Perioperative myocardial infarction—aetiology and prevention

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Perioperative myocardial infarction (PMI) is one of the most important predictors of short- and long-term morbidity and mortality associated with non-cardiac surgery. Prevention of a PMI is thus a prerequisite for an improvement in overall postoperative outcome. The aetiology of PMI is multifactorial. The perioperative period induces large, unpredictable and unphysiological alterations in coronary plaque morphology, function and progression, and may trigger a mismatch of myocardial oxygen supply and demand. With many diverse factors involved, it is unlikely that one single intervention will successfully improve cardiac outcome following non-cardiac surgery. A multifactorial, step-wise approach is indicated. Based on increasing knowledge of the nature of atherosclerotic coronary artery disease, and in view of the poor positive predictive value of non-invasive cardiac stress tests, and the considerable risk of coronary angiography and coronary revascularization in high-risk patients, the paradigm is shifting from an emphasis on extensive non-invasive preoperative risk stratification to a combination of selective non-invasive testing and aggressive pharmacological perioperative therapy. Perioperative plaque stabilization by pharmacological means may be as important in the prevention of PMI as an increase in myocardial oxygen supply or a reduction in myocardial oxygen demand.

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Perioperative myocardial infarction (PMI) is one of the most important predictors of short- and long-term morbidity and mortality associated with non-cardiac surgery. Prevention of a PMI is thus a prerequisite for the improvement in overall postoperative outcome. The design of effective preventive measures requires basic knowledge of the aetiology of PMI. Unfortunately, the exact nature of PMI remains an area of uncertainty and the subject of continued debate and controversy. Accordingly, the first part of this article will address the aetiology of PMI, with consideration of the aetiology and pathophysiology of acute coronary syndromes, and of the diagnosis of MI (recently reviewed in detail in reference). The second part will address strategies and means of preventing a PMI.

Aetiology of PMI

Acute coronary syndrome

Aetiology

Acute coronary syndromes (ACS) are associated with structurally as well as functionally complex plaques and coronary artery stenoses, coronary endothelial lesions, and plaque inflammation. Structural morphology, cellular composition, and biological activity of coronary plaques appear to be closely linked. Plaque instability correlated more with biological activity and cellular composition than with angiographical findings. The interaction between morphological and functional factors is unpredictable. Exogenous factors (e.g. mechanical stress, vasomotor tone, infection, blood viscosity, coagulability) further modify such interaction, making the final outcome even less predictable. Systemic or multi-focal arterial inflammation may be independent risk factors for acute coronary events, supporting the broader concept of the ‘vulnerable patient’.

Pathophysiology

Plaque progression is frequently abrupt, mostly unpredictable, and often related to episodes of thrombosis (which, in turn, are triggered by plaque rupture, erosion, endothelial activation, or inflammation). In the absence of a hypercoagulable state, thrombi may remain mural rather than become occlusive, and may thus produce few if any symptoms (unless they embolize). If subsequent lysis is incomplete and is followed by re-endothelialization, the plaque will grow. The unpredictability of plaque progression is probably related to fluctuations in risk factors and triggers, for
example physical activity, mental stress, environmental temperature, smoking, infection, hydration, and arterial pressure; to heterogeneity of plaque histology; and to differences in the physical forces to which plaques are exposed. It is impossible to predict the time it will take the vulnerable plaque to become unstable, or the trigger that causes the plaque to rupture (i.e., mechanical stress, coronary vasospasm, widespread acute inflammatory endothelial activation, or the chronic inflammatory component of atherosclerosis). In a substantial percentage of culprit lesions, thrombosed plaques without detectable fissures were observed. In such cases, plaque vulnerability is probably caused by thrombogenic or high-risk blood and/or local pro-inflammatory cytokines that trigger thrombosis, sometimes even in the absence of inflammatory cell infiltration and a lipid core.

Rupture of the intimal surface of a plaque is the result of a combination of cellular processes that promote plaque instability, and of physical (haemodynamic) processes that influence the magnitude and distribution of stress on the plaque. The size of the thrombus that forms at the site of plaque rupture and the clinical consequences will depend on several key factors: the degree of plaque disruption (ulceration, fissure, or erosion) and substrate exposure as a major determinant of thrombogenicity at the local coronary artery site; the composition of the plaque; the magnitude of the stenosis; and the extent of platelet activation and intrinsic fibrinolytic activity.

Plaque rupture is more common during various kinds of strenuous physical activity and emotional stress. Activation of the sympathetic nervous system in these situations leads to increased plasma concentrations of catecholamines, blood viscosity, and of arterial pressure and heart rate, which are accompanied by detectable increases in platelet aggregation and decreases in fibrinolytic activity that both tend to favour thrombosis. This combination of increased prothrombotic and reduced fibrinolytic activity could initiate propagation and total occlusion of the coronary artery by a mural thrombus overlaying a small plaque erosion that might otherwise have been harmless. The periprocedural period is characterized by comparable adrenergic stimulation, and increased prothrombotic and reduced fibrinolytic activity.

In the event of plaque rupture, thrombus growth depends not only on the size and thrombogenicity of the fissured plaque, but also on the number and activation of exposed inflammatory cells. Inflammatory activation of the endothelium can turn its physiological vasodilatory and anti-thrombotic properties into pathological vasoconstrictor and prothrombotic properties. In addition, the inflammatory response of the circulating blood may activate coagulation. These many variables explain why coronary lesions that are angiographically fairly small may progress acutely to severe stenosis or total occlusion.

When intraluminal thrombi attach to a ruptured plaque, total occlusion of an epicardial coronary artery may occur resulting in total interruption of nutrient blood flow to the myocardium. The situation may be worsened by distal embolization of microthrombi and by coronary vasoconstriction caused by local mediator release or systemic sympathetic activation. If coronary blood flow is interrupted for longer than 30 min, a MI may result. Persistent coronary artery occlusion will cause a progressive increase in infarct size. Loss of functional myocardium results in impaired left ventricular function, which may impair quality of life, and usually leads to premature death.

Any discussion of the aetiology of PMI must take into account the extreme variations in clinical presentation of ACS in general. At one end of the spectrum are those patients who suffer a sudden cardiac death or an MI without any preceding episode of angina, and not followed by recurrent instability. At the other end of the spectrum are those patients who develop an MI after episodes of unstable angina over a period of days to weeks, and who often develop post-infarction angina and/or re-infarction. It is conceivable that the triggers of instability differ between such groups of patients.

**Perioperative MI**

**Aetiology**

There is pathological and angiographic evidence that the aetiology of PMI resembles that in the non-surgical setting. In PMI, acute plaque disruption and haemorrhage in the infarct-related coronary artery seems to be common, but the severity of underlying coronary artery stenosis does not necessarily predict the infarct territory. The high incidence of histologically confirmed transmural infarctions seems to be in contradiction to the ECG finding of almost exclusively non-Q-wave PMIs. On the other hand, the presence of circumferential PMIs is consistent with a myocardial oxygen supply/demand mismatch being the main trigger of myocardial injury. However, myocardial oxygen supply/demand mismatch and plaque rupture are not mutually exclusive mechanisms, and MIs may develop by different mechanisms at different locations in the same patient.

