



Preoperative cardiac management of the patient for non-cardiac surgery: an individualized and evidence-based approach

H.-J. Priebe *

University Hospital Freiburg, Freiburg 79106, Germany

* E-mail: hans-joachim.priebe@uniklinik-freiburg.de

Editor's key points

- Preoperative risk stratification allows intelligent preoperative testing and intervention, reducing risk, and improving outcome.
- An individualized approach is needed, given the population-oriented classifications available and the enormous variation between patients in other factors.
- Functional capacity remains one of our most important tools in establishing perioperative cardiovascular risk.

Summary. Preoperative cardiovascular management is an essential component of overall perioperative cardiovascular care. It involves preoperative detection and management of cardiovascular disease and prediction of both short- and long-term cardiovascular risk. It thereby not only affects anaesthetic perioperative management (e.g. choice of anaesthetic drug and method, type of monitoring, and postoperative care) but also surgical decision-making (e.g. postponement, modification, and cancellation of surgical procedure). The ultimate goal of preoperative cardiovascular management is to improve overall patient outcome. This requires individualized management. Although preoperative cardiac management has improved during the past decades, we are not yet in the situation where we can accurately predict individual perioperative risk. The individual stress response and the individual interactions between pharmacological intervention and intra- and postoperative risk factors are highly variable. More importantly, preoperative cardiac management is only one aspect of overall perioperative care. There are numerous intra- and postoperative factors which have been shown to affect overall outcome. However, not all of them can reliably be predicted or modified in a way to positively affect overall outcome. Recognition of such factors and aggressive attempts at appropriate intervention may reduce overall risk more than preoperative management in isolation. Without defining and subsequently targeting intra- and postoperative risk factors, the benefit of preoperative cardiac management will be limited.

Keywords: cardiac management, preoperative; surgery, non-cardiac; surgery, preoperative period

Major non-cardiac surgery is associated with an incidence of perioperative cardiac death of 0.5–1.5%, and of major cardiovascular complications (non-fatal cardiac arrest, non-fatal myocardial infarction, heart failure, clinically relevant arrhythmias, and stroke) of 2.0–3.5%. Underlying cardiovascular disease significantly contributes to perioperative morbidity and mortality.¹ Depending on the type of surgery and patient age, the prevalence of various cardiovascular diseases in patients undergoing non-cardiac surgery ranges from <5% to 70%, being highest in patients older than 70 yr undergoing major vascular surgery.¹

Preoperative cardiovascular management is an essential component of overall perioperative cardiovascular care. It involves preoperative detection and management of cardiovascular disease, and prediction of both short- and long-term cardiovascular risk. It thereby not only affects anaesthetic perioperative management (e.g. choice of anaesthetic drug and method, type of monitoring, postoperative care) but also surgical decision-making (e.g. postponement, modification, and cancellation of surgical procedure). By

modifying intra- and postoperative patient care, preoperative cardiac management is hoped to improve overall perioperative outcome. The immediate aims of preoperative cardiac management are: (i) identification of patients with potentially life-threatening cardiac disease that requires preoperative assessment and treatment by a cardiologist; (ii) identification of the most appropriate testing and avoidance of unnecessary testing (an important aspect because non-invasive and invasive testing are not only associated with patient discomfort and financial burden, but also with morbidity and mortality related to the test procedure, false test results, and postponement of required surgery); and (iii) identification and implementation of most appropriate medical (e.g. initiation, continuation, or optimization of cardiovascular medication) and interventional cardiovascular treatment strategies (e.g. preoperative coronary revascularization or cardiac valve replacement). The ultimate goal of preoperative cardiovascular management is to improve overall patient outcome. This requires individualized management.

Preoperative assessment

Active cardiac conditions, a high-risk surgical procedure, and poor exercise tolerance are the strongest independent predictors of adverse perioperative cardiac outcome.

Active cardiac conditions

Active/unstable cardiac conditions [unstable angina pectoris, acute heart failure, significant cardiac arrhythmias, symptomatic valvular heart disease (VHD), and recent myocardial infarction with residual myocardial ischaemia] are associated with very poor perioperative outcome. They thus need to be identified and, if present, evaluated and treated by a cardiologist according to respective national or international guidelines. Subsequent management (delay, modification, or cancellation of planned procedure) will depend on test results and response to treatment.

Heart failure

Heart failure is a major independent predictor of adverse perioperative outcome in non-cardiac surgery.^{2, 3} It carries a greater perioperative risk than ischaemic heart disease.² The perioperative prognostic value of heart failure with preserved left ventricular (LV) ejection fraction (previously referred to as diastolic heart failure) remains to be determined. The present guidelines on perioperative cardiac care by the European Society of Cardiology (ESC)¹ recommend comparable perioperative management in patients with impaired and preserved LV ejection fraction.

Patients with suspected or known heart failure should undergo preoperative evaluation by a specialist to assess the severity of the disease and to ensure optimal medical therapy. The findings on stress echocardiography and the serum concentrations of brain natriuretic peptide (BNP) or its inactive precursor N-terminal pro-B-type natriuretic peptide (NT-proBNP) may be used for risk stratification. This patient population must be expected to be taking multiple, long-term medications, including angiotensin-converting enzyme (ACE) inhibitors, angiotensin-II-receptor blockers, β -blockers, aldosterone antagonists, and diuretics, all with associated side-effects (mostly electrolyte disturbances, renal insufficiency, and intraoperative therapy-resistant hypotension). As there is evidence that the perioperative use of ACE inhibitors, β -blockers, statins, and aspirin improves outcome in patients with LV dysfunction undergoing major vascular surgery, perioperative continuation of such therapy is recommended in this patient population.

Valvular heart disease

As patients with VHD are, in general, at increased risk of perioperative cardiac complications during non-cardiac surgery, echocardiography should be considered in all patients with suspected VHD (class of recommendation IIa, level of evidence grade B) (for definitions of class of recommendation and level of evidence, see Tables 1 and 2). In all patients with severe VHD, clinical and echocardiographic evaluation

Table 1 Classes of recommendations¹

Classes	Definitions
I	Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, and effective
II	Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure
IIa	Weight of evidence/opinion is in favour of usefulness/efficacy
IIb	Usefulness/efficacy is less well established by evidence/opinion
III	Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful

Table 2 Levels of evidence¹

A	Data derived from multiple randomized clinical trials or meta-analyses
B	Data derived from a single randomized clinical trial or large non-randomized studies
C	Consensus of opinion of the experts and/or small studies, retrospective studies, registries

should be performed (I, C) and, if indicated, appropriately treated before operation.

Of all forms of VHD, severe aortic stenosis (AS) (aortic valve area $<1 \text{ cm}^2$ or $<0.6 \text{ cm}^2 \text{ m}^{-2}$) carries the highest perioperative cardiovascular morbidity and mortality in non-cardiac surgery. The key factors in the preoperative decision-making are severity of stenosis and clinical condition. The preoperative management of patients with *asymptomatic* but severe AS remains problematic. They usually tolerate low- to intermediate-risk surgery. If undergoing high-risk surgery, evaluation by a specialist is advisable. In medical patients with asymptomatic severe AS, independent predictors of adverse outcome were female sex, peak aortic-jet velocity, and BNP at baseline.⁴ The score which was developed on these independent predictors may be useful in selecting those patients who might benefit from preoperative valve replacement or balloon aortic valvuloplasty.

Management of *symptomatic* patients with severe AS is particularly challenging. These and certain asymptomatic patients with severe AS undergoing high-risk surgery are candidates for aortic valve replacement which should preferably be performed before non-cardiac surgery. In patients with severe AS who cannot undergo surgical valve replacement (advanced age, presence of severe LV dysfunction, multiple and serious co-morbidities, relative urgency of surgery), preoperative transcatheter valve implantation (transapical or transfemoral) should be considered.⁵ Considering the very poor short-term prognosis in general, and the very poor

Table 3 Cardiac risk stratification (combined incidence of cardiac death and non-fatal myocardial infarction within 30 days of surgery) according to surgical risk. *These procedures do not generally require further preoperative cardiac testing. On the basis of guidelines published by the European Society of Cardiology (ESC)¹

Low risk (<1%)*	Intermediate risk (1–5%)	High risk (>5%)
Breast	Intraperitoneal/intrathoracic	Aortic—open
Dental	Vascular (peripheral arterial angioplasty/carotid/endovascular aneurysm repair)	Peripheral vascular—major
Endocrine	Head and neck surgery	
Eye	Neurological/orthopaedic—major (hip and spine surgery)	
Gynaecology	Lung/kidney/liver transplantation	
Reconstructive	Urologic—major	
Orthopaedic—minor (e.g. knee surgery)		
Urologic—minor		

perioperative outcome in this patient population, transcatheter valve implantation carries acceptable peri-procedural morbidity and mortality.^{6–9} At 1 month after transcatheter aortic valve implantation, 88% of 244 high-surgical-risk patients with a mean age of 82 (7) yr were in NYHA class II or less, and 30 day mortality was about 12%.⁹

Surgical risk

On the basis of an expected combined incidence of cardiac death and non-fatal myocardial infarction within 30 days of surgery, surgical procedures can be separated into those with low, intermediate, and high risk (Table 3). In general, patients undergoing vascular surgery carry the highest risk of suffering a perioperative cardiac event. However, surgical risk differs between vascular procedures. Whereas abdominal aortic aneurysm repair or major lower extremity arterial revascularization are classified as high-risk procedures, endovascular procedures, carotid endarterectomy, and peripheral angioplasty are classified as intermediate-risk procedures.

