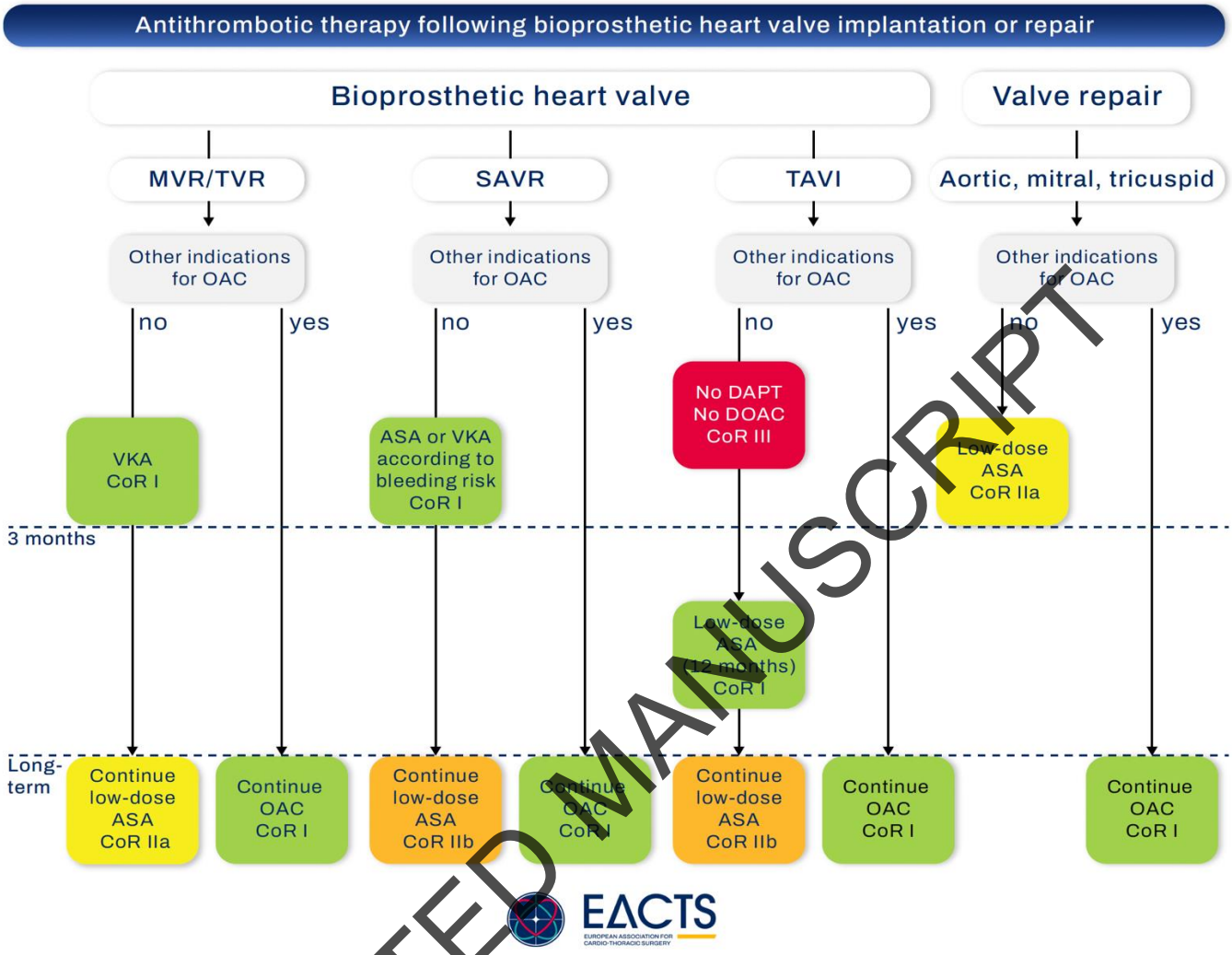

Figure 4: Antithrombotic therapy after bioprosthetic heart valve implantation and valve repair.

ASA: acetylsalicylic acid; CoR: class of recommendation; DAPT: dual antiplatelet therapy; DOAC: direct oral anticoagulants; MVR: mitral valve replacement: OAC; oral anticoagulation; SAVR: surgical aortic valve replacement; TAVI: transcatheter aortic valve implantation; TVR: tricuspid valve replacement; VKA: vitamin K antagonist. Colour coding corresponds to the assigned classes of recommendations.

4.5.5 Deep venous thrombosis prophylaxis and other indications for anticoagulation

A VTE, including deep venous thrombosis and PE, significantly raises morbidity and mortality after major operations (258). In a large analysis of the USA National Inpatient Sample of nearly 400,000 patients

following CABG, the incidence of VTE was 1.3%, leading to a doubled adjusted risk of death compared with those without VTE (259). Risk factors encompass older age, previous VTE, obesity, HF, chronic obstructive pulmonary disease, prolonged immobilization, use of a central venous catheter and coagulation defects (258, 259). A comprehensive meta-analysis encompassing 16 randomized and 49 observational studies demonstrated that early VTE prophylaxis significantly reduces the risks of symptomatic PE and VTE, without markedly increasing the risk of bleeding and its complications (258). In VTE prophylaxis, both UFH and LMWH at standard prophylactic doses are effective (260), but LMWH is favoured due to its ease of administration and no need for monitoring, though the dose should be adjusted in relation to renal function. Anti-Xa activity can be measured when LMWH is used in patients with more severe renal impairment (261). UFH is preferred in situations with a higher risk of bleeding because a specific and rapid antidote (protamine sulphate) is available. The occurrence of heparin-induced thrombocytopenia should be considered, based on specific diagnostic criteria and especially on second exposure (262).

In patients with a preoperative OAC indication, other than implanting artificial heart valves and prosthetic material, the same VKA or DOAC regimen should be resumed postoperatively, as soon as it is deemed safe. Those requiring preoperative bridging due to high-risk profiles and VKA treatments should continue postoperative bridging, similar to the protocol for MHVs (Fig. 2). Notably, and different from VKA, which has a delayed anticoagulant effect and thus can be started immediately after the operation, DOACs have a direct and immediate, albeit reversible, anticoagulant effect and can confer a high risk of bleeding in the early postoperative period. Thus, DOACs should be restarted as soon as it is deemed safe, usually starting from 72 h after the operation (161).

Recommendation Table 8. Recommendations for postoperative antithrombotic drugs

Recommendations	Class[a]	Level[b]	Ref[c]
Postoperative (re)starting of oral anticoagulation			

In patients with an indication for postoperative oral anticoagulation and high thromboembolic risk[d], it is recommended to start UFH or LMWH after the operation, as soon as it is considered safe.	**I**	**B**	**(208-212)**
It is recommended to restart VKA together with bridging heparin on the first postoperative day or as soon as it is considered safe	**I**	**C**	**-**
DOACs, when indicated, should be (re)started 2 to 3 days after open-heart surgery.	**IIa**	**B**	**(161)**
Mechanical Heart Valves			
Lifelong VKAs are recommended for all patients, with anticoagulation levels consistent with valve type, position and patient characteristics.	**I**	**A**	**(204-206)**
DOACs are not recommended in patients with mechanical valve prosthesis to prevent thromboembolic events.	**III**	**A**	**(223, 224)**
The addition of low-dose ASA (75–100 mg/day) to VKA should be considered in case of concomitant significant atherosclerotic disease.	**IIa**	**B**	**(213, 225)**
In patients with MHV who develop a major thromboembolic complication despite a documented adequate INR, either an increase in the INR target or the addition of low-dose ASA should be considered.	**IIa**	**C**	**(225)**
INR self-monitoring and self-management are recommended in appropriately trained patients.	**I**	**A**	**(216, 221, 222)**

Bioprosthetic Heart Valves			
In patients with no clear indications for OAC, either low-dose ASA [75–100 mg/day) or VKA, based on the bleeding profile of the individual patient, is recommended for the first 3 months after a surgical aortic BHV implant.	**I**	**C**	**(231, 233, 234)**
In patients with no clear indications for OAC, long-term dose ASA (75–100 mg/day) may be considered after the first 3 months following a surgical aortic BHV implant.	**IIb**	**C**	**-**
In patients with no clear indications for OAC, VKAs are recommended for the first 3 months after surgical implantation of a mitral or tricuspid BHV.	**I**	**B**	**(237, 238)**
In patients with no clear indications for OAC, long-term dose ASA (75–100 mg/day) should be considered after the first 3 months following a surgical mitral or tricuspid BHV implant.	**IIa**	**C**	**-**
For patients with surgical- or transcatheter-implanted bioprostheses and an indication for OAC, long-term OAC is recommended to prevent thromboembolic events.	**I**	**C**	**-**
DOACs may be considered as an alternative to VKA 3 months after the surgical implantation of a BHV in patients with another indication for OAC.	**IIb**	**B**	**(241, 244, 245)**
Surgical valve repair			

SAPT with low-dose ASA (75–100 mg/day) should be considered for the first 3 months following valve-sparing aortic surgery and tricuspid valve repair in the absence of indications for OAC.	**IIa**	**C**	**-**
SAPT with low-dose ASA (75–100 mg/day) should be considered for the first 3 months after mitral valve repair.	**IIa**	**B**	**(246-248)**
OAC is recommended after surgical valve repair in patients who have other indications for OAC to prevent thromboembolic events.	**I**	**C**	**-**
TAVI			
Low-dose ASA (75–100 mg/day) is recommended for 12 months after TAVI in patients with no clear indication for OAC.	**I**	**A**	**(251, 252) (253, 257, 263)**
Long-term low-dose ASA (75–100 mg/day) may be considered after TAVI in patients with no clear indication for OAC.	**IIb**	**C**	**-**
OAC or DAPT is not recommended after TAVI in patients with no clear indication for OAC or DAPT, respectively.	**III**	**B**	**(252, 253)**
OAC is recommended for long-term use in patients having TAVI who have other indications for OAC.	**I**	**B**	**(255)**
DOAC may be considered rather than VKA following TAVI when there is an indication for OAC therapy.	**IIb**	**B**	**(256, 257)**
Other indications			
VTE prophylaxis with LMWH should be considered after open-heart surgery as soon as there is no safety concern.	**IIa**	**B**	**(258, 259)**

ASA: acetylsalicylic acid; BHV: bioprosthetic heart valve; DAPT: dual antiplatelet therapy; DOACs: direct oral anticoagulants; INR: international normalized ratio; LMWH: low-molecular-weight heparin; MHV: mechanical heart valve; OAC: oral anticoagulation; SAPT: single antiplatelet therapy; TAVI: transcatheter aortic valve implant; UFH: unfractionated heparin; VKA: vitamin K antagonist; VTE: venous thromboembolism.

[a]Class of recommendation.

[b]Level of evidence.

[c]References.

[d]Patients with a mechanical prosthetic heart valve, AF with rheumatic valvular disease, an acute thrombotic event within the previous 12 weeks and, potentially, patients with left ventricular apex thrombus, defects of antithrombin, protein C, protein S and factor V Leiden mutation.

[e]Based on the half-life and frequency of administration for the specific LMWH agent.

5 Antiarrhythmic drugs in new-onset postoperative atrial fibrillation

POAF is usually defined as new-onset AF early after the operation in a patient without a history of AF. The incidence of POAF after open-heart surgery ranges from 20% to 50% (155, 264) and depends on the type of cardiac operation and individual patient factors such as age, sex and comorbidities (265). The exact mechanism behind POAF is still unknown, but open-heart surgery is associated with unique pathophysiological circumstances that may facilitate its development, such as direct injury to the atrial myocardium (266), inflammation (267-270), myocardial ischaemia and ischaemia-reperfusion injury (271, 272) and sympathetic activation (273, 274).

POAF is associated with increased short- and long-term complications after open-heart surgery, and length of stay is usually extended by days in patients with POAF (265). POAF is associated with an increased risk of perioperative death, stroke, MI and AKI as well as long-term mortality, stroke, rehospitalization for HF and recurrent AF (70, 275, 276). A meta-analysis including more than 150,000 patients showed a higher adjusted mortality in patients with POAF at 10 years (29% vs 23%; OR 1.51; 95% CI 1.43–1.60; $P < 0.001$) and a fourfold increase in the risk of stroke (4% vs 1%; OR 4.09;95% CI 2.49–6.72; $P < 0.001$) (277). However, evidence of a causal relationship between POAF per se and short- and long-term complications is lacking.

Prevention of POAF is addressed in section 3 , while this section focuses on the management of POAF.

5.1 Rate versus rhythm control

In patients who are haemodynamically unstable because of POAF, emergency cardioversion and restoration of sinus rhythm are recommended (155). In haemodynamically stable patients, rhythm control of POAF has been the standard of care on the assumption that the restoration/maintenance of sinus rhythm would be a superior strategy compared with rate control. This approach is supported by historical and non-cardiac surgery data (278, 279). Evidence from an RCT including 523 patients has shown that in asymptomatic or minimally symptomatic patients there is no benefit in adopting a rhythm-control strategy, even with amiodarone (280). However, in this study, 25% of patients in the

rate control group crossed over to the rhythm control group, and vice versa, limiting the ability of the trial to show a significant benefit of one strategy over the other. Therefore, in asymptomatic or minimally symptomatic patients, a rhythm control strategy should be preferred, utilizing drugs as well as cardioversion, whereas rate control may also be an option.

5.2 Choice of agent

The choice of drug depends on patient characteristics, including haemodynamics and the LVEF. For rate control, BBs or diltiazem/verapamil (if BBs are contraindicated) is preferred in patients with preserved LVEF. BBs should be used in patients with reduced LVEF. Digoxin can be used in both settings; however, concerns about increased mortality risk, particularly in patients with non-surgical AF, have been raised (155, 281). For rhythm control, amiodarone should be used both in patients with and without preserved LVEF (77, 155).

5.3 Thromboembolism prevention in patients with postoperative atrial fibrillation

The rationale for the use of anticoagulation when POAF occurs comes from studies showing the benefit of OAC in non-surgical patients with AF together with data from several meta-analyses showing an increased long-term risk for stroke after POAF in patients having open-heart surgery (275, 277, 282). Furthermore, observational data have shown an eightfold increased risk of AF recurrence in patients with POAF after a median follow-up of 6 years (70).

The benefits of OAC in POAF long-term stroke risk are debated and controversial. A large Danish cohort of patients undergoing CABG showed that the use of OAC was associated with a reduced risk of stroke in patients with POAF (adjusted HR 0.55, 95% CI 0.32–0.95; *P* = 0.03) (282). Similar results were presented in a study by El-Chami *et al.* (283). However, a nationwide Swedish registry with a median follow-up of 4.5 years and more than 24,000 patients who had CABG showed that, even though POAF increased the risk of ischaemic stroke (adjusted HR 1.18, 95% CI, 1.05–1.32), any thromboembolism, hospitalization for HF and recurrent AF, early initiation of OAC was not associated with a reduced risk

of ischaemic stroke or any thromboembolism, but rather with an increased risk for major bleeding (adjusted HR 1.40, 95% CI 1.08–1.82) (66). Furthermore, an analysis from the Society of Thoracic Surgeons Adult Cardiac Surgery Database of almost 39,000 patients with POAF after isolated CABG showed that, after propensity score matching, OAC at discharge was associated with an increased risk of death (hazard ratio 1.16; 95% CI 1.06–1.26), no difference in the incidence of ischaemic stroke and a significantly higher risk of bleeding in patients treated with OAC (284).

