



Non-cardiac surgery in patients with coronary artery disease: risk evaluation and periprocedural management

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Abstract | Perioperative cardiovascular complications are important causes of morbidity and mortality associated with non-cardiac surgery, particularly in patients with coronary artery disease (CAD). Although preoperative cardiac risk assessment can facilitate the identification of vulnerable patients and implementation of adequate preventive measures, excessive evaluation might lead to undue resource utilization and surgical delay. Owing to conflicting data, there remains some uncertainty regarding the most beneficial perioperative strategy for patients with CAD. Antithrombotic agents are the cornerstone of secondary prevention of ischaemic events but substantially increase the risk of bleeding. Given that 5–25% of patients undergoing coronary stent implantation require non-cardiac surgery within 2 years, surgery is the most common reason for premature cessation of dual antiplatelet therapy. Perioperative management of antiplatelet therapy, which necessitates concomitant evaluation of the individual thrombotic and bleeding risks related to both clinical and procedural factors, poses a recurring dilemma in clinical practice. Current guidelines do not provide detailed recommendations on this topic, and the optimal approach in these patients is yet to be determined. This Review summarizes the current data guiding preoperative risk stratification as well as periprocedural management of patients with CAD undergoing non-cardiac surgery, including those treated with stents.

Perioperative cardiovascular events are estimated to occur in one in every 33 patients undergoing non-cardiac surgery in the USA¹. With >300 million surgical procedures performed annually worldwide, these perioperative cardiovascular complications are a substantial health-care burden². A large subset of these surgical procedures are performed in patients with established coronary artery disease (CAD), especially those with a history of percutaneous coronary intervention (PCI), in whom the risk of perioperative adverse cardiac events is potentially even higher^{3,4}.

The pathophysiological mechanisms of myocardial ischaemia during non-cardiac surgery are related either to oxygen supply–demand imbalance on a background of existing flow-limiting coronary stenosis or to rupture of vulnerable atherosclerotic plaques, both of which predispose patients with CAD to a high risk of an adverse cardiac event^{5–7}. The pro-inflammatory and hypercoagulable states induced by the surgical procedure and the haemodynamic perturbations resulting from fluid shifts and anaesthesia are all important triggers of perioperative myocardial ischaemia^{8,9}.

Moreover, although bleeding risks associated with surgical procedures generally hinder the perioperative use of antithrombotic therapies, in many cases the bleeding itself acts as a precipitating factor for ischaemia. Such a multifactorial aetiology (FIG. 1) explains why preoperative cardiac risk assessment and periprocedural management of patients with CAD are complex and transversal topics requiring collaboration between multiple medical disciplines. However, owing to the limited and often conflicting literature on this subject, practitioners are mostly dependent on consensus-based recommendations, which endorse a more generalized approach that might not always be applicable when assessing individual clinical scenarios^{10,11}. Compared with previous reports addressing specific aspects of this broad and largely debated topic, this Review aims to provide a comprehensive, multidisciplinary and up-to-date appraisal of the key evidence that should inform decision making along every step of perioperative patient care. We elaborate on the various elements of cardiac evaluation and management of patients with CAD who are referred for non-cardiac surgery, including individual

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<https://doi.org/10.1038/s41569-020-0410-z>

Key points

- Numerous prothrombotic, inflammatory and haemodynamic stressors related to surgery can exacerbate the risk of myocardial ischaemia in patients with underlying coronary artery disease (CAD).
- Preoperative cardiac risk assessment and perioperative monitoring of patients with CAD are essential to optimize risk reduction strategies and improve surgical outcomes.
- A multidisciplinary approach involving all perioperative care specialists is necessary to define the various aspects of surgical risk.
- Patients undergoing non-cardiac surgery after recent coronary stent placement have higher rates of adverse cardiac events; however, guidelines lack specific recommendations for the optimal perioperative management of this subgroup.
- Decisions regarding antiplatelet therapy during non-cardiac surgery must be made with the goal of achieving a balance between the potential benefit of preventing thrombotic events and avoiding bleeding complications.
- Bridging with intravenous antiplatelet agents is a viable strategy for patients on dual antiplatelet therapy undergoing non-deferrable surgery, but still needs to be validated in a randomized clinical study.

risk stratification, intraoperative measures, perioperative cardiac monitoring and interventions to prevent cardiovascular events. Furthermore, we also discuss the diverse thrombotic and bleeding risk factors affecting this patient population and the use of oral antithrombotic drugs and intravenous bridging agents, and provide a summary of current guidelines and areas for future research in this field.

Preoperative cardiac risk assessment

The risk of cardiac complications depends on the interplay between patient-related factors, such as clinical and comorbid conditions, and surgery-specific characteristics such as the urgency, type, invasiveness and duration of the procedure. Accurate preoperative cardiac risk assessment not only facilitates decisions regarding the appropriateness of the surgery, but also guides preventative strategies and perioperative monitoring measures. Risk indices, cardiac biomarkers and preoperative cardiac testing are useful risk assessment tools. However, owing to the complexity of assessing overall cardiac risk, a multidisciplinary stepwise approach is generally recommended^{10,11}.

Classification of surgical risk

The most commonly used risk indices for preoperative evaluation are the Revised Cardiac Risk Index (RCRI; also referred to as the Lee index)¹² and the two National Surgical Quality Improvement Program (NSQIP) risk calculators^{13,14}. The RCRI, which is a modified version of the Goldman index, was designed in 1999 to predict the risk of postoperative myocardial infarction, pulmonary

oedema, ventricular fibrillation or cardiac arrest, and complete heart block. The RCRI takes into account six variables (type of surgery, history of ischaemic heart disease, history of cerebrovascular disease, history of heart failure, preoperative treatment with insulin and preoperative creatinine levels >2 mg/dl) and has been widely validated over the past two decades^{15,16}. The NSQIP prospective registry^{17,18} was used to create two new risk indices. The Gupta Myocardial Infarction or Cardiac Arrest (MICA) model, published in 2011, was derived from the 2007 NSQIP dataset and validated in the 2008 dataset, which both contained information from >200,000 patients. The five variables identified as predictors of perioperative myocardial infarction or cardiac arrest in the MICA model were: type of surgery, functional status, creatinine level >1.5 mg/dl, American Society of Anesthesiologists class and advanced age¹³. This risk model was shown to have higher predictive accuracy than the RCRI¹³. The Universal American College of Surgeons surgical risk calculator was developed by Bilimoria and colleagues in 2013 with the use of 1,557 Current Procedural Terminology codes to define the planned surgical procedure, and includes 20 patient-related and surgery-related variables¹⁴. Although this risk model is more comprehensive than the other risk calculators, its use is more complex, requiring manual data entry of specific information and calculation through an online tool¹⁹.

The European Society of Cardiology and the European Society of Anaesthesiology guidelines provide a three-tiered classification system for different types of surgical procedures on the basis of their estimated perioperative risk of 30-day adverse cardiac events (whereby low risk means <1%, intermediate risk 1–5% and high risk >5%)^{10,20}. Findings from a study that validated this classification system broadly reflected the expected rates of adverse outcomes, thereby consolidating its use in preoperative risk assessment protocols²¹. Importantly, although the haemorrhagic risk associated with a procedure primarily depends on the extent of tissue damage and involvement of the vascular system, the risk of ischaemic events is also influenced by the underlying pathology defining the indication for surgery. For example, lower limb revascularization is associated with a low risk of bleeding but a high risk of adverse cardiac events²¹. This discordance is attributable to the unfavourable clinical comorbidities, such as CAD and diabetes mellitus, that are highly prevalent among patients with peripheral artery disease. Finally, the rate of complications specific to the surgical centre is also influenced by factors such as surgical volume, operator experience and availability of resources, all of which can influence the correct estimation of surgical risk.

The next steps in cardiac risk assessment depend on the risk estimate derived from the above indices as well as the urgency of the procedure (FIG. 2). For emergency surgery, guidelines state that the benefit of proceeding to surgery without delay generally outweighs any risk associated with forgoing additional evaluation¹¹. However, in an elective or even time-sensitive setting, the need for additional cardiac evaluation is contingent

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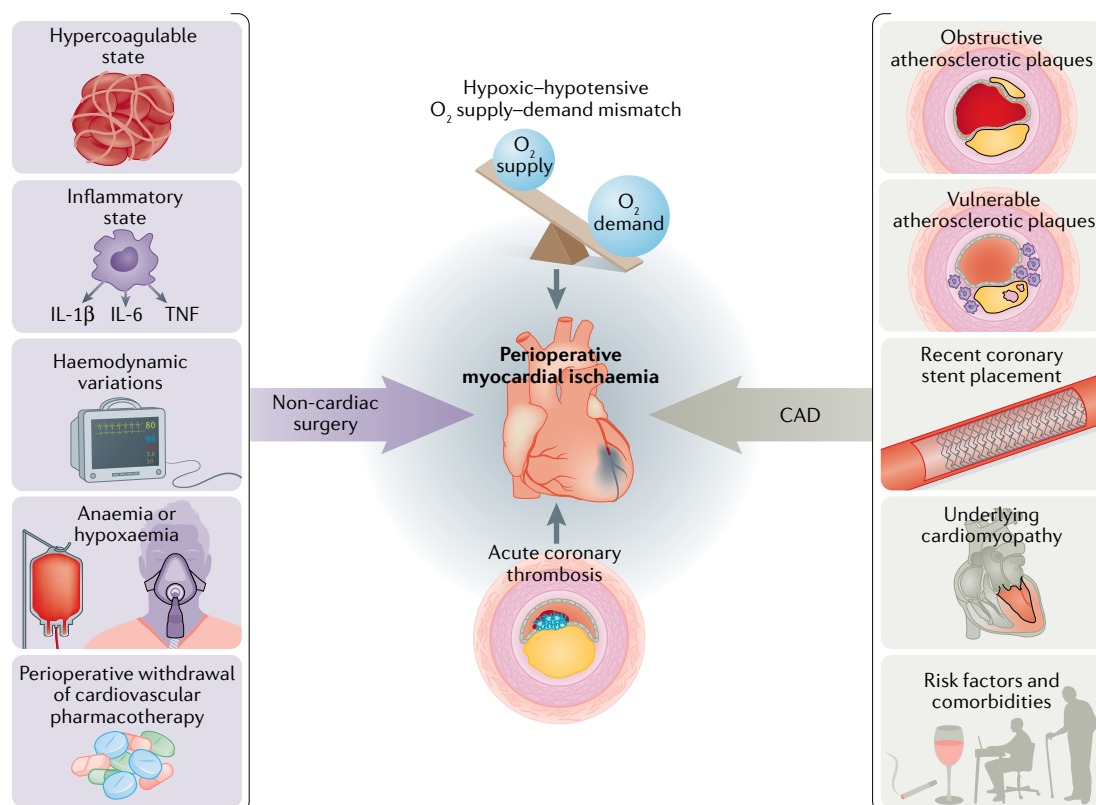


Fig. 1 | Pathogenesis of perioperative myocardial ischaemia in patients with CAD. Summary of the multifactorial aetiology and pathogenic mechanisms of perioperative myocardial ischaemia in patients with coronary artery disease (CAD) undergoing non-cardiac surgery. Perioperative myocardial ischaemia can result from either coronary oxygen supply–demand mismatch or acute thrombosis. Several surgery-related factors (depicted on the left side of the figure) secondary to the surgical trauma, surgery-induced stress (increased sympathetic activation) and perioperative use of anaesthesia and analgesia can trigger perioperative myocardial ischaemia. Furthermore, temporary withdrawal of cardiovascular medications with an antithrombotic effect (antiplatelets) or an anti-ischaemic effect (β -blockers) is often necessary throughout the perioperative period. Among patients undergoing non-cardiac surgery, the presence of CAD increases the risk of perioperative myocardial ischaemia. CAD-related factors (depicted on the right side of the figure) include the presence of obstructive flow-limiting coronary stenosis or vulnerable rupture-prone atherosclerotic plaques, recent placement of a coronary stent that is not yet fully endothelialized, underlying ischaemic cardiomyopathy, and other risk factors and comorbid conditions commonly associated with CAD (such as age, diabetes mellitus and chronic kidney disease). TNF, tumour necrosis factor.

upon the patient's cardiovascular risk¹¹. Patients with a clinical presentation suggestive of myocardial ischaemia or acute coronary syndrome (ACS) must be promptly evaluated by a cardiologist for optimal management before undergoing surgery¹¹. Furthermore, the guidelines recommend that patients with an estimated low risk of perioperative adverse cardiac events (<1%) can generally proceed to surgery without additional testing, given that risk-reduction strategies are unlikely to further improve their surgical outcomes¹¹. Conversely, for those at higher risk ($\geq 1\%$), physicians must decide whether additional cardiovascular evaluation will alter their perioperative management¹¹.

Electrocardiography

Having a baseline electrocardiogram (ECG) reading is particularly useful if postoperative ECG findings are abnormal. However, obtaining a preoperative ECG in asymptomatic patients without a known history of cardiovascular disease who are scheduled for low-risk

surgery is rarely helpful²². Although some ECG abnormalities have been associated with postoperative ischaemic events, these abnormalities did not provide incremental predictive value beyond common cardiovascular risk factors^{23,24}. Preoperative ECG is more appropriate in patients with known cardiovascular disease or in asymptomatic patients undergoing high-risk procedures^{10,11}.

Functional capacity

Determination of functional capacity is another important step in cardiac risk evaluation. Functional capacity is expressed in metabolic equivalents (METs), wherein one MET is defined as the basal metabolic rate and equates to an uptake of 3.5 ml/kg/min of oxygen. Functional capacity can be estimated by asking the patient a few simple questions related to the performance of daily activities or by using standardized questionnaires such as the Duke Activity Status Index (DASI)²⁵. Common points of reference for functional capacity include: capacity to eat,

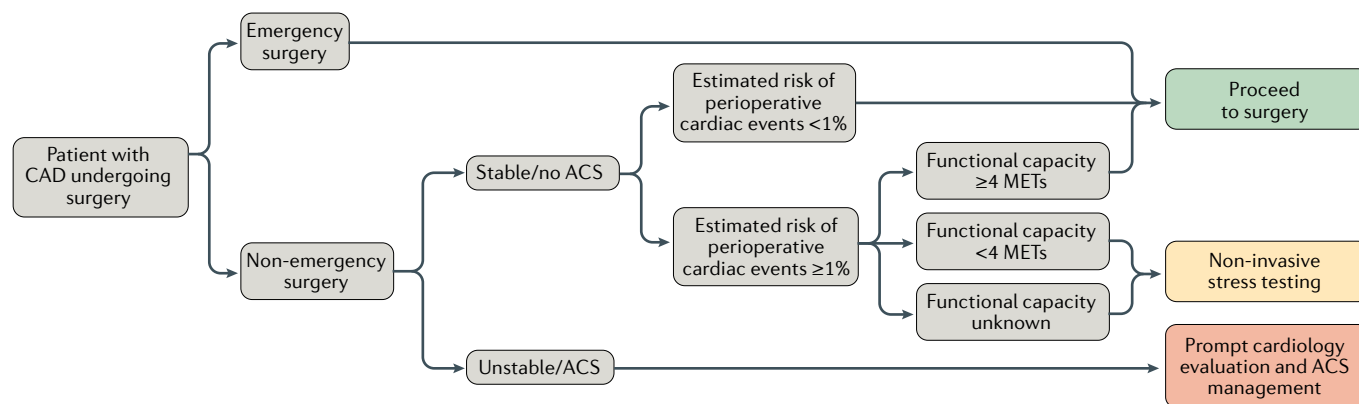


Fig. 2 | Preoperative cardiac risk assessment in patients undergoing non-cardiac surgery. The flow chart provides a stepwise approach to guide preoperative cardiac risk assessment by detailing the key factors that clinicians must consider when evaluating patients with established coronary artery disease (CAD) undergoing surgery. Adapted with permission from REF.¹¹. ACS, acute coronary syndrome; MET, metabolic equivalent. Adapted with permission from REF.¹¹, Elsevier.

dress or use the bathroom (1 MET); walking up a flight of steps or uphill (4 METs); performing heavy chores around the house or moving furniture (4–10 METs); and strenuous physical activity and sports (>10 METs). MET values <4 indicate poor functional capacity and are associated with increased incidence of postoperative adverse cardiac events¹¹. The METS study²⁶ compared the prognostic accuracy of physicians' subjective assessment of functional capacity in patients undergoing elective non-cardiac surgery with three alternative measures: the DASI questionnaire, cardiopulmonary exercise testing and serum N-terminal pro-B-type natriuretic peptide (NT-proBNP) concentrations. Subjective assessment neither accurately identified patients with poor cardiopulmonary fitness nor predicted postoperative adverse outcomes, whereas DASI scores showed significant associations with the primary outcome of death or myocardial infarction within 30 days of surgery²⁶.

Non-invasive stress testing

Several modalities are used for non-invasive stress testing, most of which combine information on both myocardial ischaemia and objectively assessed functional capacity. Stress can be induced either by exercise or by pharmacological agents in patients with limited exercise capacity. The few existing studies on the perioperative value of treadmill or cycle ergometer and cardiopulmonary exercise testing suggest an overall modest capacity to predict postoperative cardiovascular outcomes or improve risk prediction already derived from clinical evaluation^{26–30}. Imaging stress tests, namely stress echocardiography, myocardial perfusion imaging and cardiac MRI, provide accurate information on left ventricular function and structural abnormalities, as well as the presence and extent of stress-induced myocardial ischaemia, and might be useful for preoperative assessment of patients at high risk of or with established CAD^{31,32}. However, a 2019 meta-analysis evaluating the effect of preoperative stress testing on 30-day mortality in patients undergoing non-cardiac

surgery generated inconclusive results, possibly owing to the low quality and high heterogeneity of the included studies³³.

