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EACTS GUIDELINES

2017 EACTS Guidelines on perioperative medication in adult cardiac surgery

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ABBREVIATIONS AND ACRONYMS

ACEI	Angiotensin-converting enzyme inhibitor
ACS	Acute coronary syndrome
AF	Atrial fibrillation
AKI	Acute kidney injury
ARB	Angiotensin II receptor blocker
ASA	Acetylsalicylic acid
CABG	Coronary artery bypass grafting
CAD	Coronary artery disease
CHA_2DS_2-VASc	Congestive heart failure, hypertension, age ≥ 75 (2 points), diabetes, prior stroke (2 points)–vascular disease, age 65–74, sex category (female)
CI	Confidence interval
COX	Cyclo-oxygenase
CPB	Cardiopulmonary bypass
DAPT	Dual antiplatelet therapy
DM	Diabetes mellitus
EACTS	European Association for Cardio-Thoracic Surgery
ICU	Intensive care unit
INR	International normalized ratio
IV	Intravenous
LDL-C	Low-density lipoprotein cholesterol
LMWH	Low-molecular-weight heparin
LVEF	Left ventricular ejection fraction
MI	Myocardial infarction
NOAC	Non-vitamin K antagonist oral anticoagulant
NYHA	New York Heart Association
OAC	Oral anticoagulant
OR	Odds ratio
PCSK9	Proprotein convertase subtilisin/kexin type 9
POAF	Postoperative atrial fibrillation
RAAS	Renin–angiotensin–aldosterone system
RCT	Randomized controlled trial
SAP	Surgical antibiotic prophylaxis
SAPT	Single antiplatelet therapy
SSI	Surgical site infection
TAVI	Transcatheter aortic valve implantation
UFH	Unfractionated heparin
VKA	Vitamin K antagonist

1. PREAMBLE

The European Association for Cardio-Thoracic Surgery (EACTS) Guidelines Committee is part of the EACTS Quality Improvement Programme and aims to identify topics in cardiothoracic surgery where there is a need for guidance. Clinical guidelines are issued for areas where there is substantial evidence to support strong recommendations, usually derived from randomized clinical trials or large registries.

Quality criteria for developing clinical guidelines require transparency on how they are formulated. The methodology manual for the EACTS clinical guidelines was issued to standardize the developmental process of evidence-based documents [1].

Members of the task force to develop a clinical guideline on perioperative medication in adult cardiac surgery were selected for their expertise in their respective areas. To increase the credibility of evidence-based documents, EACTS aims for a collaborative process with other specialists also involved in the diagnosis or treatment of the given condition. For the current clinical guideline, non-cardiac surgeon specialists, known to be experts in their particular domains, were invited to join the task force; however, it should be noted that other scientific societies have not officially endorsed this clinical guideline.

Task force members undertook an evidence review, assisted by 2 dedicated research fellows. The level of evidence (Table 1) and the strength of the recommendations (Table 2) were weighed and graded according to predefined scales [1].

In accordance with the methodology manual for the EACTS clinical guidelines, task force members were asked to complete declarations of interest.

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 large non-randomized studies.**
Level of evidence C	**The consensus of expert opinion and/or small studies, retrospective studies, registries.**

Table 2: Classes of recommendations

Classes of recommendations	Definition	Suggested wording to use
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**

2. INTRODUCTION

Adult cardiac surgery is an essential therapeutic approach to reduce mortality and morbidity in appropriately defined patients. The outcome depends on the management of underlying conditions, and

medical treatment is key in the optimal perioperative and long-term success of the cardiac surgery. Several studies have suggested that patients who have had coronary artery bypass grafting (CABG) benefit the most from risk factor-modifying strategies [2–6].

Medical therapy affects adult cardiac surgery at 3 distinct stages: preoperative, intraoperative and postoperative [7]. Preoperatively, one might need to introduce or interrupt drugs to decrease the odds of procedural complications. Intraoperatively, control of glycaemia and prophylactic antibiotics are essential to reducing the risk for infectious complications. Postoperatively, restarting or initiating medication to prevent ischaemic events, prevent arrhythmias and manage cardiovascular risk factors and heart failure is required to impact the long-term prognosis in a positive way, especially if the medications are included in a formal programme of cardiac rehabilitation [8].

Cardiac surgery is always a major life event that is associated with increased disease awareness and represents a unique opportunity to introduce optimized medical therapy and stress the importance of lifestyle modifications, compliance with medication and lifelong follow-up. Surgical patients are often treated suboptimally [9, 10], although the benefit of a more intense postoperative patient-based medication therapy is established after cardiac surgery [10, 11].

The surgical community may be somewhat underinformed on this topic [12], despite the availability of previously published guidelines on specific drugs [13–15]. Therefore, the EACTS Clinical Guideline Committee determined that there was a need to produce an updated guideline focusing on the main pharmacological classes involved in the perioperative treatment and prevention of adverse events in patients undergoing adult cardiac surgery. Medications used for the treatment of operative complications, such as graft vasospasm after CABG, perioperative ischaemia, myocardial infarction (MI), low cardiac output syndrome, renal failure, arrhythmias except for atrial fibrillation (AF), pneumonia, wound infection and neurological complications, have been excluded. The underlying rationale for excluding these topics from the final document is the fact that they are comprehensively covered in other relevant clinical guidelines [16–22] or that these surgical complications will be included in an upcoming expert document. The following central illustration (Fig. 1) summarizes what is new and what is essential in these guidelines according to the class of recommendation.

3. ANTITHROMBOTIC MANAGEMENT

Antithrombotic treatment with anticoagulants and platelet inhibitors reduces the risk for thromboembolic complications but may increase the risk for intraoperative and postoperative bleeding complications. An individual assessment of the risk for thromboembolism and bleeding based on the medication, patient condition (elective, urgent or emergent), imaging results and planned surgical intervention is recommended within the heart team conference.

Multidisciplinary decision making

Recommendation	Class[a]	Level[b]	Ref[c]
It is recommended that the Heart Team discuss the optimal timing of stopping antithrombotic preoperative treatment of patients undergoing cardiac surgery, based on ischaemic and bleeding risk.	I	C	

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

3.1 Acetylsalicylic acid

Acetylsalicylic acid (ASA) is one of the cornerstones for the treatment of acute and chronic cardiovascular disease. Secondary prevention with ASA has been shown to reduce mortality, MI and cerebrovascular events in different subsets of patients with occlusive cardiovascular disease [23], but also to increase the risk for bleeding complications.

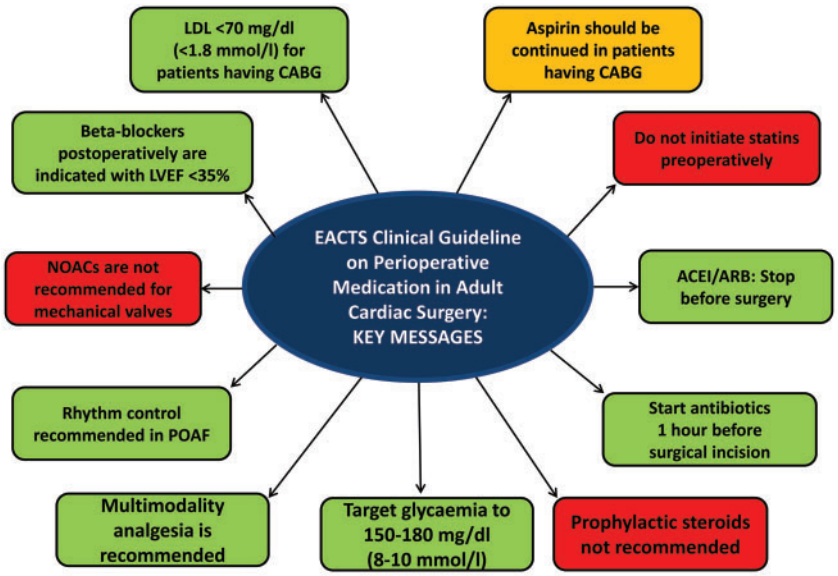

Figure 1: Central illustration with the main recommendations. ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin II receptor blocker; CABG: coronary artery bypass grafting; EACTS: European Association for Cardio-Thoracic Surgery; LDL: low-density lipoprotein; LVEF: left ventricular ejection fraction: NOACs: non-vitamin K antagonist oral anticoagulants; POAF: postoperative atrial fibrillation.

3.1.1 Discontinuation before surgery. A meta-analysis of 13 trials with 2399 patients who had CABG that compared administration of ASA preoperatively versus no treatment or treatment with a placebo [24] showed that treatment with ASA reduced the risk for perioperative MI [(odds ratio (OR) 0.56; 95% confidence interval (CI) 0.33–0.96] but did not reduce the mortality rate (OR 1.16; 95% CI 0.42–3.22). Postoperative bleeding, red cell transfusions and surgical re-exploration were increased with ASA. However, the included studies were of low methodological quality.

A recent large randomized controlled trial (RCT) compared the administration of ASA (100 mg) on the day of the operation versus the use of a placebo in patients having CABG [25] and demonstrated no significant effect of treatment with ASA on thrombotic and bleeding perioperative events. However, the included patients were eligible only if they were not using ASA preoperatively or had stopped ASA at least 4 days before the operation. Therefore, a strategy of discontinuation versus continuation was not evaluated.

Another RCT on pretreatment demonstrated that a large dose (300 mg) of ASA preoperatively was associated with increased postoperative bleeding but with a lower rate of major cardiovascular events at a 53-month follow-up [26]. Similarly, a small RCT reported that patients pretreated with ASA (300 mg) had significantly more postoperative bleeding (+25%) and that this effect was more pronounced (+137%) in carriers of the glycoprotein (GP) IIIa allele PlA2 [27]. Similar results were presented in a previous meta-analysis [28], where less bleeding was reported in patients receiving <325 mg ASA daily. Of note, stopping ASA 5 days before the operation and replacing it with low-molecular-weight heparin (LMWH) increases the risk for bleeding complications and therefore should be abandoned [29].

In summary, the continuation of ASA is associated with more blood loss but fewer ischaemic events during and after CABG surgery. Recent data suggest that the inhibiting effect of ASA on platelet aggregability is clearly susceptible to platelet transfusion [30, 31], which also argues for the continuation of ASA in patients undergoing elective or urgent CABG. However, in patients who refuse blood transfusions, who undergo non-coronary cardiac surgery or who are at high risk of re-exploration for bleeding—such as complex and redo operations, severe renal insufficiency, haematological disease and hereditary platelet function deficiencies—stopping ASA at least 5 days before surgery should be considered [32]. The increased risk for bleeding complications if ASA and other antithrombotic drugs are not discontinued must be weighed against the potentially increased risk of thrombotic complications during the preoperative cessation period.

3.1.2 Restart after surgery. In a large prospective observational trial [33], patients who restarted ASA within 48 h of CABG had a mortality rate of 1.3% compared with a rate of 4.0% among those who did not receive ASA during this period ($P < 0.001$). ASA therapy was associated with a 48% reduction in the incidence of MI ($P < 0.001$), a 50% reduction in the incidence of stroke ($P = 0.01$), a 74% reduction in the incidence of renal failure ($P < 0.001$) and a 62% reduction in the incidence of bowel infarction ($P = 0.01$). A systematic review of 7 studies showed that administration of ASA within 6 h of CABG was associated with improved graft patency without increased incidence of bleeding complications [34]. Therefore, ASA should be given to all patients having CABG as soon as there is no concern over bleeding.

