

# 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 <sub>2</sub> DS <sub>2</sub> -VASc	Congestive heart failure, hypertension, age $\geq$ 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 <sup>a</sup>	Level <sup>b</sup>	Ref <sup>c</sup>
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	

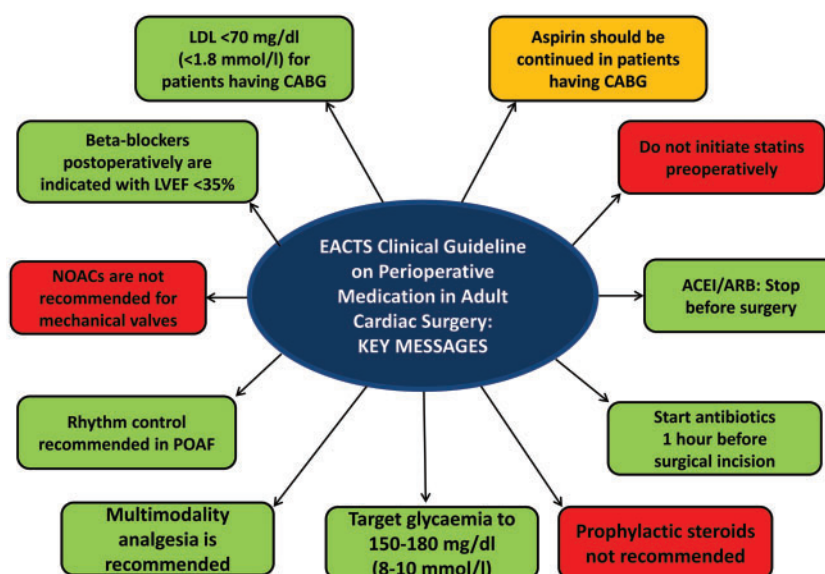
<sup>a</sup>Class of recommendation.

<sup>b</sup>Level of evidence.

<sup>c</sup>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 PIA2 [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 <sup>a</sup>	Level <sup>b</sup>	Ref <sup>c</sup>
<b>Preoperative period</b>			
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 <sup>d</sup> of re-exploration for bleeding.	IIa	C	
Bridging oral antiplatelet therapy with LMWH is not recommended.	III	B	[29]
<b>Postoperative period</b>			
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	

<sup>a</sup>Class of recommendation.

<sup>b</sup>Level of evidence.

<sup>c</sup>References.

<sup>d</sup>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.

Beside 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 reinstitute 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 <sup>a</sup>	Level <sup>b</sup>	Ref <sup>c</sup>
<b>Preoperative period</b>			
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.	Ila	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.	Ilb	B	[53, 54, 58, 60]
Bridging P2Y12 inhibitors with GPIIb/IIIa inhibitors or cangrelor may be considered in high ischaemic risk patients.	Ilb	C	
<b>Postoperative period</b>			
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).	Ilb	C	

<sup>a</sup>Class of recommendation.

<sup>b</sup>Level of evidence.

<sup>c</sup>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 <sup>a</sup>	Level <sup>b</sup>	Ref <sup>c</sup>
It is recommended to discontinue GPIIb/IIIa inhibitors at least 4 hours before surgery.	I	C	

<sup>a</sup>Class of recommendation.

<sup>b</sup>Level of evidence.

<sup>c</sup>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  $\geq 2$  days before surgery [71, 72]. In patients treated with dabigatran with creatinine clearance  $< 50$  ml/min/1.73 m<sup>2</sup>, NOAC should be stopped  $\geq 4$  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<sub>2</sub>DS<sub>2</sub>-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 <sub>max</sub>	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 <sup>a</sup>	At least 48 hours	At least 48 hours

<sup>a</sup>Discontinuation  $\geq 48$  h if creatinine clearance is  $>80$  ml/min/1.73 m<sup>2</sup>; discontinuation  $>72$  h if creatinine clearance is 50–79 ml/min/1.73 m<sup>2</sup> and discontinuation  $\geq 96$  h if creatinine clearance is  $<50$  ml/min/1.73 m<sup>2</sup>.

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 <sup>a</sup>	Level <sup>b</sup>	Ref <sup>c</sup>
<b>Preoperative period</b>			
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 <sup>e</sup> .	I	C	
Bridging of OAC is recommended in patients with any of the following indication: <ul style="list-style-type: none"> <li>• Mechanical prosthetic heart valve</li> <li>• AF with moderate to severe mitral stenosis</li> <li>• AF with a CHA<sub>2</sub>DS<sub>2</sub>-VASc score &gt;4</li> <li>• Acute thrombotic event within the previous 4 weeks.</li> </ul>	I	C	
Bridging of OACs should be considered in patients with a high acute thromboembolic risk <sup>d</sup> .	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]

<sup>a</sup>Class of recommendation.

<sup>b</sup>Level of evidence.

<sup>c</sup>References.

<sup>d</sup>Left ventricular apex thrombus, antithrombin 3 deficit and proteins C and/or S deficit.

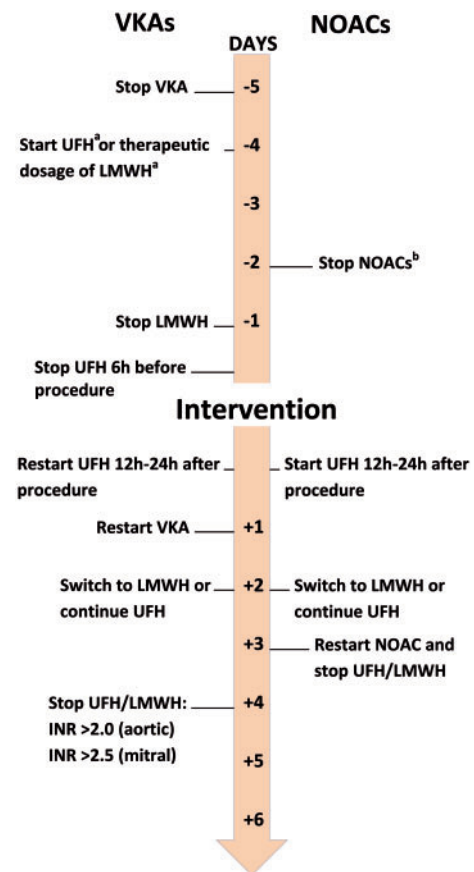
<sup>e</sup>Table 5 includes the proposition of discontinuation time for specific agents.

AF: atrial fibrillation; CHA<sub>2</sub>DS<sub>2</sub>-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

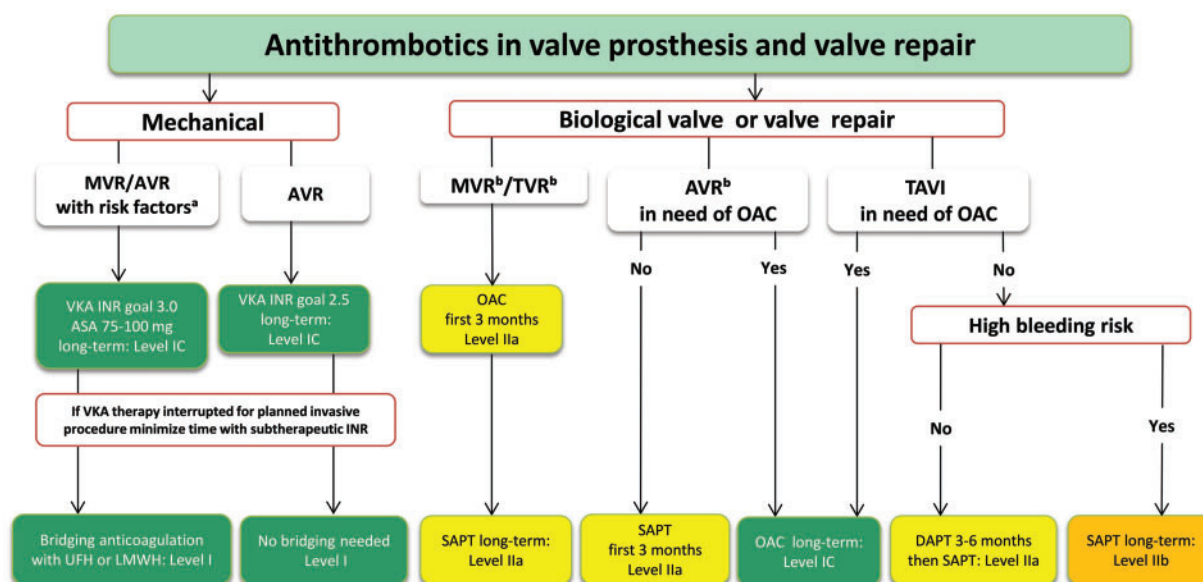
Heart valve replacement or repair increases the risk for thromboembolic complications, requiring antithrombotic therapy. Scientific evidence for the best antithrombotic strategy and duration is scarce [88], resulting in a low level of evidence for most recommendations [16].

**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. <sup>a</sup>Bridging with UFH/LMWH should start when INR values are below specific therapeutic ranges. <sup>b</sup>Discontinuation should be prolonged to >72 h if creatinine clearance is 50–79 ml/min/1.73 m<sup>2</sup> or ≥96 h if creatinine clearance is <50 ml/min/1.73 m<sup>2</sup>. 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. <sup>a</sup>Includes atrial fibrillation, previous thromboembolic events, left ventricular dysfunction and older generation mechanical AVR; <sup>b</sup>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 life-long 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 <sup>a</sup>	Level <sup>b</sup>	Ref <sup>c</sup>
<b>Postoperative bridging and (re)starting oral anticoagulation</b>			
In patients with an indication for postoperative therapeutic bridging <sup>d</sup> , 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	
<b>Mechanical prostheses</b>			
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]
<b>Bioprostheses</b>			
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]

Continued

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	
<b>TAVI</b>			
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	
<b>Other indications</b>			
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	

<sup>a</sup>Class of recommendation.<sup>b</sup>Level of evidence.<sup>c</sup>References.<sup>d</sup>Patients with a mechanical prosthetic heart valve; AF with moderate to severe mitral stenosis; AF with a CHA<sub>2</sub>DS<sub>2</sub>-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<sub>2</sub>DS<sub>2</sub>-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 <sup>a</sup>	Level <sup>b</sup>	Ref <sup>c</sup>
<b>Preoperative period</b>			
Perioperative low-dose oral beta-blocker therapy, starting 2–3 days before cardiac surgery, should be considered for the prevention of POAF.	Ila	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.	Ilb	A	[111, 128, 129]
<b>Postoperative period</b>			
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.	Ila	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.	Ila	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 <sub>2</sub> DS <sub>2</sub> -VASc risk score.	I	B	[17, 122, 133, 134]

<sup>a</sup>Class of recommendation.

<sup>b</sup>Level of evidence.

<sup>c</sup>References.

AF: atrial fibrillation; CHA<sub>2</sub>DS<sub>2</sub>-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<sub>2</sub>DS<sub>2</sub>-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, hyperkalemia 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 <sup>a</sup>	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

<sup>a</sup>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<sup>2</sup>) or hyperkalaemia (>5.0 mEq/l) [157].

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

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>	Ref <sup>c</sup>
<b>Preoperative period</b>			
It is recommended to discontinue ACEIs and ARBs preoperatively in patients undergoing cardiac surgery <sup>d</sup> .	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	
<b>Postoperative period</b>			
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 <sup>2</sup> .	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 <sup>2</sup> .	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 <sup>2</sup> .	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 <sup>2</sup> and without hyperkalaemia (>5.0 mEq/l).	I	A	[154, 155]

<sup>a</sup>Class of recommendation.

<sup>b</sup>Level of evidence.

<sup>c</sup>References.

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

<sup>a</sup>Class of recommendation.

<sup>b</sup>Level of evidence.

<sup>c</sup>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-naïve 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 <sup>a</sup>	Level <sup>b</sup>	Ref <sup>c</sup>
<b>Preoperative period</b>			
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	
<b>Postoperative period</b>			
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]

<sup>a</sup>Class of recommendation.

<sup>b</sup>Level of evidence.

<sup>c</sup>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- $\alpha$ , 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 <sup>a</sup>	Level <sup>b</sup>	Ref <sup>c</sup>
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]

<sup>a</sup>Class of recommendation.

<sup>b</sup>Level of evidence.

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

<sup>a</sup>Class of recommendation.

<sup>b</sup>Level of evidence.