Functional capacity

Preoperative functional status is probably the most important predictor of perioperative outcome. Low exercise tolerance is associated with poor perioperative outcome.^{10–15} The main purpose of preoperative assessment of functional capacity is to predict the individual's ability to increase oxygen delivery in the perioperative period. There are several methods of assessing exercise tolerance.

Duke Activity Status Index

The Duke Activity Status Index (DASI) is a structured questionnaire that grades exercise ability on the basis of a series of questions related to exercise equivalences ranging from the ability to wash and dress without breathlessness to strenuous activity such as swimming and singles tennis.¹⁶ A DASI questionnaire score above 11.6 is roughly equivalent to an oxygen consumption of 14 ml O₂ kg⁻¹ min⁻¹.¹⁷ However, as the questionnaire was developed in

Table 4 Estimated energy requirements for various activities (modified after ref. 1). MET, metabolic equivalent task. 1 MET, oxygen consumption of 3.5 ml kg⁻¹ min⁻¹

Can you ...
1 MET
<ul style="list-style-type: none"> ... take care of yourself? ... eat, dress, or use the toilet? ... walk indoors around the house? ... walk a block or two on level ground at 2–3 mph (3.2–4.8) km h⁻¹? ... do light work around the house like dusting or washing dishes?
4 METs
<ul style="list-style-type: none"> ... climb a flight of stairs or walk up a hill? ... walk on level ground at 4 mph (6.4 km h⁻¹)? ... do heavy work around the house (e.g. scrubbing floors)? ... participate in moderate recreational activities (e.g. dancing, doubles tennis)?
>10 METs
<ul style="list-style-type: none"> ... participate in strenuous sports (e.g. swimming, singles tennis, skiing)?

medical patients with cardiac disease, its predictive value in a surgical population is undetermined. The ESC¹ and American College of Cardiology/American Heart Association (ACC/AHA)¹⁸ guidelines recommend using the metabolic equivalent task (MET), a derivative of the DASI questionnaire, as an estimate of functional capacity (Table 4). One MET is defined as 3.5 ml O₂ min⁻¹ kg⁻¹, with 4 METs given as the cut-off value for acceptable functional capacity.

It is important to recognize that the definition of MET is based on a single measurement of resting oxygen consumption in a 70 kg, 40-yr-old male.¹⁹ However, the average resting metabolic rate (or 1 MET) has been reported as low as 2.56 ml (0.40 ml O₂ min⁻¹ kg⁻¹), varying primarily with body composition and (less so) with age.¹⁹ Thus, reliable individual assessment of functional capacity on the basis of multiples of METs would require knowledge of the individual's

resting oxygen uptake. Depending on the resting oxygen consumption, 4 METs may reflect very different oxygen uptakes. Without knowing the individual's resting oxygen consumption and gas exchange characteristics, and without controlling for height and speed of climbing and walking, it is impossible to know whether an individual remains below or above their anaerobic threshold (AT) at those given activities. Thus, applying an average oxygen consumption value to each individual irrespective of body composition and age must be expected to lower the predictive value. In addition, assessment relies on patient reporting and may thus not necessarily reflect the individual's true functional capacity. However, assessment of functional capacity by the DASI questionnaire or MET can be helpful when formal exercise testing is not possible (e.g. in emergency cases, in immobile or non-cooperative patients, and in patients with pain).

Incremental shuttle walk test

The incremental shuttle walk test (ISWT) is widely used for the assessment of cardiopulmonary reserve. It has the patient walk up and down a usually 10 m course (shuttle) at a speed dictated by an audio signal, with the walking speed being slowly increased at timed intervals. The test is terminated either by the patient who feels too fatigued to continue walking at the speed set by the audio signal or by the operator when the patient fails to complete the 10 m course within the allotted time. The distance completed by the patient when the test is terminated is a measure of functional capacity and correlates with peak oxygen consumption in various conditions.^{20 21} Cut-off values for walking distance predicting adverse postoperative outcome will depend on the type of surgery and have been reported as <350–400 m in patients undergoing pneumonectomy or oesophagogastrctomy.^{13 22} Although this test is technically less demanding than formal cardiopulmonary exercise testing, it does require standardization of procedures to produce reproducible and meaningful results. Obviously, immobile and patients with pain will not be able to perform this test.

Cardiopulmonary exercise testing

The gold standard for objective and comprehensive assessment of overall functional capacity is the individual measurement of oxygen uptake and carbon dioxide elimination by using a symptom-limited, submaximal, incremental cardiopulmonary exercise test (CPET). The advantage of this test is that it assesses both the cardiac and the respiratory components of exercise. It provides additional useful information on ECG changes, and on cardiac and ventilatory function. The main measures of interest are peak oxygen consumption (VO_2 peak) and AT. AT is defined as the point at which anaerobic metabolism starts to increase because oxygen delivery to the muscles no longer meets exercise-induced oxygen demand. The thresholds for classifying patients as increased risk are usually set at VO_2 peak $<15 \text{ ml O}_2 \text{ kg}^{-1} \text{ min}^{-1}$ and AT $<11 \text{ ml O}_2 \text{ kg}^{-1} \text{ min}^{-1}$.^{11 23}

If performed and interpreted appropriately, CPET provides a wealth of additional information beyond standard cardiac stress tests which can potentially assist in the perioperative management of complex cardiovascular and pulmonary disease.^{24 25} However, CPET requires complex equipment and highly trained personnel for correctly performing the test and interpreting the results; it is not feasible in the immobile patient, the individual positive predictive values of VO_2 peak and AT remain to be determined, and identification of the AT is not always straightforward. The results of the DASI questionnaire, the ISWT, and the cycle CPET do not necessarily agree. Although a significant correlation between measured oxygen consumption and both ISWT and DASI has been reported, and although both ISWT and DASI were satisfactory predictors of VO_2 peak $>15 \text{ ml O}_2 \text{ kg}^{-1} \text{ min}^{-1}$ and AT $>11 \text{ ml O}_2 \text{ kg}^{-1} \text{ min}^{-1}$, patients with unsatisfactory questionnaire scores or shuttle walk test results may have satisfactory CPET results.¹⁷ Overall, however, the CPET provided more robust information than did Duke's score and shuttle testing. It remains to be seen whether such relatively objective information modifies perioperative management in a way which improves perioperative outcome.

Cardiac risk factors

The cardiac risk factors listed in the ESC guidelines¹ (Table 5) are those of the Lee revised cardiac risk index (RCRI)²⁶ except for high-risk surgery which is not included because it is separately considered in the context of surgical risk (Table 3). The risk factors are meant to predict cardiac outcome independently. The ESC guidelines recommend using clinical risk indices for postoperative risk stratification (I, B) and specifically to use the Lee RCRI for perioperative risk stratification (I, A). Such clear recommendation is somewhat surprising because cardiac risk indices have several limitations.

First, there are general problems with using cardiac risk factors for individual risk stratification. Clinical risk factors do not specify the duration of exposure to the risk factor and thus do not reliably reflect the severity of disease. Definition and diagnosis of risk factors such as angina pectoris, prior myocardial infarction, and heart failure vary and can be highly subjective. Therefore, adding as much objective information as possible [e.g. functional capacity, results of CPET, echocardiographic LV assessment, and concentrations of BNP, NT-proBNP, and C-reactive protein (CRP) in the case of suspected heart failure] is important.

Secondly, there are statistical problems with risk indices. They have very low positive predictive value. Even in the high-risk class IV of the RCRI (≥ 3 risk factors), only 11% of the population suffered a perioperative cardiovascular event. Discrimination between classes is poor. The 95% confidence intervals of the complication rates show large overlaps in the prediction of risk between the risk classes.

The likelihood ratio is another measure of the ability of a risk index to discriminate between degrees of risk.²⁷ The accepted low and high values of likelihood ratios for

Table 5 Cardiac risk factors (modified after ref. 1)

History of angina pectoris
History of myocardial infarction
History of heart failure
History of stroke/transient ischaemic attack
Diabetes mellitus requiring treatment with insulin
Renal dysfunction (serum creatinine concentration $>170 \mu\text{mol litre}^{-1}$ (2.0 mg dl $^{-1}$) or a creatinine clearance $<60 \text{ ml min}^{-1}$)

satisfactorily discriminating between groups of patients are <0.2 and >10 , respectively. The likelihood ratios of the RCRI classes I, II, III, and IV are 0.16, 0.34, 2.72, and 4.75,²⁷ respectively, indicating that the RCRI is useful in identifying patients at low risk, but not at high risk for perioperative cardiac complications. Furthermore, it includes only preoperative predictors of outcome. A recent study failed to reproduce all of the factors of the RCRI as independent predictors of outcome, and identified additional pre- and intra-operative independent predictors of outcome (e.g. age >68 yr, BMI $>30 \text{ kg m}^{-2}$, hypertension, duration of surgery ≥ 3.8 h, red blood cell transfusion ≥ 1 unit).³ If validated, the validity of the Lee RCRI may need to be reassessed. Obviously, intra- and postoperative risk factors (e.g. duration of surgery, bleeding, blood transfusion, anaemia, and pain) may well affect short- and long-term cardiac outcome and cannot reliably be predicted before operation. In general, cardiac risk indices are suited to compare the degree of cardiac risk between different populations, but they are not useful in the prediction of individual perioperative cardiac risk.