Patients who experience a PMI have angiographic evidence of extensive coronary artery disease (CAD). Various angiographic findings were consistent with perioperative plaque rupture at sites other than critically narrowed coronary artery stenoses, as well as with the possibility that in some patients with severe but stable CAD, PMI might have developed primarily on the basis of prolonged myocardial ischaemia. Most (>80%) PMIs occur early after surgery, are asymptomatic, and are most commonly preceded by ST-segment depression rather than ST-segment elevation. Long-duration (single duration >20–30 min or cumulative duration >1–2 h) rather than merely the presence of postoperative ST-segment depression, seems to be the important factor associated with adverse cardiac outcome.
evidence of myocardial ischaemia was strongly associated with an initial postoperative low troponin level and conventional subsequent increases in serum troponin concentration.82 The frequent combination of increases in heart rate preceding the ischaemic episodes, ST-segment depression rather than elevation during all ischaemic episodes; non-Q-wave rather than Q-wave MIs in almost all cases; the lack of angiographically visible thrombus or ruptured plaques in some patients who underwent coronary angiography following PMI; and complete reversal of ECG changes to baseline in all but one of the patients with ischaemia (including those with infarction),85 are highly suggestive that prolonged stress-induced myocardial ischaemia is the likely primary cause of PMI. Repeated brief ischaemic episodes may well have a cumulative effect and ultimately cause myocardial necrosis.55

Although ST-segment depression usually reflects subendocardial ischaemia and is often regarded as reversible injury, it is not inconsistent with an MI. During the early evolution of an MI, significant ST-segment elevation may be lacking.74 For that reason, in current clinical practice, acute MI is divided into ST-segment and non-ST-segment elevation MI (which ultimately develop with little cross-over into Q-wave and non-Q-wave MI, respectively).74 In most studies on perioperative cardiac ischaemic events, the populations consisted largely of elderly patients. Thus, prolonged ST-segment depression may reflect ongoing myocardial ischaemia (ultimately leading to MI), or it may reflect the beginning of an evolving MI.

Not all investigations found an association between postoperative cardiac complications and long-duration ST-segment depression, or between changes in heart rate and postoperative ST-segment changes or troponin release. Such findings would suggest either non-ischaemic causes of ST-segment depression in the perioperative period (e.g. hyperventilation, electrolyte changes, drug effects, positional changes), compensatory mechanisms in response to myocardial ischaemia (e.g. preconditioning as a result of multiple brief episodes of myocardial ischaemia and coronary reperfusion), or functional collateral perfusion.46,137

The preponderance of non-Q-wave infarctions is clearly different from the non-surgical setting. This again might suggest that PMIs are more often the result of prolonged ischaemia than of thrombotic occlusion, similar to the presumed pathophysiology of silent ischaemia.141 However, presence or absence of a Q-wave are not determined primarily by presence or absence of an MI or by the transmural nature of the underlying MI but rather by the total size of the MI.7,112 The probability of a Q-wave infarction increases with MI size and the number of transmural segments. Transmural infarctions were of the non-Q-wave type in 29% of 100 consecutive patients with documented previous MI.112 In addition, the Q-wave takes time to develop and, accordingly, does not figure strongly in present acute-management decisions.

In the presence of severe but stable CAD, coronary thrombosis may result from a decrease in coronary blood flow and stasis.52,53 Some patients with stenotic atherosclerotic lesions may develop acute MI without evidence of plaque rupture and superimposed thrombus formation. This may happen if there is a marked decrease in myocardial oxygen supply (e.g. prolonged severe coronary vasospasm), or a marked increase in myocardial oxygen demand (e.g. tachycardia). It is thus conceivable that coronary thrombosis in the postoperative setting can be the consequence rather than the cause of prolonged myocardial ischaemia and PMI.

Most ischaemic episodes tend to start at the end of surgery and during emergence from anaesthesia.85 This period is characterized by increases in heart rate, arterial pressure, sympathetic tone, and procoagulant activity.16 Increased sympathetic tone can result in increases in arterial pressure, heart rate, contractility, coronary vasomotor tone, and coronary vascular shear stress. This, in turn, may trigger coronary vasospasm, plaque disruption, and coronary thrombosis. Increases in arterial pressure, heart rate, and cardiac contractility lead to subendocardial ischaemia by increasing myocardial oxygen demands in the presence of limited or absent coronary vasodilator reserve as a result of underlying CAD. Surgery-induced simultaneous procoagulant and anti-fibrinolytic activity may trigger coronary artery thrombosis during low-flow conditions in the presence of underlying stable CAD even in the absence of acute plaque disruption.

The ultimate fate of the thrombus and, thus, the extent of jeopardized myocardium will depend on the duration and degree of coronary occlusion. If the plaque disruption is major with extensive exposure of thrombogenic core material to the blood stream, acute total coronary occlusion with subsequent MI, or sudden death may develop. If the disruption is minor, the forming thrombus can be non-occlusive and the patient may stay asymptomatic or develop unstable angina or a non-Q-wave infarction. A concomitant increase in coagulability and coronary vasoconstriction (as is common in the perioperative setting) may, however, transform a non-occlusive thrombus to an occlusive thrombus. Ultimately, the balance between thrombosis and thrombolysis, and the flow conditions (affected by coronary vasomotor tone, perfusion pressure, and rheological properties) are the decisive factors in determining whether the clinical outcome will be myocardial ischaemia or an MI.

**Diagnosis**

A satisfactory explanation of the aetiology of PMI depends greatly on reliable data on the association between various variables and the occurrence of PMI. Such data can only be obtained if the detection of PMI is quantitatively and qualitatively reliable. However, fundamental questions remain regarding the definition and diagnostic criteria of MI in general,5 and perioperatively in particular.97 According to the definition of the World Health Organization (WHO), at least two of three criteria must be fulfilled to diagnose MI: (i) typical ischaemic chest pain; (ii) increased serum concentration of creatine kinase (CK)-MB isoenzyme; and (iii) typical electrocardiographic findings, including
development of pathological Q-waves. The perioperative period is mostly silent, and the electrocardiogram (ECG) is often difficult to interpret and frequently does not exhibit characteristic ST-segment elevation or Q-waves. Therefore, if the diagnosis of MI is based solely on the classical triad, considerable under-reporting of the true incidence of PMI is to be expected, possibly obscuring the aetiology of PMI.

The development of assays for the cardiac troponins T (cTnT) and I (cTnI) that are highly specific and sensitive for myocardial injury formed the basis of a revised definition of MI as proposed by the European Society of Cardiology and the American College of Cardiology. Either of the two following criteria satisfy the diagnosis of an acute, evolving, or a recent MI: (1) typical rise and gradual fall in cardiac troponin concentrations or more rapid rise and fall of CK-MB concentration in combination with at least one of the following: (a) typical ischaemic symptoms, (b) development of pathological Q-waves in the ECG, (c) ECG changes indicative of myocardial ischaemia (ST-segment elevation or depression), or (d) coronary artery intervention; and (2) pathological findings of an acute MI.