<sup>c</sup>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 <sup>a</sup>	Level <sup>b</sup>	Ref <sup>c</sup>
In elective patients undergoing cardiac surgery who are <i>S. aureus</i> 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 <i>S. aureus</i> 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]
<b>Timing</b>			
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]
<b>Dosing</b>			
It is recommended to use SAP according to standardized doses <sup>d</sup> .	I	B	[210, 247, 248]
<b>Duration</b>			
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. <sup>d</sup>	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]

Continued

Choice	Class	Level	Ref
First-line treatment with cefazolin or cefuroxime is recommended.	I	A	[230, 231, 254]
Clindamycin or vancomycin are recommended in patients with a documented $\beta$ -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]

<sup>a</sup>Class of recommendation.<sup>b</sup>Level of evidence.<sup>c</sup>References.<sup>d</sup>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  $\geq 24$  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<sup>a</sup>

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	1.5–2 hours
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

<sup>a</sup>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 $\beta$ -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  $\beta$ -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 remifentanyl, 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 <sup>a</sup>	Level <sup>b</sup>	Ref <sup>c</sup>
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 remifentanyl 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 <sup>d</sup> .	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]

Continued

Ketamine may be considered a postoperative analgesic adjuvant.	IIb	B	[312-314]
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<sup>a</sup>Class of recommendation.<sup>b</sup>Level of evidence.<sup>c</sup>References.<sup>d</sup>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 <sup>a</sup>	Level <sup>b</sup>	Ref <sup>c</sup>
<b>Preoperative period</b>			
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	
<b>Intraoperative period</b>			
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]
<b>ICU</b>			
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	
<b>After ICU</b>			
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	
<b>At hospital discharge</b>			
It is recommended that patients with DM or specifically, <i>de novo</i> DM, consult a diabetic specialist before discharge.	I	C	

<sup>a</sup>Class of recommendation.

<sup>b</sup>Level of evidence.

<sup>c</sup>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 re-admission [321].

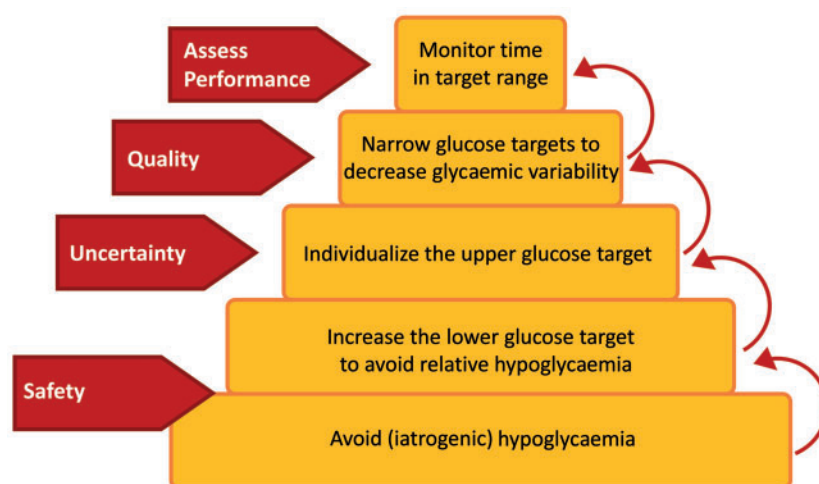
Perioperative hyperglycaemia is probably a marker of illness severity rather than a cause of poor outcomes [322]. Indeed, the degree of hyperglycaemia is related to the level of activation of the stress response. Although mild-to-moderate stress hyperglycaemia is protective, it is likely that severe 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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## REFERENCES

- [1] Sousa-Uva M, Head SJ, Thielmann M, Cardillo G, Benedetto U, Czerny M *et al.* Methodology manual for European Association for Cardio-Thoracic Surgery (EACTS) clinical guidelines. *Eur J Cardiothorac Surg* 2015;48:809–16.
- [2] Kulik A, Desai NR, Shrank WH, Antman EM, Glynn RJ, Levin R *et al.* Full prescription coverage versus usual prescription coverage after coronary artery bypass graft surgery: analysis from the post-myocardial infarction free Rx event and economic evaluation (FREEE) randomized trial. *Circulation* 2013;128:S219–25.
- [3] Zhang H, Yuan X, Zhang H, Chen S, Zhao Y, Hua K *et al.* Efficacy of chronic  $\beta$ -blocker therapy for secondary prevention on long-term outcomes after coronary artery bypass grafting surgery. *Circulation* 2015;131:2194–201.
- [4] Milojevic M, Head SJ, Parasca CA, Serruys PW, Mohr FW, Morice MC *et al.* Causes of death following PCI versus CABG in complex CAD: 5-year follow-up of SYNTAX. *J Am Coll Cardiol* 2016;67:42–55.
- [5] Hlatky MA, Solomon MD, Shilane D, Leong TK, Brindis R, Go AS. Use of medications for secondary prevention after coronary bypass surgery compared with percutaneous coronary intervention. *J Am Coll Cardiol* 2013;61:295–301.
- [6] Eisen A, Cannon CP, Blazing MA, Bohula EA, Park JG, Murphy SA *et al.* The benefit of adding ezetimibe to statin therapy in patients with prior coronary artery bypass graft surgery and acute coronary syndrome in the IMPROVE-IT trial. *Eur Heart J* 2016;37:3576–84.
- [7] Kolh P, Windecker S, Alfonso F, Collet JP, Cremer J, Falk V *et al.* 2014 ESC/EACTS guidelines on myocardial revascularization: the Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). Developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). *Eur J Cardiothorac Surg* 2014;46:517–92.
- [8] Niebauer J. Is there a role for cardiac rehabilitation after coronary artery bypass grafting? Treatment after coronary artery bypass surgery remains incomplete without rehabilitation. *Circulation* 2016;133:2529–37.
- [9] Mohr FW, Morice MC, Kappetein AP, Feldman TE, Stahle E, Colombo A *et al.* Coronary artery bypass graft surgery versus percutaneous coronary intervention in patients with three-vessel disease and left main coronary disease: 5-year follow-up of the randomised, clinical SYNTAX trial. *Lancet* 2013;381:629–38.
- [10] Park SJ, Ahn JM, Kim YH, Park DW, Yun SC, Lee JY *et al.* Trial of everolimus-eluting stents or bypass surgery for coronary disease. *N Engl J Med* 2015;372:1204–12.
- [11] Iqbal J, Zhang YJ, Holmes DR, Morice MC, Mack MJ, Kappetein AP *et al.* Optimal medical therapy improves clinical outcomes in patients undergoing revascularization with percutaneous coronary intervention or coronary artery bypass grafting: insights from the Synergy Between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery (SYNTAX) trial at the 5-year follow-up. *Circulation* 2015;131:1269–77.
- [12] Milojevic M, Head SJ, Mack MJ, Mohr FW, Morice MC, Dawkins KD *et al.* Influence of practice patterns on outcome among countries enrolled in the SYNTAX trial: 5-year results between percutaneous coronary intervention and coronary artery bypass grafting. *Eur J Cardiothorac Surg* 2017;52:445–53.

- [13] Dunning J, Versteegh M, Fabbri A, Pavie A, Kolh P, Lockowandt U *et al.* Guideline on antiplatelet and anticoagulation management in cardiac surgery. *Eur J Cardiothorac Surg* 2008;34:73-92.
- [14] Lazar HL, McDonnell M, Chipkin SR, Furnary AP, Engelman RM, Sadhu AR *et al.* The Society of Thoracic Surgeons practice guideline series: blood glucose management during adult cardiac surgery. *Ann Thorac Surg* 2009;87:663-9.
- [15] Kulik A, Ruel M, Jneid H, Ferguson TB, Hiratzka LF, Ikonomidis JS *et al.* Secondary prevention after coronary artery bypass graft surgery: a scientific statement from the American Heart Association. *Circulation* 2015;131:927-64.
- [16] Falk V, Baumgartner H, Bax JJ, De Bonis M, Hamm C, Holm PJ *et al.* ESC/EACTS Guidelines for the management of valvular heart disease. *Eur J Cardiothorac Surg* 2017;52:616-64.
- [17] Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B *et al.* 2016 ESC guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur J Cardiothorac Surg* 2016;50:e1-88.
- [18] Priors SG, Blomstrom-Lundqvist C, Mazzanti A, Blom N, Borggrefe M, Camm J *et al.* 2015 ESC guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: the Task Force for the Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death of the European Society of Cardiology (ESC). Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC). *Eur Heart J* 2015;36:2793-867.
- [19] Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS *et al.* 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J* 2016;37:2129-200.
- [20] Catapano AL, Graham I, De Backer G, Wiklund O, Chapman MJ, Drexel H *et al.* 2016 ESC/EAS guidelines for the management of dyslipidaemias. *Eur Heart J* 2016;37:2999-3058.
- [21] Roffi M, Patrono C, Collet JP, Mueller C, Valgimigli M, Andreotti F *et al.* 2015 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: task force for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J* 2016;37:267-315.
- [22] Pagano D, Milojevic M, Meesters MI, Benedetto U, Bolliger D, von Heymann C. 2017 EACTS/EACTA Guidelines on patient blood management for adult cardiac surgery. The task force on patient blood management for adult cardiac surgery of the European Association for Cardio-Thoracic Surgery (EACTS) and the European Association of Cardiothoracic Anaesthesiology (EACTA). *Eur J Cardiothorac Surg* 2017; doi:10.1093/ejcts/exz325.
- [23] Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *Br Med J* 2002;324:71-86.
- [24] Hastings S, Myles P, McIlroy D. Aspirin and coronary artery surgery: a systematic review and meta-analysis. *Br J Anaesth* 2015;115:376-85.
- [25] Myles PS, Smith JA, Forbes A, Silbert B, Jayarajah M, Painter T *et al.* Stopping vs. continuing aspirin before coronary artery surgery. *N Engl J Med* 2016;374:728-37.
- [26] Deja MA, Kargul T, Domaradzki W, Stęcel T, Mazur W, Wojakowski W *et al.* Effects of preoperative aspirin in coronary artery bypass grafting: a double-blind, placebo-controlled, randomized trial. *J Thorac Cardiovasc Surg* 2012;144:204-9.
- [27] Morawski W, Sanak M, Cisowski M, Szczeklik M, Szczeklik W, Dropinski J *et al.* Prediction of the excessive perioperative bleeding in patients undergoing coronary artery bypass grafting: role of aspirin and platelet glycoprotein IIIa polymorphism. *J Thorac Cardiovasc Surg* 2005;130:791-6.
- [28] Sun JC, Whitlock R, Cheng J, Eikelboom JW, Thabane L, Crowther MA *et al.* The effect of pre-operative aspirin on bleeding, transfusion, myocardial infarction, and mortality in coronary artery bypass surgery: a systematic review of randomized and observational studies. *Eur Heart J* 2008;29:1057-71.
- [29] Nenna A, Spadaccio C, Prestipino F, Lusini M, Sutherland FW, Beattie GW *et al.* Effect of preoperative aspirin replacement with enoxaparin in patients undergoing primary isolated on-pump coronary artery bypass grafting. *Am J Cardiol* 2016;117:563-70.
- [30] Hansson EC, Shams Hakimi C, Astrom-Olsson K, Hesse C, Wallen H, Dellborg M *et al.* Effects of ex vivo platelet supplementation on platelet aggregability in blood samples from patients treated with acetylsalicylic acid, clopidogrel, or ticagrelor. *Br J Anaesth* 2014;112:570-5.
- [31] Martin AC, Berndt C, Calmette L, Philip I, Decouture B, Gaussem P *et al.* The effectiveness of platelet supplementation for the reversal of ticagrelor-induced inhibition of platelet aggregation: an in-vitro study. *Eur J Anaesthesiol* 2016;33:361-7.
- [32] Zisman E, Erport A, Kohanovsky E, Ballagulah M, Cassel A, Quitt M *et al.* Platelet function recovery after cessation of aspirin: preliminary study of volunteers and surgical patients. *Eur J Anaesthesiol* 2010;27:617-23.
- [33] Mangano DT; Multicenter Study of Perioperative Ischemia Research Group. Aspirin and mortality from coronary bypass surgery. *N Engl J Med* 2002;347:1309-17.
- [34] Musleh G, Dunning J. Does aspirin 6 h after coronary artery bypass grafting optimise graft patency? *Interact CardioVasc Thorac Surg* 2003;2:413-5.
- [35] Yusuf S, Zhao F, Mehta SR, Chrolavicius S, Tognoni G, Fox KK. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med* 2001;345:494-502.
- [36] Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C *et al.* Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 2009;361:1045-57.
- [37] Wiviott SD, Braunwald E, McCabe CH, Montalescot G, Ruzyllo W, Gottlieb S *et al.* Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 2007;357:2001-15.
- [38] Becker RC, Bassand JP, Budaj A, Wojdyla DM, James SK, Cornel JH *et al.* Bleeding complications with the P2Y12 receptor antagonists clopidogrel and ticagrelor in the PLATElet inhibition and patient Outcomes (PLATO) trial. *Eur Heart J* 2011;32:2933-44.
- [39] Fox KA, Mehta SR, Peters R, Zhao F, Lakkis N, Gersh BJ *et al.* Benefits and risks of the combination of clopidogrel and aspirin in patients undergoing surgical revascularization for non-ST-elevation acute coronary syndrome: the Clopidogrel in Unstable angina to prevent Recurrent ischemic Events (CURE) Trial. *Circulation* 2004;110:1202-8.
- [40] Held C, Asenblad N, Bassand JP, Becker RC, Cannon CP, Claeys MJ *et al.* Ticagrelor versus clopidogrel in patients with acute coronary syndromes undergoing coronary artery bypass surgery: results from the PLATO (Platelet Inhibition and Patient Outcomes) trial. *J Am Coll Cardiol* 2011;57:672-84.
- [41] Smith PK, Goodnough LT, Levy JH, Poston RS, Short MA, Weerakkody GJ *et al.* Mortality benefit with prasugrel in the TRITON-TIMI 38 coronary artery bypass grafting cohort: risk-adjusted retrospective data analysis. *J Am Coll Cardiol* 2012;60:388-96.
- [42] Hansson EC, Jideus L, Aberg B, Bjursten H, Dreifaldt M, Holmgren A *et al.* Coronary artery bypass grafting-related bleeding complications in patients treated with ticagrelor or clopidogrel: a nationwide study. *Eur Heart J* 2016;37:189-97.
- [43] Tomsic A, Schotborgh MA, Manshanden JS, Li WW, de Mol BA. Coronary artery bypass grafting-related bleeding complications in patients treated with dual antiplatelet treatment. *Eur J Cardiothorac Surg* 2016;50:849-56.
- [44] Pickard AS, Becker RC, Schumock GT, Frye CB. Clopidogrel-associated bleeding and related complications in patients undergoing coronary artery bypass grafting. *Pharmacotherapy* 2008;28:376-92.
- [45] Purkayastha S, Athanasiou T, Malinovsky V, Tekkis P, Foale R, Casula R *et al.* Does clopidogrel affect outcome after coronary artery bypass grafting? A meta-analysis. *Heart* 2006;92:531-2.
- [46] Ferraris VA, Saha SP, Oestreich JH, Song HK, Rosengart T, Reece TB *et al.* 2012 update to the Society of Thoracic Surgeons guideline on use of antiplatelet drugs in patients having cardiac and noncardiac operations. *Ann Thorac Surg* 2012;94:1761-81.
- [47] Valgimigli M, Bueno H, Byrne RA, Collet J-P, Costa F, Jeppsson A *et al.* 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS. *Eur J Cardiothorac Surg*; doi:10.1093/ejcts/exz334.
- [48] Angiolillo DJ, Firstenberg MS, Price MJ, Tummala PE, Hutrya M, Welsby J *et al.* Bridging antiplatelet therapy with cangrelor in patients undergoing cardiac surgery: a randomized controlled trial. *JAMA* 2012;307:265-74.
- [49] Qamar A, Bhatt DL. Current status of data on cangrelor. *Pharmacol Ther* 2016;159:102-9.
- [50] Wallentin L. P2Y(12) inhibitors: differences in properties and mechanisms of action and potential consequences for clinical use. *Eur Heart J* 2009;30:1964-77.
- [51] Gherli R, Mariscalco G, Dalen M, Onorati F, Perrotti A, Chocron S *et al.* Safety of preoperative use of ticagrelor with or without aspirin compared with aspirin alone in patients with acute coronary syndromes undergoing coronary artery bypass grafting. *JAMA Cardiol* 2016;1:921-8.