Non-invasive testing

Non-invasive tests are performed to obtain information on possible LV dysfunction, myocardial ischaemia, and valvular dysfunction. Resting ECG, echocardiography, and myocardial imaging techniques and cardiac stress tests (exercise ECG, stress echocardiography, stress myocardial perfusion imaging) have very low (0–33%) positive predictive values for perioperative cardiac events¹⁸ (i.e. likely absence of perioperative cardiac events, despite abnormal test result). Stress tests will primarily detect flow-limiting lesions, but not non-flow-limiting plaques. However, the latter often consist of vulnerable plaques and are frequently the source of perioperative myocardial infarction.^{28 29} Not surprisingly then, non-invasive cardiac stress testing may not necessarily be helpful in identifying patients who might benefit from preoperative coronary angiography and coronary revascularization. The indications for performing these tests are, therefore, very restrictive (Tables 6 and 7).

Coronary angiography

In general, coronary angiography in cardiovascular high-risk patients carries the potential for life-threatening complications. In addition, there is no convincing evidence that

Table 6 Recommendations for preoperative resting electrocardiogram and echocardiography (modified after ref. 1)

Recommendations	Class	Level of evidence
Preoperative resting electrocardiogram		
<i>Recommended:</i> for patients with cardiac risk factor(s) undergoing intermediate- or high-risk surgery	I	B
<i>Should be considered:</i> for patients with cardiac risk factor(s) undergoing low-risk surgery	IIa	B
<i>May be considered:</i> for patients with no cardiac risk factor(s) undergoing intermediate-risk surgery	IIb	B
<i>Not recommended:</i> for patients with no cardiac risk factor(s) undergoing low-risk surgery	III	B
Preoperative resting echocardiography		
<i>Recommended:</i> for patients with severe valvular heart disease	I	C
<i>Should be considered:</i> for left ventricular assessment in patients undergoing high-risk surgery	IIa	C
<i>Not recommended:</i> for left ventricular assessment in asymptomatic patients	III	B

Table 7 Recommendations on preoperative cardiac stress testing (modified after ref. 1)

Recommendations	Class	Level of evidence
<i>Recommended:</i> for patients with ≥ 3 cardiac risk factors undergoing high-risk surgery	I	C
<i>May be considered</i>		
For patients with ≤ 2 cardiac risk factors undergoing high-risk surgery	IIb	B
For patients undergoing intermediate-risk surgery	IIb	C
<i>Not recommended:</i> scheduled low-risk surgery	III	C

preoperative coronary revascularization reliably improves perioperative outcome. Consequently, the indications for preoperative coronary angiography are restrictive and, in general, identical to those in the non-operative setting (Table 8). Before performing a preoperative coronary angiography, it should be clear beforehand that the patient is a potential candidate for subsequent preoperative coronary revascularization, which necessitates a prior detailed discussion of the implications of preoperative coronary revascularization (e.g. possible postponement of surgery and need for anti-platelet therapy) between medical care givers and the patient. Preoperative coronary angiography merely to confirm the existence of coronary artery disease is rarely indicated. If the coronary anatomy found on coronary

Table 8 Recommendations for preoperative coronary angiography (modified after ref. 1)

Recommendations	Class	Level of evidence
<i>Recommended:</i> for patients with ...	I	A
Acute ST-elevation myocardial infarction (STEMI)		
Non-STEMI and unstable angina		
Angina unresponsive to medical therapy		
<i>May be considered:</i> for cardiac stable patients ...	IIb	B
Undergoing high-risk surgery		
Undergoing intermediate-risk surgery	IIb	C
<i>Not recommended:</i> for cardiac stable patients	III	C
Undergoing low risk surgery		

angiography fulfils the indication(s) for coronary revascularization, a consultation between cardiologist, surgeon, anaesthetist, and patients is required to decide on the appropriate method of coronary revascularization (i.e. surgical vs interventional; if interventional, balloon angioplasty vs bare-metal stenting vs drug-eluting stenting).

Biomarkers

Coronary artery and myocardial disease are frequently accompanied by increased plasma concentrations of CRP, and of BNP and NT-proBNP reflecting the considerable inflammatory component associated with cardiovascular disease and increased myocardial wall stress, respectively.³⁰ The results of several recent systematic reviews, meta-analyses,^{31–32} and observational studies^{33–37} have shown that elevated preoperative serum concentrations of high-sensitivity CRP, and BNP or NT-proBNP are powerful, independent predictors of adverse postoperative short- and intermediate-term cardiac outcome in major non-cardiac surgery. In addition, preoperative measurements of these biomarkers provide additive prognostic information for major adverse cardiac events and mortality after high-risk surgery. In patients undergoing elective major non-cardiac surgery, both NT-proBNP (cut-off=301 ng litre⁻¹) and CRP (cut-off=3.4 mg litre⁻¹) predicted major perioperative cardiac events better than the Lee RCRI (cut-off=2). Moreover, the predictive power of the RCRI was improved three-fold by including preoperative concentrations of NT-proBNP and CRP.³⁷ Elevated CRP concentrations did not predict cardiac events better than elevated NT-proBNP concentrations.

The cut-off concentrations of CRP and of BNP and NT-proBNP associated with adverse outcome varied tremendously between studies, indicating that we are far from knowing what a 'normal' preoperative concentration of these biomarkers might be. Measurements of these biomarkers may be helpful in improving individual risk assessment by increasing the uniformly low positive predictive

values of clinical scoring systems and of preoperative cardiac stress tests, by possibly being able to estimate the severity of an underlying cardiac condition (particularly in patients with low or unknown functional capacity), and in deciding on the need for additional cardiac assessment. It is undecided whether postponement of surgery for treatment of the underlying cardiovascular disease until normalization or at least improvement of the concentrations of these biomarkers will improve perioperative outcome. It thus remains to be determined how to effectively use preoperative plasma concentrations of CRP, BNP, and NT-proBNP to improve preoperative risk stratification, before we will be able to decide whether preoperative determination of biomarkers will turn out to be the magic bullet of preoperative cardiac risk stratification.³⁸ According to the ESC guidelines¹ preoperative measurement of plasma concentrations of BNP and NT-proBNP should be considered to obtain independent prognostic information for perioperative and late cardiac events in high-risk patients (IIa, B). Routine measurements of cardiac biomarkers (BNP, NT-proBNP, and cardiac troponins) are not recommended (III, C).

Preoperative coronary revascularization

Despite numerous publications and respective guidelines and recommendations, the issue of preoperative coronary artery revascularization remains highly controversial, mostly because findings of randomized and non-randomized trials have been contradictory. In the Coronary Artery Revascularization Prophylaxis (CARP) study, preoperative coronary artery revascularization before elective vascular surgery was not associated with a survival benefit.³⁹ Even in cardiac high-risk patients (≥ 3 cardiac risk factors and extensive stress-induced myocardial ischaemia) undergoing major vascular surgery, preoperative coronary revascularization was neither associated with improved short-term⁴⁰ nor long-term outcome.⁴¹

In contrast, in a randomized, prospective trial involving patients with an RCRI ≥ 2 undergoing peripheral vascular surgery, a strategy of routine preoperative coronary angiography was associated with better short- and long-term cardiac outcome than a strategy in which coronary angiography was only performed if indicated by findings on non-invasive tests.⁴² As the only clinically relevant difference between the groups was a higher preoperative myocardial revascularization rate in the routine compared with the selective strategy group (58% vs 40%; $P=0.01$), the findings could suggest that selected patients may possibly benefit from a preoperative coronary revascularization.⁴³

Similarly, in a randomized study of patients undergoing carotid endarterectomy without any clinical and electrocardiographic signs and symptoms of coronary artery disease and normal LV ejection fraction at rest, routine compared with no preoperative coronary angiography was associated with a significantly reduced incidence of postoperative cardiac events.⁴⁴ Preoperative coronary angiography was the only independent predictor of postoperative cardiac

ischaemic events. As 30% of patients (66 of 216) undergoing coronary angiography underwent preoperative percutaneous coronary intervention (PCI) because of one or more coronary artery stenosis >75%, it is possible that the improved outcome was, again, due to preoperative coronary revascularization. In this study, preoperative angiography and coronary revascularization were seemingly associated with benefit in some circumstances (i.e. asymptomatic patients undergoing intermediate-risk vascular surgery) where the ESC management algorithm (see below) clearly does not recommend such interventions.