Debate continues as to the appropriate cut-off values of troponin concentrations for defining a clinically relevant MI. Initial cut-off values (cTnI >1.5 ng ml⁻¹ and cTnT >0.1 ng ml⁻¹ for certain assays) were derived from titration of troponin concentrations to a population of patients with clinically diagnosed MI. However, even small increases in serum concentrations of cardiac troponins are associated with adverse cardiac outcome in patients with or without ST-segment elevation ACS. Considering the high specificity of cardiac troponins for myocardial cell injury, the recent consensus document of the European Society of Cardiology and the American College of Cardiology Committee on the re-definition of MI states that in the presence of documented myocardial ischaemia, even minor increases in troponin serum concentration to greater than the 99th percentile of the normal population should be regarded as MI. As most troponin assays still lack adequate precision at such low concentrations, slightly higher cut-off values based on <10% imprecision are recommended.

In the frequent absence of typical symptoms and ECG signs of acute MI, the diagnosis of PMI has to rest heavily on changes in biochemical markers. Cardiac troponins appear to be better suited to identify PMI than the CK-MB isoenzyme. The first study using cTnT in the diagnosis of MI utilized a cut-off value for cTnT serum concentration of 3.1 ng ml⁻¹. Subsequent studies utilized cut-off values of 0.2 and 0.1 ng ml⁻¹ and as low as cTnT >0.6 and/or cTnT >0.03 ng ml⁻¹. The following example will demonstrate the dilemma of defining the ‘correct’ incidence of PMI. In the same study, depending on the biochemical marker and the cut-off values, the overall incidence of PMI varied between 2.8% (CK-MB >10%), 9% (conventional cut-off values of cTnI >1.5 ng ml⁻¹ and/or cTnT >0.1 ng ml⁻¹), and 23% (low level cut-off values of cTnI >0.6 and/or cTnT >0.03 ng ml⁻¹). Only 5.6% of patients fulfilled the revised definition of MI (presence of at least two of three criteria: prolonged chest pain, elevated CK-MB or cTn, ischaemic ECG changes). However, without routine measurements of serum concentrations of biochemical markers and continuous ECG monitoring for 3 postoperative days, MI would have been diagnosed in only those 3.6% of patients who experienced prolonged chest pain or symptoms of congestive heart failure. Similarly, whereas 12% of patients had increased cTnT concentrations during routine postoperative monitoring, only 3% had a PMI by the WHO definition.

The question remains whether a reported incidence of perioperative myocardial injury based on traditional definition underestimates the true incidence of clinically relevant myocardial injury, or whether a reported incidence based on serum concentrations of cardiac troponins overestimates it. When using exclusively biochemical markers, specificity may be sacrificed for sensitivity. Another question is whether biochemical marker-defined myocardial injury carries the same predictive value as traditionally defined infarctions, and whether mechanisms and triggers are identical in both cases. Irrespective of whether one refers to small increases in serum concentrations of troponin as ‘myocardial infarction’ or ‘subclinical myocardial injury’ or ‘at risk’, even minor increases in serum concentrations of troponins (cTnI >0.6 and/or cTnT >0.03 ng ml⁻¹) and CK-MB (CK>170 iu and CK-MB/total CK >5%) during the first 3 postoperative days were associated with approximately 50–100% increases in long-term mortality following major vascular surgery (follow-up period 1–5 years, mean 32 months). Larger, conventional increases in troponin concentration (cTnI >1.5 and/or cTnT >0.1 ng ml⁻¹) and CK-MB (CK >170 iu and CK-MB/total CK >10%) were associated with 2-fold and almost 4-fold higher long-term mortality, respectively. Postoperative increases in cTnT >0.1 ng ml⁻¹ correlated with postoperative cardiac events (admission for unstable angina, non-fatal MI, cardiac death) within the first 6 months following non-cardiac surgery; postoperative increases in cTnT more than 0.02 ng ml⁻¹ conferred a 15-fold increase in 1-yr mortality in elderly patients undergoing non-cardiac surgery, and routine cTnI measurements during the first 3 postoperative days enabled prediction of all cause mortality within the first 6 months following vascular surgery. Furthermore, prolonged postoperative myocardial ischaemia and increases in postoperative cardiac troponin concentrations correlated strongly. Postoperative myocardial ischaemic episodes of more than 30 min and more than 60 min were, in turn, associated with 2.6- and 3.7-fold increases in long-term mortality, respectively. Taken together, existing evidence clearly suggests that even small increases in serum concentrations of cardiac troponins in the perioperative period reflect clinically relevant myocardial injury with short-and long-term consequences on outcome. Perioperative
measurements in high-risk patients enable prompt initiation of appropriate diagnostic and therapeutic measures, which may affect long-term cardiac outcome.

Summary

Thus, the aetiology of PMI remains poorly understood. Existing data are inconclusive and do not allow a definitive decision on whether long-duration subendocardial myocardial ischaemia or acute coronary occlusion as a result of plaque disruption or thrombosis is the primary mechanism of perioperative MI in the individual patient. This uncertainty is to be expected considering the enormous structural and functional diversity of coronary atherosclerosis, the unpredictability of plaque progression and vulnerability, and the outstanding methodological problems of reliably detecting and diagnosing perioperative myocardial ischaemia and infarction. Plaque transformation from the stable to the vulnerable state can be acute. Widespread waxing and waning of coronary inflammation and/or of systemic blood thrombogenicity may contribute to the development of plaque vulnerability, in the absence or presence of underlying structurally vulnerable plaques. Some patients may remain vulnerable for a period of weeks to months. In such (chronically) inflamed patients it is possible that plaques will suddenly flare up and become unstable, even in the absence of inflammatory cell infiltration and a central lipid core. Plaque rupture may occur without clinical manifestations (silent plaque rupture).

Prevention of perioperative MI

Two principal strategies have been used in an attempt to reduce the incidence of PMIs and other cardiac events and complications: preoperative coronary revascularization, and pharmacological treatment.

Preoperative coronary revascularization

Controversy remains as to the appropriate management of patients identified preoperatively as having relevant but correctable CAD. The effectiveness of preoperative coronary revascularization in this population continues to be debated. Proponents of ‘prophylactic’ coronary revascularization in selected patients argue that it improves both perioperative as well as long-term outcome. Opponents of this approach point out that morbidity and mortality of percutaneous coronary intervention (PCI) and coronary artery bypass surgery (CABG) in high-risk elderly vascular patients are substantial and outweigh any benefit; that recovery from such major morbidity substantially delays and even prevents the surgery for which the intervention was undertaken; that it does not differentiate between young and old age and between patients with symptomatic CAD and those with CAD discovered by cardiac stress testing only; that only survivors of coronary revascularization are included in the various reports; and, most importantly, that no prospective randomized trial exists to date that demonstrates the effectiveness of preoperative coronary revascularization in improving short- and long-term cardiac outcome and mortality in high-risk patients undergoing high-risk surgery. However, this benefit was entirely offset by two MIIs and three deaths occurring during invasive cardiac evaluation. As a result, there was no statistically significant difference between patients who did and those who did not undergo extensive preoperative cardiac evaluation and coronary intervention in overall early and late non-fatal and fatal MI and cardiac death. These and similar findings suggest that in many patients with positive DTS undergoing high-risk surgery, coronary angiography does not necessarily confer additional useful information or benefit.