Recommendations for perioperative acetylsalicylic acid management

Recommendations	Class[a]	Level[b]	Ref[c]
Preoperative period			
In patients on ASA who need to undergo CABG surgery, continuing ASA throughout the preoperative period should be considered.	IIa	C	
Stopping ASA at least 5 days before surgery should be considered in patients who refuse blood transfusions, undergo non-coronary cardiac surgery or are at high risk[d] of re-exploration for bleeding.	IIa	C	
Bridging oral antiplatelet therapy with LMWH is not recommended.	III	B	[29]
Postoperative period			
It is recommended to (re)start ASA as soon as there is no concern over bleeding, but within 24 hours of CABG.	I	B	[33, 34]
In patients undergoing non-coronary cardiac surgery with a preoperative indication for ASA, it is recommended that treatment is restarted as soon as there is no concern over bleeding, but within 24 hours after surgery.	I	C	

[a]Class of recommendation.
[b]Level of evidence.
[c]References.
[d]Complex and redo operations, severe renal insufficiency, haematological diseases and hereditary deficiencies in platelet function.
ASA: acetylsalicylic acid; CABG: coronary artery bypass grafting; LMWH: low-molecular-weight heparin.

3.2 P2Y12 inhibitors

Dual antiplatelet therapy (DAPT) with ASA and P2Y12-receptor inhibitors (clopidogrel, ticagrelor and prasugrel) (Table 3) reduces the risk for thrombotic complications in patients with acute coronary syndrome (ACS) compared to treatment with ASA only [35–37], especially if they undergo percutaneous coronary intervention. The risk for thrombotic complications is further reduced if one of the more potent third-generation P2Y12 inhibitors (ticagrelor or prasugrel) is used instead of clopidogrel [36, 37], at the expense of increased spontaneous and surgical bleeding complications [36–38].

3.2.1 Discontinuation before surgery. Continuing DAPT until the operation increases the risk of bleeding, transfusions and re-exploration for bleeding, as shown in RCTs [39–41], observational studies [42, 43] and meta-analyses [44, 45]. It is, therefore, recommended that P2Y12-receptor inhibitors be discontinued before elective surgery whenever possible [7, 46]. Alternatively, elective operations may be postponed until the DAPT treatment period is completed. In urgent cases—most often in patients with ACS—the risk for thromboembolic episodes (stent thrombosis and MI)

Table 3: P2Y12 inhibitors

	Clopidogrel	Prasugrel	Ticagrelor	Cangrelor
Bioavailability	50%	80%	36%	100%
Half-life (active metabolite)	1-2 hours	2-15 hours	7-9 hours	3-6 minutes
Binding reversibility	Irreversible	Irreversible	Reversible	Reversible
Onset of action	2-6 hours	30 minutes	30 minutes	2 minutes
Frequency of administration	Once daily	Once daily	Twice daily	Intravenous infusion
Duration of effect	3-10 days	7-10 days	3-5 days	1-2 hours
Antidote	No	No	No	No
Discontinuation before non-acute surgery	At least 5 days	At least 7 days	At least 3 days	1 hour

while waiting for the effect of the P2Y12-receptor inhibitors to cease must be weighed against the risk for perioperative bleeding complications. In patients who are at extreme high risk for thrombotic events, e.g. recent stent implantation [47], bridging therapy may be considered [7, 46] or surgery may be performed without discontinuation of P2Y12 inhibitors. If bridging is warranted, GPIIb/GPIIIa inhibitors may be used. However, cangrelor, a new reversible intravenous P2Y12 inhibitor with an ultrashort half-life, has demonstrated a high rate of maintenance for platelet inhibition and no excessive perioperative bleeding complications [48, 49].

Safe discontinuation intervals differ according to the pharmacodynamics and pharmacokinetic profile of each P2Y12-receptor inhibitor [46]. When P2Y12-receptor inhibitors are discontinued, ASA therapy should be continued until the operation. Discontinuation of clopidogrel 5 days or more before CABG did not increase the risk for bleeding complications [39]. A longer time interval (7 days) is recommended for prasugrel due to the longer offset of platelet inhibition [50] and a higher incidence of CABG-related bleeding complications compared with that for clopidogrel [41]. In patients treated with ticagrelor, discontinuation of the drug 3 to 4 days, as opposed to 5 days or more before CABG surgery, is not associated with a higher incidence of bleeding complications (OR 0.93; 95% CI 0.53–1.64, $P = 0.80$) [42]. This finding has been confirmed in multiple studies [43, 51]. It is unlikely that the optimal discontinuation period before surgery of any of the P2Y12 inhibitors will ever be tested in an RCT with clinically relevant end points.

3.2.2 Platelet function testing. Besides the variances in platelet inhibitory effects between different P2Y12 inhibitors, there is also a significant individual variation in the magnitude and duration of the antiplatelet effect [52–54]. Residual platelet reactivity is a marker of both ischaemic and bleeding events [55], but testing platelet function to adjust P2Y12 inhibition does not improve clinical outcome in low- and high-risk patients [56, 57]. Platelet function testing (PFT) may optimize the timing for surgical procedures, especially in patients in whom the time since discontinuation is unclear (e.g. in unconscious or confused patients) or treatment compliance is unclear.

Bedside PFT has been suggested as an option to guide interruption of therapy rather than an arbitrarily specified period [7, 46]. Preoperative adenosine diphosphate-mediated platelet aggregation predicts CABG-related bleeding complications in both clopidogrel- [58–61] and ticagrelor- [54] treated patients with ACS. A strategy based on preoperative PFT 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 [62]. PFT in patients with ACS eligible for CABG appears to be a valuable approach to refine the timing of surgery. No RCT or observational study has compared perioperative bleeding complications between a fixed versus a PFT-based time delay from discontinuation to surgery. Furthermore, the cut-off levels of P2Y12 inhibition to predict perioperative bleeding are not available for all PFT devices.

3.2.3 Restart after surgery. Current guidelines recommend DAPT for all patients with ACS independently of revascularization treatment [7, 46]. This recommendation also applies to patients having CABG or other non-coronary cardiac operations. Furthermore, DAPT after CABG has been associated with reduced all-cause mortality [63, 64] and better vein graft patency (OR 0.59; 95% CI 0.43–0.82) [64], although the evidence is conflicting. The potential benefits of DAPT after CABG are offset by an increased risk for bleeding complications.

The magnitude of the benefit, i.e. a reduction in the mortality rate of more than 50% [40, 41], appears to be more pronounced in patients with ACS than in those with stable angina and with P2Y12 inhibitors that are more potent than clopidogrel [63–65]. It is recommended to restart DAPT after CABG as soon as it is considered safe in patients with ACS. There is currently no evidence to support starting routine DAPT after CABG in patients not receiving DAPT preoperatively, although starting DAPT may be considered in patients with a higher ischaemic risk due to a coronary endarterectomy or off-pump surgery.

The optimal timing for restarting should be as soon as it is deemed safe. In patients with a high risk of ischaemia, P2Y12 inhibitors should be restarted within 48 h after surgery. In contrast, it may be considered safe to reinitiate P2Y12 inhibitors 3–4 days postoperatively when the risk for ischaemia is low (e.g. recent stent implantation >1 month or ACS without stenting).

Recommendations for perioperative P2Y12 inhibitor management

Recommendations	Class[a]	Level[b]	Ref[c]
Preoperative period			
In patients on DAPT who need to undergo non-emergent cardiac surgery, postponing surgery for at least 3 days after discontinuation of ticagrelor, 5 days after clopidogrel and 7 days after prasugrel should be considered.	IIa	B	[41, 42]
Platelet function testing may be considered to guide the decision on the timing of cardiac surgery in patients who have recently received P2Y12 inhibitors.	IIb	B	[53, 54, 58, 60]
Bridging P2Y12 inhibitors with GPIIb/IIIa inhibitors or cangrelor may be considered in high ischaemic risk patients.	IIb	C	
Postoperative period			
In patients treated with DAPT after recent coronary stent implantation (within 1 month) who subsequently undergo cardiac surgery, it is recommended to resume the P2Y12 inhibitor postoperatively as soon as there is no concern over bleeding but within 48 hours of surgery, and continue DAPT until the recommended duration of therapy is completed.	I	C	
In patients treated with DAPT after coronary stent implantation (exceeding 1 month) or ACS without stenting who subsequently undergo cardiac surgery, it is recommended to resume the P2Y12 inhibitor postoperatively as soon as there is no concern over bleeding but within 96 hours of surgery, and continue DAPT until the recommended duration of therapy is completed.	I	C	
DAPT may be considered after CABG in selected patients with stable CAD (endarterectomy, off-pump).	IIb	C	

[a]Class of recommendation.
[b]Level of evidence.
[c]References.
ACS: acute coronary syndrome; CABG: coronary artery bypass grafting; CAD: coronary artery disease; DAPT: dual antiplatelet therapy; GP: glycoprotein.

3.3 Glycoprotein IIb/IIIa inhibitors

GPIIb/IIIa inhibitors (abciximab, eptifibatide and tirofiban) are almost exclusively used in conjunction with percutaneous coronary intervention but may also be used for bridging high-risk patients taking oral P2Y12 inhibitors to surgery [7, 46, 66]. The optimal time delay for discontinuation before surgery is based mainly on pharmacokinetic assumptions. Platelet function recovery is obtained within 24–48 h of discontinuing abciximab and up to 4–8 h after discontinuing eptifibatide and tirofiban [67]. However, the pooled analysis of patients from the EPILOG and EPISTENT trials shows no difference between patients treated with abciximab and placebo in terms of major blood loss (88% vs 79%, $P = 0.27$) when the study treatment was stopped within 6 h before the surgical incision [68]. In addition, other clinical studies suggest that cessation 4 h before surgery is sufficient for all GP IIb/IIIa inhibitors, including abciximab [66, 69].

Recommendation for bridging antiplatelet therapy with GPIIb/IIIa inhibitors

Recommendation	Class[a]	Level[b]	Ref[c]
It is recommended to discontinue GPIIb/IIIa inhibitors at least 4 hours before surgery.	I	C	

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

3.4 Preoperative anticoagulation and bridging

In patients treated with vitamin K antagonists (VKA) (Table 4), VKAs should be stopped 5 days before planned elective surgery to achieve a target international normalized ratio (INR) below 1.5 on the day of surgery [22, 70]. In patients treated with non-vitamin K antagonist oral anticoagulants (NOACs) who are undergoing elective surgery, NOACs should be discontinued before surgery at various time intervals according to renal function and types of drugs (Table 5). In patients taking direct factor Xa inhibitors (apixaban, edoxaban and rivaroxaban), treatment should be stopped ≥2 days before surgery [71, 72]. In patients treated with dabigatran with creatinine clearance <50 ml/min/1.73 m^2, NOAC should be stopped ≥4 days before surgery.

The decision to bridge oral anticoagulation with unfractionated heparin (UFH) or LMWH depends on the ischaemic risk for underlying diseases. Preoperative bridging imposes a risk for perioperative bleeding; therefore, not all patients on anticoagulation agents who have cardiac surgery should be bridged [73]. Therefore, bridging with oral anticoagulation is recommended in patients with mechanical prosthetic heart valves, valvular AF (moderate-to-severe mitral stenosis), AF with a CHA_2DS_2-VASc score >4 or with a recent acute thrombotic event within the previous 4 weeks defined as ischaemic stroke, ACS or pulmonary embolism. Bridging should also be considered in patients with left ventricular apex thrombus, antithrombin 3 and proteins C and S deficiencies.

