ESC GUIDELINES

Guidelines for pre-operative cardiac risk assessment and perioperative cardiac management in non-cardiac surgery

The Task Force for Preoperative Cardiac Risk Assessment and Perioperative Cardiac Management in Non-cardiac Surgery of the European Society of Cardiology (ESC) and endorsed by the European Society of Anaesthesiology (ESA)

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List of acronyms and abbreviations

AAA	abdominal aortic aneurysm
ACC	American College of Cardiology
ACE	angiotensin-converting enzyme
ACS	acute coronary syndrome
AHA	American Heart Association
AR	aortic regurgitation
ARB	angiotensin receptor blocker
AS	aortic stenosis
AF	atrial fibrillation
BBSA	β-blocker in spinal anaesthesia
BNP	brain natriuretic peptide
CABG	coronary artery bypass grafting
CARP	coronary artery revascularization prophylaxis
CASS	coronary artery surgery study
CI	confidence interval
COX-2	cyclooxygenase-2
COPD	chronic obstructive pulmonary disease
CPET	cardiopulmonary exercise testing
CPG	Committee for Practice Guidelines
CRP	C-reactive protein
CT	computed tomography
cTnI	cardiac troponin I
cTnT	cardiac troponin T
CVD	cardiovascular disease
DECREASE	Dutch Echocardiographic Cardiac Risk Evaluating Applying Stress Echo
DES	drug-eluting stent
DIPOM	Diabetes Postoperative Mortality and Morbidity
DSE	dobutamine stress echocardiography
ECG	electrocardiography
ESC	European Society of Cardiology
FEV_1	forced expiratory volume in 1 s
FRISC	fast revascularization in instability in coronary disease
HR	hazard ratio
ICU	intensive care unit
IHD	ischaemic heart disease
INR	international normalized ratio
LMWH	low molecular weight heparin
LQTS	long QT syndrome
LR	likelihood ratio
LV	left ventricular
MaVS	metoprolol after surgery
MET	metabolic equivalent
MI	myocardial infarction
MR	mitral regurgitation
MRI	magnetic resonance imaging
MS	mitral stenosis
NICE-SUGAR	normoglycaemia in intensive care evaluation and survival using glucose algorithm regulation
NSTEMI	non-ST-segment elevation myocardial infarction
NT-proBNP	N-terminal pro-brain natriuretic peptide
NYHA	New York Heart Association
OPUS	orbofiban in patients with unstable coronary syndromes
OR	odds ratio
$PaCO_2$	mixed expired volume of alveolar and dead space gas

PAH	pulmonary arterial hypertension
PETCO$_2$	end-tidal expiratory CO_2 pressure
PCI	percutaneous coronary intervention
PDA	personal digital assistant
POISE	PeriOperative ISchaemic Evaluation trial
QUO-VADIS	QUinapril On Vascular ACE and Determinants of ISchemia
ROC	receiver operating characteristic
SD	standard deviation
SMVT	sustained monomorphic ventricular tachycardia
SPECT	single photon emission computed tomography
SPVT	sustained polymorphic ventricular tachycardia
STEMI	ST-segment elevation myocardial infarction
SVT	supraventricular tachycardia
SYNTAX	synergy between percutaneous coronary intervention with taxus and cardiac surgery
TACTICS	treat angina with aggrastat and determine cost of therapy with an invasive or conservative strategy
TIA	transient ischaemic attack
TIMI	thrombolysis in myocardial infarction
TOE	transoesophageal echocardiography
UFH	unfractionated heparin
VCO$_2$	carbon dioxide production
VE	minute ventilation
VHD	valvular heart disease
VKA	vitamin K antagonist
VO$_2$	oxygen consumption
VPB	ventricular premature beat
VT	ventricular tachycardia

Preamble

Guidelines and Expert Consensus Documents aim to present management and recommendations based on the relevant evidence on a particular subject in order to help physicians to select the best possible management strategies for the individual patient suffering from a specific condition, taking into account not only the impact on outcome, but also the risk–benefit ratio of particular diagnostic or therapeutic means. Guidelines are no substitutes for textbooks. The legal implications of medical guidelines have been discussed previously.[1]

A great number of Guidelines and Expert Consensus Documents have been issued in recent years by the European Society of Cardiology (ESC) and also by other organizations or related societies. Because of the impact on clinical practice, quality criteria for development of guidelines have been established in order to make all decisions transparent to the user. The recommendations for formulating and issuing ESC guidelines and Expert Consensus Documents can be found on the ESC website in the guidelines section (www.escardio.org).

In brief, experts in the field are selected and undertake a comprehensive review of the published evidence for management and/or prevention of a given condition. A critical evaluation of diagnostic and therapeutic procedures is performed, including assessment of the risk–benefit ratio. Estimates of expected health outcomes for larger societies are included, where data exist. The level of evidence and the strength of recommendation of particular treatment options are weighted and graded according to predefined scales, as outlined in *Tables 1* and 2.

The experts of the writing panels have provided disclosure statements of all relationships they may have which might be perceived as real or potential sources of conflicts of interest. These disclosure forms are kept on file at the European Heart House, headquarters of the ESC. Any changes in conflict of interest that arise during the writing period must be notified to the ESC. The Task Force report is entirely supported financially by the ESC without any involvement of industry.

The ESC Committee for Practice Guidelines (CPG) supervises and coordinates the preparation of new Guidelines and Expert Consensus Documents produced by Task Forces, expert groups, or consensus panels. The Committee is also responsible for the endorsement process of these Guidelines and Expert Consensus Documents or statements. Once the document has been finalized and approved by all the experts involved in the Task Force, it is submitted to outside specialists for review. The document is revised, and finally approved by the CPG and subsequently published.

After publication, dissemination of the message is of paramount importance. Pocketsize versions and personal digital assistant (PDA)-downloadable versions are useful at the point of care. Some surveys have shown that the intended end-users are sometimes not aware of the existence of guidelines, or simply do not translate them into practice, so this is why implementation programmes for new guidelines form an important component of the dissemination of knowledge. Meetings are organized by the ESC, and are directed towards its member National Societies and key opinion leaders in Europe. Implementation meetings can also be undertaken at national levels, once the guidelines have been endorsed by the ESC member societies, and translated into the national language. Implementation programmes are needed because it has been shown that the outcome of disease may be favourably influenced by the thorough application of clinical recommendations.[2]

Thus, the task of writing Guidelines or Expert Consensus Documents covers not only the integration of the most recent research, but also the creation of educational tools and implementation programmes for the recommendations. The development of clinical guidelines and implementation into clinical practice can then only be completed if surveys and registries are performed to verify its use in real-life daily practices. Such surveys and registries also make it possible to evaluate the impact of implementation of the guidelines on patient outcomes. Guidelines and recommendations should help physicians and other healthcare providers to make decisions in their daily practice. However, the physician in charge of his/her care must make the ultimate judgement regarding the care of an individual patient.

Introduction

Magnitude of the problem

The present guidelines focus on the cardiological management of patients undergoing non-cardiac surgery, i.e. patients where heart

Table 1 **Classes of recommendations**

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

Table 2 **Level of evidence**

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

disease is a potential source of complications during surgery. The risk of perioperative complications depends on the condition of the patient prior to surgery, the prevalence of co-morbidities, and the magnitude and duration of the surgical procedure.[3] More specifically, cardiac complications can arise in patients with documented or asymptomatic ischaemic heart disease (IHD), left ventricular (LV) dysfunction, and valvular heart disease (VHD) who undergo procedures that are associated with prolonged haemodynamic and cardiac stress. In the case of perioperative myocardial ischaemia, two mechanisms are important: (i) chronic mismatch in the supply-to-demand ratio of blood flow response to metabolic demand, which clinically resembles stable IHD due to a flow limiting stenosis in coronary conduit arteries; and (ii) coronary plaque rupture due to vascular inflammatory processes presenting as acute coronary syndromes (ACSs). Hence, although LV dysfunction may occur for various reasons in younger age groups, perioperative cardiac mortality and morbidity are predominantly an issue in the adult population undergoing major non-cardiac surgery.

The magnitude of the problem in Europe can best be understood in terms of (i) the size of the adult non-cardiac surgical cohort; and (ii) the average risk of cardiac complications within this cohort. Unfortunately, at a European level, no systematic data are available on the annual number and type of operations, nor on patient outcome. Information is collected at the national level in several countries, but data definitions, amount of data, and data quality vary greatly. In The Netherlands, with a population of 16 million, throughout 1991–2005, 250 000 major surgical procedures were conducted on average annually in patients above the age of 20 years, implying an annual rate of 1.5%.[4] When applied to Europe, with an overall population of 490 million, this figure translates into a crude estimate of 7 million major procedures annually in patients who present with cardiac risk.

Data on cardiac outcome can be derived from the few large-scale clinical trials and registries that have been undertaken in patients undergoing non-cardiac surgery. Lee *et al.* studied 4315 patients undergoing elective major non-cardiac procedures in a tertiary care teaching hospital throughout 1989–1994.[5] They

observed that 92 (2.1%) patients suffered major cardiac complications, including cardiac death and myocardial infarction (MI). In a cohort of 108 593 consecutive patients who underwent surgery throughout 1991–2000 in a university hospital in The Netherlands, perioperative mortality occurred in 1877 (1.7%) patients, with a cardiovascular cause being identified in 543 cases (0.5%).[6] The Dutch Echocardiographic Cardiac Risk Evaluating Applying Stress Echo (DECREASE) -I, -II and -IV trials enrolled 3893 surgical patients throughout 1996–2008, and these comprised intermediate- and high-risk patients of whom 136 (3.5%) suffered perioperative cardiac death or MI.[7–9] A final piece of evidence with respect to patient outcome is derived from the Perioperative Ischaemic Evaluation (POISE) trial, which was conducted throughout 2002–2007, and enrolled 8351 patients undergoing non-cardiac surgery.[10] Perioperative mortality occurred in 226 patients (2.7%), of whom 133 (1.6%) suffered cardiovascular death, whereas non-fatal MI was observed in another 367 (4.4%) subjects. Differences in incidences between the studies are mainly explained by patient selection and endpoint MI definitions—major non-cardiac surgery is associated with an incidence of cardiac death of between 0.5 and 1.5%, and of major cardiac complications of between 2.0 and 3.5%. When applied to the population in the European Union member states these figures translate into 150 000–250 000 life-threatening cardiac complications due to non-cardiac surgical procedures annually.

Impact of the ageing population

Within the next 20 years, the acceleration in ageing of the population will have a major impact on perioperative patient management. It is estimated that elderly people require surgery four times more often than the rest of the population.[11] Although exact data regarding the number of patients undergoing surgery in Europe are lacking, it is estimated that this number will increase by 25% by 2020, and for the same time period the elderly population will increase by >50%. The total number of surgical procedures will increase even faster because of the rising frequency of interventions with age.[12] Results of the US National Hospital Discharge Survey show that, in general, the number of surgical procedures will increase in almost all age groups, but that the largest increase will occur in the middle aged and elderly (Table 3).

Demographics of patients undergoing surgery show a trend towards an increasing number of elderly patients and co-morbidities.[13] Although mortality from cardiac disease is decreasing in the general population, the prevalence of IHD, heart failure, and cardiovascular risk factors, especially diabetes, is increasing. Among the significant co-morbidities in elderly patients presenting for general surgery, cardiovascular disease (CVD) is the most prevalent. It is estimated from primary care data that in the 75–84 year age group 19% of men and 12% of women have some degree of CVD.[14] Age *per se*, however, seems to be responsible for only a small increase in the risk of complications; greater risks are associated with urgency and significant cardiac, pulmonary, and renal disease. The number of affected individuals is likely to be higher in countries with high CVD mortality, particularly in Central and Eastern Europe. These conditions should, therefore, have a greater impact on the evaluation of patient risk than age alone.

Table 3 Change in numbers of discharges for surgical procedures by age for the time periods 1994/95 and 2004/05 as reported from the 2005 US National Hospital Discharge Survey (non-federal short-stay hospitals)[15]

Age (years)	Number of procedures (in thousands)		% change
	1994/95	2004/05	
18–44	7311	7326	+2.1
45–64	4111	5210	+26.7
65–74	3069	3036	−1.1
75 and over	3479	4317	+24.1
18 and over	17 969	19 889	+10.7

Purpose

Currently there are no official ESC guidelines on pre-operative risk assessment and perioperative cardiac management. The objective is to endorse a standardized and evidence-based approach to perioperative cardiac management. The guidelines recommend a practical, stepwise evaluation of the patient, which integrates clinical risk factors and test results with the estimated stress of the planned surgical procedure. This results in an individualized cardiac risk assessment, with the opportunity to initiate medical therapy, coronary interventions, and specific surgical and anaesthetic techniques in order to optimize the patient's perioperative condition. Compared with the non-surgical setting, data from randomized clinical trials, which are the ideal evidence base for the guidelines, are sparse. Therefore, when no trials are available on a specific cardiac management regimen in the surgical setting, data from the non-surgical setting are used, and similar recommendations made, but with different levels of evidence. Emphasis is placed on the restricted use of prophylactic coronary revascularization, as this is rarely indicated simply to ensure the patient survives surgery. Pre-operative evaluation requires an integrated multidisciplinary approach from anaesthesiologists, cardiologists, internists, pulmonologists, geriatricians, and surgeons. Anaesthesiologists, who are experts on the specific demands of the proposed surgical procedure, usually coordinate the process.

Guidelines have the potential to improve post-operative outcome. However, as shown in an observational study of 711 vascular surgery patients from The Netherlands, adherence to guidelines is poor.[16–18] Although 185 of a total of 711 patients (26%) fulfilled the ACC/AHA guideline criteria for pre-operative non-invasive cardiac testing, clinicians had performed testing in only 38 of those cases (21%).[16] The guideline-recommended medical therapy for the perioperative period, namely the combination of aspirin and statins in all patients and β-blockers in patients with ischaemic heart disease, was followed in only 41% of cases.[18] Significantly, the use of evidence-based medication during the perioperative period was associated with a reduction in 3-year mortality after adjustment for clinical characteristics [hazard ratio (HR), 0.65; 95% confidence interval (CI), 0.45–0.94]. These data

highlight the existence of a clear opportunity for improving the quality of care in this high-risk group of patients.

In addition to promoting an improvement in immediate perioperative care, guidelines should provide long-term advice, as patients should live long enough to enjoy the benefits of surgery. Following the development and introduction of perioperative cardiac guidelines, their effect on outcome should be monitored. The objective evaluation of changes in outcome will be an essential part of future perioperative guideline developments.

Pre-operative evaluation

Surgical risk for cardiac events

Cardiac complications after non-cardiac surgery depend not only on specific risk factors but also on the type of surgery and the circumstances under which it takes place.[19] Surgical factors that influence cardiac risk are related to the urgency, magnitude, type, and duration of the procedure, as well as the change in body core temperature, blood loss, and fluid shifts.[12]

Every operation elicits a stress response. This response is initiated by tissue injury and mediated by neuroendocrine factors, and may induce tachycardia and hypertension. Fluid shifts in the perioperative period add to the surgical stress. This stress increases myocardial oxygen demand. Surgery also causes alterations in the balance between prothrombotic and fibrinolytic factors, resulting in hypercoagulability and possible coronary thrombosis (elevation of fibrinogen and other coagulation factors, increased platelet activation and aggregation, and reduced fibrinolysis). The extent of such changes is proportionate to the extent and duration of the intervention. All these factors may cause myocardial ischaemia and heart failure. Certainly in patients at elevated risk, attention to these factors should be given and lead, if indicated, to adaptations in the surgical plan.

Although patient-specific factors are more important than surgery-specific factors in predicting the cardiac risk for non-cardiac surgical procedures, the type of surgery cannot be ignored when evaluating a particular patient undergoing an intervention.[6,20] With regard to cardiac risk, surgical interventions can be divided into low-risk, intermediate-risk, and high-risk groups with estimated 30-day cardiac event rates (cardiac death and MI) of <1, 1–5, and >5%, respectively (*Table 4*). Although only a rough estimation, this risk stratification provides a good indication of the need for cardiac evaluation, drug treatment, and assessment of risk for cardiac events.

The high-risk group consists of major vascular interventions. In the intermediate-risk category the risk also depends on the magnitude, duration, location, blood loss, and fluid shifts related to the specific procedure. In the low-risk category the cardiac risk is negligible unless strong patient-specific risk factors are present.

The need for, and value of, pre-operative cardiac evaluation will also depend on the urgency of surgery. In the case of emergency surgical procedures, such as those for ruptured abdominal aortic aneurysm (AAA), major trauma, or for perforated viscus, cardiac evaluation will not change the course and result of the intervention but may influence the management in the immediate postoperative period. In non-emergent but urgent untreated surgical conditions such as bypass for acute limb ischaemia or treatment of bowel obstruction, the morbidity and mortality of the untreated underlying condition will outweigh the potential cardiac risk related to the intervention. In these cases, cardiological evaluation may influence the perioperative measures taken to reduce the cardiac risk, but will not influence the decision to perform the intervention. In some cases, the cardiac risk can also influence the type of operation and guide the choice to less invasive interventions, such as peripheral arterial angioplasty instead of infrainguinal bypass, or extra-anatomic reconstruction instead of aortic procedure, even when these may yield less favourable

Table 4 Surgical risk[a] estimate (modified from Boersma *et al.*[6])

Low-risk <1%	Intermediate-risk 1–5%	High-risk >5%
• Breast • Dental • Endocrine • Eye • Gynaecology • Reconstructive • Orthopaedic—minor (knee surgery) • Urologic—minor	• Abdominal • Carotid • Peripheral arterial angioplasty • Endovascular aneurysm repair • Head and neck surgery • Neurological/ orthopaedic—major (hip and spine surgery) • Pulmonary renal/ liver transplant • Urologic—major	• Aortic and major vascular surgery • Peripheral vascular surgery

[a]Risk of MI and cardiac death within 30 days after surgery.

Table 5 Lee index and Erasmus model: clinical risk factors used for pre-operative cardiac risk stratification[5,6]

Clinical characteristics	Lee index	Erasmus model
IHD (angina pectoris and/or MI)	×	×
Surgical risk	High-risk surgery	High, intermediate-high, intermediate-low, low risk
Heart failure	×	×
Stroke/transient ischaemic attack	×	×
Diabetes mellitus requiring insulin therapy	×	×
Renal dysfunction/haemodialysis	×	×
Age		×

IHD = ischaemic heart disease; MI = myocardial infarction.

results in the long term. Lastly, in some situations, the cardiac evaluation, in as far as it can reliably predict perioperative cardiac complications and estimate late survival, should be taken into consideration even when deciding whether to perform an intervention or not. This is the case in certain prophylactic interventions such as the treatment of small AAAs or asymptomatic carotid stenosis where the life expectancy of the patient and the risk of the operation are important factors in evaluating the potential benefit of the surgical intervention.

Vascular interventions are of specific interest, not only because they carry the highest risk of cardiac complications, explained by the high probability that the atherosclerotic process also affects the coronary arteries, but also because of the many studies that have shown that this risk can be influenced by adequate perioperative measures in these patients. Open aortic and infra-inguinal procedures have both to be considered as high-risk procedures.[6] Although a less extensive intervention, infra-inguinal revascularization entails a cardiac risk similar to or even higher than aortic procedures. This can be explained by the higher incidence of diabetes, renal dysfunction, IHD, and advanced age in this patient group. This also explains why the risk related to peripheral artery angioplasties, which are minimally invasive procedures, is not negligible. Several randomized trials, as well as community-based studies, have shown that the cardiac risk is substantially lower after endovascular aortic aneurysm repair compared with open repair.[21] This can be related to the lesser tissue damage and the avoidance of aortic cross-clamping and post-operative ileus. However, long-term survival does not seem to be influenced by the surgical technique that is used, but is determined by the underlying cardiac disease.[22] Carotid endarterectomy is considered to be an intermediate-risk procedure. Nevertheless, elevated cardiac risk and late survival should be taken into account in the decision-making process and can influence the choice between endarterectomy or stenting.

Laparoscopic procedures have the advantage of causing less tissue trauma and intestinal paralysis compared with open procedures, resulting in less incisional pain and diminished post-operative fluid shifts related to bowel paralysis.[23] On the other hand, the pneumoperitoneum used in these procedures results in elevated intra-abdominal pressure and a reduction in venous return. It will result in a decrease in cardiac output and an increase in systemic vascular resistance. Therefore, cardiac risk in patients with heart failure is not diminished in patients undergoing laparoscopy compared with open surgery, and both should be evaluated in the same way. This is especially true in patients undergoing interventions for morbid obesity.[24,25]

Recommendation/statement on surgical risk estimate

Recommendation/statement	Class[a]	Level[b]
Laparoscopic procedures demonstrate a cardiac stress similar to open procedures and it is recommended that patients be screened prior to intervention accordingly	I	A

[a]Class of recommendation.
[b]Level of evidence.

Functional capacity

Determination of functional capacity is considered to be a pivotal step in pre-operative cardiac risk assessment. Functional capacity is measured in metabolic equivalents (METs). One MET equals the basal metabolic rate. Exercise testing provides an objective assessment of functional capacity. Without testing, functional capacity can be estimated by the ability to perform the activities of daily living. Given that 1 MET represents metabolic demand at rest, climbing two flights of stairs demands 4 METs, and strenuous sports such as swimming >10 METS (*Figure 1*).