Both European and US guidelines on non-cardiac surgery suggest forgoing stress testing if the reported functional capacity is moderate or higher (≥ 4 METs)^{10,11} (FIG. 2). The European guidelines recommend the use of imaging stress tests in patients undergoing high-risk surgery who have two or more clinical risk factors and poor functional capacity (<4 METs)¹⁰. Similarly, the US guidelines state that pharmacological stress testing might be reasonable in patients with elevated risk and poor or unknown functional capacity if the test findings might affect perioperative management¹¹.

Cardiac biomarkers

Cardiac biomarkers measured in the perioperative setting include markers of myocardial stretching due to volume overload (such as serum B-type natriuretic peptide (BNP) and NT-proBNP levels) and myocardial tissue damage (such as serum cardiac troponin levels). Preoperative BNP and NT-proBNP levels were found to be independent predictors of 30-day adverse cardiovascular event rates after non-cardiac surgery in several meta-analyses^{34–36}. Data from a multicentre observational study involving 979 patients with at least one cardiovascular risk factor who were undergoing elective major non-cardiac surgery showed that preoperative assessment of high-sensitivity troponin T levels adds incremental prognostic information beyond that provided by the RCRI and serum NT-proBNP levels³⁷. A 2019 pilot study found that five out of ten patients undergoing vascular surgery and presenting with asymptomatic high-sensitivity troponin T elevation before surgery had obstructive CAD on subsequent coronary angiography³⁸. In current practice, preoperative assessment of cardiac biomarkers might be considered in patients at high risk of cardiac complications^{10,39}. However, guidelines also recommend against routine preoperative biomarker sampling for risk stratification or prevention of adverse cardiac events^{10,11}.

Coronary CT angiography

Coronary CT angiography (CTA) is a non-invasive and relatively accessible imaging modality that provides detailed morphological information on the coronary anatomy, making it a promising screening tool in patients undergoing major non-cardiac surgery with, or at risk of, CAD. Given the proven capability of coronary CTA to rule out suspected obstructive CAD, preoperative coronary CTA evaluation might help avoid unnecessary pharmacological and invasive approaches. In a single-centre study involving 844 patients undergoing elective non-cardiac surgery, coronary CTA assessment significantly improved the predictive value of the RCRI for perioperative cardiac risk estimation⁴⁰. In particular, the absence of clinically significant stenosis on coronary CTA successfully identified patients with very low rates of perioperative adverse cardiac events regardless of the RCRI score, thereby conferring excellent specificity and negative predictive value upon coronary CTA evaluation⁴⁰. However, in another multicentre, prospective cohort of 955 patients, preoperative coronary CTA improved risk estimation in those who experienced perioperative adverse cardiac events but inappropriately overestimated risk in patients who were event-free compared with the use of the RCRI alone⁴¹. Therefore, the use of coronary CTA in preoperative risk evaluation requires more evidence before any clear recommendations can be made.

Coronary angiography

Invasive assessment of coronary anatomy is not recommended for perioperative risk stratification in patients scheduled to undergo non-cardiac surgery^{10,11,39}. Indications for performing invasive coronary angiography are the same as those in the non-surgical setting^{10,11,39}. Nonetheless, the European guidelines also state that preoperative coronary angiography might be considered in patients with stable cardiac conditions undergoing non-urgent carotid endarterectomy¹⁰. This recommendation was formed on the basis of results from a randomized trial conducted in patients without known CAD undergoing carotid endarterectomy that investigated the outcomes of systematic preoperative coronary angiography and subsequent clinically indicated coronary revascularization (which occurred in 31% of the patients at a median time of 4 days before surgery)⁴². The number of postoperative myocardial ischaemic events, combined with the rate of complications related to coronary angiography and stenting, was significantly lower in patients who underwent systematic preoperative coronary angiography than in those who did not (0% versus 4%, $P=0.01$)⁴². However, the results of this trial might be problematic, given the unrealistic magnitude of the treatment effect and a potentially compromised randomization process³⁹.

Perioperative prevention strategies

Intraoperative measures

Given that the dominant mechanism of perioperative myocardial ischaemia is oxygen supply–demand imbalance, the main goal in the prevention of myocardial ischaemia in patients at high risk of ischaemic events is

to maintain an appropriate myocardial oxygen supply via adequate coronary perfusion pressure and to minimize myocardial oxygen demand (such as through heart rate control)^{7,43}. In a large prospective cohort involving >15,000 patients undergoing non-cardiac surgery, both intraoperative tachycardia (heart rate >100 bpm) and hypotension (systolic blood pressure <100 mmHg) were associated with postoperative myocardial ischaemia⁴⁴. Importantly, not only the absolute values, but also the overall duration of haemodynamic variations, affected the risk of adverse cardiac events^{44,45}. At present, however, a consensus on the threshold of harm for intraoperative heart rate and blood pressure has not been reached, because the acceptable threshold levels depend mainly on the clinical context⁴⁶. A 2019 expert collaboration stated that systolic arterial pressure levels <100 mmHg and mean arterial pressure levels <60–70 mmHg should be avoided during non-cardiac surgery⁴⁷. By contrast, a multicentre randomized trial in 298 patients undergoing major non-cardiac surgery showed that a strategy of targeting individualized blood pressure goals was superior to standardized management in reducing the risk of postoperative organ dysfunction⁴⁸. Furthermore, intraoperative systemic hypertension has been suggested to promote myocardial ischaemia by increasing cardiac filling pressures and ventricular wall stress, but the clinical evidence to support this association is limited⁴⁷. Postoperative hypotension and hypertension have also been suggested to be much more common than previously reported⁴⁹. To this end, implementation of a machine learning-derived automated early warning system that can predict hypotension shortly before it occurs might help prevent harmful haemodynamic fluctuations in patients undergoing non-cardiac surgery⁵⁰.

The most common cardiovascular effect of commonly used anaesthetic agents is a reduction in systemic vascular resistance⁵¹. Both inhaled and neuraxial anaesthetics decrease sympathetic tone through a number of mechanisms that ultimately result in vasodilatation and possibly hypotension^{52,53}. Intravenous anaesthetics, such as propofol, can also cause dose-dependent vasodilatation with a decrease in systemic blood pressure levels⁵⁴. Despite several studies on this topic^{55–57}, no conclusive evidence supports the use of one type of anaesthetic over another in preventing adverse cardiovascular effects. Accordingly, guidelines recommend that the choice of anaesthetic agent should be based on factors other than prevention of myocardial ischaemia^{10,11}.

Monitoring for myocardial ischaemia

Given that most ischaemic complications occur within 48 h of surgery and are often asymptomatic⁵⁸, careful clinical evaluation and close surveillance with ECG and cardiac biomarker testing are encouraged in patients at high cardiovascular risk^{10,11}. However, the value of routine postoperative cardiac biomarker testing remains controversial. The VISION study^{59,60} aimed to evaluate the prognostic importance of postoperative troponin elevation in two separate cohorts comprising >36,000 patients undergoing non-cardiac surgery. The findings showed that elevation in troponin levels after non-cardiac surgery occurred in up to 18% of

patients, and peak values measured with either standard or high-sensitivity assays predicted 30-day mortality irrespective of the concomitant presence of myocardial ischaemic features^{59,60}. These large epidemiological studies have helped establish the diagnostic criteria for the definition of myocardial injury after non-cardiac surgery, which includes an increase in postoperative serum troponin levels attributable to myocardial ischaemia (that is, with no evidence of a non-ischaemic aetiology such as sepsis or rapid atrial fibrillation) in the absence of ancillary features indicative of myocardial infarction (such as symptoms of ischaemia or evidence of ischaemia on ECG testing)^{43,61}. Given the lack of universally accepted troponin thresholds for identifying myocardial injury, elevation of serum troponin I or troponin T levels is defined as any value above the 99th upper reference limit for each specific troponin assay⁴³. The pathophysiological mechanism of myocardial injury after non-cardiac surgery is still unclear, but findings from studies investigating perioperative myocardial infarction suggest that ischaemia owing to oxygen supply–demand imbalance accounts for a majority of the events^{62–64}. In any case, the prognostic consequences of postoperative myocardial injury seem similar to those of an established diagnosis of myocardial infarction that fulfils the additional ischaemic criteria⁶⁵.

Elevated postoperative serum BNP levels have also been associated with increased risk of morbidity and mortality^{66,67}, but measurement of this biomarker has not yet been incorporated into routine clinical practice. Findings from ongoing studies will help ascertain the clinical utility of different cardiac biomarkers for perioperative risk stratification and early detection of preventable cardiovascular complications^{68,69}.

Pharmacological strategies

Antithrombotic therapy. Many elderly patients who undergo non-cardiac surgery are prescribed with long-term antiplatelet therapy (most commonly aspirin) for the secondary prevention of cardiovascular events⁷⁰. The first studies that reported on the balance between bleeding and thrombotic risk related to perioperative maintenance of antiplatelet therapy were published >15 years ago^{71,72}. The POISE-2 trial⁷³ was the largest randomized, placebo-controlled study to test a strategy of routine perioperative aspirin administration in 10,010 patients aged ≥45 years with cardiovascular disease or at risk of cardiovascular complications (defined as the presence of three or more risk criteria) who were scheduled for non-cardiac surgery. The trial excluded patients who received a bare-metal stent (BMS) <6 weeks before surgery or a drug-eluting stent (DES) <1 year before surgery. No significant difference was observed in the primary composite outcome of death or non-fatal myocardial infarction at 30 days between the aspirin (7.0%) and placebo (7.1%) groups⁷³. However, administration of aspirin increased the risk of major bleeding in the first 7 days after the surgery compared with placebo. This trial provided important evidence against the perioperative initiation or continuation of aspirin therapy in patients with, or at risk of, cardiovascular disease. Nonetheless, antithrombotic therapy

might still be appropriate in certain patients if the risk of ischaemia outweighs the risk of perioperative bleeding. A subgroup analysis from the POISE-2 study involving 470 patients with a prior coronary stent implanted >1 year before non-cardiac surgery found that perioperative aspirin therapy significantly reduced the risk of death or non-fatal myocardial infarction⁷⁴. By contrast, the STRATAGEM trial⁷⁵, which compared the effects of maintenance or interruption of aspirin therapy before intermediate-risk or high-risk non-cardiac surgery in 291 patients already receiving antiplatelet therapy for secondary prevention found no difference in the occurrence of major thrombotic or bleeding events between the two strategies.

Although observational data suggest a potential survival benefit associated with aspirin use for the treatment of perioperative myocardial infarction⁵⁸, to date, no randomized trials have evaluated this treatment strategy. Moreover, given that only a minority of patients with postoperative elevation of serum troponin levels experience ischaemic symptoms or have a diagnosis of myocardial infarction, the optimal management strategy for these patients remains a subject of debate^{60,76,77}. A pilot study comparing ticagrelor with aspirin therapy in patients with troponin elevation after major non-cardiac surgery was prematurely terminated owing to slow enrolment⁷⁸. In 2018, investigators in the MANAGE trial⁷⁹ assessed the use of dabigatran therapy to prevent major vascular complications in patients with myocardial injury after non-cardiac surgery. Patients who received 110 mg of dabigatran twice daily had fewer major adverse vascular events than those receiving placebo. No significant difference was observed in the primary safety composite end point of life-threatening, major and critical organ bleeding⁷⁹. However, several caveats need to be kept in mind when interpreting these findings⁸⁰. First, the trial was terminated early due to loss of funding and slow enrolment. Second, the measured outcomes included mostly vascular end points, and the initial primary efficacy end point of a composite of vascular mortality, nonfatal myocardial infarction, stroke, peripheral arterial thrombosis and symptomatic pulmonary embolism was broadened midway through the trial to include amputation and symptomatic venous thromboembolism to increase statistical power. Third, the rate of study drug discontinuation was almost 50%. Finally, additional cardiac testing to ascertain the mechanism of perioperative troponin elevation was performed infrequently during the trial⁸⁰. Therefore, although certain antithrombotic therapies have shown promising results, more research is needed to define the optimal approach for the detection and pharmacological treatment of perioperative myocardial ischaemia.

Other therapies. Statins, β -blockers and renin–angiotensin–aldosterone system inhibitors (angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin-receptor blockers (ARBs)) are cornerstones in the prevention of cardiovascular events. Whether to stop or to continue any cardiovascular medication perioperatively should be decided on the basis of cardiac versus surgical risk^{10,11}

Table 1 | Perioperative management of cardiovascular pharmacotherapy

Drug class	Recommendation on perioperative management	LoE/CoR	
		ACC/AHA ¹¹	ESC/ESA ¹⁰
Statins	Continuation	I/B	I/C
	Initiation if the patient requires vascular surgery	IIa/B	IIa/B
	Initiation if clinically indicated and the patient requires high-risk surgery	IIb/C	None
β-Blockers	Continuation	I/B	I/B
	Initiation if the patient is at high risk of ischaemia ^a	IIb/B	IIb/B
	Initiation on the day of the procedure or without titration	III/B	III/B
ACEIs or ARBs	Continuation	IIa/B	IIa/C
	Initiation in stable patients with HF and LV systolic dysfunction	None	IIa/C
	Transient discontinuation in patients with hypertension	None	IIa/C

ACC, American College of Cardiology; ACEI, angiotensin-converting enzyme inhibitor; AHA, American Heart Association; ARB, angiotensin receptor blocker; CoR, class of recommendation; ESA, European Society of Anaesthesiology; ESC, European Society of Cardiology; LoE, level of evidence; HF, heart failure; LV, left ventricular. ^aFor the ACC/AHA guidelines, high ischaemic risk indicates the presence of three or more Revised Cardiac Risk Index factors, or patients with intermediate-risk or high-risk preoperative test results (level IIb, class C recommendation); for the ESC/ESA guidelines, high ischaemic risk indicates the presence of two or more clinical risk factors or American Society of Anesthesiologists status ≥ 3 in patients scheduled for high-risk surgery, or the presence of known ischaemic heart disease or myocardial ischaemia.

(TABLE 1). Investigators in the POISE trial⁸¹ enrolled 8,351 patients with or at risk of CAD who were scheduled for non-cardiac surgery, and randomly assigned them to the extended-release metoprolol succinate group or placebo group. Metoprolol treatment was associated with a reduction in the occurrence of myocardial infarction, but also increased mortality and an elevated incidence of stroke and clinically important hypotension. β-Blocker-related increases in the incidence of stroke and mortality were also reported in a subsequent meta-analysis^{82–86}. On the basis of current evidence, the benefit of β-blockers as prophylactic agents in patients undergoing non-cardiac surgery is unclear. Guidelines encourage perioperative continuation of β-blocker treatment in patients who are already on long-term therapy, and initiation might be considered in naive patients scheduled for high-risk surgical procedures^{10,11}.

Statins have an unequivocal role in the secondary prevention of cardiovascular disease owing to their favourable effects on plaque stabilization, decreasing inflammation, recovery of endothelial function and reducing thrombogenicity⁸⁷. An improvement in in-hospital survival after non-cardiac surgery among patients treated perioperatively with statins was observed almost two decades ago in a propensity-matched analysis involving a large US cohort⁸⁸. Several subsequent observational studies have confirmed and extended the advantage of perioperative statin use to improve cardiovascular outcomes^{89,90}. In 2017, the LOAD randomized trial⁹¹ tested the efficacy of perioperative statin therapy in statin-naïve patients undergoing non-cardiac surgery who were at high risk of vascular complications. No significant differences in primary outcomes were observed

between patients receiving statin and those receiving placebo. By contrast, other randomized studies assessing the efficacy of perioperative statin treatment in patients already on long-term statin therapy found a significant reduction in 30-day cardiovascular end points^{92,93}. Therefore, despite both European and US guidelines being formulated before some of the above-mentioned evidence became available, recommendations to perioperatively continue statins in those already on chronic treatment remain valid^{10,11}.

The pleiotropic and cholesterol-lowering effects of statins might be protective in the perioperative period, especially in patients undergoing vascular procedures. In a randomized trial involving 100 patients undergoing vascular surgery assigned to either 20 mg atorvastatin or placebo, atorvastatin treatment was associated with a threefold lower rate of cardiovascular events at 6 months⁹⁴. Findings from other cohort studies have corroborated these results^{95–98}. Accordingly, guidelines suggest considering the initiation of statins in previously untreated patients undergoing vascular surgery^{10,11}.

Whether the perioperative use of ACEIs and ARBs should be continued at the time of non-cardiac surgery is unclear, given that several studies have shown an increased risk of perioperative hypotension, with variable effects on cardiovascular outcomes and mortality. In a prospective cohort of 4,802 patients receiving ACEIs or ARBs and undergoing non-cardiac surgery, withholding ACEIs or ARBs 24 h before surgery was associated not only with a reduction in intraoperative hypotension, but also a decrease in 30-day all-cause death, stroke or myocardial injury⁹⁹. However, in a subsequent meta-analysis that included 6,022 patients on chronic ACEI or ARB therapy, withholding these drugs on the morning of surgery was only associated with reduction in intraoperative hypotension and not mortality¹⁰⁰. Given the low quality of the available evidence, recommendations for the use of ACEIs or ARBs in the context of non-cardiac surgery are not consistent between different societies. The 2017 Canadian guidelines recommend withholding ACEIs or ARBs 24 h before non-cardiac surgery in patients on chronic therapy³⁹. A large multicentre, randomized, controlled trial is currently underway and will shed light on this subject¹⁰¹.