Bridging should be initiated according to the outline in Fig. 2. UFH is the only approved bridging method, although there is no evidence from randomized trials. Studies show that patients receiving

Table 4: Vitamin K antagonists

	Acenocoumarol	Coumadine (Warfarin)	Fluindione	Phenprocoumon
Half-life	10 hours	35–80 hours	30–40 hours	3–4 days
Steady state	2–3 days	3–6 days	3–4 days	6 days
Initial dose	4 mg	5 mg	20 mg	6 mg
Duration of effect	2–4 days	4–5 days	2–3 days	4–5 days

Table 5: Different types of direct oral anticoagulant agents

	Apixaban	Dabigatran	Edoxaban	Rivaroxaban
Target	Factor Xa	Thrombin	Factor Xa	Factor Xa
Bioavailability	51–85%	6–8%	60%	80%
T_{max}	3 hours	2 hours	1–3 hours	2–4 hours
Half-life	9–14 hours	14–17 hours	5–11 hours	9–13 hours
Frequency of administration	Twice daily	Once or twice daily	Once daily	Once or twice daily
Renal excretion	25%	80%	36–45%	66% (half inactive)
Antidote	Andexanet alfa	Idarucizumab	Andexanet alfa	Andexanet alfa
Discontinuation before non-acute surgery	At least 48 hours	At least 48-96 hours[a]	At least 48 hours	At least 48 hours

[a]Discontinuation ≥48 h if creatinine clearance is >80 ml/min/1.73 m^2; discontinuation >72 h if creatinine clearance is 50–79 ml/min/1.73 m^2 and discontinuation ≥96 h if creatinine clearance is <50 ml/min/1.73 m^2.

preoperative UFH versus LMWH had fewer postoperative re-explorations for bleeding after cardiac surgery [74]. However, UFH can only be administered in a hospital, whereas LMWH does not require hospital admission and continuous intravenous infusion. Therefore, LMWH is more practical and user-friendly and should be considered as an alternative for bridging with dose adjustment according to weight and renal function and if possible with monitoring of anti-Xa activity with a target of 0.5–1.0 U/ml. The option of bridging with fondaparinux is not recommended due to an extended half-life (17–21 h) and the lack of an adequate antidote, although it may have a role in patients with a history of heparin-induced thrombocytopenia [75].

There is no adequate evidence to support specific time intervals for stopping preoperative bridging with UFH and LMWH. Based on the pharmacokinetics of UFH, it is recommended that administration be discontinued at least 6 h preoperatively. Discontinuation of LMWH should occur >12 h preoperatively, as suggested by studies reporting high plasma concentrations if it is given twice daily [76].

Even when the patient's condition is urgent, surgery should ideally be delayed if patients are taking oral anticoagulants. The benefit associated with allowing a short delay before performing surgery should, however, be balanced against the risk of a major haemorrhage. When VKAs cannot be stopped for an appropriate time, prothrombin complex concentrate (25 IU factor IX/kg) should be given with an additional dose of 5 mg of vitamin K1 (intravenous, subcutaneous or oral) [77]. For patients taking NOACs. The timing between the last intake and the procedure should be checked, and the treatment concentration should be assessed using specific diluted thrombin times (Haemoclot®) for dabigatran and anti-factor Xa assays for the FXa inhibitors. The plasma concentration of NOACs should be considered the best way to assess the residual activity of the drug and estimate the risk for bleeding [78]. The operation may be safely performed if the plasma concentrations of dabigatran and rivaroxaban are below 30 ng/ml; with higher concentrations, the operation should be delayed for 12 h (if the concentration is 30–200 ng/ml) or 24 h (if the concentration is 200–400 ng/ml). If plasma concentrations are too high and the operation cannot be postponed, the off-label therapeutic use of both non-activated prothrombin complex concentrate (20–50 U/kg) and activated prothrombin complex concentrate (FEIBA®, 30 to 50 U/kg) may be considered [79]. Although FEIBA® and its high potential to overshoot thrombin generation might be more efficient in the case of life-threatening bleeding, this benefit should be balanced against an increased risk of thrombosis [80]. Target concentration ranges from studies on apixaban/edoxaban are lacking. Idarucizumab has recently been approved for reversing the effect of dabigatran based

on the Reversal Effects of Idarucizumab on Active Dabigatran (REVERSE-AD) trial, which demonstrated complete reversal of the anticoagulant effects within minutes [81]. No outcome data are available, and treatment duration, as well as monitoring guidelines, is still to be established [81]. The effect of andexanet alfa in reversing the effect of FXa inhibitors has shown to be promising, although clinical data are currently unavailable [82, 83].

Preoperative management of oral anticoagulants

Recommendations	Class[a]	Level[b]	Ref[c]
Preoperative period			
It is recommended that VKAs be discontinued 5 days prior to surgery to aim for an INR <1.5 on the day of the elective cardiac surgery.	I	C	
For patients on NOACs, preoperative discontinuation of therapy is recommended at least 48–96 hours prior to surgery, depending on renal function and the agent[e].	I	C	
Bridging of OAC is recommended in patients with any of the following indication: • Mechanical prosthetic heart valve • AF with moderate to severe mitral stenosis • AF with a CHA_2DS_2-VASc score >4 • Acute thrombotic event within the previous 4 weeks.	I	C	
Bridging of OACs should be considered in patients with a high acute thromboembolic risk[d].	IIa	C	
Bridging with UFH is recommended.	I	B	[74, 84]
Bridging with subcutaneous LMWH should be considered as an alternative to bridging with UFH.	IIa	B	[85, 86]
Bridging with fondaparinux is not recommended.	III	C	
In patients who are preoperatively bridged with UFH, it is recommended that UFH be stopped 6 hours before surgery.	I	C	
In patients who are preoperatively bridged with therapeutic LMWH, it is recommended that they be given the last dose 24 hours before surgery.	I	B	[76, 87]

[a]Class of recommendation.
[b]Level of evidence.
[c]References.
[d]Left ventricular apex thrombus, antithrombin 3 deficit and proteins C and/or S deficit.
[e]Table 5 includes the proposition of discontinuation time for specific agents.
AF: atrial fibrillation; CHA_2DS_2-VASc: congestive heart failure, hypertension, age ≥75 (2 points), diabetes, prior stroke (2 points)–vascular disease, age 65–74, sex category (female); INR: international normalized ratio; LMWH: low-molecular-weight heparin; NOACs: non-vitamin K antagonist oral anticoagulants; OACs: oral anticoagulants; UFH: unfractionated heparin; VKAs: vitamin K antagonists.

3.5 Postoperative antithrombotics and bridging

Heart valve replacement or repair increases the risk for thromboembolic complications, requiring antithrombotic therapy. Scientific evidence for the best antithrombotic strategy and duration is scarce [88], resulting in a low level of evidence for most recommendations [16].

3.5.1 Mechanical prostheses. Patients undergoing mechanical valve implantations require lifelong treatment with VKA guided by INR (Fig. 3, Table 4) [89, 90]. Anticoagulant treatment with UFH and VKA is started on the first postoperative day and is maintained until the INR is in the therapeutic range. However, special attention to the coagulation status and potential bleeding events is required. In the case of bleeding disorders, VKAs should be restarted whenever it is deemed safe, preferably within 48 h. Of note, similarly to preoperative bridging, UFH administered by the intravenous route remains the only approved bridging treatment after the implantation of mechanical heart valve prostheses [91], although it has never been evaluated in a randomized trial. Off-label bridging with subcutaneous LMWH is widely implemented in hospital protocols due to its logistic and cost advantages over UFH. However, prospective open-label non-randomized studies have shown subcutaneous enoxaparin to be suitable for a much

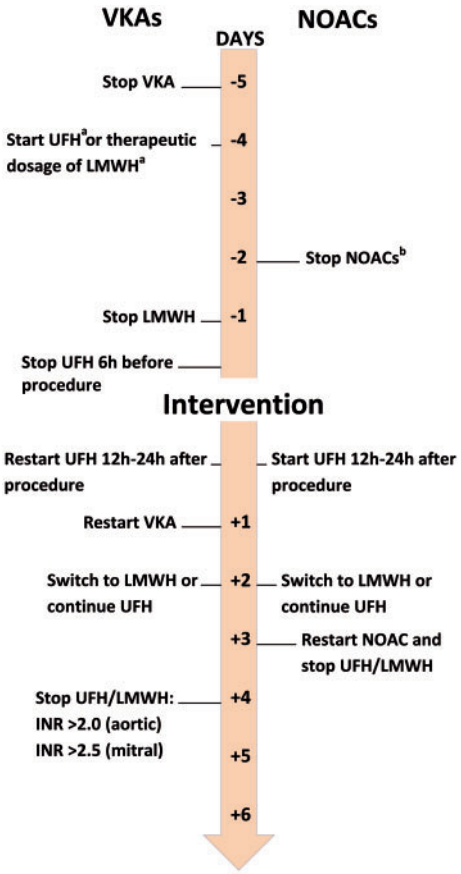

Figure 2: Management of oral anticoagulation in patients with an indication for preoperative bridging. [a]Bridging with UFH/LMWH should start when INR values are below specific therapeutic ranges. [b]Discontinuation should be prolonged to >72 h if creatinine clearance is 50–79 ml/min/1.73 m^2 or ≥96 h if creatinine clearance is <50 ml/min/1.73 m^2. INR: international normalized ratio; LMWH: low-molecular-weight heparin; NOACs: non-vitamin K antagonist oral anticoagulants; UFH: unfractionated heparin; VKAs: vitamin K antagonists.

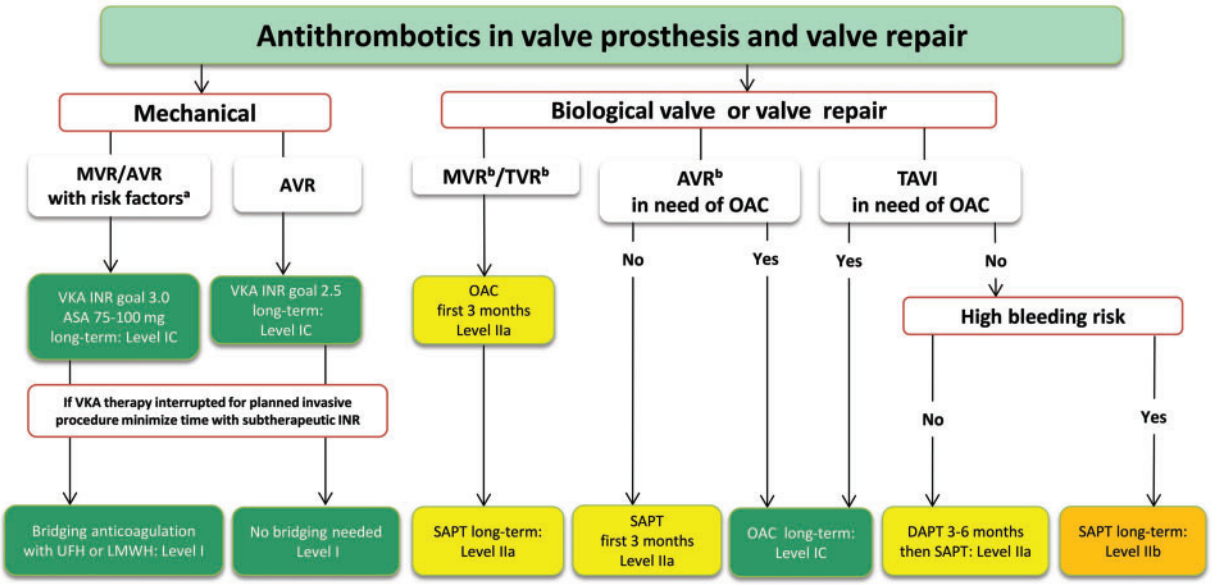

Figure 3: Proposed antithrombotic algorithm after valvular heart procedures. [a]Includes atrial fibrillation, previous thromboembolic events, left ventricular dysfunction and older generation mechanical AVR; [b]stands for replacement or repair. ASA: acetylsalicylic acid; AVR: aortic valve replacement; DAPT: dual antiplatelet therapy; INR: international normalized ratio; LMWH: low-molecular-weight heparin; MVR: mitral valve replacement; OAC: oral anticoagulant; SAPT: single antiplatelet therapy; TAVI: transcatheter aortic valve implantation; TVR: tricuspid valve replacement; UFH: unfractionated heparin; VKA: vitamin-K antagonists.

higher proportion of patients within the target anticoagulation range, when compared with UFH, and to provide similar or better safety. It should, therefore, be considered as an alternative bridging strategy to UFH [92, 93]. Once the INR is in the adequate target range, bridging should be discontinued.