The inability to climb two flights of stairs or run a short distance (<4 METs) indicates poor functional capacity and is associated with an increased incidence of post-operative cardiac events. After thoracic surgery, a poor functional capacity has been associated with an increased mortality (relative risk 18.7, 95% CI 5.9–59). However, in comparison with thoracic surgery, a poor functional status was not associated with an increased mortality after other non-cardiac surgery (relative risk 0.47, 95% CI 0.09–2.5).[28] This may reflect the importance of pulmonary function, strongly related to functional capacity, as a major predictor of survival after thoracic surgery. These findings were confirmed in a study of 5939 patients scheduled for non-cardiac surgery in which the prognostic importance of pre-operative functional capacity was measured in METs.[29] Using receiver operating characteristic (ROC) curve analysis, the association of functional capacity with post-operative cardiac events or death showed an area under

Figure 1 Estimated energy requirements for various activities. km per h = kilometres per hour; MET = metabolic equivalent. Based on Hlatky et al.[26] and Fletcher et al.[27]
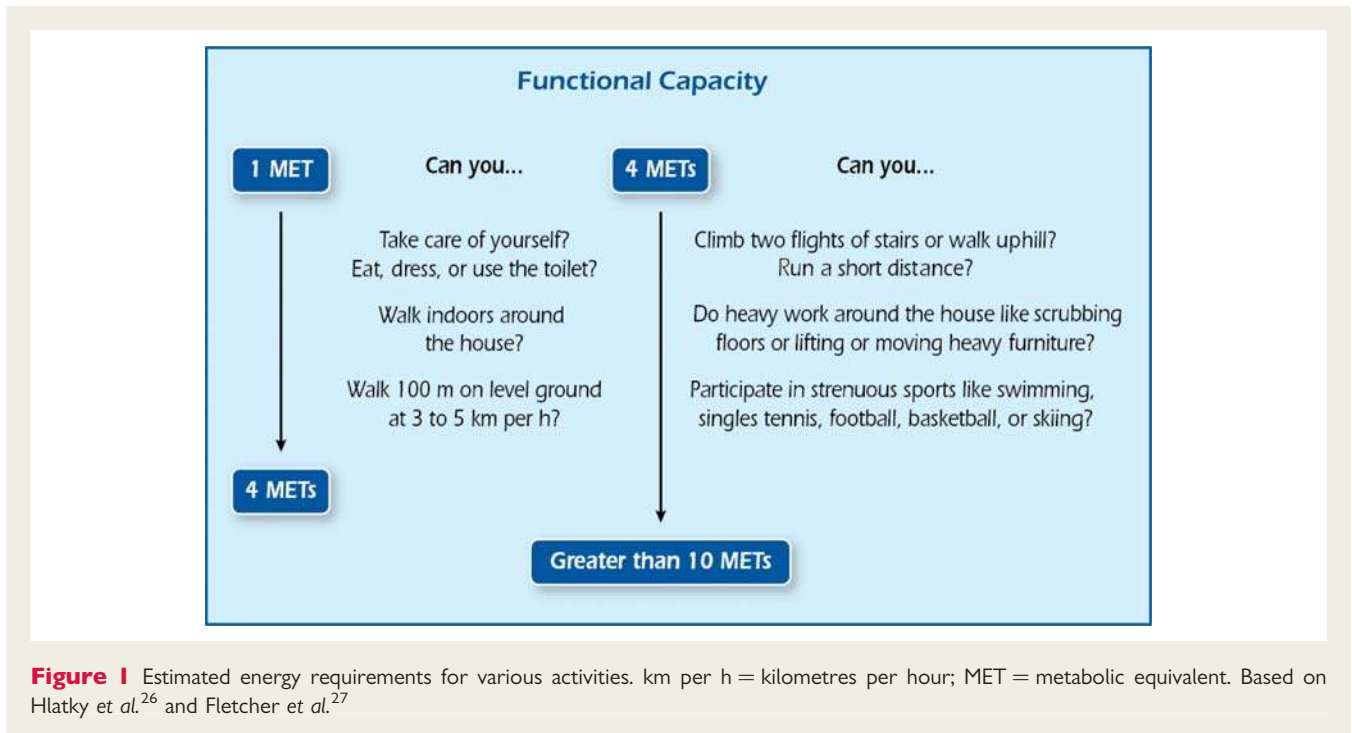
the ROC curve of just 0.664, compared with 0.814 for age. Considering the relatively weak association between functional capacity and post-operative cardiac outcome, what importance should we attach to functional capacity assessment in the pre-operative evaluation of the risk of non-cardiac surgery? When functional capacity is high, the prognosis is excellent, even in the presence of stable IHD or risk factors.[30] In this case, perioperative management will rarely be changed as a result of further cardiac testing and the planned surgical procedure can proceed. Using functional capacity evaluation prior to surgery, the ability to climb two flights of stairs or run for a short distance indicated a good functional capacity. On the other hand, when functional capacity is poor or unknown, the presence and number of risk factors in relation to the risk of surgery will determine pre-operative risk stratification and perioperative management.

Risk indices

Effective strategies aimed at reducing the risk of perioperative cardiac complications should involve cardiac evaluation using medical history prior to the surgical procedure, for two main reasons. First, patients with an anticipated low cardiac risk—after thorough evaluation—can be operated on safely without further delay. It is unlikely that risk reduction strategies can reduce the peri-operative risk further. Secondly, risk reduction by pharmacological treatment is most cost-effective in patients with a suspected increased cardiac risk. Additional non-invasive cardiac imaging techniques are tools to identify patients at higher risk. However, imaging techniques should be reserved for those patients in whom test results would influence and change management. Obviously, the intensity of the pre-operative cardiac evaluation must be tailored to the patient's clinical condition and the urgency of the circumstances requiring surgery. When emergency surgery is needed,

the evaluation must necessarily be limited. However, most clinical circumstances allow the application of a more extensive, systematic approach, with cardiac risk evaluation that is initially based on clinical characteristics and type of surgery, and then extended—if indicated—to resting electrocardiography (ECG), laboratory measurements, and non-invasive (stress) testing.

During the last 30 years, several risk indices have been developed, based on multivariable analyses of observational data, which represent the relationship between clinical characteristics and perioperative cardiac mortality and morbidity. The indices that were developed by Goldman (1977), Detsky (1986), and Lee (1999) became well known.[5,31,32] The Lee index, which is in fact a modification of the original Goldman index, is considered by many clinicians and researchers to be the best currently available cardiac risk prediction index in non-cardiac surgery. It was developed using prospectively collected data on 2893 unselected patients (and validated in another 1422 patients) who underwent a wide spectrum of procedures. They were followed systematically throughout the post-operative phase for a range of clinically relevant cardiac outcomes. The Lee index contains five independent clinical determinants of major perioperative cardiac events: a history of IHD, a history of cerebrovascular disease, heart failure, insulin-dependent diabetes mellitus, and impaired renal function. High-risk type of surgery is the sixth factor that is included in the index. All factors contribute equally to the index (with 1 point each), and the incidence of major cardiac complications is estimated at 0.4, 0.9, 7, and 11% in patients with an index of 0, 1, 2, and ≥3 points, respectively. The area under the ROC curve in the validation data set was 0.81, indicating that the index has a high capability for discriminating between patients with and without a major cardiac event.

However, the patients studied by Lee et al. cannot be considered to be an average, unselected non-cardiac surgical cohort. Patients

undergoing thoracic (12%), vascular (21%), and orthopaedic surgery (35%) were over-represented. Furthermore, despite its respectable size, the study was too underpowered to reveal a broad range of cardiac outcome determinants, as only 56 cardiac events were observed in the derivation cohort. Several external validation studies have suggested that the Lee index is probably suboptimal for identifying patients with multiple risk factors.[6] In fact, the type of surgery was only classified as two subtypes: first, high-risk, including intraperitoneal, intrathoracic, and suprainguinal vascular procedures; and, secondly, all remaining non-laparoscopic procedures, mainly including orthopaedic, abdominal, and other vascular procedures. Evidence exists that a more subtle classification, such as the Erasmus model, results in better risk discrimination.[6] In this model, an extensive description of the type of surgery and age increased the prognostic value of the model for perioperative cardiac events (area under the ROC curve for the prediction of cardiovascular mortality increased from 0.63 to 0.85).

Recommendations/statements on cardiac risk stratification

Recommendations/statements	Class[a]	Level[b]
It is recommended clinical risk indices be used for post-operative risk stratification	I	B
It is recommended that the Lee index model applying six different variables for perioperative cardiac risk be used	I	A

[a]Class of recommendation.
[b]Level of evidence.

Biomarkers

A biological marker—biomarker—is a characteristic that can be objectively measured and evaluated and which is an indicator of abnormal biological and pathogenic processes or responses to therapeutic interventions. In the perioperative setting, biomarkers can be divided into markers focusing on myocardial ischaemia and damage, inflammation, and LV function.

Cardiac troponins T and I (cTnT and cTnI) are the preferred markers for the diagnosis of MI because they demonstrate sensitivity and tissue specificity superior to other available biomarkers.[33,34] The prognostic information is independent of, and complementary to, other important cardiac indicators of risk such as ST deviation and LV function. The prognostic significance of even small elevations in troponins has been independently confirmed in community-based studies and in clinical trials (TACTICS-TIMI 18, FRISC II, OPUS-TIMI),[35,36] not only in high-risk, but also in intermediate-risk groups. cTnI and CTnT seem to be of similar value for risk assessment in ACS in the presence and absence of renal failure.[33] The prognosis for all-cause death in patients with end-stage renal disease and with even minor elevations in cTnT is 2−5 times worse than for those with undetectable values. Existing evidence suggests that even small increases in cTnT in the perioperative period reflect clinically relevant myocardial injury with worsened cardiac prognosis and outcome.[37] The development of new biomarkers, including high-sensitivity troponins, will further enhance the assessment of myocardial damage. It should be noted that troponin elevation may be observed in many other conditions. The diagnosis of non-ST-segment elevation myocardial infarction (NSTEMI) should never be made solely on the basis of biomarkers.

Inflammatory markers might identify pre-operatively those patients with an increased risk of unstable coronary plaque. C-reactive protein (CRP) is an acute-phase reactant produced in the liver. CRP is also expressed in smooth muscle cells within diseased atherosclerotic arteries and has been implicated in many aspects of atherogenesis and plaque vulnerability, including expression of adhesion molecules, induction of nitric oxide, altered complement function, and inhibition of intrinsic fibrinolysis.[38] However, in the surgical setting, no data are currently available using CRP as a marker for the initiation of risk reduction strategies.

Brain natriuretic peptide (BNP) and N-terminal pro-BNP (NT-proBNP) are produced in cardiac myocytes in response to increases in myocardial wall stress. This may occur at any stage of heart failure, independently of the presence or absence of myocardial ischaemia. Plasma BNP and NT-proBNP have emerged as important prognostic indicators in patients with heart failure, ACS, and stable IHD in non-surgical settings.[39−41] Pre-operative BNP and NT-proBNP levels have additional prognostic value for long-term mortality and for cardiac events after major non-cardiac vascular surgery.[42−46]

Data on pre-operative biomarker use from prospective controlled trials are sparse. Based on the present data, routine assessment of serum biomarkers for patients undergoing non-cardiac surgery cannot be proposed for routine use as an index of cell damage.

Recommendations/statements on biomarkers

Recommendations/statements	Class[a]	Level[b]
NT-proBNP and BNP measurements should be considered for obtaining independent prognostic information for perioperative and late cardiac events in high-risk patients.	IIa	B
Routine biomarker sampling to prevent cardiac events is not recommended	III	C

[a]Class of recommendation.
[b]Level of evidence.
BNP = brain natriuretic peptide; NT-proBNP = N-terminal pro-brain natriuretic peptide.

Non-invasive testing

Pre-operative non-invasive testing aims at providing information on three cardiac risk markers: LV dysfunction, myocardial ischaemia, and heart valve abnormalities, all major determinants of adverse post-operative outcome. LV function is assessed at rest, and various imaging modalities are available. For myocardial ischaemia detection, exercise ECG and non-invasive imaging techniques may be used. The overall theme is that the diagnostic algorithm for risk stratification of myocardial ischaemia and LV function should be similar to that proposed for patients in the non-surgical setting with known or suspected IHD.[47] Non-invasive testing should not

only be considered for coronary artery revascularization but also for patient counselling, change of perioperative management in relation to type of surgery, anaesthetic technique, and long-term prognosis. Echocardiography is preferred for evaluation of valve disease (see section on specific diseases, subheading valvular heart disease).

Non-invasive testing of cardiac disease

Electrocardiography

The 12-lead ECG is commonly performed as part of pre-operative cardiovascular risk assessment in patients undergoing non-cardiac surgery. In IHD patients, the pre-operative electrocardiogram contains important prognostic information and is predictive of long-term outcome independent of clinical findings and perioperative ischaemia.[48] However, the electrocardiogram may be normal or non-specific in a patient with either ischaemia or infarction. The routine use of ECG prior to all types of surgery is a subject of increasing debate. A retrospective study investigated 23 036 patients scheduled for 28 457 surgical procedures; patients with abnormal ECG findings had a greater incidence of cardiovascular death than those with normal ECG results (1.8% vs. 0.3%). In patients who underwent low-risk or low- to intermediate-risk surgery, the absolute difference in the incidence of cardiovascular death between those with and without ECG abnormalities was only 0.5%.[49]

Recommendations on ECG		
Recommendations	**Class**[a]	**Level**[b]
Pre-operative ECG is recommended for patients who have risk factor(s) and are scheduled for intermediate- or high-risk surgery	I	B
Pre-operative ECG should be considered for patients who have risk factor(s) and are scheduled for low-risk surgery	IIa	B
Pre-operative ECG may be considered for patients who have no risk factor and are scheduled for intermediate-risk surgery	IIb	B
Pre-operative ECG is not recommended for patients who have no risk factor and are scheduled for low-risk surgery	III	B

[a]Class of recommendation.
[b]Level of evidence.
ECG = electrocardiography.

Assessment of left ventricular function

Resting LV function can be evaluated before non-cardiac surgery by radionuclide ventriculography, gated single photon emission computed tomography (SPECT) imaging, echocardiography, magnetic resonance imaging (MRI), or multislice computed tomography (CT), with similar accuracy.[50] Routine echocardiography is not recommended for the pre-operative evaluation of LV function, but may be performed in asymptomatic patients undergoing high-risk surgery. A meta-analysis of the available data demonstrated that an LV ejection fraction of <35% had a sensitivity of 50% and a specificity of 91% for prediction of perioperative non-fatal

MI or cardiac death.[51] The limited predictive value of LV function assessment for perioperative outcome may be related to the failure to detect severe underlying IHD. Recommendations for the pre-operative evaluation of (asymptomatic) patients with cardiac murmurs are discussed in the section on VHD.

Recommendations on resting echocardiography		
Recommendations	**Class**[a]	**Level**[b]
Rest echocardiography for LV assessment should be considered in patients undergoing high-risk surgery	IIa	C
Rest echocardiography for LV assessment in asymptomatic patients is not recommended	III	B

[a]Class of recommendation.
[b]Level of evidence.
LV = left ventricular.

Non-invasive testing of ischaemic heart disease

Physiological exercise using a treadmill or bicycle ergometer is the preferred method for detection of ischaemia. Physiological exercise provides an estimate of functional capacity, provides blood pressure and heart rate response, and detects myocardial ischaemia through ST-segment changes. The accuracy of exercise ECG varies significantly among studies. Meta-analysis of the reported studies using treadmill testing in vascular surgery patients showed a rather low sensitivity (74%, 95% CI 60–88%) and specificity (69%, 95% CI 60–78%), comparable with daily clinical practice.[51] The positive predictive value was as low as 10%, but the negative predictive value was very high (98%). However, risk stratification with exercise is not suitable for patients with limited exercise capacity due to their inability to reach an ischaemic threshold. Furthermore, pre-existing ST-segment abnormalities, especially in the pre-cordial leads V_5 and V_6 at rest, hamper reliable ST-segment analysis. A gradient of severity in the test result relates to the perioperative outcome: the onset of a myocardial ischaemic response at low exercise workloads is associated with a significantly increased risk of perioperative and long-term cardiac events. In contrast, the onset of myocardial ischaemia at high workloads is associated with significantly less risk.[30] Pharmacological stress testing with either nuclear perfusion imaging or echocardiography is more suitable in patients with limited physical capabilities.

The role of myocardial perfusion imaging for pre-operative risk stratification is well established. In patients with limited exercise capacity, pharmacological stress (dipyridamole, adenosine, or dobutamine) is an alternative stressor. Images reflect myocardial blood distribution at the time of injection. Studies are performed both during stress and at rest to determine the presence of reversible defects, reflecting jeopardized ischaemic myocardium, or fixed defects, reflecting scar or non-viable tissue.

The prognostic value of the extent of ischaemic myocardium, using semi-quantitative dipyridamole myocardial perfusion imaging, has been investigated in a meta-analysis of studies in vascular surgery patients.[52] Study endpoints were perioperative

cardiac death and MI. The authors included nine studies, totalling 1179 vascular surgery patients, with a 7% 30-day event rate. In this analysis, reversible ischaemia in <20% of the LV myocardium did not change the likelihood of perioperative cardiac events, compared with those without ischaemia. Patients with more extensive reversible defects were at increased risk: 20–29% reversibility [likelihood ratio (LR) 1.6, 95% CI 1.0–2.6], 30–39% reversibility (LR 2.9, 95% CI 1.6–5.1), 40–49% reversibility (LR 2.9, 95% CI 1.4 − 6.2), and ≥50% reversibility (LR 11, 95% CI 5.8–20).

A second meta-analysis, that assessed the prognostic value of six diagnostic tests, reported a sensitivity of 83% (95% CI 77–92%) with a much lower specificity of 47% (95% CI, 41–57%) for myocardial perfusion imaging.[51–53] The positive and negative predictive values were 11 and 97%, respectively.

A third meta-analysis pooled the results of 10 studies evaluating dipyridamole thallium-201 imaging in vascular surgery candidates over a 9-year period (1985–1994).[53] The 30-day cardiac death or non-fatal MI rates were 1% in patients with normal test results, 7% in patients with fixed defects, and 9% in patients with reversible defects on thallium-201 imaging. Moreover, three out of the 10 studies analysed used semi-quantitative scoring, demonstrating a higher incidence of cardiac events in patients with two or more reversible defects.

Overall, the positive predictive value of reversible defects for perioperative death or MI has decreased over recent years. This is probably related to changes in perioperative management and surgical procedures, resulting in a reduced cardiac event rate in patients with myocardial ischaemia as detected by pre-operative cardiac stress tests. However, because of the high sensitivity of nuclear imaging studies for detecting IHD, patients with a normal scan have an excellent prognosis. Myocardial perfusion imaging using dobutamine stress has a good safety profile. Hypotension, a systolic blood pressure decrease of ≥40 mmHg, occurred in 3.4%, and serious cardiac arrhythmias in 3.8% of cases, in a consecutive series of 1076 patients. All arrhythmias terminated either spontaneously or after metoprolol administration.[54]

Stress echocardiography using exercise or pharmacological (dobutamine, dipyridamole) stress has been widely used for pre-operative cardiac risk evaluation. The test combines information on LV function at rest, heart valve abnormalities, and the presence and extent of stress-inducible ischaemia.[55] In one study, 530 patients were enrolled to evaluate the incremental value of dobutamine stress echocardiography (DSE) for the assessment of cardiac risk before non-vascular surgery.[56] Multivariable predictors of post-operative events in patients with ischaemia were found to be a history of heart failure [odds ratio (OR) 4.7, 95% CI 1.6–14.0] and ischaemic threshold <60% of age-predicted maximal heart rate (OR 7.0, 95% CI 2.8–17.6). DSE identified 60% of patients as low risk (no ischaemia), 32% as intermediate risk (ischaemic threshold ≥60%), and 8% as high risk (ischaemic threshold <60%); post-operative event rates were 0, 9, and 43%, respectively. A recent meta-analysis showed that the sensitivity and specificity of DSE for perioperative cardiac death and MI are high (85 and 70%, respectively).[51] DSE can be performed safely with reasonable patient tolerance [incidence of cardiac arrhythmias and hypotension (defined as a

systolic blood pressure decrease of ≥40 mmHg)]. DSE has some limitations, e.g. it should not be used in patients with severe arrhythmias, significant hypertension, large thrombus-laden aortic aneurysms, or hypotension.

In general, stress echocardiography has a high negative predictive value (between 90 and 100%): a negative test is associated with a very low incidence of cardiac events and indicates a safe surgical procedure. However, the positive predictive value is relatively low (between 25 and 45%); this means that the post-surgical probability of a cardiac event is low, despite wall motion abnormality detection during stress echocardiography.

In a meta-analysis of 15 studies comparing dipyridamole thallium-201 imaging and DSE for risk stratification before vascular surgery, it was demonstrated that the prognostic value of stress imaging abnormalities for perioperative ischaemic events is comparable when using available techniques, but that the accuracy varies with IHD prevalence.[53] In patients with a low incidence of IHD, the diagnostic accuracy is reduced compared with those with a high incidence of IHD.

MRI can also be used for detection of ischaemia; both perfusion and wall motion can be detected during stress and at rest.[57] Ischaemia, more than IHD, is associated with adverse postoperative cardiac events. Therefore, functional testing is preferred to the detection of anatomical stenosis. The accuracy for assessment of ischaemia is high, with a sensitivity of 83% (95% CI 79–88%) and specificity of 86% (95% CI 81–91%) when wall motion is used (14 studies, 754 patients). When perfusion is added on top of wall motion abnormalities (24 studies, 1516 patients), sensitivity in the assessment of ischaemia increases to 91% (95% CI 88–94%); however, specificity decreases to 81% (95% CI 77–85%). MRI with dobutamine stress was used in 102 patients undergoing major non-cardiac surgery.[58] New wall motion abnormalities were used as a marker of ischaemia. Applying multivariable analysis, myocardial ischaemia was the strongest predictor of perioperative cardiac events (death, MI, and heart failure). MRI enabled non-invasive angiography and meta-analysis of existing data to be undertaken, using IHD detected by coronary angiography as a reference, and demonstrated sensitivity and specificity of 75% (95% CI 68–80%) and 85% (95% CI 78–90%), respectively, on a vessel basis (16 studies, 2041 vessels); on a patient basis (13 studies, 607 subjects), sensitivity and specificity were 88% (95% CI 82–92%) and 56% (95% CI 53–68%) respectively.[59] Currently no data are available in the setting of pre-operative risk stratification.