Similarly, a population-based cohort with a mean follow-up of 4.7 years, including both isolated SAVR and combined SAVR and CABG patients, showed that POAF was associated with an increased long-term risk of death (adjusted HR 1.21; 95% CI 1.06–1.37), ischaemic stroke, any thromboembolism, hospitalization for HF and recurrent AF, whereas initiation of OAC before discharge or within 30 days after discharge was not associated with reduced risk of death, ischaemic stroke or thromboembolism (285). In view of these mixed results, no clear evidence exists on whether or when to start OAC, so the decision has to be made individually, balancing the bleeding and thromboembolic risks of individual patients (153).

In patients with persistent POAF, a therapeutic dose of either UFH or (more commonly) LMWH should be considered within 24 h from POAF onset and maintained until sinus rhythm has been restored or OAC has been initiated. OAC, either with VKA or DOACs, should be considered 48 h after POAF onset and be maintained for at least 4 weeks according to the individual patient's risk profile. Most of the evidence for OAC in POAF is available for VKAs. For patients with MHV or moderate-to-severe mitral stenosis, VKAs are recommended (155). A recent meta-analysis suggests that DOAC compared with VKA in patients with POAF without MHV is associated with a reduced risk for stroke [risk ratio (RR) 0.63, 95% CI 0.58–0.83, *P*=0.01) and bleeding (RR 0.74, 95% CI 0.62–0.89, *P*= 0.01), whereas there is no difference in mortality risk [RR 1.02 (95% CI 0.77–1.35), *P*=0.9] (286). Thus, DOACs seem to be a reasonable alternative in non-valvular POAF (287-290). The CHA_2DS_2-VASc score can be used to assess stroke risk in patients with POAF with the same predictive accuracy as in patients with non-surgical AF (291). However, it is still unclear whether CHA_2DS_2-VASc can be used to select patients for OAC treatment and, if so, at which score point should treatment be recommended (284, 291, 292). Furthermore, how bleeding risk in POAF patients should be estimated remains elusive.

Recommendation Table 9. Recommendations for antiarrhythmic drugs

Recommendations	Class[a]	Level[b]	Ref[c]
Postoperative period			
In patients with haemodynamically stable POAF, rhythm control is recommended.	**I**	**B**	**(265, 279, 280, 293)**
In patients with haemodynamically stable and asymptomatic POAF, rate control should be considered.	**IIa**	**B**	**(265, 278-280)**
In patients with haemodynamically unstable POAF, antiarrhythmic drugs for rhythm control and, if necessary, cardioversion are recommended to restore sinus rhythm.	**I**	**B**	**(293)**
Therapeutic doses of UFH or LMWH should be considered within 24 h of the onset of POAF, balancing cardioembolic and surgical bleeding risks.	**IIa**	**C**	**-**
In patients with persistent POAF at discharge, OAC therapy is recommended for at least 4 weeks followed by re-evaluation.	**I**	**B**	**(265, 275, 277, 294)**
In patients with POAF in sinus rhythm at discharge, OAC therapy for at least 4 weeks may be considered, taking bleeding risk and thromboembolic risk into consideration.	**IIb**	**B**	**(265, 275, 277, 282, 283, 294)**

LMWH: low-molecular-weight heparin; OAC: oral anticoagulation; POAF: postoperative atrial fibrillation; UFH: unfractionated heparin.

[a]Class of recommendation.

[b]Level of evidence.

[c]References.

6 Postoperative renin-angiotensin-aldosterone system inhibitors, mineralocorticoid receptor antagonist and sodium-glucose cotransporter-2 inhibitors

Renin-angiotensin-aldosterone system (RAAS) inhibitors include 4 different groups of drugs that affect the RAAS (Table 7):

1. ACEIs: Angiotensin-converting enzyme inhibitors
2. ARBs: Angiotensin II receptor blockers
3. MRA: Mineralocorticoid receptor antagonist
4. DRI: Direct renin inhibitors

The RAAS inhibitors are used to treat both systemic hypertension and heart failure with reduced ejection fraction (HFrEF). They also have been shown to have a protective effect on renal function (39, 295-299).

Table 7: Classes of drugs that affect the renin-angiotensin-aldosterone system

Class	ACEI	ARB	MRA	DRI	ARNI
Common drugs	Enalapril, captopril, lisinopril, ramipril, trandolapril	Candesartan, valsartan, losartan	Spironolactone, eplerenone	Aliskiren, imarikiren	Sacubitril/valsartan
Mechanism of action	Blocks the conversion of AT1 and its degradation and blocks the destruction of bradykinins	Inhibits the union of AT2 to its receptor	Inhibit the effect of aldosterone on the mineralocorticoid receptor	Blocks renin activity	Blockade of neprilysin that cleaves a variety of peptides such as natriuretic peptides, bradykinin, adrenomedullin, substance P, AT 1 and 2, and endothelin
Main clinical effects	Dilates blood vessels	Reduces CV effects caused by AT2	Blocks the effects of aldosterone, reducing water and sodium reabsorption	Increases renal vasodilation	Increases vasodilatory natriuretic peptides and prevents activation of AT system (reduces blood

					pressure, increases natriuresis)
Side effects	Cough, angioedaema, hyperkalaemia, hypotension, worsening CKD	Hypotension, worsening CKD, interaction with other drugs	Risk of hyperkalaemia and worsening renal function in CKD, gynaecomastia, loss of libido	Hyperkalaemia, hypotension, renal impairment	Hypotension, hyperkalaemia
Contraindications	AKI, angioedaema, bilateral renal artery stenosis, concomitant treatment with ARB, pregnancy	Concomitant treatment with ACEIs, allergy to the drug	Hyperkalaemia, severe renal dysfunction with eGFR <30 ml/min/m^2	Combination with ACEIs and ARB	Angioedaema, bilateral renal artery stenosis, pregnancy, allergy, eGFR<30

ACEI: angiotensin-converting enzyme inhibitor; AKI: acute kidney injury; ARB: angiotensin receptor blocker; ARNI: angiotensin receptor and neprilysin inhibitor; AT: angiotensin; CKD: chronic kidney disease; CV: cardiovascular; DRI: direct renin inhibitors; eGFR: estimated glomerular filtration rate; MRA: mineralocorticoid receptor antagonist.

6.1 Postoperative use of renin-angiotensin-aldosterone system inhibitors and aldosterone antagonists

Hypertension: No strong data exist for recommendations regarding ideal blood pressure levels after cardiac surgery. However, expert consensus suggests that blood pressure readings in the range of 60–90 mmHg diastolic and 110–140 mmHg systolic blood pressure are adequate (300). Medications used for the treatment of hypertension in the postoperative period include RAAS inhibitors (ACEIs, ARBs, direct renin inhibitors, MRAs), CCBs and BBs. Perioperative handling of RAAS inhibitors is discussed in section 3.

Heart failure: RAAS inhibitors have been shown to improve cardiac remodelling, reduce afterload and improve LVEF. Controversy exists, however, regarding their use in patients with normal LVEF and blood

pressure (301). Recent observational studies suggest that RAAS inhibitors improve long-term survival after cardiac surgery independently of cardiac function (47, 302, 303). Thus, the initiation of an RAAS inhibitor is recommended after cardiac surgery in patients with HF independent of LVEF (304) and may be considered in patients without HF, independently of the type of operation performed. See also section 13 about postoperative optimization. Of importance, postoperative RAAS inhibitors should be started at a low dose followed by slow up-titration as required, to avoid the development of hypotension and the impairment of renal function (302).

Of importance, ACEIs and ARBs differ regarding their mechanism of action. Whereas ACEIs reduce circulating and local levels of angiotensin II, ARBs directly block the angiotensin-receptor 1. Overactivation of the RAS has been related to inflammation and metabolic syndrome (305); thus, RAAS inhibitors may help reduce cardiovascular complications in patients with metabolic syndrome. A recent study by Manning *et al.* concluded that ARBs, due to their different mechanism of action, may have a higher protective effect in this subgroup of patients compared with ACEIs (306). ARBs may be used as an alternative to ACEIs in patients who do not tolerate ACEIs, but they should not be used concomitantly due to an increased risk of hypotension, hyperkalaemia and impaired kidney function.

MRAs (spironolactone and eplerenone) have been shown in several clinical trials to have beneficial effects on symptoms, mortality and HF hospitalizations in patients with HFrEF (307, 308). Despite there are no direct comparisons between the two agents, recent small studies have shown more favourable effects of eplerenone on cardiac remodelling parameters (309) and a larger reduction in cardiovascular deaths compared with spironolactone in a real-life cohort (310). These differences are considered to be secondary to a more favourable eplerenone side-effect profile. Based on current evidence, MRAs are recommended, in addition to RAS inhibitors, SGLT2 inhibitors ARNI and BBs, in patients with HFrEF, to reduce mortality and HF hospitalizations (304, 311)

In addition to the previously described RAAS inhibitors for patients with HFrEF, the angiotensin receptor and neprilysin inhibitor has emerged as a new medication with proven significant impact on clinical outcomes. The combination of the ARB valsartan with sacubitril (a neprilysin inhibitor) has shown a significant reduction in mortality and in HF rehospitalizations in patients with HF and reduced LVEF. In

the PARADIGM-HF (Efficacy and Safety of LCZ696 Compared to Enalapril on Morbidity and Mortality of Patients With Chronic Heart Failure) study (312), patients with LVEF <40%, BNP > 150 pg/ml or NT pro-BNP > 600 pg/ml were randomized to sacubitril/valsartan or enalapril; study results showed a significant reduction in HF readmission in the sacubitril/valsartan cohort. The PARAGON-HF (The Prospective Comparison of ARNI [angiotensin receptor–neprilysin inhibitor] with ARB [angiotensin-receptor blockers] Global Outcomes in HF with Preserved Ejection Fraction) study (313) compared sacubitril/valsartan versus valsartan in patients with HF with preserved ejection fractions. The study showed a beneficial effect of the new drug in the subgroup of patients with lower EF (40%–55%). Small Chinese studies (314, 315) assessing the use of sacubitril/valsartan in the immediate postoperative period after cardiac surgery showed significant improvement in LVEF and left ventricular end-diastolic diameter in patients receiving the drug in the postoperative period. It is worth mentioning that sacubitril/valsartan was started at low doses because many patients were hypotensive during the first days. Hence, initiation of sacubitril/valsartan as a replacement for ACEI is recommended in patients with HFrEF with reduced LVEF (≤40%) who remain symptomatic despite treatment with ACEI, beta-blockers (BBs), MRAs and an SGLT2 inhibitor. The doses should be up-titrated rapidly under close monitoring (316).

6.2 Sodium-glucose cotransporter-2 inhibitors

The SGLT2 inhibitors exert multiple effects on the heart, kidney and vasculature that lead to a reduction in the severity of HF symptoms (317). Recent RCTs, such as the EMPA-REG OUTCOME (Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes) RCT (318) and the DECLARE-TIMI (Effect of Dapagliflozin on the Incidence of Cardiovascular Events) RCT (319), have shown their significant impacts on the reduction of cardiovascular deaths and HF hospitalizations in patients with and without diabetes mellitus (DM) and patients with and without HF. The recent DAPA-HF (Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure) (320) RCT showed that randomized patients with reduced EF and an estimated glomerular filtration rate (eGFR)>30 ml/min to either dapagliflozin or placebo showed a significant reduction by dapagliflozin in the combined end point of HF rehospitalizations and

cardiovascular deaths. Similar results were shown with empagliflozin in the EMPEROR-Reduced (Empagliflozin Outcome Trial in Patients with Chronic Heart Failure and Reduced Ejection Fraction) RCT (321).

Although no dedicated studies are currently examining the role of SGLT2 inhibitors in patients undergoing cardiac surgery, there is enough evidence to recommended their use in patients with HF, independently of their LVEF (304, 311, 322). Nevertheless, concerns exist about data reporting the risk of euglycemic ketoacidosis and an increased risk of urinary tract infections and genital mycoses in patients undergoing surgery while treated with SGLT2 inhibitors, with or without DM. For further evidence and detailed recommendations regarding the perioperative management of SGLT2 inhibitors to prevent the risk of those serious complications in cardiac surgical contexts, readers are referred to section 11, which reports the available evidence more comprehensively.

Recommendation Table 10. Recommendations for postoperative renin-angiotensin-aldosterone system inhibitors, aldosterone antagonists and sodium-glucose cotransporter-2 inhibitors

Recommendations	Class[a]	Level[b]	Ref[c]
In patients with HF, it should be considered to (re)start short-acting, low-dose RAS inhibitors (ACEIs or ARBs) as soon as it is deemed safe after open-heart surgery, based on haemodynamic stability and renal function.	**IIa**	**C**	**(302)**
Long-term optimal-dose RAS inhibition (ACEIs or ARBs) is recommended after cardiac surgery in patients with HF and/or HTA.	**I**	**B**	**(4, 303, 304, 323)**
In ACEI-intolerant patients, an ARB is recommended in patients with a reduced LVEF (≤40%).	**I**	**A**	**(304, 324, 325)**
Sacubitril/valsartan is recommended as a replacement for an ACEI in ambulatory patients with reduced LVEF (≤40%) who remain	**I**	**B**	**(304, 311, 312)**

symptomatic despite optimal treatment with an ACEI, a BB, a MRA and an SGLT 2 inhibitor.			
Long-term MRA in addition to BBs and ACEI therapy is recommended after cardiac surgery in patients with HF and reduced LVEF (≤35%), eGFR >30 ml/min/1.73 m^2 and without hyperkalaemia.	**I**	**A**	**(307, 308)**
SGLT2 inhibitors are recommended for patients with HF.	**I**	**A**	**(311, 320, 326)**
Long-term optimal-dose RAAS inhibition may be considered in patients following CABG and/or SAVR, and in post-TAVI patients.	**IIb**	**B**	**(4, 303, 327)**

ACEI: angiotensin-converting enzyme inhibitors; ARB: angiotensin receptor blockers; BB: beta-blockers; CABG: coronary artery bypass grafting; eGFR: estimated glomerular filtration rate; HF: heart failure; HTA: arterial hypertension; LVEF: left ventricular ejection fraction; MRA: mineralocorticoid receptor antagonist; RAAS: renin-angiotensin-aldosterone system; SAVR: surgical aortic valve replacement; SGLT2: sodium-glucose cotransporter protein 2; TAVI: transcatheter aortic valve implant.

[a]Class of recommendation.

[b]Level of evidence.

[c]References.

7 Postoperative beta-blockers

The use of BBs after open-heart surgery continues to be debated. As discussed in section 5 regarding AF, postoperative administration of BBs or restarting BBs after cardiac surgery has been shown to be associated with a reduced incidence of postoperative AF and of supraventricular and ventricular arrhythmias (34, 328). In a recent meta-analysis, the postoperative use of BBs reduced hospitalization time (328). Moreover, use of beta-1 specific BBs (bisoprolol, carvedilol, metoprolol and nebivolol) reduced mortality in MI patients with LVEF <35% (329, 330). Based on current evidence, starting or continuing BB therapy is recommended after cardiac surgery in these patient subgroups (331).

However, conflicting data exist regarding the long-term use of BBs in patients without a previous MI or reduced LVEF undergoing cardiac surgery. Recent studies based on the SWEDEHEART (Swedish Web System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies) registry data showed no mortality benefit with BB use after CABG (4) and SAVR (332). Moreover, Park *et al.* (333) recently reported no beneficial effect of the use of BBs in patients undergoing CABG after the 1-year follow-up. Furthermore, the only RCT with BBs in patients who had CABG did not show any advantages with the use of BBs (334). Although long-term treatment with BBs did not reduce the risk of death or of a new MI in patients with acute MI who underwent early coronary angiography and had a preserved LVEF (≥50%) (335), further research is needed to assess the benefits of BBs in stable post-cardiac surgery patients before issuing strong recommendations for their use.