- [52] Gurbel PA, Bliden KP, Butler K, Tantry US, Gesheff T, Wei C *et al.* Randomized double-blind assessment of the ONSET and OFFSET of the antiplatelet effects of ticagrelor versus clopidogrel in patients with stable coronary artery disease: the ONSET/OFFSET study. *Circulation* 2009;120:2577-85.
- [53] Storey RF, Bliden KP, Ecob R, Karunakaran A, Butler K, Wei C *et al.* Earlier recovery of platelet function after discontinuation of treatment with ticagrelor compared with clopidogrel in patients with high antiplatelet responses. *J Thromb Haemost* 2011;9:1730-7.
- [54] Malm CJ, Hansson EC, Akesson J, Andersson M, Hesse C, Shams Hakimi C *et al.* Preoperative platelet function predicts perioperative bleeding complications in ticagrelor-treated cardiac surgery patients: a prospective observational study. *Br J Anaesth* 2016;117:309-15.
- [55] Aradi D, Kirtane A, Bonello L, Gurbel PA, Tantry US, Huber K *et al.* Bleeding and stent thrombosis on P2Y12-inhibitors: collaborative analysis on the role of platelet reactivity for risk stratification after percutaneous coronary intervention. *Eur Heart J* 2015;36:1762-71.
- [56] Collet JP, Cuisset T, Range G, Cayla G, Elhadad S, Pouillot C *et al.* Bedside monitoring to adjust antiplatelet therapy for coronary stenting. *N Engl J Med* 2012;367:2100-9.
- [57] Cayla G, Cuisset T, Silvain J, Leclercq F, Manzo-Silberman S, Saint-Etienne C *et al.* Platelet function monitoring to adjust antiplatelet therapy in elderly patients stented for an acute coronary syndrome (ANTARCTIC): an open-label, blinded-endpoint, randomised controlled superiority trial. *Lancet* 2016;388:2015-22.
- [58] Kwak YL, Kim JC, Choi YS, Yoo KJ, Song Y, Shim JK. Clopidogrel responsiveness regardless of the discontinuation date predicts increased blood loss and transfusion requirement after off-pump coronary artery bypass graft surgery. *J Am Coll Cardiol* 2010;56:1994-2002.
- [59] Ranucci M, Baryshnikova E, Soro G, Ballotta A, De Benedetti D, Conti D. Multiple electrode whole-blood aggregometry and bleeding in cardiac surgery patients receiving thienopyridines. *Ann Thorac Surg* 2011;91:123-9.
- [60] Ranucci M, Colella D, Baryshnikova E, Di Dedda U, Hemmings HC; Surgical and Clinical Outcome Research (SCORE) Group. Effect of preoperative P2Y12 and thrombin platelet receptor inhibition on bleeding after cardiac surgery. *Br J Anaesth* 2014;113:970-6.
- [61] Mahla E, Pruehler F, Farzi S, Pregartner G, Raggam RB, Beran E *et al.* Does platelet reactivity predict bleeding in patients needing urgent coronary artery bypass grafting during dual antiplatelet therapy? *Ann Thorac Surg* 2016;102:2010-7.
- [62] Mahla E, Suarez TA, Bliden KP, Rehak P, Metzler H, Sequeira AJ *et al.* Platelet function measurement-based strategy to reduce bleeding and waiting time in clopidogrel-treated patients undergoing coronary artery bypass graft surgery: the timing based on platelet function strategy to reduce clopidogrel-associated bleeding related to CABG (TARGET-CABG) study. *Circ Cardiovasc Interv* 2012;5:261-9.
- [63] Verma S, Goodman SG, Mehta SR, Latter DA, Ruel M, Gupta M *et al.* Should dual antiplatelet therapy be used in patients following coronary artery bypass surgery? A meta-analysis of randomized controlled trials. *BMC Surg* 2015;15:112.
- [64] Deo SV, Dunlay SM, Shah IK, Altarabsheh SE, Erwin PJ, Boilson BA *et al.* Dual anti-platelet therapy after coronary artery bypass grafting: is there any benefit? A systematic review and meta-analysis. *J Card Surg* 2013;28:109-16.
- [65] van Diepen S, Fuster V, Verma S, Hamza TH, Siami FS, Goodman SG *et al.* Dual antiplatelet therapy versus aspirin monotherapy in diabetics with multivessel disease undergoing CABG: FREEDOM insights. *J Am Coll Cardiol* 2017;69:119-27.
- [66] Savonitto S, D'Urbano M, Caracciolo M, Barlocco F, Mariani G, Nichelatti M *et al.* Urgent surgery in patients with a recently implanted coronary drug-eluting stent: a phase II study of 'bridging' antiplatelet therapy with tirofiban during temporary withdrawal of clopidogrel. *Br J Anaesth* 2010;104:285-91.
- [67] Patrono C, Collier B, FitzGerald GA, Hirsh J, Roth G. Platelet-active drugs: the relationships among dose, effectiveness, and side effects: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest* 2004;126:234S-64S.
- [68] Lincoff AM, LeNarz LA, Despotis GJ, Smith PK, Booth JE, Raymond RE *et al.* Abciximab and bleeding during coronary surgery: results from the EPILOG and EPISTENT trials. Improve long-term outcome with abciximab GP IIb/IIIa blockade. Evaluation of platelet IIb/IIIa inhibition in STENTING. *Ann Thorac Surg* 2000;70:516-26.
- [69] De Carlo M, Maselli D, Cortese B, Ciabatti N, Gistri R, Levantino M *et al.* Emergency coronary artery bypass grafting in patients with acute myocardial infarction treated with glycoprotein IIb/IIIa receptor inhibitors. *Int J Cardiol* 2008;123:229-33.
- [70] Birnie DH, Healey JS, Wells GA, Verma A, Tang AS, Krahn AD *et al.* Pacemaker or defibrillator surgery without interruption of anticoagulation. *N Engl J Med* 2013;368:2084-93.
- [71] Heidbuchel H, Verhamme P, Alings M, Antz M, Diener HC, Hacke W *et al.* Updated European Heart Rhythm Association practical guide on the use of non-vitamin K antagonist anticoagulants in patients with non-valvular atrial fibrillation. *Europace* 2015;17:1467-507.
- [72] Faraoni D, Levy JH, Albaladejo P, Samama CM; Groupe d'Intérêt en Hémostase Périscopérotoire. Updates in the perioperative and emergency management of non-vitamin K antagonist oral anticoagulants. *Crit Care* 2015;19:203.
- [73] Douketis JD, Spyropoulos AC, Kaatz S, Becker RC, Caprini JA, Dunn AS *et al.* Perioperative bridging anticoagulation in patients with atrial fibrillation. *N Engl J Med* 2015;373:823-33.
- [74] Jones HU, Muhlestein JB, Jones KW, Bair TL, Lavasani F, Sohrevardi M *et al.* Preoperative use of enoxaparin compared with unfractionated heparin increases the incidence of re-exploration for postoperative bleeding after open-heart surgery in patients who present with an acute coronary syndrome: clinical investigation and reports. *Circulation* 2002;106(12 Suppl 1):119-22.
- [75] Gellatly RM, Leet A, Brown KE. Fondaparinux: an effective bridging strategy in heparin-induced thrombocytopenia and mechanical circulatory support. *J Heart Lung Transplant* 2014;33:118.
- [76] O'Donnell MJ, Kearon C, Johnson J, Robinson M, Zondag M, Turpie I *et al.* Brief communication: preoperative anticoagulant activity after bridging low-molecular-weight heparin for temporary interruption of warfarin. *Ann Intern Med* 2007;146:184-7.
- [77] Kozek-Langenecker SA, Afshari A, Albaladejo P, Santullano CA, De Robertis E, Filipescu DC *et al.* Management of severe perioperative bleeding: guidelines from the European Society of Anaesthesiology. *Eur J Anaesthesiol* 2013;30:270-382.
- [78] Pernod G, Albaladejo P, Godier A, Samama CM, Susen S, Gruel Y *et al.* Management of major bleeding complications and emergency surgery in patients on long-term treatment with direct oral anticoagulants, thrombin or factor-Xa inhibitors: proposals of the working group on perioperative haemostasis (GIHP)—March 2013. *Arch Cardiovasc Dis* 2013;106:382-93.
- [79] Levy JH, Spyropoulos AC, Samama CM, Douketis J. Direct oral anticoagulants: new drugs and new concepts. *JACC Cardiovasc Interv* 2014;7:1333-51.
- [80] Dickneite G, Hoffman M. Reversing the new oral anticoagulants with prothrombin complex concentrates (PCCs): what is the evidence? *Thromb Haemost* 2013;111:189-98.
- [81] Pollack CV Jr, Reilly PA, Eikelboom J, Glund S, Verhamme P, Bernstein RA *et al.* Idarucizumab for dabigatran reversal. *N Engl J Med* 2015;373:511-20.
- [82] Connolly SJ, Milling TJ Jr, Eikelboom JW, Gibson CM, Curnutte JT, Gold A *et al.* Andexanet alfa for acute major bleeding associated with factor Xa inhibitors. *N Engl J Med* 2016;375:1131-41.
- [83] Siegal DM, Curnutte JT, Connolly SJ, Lu G, Conley PB, Wiens BL *et al.* Andexanet alfa for the reversal of factor Xa inhibitor activity. *N Engl J Med* 2015;373:2413-24.
- [84] Spyropoulos AC, Turpie AG, Dunn AS, Kaatz S, Douketis J, Jacobson A *et al.* Perioperative bridging therapy with unfractionated heparin or low-molecular-weight heparin in patients with mechanical prosthetic heart valves on long-term oral anticoagulants (from the REGIMEN Registry). *Am J Cardiol* 2008;102:883-9.
- [85] Douketis JD, Johnson JA, Turpie AG. Low-molecular-weight heparin as bridging anticoagulation during interruption of warfarin: assessment of a standardized periprocedural anticoagulation regimen. *Arch Intern Med* 2004;164:1319-26.
- [86] Spyropoulos AC, Turpie AG, Dunn AS, Spandorfer J, Douketis J, Jacobson A *et al.* Clinical outcomes with unfractionated heparin or low-molecular-weight heparin as bridging therapy in patients on long-term oral anticoagulants: the REGIMEN registry. *J Thromb Haemost* 2006;4:1246-52.
- [87] Kovacs MJ, Kearon C, Rodger M, Anderson DR, Turpie AG, Bates SM *et al.* Single-arm study of bridging therapy with low-molecular-weight heparin for patients at risk of arterial embolism who require temporary interruption of warfarin. *Circulation* 2004;110:1658-63.
- [88] Dentali F, Douketis JD, Lim W, Crowther M. Combined aspirin-oral anticoagulant therapy compared with oral anticoagulant therapy alone among patients at risk for cardiovascular disease: a meta-analysis of randomized trials. *Arch Intern Med* 2007;167:117-24.