Interventional strategies

The presence of CAD is associated with an increased risk of perioperative adverse cardiac events. A meta-analysis of 11 studies that assessed coronary CTA before non-cardiac surgery showed a progressive increase in perioperative adverse cardiac events with increasing severity of CAD¹⁰². Nonetheless, coronary revascularization before surgery does not seem to improve perioperative outcomes. In the CARP trial¹⁰³, 510 patients with stable obstructive CAD undergoing major vascular surgery were randomly assigned to either pre-planned, preoperative coronary revascularization (with PCI or coronary artery bypass graft (CABG) surgery) or no revascularization. At 2.7 years after randomization, mortality was not significantly different between

the treatment groups. The incidence of myocardial infarction was also not different within 30 days of surgery¹⁰³. However, a subgroup analysis of combined registry and randomized data suggested that patients with unprotected left main coronary artery stenosis had improved outcomes with revascularization before non-cardiac surgery¹⁰⁴. Therefore, routine prophylactic coronary revascularization is not recommended before non-cardiac surgery in patients who are stable and asymptomatic for the sole purpose of reducing perioperative adverse cardiac events^{10,11}. Nonetheless, in clinical scenarios in which preoperative revascularization is performed, use of newer-generation DES is preferred over BMS in the light of evidence demonstrating the safety and efficacy of both polymer-free and durable-polymer DES with only 1 month of dual antiplatelet therapy (DAPT)^{105,106}.

Platelet function assessment

Platelet function tests enable the assessment of the degree of on-treatment platelet reactivity in response to a stimulating agonist. Platelet reactivity is generally referred to as low in the case of effective platelet inhibition, or high if platelet responsiveness is substantially preserved¹⁰⁷. A wide variety of platelet function assays are currently available, each with specific clinical applications. In a surgical setting, if antiplatelet therapy needs to be preoperatively withdrawn owing to bleeding concerns, sufficient time for recovery of platelet function is required to guarantee adequate haemostatic competence. At the same time, prolonged exposure to high platelet reactivity while awaiting surgery might increase the risk of thrombotic complications, particularly in patients with an indication for DAPT¹⁰⁸. Several scientific societies have issued standard timeline recommendations for preoperative antiplatelet discontinuation, which essentially depends on the type of drug and surgery^{109–111}. However, such a 'one size fits all' approach does not take into account the well-documented inter-individual variability in pharmacodynamic responsiveness (especially to clopidogrel) and recovery of platelet function after antiplatelet drug discontinuation^{112–114}. To this end, point-of-care platelet function monitoring might help identify patients who can safely proceed to surgery as soon as platelet reactivity has been restored¹¹⁵. A number of observational studies have examined the benefit of preoperative platelet function monitoring in reducing bleeding complications after cardiac surgery, and guidelines have advocated for their use to inform timing of cardiac surgery in patients receiving DAPT or P2Y purinoceptor 12 (P2Y₁₂) inhibitors^{110,116–118}. Another potential role for platelet function testing is to guide management of perioperative bleeding associated with cardiac surgery-related coagulopathy within the context of blood transfusion algorithms^{118,119}.

The clinical utility of platelet function testing is less clear in patients undergoing non-cardiac surgery. The BIANCA observational study¹²⁰ explored the association between platelet reactivity and bleeding in 197 patients treated with clopidogrel with or without aspirin during the 7 days before surgery. The incidence of bleeding was found to decrease with increasing recovery of

platelet function, thereby suggesting that an individualized preoperative waiting period derived from objective assessment of platelet reactivity rather than a standard prespecified waiting period might better predict bleeding and guide the timing of the procedure even in patients undergoing non-cardiac surgery¹²⁰.

Coronary stents and non-cardiac surgery

Up to 25% of patients undergoing coronary stent implantation require non-cardiac surgery in the subsequent 2 years¹²¹. Compelling evidence from observational studies indicates that among all surgical candidates, those with a coronary stent experience higher rates of both ischaemic and bleeding complications in the perioperative period^{122,123}. Of note, ascertainment bias might have affected the findings from these observational studies, because the probability of diagnosing an event is potentially higher in patients with prior coronary stents owing to closer perioperative monitoring and troponin surveillance⁴.

In the early era of PCI, the first case series documented catastrophic outcomes in patients undergoing non-cardiac surgery within a few weeks of stent placement, the majority of which were presumed to be related to stent thrombosis¹²⁴. Stent thrombosis is a rare but life-threatening complication of PCI with a fatality rate as high as 45%¹²⁵, and involves the abrupt closure of the vessel in a previously stented segment that can lead to acute myocardial infarction and death. The pathogenic mechanism of stent thrombosis is multifactorial and depends on numerous patient-related, device-related and procedure-related factors¹²⁶. Over the past 15 years, the introduction of new stent platforms, advances in revascularization techniques and widespread adoption of DAPT have led to a substantial reduction in the incidence of stent thrombosis¹²⁶. As a result, non-cardiac surgery after PCI has become more safe and feasible, but thrombotic risk still remains¹²⁷. Although stent-related complications generate the most concern for both patients and physicians, these complications are not the only factor responsible for perioperative adverse cardiac events. In fact, de novo coronary lesions and oxygen supply-demand mismatch were shown to account for the majority of myocardial infarctions related to non-cardiac surgery^{122,127,128}. In this context, the management of antiplatelet therapy in patients with recent coronary stent implantation assumes a major prognostic role and has many important challenges¹²⁹. Misperception of individual thrombotic and bleeding risk in patients with recent PCI undergoing surgery might lead to inappropriate use of antithrombotic agents, potentially triggering rather than preventing perioperative complications. Therefore, defining the risk–benefit trade-off of continuing or withholding antiplatelet therapy requires an understanding of the key determinants of thrombotic and bleeding risk in the surgical setting.

Determinants of thrombotic risk

Several well-known predictors of thrombotic events consisting of patient-related clinical and angiographic characteristics and PCI-related features are relevant to individuals undergoing surgery^{129,130} (TABLE 2).

Table 2 | Determinants of thrombotic risk

Determinants of thrombotic risk ^a	Features of thrombotic risk ^{110,143}
Patient-related factors	
Clinical variables	Recent acute coronary syndrome (<1 year)
	History of multiple myocardial infarctions
	History of stent thrombosis despite adequate antiplatelet therapy
	Advanced age (≥75 years)
	Comorbid diabetes mellitus
	Comorbid chronic renal disease (eGFR < 60 ml/min)
	Left ventricular ejection fraction <40%
Angiographic variables	Multivessel coronary artery disease
PCI-related factors	
Time from PCI to surgery	<1 month (high risk)
	1–6 months (intermediate risk)
Stent type	First-generation drug-eluting stent
	Bioresorbable scaffold
PCI complexity	Minimum of three stents implanted
	Minimum of three lesions treated
	Bifurcation with two stents implanted
	Total stent length >60 mm
	Small stent diameter (<3 mm)
	Treatment of in-stent restenosis
	Treatment of chronic total occlusion
	Treatment of the last remaining patent coronary artery

eGFR, estimated glomerular filtration rate; PCI, percutaneous coronary intervention.

^aThe presence of thrombotic risk features identify patients with moderate-to-high risk of thrombosis; stratification between moderate-risk and high-risk categories should be assessed individually.

Clinical characteristics. In patients undergoing non-cardiac surgery, the presence of prior coronary stenting per se is indicative of an older and sicker subgroup with greater prevalence of cardiovascular risk factors^{122,127,131}. As in the general population, history of recent myocardial infarction is among the strongest predictors of adverse cardiac events in patients undergoing surgery^{132–136}. Additional key prognostic variables include advanced age and presence of comorbid conditions such as heart failure, diabetes and chronic kidney disease^{123,127,128,136–139}.

ACS encompasses a spectrum of pathological events associated with atherosclerotic plaque instability and prolonged activation of the coagulation pathways^{140,141}. Patients with ACS have increased cardiovascular risk, which remains elevated for a longer time than in patients with chronic coronary syndromes, even after successful revascularization¹⁴². Accordingly, guidelines recommend that patients with ACS be prescribed a more intensive antiplatelet regimen^{110,143}. Therefore, major surgical procedures requiring temporary interruption of antiplatelet therapy might precipitate the risk of cardiovascular complications by inducing a heightened inflammatory and prothrombotic status, especially in patients with recent ACS^{144–146}.

Angiographic characteristics. The anatomical extent and complexity of CAD correlate with the risk of cardiovascular events after PCI and are of paramount importance in guiding treatment strategy^{147,148}. Patients with high-risk vulnerable plaques on coronary CTA are more likely to develop ACS^{149,150}. Therefore, coronary plaque burden and composition evaluated with the use of non-invasive imaging techniques can provide further information on the thrombotic risk of a patient undergoing surgery. Ultimately, conditions that reduce the chance of achieving a successful or complete coronary revascularization can increase the likelihood of perioperative cardiac events¹⁵¹.

Time from PCI to surgery. The time period between stent placement and surgery is widely reported as one of the most important determinants of a poor prognosis, with several studies highlighting an inverse relationship between the risk of perioperative cardiac events and the timing of surgery after PCI^{136,139,145,146,152,153}. Observational data indicates that the risk of thrombotic complications is highest when surgery is performed within 4–6 weeks of stenting^{144,154–156}. Although thrombotic risk is gradually attenuated over time, this risk can remain elevated for at least 6 months and for as long as 2–3 years after PCI¹³⁴. Of note, however, many of these studies lack adequate controls to assess whether surgery has a truly additive effect on the thrombotic risk of patients with recent PCI. Indeed, even in the absence of surgical procedures, the risk of adverse events, including stent thrombosis, prevails in the initial period after PCI^{157,158}. To address this limitation in study design, a large Veterans Affairs cohort study matched patients undergoing non-cardiac surgery within 2 years of coronary stenting with those undergoing coronary stenting only¹³⁵. Despite a higher incidence of adverse cardiac events early after PCI in both groups, non-cardiac surgery conferred an incremental risk that peaked if surgery occurred in the first 6 weeks after PCI, and stabilized after 6 months¹³⁵. Consistent findings were reported in studies comparing outcomes in patients undergoing surgery with and without previous stenting^{4,122,123}.

Different potential mechanisms contribute to this time-dependent pattern. Given that most surgery, especially major surgery, requires perioperative interruption of DAPT, allowing sufficient time for endothelial coverage of stent struts is necessary to prevent thrombotic complications¹⁵⁹. Furthermore, a large proportion of the surgical procedures occurring in the first few months after PCI are implicitly associated with a higher risk than those occurring later owing to their life-saving and thus non-deferrable nature^{121,134}.

According to the European guidelines, elective surgery requiring discontinuation of P2Y₁₂ inhibitors should be considered after 1 month following PCI, irrespective of the stent type, if aspirin treatment can be maintained throughout the perioperative period¹¹⁰. However, in patients with ACS at the time of the index PCI or at high thrombotic risk, elective surgery might be postponed for up to 6 months¹¹⁰. Conversely, the US guidelines provide timeline recommendations based on the type of stent implanted¹⁴³. Elective surgery with

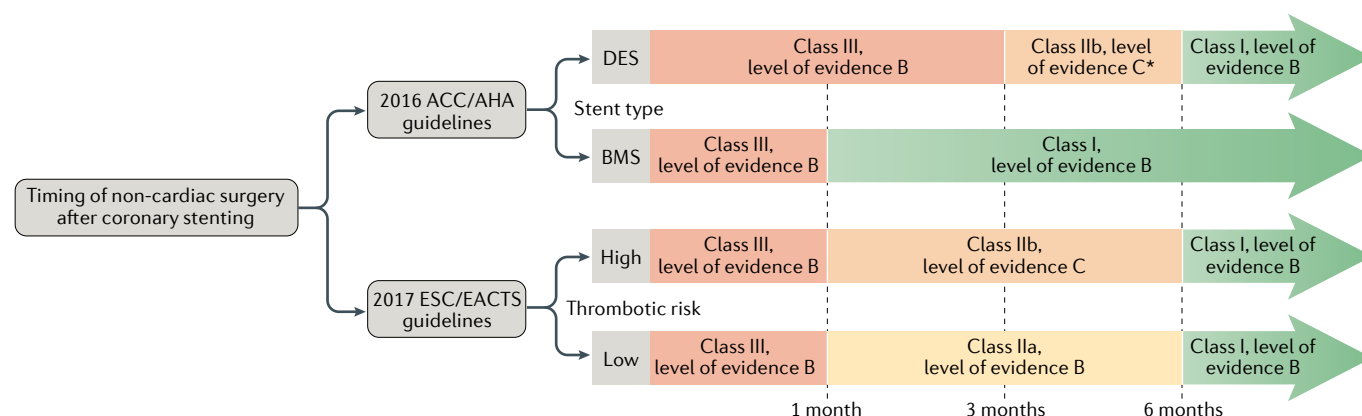


Fig. 3 | Guideline-recommended timing of non-cardiac surgery in patients on DAPT with a coronary stent. The figure shows a comparison of the 2016 American College of Cardiology (ACC)/American Heart Association (AHA)¹⁴³ and the 2017 European Society of Cardiology (ESC)/European Association for Cardio-Thoracic Surgery (EACTS)¹¹⁰ guideline recommendations on the timing of elective non-cardiac surgery requiring discontinuation of the P2Y₁₂ inhibitor after percutaneous coronary intervention (PCI). The US guidelines provide timeline recommendations on the basis of stent type, whereas the European guidelines only take into consideration thrombotic risk regardless of the stent implanted. Thrombotic risk includes presentation of acute coronary syndrome at the time of the index PCI or presence of risk factors such as those summarized in TABLE 2. BMS, bare-metal stent; DAPT, dual antiplatelet therapy; DES, drug-eluting stent. *If the risk of further delay of surgery is greater than the expected risk of stent thrombosis.

discontinuation of DAPT should ideally be performed >6 months after DES implantation, but can be considered 3–6 months if the risk of delaying surgery is greater than the risk of stent thrombosis. In patients implanted with a BMS, surgery can be safely performed 1 month after PCI¹⁴³ (FIG. 3).

Stent type. DES were developed to address the high rates of restenosis and repeat revascularization associated with BMS¹⁶⁰. However, the antiproliferative mechanism through which DES maintain luminal patency mandates longer duration of DAPT. As discussed above, the US guidelines recommend that timing of surgery after PCI be decided according to stent type, but the evidence in support of this recommendation is weak^{135,153}. Several studies failed to demonstrate any relationship between stent type and postoperative outcomes^{128,136,144,155}. By contrast, a multicentre Italian registry described an important interplay between timing of surgery and stent type in relation to ischaemic events after surgery¹³⁹. Compared with BMS, new-generation DES seemed safer when surgery was performed 0–6 months after PCI, whereas old-generation DES were associated with worse outcomes at all time points¹³⁹.

In current practice, stent selection is predominantly influenced by patient characteristics and other circumstances such as need for imminent surgery¹⁵⁵. Therefore, whether the stent type is the primary cause of thrombotic events or merely a marker of risk remains unclear. Additional PCI-related factors other than stent type might plausibly have a greater influence on patient outcomes after surgery, especially since new-generation devices were proven safe after a short course of DAPT¹⁰⁵.

PCI complexity. Lesional and procedural characteristics that increase the risk of early and late stent thrombosis are used to define PCI complexity and include features

such as multivessel PCI, total stent length and treatment of a bifurcation lesion with two stents^{125,161,162}. Complex anatomy of the target lesion has been associated with higher incidence of perioperative adverse cardiac events^{127,134,146}. Given that post hoc analyses of clinical trials have demonstrated a potential benefit of extending DAPT duration to at least 12 months in patients with complex PCI^{163,164}, major non-cardiac surgical procedures requiring early DAPT interruption in these patients warrant caution.

Determinants of bleeding risk

Characterization of bleeding risk in patients undergoing surgery depends on two factors: the anticipated risk of haemorrhagic complications of a specific surgery and the presence of baseline clinical conditions that increase the propensity for bleeding (Supplementary Table 1).

Surgery-related factors. The bleeding risk associated with a specific surgery type is contingent on the potential quantity of blood loss as well as the expected difficulty in achieving local haemostasis¹³⁰. Of note, poor haemostasis might, in some surgical procedures, be clinically detrimental despite only a modest quantitative risk of blood loss. On the basis of these principles, a multidisciplinary collaboration of experts provided a practical classification of bleeding risk for various types of interventions across different surgical specialties¹³⁰. However, this formal attempt at systematically grading surgical risk applied only to a limited number of procedures^{130,165}. The countless potential interventions and techniques within a myriad of possible clinical scenarios make a single, all-inclusive classification difficult to achieve.

Another critical aspect affecting perioperative bleeding risk is related to the circumstances under which the surgery occurs. Elective surgery might be planned with sufficient time for careful evaluation of individual risk and restoration of platelet function if DAPT

interruption is needed, whereas non-deferrable procedures understandably pose a higher risk of bleeding complications¹⁶⁶.