Recommendation Table 11. Recommendations for postoperative beta-blockers

Recommendation	Class[a]	Level[b]	Ref[c]
Long-term cardioselective BBs are recommended in patients with HF and in those with recent MI and reduced LVEF.	**I**	**A**	**(329-331)**

BBs: beta-blockers; HF: heart failure; LVEF: left ventricular ejection fraction; MI: myocardial infarction.

[a]Class of recommendation.

[b]Level of evidence.

[c]References.

8 Lipid-lowering drugs

8.1 Preoperative statins

Results from observational studies and small RCTs have suggested that initiation of preoperative statin therapy before cardiac surgery reduced mortality, POAF and AKI (336). However, in the STICS (Statin Therapy in Cardiac Surgery) RCT that randomized 1,922 patients undergoing elective cardiac surgery, the initiation of rosuvastatin (20 mg/day) before cardiac surgery did not prevent perioperative myocardial damage or reduce the risk of POAF (83). AKI was significantly more common among patients who received rosuvastatin than among those who received a placebo (83). In another RCT of patients undergoing cardiac surgery, high-dose atorvastatin started the day before the operation and continued perioperatively did show a significantly higher rate of AKI in patients with CKD compared with placebo (84). The trial was terminated prematurely due to futility (84). In summary, current evidence does not support the preoperative initiation of statin therapy in statin-naïve patients undergoing cardiac surgery. No new data are available on whether patients already taking statins should continue or discontinue therapy preoperatively, although statins are continued perioperatively in common practice. No new data are available on whether patients already taking statins should continue or discontinue therapy preoperatively, although in common practice statins are continued perioperatively.

8.2 Postoperative statins

Intense or maximally tolerated statin therapy has been recommended with a low-density lipoprotein cholesterol (LDL-C) target of <55 m/dl (1.4 mmol/L) and >50% LDL-C reduction in patients with coronary artery disease (337). In the TNT (Treating to New Targets) RCT, which randomized >4,000 patients, intense LDL-C lowering [to a mean of 79 mg/dl (2.05 mmol/L)] with atorvastatin 80 mg/day in patients with previous CABG, reduced major cardiovascular events by 27% and the need for repeat revascularization by 30%, compared with less intensive cholesterol lowering to a mean of 101 mg/dl (2.61 mmol/L) with atorvastatin 10 mg/day (338). For patients with statin intolerance during the follow-up period, the European Atherosclerosis Society has developed a scheme for statin re-exposure (339).

In a large national registry database, the use of statins after CABG was associated with a long-term lower mortality risk after adjustment (HR: 0.56; 95% CI 0.52–0.60) (4). The importance of close adherence to the use of statins, at 8 years, was demonstrated by the greater reductions in mortality risk with longer exposure time. Further evidence from the same national registries showed that ongoing statin treatment was associated with a markedly reduced risk of major adverse cardiovascular events (MACE), all-cause mortality, cardiovascular death, MI, stroke and new revascularization, irrespective of the statin dose (340). Close long-term adherence to statin therapy is therefore recommended after CABG to reduce mortality and thromboembolic events.

In patients who underwent aortic valve replacement for aortic stenosis or aortic regurgitation, there is observational data showing that treatment with statins is associated with a reduced risk of all-cause death, MI and stroke (341, 342). These results suggest that statin therapy might be beneficial for patients after surgical aortic valve replacement.

8.3 Non-statin lipid-lowering agents

In patients after CABG surgery in whom the LDL-C target <55 mg/dl (1.4 mmol/L) is not reached despite an intense or maximally tolerated statin dose, the addition of a cholesterol absorption inhibitor, ezetimibe, is recommended (343). In a post-hoc analysis of the IMPROVE-IT (IMProved Reduction of Outcomes: Vytorin Efficacy International Trial), patients with a prior CABG operation who received ezetimibe plus a statin versus a statin alone had a substantial reduction in cardiovascular deaths, major cardiovascular events or stroke during a 6-year median follow-up period (344).

For patients in whom the LDL-C target is not reached despite a high or maximally tolerated statin and ezetimibe dose, the addition of a proprotein convertase subtilisin/kexin type 9 inhibitor is recommended (337, 345). Although there are no dedicated studies of bempedoic acid in patients having cardiac surgery, indirect evidence provides support for its beneficial effects because it reduces cardiovascular deaths, MIs and new revascularizations in patients at high cardiovascular risk who are statin-intolerant (346-348). For proprotein convertase subtilisin/kexin type 9 inhibitors, there is also evidence for their efficacy in high cardiovascular risk patients (349-352). In a prespecified substudy of

the ODYSSEY OUTCOMES (Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab) RCT with elevated LDL-C despite high-intensity statin therapy, alirocumab was associated with reductions in MACE and in deaths in patients who underwent CABG (353).

A meta-analysis of 18 RCTs and 45,058 patients showed that fibrates, agonists of peroxisome proliferator-activated receptor-alfa, could reduce major cardiovascular events predominantly by prevention of coronary events, but with no impact on mortality (354). However, in recent studies, no additional benefit of fibrate treatment on top of statin therapy has been demonstrated (355).

Current European Society of Cardiology guidelines recommend treatment of hypertriglyceridaemia to improve cardiac outcomes in patients undergoing coronary revascularization (337). The first line of treatment is statins. If they are not effective, statins combined with icosapent ethyl should be considered. The REDUCE-IT (Reduction of Cardiovascular Events With Icosapent Ethyl–Intervention Trial) showed that icosapent ethyl was associated with a significant reduction of ischaemic events in patients with a history of CABG (356)

Recommendation Table 12. Recommendations for lipid-lowering drugs

Recommendations	Class[a]	Level[b]	Ref[c]
Preoperative period			
It is not recommended to initiate statin therapy shortly before elective cardiac surgery due to the associated risk of acute renal failure.	**III**	**A**	**(83, 84)**
It should be considered to continue statin therapy at the preoperative dose during the perioperative period.	**IIa**	**B**	**(85, 357)**
Postoperative period			
LDL-C is recommended as the primary target of lipid-lowering drugs.	**I**	**A**	**(338)**

Intense or maximally tolerated statin therapy is recommended in patients after CABG surgery to reach the LDL-C target <55 mg/dl (1.4 mmol/L) or >50% LDL-C reduction if the baseline LDL-C is between 1.4 and 2.8 mmol/L (55 and 110 mg/dl).	**I**	**A**	**(338, 345, 351)**
In patients in whom the LDL-C target <55 mg/dl (1.4 mmol/L) is not reached by statin therapy after CABG surgery, a combination of a statin with ezetimibe is recommended.	**I**	**B**	**(345, 348)**
Bempedoic acid is recommended with or without ezetimibe in patients who are statin-intolerant[d].	**I**	**B**	**(346, 347)**
Use of PCSK9 inhibitors is recommended to reach the LDL-C target if the LDL-C goal is not reached with maximally tolerated statin therapy, despite the addition of ezetimibe.	**I**	**A**	**(350-352)**
High adherence and persistence to statin therapy are recommended after CABG to reduce mortality and thromboembolic events.	**I**	**B**	**(4, 340)**
In patients undergoing SAVR or TAVI, long-term statin therapy may be considered to improve outcomes.	**IIb**	**B**	**(341, 342)**

CABG: coronary artery bypass grafting; LDL-C: low-density lipoprotein cholesterol; PCSK9: proprotein convertase subtilisin/kexin type 9; SAVR: surgical aortic valve replacement; TAVI: transcatheter aortic valve implantation.

[a]Class of recommendation.

[b]Level of evidence.

[c]References.

[d]Patients who were unable or unwilling to take statins or unable to tolerate maximum recommended doses to reach the LDL target.

9 Steroids

Major surgery and initiation of CPB trigger a systemic inflammatory response, which can lead to various adverse clinical effects, including neurological and haemorrhagic events, respiratory dysfunction and multi-organ failure (358). Steroids have been used as anti-inflammatory interventions in cardiac surgery for nearly 4 decades, although there is concern over increased risks of infections and MIs.

The results of early studies included in a 2008 meta-analysis of 44 RCTs totalling 3,205 patients undergoing on-pump CABG indicated that corticosteroids may reduce postoperative AF, bleeding and ICU stays but did not lower mortality rates (359). These findings did not suggest an increase in MIs or infection risks and were the basis for subsequent RCTs. A recent Cochrane Review, which summarized findings from 72 RCTs on the organ-protective effects of corticosteroids in cardiac surgery with CPB, found minimal to no impact on mortality, GI bleeding and renal failure (360). The review revealed mixed effects on cardiac and pulmonary complications, but corticosteroids may elevate the risk of cardiac complications while potentially reducing pulmonary issues with low certainty of these findings.

The SIRS (Steroids In caRdiac Surgery) study, which included 7,507 patients with a high risk of morbidity and mortality (EuroSCORE ≥ 6) with no use of systemic corticosteroids or history of bacterial or fungal infections in the last 30 days undergoing cardiac surgery with CPB, compared methylprednisolone with placebo (361). No significant differences were found in 30-day mortality or in a composite end point of mortality, MI, stroke, renal failure and respiratory failure, although a concern was raised due to a higher occurrence of myocardial injury in the steroid group (361). Similarly, the DECS (Dexamethasone for Cardiac Surgery) trial, which enrolled nearly 4,500 patients, showed no benefit of corticosteroids over placebo in terms of mortality, MI, stroke and renal or respiratory failure (362).

An individual patient data meta-analysis of the SIRS and DECS trials showed that steroid administration did not reduce the risk of death, MI, stroke, renal failure, new onset AF or transfusions (82). Furthermore, an increased risk of myocardial injury was observed in both the SIRS and DECS trials. On the other hand, corticosteroids were also associated with a lower risk of respiratory failure and infection and contributed to a shorter duration of both ICU and hospital stays. These findings are consistent with those of another 2018 meta-analysis of 56 RCTs, which likewise failed to demonstrate conclusively the

benefits of corticosteroids in reducing mortality post-cardiac surgery (363). Notably, the DECS and SIRS trials accounted for a significant portion—75%—of the total participants in the meta-analysis, highlighting a general pattern of similarity in results.

In summary, routine prophylactic administration of steroids in cardiac surgery is not recommended. However, subgroup analyses stratified by age in the DECS trial and a recent meta-analysis of RCTs suggested a potential benefit for patients under 65 years of age (362, 364), who often exhibit a strong inflammatory response, but more research is needed. Patients who are already on long-term corticosteroid treatment should continue their preoperative dosage including the day of the operation.

Recommendation Table 13. Recommendation for prophylactic use of steroids

Recommendation	Class[a]	Level[b]	Ref[c]
The routine use of prophylactic steroids for patients undergoing open-heart surgery is not recommended.	**III**	**A**	**(82, 359-362)**

[a]Class of recommendation.
[b]Level of evidence.
[c]References.

10 Antibiotics

Infectious complications following open-heart surgery have been observed in up to 20% of the patients (365). Surgical site infections (SSIs) at the sternal wound and especially at the graft harvesting site are one of the most common complications, and, in severe cases, they are potentially fatal. Deep sternal wound infection (DSWI), including mediastinitis, remains a significant clinical problem because it is associated with a prolonged hospital stay, increased costs and mortality (366). Risk factors associated with SSIs include obesity, hypoalbuminaemia, hyperglycaemia, smoking and nasal colonization with *Staphylococcus aureus* (366, 367).

In a nationwide, retrospective, population-based cohort study including more than 114,000 patients undergoing isolated CABG, isolated valve surgery or their combination, DSWI, defined as a DWL of the sternal wound requiring reoperation within 90 days postoperatively, was observed in 1.3% of the patients (368). In the aforementioned registry, patients undergoing combined valve and CABG surgery had a slightly higher incidence (2.1%) of DSWI compared with patients undergoing isolated CABG or valve procedures. DSWI was associated with increased mortality at 90 days (7.9% vs 3.0%, with and without infection, respectively, $P < 0.001$) and at 1 year (12.8% vs 4.5%, $P < 0.001$) (368).

Thus, antibiotic prophylaxis is central to prevent SSIs in open-heart surgery and is therefore addressed in this guideline, while treatment of SSIs is addressed in a previous EACTS consensus document (369).

10.1 Preoperative screening and choice of the agent

Antibiotic prophylaxis in open-heart surgery reduces the rate of SSIs almost fivefold (370, 371) and also the associated morbidity and mortality. The most common agents associated with SSIs are Gram positive bacteria *(S. aureus* and *coagulase-negative Staphylococci*, including *S. epidermidis)*. Gram negative pathogens, including *Pseudomonas, Acinetobacter* and *Proteus mirabilis* anaerobic bacteria, fungi and mycobacteria, are less common (366, 369, 372, 373).

10.1.1 Preoperative screening

Occurrence of SSIs or bloodstream infections in patients colonized with *S. aureus* (nose, throat and perineum) was 2.5% in a mixed surgical population comprising 5,000 screened patients from 33 European surgical centres in 10 countries, with an adjusted HR of 4.4 (CI, 2.19–8.76) for *S. aureus* carriers to develop postoperative SSIs or bloodstream infection (367). A large, placebo-controlled RCT showed that intranasal mupirocin twice daily for 5 days significantly reduced the rate of SSIs in patients with a documented *S. aureus* colonization by nearly 60% (3.4 vs 7.7%, in the mupirocin and placebo groups, respectively; relative risk 0.42; 95% CI: 0.23–0.75) (374). In this RCT, *S. aureus* colonization was 19%, whereas it was 67% among 5,004 patients in a recent multicentre European Union registry (367). The differences in incidence may relate to the study population but also to the detection methods. However, the benefit of routine presurgical screening and mupirocin prophylaxis for all patients who are candidates for open-heart surgery remains to be investigated.

10.1.2 Choice of the agent

To ensure that the most frequent pathogens are targeted and resistance is prevented (373), prophylaxis with antibiotic agents needs to be chosen based on the local antimicrobial environment and resistance patterns reports as well as on the specific patient's characteristics. In a small, recent study, swabs from sternal skin prior to and after CABG surgery in 24 patients showed that >90% of the isolated pathogens were cefazolin-sensitive, i.e. the minimal inhibitory concentrations were <8 mg/L (375). Moreover, a larger, single-centre, observational study showed no difference in SSI between cefazolin and cefuroxime prophylaxis in 1029 patients (376). This comparison was, however, not randomized because the change in antibiotic prophylaxis was made in a context of antibiotic stewardship (376).

Cefazolin and cefuroxime are the most used, first-line prophylaxis agents based on studies showing their effectiveness in open-heart surgery (377-379). In patients colonized with cephalosporin-insensitive methicillin-resistant *Staphylococcus aureus*, vancomycin is recommended (380, 381).

10.1.3 β-lactam allergy

In patients with a documented allergy to β-lactam, clindamycin or vancomycin can be used to prevent Gram-positive bacterial infections (382-386). Importantly, up to 15% of hospitalized patients self-report an allergy to penicillin, but when allergy was tested, in 90–99% of the patients it could not be objectively documented (387). Therefore, proper allergy testing in patients who self-report penicillin allergy can avoid the use of vancomycin, clindamycin and quinolones prophylaxis and thus avoid the increase in vancomycin-resistant Enterococcus species, methicillin-resistant *Staphylococcus aureus* and *Clostridium difficile* resistant species (388, 389) and also lower the associated mortality, morbidity and prolonged hospitalization. Therefore, implementation of hospital protocols, including preoperative skin testing and testing for referred allergy, could optimize prophylaxis and reduce intrahospital infections, resistance and costs and improve the patients' outcomes (387, 390).