CT can be used to detect coronary calcium, which reflects coronary atherosclerosis. In addition, both electron beam and multislice CT have been used for non-invasive angiography, and a meta-analysis of existing data, using IHD detected by coronary angiography as a reference, demonstrated a sensitivity and a specificity of 82% (95% CI 80–85%) and 91% (95% CI 90–92%), respectively, on a vessel basis (eight studies, 2726 vessels); on a patient basis (21 studies, 1570 patients), sensitivity and specificity were 96% (95% CI 94–98%) and 74% (95% CI 65–84%), respectively.[60] Data in the setting of pre-operative risk stratification are not yet available. A word of caution should be given with respect to the risk of radiation.[61] In patients undergoing heart valve surgery, CT angiography has been used to exclude

concomitant IHD, thereby avoiding the need for invasive coronary angiography.[62] This approach may also be of use for pre-operative risk stratification; however, currently no data are available in the setting of pre-operative risk stratification.

How can these data be put into a practical algorithm? Testing should only be performed if it changes perioperative management. Patients with extensive stress-induced ischaemia represent a high-risk population in whom standard medical therapy appears to be insufficient to prevent perioperative cardiac events.[63] Pre-operative testing may be considered in high-risk surgery patients with fewer than three clinical risk factors. However, in these patients, the beneficial effect of cardioprotective therapy appears to be sufficient to preclude pre-operative stress testing. The results of the randomized, multicentre DECREASE-II study showed that the perioperative cardiac event rate of vascular surgery patients on β-blocker therapy was already so reduced that test results and subsequent alteration in perioperative management were redundant.[8] No differences in cardiac death and MI at 30 days were observed between 770 patients assigned to no cardiac stress testing vs. testing (1.8 vs. 2.3%; OR 0.78; 95% CI 0.28–2.1). Importantly, pre-operative testing delayed surgery for >3 weeks. Likewise, similar recommendations are given for intermediate-risk surgery patients, although no data from randomized trials are available. Considering the low event rate of patients scheduled for low-risk surgery, it is unlikely that test results in cardiac-stable patients will alter perioperative management.

Recommendations on stress testing prior to surgery		
Recommendations	**Class**[a]	**Level**[b]
Stress testing is recommended in high-risk surgery patients with ≥3 clinical factors[c]	I	C
Stress testing may be considered in high-risk surgery patients with ≤2 clinical factors	IIb	B
Stress testing may be considered in intermediate-risk surgery	IIb	C
Stress testing is not recommended in low-risk surgery	III	C

[a]Class of recommendation.
[b]Level of evidence.
[c]Clinical risk factors are presented in Table 13.

Integrated assessment of cardiopulmonary function

Cardiopulmonary exercise testing (CPET) provides a global assessment of the integrated response to exercise involving the pulmonary, cardiovascular, and skeletal muscle systems. CPET is a programmed exercise test on either a cycle ergometer or a treadmill during which inspired and expired gases are measured through a facemask or a mouthpiece. This test provides information on oxygen uptake and utilization.[64] The most commonly used data from this test are O_2 consumption at peak exercise (VO_{2peak}) and at anaerobic threshold (VO_{2AT}), defined as the point when metabolic demands exceed oxygen delivery, and

anaerobic metabolism begins to occur. The thresholds for classifying patients as low risk are usually taken as VO_{2peak} >15 mL/kg/min and VO_{2AT} >11 mL/kg/min. These thresholds roughly equate to 4 METs.[65] CPET before lung resection may help in stratifying the surgical risk and optimizing perioperative care. In a cohort of 204 consecutive patients who had undergone pulmonary lobectomy or pneumonectomy, a VO_2 peak <20 mL/kg/min was a predictor of pulmonary complications, cardiac complications, and mortality; a VO_{2peak} <12 mL/kg/min was associated with a 13-fold higher rate of mortality.[66] In a study of 187 elderly patients VO_{2AT} was measured before major abdominal surgery.[67] The overall mortality was 5.9%. Patients who had a VO_{2AT} <11 mL/kg/min ($n = 55$) had a mortality of 18% compared with those who had a VO_{2AT} >11 mL/kg/min ($n = 132$) whose mortality was 0.8% (risk ratio 24, 95% CI 3.1–183). In patients who exhibited signs of myocardial ischaemia during testing, the mortality was 42% for patients whose VO_{2AT} was <11 mL/kg/min and only 4% for those whose VO_{2AT} was >11 mL/kg/min (P <0.001). CPET also carries accurate prognostic information in the setting of heart failure patients: an abnormally high relationship between minute ventilation (VE) and carbon dioxide production (VCO_2), expressed as the VE/VCO_2 slope measured between the onset of loaded exercise and the end of the isocapnic buffering period, identified by the rise in the VE/VCO_2 slope and the reduction of end-tidal expiratory CO_2 pressure ($PETCO_2$) (or mixed expired value of alveolar and dead space gas, $PaCO_2$), is associated with a poor outcome, as is an oscillatory pattern of ventilation during exercise, defined as cyclic fluctuations in minute ventilation at rest that persist during effort.[68] There are potential discrepancies between a CPET and functional assessment using METs that preclude a widespread use of CPET. Non-cardiac and non-respiratory factors such as skeletal muscle function and physical training can underestimate aerobic metabolic activity. A further consideration must be the availability of CPET testing, which at present is not available in all centres. The role of CPET in pre-operative risk assessment has not been established and CPET should not be considered to be a substitute for stress testing in routine practice.

Angiography

Coronary angiography is a well-established invasive diagnostic procedure but is rarely indicated to assess the risk of non-cardiac surgery. There is a lack of information derived from randomized clinical trials on its usefulness in patients scheduled for non-cardiac surgery. Moreover, adopting an invasive coronary angiography assessment may cause an unnecessary and unpredictable delay in an already planned surgical intervention. Nevertheless, IHD may be present in a significant number of patients in whom non-cardiac surgery is indicated. In patients with known IHD, indications for pre-operative coronary angiography and revascularization are similar to angiography indications in the non-surgical setting.[47,69–71] The control of ischaemia before surgery, either medically or with intervention, is recommended whenever non-cardiac surgery procedures can be delayed.

Recommendations on pre-operative coronary angiography

Recommendations	Class[a]	Level[b]
Pre-operative angiography is recommended in patients with acute STEMI	I	A
Pre-operative angiography is recommended in patients with NSTEMI and unstable angina	I	A
Pre-operative angiography is recommended in patients with angina not controlled with adequate medical therapy	I	A
Pre-operative angiography may be considered in cardiac-stable patients undergoing high-risk surgery	IIb	B
Pre-operative angiography may be considered in cardiac-stable patients undergoing intermediate-risk surgery	IIb	C
Pre-operative angiography is not recommended in cardiac-stable patients undergoing low-risk surgery	III	C

[a]Class of recommendation.
[b]Level of evidence.
STEMI = ST-segment elevation myocardial infarction; NSTEMI = non-ST-segment elevation myocardial infarction.

Risk reduction strategies

Pharmacological

The occurrence of MI during the intra- or early post-operative period is frequently preceded by prolonged or recurrent myocardial ischaemia. The stress of surgery and anaesthesia may trigger ischaemia through an imbalance between myocardial oxygen demand and supply. Besides specific risk reduction strategies adapted to patient characteristics and the type of surgery, pre-operative evaluation is an opportunity to check and optimize the control of all cardiovascular risk factors.

β-Blockers

During the perioperative period, there is a catecholamine surge, resulting in an increased heart rate and myocardial contractility and subsequent increased myocardial oxygen consumption. The main rationale for perioperative β-blocker use is to decrease myocardial oxygen consumption by reducing heart rate, resulting in a lengthening of the diastolic filling period, and decreased myocardial contractility.[72] Additional cardioprotective factors are redistribution of coronary blood flow to the subendocardium, plaque stabilization, and an increase in the threshold for ventricular fibrillation.[72] Randomized studies have shown that β-blockers and other drugs that lower the heart rate can reduce perioperative myocardial ischaemia as assessed by continuous ST-segment monitoring.[73] However, whether this translates into a clinical benefit can be established only through trials analysing the incidence of cardiovascular events. Seven multicentre randomized trials evaluating the effect of perioperative β-blockade on clinical endpoints have been published in peer-reviewed journals (Table 6 and Figure 2).[9,10,74–78]

Table 6 Summary of randomized controlled trials evaluating the effect of perioperative β-blockade on post-operative mortality and non-fatal MI

Study	n	Vascular surgery (%)	β-Blocker Type	Onset (before surgery)	Duration (days after surgery)	Dose titration	Patient selection according to cardiac risk	30-day mortality (%) β-Blocker	30-day mortality (%) Control	30-day rate of non-fatal MI (%) β-Blocker	30-day rate of non-fatal MI (%) Control
Mangano et al.[76]	200	40	Atenolol	30 min	7	No	IHD or ≥2 risk factors	5/99 (5.1[a])	12/101 (11.9[a])	–	–
DECREASE[9]	112	100	Bisoprolol	7 days	30	Yes	Positive DSE	2/59 (3.4)	9/53 (17.0)	0/59 (0)	9/53 (17.0)
POBBLE[74]	103	100	Metoprolol tartrate	<24 h	7	No	No	3/55 (5.4)	1/48 (2.1)	3/55 (5.5)	5/48 (10.4)
MaVS[77]	496	100	Metoprolol succinate	2 h	5	No	no	0/246 (0)	4/250 (1.6)	19/246 (7.7)	21/250 (8.4)
DIPOM[75]	921	7	Metoprolol succinate	12 h	8	No	diabetes	74/462 (16.0)	72/459 (15.7)	3/462 (0.6)	4/459 (0.9)
BBSA[78]	219	5	Bisoprolol	>3 h	10	Yes	IHD or ≥2 risk factors	1/110 (0.9)	0/109 (0)	0/110 (0)	0/109 (0)
POISE[10]	8351	41	Metoprolol succinate	2–4 h	30	No	IHD or atherosclerosis or major vascular surgery or ≥3 risk factors	129/4174 (3.1)	97/4177 (2.3)	152/4174 (3.6)	215/4177 (5.1)

[a]At 6 months.
DSE = dobutamine stress echocardiography; IHD = ischaemic heart disease; MI = myocardial infarction.
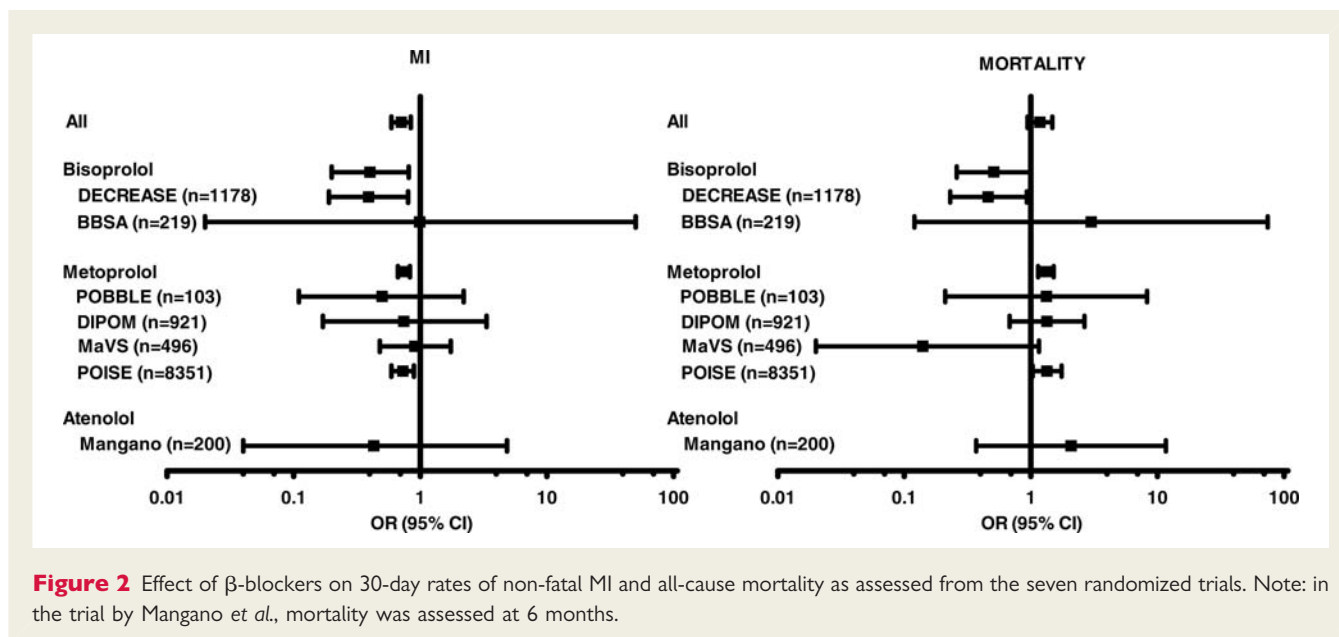
Figure 2 Effect of β-blockers on 30-day rates of non-fatal MI and all-cause mortality as assessed from the seven randomized trials. Note: in the trial by Mangano *et al.*, mortality was assessed at 6 months.

Three trials targeted patients at high risk for perioperative complications because of the type of surgery, the presence of IHD, or risk factors for perioperative cardiac complications.[9,76,78] Three other trials did not require the presence of clinical risk factors, except for diabetes in one case.[74,75,77] The POISE trial included patients with a wide spectrum of risk of perioperative cardiac complications.[10]

The first trial randomized 200 patients with at least two risk factors for IHD or with known IHD, who were scheduled for non-cardiac surgery under general anaesthesia, including 40% major vascular surgery procedures.[76] Atenolol was associated with a significant decrease in overall mortality and an increase in event-free survival at 6 months, and this benefit was sustained for up to 2 years. The Dutch Echographic Cardiac Risk Evaluating Applying Stress Echo (DECREASE) trial selected 112 out of 1453 vascular surgery patients who combined at least one clinical risk factor and positive DSE, excluding patients with extensive wall motion abnormalities.[9] Patients were randomized to standard care or bisoprolol, which was started at least 1 week before surgery and titrated according to heart rate. There was an 89% reduction in cardiac mortality and/or MI in the bisoprolol group (3.4% vs. 34%, *P* <0.001), which was sustained for up to 3 years.

The PeriOperative Beta-BlockadE (POBBLE) trial included 103 low-risk patients undergoing elective infrarenal vascular surgery, randomized to metoprolol tartrate or placebo.[74] The incidence of death, MI, or stroke at 30 days did not differ between the metoprolol and placebo groups (13 and 15%, respectively, *P* = 0.78). Patients were at low cardiac risk and those with a history of MI within the previous 2 years were excluded. In the Metoprolol after Vascular Surgery (MaVS) trial, 497 patients undergoing abdominal or infrainguinal vascular surgery were randomized to metoprolol succinate or placebo.[77] The combined endpoint of death, MI, heart failure, arrhythmias, or stroke at 30 days did not differ between the metoprolol and placebo groups (10.2 and 12%, respectively, *P* = 0.57). The Lee index was ≤2 in 90% of patients and ≤1 in 60%.

The Diabetes Postoperative Mortality and Morbidity (DIPOM) trial selected 921 patients with diabetes, age >39 years, and a duration of surgery of >1 h (39% low-risk surgery).[75] Patients were randomized to receive metoprolol succinate or placebo. The combined endpoint of death, MI, unstable angina, or heart failure at 30 days did not differ between the metoprolol and placebo groups (6 and 5%, respectively, *P* = 0.66). However, only 54% of the patients had a history of IHD, or an additional cardiac risk factor, and underwent high- or intermediate-risk surgery.

In the POISE trial, 8351 patients were randomized to metoprolol succinate or placebo.[10] Patients were aged ≥45 years and were included if they had known CVD, at least three out of seven clinical risk factors, or were scheduled for major vascular surgery. Treatment consisted of metoprolol succinate, 100 mg 2–4 h prior to surgery, 100 mg during the first 6 h after surgery, but withheld if systolic blood pressure dipped below 100 mmHg. Maintenance therapy was started 12 h later, bringing the total dose of metoprolol succinate in the first 24 h to 400 mg, at least in a number of patients. There was a 17% decrease in the composite endpoint, defined as death, MI, or non-fatal cardiac arrest at 30 days (5.8% vs. 6.9%, *P* = 0.04). However, the 30% decrease in non-fatal MI (3.6% vs. 5.1%, *P* <0.001) was partially offset by a 33% increase in total mortality (3.1% vs. 2.3%, *P* = 0.03) and a 2-fold increase in stroke (1.0% vs. 0.5%, *P* = 0.005). Hypotension was more frequent in patients receiving metoprolol (15.0% vs. 9.7%, *P* <0.0001). *Post hoc* analysis showed that hypotension had the largest population-attributable risk for death and stroke.

Seven meta-analyses have pooled 5, 11, 6, 15, 8, 22 and 33 randomized published trials on perioperative β-blockers, totalling respectively 586, 866, 632, 1077, 2437, 2057, and 12 306 patients.[79–85] Five meta-analyses gave consistent results showing a significant reduction in perioperative myocardial ischaemia and MI in patients receiving β-blockers.[79–83] These meta-analyses gave consistent results showing a significant reduction in perioperative myocardial ischaemia, MI, and cardiac mortality in patients

receiving β-blockers.[84,85] Risk reduction was more marked in high-risk patients. The most recent meta-analysis concluded that β-blockers result in 16 fewer non-fatal MIs per 1000 patients treated, but at the expense of three non-fatal disabling strokes and (possibly) three fatal cardiac or non-cardiac complications.[83] However, it should be acknowledged that the recent POISE trial had the greatest weight in all of the above analyses. Indeed, ∼80% of the deaths, MIs, and strokes in this meta-analysis are derived from POISE, and this proportion was as high as 84% in the trials labelled low-bias risk. Hence, a more detailed analysis of the results of POISE compared with non-POISE trials is warranted (Table 7). First, in POISE, all-cause mortality was increased by 34% in patients receiving β-blockers; in the non-POISE trials the point estimate of treatment effect was consistent with a reduced, although not statistically significant, all-cause and cardiovascular mortality by β-blockers. The differential treatment effect seems to be caused by the high mortality in POISE patients who are given β-blockers (3.1% vs. 1.9% in non-POISE trials), and not by differences in patients allocated to control therapy (2.3% vs. 2.5%). Therefore, understanding of the cause and timing of deaths in POISE is important. Perioperative death in POISE patients allocated to metoprolol succinate was associated with perioperative hypotension, bradycardia, and stroke. A history of cerebrovascular disease was associated with an increased risk of stroke. Hypotension can be related to the use of a high dose of metoprolol without dose titration. It is considered that 200 mg of metoprolol has approximately the same strength of β-blockade as 100 mg of atenolol and 10 mg of bisoprolol.

Discrepancies in the protective role of β-blockers can be explained by differences in patient characteristics, type of surgery, and the modalities of β-blockade (timing of onset, duration, dose titration, and type of drug). Also, these findings may be hampered by the inclusion of numerous trials which were not designed to assess the effect on perioperative cardiac risk or which used only a single β-blocker dose before anaesthesia without continuation after surgery.[84] A recent meta-analysis suggested that most differences between trials on the cardioprotective effect of β-blockers could be attributed to the variability in heart rate response.[86] In particular, the decrease in post-operative MI was highly significant when there was tight heart rate control.

Although observational studies should be interpreted with caution, they provide additional insights into the interactions between risk stratification and perioperative β-blockade.

In a prospective cohort comprising 1351 patients undergoing vascular surgery, 360 (27%) were treated using β-blockers.[63] In a study population of 1351 patients, 83% had <3 clinical risk factors. They experienced a lower risk of death or MI when using β-blockers (0.8%) than without (2.3%). In the 17% of patients who had ≥3 risk factors, the risk of death or MI was reduced using β-blockers from 5.8 to 2.0% when stress-induced ischaemia was absent and from 33 to 2.8% when stress-induced ischaemia was limited (1−4 myocardial segments). Patients with extensive stress-induced ischaemia (≥5/16 myocardial segments) had a particularly high risk of death or MI whatever the treatment used (33% with β-blockers and 36% without). A large retrospective cohort drawn from a quality of care database analysed 663 635 patients undergoing non-cardiac surgery (30% high risk surgery).[87] The

Table 7 Meta-analysis of perioperative effects of β-blockers in non-cardiac surgery; all-cause mortality and cardiovascular mortality[95]

	All-cause-mortality					Cardiovascular mortality				
	n	Deaths (%)	OR (95% CI)	P-value for homogeneity of ORs	Benefit per 1000 (SD)	n	Deaths (%)	OR (95% CI)	P-value for homogeneity of ORs	Benefit per 1000 (SD)
POISE										
β-Blocker	4174	129 (3.1)	1.34 (1.03–1.75)	0.027	−7.7 (3.6)	4174	75 (1.8)	1.30 (0.92–1.84)	0.086	−4.1 (2.7)
Control	4177	97 (2.3)				4177	58 (1.4)			
Non-POISE										
β-Blocker	1896	36 (1.9)	0.74 (0.47–1.17)		6.4 (5.0)	1866	18 (1.0)	0.70 (0.37–1.31)		4.1 (3.7)
Control	1615	41 (2.5)				1598	22 (1.4)			
Non-POISE, strokes reported										
β-Blocker	1536	31 (2.0)	1.01 (0.60–1.69)	0.017	−0.1 (5.2)	1536	16 (1.0)	1.08 (0.52–2.25)	0.021	−0.8 (3.7)
Control	1346	27 (2.0)				1346	13 (1.0)			
Non-POISE, strokes not reported										
β-blocker	360	5 (1.4)	0.26 (0.09–0.72)		38.2 (14.9)	330	2 (0.6)	0.16 (0.04–0.77)		29.7 (12.4)
Control	269	14 (5.2)				252	9 (3.6)			

comparison of in-hospital mortality between 119 632 patients receiving β-blockers and 216 220 propensity-matched patients without β-blockers showed no difference overall (2.3% vs. 2.4%, respectively, $P = 0.68$). However, there were marked differences according to patient risk profile. β-Blocker use was associated with a significant decrease in mortality when the Lee index was ≥3. No significant difference was observed for a Lee index of 1 or 2. Mortality was increased in the lowest risk group (Lee index of 0).

Randomized trials selecting high-risk patients, cohort studies, and meta-analyses provide consistent evidence supporting a decrease in cardiac mortality and MI by β-blockers in patients with clinical risk factors undergoing high-risk (mainly vascular) surgery. Perioperative β-blockade is also cost-effective in these patients. However, patients with extensive ischaemia as demonstrated by stress testing are at particularly high risk of perioperative cardiac complications, despite perioperative β-blockers.