Patient-related factors. Bleeding risk assessment before an invasive procedure involves obtaining information on previous bleeding events, the presence of pro-haemorrhagic clinical and comorbid conditions, and any medications that might interfere with clotting activity. In patients with inherited or acquired bleeding disorders, such as haemophilia, platelet defects or von Willebrand disease, there is an increased need to focus on perioperative haemostatic care. Nonetheless, most invasive procedures can be safely performed with an optimal surgical plan and judicious use of haemostatic agents and blood products^{167,168}. Bleeding abnormalities might also be encountered in patients with chronic kidney disease or liver disease owing to multifactorial mechanisms such as alterations in the coagulation cascade, platelet and vessel wall dysfunction, and reduced clearance of antithrombotic medications^{169,170}. Although studies in patients undergoing surgery have focused mainly on those with severe and end-stage conditions, the findings clearly suggest an excess in bleeding complications and reduced survival^{171,172}. Anaemia and thrombocytopenia, either previously diagnosed or identified upon preoperative testing, usually coincide with advanced age and multiple comorbidities, and thus represent strong predictors of mortality and the need for perioperative blood transfusion^{173–176}. Notably, a 2019 academic collaboration provided a consensus-based definition of high bleeding risk in patients undergoing PCI that encompasses most of the above-mentioned criteria¹⁷⁷.

Perioperative antiplatelet management

Premature DAPT discontinuation is an undisputed predictor of stent thrombosis^{125,161,178–180}. Nevertheless, the effect of antiplatelet therapy withdrawal in patients undergoing non-cardiac surgery has long been debated⁷². A landmark analysis from the PARIS registry¹⁷⁸ suggested that a temporary DAPT interruption driven by the need for surgery increases the risk of adverse cardiac events only if DAPT withdrawal occurs within 6 months of PCI. However, the control group in this analysis were all patients who remained on DAPT, irrespective of whether they underwent surgery.

Most data on perioperative antiplatelet management are derived from small observational studies that are limited by exposure to non-randomized variables¹⁸¹. In addition, all such studies were conducted on patients who actually underwent surgery. Therefore, exclusion of patients who had cancellations of their surgery because of an adverse event after DAPT interruption but before the scheduled procedure introduced an important selection bias¹⁸².

To date, the available evidence to guide perioperative antiplatelet management in patients with a stent remains controversial¹⁸¹. Numerous studies have not demonstrated any significant association between adverse cardiac events and antiplatelet therapy at the time of surgery^{134,136,152,183}. Conversely, other studies

have shown that interrupting DAPT in patients with recent coronary stenting increases the risk of adverse outcomes, especially if interruption occurred early after PCI, for both aspirin and thienopyridine therapy, and >5 days before surgery^{128,184–187}. With regard to surgical bleeding risk, the causative role of antiplatelet therapy is more intuitive and the evidence more consistent^{73,183,188–190}. In general, when interpreting the observational data, antiplatelet management should be considered as a marker of the perceived thrombotic and bleeding risk more than as an effect modifier. Before randomized trial data that can inform on the role of perioperative antiplatelet therapy in patients with a coronary stent become available, large prospective registries are needed to characterize current real-world practice and ascertain the burden of this public health issue (TABLE 3).

Recommendations. In line with current guidelines, the perioperative management of antiplatelet therapy requires a multidisciplinary discussion between the cardiologist, the surgeon and other perioperative care specialists (such as the anaesthesiologist) to assess the trade-off between thrombotic and bleeding risk^{109,110,143}. Of note, many risk factors are associated with both bleeding and thrombosis, because these two conditions can frequently coexist^{128,177}. To further compound matters, the risk of thrombotic events is heightened in patients who experience perioperative bleeding events^{73,122,191}. This complex conundrum is reflected in the delicate balance between thrombosis and bleeding preventative strategies. However, given the absence of conclusive evidence to support specific recommendations, current guidelines provide only limited insights and general guidance^{110,143}. To address this gap in knowledge, a number of expert collaborations from different national societies have issued practical recommendations to standardize antiplatelet management in various surgical settings on the basis of the predicted individual risk of thrombotic events and the anticipated risk of bleeding complications^{130,165,192} (TABLE 4). Overall, most surgical procedures can be safely performed in patients who are on aspirin therapy, except for the procedures associated with a very high risk of haemorrhagic complications^{130,165,192}. In patients with an indication for DAPT owing to recent stent implantation or ACS, if elective surgery requires discontinuation of the P2Y₁₂ inhibitor therapy, postponing surgery beyond the recommended DAPT course should always be considered and weighed against the possible implications of this delay. If surgery is time-sensitive and not deferrable beyond timeline recommendations, considerations for bridging with an intravenous antiplatelet agent should be made if DAPT needs to be discontinued. A proposed algorithm summarizing perioperative management of antiplatelet therapy in patients with CAD with or without coronary stents is shown in FIG. 4.

The optimal duration of antiplatelet therapy discontinuation before non-cardiac surgery corresponds to the minimal time interval that allows offsetting of the bleeding risk associated with the antiplatelet effect.

Table 3 | Ongoing studies on the perioperative management of patients at risk of cardiovascular complications

Study name	Study design	Number of patients	Study aims	Study intervention	Primary outcome	Refs
Cardiac risk assessment						
MET-REPAIR	Prospective observational registry	15,000	Determine the capacity of metabolic equivalent (estimated using a questionnaire) to predict perioperative cardiovascular events and improve risk stratification of established risk scores	NA	In-hospital cardiovascular mortality, non-fatal cardiac arrest, acute MI, stroke or congestive heart failure	230
Perioperative management						
PROTECT	Randomized, single-blind, controlled trial	5,100	Evaluate the efficacy of aggressive perioperative warming	Aggressive thermal management (target intraoperative core temperature 37.0–37.5 °C) versus routine thermal management (>35.5 °C)	Myocardial injury, non-fatal cardiac arrest or all-cause mortality at 30 days	231
PRINCE	Randomized, double-blind, sham-controlled trial	1,100	Assess the efficacy of preoperative remote ischaemic preconditioning in patients with ongoing or recently suspended antiplatelet therapy	Three cycles of 5-min ischaemic preconditioning through a BP cuff inflated to 200 mmHg, followed by 5-min reperfusion while the cuff is deflated	Myocardial injury at 1 week	232
NORMALIZE	Randomized, single-blind, controlled trial	420	Compare standardized BP management with individualized BP management using noradrenaline infusion	Standardized BP management (target mean BP >65 mmHg and systolic BP <160 mmHg) versus individualized BP management (target of 20% variation from preoperative BP)	Myocardial injury at 1 day	233
iPEGASUS	Randomized, single-blind, controlled trial	380	Test the efficacy of perioperative, algorithm-driven haemodynamic therapy on the basis of individualized fluid and cardiac output optimization	Individualized goal-directed therapy versus established basic treatment goals	Morbidity and mortality at 28 days	234
Pharmacological strategies						
POISE-3	Randomized, double-blind, placebo-controlled trial with partial factorial design	10,000	Aim 1: evaluate the efficacy of perioperative tranexamic acid in preventing bleeding complications	Aim 1: tranexamic acid (1 g) 20 min before the procedure and another dose (1 g) at the end of the procedure versus placebo	Aim 1: life-threatening, major or critical organ bleeding at 30 days (superiority); presence of MI, non-haemorrhagic stroke, peripheral arterial thrombosis or symptomatic proximal venous thromboembolism at 30 days (non-inferiority)	235
			Aim 2: determine the efficacy of a hypotension-avoidance strategy in preventing adverse vascular events	Aim 2: perioperative hypotension-avoidance strategy versus perioperative hypertension-avoidance strategy	Aim 2: vascular death, MI, stroke or non-fatal cardiac arrest at 30 days	
STOP-or-NOT	Randomized, open-label, controlled trial	2,222	Assess the effect of perioperative RAAS inhibitor management in patients on chronic RAAS-inhibitor therapy	Perioperative continuation versus discontinuation (48 h before surgery) of RAAS inhibitor therapy	All-cause mortality or major postoperative complications at 28 days	101,236
ORION	Randomized, double-blind, placebo-controlled trial	600	Evaluate the efficacy of perioperative metoprolol therapy	Up to three intravenous doses of 5 mg of metoprolol before extubation, followed by 25 mg oral metoprolol three times a day for 72 h	Myocardial injury at 72 h	237

Table 3 (cont.) | Ongoing studies on the perioperative management of patients at risk of cardiovascular complications

Study name	Study design	Number of patients	Study aims	Study intervention	Primary outcome	Refs
Pharmacological strategies (cont.)						
IMPROVE	Randomized, double-blind, placebo-controlled trial	230	Evaluate the efficacy of perioperative levosimendan therapy	Levosimendan infusion (12.5 mg) started after surgical skin incision	Serum NT-proBNP levels at 5 days	238
COPMAN	Randomized, double-blind, placebo-controlled trial	180	Determine the feasibility of perioperative colchicine therapy	Colchicine (0.6 mg) 1 h before surgery, then a 0.6-mg dose twice daily for 7 days or until hospital discharge	Number of eligible patients recruited in 3 months (primary outcome); myocardial injury at 7 days (secondary outcome)	239
Antiplatelet management						
ASSURE-DES	Randomized, open-label, controlled trial	900	Assess the safety and efficacy of perioperative antiplatelet therapy 12 months after drug-eluting stent implantation	Aspirin versus no antiplatelet therapy	All-cause death, stent thrombosis, MI or stroke at 30 days	240
CNCS	Prospective observational registry	12,000	Investigate the contemporary antithrombotic management of patients referred for cardiac and non-cardiac surgery while on chronic antiplatelet and/or anticoagulant therapy	NA	Death, MI, ischaemic stroke, need for urgent revascularization, or bleeding from 14 days before non-cardiac surgery to 30 days after non-cardiac surgery	241
MONET BRIDGE	Randomized, double-blind, placebo-controlled trial	140	Assess the safety of preoperative bridging with cangrelor therapy in patients undergoing non-deferrable cardiac or non-cardiac surgery who discontinue P2Y ₁₂ inhibitor therapy	Cangrelor infusion (0.75 µg/kg/min) started after P2Y ₁₂ inhibitor therapy discontinuation throughout the preoperative period	Residual platelet reactivity within 1–2 h of infusion initiation (primary outcome); BARC 3–5 bleeding at 30 days (secondary outcome)	212

BARC, Bleeding Academic Research Consortium; BP, blood pressure; MI, myocardial infarction; NA, not applicable; NT-proBNP, N-terminal pro-B-type natriuretic peptide; P2Y₁₂, P2Y purinoceptor 12; RAAS, renin–angiotensin–aldosterone system.

Discontinuation of oral P2Y₁₂ inhibitors should be judiciously timed according to the date of surgery. The minimum delay for non-cardiac surgery after P2Y₁₂ inhibitor discontinuation is 5 days for clopidogrel, 3 days for ticagrelor and 7 days for prasugrel¹¹⁰. However, these time frames vary according to different national and specialty guidelines, with a recommended discontinuation period for P2Y₁₂ inhibitors as long as 7–10 days before surgery^{109,111,192}. If aspirin also needs to be interrupted, the clearance of its irreversible antiplatelet effect requires 7–10 days (corresponding to the average lifespan of a platelet) for complete turnover of circulating platelets. Nonetheless, full restoration of aspirin-inhibited platelet function is not necessary to achieve sufficient haemostatic competence^{193–195}. Therefore, discontinuing aspirin 3–5 days before surgery might be sufficient for most major invasive procedures^{39,192,196}.

After surgery and once haemostasis has been achieved, oral P2Y₁₂ inhibitors should be restarted with a loading dose as soon as possible (optimally within 48 h)^{110,143}. In patients at high risk of bleeding complications, clopidogrel should be favoured over more potent agents. If gastrointestinal function is impaired postoperatively (such as in patients who have undergone abdominal surgery), intravenous infusion of antiplatelet agents can be used until recovery¹³⁰.

Non-deferrable surgery

Restoration of platelet function

If urgent or emergency major procedures are indicated in patients on antiplatelet therapy, restoration of platelet function might be attempted via platelet transfusion^{197,198}. Platelet transfusions should be given only after the active metabolites of the oral antiplatelet agents are no longer detectable in the bloodstream to avoid inhibition of the newly transfused platelets. In particular, platelet transfusions should be avoided within 4–6 h of the last dose of thienopyridine and 10–12 h of the last dose of ticagrelor¹⁹⁹. However, these time constraints might limit the feasibility of platelet transfusions, especially in situations that require immediate neutralization of the antiplatelet effect that is causing the excessive bleeding.

At present, rapid-acting reversal agents for antiplatelet drugs are not commercially available. A recombinant human monoclonal antibody-based antidote for ticagrelor is currently under clinical development and has already shown promising results in healthy volunteers²⁰⁰.

Bridging protocols

Bridging of antiplatelet therapy involves a temporary shift from an oral to an intravenous antiplatelet regimen^{129,201}. The reason for considering an intravenous agent is the

rapid onset and offset of its antiplatelet effects. This strategy might be useful in patients on DAPT undergoing non-deferrable surgery, in whom withholding or continuing antiplatelet therapy entails a prohibitive risk of either thrombotic or bleeding complications¹³⁰. Of note, bridging patients requiring DAPT implies the use of an antiplatelet, and not an anticoagulant, agent²⁰¹. Indeed, perioperative use of parenteral anticoagulants (such as unfractionated heparin and low-molecular-weight heparin) is associated with an increased risk of bleeding^{202,203}. Moreover, unfractionated heparin is an inducer of platelet activation that potentially favours the occurrence of thromboembolic events^{202–205}.

Cangrelor and small-molecule glycoprotein IIb/IIIa (GPIIb/IIIa) inhibitors are the only intravenous antiplatelet agents available for clinical use, but the two drug types have different pharmacological properties^{206–208} (FIG. 5). Cangrelor induces immediate platelet inhibition through reversible binding of the P2Y₁₂ receptor. Given the short half-life of cangrelor (3–5 min), platelet function is restored within 30–60 min of cessation of infusion²⁰⁹. Cangrelor has been evaluated as a bridging therapy for surgery in the randomized, placebo-controlled, phase II BRIDGE trial²¹⁰, which involved thienopyridine-treated patients undergoing CABG surgery. This trial included a dose-finding phase, which identified a dosing regimen defined as ‘thienopyridine-like’ that did not suppress platelet reactivity to the extent of the PCI dosing regimen of cangrelor, with the goal of minimizing bleeding complications when used as a bridging agent. However, real-world data on clinical experience remain limited²¹¹. The MONET BRIDGE trial is currently underway and will help to uncover the utility of cangrelor in patients who need to discontinue DAPT because of non-cardiac surgery within 12 months of stent placement²¹².

Small-molecule GPIIb/IIIa inhibitors (eptifibatide or tirofiban) provide nearly complete suppression of platelet aggregation by targeting the GPIIb/IIIa receptor on the platelet surface²¹³. In contrast to cangrelor, no dedicated bridging dose regimen with GPIIb/IIIa inhibitors has been established. GPIIb/IIIa inhibitors are currently used at the PCI dose known to have a

slower offset of action, and require dose adjustments in patients with reduced creatinine clearance^{208,213}. Overall, these characteristics increase the potential for perioperative bleeding complications and have resulted in reduced frequency of the use of GPIIb/IIIa inhibitors in contemporary practice, being mainly limited to bail-out situations for large intraprocedural thrombus burden²⁰⁸. Although small-molecule GPIIb/IIIa inhibitors might be considered an alternative to cangrelor for perioperative bridging, specific data from patients with recent stent implantation undergoing non-deferrable surgery are scarce, and previous experience in other clinical settings suggests that concern over safety in their use is warranted^{208,214,215}.

According to the European guidelines, a bridging strategy with intravenous antiplatelet agents might be considered if both aspirin and P2Y₁₂ inhibitor therapy have to be discontinued perioperatively, especially within 1 month of PCI¹⁰. By contrast, the US guidelines do not provide specific recommendations on bridging and acknowledge the absence of convincing evidence in support of this practice²¹⁶.

Perioperative management of OAC therapy

Two key scenarios involving the management of patients with CAD on oral anticoagulant (OAC) therapy undergoing non-cardiac surgery can occur, which essentially depend on whether the patient has had previous PCI. A patient with previous PCI can theoretically be referred for surgery while on triple antithrombotic therapy, dual antithrombotic therapy or OAC therapy alone²¹⁷. Conversely, patients with stable CAD who have not had PCI will generally be on OAC therapy alone, unless a high risk of ischaemic events is perceived that outweighs the risk of bleeding, justifying the addition of a single antiplatelet agent^{218,219}. However, this strategy is not supported by the results of the 2019 AFIRE trial²²⁰, which demonstrated that the addition of aspirin or a P2Y₁₂ inhibitor to rivaroxaban increased the risk of all-cause death. Given that OAC use in the setting of non-cardiac surgery is a risk factor for bleeding, considerations on the risk–benefit trade-off of antithrombotic therapy might lead to re-evaluation and simplification of the initial antiplatelet strategy in patients with CAD with or without a coronary stent¹⁷⁷.

Approximately one quarter of patients on OAC therapy require temporary interruption within 2 years of initiation of therapy owing to the need for an invasive procedure²²¹. In warfarin-treated patients, the BRIDGE trial²²² showed that foregoing bridging anticoagulation is non-inferior to bridging with low-molecular-weight heparin with regard to the incidence of arterial thromboembolism, and is associated with fewer bleeding events. In the PAUSE study²²³, standardized risk-adjusted protocols to guide perioperative non-vitamin K OAC (NOAC) interruption without heparin bridging or coagulation testing were associated with overall low rates of major bleeding and arterial thromboembolism.