10.2 Dosing

To date, because of its safety, effectiveness and ease of use, systemic antibiotic prophylaxis in cardiac surgery is routinely based on fixed rather than body weight-adjusted doses. During open-heart surgery, haemodilution during CPB, adhesion to extracorporeal circuit material and reduced protein binding may all lead to concentrations of the antibiotic drug in plasma and tissue below the minimum inhibitory concentration, which may increase the risk of both infection complications and resistances (373). Thus, many centres routinely administer an additional dose of the chosen antibiotic upon initiation of CPB. Intraoperative redosing should be considered based on patient characteristics, haemodilution and procedure duration if it exceeds 2 half-lives of the antibiotic agent (Table 8), or when there is excessive intraoperative blood loss. Based on the limited evidence for optimal dosing in patients who are obese (391, 392), the dose of cephalosporin should not routinely exceed the standard dose. However, evidence indicating a need for dose adjustment in patients with more severe obesity is limited. For patients with renal failure, dosing should be adjusted according to the creatinine clearance in relation to the drug's clearance (393).

10.3 Timing of first administration and redosing

In order to reduce SSI, the time of parenteral administration (intramuscular or IV) of an antibiotic drug in relation to the operation is important. In patients treated with cefuroxime, the optimal timing was between 0 and 30 min before the incision because, within this time frame, the lowest occurrence of SSI was observed compared with 30–60 min and 60–120 min (394). Importantly, differences in pharmacokinetics of individual antibiotic drugs should be considered (Table 8) to optimize the timing of IV administration, provided that the antibiotic agent is always administered before the skin incision to allow adequate concentrations in the plasma and tissues. Furthermore, the incidence of infection after cardiac surgery decreases in patients with higher versus lower antibiotic serum concentrations at the time CPB is started as well as at the end of the operation (395, 396).

Dosing antibiotics for prophylaxis during CPB shows some pharmacological complexity. A recent review of antibiotic pharmacokinetics during open-heart cardiac surgery reported that, in the majority of studies, CPB is associated with an increase in volume of distribution of up to 58% and an altered drug clearance of up to 20%. Major changes in pharmacokinetics are related to haemodilution, retention of antibiotics in the extracorporeal circuit, increased volume of distribution, changes in blood protein content and clearance (373, 375), with consequent major changes in the circulating antibiotic's concentrations during CPB (375). Consistently, pharmacokinetic population models based on real-world data indicate a low probability of target attainment by cefazolin during cardiac surgery (397). Thus, based on the preceding evidence, an additional dose of antibiotics can be administered shortly after initiation of CPB, or the cefazolin dose can be doubled both before the skin incision and after CPB without an increase in adverse effects (375). These strategies, however, cannot be generalized to other antibiotics because the result depends on the individual drug's pharmacokinetics.

Kidney function can affect renal clearance of both cefuroxime and cefazolin (Table 8), and dose adjustment should be performed according to renal clearance measured as the eGFR, especially if the eGFR is below 50 ml/min.

10.4 Postoperative antibiotic prophylaxis

A randomized trial of 838 patients comparing a single-dose versus a 24-h multiple-dose of cefazolin in patients post open-heart surgery reported higher SSI rates with the single dosing (398). Furthermore, a recent meta-analysis of 12 RCTs with 7893 patients showed that prophylactic antibiotics administered >24 h (most commonly between 24 and 72 h) versus <24 h significantly reduced the risk of SSI by 38% (95% CI 13–69, *P* = 0.002) and the risk of DSWI by 68% (95% CI 12–153, *P* = 0.01) (399). Other studies have failed to show the benefit of prolonging prophylactic antibiotics to >48 h (400, 401), and this practice most likely increases the risk of antibiotic resistance compared with shorter prophylaxis as well (402-404). Therefore, based on current evidence, the optimal length of prophylactic antibiotics in adult post-open-heart surgery is 24 h and should not exceed 48 h. Whether intermittent or continuous prophylactic administration of antibiotics should be preferred remains unclear, although some evidence suggests that continuous infusion may reduce postoperative infectious complications (405). For intermittent administration, the exact timing of redosing depends on the half-life of the antibiotic agent (Table 8). Furthermore, it should be adjusted according to the postoperative renal function with special caution in patients on haemodialysis (375, 406-408).

10.5 Topical agents

In addition to IV antibiotic prophylaxis, topical agents may reduce the incidence of SSIs. The gentamicin–collagen sponge has been developed to maintain a high local concentration in tissues surrounding wounds. A meta-analysis including observational studies and RCTs showed approximately 40% relative reduction in sternal wound infections associated with gentamicin–collagen sponge use versus non-use (409). Another meta-analysis with over 40,000 patients, including 7 RCTs, showed that topical vancomycin reduced the risk of sternal wound infection by almost 70% compared with the control group [risk ratio, 95% CI 0.31 (0.23–0.43); *P* < 0.00001] (410). Due to the heterogeneity throughout the studies regarding the type of drug, doses, application protocols and SSIs definition, general recommendations are still challenging. However, topical vancomycin and the gentamicin–collagen sponge have some supporting evidence (411).

Table 8: Pharmacokinetics for selected antibiotics

Antibiotic agent	Time to peak	Protein binding (%)	Renal excretion (%)	Half-life (hours)[†]	Biotransformation and clinically relevant DDIs
Ampicillin	30 min (i.v)	15–25	90	1	No biotransformation
	1 h (i.m.)				No relevant DDIs
	2 h (oral)				
Amoxicillin (oral)	1.5 h	<20	60	1.5	Non-CYP450-mediated biotransformation
					May prolong the prothrombin time
Amoxicillin/clavulanate (oral)	1–1.5 h	25/18	40–70/40–45	1	Non-CYP450-mediated biotransformation
					No relevant DDIs
Cefazolin	5 min (i.v.)	80	80–100 (unchanged)	1.5	Minimally metabolized
	0.5–2 h (i.m.)				No relevant DDIs
	1 h (oral)				
Cefotaxime	5 min (i.v.)	40	60	1–1.5	Non-CYP450-mediated biotransformation
	30 min (i.m.)				No relevant DDIs
Ceftriaxone	Immediate (i.v.)	85–95	50–60	7–8	No relevant biotransformation
	1–3 h (i.m.)				No relevant DDIs
Cefuroxime	2–3 min (i.v.)	33–50	85–90	1–2	No relevant biotransformation
	30–60 min (i.m.)				No relevant DDIs
	2–3 h (oral)				
Ciprofloxacin (oral)	1–2 h	20–40	61.5	4–7	Metabolized in the liver
					Inhibits CYP1A2. Avoid coadministration with tizanidine, theophylline and QT-prolonging drugs. With glucose-lowering drugs: monitor blood glucose. With warfarin: monitor the INR
Clindamycin	45 min (oral)	94	10–20	2.5–3	Biotransformation via CYP3A4/5

	3 h (i.m.)				Strong CYP3A4 inhibitors and inducers may increase or decrease clindamycin plasma levels, respectively
Gentamycin (i.v.)	30 min (i.v.)	<10	>90	2–3	No relevant biotransformation
	30–90 min (i.m.)				Avoid concurrent use with loop diuretics (increased risk of ototoxicity and increased gentamicin plasma levels)
Imipenem/cilastin (i.v.)	Immediate	20/40	70/70–80	1	Metabolized in the kidney (dehydropeptidase I)
					Avoid coadministration with ganciclovir and probenecid. Reduces the concentration of valproic acid.
Levofloxacin	Immediate (i.v.)	24–38	87	6–8	No relevant biotransformation
	1–2 h (oral)				Monitor blood glucose when co-administered with glucose-lowering drugs. Monitor INR when co-administered with warfarin.
Meropenem (i.v.)	Immediate	2	70	1	Hepatic hydrolysis
					Meropenem reduces valproic acid plasma levels.
Metronidazole	Immediate (i.v.)	<20	60–80	8	Extensively metabolized
	1–2 h (oral)				Increases serum lithium levels and potentiates the effect of VKAs
Piperacillin/ tazobactam (i.v.)	Immediate	30/30	68/80	0.7–1.2	No relevant biotransformation
					Monitor kidney function if co-administered with vancomycin. Monitor coagulation parameters in patients receiving heparin or oral anticoagulants. Reduces tobramycin levels. May prolong the neuromuscular blockade of vecuronium.
Tobramycin (i.m.)	30–60 min (i.m.)	<10	90–95	2–3	No relevant biotransformation
	30 min (i.v.)				Avoid the use of nephrotoxic and ototoxic drugs. Embryo-fetal toxicity.
Vancomycin (i.v.)	Immediate	30–55	80–90	4–6	No relevant biotransformation

					No relevant DDIs

[†]Repeat intraoperative dosing if the duration of the procedure exceeds 2 half-lives of the antibiotic agent or when there is excessive intraoperative blood loss or haemodilution.

CYP: cytochrome P450; DDIs: drug–drug interactions; h: hours; i.m.: intramuscular; i.v.: intravenous; min: minutes; VKAs: vitamin K antagonists.

Recommendation Table 14. Recommendations for antibiotics

Recommendations	Class[a]	Level[b]	Ref[c]
In patients undergoing open-heart surgery who are *Staphylococcus aureus* carriers, intranasal mupirocin twice daily is recommended starting 4 days before surgery.	I	B	(367, 374, 412)
General prophylaxis			
Antibiotic prophylaxis is recommended to prevent infectious-related complications.	I	A	(394, 413-415)
Timing			
It is recommended to complete the first dose of antibiotic[d] prophylaxis infusion within 30–60 min before skin incision.	I	B	(394, 415-417)
Dosing			
Antibiotic prophylaxis dosage is recommended to be individualized according to patient characteristics, including underweight, obesity and renal function, with appropriate adjustments.	I	C	-
Duration			
A prophylaxis duration of 24 h and no longer than 48 h post-open-heart surgery should be considered.	IIa	A	(399-401, 418, 419)

Intraoperative antibiotic redosing should be considered based on patient characteristics, haemodilution or blood loss or if the procedure exceeds 2 half-lives of the antibiotic agent.	**IIa**	**B**	**(408, 416, 420-422)**
Selection of antibiotic agent			
It is recommended that prophylactic agents and dosage are chosen based on local antimicrobial environment reports and resistance patterns and are tailored to the patient's characteristics.	**I**	**C**	**-**
Cefazolin or cefuroxime should be considered as first-line treatment in non-allergic patients.	**IIa**	**A**	**(379, 422, 423)**
Vancomycin or clindamycin should be considered in patients with a documented β-lactam allergy.	**IIa**	**B**	**(382, 384, 385)**
Vancomycin should be considered for prophylaxis in patients with a documented methicillin-resistant *Staphylococcus aureus* colonization.	**IIa**	**B**	**(380, 381, 424, 425)**
Topical vancomycin or gentamicin–collagen sponges may be considered as adjunctive measures to prevent surgical site infections.	**IIb**	**B**	**(409-411)**

MRSA, methicillin-resistant *Staphylococcus aureus*.

[a]Class of recommendation.

[b]Level of evidence.

[c]References.

[d]See Table 8 for different antibiotics.

11 Blood glucose management

Based on recent estimates, up to 40% of patients with the diagnosis of DM undergo cardiac surgery (426) with increased morbidity and mortality compared with patients who do not have DM (426, 427). This estimate is consistent with DM being a major risk factor for cardiovascular disease due to endothelial dysfunction, platelet activation and hypercoagulation (428) as well as for infections (429). Moreover, around 25–29% of all patients undergoing cardiac surgery have newly discovered fasting hyperglycaemia detected before the procedure (426). This finding is important because patients with presurgical fasting hyperglycaemia (blood glucose >120 mg/dl or 6.6 mmol/L) have a higher incidence of perioperative hyperglycaemia (defined as blood glucose >180 mg/dl or >10 mmol/L), vascular and infectious complications and worse general outcomes after cardiac surgery compared with individuals without DM and with those patients with already-diagnosed DM who are under treatment (426) Therefore, preoperative assessment of blood fasting glucose is recommended routinely at hospital admission. If fasting hyperglycaemia is present, the diagnostic workup for DM should be completed preoperatively, including haemoglobin A1c (HbA1c) determination (Fig. 5). Although data on hyperglycaemia detected before cardiac surgery show a consistently significant association with postoperative complications (426, 427, 430), studies on preoperative HbA1c levels as a perioperative risk factor in cardiac surgery are more heterogeneous. Some studies report an association between higher HbA1c, with or without known DM, and increased early postoperative complications including stroke, AKI, sternal wound infections, prolonged stay in the ICU, inferior graft patency and/or increased 30-day mortality, even though HbA1c thresholds differ across studies (between >5.5% and >7%) (426, 431-434). Other studies did not report any association between preoperative HbA1c levels and adverse outcomes, including a large retrospective analysis of 431,480 operations from the Duke University Health System, whereas a significant association between preoperative hyperglycaemia and mortality was observed in the same cohort (427).

A multidisciplinary ‘diabetes team’ should be in charge of perioperative insulin infusion protocols, treatment algorithms for the transition to subcutaneous insulin after enteral feeding has been reestablished, nutritional management and switch to preoperative glucose-lowering drugs, using hospitalization as a ‘window of opportunity’ for patient education, treatment selection and dose

adjustment (Fig. 5). Before hospital discharge, patients with a previous DM diagnosis, with new-onset DM or hyperglycaemia in the perioperative period, should have an endocrinology consultation and dietary counselling, strict post discharge monitoring and regular follow up. The postoperative choice of glucose-lowering therapies should be aimed at preventing major cardiovascular complications and keeping HbA1c <7% in order to optimize long-term postoperative results (435, 436).

Independently of a previous diagnosis of DM, recent observational studies estimate that intraoperative and ICU hyperglycaemia (defined as > 180 mg/dL or 10 mmol/L) affects 30–40% of all cardiac surgery patients, likely triggered by surgery-related stressors, inotropes, underlying patient characteristics (e.g. obesity, pre-existing DM, presurgery hyperglycaemia) (426, 430, 437). Overall, perioperative hyperglycaemia, independently of a previous diagnosis of DM, is associated with worse outcomes early after cardiac surgery such as longer hospitalization, arrhythmias, AKI, infections and death compared with patients with no hyperglycaemia (426, 427, 430, 438, 439).

The relevance of controlling perioperative hyperglycaemia is confirmed by randomized studies showing that perioperative (including ICU and post-ICU) blood glucose control using an insulin infusion reduces mortality and adverse events in patients undergoing cardiac surgery (426, 440-442). Thus, blood glucose control and, if needed, IV insulin are currently the standard treatments for hyperglycaemia to keep values <180 mg/dL or 10 mmol/L (443). However, the optimal blood glucose range in cardiac surgery is still debated. In particular, the lower threshold of the range has non-conclusive evidence for different reasons, including the practical consideration that a too-low threshold may increase the risk of hypoglycaemic episodes in the ICU (444). In particular, the tested glucose ranges vary across studies, and there are few head-to-head comparisons of different ranges. The categories usually defined as ‘tight’ versus ‘conventional’ are heterogeneous. Too tight glycaemic control (blood glucose <100–110 mg/dL) has been associated with an increased risk of hypoglycaemia in some trials post-CABG (445-448), whereas the small GLUCO-CABG (Intensive versus conservative glucose control in patients undergoing coronary artery bypass graft surgery) RCT showed that tight insulin therapy (glucose target 100–140 mg/dL) was similar to less intensive treatment (glucose target 141–180 mg/dL) for efficacy and safety, including no differences in hypoglycemia (449). A 2023 Cochrane Review for patients with DM undergoing all cardiac and non-cardiac major surgery showed no difference between tight and

conventional perioperative glycaemic control for all-cause mortality, AKI and ICU length of stay and showed a trend of reduced infections for tight glucose control (RR 0.75, 95% CI 0.55–1.04; *P* = 0.09), an increase in severe and non-severe hypoglycaemic events (RR 3.36, 95% CI 1.69–6.67; I^2 = 64%, n=2410) and no significant increase in mortality (RR 1.08, 95% CI 0.88–1.33; I^2 = 0%; n=2551) (450). Furthermore, in a large cohort of 6,393 cardiac operations, the correlation between blood glucose levels and 30-day mortality followed a U-shaped relationship, whereby mortality was 4.5% at 100 mg/dL, 1.5% at 140 mg/dL and 6.9% at 200 mg/dL (427), this being in agreement with previous data from a general ICU cohort (451, 452). This finding suggests a similar imbalance in glucose regulation and needs in the 2 extreme situations. Interestingly, the U-shaped association was not observed in non-cardiac surgery, where the correlation between blood glucose and death was linear instead (427). Moreover, perioperative hyperglycaemia seems to have a worse prognosis and therefore a need for tighter control in patients without known DM compared with previously diagnosed DM already under treatment (426, 449). Currently, management of blood glucose levels by insulin infusion is recommended until normal feeding is fully restored.