- [89] Cannegieter SC, Rosendaal FR, Briet E. Thromboembolic and bleeding complications in patients with mechanical heart valve prostheses. *Circulation* 1994;89:635-41.
- [90] Mok CK, Boey J, Wang R, Chan TK, Cheung KL, Lee PK *et al*. Warfarin versus dipyridamol-aspirin and pentoxifylline-aspirin for the prevention of prosthetic heart valve thromboembolism: a prospective randomized clinical trial. *Circulation* 1985;72:1059-63.
- [91] Vahanian A, Alfieri O, Andreotti F, Antunes MJ, Baron-Esquivias G, Baumgartner H *et al*. Guidelines on the management of valvular heart disease (version 2012): the Joint Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). *Eur J Cardiothorac Surg* 2012;42:S1-44.
- [92] Ferreira I, Dos L, Tornos P, Nicolau I, Permanyer-Miranda G, Soler-Soler J. Experience with enoxaparin in patients with mechanical heart valves who must withhold acenocumarol. *Heart* 2003;89:527-30.
- [93] Meurin P, Tabet JY, Weber H, Renaud N, Ben Driss A. Low-molecular-weight heparin as a bridging anticoagulant early after mechanical heart valve replacement. *Circulation* 2006;113:564-9.
- [94] Jung B, Rodes-Cabau J. The optimal management of anti-thrombotic therapy after valve replacement: certainties and uncertainties. *Eur Heart J* 2014;35:2942-9.
- [95] Grzymala-Lubanski B, Svensson PJ, Renlund H, Jeppsson A, Sjalander A. Warfarin treatment quality and prognosis in patients with mechanical heart valve prosthesis. *Heart* 2017;103:198-203.
- [96] Heneghan C, Ward A, Perera R, Bankhead C, Fuller A, Stevens R *et al*. Self-monitoring of oral anticoagulation: systematic review and meta-analysis of individual patient data. *Lancet* 2012;379:322-34.
- [97] Heneghan CJ, Garcia-Alamino JM, Spencer EA, Ward AM, Perera R, Bankhead C *et al*. Self-monitoring and self-management of oral anticoagulation. *Cochrane Database Syst Rev* 2016;7:CD003839.
- [98] Head SJ, Celik M, Kappetein AP. Mechanical versus bioprosthetic aortic valve replacement. *Eur Heart J* 2017; doi:10.1093/eurheartj/ehx141.
- [99] Eikelboom JW, Connolly SJ, Brueckmann M, Granger CB, Kappetein AP, Mack MJ *et al*. Dabigatran versus warfarin in patients with mechanical heart valves. *N Engl J Med* 2013;369:1206-14.
- [100] Hansen ML, Sorensen R, Clausen MT, Fog-Petersen ML, Raunso J, Gadsboll N *et al*. Risk of bleeding with single, dual, or triple therapy with warfarin, aspirin, and clopidogrel in patients with atrial fibrillation. *Arch Intern Med* 2010;170:1433-41.
- [101] Brennan JM, Edwards FH, Zhao Y, O'Brien S, Booth ME, Dokholyan RS *et al*. Early anticoagulation of bioprosthetic aortic valves in older patients: results from the Society of Thoracic Surgeons Adult Cardiac Surgery National Database. *J Am Coll Cardiol* 2012;60:971-7.
- [102] Merie C, Kober L, Skov Olsen P, Andersson C, Gislason G, Skov Jensen J *et al*. Association of warfarin therapy duration after bioprosthetic aortic valve replacement with risk of mortality, thromboembolic complications, and bleeding. *JAMA* 2012;308:2118-25.
- [103] Rafiq S, Steinbrüchel DA, Lilleør NB, Möller CH, Lund JT, Thiis JJ *et al*. Antithrombotic therapy after bioprosthetic aortic valve implantation: warfarin versus aspirin, a randomized controlled trial. *Thromb Res* 2017;150:104-10.
- [104] Nombela-Franco L, Webb JG, de Jaegere PP, Toggweiler S, Nuis RJ, Dager AE *et al*. Timing, predictive factors, and prognostic value of cerebrovascular events in a large cohort of patients undergoing transcatheter aortic valve implantation. *Circulation* 2012;126:3041-53.
- [105] Makkar RR, Fontana G, Jilaihawi H, Chakravarty T, Kofoed KF, de Backer O *et al*. Possible subclinical leaflet thrombosis in bioprosthetic aortic valves. *N Engl J Med* 2015;373:2015-24.
- [106] Abdul-Jawad Altisent O, Durand E, Munoz-Garcia AJ, Nombela-Franco L, Cheema A, Kefer J *et al*. Warfarin and antiplatelet therapy versus warfarin alone for treating patients with atrial fibrillation undergoing transcatheter aortic valve replacement. *JACC Cardiovasc Interv* 2016;9:1706-17.
- [107] Steinberg BA, Zhao Y, He X, Hernandez AF, Fullerton DA, Thomas KL *et al*. Management of postoperative atrial fibrillation and subsequent outcomes in contemporary patients undergoing cardiac surgery: insights from the Society of Thoracic Surgeons CAPS-Care Atrial Fibrillation Registry. *Clin Cardiol* 2014;37:7-13.
- [108] Mariscalco G, Klersy C, Zanobini M, Banach M, Ferrarese S, Borsani P *et al*. Atrial fibrillation after isolated coronary surgery affects late survival. *Circulation* 2008;118:1612-8.
- [109] Ahlsson A, Fengsrud E, Bodin L, Englund A. Postoperative atrial fibrillation in patients undergoing aortocoronary bypass surgery carries an eightfold risk of future atrial fibrillation and a doubled cardiovascular mortality. *Eur J Cardiothorac Surg* 2010;37:1353-9.
- [110] Dunning J, Treasure T, Versteegh M, Nashef SA, Audit E, Guidelines C. Guidelines on the prevention and management of de novo atrial fibrillation after cardiac and thoracic surgery. *Eur J Cardiothorac Surg* 2006;30:852-72.
- [111] Arsenault KA, Yusuf AM, Crystal E, Healey JS, Morillo CA, Nair GM *et al*. Interventions for preventing post-operative atrial fibrillation in patients undergoing heart surgery. *Cochrane Database Syst Rev* 2013;1:CD003611.
- [112] Sear JW, Foex P. Recommendations on perioperative beta-blockers: differing guidelines: so what should the clinician do? *Br J Anaesth* 2010;104:273-5.
- [113] Chatterjee S, Sardar P, Mukherjee D, Lichstein E, Aikat S. Timing and route of amiodarone for prevention of postoperative atrial fibrillation after cardiac surgery: a network regression meta-analysis. *Pacing Clin Electrophysiol* 2013;36:1017-23.
- [114] Heidarsdottir R, Arnar DO, Skuladottir GV, Torfason B, Edvardsson V, Gottskalksson G *et al*. Does treatment with n-3 polyunsaturated fatty acids prevent atrial fibrillation after open heart surgery? *Eurpace* 2010;12:356-63.
- [115] Calo L, Bianconi L, Colivicchi F, Lamberti F, Loricchio ML, de Ruvo E *et al*. N-3 Fatty acids for the prevention of atrial fibrillation after coronary artery bypass surgery: a randomized, controlled trial. *J Am Coll Cardiol* 2005;45:1723-8.
- [116] Miller S, Crystal E, Garfinkle M, Lau C, Lashevsky I, Connolly SJ. Effects of magnesium on atrial fibrillation after cardiac surgery: a meta-analysis. *Heart* 2005;91:618-23.
- [117] Heldal M, Atar D. Pharmacological conversion of recent-onset atrial fibrillation: a systematic review. *Scand Cardiovasc J Suppl* 2013;47:2-10.
- [118] Kowey PR, Dorian P, Mitchell LB, Pratt CM, Roy D, Schwartz PJ *et al*. Vernakalant hydrochloride for the rapid conversion of atrial fibrillation after cardiac surgery: a randomized, double-blind, placebo-controlled trial. *Circ Arrhythm Electrophysiol* 2009;2:652-9.
- [119] Gillinov AM, Bagiella E, Moskowitz AJ, Raiten JM, Groh MA, Bowdish ME *et al*. Rate control versus rhythm control for atrial fibrillation after cardiac surgery. *N Engl J Med* 2016;374:1911-21.
- [120] Vamos M, Erath JW, Hohnloser SH. Digoxin-associated mortality: a systematic review and meta-analysis of the literature. *Eur Heart J* 2015;36:1831-8.
- [121] Gialdini G, Nearing K, Bhavne PD, Bonuccelli U, Iadecola C, Healey JS *et al*. Perioperative atrial fibrillation and the long-term risk of ischemic stroke. *JAMA* 2014;312:616-22.
- [122] Anderson E, Dyke C, Levy JH. Anticoagulation strategies for the management of postoperative atrial fibrillation. *Clin Lab Med* 2014;34:537-61.
- [123] Giugliano RP, Ruff CT, Braunwald E, Murphy SA, Wiviott SD, Halperin JL *et al*. Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2013;369:2093-104.
- [124] Seeger J, Gonska B, Rodewald C, Rottbauer W, Wöhrle J. Apixaban in patients with atrial fibrillation after transfemoral aortic valve replacement. *JACC Cardiovasc Interv* 2017;10:66-74.
- [125] Blessberger H, Kammler J, Domanovits H, Schlager O, Wildner B, Azar D *et al*. Perioperative beta-blockers for preventing surgery-related mortality and morbidity. *Cochrane Database Syst Rev* 2014;9:CD004476.
- [126] Brinkman W, Herbert MA, O'Brien S, Filardo G, Prince S, Dewey T *et al*. Preoperative beta-blocker use in coronary artery bypass grafting surgery: national database analysis. *JAMA Intern Med* 2014;174:1320-7.
- [127] Connolly SJ, Cybulsky I, Lamy A, Roberts RS, O'Brien B, Carroll S *et al*. Double-blind, placebo-controlled, randomized trial of prophylactic metoprolol for reduction of hospital length of stay after heart surgery: the beta-Blocker Length Of Stay (BLOS) study. *Am Heart J* 2003;145:226-32.
- [128] White CM, Caron MF, Kalus JS, Rose H, Song J, Reddy P *et al*. Intravenous plus oral amiodarone, atrial septal pacing, or both strategies to prevent post-cardiothoracic surgery atrial fibrillation: the Atrial Fibrillation Suppression Trial II (AFIST II). *Circulation* 2003;108:1200-6.
- [129] Mitchell LB, Exner DV, Wyse DG, Connolly CJ, Prystai GD, Bayes AJ *et al*. Prophylactic oral amiodarone for the prevention of arrhythmias that begin early after revascularization, valve replacement, or repair: PAPA-BEAR: a randomized controlled trial. *JAMA* 2005;294:3093-100.
- [130] Lee JK, Klein GJ, Krahn AD, Yee R, Zarnke K, Simpson C *et al*. Rate-control versus conversion strategy in postoperative atrial fibrillation: trial design and pilot study results. *Card Electrophysiol Rev* 2003;7:178-84.



