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2014 ESC/ESA Guidelines on non-cardiac surgery: cardiovascular assessment and management

The Joint Task Force on non-cardiac surgery: cardiovascular assessment and management of the European Society of Cardiology (ESC) and the European Society of Anaesthesiology (ESA)

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Abbreviations and acronyms

AAA	abdominal aortic aneurysm
ACEI	angiotensin converting enzyme inhibitor
ACS	acute coronary syndromes
AF	atrial fibrillation
AKI	acute kidney injury
AKIN	Acute Kidney Injury Network
ARB	angiotensin receptor blocker
ASA	American Society of Anesthesiologists
b.i.d.	bis in diem (twice daily)
BBSA	Beta-Blocker in Spinal Anesthesia
BMS	bare-metal stent
BNP	B-type natriuretic peptide
bpm	beats per minute
CABG	coronary artery bypass graft
CAD	coronary artery disease
CARP	Coronary Artery Revascularization Prophylaxis
CAS	carotid artery stenting
CASS	Coronary Artery Surgery Study
CEA	carotid endarterectomy
CHA_2DS_2-VASc	cardiac failure, hypertension, age $\geq$75 (doubled), diabetes, stroke (doubled)-vascular disease, age 65–74 and sex category (female)
CI	confidence interval
CI-AKI	contrast-induced acute kidney injury
CKD	chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
C_{max}	maximum concentration
CMR	cardiovascular magnetic resonance
COPD	chronic obstructive pulmonary disease
CPG	Committee for Practice Guidelines
CPX/CPET	cardiopulmonary exercise test
CRP	C-reactive protein
CRT	cardiac resynchronization therapy
CRT-D	cardiac resynchronization therapy defibrillator
CT	computed tomography
cTnI	cardiac troponin I
cTnT	cardiac troponin T
CVD	cardiovascular disease
CYP3a4	cytochrome P3a4 enzyme
DAPT	dual anti-platelet therapy
DECREASE	Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography
DES	drug-eluting stent
DIPOM	DIabetic Post-Operative Mortality and Morbidity
DSE	dobutamine stress echocardiography
ECG	electrocardiography/electrocardiographically/electrocardiogram
eGFR	estimated glomerular filtration rate
ESA	European Society of Anaesthesiology
ESC	European Society of Cardiology
EVAR	endovascular abdominal aortic aneurysm repair
FEV_1	Forced expiratory volume in 1 second
HbA_{1c}	glycosylated haemoglobin
HF-PEF	heart failure with preserved left ventricular ejection fraction
HF-REF	heart failure with reduced left ventricular ejection fraction
ICD	implantable cardioverter defibrillator
ICU	intensive care unit
IHD	ischaemic heart disease
INR	international normalized ratio
IOCM	iso-osmolar contrast medium
KDIGO	Kidney Disease: Improving Global Outcomes
LMWH	low molecular weight heparin
LOCM	low-osmolar contrast medium
LV	left ventricular
LVEF	left ventricular ejection fraction
MaVS	Metoprolol after Vascular Surgery
MDRD	Modification of Diet in Renal Disease
MET	metabolic equivalent
MRI	magnetic resonance imaging
NHS	National Health Service
NOAC	non-vitamin K oral anticoagulant
NSQIP	National Surgical Quality Improvement Program
NSTE-ACS	non-ST-elevation acute coronary syndromes
NT-proBNP	N-terminal pro-BNP
O_2	oxygen
OHS	obesity hypoventilation syndrome
OR	odds ratio
P gp	platelet glycoprotein
PAC	pulmonary artery catheter
PAD	peripheral artery disease
PAH	pulmonary artery hypertension
PCC	prothrombin complex concentrate
PCI	percutaneous coronary intervention
POBBLE	Peri-Operative Beta-BLockadE
POISE	Peri-Operative ISchemic Evaluation
POISE-2	Peri-Operative ISchemic Evaluation 2
q.d.	quaque die (once daily)
RIFLE	Risk, Injury, Failure, Loss, End-stage renal disease
SPECT	single photon emission computed tomography
SVT	supraventricular tachycardia
SYNTAX	Synergy between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery
TAVI	transcatheter aortic valve implantation
TdP	torsades de pointes
TIA	transient ischaemic attack
TOE	transoesophageal echocardiography
TOD	transoesophageal doppler
TTE	transthoracic echocardiography
UFH	unfractionated heparin
VATS	video-assisted thoracic surgery
VHD	valvular heart disease
VISION	Vascular Events In Noncardiac Surgery Patients Cohort Evaluation
VKA	vitamin K antagonist
VPB	ventricular premature beat
VT	ventricular tachycardia

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1. Preamble

Guidelines summarize and evaluate all available evidence, at the time of the writing process, on a particular issue with the aim of assisting health professionals in selecting the best management strategies for an individual patient with a given condition, taking into account the impact on outcome, as well as the risk–benefit ratio of particular diagnostic or therapeutic means. Guidelines and recommendations should help health professionals to make decisions in their daily practice; however, the final decisions concerning an individual patient must be made by the responsible health professional(s), in consultation with the patient and caregiver as appropriate.

A great number of guidelines have been issued in recent years by the European Society of Cardiology (ESC) and the European Society of Anaesthesiology (ESA), as well as by other societies and organisations. Because of their impact on clinical practice, quality criteria for the development of guidelines have been established in order to make all decisions transparent to the user. The recommendations for formulating and issuing ESC/ESA Guidelines can be found on the ESC web site (http://www.escardio.org/guidelines-surveys/esc-guidelines/about/Pages/rules-writing.aspx). These ESC/ESA guidelines represent the official position of these two societies on this given topic and are regularly updated.

Members of this Task Force were selected by the ESC and ESA to represent professionals involved with the medical care of patients with this pathology. Selected experts in the field undertook a comprehensive review of the published evidence for management (including diagnosis, treatment, prevention and rehabilitation) of a given condition, according to the ESC Committee for Practice Guidelines (CPG) and ESA Guidelines Committee policy. A critical evaluation of diagnostic and therapeutic procedures was performed, including assessment of the risk–benefit ratio. Estimates of expected health outcomes for larger populations were included, where data exist. The level of evidence and the strength of recommendation of particular management options were weighed and graded according to pre-defined scales, as outlined in *Tables 1* and *2*.

The experts of the writing and reviewing panels completed 'declarations of interest' forms which might be perceived as real or potential sources of conflicts of interest. These forms were compiled into one file and can be found on the ESC web site (http://www.escardio.org/guidelines). Any changes in declarations of interest that arise during the writing period must be notified to the ESC/ESA and updated. The Task Force received its entire financial support from the ESC and ESA, without any involvement from the healthcare industry.

The ESC CPG supervises and co-ordinates the preparation of new guidelines produced by Task Forces, expert groups or consensus panels. The Committee is also responsible for the endorsement process of these guidelines. The ESC and Joint Guidelines undergo extensive review by the CPG and partner Guidelines Committee and external experts. After appropriate revisions it is approved by all the experts involved in the Task Force. The finalized document is approved by the CPG/ESA for simultaneous publication in the European Heart Journal and joint partner journal, in this instance the European Journal of Anaesthesiology. It was developed after careful consideration of the scientific and medical knowledge and the evidence available at the time of their dating.