The perioperative use of the SGLT2 inhibitors approved for DM, HF and CKD is associated with an increased risk of euglycemic ketoacidosis, a rare, but potentially life-threatening side effect, favoured by perioperative fasting and metabolic changes caused by surgical stress (453). Thus, for all elective major surgery, the United States Food and Drug Administration advises that SGLT2 inhibitors be stopped for at least 3 or 4 days, depending on the specific agent, before the scheduled operation (453), whereas the European Medicines Agency generically advises to stop treatment '*temporarily and to restart SGLT2 inhibitor once the patient's condition has stabilized*' (454). The interruption of SGTL2 is also advised to prevent postoperative severe urinary and genital mycotic infections, which are increased by these drugs and can be worsened by urinary catheters. For emergency open-heart surgery in patients on SGLT2 inhibitors for DM, HF or CKD, the risk factors triggering euglycemic ketoacidosis remain unknown (455). Therefore, monitoring symptoms, blood and urine ketones, arterial pH, serum bicarbonate and the anion gap is of central importance to prevent fatal complications (456-458). Thus, based on the arterial blood gases, acidosis in the presence of normoglycemia should raise suspicion, and measurement of ketones in blood and urine can further support the diagnosis.

Aside from insulin, glucose-lowering drugs are re-introduced upon resumption of normal feeding, and SGLT2 inhibitors, when the patient is haemodynamically stable. Regarding the long-term postoperative use of SGLT2 inhibitors, a post-hoc analysis of the EMPA-REG (Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes) RCT on a subgroup of patients who self-reported a history of CABG at trial entry, showed that empagliflozin significantly reduced cardiovascular and all-cause mortality, hospitalization for HF and incident or worsening CKD, versus placebo, consistent with the entire trial cohort (459). The ongoing open-label, small randomized DAPA-TAVI (Dapagliflozin after Transcatheter Aortic Valve Implantation) RCT is testing the risk/benefit of dapagliflozin in patients with severe aortic stenosis and HF randomized within 2 weeks post-TAVI (460).

Glucagon-like peptide-1 receptor agonists (GLP-1RA) have been approved initially for DM and, more recently, some of them, for treating obesity in the absence of DM (461). Recent data suggested an increase in pulmonary aspiration associated with the use of these drugs due to gastroparesis (462-464)). Although the data still conflict (464), caution should be exerted preoperatively, and the last dose of GLP-1RA should be withheld until either the day or the week before the operation, depending on the type of drug.

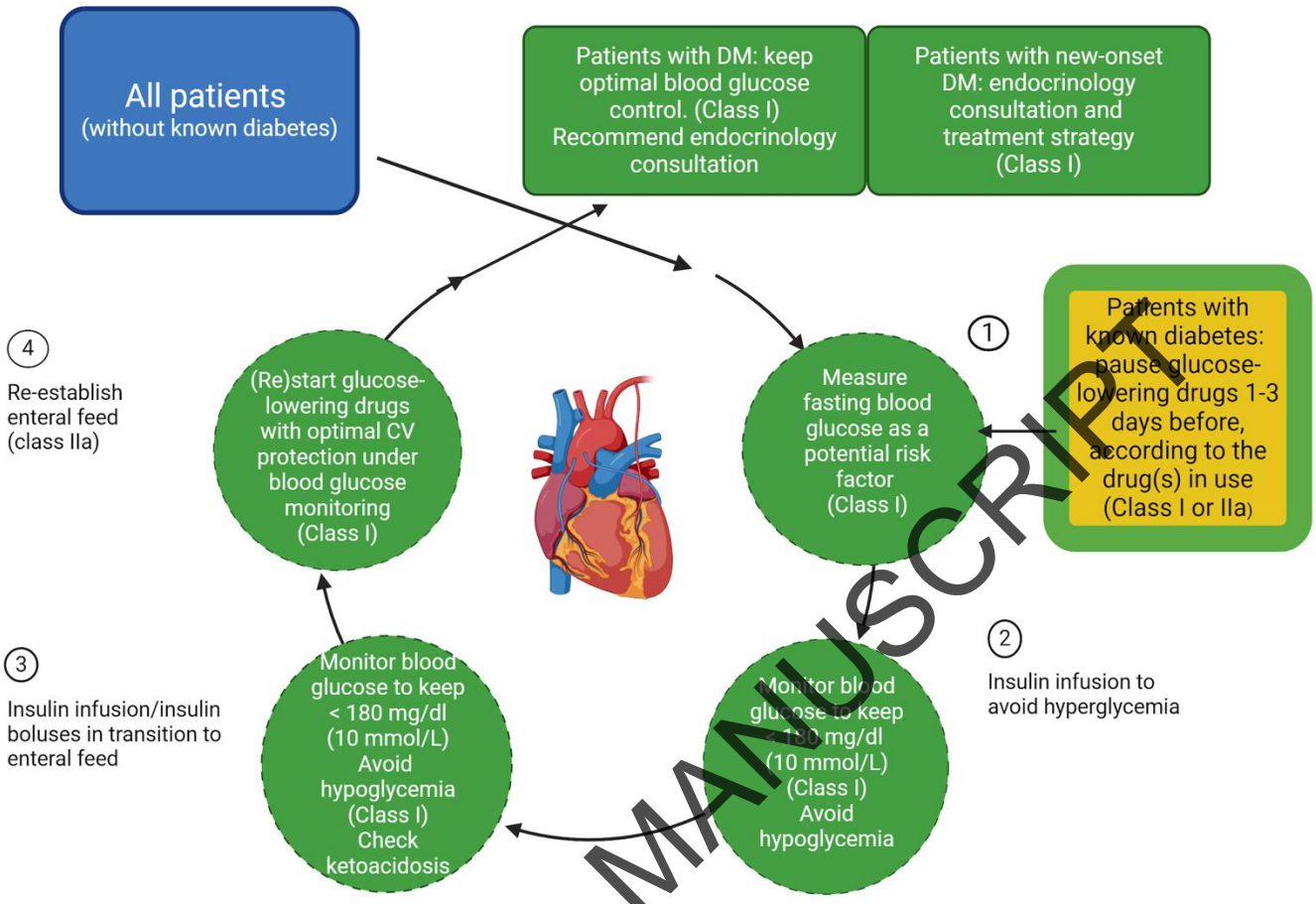

Figure 5: Management of blood glucose monitoring and control before, during and after cardiac surgery. CV: cardiovascular; DM: diabetes mellitus.

Small randomized trials tested GLP-1RA as an adjunctive therapy to perioperative insulin infusion, suggesting better glucose control when liraglutide (465, 466) was combined with insulin, because the combination reduced insulin requirements and improved perioperative glycaemic control during CABG and non-CABG cardiac surgery, compared with placebo and insulin, in patients with and without DM (465-467), similarly to non-cardiac surgery (468). However, the perioperative data are too preliminary for any specific recommendation.

Caution should be exerted with the use of thiazolidinediones, which increase the risk of fluid retention, and these drugs are contraindicated in patients with DM and HF (469).

Recommendation Table 15. Recommendations for blood glucose management

Recommendations	Class[a]	Level[b]	Ref[c]
Preoperative period			
It is recommended to discontinue oral and subcutaneous non-insulin glucose-lowering drugs and long-acting insulins, at least 24 h before surgery, taking into account the half-life of each agent.	**I**	**C**	**-**
Discontinuation of SGLT2 inhibitors should be considered at least 72 h before open-heart surgery to reduce the risk of euglycemic ketoacidosis.[d]	**IIa**	**B**	**(455, 456, 470, 471)**
In the 24 h before the operation, blood glucose levels should be maintained between 120 and 180 mg/dl (6.7–10 mmol/l) by using short-acting insulin.	**IIa**	**C**	**-**
Intraoperative period			
In patients without DM, blood glucose monitoring is recommended during open-heart surgery; for persistent levels >180 mg/dl (>10 mmol/l), intravenous insulin is recommended.	**I**	**B**	**(472-474)**
In patients with DM, it is recommended to maintain a blood glucose level <180 mg/dl (<10 mmol/l) by continuous IV insulin infusion, which is started and maintained throughout the operation with glucose monitoring.	**I**	**B**	**(450, 475)**
Intensive care unit			
In patients with or without DM in the ICU, it is recommended to maintain blood glucose levels <180 mg/dl (10 mmol/l) by continuous insulin IV infusion, if needed.	**I**	**B**	**(438, 449, 476)**
Post-intensive care unit			

A combination of short-acting and long-acting subcutaneous insulin should be started at 50% of total previous 24-h insulin dose in the ICU and then titrated when the patient restarts a regular diet.	**IIa**	**C**	**-**
It should be considered to check blood glucose levels every 4 h to target <180 mg/dl (10 mmol/l) and adjust insulin dosing as needed.	**IIa**	**C**	**-**
It may be considered to restart preoperative glucose-lowering drugs at 50% of the preoperative dose when the patient restarts a regular diet.	**IIb**	**C**	**-**
It may be considered to restart SGLT2 inhibitors when the patient is haemodynamically stable.[d]	**IIb**	**C**	**-**
At hospital discharge			
It is recommended to consult a diabetes specialist before discharge for patients with DM and de novo persistent hyperglycaemia to plan short- and long-term management and target HbA1c <7%.	**I**	**B**	**(432, 476-479)**
In patients with DM, it is recommended to reconsider oral glucose-lowering therapy and prioritize the use of agents with CV proven benefit over those without.	**I**	**C**	**-**
Thiazolidinediones are not recommended in patients with DM and HF.	**III**	**A**	**(480-483)**

CV: cardiovascular; DM: diabetes mellitus; HbA1c: haemoglobin A1c; HF: heart failure; ICU: intensive care unit; IV: intravenous; SGLT2: sodium glucose cotransporter-2 inhibitors.

[a]Class of recommendation.

[b]Level of evidence.

[c]References.

[d]This recommendation applies to all approved indications for SGLT2 inhibitors.

12 Antidepressants

Depression and delirium are increasingly associated with open-heart surgery, and affect both morbidity and mortality. In fact, they often result in rehospitalization, extended hospital stay, need for rehabilitation and long-term care, impaired postoperative cognitive function and quality of life, thus predisposing to several postoperative complications and can undermine the success of the operation (484). Depression has also been shown to be associated with increased sympathetic tone, higher cortisol and catecholamine levels, inflammatory markers and platelet activation, all factors that can worsen cardiovascular outcomes (484). The incidence of depression has been reported as high as 60% among patients undergoing open-heart surgery (484, 485). Furthermore, preexisting depression (even if latent), older age and female sex are known risk factors for post-heart surgery depression.

The most widely used antidepressant drugs in patients undergoing cardiac surgery are selective serotonin reuptake inhibitors (SSRIs) (escitalopram, citalopram, fluoxetine, paroxetine and sertraline), and, less frequently, serotonin and noradrenaline reuptake inhibitors (SNRIs) (i.e. desvenlafaxine, duloxetine, levomilnacipran, milnacipran and venlafaxine). Both drug classes appear to be effective and safe when used peri- and/or post-open-heart surgery (484, 485). SSRIs competitively inhibit the presynaptic uptake of serotonin, consequently increasing serotonin levels within the brain. Outside the central nervous system, SSRIs have been reported to have some anti-inflammatory effects and to weakly inhibit platelet function by blocking serotonin uptake. These mechanisms have been hypothesized to reduce cardiovascular risk on one side, and to potentially increase bleeding risk on the other side (486). However, large case–control studies showed that the perioperative use of SSRIs and SNRIs did not increase postoperative bleeding or 30-day cardiovascular adverse outcomes in patients undergoing CABG (487, 488) or other types of cardiac operations (489). A meta-analysis involving 437 patients reported no increase in major bleeding or mortality rates (490). Some SSRIs not only block the presynaptic uptake of serotonin but also inhibit the cytochrome P450 2D6 enzyme, which can lead to clinically relevant interactions with other agents used in the peri- and/or intraoperative periods. In particular, SSRIs may increase blood concentrations of benzodiazepines, barbiturates, BBs and some antiarrhythmics (flecainide, mexiletine, propafenone) and can also reduce the conversion of prodrugs such as tramadol, codeine and oxycodone into their active metabolites, thus reducing the analgesic

effect of these pharmacological agents (491-493). SSRIs should also be used with caution in patients with vasospastic angina, because serotonin can be a trigger of coronary artery spasm. Moreover, citalopram and escitalopram should be avoided in people with known QT interval prolongation or in patients taking other medicines that prolong the QT interval (494). Thus, drug interactions should be carefully assessed in patients receiving polypharmacy. The co-administration of SSRI and methylene blue has been associated with the occurrence of serotonin syndrome, due to the reversible inhibition of monoamine oxidase enzymes responsible for the metabolism of serotonin (495), which can be serious after cardiac surgery. Caution is also recommended when administering SSRI and non-steroidal anti-inflammatory drugs (NSAID) for pain control because the risk of GI bleeding is increased when NSAIDs are administered together with SSRI compared with NSAIDs alone (496, 497).

Delirium post-open-heart surgery has been reported in 10% to 50% of the patients, depending on the studied cohorts and how delirium is defined (498), usually in the first postoperative days. Delirium tends to be associated with older age, preoperative depression, cognitive impairment and other major co-morbidities (499). Moreover, delirium is associated with prolonged length of stay, hospital readmission, long-term cognitive and functional decline and death after surgery (500, 501). Preoperative evaluation of patients' anxiety, symptoms of depression and cognitive tests have been suggested to lower the risk of postoperative delirium (498). Heterogeneous and non-conclusive evidence exists that peri- and intraoperative benzodiazepine administration causes postoperative delirium in open-heart surgery, especially in elderly patients (502). A recent large survey of >65,000 patients and 33 Canadian institutions showed a wide variability in the pattern of usage and doses, specifically in cardiac surgery (503), reflecting the uncertain evidence. For elderly patients, use of benzodiazepines should be minimized or avoided before and after surgery (503, 504). The B-Free (Benzodiazepine-Free Cardiac Anaesthesia for Reduction of Postoperative Delirium) RCT failed to show that a restrictive use of benzodiazepines during cardiac surgery could reduce the incidence of delirium within 72 h after cardiac surgery compared with a liberal use (505, 506)

Lastly, given their cardiotoxicity, tricyclic antidepressants should be avoided or discontinued under psychiatric consultation in patients undergoing cardiac surgery (507, 508).

