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Review Article

Peri-operative cardiac protection for non-cardiac surgery

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Summary

Cardiovascular complications are an important cause of morbidity and mortality after non-cardiac surgery. Pre-operative identification of high-risk individuals and appropriate peri-operative management can reduce cardiovascular risk. It is important to continue chronic beta-blocker and statin therapy. Statins are relatively safe and peri-operative initiation may be beneficial in high-risk patients and those scheduled for vascular surgery. The pre-operative introduction of beta-blockers reduces myocardial injury but increases rates of stroke and mortality, possibly due to hypotension. They should only be considered in high-risk patients and the dose should be titrated to heart rate. Alpha-2 agonists may also contribute to hypotension. Aspirin continuation can increase the risk of major bleeding and offset the benefit of reduced myocardial risk. Contrary to the initial ENIGMA study, nitrous oxide does not seem to increase the risk of myocardial injury. Volatile anaesthetic agents and opioids have been shown to be cardioprotective in animal laboratory studies but these effects have, so far, not been conclusively reproduced clinically.

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Introduction

As the worldwide population ages, more patients with significant cardiovascular morbidities undergo surgery. Anaesthesia is generally safe [1, 2], but surgical stress can result in major adverse cardiac events and this accounts for significant morbidity and mortality [3]. For example, a large prospective cohort study showed that 1200 of 15 000 patients recorded troponin concentrations > 0.03 ng.ml^{-1} within three days of surgery. This troponin release was independently associated with death and 1 in 10 of these patients died within one month of surgery, although more than half did not fulfil criteria for acute coronary syndrome [4]. This suggests that we may underestimate the rate of adverse events associated with myocardial injury.

Pathophysiological mechanisms behind myocardial infarction include acute coronary syndrome due to thrombosis of an unstable atherosclerotic plaque and an imbalance of myocardial oxygen supply and demand in the presence of coronary artery stenosis [5]. Strategies to reduce peri-operative cardiac complications aim to attenuate these pathophysiologic changes. In this review, we will discuss the role of pre-operative drugs and other interventions, as well as the use of intra-operative anaesthetic agents and opioids.

Peri-operative drugs

Beta-blockers

The use of peri-operative beta-blockers for cardiac protection is controversial. Beta-blockers reduce heart rate

and systemic blood pressure, thereby improving the balance of myocardial oxygen supply and demand [5]. In addition, they shift myocardial metabolism towards glucose and reduce free fatty acid concentrations and inflammation, which can stabilise atherosclerotic plaques [6–8]. Support for the peri-operative use of beta-blockers initially came from a prospective trial that showed atenolol markedly reduced mortality after non-cardiac surgery [9]. The even more dramatic results of the subsequent DECREASE trial [10] lent further support. However, several ensuing studies failed to replicate these benefits [11–13]. The POISE 1 multicentre randomised, controlled trial compared extended release metoprolol with placebo in over 8000 patients undergoing non-cardiac surgery. The intervention started 2–4 h before surgery and continued for 30 postoperative days [14]. Metoprolol reduced myocardial infarctions, hazard ratio (95% CI) 0.73 (0.60–0.89), but increased deaths and strokes, hazard ratios (95% CI) of 1.33 (1.03–1.74) and 2.17 (1.26–3.74), respectively. Support for pre-operative beta-blockade was further undermined when the validity of the DECREASE trials became uncertain due to scientific misconduct by Poldermans and his colleagues [15, 16]. While the DECREASE 1 trial was never investigated, the other DECREASE trials were found to have major scientific flaws.

A recent meta-analysis included nine randomised, controlled trials of 10 529 patients and excluded the DECREASE trials [17]. It showed that beta-blockers reduced non-fatal myocardial infarction, relative risk (95% CI) 0.73 (0.61–0.88), but increased 30-day all-cause mortality and stroke, relative risk (95% CI) 1.27 (1.01–1.60) and 1.73 (1.00–2.99), respectively. One limitation of the meta-analysis is that the results were hugely influenced by the POISE 1 trial. The dose of metoprolol used in that trial has been criticised [18]: the maximum recommended starting dose for extended metoprolol dose is 100 mg daily [19] but some patients in the POISE 1 trial received up to 400 mg on the day of surgery, given in divided doses, followed by 200 mg daily for 30 days [14]. Theoretically, this high, untitrated dose could account for more adverse effects.