The task of developing ESC/ESA guidelines covers not only the integration of the most recent research, but also the creation of educational tools and implementation programmes for the recommendations. To implement the guidelines, condensed pocket versions, summary slides, booklets with essential messages, summary cards for non-specialists, electronic versions for digital applications (smart phones etc.) are produced. These versions are abridged and thus, if needed, one should always refer to the full-text version, which is freely available on the ESC and ESA web sites. The national societies of the ESC and of the ESA are encouraged to endorse, translate and implement the ESC guidelines. Implementation programmes

Table 1 Classes of recommendations

Classes of recommendations	Definition	Suggested wording to use
Class I	Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective.	Is recommended/is indicated
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.*	Should be considered
Class IIb	*Usefulness/efficacy is less well established by evidence/opinion.*	May be considered
Class III	Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful.	Is not recommended

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are needed because it has been shown that the outcome of disease may be favourably influenced by the thorough application of clinical recommendations.

Surveys and registries are needed to verify that real-life daily practice is in keeping with what is recommended in the guidelines, thus completing the loop between clinical research, writing of guidelines, disseminating them and implementing them into clinical practice.

Health professionals are encouraged to take the ESC/ESA guidelines fully into account when exercising their clinical judgment, as well as in the determination and the implementation of preventive, diagnostic or therapeutic medical strategies; however, the ESC/ESA guidelines do not, in any way whatsoever, override the individual responsibility of health professionals to make appropriate and accurate decisions in consideration of the condition of each patient's health and in consultation with that patient and, where appropriate and/or necessary, the patient's caregiver. It is also the health professional's responsibility to verify the rules and regulations applicable to drugs and devices at the time of prescription.

Table 2 Levels 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.

2. Introduction

2.1 The magnitude of the problem

The present Guidelines focus on the cardiovascular management of patients in whom heart disease is a potential source of complications during non-cardiac surgery. The risk of peri-operative complications depends on the condition of the patient before surgery, the prevalence of comorbidities, and the urgency, magnitude, type, and duration of the surgical procedure.

More specifically, cardiac complications can arise in patients with documented or asymptomatic ischaemic heart disease (IHD), left ventricular (LV) dysfunction, valvular heart disease (VHD), and arrhythmias, who undergo surgical procedures that are associated with prolonged haemodynamic and cardiac stress. In the case of peri-operative myocardial ischaemia, two mechanisms are important: (i) a mismatch in the supply–demand ratio of blood flow, in response to metabolic demand due to a coronary artery stenosis that may become flow-limiting by peri-operative haemodynamic fluctuations and (ii) acute coronary syndromes (ACS) due to stress-induced rupture of a vulnerable atherosclerotic plaque in combination with vascular inflammation and altered vasomotion, as well as haemostasis. LV dysfunction and arrhythmias may occur for various reasons at all ages. Because the prevalence of not only IHD but also VHD and arrhythmias increases with age, peri-operative 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 group and (ii) the average risk of cardiac complications in this cohort. Unfortunately, systematic data on the annual number and type of operations—and on patient outcomes—are only available at a national level in 23 European countries (41%).[1] Additionally, data definitions vary, as do data quantity and quality. A recent modelling strategy, based on worldwide data available in 2004, estimated the number of major operations to be at the rate of 4% of the world population per year.[1] When applied to Europe, with an overall population of over 500 million, this figure translates into a crude estimate of 19 million major procedures annually. While the majority of these procedures are performed in patients with minimal cardiovascular risk, 30% of patients undergo extensive surgical procedures in the presence of cardiovascular comorbidity; hence, 5.7 million procedures annually are performed in European patients who present with increased risk of cardiovascular complications.

Worldwide, non-cardiac surgery is associated with an average overall complication rate of 7–11% and a mortality rate of 0.8–1.5%, depending on safety precautions.[2] Up to 42% of these are caused by cardiac complications.[3] When applied to the population in the European Union member states, these figures translate into at least 167 000 cardiac complications annually due to non-cardiac surgical procedures, of which 19 000 are life-threatening.

2.2 Change in demographics

Within the next 20 years, the ageing of the population will have a major impact on peri-operative patient management. It is estimated that elderly people require surgery four times as often than the rest of the population.[4] In Europe, it is estimated that the number of patients undergoing surgery will increase by 25% by 2020. Over the same time period, the elderly population will increase by 50%. The total number of surgical procedures may increase even faster because of the rising frequency of interventions with age.[5] The results of the United States National Hospital Discharge Survey show that the number of surgical procedures will increase in almost all age groups and that the largest increase will occur in the middle-aged and elderly. Demographics of patients undergoing surgery show a trend towards an increasing number of elderly patients and comorbidities.[6] 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 comorbidities in elderly patients presenting for general surgery, cardiovascular disease (CVD) is the most prevalent.[7] 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; thus, these conditions should have greater impact on the evaluation of patient risk than age alone.

2.3 Purpose and organization

These Guidelines are intended for physicians and collaborators involved in the pre-operative, operative, and post-operative care of patients undergoing non-cardiac surgery.

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Table 3 Surgical risk estimate according to type of surgery or intervention[a,b]

Low-risk: < 1%	Intermediate-risk: 1–5%	High-risk: > 5%
• Superficial surgery • Breast • Dental • Endocrine: thyroid • Eye • Reconstructive • Carotid asymptomatic (CEA or CAS) • Gynaecology: minor • Orthopaedic: minor (meniscectomy) • Urological: minor (transurethral resection of the prostate)	• Intraperitoneal: splenectomy, hiatal hernia repair, cholecystectomy • Carotid symptomatic (CEA or CAS) • Peripheral arterial angioplasty • Endovascular aneurysm repair • Head and neck surgery • Neurological or orthopaedic: major (hip and spine surgery) • Urological or gynaecological: major • Renal transplant • Intra-thoracic: non-major	• Aortic and major vascular surgery • Open lower limb revascularization or amputation or thromboembolectomy • Duodeno-pancreatic surgery • Liver resection, bile duct surgery • Oesophagectomy • Repair of perforated bowel • Adrenal resection • Total cystectomy • Pneumonectomy • Pulmonary or liver transplant

CAS = carotid artery stenting; CEA = carotid endarterectomy.
[a]Surgical risk estimate is a broad approximation of 30-day risk of cardiovascular death and myocardial infarction that takes into account only the specific surgical intervention, without considering the patient's comorbidities.
[b]Adapted from Glance *et al.*[11]

The objective is to endorse a standardized and evidence-based approach to peri-operative cardiac management. The Guidelines recommend a practical, stepwise evaluation of the patient that 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 of initiating medical therapy, coronary interventions, and specific surgical and anaesthetic techniques in order to optimize the patient's peri-operative condition.

Compared with the non-surgical setting, data from randomized clinical trials—which provide the ideal evidence-base for the guidelines—are sparse. Consequently, when no trials are available on a specific cardiac-management regimen in the surgical setting, data from the non-surgical setting are extrapolated and similar recommendations made, but with different levels of evidence. Anaesthesiologists, who are experts on the specific demands of the proposed surgical procedure, will usually co-ordinate the pre-operative evaluation. The majority of patients with stable heart disease can undergo low and intermediate-risk surgery (*Table 3*) without additional evaluation. Selected patients require evaluation by a team of integrated multidisciplinary specialists including anaesthesiologists, cardiologists, and surgeons and, when appropriate, an extended team (e.g. internists, intensivists, pulmonologists or geriatricians).[8] Selected patients include those identified by the anaesthesiologist because of suspected or known cardiac disease with sufficient complexity to carry a potential peri-operative risk (e.g. congenital heart disease, unstable symptoms or low functional capacity), patients in whom pre-operative medical optimization is expected to reduce peri-operative risk before low- and intermediate-risk surgery, and patients with known or high risk of cardiac disease who are undergoing high-risk surgery. Guidelines have the potential to improve post-operative outcomes and 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 peri-operative care, guidelines should provide long-term advice.