Recommendation Table 16. Recommendations for antidepressants

Recommendations	Class[a]	Level[b]	Ref[c]
Continuation of SSRIs should be considered throughout the perioperative period in patients already on treatment, with careful consideration of drug interactions.	IIa	B	(484, 487-490)
In patients on SSRIs, gastroprotectant drugs are recommended.	I	B	(496, 497)
NSAIDs are not recommended in cardiac surgery patients on SSRIs due to the risk of gastrointestinal bleeding.	III	B	(496, 497)
It is recommended to discontinue tricyclic antidepressants before open-heart surgery, in consultation with a psychiatric specialist.	I	C	-
SSRIs in patients with QT prolongation or vasospastic angina are not recommended.	III	B	(509, 510)

NSAIDs: non-steroidal anti-inflammatory drugs; SSRI: selective serotonin reuptake inhibitor.

[a]Class of recommendation.

[b]Level of evidence.

[c]References.

13 Postoperative optimization

Cardiac surgery has become increasingly effective in enhancing both survival and quality of life, especially by treating severe forms of coronary artery disease, heart valve disease and acute and chronic syndromes of the aorta (6-8, 511, 512). Despite these advancements, a significant risk of long-term complications remains. This finding underscores the importance of secondary prevention medication and lifestyle modifications to prevent future cardiovascular symptoms and complications. These medications function through various mechanisms, such as slowing the progression of native coronary artery disease, inhibiting atherosclerosis in arterial and venous grafts, reducing calcification in BHV and lowering the risk of thrombosis in both native and artificial grafts and valves (513-515). The role and definition of guideline-directed medical therapy (GDMT) are constantly evolving, driven by emerging evidence and the development of new medications (6, 7). Regular updates and adjustments to GDMT are crucial to fully capitalize on the benefits of cardiac surgery and ensure better short- and long-term patient outcomes.

13.1 Guideline-directed medical therapy after coronary surgery

GDMT post-CABG is essential for preventing not only perioperative and short-term complications but also for enhancing long-term outcomes. Its importance is increasingly recognized by all stakeholders (clinicians, payers, patients, healthcare authorities) (515, 516). Secondary prevention strategies are central to prevent the progression of underlying coronary atherothrombosis, especially in residual disease not suitable for revascularization and in maintaining conduit patency (114, 517). Despite the well-documented benefits of secondary prevention in maximizing CABG results, adherence to and persistence with GDMT remain suboptimal, even in rigorously conducted clinical trials that emphasize GDMT as a crucial aspect of their study protocols (2, 518). Factors such as polypharmacy and comorbidities like CKD and DM contribute to this reduced adherence to and persistence with GDMT, consequently increasing the risk of adverse events and negatively affecting long-term survival (519-522).

Adherence to recommended SAPT at discharge, typically low-dose ASA, varies from 85% to 100% among countries enrolled in multicentric trials (523, 524). Although it is recommended for virtually all patients having CABG, low-dose ASA is sometimes omitted due to concurrent OAC use, though there are no data supporting this practice. Statin utilization at discharge ranges in clinical trials from 40% to 90%, with adherence to other components of GDMT, particularly BBs and ACEIs/ARBs, generally even lower (3, 524).

Thus, medication dispensing tends to decrease gradually over time post-discharge, a trend reflected in various "real-world" observational studies (4, 5, 525). A national analysis from Sweden, including nearly 30,000 patients undergoing isolated CABG from 2006 to 2015 who survived at least 6 months post-discharge, showed that statins were dispensed to 94% of patients at 6 months and to 77% eight years later (4). Similarly, BBs were dispensed to 91% and 76%, ACEIs/ARBs to 73% and 66% and antiplatelet drugs to 93% and 80% at 6 months and 8 years, respectively. Persistence with statins, RAS inhibitors and antiplatelet drugs (ASA alone or with a $P2Y_{12}$-receptor inhibitor when indicated) was each independently associated with a lower mortality risk after adjusting for baseline characteristics and other drug use (4, 526). Other studies have also demonstrated that patients who adhere to recommended drugs after CABG experience significantly higher MACE-free survival (3, 5, 340). In a meta-analysis of 5 landmark RCTs comparing bypass surgery with PCI, GDMT compliance was poor in CABG and substantially worse than in patients who had PCI (2). One-year post CABG, only 67% of patients were on combined antiplatelet therapy, statins and BBs, decreasing to 53% at 5 years. Including ACEIs, compliance further dropped to 40%. Meta-regression analysis suggests that poor adherence to GDMT significantly worsens long-term outcomes, including an increased risk of MI at 5 years (2). These notable differences in event-free survival between groups emphasize the importance of adherence to and persistence with medical therapy after CABG that must be vigorously pursued.

In accordance with the recommendations previously outlined, post-CABG care should include life-long low-dose ASA and a lipid-lowering medication for all patients, unless contraindicated or not tolerated, along with temporary DAPT following recent ACS or PCI. ACEIs or ARBs are also recommended for all patients after CABG. Their effects are found to be consistent irrespective of baseline characteristics, including in patients with hypertension, DM, CKD or reduced left ventricular function. BBs are

recommended for patients in whom CABG is not expected to relieve all angina symptoms, with previous MI, reduced LVEF and/or some rhythm disorders. Additionally, comprehensive management should include addressing other cardiovascular risk factors through both medication and lifestyle changes, such as a balanced diet, weight control, regular exercise and smoking cessation, although these are beyond the scope of this document (515).

13.2 Guideline-directed medical therapy after open-heart non-coronary cardiac surgery

Despite comprising nearly half of the cardiac surgery population, prospective research on the impact of secondary prevention measures on long-term outcomes following valve and other non-CABG cardiac interventions remains limited (525, 527). Observational data suggest that statins and ACEIs/ARBs are beneficial for patients undergoing SAVR and TAVI, whereas the effectiveness of these drugs in other surgical settings is not well-established.

In a nationwide Swedish study of 10,000 patients with aortic stenosis who underwent isolated SAVR with mechanical or bioprosthetic prostheses from 2006 to 2017, statins were dispensed to 49% of the patients at both 6 months and 10 years post-discharge. ACEIs/ARBs followed a similar pattern, with 51% and 54% of patients receiving them in these respective time frames, while the prescription of BBs decreased from 79% initially to 61% after 10 years. Continuous adherence to statins and RAS inhibitors was significantly associated with reduced mortality risk. In contrast, BBs did not show a comparable impact on mortality (332). An extended analysis until 2020 showed that treatment with ACEIs/ARBs post-SAVR was associated with a 13% reduced risk of the composite outcome of all-cause death, stroke or MI and a 21% lower risk of all-cause death (303). In a further investigation of the same patient cohort, ongoing statin treatment post-isolated SAVR for stenosis showed a consistent reduction in MACE and in all-cause and cardiovascular mortality across all patient subgroups (341). Altogether, these findings underscore the benefits of statins post-SAVR (528, 529). Notably, the beneficial effects of long-term ACEIs/ARBs and statins also include SAVR for aortic regurgitation. However, in this broader application, the effectiveness of BBs presents a more complex picture, delivering mixed outcomes that necessitate further exploration (342). Thus, the role of BBs needs to be further investigated.

ACEIs/ARBs and statins show broad indications in patients following AV interventions, as seen in patients who undergo TAVI, where RAAS inhibitor use at hospital discharge significantly reduces mortality and HF readmission (530, 531). This observation is supported by the PARTNER (Placement of Aortic Transcatheter Valves) and Sapien RCTs and registries, which associated statin use with lower 2-year all-cause mortality rates (532). Additionally, TAVI patients on ACEIs/ARBs and statins demonstrate lower three-year mortality (533), mirroring benefits seen in studies of patient having SAVR.

13.3 Strategies to improve guideline-directed medical therapy

Hospitalization for cardiac surgery is an important opportunity for physicians to start or adjust secondary prevention therapies at discharge and during follow-ups to improve treatment adherence and persistence. However, GDMT adoption rates post-coronary revascularization and valve surgery are often below 60%, and these rates decrease over time (2, 4, 332, 534-536). Similarly, adherence to pharmacological therapies, including immunosuppressants, is often suboptimal following a heart transplant (537). Factors contributing to the underuse of GDMT include lack of emphasis and understanding its importance, misconceptions about its necessity post-surgery and inadequate reporting in clinical trials. Reluctance to commit to lifelong medication, particularly when asymptomatic or experiencing side effects, polypharmacy, drug interactions and high drug costs, especially in low- and middle-income countries, and loneliness further reduce compliance (537-539).

Improving adherence to GDMT is crucial to decrease preventable deaths and disabilities from cardiovascular disease. Cardiac surgery institutions, in collaboration with patients and care physicians, must ensure early and sustained adherence to GDMT (540). Providing comprehensive education about the benefits of adhering to GDMT is essential to derive the most from the intervention, including improved survival and a better quality of life. Innovations like fixed-dose drug combinations, the so-called ‘polypill’, which simplifies multiple drug regimens, and avoidance of preventable drug–drug interactions, thus reducing adverse events, can boost compliance and improve outcomes while reducing costs (541). Importantly, patients living with cardiovascular diseases who are exposed to major open-heart procedures are particularly exposed to polypharmacy (i.e. the use of ≥ 5 drugs) (542), which

is often necessary in complex, chronic, co-morbid, often older patients. Polypharmacy is a known risk factor for potential drug–drug interactions, which, only if clinically relevant, may ultimately lead to toxicity or therapeutic failure with a negative impact on the patient's quality of life, mortality, health system costs due to (re)hospitalization and worse long-term outcomes (543, 544), possibly including safety and efficacy of the GDMT. Careful revision of drugs in multimorbid and multitreated patients is needed to screen for and avoid clinically relevant drug interactions.

Until these approaches are widely available and adopted in secondary prevention, focusing on long-term adherence to GDMT through quality assurance programs is vital (545-547). Certainly, developing institutional algorithms and protocols that reflect their clinical, cultural, religious and legal environments to improve discharge adherence, in agreement with the present recommendations, is an essential step toward the long-term goals.

Quality indicators may play a valuable role in improving treatment adherence and providing important insights from real-world data (548). Integrating guideline-based quality indicators into healthcare programs can guide improvements in adherence, persistence and patient outcomes, raising care standards while ensuring that evidence-based practices are thoughtfully applied. As care for cardiac surgery patients shifts to primary and secondary prevention, collaborative efforts (549), such as remote medication monitoring (550) with or without application of artificial intelligence, become crucial in maintaining a high quality of care and continuously promoting better treatment adherence.

Recommendation Table 17. Recommendations for postoperative optimization of medical therapies

Recommendations	Class[a]	Level[b]	Ref[c]
Postoperative period			
Long-term GDMT, including low-dose ASA (75–100 mg), lipid-lowering therapy and a RAS inhibitor (ACEI or ARB), is recommended post-CABG at discharge, in the absence of contraindications[d].	**I**	**B**	**(2-5)**

In patients with recent ACS or PCI, long-term GDMT, including DAPT for the indicated duration followed by low-dose ASA (75–100 mg), lipid-lowering therapy, RAS inhibitor (ACEI or ARB), is recommended post-CABG at discharge, in the absence of contraindications[d].	**I**	**C**	**-**
In patients with HF and reduced LVEF <40%, long-term GDMT, including low-dose ASA (75–100 mg), lipid-lowering therapy, a RAS inhibitor, MRA, SGLT2 inhibitor and BB are recommended post CABG at discharge, in the absence of contraindications[d].	**I**	**C**	**-**
Long-term GDMT, including an indicated antithrombotic regimen, lipid-lowering therapy and a RAS inhibitor (ACEI or ARB), may be considered post-SAVR and post-TAVI, in the absence of contraindications[d].	**IIb**	**B**	**(303, 332, 341, 530, 532, 533)**
In patients with HF and reduced LVEF ≤40%, long-term GDMT, including recommended antithrombotic regimen, lipid-lowering therapy, a RAS inhibitor, MRA, SGLT2 inhibitor and BB may be considered after valvular heart surgery, in the absence of contraindications[d].	**IIb**	**C**	**-**
It is recommended that patients undergo regular examinations and strictly adhere to their prescribed GDMT over time, to derive the most long-term benefits from the operation.	**I**	**A**	**(2, 535-537)**
Quality assurance initiatives that systematically measure adherence to GDMT, along with quality improvement programs, are recommended to enhance adherence to and persistence with GDMT.	**I**	**C**	**(549)**

ACEI: angiotensin-converting enzyme inhibitor; ACS: acute coronary syndrome; ARB: angiotensin II receptor blockers; ASA: acetylsalicylic acid; BB: beta blocker; CABG: coronary artery bypass grafting; DAPT: dual antiplatelet therapy; GDMT: guideline directed medical therapy; HF: heart failure; LVEF: left ventricular ejection fraction; MRA: mineralocorticoid receptor antagonist; PCI: percutaneous coronary intervention; RAS: renin-

angiotensin system; RAS: renin-angiotensin system; SAVR: surgical aortic valve replacement; SGLT2: sodium glucose cotransporter-2; TAVI: transcatheter aortic valve implantation.

[a]Class of recommendation.

[b]Level of evidence.

[c]References.

[d]If so, substitution with similar medications from the same or a similar drug class is recommended to achieve the desired effects.

14 Gaps in knowledge

The management of perioperative medication in cardiac surgery area requires thorough investigation to effectively address each stage of treatment.

Section 3

Preoperative management

- The timing of discontinuation and subsequent re-initiation of RAAS inhibitors in relation to open-heart surgery need further investigation.
- The initiation of BB agents shortly before surgery to prevent postoperative arrhythmias requires prospective studies.
- The impact of weight reduction, with and without medications, in preparation to open-heart surgery needs more studies to understand its effects on both short- and long-term outcomes.

Section 4

- There is a need for better understanding the bleeding risk vs. thrombotic risk to optimize handling of antithrombotic drugs preoperatively.

Antiplatelet drugs

- Studies are needed to compare continuing ASA versus discontinuing ASA before cardiac surgery.
- Whether ASA should be started before CABG in ASA-naïve patients needs to be investigated.
- Safety and efficacy of a $P2Y_{12}$-receptor inhibitor vs ASA as single antiplatelet long-term treatment after CABG needs to be investigated.
- Whether DAPT is superior to SAPT in patients with CCS after CABG remains to be investigated.

Anticoagulant drugs

- The safety and efficacy of DOAC-specific antidotes in cardiac surgery, particularly for andexanet alfa, needs more data.
- The safety and efficacy of alternative reversal strategies for anti-FXa DOACs, namely for PCC and haemoadsorptive column devices, in cardiac surgery need further studies.

- The efficacy and safety of ASA versus VKA or DOACs in the first 3 months following bioprosthetic SAVR and valve repair need to be compared.
- The efficacy and safety of ASA beyond 12 months after bioprosthetic AVR or TAVI remain unknown.
- The benefit and risks of DOAC versus VKA post-TAVI in patients with an indication for OAC remains unknown and needs to be investigated.

Sections 5

- How thromboembolic risk and bleeding risk should be assessed in patients with POAF remain to be investigated.
- It needs to be established in which patients with POAF should be treated with OAC.
- The optimal duration of OAC in patients with POAF remains to be defined.

Section 6

- When and at which dose should RAAS inhibitors ideally be restarted after open-heart surgery need further investigation.

Section 7

- The role of BBs in cardiac surgery patients without heart failure needs to be established.

Section 8

- Whether patients already on statins should continue or discontinue therapy preoperatively remains uncertain.
- The role of long-term treatment with statins in patients undergoing non-CABG cardiac surgery remains unclear.