Preoperative coronary angiography

Following preoperative percutaneous transluminal coronary angioplasty (PTCA) in patients undergoing non-cardiac surgery, the reported incidences of non-fatal MI and perioperative cardiac death were low. However, neither of these studies is of adequate size or design to allow any conclusion regarding the effectiveness of preoperative PTCA. None of these reports contained control groups of patients with CAD that were not subjected to preoperative PTCA. In a retrospective, case-matched study, preoperative PTCA was associated with reduced overall perioperative cardiac events when compared with patients with CAD that had not undergone PTCA. However, the overall reduction in cardiac events was because of a reduction in the incidence of angina pectoris and congestive heart failure but not in non-fatal MI and mortality. Furthermore, if PTCA had been performed less than 90 days before surgery, any potential benefit was lost.

Coronary stenting. Patients who have recently been subjected to coronary stenting run a high risk of suffering a PMI and serious bleeding. Of 40 patients who underwent coronary stenting within 6 weeks of major non-cardiac surgery, seven suffered a PMI, 11 experienced major bleeding, and eight died. All PMIs, deaths, and haemorrhages occurred in patients who had undergone stenting within 14 days of surgery. Fatal cardiac events were mostly caused by stent thrombosis (likely a result of
interruption of antiplatelet medication 1–2 days before surgery. In contrast, severe bleeding occurred in patients whose antiplatelet medication was continued.

Eight (4%) of 207 patients undergoing non-cardiac surgery in the 2 months following successful coronary stenting suffered major cardiac events (non-fatal PMI one, fatal PMI two, deaths six).162 All of these eight patients were among those 168 patients who underwent surgery within 6 weeks of stent placement. No major complication was observed in the 39 patients who had surgery 7–9 weeks after stent placement.

Preoperative surgical coronary revascularization
Numerous reports include a substantial number of patients who underwent high-risk vascular surgery following CABG.37486484138 Unfortunately, no prospective, randomized trial exists on the effect of preoperative CABG on cardiac outcome. Several retrospective studies,25374548118 and one prospective non-randomized study82 have suggested that in survivors of preoperative CABG surgery, perioperative morbidity and mortality of subsequent major non-cardiac surgery is comparable with patients without clinical evidence of CAD. In a retrospective analysis of 3368 operations in patients enrolled in the Coronary Artery Surgery Study registry, prior CABG improved outcome in major non-cardiac surgery (abdominal, thoracic, vascular, head, and neck).37 Compared with medically treated patients, the perioperative event rate was lower in patients who had previously undergone CABG (PMI 0.8 vs 2.7%, mortality 1.7 vs 3.3%). The event-lowering effect of CABG was most pronounced in patients with advanced angina and/or multi-vessel CAD. No difference in cardiac outcome was observed during minor surgery. Although these findings seem to suggest a cardioprotective effect of preoperative CABG in patients with CAD undergoing major non-cardiac surgery, the analysis did not take into account the added risks of coronary angiography and myocardial revascularization.

Timing of non-cardiac surgery following CABG may be crucial. In a retrospective, case-control study, patients who underwent high-risk vascular surgery within 1 month of CABG had a higher mortality and a trend towards a higher incidence of MI than those undergoing surgery at a later date.15 This confirms previous findings of increased mortality associated with simultaneous CABG and vascular surgery,134 or with non-cardiac surgery within 1–6 months of CABG compared with surgery performed later than 6 months following CABG.26

Risk calculation in preoperative coronary revascularization
In the individual patient, the combined risk of preoperative coronary interventions (coronary angiography, PCI, or CABG) and scheduled non-cardiac surgery may well exceed the perioperative risk of non-cardiac surgery alone in patients without prior CABG. Any potential benefit of preoperative coronary revascularization will be restricted to those patients who survived the preoperative coronary evaluation and revascularization.

In patients with peripheral vascular disease, in-hospital and long-term outcomes (MI, transient ischaemic attack, stroke, bleeding complications) following PCI were substantially worse and procedural success lower than in patients without peripheral vascular disease.142 In such a patient population, coronary angiography was associated with an incidence of MI and mortality of 0.07–0.25% and 1.0–2.5%, respectively.104 Percutaneous intervention and CABG carry a 3–10% risk of MI, and a mortality of 1–2.5% and 2–8.5% (depending on urgency of CABG), respectively.104121 Depending on the type and extent of CAD, vascular surgery alone is associated with an incidence of PMI of 0.5–15% and a mortality of 0.8–20%.104

It is obvious from these numbers that in individual patients overall perioperative cardiac morbidity and mortality may well be lower when undergoing vascular surgery without prior coronary revascularization. Decision analysis suggested that on average, vascular surgery without preoperative coronary intervention results in better perioperative outcome.102 However, the overall long-term outcome might well be comparable because those patients who did not undergo preoperative coronary angiography and coronary revascularization will be faced at some time postoperatively with just those coronary interventions and their associated risks. In addition, there is evidence that the results of PCI in high-risk patients has improved in recent years.142 This is likely a result of more routine coronary stenting, increased use of drug-eluting stents and stents that are easier to deploy, and advances in pharmacotherapy.12 It is conceivable that such advances might shift the risk/benefit balance towards preoperative PCI.

Recommendations for preoperative coronary angiography
In general, indications for preoperative coronary angiography are similar to those in the non-operative setting. The Class I recommendations for preoperative coronary angiography are accordingly restrictive, apply only to patients with suspected or known CAD and include: (i) evidence for high risk of adverse outcome based on non-invasive test results; (ii) angina pectoris unresponsive to adequate medical therapy; (iii) unstable angina, particularly when facing intermediate or high risk non-cardiac surgery; and (iv) equivocal non-invasive test results in patients at high clinical risk undergoing high risk surgery.3435

Recommendations for preoperative coronary intervention
In view of the considerable risk of percutaneous intervention in high-risk patients, it is highly unlikely that prophylactic PCI to merely ‘get the patient through surgery’ will reduce the incidence of PMI. PCI with or without stenting should thus be reserved for patients who have a medical indication for such intervention unrelated to surgery.

PTCA. The indications for preoperative PTCA are identical to those in the non-operative setting.144 Following balloon
angioplasty without coronary stenting, surgery should be delayed for at least a week.\textsuperscript{34,35} This is beyond the time period of within hours to days of the intervention during which arterial recoil and acute thrombosis at the site of angioplasty are most likely to occur, and it allows healing of the vessel injury at the site of balloon treatment.

**Coronary stenting.** Stent thrombosis is a serious complication and mostly results in Q-wave infarction or death.\textsuperscript{28} In patients not undergoing surgery, stent thrombosis most commonly occurs within hours to days of stent placement.\textsuperscript{28} Dual antiplatelet medication with a thienopyridine (mostly clopidogrel) and aspirin reduces the incidence of early stent thrombosis to less than 1%.\textsuperscript{163} The risk of stent thrombosis (clopidogrel and aspirin) to be continued perioperatively, a drug-eluting stent can be placed. If surgery (or the surgeon) does not allow perioperative continuation of dual antiplatelet therapy, a drug-eluting stent should probably not be used. In such a case, heparin- or phosphorylcholine-coated stents may possibly reduce the risk of stent thrombosis in the absence of clopidogrel. This possibility is, however, not supported by any data. Under certain circumstances, PTCA without stent placement may be the most appropriate option. Needless to say, the choice for the type of stent (bare metal $\text{vs}$ drug eluting $\text{vs}$ coated) and the type of PCI (angioplasty with or without stenting) rests entirely with the interventionalist. However, as the anaesthetist will be involved in the perioperative management of these high-risk patients, and as the perioperative period differs considerably from the non-operative setting, the interventionalist may benefit from the anaesthetist’s knowledge and feedback. Close preoperative consultation between interventionalist and anaesthetist is required to minimize the risk of perioperative cardiac and overall morbidity and mortality.