The INR target in patients with mechanical prostheses depends on certain patient characteristics (e.g. previous thrombosis and AF) and on the prosthesis thrombogenicity and implantation site (e.g. aortic, mitral or tricuspid) [16]. A median target INR of 2.5 (range 2.0–3.0) is consistently recommended for aortic prostheses without additional risk factors for thromboembolism [16, 94], whereas higher targets are recommended in patients with risk factors (e.g. AF, venous thromboembolism, hypercoagulable state and left ventricular ejection fraction [LVEF] <35%) and/or mitral and tricuspid prostheses (median target INR >3.0). Of interest in patients with mechanical heart valves, the time in the therapeutic range is better associated with safety than the target INR range [95], supporting the use of INR self-management [96–98].

The Randomized, Phase II Study to Evaluate the Safety and Pharmacokinetics of Oral Dabigatran in Patients after Heart Valve Replacement (RE-ALIGN) trial investigated whether dabigatran versus VKAs was safe and effective in patients with mechanical heart valves [99]. The trial was prematurely stopped because of an increased risk for both thromboembolic complications and major bleeding with dabigatran. Therefore, NOACs currently have no role in any patient with a mechanical heart prosthesis.

In patients with concomitant atherosclerotic disease, the addition of low-dose (75–100 mg) ASA to VKAs may be considered, although the evidence is limited. Furthermore, a low dose of ASA may also be added if thromboembolism occurs despite an adequate INR. However, combined antithrombotic therapy is associated with a significant increase in the risk for bleeding, which carries an ominous prognosis [100]. Therefore, it should be reserved for patients with a very high risk of a thromboembolism. For patients who are candidates for triple oral antithrombotic therapy, i.e. patients with a mechanical valve and an absolute indication for DAPT (e.g. recent stent implantation or ACS), a short period (1 month) of triple therapy comprising VKA, low-dose ASA and clopidogrel [16], followed by interruption of either ASA or clopidogrel should be considered. Ticagrelor and prasugrel are not recommended in a triple therapy setting due to the safety hazard [16].

3.5.2 Bioprostheses. The optimal anticoagulation strategy early after implantation of an aortic bioprosthesis remains controversial. One should consider either anticoagulation with VKA or single antiplatelet therapy with ASA during the first 3 months. A large 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 alone or with VKAs alone for 3 months after bioprosthetic aortic valve replacement, whereas combined ASA and VKA therapy reduced the numbers of deaths and embolic events but significantly increased bleeding [101]. A Danish registry study showed a higher incidence of thromboembolic events and cardiovascular deaths in patients discontinuing warfarin during the first 6 postoperative months [102], although this cannot be directly translated into an increased risk if warfarin treatment is not initiated. A recent small RCT of 370 patients found that warfarin for 3 months versus ASA therapy significantly increased major bleeding but did not reduce the number of deaths or thromboembolic events [103]. There are no data on continuing lifelong ASA after an initial 3 months of treatment in patients with surgical bioprostheses who do not have any other indication for ASA.

Three months of treatment with VKA is recommended in all patients with a bioprosthesis implanted in the mitral or tricuspid position.

3.5.3 Valve repair. It is recommended to consider oral anticoagulation with VKA during the first 3 months after valve-sparing aortic root surgery and after mitral and tricuspid repair, although strong evidence is lacking. As for other indications, the risk for thromboembolic and bleeding complications must be taken into account when the antithrombotic treatment is planned.

Postoperative management of oral anticoagulants and indications for long-term antithrombotic treatments

Recommendations	Class[a]	Level[b]	Ref[c]
Postoperative bridging and (re)starting oral anticoagulation			
In patients with an indication for postoperative therapeutic bridging[d], it is recommended to start UFH 12–24 hours after surgery.	I	C	
LMWH should be considered as an alternative bridging strategy to UFH 24–48 hours after surgery.	IIa	C	
It is recommended to (re)-initiate VKAs on the first postoperative day.	I	C	
Delaying the restarting of NOACs for 72 hours after surgery should be considered.	IIa	C	
Mechanical prostheses			
Lifelong oral anticoagulation using a VKA is recommended for all patients.	I	B	[89, 90]
NOACs are not recommended in patients with a mechanical valve prosthesis.	III	B	[99]
The addition of low-dose ASA (75–100 mg/day) to VKA should be considered in the case of concomitant atherosclerotic disease.	IIa	C	
The addition of lifelong low-dose ASA (75–100 mg/day) to VKA should be considered after thromboembolism despite an adequate INR.	IIa	C	
Triple therapy comprising VKAs, ASA (75–100 mg/day) and clopidogrel (75 mg/day) should be considered for a duration of 1 month after ACS or recent stent implantation, followed by VKAs and low ASA (75–100 mg/day) or clopidogrel (75 mg/day).	IIa	C	
INR self-management is recommended provided that appropriate training and quality control are performed.	I	B	[96]
Bioprostheses			
Oral anticoagulation is recommended on a lifelong basis for patients with surgically or transcatheter implanted bioprostheses who have other indications for anticoagulation.	I	C	
Oral anticoagulation may be considered for the first 3 months after surgical implantation of an aortic bioprosthesis.	IIb	B	[101, 103]
Low-dose ASA (75–100 mg/day) should be considered for the first 3 months after surgical implantation of an aortic bioprosthesis or valve-sparing aortic surgery.	IIa	B	[101, 103]
Oral anticoagulation using a VKA should be considered for the first 3 months after mitral or tricuspid valve repair or bioprosthetic valve replacement.	IIa	C	
TAVI			
DAPT should be considered for the first 3–6 months after TAVI, followed by lifelong ASA in patients who do not need OACs for other reasons.	IIa	C	
ASA monotherapy may be considered after TAVI in cases where there is a high risk for bleeding.	IIb	C	
Other indications			
In patients undergoing cardiac surgery with a preoperative indication for oral anticoagulation, it is recommended that the preoperative regimen of VKAs or NOACs be restarted after surgery.	I	C	

Continued

[a]Class of recommendation.
[b]Level of evidence.
[c]References.
[d]Patients with a mechanical prosthetic heart valve; AF with moderate to severe mitral stenosis; AF with a CHA_2DS_2-VASc score >4; an acute thrombotic event within the previous 4 weeks and, potentially, patients with left ventricular apex thrombus, antithrombin 3 deficit, protein C and/or protein S deficits.

ACS: acute coronary syndrome; AF: atrial fibrillation; ASA: acetylsalicylic acid; CHA_2DS_2-VASc: Congestive heart failure, hypertension, age >75 (2 points), diabetes, prior stroke (2 points)–vascular disease, age 65–74, sex category (female); DAPT: dual antiplatelet therapy; INR: international normalised ratio; LMWH: low-molecular-weight heparin; NOACs: non-vitamin K antagonist oral anticoagulants; OACs: oral anticoagulants; TAVI: transcatheter aortic valve implantation; UFH: unfractionated heparin; VKAs: vitamin K antagonists.

3.5.4 Transcatheter aortic valve implantation. The decision for (dual) antiplatelet therapy or oral anticoagulation after transcatheter aortic valve implantation (TAVI) is complicated due to multiple factors associated with (i) a prothrombotic environment after valve implantation, (ii) combined TAVI and stent implantation in 30% of patients and (iii) an elderly patient population that frequently has comorbidities and frailty characteristics and should be considered at high risk for bleeding. DAPT remains the most widely used antithrombotic strategy after TAVI, being used in >60% of patients, whereas VKAs are used in <20% of patients [104]. However, subclinical valve thrombosis is another challenging issue, because it may occur soon after TAVI with antiplatelet treatment and may only be reversed after exposure to oral anticoagulant (OAC) therapy [105]. Indeed, recent evidence demonstrates that VKA alone versus VKA plus ASA produced comparable rates of thromboembolic events and deaths while reducing bleeding events [106]. Which antithrombotic regimen (e.g. antiplatelet, VKA or NOAC) is

most appropriate after TAVI is currently being tested in several ongoing trials (NCT02247128, NCT02556203 and NCT02664649). For the moment, there is a consensus that DAPT should be used soon after TAVI when there is no indication for OACs.

3.5.5 Other indications. In patients undergoing any cardiac operation with a preoperative indication for OACs other than heart valve replacement or repair, the preoperative regimen of VKAs or NOACs should be reinitiated after surgery. Patients with a preoperative indication for bridging should also receive postoperative bridging, following the same scheme as that used for mechanical prosthetic heart valves shown in Fig. 2. In contrast to VKAs, one should restart NOACs after surgery with caution due to the more immediate antithrombotic effects and the increased risk for bleeding [99].

4. ATRIAL FIBRILLATION

4.1 Preoperative atrial fibrillation prophylaxis

The most common arrhythmia in the period after cardiac surgery is AF. It is associated with a longer hospital stay and with higher rates of strokes and mortality [107–109]. It is also a predictor of the occurrence of AF years after surgery [109]. Since the publication of the previous comprehensive version of the guidelines on the Prevention and Management of *de novo* Atrial Fibrillation after Cardiac and Thoracic Surgery [110], numerous studies have addressed the safety and efficacy of medication to prevent postoperative AF (POAF) [17]. Treatment with beta-blockers has been shown to reduce POAF [107, 111]. Therefore, patients who are already taking beta-blockers should continue to take them before and after surgery. Patients who are not taking beta-blockers may derive some benefit, i.e. a lower incidence of POAF, from starting beta-blockers 2–3 days before the operation (if tolerated) and being carefully up-titrated according to blood pressure and heart rate [112]. Amiodarone taken 6 days preoperatively followed by 6 days postoperatively has been shown to be more effective than beta-blockers, but it is associated with more acute and long-term complications [111, 113]. It may be considered in patients who are unable to tolerate beta-blockers. Studies suggest that both magnesium and fish oil may prevent POAF, but RCTs have shown conflicting evidence [114–116]. Therefore, a clear recommendation for their use cannot be provided at the moment. There is currently no evidence from clinical trials to support the use of colchicine, steroids or statins to prevent POAF.

4.2 Management of postoperative atrial fibrillation

In patients who are haemodynamically unstable because of POAF, we recommend cardioversion and antiarrhythmic drugs to restore sinus rhythm. Both amiodarone and vernakalant are effective for restoring sinus rhythm after POAF [117, 118].