However, the limiting factor of this study is that coronary angiography was used as the primary and only means of detecting coronary artery disease. It is thus possible that outcome in the patients not undergoing preoperative angiography was worse because they were not adequately assessed for clinically relevant coronary artery disease. It is likely that several of the control patients had poor or unknown functional capacity and ≥ 3 cardiac risk factors. If these had been managed according to the ESC algorithm (see below), they would have undergone additional preoperative non-invasive cardiac testing. The results of such testing might have affected subsequent management in a way which might have improved outcome in the control group.

Numerous variables must be expected to affect the impact of preoperative coronary artery revascularization on perioperative cardiac outcome. They include morbidity and mortality associated with coronary angiography and revascularization, especially in cardiac high-risk patients,⁴⁵ underlying cardiac risk (high vs intermediate risk findings on cardiac stress tests; high vs intermediate-risk coronary anatomy),⁴⁶ surgical risk (high- vs intermediate-risk surgery),⁴⁷ indication for coronary artery revascularization (prophylactic to 'get the patient through surgery' vs class IA indication; for symptoms vs for prognosis; class I vs class II recommendation),⁴⁸ type of coronary artery revascularization (interventional vs surgical),^{49 50} completeness of coronary artery revascularization,⁵⁰ and, possibly most importantly, perioperative management of anti-ischaemic, plaque-stabilizing, and anti-platelet medication.⁵¹ In general, because of lack of clear evidence for an outcome benefit of preoperative coronary artery revascularization, and the risk associated with coronary artery revascularization in general (an estimated 5–30% of patients undergoing PCI have evidence of a peri-procedural myocardial infarction),⁴⁵ the indications for preoperative coronary artery revascularization should be handled very restrictively⁵² and are, in general, the same as those in the non-surgical setting (Table 9). However, in this high-risk patient population, the ultimate decision has to be based on individual assessment of medical and surgical short- and long-term prognosis, and on informed patient consent based on such assessment. If preoperative coronary revascularization is to be performed, it must be remembered that the surgical procedure needs to be postponed for at least 2 weeks after balloon angioplasty, 3 months after placement of a bare-metal stent, and

Table 9 Recommendations for coronary revascularization (modified after ref. 1). STEMI, ST-segment elevation myocardial infarction (MI); NSTEMI, non-ST-segment elevation MI; LAD, left anterior descending; LV, left ventricular. Class of recommendation and level of evidence in parentheses

Patients with acute coronary syndrome
All patients with STEMI (I,A)
Patients with NSTEMI at high risk (elevated serum troponin concentration and ST-segment depression at baseline, ongoing symptoms, high thrombotic risk, advanced age, diabetes mellitus) (I,A)
Patients with stable angina pectoris or silent ischaemia and ...
Left main coronary artery stenosis >50% (I,A)
Any proximal LAD coronary artery stenosis >50% (I,A)
2- or 3-vessel coronary artery disease with impaired LV function (I,B)
Documented LV ischaemic area >10% (I,B)
Single remaining patent vessel with >50% stenosis and impaired LV function (I,C)
Patients with persistent signs of extensive ischaemia or a high cardiac risk undergoing high-risk vascular surgery (IIb, B)

12 months after placement of a drug-eluting stent. If surgical revascularization is to be performed, non-cardiac surgery generally needs to be delayed for about 30 days after revascularization coronary artery bypass graft.⁵³

Cardiac risk assessment algorithm for non-cardiac surgery

The ESC guidelines¹ recommend a systematic, step-wise approach to preoperative cardiac risk assessment for individual risk assessment (Fig. 1). The extent of preoperative cardiac evaluation will depend on the urgency of the procedure, and on patient and surgical characteristics.

Step 1: assessment of urgency of surgical procedure

In the case of emergency/urgent surgery, no additional preoperative cardiac evaluation or treatment is possible.

Step 2: assessment of presence of active cardiac conditions

In the case of elective surgery, potentially life-threatening active/unstable cardiac conditions (see above) need to be ruled out. Subsequent management (delay, modification or cancellation of planned procedure) will depend on test results and response to treatment.

Step 3: assessment of surgical risk

If a low-risk surgical procedure (Table 3) is planned, surgery can usually be performed without additional cardiac testing. Otherwise, further risk stratification is required.

Step 4: assessment of functional capacity

In the case of intermediate- or low-risk surgery (Table 3), functional capacity (Table 4) should be assessed. If the

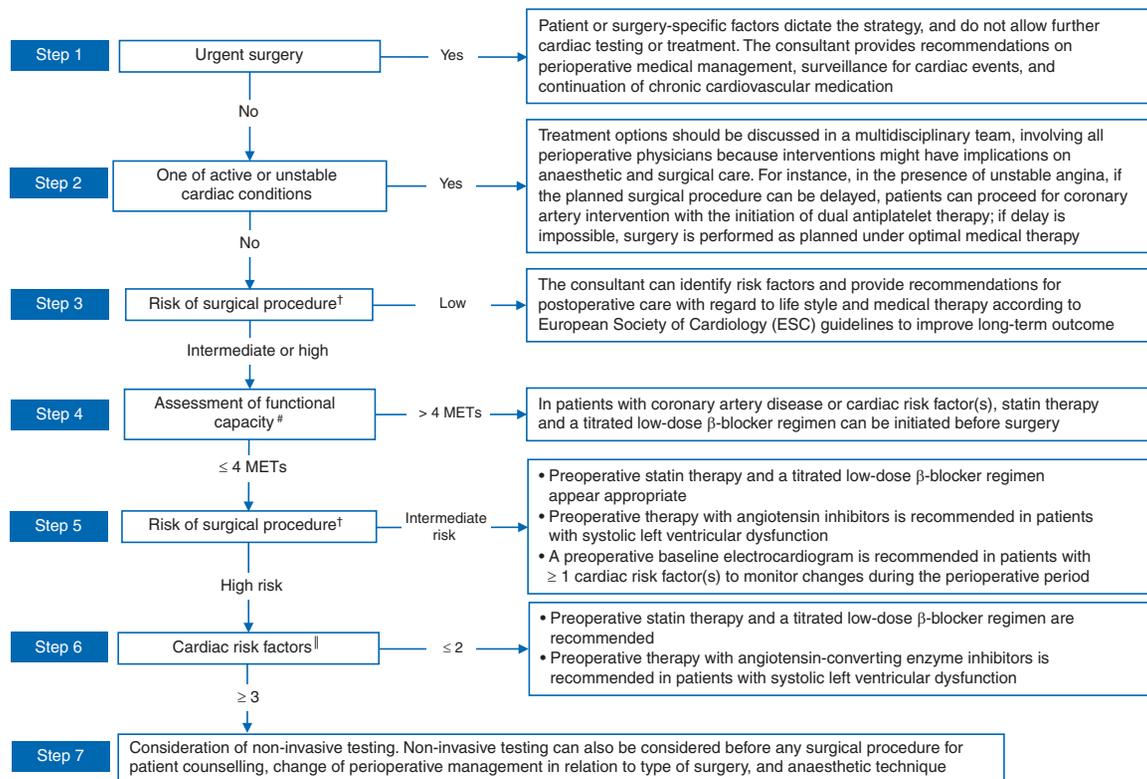


Fig 1 Algorithm for preoperative cardiac risk assessment and management. Modified after the ESC algorithm for preoperative cardiac risk assessment and management.¹ MET, metabolic equivalent task. [†]See Table 3 for risk of surgical procedure. [#]See Table 4 for assessment of functional capacity. ^{||}See Table 5 for cardiac risk factors.

patient is able to generate >4 METs in daily life (as indicated by confirmatory answers to the respective questions), perioperative prognosis is usually good (independent of a history of cardiac disease) and surgery can be performed as planned without additional cardiac testing. In patients with documented coronary artery disease or cardiac risk factors, preoperative initiation of statin therapy and a titrated low-dose β -blocker regimen can be considered.

Step 5: re-assessment of surgical risk

As patients with reduced functional reserve carry an increased perioperative cardiac risk, re-assessment of the cardiac risk of the surgical procedure is recommended in patients with unknown or a functional capacity of ≤ 4 METs. Such patients may undergo intermediate-risk surgery without additional cardiac testing. In this case, optimal cardiovascular medication should be assured and a baseline ECG obtained in patients with cardiac risk factors. If high-risk surgery is planned, cardiac risk factors need to be assessed.