**Recommendation for preoperative surgical coronary revascularization**

The indications for preoperative surgical coronary revascularization are essentially identical to those in the non-operative setting.\textsuperscript{36,62} They include patients with: (i) acceptable coronary revascularization risk and suitable viable myocardium with left main stenosis; (ii) three-vessel CAD in conjunction with left ventricular dysfunction; (iii) two-vessel disease involving severe proximal left anterior descending artery obstruction; and (iv) intractable coronary ischaemia despite maximal medical therapy. If major non-cardiac surgery is indicated following recent CABG, timing appears crucial. Limited data would suggest postponing elective major surgery for at least 4–6 weeks,\textsuperscript{15,134,151} possibly for even up to 6 months after CABG.\textsuperscript{26}

**Conclusions**

Thus, prospective, randomized investigations on the effect of preoperative coronary revascularization on short- and long-term cardiac and overall outcome do not exist. Survivors of coronary revascularization tend to have a better perioperative and long-term cardiac outcome than patients with comparable CAD without preoperative coronary revascularization.

However, in this analysis the high cardiac morbidity and mortality associated with preoperative coronary angiography and coronary revascularization (PCI or CABG) in high-risk patients are not taken into account. In addition, survivors of PCI face the perioperative risk of coronary (stent) thrombosis or haemorrhage associated with discontinuation or continuation of dual antiplatelet therapy, respectively. Overall outcome may thus be comparable between preoperatively revascularized and non-revascularized patients — it may be even worse in individual revascularized
patients. The decision for or against preoperative coronary revascularization, and for or against PCI or CABG, should therefore be based entirely on universally accepted medical indications for coronary revascularization and the appropriate technique. The philosophy of performing preoperative coronary revascularization merely ‘to get the patient through surgery’ is contrary to all available evidence. If the decision for preoperative coronary revascularization is made, timing with respect to the subsequent surgery appears crucial. If these caveats are being observed, it is conceivable that carefully selected patients might benefit from preoperative coronary revascularization. However, only prospective randomized trials can tell.

**Pharmacological treatment**

**Beta-blockers**

Perioperative β-blocker therapy has been listed as a ‘top-tier’ patient safety practice by the Institute of Medicine.140 Several prospective and retrospective studies suggest that perioperative β-blockade improves cardiac outcome in patients with or at risk CAD,100 157 and in patients with documented inducible myocardial ischaemia undergoing non-cardiac surgery.14 129 130 It has been suggested that β-adrenoceptor-antagonists (‘β-blockers’) should be administered to almost all patients with one or more factors that are known to be associated with a higher perioperative cardiac risk.76

**Rationale for the use of perioperative β-blocker therapy**

Numerous cardiovascular and other effects (anti-arrhythmic, anti-inflammatory, altered gene expression and receptor activity, protection against apoptosis) of β-blockers may account for their cardioprotective effect in the operative and non-operative setting.670 94 All β-blockers, except those with intrinsic sympathetic activity, reduce mortality in both MI,51 57 143 and heart failure patients.68 149 Randomized clinical trials involving more than 24 000 patients have shown that β-adrenoceptor-antagonism (‘β-blockade’) reduces post-myocardial infarction mortality, probably by a reduction in infarct size and ventricular arrhythmias.147 On the basis of such data it seems logical that perioperative β-blocker therapy should be beneficial during the period of perioperative stress.

Activation of the hypothalamus–pituitary–adrenal axis persists for at least 1 week following surgery. Adrenal cortical stimulation is accompanied by sympathetic nervous system-induced adrenal medullary activation, resulting in the release of catecholamines with subsequent stimulation of adrenergic receptors. Adrenergic receptors are located in virtually every organ. In the human heart, they mediate numerous biological responses, including inotropy, chronotropy, myocyte apoptosis, and direct myocyte toxicity.

Catecholamines increase each of the four determinants of myocardial oxygen consumption (i.e. heart rate, preload, afterload, and contractility). β-Blockers have the potential of reducing myocardial O2 consumption (thus improving the myocardial O2 supply/demand balance) by decreasing sympathetic tone and myocardial contractility, in turn resulting in decreases in heart rate and arterial pressure. Furthermore, they decrease β2-adrenoceptor-mediated release of intracardiac norepinephrine during ischaemia (reducing cardiac toxicity); they attenuate exercise-induced coronary vasoconstriction (improving exercise capacity); and they have antiarrhythmic properties (increasing the threshold for ventricular fibrillation during myocardial ischaemia).

**Effect on perioperative cardiac mortality.** The effect of perioperative β-blocker therapy on cardiac outcome has been assessed in two, much discussed studies.100 130 In a randomized, double-blind, placebo-controlled study, the benefit of perioperative atenolol in patients with or at risk for CAD undergoing major non-cardiac surgery under general anaesthesia was examined.100 Atenolol (n=99) or placebo (n=101) were started intravenously approximately 30 min before induction of anaesthesia and continued until hospital discharge or for up to 7 days postoperatively. Outcome variables included cardiac death (death because of MI, dysrhythmia, or congestive heart failure), and cardiac events (non-fatal MI, unstable angina and/or congestive heart failure requiring admission and treatment, myocardial revascularization) during the 2 yr following hospital discharge (i.e. in-hospital cardiac morbidity and mortality were not included in the analysis). Over the 2-yr follow-up period, overall mortality after hospital discharge was significantly lower in the atenolol (10%) than in the placebo group (21%, P=0.019). This amounts to a relative risk reduction of 55%. The main reason for this difference was a reduction in cardiac deaths during the first 6 months in the atenolol-treated patients. The combined cardiovascular outcomes were similarly reduced in the atenolol group.

The study has been criticized on numerous grounds. (i) Only those adverse events were included in the analysis that occurred after hospital discharge when patients had stopped taking β-blockers. However, four patients in the atenolol, and two patients in the control group died during hospitalization. It is inappropriate to exclude these in-hospital events from the overall analysis. If they are included, the difference in deaths between the atenolol (n=13) and the placebo group (n=23) loses statistical significance (P=0.1). (ii) The potential for acute β-withdrawal symptoms in the control group cannot be excluded. Eight patients on chronic β-blocker medication were acutely taken off their β-blockers when they were randomized to the control group. Thus, acute β-withdrawal symptoms could possibly have contributed to the less favourable outcome in the placebo group. (iii) Approximately 40% of patients did not tolerate the full dose, and roughly 15% did not tolerate atenolol at all. (iv) Female gender was under-represented. (v) The exact number of patients with intermediate rather
than high risk for adverse perioperative cardiac outcome was not specified. (vi) There was a trend towards a more severe cardiac history (previous MI, angina, diabetes, coronary revascularizations, advanced age) in the placebo group, and a trend towards more effective cardiac therapy (i.e. β-blockers, angiotensin-converting enzyme inhibitors) at hospital discharge in the atenolol group. Given the many study limitations (mainly the overall small number of events, the unrealistically high treatment effect of 55% and no statistically significant difference between groups when in-hospital deaths are included), one has to question the appropriateness of the recommendation for perioperative β-blocker therapy by the American College of Physicians that was based on this study.\textsuperscript{125}