The 2018 European Heart Rhythm Association guidelines on the use of NOACs in patients with atrial fibrillation provide practical recommendations for their perioperative management on the basis of surgical

Table 4 | Perioperative antiplatelet management according to thrombotic and bleeding risk

Bleeding risk	Thrombotic risk		
	Low	Intermediate	High
Low	Aspirin: continue ^a	Aspirin: continue	Aspirin: continue
	P2Y ₁₂ inhibitor: stop	P2Y ₁₂ inhibitor: continue ^a	P2Y ₁₂ inhibitor: continue
Intermediate	Aspirin: continue ^a	Aspirin: continue	Aspirin: continue
	P2Y ₁₂ inhibitor: stop	P2Y ₁₂ inhibitor: stop	P2Y ₁₂ inhibitor: stop Consider bridging
High	Aspirin: stop ^b	Aspirin: continue ^b	Aspirin: continue
	P2Y ₁₂ inhibitor: stop	P2Y ₁₂ inhibitor: stop	P2Y ₁₂ inhibitor: stop Consider bridging

Based on REFS^{130,165,192}. P2Y₁₂, P2Y purinoceptor 12. ^aExcept for neurosurgery. ^bConsensus-based recommendations among different surgical specialties show partial agreement.

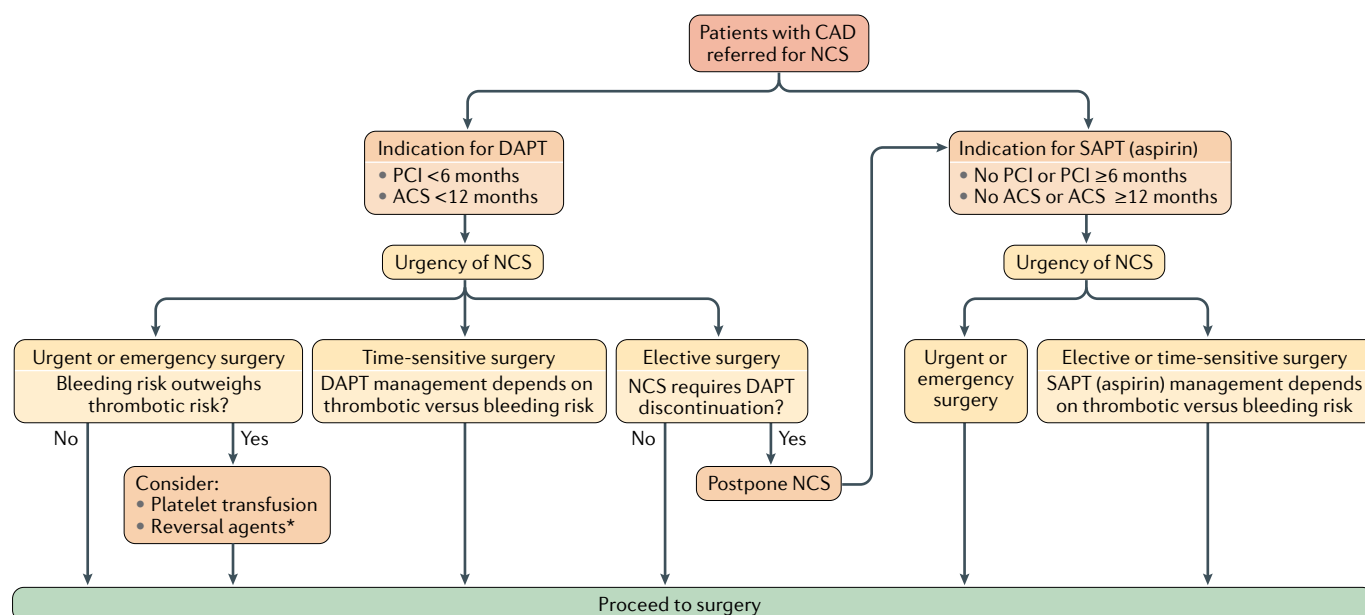


Fig. 4 | Proposed algorithm for perioperative management of antiplatelet therapy in patients with CAD referred for non-cardiac surgery. Perioperative management of antiplatelet therapy in patients with coronary artery disease (CAD) referred for non-cardiac surgery (NCS) primarily depends on the clinical indication for the antiplatelet therapy. In patients receiving dual antiplatelet therapy (DAPT) because of a recent percutaneous coronary intervention (PCI) or acute coronary syndrome (ACS), the first step is to determine the urgency of surgery. In case of emergency (that is, required to be in the operating room within 6 h) or urgent procedures (that is, required to be in the operating room between 6–24 h), the use of platelet transfusion or antiplatelet reversal agents might be considered before proceeding to surgery if the bleeding risk is high and outweighs the thrombotic risk. A time-sensitive procedure (that is, whereby a surgical delay of 1–6 weeks will negatively affect outcomes) allows sufficient time to manage perioperative DAPT on the basis of individual evaluation of bleeding versus thrombotic risk (TABLE 4). Elective procedures requiring discontinuation of DAPT owing to bleeding risk concerns should be postponed beyond the recommended DAPT course. In patients with an indication for single antiplatelet therapy (SAPT; most commonly aspirin) undergoing non-emergency or non-urgent NCS, the decision to continue SAPT perioperatively must be made on the basis of individual evaluation of bleeding versus thrombotic risk. *At present, no reversal agents are available for antiplatelet drugs; an antidote for ticagrelor is under clinical development.

bleeding risk²²⁴. Minor surgical procedures with minimal bleeding risk can be safely performed without NOAC interruption. In invasive surgeries with low bleeding risk, the last dose of NOAC should be taken 24 h before the procedure if renal function is normal. In the setting of renal dysfunction, the timing of NOAC interruption should be carefully adjusted according to the estimated creatinine clearance, especially in patients receiving dabigatran. For surgical procedures associated with a high risk of bleeding, these time intervals are doubled. In keeping with the results of the BRIDGE²¹⁰ and PAUSE²²³ trials, bridging is not recommended²²⁴. NOAC therapy can be resumed as early as 6–8 h after surgery, although this interval can be longer depending on the haemostatic conditions.

At present, no specific recommendations have been made for the perioperative management of patients treated with a combination of OAC and antiplatelet agents. However, evidence derived from other clinical settings can be used to guide the treatment strategy. The risk of thromboembolic events in patients with atrial fibrillation who are not on OAC therapy has been shown to increase gradually over time^{225,226}. Conversely, thrombotic events associated with the cessation of antiplatelet therapy in patients with recent stent implantation tend to occur, most often, immediately after withdrawal

of platelet inhibition¹⁷⁸. The differential effect of OAC compared with antiplatelet therapy on bleeding complications remains unclear and largely depends on the type and combination of agents being considered, but historical evidence suggests that aspirin monotherapy is the safest regimen in terms of bleeding risk²²⁷. Furthermore, perioperative interruption of NOAC therapy might be more practical than interruption of antiplatelet therapy owing to their rapid offset of action and proven safety even in the absence of bridging protocols²²³. Together, these observations suggest that in patients with both atrial fibrillation and recent PCI on dual or triple antithrombotic therapy who are referred for non-cardiac surgery, perioperative maintenance of antiplatelet therapy and interruption of OAC treatment might often be the most appropriate strategy.

Finally, if an emergency intervention is required, OAC therapy should be promptly interrupted. For urgent procedures, reversal of dabigatran with idarucizumab should be considered²²⁸. The use of andexanet alfa as an antidote for factor Xa inhibitors has not been studied in the setting of non-deferrable surgery²²⁹. If specific reversal agents are not available, use of prothrombin complex concentrates is a viable option. Urgent procedures should be deferred, if possible, for 12–24 h after the last NOAC dose. In such

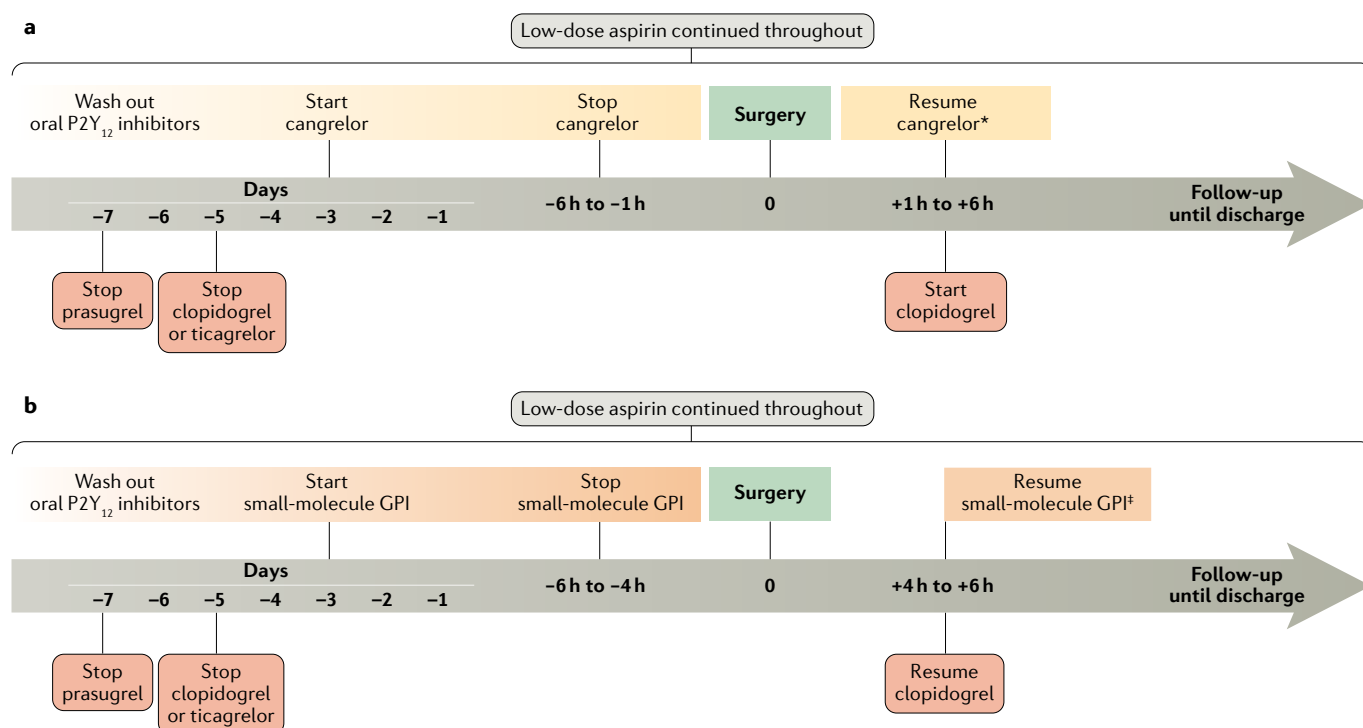


Fig. 5 | Perioperative bridging protocols in patients on DAPT undergoing non-cardiac surgery. a | The figure shows a bridging protocol with cangrelor. A bridging-dose regimen of cangrelor (0.75 µg/kg/min) can be started at the time of the next expected dose of the oral P2Y₁₂ purinoceptor 12 (P2Y₁₂) inhibitor. However, given the presence of residual platelet inhibition after discontinuation of dual antiplatelet therapy (DAPT), the infusion can be postponed for up to 3–4 days after the last dose of prasugrel and 2–3 days after the last dose of clopidogrel or ticagrelor. Infusion with cangrelor should be stopped 1–6 h before surgery. After surgery, clopidogrel therapy should be restarted with a loading dose (300–600 mg) as soon as the bleeding risk is acceptable. Prasugrel and ticagrelor administration is discouraged early after surgery. **b** | The figure shows a bridging protocol using the small-molecule glycoprotein IIb/IIIa inhibitor (GPI) tirofiban or eptifibatide. A bridging dose of small-molecule GPI (tirofiban 0.1 µg/kg/min or eptifibatide 2.0 µg/kg/min) should be started 3–4 days after the last dose

of prasugrel and 2–3 days after the last dose of clopidogrel or ticagrelor, and stopped 4–6 h before surgery. In patients with impaired renal function (creatinine clearance <50 ml/min), dose reduction (tirofiban 0.05 µg/kg/min or eptifibatide 1.0 µg/kg/min) and earlier pre-procedural discontinuation (between 8 h and 12 h) of small-molecule GPI is warranted. Post-surgery management is as described in panel **a**. *If oral administration of P2Y₁₂ inhibitors is not possible, postoperative bridging with cangrelor might be considered. †If oral administration of P2Y₁₂ inhibitors is not possible, postoperative bridging with small-molecule GPI might be considered. Part **a** adapted with permission from Angiolillo et al. International expert consensus on switching platelet P2Y₁₂ receptor-inhibiting therapies. *Circulation* **136**, 1955–1975 (2017)²⁰⁶, Wolters Kluwer. Part **b** adapted with permission from Capodanno. & Angiolillo Management of antiplatelet therapy in patients with coronary artery disease requiring cardiac and noncardiac surgery. *Circulation* **128**, 2785–2798 (2013)²⁰⁷, Wolters Kluwer.

situations, a full panel of coagulation assays should be obtained²²⁴.

Conclusions

Patients with CAD are a vulnerable subgroup of the population undergoing non-cardiac surgery owing to their increased susceptibility to adverse cardiac events caused by surgical stress. Clinical decisions regarding preoperative risk assessment and perioperative management are complex and need to be individualized. The estimation of the cardiac risk specific to each patient is contingent on the careful evaluation of the clinical profile within the context of the type and urgency of the surgical procedure. During the past two decades conflicting evidence on the role of different pharmacological and interventional strategies aimed at reducing perioperative complications in patients with established cardiovascular disease has been generated, leaving several questions unanswered (BOX 1). These uncertainties have resulted in international societies issuing recommendations with limited applicability to daily practice. In particular, ambiguity surrounding

the perioperative management of DAPT in patients with recent coronary stenting raises the most concern. Although this ambiguity might partly be a knee-jerk reaction to past experiences of late stent thrombosis with first-generation devices, there remains a subset of surgical patients in whom perioperative withdrawal of antiplatelet therapy could be potentially fatal. As a general rule, the postponement of elective non-cardiac surgery should be considered until completion of the recommended DAPT course. If the surgery cannot be deferred, the decision to continue or withhold antiplatelet therapy must involve all multidisciplinary specialists involved in perioperative care. Such a collaborative approach is critical to understanding the relative influence of several patient-related and surgery-related factors on the risk of bleeding and thrombotic complications. Bridging protocols with intravenous antiplatelet agents have been proposed for the perioperative management of selected patients at high risk of cardiac complications; however, clinical data in support of these practices are still limited. Ultimately, as the treatment paradigm of CAD keeps evolving, there

Box 1 | Non-cardiac surgery in patients with CAD: gaps in knowledge

Individualized treatment is crucial for optimizing clinical outcomes in patients at high risk of cardiac complications undergoing non-cardiac surgery, but can only be achieved through a direct collaboration between the various medical specialties involved in perioperative care. Research has evolved in different directions to address the numerous issues within this multidisciplinary field. Advances in cardiac risk assessment, intraoperative monitoring and treatment in patients undergoing non-cardiac surgery have contributed to the progressive decline in risk-adjusted mortality. Nonetheless, important gaps in knowledge still exist and many proposed risk-reduction strategies have yet to be proven effective. Although research efforts should continue to aim for the most rigorous scientific evidence through randomized clinical trials, alternative study designs that are more feasible and inexpensive (such as observational registries and pragmatic registry-based trials) are also necessary to advance our knowledge on the many aspects relevant to this patient population.

Cardiac biomarkers

Widespread availability of cardiac biomarker assays has highlighted prognostic implications of perioperative myocardial injury, especially in asymptomatic patients^{59,60,67}. However, the aetiology of this phenomenon is complex and often involves multiple mechanisms that are not always apparent or preventable. Whether prompt and systematic detection of cardiac biomarker levels has the potential to translate into a real clinical benefit remains unclear. Identification of actionable causes leading to the elevation of cardiac biomarkers is essential for the identification of appropriate treatment strategies.

Cardiac imaging

Advanced cardiac imaging modalities, such as coronary CT angiography and cardiac MRI, allow accurate morphological and functional assessment of the myocardium, and are thus valuable tools for perioperative screening and risk stratification of patients with coronary artery disease (CAD)^{40,41}. However, given that these techniques are limited by high costs and patient exposure to ionizing radiation, pharmacological stressors and contrast media, detailed recommendations on their appropriate use in the perioperative setting are needed.

Platelet function

Tailoring the timing of surgery on the basis of platelet function assessment in patients who require preoperative discontinuation of antiplatelet therapy is an example of an individualized management strategy to improve outcomes, shorten the length of hospital stay and reduce costs. Studies have consistently demonstrated a strong association between levels of platelet reactivity and risk of bleeding and thrombosis, but the clinical applications of platelet function assessment remain limited¹¹⁵. Dedicated clinical trials are needed to define the appropriate cut-off values of platelet reactivity that dictate when surgery can be safely performed.

Intraoperative measures

Growing data suggest that individualizing goals for perioperative haemodynamic management can reduce surgical complications⁴⁸. Development of artificial intelligence-based systems might help facilitate prompt detection and response to imminent adverse events⁵⁰. Despite limited evidence on this topic, initial findings are promising and dedicated research is underway.