Section 9

- The potential benefit of prophylactic steroids for younger patients (age <65 years) needs further investigation.

Section 10

- The relevance of routine presurgical screening for cutaneous bacterial colonization and the use of topical antibiotic prophylaxis for patients undergoing open-heart surgery remain to be investigated.
- The efficacy of administering an extra dose of antibiotics at the beginning of or during surgery due to haemodilution and blood composition changes during CPB and/or a long procedure time needs to be established.
- How to adjust fixed or body-weight-adjusted dosing in special clinical settings, such as the extremes of body weight (either underweight or moderate to severe obesity), in older patients and/or in patients with DM needs further investigations.
- The benefit of the gentamicin–collagen sponge on sternal wound healing and post-operative infectious complications needs to be investigated.

Section 11

- The significance of preoperative HbA1c level as a risk factor for cardiac surgery complications is currently unknown.
- The optimal perioperative blood glucose ranges during and early after cardiac surgery, in particular for those at the lower threshold, needs to be established.
- Whether the contemporary, improved technology of continuous blood glucose monitoring may play a role in redefining and identifying safer upper and lower thresholds of glucose management in cardiac surgery, for individuals with DM and those without DM, needs to be investigated.
- Whether the same blood glucose range should apply to all types of cardiac operations (e.g. CABG and non-CABG) and should be similar in patients with and without a known DM diagnosis remains to be established.

- The duration of insulin-based blood glucose monitoring needs further investigation.
- Further data are needed on the timing of interruption of different SGLT2 inhibitors in relation to cardiac surgery to avoid euglycemic ketoacidosis, and of the different GLP-1RA before cardiac surgery to avoid complications associated with drug-induced gastroparesis.
- The benefit of GLP-1RA as an add-on therapy to insulin as perioperative glucose control needs to be investigated.

Section 12

- The benefit/risk ratio of using benzodiazepines during cardiac surgery needs further investigation.
- More data are needed on SNRIs in patients undergoing cardiac surgery.
- The benefit of preventing postoperative delirium in the ICU, needs further data.

Section 13

- There is a critical need for prospective studies to assess the utilization and effectiveness of GDMT after cardiac operations, especially beyond CABG. These studies are crucial for physicians and decision makers to improve adherence to recommended medical therapies and outcomes.
- It is essential to investigate how GDMT affects different patient demographics in order to refine treatment protocols and enhance adherence to GMDT across diverse populations.

15 Key messages

Given the complexity and continuous growth of the cardiovascular therapeutic armamentarium on one side and of patient characteristics (co-morbidities, ageing, polypharmacy) on the other side, the management of perioperative medications in adult individuals undergoing major cardiac surgery imposes a comprehensive, multidisciplinary collaboration among cardiac surgeons, cardiologists, anaesthesiologists, intensivists and clinical pharmacologists, together with the active participation of the patient, to maximize benefit and minimize risks in the short and long term after cardiac interventions.

This guideline, updated by a multidisciplinary group under the auspices of the EACTS, integrates the latest available evidence from its previous edition. It strives to offer updated, evidence-based recommendations wherever possible and to provide consensus-based recommendations in areas lacking robust evidence, thereby facilitating decision making relevant to clinical encounters. Moreover, the guideline calls for expanded collaborations among scientific (mostly cardiovascular) societies, healthcare authorities and patient representatives. Such collaborations are intended to enhance adherence to recommended medical therapies, improve the quality of care around cardiac surgery, reduce the risk of complications and enhance the patient's quality of life.

The guideline provides practical recommendations designed to prevent perioperative complications in different clinical settings (e.g. patients with ongoing antithrombotic therapy, diabetes, hypertension, dyslipidaemia and depression under treatment). It establishes key strategies to optimize long-term outcomes following cardiac interventions, as summarized in Fig. 6. Additionally, the guideline underscores the need for a better understanding and usage of various medications and paves the way for further research, calling for urgent investigations of the most crucial and still unaddressed aspects of care and prevention.

In summary, the goal of this guideline is to optimize perioperative medication protocols to ensure (i) optimal transition from ongoing treatments to surgery, (ii) timing and indications for new and perioperative-related protocols (infection prevention, optimal blood glucose levels, arrhythmias) and

(iii) post-discharge, long-term management achieved through evidence-based data and comprehensive interdisciplinary cooperation.

Practical recommendations serve as foundational elements to guide clinical practice, mitigate perioperative risks and support long-term patient benefits and optimal quality of life after cardiac interventions, with an impact on healthcare costs and resources.

Figure 6: Key messages from the Multidisciplinary Perioperative Medication Guidelines in Adult Cardiac Surgery. The colours of the boxes correspond to the established classes of recommendations. ACS: acute coronary syndrome; ASA: acetylsalicylic acid; BB: beta-blocker; BHV: bioprosthetic heart valve; CCB: calcium channel blocker; DAPT: dual antiplatelet therapy; DM: diabetes mellitus; DOAC: direct oral anticoagulants; GDMT: guideline-directed medical therapy; HF: heart failure; HTA: arterial hypertension; INR: international normalized ratio; LMWH: low-molecular-weight heparin; LVEF: left ventricular ejection fraction; MHV: mechanical heart valve; NSAID: non-steroidal anti-inflammatory drugs; OAC: oral anticoagulation; PCI: percutaneous coronary intervention; POAF: postoperative atrial fibrillation; RAAS: renin-angiotensin-aldosterone system; SGLT2: sodium glucose cotransporter-2; SSRI: serotonin reuptake inhibitor; TAVI: transcatheter aortic valve implantation; UFH: unfractionated heparin; VKA: vitamin K antagonist.

16 Supplementary data

Supplementary data are available online.

Data availability statement

No new data were generated or analysed in support of this research.

Conflict of interests

Anders Jeppsson reports grants from the Swedish Heart-Lung Foundation and from the Swedish State (both to the institution). Anders Jeppsson also reports direct personal consulting fees from AstraZeneca, Pharmacosmos, Novo Nordisk, Werfen , and LFB Biotechnologies, and honoraria from Bayer and Boehringer-Ingelheim. Bianca Rocca reports consulting fees from Aboca SRL and participation on a Bayer AG Advisory Board for anti-XI drugs. Stefan James reports institutional research grants from Astra Zeneca, Elixir, Jansen, Amgen, BMS. Stefan James also reports consulting fees from Medtronic inc. Pedro Magro reports receiving support for attending the 2024 AATS meeting from Assoc. MINICOR and SPCCTV and from the Portuguese society of cardiology for attending the 2024 SPC meeting .Miguel Sousa-Uva reports holding a leadership position as President of the Portuguese Society of Cardiac Thoracic and Vascular Surgery. Milan Milojevic reports participation in meeting sponsored by Corcym in relation to ERAS and participation in meeting sponsored by Medtronic in relation to CPB. Milan Milojevic also reports a role of Guidelines Program Director at EACTS.

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Management of medications in adult patients undergoing cardiac surgery

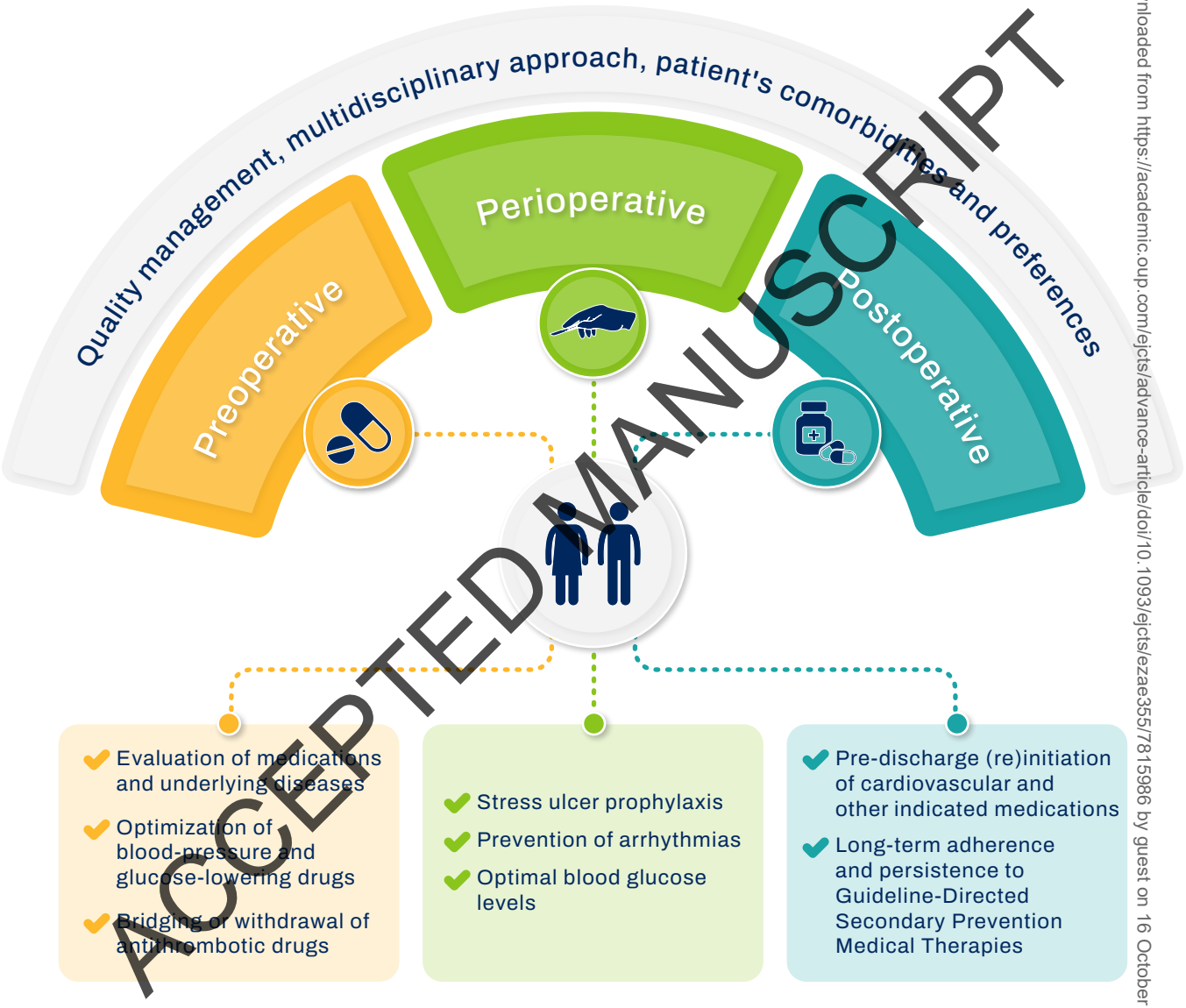

Figure 1

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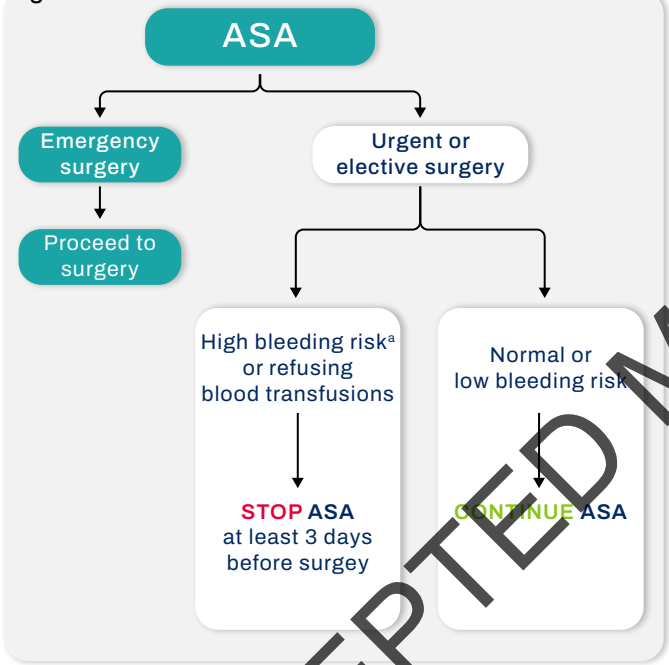