A subsequent study looked at the benefit of perioperative bisoprolol in patients with documented CAD (diagnosed by new wall motion abnormalities on dobutamine stress echocardiography) undergoing major vascular surgery.\textsuperscript{130} 1351 patients undergoing elective major vascular surgery were screened for cardiac risk factors (age over 70 yr, angina, prior MI, compensated or a history of congestive heart failure, current treatment for ventricular arrhythmias, current treatment for diabetes mellitus, limited exercise capacity). 846 of the 1352 patients had at least one of these cardiac risk factors and were, in turn, screened for a positive dobutamine stress echocardiogram (DSE). Of the 846 patients, 173 had a positive DSE. Of these, 61 were excluded from further study because of either extensive wall motion abnormalities on DSE, strong evidence on DSE for left main or severe three-vessel CAD, or because they were already taking β-blockers. The remaining 112 patients were randomized to receive either bisoprolol \((n=59)\) or ‘standard care’ \((n=53)\). Bisoprolol was started on average 37 (range 7–89) days before surgery and was continued for 30 days postoperatively. Outcome variables included cardiac death and non-fatal MI during the first 30 days following surgery. The authors reported a 10-fold lower rate of perioperative cardiac events in the bisoprolol group compared with the ‘standard care’ group \((3.4 \div 34\% ; P=0.001)\).

Although the results strongly suggest that patients with documented CAD disease undergoing high-risk surgery benefit from perioperative β-blockade, this investigation also has several limitations: (i) the study included only 112 patients and a total of merely 20 events. In view of the small sample size, the possibility cannot be ruled out that the observed 90% relative reduction in 30-day adverse outcome occurred by chance alone. The number of 3.2 needed to treat for prevention of PMI and mortality is 10-fold lower than a meta-analysis-derived number of 42 for secondary prevention after MI in the medical setting.\textsuperscript{9,51} (ii) The trial was terminated early because the interim analysis had suggested a large treatment effect. However, unexpectedly large beneficial effects suggested by studies that are terminated early are cause for scepticism.\textsuperscript{159} (iii) Treatment was not blinded. (iv) Standard care (given to the control group) was not defined. (v) The study population was highly selective: of the 1351 initially screened patients, only 112 (8\%) were eventually included in the actual study. Thus, the results are not necessarily representative of a broader patient population. (vi) Patients with severe CAD were excluded. (vii) Finally, the 34% complication rate in the standard care group (nine cardiac deaths, nine MIs) is rather high. A high complication rate in the control group generally tends to favour the treatment group. Despite the various limitations, the accompanying editorial\textsuperscript{87} stated that ‘... In the absence of major contraindications therapeutic doses of beta-adrenergic antagonists should be given to patients with an intermediate or high risk of cardiac complications’.

\textbf{Unanswered questions}

The repeated recommendations for perioperative β-blockade in patients with suspected or documented CAD\textsuperscript{71,87,125} is mainly based on the findings of those two prospective, randomized controlled trials in a little over 300 patients. Several unanswered questions remain.

\textbf{Should β-blockers be administered together with other sympatholytic therapies?} The safety of simultaneously administering β-blockers in patients receiving thoracic epidural anaesthesia or α\textsubscript{2}-adrenergic agonists has not been established. It is conceivable that the interaction between treatments causes an unacceptably high incidence of bradycardia and hypotension, counteracting any potential cardioprotective effect of β-blocker therapy. At present, it remains unknown whether it is necessary to add β-blockers to treatments like α\textsubscript{2}-adrenergic agonists that have themselves demonstrated cardioprotection in the perioperative period.\textsuperscript{158,161}

\textbf{Is there a β-blocker of choice for perioperative β-blocker therapy?} Blocking or blunting the perioperative adrenergic stress response is most likely the key pathophysiological intervention that associates perioperative β-blocker therapy with improved cardiac outcome. Therefore, although not proven yet, it is rather unlikely that pharmacological differences between β-blockers (e.g. in receptor selectivity and affinity, lipophilicity, intrinsic sympathomimetic activity) have any impact on efficacy and safety of treatment. Choice of the β-blocker should be based on those, admittedly very few, controlled randomized trials that have demonstrated effectiveness of perioperative β-blocker therapy.\textsuperscript{100,130} Any cardioselective β-blocker (such as atenolol, bisoprolol, or metoprolol) is probably an acceptable choice.

\textbf{When should perioperative β-blockade be started?} Perioperative cardioprotection was demonstrated when the medication had been initiated either weeks before the scheduled surgery,\textsuperscript{130} or as late as during premedication\textsuperscript{148} and induction of anaesthesia.\textsuperscript{100} The recently revised ACC/AHA guidelines on perioperative cardiovascular evaluation for non-cardiac surgery\textsuperscript{37} recommend that in patients with
Class I indications for perioperative β-blocker therapy (see below), β-blockers be started days or weeks before elective surgery. This makes sense as it will allow titration of the β-blocker to the targeted heart rate.

What should be the therapeutic goal? It is assumed that cardiovascular and sympathetic suppression is required to produce cardiac protection. The extent of such suppression is difficult to assess clinically. Basically all studies on the perioperative use of β-blockers have, therefore, taken heart rate as a physiological surrogate of sympathetic tone. Preoperatively, β-blockers were titrated to achieve heart rates below 50 and 60 beats min⁻¹. Postoperatively, heart rates of less than 80 beats min⁻¹ or 20% below the preoperative ischaemic threshold were aimed at. The revised ACC/AHA Guidelines recommend that the preoperative dose is titrated to achieve a resting heart rate between 50 and 60 beats min⁻¹.

For how long should β-blocker therapy be continued postoperatively? In the two main controlled, randomized trials on the effectiveness of perioperative β-blocker therapy, β-blockers were continued for up to a week and up to a month following surgery. In the latter study, following the initial study period of 30 postoperative days, the survivors continued to receive either bisoprolol therapy or standard care according to their initial randomization. In the bisoprolol group, the dose was adjusted to achieve a heart rate between 50 and 60 beats min⁻¹. Patients were followed for 11–30 months after surgery. Cardiac events (cardiac death and non-fatal MI) occurred in seven (12%) patients in the bisoprolol group and in 14 (32%) patients in the standard care group (P=0.025). These results suggest that long-term postoperative β-blockade reduces the incidence of late cardiac events, certainly among survivors of major vascular surgery who had received perioperative β-blockade.

It appears obvious that those patients with objective indications for the use of β-blockers should continue β-blocker therapy after hospital discharge. In patients without clear indications for long-term β-blocker therapy, β-blockers should probably be continued for at least the time of hospitalization, and preferably for up to 1 month postoperatively. In those patients in whom β-blocker therapy is going to be discontinued after discharge, the dose should be tapered slowly to avoid acute withdrawal symptoms. In those patients in whom β-blocker therapy is going to be continued after discharge, the dose should be adjusted as indicated.