Conversely, randomized trials including low-risk patients and cohort studies suggest that perioperative β-blockade does not decrease the risk of cardiac complications in patients without clinical risk factors. The possibility of a harmful effect on mortality has been suggested by a retrospective cohort[87] and the POISE trial.[10] Bradycardia and hypotension may be harmful in patients with atherosclerosis, and possibly favour stroke.

This does not justify exposing low-risk patients to potential side effects in the absence of proven benefit. The issue remains debatable in intermediate-risk patients, i.e. those with one or two clinical risk factors. Results of the DECREASE IV trial suggest that β-blockers should also be used in patients undergoing intermediate-risk surgery.[88] Patients randomized to bisoprolol ($n = 533$) had a lower incidence of the primary efficacy endpoint than those randomized to bisoprolol-control therapy (2.1% vs. 6.0% events, HR 0.34, 95% CI 0.17–0.67). An increased mortality following pre-operative β-blocker withdrawal has been reported in observational studies.[89,90] β-Blockers should be continued when prescribed for IHD or arrhythmias. When β-blockers are prescribed for hypertension, the absence of evidence in favour of a perioperative cardioprotective effect with other antihypertensive drugs does not support a change of therapy. β-Blockers should not be withdrawn in patients treated for stable heart failure due to LV systolic dysfunction. In decompensated heart failure, β-blocker therapy may need to be reduced, or temporarily omitted.[91] If possible, non-cardiac surgery should be deferred so that it can be performed under optimal medical therapy in a stable condition. Contra-indications to β-blockers (asthma, severe conduction disorders, symptomatic bradycardia, and symptomatic hypotension) should be respected. β-Blockers are not contra-indicated in patients with intermittent claudication, as in randomized trials, worsening of symptoms has not been shown to occur more frequently.[92] Furthermore, a recent study showed that cardioselective β-blockers were associated with reduced mortality in patients with chronic obstructive pulmonary disease (COPD) undergoing vascular surgery.[93] In the absence of contra-indications, β-blocker dose should be titrated to achieve a heart rate between 60 and 70 beats/min. β_1-Selective blockers without intrinsic sympathomimetic activity are favoured.

Recommendations on β-blockers[a]

Recommendations	Class[b]	Level[c]
β-Blockers are recommended in patients who have known IHD or myocardial ischaemia according to pre-operative stress testing[a]	I	B
β-Blockers are recommended in patients scheduled for high-risk surgery[a]	I	B
Continuation of β-blockers is recommended in patients previously treated with β-blockers because of IHD, arrhythmias, or hypertension	I	C
β-Blockers should be considered for patients scheduled for intermediate-risk surgery[a]	IIa	B
Continuation in patients previously treated with β-blockers because of chronic heart failure with systolic dysfunction should be considered	IIa	C
β-Blockers may be considered in patients scheduled for low-risk surgery with risk factor(s)	IIb	B
Perioperative high-dose β-blockers without titration are not recommended	III	A
β-Blockers are not recommended in patients scheduled for low-risk surgery without risk factors	III	B

[a]Treatment should be initiated optimally between 30 days and at least 1 week before surgery. Target: heart rate 60–70 beats/min, systolic blood pressure >100 mmHg.
[b]Class of recommendation.
[c]Level of evidence.
IHD = ischaemic heart disease.

Treatment onset and the choice of the optimal dose of β-blockers are closely linked. Perioperative myocardial ischaemia and troponin release are reduced, and long-term outcome is improved, in patients who have a lower heart rate.[94] On the other hand, bradycardia and hypotension should be avoided. This highlights the importance of preventing overtreatment with fixed high initial doses. The dose of β-blockers should be titrated, which requires that treatment be initiated optimally between 30 days and at least 1 week before surgery. It is recommended that treatment start with a daily dose of 2.5 mg of bisoprolol or 50 mg of metoprolol succinate which should then be adjusted *before* surgery to achieve a resting heart rate of between 60 and 70 beats/min with systolic blood pressure >100 mmHg. The goal for heart rate is the same during the whole perioperative period, using i.v. administration when oral administration is not possible. Post-operative tachycardia should result in the first instance in the treatment of the underlying cause, for example hypovolaemia, pain, blood loss, or infection, rather than the β-blocker dose simply being increased.

The optimal duration of perioperative β-blocker therapy cannot be derived from randomized trials. The occurrence of delayed cardiac events is an incentive to continue β-blocker therapy for at least several months. Long-term β-blocker therapy should be used in patients who had a positive pre-operative stress test. Current concepts of cardioprotection have led to recommendations to use selective β_1-blockers without intrinsic sympathomimetic activity and with a long half-life, e.g. bisoprolol.

Statins

3-Hydroxy-3-methylglutaryl co-enzyme A reductase inhibitors (statins) are widely prescribed in patients with or at risk of IHD because of their lipid-lowering effect. Patients with non-coronary atherosclerosis (carotid, peripheral, aortic, renal) should receive statin therapy for secondary prevention, independently of non-cardiac surgery.[96] Statins also induce coronary plaque stabilization by decreasing lipid oxidation, inflammation, matrix metalloproteinase, and cell death, and by increasing tissue inhibitor of metalloproteinase and collagen. These so-called non-lipid or pleiotropic effects may prevent plaque rupture and subsequent MI in the perioperative period.[97]

Multiple large clinical trials and observational studies have demonstrated a beneficial effect of perioperative statin use.[98,99] In the first prospective, randomized controlled trial, 100 patients scheduled for vascular surgery were allocated to 20 mg of atorvastatin or placebo once a day for 45 days, irrespective of their serum cholesterol concentration.[100] Vascular surgery was performed on average 31 days after randomization, and patients were followed-up over 6 months. During these 6 months of follow-up, atorvastatin significantly reduced the incidence of cardiac events (8% vs. 26%, $P = 0.03$). A meta-analysis of 223 010 patients from 12 retrospective and three prospective trials showed that statins reduced mortality significantly by 44% in non-cardiac surgery and by 59% in vascular surgery.[98] The most recent randomized controlled trial was the DECREASE III study. A total of 497 vascular surgery patients were allocated to either fluvastatin (extended release 80 mg once daily) or placebo, starting 37 days prior to surgery. The incidence of myocardial ischaemia in patients allocated to fluvastatin or placebo was 10.8% vs. 19.0%, respectively (OR 0.55, 95% CI 0.34−0.88). The incidence of cardiac death or MI in the two study groups was 4.8% vs. 10.2%, respectively (OR 0.47, 95% CI 0.24−0.94).[101]

A concern related to the use of perioperative statin therapy has been the risk of statin-induced myopathy and rhabdomyolysis. Perioperatively, factors increasing the risk of statin-induced myopathy are numerous, e.g. the impairment of renal function after major surgery, and multiple drug use during anaesthesia. Furthermore, the use of analgesic drugs and post-operative pain may mask signs of myopathy. Failure to detect statin-induced myopathy may then lead to the statin being continued and the subsequent development of rhabdomyolysis and acute renal failure. However, no studies have been published that support this concern, except for some case reports. In a retrospective study of 981 consecutive patients undergoing vascular surgery, no cases of rhabdomyolysis, significantly higher creatine kinase level, or increased incidence of myopathy were observed in statin users.[102]

Recently it has been suggested that discontinuation of statins may cause a rebound effect and be disadvantageous.[99,103] A potential limitation of perioperative statin use is the lack of an i.v. formulation.

Therefore, statins with a long half-life or extended release formulations such as rosuvastatin, atorvastatin, and fluvastatin extended release are recommended, to bridge the period immediately after surgery when oral intake is not feasible.

Recommendations on statins

Recommendations	Class[a]	Level[b]
It is recommended that statins be started in high-risk surgery patients, optimally between 30 days and at least 1 week before surgery	I	B
It is recommended that statins be continued perioperatively	I	C

[a]Class of recommendation.
[b]Level of evidence.

Nitrates

Nitroglycerin is well known to reverse myocardial ischaemia. One small but controlled study has demonstrated decreased perioperative myocardial ischaemia in patients with stable angina given i.v. nitroglycerin during non-cardiac surgery.[104] However, no effect was observed on the incidence of MI or cardiac death. These observations were confirmed in a similar study, showing no effect on either myocardial ischaemia, MI, or cardiac death.[105] Furthermore, perioperative use of nitroglycerin may pose a significant haemodynamic risk to the patients. Decreased preload may lead to tachycardia, and hypotension.

Recommendations on nitrates

Recommendations	Class[a]	Level[b]
Perioperative nitroglycerin use for the prevention of adverse ischaemic events may be considered	IIb	B

[a]Class of recommendation.
[b]Level of evidence.

Angiotensin-converting enzyme inhibitors

Independently of the blood pressure-lowering effect, angiotensin-converting enzyme (ACE) inhibitors preserve organ function. This effect is related to improvement of endothelial function, anti-inflammatory properties, and a direct interference with atherogenesis.[106] The inhibition of ACE may prevent events related to myocardial ischaemia and LV dysfunction. Therefore, it seems reasonable to suggest that perioperative treatment with ACE inhibitors may have beneficial effects on post-operative outcome.

The QUO VADIS study compared the effect of the ACE inhibitors quinapril with that of placebo in patients undergoing cardiac surgery. Quinapril treatment was started 4 weeks before elective surgery and was continued up to 1 year after surgery.[107] This trial demonstrated that post-operative cardiovascular events were significantly reduced (HR 0.23, 95% CI 0.06−0.87) in patients treated with quinapril. The beneficial effect in the QUO VADIS study, however, could be the result of the post-operative treatment. A recent review provided conflicting data concerning ACE inhibitors after cardiac surgery.[108]

Additionally, perioperative use of ACE inhibitors carries a risk of severe hypotension under anaesthesia, in particular following induction and concomitant β-blocker use. Hypotension is less frequent when ACE inhibitors are discontinued the day before surgery. Although this remains debated, ACE inhibitor withdrawal may be considered 24 h before surgery when they are prescribed for hypertension. They should be resumed after surgery as soon as volume is stable. The risk of hypotension is at least as high with angiotensin receptor blockers (ARBs) as with ACE inhibitors, and the response to vasopressors may be impaired. In patients with LV systolic dysfunction who are in a stable clinical condition, it seems reasonable to continue ACE inhibitors during the perioperative period under close monitoring. When LV dysfunction is discovered during pre-operative evaluation in untreated patients in stable condition, surgery should be postponed, if possible, to introduce ACE inhibitors and β-blockers as recommended by the ESC Guidelines on heart failure.[91]

Recommendations on ACE inhibitor use

Recommendations	Class[a]	Level[b]
It is recommended that ACE inhibitors be continued during non-cardiac surgery in stable patients with LV systolic dysfunction.	I	C
ACE inhibitors are recommended in cardiac-stable patients with LV systolic dysfunction scheduled for high-risk surgery	I	C
ACE inhibitors should be considered in cardiac-stable patients with LV systolic dysfunction scheduled for low-/intermediate-risk surgery	IIa	C
Transient discontinuation of ACE inhibitors before non-cardiac surgery in hypertensive patients should be considered.	IIa	C

[a]Class of recommendation.
[b]Level of evidence.
ACE = angiotensin-converting enzyme; LV = left ventricular.

Calcium channel blockers

The effect of calcium channel blockers on the balance between myocardial oxygen supply and demand makes them theoretically suitable for risk reduction strategies. It is necessary to distinguish between dihydropyridines that do not act directly on heart rate and diltiazem or verapamil that lower the heart rate.

The relevance of randomized trials assessing the perioperative effect of calcium channel blockers is limited by their small size, the lack of risk stratification, and the absence of the systematic reporting of cardiac death and MI. A meta-analysis pooled 11 randomized trials totalling 1007 patients. All patients underwent non-cardiac surgery under calcium channel blockers (diltiazem in seven trials, verapamil in two, and nifedipine in one, and one other trial incorporated three arms: control, diltiazem, and nifedipine).[109] There was a significant reduction in the number of episodes of myocardial ischaemia and supraventricular tachycardia (SVT) in the pooled analyses on calcium channel blockers. However, the decrease in mortality and MI reached statistical

significance only when both endpoints were combined in a composite endpoint of death and/or MI (relative risk 0.35, 95% CI 0.08–0.83, *P* = 0.02). Subgroup analyses favoured diltiazem. Another study in 1000 patients having acute or elective aortic aneurysm surgery showed that dihydropyridine calcium channel blocker use was independently associated with an increased incidence of perioperative mortality.[110] The use of short-acting dihydropyridines, in particular nifedipine capsules, should be avoided.

Thus, although heart rate-reducing calcium channel blockers are not indicated in patients with heart failure and systolic dysfunction, in patients who have contra-indications to β-blockers the continuation or the introduction of heart rate-reducing calcium channel blockers may be considered.

Recommendations on calcium channel blockers

Recommendations	Class[a]	Level[b]
It is recommended that calcium channel blockers be continued during non-cardiac surgery in patients with Prinzmetal angina pectoris	I	C
Heart rate-reducing calcium channel blockers, in particular diltiazem, may be considered before non-cardiac surgery in patients who have contra-indications to β-blockers	IIb	C
Routine use of calcium channel blockers to reduce the risk of perioperative cardiovascular complications is not recommended	III	C

[a]Class of recommendation.
[b]Level of evidence.

Ivabradine

Ivabradine is a specific inhibitor of the pacemaker in the sino-atrial node and reduces heart rate independently of sympathetic activation. It does not affect blood pressure or myocardial contractility. In a randomized trial of 111 vascular surgery patients, both ivabradine and metoprolol succinate reduced the incidence of ischaemia and MI significantly when compared with placebo. These preliminary findings need to be confirmed by future studies; ivabradine might be considered for patients with strict contra-indications to β-blockers.[111]

α₂ Receptor agonists

α_2 Receptor agonists reduce post-ganglionic noradrenaline output and therefore might reduce the catecholamine surge during surgery. The European Mivazerol trial randomized 1897 patients with IHD who underwent intermediate- or high-risk non-cardiac surgery.[112] Mivazerol did not decrease the incidence of death or MI in the whole population. However, there was a reduction of post-operative death or MI observed in a subpopulation of 904 vascular surgery patients. A more recent study including 190 patients with clinical risk factors or IHD showed a decrease in 30-day and 2-year mortality after perioperative use of clonidine.[113] However, there was no decrease in MI. A meta-analysis pooled 23 randomized trials, which included cardiac surgery in 10, vascular surgery in eight, and non-vascular surgery in three cases.[114]

Perioperative use of α_2 receptor agonists was associated with a decrease in mortality and MI only in the subgroup having vascular surgery, while there was no benefit in non-vascular surgery.

Recommendations on α_2 receptor agonists

Recommendations	Class[a]	Level[b]
α_2 Receptor agonists may be considered to reduce the risk of perioperative cardiovascular complications in vascular surgery patients	IIb	B

[a]Class of recommendation.
[b]Level of evidence.

Diuretics

Diuretics are a frequent pharmacological treatment in patients with hypertension or heart failure as underlying diseases. In hypertension, diuretics are usually used at low dose with relatively moderate blood pressure-lowering effect. In general, diuretics for hypertension can be discontinued on the day of surgery, and resumed orally when possible. If blood pressure reduction is required before oral therapy can be continued, other antihypertensive agents given i.v. may be preferred. In heart failure, diuretics are often used at high dose. Dosage increase should be considered if signs of fluid retention are present. Dosage reduction should be considered if there is risk of hypovolaemia, hypotension, and electrolyte disturbances. In general, diuretic treatment, if necessary to control heart failure, should be continued up to the day of surgery, and resumed orally when possible. In the perioperative period, volume status in patients with heart failure should be carefully monitored and loop diuretics may be given i.v. to control volume overload.

In any patient given diuretics, the possibility of electrolyte disturbance should be considered, as diuretics increase renal excretion of K and Mg. Hypokalaemia is reported to occur in up to 34% of patients undergoing surgery (mostly non-cardiac).[115] Hypokalaemia is well known to increase significantly the risk of ventricular tachycardia (VT) and ventricular fibrillation in cardiac disease.[116] In a study of 688 patients with cardiac disease undergoing non-cardiac surgery, hypokalaemia was independently associated with perioperative mortality.[117] On the other hand, in a study of 150 patients undergoing non-cardiac surgery, no increase in intraoperative arrhythmias was observed with hypokalaemia.[115] However, this latter study was relatively small and most patients had no evidence of cardiac disease. Significantly, the use of K- and Mg-sparing diuretics, i.e. aldosterone antagonists (spironolactone and eplerenone), is now well known to reduce mortality in severe heart failure.[118] In general, K and Mg homeostasis should be evaluated pre-operatively. Special attention should be given to patients on diuretics and patients prone to develop arrhythmia. Any electrolyte disturbance—especially hypokalaemia and hypomagnesaemia—should be corrected in due time before surgery. Dietary advice to increase intake of K and Mg should be given; depleting drugs should, if possible, be reduced; sparing diuretics may be added or preferred; and supplementation may be given. Acute pre-operative repletion in asymptomatic patients may be associated with more risks than benefits. Thus, minor, asymptomatic electrolyte disturbances should not delay acute surgery.

Recommendations on diuretics

Recommendations	Class[a]	Level[b]
It is recommended that electrolyte disturbances be corrected before surgery	I	B
It is recommended that hypertensive patients discontinue low-dose diuretics on the day of surgery and resume orally when possible	I	C
It is recommended that diuretics be continued in heart failure patients up to the day of surgery, resumed intravenously perioperatively, and continued orally when possible	I	C

[a]Class of recommendation.
[b]Level of evidence.

Aspirin

Though aspirin is widely used in patients with IHD and especially after coronary stent placement, the evidence of aspirin in the perioperative period setting is limited. In a randomized trial of 232 patients undergoing carotid endarterectomy, aspirin was shown to be effective in preventing intraoperative and postoperative stroke, though no effect on death or MI was noted.[119] A meta-analysis in 2001 demonstrated a reduction in serious vascular events and vascular death in vascular surgery patients.[120] This study included 10 trials of antiplatelet treatment in lower limb bypass surgery of which six involved aspirin treatment. However, the benefit of antiplatelet therapy did not reach statistical significance for the combined endpoint of vascular events (OR = 0.8, 95% CI 0.5–1.1) in this vascular surgery population.

Concerns of promoting perioperative haemorrhagic complications often led to the discontinuation of aspirin in the perioperative period. A large meta-analysis, including 41 studies in 49 590 patients, which compared perioprocedural withdrawal vs. bleeding risks of aspirin, concluded that the risk of bleeding complications was increased by 1.5 but that aspirin did not lead to higher severity levels of bleeding complications.[121] A systematic review in subjects at risk of or with IHD demonstrated that aspirin non-adherence/withdrawal was associated with a 3-fold higher risk of major adverse cardiac events (OR = 3.14, 95% CI 1.8–5.6).[122] Aspirin should only be discontinued if the bleeding risk outweighs the potential cardiac benefit. Prior to minor surgical or endoscopic procedures, a careful consideration should be given to the question of withdrawing antithrombotic medications. In principle and based on individualized 'risk to benefit' assessments, there is often no need for stopping the antiplatelet treatment prior to the aforementioned procedures in patients who are taking antiplatelet medications. For patients receiving antiplatelet therapy, i.e. aspirin, clopidogrel, or both, with excessive or life-threatening perioperative bleeding, transfusion of platelets or administration of other prohaemostatic agents is recommended.

Recommendations on aspirin

Recommendations	Class[a]	Level[b]
Continuation of aspirin in patients previously treated with aspirin should be considered in the perioperative period	IIa	B
Discontinuation of aspirin therapy in patients previously treated with aspirin should be considered only in those in whom haemostasis is difficult to control during surgery	IIa	B

[a]Class of recommendation.
[b]Level of evidence.

Anticoagulant therapy

Anticoagulant therapy is associated with increased bleeding during non-cardiac surgery. In some patients, this risk will be outweighed by the benefit of anticoagulant therapy, and drug therapy should be maintained or modified, whereas in other patients with low risk of thrombosis, therapy should be stopped in order to minimize bleeding complications.

Patients treated with oral anticoagulant therapy with vitamin K antagonists (VKAs) have an increased risk of periprocedural and post-procedural bleeding. If the international normalized ratio (INR) is <1.5, surgery can be performed safely (Table 8). However, in patients with a high risk of thromboembolism, discontinuation of VKAs is hazardous and these patients will need bridging therapy with unfractionated heparin (UFH) or therapeutic-dose low molecular weight heparin (LMWH) i.v. or s.c.[123-125] A high thromboembolic risk is present among other conditions, in patients with atrial fibrillation (AF), mechanical prosthetic heart valves, biological prosthetic heart valves or mitral valvular repair within the last 3 months, or recent venous thromboembolism (<3 months) plus thrombophilia. Bridging therapy is now most often performed with therapeutic-dose s.c. LMWH. VKAs are stopped 5 days (i.e. five doses of VKA) prior to surgery; LMWH or UFH are started 1 day after acenocoumarol interruption, and 2 days after warfarin interruption. In high thromboembolic risk patients, 70 U/kg of antifactor Xa twice daily are recommended and prophylactic once-daily doses in low-risk patients (Table 9).[126] The last dose of LMWH should be administered at least 12 h before the procedure. In patients with mechanical prosthetic heart valves, the evidence for i.v. UFH is more solid. Thus, in some centres these patients are hospitalized and treated with i.v. UFHs up until 4 h prior to surgery, and treatment with UFH is resumed after surgery until the INR is in the therapeutic range.[124] On the day of the procedure, the INR is checked.

Table 8   Bridging therapy of VKA with UFH or LMWH in high- and low-risk patients/procedures[125]

Low thromboembolic risk/low bleeding risk
▪ Continue anticoagulant therapy with INR in therapeutic range.