Step 6: assessment of cardiac risk factors

Whereas the first four steps of the management algorithm meet the objective of the ESC guidelines for 'individualized

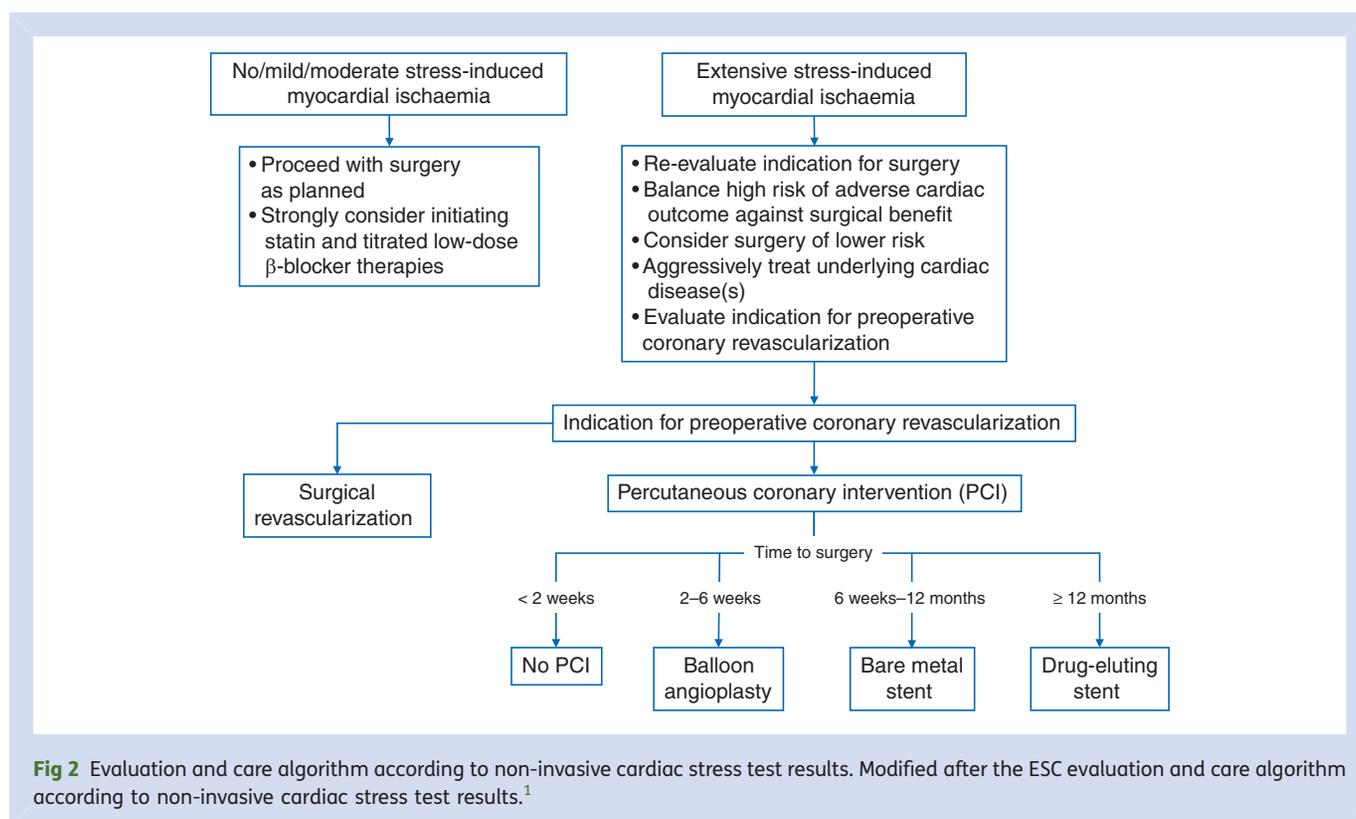
cardiac risk assessment',¹ this is not the case with the following steps because they are based on the RCRI, a population-derived risk index with poor discriminative power. Despite this limitation, it is used in the decision-making for subsequent non-invasive cardiac testing. If such testing would reliably discriminate between low and high risk, the poor discriminative power of the RCRI would not be of a major concern. However, as mentioned above, the positive predictive values of cardiac stress tests are also uniformly very low. The ESC algorithm states that in patients with up to two clinical cardiac risk factors (Table 5), surgery can be performed as planned after optimization of cardiovascular medication.

Step 7: consideration of non-invasive testing

Because of the uniformly low positive predictive values of cardiac stress test, cardiac stress testing is strongly recommended only in patients with ≥ 3 clinical risk factors undergoing high-risk surgery (i.e. open aortic surgery or open lower extremity arterial surgery) (Table 7).

Step 8: interpretation of stress test results

If cardiac stress testing shows no or only mild stress-inducible myocardial ischaemia, the ESC guidelines



do not make additional invasive testing mandatory, but recommend to start therapy with statins and titrated low-dose β -blockers (Fig. 2). Patients with extensive stress-inducible myocardial ischaemia present a challenge. On the one hand, even optimal medical treatment will not necessarily provide sufficient cardioprotection. On the other hand, preoperative prophylactic coronary revascularization usually does not improve perioperative outcome in this patient population. Under these circumstances, a highly individualized approach is required. The very high cardiac risk of the planned surgical procedure needs to be balanced against the possible harms of not performing surgery (e.g. risk of rupture of an abdominal aneurysm). If there is an indication for coronary revascularization, the angiographic findings, patient preference, and the anticipated time interval between coronary revascularization and surgery will influence the method of coronary revascularization (Fig. 2).

Pharmacological management

When considering the pathophysiology of coronary artery disease,^{28 54 55} the proven cardioprotective efficacy of optimal medical therapy in patients with clinically relevant coronary artery disease and the questionable additional benefit of additional coronary revascularization in secondary cardiac prevention,^{51 56-59} the morbidity and mortality associated with coronary artery revascularization,⁴⁵ the lack of proven benefit of a prophylactic preoperative coronary revascularization,^{39-41 52} and the increased perioperative risk of patients with coronary artery stents,^{53 60} great

emphasis must be placed on optimal perioperative medical therapy in high-risk patients. Pharmacological stabilization of coronary plaques (by statins, aspirin, β -blockers, and ACE inhibitors) is probably more effective in reducing perioperative cardiac morbidity and mortality than increasing myocardial oxygen delivery by coronary revascularization. Preoperative optimization of cardiovascular medication is certainly one of the most important, if not *the* most important aspect of preoperative cardiac management.^{61 62}

β -Blockers

As a consequence of the results of the POISE study,⁶³ the focused update on perioperative β -blockade by the ACC and AHA^{18 64} list only one class I indication for perioperative β -blocker therapy: continuation of β -blockers in patients undergoing surgery who are receiving β -blockers for treatment of conditions with ACC/AHA class I guideline indications (level of evidence: C). In contrast, the ESC guidelines¹ list three class I indications for perioperative β -blocker therapy: (i) patients with known coronary artery disease or myocardial ischaemia on preoperative stress testing (level of evidence: B); (ii) patients undergoing high-risk surgery (level of evidence: B); and (iii) patients previously treated with β -blockers for coronary artery disease, arrhythmias, or hypertension (level of evidence: C). The third class I indication is identical with that of the ACC/AHA. However, the other two class I indications are not supported by findings of the POISE study. Both guidelines emphasize early start and dose titration of β -blockers. The ACC/AHA guidelines¹⁸

⁶⁴ recommend that treatment be started days to weeks before surgery, aiming at a heart rate of 60–80 beats min^{-1} while avoiding hypotension. The ESC guidelines¹ recommend that treatment be started optimally between 30 days and at least 1 week before surgery, aiming at a heart rate of 60–70 beats min^{-1} and a systolic arterial pressure >100 mm Hg. It remains to be seen whether these recommendations can be fulfilled in daily clinical practice.

The importance of strict heart rate control as an independent predictor of outcome remains open to debate. A thorough search for causes of tachycardia other than myocardial ischaemia must be conducted before an elevated heart rate is symptomatically treated with β -blockers. Persistent perioperative tachycardia may well be due to hypovolaemia, pain, anxiety, anaemia, hypothermia, infection, latent heart failure, or pulmonary embolism. In such situations, heart rate control by β -blockers could endanger lives. Especially, anaemic patients may not be tolerating aggressive, heart rate-controlled perioperative β -blocker therapy.^{65–67}

Statins

In addition to their lipid-lowering effect, statins have the so-called pleiotropic effects which by various mechanisms improve endothelial morphology and function and stabilize coronary plaques.^{68–71} A few non-randomized studies,^{72–73} reviews,⁷⁴ and meta-analyses^{75–76} and a randomized controlled trial including 497 vascular surgery patients⁷⁷ have documented perioperative cardioprotection by statins. There is also evidence that preoperative discontinuation of chronic statin therapy is associated with adverse perioperative outcome.^{78–79} Overall evidence suggests a benefit of perioperative statin therapy in patients at increased perioperative cardiac risk.^{80–82} Statin therapy may be of benefit even if started only the day before a myocardial ischaemic insult. A single, high loading dose of statin only 1 day before PCI reduced the incidence of periprocedural myocardial injury in elective PCI.^{83–84} On the basis of the present evidence, it is recommended to start statin therapy in high-risk patients, optimally between 30 days and at least 1 week before surgery (I, B), and to not discontinue chronic statin therapy before operation (I, C).¹ If statin therapy is discontinued for whatever reason, it should be restarted as soon as possible.

Angiotensin II inhibitors

ACE inhibitors and angiotensin II receptor blockers (ARBs) exert beneficial effects on cardiovascular and other organ (e.g. kidney) function,⁸⁵ which may result in amelioration of myocardial ischaemia and LV dysfunction. Perioperative management of ACE inhibitors or ARBs has traditionally been controversial because the risk of worsening myocardial conditions associated with preoperative discontinuation of these drugs must be weighted against the risk of severe hypotension associated with their continuation. Decision-making is helped by considering the indication for therapy.