Is there a risk of discontinuing perioperative β-blockade? It is conceivable that acute withdrawal symptoms could develop when β-blockade is abruptly discontinued in patients at increased cardiac risk who were started preoperatively on β-blockers. Although neither of the controlled randomized trials reported such adverse effects of discontinuation of β-blockers results of a retrospective analysis in a small number of patients would suggest that discontinuation of β-blockers in vascular surgery patients may be associated with an increased risk of postoperative morbidity and mortality. It seems advisable to discontinue β-blocker therapy gradually (and only after a period of preferably 30 days postoperatively) in those patients considered not to have a clear indication for long-term therapy.

Is ‘routine’ chronic β-blocker therapy continued perioperatively as effective as acutely initiated, closely monitored, heart rate-targeted perioperative β-blocker therapy? Those 53 patients who were excluded from the bisoprolol study because they were already taking β-blockers, subsequently underwent planned vascular surgery under continued but not specified β-blocker therapy. In this population, the 30-day perioperative cardiac mortality was 7.5%, which is twice as high as that reported in the randomized part of the trial. These findings suggest that perioperative β-blocker therapy might be less effective when not closely monitored and strictly heart rate-targeted.

The total cohort of 1351 consecutive patients initially screened in the randomized trial on bisoprolol was retrospectively re-analyzed. Patients received β-blockers perioperatively, whereas 991 (73%) did not. Except for those 59 patients who were part of the randomized trial, β-blocker management was not specified in those 360 patients. The perioperative cardiac event rate (non-fatal MI, cardiac death) was 2.2% (n=8) in the β-blocker-treated patients (which is comparable with the 3.4% event rate reported in the randomized part of the trial), and 3.7% (n=37) in the non-β-blocked patients (which is almost 10-fold lower than the 34% event rate reported in the randomized part of the trial). The finding of a comparably low perioperative cardiac event rate in this larger population of β-blocked patients (who, presumably, were less intensively monitored than those patients who participated in the prospective, controlled trial) could be interpreted as suggestive evidence that ‘routine’ chronic β-blocker therapy continued perioperatively is, in fact, as effective as acute, closely monitored, heart rate-targeted perioperative β-blocker therapy.

Who should receive perioperative β-blocker therapy? Of the 1351 patients initially screened in the randomized trial on bisoprolol, 1118 (83%) had at most one or two clinical risk factors (defined as age >70 yr, current angina, prior MI, congestive heart failure, prior cerebrovascular event, diabetes mellitus, renal failure). Among this subgroup of patients with relatively low cardiac risk, those receiving β-blockers perioperatively had a significantly lower cardiac event rate (2/263 patients, 0.8%) than those not receiving β-blockers (20/855 patients, 2.3%). Amongst a further subset of 375 patients with no clinical risk factor at all, cardiac event rates were comparably low between those receiving (0/48 patients, 0%) and those not receiving β-blockers (4/327 patients, 1.2%).
In contrast, in the subgroup of 233 (17%) patients with more than/equal to three clinical risk factors, those receiving β-blockers had a cardiac event rate of 6.2% (6/97 patients) compared with a cardiac event rate of 12.5% (17/136 patients) in those not receiving β-blockers. Within this subgroup of patients with more than/equal to three clinical risk factors, 207 patients had four or fewer new wall motion abnormalities on dobutamine stress echocardiography. Those receiving β-blockers perioperatively had a lower cardiac event rate (2/86 patients, 2.3%) than those not receiving β-blockers (12/121 patients, 10.6%). However, in a further subgroup of 26 patients with more than/equal to three clinical risk factors and five or more new wall motion abnormalities on dobutamine stress echocardiography, there was no difference in the cardiac event rates between those receiving β-blockers perioperatively (4/11 patients, 36%) and those not receiving β-blockers (5/15 patients, 33%).

These data are based on retrospective analysis, treatments were neither controlled nor randomized or blinded, and the number of patients in some of the subgroups was too small to allow valid statistical analysis. Taking these limitations into due consideration, the results would suggest that in patients undergoing vascular surgery, perioperative β-blocker therapy may possibly be beneficial in all but subsets of very low or very high risk patients. The findings would further suggest indirectly that aggressive β-blockade in high-risk patients undergoing high-risk surgery may reduce the need for additional preoperative non-invasive cardiac testing, and coronary angiography and revascularization. It is likely that the combined morbidity and mortality from the three sequential procedures, coronary angiography, coronary revascularization and subsequent major vascular surgery, is higher than the 3.4% incidence of major cardiac complications in patients receiving perioperative bisoprolol. Only in a subset of patients with extensive myocardial ischaemia, may perioperative β-blocker therapy not be sufficiently protective.

Based on the results of various studies, the revised ACC/AHA Guidelines list several conditions as Class I indications for perioperative β-blocker therapy (i.e. conditions for which there is evidence for and/or general agreement that the therapy is useful and effective): (i) the need for β-blockers in the recent past to control symptoms of angina; (ii) patients with symptomatic arrhythmias or hypertension; and (iii) patients at high risk for a perioperative cardiac event based on the finding of myocardial ischaemia on perioperative testing who are undergoing vascular surgery. Class IIa indications for perioperative β-blocker therapy (i.e. conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the performed therapy, with the weight of evidence/opinion in favour of usefulness/efficacy of the performed therapy) include preoperative identification of untreated hypertension, known CAD, or major risk factors for CAD.

When it comes to defining the contraindications for the use of β-blockers, it is helpful to remember that the 2001 AHA/ACC Guidelines for secondary prevention of MI and death recommend to initiate β-blockade in all post-MI patients and to continue such therapy indefinitely. They list as absolute contraindications for the use of β-blockers symptomatic bradycardia (usually a heart rate <50–60 beats min⁻¹), symptomatic hypotension (usually a systolic arterial pressure <90–100 mm Hg), severe heart failure requiring i.v. diuretics or inotropes, cardiogenic shock, asthma or reactive airway disease requiring bronchodilator and/or steroids, and 2° or 3° AV block.

**Proposed algorithm for the use of perioperative β-blocker therapy**

An algorithm for the use of perioperative β-blocker therapy based on various studies on perioperative β-blocker therapy and preoperative risk stratification has been suggested. In high-risk patients with more than/equal to three major clinical risk factors (high-risk surgical procedure, CAD, cerebrovascular disease, insulin-dependent diabetes mellitus, chronic renal insufficiency) and a positive non-invasive cardiac stress test (DTS, DSE), additional coronary angiography and coronary revascularization should be considered because the perioperative cardiac event rate will remain in the 6.5–16% range even with perioperative β-blocker therapy. In high-risk patients with negative non-invasive test results, and in clinically intermediate risk patients [1–2 major clinical risk factors or any of two minor risk factors such as age ≥65 yr, hypertension, current smoker, serum cholesterol ≥6.18 mmol litre⁻¹ (≥240 mg dl⁻¹), non-insulin-requiring diabetes mellitus] with good functional capacity and without evidence of angina or peripheral vascular disease, β-blocker therapy is started preoperatively and surgery is performed as planned.

In clinically intermediate-risk patients with poor functional capacity and with evidence of angina or peripheral vascular disease, additional therapies and/or interventions (coronary angiography and revascularization) should be considered. Finally, in low-risk patients without clinical risk factors, the perioperative cardiac event rate is low with (0.4%) or without (0.4–1.0%) perioperative β-blockade, so that perioperative β-blockade is deemed unnecessary.