Low thromboembolic risk/high bleeding risk
▪ Discontinue anticoagulant therapy 5 days before the procedure.
▪ Start LMWH prophylaxis once daily or UFH i.v. 1 day after acenocoumarol interruption, and 2 days after warfarin interruption. Administer the last dose of LMWH at least 12 h before the procedure or give UFH i.v. up to 4 h prior to surgery.
▪ Resume LMWH or UFH at the pre-procedural dose 1–2 days (at least 12 h) after the procedure according to haemostatic status. Resume anticoagulant therapy 1 to 2 days after surgery at the pre-procedural dose + 50% boost dose for two consecutive days according to the haemostatic status.
▪ LMWH or UFH is continued until the INR has returned to therapeutic levels.

High thromboembolic risk
▪ Discontinue anticoagulant therapy 5 days before the procedure.
▪ Start therapeutic LMWH twice daily or UFH i.v. 1 day after acenocoumarol interruption, and 2 days after warfarin interruption. Administer the last dose of LMWH at least 12 h before the procedure or give UFH i.v. up to 4 h prior to surgery.
▪ Resume LMWH or UFH at the pre-procedural dose 1–2 days (at least 12 h) after the procedure according to haemostatic status. Resume anticoagulant therapy 1–2 days after surgery at the pre-procedural dose + 50% boost dose for two consecutive days according to haemostatic status.
▪ LMWH or UFH is continued until the INR has returned to therapeutic levels.

INR = international normalized ratio; LMWH = low molecular weight heparin; UFH = unfractionated heparin.

Table 9 Anticoagulation protocols applied according to patient thromboembolic risk[126]

Weight, kg	Patients at high thromboembolic risk		Patients at low thromboembolic risk	
	Nadroparin (twice daily, s.c.) (IU)	Enoxaparin (twice daily, s.c.) (IU)	Nadroparin (once daily, s.c.) (IU)	Enoxaparin (once daily, s.c.) (IU)
<50	2850	2000	2850	4000
50–69	3800	4000	3800	4000
70–89	5700	6000	5700	4000
90–110	7600	8000	5700	4000
>110	9500	10 000	5700	4000

IU = international units; LMWH = low molecular weight heparin; SC = subcutaneous.

Consideration should be given to postponing the procedure if the INR is >1.5. LMWH or UFH is resumed at the pre-procedural dose 1–2 days after surgery, depending on the haemostatic status, but at least 12 h after the procedure. Oral anticoagulants should be resumed on day 1 or 2 after surgery depending on haemostasis sufficiency (if the patient can take oral therapy) at the pre-operative maintenance dose plus a boost dose of 50% for two consecutive days; the maintenance dose should be administrated thereafter. LMWH or UFH should be continued until the INR returns to therapeutic levels.

Furthermore, the type of surgical procedure should be taken into consideration, as the bleeding risk varies considerably and affects the ability to ensure haemostatic control. Procedures with a high risk of serious bleeding complications are those where compression cannot be performed. In these cases, discontinuation of oral anticoagulants and bridging therapy with LMWH are warranted. In patients undergoing surgery with a low risk of serious bleeding, such as cataract surgery, no changes in oral anticoagulation therapy are needed.

In patients who are receiving VKAs and require reversal of the anticoagulant effect for an urgent surgical procedure, low-dose (2.5–5.0 mg) i.v. or oral vitamin K is recommended. For more immediate reversal of the anticoagulant effect of VKAs, treatment with fresh-frozen plasma or another prothrombin concentrate in addition to low-dose i.v. or oral vitamin K is recommended. In patients receiving UFH and requiring reversal of the anticoagulant effect for an urgent surgical procedure, cessation of therapy is enough. When given as an infusion, the anticoagulant effect of UFH reaches steady state within 4–6 h. So on cessation of an infusion, coagulation should be mostly normal after 4 h. When UFH is given s.c., the anticoagulant effect is more prolonged. For immediate reversal, the antidote is protamine sulfate. However, protamine sulfate can potentially provoke anaphylactic reactions with cardiovascular collapse, especially if infused too quickly. The dose of protamine sulfate can be calculated by the assessment of the amount of heparin received in the previous 2 h. The dose of protamine sulfate for reversal for a heparin infusion then is

1 mg per 100 U of heparin sodium. If the heparin infusion was stopped for >30 min but <2 h, then use half the dose of protamine sufate; if the heparin infusion was stopped for >2 h but <4 h, then use a quarter of the dose. The maximum dose of protamine sulfate is 50 mg. In patients who are receiving LMWH the anticoagulant effect may be reversed within 8 h of the last dose because of the short half-life. If immediate reversal is required, i.v. protamine sulfate can be used, but anti-Xa activity is never completely neutralized (maximum of 60–75%).

A summary of the recommended way to minimize bleeding and thromboembolic events during surgery is given in *Table 8*.

Revascularization

The main objective of prophylactic myocardial revascularization is the prevention of potentially lethal perioperative MI. While revascularization may be particularly effective in treating high-grade stenoses, it cannot prevent rupture of vulnerable plaques during the stress of surgery. The latter mechanism has been advocated in at least half of fatal cases of perioperative MI and may explain the lack of specificity of stress imaging techniques in predicting infarct-related coronary artery lesions.[37,127]

Patients who are clinically stable in the years after coronary artery bypass grafting (CABG) have a diminished risk of cardiac complications after subsequent non-cardiac surgery. Data from the CASS registry indicate that this is particularly the case in patients with triple vessel disease and/or depressed LV function but also in the case of high-risk surgery.[128] Therefore, patients who had CABG within the previous 5 years can be sent for surgery, if their clinical condition has remained unchanged since their last examination.

Patients with previous percutaneous revascularization may be at higher risk of cardiac events during or after subsequent non-cardiac surgery, particularly in cases of unplanned or urgent surgery after coronary stenting. After the introduction of angioplasty, it seemed that conventional percutaneous coronary intervention (PCI) did not worsen outcomes after surgery, even if

performed as early as 11 days after PCI.[129] The advent of stenting in the mid 1990s dramatically changed the scenario. Indeed, extremely high mortality rates (up to 20%) were reported in relation to acute stent thrombosis at the time of surgery if performed within weeks after coronary stenting with discontinuation of antiplatelet therapy.[130,131] Therefore, it is preferred that elective surgery be postponed for a minimum period of 6 weeks and optimally up to 3 months after bare metal stent implantation and that dual antiplatelet therapy be continued. When surgery was performed within this period, discontinuation of dual antiplatelet therapy was associated with an increased incidence of stent thrombosis.[130,131] After 3 months, patients can be sent for non-cardiac surgery, with continuation of at least aspirin therapy.[132] (Figure 3).

In 2002, DESs were introduced in Europe and became widely accepted as an efficient tool to reduce in-stent restenosis further. However, their major drawback is the need for prolonged dual antiplatelet therapy by aspirin and clopidogrel for at least 12 months. When surgery was performed within this period, discontinuation of dual antiplatelet therapy was associated with an increased incidence of stent thrombosis. It is now generally accepted that after DES implantation, elective surgery should not take place until after at least 12 months of continuous dual antiplatelet therapy[133] (Figure 3). After 12 months, patients can be sent for non-cardiac surgery, with continuation of at least aspirin therapy. The need for surgery in relation to its timing and the specific pathology (e.g. malignant tumour, vascular aneurysm repair) should be balanced against the excessive risk of stent thrombosis during the first year following DES implantation and a careful 'case-by-case' consideration is advisable. Discussion between the surgeon, the anaesthesiologist, and the treating cardiologist about this matter is recommended in order to achieve a reasonable expert consensus.

In patients who require temporary interruption of aspirin- or clopidogrel-containing drugs before surgery or a procedure it is recommended that this treatment be stopped at least 5 days and, preferably as much as 10 days, prior to the procedure. Therapy can be resumed after ~24 h (or the next morning) after surgery when there is adequate haemostasis. In patients in need of an urgent surgical or other invasive procedure, with potential excessive or life-threatening perioperative bleeding, transfusion of platelets or administration of other prohaemostatic agents is recommended.[134]

Recommendations on timing of non-cardiac surgery in cardiac-stable/asymptomatic patients with prior revascularization

Recommendations	Class[a]	Level[b]
It is recommended that patients with previous CABG in the last 5 years be sent for non-cardiac surgery without further delay	I	C
It is recommended that non-cardiac surgery be performed in patients with recent bare metal stent implantation after a minimum 6 weeks and optimally 3 months following the intervention	I	B
It is recommended that non-cardiac surgery be performed in patients with recent drug-eluting stent implantation no sooner than 12 months following the intervention	I	B
Consideration should be given to postponing non-cardiac surgery in patients with recent balloon angioplasty until at least 2 weeks following the intervention	IIa	B

[a]Class of recommendation.
[b]Level of evidence.
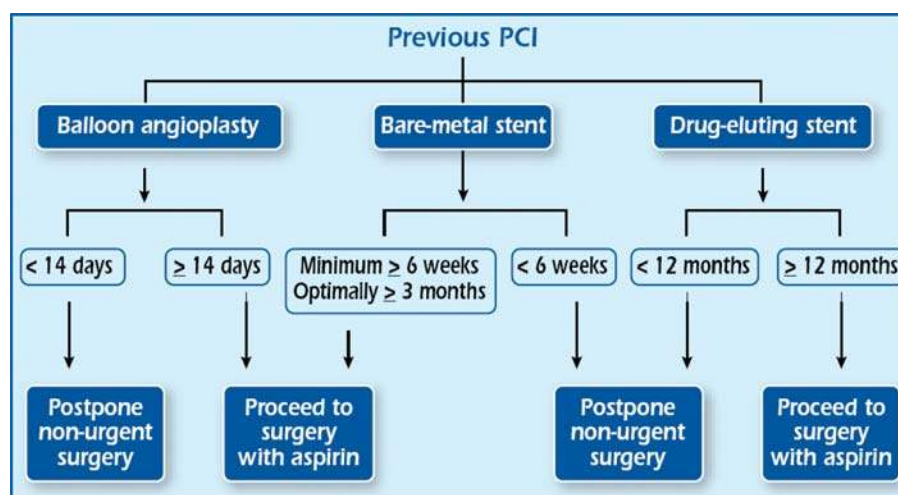CABG = coronary artery bypass grafting.

Figure 3 Recommendations for timing of non-cardiac surgery after PCI.[133] PCI = percutaneous coronary intervention.

Prophylactic revascularization in patients with stable ischaemic heart disease

Only two randomized studies have addressed the role of prophylactic revascularization prior to non-cardiac surgery in stable patients scheduled for vascular surgery. The Coronary Artery Revascularization Prophylaxis (CARP) trial was the first to compare optimal medical therapy with revascularization (by CABG or PCI) in patients with stable IHD prior to major vascular surgery.[135] Of 5859 patients screened at 18 US Veterans Affairs hospitals, 510 patients were randomized to one or other of the treatment options. Patients were included on the basis of a combination of cardiovascular risk factors and the detection of ischaemia on non-invasive testing as assessed by the consultant cardiologist. There was no difference in the primary endpoint of long-term mortality at 2.7 years after randomization: 22% (revascularization) vs. 23% (no-intervention) ($P = 0.92$). Furthermore, there was no difference in perioperative MI: 12% vs. 14%, respectively ($P = 0.37$). The second trial, DECREASE-V, was a pilot study and applied a different, more precise screening methodology and a more contemporary perioperative medical management.[136] A total of 1880 patients scheduled for surgery were screened for the presence of the following risk factors: age >70 years, angina pectoris, prior MI, compensated or a history of congestive heart failure, drug therapy for diabetes mellitus, renal dysfunction, and prior stroke or transient ischaemic attack (TIA). In the presence of ≥3 risk factors, DSE or nuclear stress testing was performed and in the presence of extensive ischaemia (>5/16 segments or >3/6 walls), patients were randomized to either revascularization or no revascularization. Importantly, β-blocker therapy was initiated and aspirin was continued during surgery in all patients. Three-vessel or left main disease was present in 75% of cases. Also 43% of patients had a depressed ejection fraction of ≤35%. PCI was performed in 65% of patients ($n = 32$, of whom 30 had DESs). There was no difference in the composite primary endpoint (all-cause mortality and non-fatal MI at 30 days): 43% for revascularization vs. 33% for no revascularization ($P = 0.30$).

CARP was the first trial to indicate that prophylactic revascularization prior to vascular surgery does not improve clinical outcomes in stable patients. Nevertheless, inclusion in the trial was based on subjective indicators and the study population was a relatively low risk group. DECREASE-V included high risk patients with extensive stress-induced ischaemia, as assessed by non-invasive stress testing. Despite the relatively small study cohort, DECREASE-V extends the conclusions of CARP to a higher risk population, with a majority of patients having three-vessel disease and a substantial proportion having asymptomatic LV dysfunction.

Successful achievement of a vascular procedure without prophylactic revascularization in a stable coronary patient does not imply that this patient would not need any revascularization afterwards. The limited data from DECREASE-V indicate a potential late catch-up phenomenon in the medically treated group.[136] Despite the lack of more scientific data, myocardial revascularization may therefore be recommended in patients prior to foreseen non-cardiac surgery without complications and who present with or have persistent signs of extensive ischaemia, according to the ESC Guidelines for non-surgical settings.

Both CARP and DECREASE-V have been conducted in the setting of vascular surgery, a type of surgery presenting particular risk to the patient with coronary heart disease. Despite this limitation, the conclusions of these trials can probably be extrapolated to other types of surgery.

Recommendation for prophylactic revascularization in stable/asymptomatic patients

Recommendation	Class[a]	Level[b]
Late revascularization after successful non-cardiac surgery should be considered in accordance with ESC Guidelines on stable angina pectoris	IIa	C
Prophylactic myocardial revascularization prior to high-risk surgery may be considered in patients with proven IHD	IIb	B
Prophylactic myocardial revascularization prior to intermediate-risk surgery in patients with proven IHD is not recommended	III	B
Prophylactic myocardial revascularization prior to low-risk surgery patients with proven IHD is not recommended	III	C

[a]Class of recommendation.
[b]Level of evidence.
IHD = ischaemic heart disease.

Type of prophylactic revascularization in patients with stable ischaemic heart disease

Occasionally, patients with stable IHD may require elective surgery, meaning that surgery may be postponed for several months or even up to ≥1 year. There are no solid data to guide a revascularization strategy in this case, and recommendations can therefore only be based on experts' recommendations. Yet, these patients may to some extent be compared with patients who had previous revascularization. It seems therefore reasonable to propose a cardiovascular work-up according to the ESC Guidelines on stable angina pectoris.[47] CABG should be performed to improve prognosis and relieve symptoms in patients with significant left main disease or its equivalent, for significant three-vessel disease, in particular in the case of depressed LV function, as stated in these guidelines. PCI should be performed to improve symptoms in stable symptomatic patients with single or multivessel disease in whom intervention is technically suitable and in whom the procedural risk does not outweigh the potential benefit.[70]

The choice between PCI and CABG, often a matter of debate, will depend on several factors. Recently, the 1 year results of the SYNTAX trial, in which 1800 patients with three-vessel or left main IHD were randomized to undergo CABG or PCI, have been published.[137] They indicate that CABG remains the treatment of choice in these patients but that PCI is a valuable alternative. As mentioned before, current guidelines on the management of stable angina indicate a role for both treatments. Nevertheless, if PCI is performed prior to non-cardiac surgery the use of bare metal stents, in order not to delay surgery unnecessarily, is recommended.

Recommendation on type of prophylactic revascularization in stable patients

Recommendation	Class[a]	Level[b]
It is recommended that PCI or CABG be performed according to the applicable guidelines for management in stable angina pectoris	I	A

[a]Class of recommendation.
[b]Level of evidence.
CABG = coronary artery bypass grafting; PCI = percutaneous coronary intervention.

Revascularization in patients with unstable ischaemic heart disease

No trial has investigated the role of prophylactic revascularization in patients with unstable angina pectoris requiring non-cardiac surgery. Unstable angina pectoris, in particular non-ST-segment elevation ACS, is considered to be a high-risk clinical entity and requires prompt diagnosis, risk stratification, and revascularization. Therefore, as long as the clinical condition for non-cardiac surgery is not life threatening, priority should be given to the diagnosis and proper treatment of unstable angina. In this case, the recent ESC Guidelines on the management of non-ST-segment elevation ACS apply.[69] The cornerstone of treatment includes antiplatelet and anticoagulant therapy, β-blocking agents, and prompt revascularization. Careful attention should be paid to avoiding overt anticoagulation and/or antithrombotic management of unstable coronary patients with concomitant surgical conditions, due to the risk of increased bleeding tendency secondary to the background surgical disease (malignancy, etc.). Except for the previously mentioned well-recognized indications for emergency CABG, most patients undergo PCI. In the exceptional situation of unstable angina and the need for subsequent non-cardiac surgery, preference should again be given to bare metal stents, in order not to delay surgery beyond 3 months.

Recommendations on prophylactic myocardial revascularization in patients with unstable IHD

Recommendations	Class[a]	Level[b]
If non-cardiac surgery can be postponed safely, it is recommended that patients be diagnosed and treated in line with the guidelines on unstable angina management	I	A
In the unlikely combination of a life-threatening clinical condition requiring urgent non-cardiac surgery and ACS, it is recommended that surgery be given priority	I	C
However, on follow-up, aggressive medical treatment and myocardial revascularization according to the guidelines on unstable angina pectoris management is recommended	I	B
If PCI is indicated, the use of bare metal stents or even balloon angioplasty is recommended	I	C

[a]Class of recommendation.
[b]Level of evidence.
ACS = acute coronary syndrome; IHD = ischaemic heart disease; PCI = percutaneous coronary intervention.

Specific diseases

So far, the guidelines have discussed cardiac risk markers and risk reduction strategies. However, patients presenting with specific diseases prior to surgery benefit from an integrated evaluation and management of their disease in the perioperative period. In the following sections the most common cardiovascular diseases are discussed.

Chronic heart failure

The prevalence of chronic heart failure in the adult population in the UK has been estimated to be 1.8%, and this increases with age. In patients >75 years the prevalence is a high as 8.0%.

The predictive value of heart failure for perioperative cardiac events is well recognized and is an important factor of clinical risk indices, such as Goldman's or Detsky's risk score.[31,32] A study evaluating LV function prior to vascular surgery in 1988 found an LV ejection fraction of ≤35% to be an optimal predictor of post-operative cardiac events.[138] In 2008, another study confirmed these findings and concluded that elderly patients with chronic heart failure scheduled for vascular surgery have higher risks of operative mortality and hospital readmission than other patients (including those with IHD) admitted for the same procedure.[139] The prognostic pre-operative value of heart failure with preserved LV ejection fraction is ill defined. Long-term outcome is similar to that of patients with reduced LV ejection fraction.[140] These patients could present an increased cardiovascular risk when undergoing surgery. In the absence of evidence-based studies, the committee recommends similar perioperative management in patients with preserved LV ejection fraction as in patients with a reduced ejection fraction.

The ability to assess myocardial viability during stress testing has allowed further risk stratification of cases with LV dysfunction. As shown in a study of 295 patients with a LV ejection fraction <35% scheduled for vascular surgery, post-operative cardiac events were related to the presence of stress-induced ischaemia and scar tissue.[141] However, there was an inverse relationship to the presence and extent of dysfunctional but viable segments, showing an improved function without signs of ischaemia during inotropic stimulation. Using multivariable analysis, the number of ischaemic segments was associated with perioperative cardiac events (OR per segment 1.6, 95% CI 1.05−1.8), whereas the number of segments with sustained improvement was associated with improved outcome (OR per segment 0.2, 95% CI 0.04−0.7). The stratification using stress testing enables the physician to identify a subgroup of patients with sustained improvement who have a relatively benign post-operative outcome, unlike patients with a predominantly ischaemic response.

Current ESC Guidelines recommend the use of ACE inhibitors (or ARBs in patients intolerant of ACE inhibitors) and β-blockers as primary treatment in chronic heart failure patients, to improve morbidity and mortality.[91] Unless contra-indicated or not tolerated, they should be given in optimal doses in all patients with symptomatic heart failure and an LV ejection fraction ≤40%. Either an ARB or an aldosterone antagonist may subsequently be added, depending on clinical condition and patient characteristics. In all patients with an LV ejection fraction ≤35% who remain severely symptomatic [New York Heart Association (NYHA) functional class III or IV], the addition of a low dose of aldosterone antagonist should be considered (in the absence of hyperkalaemia and significant renal

dysfunction). As an alternative option, addition of an ARB is recommended in heart failure patients with an LV ejection fraction ≤40% who remain symptomatic despite optimal treatment with an ACE inhibitor and β-blocker, unless also taking an aldosterone antagonist. Diuretics are recommended in heart failure patients with signs or symptoms of congestion.

It has been concluded that the perioperative use of ACE inhibitors, β-blockers, statins, and aspirin is independently associated with a reduced incidence of in-hospital mortality in patients with LV dysfunction who are undergoing major non-cardiac vascular surgery.[142] Thus, it is recommended that life-saving therapies in stable heart failure patients be continued up until the surgery and that they be reinstituted post-operatively, as soon as clinical conditions are satisfactory.

The diagnosis of post-operative heart failure is often difficult to make since it often presents atypically and may have a different aetiology compared with the non-surgical setting. The evaluation should include physical examination, ECG, serial biomarker measurements, X-ray, and echocardiography. Special attention should be given to the patient's volume status since high-volume infusion is often needed in the intra- and immediate post-operative setting. In the period after surgery, fluids given during the operation may be mobilized to cause hypervolaemia and even heart failure, if not adequately handled. Fluid overloading may cause decompensation of chronic heart failure or development of de novo acute heart failure. Heart failure may develop perioperatively either immediately after surgery (due to prolonged procedure, myocardial ischaemia, rapid fluid shift) or some days later (due to third-space fluid re-absorption). According to the recent ESC Guidelines on heart failure, an attempt should be made to optimize pharmacological therapy before surgery. This may be of particular importance for β-blockers, which are recommended in the perioperative period in all high-risk patients. To avoid uncontrolled hypotension, routine use of i.v. β-blockers is not recommended. Importantly, if a heart failure patient is not receiving a β-blocker, such therapy should be initiated early enough before elective surgery to ensure optimal dose uptitration.