Another meta-analysis reviewed whether starting beta-blockers less than 45 days before non-cardiac surgery reduced cardiovascular morbidity and mortality at one postoperative month [20]. The meta-analysis included 17 studies (16 randomised control trials and one cohort study) and over 12 000 patients. Beta-blockers were associated with more strokes, hypotension, and bradycardia, relative risks (95% CI) 1.76 (1.07–2.91), 1.47 (1.34–1.60) and 2.61 (2.18–3.12), respectively, but fewer myocardial infarctions, relative risk (95% CI) 0.69 (0.58–0.82). When both the POISE and DECREASE trials were excluded, the remaining studies did not show a significant effect of beta-blockers on any outcome, including myocardial infarction, mortality or stroke. However, the remaining pooled sample size of 1200 in each arm might be too small to exclude an important clinical effect. The remaining studies fail to exclude the possibility that initiation of peri-operative beta-blockers may be harmful even when using doses lower than in the POISE trial, and that adverse effects may not only be associated with the drug dosing regimen. Many trials did not stratify patient risk when administering beta-blockers. For example, revised cardiac risk indices were not recorded and non-invasive stress testing was not done in the POISE trial, in which less than half of the patients had a history of ischaemic heart disease [14].

Retrospective studies have associated peri-operative beta-blockade with reduced mortality and cardiac complications in patients with revised cardiac risk indices of more than one [21, 22]. One retrospective study of more than 38 000 patients associated fewer postoperative deaths at 30 days and 1 year with beta-blockade when it was started and continued according to an individual patient's cardiovascular risk [23]. These studies suggest that there may be benefit in starting beta-blockers in patients with high baseline cardiovascular risk. It has also been suggested that beta-blockers would improve outcomes more if given for longer before surgery. It takes time to gradually titrate the dose to achieve an optimal heart rate without hypotension, which would also allow anti-inflammatory effects to develop [24]. Beta-blockers have been started one day or less before surgery in the majority of trials. The acute administration of beta-blockers is associated with increased mortality compared with chronic beta-blockade [24, 25]. However, the strongest support for prolonged pre-operative beta-blockade comes from the

discredited DECREASE trials. Overall, evidence to support the early administration of beta-blockers is not strong. If one is going to start beta-blockers pre-operatively, it may be better to do so several days before surgery to assess how the patient tolerates them, which is a class 2b recommendation in the ACC/AHA guidelines [26].

The titration of drug dose to heart rate improves the balance between myocardial oxygen supply and demand. In addition, an elevated heart rate is associated with atherosclerotic plaque disruption [27]. One study showed that better control of heart rate was associated with improved cardioprotection [28], but another did not show an association between heart rate control and cardiac complications [29]. Tight heart rate control is not without risk as it promotes bradycardia, hypotension and congestive heart failure [28, 29]. Titration of effect can be difficult with beta-blockers; many patients on peri-operative beta-blockers still had high heart rates at the time of surgery [28, 30]. The type of beta-blocker may also be important. A large retrospective observational study reported more deaths in patients on metoprolol than atenolol [31]. One hypothesis is that the longer action of atenolol diminishes the frequency and effect of missed doses. The initiation of beta-blockade with atenolol or bisoprolol instead of metoprolol is a class 2b recommendation in the 2014 ESC/ESA guidelines for cardiovascular assessment and management in non-cardiac surgery [32]. Currently, the only class 1 recommendation for beta-blockers, in both the 2014 ACC/AHA and ESC/ESA guidelines, is to continue them peri-operatively in patients on chronic treatment [26, 32]. This is supported by observational studies that associate increased mortality with withdrawal of beta-blockers [23, 33, 34]. The current guidelines are less supportive than previous guidelines about starting beta-blockers before surgery. In the ACC/AHA guidelines, it is only a class 2b recommendation in patients with 'intermediate or high-risk myocardial ischaemia noted in pre-operative risk stratification tests', as well as in patients with three or more revised cardiac risk indices [26]. The ESC/ESA guideline recommends considering pre-operative beta-blockade in patients with evidence of ischaemic heart disease and in patients with two or more clinical risk factors, or an ASA status of 3 or more (grade 2b) [32]. The ACC/AHA recommends against starting beta-blockers on the day of surgery [26]. The ESC/ESA guideline advises against starting high-dose beta-blockers without titration and against starting beta-blockers in patients scheduled for low-risk surgery [32].