- [131] Hagens VE, Van Gelder IC, Crijns HJ. The RACE study in perspective of randomized studies on management of persistent atrial fibrillation. *Card Electrophysiol Rev* 2003;7:118-21.
- [132] January CT, Wann LS, Alpert JS, Calkins H, Cigarroa JE, Cleveland JC *et al.* 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: executive summary. A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. *Circulation* 2014;130:2071-104.
- [133] Al-Khatib SM, Hafley G, Harrington RA, Mack MJ, Ferguson TB, Peterson ED *et al.* Patterns of management of atrial fibrillation complicating coronary artery bypass grafting: results from the PROject of Ex-vivo Vein graft ENgineering via Transfection IV (PREVENT-IV) Trial. *Am Heart J* 2009;158:792-8.
- [134] Mason PK, Lake DE, DiMarco JP, Ferguson JD, Mangrum JM, Bilchick K *et al.* Impact of the CHA2DS2-VASc score on anticoagulation recommendations for atrial fibrillation. *Am J Med* 2012;125:603.e1-6.
- [135] Lewis EJ, Hunsicker LG, Bain RP, Rohde RD. The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. The Collaborative Study Group. *N Engl J Med* 1993;329:1456-62.
- [136] Bhatia M, Arora H, Kumar PA. Pro: ACE inhibitors should be continued perioperatively and prior to cardiovascular operations. *J Cardiothorac Vasc Anesth* 2016;30:816-9.
- [137] Disque A, Neelankavil J. Con: ACE inhibitors should be stopped prior to cardiovascular surgery. *J Cardiothorac Vasc Anesth* 2016;30:820-2.
- [138] Mangieri A. Renin-angiotensin system blockers in cardiac surgery. *J Crit Care* 2015;30:613-8.
- [139] Zou Z, Yuan HB, Yang B, Xu F, Chen XY, Liu GJ *et al.* Perioperative angiotensin-converting enzyme inhibitors or angiotensin II type 1 receptor blockers for preventing mortality and morbidity in adults. *Cochrane Database Syst Rev* 2016;1:CD009210.
- [140] Bertrand M, Godet G, Meerschaert K, Brun L, Salcedo E, Coriat P. Should the angiotensin II antagonists be discontinued before surgery? *Anesth Analg* 2001;92:26-30.
- [141] Rouleau JL, Warnica WJ, Baillet R, Block PJ, Chocron S, Johnstone D *et al.* Effects of angiotensin-converting enzyme inhibition in low-risk patients early after coronary artery bypass surgery. *Circulation* 2008;117:24-31.
- [142] Zhang Y, Ma L. Effect of preoperative angiotensin-converting enzyme inhibitor on the outcome of coronary artery bypass graft surgery. *Eur J Cardiothorac Surg* 2015;47:788-95.
- [143] Argenziano M, Chen JM, Choudhri AF, Cullinane S, Garfein E, Weinberg AD *et al.* Management of vasodilatory shock after cardiac surgery: identification of predisposing factors and use of a novel pressor agent. *J Thorac Cardiovasc Surg* 1998;116:973-80.
- [144] Carrel T, Englberger L, Mohacsi P, Neidhart P, Schmidli J. Low systemic vascular resistance after cardiopulmonary bypass: incidence, etiology, and clinical importance. *J Card Surg* 2000;15:347-53.
- [145] James PA, Oparil S, Carter BL, Cushman WC, Dennison-Himmelfarb C, Handler J *et al.* 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). *JAMA* 2014;311:507-20.
- [146] Parati G, Stergiou G, O'Brien E, Asmar R, Beilin L, Bilo G *et al.* European Society of Hypertension practice guidelines for ambulatory blood pressure monitoring. *J Hypertens* 2014;32:1359-66.
- [147] Crystal E, Garfinkle MS, Connolly SS, Ginger TT, Yusuf SS. Interventions for preventing post-operative atrial fibrillation in patients undergoing heart surgery. *Cochrane Database Syst Rev* 2004;4:CD003611.
- [148] Pfeffer MA, McMurray JJ, Velazquez EJ, Rouleau JL, Kober L, Maggioni AP *et al.* Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both. *N Engl J Med* 2003;349:1893-906.
- [149] McMurray JJ, Ostergren J, Swedberg K, Granger CB, Held P, Michelson EL *et al.* Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function taking angiotensin-converting-enzyme inhibitors: the CHARM-Added trial. *Lancet* 2003;362:767-71.
- [150] Pfeffer MA, Swedberg K, Granger CB, Held P, McMurray JJ, Michelson EL *et al.* Effects of candesartan on mortality and morbidity in patients with chronic heart failure: the CHARM-Overall programme. *Lancet* 2003;362:759-66.
- [151] Oosterga M, Voors AA, Pinto YM, Buikema H, Grandjean JG, Kingma JH *et al.* Effects of quinapril on clinical outcome after coronary artery bypass grafting (The QUO VADIS Study). *QUINapril on Vascular Ace and Determinants of Ischemia*. *Am J Cardiol* 2001;87:542-6.
- [152] Arora P, Rajagopalam S, Ranjan R, Kolli H, Singh M, Venuto R *et al.* Preoperative use of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers is associated with increased risk for acute kidney injury after cardiovascular surgery. *Clin J Am Soc Nephrol* 2008;3:1266-73.
- [153] Savarese G, Costanzo P, Cleland JGF, Vassallo E, Ruggiero D, Rosano G *et al.* A meta-analysis reporting effects of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers in patients without heart failure. *J Am Coll Cardiol* 2013;61:131-42.
- [154] Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A *et al.* The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. *N Engl J Med* 1999;341:709-17.
- [155] Zannad F, McMurray JJ, Krum H, van Veldhuisen DJ, Swedberg K, Shi H *et al.* Eplerenone in patients with systolic heart failure and mild symptoms. *N Engl J Med* 2011;364:11-21.
- [156] Jneid H, Moukarbel GV, Dawson B, Hajjar RJ, Francis GS. Combining neuroendocrine inhibitors in heart failure: reflections on safety and efficacy. *Am J Med* 2007;120:1090.e1-8.
- [157] Pitt B, Pedro Ferreira J, Zannad F. Mineralocorticoid receptor antagonists in patients with heart failure: current experience and future perspectives. *Eur Heart J Cardiovasc Pharmacother* 2017;3:48-57.
- [158] SOLVD Investigators, Yusuf S, Pitt B, Davis CE, Hood WB Jr, Cohn JN. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. *N Engl J Med* 1991;325:293-302.
- [159] Pfeffer MA, Braunwald E, Moye LA, Basta L, Brown EJ Jr, Cuddy TE *et al.* Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. Results of the survival and ventricular enlargement trial. *N Engl J Med* 1992;327:669-77.
- [160] CONSENSUS Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). The CONSENSUS Trial Study Group. *N Engl J Med* 1987;316:1429-35.
- [161] McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR *et al.* Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med* 2014;371:993-1004.
- [162] Chan AY, McAlister FA, Norris CM, Johnstone D, Bakal JA, Ross DB. Effect of beta-blocker use on outcomes after discharge in patients who underwent cardiac surgery. *J Thorac Cardiovasc Surg* 2010;140:182-7, 7.e1.
- [163] ten Broecke PW, De Hert SG, Mertens E, Adriaensen HF. Effect of preoperative beta-blockade on perioperative mortality in coronary surgery. *Br J Anaesth* 2003;90:27-31.
- [164] Daumerie G, Fleisher LA. Perioperative beta-blocker and statin therapy. *Curr Opin Anaesthesiol* 2008;21:60-5.
- [165] Blessberger H, Kammler J, Steinwender C. Perioperative use of beta-blockers in cardiac and noncardiac surgery. *JAMA* 2015;313:2070-1.
- [166] Carl M, Alms A, Braun J, Dongas A, Erb J, Goetz A *et al.* S3 guidelines for intensive care in cardiac surgery patients: hemodynamic monitoring and cardiocirculatory system. *Ger Med Sci* 2010;8:Doc12.
- [167] Sjoland H, Caidahl K, Lurje L, Hjalmarson A, Herlitz J. Metoprolol treatment for two years after coronary bypass grafting: effects on exercise capacity and signs of myocardial ischaemia. *Br Heart J* 1995;74:235-41.
- [168] Puymirat E, Riant E, Aissoui N, Soria A, Ducrocq G, Coste P *et al.*  $\beta$  blockers and mortality after myocardial infarction in patients without heart failure: multicentre prospective cohort study. *Br Med J* 2016;354:i4801.
- [169] Booij HG, Damman K, Warnica JW, Rouleau JL, van Gilst WH, Westenbrink BD.  $\beta$ -blocker therapy is not associated with reductions in angina or cardiovascular events after coronary artery bypass graft surgery: insights from the IMAGINE Trial. *Cardiovasc Drugs Ther* 2015;29:277-85.
- [170] Lin T, Hasaniya NW, Krider S, Razzouk A, Wang N, Chiong JR. Mortality reduction with beta-blockers in ischemic cardiomyopathy patients undergoing coronary artery bypass grafting. *Congest Heart Fail* 2010;16:170-4.
- [171] The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. *Lancet* 1999;353:9-13.
- [172] Brophy JM, Joseph L, Rouleau JL. Beta-blockers in congestive heart failure. A Bayesian meta-analysis. *Ann Intern Med* 2001;134:550-60.