Once the aetiology of post-operative heart failure is diagnosed, treatment is similar to the non-surgical setting. Patients with heart failure have a significantly higher risk of hospital readmission after surgical procedures. This confirms the need for careful discharge planning and close follow-up, optimally using a multidisciplinary approach.

Arterial hypertension

In general, the presence of arterial hypertension is not considered to be an independent risk factor for cardiovascular complications in non-cardiac surgery. Pre-operative evaluation allows the identification of patients with hypertension, enables a search for target organ damage and evidence of associated cardiovascular pathology to be undertaken, and allows initiation of appropriate therapy. This is particularly important for those with concomitant risk factors.

There is no clear evidence favouring one mode of antihypertensive therapy over another in patients undergoing non-cardiac surgery. Patients with arterial hypertension should be managed according to existing ESC Guidelines.[143] However, in hypertensive patients with concomitant IHD who are at high risk of cardiovascular complications, perioperative administration of β-blockers is recommended. In patients with hypertension, antihypertensive therapy should be continued up to the morning of surgery and

restarted promptly in the post-operative period.[144] In patients with grade 1 or 2 hypertension,[143] there is no evidence that delay in surgery in order to optimize therapy is beneficial. In these cases, antihypertensive medications should be continued during the perioperative period. In patients with grade 3 hypertension (systolic blood pressure ≥180 mmHg and/or diastolic blood pressure ≥110 mmHg), the potential benefits of delaying surgery to optimize the pharmacological therapy should be weighed against the risk of delaying the surgical procedure.[20,144]

Valvular heart disease

Patients with VHD are at higher risk of perioperative cardiovascular complications during non-cardiac surgery.[124] Echocardiography should be performed in patients with known or suspected VHD, to assess its severity and consequences. On the basis of existing data, the following recommendations are particularly applicable in these patients.[20,124]

Recommendation on VHD		
Recommendation	**Class**[a]	**Level**[b]
In the presence of severe VHD it is recommended that a clinical and echocardiographic evaluation be performed and, if needed, treatment before non-cardiac surgery	I	C

[a]Class of recommendation.
[b]Level of evidence.
VHD = valvular heart disease.

Aortic stenosis

Aortic stenosis (AS) is the most common VHD in Europe, particularly among the elderly.[145] Severe AS (defined as aortic valve area <1 cm^2, <0.6 cm^2/m^2 body surface area) constitutes a well established risk factor for perioperative mortality and MI.[146] In the case of urgent non-cardiac surgery in patients with severe AS, such procedures should be performed under haemodynamic monitoring.[124] In the case of elective non-cardiac surgery, the presence of symptoms is a key for decision making.

In symptomatic patients, aortic valve replacement should be considered before elective surgery. In patients who are not candidates for valve replacement either due to high risks associated with serious co-morbidities or those who refuse, non-cardiac surgery should be performed only if is essential. In these patients, balloon aortic valvuloplasty or transcatheter valve implantation may be a reasonable therapeutic option before surgery.[124,147]

In asymptomatic patients, non-cardiac surgery of low to intermediate risk can be safely performed. If high-risk surgery is planned, further clinical assessment is necessary for aortic valve replacement. In those at high risk for aortic valve replacement, elective surgery under strict haemodynamic monitoring should be performed only if strictly needed. In the remaining patients, aortic valve replacement should be considered as the initial procedure.[124]

Mitral stenosis

Non-cardiac surgery can be performed at relatively low risk in patients with non-significant mitral stenosis (MS) (valve area >1.5 cm^2) and in

asymptomatic patients with significant MS (valve area <1.5 cm^2) and systolic pulmonary artery pressure <50 mmHg. Pre-operative surgical correction of MS in these patients is not indicated. It needs to be remembered that control of heart rate is essential to avoid tachycardia, which may cause pulmonary oedema. Strict control of fluid overload is also important. Also development of AF may cause serious clinical deterioration.[20,124] With the high risk of embolism, anticoagulation control is important. In asymptomatic patients with significant MS and systolic pulmonary artery pressure >50 mmHg and in symptomatic patients, the risk related to the non-cardiac procedure is significantly higher, and these patients may benefit from percutaneous mitral commissurotomy (or open surgical repair) particularly before high-risk surgery.[20,124]

Aortic regurgitation and mitral regurgitation

Non-significant aortic regurgitation (AR) and mitral regurgitation (MR) do not independently increase the risk of cardiovascular complications during non-cardiac surgery. In asymptomatic patients with severe AR and MR (detailed classification presented in the ESC Guidelines[124]) and preserved LV function, non-cardiac surgery can be performed without additional risk. Symptomatic patients and those who are asymptomatic with severely impaired LV ejection fraction (<30%) are at high risk of cardiovascular complications, and non-cardiac surgery should be performed only if necessary.[124] Patients with severe MR and AR may benefit from optimization of pharmacological therapy to produce maximal haemodynamic stabilization before high-risk surgery.

Patients with prosthetic valve(s)

Patients who have undergone surgical correction of VHD and have a prosthetic valve can undergo non-cardiac surgery without additional risk, when there is no evidence of valve or ventricular dysfunction. In these patients, endocarditis prophylaxis is recommended and a modification of the anticoagulation regimen needs to be considered in the perioperative period, with oral anticoagulants being temporarily replaced by i.v. UFH, s.c. UFH, or s,c LMWH at therapeutic doses.

Prophylaxis of infective endocarditis

In patients with VHD and those with prosthetic valves who are undergoing non-cardiac surgery at risk of bacteraemia, antibiotic prophylaxis against infective endocarditis should be initiated. This issue is discussed in detail in the ESC and AHA guidelines.[148,149]

Arrhythmias

The occurrence of perioperative arrhythmias has been reported in 70% of patients subjected to general anaesthesia for various surgical procedures.[150,151] The incidence has been reported to vary from 16 to 62% with intermittent ECG monitoring[152] and 89% with continuous Holter monitoring.[153]

Ventricular arrhythmias

Almost half of all high-risk patients undergoing non-cardiac surgery have frequent ventricular premature beats (VPBs) or non-sustained VT. There is no evidence that VPBs or non-sustained VTs alone are associated with a worse prognosis. ACC/AHA/ESC Guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death recommend approaches based on large clinical trials.[154] Regardless of the cause, sustained monomorphic ventricular tachycardia (SMVT) with serious haemodynamic compromise must be treated promptly with electric cardioversion.[154] I.v. amiodarone can be used for initial treatment of patients with stable SMVT.[154] It is also reasonable in patients with SMVT that is haemodynamically unstable, refractory to conversion with countershock, or recurrent despite other agents. In sustained polymorphic ventricular tachycardia (SPVT), if haemodynamic compromise is present, immediate electrical cardioversion should be performed. β-Blockers are useful for patients with recurrent SPVT, especially if ischaemia is suspected or cannot be excluded. Amiodarone is reasonable for patients with recurrent SPVT in the absence of long QT syndrome (LQTS).[154] Torsades de Pointes rarely occurs, and withdrawal of any offending drugs and correction of electrolyte abnormalities are recommended. Management with magnesium sulfate is reasonable for patients with Torsades de Pointes and LQTS. β-Blockade combined with pacing is suggested in patients who have Torsades de Pointes and sinus bradycardia. Isoproterenol is recommended in patients with recurrent pause-dependent Torsades de Pointes who do not have congenital LQTS.[154] In the event of perioperative pulseless VT or ventricular fibrillation, immediate defibrillation is required.

Supraventricular arrhythmias

A greater number of patients undergoing non-cardiac surgery may suffer from SVT and AF compared with ventricular arrhythmias.[153–158] Sympathetic activity is the primary autonomic mechanism responsible for the trigger of AF.[159] Vagal manoeuvres may terminate SVT in some cases and these arrhythmias respond well to treatment with adenosine. When SVT is refractory to adenosine, effective therapy for termination of the arrhythmia includes a short-acting β-blocking agent or a non-dihydropyridine calcium channel blocker (diltiazem and verapamil) or amiodarone i.v.[160–162] Verapamil should be used with care because of its negative inotropic effect. The use of calcium channel blockers is not recommended in pre-excited SVT/AF. For perioperative AF, the goal of management is ventricular rate control.[163] β-Blockers and non-dihydropyridine calcium channel blockers (diltiazem and verapamil) are the drugs of choice for the rate control in AF. Digoxin may be used as a first-line drug only in patients with chronic heart failure, since it is not effective in high adrenergic states such as surgery. β-Blockers have been shown to accelerate the conversion of AF to sinus rhythm after non-cardiac surgery.[164] In several studies, the pre-operative administration of β-blockers was associated with better control of arrhythmias.[165,166]

Bradyarrhythmias

Severe perioperative bradyarrhythmias requiring treatment have been reported in 0.4% of 17 021 patients, 6.4% of whom were American Association of Anaesthesiologists physical status 3 or 4.[151] These patients were monitored with routine intraoperative and early post-operative ECG monitoring. In general, perioperative bradyarrhythmias respond well to short-term pharmacological therapy, non-invasive transoesophageal atrial pacing in

anaesthetized individuals, or non-invasive transcutaneous pacing in awake or anaesthetized patients.[160] Temporary cardiac pacing is rarely required, even in the presence of pre-operative asymptomatic bifascicular block or left bundle branch block.[167] The indications for temporary pacemakers during the perioperative period are generally the same as those for permanent pacemakers.[168] Asymptomatic bifascicular block, with or without first degree atrio-ventricular block, is not an indication for temporary endocardial pacing.[169,170]

Pacemaker/implantable cardioverter defibrillator

The use of unipolar electrocautery represents a significant risk to pacemaker-dependent patients. The electrical stimulus from electrocautery may inhibit demand pacemakers or may reprogramme the pacemaker. However, these problems can be avoided by positioning the ground plate for the electrical circuit, such that the electrical current travels away from the generator. Keeping the electrocautery device away from the pacemaker, giving only brief, bursts and using the lowest possible amplitude may decrease the interference. In many studies, the authors recommended setting the pacemaker in an asynchronous or non-sensing mode in patients who are pacemaker dependent and whose underlying rhythm is unreliable, and interrogating the device after surgery to ensure appropriate programming and sensing pacing thresholds.[171–174] Interference with implantable cardioverter defibrillator function can also occur during non-cardiac surgery as a result of electrical current generated by electrocautery.[175,176] The implantable cardioverter defibrillator should be turned off during surgery and switched on in the recovery phase before discharge to the ward. In addition, it is recommended that written instructions regarding the responsibility for surveillance and restarting of the implantable cardioverter defibrillator should be available.

Recommendations on ventricular arrhythmias

Recommendations	Class[a]	Level[b]
Anti-arrhythmic drugs are recommended for patients with recurrent sustained VT	I	B
Continuation of amiodarone and β-blockers before surgery is recommended	I	C
It is recommended that wide QRS tachycardia be considered to be VT if the diagnosis is unclear	I	C
Prompt electrical cardioversion in patients with sustained VT with haemodynamic compromise is recommended	I	C
Anti-arrhythmic drugs for initial treatment of patients with stable sustained monomorphic VT should be considered	IIa	B
Anti-arrhythmic drugs for patients with non sustained VT are not recommended	III	B
Anti-arrhythmic drugs for patients with VPBs are not recommended	III	A

[a]Class of recommendation.
[b]Level of evidence.
VPB = ventricular premature beat; VT = ventricular tachycardia.

Recommendations on supraventricular arrhythmias

Recommendations	Class[a]	Level[b]
Ventricular rate control is recommended in patients with AF without haemodynamic instability	I	A
Continuation of oral anti-arrhythmic drugs before surgery is recommended	I	C
Electrical cardioversion when haemodynamic instability occurs is recommended	I	C
Vagal manoeuvres and anti-arrhythmic therapy for termination of SVT in haemodynamic stable patients is recommended	I	C

[a]Class of recommendation.
[b]Level of evidence.
AF = atrial fibrillation; SVT = supraventricular tachycardia.

Recommendations on implantable devices

Recommendations	Class[a]	Level[b]
Interrogation of implantable devices pre-operatively and post-operatively is recommended	I	C
It is recommended that the hospital management state who is responsible for programming the devices before and after surgery	I	C

[a]Class of recommendation.
[b]Level of evidence.

Renal disease

Reduced kidney function is an independent risk factor for adverse post-operative cardiovascular outcomes including MI, stroke, and progression of heart failure. In most risk indices, renal function is taken into account. Traditionally, this function is assessed by serum creatinine concentration. For example, the serum creatinine cut-off value of >2.0 mg/dL (177 μmol/L) is used in the Lee index.[5] However, estimated creatinine clearance (mL/min) incorporating serum creatinine, age, and weight provides a more accurate assessment of renal function than serum creatinine alone. Most commonly used is the Cockcroft–Gault formula {[(140 − age in years) × (weight in kg)]/[72 × serum creatinine in mg/dL]} × (0.85 for females).[177] An evaluation of 852 subjects undergoing major vascular surgery demonstrated an increase in mortality when serum creatinine was >2.0 mg/dL with an OR for perioperative mortality of 5.2, 95% CI 2.9–10.8.[178] However, it might be argued that patients with less pronounced renal insufficiency also do worse compared with patients with normal serum creatinine values. A 10 mL/min decrease in creatinine clearance was associated with a 40% increased risk of post-operative mortality (OR 1.4, 95% CI 1.2–1.5; ROC area: 0.70, 95% CI 0.63–0.76). ROC curve analysis showed that the cut-off value of 64 mL/min for creatinine clearance yielded the highest sensitivity/specificity to predict post-operative mortality.[178]

In addition to the pre-operative renal function, worsening of function after surgery is a prognostic factor for adverse late outcome. In 1324 patients who underwent elective open AAA surgery, creatinine clearance was measured pre-operatively and on days 1, 2, and 3 after surgery.[179] Patients were divided into three groups according to the change in renal function after surgery compared with baseline. Group 1 showed an improved or no change (change in creatinine clearance, ± 10% of function compared with baseline); group 2 showed a temporary worsening (worsening >10% at day 1 or 2, then complete recovery within 10% of baseline at day 3); and group 3 experienced a persistent worsening (>10% decrease compared with baseline). Mortality during 30 days after surgery was 1.3, 5.0, and 12.6% in groups 1, 2, and 3, respectively. Adjusted for baseline characteristics and post-operative complications, 30-day mortality was highest in patients with persistent worsening of renal function (HR 7.3, 95% CI 2.7–19.8), followed by those with temporary worsening (HR 3.7, 95% CI 1.4–9.9). During 6.0 ± 3.4 years of follow-up, 348 patients (36.5%) died. The risk of late mortality was 1.7 (95% CI 1.3–2.3) in the persistent worsening group followed by those with temporary worsening (HR 1.5, 95% CI 1.2–1.4). This study showed that, although renal function may recover completely after aortic surgery, temporary worsening of renal function was associated with an increased long-term mortality.[179]

Identification of patients who might experience perioperative worsening of renal function is important in order to initiate supportive measures such as maintenance of adequate intravascular volume for renal perfusion and vasopressor use. In a large retrospective study, risk factors for post-operative acute renal failure within the first 7 days after major non-cardiac surgery among patients with previously normal renal function were evaluated.[180] Thirty-day, 60-day, and 1-year all-cause mortality was also assessed. A total of 65 043 cases throughout 2003 and 2006 were reviewed. Of these, 15 102 patients met the inclusion criteria; 121 patients developed acute renal failure (0.8%), and 14 required renal replacement therapy (0.1%). Seven independent pre-operative predictors were identified (P <0.05): age, emergency surgery, liver disease, high body mass index, high-risk surgery, peripheral arterial occlusive disease, and COPD necessitating chronic bronchodilator therapy.

Contrast-induced nephropathy, caused by renal hypoperfusion and direct tubular toxicity, occurs in up to 15% of patients with chronic renal dysfunction undergoing radiographic procedures.[181] Between 0.5 and 12% of these patients require haemodialysis and prolonged hospitalization. A considerable number of patients experience worsening of renal function, possibly progressing to end-stage renal failure. The cornerstone of prevention consists of periprocedural hydration and antioxidant drugs. Recently, three randomized studies have compared the effects of sodium bicarbonate vs. isotonic saline in humans, resulting in an impressive reduction in contrast nephropathy in the sodium bicarbonate group, with an incidence <2%.[182] These results were recently evaluated in an adequately powered randomized trial comparing the efficacy of hydration with sodium bicarbonate vs. isotonic saline in addition to oral N-acetylcysteine for prophylaxis of contrast-induced nephropathy in a population of patients with chronic kidney dysfunction undergoing planned coronary angiography or intervention. A total of 502 patients with an estimated creatinine clearance <60 mL/min were randomized to receive infusion of either saline (0.9% NaCl) or sodium bicarbonate before and after administration of contrast medium on top of N-acetylcysteïne orally (600 mg b.i.d.).[183] Treatment with isotonic saline consisted of 1 mL/kg/h 0.9% sodium chloride for 12 h before and after the procedure, and treatment with sodium bicarbonate (154 mEq/L in dextrose and water) consisted of 3 mL/kg for 1 h before the contrast medium, followed by an infusion of 1 mL/kg/h for 6 h after the procedure. Contrast-induced nephropathy was defined as an absolute increase in serum creatinine ≥0.5 mg/dL measured within 5 days after contrast exposure. No difference was observed between the two study groups; contrast-induced nephropathy occurred in 54 patients (10.8%); 25 (10%) were treated with sodium bicarbonate and 29 (11.5%) with saline (P = 0.60). Thus, hydration with sodium bicarbonate plus oral N-acetylcysteine before contrast medium exposure was no more effective than hydration with isotonic sodium chloride plus oral N-acetylcysteine for prophylaxis of contrast-induced nephropathy in patients with moderate renal dysfunction. The discrepancies among randomized studies might be explained by differences in the concomitant use of N-acetylcysteine, use of contrast medium, or baseline renal dysfunction among randomized patients. Sodium bicarbonate requires only 1 h of pretreatment and may represent an option in patients scheduled for urgent agent injection or for outpatient procedures.

Recommendation/statement for renal function		
Recommendation/statement	Class[a]	Level[b]
It is recommended that pre-operative renal function be considered as an independent cardiac risk factor for perioperative and long-term prognosis	I	B
For patients at risk of developing contrast-induced nephropathy (CIN), hydration with isotonic sodium chloride (with or without oral N-acetylcysteine) for prophylaxis of CIN is recommended prior to cardiac imaging procedures that are involved with administration of contrast medium injection (e.g. coronary and/or peripheral angiography)	I	B

[a]Class of recommendation.
[b]Level of evidence.

Cerebrovascular disease

Cerebrovascular disease is the third leading cause of death in Western countries, with ~500 TIAs and 2400 new strokes per million inhabitants. One-third of new stroke patients die within 1 year, and <50% make a full recovery and regain independence. An increasing number of elderly patients are referred for non-cardiac surgery, including those with concomitant vascular diseases affecting the cerebral circulation. Risk factors for perioperative symptomatic or asymptomatic transient or permanent cerebrovascular events (TIA/stroke) are embolism or haemodynamic compromise in large (aorta, carotid, vertebral, and main cerebral arteries intracranially) or small vessels (perforating

and penetrating arterioles and capillaries). Although fatal and non-fatal stroke can be reduced significantly in symptomatic patients with moderate/severe carotid stenosis associated with ipsilateral symptoms, in particular if treated early (2–4 weeks, but at least within 3–6 months after the onset of symptoms), the benefit of this interventional/surgical treatment is smaller in neurologically asymptomatic subjects. Thus medical measures to prevent stroke are of utmost general importance and include a multifaceted strategy aimed at control of hypertension, hyperlipidaemia, diabetes, etc. The usefulness of specific antiplatelet agents or anticoagulants has been demonstrated in many randomized controlled trials for primary and secondary prevention, and may even be increased in elderly subjects undergoing non-cardiac surgery and anaesthesia.[184]

Apart from stroke and TIA, transient or permanent changes in mental status characterized by disturbances of attention, orientation, memory dysfunction, illusions, hallucinations, aphasia, etc. (the key diagnostic features of delirium) may occur, including anxiety and depression, which are often under-recognized or misdiagnosed. They may be due to perioperative medication, surgery itself, intraoperative hypo- or hypertension, and cerebral microembolism causing multiple small vessel occlusion and ischaemia, evidenced by transcranial Doppler and MRI diffusion-weighted imaging. In cardiac surgery, mental changes are common and may be associated with transient and occasionally even permanent cognitive dysfunction (25–30%). It is very likely that they also occur in the elderly high-risk patient undergoing non-cardiac surgery.

Current concepts of perioperative stroke are summarized in three major reviews[185–187] which compare the incidence of stroke for various surgical procedures (0.08–0.07% in general surgery, 1–5% in peripheral and carotid surgery, and 2–10% in cardiac surgery). Contrary to common belief, most strokes are not related to hypoperfusion, but occur mainly in the presence of an intact cerebral autoregulation.[187] Ischaemic and embolic mechanisms are far more common than haemodynamic compromise. Delayed stroke is mainly attributed to various sources of cardiac embolism, followed by hypercoagulability and increased risk of thrombogenic events. Many strokes remain undiagnosed because of a lack of major sensory–motor symptoms or the presence of only subtle neuropsychological deficits, which are more difficult to identify. Several patient- and procedure-related factors are associated with an increased risk of perioperative stroke—they should be investigated carefully to evaluate the individual risk/benefit ratio and optimize care, including appropriate risk modification and timing of surgery. A history of recent stroke or TIA is the strongest predictor for perioperative stroke and should be identified after evaluating the history and the neurological status of each patient. In such cases, and if in doubt, additional brain and vascular images are recommended. In patients with both carotid and cardiac disease, death rates from cardiac causes exceed the risk of stroke; a review of the literature from 1970 to 2000 showed that patients with significant asymptomatic carotid stenosis are at high risk for fatal and non-fatal cardiac events (8%/year), but not for stroke (1–2%/year).[96] However, the overall perioperative stroke risk tends to be overstated. There is no evidence-based recommendation to treat carotid stenosis prior to non-cardiac surgery, but there are exceptional cases prior to cardiac surgery.