Because of the availability of new evidence and the international impact of the controversy over the DECREASE trials, the ESC/ESA and American College of Cardiology/American Heart Association both began the process of revising their respective guidelines concurrently. The respective writing committees independently performed their literature review and analysis, and then developed their recommendations. Once peer review of both guidelines was completed, the writing committees chose to discuss their respective recommendations regarding beta-blocker therapy and other relevant issues. Any differences in recommendations were discussed and clearly articulated in the text; however, the writing committees aligned a few recommendations to avoid confusion within the clinical community, except where international practice variation was prevalent.

Following the development and introduction of peri-operative cardiac guidelines, their effect on outcome should be monitored. The objective evaluation of changes in outcome will form an essential part of future peri-operative guideline development.

Recommendations on pre-operative evaluation

Recommendations	Class[a]	Level[b]	Ref.[c]
Selected patients with cardiac disease undergoing low-and intermediate-risk non-cardiac surgery may be referred by the anaesthesiologist for cardiological evaluation and medical optimization.	IIb	C	
A multidisciplinary expert team should be considered for pre-operative evaluation of patients with known or high risk of cardiac disease undergoing high-risk non-cardiac surgery.	IIa	C	8

[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

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3. Pre-operative evaluation

3.1 Surgical risk for cardiac events

Cardiac complications after non-cardiac surgery depend on patient-related risk factors, on the type of surgery, and on the circumstances under which it takes place.[9] Surgical factors that influence cardiac risk are related to the urgency, invasiveness, type, and duration of the procedure, as well as the change in body core temperature, blood loss, and fluid shifts.[5] Every operation elicits a stress response. This response is initiated by tissue injury and mediated by neuro-endocrine factors, and may induce sympathovagal imbalance. Fluid shifts in the peri-operative period add to the surgical stress. This stress increases myocardial oxygen demand. Surgery also causes alterations in the balance between prothrombotic and fibrinolytic factors, potentially resulting in increased coronary thrombogenicity. The extent of such changes is proportionate to the extent and duration of the intervention. These factors, together with patient position, temperature management, bleeding, and type of anaesthesia, may contribute to haemodynamic derangements, leading to myocardial ischaemia and heart failure. General, locoregional, and neuraxial anaesthesia differ in terms of the stress response evoked by surgery. Less invasive anaesthetic techniques may reduce early mortality in patients at intermediate-to-high cardiac risk and limit post-operative complications.[10] 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.[9]

With regard to cardiac risk, surgical interventions—which include open or endovascular procedures—can be broadly divided into low-risk, intermediate-risk, and high-risk groups, with estimated 30-day cardiac event rates (cardiac death and myocardial infarction) of $<1\%$, $1-5\%$, and $>5\%$, respectively (*Table 3*).

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 a perforated viscus, cardiac evaluation will not alter the course or result of the intervention but may influence management in the immediate peri-operative period. In non-emergency but urgent surgical conditions, such as bypass for acute limb ischaemia or treatment of bowel obstruction, the morbidity and mortality of the untreated underlying condition may outweigh the potential cardiac risk related to the intervention. In these cases, cardiological evaluation may influence the peri-operative measures taken to reduce 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 infra-inguinal bypass, or extra-anatomical reconstruction instead of an aortic procedure, even when these may yield less favourable results in the long term. Finally, in some situations, the cardiac evaluation (in as far as it can reliably predict peri-operative cardiac complications and late survival) should be taken into consideration when deciding whether to perform an intervention or manage conservatively. 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.

3.2 Type of surgery

In general, endoscopic and endovascular techniques speed recovery, decrease hospital stay, and reduce the rate of complications.[12] However, randomized clinical trials comparing laparoscopic with open techniques exclude older, sicker, and 'urgent' patients, and results from an expert-based randomized trial (laparoscopic vs. open cholecystectomy) have shown no significant differences in conversion rate, pain, complications, length of hospital stay, or re-admissions.[13]

The wide variety of surgical procedures, in a myriad of different contexts, makes difficult the assignation of a specific risk of a major adverse cardiac event to each procedure. When alternative methods to classical open surgery are considered, either through endovascular or less-invasive endoscopic procedures, the potential trade-offs between early benefits due to reduced morbidity and mid- to long-term efficacy need to be taken into account.

3.2.1 Endovascular vs. open vascular procedures

Vascular interventions are of specific interest, not only because they carry the highest risk of cardiac complications, but also because of the many studies that have shown that this risk can be influenced by adequate peri-operative measures in these patients.[14] Open aortic and infra-inguinal procedures must both be regarded as high-risk procedures. Although it is a less-extensive intervention, infra-inguinal revascularization entails a cardiac risk similar to—or even higher than—that of 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.

Endovascular AAA repair (EVAR) has been associated with lower operative mortality and morbidity than open repair but this advantage reduces with time, due to more frequent graft-related complications and re-interventions in patients who underwent EVAR, resulting in similar long-term AAA-related mortality and total mortality.[15–17]

A meta-analysis of studies, comparing open surgical with percutaneous transluminal methods for the treatment of femoro-popliteal arterial disease, showed that bypass surgery is associated with higher 30-day morbidity [odds ratio (OR) 2.93; 95% confidence interval (CI) 1.34–6.41] and lower technical failure than endovascular treatment, with no differences in 30-day mortality; however, there were higher amputation-free and overall survival rates in the bypass group at 4 years.[18] Therefore, multiple factors must be taken into consideration when deciding which type of procedure serves the patient best. An endovascular-first approach may be advisable in patients with significant comorbidity, whereas a bypass procedure may be offered as a first-line interventional treatment for fit patients with a longer life expectancy.[19] Carotid artery stenting has appeared as an attractive, less-invasive alternative to CEA; however, although CAS reduces the rate of

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periprocedural myocardial infarction and cranial nerve palsy, the combined 30-day rate of stroke or death is higher than CEA, particularly in symptomatic and older patients, driven by a difference in the risk of periprocedural non-disabling stroke.[20,21] The benefit of carotid revascularization is particularly high in patients with recent (<3 months) transient ischaemic attack (TIA) or stroke and a >60% carotid artery bifurcation stenosis.[22] In neurologically asymptomatic patients, carotid revascularization benefit is questionable, compared with modern medical therapy, except in patients with a >80% carotid stenosis and an estimated life expectancy of >5 years.[21] The choice between CEA and CAS must integrate operator experience and results, anatomical characteristics of the arch vessels, neck features, and comorbidities.[21–23]