Statins

Statins reduce plasma lipid levels by inhibiting 3-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA) reductase. They also have numerous pleiotropic effects that include improved endothelial function, vasodilation, anticoagulation, platelet inhibition, the reduction in vascular inflammation and oxidisation and the stabilisation of atherosclerotic plaques [35, 36]. Endothelial function can improve within 24 h of initiating treatment [37]. Observational studies have associated reduced mortality and cardiovascular outcomes with the use of statins in non-cardiac surgery [38–41]. In addition, withdrawal of peri-operative statin therapy for at least four days was associated with myocardial injury [42]. All these studies support the class 1 recommendation to continue peri-operative statins in patients on chronic therapy in both the ACC/AHA and ESC/ESA guidelines. Two meta-analyses showed that initiation of statins in statin-naïve patients reduced peri-operative myocardial infarction [43, 44], mortality and atrial fibrillation in cardiac surgery and cardiac procedures [44]. The benefit in non-cardiac surgery is less clear. The ACC/AHA and ESC/ESA guidelines give a class 2a recommendation for initiation of peri-operative statins for patients undergoing vascular surgery [26, 32]. This is mainly supported by a prospective, double-blind, randomised, controlled trial of peri-operative atorvastatin that reduced cardiac events, including: death from cardiac causes; myocardial infarction; stroke; and unstable angina [45]. Another meta-analysis showed that peri-operative statins significantly reduced the rates of mortality and myocardial infarction, but this included results from the controversial DECREASE trials [44]. A Cochrane meta-analysis, which excluded the DECREASE III trial, included three randomised, controlled trials involving 178 statin-naïve patients started on a statin for vascular surgery. It did not show an effect on mortality or

myocardial infarction [46]. Another meta-analysis also reported no effect of starting statins before non-cardiac surgery, after excluding results from the DECREASE trials [43]. Exclusion of DECREASE trial data significantly weakens the evidence of benefit in non-cardiac surgery. The safety of starting statins is an important consideration, as with any drug including beta-blockers. Fortunately, statins are generally safe with a low incidence of adverse effects. Concerns are mainly related to muscular and hepatic effects. A prospective observational study did not show any increase in adverse muscular events in patients on long-term statin therapy after knee and hip surgery [47]. Muscle pain occurs in up to 1 in 100 patients taking statins, but life-threatening rhabdomyolysis affects about one in 2000 patients [48–50]. Asymptomatic increases in liver enzymes are also rare and liver function measurements when starting statins are not recommended [48–50]. The relatively benign safety profile of statins favours their peri-operative use, as opposed to beta-blockers, particularly for vascular surgery [45]. Patients with a higher baseline cardiovascular risk are more likely to benefit from peri-operative treatment [38] and nowadays it is very likely that such patients are already on treatment anyway.

Alpha-2 agonists and aspirin

Alpha-2 agonists act on the locus coeruleus to reduce central sympathetic activity and peripheral noradrenaline release [51–53]. This can attenuate the adrenergic stress response to surgery and the reduction in heart rate can improve myocardial oxygen balance. A double-blind, randomised, controlled trial involving 190 patients with or at risk of ischaemic heart disease undergoing non-cardiac surgery showed that peri-operative clonidine significantly reduced myocardial ischaemia and mortality with minimal haemodynamic effects [54]. A meta-analysis that included studies of clonidine, dexmedetomidine and mivazerol showed that alpha-2 agonists reduced mortality and myocardial infarction after vascular surgery [55]. Another meta-analysis, restricted to dexmedetomidine, did not show a significant improvement in cardiac outcomes, but hypotension and bradycardia were increased [56]. The POISE 2 trial was a large, multicentre, blinded, randomised controlled trial with a two-by-two factorial design used to separately investigate the effects of peri-operative low-dose clonidine and aspirin in patients with, or at risk of, atherosclerotic disease undergoing non-cardiac surgery. Low-dose clonidine did not reduce death or myocardial infarction, but significantly increased the rate of non-fatal cardiac arrest, bradycardia and hypotension [57]. Hypotension was an independent predictor of myocardial infarction, suggesting that clonidine may actually worsen outcomes [57]. Unlike the POISE 1 trial, the dosing regimen in POISE 2 was not high. Although some other studies show benefit with clonidine, the sample sizes were much smaller than the POISE 2 trial. The increase in rates of hypotension and bradycardia demonstrated in the POISE 2 trial concurs with the results from the previous meta-analysis evaluating the effects of dexmedetomidine [56]. Alpha-2 agonists should probably not be used for 'cardioprotection' in non-cardiac surgery, and this opinion is reflected in the most recent ACC/AHA and ESC/ESA guidelines [26, 32].