Management of antiplatelet therapy

Advances in stent technology, adoption of intravenous antiplatelet bridging regimens and the development of novel therapeutic targets will inevitably alter the perioperative management of patients with CAD undergoing surgery, with the possible advantage of reducing surgical waiting times in those who have undergone recent stent implantation. Prospective studies are needed to assess how contemporary advances in both drug and device therapy will change clinical practice and inform future updates of guideline recommendations.

remains a compelling need for evidence that is relevant to a more contemporary population. Refined stent technologies and novel therapeutic targets, including inflammation, have broadened the armamentarium of treatment options in patients with CAD. Whether these innovations

have the potential to improve quality of care and clinical outcomes in patients with CAD undergoing non-cardiac surgery is yet to be seen.

Published online: 05 August 2020

- Smilowitz, N. R. et al. Perioperative major adverse cardiovascular and cerebrovascular events associated with noncardiac surgery. *JAMA Cardiol.* **2**, 181–187 (2017).
- Weiser, T. G. et al. Estimate of the global volume of surgery in 2012: an assessment supporting improved health outcomes. *Lancet* **385**, S11 (2015).
- Sabaté, S. et al. Incidence and predictors of major perioperative adverse cardiac and cerebrovascular events in non-cardiac surgery. *Br. J. Anaesth.* **107**, 879–890 (2011).
- Holcomb, C. N. et al. The incremental risk of coronary stents on postoperative adverse events. *Ann. Surg.* **263**, 924–930 (2016).
- Cohen, M. C. & Aretz, T. H. Histological analysis of coronary artery lesions in fatal postoperative myocardial infarction. *Cardiovasc. Pathol.* **8**, 133–139 (1999).
- Biccard, B. M. & Rodseth, R. N. The pathophysiology of peri-operative myocardial infarction. *Anaesthesia* **65**, 733–741 (2010).
- Landesberg, G., Beattie, W. S., Mosseri, M., Jaffe, A. S. & Alpert, J. S. Perioperative myocardial infarction. *Circulation* **119**, 2936–2944 (2009).
- Ellis, S. G., Hertzner, N. R., Young, J. R. & Brenner, S. Angiographic correlates of cardiac death and myocardial infarction complicating major nonthoracic vascular surgery. *Am. J. Cardiol.* **77**, 1126–1128 (1996).
- Dawood, M. M. et al. Pathology of fatal perioperative myocardial infarction: implications regarding pathophysiology and prevention. *Int. J. Cardiol.* **57**, 37–44 (1996).
- Kristensen, S. D. et al. 2014 ESC/ESA guidelines on non-cardiac surgery: cardiovascular assessment and management: The Joint Task Force on non-cardiac surgery: cardiovascular assessment and management of the European Society of Cardiology (ESC) and the European Society of Anaesthesiology (ESA). *Eur. Heart J.* **35**, 2383–2431 (2014).
- Fleisher, L. A. et al. 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines. *J. Am. Coll. Cardiol.* **64**, e77–e137 (2014).
- Lee, T. H. et al. Derivation and prospective validation of a simple index for prediction of cardiac risk of major noncardiac surgery. *Circulation* **100**, 1043–1049 (1999).
- Gupta, P. K. et al. Development and validation of a risk calculator for prediction of cardiac risk after surgery. *Circulation* **124**, 381–387 (2011).
- Bilimoria, K. Y. et al. Development and evaluation of the universal ACS NSQIP surgical risk calculator: a decision aid and informed consent tool for patients and surgeons. *J. Am. Coll. Surg.* **217**, 833–842.e3 (2013).
- Ford, M. K., Beattie, W. S. & Wijesundera, D. N. Systematic review: prediction of perioperative cardiac complications and mortality by the revised cardiac risk index. *Ann. Intern. Med.* **152**, 26–35 (2010).

16. Andersson, C. et al. Age-specific performance of the revised cardiac risk index for predicting cardiovascular risk in elective noncardiac surgery. *Circ. Cardiovasc. Qual. Outcomes* **8**, 103–108 (2015).
17. Shiloach, M. et al. Toward robust information: data quality and inter-rater reliability in the American College of Surgeons National Surgical Quality Improvement Program. *J. Am. Coll. Surg.* **210**, 6–16 (2010).
18. Cohen, M. E. et al. Optimizing ACS NSQIP modeling for evaluation of surgical quality and risk: patient risk adjustment, procedure mix adjustment, shrinkage adjustment, and surgical focus. *J. Am. Coll. Surg.* **217**, 336–346.e1 (2013).
19. Raymond, B. L. et al. Use of the American College of Surgeons National Surgical Quality Improvement Program Surgical Risk Calculator during preoperative risk discussion: the patient perspective. *Anesth. Analg.* **128**, 643–650 (2019).
20. Glance, L. G. et al. The Surgical Mortality Probability Model: derivation and validation of a simple risk prediction rule for noncardiac surgery. *Ann. Surg.* **255**, 696–702 (2012).
21. Norderud, K. et al. Validation of the European Society of Cardiology and European Society of Anaesthesiology non-cardiac surgery risk score in patients treated with coronary drug-eluting stent implantation. *Eur. Heart J. Qual. Care Clin. Outcomes* **5**, 22–27 (2019).
22. Schein, O. D. et al. The value of routine preoperative medical testing before cataract surgery. *N. Engl. J. Med.* **342**, 168–175 (2000).
23. van Klei, W. A. et al. The value of routine preoperative electrocardiography in predicting myocardial infarction after noncardiac surgery. *Ann. Surg.* **246**, 165–170 (2007).
24. Richardson, K. M. et al. Prognostic significance and clinical utility of intraoperative conduction delays on the preoperative electrocardiogram. *Am. J. Cardiol.* **121**, 997–1003 (2018).
25. Hlatky, M. A. et al. A brief self-administered questionnaire to determine functional capacity (the Duke Activity Status Index). *Am. J. Cardiol.* **64**, 651–654 (1989).
26. Wijesundera, D. N. et al. Assessment of functional capacity before major non-cardiac surgery: an international, prospective cohort study. *Lancet* **391**, 2631–2640 (2018).
27. Carliner, N. H. et al. Routine preoperative exercise testing in patients undergoing major noncardiac surgery. *Am. J. Cardiol.* **56**, 51–58 (1985).
28. Gauss, A. et al. Electrocardiographic exercise stress testing for cardiac risk assessment in patients undergoing noncardiac surgery. *Anesthesiology* **94**, 38–46 (2001).
29. Young, E. L. et al. A systematic review of the role of cardiopulmonary exercise testing in vascular surgery. *Eur. J. Vasc. Endovasc. Surg.* **44**, 64–71 (2012).
30. Stubbs, D. J., Grimes, L. A. & Ercole, A. Performance of cardiopulmonary exercise testing for the prediction of post-operative complications in non cardiopulmonary surgery: a systematic review. *PLoS ONE* **15**, e0226480 (2020).
31. Boersma, E. et al. Predictors of cardiac events after major vascular surgery: role of clinical characteristics, dobutamine echocardiography, and β -blocker therapy. *JAMA* **285**, 1865–1873 (2001).
32. Das, M. K. et al. Assessment of cardiac risk before nonvascular surgery: dobutamine stress echocardiography in 530 patients. *J. Am. Coll. Cardiol.* **35**, 1647–1653 (2000).
33. Kalesan, B., Nicewarner, H., Intwala, S., Leung, C. & Balady, G. J. Pre-operative stress testing in the evaluation of patients undergoing non-cardiac surgery: a systematic review and meta-analysis. *PLoS ONE* **14**, e0219145 (2019).
34. Karthikeyan, G. et al. Is a pre-operative brain natriuretic peptide or N-terminal pro-B-type natriuretic peptide measurement an independent predictor of adverse cardiovascular outcomes within 30 days of noncardiac surgery? A systematic review and meta-analysis of observational studies. *J. Am. Coll. Cardiol.* **54**, 1599–1606 (2009).
35. Rodseth, R. N., Padayachee, L. & Biccadd, B. M. A meta-analysis of the utility of pre-operative brain natriuretic peptide in predicting early and intermediate-term mortality and major adverse cardiac events in vascular surgical patients. *Anaesthesia* **63**, 1226–1233 (2008).
36. Ryding, A. D., Kumar, S., Worthington, A. M. & Burgess, D. Prognostic value of brain natriuretic peptide in noncardiac surgery: a meta-analysis. *Anesthesiology* **111**, 311–319 (2009).
37. Weber, M. et al. Incremental value of high-sensitive troponin T in addition to the revised cardiac index for peri-operative risk stratification in non-cardiac surgery. *Eur. Heart J.* **34**, 853–862 (2013).
38. Mol, K. et al. Preoperative coronary angiography in vascular surgery patients with asymptomatic elevated high-sensitivity troponin T: a case series. *Br. J. Anaesth.* **123**, 565–569 (2019).
39. Ducepe, E. et al. Canadian Cardiovascular Society guidelines on perioperative cardiac risk assessment and management for patients who undergo noncardiac surgery. *Can. J. Cardiol.* **33**, 17–32 (2017).
40. Hwang, J. W. et al. Assessment of perioperative cardiac risk of patients undergoing noncardiac surgery using coronary computed tomographic angiography. *Circ. Cardiovasc. Imaging* **8**, e002582 (2015).
41. Sheth, T. et al. Prognostic capabilities of coronary computed tomographic angiography before non-cardiac surgery: prospective cohort study. *BMJ* **350**, h1907 (2015).
42. Illuminati, G. et al. Systematic preoperative coronary angiography and stenting improves postoperative results of carotid endarterectomy in patients with asymptomatic coronary artery disease: a randomised controlled trial. *Eur. J. Vasc. Endovasc. Surg.* **39**, 139–145 (2010).
43. Thygesen, K. et al. Fourth universal definition of myocardial infarction (2018). *Eur. Heart J.* **40**, 237–269 (2019).
44. Abbott, T. E. F. et al. Preoperative heart rate and myocardial injury after non-cardiac surgery: results of a predefined secondary analysis of the VISION study. *Br. J. Anaesth.* **117**, 172–181 (2016).
45. van Waes, J. A. et al. Association between intraoperative hypotension and myocardial injury after vascular surgery. *Anesthesiology* **124**, 35–44 (2016).
46. Sessler, D. I. & Khanna, A. K. Perioperative myocardial injury and the contribution of hypotension. *Intensive Care Med.* **44**, 811–822 (2018).
47. Sessler, D. I. et al. Perioperative quality initiative consensus statement on intraoperative blood pressure, risk and outcomes for elective surgery. *Br. J. Anaesth.* **122**, 563–574 (2019).
48. Futier, E. et al. Effect of individualized vs standard blood pressure management strategies on postoperative organ dysfunction among high-risk patients undergoing major surgery: a randomized clinical trial. *JAMA* **318**, 1346–1357 (2017).
49. Turan, A. et al. Incidence, severity, and detection of blood pressure perturbations after abdominal surgery: a prospective blinded observational study. *Anesthesiology* **130**, 550–559 (2019).
50. Wijnberge, M. et al. Effect of a machine learning-derived early warning system for intraoperative hypotension vs standard care on depth and duration of intraoperative hypotension during elective noncardiac surgery: the HYPE randomized clinical trial. *JAMA* **323**, 1052–1060 (2020).
51. Akata, T. General anesthetics and vascular smooth muscle: direct actions of general anesthetics on cellular mechanisms regulating vascular tone. *Anesthesiology* **106**, 365–391 (2007).
52. Torri, G. Inhalation anesthetics: a review. *Minerva Anestesiol.* **76**, 215–228 (2010).
53. Veering, B. T. & Cousins, M. J. Cardiovascular and pulmonary effects of epidural anaesthesia. *Anaesth. Intensive Care* **28**, 620–635 (2000).
54. de Wit, F. et al. The effect of propofol on haemodynamics: cardiac output, venous return, mean systemic filling pressure, and vascular resistances. *Br. J. Anaesth.* **116**, 784–789 (2016).
55. Guay, J. et al. Neuraxial blockade for the prevention of postoperative mortality and major morbidity: an overview of Cochrane systematic reviews. *Cochrane Database Syst. Rev.* **1**, CD010108 (2014).
56. Guay, J. & Kopp, S. Epidural pain relief versus systemic opioid-based pain relief for abdominal aortic surgery. *Cochrane Database Syst. Rev.* **1**, CD005059 (2016).
57. Uhlig, C. 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* **124**, 1230–1245 (2016).
58. Devereaux, P. J. et al. Characteristics and short-term prognosis of perioperative myocardial infarction in patients undergoing noncardiac surgery: a cohort study. *Ann. Intern. Med.* **154**, 523–528 (2011).
59. Devereaux, P. J. et al. Association between postoperative troponin levels and 30-day mortality among patients undergoing noncardiac surgery. *JAMA* **307**, 2295–2304 (2012).
60. Devereaux, P. J. et al. Association of postoperative high-sensitivity troponin levels with myocardial injury and 30-day mortality among patients undergoing noncardiac surgery. *JAMA* **317**, 1642–1651 (2017).
61. Devereaux, P. J. & Szczeklik, W. Myocardial injury after non-cardiac surgery: diagnosis and management. *Eur. Heart J.* <https://doi.org/10.1093/eurheartj/ehz301> (2019).
62. Duvall, W. L. et al. Angiographic investigation of the pathophysiology of perioperative myocardial infarction. *Catheterization Cardiovasc. Interv.* **80**, 768–776 (2012).
63. Sheth, T. et al. Incidence of thrombosis in perioperative and non-operative myocardial infarction. *Br. J. Anaesth.* **120**, 725–733 (2018).
64. Helwani, M. A. et al. Etiology of acute coronary syndrome after noncardiac surgery. *Anesthesiology* **128**, 1084–1091 (2018).
65. Puelacher, C. et al. Perioperative myocardial injury after noncardiac surgery: incidence, mortality, and characterization. *Circulation* **137**, 1221–1232 (2018).
66. Rodseth, R. N. et al. Postoperative B-type natriuretic peptide for prediction of major cardiac events in patients undergoing noncardiac surgery: systematic review and individual patient meta-analysis. *Anesthesiology* **119**, 270–283 (2013).
67. Rodseth, R. N. et al. The prognostic value of pre-operative and post-operative B-type natriuretic peptides in patients undergoing noncardiac surgery: B-type natriuretic peptide and N-terminal fragment of pro-B-type natriuretic peptide: a systematic review and individual patient data meta-analysis. *J. Am. Coll. Cardiol.* **63**, 170–180 (2014).
68. US National Library of Medicine. *ClinicalTrials.gov* <https://clinicaltrials.gov/ct2/show/NCT03765372> (2019).
69. US National Library of Medicine. *ClinicalTrials.gov* <https://clinicaltrials.gov/ct2/show/NCT03436238> (2019).
70. Luepker, R. V. et al. Population trends in aspirin use for cardiovascular disease prevention 1980–2009: the Minnesota Heart Survey. *J. Am. Heart Assoc.* **4**, e002320 (2015).
71. Merritt, J. C. & Bhatt, D. L. The efficacy and safety of perioperative antiplatelet therapy. *J. Thromb. Thrombolysis* **17**, 21–27 (2004).
72. Burger, W., Chemnitz, J. M., Kneissl, G. D. & Rucker, G. Low-dose aspirin for secondary cardiovascular prevention – cardiovascular risks after its perioperative withdrawal versus bleeding risks with its continuation – review and meta-analysis. *J. Intern. Med.* **257**, 399–414 (2005).
73. Devereaux, P. J. et al. Aspirin in patients undergoing noncardiac surgery. *N. Engl. J. Med.* **370**, 1494–1503 (2014).
74. Graham, M. M. et al. Aspirin in patients with previous percutaneous coronary intervention undergoing noncardiac surgery. *Ann. Intern. Med.* **168**, 237–244 (2018).
75. Mantz, J. et al. Impact of preoperative maintenance or interruption of aspirin on thrombotic and bleeding events after elective non-cardiac surgery: the multicentre, randomized, blinded, placebo-controlled, STRATAGEM trial. *Br. J. Anaesth.* **107**, 899–910 (2011).
76. van Waes, J. A. et al. Myocardial injury after noncardiac surgery and its association with short-term mortality. *Circulation* **127**, 2264–2271 (2013).
77. Botto, F. et al. Myocardial injury after noncardiac surgery: a large, international, prospective cohort study establishing diagnostic criteria, characteristics, predictors, and 30-day outcomes. *Anesthesiology* **120**, 564–578 (2014).
78. US National Library of Medicine. *ClinicalTrials.gov* <https://clinicaltrials.gov/ct2/show/NCT02291419> (2017).
79. Devereaux, P. J. et al. Dabigatran in patients with myocardial injury after non-cardiac surgery (MANAGE): an international, randomised, placebo-controlled trial. *Lancet* **391**, 2325–2334 (2018).
80. Adriaenssens, T. & Sinnaeve, P. Direct oral anticoagulants for postoperative myocardial injury. *Lancet* **391**, 2297–2298 (2018).
81. Group, P. S. Effects of extended-release metoprolol succinate in patients undergoing non-cardiac surgery (POISE trial): a randomised controlled trial. *Lancet* **371**, 1839–1847 (2008).
82. Bourri, S., Shun-Shin, M. J., Cole, G. D., Mayet, J. & Francis, D. P. Meta-analysis of secure randomised controlled trials of β -blockade to prevent perioperative