Historically, in haemodynamically stable patients, rhythm control of POAF has been the norm because of the assumption that the restoration/maintenance of sinus rhythm would be a superior strategy to rate control. More recent evidence from a randomized trial 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 [119]. However, 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 the preferred strategy, whereas rate control may also be an option. For rate control, beta-blockers or diltiazem/verapamil (if beta-blockers are contraindicated) are preferred over digoxin [17, 120]. The choice of drug depends on patient characteristics, including haemodynamics and LVEF. A combination of beta-blockers and digoxin may be required.

Recommendations for prevention in and treatment of patients with atrial fibrillation

Recommendations	Class[a]	Level[b]	Ref[c]
Preoperative period			
Perioperative low-dose oral beta-blocker therapy, starting 2–3 days before cardiac surgery, should be considered for the prevention of POAF.	IIa	B	[125–127]
If beta-blockers are initiated preoperatively, careful up-titration, according to blood pressure and heart rate, starting several days before surgery, is recommended.	I	C	
Perioperative amiodarone, starting 5–6 days before cardiac surgery, may be considered for the prevention of POAF.	IIb	A	[111, 128, 129]
Postoperative period			
In patients with postoperative haemodynamically stable POAF, rhythm control is recommended.	I	B	[119, 130]
In patients with postoperative haemodynamically stable and asymptomatic POAF, rate control should be considered.	IIa	B	[119, 130]
In patients with postoperative haemodynamically unstable POAF, cardioversion and antiarrhythmic drugs to restore sinus rhythm are recommended.	I	B	[131, 132]
Anticoagulation with therapeutic doses of UFH or LMWH should be considered within 12–48 hours of AF in patients with POAF, balancing the risks for stroke and surgical bleeding.	IIa	C	
In patients with POAF at discharge, it is recommended to initiate OAC therapy and continue for at least 4 weeks (or longer), depending on the CHA_2DS_2-VASc risk score.	I	B	[17, 122, 133, 134]

[a]Class of recommendation.
[b]Level of evidence.
[c]References.
AF: atrial fibrillation; CHA_2DS_2-VASc: Congestive heart failure, hypertension, age >75 (2 points), diabetes, prior stroke (2 points)–vascular disease, age 65–74, sex category (female); LMWH: low-molecular-weight heparin; OAC: oral anticoagulant; POAF: postoperative atrial fibrillation; UFH: unfractionated heparin.

4.3 Thromboembolism prevention for postoperative atrial fibrillation

Anticoagulation therapy is necessary for patients who have had cardiac surgery who develop AF to avoid early stroke and death [121]. OAC reduces postoperative mortality rates in patients discharged with POAF. Nevertheless, there is no clear evidence on when to start anticoagulation, and the decision has to be made based on balancing the risks for bleeding and thromboembolisms. Starting early with a therapeutic dose of UFH or LMWH should be considered within 12–48 h after surgery. OAC should commence 48 h after surgery and be maintained for at least 4 weeks according to the CHA_2DS_2-VASc score [17, 122]. Most of the evidence for anticoagulation of POAF has been obtained with VKAs. For patients with mechanical valve prostheses or moderate-to-severe mitral stenosis, VKAs are highly recommended [17]. There is evidence supporting a greater benefit of NOACs over VKA in non-valvular POAF, including patients with a bioprosthetic valve [123, 124].

5. RENIN–ANGIOTENSIN–ALDOSTERONE SYSTEM INHIBITORS

Four classes of drugs may be used to inhibit the renin–angiotensin–aldosterone system (RAAS): (i) angiotensin-converting enzyme inhibitors (ACEIs); (ii) angiotensin II receptor blockers (ARBs); (iii) aldosterone receptor antagonists and (iv) direct renin inhibitors. RAAS blockers are mainly used to treat hypertension and heart failure but also have a protective effect against the development of nephropathy through their inherent properties, which are not directly related to their effects on lowering blood pressure [135, 136]. Nevertheless, the use of RAAS blockers in some patients is fraught with controversy [136–139]. The role of newly developed direct renin inhibitors in cardiac surgical patients is uncertain, and data are currently lacking.

5.1 Preoperative discontinuation

It has been debated whether ACEIs should be discontinued before CABG [136, 137, 140]. The Ischemia Management With Accupril Post Bypass Graft Via Inhibition of the coNverting Enzyme (IMAGINE) study did not show any benefit of quinapril compared to placebo initiated early within 7 days of surgery; greater rates of morbidity and mortality have been observed at 3 months in the quinapril group [141]. However, the exact timing of the discontinuation and reinstitution of these drugs is poorly defined [138, 141]. RAAS inhibitors, including the ARBs and ACEIs, can also increase the risk for perioperative hypotension [142] and vasodilatory shock [143], causing decreased systemic vascular resistance [138]. Therefore, the use of inotropes and vasopressors is increased, and the time patients spend on ventilators and in the intensive care unit (ICU) is extended [137, 144]. For these reasons, there is a consensus on discontinuing RAAS blockers before cardiac surgery (Table 6) [136, 137, 140]. In patients with preoperatively uncontrolled hypertension, long-acting ACEIs and ARBs may be switched to short-acting ACEIs. Additionally, patients treated with sacubitril/valsartan should have the same preoperative assessment as other patients treated with RAAS inhibitors. There are currently no data on whether aldosterone receptor antagonists should be stopped or continued until surgery.

5.2 Postoperative use

The ideal blood pressure following CABG is not well studied, but a pressure of less than 140/90 mmHg has been suggested to be optimal [145, 146]. Therapy for postoperative hypertension frequently involves beta-blockers, because they also reduce the risk for AF/flutter and improve the clinical outcomes of patients with heart failure and reduced LVEF [147]. ACEIs, however, should also be considered, often in addition to beta-blockers, in patients with postoperative hypertension and/or a reduced LVEF [138, 145, 146]. Furthermore, treatment with sacubitril/valsartan is recommended for patients who remain symptomatic with chronic heart failure [New York Heart Association (NYHA) Class III and IV] and who have a reduced LVEF (<40%) as a replacement for an ACEI to further reduce the risk for death and readmission [19]. ARBs can be used as an alternative therapy for blood pressure in patients with reduced LVEF who are intolerant to ACEIs [148, 149] but should not be used concomitantly with ACEIs due to increased rates of hypotension, hyperkalaemia and impaired kidney function, especially if aldosterone antagonists are also used [150]. For other patients without hypertension or a reduced LVEF, the routine use of ACEIs is not indicated, because it may potentially lead to more

Table 6: Different types of renin–angiotensin–aldosterone system inhibitors

	Captopril	Enalapril	Lisinopril	Ramipril	Losartan	Valsartan
Mechanism of action	**ACEI**	**ACEI**	**ACEI**	**ACEI**	**ARB**	**ARB**
Half-life[a]	2 hours	35-38 hours	12 hours	13-17 hours	6-9 hours	6-9 hours
Frequency of administration	Twice or thrice daily	Once or twice daily	Once daily	Once or twice daily	Once or twice daily	Once or twice daily
Maximum dose	450 mg/day	40 mg/day	40 mg/day	20 mg/day	100 mg/day	320 mg/day
Renal excretion	95%	61%	100%	60%	4%	13%
Discontinuation before non-acute surgery	12 hours	24 hours	24 hours	24 hours	24 hours	24 hours

[a]Including the half-life of its pharmacologically active metabolite.
ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin II receptor blocker.

adverse events [141, 151]. The occurrence of low cardiac output syndrome in the early postoperative phase may result in a prolonged stay in the ICU and the need for inotropes or vasopressor support, which is associated with ischaemia and renal complications [152].

After the early postoperative phase, RAAS blockers have protective effects in patients with reduced LVEF and impaired kidney function [138] who have had CABG, mainly for long-term prevention of adverse events [153]. In addition to ACEIs and ARBs, aldosterone receptor antagonists may also benefit patients with chronic heart failure or a reduced LVEF. This benefit was shown in the Randomized Aldactone Evaluation Study (RALES) trial, where aldactone reduced overall mortality rates, heart failure symptoms and readmission due to heart failure [154]. Eplerenone, another aldosterone antagonist, has subsequently shown, in the Eplerenone in Mild Patients Hospitalisation and Survival Study in Heart Failure (EMPHASIS-HF), to reduce the risk for death and rehospitalization for heart failure in patients with an LVEF <35% and NYHA Class II [155]. Aldosterone antagonists can be used together with beta-blockers and ACEIs in patients following CABG but should be limited to patients with reduced LVEF and NYHA Class II–IV heart failure symptoms [155–157]. They should, however, be avoided in patients with kidney failure (estimated glomerular filtration rate <30 ml/min/1.73 m^2) or hyperkalaemia (>5.0 mEG/l) [157].

Management of patients with renin-angiotensin-aldosterone system inhibitors and indications for long-term treatment

Recommendations	Class[a]	Level[b]	Ref[c]
Preoperative period			
It is recommended to discontinue ACEIs and ARBs preoperatively in patients undergoing cardiac surgery[d].	I	C	
In patients with preoperative uncontrolled arterial hypertension, switching long-acting ACEI or ARB treatment to short-acting ACEIs should be considered.	IIa	C	
Postoperative period			
It should be considered to start short-acting ACEIs at a low dose no earlier than 48 hours after cardiac surgery in patients with a reduced LVEF (<40%) and an eGFR >30 ml/min/1.73 m^2.	IIa	C	
In ACEI-intolerant patients, an ARB is recommended in patients with a reduced LVEF (<40%) and an eGFR >30 ml/min/1.73 m^2.	I	A	[148, 149]
Long-term optimal-dose ACEI or ARB treatment is recommended after cardiac surgery in patients with reduced LVEF (<40%) and an eGFR >30 ml/min/1.73 m^2.	I	A	[158–160]
Sacubitril/valsartan is recommended as a replacement for an ACEI in ambulatory patients with reduced LVEF (<40%) who remain symptomatic despite optimal treatment with an ACEI, a beta-blocker and aldosterone antagonists.	I	B	[161]
Long-term aldosterone antagonist addition to beta-blockers and ACEI therapy is recommended after cardiac surgery in patients with HF and a reduced LVEF (<35%), an eGFR >30 ml/min/1.73 m^2 and without hyperkalaemia (>5.0 mEG/l).	I	A	[154, 155]

[a]Class of recommendation.
[b]Level of evidence.
[c]References.
[d]Table 6 includes the proposition of discontinuation time for specific agents.
ACEIs: angiotensin-converting enzyme inhibitors; ARBs: angiotensin II receptor blockers; LVEF: left ventricular ejection fraction; eGFR: estimated glomerular filtration rate; HF: heart failure.

6. BETA-BLOCKERS

6.1 Preoperative beta-blockers

Current evidence recommends that patients should continue beta-blockers before elective and non-elective cardiac surgery [162–164], because doing so results in a consistent survival benefit plus a reduction in arrhythmic events in the early postoperative period [165]. However, the effectiveness of catecholamine in the early postoperative period may be limited by concurrent treatment with beta-blockers until the day of the operation [166]. Therefore, it may be cumbersome to control patients with preoperative long-acting agents. Therefore, one should consider switching to short-acting agents to limit adverse events.

Whether one should initiate a beta-blocker in the preoperative or postoperative period is less clear [167], and such a decision should be individualized, which involves weighing the risks and benefits. As discussed in the section on AF, initiating beta-blockers preoperatively may be considered for the prevention of POAF. Whether beta-blockers prevent perioperative MI and death is controversial. Studies have shown that beta-blockers are particularly beneficial in patients with a recent MI [168]. Indeed, it is suggested that the benefit of beta-blockers before CABG to prevent MI and death is limited only to patients with a recent MI [169]. There is conflicting evidence on whether preoperative beta-blockers are beneficial in patients with reduced LVEF but without a recent MI [126]. However, if beta-blockers are initiated preoperatively, careful up-titration of short-acting agents according to blood pressure and heart rate, starting several days before surgery, is recommended.