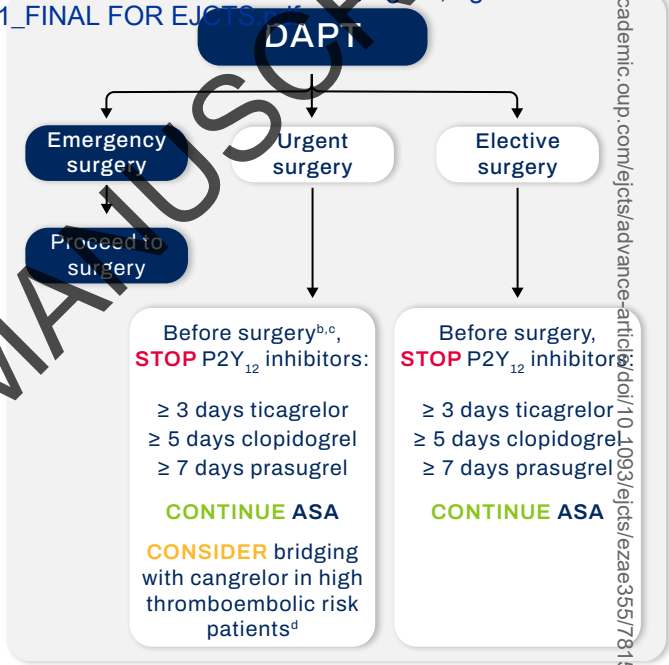

Figure 2

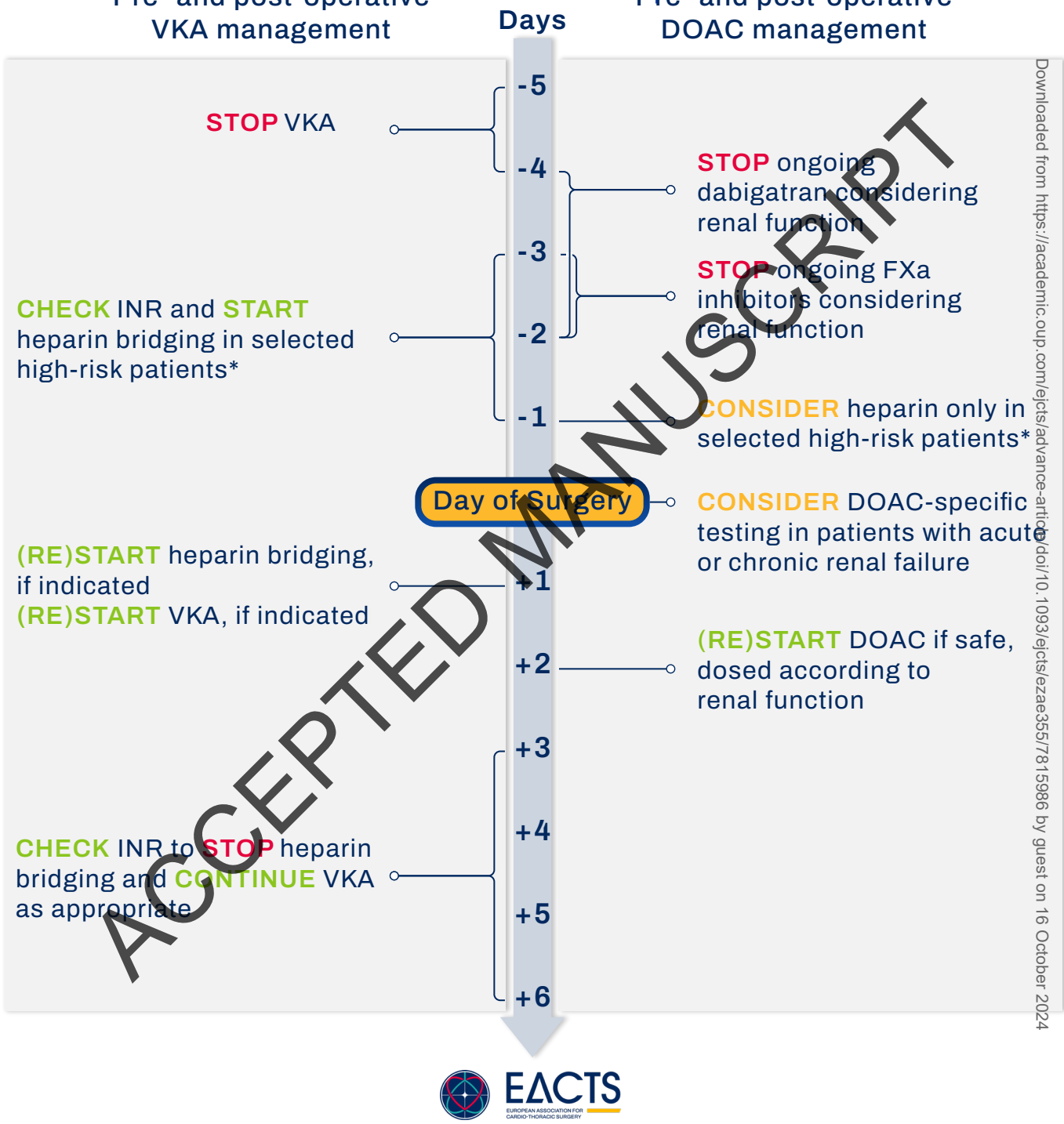

Figure 3

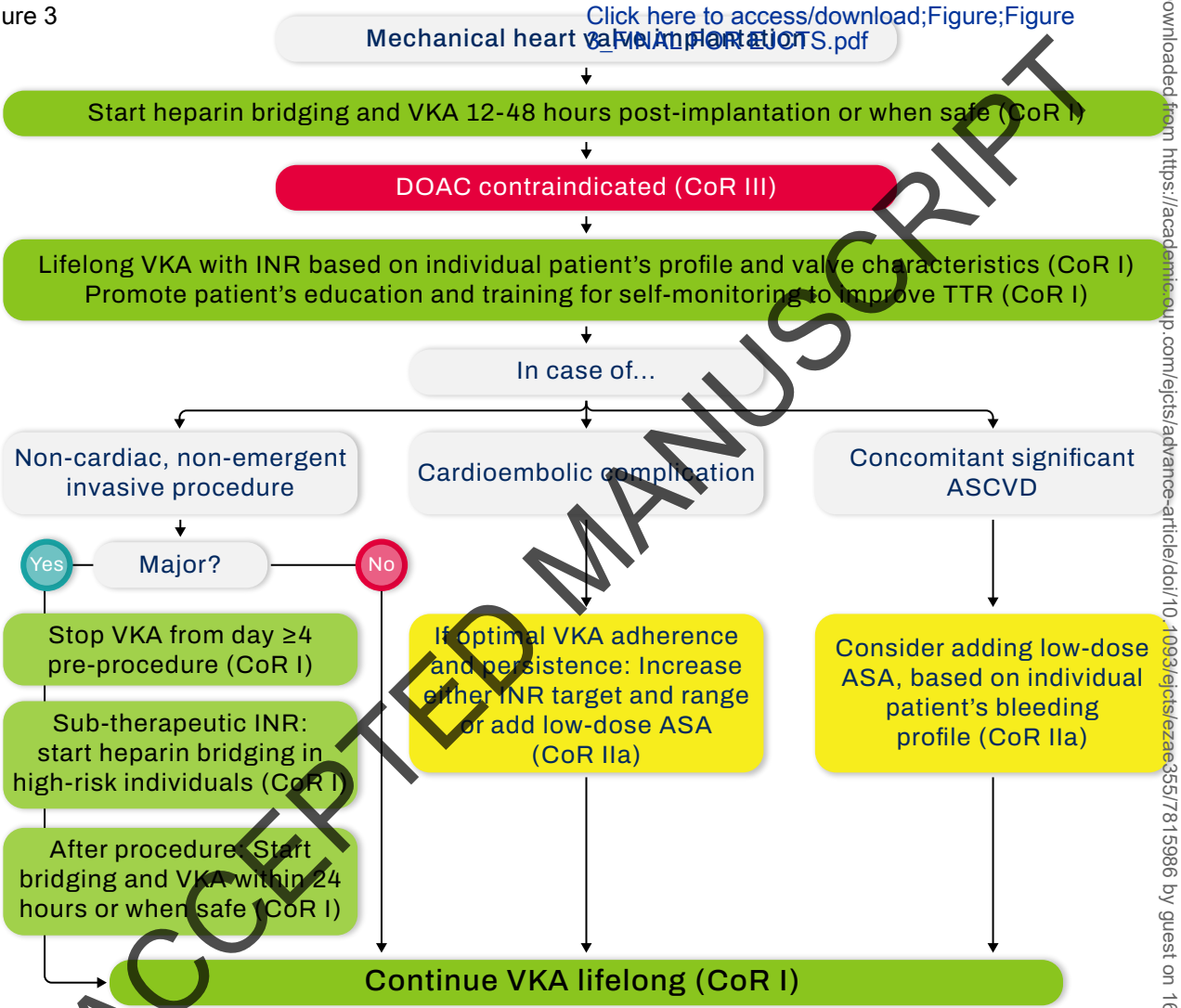

Figure 4

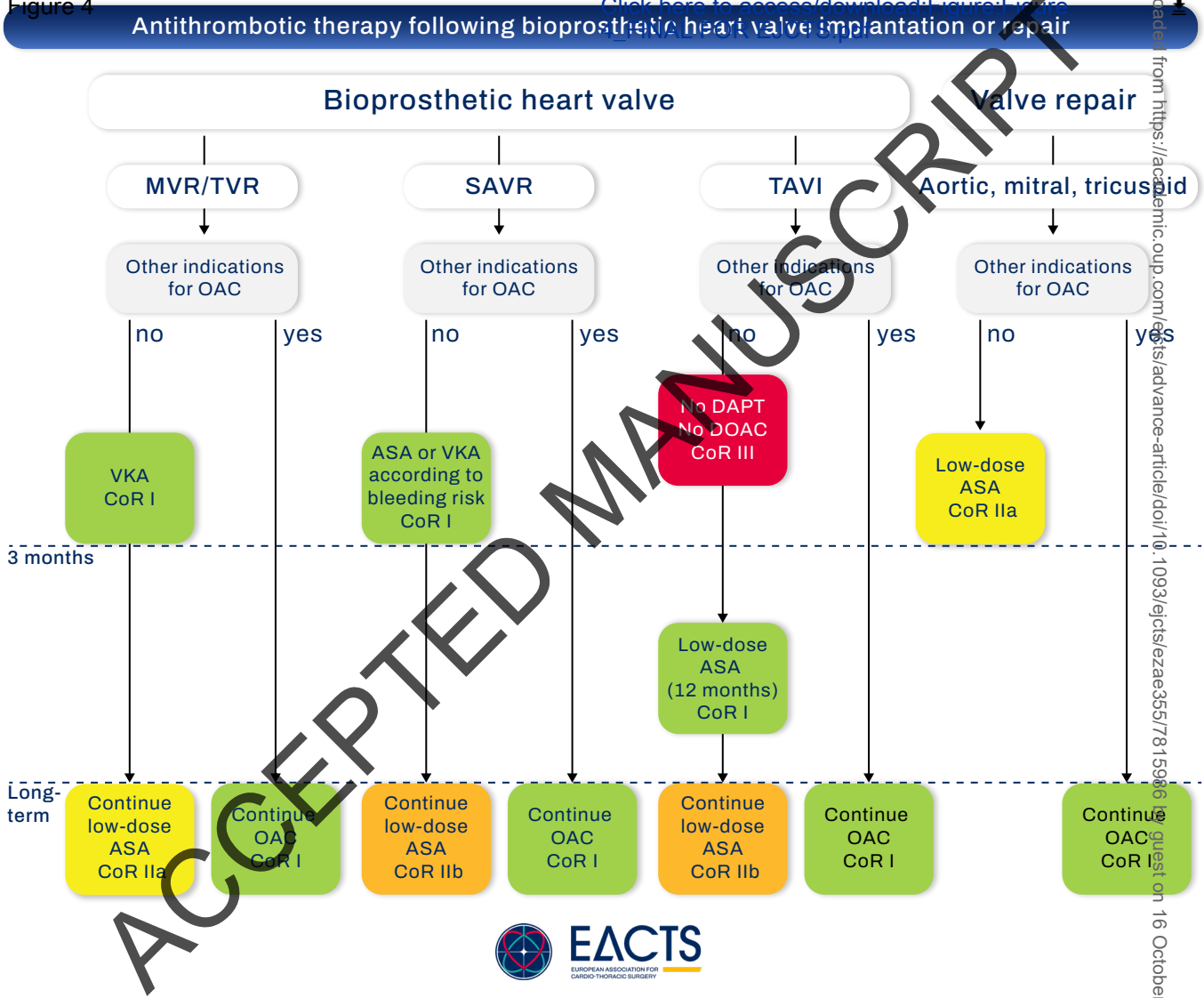

Figure 5

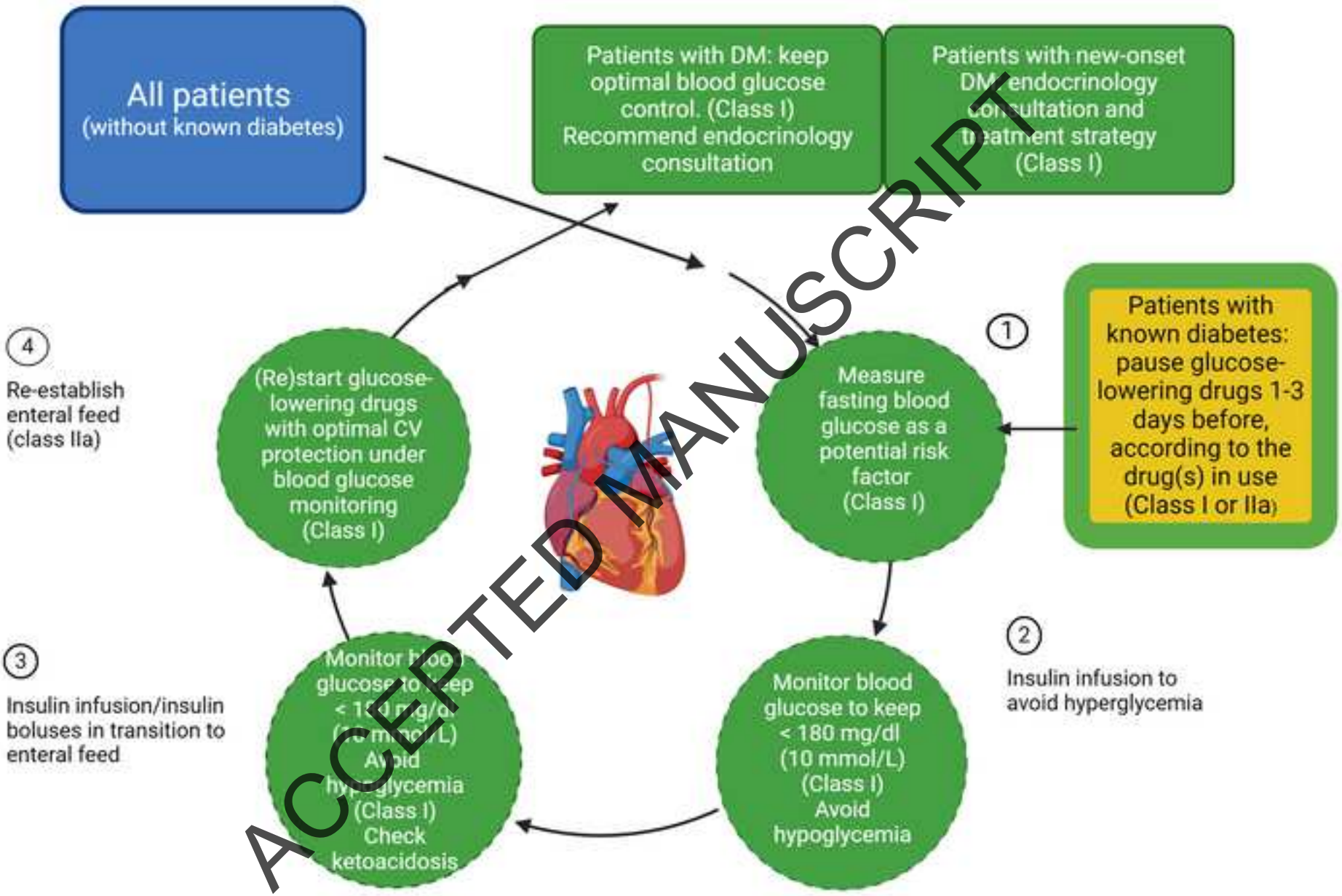

Figure 6

It is recommended to:

- Continue BB, CCB, and diuretics and administer gastroprotectant preoperatively
- Continue ASA throughout the perioperative period
- Bridge VKAs with UFH or LMWH in patients with high thrombotic risk
- Use mupirocin intranasal twice daily for S. Aureus carriers starting 4 days before open-heart surgery
- Start antibiotic prophylaxis infusion within 30-60 minutes before skin incision
- Resume or start DAPT after open-heart surgery in patients with recent ACS and/or PCI
- Use life-long VKA with INR self-monitoring in trained patients after MHV implantation
- Use VKAs for the first 3 months after mitral or tricuspid BHV implantation
- Use OAC for at least 4 weeks in patients with persistent POAF at discharge, followed by re-evaluation
- Use long-term optimal-dose RAAS inhibition in HF and/or HTA patients
- Use long-term cardioselective BB and SGLT2 inhibitors in HF patients with reduced LVEF
- Regular examinations and strict adherence to prescribed GDMT for long-term benefits from surgery
- Adhere to quality assurance initiatives and quality improvement programs to enhance adherence and persistence with GDMT

It should be considered to:

- Postpone surgery ≥3 days after discontinuation of ticagrelor, ≥5 days after clopidogrel, and ≥7 days after prasugrel
- Administer idarucizumab in emergency open-heart surgery to reverse dabigatran
- Continue statin therapy at the pre-surgery dose during the perioperative period
- Discontinue SGLT2 inhibitors at least 72 hours before open-heart surgery
- Maintain blood glucose levels in diabetic patients between 120-180 mg/dl (6.7-10 mmol/l)
- Continue SSRI throughout the perioperative period
- Administer antibiotic prophylactic with cefazolin or cefuroxime set to 24 hours, and no longer than 48 hours
- (Re)start RAAS inhibitors as soon as it is deemed safe after open-heart surgery
- Prescribe ASA for the first 3 months after aortic, mitral, and tricuspid valve repair in patients with no other indication for OAC

It is not recommended to:

- Use prophylactic steroids and statins preoperatively
- Administer andexanet alpha in patients on anti-Xa DOACs preoperatively
- Use DOACs for thromboembolic prophylaxis in patients with mechanical valves
- Prescribe OAC or DAPT after TAVI in patients with no baseline indications for OAC
- Use thiazolidinediones in patients with DM and HF
- Use NSAIDs in patients with SSRI
- Prescribe SSRI in patients with QT prolongation or vasospastic angina

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