3.2.2 Open vs. laparoscopic or thoracoscopic procedures

Laparoscopic procedures, compared with open procedures, have the advantage of causing less tissue trauma and intestinal paralysis, resulting in less incisional pain, better post-operative pulmonary function, significantly fewer wall complications, and diminished post-operative fluid shifts related to bowel paralysis.[24] However, the pneumoperitoneum required for these procedures results in elevated intra-abdominal pressure and a reduction in venous return. Typical physiological *sequelae* are secondary to increased intra-abdominal pressure and absorption of the gaseous medium used for insufflation. While healthy individuals on controlled ventilation typically tolerate pneumoperitoneum, debilitated patients with cardiopulmonary compromise and obese patients may experience adverse consequences.[25] Pneumoperitoneum and Trendelenburg position result in increased mean arterial pressure, central venous pressure, mean pulmonary artery, pulmonary capillary wedge pressure, and systemic vascular resistance impairing cardiac function.[26,27] Therefore, compared with open surgery, cardiac risk in patients with heart failure is not reduced in patients undergoing laparoscopy, and both should be evaluated in the same way. This is especially true in patients undergoing interventions for morbid obesity, but also in other types of surgery, considering the risk of conversion to an open procedure.[28,29] Superior short-term outcomes of laparoscopic vs. open procedures have been reported, depending on type of surgery, operator experience and hospital volume, but few studies provide direct measures of cardiac complications.[30–32] Benefit from laparoscopic procedures is probably greater in elderly patients, with reduced length of hospital stay, intra-operative blood loss, incidence of post-operative pneumonia, time to return of normal bowel function, incidence of post-operative cardiac complications, and wound infections.[33] Few data are available for video-assisted thoracic surgery (VATS), with no large, randomized trial comparing VATS with open thoracic lung resection. In one study involving propensity-score-matched patients, VATS lobectomy was associated with no significant difference in mortality, but with significantly lower rates of overall peri-operative morbidity, pneumonia, and atrial arrhythmia.[34]

Recommendations on the selection of surgical approach and its impact on risk

Recommendations	Class[a]	Level[b]	Ref.[c]
It is recommended that patients should undergo pre-operative risk assessment independently of an open or laparoscopic surgical approach.[d]	I	C	26,27, 35
In patients with AAA ≥55 mm, anatomically suited for EVAR, either open or endovascular aortic repair is recommended if surgical risk is acceptable.	I	A	15–17
In patients with asymptomatic AAA who are unfit for open repair, EVAR, along with best medical treatment, may be considered.	IIb	B	15,35
In patients with lower extremity artery disease requiring revascularization, the best management strategy should be determined by an expert team considering anatomy, comorbidities, local availability, and expertise.	IIa	B	18

AAA = abdominal aortic aneurysm; EVAR = endovascular aortic reconstruction.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.
[d]Since laparoscopic procedures demonstrate a cardiac stress similar to that of open procedures.

3.3 Functional capacity

Determination of functional capacity is a pivotal step in pre-operative cardiac risk assessment and 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 from the ability to perform the activities of daily living. One 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).[38] This may

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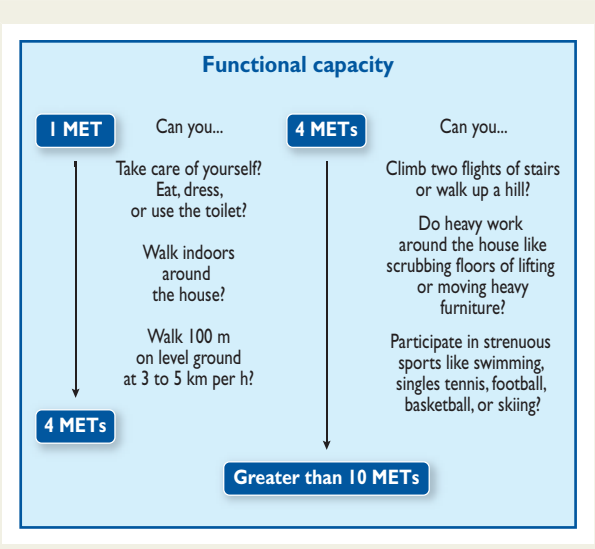

Figure 1 Estimated energy requirements for various activities. Based on Hlatky *et al.* and Fletcher *et al.*[36,37] km per h = kilometres per hour; MET = metabolic equivalent.

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 pre-operative functional capacity measured in METs showed a relatively weak association with post-operative cardiac events or death.[39] Notably, when functional capacity is high, the prognosis is excellent, even in the presence of stable IHD or risk factors;[40] otherwise, 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 peri-operative management.

3.4 Risk indices

For two main reasons, effective strategies aimed at reducing the risk of peri-operative cardiac complications should involve cardiac evaluation, using medical history before the surgical procedure,. Firstly, 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 will further reduce the peri-operative risk. 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. Clearly, 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, or other non-invasive assessments.

Several risk indices have been developed during the past 30 years, based on multivariate analyses of observational data, which represent the relationship between clinical characteristics and peri-operative cardiac mortality and morbidity. The indices developed by Goldman *et al.* (1977),[41] Detsky *et al.* (1986),[42] and Lee *et al.* (1999)[43] have become well-known.

Although only a rough estimation, the older risk-stratification systems may represent useful clinical tools for physicians in respect of the need for cardiac evaluation, drug treatment, and assessment of risk for cardiac events. The Lee index or 'revised cardiac risk' index, a modified version of the original Goldman index, was designed to predict post-operative myocardial infarction, pulmonary oedema, ventricular fibrillation or cardiac arrest, and complete heart block. This risk index comprises six variables: type of surgery, history of IHD, history of heart failure, history of cerebrovascular disease, pre-operative treatment with insulin, and pre-operative creatinine >170 μmol/L (>2 mg/dL), and used to be considered by many clinicians and researchers to be the best currently available cardiac-risk prediction index in non-cardiac surgery.

All of the above-mentioned risk indices were, however, developed years ago and many changes have since occurred in the treatment of IHD and in the anaesthetic, operative and peri-operative management of non-cardiac surgical patients. A new predictive model was recently developed to assess the risk of intra-operative/post-operative myocardial infarction or cardiac arrest, using the American College of Surgeons National Surgical Quality Improvement Program (NSQIP) database.[44] This NSQIP MICA model was built on the 2007 data set, based on patients from 180 hospitals, and was validated with the 2008 data set, both containing >200 000 patients and having predictability. The primary endpoint was intra-operative/post-operative myocardial infarction or cardiac arrest up to 30 days after surgery. Five predictors of peri-operative myocardial infarction/cardiac arrest were identified: type of surgery, functional status, elevated creatinine (>130 μmol/L or >1.5 mg/dL), American Society of Anesthesiologists (ASA) class (*Class I*, patient is completely healthy; *Class II*, patient has mild systemic disease; *Class III*, patient has severe systemic disease that is not incapacitating; *Class IV*, patient has incapacitating disease that is a constant threat to life; and *Class V*, a moribund patient who is not expected to live for 24 hours, with or without the surgery), and age. This model is presented as an interactive risk calculator (http://www.surgicalriskcalculator.com/miorcardiacarrest) so that the risk can be calculated at the bedside or clinic in a simple and accurate way. Unlike other risk scores, the NSQIP model did not establish a scoring system but provides a model-based estimate of the probability of myocardial infarction/cardiac arrest for an individual patient. The risk calculator performed better than the Lee risk index, with some reduction in performance in vascular patients, although it was still superior; however, some peri-operative cardiac complications of interest to clinicians, such as pulmonary oedema and complete heart block, were not considered in the NSQIP model because those variables were not included in the NSQIP database. By contrast, the Lee index allows estimation of the risk of peri-operative pulmonary

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oedema and of complete heart block, in addition to death and myocardial infarction (http://www.mdcalc.com/revised-cardiac-risk-index-for-pre-operative-risk/). A recent systematic review of 24 studies covering >790 000 patients found that the Lee index discriminated moderately well patients at low vs. high risk for cardiac events after mixed non-cardiac surgery, but its performance was hampered when predicting cardiac events after vascular non-cardiac surgery or predicting death.[45] Therefore, the NSQIP and Lee risk index models provide complementary prognostic perspectives and can help the clinician in the decision-making process.