Discontinuation of warfarin or antiplatelet agents in anticipation of surgery exposes patients to an increased risk of perioperative stroke. A review of perioperative outcome in patients requiring warfarin showed 0.6% thromboembolic events in those who continued therapy vs. 7.0% in patients who received i.v. heparin as bridging therapy.[188] Whether this is due to insufficient control or dosage of heparin administration is uncertain. In knee or hip replacement, continued use of moderate dose warfarin therapy during the perioperative period was safe and effective and was similar to patients undergoing dental procedures, cataract surgery, and diagnostic endoscopy without interrupting their antiplatelet agents or oral anticoagulants regimen. Lengthy operations are associated with higher risks for perioperative stroke; the choice of surgical technique is also important and the types of anaesthesia and anaesthetic agents require additional consideration. Optimal selection of individually guided best levels of blood pressure during surgery and thereafter, as well as management of the patient's body temperature and control of blood glucose, are suggested to reduce rates of incidental stroke and death. Pre-, intra-, and post-operative use of antiplatelet agents is useful. Whether or not so-called neuroprotective agents are needed is a matter of controversy.

Recommendations on stroke/transient ischaemic attack (TIA)

Recommendations	Class[a]	Level[b]
If carotid stenosis is >70%, additional therapy such as antiplatelet therapy and/or surgery is recommended	I	A
Routine pre-operative screening for symptomatic or asymptomatic carotid stenosis may be considered	IIb	C

[a]Class of recommendation.
[b]Level of evidence.

Pulmonary disease

The co-existence of pulmonary disease in patients having non-cardiac surgery may increase the risk of operation. Such diseases include acute respiratory infections, COPD, asthma, cystic fibrosis, interstitial lung disease, and other conditions causing impairment of respiratory function. Pre-existing pulmonary disease has a significant impact on perioperative risk, but the most common effect is to increase the risk of post-operative pulmonary complications. These complications are mainly a consequence of the development of atelectasis during general anaesthesia. Post-operative shallow breathing, reduced lung expansion,and other factors may cause the lung collapse to persist and promote respiratory infection. These complications occur especially after abdominal or thoracic surgery, and the risk seems to be increased in smokers. Specific perioperative management is required to reduce the risks of pulmonary complications. There are some

respiratory conditions which are associated with cardiovascular abnormalities and which may require special cardiac risk assessment and management in addition to dealing with pulmonary complications *per se*. Two such conditions are COPD and pulmonary arterial hypertension (PAH).

COPD, defined as airways obstruction which is not completely reversible, is well recognized as a major cause of morbidity and mortality. The prevalence of COPD in adults in Europe has been found to vary between ~5 and 10%, with rates tending to be higher in males than females. Thus, up to one in 10 patients having non-cardiac surgery may have COPD.

Cor pulmonale with right heart failure is a direct complication of severe COPD. However, COPD is also associated with an increased risk of coronary heart disease. In a systematic review of 12 population cohort studies, those with a reduced forced expiratory volume in 1 s (FEV_1) had a 75% increased risk of cardiovascular mortality compared with those with a normal FEV_1.[189] Reduced expiratory flow has also been associated with a higher incidence of non-fatal coronary heart disease and stroke, carotid stenosis, low ankle–brachial index, and cerebral white matter lesions. These associations occur in both men and women and, despite a strong relationship of smoking with both COPD and CVD, are independent of traditional cardiovascular risk factors. For every 10% decrease in FEV_1, cardiovascular mortality increases by ~30% and non-fatal coronary events by ~20%.

In patients undergoing aortic aneurysm repair, conflicting results have been found with short-term mortality (often due to cardiac complications). For example, COPD has been associated with operative death, but not 30-day mortality. In vascular surgery patients as a whole, COPD has not been associated with increased 30-day mortality. Thus, despite an association with CVD, there is no convincing evidence that COPD is related to a higher risk of perioperative cardiac complications.

PAH may be idiopathic, due to congenital heart disease, familial, or associated with specific conditions such as collagen vascular disease. It must be distinguished from other causes of PAH due to COPD, thromboembolism, and congenital disease. The diagnosis is based on a mean arterial pulmonary pressure of >25 mmHg at rest and a pulmonary wedge pressure of ≤15 mmHg. In surveys in Europe, the prevalence has varied between about 15 and 50 cases per million adults. Half the cases were idiopathic. The prevalence is thus low and consequently the condition is uncommon in surgical practice.

PAH increases surgical complications, especially right ventricular failure, myocardial ischaemia, and post-operative hypoxia. In patients having cardiopulmonary bypass surgery, a mean pre-operative arterial pressure >30 mmHg is an independent predictor of mortality. In a study of patients with pulmonary hypertension undergoing non-cardiac surgery, of whom over half had PAH, outcome predictors included NYHA functional class ≥II, intermediate- to high-risk surgery, right ventricular function, and duration of anaesthesia.[190] There is a need for further research on factors predicting poor outcomes. However, the study above did confirm that such patients are at high risk, the perioperative cardiopulmonary complication rate being 38% and mortality 7%.

Pre-existing COPD is often considered in terms of the risk of post-operative pulmonary complications. For perioperative cardiac risk, the lack of convincing evidence that COPD increases risk may have arisen because in COPD patients extra care was taken with cardiac management, thus negating any association. Nevertheless, COPD has not been included in pre-operative cardiac risk indices, such as Goldman, Detsky, and Lee and, indeed, no improvement was found in the prognostic value of the Lee index in vascular surgery patients when COPD was included.[191] For PAH, on the other hand, the condition is so uncommon that its inclusion in an integrated risk model has not been considered.

In patients with pulmonary disease having non-cardiac surgery, the treatment goals pre-operatively are to optimize pulmonary function and minimize respiratory complications. For COPD, treatment goals would include eliminating active infection with antibiotics; minimizing wheeze associated with any reversible disease using inhaled bronchodilators or steroids; reducing right and LV failure with diuretics; ensuring adequate oxygenation; and, finally, encouraging smoking cessation prior to surgery. In relation to perioperative cardiac management, patients with COPD should be managed in the same way as those without COPD and, in particular, there are no special contra-indications to the use of cardioselective β-blockers or statins in COPD patients.[93,192]

PAH is incurable and the treatment goal is to reduce symptoms, and improve exercise capacity and right ventricular function. Anaesthesia and surgery may be complicated by acute right heart failure due to increase of pulmonary vascular resistance related to the impairment of lung ventilation, typical of the operative and post-operative state of thoracic and abdominal surgery. Specific drug therapy for PAH includes calcium channel blockers (only for the few patients who are responders to the acute vasoreactivity test), prostanoids, endothelin receptor antagonists, and phosphodiesterase type-5 inhibitors.[143,193] Ideally, patients with PAH should have an optimized treatment regimen before any surgical intervention. It is recommended also that PAH-specific drug therapy is not withheld for >12 h due to the perioperative fasting state. In case of progression of right heart failure in the post-operative period, it is recommended that the diuretic dose be optimized and, if necessary, that inotropic support with dobutamine be initiated. The role of starting new specific PAH drug therapy in the perioperative period has not been established. In the case of severe right heart failure, not responsive to supportive therapy, the administration of temporary inhaled nitric oxide or i.v. epoprostenol with the guidance of a physician experienced in the treatment of PAH may be indicated. In this case, a period of progressive weaning from these medications may be required.

Patients with COPD and PAH have a relatively high frequency of heart failure and coronary heart disease. There is no consistent evidence indicating that COPD patients are at higher risk of perioperative cardiac complications and death, so that they can be managed in the same way as patients without COPD. On the other hand, PAH increases perioperative risk, and requires pre-operative assessment and, if severe, perioperative treatment.

Recommendations on pulmonary diseases

Recommendations	Class[a]	Level[b]
It is recommended that patients with pulmonary arterial hypertension have an optimized treatment regimen before any surgical intervention	I	C
In case of progression of right heart failure in the post-operative period of patients with pulmonary arterial hypertension, it is recommended the diuretic dose be optimized and if necessary that inotropic support with dobutamine be initiated	I	C
In the case of severe right heart failure not responsive to supportive therapy the temporary administration of inhaled nitric oxide or i.v. epoprostenol may be considered with the guidance of a physician experienced in the treatment of pulmonary arterial hypertension	IIb	C
Special perioperative cardiac risk management for patients with COPD is not recommended	III	C

[a]Class of recommendation.
[b]Level of evidence.
COPD = chronic obstructive pulmonary disease.

Perioperative monitoring

Electrocardiography

Although even a single post-operative ECG demonstrating ischaemia in the recovery room is predictive of a major cardiac complication later during the hospital stay, ECG monitoring alone is not adequate to detect ischaemia in real time in the intensive care unit (ICU) and intraoperative settings.[194–196] Specifically, conventional visual ECG monitoring for the detection of transient ST-segment changes is inaccurate.[196] Although lead V_5 has been known as the best choice for the detection of intraoperative ischaemia for many years,[197,198] one study found that lead V_4 was more sensitive and appropriate than lead V_5 for detecting prolonged post-operative ischaemia and infarction.[199] Leads are not specific for ischaemic events, and, furthermore, ischaemic events are dynamic and may not always appear in the same lead. If a single lead is used for monitoring, there is an increased risk of missing ischaemic events. With the use of selected lead combinations, more ischaemic events can be precisely diagnosed in the intraoperative setting. In one study, although the best sensitivity was obtained with lead V_5 (75%), followed by lead V_4 (61%), combining leads V_4 and V_5 increased the sensitivity to 90%.[198] In the same study, when three leads (II, V_4, and V_5) were used simultaneously, the sensitivity increased to 96%.[198] Similarly, in another study in which two or more pre-cordial leads were used, the sensitivity of ECG monitoring was >95% for detection of perioperative ischaemia and infarction.[199] It was also shown that ECG monitoring with fewer leads (as few as three leads) had lower sensitivity than monitoring with 12 leads, and there was a statistically significant association, independent of perioperative troponin values,

between perioperative ischaemia on a 12-lead ECG and long-term mortality.[200–202] Thus, 12-lead ECG monitoring is recommended especially with high-risk patients.

ST-segment monitoring has been shown to be limited in patients who have intraventricular conduction defects (e.g. left bundle branch block) and ventricular paced rhythms.[203] The secondary ST–T changes, which were present in these patients, were due to abnormal depolarization, which also distorted the repolarization process. The distorted ST-segments can limit the sensitivity of the ST-segment monitoring system.[203] Because detection of ST-segment changes of the electrocardiogram by visual inspection is poor, computerized analysis has become standard in modern monitors. Continuous automated ST trending monitors are included in most new operating room ECG monitors to facilitate ischaemia detection. Such devices increase the sensitivity of ECG ischaemia detection.[196] In one study, Holter recordings were used as the reference standard for detection of intraoperative ischaemia, and the ST trending monitors were found to have overall sensitivity and specificity of 74 and 73%, respectively. Several conditions contributed to the inaccuracy of ST trend monitoring, and additional modification of their performance was necessary to achieve better agreement with the Holter analysis.[196]

In a series of studies during the past decade, the presence of ECG changes during monitoring in high-risk cohorts has been linked to a higher incidence of perioperative MI and cardiac events. In addition, the duration of ST-segment changes positively correlates with the incidence of perioperative MI.[204] Therefore, when ST-segment changes occur, the clinician should assume that myocardial ischaemia is present.[205] However, it is not clear if ECG monitoring is sufficiently sensitive to identify patients at low risk.[206,207] In addition, the usefulness of this test in the general population is limited because many studies have excluded patients with ECG findings that preclude accurate evaluation of ischaemia.

Recommendations on 12-lead ECG monitoring

Recommendations	Class[a]	Level[b]
12-lead ECG monitoring is recommended for all patients undergoing surgery	I	C
Selected lead combinations for better ischaemia detection in operation room should be considered	IIa	B

[a]Class of recommendation.
[b]Level of evidence.
ECG = electrocardiography.

Transoesophageal echocardiography

Transoesophageal echocardiography (TOE) has frequently been used as a monitoring tool during cardiac surgery since the mid 1980s. However, few evidence-based data support TOE use in non-cardiac surgery. TOE has several advantages over alternative monitoring methods, such as the use of a pulmonary artery catheter. It is rapidly available, relatively non-invasive, and provides more versatile and comprehensive information. However, although TOE is in general a safe procedure, serious adverse events can

occur. The complication rates relate to the experience of the operator and the presence of severe oesophageal or gastric diseases. Specific training of users is mandatory to avoid inaccurate interpretation.

Myocardial ischaemia can be identified by abnormalities in regional wall motion and thickening. The concordance between intraoperative TOE and ECG is rather weak.[208] Both ST-segment changes and regional wall motion abnormalities can be present in the absence of acute ischaemia. Wall motion abnormalities may be difficult to interpret in the presence of left bundle branch block, ventricular pacing, AF, or right ventricular overload. The resolution of ischaemia is not necessarily detectable if ischaemia is followed by myocardial stunning. Episodes of new or worsened wall motion abnormalities have been shown to be relatively infrequent (20%) in high-risk patients undergoing non-cardiac surgery.[208] They were more common in patients submitted to aortic vascular surgery. Episodes were poorly correlated with post-operative cardiac complications.[208]

When compared with pre-operative clinical data and intraoperative monitoring using 2-lead ECG, routine monitoring for myocardial ischaemia with TOE or 12-lead ECG during non-cardiac surgery has little incremental clinical value in identifying patients at high risk of perioperative ischaemic outcomes.[209]

Recommendations on intraoperative and/or perioperative transoesophageal echocardiography for detection of myocardial ischaemia

Recommendations	Class[a]	Level[b]
The use of TOE should be considered in patients who develop ST-segment changes on intraoperative or perioperative ECG monitoring	IIa	C
The use of TOE may be considered in patients at high risk of developing myocardial ischaemia who undergo major non-cardiac surgery	IIb	C

[a]Class of recommendation.
[b]Level of evidence.
ECG = electrocardiography; TOE = transoesophageal echocardiography.

TOE is recommended if acute and severe haemodynamic instability or life-threatening abnormalities develop during or after surgery.[210] The main advantage of TOE over pulmonary artery catheterization is the more comprehensive evaluation of cardiac structure and function. Information is quickly available on regional or global, right and/or LV dysfunction, the presence of tamponade or cardiac thrombi, and preload estimation through the measurement of end-diastolic volume. Numerous indices of ventricular and atrial function have been proposed. However, most parameters are load dependent.

The role of TOE for haemodynamic monitoring in patients at risk is more controversial. Automated analysis systems exist but are not yet sufficiently validated. There is no evidence that haemodynamic monitoring by TOE accurately stratifies risk or predicts outcome.

TOE can be useful in the operating room in patients with severe valvular lesions. The loading conditions during general anaesthesia

differ from those present in the pre-operative evaluation. Functional and ischaemic mitral regurgitation are usually reduced during general anaesthesia. Organic mitral regurgitation can, conversely, increase. In the setting of severe mitral regurgitation, the LV ejection fraction overestimates LV function, and other parameters may be more accurate, such as myocardial velocities or deformation obtained by tissue Doppler imaging or 2D speckle tracking, an angle-independent method. These are promising techniques, but more validation is needed before they can be used routinely in this setting. In patients with severe aortic stenosis, appropriate preload is important during surgery. Monitoring of LV end-diastolic volume may be more accurate than that of pulmonary capillary pressure. An appropriate heart rate is crucial in patients with mitral stenosis and aortic regurgitation: a long diastolic period in the former and shorter duration of diastole in the latter. When inappropriate control of heart rate occurs, the consequences should be assessed: changes in transmitral mean gradient and pulmonary arterial pressures in mitral stenosis and changes in LV volumes and indices of LV function in aortic regurgitation.

Recommendations on intraoperative and/or perioperative transoesophageal echocardiography in patients with or at risk of haemodynamic instability

Recommendations on intraoperative and/or perioperative TOE in patients with or at risk of haemodynamic instability	Class[a]	Level[b]
TOE is recommended when acute sustained severe haemodynamic disturbances develop during surgery or in the perioperative period	I	C
TOE monitoring may be considered in patients at increased risk of significant haemodynamic disturbances during and after major non-cardiac surgery	IIb	C
TOE monitoring may be considered in patients who present severe valvular lesions during major non-cardiac surgical procedures accompanied by significant haemodynamic stresses	IIb	C

[a]Class of recommendation.
[b]Level of evidence.
TOE = transoesophageal echocardiography.

Right heart catherization

Most post-operative ischaemic episodes are silent and not accompanied by changes in pulmonary capillary wedge pressure. Right heart catheterization is not recommended for monitoring patients with intraoperative ischaemia. Indeed, both a large observational study and a randomized multicentre clinical trial did not show a benefit associated with the use of right heart catheterization after major non-cardiac surgery.[211,212] A case−control analysis was carried out on a subset of patients from the observational study who underwent pulmonary artery catheter placement and who were matched with a similar number of patients who did not undergo right heart catheterization. Patients, who were adjusted for surgical procedure and propensity of catheterization,

demonstrated a higher incidence of post-operative heart failure and non-cardiac events in the group submitted to catheterization.[211]

In the randomized study, no difference in mortality and hospital duration was found, but patients submitted to right heart catheterization had a higher incidence of pulmonary embolism.[212]

Disturbed glucose metabolism

Diabetes mellitus is an important risk factor for perioperative cardiac complications and death. This condition promotes atherosclerosis, endothelial dysfunction, and activation of platelets and proinflammatory cytokines. Surgical stress is associated with haemodynamic stress and vasospasm and further enhances the prothrombotic state, while inhibiting fibrinolysis. This may lead to instability of pre-existing coronary plaques, thrombus formation, vessel occlusion, and MI. Also, hyperglycaemia in the absence of established diabetes plays an important role, emphasizing the need for pre-operative management of hyperglycaemia where possible. This is illustrated by studies on patients with pre-diabetes glucose levels who undergo non-cardiac vascular or non-vascular surgery, showing ~2- to 4-fold increases in risk of myocardial ischaemia, troponin release, 30-day and long-term cardiac events, and risk of death or cardiovascular mortality in particular.[213,214] Importantly, impaired glucose tolerance is often identified only after glucose loading. Critical illness is another condition characterized by disturbed glucose homeostasis ('stress diabetes' or 'diabetes of injury'), which develops independent of previously diagnosed diabetes and has repeatedly been identified as an important risk factor for morbidity and/or mortality.

Data from the International Diabetes Foundation reveal a high and increasing prevalence of diabetes in Europe, rising from 7.8% in 2003 to 8.4% in 2007, with an estimated prevalence of at least 9.1% by 2025.[215] More than 30% of the cases were previously undiagnosed, pointing to underestimation of the problem. With ~48 million people affected, diabetes has become one of the main causes of morbidity and mortality in Europe. According to the World Health Organization, ~50% of these patients die of CVDs. It has been well established that surgery in patients with diabetes is associated with longer hospital stay, higher healthcare resource utilization, and greater perioperative mortality. More recently, the emphasis has shifted from diabetes to hyperglycaemia on its own. New-onset hyperglycaemia, as compared with hyperglycaemia in known diabetics, may hold a much higher risk of adverse outcome.[216]

Evidence for strict blood glucose control for patients without known diabetes undergoing non-cardiac surgery is largely derived from studies in critically ill patients.[217] In 2001 the landmark Leuven prospective randomized controlled study demonstrated major clinical benefits for surgical ICU patients whose blood glucose levels were maintained normal (5.0−5.6 mmol/L; 90−100 mg/dL) with intensive insulin therapy, compared with patients who received conventional glucose management and developed hyperglycaemia (8.3−8.9 mmol/L; 150−160 mg/dL).[218] These benefits included lower ICU and in-hospital mortality and prevention of several critical illness-associated complications (critical illness polyneuropathy, severe infections, acute renal failure, and prolonged dependency on mechanical ventilation and intensive care). Also, long-term outcome improved, as shown for the cardiac surgery subgroup. Five years later the Leuven group reported findings from the medical ICU, showing prevention of morbidity, but no mortality benefit from intensive glucose control, except in a subgroup requiring critical care for ≥3 days.[219] Based on these two trials recommendations were made aiming at tight glucose control. Several observational implementation studies on tight glucose management or small, randomized studies in selected ICU patient groups supported the clinical benefits of the Leuven studies.[217] Pooled analysis of the Leuven studies revealed reduced mortality and morbidity for all major clinical diagnostic subgroups, including cardiovascular, respiratory, gastrointestinal/hepatic disease or surgery, active malignancy, and sepsis upon ICU admission. Patients with known diabetes tended to experience less morbidity but a survival benefit appeared absent. All studies described above started glucose control after ICU admission. Timing of initiating insulin therapy is controversial, but a recent medical ICU study showed better outcome when initiated within the first 48 h than after 48 h. Tight intraoperative glucose control may provide additional benefit but appears a challenge and, so far, studies have mainly been set up for cardiac surgery. Moderate intraoperative glycaemic control during CABG (not continued in the ICU) resulted in decreased need for pacing, lower incidence of AF and infections, shortening of the ICU and hospital stay, and decreased recurrent ischaemic events in the long-run. In contrast, implementation of glycaemic control during cardiac surgery, superimposed upon post-operative ICU glycaemic control, did not further reduce perioperative mortality or morbidity.[220] In an observational study, stricter glucose control during liver transplantation was associated with a lower infection rate and 1-year mortality than poor glycaemic control.[221]

Studies in the field of critical care have demonstrated the detrimental effect of hyperglycaemia, due to an adverse effect on renal and hepatic function, endothelial function, and immune response, particularly in patients without underlying diabetes. In the Leuven studies, risk of death and degree of hyperglycaemia were positively correlated. Unequivocal demonstration that glycaemic control rather than direct insulin effects mediated the survival and most morbidity benefits of insulin therapy was provided in a rabbit model of critical illness.[222] Several risk factors for cardiac events after non-cardiac surgery are attenuated with strict blood glucose control in the ICU, including endothelial injury/dysfunction, CRP, and asymmetric dimethylarginine, apart from effects on mitochondrial damage, serum lipid profile, and the cortisol response. No effects, or only marginal ones, were seen on cytokines, coagulation, and fibrinolysis.