Patients may be receiving ACE inhibitors or ARBs to primarily treat hypertension or LV systolic dysfunction (e.g. after myocardial infarction). Taking into account the high risk associated with decompensation of LV function, in cardiovascular stable patients taking ACE inhibitors or ARBs for treatment of LV dysfunction, the medication should be continued when undergoing high-risk surgery (I, C), and continuation should be considered when undergoing low- or intermediate-risk surgery (IIa, C).¹ In patients taking the medication for treatment of hypertension, transient discontinuation should be considered (IIb, C). All of these recommendations are based on low level evidence, reflecting lack of scientifically solid data.

Antiplatelet therapy

Aspirin

Discontinuation of aspirin may be responsible for 15% of all recurrent acute coronary syndromes in patients with documented stable coronary artery disease.^{86–87} Thus, aspirin taken for secondary cardiac prevention should, in general, not be discontinued.⁸⁸ Perioperatively, aspirin should only be discontinued if the expected risk of bleeding and its possible sequelae are similar or even higher (e.g. intracranial, posterior eye chamber, prostate surgery) than the known cardiovascular risks of acute discontinuation of aspirin (e.g. non-fatal and fatal myocardial infarction, stroke).^{1 53 60 89 90}

Dual antiplatelet therapy

After PCI, premature discontinuation of dual antiplatelet therapy (aspirin and an ADP receptor antagonist) is generally associated with increased incidence of acute coronary syndromes and mortality.^{91–94} The recommendations of international cardiology societies regarding the management of patients after acute coronary syndromes or PCI in the non-operative setting^{95–99} form the basis for respective perioperative recommendations.^{1 18 53 98 100 101} Elective surgery should be postponed for at least 6 weeks (preferably 3 months) after placement of a bare-metal stent, and at least 12 months after implantation of a drug-eluting stent to guarantee a sufficient duration of ADP receptor antagonist therapy (e.g. clopidogrel, prasugrel, and ticagrelor) for adequate endothelialization. Premature discontinuation increases perioperative cardiac morbidity and mortality without significantly reducing risk of bleeding.^{102 103} If surgery needs to be performed within 3 months after placement of a bare-metal stent, and within the first year after implantation of a drug-eluting stent, then similar to the perioperative management of aspirin therapy, dual antiplatelet therapy with aspirin and an ADP receptor antagonist should only be discontinued before operation if the expected risk of bleeding and its possible sequelae are considerably higher (e.g. intracranial, intraspinal, and posterior eye chamber surgery) than the considerable cardiovascular risks associated with acute discontinuation of dual antiplatelet therapy (e.g. non-fatal and fatal myocardial infarction, stroke), and only if surgery cannot be postponed.^{1 18 90}

If surgery cannot be postponed, at least aspirin should be continued whenever possible.

Conclusion

Although preoperative cardiac management has improved during the past decades, we are not yet in the situation where we can accurately predict individual perioperative risk.¹⁰⁴ There are several reasons for that. First, the individual stress response (e.g. cardiovascular and endocrine) to a given stressor (e.g. a given surgical procedure, haematocrit value) and the individual interactions between pharmacological intervention (e.g. antiplatelet and cardiovascular medication) and intra- and postoperative risk factors (e.g. anaemia, hypercoagulability, hypovolaemia, inflammatory response, and cardiovascular depression) are highly variable.

Secondly, and probably more important, preoperative cardiac management is only one aspect of overall perioperative care. There are numerous intra- and postoperative factors (e.g. haemodynamic, endocrine, metabolic, and inflammatory responses; surgical care issues; duration of surgery; hypovolaemia; hypothermia; anaemia; thromboembolism; pulmonary dysfunction; pain) which have been shown to affect overall outcome.^{3 105} Not all of them can reliably be predicted or modified in a way to positively affect overall outcome. However, recognition of such factors and aggressive attempts at appropriate intervention may reduce overall risk more than preoperative management in isolation. Such approach may render the before operation high-risk patient a low(er)-risk patient. Conversely, ignoring such approach may render the before operation low-risk patient a high-risk patient. Even optimal preoperative management will only have a positive impact, if antibiotics, intravascular volume, blood components, and nutrition are managed appropriately; minimally invasive surgery with reduced use of surgical tubes and drains is attempted; and adequate postoperative pain relief and care are provided.^{105 106} Without defining and subsequently targeting intra- and postoperative risk factors, the benefit of preoperative cardiac management will be limited.

Conflict of interest

None declared.

References

- Poldermans D, Bax J, Boersma E, et al. Guidelines for pre-operative cardiac risk assessment and peri-operative cardiac management in non-cardiac surgery: the Task Force for Pre-operative Cardiac Risk Assessment and Peri-operative Cardiac Management in Non-cardiac Surgery of the European Society of Cardiology (ESC) and endorsed by the European Society of Anaesthesiology (ESA). *Eur Heart J* 2009; **30**: 2769–812
- Hammill BG, Curtis LH, Bennett-Guerrero E, et al. Impact of heart failure on patients undergoing major noncardiac surgery. *Anesthesiology* 2008; **108**: 559–67
- Kheterpal S, O'Reilly M, Englesbe M, et al. Pre-operative and intra-operative predictors of cardiac adverse events after general, vascular, and urological surgery. *Anesthesiology* 2009; **110**: 58–66
- Monin J-L, Lancellotti P, Monchi M, et al. Risk score for predicting outcome in patients with asymptomatic aortic stenosis. *Circulation* 2009; **120**: 69–75
- Leon MB, Smith CR, Mack M, et al. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. *N Engl J Med* 2010; **363**: 1597–607
- Tamburino C, Capodanno D, Ramando A, et al. Incidence and predictors of early and late mortality after transcatheter aortic valve implantation in 663 patients with severe aortic stenosis. *Circulation* 2011; **123**: 299–308
- Buellesfeld L, Windecker S. Transcatheter aortic valve implantation: the evidence is catching up with reality. *Eur Heart J* 2011; **32**: 133–7
- Eltchaninoff H, Prat A, Gilard M, et al. Transcatheter aortic valve implantation: early results of the FRANCE (FRench Aortic National CoreValve and Edwards) registry. *Eur Heart J* 2011; **32**: 191–7
- Zahn R, Gerckens U, Grube E, et al. Transcatheter aortic valve implantation: first results from a multi-centre real-world registry. *Eur Heart J* 2011; **32**: 198–204
- Older P, Smith R, Courtney P, Hone R. Pre-operative evaluation of cardiac failure and ischemia in elderly patients by cardiopulmonary exercise testing. *Chest* 1993; **104**: 701–4
- Older P, Hall A, Hader R. Cardiopulmonary exercise testing as a screening test for peri-operative management of major surgery in the elderly. *Chest* 1999; **116**: 355–62
- Win T, Jackson A, Sharples L, et al. Cardiopulmonary exercise tests and lung cancer surgical outcome. *Chest* 2005; **127**: 1159–65
- Murray P, Whiting P, Hutchinson SP, Ackroyd R, Stoddard CJ, Billings C. Pre-operative shuttle walking testing and outcome after oesophagogastrctomy. *Br J Anaesth* 2007; **99**: 809–11
- Carlisle J, Swart M. Mid-term survival after abdominal aortic aneurysm surgery predicted by cardiopulmonary exercise testing. *Br J Surg* 2007; **94**: 966–9
- Crawford RS, Cambria RP, Abularrage CJ, et al. Pre-operative functional status predicts peri-operative outcomes after infringuinal bypass surgery. *J Vasc Surg* 2010; **51**: 351–9
- Hlatky MA, Boineau RE, Higginbotham MB, et al. A brief self-administered questionnaire to determine functional capacity (the Duke Activity Status Index). *Am J Cardiol* 1989; **64**: 651–4
- Struthers R, Erasmus P, Holmes K, Warman P, Collingwood A, Sneyd JR. Assessing fitness for surgery: a comparison of questionnaire, incremental shuttle walk, and cardiopulmonary exercise testing in general surgical patients. *Br J Anaesth* 2008; **101**: 774–80
- Fleisher LA, Beckman JA, Brown KA, et al. 2009 ACCF/AHA focused update on peri-operative beta blockade incorporated into the ACC/AHA 2007 guidelines on peri-operative cardiovascular evaluation and care for noncardiac surgery: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation* 2009; **120**: e169–276; *J Am Coll Cardiol* 2009; **54**: 13–118
- Byrne NM, Hills AP, Hunter GR, Weinsier RL, Schutz Y. Metabolic equivalent: one size does not fit all. *J Appl Physiol* 2005; **99**: 1112–9