Risk models do not dictate management decisions but should be regarded as one piece of the puzzle to be evaluated, in concert with the more traditional information at the physician's disposal.

3.5 Biomarkers

A biological marker, or 'biomarker', is a characteristic that can be objectively measured and which is an indicator of biological processes. In the peri-operative 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, respectively) are the preferred markers for the diagnosis of myocardial infarction because they demonstrate sensitivity and tissue specificity better than other available biomarkers.[46] The prognostic information is independent of—and complementary to—other important cardiac indicators of risk, such as ST deviation and LV function. It seems that cTnI and cTnT are of similar value for risk assessment in ACS in the presence and absence of renal failure. Existing evidence suggests that even small increases in cTnT in the peri-operative period reflect clinically relevant myocardial injury with worsened cardiac prognosis and outcome.[47–49] The development of new biomarkers, including high-sensitivity troponins, will probably further enhance the assessment of myocardial damage.[48] Assessment of cardiac troponins in high-risk patients, both before and 48–72 hours after major surgery, may therefore be considered.[3] It should be noted that troponin elevation may also be observed in many other conditions; the diagnosis of non-ST-segment elevation myocardial infarction should never be made solely on the basis of biomarkers.

Inflammatory markers might pre-operatively identify those patients with an increased risk of unstable coronary plaque; however, in the surgical setting, no data are currently available on how inflammatory markers would alter risk-reduction strategies.

B-type 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 across many cardiac diseases in non-surgical settings.[50] 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.[51–53]

Data from prospective, controlled trials on the use of pre-operative biomarkers are sparse. Based on the existing data, assessment of serum biomarkers for patients undergoing non-cardiac surgery cannot be proposed for routine use, but may be considered in high-risk patients (METs ≤4 or with a revised cardiac risk index value >1 for vascular surgery and >2 for non-vascular surgery).

Recommendations on cardiac risk stratification

Recommendations	Class[a]	Level[b]	Ref.[c]
Clinical risk indices are recommended to be used for peri-operative risk stratification.	I	B	43,44
The NSQIP model or the Lee risk index are recommended for cardiac peri-operative risk stratification.	I	B	43,44,54
Assessment of cardiac troponins in high-risk patients, both before and 48–72 hours after major surgery, may be considered.	IIb	B	3,48,49
NT-proBNP and BNP measurements may be considered for obtaining independent prognostic information for peri-operative and late cardiac events in high-risk patients.	IIb	B	52,53,55
Universal pre-operative routine biomarker sampling for risk stratification and to prevent cardiac events is not recommended.	III	C	

BNP = B-type natriuretic peptide; NT-proBNP = N-terminal pro-brain natriuretic peptide.
NSQIP = National Surgical Quality Improvement Program.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

3.6 Non-invasive testing

Pre-operative non-invasive testing aims to provide information on three cardiac risk markers: LV dysfunction, myocardial ischaemia, and heart valve abnormalities, all of which are major determinants of adverse post-operative outcome. LV function is assessed at rest, and various imaging methods are available. For detection of myocardial ischaemia, exercise ECG and non-invasive imaging techniques may be used. Routine chest X-ray before non-cardiac surgery is not recommended without specific indications. 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.[56] Non-invasive testing should be considered not only for coronary artery revascularization but also for patient counselling, change of peri-operative management in relation to type of surgery, anaesthetic technique, and long-term prognosis.

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3.6.1 Non-invasive testing of cardiac disease

3.6.1.1 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 ECG offers important prognostic information and is predictive of long-term outcome, independent of clinical findings and peri-operative ischaemia.[57] However, the ECG may be normal or non-specific in patients with myocardial ischaemia or even with infarction.

Recommendations on routine pre-operative ECG

Recommendations	Class[a]	Level[b]	Ref.[c]
Pre-operative ECG is recommended for patients who have risk factor(s)[d] and are scheduled for intermediate- or high-risk surgery.	I	C	57
Pre-operative ECG may be considered for patients who have risk factor(s) and are scheduled for low-risk surgery.	IIb	C	
Pre-operative ECG may be considered for patients who have no risk factors, are above 65 years of age, and are scheduled for intermediate-risk surgery.	IIb	C	
Routine pre-operative ECG is not recommended for patients who have no risk factors and are scheduled for low-risk surgery.	III	B	71

ECG = electrocardiography.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.
[d]Clinical risk factors in *Table 4*.

3.6.1.2 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), echocardiography, magnetic resonance imaging (MRI) or multislice computed tomography (CT), all with similar accuracy. Echocardiography is the most readily available and versatile tool for evaluating ventricular function. Routine echocardiography is not recommended for the pre-operative evaluation of ventricular function but may be performed in asymptomatic patients with high surgical risk.[58] Pre-operative LV systolic dysfunction, moderate-to-severe mitral regurgitation, and increased aortic valve gradients are associated with major cardiac events.[59] The limited predictive value of LV function assessment for peri-operative outcome may be related to the failure to detect severe underlying IHD.

Recommendations on resting echocardiography in asymptomatic patients without signs of cardiac disease or electrocardiographic abnormalities

Recommendations	Class[a]	Level[b]
Rest echocardiography may be considered in patients undergoing high-risk surgery.	IIb	C
Routine echocardiography is not recommended in patients undergoing intermediate- or low-risk surgery.	III	C

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

3.6.2 Non-invasive testing of ischaemic heart disease

Physical exercise, using a treadmill or bicycle ergometer, provides an estimate of functional capacity, evaluates blood pressure and heart rate response, and detects myocardial ischaemia through ST-segment changes. The accuracy of exercise ECG varies significantly among studies.[56] Risk stratification with an exercise test is not suitable for patients with limited exercise capacity, owing to their inability to reach their target heart rate. Also, pre-existing ST-segment abnormalities at rest—especially in precordial leads V5 and V6—hamper reliable ST-segment analysis. A gradient of severity in the test result relates to the peri-operative outcome: the onset of a myocardial ischaemic response at low exercise workloads is associated with a significantly increased risk of peri-operative and long-term cardiac events. In contrast, the onset of myocardial ischaemia at high workloads is associated with only a minor risk increase, but higher than a totally normal test. Pharmacological stress testing with either nuclear perfusion imaging or echocardiography is more suitable in patients with limited exercise tolerance.

The role of myocardial perfusion imaging for pre-operative risk stratifications is well established. In patients with limited exercise capacity, pharmacological stress (dipyridamole, adenosine, or dobutamine) is an alternative stressor. 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 patients undergoing vascular surgery.[60] Study endpoints were peri-operative cardiac death and myocardial infarction. The authors included nine studies, totalling 1179 patients undergoing vascular surgery, with a 7% 30-day event rate. In this analysis, reversible ischaemia in $<20\%$ of the LV myocardium did not alter the likelihood of peri-operative cardiac events, compared with those without ischaemia. Patients with more extensive reversible defects from 20–50% were at increased risk.

A second meta-analysis pooled the results of 10 studies evaluating dipyridamole thallium-201 imaging in candidates for vascular surgery over a 9-year period from 1985 to 1994.[61] The 30-day cardiac death or non-fatal myocardial infarction 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 of the 10 studies analysed used semi-quantitative scoring, demonstrating a higher incidence of cardiac events in patients with two or more reversible defects.