Aspirin prevents myocardial infarction in patients with coronary artery disease [58]. Trials have shown aspirin to be ineffective in preventing the onset of cardiovascular disease. Meta-analysis of pooled data demonstrates a small but statistically significant reduction in cardiovascular events that is counterbalanced by an equally small but significant risk of bleeding. On balance, the US Food and Drug Administration concluded that the totality of evidence does not favour aspirin for primary prevention of cardiovascular disease [59]. Since surgery results in a pro-thrombotic and pro-inflammatory state with increased platelet aggregation [60, 61], it was thought that the antiplatelet and anti-inflammatory effects of aspirin may be cardioprotective during the peri-operative period. The POISE 2 trial sought to investigate the effects of starting and withdrawing aspirin during the peri-operative period in non-cardiac surgery. Over 10 000 patients were randomly assigned to receive aspirin or placebo, and patients were further stratified according to whether they were taking aspirin before the study. Administration of low-dose aspirin peri-operatively did not reduce the rates of mortality and myocardial infarction [62]. In addition, aspirin withdrawal for at least three days (usually seven days) did not increase

mortality or cardiac morbidity. Instead, aspirin is associated with an increased rate of major bleeding and aspirin withdrawal may reduce bleeding risk [62]. Increased bleeding with peri-operative aspirin has also been demonstrated in other studies [63, 64]. POISE-2 investigators suggested stopping aspirin for three or more days pre-operatively and advise that it can be resumed 8–10 days postoperatively when the bleeding risk is diminished. On the other hand, a randomised controlled trial of 220 patients undergoing non-cardiac surgery showed that aspirin withdrawal was associated with a significantly higher rate of major adverse cardiovascular events [65]. A review of observational studies suggested an increased risk of cardiovascular morbidity with aspirin withdrawal, and that while aspirin increased bleeding complications, it did not increase the severity of bleeding [64]. Another review of studies recommended continuation of aspirin in patients with ischaemic heart disease, cerebrovascular disease or peripheral artery disease for most non-cardiac surgeries, with the exception of middle ear, posterior chamber of the eye, intracranial, intramedullary spine and maybe transurethral resection of prostrate surgeries [66]. It is important to note that only 23% of the patients in the POISE 2 trial had known ischaemic heart disease, and that patients less than 6 weeks after placement of a bare metal stent or within a year after placement of drug-eluting coronary stents were excluded from the study [62]. Furthermore, patients requiring aspirin for either primary or secondary prevention made up no more than 36.3% of those assigned to the aspirin group and it has been suggested that the high-risk group may have been diluted with lower risk patients [67]. Thus, it is still not possible to conclude whether temporary cessation of aspirin therapy for surgery in high-risk groups is safe. It may be prudent to stop aspirin in patients having surgery that is associated with significant blood loss or closed spaces. Patients with a high cardiovascular risk undergoing surgery with relatively low bleeding risk (e.g. endovascular surgery) may still benefit from peri-operative aspirin. Patients with coronary stents who need to have their $P2Y_{12}$ platelet receptor-inhibitor stopped for non-cardiac surgery should continue aspirin if possible [26]. Ultimately, use of peri-operative aspirin should be based on each individual patient by balancing cardiovascular morbidity and peri-operative bleeding risks.

Other peri-operative interventions

The latest ACC/AHA guidelines recommend against coronary revascularisation before non-cardiac surgery [26]. Pre-operative coronary artery revascularisation did not reduce long-term mortality or postoperative myocardial infarction compared with drugs in a study of over 5000 patients having vascular surgery [68]. In subgroup analysis, patients with unprotected left main coronary disease and those with abnormal cardiac imaging before abdominal aortic aneurysm had improved outcomes with prophylactic revascularisation [69, 70]. However, these represent a very small proportion of patients with very high cardiovascular risk. Coronary artery bypass and percutaneous coronary intervention are procedures that are associated with significant risk. Patients with coronary stents after percutaneous coronary intervention are at risk of in-stent thrombosis during surgery, particularly if antiplatelet drugs are stopped peri-operatively. Revascularisation before non-cardiac surgery is only recommended for patients in whom revascularisation is indicated regardless of surgery [26].