- 20 Singh SJ, Morgan MD, Hardman AE, Rowe C, Bardsley PA. Comparison of oxygen uptake during a conventional treadmill test and the shuttle walking test in chronic airflow limitation. *Eur Respir J* 1994; **7**: 2016–20
- 21 Onorati P, Antonucci R, Valli G, et al. Non-invasive evaluation of gas exchange during a shuttle walking test vs. a 6-min walking test to assess exercise tolerance in COPD patients. *Eur J Appl Physiol* 2003; **89**: 331–6
- 22 Win T, Jackson A, Groves AM, Sharples LD, Charman SC, Laroche CM. A comparison of shuttle walk with measured peak oxygen consumption in patients with operable lung cancer. *Thorax* 2006; **61**: 57–60
- 23 Older P, Smith R. Experience with the pre-operative invasive measurement of haemodynamic, respiratory and renal function in 100 elderly patients scheduled for major abdominal surgery. *Anaesth Intensive Care* 1988; **16**: 395–8
- 24 Balady GJ, Arena R, Sietsema K, et al. Clinician's guide to cardiopulmonary exercise testing in adults. A scientific statement from the American Heart Association. *Circulation* 2010; **122**: 191–225
- 25 Arena R, Sietsema KE. Cardiopulmonary exercise testing in the clinical evaluation of patients with heart and lung disease. *Circulation* 2011; **123**: 668–80
- 26 Lee TH, Marcantonio ER, Mangione CM, et al. Derivation and prospective validation of a simple index for prediction of cardiac risk of major noncardiac surgery. *Circulation* 1999; **100**: 1043–9
- 27 Ridley S. Cardiac scoring systems—what is there value? *Anaesthesia* 2003; **58**: 985–91
- 28 Priebe HJ. Peri-operative myocardial infarction—etiology and prevention. *Br J Anaesth* 2005; **95**: 3–19
- 29 Landesberg G, Beattie WS, Mosseri M, Jaffe AS, Alpert JS. Peri-operative myocardial infarction. *Circulation* 2009; **119**: 2936–44
- 30 Braunwald E. Biomarkers in heart failure. *N Engl J Med* 2008; **358**: 2148–59
- 31 Karthikeyan G, Moncur RA, Levine O, et al. Is a pre-operative brain natriuretic peptide or N-terminal pro-B-type natriuretic peptide measurement an independent predictor of adverse cardiovascular outcomes within 30 days of noncardiac surgery? A systematic review and meta-analysis of observational studies. *J Am Coll Cardiol* 2009; **54**: 1599–606
- 32 Ryding A, Kumar S, Worthington AM, Burgess D. Prognostic value of brain natriuretic peptide in noncardiac surgery: a meta-analysis. *Anesthesiology* 2009; **111**: 311–9
- 33 Feringa HHH, Schouten O, Dunkelgrun M, et al. Plasma N-terminal pro-B-type natriuretic peptide as long-term prognostic marker after major vascular surgery. *Heart* 2007; **93**: 226–31
- 34 Owens CD, Ridker PM, Belkin M, et al. Elevated C-reactive protein levels are associated with postoperative events in patients undergoing lower extremity vein bypass surgery. *J Vasc Surg* 2007; **45**: 2–9
- 35 Bolliger D, Seeberger M, Lurati Buse GAL, et al. A preliminary report on the prognostic significance of pre-operative brain natriuretic peptide and postoperative cardiac troponin in patients undergoing major vascular surgery. *Anesth Analg* 2009; **108**: 1069–75
- 36 Goei D, Hoeks SE, Boersma E, et al. Incremental value of high-sensitivity C-reactive protein and N-terminal pro-B-type natriuretic peptide for the prediction of postoperative cardiac events in noncardiac vascular surgery patients. *Coron Art Dis* 2009; **20**: 219–24
- 37 Choi J-H, Cho DK, Song Y-B, et al. Pre-operative NT-proBNP and CRP predict peri-operative major cardiovascular events in non-cardiac surgery. *Heart* 2010; **96**: 56–62
- 38 Bolliger D, Seeberger MD, Filipovic M. Pre-operative cardiac risk assessment in noncardiac surgery: are natriuretic peptides the magic bullet? *J Am Coll Cardiol* 2009; **54**: 1607–8
- 39 McFalls EO, Ward HB, Moritz TE, et al. Coronary-artery revascularization before elective major vascular surgery. *N Engl J Med* 2004; **351**: 2795–804
- 40 Poldermans D, Schouten O, Vidakovic R, et al. A clinical randomized trial to evaluate the safety of a noninvasive approach in high-risk patients undergoing major vascular surgery: the DECREASE-V Pilot Study. *J Am Coll Cardiol* 2007; **49**: 1763–9
- 41 Schouten O, van Kuijk J-P, Flu W-J, et al. Long-term outcome of prophylactic coronary revascularization in cardiac high-risk patients undergoing major vascular surgery (from the randomized DECREASE-V pilot study). *Am J Cardiol* 2009; **103**: 897–901
- 42 Monaco M, Stassano P, Di Tommaso L, et al. Systematic strategy of prophylactic coronary angiography improves long-term outcome after major vascular surgery in medium- to high-risk patients: a prospective, randomized study. *J Am Coll Cardiol* 2009; **54**: 989–96
- 43 Landesberg G, Mosseri M. Prophylactic pre-operative coronary revascularization: is the phoenix awakening? *J Am Coll Cardiol* 2009; **54**: 997–8
- 44 Illuminati G, Ricco J-B, Greco C, et al. Systematic pre-operative coronary angiography and stenting improves postoperative results of carotid endarterectomy in patients with asymptomatic coronary artery disease: a randomised controlled trial. *Eur J Vasc Endovasc Surg* 2010; **39**: 139–45
- 45 Prasad A, Herrmann J. Myocardial infarction due to percutaneous coronary intervention. *N Engl J Med* 2011; **364**: 453–64
- 46 Garcia S, Moritz TE, Ward HB, et al. Usefulness of revascularization of patients with multivessel coronary artery disease before elective vascular surgery for abdominal aortic and peripheral occlusive disease. *Am J Cardiol* 2008; **102**: 809–13
- 47 Schouten O, Dunkelgrun M, Feringa HHH, et al. Myocardial damage in high-risk patients undergoing elective endovascular or open infrarenal abdominal aortic aneurysm repair. *Eur J Vasc Endovasc Surg* 2007; **33**: 544–9
- 48 Wijns W, Kolh P, Danchin N, et al. Guidelines on myocardial revascularization. The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J* 2010; **31**: 2501–55
- 49 Ward HB, Kelly RF, Thottapurathu L, et al. Coronary artery bypass grafting is superior to percutaneous coronary intervention in prevention of peri-operative myocardial infarctions during subsequent vascular surgery. *Ann Thorac Surg* 2006; **82**: 795–801
- 50 Biccard BM, Rodseth RN. A meta-analysis of the prospective randomised trials of coronary revascularisation before noncardiac vascular surgery with attention to the type of coronary revascularisation performed. *Anaesthesia* 2009; **64**: 1105–13
- 51 Boden WE, O'Rourke RA, Teo KK, et al. Optimal medical therapy with or without PCI for stable coronary disease. *N Engl J Med* 2007; **356**: 1503–16
- 52 Mythen M. Pre-operative coronary revascularisation before non-cardiac surgery: think long and hard before making a pre-operative referral. *Anaesthesia* 2009; **64**: 1048–50