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Table 4 Clinical risk factors according to the revised cardiac risk index[43]

• Ischaemic heart disease (angina pectoris and/or previous myocardial infarction[a])
• Heart failure
• Stroke or transient ischaemic attack
• Renal dysfunction (serum creatinine >170 μmol/L or 2 mg/dL or a creatinine clearance of <60 mL/min/1.73 m^2)
• Diabetes mellitus requiring insulin therapy

[a]According to the universal definition of myocardial infarction.[49]

Overall, the positive predictive value of reversible defects for peri-operative death or myocardial infarction has decreased in more recent studies. This is probably related to changes in peri-operative management and surgical procedures; however, because of the high sensitivity of nuclear imaging studies for detecting IHD, patients with a normal scan have an excellent prognosis.

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.[62] 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.[63] Multivariate predictors of post-operative events in patients with ischaemia were found to be a history of heart failure (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 has some limitations: it should not, for example, 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 and a negative test is associated with a very low incidence of cardiac events in patients undergoing surgery; however, the positive predictive value is relatively low (between 25% and 45%); this means that the postsurgical probability of a cardiac event is low, despite wall motion abnormality detection during stress echocardiography.

A negative DSE, performed before scheduled aortic surgery, does not, however, rule out post-operative myocardial necrosis.[64] Failure to achieve target heart rate is not uncommon, despite an aggressive DSE regimen. A negative DSE without resting wall motion abnormalities has excellent negative predictive value, regardless of the heart rate achieved. Patients with resting wall motion abnormalities are at increased risk for peri-operative events, even if ischaemia cannot be induced.[65]

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 peri-operative ischaemic events is similar with both pharmacological stressors, but that the accuracy varies with IHD prevalence.[61] In patients with a low prevalence of IHD, the diagnostic accuracy is reduced, compared with those with a high incidence of IHD.

Cardiovascular magnetic resonance (CMR) imaging can be used for detection of ischaemia; both perfusion and wall motion can be detected during stress and at rest.[66] Its accuracy in assessment of ischaemia is high, with a sensitivity of 83% and a specificity of 86% when wall motion is used (14 studies; 754 patients). When perfusion is assessed (24 studies; 1516 patients), its sensitivity was 91% and specificity 81%. When evaluated prospectively in a multicentre study, the sensitivity was 67% and the specificity was 61%.[67] There are limited data on CMR in the pre-operative setting; in one study dobutamine stress CMR was used in 102 patients undergoing major non-cardiac surgery; in multivariate analysis, myocardial ischaemia was the strongest predictor of peri-operative cardiac events (death, myocardial infarction, and heart failure).[68] Currently no data are available in the setting of pre-operative risk stratification.

Computed tomography can be used to detect coronary calcium, which reflects coronary atherosclerosis, and CT angiography is useful for excluding coronary artery disease (CAD) in patients who are at low risk of atherosclerosis.[69] Currently, no data are available in the setting of pre-operative risk stratification. All the various imaging tests have their intrinsic risks and these need to be taken into account when they are used.[70]

Recommendations on imaging stress testing before surgery in asymptomatic patients

Recommendations	Class[a]	Level[b]
Imaging stress testing is recommended before high-risk surgery in patients with more than two clinical risk factors and poor functional capacity (<4 METs).[c]	I	C
Imaging stress testing may be considered before high- or intermediate-risk surgery in patients with one or two clinical risk factors and poor functional capacity (<4 METs).[c]	IIb	C
Imaging stress testing is not recommended before low-risk surgery, regardless of the patient's clinical risk.	III	C

MET = metabolic equivalent
[a]Class of recommendation.
[b]Level of evidence.
[c]Clinical risk factors in *Table 4*.

How can these data contribute to a practical algorithm? Testing should only be performed if its results might influence peri-operative management. Patients with extensive stress-induced ischaemia represent a high-risk population in whom standard medical therapy appears insufficient to prevent a peri-operative cardiac event. Pre-operative testing is recommended in the case of high-risk surgery in patients with poor functional capacity (<4 METS) and more than two of the clinical risk factors listed in *Table 4*, but may also be considered in patients with fewer than three of these risk factors. Importantly, pre-operative testing might delay surgery. A similar recommendation is made 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 will alter peri-operative management in stable cardiac patients.

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3.7 Invasive coronary angiography

Coronary angiography is a well-established, invasive, diagnostic procedure but is rarely indicated for assessing the risk of patients undergoing non-cardiac surgery. There is a lack of information from randomized clinical trials, relating to its usefulness in patients scheduled for non-cardiac surgery. Also, adopting an invasive coronary angiography assessment may cause an unnecessary and unpredictable delay in an already planned surgical intervention, as well as adding an independent procedural risk to the overall risk. Despite the fact that CAD may be present in a significant number of patients requiring non-cardiac surgery, indications for pre-operative coronary angiography and revascularization are similar to angiography indications in the non-surgical setting.[56,72–75] Pre-operative treatment of myocardial ischaemia, either medically or with intervention, is recommended whenever non-cardiac surgery can be delayed.

Recommendations on pre-operative coronary angiography

Recommendations	Class[a]	Level[b]	Ref.[c]
Indications for pre-operative coronary angiography and revascularization are similar to those for the non-surgical setting.	I	C	56
Urgent angiography is recommended in patients with acute ST-segment elevation myocardial infarction requiring non-urgent, non-cardiac surgery.	I	A	75
Urgent or early invasive strategy is recommended in patients with NSTE-ACS requiring non-urgent, non-cardiac surgery according to risk assessment.	I	B	73
Pre-operative angiography is recommended in patients with proven myocardial ischaemia and unstabilized chest pain (Canadian Cardiovascular Society Class III–IV) with adequate medical therapy requiring non-urgent, non-cardiac surgery.	I	C	56,72
Pre-operative angiography may be considered in stable cardiac patients undergoing non-urgent carotid endarterectomy surgery.	IIb	B	76
Pre-operative angiography is not recommended in cardiac-stable patients undergoing low-risk surgery.	III	C	

NSTE-ACS = non-ST-segment elevation acute coronary syndromes.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

4. Risk-reduction strategies

4.1 Pharmacological

The stress of surgery and anaesthesia may trigger ischaemia through an increase in myocardial oxygen demand, a reduction in myocardial oxygen supply, or both. Besides specific risk-reduction strategies adapted to patient characteristics and type of surgery, pre-operative evaluation can check and optimize the control of cardiovascular risk factors.

4.1.1 Beta-blockers

Concerns were raised over a number of studies of the Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography (DECREASE) family,[77] and the results of these studies were not included in the present Guidelines.

The main rationale for peri-operative beta-blocker use is to decrease myocardial oxygen consumption by reducing heart rate, leading to a longer diastolic filling period and decreased myocardial contractility. Additional cardioprotective factors have been suggested; however, the answer to whether or not this translates into clinical benefit requires randomized trials analysing the incidence of cardiovascular events. Six randomized trials evaluating the effect of peri-operative beta-blockade on clinical endpoints have been published in English in peer-reviewed journals (*Table 5*).[78–83]

Two trials targeted patients at high risk for peri-operative complications relating to the type of surgery, the presence of IHD, or risk factors for peri-operative cardiac complications.[79,83] Three other trials did not require clinical risk factors, except for diabetes in one case.[80–82] The Peri-Operative ISchemic Evaluation (POISE) trial covered a wide spectrum of risk of peri-operative cardiac complications.[78] One trial randomized 200 patients with at least two IHD risk factors or with known IHD, who were scheduled for non-cardiac surgery under general anaesthesia, including 40% for major vascular surgery.[83] Atenolol was associated with a significant decrease in overall mortality at 6 months, which was sustained for up to 2 years; however, seven in-hospital deaths, five in the atenolol group and two in the placebo group, were not taken into account. The Peri-Operative Beta-BLockadE (POBBLE) trial randomized 103 low-risk patients undergoing elective infrarenal vascular surgery to metoprolol tartrate or placebo,[82] resulting in a similar incidence of death, myocardial infarction or stroke at 30 days (13% and 15%, respectively; $P = 0.78$). Patients at low cardiac risk and those with a history of myocardial infarction within the past 2 years were excluded. The Metoprolol after Vascular Surgery (MaVS) trial randomized 497 patients undergoing abdominal or infra-inguinal vascular surgery to metoprolol succinate or placebo.[80] The combined incidence of death, myocardial infarction, heart failure, arrhythmias, or stroke at 30 days was similar (10.2% and 12.0%, respectively; $P = 0.57$). The revised cardiac risk index was ≤ 2 in 90% of patients and ≤ 1 in 60%.