6.2 Postoperative beta-blockers

In addition to a preoperative beta-blockade in patients with reduced LVEF, continuing beta-blockers during the early postoperative phase has also been shown to significantly reduce the 30-day mortality rate following CABG [170]. Strong evidence suggests that beta-blockers reduce the number of deaths in patients with a recent MI or reduced LVEF (<35%) [171, 172]. Therefore, it is crucial that beta-blockers be continued upon discharge for long-term secondary prevention in patients with a recent MI or reduced LVEF [173–175]. Approved beta-blockers are metoprolol succinate, bisoprolol, nebivolol and carvedilol [19].

Management of treatment with beta-blockers in perioperative settings

Recommendations	Class[a]	Level[b]	Ref[c]
Preoperative period			
It should be considered to continue beta-blocker therapy prior to cardiac surgery.	IIa	B	[125, 126, 176]
Postoperative period			
Postoperative long-term beta-blocker therapy is recommended in patients with a recent MI or reduced LVEF (<35%).	I	A	[171, 173–175]

[a]Class of recommendation.
[b]Level of evidence.
[c]References.
LVEF: left ventricular ejection fraction; MI: myocardial infarction.

7. DYSLIPIDAEMIA

7.1 Statins

7.1.1 Preoperative therapy. Results from observational studies and small RCTs have suggested that initiation of preoperative statin therapy before cardiac surgery reduced mortality, POAF and acute kidney injury (AKI) [177, 178]. However, in the Statin Therapy in Cardiac Surgery (STICS) trial that randomized 1922 patients undergoing elective cardiac surgery, the initiation of rosuvastatin therapy (20 mg/day) before cardiac surgery did not prevent perioperative myocardial damage or reduce the risk for POAF [179]. AKI was significantly more common among patients who received rosuvastatin than among those who received a placebo [179]. In another trial of patients undergoing cardiac surgery, initiation of a high dose of atorvastatin on the day before surgery that continued perioperatively did show a significantly higher rate of AKI in patients with chronic kidney disease compared with placebo [180]. The trial was later prematurely terminated on the grounds of futility [181].

In summary, these recent data do not support the preoperative initiation of statin therapy in statin-naive patients undergoing cardiac surgery. No data are available on whether patients already taking statins should continue or discontinue therapy preoperatively, although in common practice statins are continued perioperatively.

7.1.2 Postoperative use. Intense or maximally tolerated statin therapy is recommended with a low-density lipoprotein cholesterol (LDL-C) target of <70 mg/dl (1.8 mmol/l) or >50% LDL-C reduction in patients with coronary artery disease. In the Treating to New Targets (TNT) trial, which included >4000 randomized patients, intense lowering of LDL-C [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 lowering of the cholesterol level to a mean of 101 mg/dl (2.61 mmol/l) with atorvastatin 10 mg/day [182]. In patients with statin intolerance during the follow-up period, the European Atherosclerosis Society has recently developed a scheme for statin re-exposure [183].

7.2 Non-statin, lipid-lowering agents

In patients after CABG surgery in whom the LDL-C target <70 mg/dl (1.8 mmol/l) is not reached, despite an intense or maximally tolerated statin dose, the addition of a cholesterol absorption inhibitor, ezetimibe, should be considered. In a recent analysis of the IMProved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) study, it was observed that patients who had a previous CABG operation who received ezetimibe plus a statin versus a statin alone had a substantial reduction in cardiovascular events during a 6-year median follow-up period [6].

Although no direct evidence for the use of proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor after cardiac surgery exists, circumstantial evidence provides enough facts for its beneficial effects after CABG surgery [184]. Patients in whom the LDL-C target <70 mg/dl (1.8 mmol/l) is not reached, despite an intense or maximally tolerated dose of statin and ezetimibe, the recently developed PCSK9 inhibitors have been shown to reduce

Management of patients with dyslipidaemia

Recommendations	Class[a]	Level[b]	Ref[c]
Preoperative period			
It is not recommended to initiate statin therapy shortly before cardiac surgery.	III	A	[177–180]
Continuing statin therapy before cardiac surgery should be considered.	IIa	C	
Postoperative period			
LDL-C is recommended as the primary target.	I	A	[189]
Intense or maximally tolerated statin therapy is recommended in patients after CABG surgery to reach the LDL-C target <70 mg/dl (1.8 mmol/l) or >50% LDL-C reduction if the baseline LDL-C is between 1.8–3.5 mmol/l (70–135 mg/dl).	I	A	[20, 182, 189]
In patients after CABG surgery in whom the LDL-C target <70 mg/dl (1.8 mmol/l) is not reached by using statin therapy, a combination of a statin with a cholesterol absorption inhibitor (ezetimibe) should be considered.	IIa	B	[6, 189]
In patients after CABG surgery who have a persistently high LDL-C (>140 mg/dl or 3.6 mmol/l) level, despite treatment with the maximal tolerated statin dose (in combination with ezetimibe), a PCSK9 inhibitor should be considered.	IIa	B	[184, 190, 191]

[a]Class of recommendation.
[b]Level of evidence.
[c]References.
CABG: coronary artery bypass grafting; LDL-C: low-density lipoprotein cholesterol; PCSK9: proprotein convertase subtilisin/kexin type 9.

cardiovascular events during follow-up in patients at high cardiovascular risk [185, 186]. Therefore, the addition of PCSK9 inhibitors should be considered in selected patients.

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 preventing coronary events but had no impact on mortality rates [187]. However, in recent studies, no additional benefit of treatment with fibrate on top of statin therapy has been demonstrated [188]. Bile acid sequestrants (cholestyramine, colestipol and colesevelam) reduce LDL-C by 18–25% and may be used in combination with statins [20]. However, gastrointestinal adverse events and drug interactions limit their use.

8. ULCER PREVENTION AND STEROIDS

8.1 Ulcer prevention

Based on older studies, the incidence of upper gastrointestinal ulceration and bleeding is around 1% after cardiac surgery and is associated with significant morbidity and mortality (30–40%) [192]. However, patients undergoing contemporary cardiac surgery are aggressively treated with antithrombotic medication, and the incidence may therefore be underestimated. The impact of gastrointestinal ulcers and bleeding may be larger due to higher comorbidities and more potent antithrombotic medication.

Studies have shown that patients continue to have gastrointestinal complications, despite intraoperative histamine 2 antagonist therapy, and that more robust prophylaxis is required [193]. A summary of the available evidence concluded that a proton-pump inhibitor, but not an histamine 2 antagonist, reduced gastrointestinal complications [194]. Indeed, a large randomized trial of 210 patients undergoing cardiac surgery randomly assigned patients to teprenone, ranitidine or rabeprazole and found that patients treated with a proton-pump inhibitor (rabeprazole) had a significantly lower rate of active ulcers (4.3%) compared with 21.4% and 28.6% in patients treated with the histamine 2 antagonist (ranitidine) and the mucosal protector (teprenone), respectively [195]. Therefore, prophylaxis with a proton-pump inhibitor should be considered, despite a concern that routine prophylaxis may increase the incidence of postoperative pneumonia [196]. Although, there is conflicting evidence to support this statement [197].

Recommendations for stress ulcer prophylaxis

Recommendations	Class[a]	Level[b]	Ref[c]
The prophylactic use of a PPI for patients undergoing cardiac surgery should be considered to reduce gastric complications.	IIa	B	[194, 195, 198]
The prophylactic use of an H2 antagonist for patients undergoing cardiac surgery may be considered to reduce gastric complications.	IIb	B	[193–195]

[a]Class of recommendation.
[b]Level of evidence.
[c]References.
PPI: proton-pump inhibitor; H2 antagonist: histamine 2 antagonist.

8.2 Steroids

The use of cardiopulmonary bypass (CPB) initiates a systemic inflammatory response that is associated with adverse clinical outcomes such as respiratory failure, bleeding, adverse neurological function and multiple organ failure [199]. Because steroids attenuate this systemic inflammatory response, theoretically steroids have a potential benefit for patients undergoing cardiac surgery with CPB, although steroids may also increase the risk for infective complications and MI.

A meta-analysis of 44 RCTs ($n = 3205$) looking at the use of steroids in patients undergoing on-pump CABG showed that steroids reduced POAF, postoperative bleeding and the duration of the stay in the ICU but failed to show a reduction in the mortality rate [200]. Steroids did not increase the rate of MI or infective complications. The Steroids in Cardiac Surgery (SIRS) trial was conducted [201] on the basis of this analysis. In the trial, 7507 patients with a EuroSCORE >5 who underwent cardiac surgery with CPB were randomized between methylprednisolone or placebo showed no difference in the risk for 30-day mortality (4% vs 5%, respectively) or the risk for mortality and major morbidity (24% vs 24%, respectively). Although there was no difference in the rate of infections or delirium, there was a safety concern due to significantly higher rates of myocardial injury. The Dexamethasone for Cardiac Surgery (DECS) trial randomized nearly 4500 patients undergoing cardiac surgery with CPB and confirmed that no benefit was found with steroids over placebo in the composite of mortality, MI, stroke, renal failure or respiratory failure [202].

In summary, the routine use of prophylactic steroids is not indicated for patients undergoing cardiac surgery. However, a subgroup analysis of the Dexamethasone for Cardiac Surgery trial demonstrated an interaction according to age, suggesting that patients younger than 65 years may benefit from the preoperative use of steroids [203]. Indeed, younger patients generally have a more pronounced inflammatory response than elderly patients; therefore, suppression of this effect with steroids could have a potential benefit. Patients on chronic steroid therapy should receive their usual preoperative dose of steroids on the day of the operation. Additional perioperative stress-dose steroids for these patients are reasonable but are not evidence-based [204].

Recommendation for routine use of steroids

Recommendation	Class[a]	Level[b]	Ref[c]
The routine use of prophylactic steroids for patients undergoing cardiac surgery is not recommended.	III	A	[200–202]

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

9. ANTIBIOTIC PROPHYLAXIS

Perioperative infections following cardiac surgery, including surgical site infections (SSIs), bloodstream infections, pneumonia and *Clostridium difficile* colitis, dramatically affect survival, are the cause of prolonged hospitalization or readmission and

Recommendations for antibiotic prophylaxis

Recommendations	Class[a]	Level[b]	Ref[c]
In elective patients undergoing cardiac surgery who are *S. aureus* carriers, mupirocin twice daily intranasally is recommended, starting 4 days before surgery.	I	B	[226, 227]
In elective patients undergoing cardiac surgery with an unknown intranasal *S. aureus* colonization status, a strategy of testing well in advance of cardiac surgery to allow the appropriate preoperative duration of mupirocin eradication treatment in colonized patients should be considered over routine mupirocin treatment.	IIa	C	
Primary SAP is recommended to prevent infectious complications.	I	A	[242–244]
Timing			
Administration of the first dose of antimicrobial therapy within the 60 min before surgical incision is recommended.	I	B	[243, 246]
Administration of vancomycin and fluoroquinolones within the 120 min before surgical incision is recommended.	I	B	[243, 245]
Dosing			
It is recommended to use SAP according to standardized doses[d].	I	B	[210, 247, 248]
Duration			
It should be considered that the optimal duration of SAP is 24 hours and should not exceed 48 hours following cardiac surgery.	IIa	A	[212, 231, 249, 250]
Intraoperative redosing either with half a dose or a full dose depending on the antibiotic that is used, the length of operation, BMI and renal function should be considered to obtain adequate serum and tissue concentrations of the antimicrobial agent if the duration of the procedure exceeds two half-lives of the antimicrobial treatment.[d]	IIa	B	[222, 243, 251]
Intraoperative redosing either with half a dose or a full dose depending on the antibiotic that is used, the length of the operation, BMI and renal function should be considered to obtain adequate serum and tissue concentrations of the antimicrobial agent if there is haemodilution during CPB or excessive blood loss.	IIa	B	[252, 253]
Choice			
First-line treatment with cefazolin or cefuroxime is recommended.	I	A	[230, 231, 254]
Clindamycin or vancomycin are recommended in patients with a documented ß-lactam allergy.	I	B	[232–235]
Vancomycin should be considered for prophylaxis in patients known to be colonized with MRSA.	IIa	B	[239–241, 255]

Continued

[a]Class of recommendation.
[b]Level of evidence.
[c]References.
[d]Table 7 includes the half-time of the most used antibiotics for SAP.
BMI: body mass index; CPB: cardiopulmonary bypass; MRSA: methicillin-resistant *Staphylococcus aureus*; SAP: surgical antibiotic prophylaxis.

significantly increase costs [205]. Moreover, these major infections are of particular importance, because they have a relatively high prevalence of nearly 5% in the total cardiosurgical population [206].