- death in non-cardiac surgery. *Heart* **100**, 456–464 (2014).
83. Wijesundera, D. N. et al. Perioperative beta blockade in noncardiac surgery: a systematic review for the 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines. *J. Am. Coll. Cardiol.* **64**, 2406–2425 (2014).
84. Blessberger, H. et al. Perioperative beta-blockers for preventing surgery-related mortality and morbidity. *Cochrane Database of Syst. Rev.* **9**, CD004476 (2014).
85. Bangalore, S. et al. Perioperative β blockers in patients having non-cardiac surgery: a meta-analysis. *Lancet* **372**, 1962–1976 (2008).
86. Devereaux, P. et al. How strong is the evidence for the use of perioperative β blockers in non-cardiac surgery? Systematic review and meta-analysis of randomised controlled trials. *BMJ* **331**, 313–321 (2005).
87. Maron, D. J., Fazio, S. & Linton, M. F. Current perspectives on statins. *Circulation* **101**, 207–213 (2000).
88. Lindenauer, P. K., Pekow, P., Wang, K., Gutierrez, B. & Benjamin, E. M. Lipid-lowering therapy and in-hospital mortality following major noncardiac surgery. *JAMA* **291**, 2092–2099 (2004).
89. Berwanger, O. et al. Association between pre-operative statin use and major cardiovascular complications among patients undergoing non-cardiac surgery: the VISION study. *Eur. Heart J.* **37**, 177–185 (2016).
90. London, M. J., Schwartz, G. G., Hur, K. & Henderson, W. G. Association of perioperative statin use with mortality and morbidity after major noncardiac surgery. *JAMA Intern. Med.* **177**, 231–242 (2017).
91. Berwanger, O. et al. Atorvastatin for high-risk statin-naïve patients undergoing noncardiac surgery: the Lowering the Risk of Operative Complications Using Atorvastatin Loading Dose (LOAD) randomized trial. *Am. Heart J.* **184**, 88–96 (2017).
92. Xia, J., Qu, Y., Yin, C. & Xu, D. Preoperative rosuvastatin protects patients with coronary artery disease undergoing noncardiac surgery. *Cardiology* **131**, 30–37 (2015).
93. Xia, J., Qu, Y., Shen, H. & Liu, X. Patients with stable coronary artery disease receiving chronic statin treatment who are undergoing noncardiac emergency surgery benefit from acute atorvastatin reload. *Cardiology* **128**, 285–292 (2014).
94. Durazzo, A. E. et al. Reduction in cardiovascular events after vascular surgery with atorvastatin: a randomized trial. *J. Vasc. Surg.* **39**, 967–975 (2004).
95. Kennedy, J., Quan, H., Buchan, A. M., Ghali, W. A. & Feasby, T. E. Statins are associated with better outcomes after carotid endarterectomy in symptomatic patients. *Stroke* **36**, 2072–2076 (2005).
96. Verzini, F. et al. Effects of statins on early and late results of carotid stenting. *J. Vasc. Surg.* **53**, 71–79 (2011).
97. O'Donnell, T. F. X. et al. Statin therapy is associated with higher long-term but not perioperative survival after abdominal aortic aneurysm repair. *J. Vasc. Surg.* **68**, 392–399 (2018).
98. Hussain, M. A. et al. Association between statin use and cardiovascular events after carotid artery revascularization. *J. Am. Heart Assoc.* **7**, e009745 (2018).
99. Roshanov, P. S. et al. Withholding versus continuing angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers before noncardiac surgery: an analysis of the vascular events in noncardiac surgery patients cohort evaluation prospective cohort. *Anesthesiology* **126**, 16–27 (2017).
100. Hollmann, C., Fernandes, N. L. & Biccadd, B. M. A systematic review of outcomes associated with withholding or continuing angiotensin-converting enzyme inhibitors and angiotensin receptor blockers before noncardiac surgery. *Anesth. Analg.* **127**, 678–687 (2018).
101. Legrand, M. et al. Impact of renin-angiotensin system inhibitors continuation versus discontinuation on outcome after major surgery: protocol of a multicenter randomized, controlled trial (STOP-or-NOT trial). *Trials* **20**, 160 (2019).
102. Koshy, A. N. et al. Computed tomographic coronary angiography in risk stratification prior to non-cardiac surgery: a systematic review and meta-analysis. *Heart* **105**, 1335–1342 (2019).
103. McFalls, E. O. et al. Coronary-artery revascularization before elective major vascular surgery. *N. Engl. J. Med.* **351**, 2795–2804 (2004).
104. Garcia, S. et al. Usefulness of revascularization of patients with multivessel coronary artery disease before elective vascular surgery for abdominal aortic and peripheral occlusive disease. *Am. J. Cardiol.* **102**, 809–815 (2008).
105. Urban, P. et al. Polymer-free drug-coated coronary stents in patients at high bleeding risk. *N. Engl. J. Med.* **373**, 2038–2047 (2015).
106. Windecker, S. et al. Polymer-based or polymer-free stents in patients at high bleeding risk. *N. Engl. J. Med.* **382**, 1208–1218 (2020).
107. Tantry, U. S. et al. Consensus and update on the definition of on-treatment platelet reactivity to adenosine diphosphate associated with ischemia and bleeding. *J. Am. Coll. Cardiol.* **62**, 2261–2273 (2013).
108. Gurbel, P. A., Mahla, E. & Tantry, U. S. Peri-operative platelet function testing: the potential for reducing ischaemic and bleeding risks. *Thromb. Haemost.* **106**, 248–252 (2011).
109. Douketis, J. D. et al. Perioperative management of antithrombotic therapy: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* **141**, e326S–e350S (2012).
110. Valgimigli, M. et al. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS: The Task Force for dual antiplatelet therapy in coronary artery disease of the European Society of Cardiology (ESC) and of the European Association for Cardio-Thoracic Surgery (EACTS). *Eur. Heart J.* **39**, 213–260 (2018).
111. Horlocker, T. T. et al. Regional anesthesia in the patient receiving antithrombotic or thrombolytic therapy: American Society of Regional Anesthesia and Pain Medicine Evidence-Based Guidelines (Fourth Edition). *Reg. Anesth. Pain. Med.* **43**, 263–309 (2018).
112. Gurbel, P. A., Bliden, K. P., Hiatt, B. L. & O'Connor, C. M. Clopidogrel for coronary stenting: response variability, drug resistance, and the effect of pretreatment platelet reactivity. *Circulation* **107**, 2908–2913 (2003).
113. Angiolillo, D. J. et al. Variability in individual responsiveness to clopidogrel: clinical implications, management, and future perspectives. *J. Am. Coll. Cardiol.* **49**, 1505–1516 (2007).
114. Price, M. J. et al. Recovery of platelet function after discontinuation of prasugrel or clopidogrel maintenance dosing in aspirin-treated patients with stable coronary disease: the Recovery Trial. *J. Am. Coll. Cardiol.* **59**, 2338–2343 (2012).
115. Sibbing, D. et al. Updated expert consensus statement on platelet function and genetic testing for guiding P2Y₁₂ receptor inhibitor treatment in percutaneous coronary intervention. *JACC Cardiovasc. Interv.* **12**, 1521–1537 (2019).
116. Mahla, E. 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. *Circulation. Cardiovasc. Interv.* **5**, 261–269 (2012).
117. Mahla, E., Tantry, U. S., Pruller, F. & Gurbel, P. A. Is there a role for preoperative platelet function testing in patients undergoing cardiac surgery during antiplatelet therapy? *Circulation* **138**, 2145–2159 (2018).
118. Pagano, D. et al. 2017 EACTS/EACTA guidelines on patient blood management for adult cardiac surgery. *Eur. J. Cardiothorac. Surg.* **53**, 79–111 (2018).
119. Karkouti, K. et al. Point-of-care hemostatic testing in cardiac surgery: a stepped-wedge clustered randomized controlled trial. *Circulation* **134**, 1152–1162 (2016).
120. Mahla, E. et al. Platelet inhibition and bleeding in patients undergoing non-cardiac surgery — the BIANCA observational study. *Thrombosis Haemost.* **118**, 864–872 (2018).
121. Hawn, M. T. et al. The incidence and timing of noncardiac surgery after cardiac stent implantation. *J. Am. Coll. Surg.* **214**, 658–666 (2012).
122. Mahmoud, K. D. et al. Perioperative cardiovascular risk of prior coronary stent implantation among patients undergoing noncardiac surgery. *J. Am. Coll. Cardiol.* **67**, 1038–1049 (2016).
123. Egholm, G. et al. Risk associated with surgery within 12 months after coronary drug-eluting stent implantation. *J. Am. Coll. Cardiol.* **68**, 2622–2632 (2016).
124. Kaluza, G. L., Joseph, J., Lee, J. R., Razinzer, M. E. & Razinzer, A. E. Catastrophic outcomes of noncardiac surgery soon after coronary stenting. *J. Am. Coll. Cardiol.* **35**, 1288–1294 (2000).
125. Iakovou, I. et al. Incidence, predictors, and outcome of thrombosis after successful implantation of drug-eluting stents. *JAMA* **293**, 2126–2130 (2005).
126. Gori, T. et al. Predictors of stent thrombosis and their implications for clinical practice. *Nat. Rev. Cardiol.* **16**, 243–256 (2019).
127. Berger, P. B. et al. Frequency of major noncardiac surgery and subsequent adverse events in the year after drug-eluting stent placement: results from the EVENT (Evaluation of Drug-Eluting Stents and Ischemic Events) registry. *JACC Cardiovasc. Interv.* **3**, 920–927 (2010).
128. Albaladejo, P. et al. Non-cardiac surgery in patients with coronary stents: the RECO study. *Heart* **97**, 1566–1572 (2011).
129. Banerjee, S. et al. Use of antiplatelet therapy/DAPT for post-PCI patients undergoing noncardiac surgery. *J. Am. Coll. Cardiol.* **69**, 1861–1870 (2017).
130. Rossini, R. et al. A multidisciplinary approach on the perioperative antithrombotic management of patients with coronary stents undergoing surgery: surgery after stenting 2. *JACC Cardiovasc. Interv.* **11**, 417–434 (2018).
131. Rodriguez, A. et al. Management of antiplatelet therapy in patients with coronary stents undergoing noncardiac surgery: association with adverse events. *Br. J. Anaesth.* **120**, 67–76 (2018).
132. Bhatt, D. L. et al. Comparative determinants of 4-year cardiovascular event rates in stable outpatients at risk of or with atherothrombosis. *JAMA* **304**, 1350–1357 (2010).
133. Livhits, M. et al. Risk of surgery following recent myocardial infarction. *Ann. Surg.* **253**, 857–864 (2011).
134. Anwaruddin, S. et al. Characterization of post-operative risk associated with prior drug-eluting stent use. *JACC Cardiovasc. Interv.* **2**, 542–549 (2009).
135. Holcomb, C. N. et al. The incremental risk of noncardiac surgery on adverse cardiac events following coronary stenting. *J. Am. Coll. Cardiol.* **64**, 2730–2739 (2014).
136. Hawn, M. T. et al. Risk of major adverse cardiac events following noncardiac surgery in patients with coronary stents. *JAMA* **310**, 1462–1472 (2013).
137. Wu, W. C. et al. Preoperative hematocrit levels and postoperative outcomes in older patients undergoing noncardiac surgery. *JAMA* **297**, 2481–2488 (2007).
138. Smilowitz, N. R., Banco, D., Katz, S. D., Beckman, J. A. & Berger, J. S. Association between heart failure and perioperative outcomes in patients undergoing noncardiac surgery. *Eur. Heart J. Qual. Care Clin. Outcomes* <https://doi.org/10.1093/ehjqcco/qcz066> (2019).
139. Saia, F. et al. Risk of adverse cardiac and bleeding events following cardiac and noncardiac surgery in patients with coronary stent: how important is the interplay between stent type and time from stenting to surgery? *Circ. Cardiovasc. Qual. Outcomes* **9**, 39–47 (2016).
140. Merlini, P. A. et al. Persistent activation of coagulation mechanism in unstable angina and myocardial infarction. *Circulation* **90**, 61–68 (1994).
141. Hong, M. K. et al. Comparison of coronary plaque rupture between stable angina and acute myocardial infarction: a three-vessel intravascular ultrasound study in 235 patients. *Circulation* **110**, 928–933 (2004).
142. Kereiakes, D. J. et al. DAPT score utility for risk prediction in patients with or without previous myocardial infarction. *J. Am. Coll. Cardiol.* **67**, 2492–2502 (2016).
143. Levine, G. N. et al. 2016 ACC/AHA guideline focused update on duration of dual antiplatelet therapy in patients with coronary artery disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J. Am. Coll. Cardiol.* **68**, 1082–1115 (2016).
144. Cruden, N. L. et al. Previous coronary stent implantation and cardiac events in patients undergoing noncardiac surgery. *Circ. Cardiovasc. Interv.* **3**, 236–242 (2010).
145. Holcomb, C. N. et al. Association of coronary stent indication with postoperative outcomes following noncardiac surgery. *JAMA Surg.* **151**, 462–469 (2016).
146. Armstrong, E. J. et al. Patient and lesion-specific characteristics predict risk of major adverse cardiovascular events among patients with previous percutaneous coronary intervention undergoing noncardiac surgery. *Catheter. Cardiovasc. Interv.* **89**, 617–627 (2017).