Recently, the favourable outcomes of the Leuven findings using tight glucose control were questioned. The NICE-SUGAR study investigators randomized >6000 patients (63% medical ICU and 37% surgical ICU) to either tight glucose control (target glucose level, 4.5−6.0 mmol/L; 81−108 mg/dL) or conventional glucose control (target glucose level, 8.0−10.0 mmol/L; 144−180 mg/dL).[223] Patients were randomized to treatment within 24 h after admission using i.v. insulin infusions for glucose control. The primary endpoint, death by 90 days after randomization, was increased with intensive glucose control (27.5%) as compared with 24.9% with conventional control. There was no morbidity difference between the two study groups, and hence the excess

mortality remains unexplained. As could be expected, hypoglycaemia (<40 mg/dL) occurred in more patients in the intensive-control group than in the conventional-control group (6.8% vs. 0.5%, $P <0.001$). The strength of the NICE-SUGAR trial was its large and multicentre design using a computer-guided insulin infusion protocol. However, this protocol used an if–then algorithm based upon inaccurate and non-standardized stand-alone glucometers for blood glucose measurements. In addition, NICE-SUGAR had an open-label design, a small imbalance between the groups with respect to corticosteroid therapy, and 10% of patients randomized to intensive glucose control discontinued the study prematurely. The differences in outcome between the two studies should be explained.

(i) The Leuven trials were performed in a single centre with standardized care which included early parenteral nutrition supplementing enteral feeding, whereas in the NICE-SUGAR trial enteral nutrition predominated, resulting in hypocaloric feeding in particular during the first week after admission to ICU.
(ii) The target for initiating insulin in the standard treatment group was different, with insulin being advocated in the Leuven study only when blood glucose exceeded the renal threshold of >215 mg/dL, an approach that considers hyperglycaemia as a possible beneficial adaptation, whereas in NICE-SUGAR a target of 144–180 mg/dL was used in the standard group, which resulted in 70% of the patients receiving insulin and reaching an average blood glucose level of 8.0 mmol/L (144 mg/dL).
(iii) Also in the intervention group of NICE-SUGAR, the compliance to therapy was much lower than in the Leuven studies, which resulted in an average glucose level of 6.6 mmol/L (118 mg/dL) and a very large overlap with the glucose levels in the control group.
(iv) The use of inaccurate glucometers in NICE-SUGAR may have misguided the insulin therapy and may have overlooked hypokalaemia, a possible cause of excess cardiovascular mortality, which is prevented with the use of blood gas analysers for glucose measurement.
(v) The nurse experience with the intervention in NICE-SUGAR was much less than in the Leuven studies, in view of the limited number of patients recruited per centre ($<15\%$ of all patients screened in the participating ICUs) as compared with 70–95% in the Leuven studies.

The results of the NICE-SUGAR trial may suggest that intensive glucose control could harm patients admitted to the ICU, in terms of death, when glucose levels are below the range of 7.8–10.0 mmol/L (140–180 mg/dL). In contrast, evidence derived from previous studies suggests the clinical benefit of maintenance of normoglycaemia (4.4–6.1 mmol/L; 80–110 mg/dL) as compared with tolerating hyperglycaemia up to 11.9 mmol/L (215 mg/dL) for adult critically ill patients (*Table 10*).

Until further data become available clarifying the reasons for the different outcomes between the studies, it is recommended that the management of blood glucose in the ICU be optimized, avoiding the extremes of hyperglycaemia and also hypoglycaemia. The available data indicate that this therapy should be started immediately after ICU admission. It may be advisable to target a level of ~8.0 mmol/L (144 mg/dL) for settings and patient populations that are comparable with those studied in NICE-SUGAR.

Table 10 Clinical benefits of intensive insulin therapy in critically ill patients with a non-cardiac diagnosis upon ICU admission[218,219]

	ICU stay $\geq$3 days		*P*-value
	CIT (*n* = 643)	**IIT** (*n* = 648)	
ICU mortality	27.4%	22.7%	0.05
In-hospital mortality	38.7%	32.1%	0.01
Renal replacement therapy	11.2%	7.3%	0.02
Critical illness polyneuropathy[a]	51.3%	34.4%	<0.01
Bacteraemia	13.5%	10.6%	0.11
Mechanical ventilation (days)[b]	8 (4–17)	7 (3–13)	0.01
ICU stay (days)[b]	9 (4–18)	8 (4–15)	0.05

[a]Percentage of those screened of screened.
[b]Median (interquartile range).
CIT = conventional insulin therapy; ICU = intensive care unit; IIT = intensive insulin therapy.

Recommendations on blood glucose control

Recommendations	Class[a]	Level[b]
Post-operative prevention of hyperglycaemia [targeting levels at least below 10.0 mmol/L (180 mg/dL)] with intensive insulin therapy is recommended in adults after high-risk or complicated major surgery requiring admission to ICU	I	B
Intraoperative prevention of hyperglycaemia with insulin may be considered	IIb	C
Post-operative prevention of hyperglycaemia with insulin after uncomplicated elective surgery may be considered	IIb	C

[a]Class of recommendation.
[b]Level of evidence.
ICU = intensive care unit.

Anaesthesia

An optimal perioperative course stems from a close cooperation between cardiologists, surgeons, pulmonologists, and anaesthesiologists. Pre-operative risk assessment and pre-operative optimization of cardiac disease should be performed jointly.

There is a paucity of strong evidence-based data supporting the choice of a particular perioperative approach and thus several options are available. Sufficiently powered randomized trials addressing the potential relationship between patient outcome and perioperative management are still lacking for cardiac patients undergoing non-cardiac surgery.

Intraoperative anaesthetic management

The choice of the anaesthetic agent has been considered to be of little importance with regard to patients' outcome provided the vital functions are adequately supported. There is conflicting evidence from cardiac surgery over whether a specific method is advantageous in cardiac disease, but there is no evidence of superiority of any specific anaesthetic agent in non-cardiac surgery.[224,225]

Most anaesthetic techniques reduce sympathetic tone, leading to vasodilatation and reduction in systemic blood pressure. Thus, anaesthesiological management must ensure the proper maintenance of organ perfusion pressure.

Neuraxial techniques

Spinal and epidural anaesthesia also induce sympathetic blockade. Depending on the height of the block, it induces peripheral vasodilation with fall in blood pressure. When reaching the thoracic dermatome level 4, a reduction in cardiac sympathetic drive with subsequent reduction in myocardial contractility, heart rate, and change in cardiac loading conditions will appear. The speed and strength of sympathetic blockade will depend on dosage and drugs as well as the patient's condition. There is conflicting evidence on the effect of neuraxial blocks on patient outcome after non-cardiac surgery. One meta-analysis reported significantly improved survival and reduced incidence of post-operative thromboembolic, cardiac and pulmonary complications with neuraxial blockade compared with general anaesthesia.[226] A major criticism of this study has been the inclusion of older studies, which may have made the results invalid for current practice. A recent analysis of a large cohort of patients (10 564 patients without and 2253 patients with epidural) undergoing colon resection confirmed the improved survival with epidural analgesia at 7 and 30 days after surgery, but it was not possible to identify the cause of death.[227] Also cardiac morbidity was not different between the two groups.

Randomized studies and a meta-analysis of several randomized clinical trials in non-cardiac surgery patients, comparing outcome with regional and general anaesthetic techniques have shown little consistent evidence of improved outcome and reduced post-operative morbidity and mortality.[228–230] It has been estimated that the number of patients needed for a randomized clinical trial to determine whether epidural anaesthesia and analgesia would affect mortality in patients undergoing high-risk vascular surgery would be ~24 000, while enrolment of 1.2 million would be needed in a low-risk procedure.[227] Thus, present studies are underpowered for a valid analysis of risk of death for procedures with low surgical risk. No study has clearly demonstrated a difference in outcome with different monitoring techniques, fluid management, or transfusion strategies. Most studies have used different pre-determined therapeutic goals, often requiring inotropic support, a factor that may have been of importance for the results.[212] The importance of skilled anaesthesiological management in keeping adequate circulation is often underlined.[231]

Post-operative pain management

Post-operative pain is a major concern, reported in 5–10% of the patients. It may increase sympathetic drive and delay recovery.[232,233] The evidence that pain causes organ complications after surgery is less clear. Neuroaxial analgesia with local anaesthetics/opioids and/or α_2-agonists, i.v. opioids alone or in combination with non-steroid anti-inflammatory drugs seems to be the most effective. The benefit of invasive analgesic techniques should be weighed against potential dangers. This is of special importance when considering the use of neuraxial blockade in patients under chronic antithrombotic therapy due to increased potential of a neuraxial haematoma. It is beyond the scope of these guidelines to give recommendations for the use of neuraxial blocks in patients with coagulation disturbances.

Patient-controlled analgesia is an alternative for post-operative pain relief. Recent meta-analyses of controlled randomized trials show that patient-controlled analgesia has some advantage with regard to patient satisfaction over nurse-controlled or on-demand analgesia.[234] No difference with regard to morbidity or final outcome was demonstrated. Patient-controlled analgesia is an adequate alternative in patients and situations not suited for regional anaesthesia. Routines for follow-up and documentation of effects should be in place.[232,235–237] Non-steroid anti-inflammatory drugs and the cyclooxygenase-2 (COX-2) inhibitors have the potential for promoting heart and renal failure as well as thromboembolic events and should be avoided in patients with myocardial ischaemia. The COX-2 inhibitors cause less gastrointestinal ulceration and bronchospasm. The final role for these drugs in the treatment of post-operative pain in cardiac patients undergoing non-cardiac surgery has not been defined. The drugs should be avoided in patients with renal and heart failure, elderly patients, patients on diuretics, as well as patients with unstable haemodynamics.[238]

Recommendations on anaesthesia

Recommendations	Class[a]	Level[b]
Consideration should be given to performing thoracic epidural anaesthesia in high-risk surgery for patients with cardiac disease	IIa	A
Use of non-steroidal anti-inflammatory drugs and COX-2 inhibitors for post-operative pain control is not recommended in patients with renal and heart failure, myocardial ischaemia, elderly patients, as well as in patients taking diuretics or having unstable haemodynamics	III	B

[a]Class of recommendation.
[b]Level of evidence.
COX-2 = cyclooxygenase-2.

Putting the puzzle together

Figure 4 presents in algorithmic form an evidence-based stepwise approach for determining which patient benefits from cardiac testing, coronary artery revascularization, and cardiovascular therapy prior to surgery. For each step the committee has included the level of the recommendations and the strength of evidence in the accompanying *Table 11*.

Step 1. The urgency of the surgical procedure should be assessed. In urgent cases, patient- or surgical-specific factors dictate the
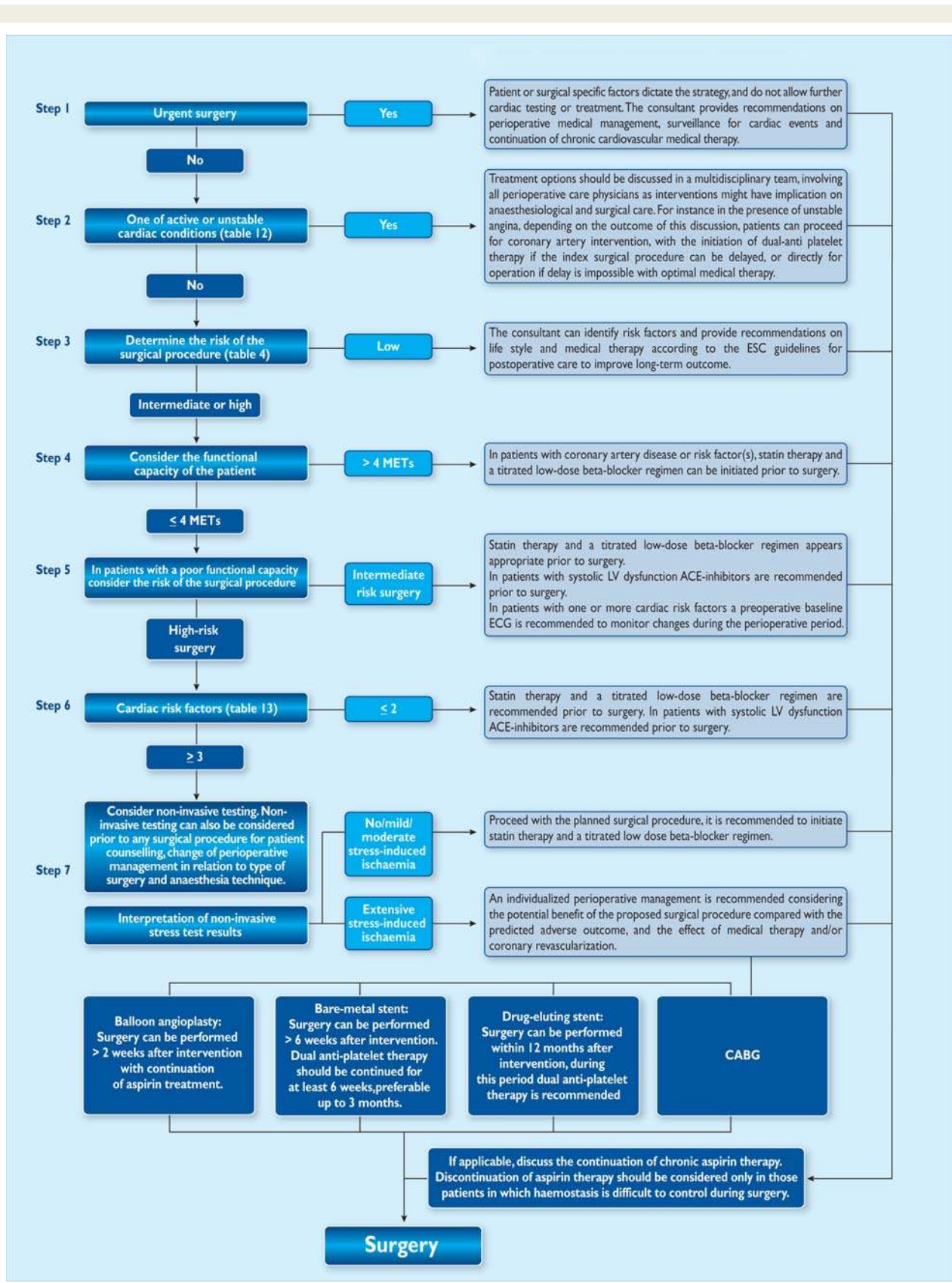
Figure 4 Summary of pre-operative cardiac risk evaluation and perioperative management.

Table 11   Summary of pre-operative cardiac risk evaluation and perioperative management

Step	Urgency	Cardiac condition	Type of surgery[a]	Functional capacity	Number of clinical risk factors[b]	LV echo	ECG	Stress Testing[e]	ß-Blockers[d]	ACE-inhibitors[d/e]	Aspirin[d]	Statins[d]	Coronary Revascularisation[f]
1	Urgent surgery					III C	IIa C	III C	I C	I C	I C	I C	III C
2	Elective surgery	Unstable				I C	I C	III C					I C
3	Elective surgery	Stable	Low risk (< 1%)		None	III B	III B	III C	III B	IIa C	IIb C	IIa B	III C
					≥ 1	III B	IIa B	III C	IIb B (titration) / III A (no titration)	IIa C	IIb C	IIa B	III C
4				Excellent or good		III B	IIa B	III C	IIb B (titration) / III A (no titration)	IIa C	IIb C	IIa B	III C
5	Elective surgery		Intermediate risk (1 - 5 %)	Moderate or poor	None	III B	IIb B	IIb C	IIa B (titration) / III A (no titration)	I C	IIb C	IIa B	III B
					≥ 1	III B	I B	IIb C	IIa B (titration) / III A (no titration)	I C	IIb C	IIa B	III B
6	Elective surgery		High risk (> 5%)	Moderate or poor	≤ 2	IIa C	I B	IIb B	I B (titration) / III A (no titration)	I C	IIb C	I B	IIb B
					≥ 3	IIa C	I B	I C	I B (titration) / III A (no titration)	I C	IIb C	I B	IIb B

[a]Type of surgery (*Table 4*): risk of MI and cardiac death within 30 days after surgery.
[b]Risk factors (*Table 13*): angina pectoris, MI, heart failure, stroke/transient ischaemic attack, renal dysfunction (creatinine >170 μmol/L or 2 mg/dL or a creatine clearance of <60 mL/min), diabetes mellitus.
[c]Non-invasive testing not only for revascularization but also for patient counselling, change of perioperative management in relation to type of surgery, and anaesthesia technique.
[d]Initiation of medical therapy, but in case of emergency surgery continuation of current medical therapy. Aspirin should be continued after stent replacement.
[e]In the presence of LV dysfunction (ejection fraction ≤40%).
[f]Class I recommendations for revascularization are consistent with the 2004 ACC/AHA guidelines: 1 = stable angina and significant left main disease; 2 = stable angina and three-vessel disease, especially when LV ejection fraction is <50%; 3 = stable angina and two-vessel disease with significant proximal left anterior descending coronary artery stenosis and either LV ejection fraction <50% or demonstrable ischaemia on non-invasive testing; 4 = high-risk unstable angina or non-STEMI; 5 = acute STEMI.

strategy, and do not allow further cardiac testing or treatment. In these cases, the consultant provides recommendations on perioperative medical management, surveillance for cardiac events, and continuation of chronic cardiovascular medical therapy.

Step 2. If the patients is unstable, as presented in *Table 12*, this condition should be clarified and treated appropriately prior to surgery. Examples are unstable coronary syndromes, decompensated heart failure, severe arrhythmias, or symptomatic valvular disease. This usually leads to cancellation or delay of the surgical procedure. For instance, patients with unstable angina pectoris should be referred for coronary angiography to assess the therapeutic options. Treatment options should be discussed in a multidisciplinary team, involving all perioperative care physicians, because interventions might have implications

Table 12   Unstable cardiac conditions

Unstable angina pectoris
Acute heart failure
Significant cardiac arrhythmias
Symptomatic valvular heart disease
Recent MI[a] and residual myocardial ischemia

[a]An MI within 30 days, according to the universal definition of MI.[34]

for anaesthesiological and surgical care. For example, the initiation of dual antiplatelet therapy after coronary artery stent placement might complicate loco-regional anaesthesia or

specific surgical procedures. Depending on the outcome of this discussion, patients can proceed for coronary artery intervention, namely CABG, balloon angioplasty, or stent placement with the initiation of dual antiplatelet therapy if the index surgical procedure can be delayed, or directly for operation if delay is incompatible with optimal medical therapy.

Step 3. Determine the risk of the surgical procedure (*Table 4*). If the estimated 30-day cardiac risk of the procedure in cardiac-stable patients is low, <1%, it is unlikely that test results will change management and it would be appropriate to proceed with the planned surgical procedure. The consultant can identify risk factors and provide recommendations on lifestyle and medical therapy according to the ESC Guidelines for post-operative care to improve long-term outcome.

Step 4. Consider the functional capacity of the patient. If an asymptomatic or cardiac-stable patient has moderate or good functional capacity, >4 METs, perioperative management is unlikely to be changed on the basis of test results irrespective of the planned surgical procedure. Even in the presence of clinical risk factors, it is appropriate to refer the patient for surgery. In patients with IHD or risk factor(s), statin therapy and a titrated low-dose β-blocker regimen can be initiated prior to surgery, as outlined in *Table 11*.

Step 5. It is recommended that chronic aspirin therapy be continued. Discontinuation of aspirin therapy should be considered only in those patients in which haemostasis is difficult to control during surgery.

Step 6. In patients with a moderate or poor functional capacity, consider the risk of the surgical procedure, as outlined in *Table 4*. Patients scheduled for intermediate-risk surgery can proceed for surgery; statin therapy and a titrated low-dose β-blocker regimen appears appropriate prior to surgery. In patients with systolic LV dysfunction, evidenced by LV ejection fraction <40%, ACE inhibitors (or ARBs in patients intolerant of ACE inhibitors) are recommended before surgery. In patients with one or more clinical risk factors, a pre-operative baseline ECG is recommended to monitor changes during the perioperative period. In patients scheduled for high-risk surgery, as described in *Table 4*, clinical risk factors (*Table 13*) are noted. In patients with up to two clinical risk factors, statin therapy and a titrated low-dose β-blocker regimen are recommended prior to surgery. In patients with systolic LV dysfunction, evidenced by LV ejection fraction <40%, ACE inhibitors (or ARBs in patients intolerant of ACE inhibitors) are recommended before surgery.

Table 13   **Clinical risk factors**
Angina pectoris
Prior MI[a]
Heart failure
Stroke/transient ischaemic attack
Renal dysfunction (serum creatinine >170 μmol/L or 2 mg/dL or a creatinine clearance of <60 mL/min)
Diabetes mellitus requiring insulin therapy

[a]According to the universal definition of MI.[34]

Consider non-invasive testing in patients with ≥3 clinical risk factors (*Table 13*). Non-invasive testing can also be considered prior to any surgical procedure for patient counselling, or change of perioperative management in relation to type of surgery and anaesthesia technique.

Step 7. Interpretation of non-invasive stress test results. Patients without stress-induced ischaemia, or mild to moderate ischaemia suggestive of one- or two-vessel disease, can proceed with the planned surgical procedure. It is recommended that statin therapy and a titrated low-dose β-blocker regimen be initiated. In patients with extensive stress-induced ischaemia, as assessed by non-invasive testing, individualized perioperative management is recommended, taking into consideration the potential benefit of the proposed surgical procedure compared with the predicted adverse outcome. Also, the effect of medical therapy and/or coronary revascularization must be assessed, not only for immediate post-operative outcome, but also for long-term follow-up. In patients referred for percutaneous coronary artery intervention, the initiation and duration of antiplatelet therapy will interfere with the planned surgical procedure. In patients referred for angioplasty, non-cardiac surgery can be performed within 2 weeks after intervention with continuation of aspirin treatment. In patients with bare metal stent placement, non-cardiac surgery can be performed after 6 weeks to 3 months following intervention. Dual antiplatelet therapy should be continued for at least 6 weeks, preferably for up to 3 months. After this period, at least aspirin therapy should be continued. In patients with recent DES placement, non-cardiac surgery can be performed after 12 months following intervention, before which time dual antiplatelet therapy is recommended. After this period, at least aspirin therapy should be continued.

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