Intra-operative anaesthesia

Volatile anaesthetic agents protect rabbit myocardium from subsequent ischaemia caused by coronary occlusion [71, 72], which led to the concept of anaesthetic pre-conditioning. In addition, volatile anaesthetics were effective in postconditioning, where exposure at the beginning of reperfusion after ischaemia was cardioprotective [73, 74]. The mechanism of action involves G-protein coupled receptors, protein kinase C, adenosine receptors, reactive oxygen species, intracellular signalling kinases, nitrogen species, caveolae, sarcolemmal and mitochondrial potassium channels and mitochondrial metabolism [72, 75, 76].

Propofol has cardioprotective effects mediated via free radical scavenging and cardiac L-type calcium channel antagonism. It enhances mechanical recovery and tissue ATP levels in the heart after ischaemia and reperfusion [77]. In a randomised controlled trial of 54 patients having cardiopulmonary bypass, large doses of propofol resulted in a lower mean troponin I level, a

higher mean cardiac index, and a lower mean malondialdehyde level (a marker of oxidative stress) than small doses of propofol or isoflurane anaesthesia [78]. The combination of isoflurane pre-conditioning and propofol postconditioning was associated with lower plasma levels of troponin I and creatinine kinase MB after cardiopulmonary bypass surgery [79]. However, evidence is conflicting [72, 80].

Several randomised controlled trials have compared volatile agent anaesthesia with propofol-based total intravenous anaesthesia in cardiac surgery. Volatile agents reduced myocardial injury and mortality [81–86]. A retrospective analysis of a database of 10 535 cardiac surgical procedures associated fewer in-hospital deaths after propofol than after sevoflurane, but only for a subgroup who had had urgent cardiopulmonary bypass, $p = 0.03$, and only after the exclusion of patients with acute coronary syndrome [87]. Since patients undergoing urgent cardiopulmonary bypass surgery are suffering from critical ischaemia and haemodynamic compromise, this result suggests that propofol may be more beneficial in those with severe ischaemia and cardiovascular instability. Sevoflurane appeared to be superior to propofol in patients with little or no ischaemic heart disease (such as CABG without severe pre-operative ischaemia). In-hospital 30-day mortality caused by infection, pulmonary causes, or renal causes in the propofol group was significantly lower, $p = 0.004$. This is probably because sevoflurane is unlikely to offer any additional benefit when ischaemic pre-conditioning already exists since the mechanisms of both are the same. In contrast, the protective effects of propofol are most likely secondary to antioxidant effects and this different mechanism could confer an advantage where ischaemic pre-conditioning already exists.

Randomised controlled trials comparing volatile anaesthetic drugs with propofol in non-cardiac surgery report no differences in cardiovascular outcomes [88–90]. One randomised, controlled trial compared anaesthesia using sevoflurane and fentanyl with anaesthesia using propofol and remifentanil for elective abdominal aortic surgery: there were no differences in postoperative troponin T levels, mortality or coronary events, although patients in the sevoflurane group required less inotropic support [88]. The use of different opioids for the two groups has been criticised as a confounding factor [91]. The monitoring of troponin levels for only the first postoperative day has been criticised as inadequate [92]. Another randomised, controlled trial compared sevoflurane with propofol in 385 patients undergoing various non-cardiac surgeries who had coronary artery disease, or more than one risk factor for coronary artery disease: there was no difference in the rate of myocardial ischaemia [90]. Again, this study was criticised for not monitoring myocardial ischaemia for longer [93]. There are many reasons why the apparent cardioprotective effect of volatile agents cannot be reproduced in clinical studies. Unlike controlled animal models, patients involved in clinical trials have other confounding factors. Normal hearts used in animal laboratory studies may respond differently from diseased human hearts. Patients with the greatest cardiovascular risk may already be pre-conditioned with chronic myocardial ischaemia, and thus may benefit little from anaesthetic pre-conditioning or postconditioning. Many patients with cardiovascular risk have diabetes and hyperglycaemia, and these have been shown to attenuate anaesthetic cardioprotection [94–96]. In addition, drugs such as beta-blockers and the oral hypoglycaemic drug glibenclamide can attenuate cardioprotection [97, 98]. Currently, there is no evidence to support the clinical use of volatile anaesthetic agents for cardioprotection in non-cardiac surgery, and this opinion is reflected in the recent AHA/ACC guidelines [26].