The Diabetes Post-Operative Mortality and Morbidity (DIPOM) trial randomized 921 patients with diabetes, age >39 years, and duration of surgery of >1 hour (39% low-risk surgery) to receive metoprolol succinate or placebo.[81] The combined incidence of death, myocardial infarction, unstable angina, or heart failure at 30 days was again similar (6% and 5%, respectively; $P = 0.66$); however, only 54% of patients had a history of IHD or an additional cardiac risk factor, and underwent high- or intermediate-risk surgery.

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Table 5 Summary of randomized, controlled trials evaluating the effect of peri-operative beta-blockade on post-operative mortality and non-fatal myocardial infarction

Study	n	Vascular Surgery (%)	Beta-blocker				Patient selection according to cardiac risk	30-day mortality, n/N (%)		30-day rate of non-fatal MI, n/N (%)	
			Type	Onset (before Surgery)	Duration (days after) surgery)	Dose Titration		Beta-blocker	Control	Beta-blocker	Control
Mangano et al.[83]	200	40	Atenolol	30 min	7	No	IHD or ≥2 risk factors	5/99 (5.1[a])	10/101 (9.9[a])	-	-
POBBLE[82]	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[80]	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[81]	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[79]	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[78]	8351	41	Metoprolol succinate	2–4 h	30	No	IHD or atherosclerosis or major vascular surgery or ≥3 risk factors	129/4174 (3.1)[b]	97/4177 (2.3)	152/4174 (3.6)[c]	215/4177 (5.1)

BBSA = Beta-Blocker in Spinal Anesthesia; DIPOM = Diabetic Postoperative Mortality and Morbidity; IHD = ischaemic heart disease; MaVS = Metoprolol after Vascular Surgery; MI = myocardial infarction; POBBLE = PeriOperative Beta-BlockadE; POISE = PeriOperative ISchemic Evaluation.
[a]At 6 months and including in-hospital deaths.
[b]$P = 0.0317$.
[c]$P = 0.0008$.

The POISE trial randomized 8351 patients to metoprolol succinate or placebo.[78] Patients were aged ≥45 years and had known CVD, or at least three of seven clinical risk factors for high-risk surgery, or were scheduled for major vascular surgery. Treatment consisted of metoprolol succinate 100 mg 2–4 hours before surgery, 100 mg during the first 6 hours after surgery, but medication was withheld if systolic blood pressure dipped below 100 mm Hg. Maintenance therapy started 12 hours later, bringing the total dose of metoprolol succinate in the first 24 hours to 400 mg in some patients. There was a 17% decrease in the primary composite endpoint of death, myocardial infarction, or non-fatal cardiac arrest at 30 days (5.8% vs. 6.9%; $P = 0.04$); however, the 30% decrease in non-fatal myocardial infarction (3.6% vs. 5.1%; $P < 0.001$) was offset by a 33% increase in total mortality (3.1% vs. 2.3%; $P = 0.03$) and a doubling of stroke incidence (1.0% vs. 0.5%; $P = 0.005$). Hypotension was more frequent with metoprolol (15.0% vs. 9.7%; $P < 0.0001$). *Post-hoc* analysis showed that hypotension carried the greatest attributable risk of death and stroke.[84]

Eight meta-analyses have pooled 9, 25, 5, 11, 6, 8, 22, and 33 published, randomized trials on peri-operative beta-blockers, totalling, respectively, 10 529, 12 928, 586, 866, 632, 2437, 2057, and 12 306 patients.[85–92] Four meta-analyses showed a significant reduction in peri-operative myocardial ischaemia and myocardial infarction in patients receiving beta-blockers,[88,89,91,92] this being more marked in high-risk patients. Two meta-analyses showed no significant reduction in peri-operative myocardial infarction or cardiac mortality in patients receiving beta-blockers.[87,90] These meta-analyses (except the two most recent ones)[85,86] have been criticized because of heterogeneity of included studies and types of surgery, inclusion of studies of the DECREASE family, imprecision regarding patients' cardiac risk profiles, and variable timing of beta-blocker administrations, doses, and targets.[93] The recent POISE trial had the greatest weight in all of these analyses. In POISE, all-cause mortality increased by 33% in patients receiving beta-blockers; peri-operative death in patients receiving metoprolol succinate were associated with peri-operative hypotension, bradycardia, and stroke. A history of cerebrovascular disease was associated with an increased risk of stroke. Hypotension was related to high-dose metoprolol without dose titration.

In a meta-analysis that excluded the DECREASE trials,[85] peri-operative beta-blockade was associated with a statistically significant 27% (95% CI 1–60) increase in mortality (nine trials, 10 529 patients) but the POISE trial again largely explained this result,[78] and also the reduced incidence of non-fatal myocardial infarction and increased incidence of non-fatal strokes. Another recent meta-analysis, involving 12 928 patients, examined the influence of beta-blockade on all-

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cause and cardiovascular mortality according to surgery-specific risk groups, beta-blocker treatment duration, and whether beta-blockade was titrated to targeted heart rate.[86] The benefit of beta-blockade was found in five high-risk surgery studies and in six studies using titration to targeted heart rate, of which one and two trials, respectively, were of the DECREASE family.

Discrepancies in the effects of beta-blockers can be explained by differences in patient characteristics, type of surgery, and the methods of beta-blockade (timing of onset, duration, dose titration, and type of drug). Also, problems arose by the inclusion of trials not designed to assess the effect on peri-operative cardiac risk or which used only a single beta-blocker dose before anaesthesia, without continuation after surgery.[87] Two meta-analyses suggested that differences between trials on the cardioprotective effect of beta-blockers could be attributed to variability in heart rate response.[86,94] In particular, the decrease in post-operative myocardial infarction was highly significant, with tight heart rate control.

In patients with clinical risk factors undergoing high-risk (mainly vascular) surgery, randomized trials, cohort studies, and meta-analyses provide some evidence supporting a decrease in cardiac mortality and myocardial infarction with beta-blockers (mainly atenolol). Peri-operative beta-blockade is also cost-effective in these patients; however, patients with myocardial ischaemia as demonstrated by stress testing are at high risk of peri-operative cardiac complications despite peri-operative beta-blocker use.

Conversely, in patients without clinical risk factors, randomized trials and cohort studies suggest that peri-operative beta-blockade does not decrease the risk of cardiac complications and may even increase this risk. A possible increase in mortality has been suggested by a retrospective cohort.[95] Bradycardia and hypotension may be harmful in patients with atherosclerosis, and enhance the risk of stroke and death. Also, peri-operative beta-blocker administration may enhance post-operative delirium in patients undergoing vascular surgery.