- [173] Dargie HJ. Effect of carvedilol on outcome after myocardial infarction in patients with left-ventricular dysfunction: the CAPRICORN randomised trial. *Lancet* 2001;357:1385-90.
- [174] Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in-Congestive Heart Failure (MERIT-HF). *Lancet* 1999;353:2001-7.
- [175] Chatterjee S, Biondi-Zoccai G, Abbate A, D'Ascenzo F, Castagno D, Van Tassel B *et al.* Benefits of  $\beta$  blockers in patients with heart failure and reduced ejection fraction: network meta-analysis. *Br Med J* 2013;346:f55.
- [176] Ferguson TB Jr, Coombs LP, Peterson ED; Society of Thoracic Surgeons National Adult Cardiac Surgery Database. Preoperative beta-blocker use and mortality and morbidity following CABG surgery in North America. *JAMA* 2002;287:2221-7.
- [177] Mannacio VA, Iorio D, De Amicis V, Di Lello F, Musumeci F. Effect of rosuvastatin pretreatment on myocardial damage after coronary surgery: a randomized trial. *J Thorac Cardiovasc Surg* 2008;136:1541-8.
- [178] Kuhn EW, Slottosch I, Wahlers T, Liakopoulos OJ. Preoperative statin therapy for patients undergoing cardiac surgery. *Cochrane Database Syst Rev* 2015;8:CD008493.
- [179] Zheng Z, Jayaram R, Jiang L, Emberson J, Zhao Y, Li Q *et al.* Perioperative rosuvastatin in cardiac surgery. *N Engl J Med* 2016;374:1744-53.
- [180] Billings FT, Hendricks PA, Schildcrout JS, Shi Y, Petracek MR, Byrne JG *et al.* High-dose perioperative atorvastatin and acute kidney injury following cardiac surgery. A randomized clinical trial. *JAMA* 2016;315:877-88.
- [181] Bellomo R. Perioperative statins in cardiac surgery and acute kidney injury. *JAMA* 2016;315:873-4.
- [182] Shah SJ, Waters DD, Barter P, Kastelein JJ, Shepherd J, Wenger NK *et al.* Intensive lipid-lowering with atorvastatin for secondary prevention in patients after coronary artery bypass surgery. *J Am Coll Cardiol* 2008;51:1938-43.
- [183] Stroes ES, Thompson PD, Corsini A, Vladutiu GD, Raal FJ, Ray KK *et al.* Statin-associated muscle symptoms: impact on statin therapy-European Atherosclerosis Society Consensus Panel Statement on Assessment, Aetiology and Management. *Eur Heart J* 2015;36:1012-22.
- [184] Sabatine MS, Giugliano RP, Keech AC, Honarpour N, Wiviott SD, Murphy SA *et al.* Evolocumab and clinical outcomes in patients with cardiovascular disease. *N Engl J Med* 2017;376:1713-22.
- [185] Robinson JG, Farnier M, Krempf M, Bergeron J, Luc G, Aversa M *et al.* Efficacy and safety of alirocumab in reducing lipids and cardiovascular events. *N Engl J Med* 2015;372:1489-99.
- [186] Lipinski MJ, Benedetto U, Escarcega RO, Biondi-Zoccai G, Lhermusier T, Baker NC *et al.* The impact of proprotein convertase subtilisin-kexin type 9 serine protease inhibitors on lipid levels and outcomes in patients with primary hypercholesterolaemia: a network meta-analysis. *Eur Heart J* 2016;37:536-45.
- [187] Jun M, Foote C, Lv J, Neal B, Patel A, Nicholls SJ *et al.* Effects of fibrates on cardiovascular outcomes: a systematic review and meta-analysis. *Lancet* 2010;375:1875-84.
- [188] ACCORD Study Group, Ginsberg HN, Elam MB, Lovato LC, Crouse JR 3rd, Leiter LA, Linz P *et al.* Effects of combination lipid therapy in type 2 diabetes mellitus. *N Engl J Med* 2010;362:1563-74.
- [189] Cholesterol Treatment Trialists' Collaboration, Fulcher J, O'Connell R, Voysey M, Emberson J, Blackwell L *et al.* Efficacy and safety of LDL-lowering therapy among men and women: meta-analysis of individual data from 174,000 participants in 27 randomised trials. *Lancet* 2015;385:1397-405.
- [190] Sattar N, Preiss D, Robinson JG, Djedjos CS, Elliott M, Somaratne R *et al.* Lipid-lowering efficacy of the PCSK9 inhibitor evolocumab (AMG 145) in patients with type 2 diabetes: a meta-analysis of individual patient data. *Lancet Diabetes Endocrinol* 2016;4:403-10.
- [191] Navarese EP, Kolodziejczak M, Schulze V, Gurbel PA, Tantry U, Lin Y *et al.* Effects of proprotein convertase subtilisin/kexin type 9 antibodies in adults with hypercholesterolemia: a systematic review and meta-analysis. *Ann Intern Med* 2015;163:40-51.
- [192] Filsoufi F, Rahmani PB, Castillo JG, Scurlock C, Legnani PE, Adams DH. Predictors and outcome of gastrointestinal complications in patients undergoing cardiac surgery. *Ann Surg* 2007;246:323-9.
- [193] van der Voort PH, Zandstra DF. Pathogenesis, risk factors, and incidence of upper gastrointestinal bleeding after cardiac surgery: is specific prophylaxis in routine bypass procedures needed? *J Cardiothorac Vasc Anesth* 2000;14:293-9.
- [194] Shin JS, Abah U. Is routine stress ulcer prophylaxis of benefit for patients undergoing cardiac surgery? *Interact CardioVasc Thorac Surg* 2012;14:622-8.
- [195] Hata M, Shiono M, Sekino H, Furukawa H, Sezai A, Iida M *et al.* Prospective randomized trial for optimal prophylactic treatment of the upper gastrointestinal complications after open heart surgery. *Circ J* 2005;69:331-4.
- [196] Eom CS, Jeon CY, Lim JW, Cho EG, Park SM, Lee KS. Use of acid-suppressive drugs and risk of pneumonia: a systematic review and meta-analysis. *CMAJ* 2011;183:310-9.
- [197] Othman F, Crooks CJ, Card TR. Community acquired pneumonia incidence before and after proton pump inhibitor prescription: population based study. *Br Med J* 2016;355:i5813.
- [198] Patel AJ, Som R. What is the optimum prophylaxis against gastrointestinal haemorrhage for patients undergoing adult cardiac surgery: histamine receptor antagonists, or proton-pump inhibitors? *Interact CardioVasc Thorac Surg* 2013;16:356-60.
- [199] Day JR, Taylor KM. The systemic inflammatory response syndrome and cardiopulmonary bypass. *Int J Surg* 2005;3:129-40.
- [200] Whitlock RP, Chan S, Devereaux PJ, Sun J, Rubens FD, Thorlund K. Clinical benefit of steroid use in patients undergoing cardiopulmonary bypass: a meta-analysis of randomized trials. *Eur Heart J* 2008;29:2592-600.
- [201] Whitlock RP, Devereaux PJ, Teoh KH, Lamy A, Vincent J, Pogue J *et al.* Methylprednisolone in patients undergoing cardiopulmonary bypass (SIRS): a randomised, double-blind, placebo-controlled trial. *Lancet* 2015;386:1243-53.
- [202] Dieleman JM, Nierich AP, Rosseel PM, van der Maaten JM, Hofland J, Diephuis JC *et al.* Intraoperative high-dose dexamethasone for cardiac surgery: a randomized controlled trial. *JAMA* 2012;308:1761-7.
- [203] Dieleman JM, Van Dijk D. Corticosteroids for cardiac surgery: a summary of two large randomised trials. *Neth J Crit Care* 2016;24:6-10.
- [204] Liu MM, Reidy AB, Saatee S, Collard CD. Perioperative steroid management: approaches based on current evidence. *Anesthesiology* 2017;127:166-72.
- [205] Fowler VG, O'Brien SM, Muhlbaier LH, Corey GR, Ferguson TB, Peterson ED. Clinical predictors of major infections after cardiac surgery. *Circulation* 2005;112(9 suppl):1358-65.
- [206] Gelijns AC, Moskowitz AJ, Acker MA, Argenziano M, Geller NL, Puskas JD *et al.* Management practices and major infections after cardiac surgery. *J Am Coll Cardiol* 2014;64:372-81.
- [207] Kowalewski M, Pawluszak W, Zaborowska K, Navarese EP, Szwed KA, Kowalkowska ME *et al.* Gentamicin-collagen sponge reduces the risk of sternal wound infections after heart surgery: meta-analysis. *J Thorac Cardiovasc Surg* 2015;149:1631-40.e1-6.
- [208] Zelenitsky SA, Ariano RE, Harding GK, Silverman RE. Antibiotic pharmacodynamics in surgical prophylaxis: an association between intraoperative antibiotic concentrations and efficacy. *Antimicrob Agents Chemother* 2002;46:3026-30.
- [209] Forse RA, Karam B, MacLean LD, Christou NV. Antibiotic prophylaxis for surgery in morbidly obese patients. *Surgery* 1989;106:750-6; discussion 6-7.
- [210] Falagas ME, Karageorgopoulos DE. Adjustment of dosing of antimicrobial agents for bodyweight in adults. *Lancet* 2010;375:248-51.
- [211] Pai MP, Bearden DT. Antimicrobial dosing considerations in obese adult patients. *Pharmacotherapy* 2007;27:1081-91.
- [212] Tamayo E, Gualis J, Florez S, Castrodeza J, Eiros Bouza JM, Alvarez FJ. Comparative study of single-dose and 24-hour multiple-dose antibiotic prophylaxis for cardiac surgery. *J Thorac Cardiovasc Surg* 2008;136:1522-7.
- [213] Mertz D, Johnstone J, Loeb M. Does duration of perioperative antibiotic prophylaxis matter in cardiac surgery? A systematic review and meta-analysis. *Ann Surg* 2011;254:48-54.
- [214] Harbarth S, Samore MH, Lichtenberg D, Carmeli Y. Prolonged antibiotic prophylaxis after cardiovascular surgery and its effect on surgical site infections and antimicrobial resistance. *Circulation* 2000;101:2916-21.
- [215] Bratzler DW, Houck PM, Richards C, Steele L, Dellinger EP, Fry DE *et al.* Use of antimicrobial prophylaxis for major surgery: baseline results from the National Surgical Infection Prevention Project. *Arch Surg* 2005;140:174-82.
- [216] Sandoe JA, Kumar B, Stoddart B, Milton R, Dave J, Nair UR *et al.* Effect of extended perioperative antibiotic prophylaxis on intravascular catheter colonization and infection in cardiothoracic surgery patients. *J Antimicrob Chemother* 2003;52:877-9.
- [217] Niederhauser U, Vogt M, Vogt P, Genoni M, Kunzli A, Turina M. Cardiac surgery in a high-risk group of patients: is prolonged postoperative antibiotic prophylaxis effective? *J Thorac Cardiovasc Surg* 1997;114:162-8.