Surgical antibiotic prophylaxis (SAP) before cardiac surgery is recommended to decrease the incidence of major infections. In addition to the administration of intravenous SAP, the gentamicin–collagen sponge has been developed to keep a high concentration of the agents in the local tissues surrounding postoperative wounds. The results from a recent meta-analysis showed significant reduction of the risk for sternal wound infection after implantation of gentamicin–collagen sponges [207]. However, the heterogeneity among studies was large, and powerful studies to confirm the benefit of additional local intervention in certain patient populations are warranted.

9.1 Dosing of surgical antibiotic prophylaxis

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 [208, 209]. To date, because of its safety, effectiveness and user-friendliness, SAP in cardiac surgery is routinely based on standardized doses rather than on weight-based doses, which avoid the need for individual patient calculations and therefore clearly reduce the risk for dosing errors (Table 7). Nevertheless, based on the limited evidence that exists for optimal dosing in obese patients [210, 211], the dose of cephalosporin should not routinely exceed the usual adult dose. For patients with renal failure, dosing should be adjusted according to the creatinine clearance.

9.2 Duration of surgical antibiotic prophylaxis

Repeat intraoperative dosing is recommended to ensure adequate serum and tissue concentrations if the duration of the procedure exceeds 2 half-lives of the antibiotic agent or when there is excessive intraoperative blood loss. Indeed, a

randomized trial of 838 patients comparing a single-dose versus a 24-h multiple-dose cefazolin regimen in patients undergoing cardiac surgery reported higher SSI rates with the single-dose regimen [212]. A recent meta-analysis of 12 RCTs with 7893 patients showed that SAP administered ≥24 h versus <24 h significantly reduced the risk for SSI by 38% (95% CI 13–69%, $P = 0.002$) and the risk for deep sternal wound infections by 68% (95% CI 12–153%, $P = 0.01$) [213]. Other studies have failed to show the benefit of prolonging SAP to >48 h [214, 215], although this practise does increase the risk of acquired antibiotic resistance compared with shorter prophylaxis [216–218]. Therefore, based on current evidence, the optimal length of SAP in adult cardiac surgery is 24 h and should not exceed 48 h. Whether intermittent or continuous administration of antibiotics should be preferred remains unclear, although some evidence suggests that continuous infusion may reduce postoperative infectious complications [219]. For a strategy of intermittent administration, the exact timing of redosing depends on the half-life of the antibiotic agent that is used. It should, furthermore, be adjusted for a prolonged antibiotic half-life in patients with renal failure [220–223]. Moreover, repeating SAP shortly after initiation of CPB has recently been shown to ensure adequate drug levels [223].

Table 7: Half-life of the most frequently used antibiotics for SAP[a]

Antibiotic agent	Half-life
Ampicilline	60 minutes
Ampicilline/sulbactam	60 minutes
Amoxicilline	60 minutes
Amoxicilline/clavulanate	60 minutes
Cefazolin	94 minutes
Cefotaxime	60 minutes
Cefotiam	45 minutes
Ceftriaxone	7–8 hours
Cefuroxime	70 minutes
Ciprofloxacin	3–5 hours
Clindamycin	2.5 hours
Gentamicin	1.5–2hours
Imipenem	60 minutes
Levofloxacin	7–8 hours
Meropenem	60 minutes
Metronidazole	7 hours
Piperacillin	60 minutes
Piperacillin/Tazobactam	45 minutes
Tobramycin	1.5–2 hours
Vancomycin	6 hours

[a]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.

SAP: surgical antibiotic prophylaxis.

9.3 Choice of surgical antibiotic prophylaxis

The majority of pathogenic organisms isolated from patients with SSIs after cardiac surgery are Gram-positive bacteria, which are followed by Gram-negative bacteria. Only a minority of other bacteria, anaerobes, fungi and parasites have been identified [224, 225].

Particularly due to the rising numbers of methicillin-resistant *Staphylococcus aureus* infections among patients undergoing cardiac surgery, the importance of eradicating intranasal *S. aureus* colonization is stressed. There is clear evidence from a large RCT that intranasal mupirocin twice daily for 4 days prior to cardiac surgery significantly reduces SSIs in patients known to be colonized with *S. aureus* [226, 227]. However, for patients in whom the status of colonization is unknown, testing for colonization well in advance of cardiac surgery should be considered to allow the appropriate preoperative duration of mupirocin eradication treatment in colonized patients. Although this practice introduces logistical difficulties and has cost implications, such a strategy should be preferred over routine mupirocin treatment in patients with an unknown colonization status.

For systemic antibiotic prophylaxis, numerous studies have clearly shown that antibiotic prophylaxis with first- and second-generation cephalosporins can effectively reduce the incidence of SSI and postoperative infectious complications in patients undergoing cardiac surgery (Table 8) [228–230], even though a

Table 8: Recommendations for the choice of SAP

Type of procedure	Recommended agents	Alternative agents in patients with ß-lactam allergy	Strength of evidence
CABG	Cefazolin, cefuroxime	Clindamycin, vancomycin	A
Cardiac device implantation (e.g. pacemaker)	Cefazolin, cefuroxime	Clindamycin, vancomycin	A
Ventricular assist devices	Cefazolin, cefuroxime	Clindamycin, vancomycin	C
Heart, lung, heart-lung transplant	Cefazolin	Clindamycin, vancomycin	A

CABG: coronary artery bypass grafting; SAP: surgical antibiotic prophylaxis.

meta-analysis showed that second-generation cephalosporins might be superior in reducing SSIs [231]. In patients with an allergy to ß-lactam who cannot tolerate cephalosporins, clindamycin or vancomycin is sufficient for Gram-positive coverage [232–235]. However, up to 15% of hospitalized patients reported an allergy to penicillin, but after a formal allergy evaluation, between 90% and 99% of these patients were found to be able to safely undergo penicillin treatments [236]. Importantly, these patients are more likely to be treated with vancomycin, clindamycin and quinolones with the increased risk for developing drug-resistant infections such as vancomycin-resistant *Enterococcus* species and *C. difficile* [237], leading to increased mortality, morbidity and prolonged hospital stays. Therefore, implementation of hospital protocols, including preoperative skin testing, may be effective therapeutic tools to reduce the rates of intrahospital infections, lower the costs of antibiotics and improve the patients' outcomes [236, 238].

In patients colonized with methicillin-resistant *S. aureus* in whom cephalosporins are insufficient, the administration of vancomycin is recommended [239–240].

10. ANAESTHESIA AND POSTOPERATIVE ANALGESIA

Anaesthetic agents and techniques might affect clinically relevant postoperative outcomes through pharmacological organ-protective mechanisms [256, 257] and by blunting the stress response [258]. Halogenated anaesthetics (isoflurane, desflurane and sevoflurane) are commonly used anaesthetic drugs with hypnotic, analgesic and muscle-relaxant properties. In addition, halogenated anaesthetics versus total intravenous anaesthetics result in additional organ protection and improvements in clinically relevant end-points after CABG, including reduction of mortality rates and perioperative MIs [256, 257, 259–264].

Postoperative pain following cardiac surgery still occurs frequently, both in patients in the ICU and in the general ward [265]. It is often underdiagnosed and undertreated, especially in patients who are unable to self-report pain. Overall, more than half of the operated patients report pain as the most traumatic experience of their postoperative stay [266, 267]. General recommendations for pain assessment developed for general surgical patients and those in the ICU are also indicated in cardiac surgery patients. Adequate pain relief is associated with improved outcomes through better respiratory function (e.g. an effective cough), early mobilization, prevention of delirium and a reduction of cardiovascular complications, which lead to a reduced stay in the ICU and lower associated costs. Poorly treated pain can have long-term sequelae that negatively affect the patient's quality of life and increase healthcare-related costs [268, 269].

10.1 Regional anaesthesia for perioperative pain control

Loco-regional techniques (epidural, intrathecal analgesics, paravertebral block, intercostal nerve block and wound infiltration) provide excellent postoperative pain control with different documented impacts on clinically relevant outcomes [270–274].

Epidural analgesia started before the operation and following published guidelines for epidural catheter positioning and removal [269] is also associated with a possible reduction in the mortality rate [258] and a low risk for epidural haematoma [275]. Intrathecal ('spinal') administration of morphine has been demonstrated to reduce postoperative opioid consumption and may be an alternative to epidural analgesia, because it is associated with a reduced risk for epidural haematoma [270, 276]. Administration of intrathecal clonidine, in addition to morphine, may provide additional benefits in terms of pain control and duration of mechanical ventilation, but it may also increase the risk for hypotension [271, 272, 277].

The paravertebral block is another alternative to the neuraxial techniques. Compared with epidural analgesia, the paravertebral block showed a similar analgesic efficacy and a lower incidence of minor complications in patients undergoing thoracotomy [278]. However, evidence in cardiac surgery patients is extremely limited. In patients undergoing median sternotomy, the bilateral paravertebral block should be performed. Although this approach appears safe and is probably associated with fewer complications compared to epidural analgesia, it requires further investigation [279].

Infiltration of local anaesthetics along the sternal wound may also be effective in reducing postoperative opioid consumption [280]. However, continuous infusion through a parasternal catheter has been associated with increased risk of sternal wound infection [281]. A single injection may be effective but requires further investigation [282].

10.2 Postoperative pain assessment

Routine assessment of pain and its severity improves pain management, both in the ICU and on the ward and allows the verification of the effectiveness of analgesic medications. It permits the monitoring of the response to therapy and detection of complications and side effects. Multimodal analgesia (e.g. analgesia through different techniques or drugs acting on different pathways) is more effective than analgesia that relies on a single technique in the overall surgical population, and there is no reason to doubt that this also applies to the cardiac surgical setting [269].

Several analgesic techniques and drug classes are currently available. Intravenous opioids are currently considered 'standard of care' in the management of significant postoperative pain for patients in the ICU after cardiac surgery. In cooperative patients, patient-controlled analgesia is superior to nurse-controlled analgesia for pain control [283]. Several opioids are available, with no clear evidence of the superiority of one over the others. A possible exception might be remifentanil, which has shown cardioprotective effects [284] and superiority in pain control [285, 286]. Use of paracetamol (acetaminophen) is safe and reduces opioid consumption [287–290], making it the best agent to manage postoperative pain after opioid-based cardiac anaesthesia and in combination with postoperative opioids.