Opioids have been shown to confer cardiac pre-conditioning and postconditioning in animal models [99–104]. Underlying mechanisms are complex. In particular, activation of κ and δ-opioid receptors is directly involved in cardioprotection, while the effect of μ-opioid receptor activation is less definite [105]. Children randomly allocated to intra-cardiac injection of morphine during correction of tetralogy of Fallot had lower peak postoperative troponin I levels, higher cardiac output, shorter intensive care unit stay, and reduced duration of mechanical ventilation compared with the control group, indicating that morphine could protect against ischaemia and reperfusion injury [106]. A randomised trial compared intravenous fentanyl 50–100 μg with sublingual diazepam 5 mg at least 5 min before balloon inflation during elective coronary

angioplasty: there were no differences in postprocedure myocardial infarction or troponin T levels [107]. However, the fentanyl dose may not have been high enough to provide significant cardioprotection. In addition, the absence of an effect for fentanyl may be because it is less active at δ opioid receptors than morphine [105]. Theoretically, remifentanil could provide greater cardioprotection compared with other opioids as very high doses can be given intra-operatively without delaying recovery. A small randomised trial showed that a 10 min infusion of remifentanil (5 $\mu g.kg^{-1}$) reduced postoperative troponin I levels in patients undergoing coronary artery bypass grafting [108]. In another small randomised controlled trial involving 20 patients, remifentanil infusion at 0.5 $\mu g.kg^{-1}.min^{-1}$ during coronary artery bypass grafting did not affect postoperative cardiac marker levels, but was instead associated with early postoperative cardiac depression [109]. A meta-analysis of trials that studied more than 1400 patients having cardiac surgery showed that remifentanil significantly reduced postoperative troponin I levels, length of stay in intensive care, and duration of mechanical ventilation compared with fentanyl or sufentanil [110]. Although opioids such as remifentanil provide cardioprotection with a clear mechanistic rationale in animal studies, there is currently limited evidence for their use in cardiac surgery and none for non-cardiac surgery.

Nitrous oxide increases levels of homocysteine by inhibiting methionine synthetase, which is a risk factor for coronary artery and cerebrovascular disease. In the ENIGMA-1 trial, the adjusted odds ratio (95% CI) for myocardial infarction during a median follow up 3.5 years was 1.59 (1.01–2.51), p = 0.04 [111]. However, the primary outcome of the ENIGMA-1 trial was not the incidence of cardiovascular complications. A meta-analysis of 13 trials concluded that there was insufficient evidence to show effects of nitrous oxide on mortality and cardiovascular complications [112]. Recently, the effect of nitrous oxide on postoperative cardiovascular complications was assessed in the ENIGMA-2 trial, a large multicentre randomised, controlled trial involving over 7000 patients at risk of cardiovascular complications. Use of intra-operative nitrous oxide was not associated with increased risk of the composite of death and cardiovascular complications (non-fatal myocardial infarction, stroke, cardiac arrest or pulmonary embolism) within 30 days after surgery [113]. This study provides the most conclusive evidence demonstrating the cardiovascular safety of nitrous oxide. However, the study only looked at cardiovascular events in the first 30 days, and the risk of late myocardial infarction with nitrous oxide suggested in ENIGMA-I was not addressed in the second trial. Remifentanil, which has a fast offset, potent analgesic effects and cardioprotective properties, may be a better alternative to nitrous oxide.

Conclusion

Cardiovascular complications remain a major cause of morbidity and mortality after non-cardiac surgery. Patients with high cardiovascular risk need to be identified pre-operatively with appropriate interventions provided if appropriate. Patients on chronic beta-blockers and statins should have their medications continued peri-operatively. Initiation of beta-blockers in previously naïve patients may cause more harm than benefit. They may be considered for patients with high cardiovascular risk, but cautious titration of dose is appropriate to reduce adverse effects. While there is evidence to support initiation of statins for cardiac surgery and procedures, the evidence for non-cardiac surgery is not strong. They may be more useful in high-risk patients and patients undergoing vascular surgery. Results from the POISE 2 trial do not support the use of aspirin and alpha-2 agonists. Pre-operative revascularisation is not indicated for reducing cardiovascular risk before surgery. More clinical studies are needed to determine the clinical effectiveness of volatile anaesthetic agents and opioids, which have been shown to be cardioprotective in animal laboratory studies. Remifentanil, in particular, may be more cardioprotective than other opioids in the clinical setting.

Competing interests

No external funding or competing interests declared. Michael Irwin is an Editor of *Anaesthesia* and this article has undergone external review as a result.

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