- [218] Conte JE Jr, Cohen SN, Roe BB, Elashoff RM. Antibiotic prophylaxis and cardiac surgery. A prospective double-blind comparison of single-dose versus multiple-dose regimens. *Ann Intern Med* 1972;76:943-9.
- [219] Trent Magruder J, Grimm JC, Dungan SP, Shah AS, Crow JR, Shoulders BR *et al*. Continuous intraoperative cefazolin infusion may reduce surgical site infections during cardiac surgical procedures: a propensity-matched analysis. *J Cardiothorac Vasc Anesth* 2015;29:1582-7.
- [220] Bratzler DW, Houck PM. Antimicrobial prophylaxis for surgery: an advisory statement from the National Surgical Infection Prevention Project. *Clin Infect Dis* 2004;38:1706-15.
- [221] Scher KS. Studies on the duration of antibiotic administration for surgical prophylaxis. *Am Surg* 1997;63:59-62.
- [222] Swoboda SM, Merz C, Kostuik J, Trentler B, Lipsett PA. Does intraoperative blood loss affect antibiotic serum and tissue concentrations? *Arch Surg* 1996;131:1165-71; discussion 71-2.
- [223] Lanckohr C, Horn D, Voeller S, Hempel G, Fobker M, Welp H *et al*. Pharmacokinetic characteristics and microbiologic appropriateness of cefazolin for perioperative antibiotic prophylaxis in elective cardiac surgery. *J Thorac Cardiovasc Surg* 2016;152:603-10.
- [224] Gardlund B, Bitkover CY, Vaage J. Postoperative mediastinitis in cardiac surgery—microbiology and pathogenesis. *Eur J Cardiothorac Surg* 2002;21:825-30.
- [225] Gudbjartsson T, Jeppsson A, Sjogren J, Steingrimsson S, Geirsson A, Friberg O *et al*. Sternal wound infections following open heart surgery—a review. *Scand Cardiovasc J* 2016;50:341-8.
- [226] Allegranzi B, Bischoff P, de Jonge S, Kubilay NZ, Zayed B, Gomes SM *et al*. New WHO recommendations on preoperative measures for surgical site infection prevention: an evidence-based global perspective. *Lancet Infect Dis* 2016;16:e276-87.
- [227] Bode LGM, Kluytmans JAJW, Wertheim HFL, Bogaers D, Vandenbroucke-Grauls CMJE, Roosendaal R *et al*. Preventing surgical-site infections in nasal carriers of *Staphylococcus aureus*. *N Engl J Med* 2010;362:9-17.
- [228] Sisto T, Laurikka J, Tarkka MR. Ceftriaxone vs cefuroxime for infection prophylaxis in coronary bypass surgery. *Scand J Thorac Cardiovasc Surg* 1994;28:143-8.
- [229] Nooyen SM, Overbeek BP, Brutel de la Riviere A, Storm AJ, Langemeyer JJ. Prospective randomised comparison of single-dose versus multiple-dose cefuroxime for prophylaxis in coronary artery bypass grafting. *Eur J Clin Microbiol Infect Dis* 1994;13:1033-7.
- [230] Kriaras I, Michalopoulos A, Turina M, Geroulanos S. Evolution of antimicrobial prophylaxis in cardiovascular surgery. *Eur J Cardiothorac Surg* 2000;18:440-6.
- [231] Lador A, Nasir H, Mansur N, Sharoni E, Biderman P, Leibovici L *et al*. Antibiotic prophylaxis in cardiac surgery: systematic review and meta-analysis. *J Antimicrob Chemother* 2012;67:541-50.
- [232] Bolon MK, Morlote M, Weber SG, Koplan B, Carmeli Y, Wright SB. Glycopeptides are no more effective than beta-lactam agents for prevention of surgical site infection after cardiac surgery: a meta-analysis. *Clin Infect Dis* 2004;38:1357-63.
- [233] Cunha BA. Antibiotic selection in the penicillin-allergic patient. *Med Clin North Am* 2006;90:1257-64.
- [234] Massias L, Dubois C, de Lentdecker P, Brodaty O, Fischler M, Farinotti R. Penetration of vancomycin in uninfected sternal bone. *Antimicrob Agents Chemother* 1992;36:2539-41.
- [235] Finkelstein R, Rabino G, Mashiah T, Bar-El Y, Adler Z, Kertzman V *et al*. Vancomycin versus cefazolin prophylaxis for cardiac surgery in the setting of a high prevalence of methicillin-resistant staphylococcal infections. *J Thorac Cardiovasc Surg* 2002;123:326-32.
- [236] Blumenthal KG, Shenoy ES, Varughese CA, Hurwitz S, Hooper DC, Banerji A. Impact of a clinical guideline for prescribing antibiotics to inpatients reporting penicillin or cephalosporin allergy. *Ann Allergy Asthma Immunol* 2015;115:294-300.e2.
- [237] Macy E, Contreras R. Health care use and serious infection prevalence associated with penicillin "allergy" in hospitalized patients: a cohort study. *J Allergy Clin Immunol* 2014;133:790-6.
- [238] Frigas E, Park MA, Narr BJ, Volcheck GW, Danielson DR, Markus PJ *et al*. Preoperative evaluation of patients with history of allergy to penicillin: comparison of 2 models of practice. *Mayo Clin Proc* 2008;83:651-62.
- [239] Anderson DJ, Podgorny K, Berríos-Torres SI, Bratzler DW, Dellinger EP, Greene L *et al*. Strategies to prevent surgical site infections in Acute Care Hospitals: 2014 update. *Infect Control Hosp Epidemiol* 2014;35:605-27.
- [240] Zangrillo A, Landoni G, Fumagalli L, Bove T, Bellotti F, Sottocorna O *et al*. Methicillin-resistant *Staphylococcus* species in a cardiac surgical intensive care unit: a 5-year experience. *J Cardiothorac Vasc Anesth* 2006;20:31-7.
- [241] Bull AL, Worth LJ, Richards MJ. Impact of vancomycin surgical antibiotic prophylaxis on the development of methicillin-sensitive *Staphylococcus aureus* surgical site infections: report from Australian Surveillance Data (VICNISS). *Ann Surg* 2012;256:1089-92.
- [242] Classen DC, Evans RS, Pestotnik SL, Horn SD, Menlove RL, Burke JP. The timing of prophylactic administration of antibiotics and the risk of surgical-wound infection. *N Engl J Med* 1992;326:281-6.
- [243] Steinberg JP, Braun BI, Hellinger WC, Kusek L, Bozakis MR, Bush AJ *et al*. Timing of antimicrobial prophylaxis and the risk of surgical site infections: results from the Trial to Reduce Antimicrobial Prophylaxis Errors. *Ann Surg* 2009;250:10-6.
- [244] van Kasteren ME, Mannien J, Ott A, Kullberg BJ, de Boer AS, Gyssens IC. Antibiotic prophylaxis and the risk of surgical site infections following total hip arthroplasty: timely administration is the most important factor. *Clin Infect Dis* 2007;44:921-7.
- [245] Weber WP, Marti WR, Zwahlen M, Misteli H, Rosenthal R, Reck S *et al*. The timing of surgical antimicrobial prophylaxis. *Ann Surg* 2008;247:918-26.
- [246] Garey KW, Dao T, Chen H, Amrutkar P, Kumar N, Reiter M *et al*. Timing of vancomycin prophylaxis for cardiac surgery patients and the risk of surgical site infections. *J Antimicrob Chemother* 2006;58:645-50.
- [247] Kreter B, Woods M. Antibiotic prophylaxis for cardiothoracic operations. Meta-analysis of thirty years of clinical trials. *J Thorac Cardiovasc Surg* 1992;104:590-9.
- [248] Vuorisalo S, Pokela R, Syrjala H. Is single-dose antibiotic prophylaxis sufficient for coronary artery bypass surgery? An analysis of peri- and postoperative serum cefuroxime and vancomycin levels. *J Hosp Infect* 1997;37:237-47.
- [249] Lin MH, Pan SC, Wang JL, Hsu RB, Lin Wu FL, Chen YC *et al*. Prospective randomized study of efficacy of 1-day versus 3-day antibiotic prophylaxis for preventing surgical site infection after coronary artery bypass graft. *J Formos Med Assoc* 2011;110:619-26.
- [250] Gupta A, Hote MP, Choudhury M, Kapil A, Bisoi AK. Comparison of 48 h and 72 h of prophylactic antibiotic therapy in adult cardiac surgery: a randomized double blind controlled trial. *J Antimicrob Chemother* 2010;65:1036-41.
- [251] Zanetti G, Giardina R, Platt R. Intraoperative redosing of cefazolin and risk for surgical site infection in cardiac surgery. *Emerg Infect Dis* 2001;7:828-31.
- [252] Krivoy N, Yanovsky B, Kophit A, Zaher A, Bar-El Y, Adler Z *et al*. Vancomycin sequestration during cardiopulmonary bypass surgery. *J Infect* 2002;45:90-5.
- [253] Fellingner EK, Leavitt BJ, Hebert JC. Serum levels of prophylactic cefazolin during cardiopulmonary bypass surgery. *Ann Thorac Surg* 2002;74:1187-90.
- [254] Mastoraki S, Michalopoulos A, Kriaras I, Geroulanos S. Cefuroxime as antibiotic prophylaxis in coronary artery bypass grafting surgery. *Interact CardioVasc Thorac Surg* 2007;6:442-6.
- [255] Sakoulas G, Moise-Broder PA, Schentag J, Forrest A, Moellering RC Jr, Eliopoulos GM. Relationship of MIC and bactericidal activity to efficacy of vancomycin for treatment of methicillin-resistant *Staphylococcus aureus* bacteremia. *J Clin Microbiol* 2004;42:2398-402.
- [256] Uhlig C, Bluth T, Schwarz K, Deckert S, Heinrich L, De Hert S *et al*. Effects of volatile anesthetics on mortality and postoperative pulmonary and other complications in patients undergoing surgery: a systematic review and meta-analysis. *Anesthesiology* 2016;124:1230-45.
- [257] Landoni G, Greco T, Biondi-Zoccai G, Nigro Neto C, Febres D, Pintaudi M *et al*. Anaesthetic drugs and survival: a Bayesian network meta-analysis of randomized trials in cardiac surgery. *Br J Anaesth* 2013;111:886-96.
- [258] Landoni G, Isella F, Greco M, Zangrillo A, Royce CF. Benefits and risks of epidural analgesia in cardiac surgery. *Br J Anaesth* 2015;115:25-32.
- [259] Bignami E, Greco T, Barile L, Silvetti S, Nicolotti D, Fochi O *et al*. The effect of isoflurane on survival and myocardial infarction: a meta-analysis of randomized controlled studies. *J Cardiothorac Vasc Anesth* 2013;27:50-8.
- [260] Bignami E, Biondi-Zoccai G, Landoni G, Fochi O, Testa V, Sheiban I *et al*. Volatile anesthetics reduce mortality in cardiac surgery. *J Cardiothorac Vasc Anesth* 2009;23:594-9.
- [261] De Hert S, Vlasselaers D, Barbe R, Ory JP, Dekegel D, Donnadonni R *et al*. A comparison of volatile and non volatile agents for cardioprotection during on-pump coronary surgery. *Anaesthesia* 2009;64:953-60.
- [262] Jakobsen CJ, Berg H, Hindsholm KB, Faddy N, Sloth E. The influence of propofol versus sevoflurane anesthesia on outcome in 10, 535 cardiac surgical procedures. *J Cardiothorac Vasc Anesth* 2007;21:664-71.



- [263] Landoni G, Biondi-Zoccai GG, Zangrillo A, Bignami E, D'Avolio S, Marchetti C *et al.* Desflurane and sevoflurane in cardiac surgery: a meta-analysis of randomized clinical trials. *J Cardiothorac Vasc Anesth* 2007;21:502-11.
- [264] Likhvantsev VV, Landoni G, Levikov DI, Grebenchikov OA, Skripkin YV, Cherpakov RA. Sevoflurane versus total intravenous anesthesia for isolated coronary artery bypass surgery with cardiopulmonary bypass: a randomized trial. *J Cardiothorac Vasc Anesth* 2016;30:1221-7.
- [265] Mazzeffi M, Khelemsky Y. Poststernotomy pain: a clinical review. *J Cardiothorac Vasc Anesth* 2011;25:1163-78.
- [266] Gelinac C. Management of pain in cardiac surgery ICU patients: have we improved over time? *Intensive Crit Care Nurs* 2007;23:298-303.
- [267] Schelling G, Richter M, Rooszendaal B, Rothenhausler HB, Krauseneck T, Stoll C *et al.* Exposure to high stress in the intensive care unit may have negative effects on health-related quality-of-life outcomes after cardiac surgery. *Crit Care Med* 2003;31:1971-80.
- [268] Barr J, Fraser GL, Puntillo K, Ely EW, Gelinac C, Dasta JF *et al.* Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. *Crit Care Med* 2013;41:263-306.
- [269] Chou R, Gordon DB, de Leon-Casasola OA, Rosenberg JM, Bickler S, Brennan T *et al.* Management of postoperative pain: a clinical practice guideline from the American Pain Society, the American Society of Regional Anesthesia and Pain Medicine, and the American Society of Anesthesiologists' Committee on Regional Anesthesia, Executive Committee, and Administrative Council. *J Pain* 2016;17:131-57.
- [270] Zangrillo A, Bignami E, Biondi-Zoccai GG, Covello RD, Monti G, D'Arpa MC *et al.* Spinal analgesia in cardiac surgery: a meta-analysis of randomized controlled trials. *J Cardiothorac Vasc Anesth* 2009;23:813-21.
- [271] Nader ND, Li CM, Dosluoglu HH, Ignatowski TA, Spengler RN. Adjuvant therapy with intrathecal clonidine improves postoperative pain in patients undergoing coronary artery bypass graft. *Clin J Pain* 2009;25:101-6.
- [272] Lena P, Balarac N, Arnulf JJ, Bigeon JY, Tapia M, Bonnet F. Fast-track coronary artery bypass grafting surgery under general anesthesia with remifentanyl and spinal analgesia with morphine and clonidine. *J Cardiothorac Vasc Anesth* 2005;19:49-53.
- [273] White PF, Rawal S, Latham P, Markowitz S, Issioui T, Chi L *et al.* Use of a continuous local anesthetic infusion for pain management after median sternotomy. *Anesthesiology* 2003;99:918-23.
- [274] McDonald SB, Jacobsohn E, Kopacz DJ, Desphande S, Helman JD, Salinas F *et al.* Parasternal block and local anesthetic infiltration with levobupivacaine after cardiac surgery with desflurane: the effect on postoperative pain, pulmonary function, and tracheal extubation times. *Anesth Analg* 2005;100:25-32.
- [275] Cook TM, Counsell D, Wildsmith JA; Royal College of Anaesthetists Third National Audit Project. Major complications of central neuraxial block: report on the Third National Audit Project of the Royal College of Anaesthetists. *Br J Anaesth* 2009;102:179-90.
- [276] Richardson L, Dunning J, Hunter S. Is intrathecal morphine of benefit to patients undergoing cardiac surgery. *Interact CardioVasc Thorac Surg* 2009;8:117-22.
- [277] Engelman E, Marsala C. Efficacy of adding clonidine to intrathecal morphine in acute postoperative pain: meta-analysis. *Br J Anaesth* 2013;110:21-7.
- [278] Yeung JH, Gates S, Naidu BV, Wilson MJ, Gao Smith F. Paravertebral block versus thoracic epidural for patients undergoing thoracotomy. *Cochrane Database Syst Rev* 2016;2:CD009121.
- [279] Canto M, Sanchez MJ, Casas MA, Bataller ML. Bilateral paravertebral blockade for conventional cardiac surgery. *Anaesthesia* 2003;58:365-70.
- [280] Nasr DA, Abdelhamid HM, Mohsen M, Aly AH. The analgesic efficacy of continuous presternal bupivacaine infusion through a single catheter after cardiac surgery. *Ann Card Anaesth* 2015;18:15-20.
- [281] Agarwal S, Nuttall GA, Johnson ME, Hanson AC, Oliver WC Jr. A prospective, randomized, blinded study of continuous ropivacaine infusion in the median sternotomy incision following cardiac surgery. *Reg Anesth Pain Med* 2013;38:145-50.
- [282] Kocabas S, Yedicocuklu D, Yuksel E, Uysallar E, Askar F. Infiltration of the sternotomy wound and the mediastinal tube sites with 0.25% levobupivacaine as adjunctive treatment for postoperative pain after cardiac surgery. *Eur J Anaesthesiol* 2008;25:842-9.
- [283] Bainbridge D, Martin JE, Cheng DC. Patient-controlled versus nurse-controlled analgesia after cardiac surgery—a meta-analysis. *Can J Anaesth* 2006;53:492-9.
- [284] Greco M, Landoni G, Biondi-Zoccai G, Cabrini L, Ruggeri L, Pasculli N *et al.* Remifentanyl in cardiac surgery: a meta-analysis of randomized controlled trials. *J Cardiothorac Vasc Anesth* 2012;26:110-6.
- [285] Alavi SM, Ghoreishi SM, Chitsazan M, Ghandi I, Fard AJ, Hosseini SS *et al.* Patient-controlled analgesia after coronary bypass: remifentanyl or sufentanil? *Asian Cardiovasc Thorac Ann* 2014;22:694-9.
- [286] Baltali S, Turkoz A, Bozdogan N, Demirturk OS, Baltali M, Turkoz R *et al.* The efficacy of intravenous patient-controlled remifentanyl versus morphine anesthesia after coronary artery surgery. *J Cardiothorac Vasc Anesth* 2009;23:170-4.
- [287] Mamoun NF, Lin P, Zimmerman NM, Mascha EJ, Mick SL, Insler SR *et al.* Intravenous acetaminophen analgesia after cardiac surgery: a randomized, blinded, controlled superiority trial. *J Thorac Cardiovasc Surg* 2016;152:881-9.e1.
- [288] Jelacic S, Bollag L, Bowdle A, Rivat C, Cain KC, Richebe P. Intravenous acetaminophen as an adjunct analgesic in cardiac surgery reduces opioid consumption but not opioid-related adverse effects: a randomized controlled trial. *J Cardiothorac Vasc Anesth* 2016;30:997-1004.
- [289] Cattabriga I, Pacini D, Lamazza G, Talarico F, Di Bartolomeo R, Grillone G *et al.* Intravenous paracetamol as adjunctive treatment for postoperative pain after cardiac surgery: a double blind randomized controlled trial. *Eur J Cardiothorac Surg* 2007;32:527-31.
- [290] Ahlers SJ, Van Gulik L, Van Dongen EP, Bruins P, Tibboel D, Knibbe CA. Aminotransferase levels in relation to short-term use of acetaminophen four grams daily in postoperative cardiothoracic patients in the intensive care unit. *Anaesth Intensive Care* 2011;39:1056-63.
- [291] Kulik A, Bykov K, Choudhry NK, Bateman BT. Non-steroidal anti-inflammatory drug administration after coronary artery bypass surgery: utilization persists despite the boxed warning. *Pharmacoevidence Drug Saf* 2015;24:647-53.
- [292] Coxib and traditional NSAID Trialists' (CNT) Collaboration, Bhala N, Emberson J, Merhi A, Abramson S, Arber N *et al.* Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: meta-analyses of individual participant data from randomised trials. *Lancet* 2013;382:769-79.
- [293] Schjerning Olsen AM, Fosbol EL, Lindhardtsen J, Folke F, Charlot M, Selmer C *et al.* Duration of treatment with nonsteroidal anti-inflammatory drugs and impact on risk of death and recurrent myocardial infarction in patients with prior myocardial infarction: a nationwide cohort study. *Circulation* 2011;123:2226-35.
- [294] Qazi SM, Sindby EJ, Norgaard MA. Ibuprofen—a safe analgesic during cardiac surgery recovery? A randomized controlled trial. *J Cardiovasc Thorac Res* 2015;7:141-8.
- [295] Rafiq S, Steinbruchel DA, Wanscher MJ, Andersen LW, Navne A, Lilleoer NB *et al.* Multimodal analgesia versus traditional opiate based analgesia after cardiac surgery, a randomized controlled trial. *J Cardiothorac Surg* 2014;9:52.
- [296] Horbach SJ, Lopes RD, da C Guaragna JC, Martini F, Mehta RH, Petracco JB *et al.* Naproxen as prophylaxis against atrial fibrillation after cardiac surgery: the NAFARM randomized trial. *Am J Med* 2011;124:1036-42.
- [297] Stepensky D, Rimon G. Competition between low-dose aspirin and other NSAIDs for COX-1 binding and its clinical consequences for the drugs' antiplatelet effects. *Expert Opin Drug Metab Toxicol* 2015;11:41-52.
- [298] Acharya M, Dunning J. Does the use of non-steroidal anti-inflammatory drugs after cardiac surgery increase the risk of renal failure? *Interact CardioVasc Thorac Surg* 2010;11:461-7.
- [299] Bainbridge D, Cheng DC, Martin JE, Novick R; Evidence-Based Perioperative Clinical Outcomes Research Group. NSAID-analgesia, pain control and morbidity in cardiothoracic surgery. *Can J Anaesth* 2006;53:46-59.
- [300] Fayaz MK, Abel RJ, Pugh SC, Hall JE, Djaiani G, Mecklenburgh JS. Opioid-sparing effects of diclofenac and paracetamol lead to improved outcomes after cardiac surgery. *J Cardiothorac Vasc Anesth* 2004;18:742-7.
- [301] Kulik A, Ruel M, Bourke ME, Sawyer L, Penning J, Nathan HJ *et al.* Postoperative naproxen after coronary artery bypass surgery: a double-blind randomized controlled trial. *Eur J Cardiothorac Surg* 2004;26:694-700.
- [302] Oliveri L, Jerzewski K, Kulik A. Black box warning: is ketorolac safe for use after cardiac surgery? *J Cardiothorac Vasc Anesth* 2014;28:274-9.
- [303] Engoren MC, Habib RH, Zacharias A, Dooner J, Schwann TA, Riordan CJ *et al.* Postoperative analgesia with ketorolac is associated with decreased mortality after isolated coronary artery bypass graft surgery