- 53 Howard-Alpe GM, de Bono J, Hudsmith L, Orr WP, Foex P, Sear JW. Coronary artery stents and non-cardiac surgery. *Br J Anaesth* 2007; **98**: 560–74
- 54 Libby P, Theroux P. Pathophysiology of coronary artery disease. *Circulation* 2005; **111**: 3481–8
- 55 Levin R. Plaque vulnerability: pathologic form and patient fate. *J Am Coll Cardiol* 2010; **55**: 133–4
- 56 Diamond GA, Kaul S. COURAGE under fire: on the management of stable coronary disease. *J Am Coll Cardiol* 2007; **50**: 1604–9
- 57 Hochman JS, Steg PG. Does preventive PCI work? *N Engl J Med* 2007; **356**: 1572–4
- 58 O'Rourke RA. Optimal medical therapy is a proven option for chronic stable angina. *J Am Coll Cardiol* 2008; **52**: 905–7
- 59 Peterson ED, Rumsfeld JS. Finding the courage to reconsider medical therapy for stable angina. *N Engl J Med* 2008; **359**: 751–3
- 60 Spahn DR, Howell SJ, Delabays A, Chassot P-G. Coronary stents and peri-operative anti-platelet regimen: dilemma of bleeding and stent thrombosis. *Br J Anaesth* 2006; **96**: 675–7
- 61 Flu WJ, Hoeks SE, van Kuijk JP, Bax JJ, Poldermans D. Treatment recommendations to prevent myocardial ischemia and infarction in patients undergoing vascular surgery. *Curr Treat Options Cardiovasc Med* 2009; **11**: 33–44
- 62 Voûte MT, Winkel TA, Poldermans D. Optimal medical management around the time of surgery. *Heart* 2010; **96**: 1842–8
- 63 POISE Study Group. Effects of extended-release metoprolol succinate in patients undergoing non-cardiac surgery (POISE trial): a randomised controlled trial. *Lancet* 2008; **371**: 1839–47
- 64 Fleischmann KE, Beckman JA, Buller CE, et al. ACCF/AHA focused update on peri-operative beta blockade. *Circulation* 2009; **120**: 2123–51
- 65 Ragoonanan TE, Beattie WS, Mazer CD, et al. Metoprolol reduces cerebral tissue oxygen tension after acute hemodilution in rats. *Anesthesiology* 2009; **111**: 988–1000
- 66 Weiskopf RB. Peri-operative use of β -adrenergic antagonists and anemia: known knowns, known unknowns, unknown unknowns; and unknown knowns. *Anesthesiology* 2010; **112**: 12–5
- 67 Beattie WS, Wijeyesundera DN, Karkouti K, et al. Acute surgical anemia influences the cardioprotective effects of β -blockade: a single-center, propensity-matched cohort study. *Anesthesiology* 2010; **112**: 25–33
- 68 Libby P, Aikawa M. Mechanisms of plaque stabilization with statins. *Am J Cardiol* 2003; **91**: 4B–8B
- 69 Ito MK, Talbert RL, Tsimikas S. Statin-associated pleiotropy: possible beneficial effects beyond cholesterol reduction. *Pharmacotherapy* 2006; **26**: 85S–97S
- 70 Ray KK, Cannon CP. The potential relevance of the multiple lipid-independent (pleiotropic) effects of statins in the management of acute coronary syndromes. *J Am Coll Cardiol* 2005; **46**: 1425–33
- 71 Klingenberg R, Hansson GK. Treating inflammation in atherosclerotic cardiovascular disease: emerging therapies. *Eur Heart J* 2009; **30**: 2838–44
- 72 Hindler K, Shaw A, Samuels J, Fulton S, Collard C, Riedel B. Improved postoperative outcomes associated with pre-operative statin therapy. *Anesthesiology* 2006; **105**: 1260–72
- 73 Feringa HHH, Schouten O, Karagiannis SE, et al. Intensity of statin therapy in relation to myocardial ischemia, troponin T release, and clinical cardiac outcome in patients undergoing major vascular surgery. *J Am Coll Cardiol* 2007; **50**: 1649–56
- 74 Boushra NN, Muntazar M. Review article: the role of statins in reducing peri-operative cardiac risk: physiologic and clinical perspectives. *Can J Anaesth* 2006; **53**: 1126–47
- 75 Kapoor AS, Kanji H, Buckingham J, Devereaux PJ, McAlister FA. Strength of evidence for peri-operative use of statins to reduce cardiovascular risk: systematic review of controlled studies. *Br Med J* 2006; **333**: 1149–56
- 76 Biccard BM. A peri-operative statin update for non-cardiac surgery. Part II: Statin therapy for vascular surgery and peri-operative statin trial design. *Anaesthesia* 2008; **63**: 162–71
- 77 Schouten O, Boersma E, Hoeks SE, et al. Fluvastatin and peri-operative events in patients undergoing vascular surgery. *N Engl J Med* 2009; **361**: 980–9
- 78 Le Manach Y, Godet G, Coriat P, et al. The impact of postoperative discontinuation or continuation of chronic statin therapy on cardiac outcome after major vascular surgery. *Anesth Analg* 2007; **104**: 1326–33
- 79 Schouten O, Hoeks SE, Welten GMJM, et al. Effect of statin withdrawal on frequency of cardiac events after vascular surgery. *Am J Cardiol* 2007; **100**: 316–20
- 80 Kersten JR, Fleisher LA. Statins. The next advance in cardioprotection? *Anesthesiology* 2006; **105**: 1079–80
- 81 Feldman LS, Broman DJ. Peri-operative statins: more than lipid-lowering? *Cleveland Clin J Med* 2008; **75**: 654–62
- 82 Poldermans D. Statins and noncardiac surgery: current evidence and practical considerations. *Cleveland Clin J Med* 2009; **76** (Suppl 4): S79–83
- 83 Briguori C, Visconti G, Focaccio A, et al. Novel approaches for preventing or limiting events (Naples) II trial: impact of a single high loading dose of atorvastatin on periprocedural myocardial infarction. *J Am Coll Cardiol* 2009; **54**: 2157–63
- 84 Cay S, Cagirci G, Sen N, Balbay Y, Durmaz T, Aydogdu S. Prevention of peri-procedural myocardial injury using a single high loading dose of rosuvastatin. *Cardiovasc Drug Ther* 2010; **24**: 41–7
- 85 Sun Y-P, Zhu B-Q, Browne AEM, et al. Comparative effects of ACE inhibitors and an angiotensin receptor blocker on atherosclerosis and vascular function. *J Cardiovasc Pharmacol Ther* 2001; **6**: 175–81
- 86 Ferrari E, Benhamou M, Cerboni P, Baudouy M. Coronary syndromes following aspirin withdrawal: a special risk for late stent thrombosis. *J Am Coll Cardiol* 2005; **45**: 456–9
- 87 Biondi-Zoccai GGL, Lotrionte M, Agostoni P, et al. A systematic review and meta-analysis on the hazards of discontinuing or not adhering to aspirin among 50 279 patients at risk for coronary artery disease. *Eur Heart J* 2006; **27**: 2667–74
- 88 Smith SC Jr, Allen J, Blair SN, et al. AHA/ACC guidelines for secondary prevention for patients with coronary and other atherosclerotic vascular disease: 2006 update: endorsed by the National Heart, Lung, and Blood Institute. *Circulation* 2006; **113**: 2363–72 (Correction: *Circulation* 2006; **113**: e847)
- 89 Burger W, Chemnitz J-M, Kneissl GD, Rucker G. Low-dose aspirin for secondary cardiovascular prevention—cardiovascular risks after its peri-operative withdrawal versus bleeding risks with its continuation—review and meta-analysis. *J Intern Med* 2005; **257**: 399–414
- 90 Chassot P-G, Delabays A, Spahn DR. Peri-operative antiplatelet therapy: the case for continuing therapy in patients at risk of myocardial infarction. *Br J Anaesth* 2007; **99**: 316–28
- 91 Collet JP, Montalescot G, Blanchet B, et al. Impact of prior use or recent withdrawal of oral antiplatelet agents on acute coronary syndromes. *Circulation* 2004; **110**: 2361–7
- 92 Iakovou I, Schmidt T, Bonizzoni E, et al. Incidence, predictors, and outcome of thrombosis after successful implantation of drug-eluting stents. *J Am Med Assoc* 2005; **293**: 2126–30

- 93 Eisenstein EL, Anstrom KJ, Kong DF, et al. Clopidogrel use and long-term clinical outcomes after drug-eluting stent implantation. *J Am Med Assoc* 2007; **297**: 159–68
- 94 Ho PM, Peterson ED, Wang L, et al. Incidence of death and acute myocardial infarction associated with stopping clopidogrel after acute coronary syndrome. *J Am Med Assoc* 2008; **299**: 532–9
- 95 Silber S, Albertsson P, Avilès FF, et al. Guidelines for percutaneous coronary interventions: the Task Force for Percutaneous Coronary Interventions of the European Society of Cardiology. *Eur Heart J* 2005; **26**: 804–47
- 96 Bassand JP, Hamm CW, Ardissino D, et al. Guidelines for the diagnosis and treatment of non-ST-segment elevation acute coronary syndromes. *Eur Heart J* 2007; **28**: 1598–660
- 97 Van de Werf F, Bax J, Betriu A, et al. Management of acute myocardial infarction in patients presenting with persistent ST-segment elevation: the Task Force on the management of ST-segment elevation acute myocardial infarction of the European Society of Cardiology. *Eur Heart J* 2008; **29**: 2909–45
- 98 Grines CL, Bonow RO, Casey DE, et al. Prevention of premature discontinuation of dual antiplatelet therapy in patients with coronary artery stents. A science advisory from the American Heart Association, American College of Cardiology, Society for Cardiovascular Angiography and Interventions, American College of Surgeons, and American Dental Association, with representation from the American College of Physicians. *Circulation* 2007; **115**: 813–8
- 99 Casterella PJ, Tchong JE. Review of the 2005 American College of Cardiology, American Heart Association, and Society for Cardiovascular Interventions guidelines for adjunctive pharmacologic therapy during percutaneous coronary interventions: practical implications, new clinical data, and recommended guideline revisions. *Am Heart J* 2008; **155**: 781–90
- 100 Riddell JW, Chiche L, Plaud B, Hamon M. Coronary stents and noncardiac surgery. *Circulation* 2007; **116**: e378–82
- 101 Practice alert for the peri-operative management of patients with coronary artery stents: a report by the American Society of Anesthesiologists Committee on Standards and Practice Parameters. *Anesthesiology* 2009; **110**: 22–3
- 102 Schouten O, van Domburg RT, Bax JJ, et al. Noncardiac surgery after coronary stenting: early surgery and interruption of antiplatelet therapy are associated with an increase in major adverse cardiac events. *J Am Coll Cardiol* 2007; **49**: 122–4
- 103 Rabbitts JA, Nuttall GA, Brown MJ, et al. Cardiac risk of noncardiac surgery after percutaneous coronary intervention with drug-eluting stents. *Anesthesiology* 2008; **109**: 596–604
- 104 Reilly CS. Can we accurately assess an individual's peri-operative risk? *Br J Anaesth* 2008; **101**: 747–9
- 105 Kehlet H, Mythen M. Why is the surgical high-risk patient still at risk? *Br J Anaesth* 2011; **106**: 289–91
- 106 Grocott MPW, Pearse RM. Prognostic studies of peri-operative risk: robust methodology is needed. *Br J Anaesth* 2010; **105**: 243–5