In conclusion, although perioperative β-blocker therapy has been designated as one of 11 specific practices with sufficient clinical-based evidence for patient safety to justify immediate and widespread implementation, before a final recommendation for a liberal use of perioperative β-blockade can be made safely, several caveats have to be kept in mind. All studies that support use of perioperative β-blocker therapy have included rather small numbers of patients (as few as 26154). Often, recruitment of patients was highly selective and consecutive (recruitment rate as low as 8%130), excluding application of the results to an unselected surgical population. Furthermore, the beneficial effects were probably not only because of a rather aggressive therapy (targeted heart rates maximally 80 beats min⁻¹), but also (and perhaps even more importantly) because of continuous
close monitoring of the patient. This will ensure both optimal cardioprotection and patient safety. More uncontrolled but equally aggressive postoperative administration of β-blockers on ordinary surgical wards might well result in more adverse side-effects, possibly negating any beneficial effects. Although current evidence suggests that selected patients are likely to benefit from perioperative β-blocker therapy, we have to acknowledge that data on risks and benefits of such therapy are still few and inconclusive.32 A large definitive trial on perioperative β-blocker therapy is needed.31 Until the results of such a trial are available, it seems fair to conclude: ‘Peri-operative β-blockade: a useful treatment that should be greeted with cautious enthusiasm’.66

Alpha-2 adrenoceptor agonists
Alpha-2 adrenoceptor agonists improve cardiovascular morbidity and mortality following non-cardiac and cardiac surgery.33 108 119 122 158 161 In a prospective, randomized, double-blinded study in 190 patients undergoing non-cardiac surgery, prophylactic clonidine (0.2 mg orally and as dermal patch for 4 days) reduced perioperative myocardial ischaemia and improved 30-day and 2-yr mortality but had no effect on PMI.158 The long-term beneficial effect could have been a result of the reduction in perioperative myocardial ischaemia.

The mechanism of the protective effect is likely to be manifold. Alpha-2 adrenoceptor agonists attenuate perioperative haemodynamic instability,108 inhibit central sympathetic discharge,114 reduce peripheral norepinephrine release,38 and dilate post-stenotic coronary vessels.65

Aspirin
Early postoperative administration of aspirin improved outcome following coronary artery bypass surgery.99 Aspirin is known to reduce cardiac events in patients with ACS and in patients not known to have CAD.23 It eliminates the diurnal variation in plaque rupture.136 Compared with controls, patients with unstable angina had more than twice the blood concentrations of interleukin-6, CRP, and macrophage colony-stimulating factor.99 Those concentrations decreased after 6 weeks of aspirin treatment. Aspirin will, of course, reduce platelet aggregability, but its ability to reduce future MI appears greatest in individuals with serological evidence of increased inflammation.135 Thus, the anti-inflammatory effect of aspirin may be additive to its antithrombotic effect in patients with plaque instability. This effect may be of particular relevance in the perioperative setting.

Statins
Perioperative use of statins may be associated with reduced perioperative mortality in patients undergoing major vascular surgery.77 128 In a multicentre observational study including over 780 000 individuals, lipid-lowering therapy (primarily statins) during the first two days of hospitalization was associated with decreased mortality in patients undergoing non-cardiac surgery (2.13 vs 3.05% in non-treated patients).93 These findings are consistent with results of a cohort study in almost 20 000 patients with ACS.145 Patients who were taking statins when experiencing ACS had fewer MIs than patients not taking statins. Institution of aggressive statin therapy in patients with acute coronary syndrome resulted in reduced plaque volume at 6-month follow-up.120 It thus appears that statin therapy may modulate early pathophysiological processes during ischaemic cardiac events.

‘Pleiotropic’ effects of statins independent of their lipid-lowering action have been proposed as the mechanisms of their beneficial effects. These pleiotropic effects include reversal of endothelial dysfunction,91 155 modulation of macrophage activation,3 immunological effects,3 and anti-inflammatory,3 antithrombotic,155 and antiproliferative actions (possibly mediated by the induction of heme oxygenase-1).89 The direct effect of statins on vascular function may result in coronary plaque stabilization.

Miscellaneous preventive measures
Postoperative myocardial ischaemia has been shown to be associated with postoperative anaemia,116 hypothermia,49 50 and pain.11 101 All of them activate sympathetic tone with adverse effects on cardiovascular function and coagulation. The result will be an increase in myocardial oxygen consumption in the presence of a decrease in delivery. As perioperative myocardial ischaemia is a predictor of adverse short- and long-term cardiac outcome, maintenance of an appropriate haemoglobin concentration, normothermia, and adequate pain control are essential preventive measures.

Conclusions
The aetiology of PMI is multifactorial. The perioperative period induces large, unpredictable and unphysiological changes in sympathetic tone, cardiovascular performance, coagulation and inflammatory response (to name just a few). These changes induce, in turn, unpredictable alterations in plaque morphology, function and progression. Simultaneous perioperative alterations in homeostasis and coronary plaque characteristics may trigger a mismatch of myocardial oxygen supply and demand by numerous mechanisms. If not alleviated in time, it will ultimately result in MI, irrespective of its aetiology (morphologically, haemodynamically, inflammatory, or coagulation induced). With these many and diverse factors involved, it is highly unlikely that one single intervention will successfully improve cardiac outcome following non-cardiac surgery. A multifactorial, step-wise approach is indicated.20 22 59 79 113

Based on increasing knowledge of the nature of atherosclerotic CAD, and in view of the poor positive predictive value of non-invasive cardiac stress tests and the considerable risk of coronary angiography and coronary revascularization in high-risk patients, the paradigm is shifting from an emphasis on extensive non-invasive preoperative risk stratification to an emphasis on a combination of selective
non-invasive testing (to reliably identify those patients who truly benefit from preoperative intervention, such as cancel-
lation of surgery, preoperative coronary revascularization, initiation or optimization of cardioprotective medication),
and aggressive perioperative pharmacological therapy.59,63 Perioperative plaque stabilization by pharmacological
means (statins, aspirin, β-blockers) may be as important in the prevention of PMI as an increase in myocardial oxygen
supply (by coronary revascularization), or a reduction in myocardial oxygen demand (by β-blockers or α2-agonists).

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Addendum

Since preparation of the manuscript, the results of a randomized study were published which investigated the effect of preoperative coronary revascularization (by either percutaneous coronary intervention or bypass surgery) on long-term outcome in 510 patients undergoing vascular surgery.1 Patients with severe coronary artery disease, poor left ventricular function or severe aortic stenosis were excluded from randomization. At a median follow-up time of 2.7 yr, there was no difference in mortality between the revascularized and non-revascularized groups (22% and 23%, respectively). Twenty-four months after randomization, the vast majority of patients were taking beta-blockers (approx. 80%), statins (approx. 70%), aspirin (approx. 85%) and angiotensin-converting-enzyme inhibitors (approx. 55%). The results suggest that in patients with stable coronary artery disease and unimpaired left ventricular function who receive excellent perioperative medical therapy, coronary revascularization before vascular surgery does not improve long-term outcome.