- in patients already receiving aspirin: a propensity-matched study. *J Cardiothorac Vasc Anesth* 2007;21:820-6.
- [304] Ott E, Nussmeier NA, Duke PC, Feneck RO, Alston RP, Snabes MC *et al.* Efficacy and safety of the cyclooxygenase 2 inhibitors parecoxib and valdecoxib in patients undergoing coronary artery bypass surgery. *J Thorac Cardiovasc Surg* 2003;125:1481-92.
- [305] Nussmeier NA, Whelton AA, Brown MT, Langford RM, Hoeft A, Parlow JL *et al.* Complications of the COX-2 inhibitors parecoxib and valdecoxib after cardiac surgery. *N Engl J Med* 2005;352:1081-91.
- [306] Grosen K, Drewes AM, Hojsgaard A, Pfeiffer-Jensen M, Hjortdal VE, Pilegaard HK. Perioperative gabapentin for the prevention of persistent pain after thoracotomy: a randomized controlled trial. *Eur J Cardiothorac Surg* 2014;46:76-85.
- [307] Mishriky BM, Waldron NH, Habib AS. Impact of pregabalin on acute and persistent postoperative pain: a systematic review and meta-analysis. *Br J Anaesth* 2015;114:10-31.
- [308] Neshar N, Serovian I, Marouani N, Chazan S, Weinbroum AA. Ketamine spares morphine consumption after transthoracic lung and heart surgery without adverse hemodynamic effects. *Pharmacol Res* 2008;58:38-44.
- [309] Tabatabaie O, Matin N, Heidari A, Tabatabaie A, Hadaegh A, Yazdanynejad S *et al.* Spinal anesthesia reduces postoperative delirium in opium dependent patients undergoing coronary artery bypass grafting. *Acta Anaesthesiol Belg* 2015;66:49-54.
- [310] Mehta Y, Kulkarni V, Juneja R, Sharma KK, Mishra Y, Raizada A *et al.* Spinal (subarachnoid) morphine for off-pump coronary artery bypass surgery. *Heart Surg Forum* 2004;7:E205-10.
- [311] Zakkar M, Frazer S, Hunt I. Is there a role for gabapentin in preventing or treating pain following thoracic surgery? *Interact CardioVasc Thorac Surg* 2013;17:716-9.
- [312] Lahtinen P, Kokki H, Hakala T, Hynynen M. S(+)-ketamine as an analgesic adjunct reduces opioid consumption after cardiac surgery. *Anesth Analg* 2004;99:1295-301.
- [313] Neuhauser C, Preiss V, Feurer MK, Muller M, Scholz S, Kwapisz M *et al.* Comparison of S-(+)-ketamine- with sufentanil-based anaesthesia for elective coronary artery bypass graft surgery: effect on troponin T levels. *Br J Anaesth* 2008;100:765-71.
- [314] Neshar N, Ekstein MP, Paz Y, Marouani N, Chazan S, Weinbroum AA. Morphine with adjuvant ketamine vs higher dose of morphine alone for immediate postthoracotomy analgesia. *Chest* 2009;136:245-52.
- [315] Kubal C, Srinivasan AK, Grayson AD, Fabri BM, Chalmers JA. Effect of risk-adjusted diabetes on mortality and morbidity after coronary artery bypass surgery. *Ann Thorac Surg* 2005;79:1570-6.
- [316] Ascione R, Rogers CA, Rajakaruna C, Angelini GD. Inadequate blood glucose control is associated with in-hospital mortality and morbidity in diabetic and nondiabetic patients undergoing cardiac surgery. *Circulation* 2008;118:113-23.
- [317] Gandhi GY, Nuttall GA, Abel MD, Mullany CJ, Schaff HV, O'Brien PC *et al.* Intensive intraoperative insulin therapy versus conventional glucose management during cardiac surgery: a randomized trial. *Ann Intern Med* 2007;146:233-43.
- [318] van den Berghe G, Wouters P, Weekers F, Verwaest C, Bruyninckx F, Schetz M *et al.* Intensive insulin therapy in critically ill patients. *N Engl J Med* 2001;345:1359-67.
- [319] Haga KK, McClymont KL, Clarke S, Grounds RS, Ng KY, Glyde DW *et al.* The effect of tight glycaemic control, during and after cardiac surgery, on patient mortality and morbidity: a systematic review and meta-analysis. *J Cardiothorac Surg* 2011;6:3.
- [320] Giakoumidakis K, Eltheni R, Patelarou E, Theologou S, Patris V, Michopanou N *et al.* Effects of intensive glycaemic control on outcomes of cardiac surgery. *Heart Lung* 2013;42:146-51.
- [321] Halkos ME, Puskas JD, Lattouf OM, Kilgo P, Kerendi F, Song HK *et al.* Elevated preoperative hemoglobin A1c level is predictive of adverse events after coronary artery bypass surgery. *J Thorac Cardiovasc Surg* 2008;136:631-40.
- [322] Marik PE. Tight glycaemic control in acutely ill patients: low evidence of benefit, high evidence of harm! *Intensive Care Med* 2016;42:1475-7.
- [323] Preiser JC, Straaten HM. Glycemic control: please agree to disagree. *Intensive Care Med* 2016;42:1482-4.
- [324] Bhamidipati CM, LaPar DJ, Stukenborg GJ, Morrison CC, Kern JA, Kron IL *et al.* Superiority of moderate control of hyperglycemia to tight control in patients undergoing coronary artery bypass grafting. *J Thorac Cardiovasc Surg* 2011;141:543-51.
- [325] Lazar HL, McDonnell MM, Chipkin S, Fitzgerald C, Bliss C, Cabral H. Effects of aggressive versus moderate glycaemic control on clinical outcomes in diabetic coronary artery bypass graft patients. *Ann Surg* 2011;254:458-63; discussion 63-4.
- [326] Buchleitner AM, Martinez-Alonso M, Hernandez M, Sola I, Mauricio D. Perioperative glycaemic control for diabetic patients undergoing surgery. *Cochrane Database Syst Rev* 2012;9:CD007315.
- [327] Desai SP, Henry LL, Holmes SD, Hunt SL, Martin CT, Hebsur S *et al.* Strict versus liberal target range for perioperative glucose in patients undergoing coronary artery bypass grafting: a prospective randomized controlled trial. *J Thorac Cardiovasc Surg* 2012;143:318-25.
- [328] Umpierrez G, Cardona S, Pasquel F, Jacobs S, Peng L, Unigwe M *et al.* Randomized controlled trial of intensive versus conservative glucose control in patients undergoing coronary artery bypass graft surgery: GLUCO-CABG trial. *Diabetes Care* 2015;38:1665-72.
- [329] NICE-SUGAR Study Investigators, Finfer S, Chittock DR, Su SY, Blair D, Foster D *et al.* Intensive versus conventional glucose control in critically ill patients. *N Engl J Med* 2009;360:1283-97.
- [330] Kotagal M, Symons RG, Hirsch IB, Umpierrez GE, Dellinger EP, Farrokhi ET *et al.* Perioperative hyperglycemia and risk of adverse events among patients with and without diabetes. *Ann Surg* 2015;261:97-103.
- [331] Greco G, Ferret BS, D'Alessandro DA, Shi W, Horvath KA, Rosen A *et al.* Diabetes and the association of postoperative hyperglycemia with clinical and economic outcomes in cardiac surgery. *Diabetes Care* 2016;39:408-17.
- [332] Mathioudakis N, Golden SH. A comparison of inpatient glucose management guidelines: implications for patient safety and quality. *Curr Diab Rep* 2015;15:13.
- [333] Doenst T, Wijeyesundera D, Karkouti K, Zechner C, Maganti M, Rao V *et al.* Hyperglycemia during cardiopulmonary bypass is an independent risk factor for mortality in patients undergoing cardiac surgery. *J Thorac Cardiovasc Surg* 2005;130:1144.
- [334] Hua J, Chen G, Li H, Fu S, Zhang LM, Scott M *et al.* Intensive intraoperative insulin therapy versus conventional insulin therapy during cardiac surgery: a meta-analysis. *J Cardiothorac Vasc Anesth* 2012;26:829-34.
- [335] Furnary AP, Gao G, Grunkemeier GL, Wu Y, Zerr KJ, Bookin SO *et al.* Continuous insulin infusion reduces mortality in patients with diabetes undergoing coronary artery bypass grafting. *J Thorac Cardiovasc Surg* 2003;125:1007-21.