147. Neumann, F. J. et al. 2018 ESC/EACTS guidelines on myocardial revascularization. *Eur. Heart J.* **40**, 87–165 (2019).
148. Serruys, P. W. et al. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. *N. Engl. J. Med.* **360**, 961–972 (2009).
149. Motoyama, S. et al. Plaque characterization by coronary computed tomography angiography and the likelihood of acute coronary events in mid-term follow-up. *J. Am. Coll. Cardiol.* **66**, 337–346 (2015).
150. Thomsen, C. & Abdulla, J. Characteristics of high-risk coronary plaques identified by computed tomographic angiography and associated prognosis: a systematic review and meta-analysis. *Eur. Heart J. Cardiovasc. Imaging* **17**, 120–129 (2016).
151. Armstrong, E. J. et al. Incomplete revascularization is associated with an increased risk for major adverse cardiovascular events among patients undergoing noncardiac surgery. *JACC Cardiovasc. Interv.* **10**, 329–338 (2017).
152. van Kuijk, J.-P. et al. Timing of noncardiac surgery after coronary artery stenting with bare metal or drug-eluting stents. *Am. J. Cardiol.* **104**, 1229–1234 (2009).
153. Wijeyesundera, D. N. et al. Risk of elective major noncardiac surgery after coronary stent insertion: a population-based study. *Circulation* **126**, 1355–1362 (2012).
154. Vicenzi, M. N. et al. Coronary artery stenting and non-cardiac surgery—a prospective outcome study. *Br. J. Anaesth.* **96**, 686–693 (2006).
155. Tokushige, A. et al. Incidence and outcome of surgical procedures after coronary bare-metal and drug-eluting stent implantation: a report from the CREDO-Kyoto PCI/CABG registry cohort-2. *Circ. Cardiovasc. Interv.* **5**, 237–246 (2012).
156. Wilson, S. H. et al. Clinical outcome of patients undergoing non-cardiac surgery in the two months following coronary stenting. *J. Am. Coll. Cardiol.* **42**, 234–240 (2003).
157. Daemen, J. et al. Early and late coronary stent thrombosis of sirolimus-eluting and paclitaxel-eluting stents in routine clinical practice: data from a large two-institutional cohort study. *Lancet* **369**, 667–678 (2007).
158. Giustino, G. et al. Characterization of the average daily ischemic and bleeding risk after primary PCI for STEMI. *J. Am. Coll. Cardiol.* **70**, 1846–1857 (2017).
159. Finn, A. V. et al. Pathological correlates of late drug-eluting stent thrombosis: strut coverage as a marker of endothelialization. *Circulation* **115**, 2435–2441 (2007).
160. Stefanini, G. G. & Holmes, D. R. Jr. Drug-eluting coronary-artery stents. *N. Engl. J. Med.* **368**, 254–265 (2013).
161. van Werkum, J. W. et al. Predictors of coronary stent thrombosis: the Dutch Stent Thrombosis registry. *J. Am. Coll. Cardiol.* **53**, 1399–1409 (2009).
162. Holmes, D. R. Jr. et al. Stent thrombosis. *J. Am. Coll. Cardiol.* **56**, 1357–1365 (2010).
163. Giustino, G. et al. Efficacy and safety of dual antiplatelet therapy after complex PCI. *J. Am. Coll. Cardiol.* **68**, 1851–1864 (2016).
164. Yeh, R. W. et al. Lesion complexity and outcomes of extended dual antiplatelet therapy after percutaneous coronary intervention. *J. Am. Coll. Cardiol.* **70**, 2213–2223 (2017).
165. Vivas, D. et al. Perioperative and periprocedural management of antithrombotic therapy: consensus document of SEC, SEDAR, SEACV, SECTCV, AEC, SECPRE, SEPD, SEGO, SEHH, SETH, SEMERGEN, SEMFYC, SEMG, SEMICVUC, SEMI, SEMES, SEPAR, SENEC, SEO, SEPA, SERVEI, SECOT and AEU. *Rev. Esp. Cardiol.* **71**, 553–564 (2018).
166. Albaladejo, P. et al. Bleeding complications in patients with coronary stents during non-cardiac surgery. *Thrombosis Res.* **134**, 268–272 (2014).
167. Hermans, C. et al. Replacement therapy for invasive procedures in patients with haemophilia: literature review, European survey and recommendations. *Haemophilia* **15**, 639–658 (2009).
168. Mensah, P. K. & Pavord, S. Managing preoperative hemostasis in patients with inherited and acquired bleeding disorders. *Semin. Thromb. Hemost.* **46**, 17–25 (2019).
169. Kaw, D. & Malhotra, D. Platelet dysfunction and end-stage renal disease. *Semin. Dialysis* **19**, 317–322 (2006).
170. Tripodi, A. & Mannucci, P. M. The coagulopathy of chronic liver disease. *N. Engl. J. Med.* **365**, 147–156 (2011).
171. Acedillo, R. R. et al. The risk of perioperative bleeding in patients with chronic kidney disease: a systematic review and meta-analysis. *Ann. Surg.* **258**, 901–913 (2013).
172. Ziser, A. et al. Morbidity and mortality in cirrhotic patients undergoing anesthesia and surgery. *Anesthesiology* **90**, 42–53 (1999).
173. Beattie, W. S., Karkouti, K., Wijeyesundera, D. N. & Tait, G. Risk associated with preoperative anemia in noncardiac surgery: a single-center cohort study. *Anesthesiology* **110**, 574–581 (2009).
174. Musallam, K. M. et al. Preoperative anaemia and postoperative outcomes in non-cardiac surgery: a retrospective cohort study. *Lancet* **378**, 1396–1407 (2011).
175. Baron, D. M. et al. Preoperative anaemia is associated with poor clinical outcome in non-cardiac surgery patients. *Br. J. Anaesth.* **113**, 416–423 (2014).
176. Glance, L. G. et al. Preoperative thrombocytopenia and postoperative outcomes after noncardiac surgery. *Anesthesiology* **120**, 62–75 (2014).
177. Urban, P. et al. Defining high bleeding risk in patients undergoing percutaneous coronary intervention: a consensus document from the Academic Research Consortium for High Bleeding Risk. *Circulation* **140**, 240–261 (2019).
178. Mehran, R. et al. Cessation of dual antiplatelet treatment and cardiac events after percutaneous coronary intervention (PARIS): 2 year results from a prospective observational study. *Lancet* **382**, 1714–1722 (2013).
179. Airoldi, F. et al. Incidence and predictors of drug-eluting stent thrombosis during and after discontinuation of thienopyridine treatment. *Circulation* **116**, 745–754 (2007).
180. Genereux, P. et al. Stent thrombosis and dual antiplatelet therapy interruption with everolimus-eluting stents: insights from the Xience V coronary stent system trials. *Circ. Cardiovasc. Interv.* **8**, e001362 (2015).
181. Childers, C. P. et al. Perioperative management of antiplatelet therapy in patients undergoing non-cardiac surgery following coronary stent placement: a systematic review. *Syst. Rev.* **7**, 4 (2018).
182. Graham, L. A., Hollis, R. H., Richman, J. S. & Hawn, M. T. Frequency of surgery cancellations associated with myocardial infarction or death 6 months after coronary stent placement. *JAMA Surg.* **150**, 1199–1201 (2015).
183. Howell, S. et al. Prospective observational cohort study of the association between antiplatelet therapy, bleeding and thrombosis in patients with coronary stents undergoing noncardiac surgery. *Br. J. Anaesth.* **122**, 170–179 (2019).
184. Schouten, O., Bax, J. J., Damen, J. & Poldermans, D. Coronary artery stent placement immediately before noncardiac surgery: a potential risk? *Anesthesiology* **106**, 1067–1069 (2007).
185. Hong, S.-J. et al. Effect of perioperative antiplatelet therapy on outcomes in patients with drug-eluting stents undergoing elective noncardiac surgery. *Am. J. Cardiol.* **123**, 1414–1421 (2019).
186. Egholm, G. et al. Dual anti-platelet therapy after coronary drug-eluting stent implantation and surgery-associated major adverse events. *Thrombosis Haemost.* **116**, 172–180 (2016).
187. Rossini, R. et al. Perioperative management of oral antiplatelet therapy and clinical outcomes in coronary stent patients undergoing surgery. *Thrombosis Haemost.* **114**, 272–282 (2015).
188. Columbo, J. A. et al. A meta-analysis of the impact of aspirin, clopidogrel, and dual antiplatelet therapy on bleeding complications in noncardiac surgery. *Ann. Surg.* **267**, 1–10 (2018).
189. Siller-Matula, J. M. et al. Impact of preoperative use of P2Y12 receptor inhibitors on clinical outcomes in cardiac and non-cardiac surgery: a systematic review and meta-analysis. *Eur. Heart J. Acute Cardiovasc. Care* **6**, 753–770 (2017).
190. Ernst, A., Eberhardt, R., Wahidi, M., Becker, H. D. & Herth, F. J. Effect of routine clopidogrel use on bleeding complications after transbronchial biopsy in humans. *Chest* **129**, 734–737 (2006).
191. Kamel, H. et al. Association between major perioperative hemorrhage and stroke or Q-wave myocardial infarction. *Circulation* **126**, 207–212 (2012).
192. Godier, A. et al. Management of antiplatelet therapy in patients undergoing elective invasive procedures: proposals from the French Working Group on Perioperative Hemostasis (GIHP) and the French Study Group on Thrombosis and Hemostasis (GFHT). In collaboration with the French Society for Anesthesia and Intensive Care (SFAR). *Arch. Cardiovasc. Dis.* **111**, 210–223 (2018).
193. Zisman, E. et al. Platelet function recovery after cessation of aspirin: preliminary study of volunteers and surgical patients. *Eur. J. Anaesthesiol.* **27**, 617–623 (2010).
194. Le Manach, Y. et al. Impact of aspirin and clopidogrel interruption on platelet function in patients undergoing major vascular surgery. *PLoS ONE* **9**, e104491 (2014).
195. Li, C., Hirsh, J., Xie, C., Johnston, M. A. & Eikelboom, J. W. Reversal of the anti-platelet effects of aspirin and clopidogrel. *J. Thromb. Haemost.* **10**, 521–528 (2012).
196. Gogarten, W. et al. Regional anaesthesia and antithrombotic agents: recommendations of the European Society of Anaesthesiology. *Eur. J. Anaesthesiol.* **27**, 999–1015 (2010).
197. O'Connor, S. A. et al. Efficacy of ex vivo autologous and in vivo platelet transfusion in the reversal of P2Y12 inhibition by clopidogrel, prasugrel, and ticagrelor: the APTITUDE study. *Circ. Cardiovasc. Interv.* **8**, e002786 (2015).
198. Zafar, M. U. et al. Impact of timing on the functional recovery achieved with platelet supplementation after treatment with ticagrelor. *Circ. Cardiovasc. Interv.* **10**, e005120 (2017).
199. Franchi, F. & Angiolillo, D. J. Novel antiplatelet agents in acute coronary syndrome. *Nat. Rev. Cardiol.* **12**, 30–47 (2015).
200. Bhatt, D. L. et al. Antibody-based ticagrelor reversal agent in healthy volunteers. *N. Engl. J. Med.* **380**, 1825–1833 (2019).
201. Capodanno, D. & Angiolillo, D. J. Pretreatment with antiplatelet drugs in invasively managed patients with coronary artery disease in the contemporary era: review of the evidence and practice guidelines. *Circ. Cardiovasc. Interv.* **8**, e002301 (2015).
202. Capodanno, D. et al. Impact of bridging with perioperative low-molecular-weight heparin on cardiac and bleeding outcomes of stented patients undergoing non-cardiac surgery. *Thromb. Haemost.* **114**, 425–431 (2015).
203. Gotoh, S., Yasaka, M., Nakamura, A., Kuwashiro, T. & Okada, Y. Management of antithrombotic agents during surgery or other kinds of medical procedures with bleeding: the MARK study. *J. Am. Heart Assoc.* **9**, e012774 (2020).
204. Schneider, D. J., Tracy, P. B., Mann, K. G. & Sobel, B. E. Differential effects of anticoagulants on the activation of platelets ex vivo. *Circulation* **96**, 2877–2883 (1997).
205. Xiao, Z. & Theroux, P. Platelet activation with unfractionated heparin at therapeutic concentrations and comparisons with a low-molecular-weight heparin and with a direct thrombin inhibitor. *Circulation* **97**, 251–256 (1998).
206. Angiolillo, D. J. et al. International expert consensus on switching platelet P2Y12 receptor-inhibiting therapies. *Circulation* **136**, 1955–1975 (2017).
207. Capodanno, D. & Angiolillo, D. J. Management of antiplatelet therapy in patients with coronary artery disease requiring cardiac and noncardiac surgery. *Circulation* **128**, 2785–2798 (2013).
208. Capodanno, D., Milluzzo, R. P. & Angiolillo, D. J. Intravenous antiplatelet therapies (glycoprotein IIb/IIIa receptor inhibitors and cangrelor) in percutaneous coronary intervention: from pharmacology to indications for clinical use. *Ther. Adv. Cardiovasc. Dis.* **13**, 1753944719893274 (2019).
209. Franchi, F., Rollini, F., Muniz-Lozano, A., Cho, J. R. & Angiolillo, D. J. Cangrelor: a review on pharmacology and clinical trial development. *Expert. Rev. Cardiovasc. Ther.* **11**, 1279–1291 (2013).
210. Angiolillo, D. J. et al. Bridging antiplatelet therapy with cangrelor in patients undergoing cardiac surgery: a randomized controlled trial. *JAMA* **307**, 265–274 (2012).
211. Dargham, B. B. et al. Intravenous antiplatelet therapy bridging in patients undergoing cardiac or non-cardiac surgery following percutaneous coronary intervention. *Cardiovasc. Revasc. Med.* **20**, 805–811 (2019).
212. US National Library of Medicine. *ClinicalTrials.gov* <https://clinicaltrials.gov/ct2/show/NCT03862651> (2019).
213. Muniz-Lozano, A., Rollini, F., Franchi, F. & Angiolillo, D. J. Update on platelet glycoprotein IIb/IIIa inhibitors: recommendations for clinical practice. *Ther. Adv. Cardiovasc. Dis.* **7**, 197–213 (2013).

214. Savonitto, S. 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.* **104**, 285–291 (2010).
215. Alshawabkeh, L. I. et al. Outcomes of a preoperative "bridging" strategy with glycoprotein IIb/IIIa inhibitors to prevent perioperative stent thrombosis in patients with drug-eluting stents who undergo surgery necessitating interruption of thienopyridine administration. *Europe PCR* **9**, 204–211 (2013).
216. Capodanno, D., Alfonso, F., Levine, G. N., Valgimigli, M. & Angiolillo, D. J. ACC/AHA versus ESC guidelines on dual antiplatelet therapy: JACC guideline comparison. *J. Am. Coll. Cardiol.* **72**, 2915–2931 (2018).
217. Capodanno, D. et al. Management of antithrombotic therapy in atrial fibrillation patients undergoing PCI: JACC state-of-the-art review. *J. Am. Coll. Cardiol.* **74**, 83–99 (2019).
218. Knuuti, J. et al. 2019 ESC guidelines for the diagnosis and management of chronic coronary syndromes. *Eur. Heart J.* **41**, 407–477 (2020).
219. Angiolillo, D. J. et al. Antithrombotic therapy in patients with atrial fibrillation treated with oral anticoagulation undergoing percutaneous coronary intervention. *Circulation* **138**, 527–536 (2018).
220. Yasuda, S. et al. Antithrombotic therapy for atrial fibrillation with stable coronary disease. *N. Engl. J. Med.* **381**, 1103–1113 (2019).
221. Healey, J. S. et al. Periprocedural bleeding and thromboembolic events with dabigatran compared with warfarin: results from the randomized evaluation of long-term anticoagulation therapy (RE-LY) randomized trial. *Circulation* **126**, 343–348 (2012).
222. Douketis, J. D. et al. Perioperative bridging anticoagulation in patients with atrial fibrillation. *N. Engl. J. Med.* **373**, 823–833 (2015).
223. Douketis, J. D. et al. Perioperative management of patients with atrial fibrillation receiving a direct oral anticoagulant. *JAMA Intern. Med.* **179**, 1469–1478 (2019).
224. Steffel, J. et al. The 2018 European Heart Rhythm Association practical guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation. *Eur. Heart J.* **39**, 1330–1393 (2018).
225. Olesen, J. B. et al. Validation of risk stratification schemes for predicting stroke and thromboembolism in patients with atrial fibrillation: nationwide cohort study. *BMJ* **342**, d124 (2011).
226. Nielsen, P. B., Larsen, T. B., Skjoth, F., Overvad, T. F. & Lip, G. Y. Stroke and thromboembolic event rates in atrial fibrillation according to different guideline treatment thresholds: a nationwide cohort study. *Sci. Rep.* **6**, 27410 (2016).
227. Hansen, M. L. et al. Risk of bleeding with single, dual, or triple therapy with warfarin, aspirin, and clopidogrel in patients with atrial fibrillation. *Arch. Intern. Med.* **170**, 1433–1441 (2010).
228. Pollack, C. V. Jr. et al. Idarucizumab for dabigatran reversal – full cohort analysis. *N. Engl. J. Med.* **377**, 431–441 (2017).
229. Connolly, S. J. et al. Andexanet alfa for acute major bleeding associated with factor Xa inhibitors. *N. Engl. J. Med.* **375**, 1131–1141 (2016).
230. US National Library of Medicine. *ClinicalTrials.gov* <https://clinicaltrials.gov/ct2/show/NCT03016936> (2019).
231. US National Library of Medicine. *ClinicalTrials.gov* <https://clinicaltrials.gov/ct2/show/NCT03111875> (2020).
232. US National Library of Medicine. *ClinicalTrials.gov* <https://clinicaltrials.gov/ct2/show/NCT02427867> (2020).
233. US National Library of Medicine. *ClinicalTrials.gov* <https://clinicaltrials.gov/ct2/show/NCT03715712> (2019).
234. US National Library of Medicine. *ClinicalTrials.gov* <https://clinicaltrials.gov/ct2/show/NCT03021525> (2019).
235. US National Library of Medicine. *ClinicalTrials.gov* <https://clinicaltrials.gov/ct2/show/NCT03505723> (2020).
236. US National Library of Medicine. *ClinicalTrials.gov* <https://clinicaltrials.gov/ct2/show/NCT03374449> (2020).
237. US National Library of Medicine. *ClinicalTrials.gov* <https://clinicaltrials.gov/ct2/show/NCT03138603> (2018).
238. US National Library of Medicine. *ClinicalTrials.gov* <https://clinicaltrials.gov/ct2/show/NCT04329624> (2020).
239. US National Library of Medicine. *ClinicalTrials.gov* <https://clinicaltrials.gov/ct2/show/NCT04139655> (2019).
240. US National Library of Medicine. *ClinicalTrials.gov* <https://clinicaltrials.gov/ct2/show/NCT02797548> (2020).
241. US National Library of Medicine. *ClinicalTrials.gov* <https://clinicaltrials.gov/ct2/show/NCT03695159> (2020).

Author contributions

D.Cao, R.C. and R.M. researched data for the article. All authors contributed to discussion of content, wrote the article and reviewed and edited the manuscript before submission.

Competing interests

D.Capodanno has received consulting fees or honoraria from Amgen, AstraZeneca, Bayer, Biosensors, Boehringer Ingelheim, Daiichi Sankyo and Sanofi. D.J.A. has received grant support, consulting fees and honoraria from Abbott, Amgen, Aralez, Bayer, Biosensors, Boehringer Ingelheim, Bristol Myers Squibb, Chiesi, Daiichi Sankyo, Eli Lilly, Janssen, Merck and Sanofi; consulting fees and honoraria from Haemonetics, the Medicines Company, PhaseBio, PLX Pharma and Pfizer; grant support and fees for review activities from CeloNova; fees for review activities from St Jude Medical; and grant support from CSL Behring, Eisai, Gilead, Idorsia Pharmaceuticals, Matsutani Chemical Industry, Novartis, Osprey Medical, RenalGuard Solutions and the Scott R. MacKenzie Foundation. R.M. has received institutional grants from Abbott, AstraZeneca, Bayer, Beth Israel Deaconess, Bristol Myers Squibb, Chiesi, Concept Medical, CSL Behring, DSI, Medtronic, Novartis Pharmaceuticals, OrbusNeich; has received personal fees from Abbott, Boston Scientific, Janssen Scientific Affairs, Medscape, Medtelligence (Janssen Scientific Affairs), Roivant Sciences, Sanofi and Siemens Medical Solutions; has received consultant fees paid to the institution from Abbott and Bristol Myers Squibb; has received advisory board funding paid to the institution from Spectranetics/Philips/Volcano Corp; has <1% equity in Claret Medical and Elixir Medical; has received Data and Safety Monitoring Board Membership fees paid to the institution from Watermark Research Partners; has been a consultant (no fee) for Idorsia Pharmaceuticals and Regeneron Pharmaceuticals; and her spouse has received consultant fees from Abiomed and The Medicines Company. All other authors declare no competing interests.

Peer review information

Nature Reviews Cardiology thanks J.-P. Collet, J. Douketis, K. Eagle and L. Fleisher for their contribution to the peer review of this work.

Publisher's note

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Supplementary information

Supplementary information is available for this paper at <https://doi.org/10.1038/s41569-020-0410-z>.

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