Non-steroidal anti-inflammatory drugs are still used in cardiac surgery [291], despite worsening renal function in some patients. The concomitant administration of other non-steroidal anti-inflammatory drugs can theoretically diminish the antiplatelet effects of low-dose aspirin, increasing the risk for thromboembolic effects (MI and stroke) [292–297].

Treatment options in managing perioperative pain

Recommendations	Class[a]	Level[b]	Ref[c]
Multimodal analgesia is recommended over single-technique analgesia.	I	B	[269]
It is recommended that adult patients undergoing cardiac surgery undergo routine assessment of pain presence and severity for optimal analgesia.	I	B	[268, 269]
It is recommended that an anaesthesia plan including a halogenated agent (isoflurane, desflurane or sevoflurane) is used in CABG patients.	I	B	[256, 257]
The use of epidural analgesia may be considered after careful consideration of benefits and risks.	IIb	B	[258]
Preoperative intrathecal morphine administration may be considered to reduce postoperative opioid consumption.	IIb	B	[276, 309, 310]
The paravertebral block may be considered as an alternative to neuraxial techniques.	IIb	B	[279]
Parasternal continuous infusion of analgesia is not recommended in cardiac surgery.	III	B	[281]
Perioperative remifentanil infusion should be considered in all patients undergoing cardiac surgery.	IIa	B	[284]
PAC should be considered over a nurse-driven protocol.	IIa	B	[283]
IV opioids plus IV paracetamol should be considered as first-line treatment for postoperative pain in the ICU after cardiac surgery.	IIa	B	[287–289]
Routine NSAIDs are not recommended as first-line agents in unselected cardiac surgical patients.	III	A	[292–294]
Short-term low-dose NSAIDs may be considered as second-line agents in selected patients with a low risk of postoperative AKI and no contraindications to NSAIDs[d].	IIb	B	[298, 299, 301, 302]
COX-2 inhibitors are not recommended in cardiac surgical patients.	III	A	[304, 305]
It may be considered to start gabapentin or pregabalin before surgery as postoperative analgesic adjuvants.	IIb	B	[306, 307, 311]
Ketamine may be considered a postoperative analgesic adjuvant.	IIb	B	[312–314]

[a]Class of recommendation.
[b]Level of evidence.
[c]References.
[d]For example, allergies, ulcer and liver disease.
AKI: acute kidney injury; CABG: coronary artery bypass grafting; COX: cyclo-oxygenase; ICU: intensive care unit; IV: intravenous; NSAIDs: non-steroidal anti-inflammatory drugs; PAC: patient-controlled analgesia.

Nevertheless, RCTs and meta-analyses have shown that the use of low-dose non-steroidal anti-inflammatory drugs in selected patients at low risk of adverse events is effective in reducing pain and opioid consumption and may shorten mechanical ventilation time and stay in the ICU [298–302]. A single propensity-matched study suggested a possible reduction in mortality associated with the use of ketorolac [303]. Therefore, their use as a second-line agent in patients without contraindications may be considered. On the contrary, RCTs showed that selective cyclo-oxygenase-2 inhibitors are associated with an increase in adverse cardiovascular events and should, therefore, not be routinely administered [304, 305]. Analgesic adjuvants can reduce postoperative pain if given preoperatively (gabapentine or pregabalin) or postoperatively (ketamine) [271, 306–308].

11. BLOOD GLUCOSE MANAGEMENT

Hyperglycaemia affects over 40% of patients after cardiac surgery, due to stress and the use of inotropes [206]. Controlled studies show that patients with diabetes mellitus (DM) have increased rates of morbidity and mortality after cardiac surgery [315]. Perioperative hyperglycaemia, *per se*, even in non-DM patients, is associated with negative outcomes after cardiac surgery. Moreover, roughly 20–30% of cardiac surgery patients have pre-existing DM [316]. DM is associated with endothelial and platelet dysfunction, leading to prothrombotic states, adverse vascular events and increased infection risk. The prevalence of unrecognized DM and pre-DM in patients undergoing cardiac surgery contributes heavily to high blood glucose concentrations (BGCs) in the perioperative period [316]. Small increases in perioperative BGCs are associated with significant increases in rates of hospital mortality and morbidity [316, 317]. Therefore, preoperative documentation in the diagnosis of diabetes and its type should be a universal practice. Patients undergoing adult cardiac surgery should have a fast glucose measurement at hospital admission and if >120 mg/dl (6.6 mmol/l) the level of haemoglobin A1c (HbA1c) should be determined.

Preoperative and post-ICU glucose management techniques have no solid scientific evidence and are based on expert opinion. ICU data are controversial and should be interpreted cautiously. However, there is randomized evidence that perioperative BGC control reduces the risk for death and adverse events in patients having cardiac surgery [318–320]. There is also

Specific recommendations for perioperative blood glucose management

Recommendations	Class[a]	Level[b]	Ref[c]
Preoperative period			
It is recommended that oral antidiabetics and long-acting subcutaneous insulin be omitted the day before surgery.	I	C	
It should be considered that preoperative short-acting subcutaneous insulin is used while patients await surgery to maintain blood glucose levels between 120–180 mg/dl (6.7–10 mmol/l), with a check every 4 hours.	IIa	C	
Intraoperative period			
It should be considered that non-DM patients have a small (5 IU) bolus IV of insulin if the blood glucose level is >180 mg/dl (>10 mmol/l), as well as hourly checks.	IIa	C	
It should be considered that in non-DM patients a continuous IV insulin infusion is started to maintain a blood glucose of 150–180 mg/dl (8.3–10 mmol/l) during surgery if blood glucose is persistently >180 mg/dl (<10 mmol/l).	IIa	B	[317, 333, 334]
In diabetic patients, it is recommended that a continuous IV insulin infusion is started at the beginning of surgery and continued throughout to maintain a blood glucose level >150 (>8.3 mmol/l) and <180 mg/dl (<10 mmol/l).	I	B	[326, 335]
ICU			
With diabetic and non-DM patients, continuous IV insulin infusion is recommended if the blood glucose level is >180 mg/dl (>10 mmol/l) for a target of 150–180 mg/dl (8.3–10 mmol/l) during the ICU stay.	I	B	[328–330]
It is recommended that blood glucose levels are checked hourly if not stable and every 4 hours if stable during the ICU stay.	I	C	
After ICU			
It should be considered to start a combination of short-acting and long-acting subcutaneous insulin at 50% of the total previous 24-hour insulin dose (in ICU) and then titrated.	IIa	C	
Checking the blood glucose level every 4 hours and adjusting insulin doses to a target of 150–180 mg/dl (8.3–10 mmol/l) should be considered.	IIa	C	
It may be considered to restart oral antidiabetics at 50% of the preoperative dose when the patient is on oral feeding.	IIb	C	
At hospital discharge			
It is recommended that patients with DM or specifically, *de novo* DM, consult a diabetic specialist before discharge.	I	C	

[a]Class of recommendation.
[b]Level of evidence.
[c]References.
DM: diabetes mellitus; ICU: intensive care unit; IU: international unit; IV: intravenous.

evidence that blood glucose control should be started before the operation and not deferred until after surgery. The overall adequacy of BGC monitoring in the weeks before surgery, as reflected by the preoperative HbA1c level, is associated with several perioperative complications including death, stroke, renal failure, sternal wound infections, prolonged ICU stays and readmission [321].

Perioperative hyperglycaemia is probably a marker of illness severity rather than a cause of poor outcomes [322]. Indeed, the degree of hyperglycaemia is related to the level of activation of the stress response. Although mild-to-moderate stress hyperglycaemia is protective, it is likely that severe stress hyperglycaemia may be deleterious. However, the blood glucose threshold above which stress hyperglycaemia becomes harmful is still unknown. Many observational studies have been carried out to find the most reliable approach to blood glucose levels, and a U-shaped association between mean blood glucose levels and death was found, with the lowest mortality rate observed for the 125–160 mg/dl range [323].

Importantly, evidence points towards an increased risk of hypoglycaemic events with aggressive glycaemic control and suggests that moderate control can achieve clinically relevant improvements [324–327]. The Controlled Trial of Intensive Versus Conservative Glucose Control in Patients Undergoing Coronary Artery Bypass Graft Surgery (GLUCO-CABG) showed that intensive insulin therapy to achieve the target glucose level between 100 and 140 mg/dl in the ICU did not significantly reduce perioperative complications compared with the target glucose level between 141 and 180 mg/dl after CABG [328]. Moreover, the Normoglycemia in Intensive Care Evaluation and Surviving Using Glucose Algorithm Regulation (NICE-SUGAR) trial showed that a blood glucose level between 81 and 108 mg/dl was associated with a significant increase in all-cause mortality in ICU patients compared with a target of 180 mg/dl or less, including both surgical and non-surgical patients [329]. Observational studies suggest that, particularly in patients with insulin-treated DM, glucose levels below the recommended threshold of 180 mg/dl are associated with increased complications. In patients without DM and non-insulin-dependent DM, higher blood glucose levels were associated with more complications than lower blood glucose levels [330, 331]. Whether differential glucose thresholds should be stratified according to previous diabetic status requires further large prospective randomized studies.

There is high variability in methods of and indications for insulin therapy, management of non-insulin agents and blood glucose monitoring among glucose management guidelines issued by several professional organizations due to controversial findings and the lack of high-quality studies [332]. A multidisciplinary diabetes team should be in charge of continuous intravenous insulin-infusion protocols, treatment algorithms for the transition to subcutaneous insulin after discharge from the ICU, nutritional requirements and the reintroduction of oral antidiabetic agents, using hospitalization as a 'window of opportunity' for patient education, treatment selection and dose adjustment (Fig. 4).

Before hospital discharge, the patients with a diagnosis of DM or pre-DM should have an endocrinology consultation and dietary counselling. Post discharge, plasma glucose and HbA1c levels should be followed up regularly, with appropriate adjustments made in insulin and oral hypoglycaemic therapies with the aim of keeping HbA1c <7%.

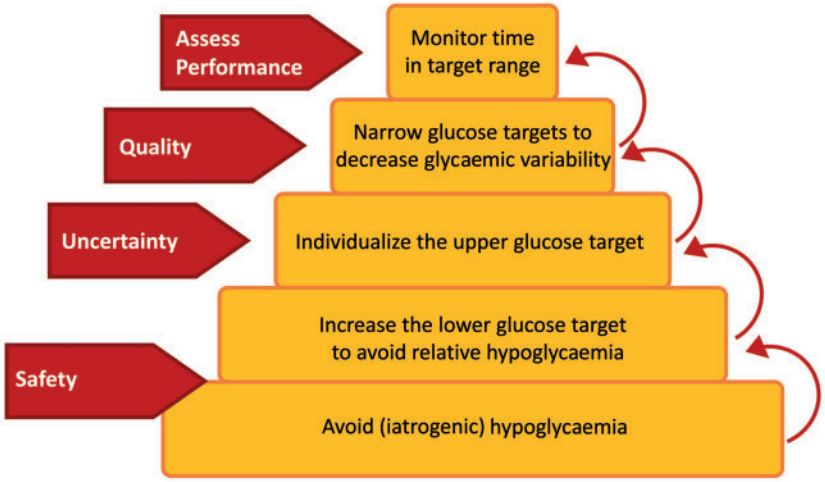

Figure 4: A recommended bottom-to-top stepwise strategy to implement perioperative blood glucose control (reproduced from Preiser *et al*. [323] with permission from Springer).

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