One cannot justify exposing low-risk patients to potential adverse 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. Increased mortality following pre-operative beta-blocker withdrawal has been reported in four observational studies.[96–99] Beta-blockers should be continued when prescribed for IHD or arrhythmias. When beta-blockers are prescribed for hypertension, the absence of evidence for a peri-operative cardioprotective effect with other antihypertensive drugs does not support a change of therapy. Beta-blockers should not be withdrawn in patients treated for stable heart failure due to LV systolic dysfunction. In decompensated heart failure, beta-blocker therapy should be adjusted to the clinical condition. If possible, non-cardiac surgery should be deferred so it can be performed under optimal medical therapy in a stable patient. Contra-indications to beta-blockers (asthma, severe conduction disorders, symptomatic bradycardia, and symptomatic hypotension) should be respected. In patients with intermittent claudication, beta-blockers have not been shown to worsen symptoms and are therefore not contra-indicated. In the absence of contra-indications, beta-blocker dose should be slowly up-titrated, starting at a low dose of a beta1-selective agent, to achieve a resting heart rate between 60 and 70 beats per minute (bpm). Beta1-selective blockers without intrinsic sympathomimetic activity are favoured and evidence exists that atenolol and bisoprolol are superior to metoprolol,[97,100–102] possibly due to the CYP2D6-dependent metabolism of metoprolol. Trials using metoprolol did not show a clear benefit.[78,80–82] A recent single-centre cohort study in 2462 pair-matched patients suggested that metoprolol or atenolol (analysed together) are associated with increased risk of post-operative stroke, compared with bisoprolol.[102]

Recommendations on beta-blockers

Recommendations	Class[a]	Level[b]	Ref.[c]
Peri-operative continuation of beta-blockers is recommended in patients currently receiving this medication.	I	B	96–99
Pre-operative initiation of beta-blockers may be considered in patients scheduled for high-risk surgery and who have ≥2 clinical risk factors or ASA status ≥3.[d]	IIb	B	86,95, 97
Pre-operative initiation of beta-blockers may be considered in patients who have known IHD or myocardial ischaemia.[d]	IIb	B	83,88, 106
When oral beta-blockade is initiated in patients who undergo non-cardiac surgery, the use of atenolol or bisoprolol as a first choice may be considered.	IIb	B	97,100 –102
Initiation of peri-operative high-dose beta-blockers without titration is not recommended.	III	B	78
Pre-operative initiation of beta-blockers is not recommended in patients scheduled for low-risk surgery.	III	B	86,97

ASA = American Society of Anesthesiologists; IHD = ischaemic heart disease.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.
[d]Treatment should ideally be initiated between 30 days and (at least) 2 days before surgery, starting at a low dose, and should be continued post-operatively.[83,98,103] The target is a resting heart rate 60–70 bpm,[86] and systolic blood pressure >100 mm Hg.[79,83]

Initiation of treatment and the optimal choice of beta-blocker dose are closely linked. Bradycardia and hypotension should be avoided. It is important to prevent overtreatment with fixed, high, initial doses, and doses should be decreased if this occurs. Beta-blocker dose should be slowly up-titrated and tailored to appropriate heart rate and blood pressure targets, requiring that treatment be initiated ideally more than 1 day (when possible at least 1 week and up to 30 days) before surgery, starting with a low dose.[83,98,103] In patients with normal renal function, atenolol treatment should start with a 50 mg daily dose, then adjusted before surgery to achieve a resting heart rate of 60-70 bpm[86] with systolic blood pressure >100 mm Hg.[83] The heart rate goal applies to the whole peri-operative period, using intravenous administration when oral administration is not possible. High doses should be avoided, particularly immediately before surgery. A retrospective study suggests that intra-operative

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mean arterial pressure should remain above 55 mm Hg.[104] Post-operative tachycardia should firstly lead to treatment of the underlying cause—for example, hypovolaemia, pain, blood loss, or infection—rather than simply increasing the beta-blocker dose.

When beta-blockers are indicated, the optimal duration of peri-operative beta-blockade cannot be derived from randomized trials. The occurrence of delayed cardiac events indicates a need to continue beta-blocker therapy for several months. For patients testing positive for pre-operative stress, long-term beta-blocker therapy should be used.

A high priority needs to be given to new, randomized, clinical trials to better identify which patients derive benefit from beta-blocker therapy in the peri-operative setting, and to determine the optimal method of beta-blockade.[105]

4.1.2 Statins

3-Hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) are widely prescribed in patients with or at risk of IHD. Patients with non-coronary atherosclerosis (carotid, peripheral, aortic, renal) should receive statin therapy for secondary prevention, irrespective of non-cardiac surgery. Statins also induce coronary plaque stabilization through pleiotropic effects, which may prevent plaque rupture and subsequent myocardial infarction in the peri-operative period.

Multiple observational studies have suggested that peri-operative statin use has a beneficial effect on the 30-day rate of death or myocardial infarction, and on long-term mortality and cardiovascular event rates.[107–110] In a prospective, randomized, controlled trial, 100 patients scheduled for vascular surgery were allocated to 20 mg of either atorvastatin or placebo once daily for 45 days, irrespective of their serum cholesterol concentrations.[111] At 6-month follow-up, atorvastatin significantly reduced the incidence of cardiac events (8% vs. 26%; $P = 0.03$). In patients in whom statins were introduced before intervention, two meta-analyses showed a significant reduction in the risk of post-operative myocardial infarction following invasive procedures,[112,113] however, these meta-analyses included more clinical trials relating to cardiac surgery or percutaneous procedures than to non-cardiac surgery. All-cause post-operative mortality was not reduced in most series, except in one observational study that used propensity score adjustment to account for differences in patient characteristics according to the treatment.[114] A recent Cochrane review focusing on vascular surgery in statin-naïve patients did not find any significant difference between statin-treated and control groups for the separate endpoints of all-cause mortality, cardiovascular mortality, and myocardial infarction, but these endpoints were assessed in only 178 patients.[115] Statins have also been associated with a decreased risk of complications after endovascular repair of AAA and a decreased risk of stroke after carotid stenting.[116,117]

Observational series suggest that peri-operative statin therapy is also associated with a lower risk of acute renal failure and with lower mortality in patients experiencing post-operative complications or multiple organ dysfunction syndrome.[114] Statins may decrease the risk of post-operative atrial fibrillation (AF) following major non-cardiac surgery.

Statin withdrawal more than four days after aortic surgery is associated with a three-fold higher risk of post-operative myocardial ischaemia.[118] A potential limitation of peri-operative statin use is the lack of a parenteral formulation; therefore, statins with a long half-life (e.g. atorvastatin) or extended release formulations (e.g. lovastatin) may be favoured to bridge the period immediately after surgery when oral intake is not feasible.

A concern relating to the use of peri-operative statin therapy has been the risk of statin-induced myopathy and rhabdomyolysis. Peri-operatively, 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. Early introduction of statins allows for better detection of potential side-effects.

According to current guidelines, most patients with peripheral artery disease (PAD) should receive statins. If they have to undergo open vascular surgery or endovascular intervention, statins should be continued afterwards. In patients not previously treated, statins should ideally be initiated at least 2 weeks before intervention for maximal plaque-stabilizing effects and continued for at least 1 month after surgery. In patients undergoing non-vascular surgery, there is no evidence to support pre-operative statin treatment if there is no other indication.

Recommendations on statins

Recommendations	Class[a]	Level[b]	Ref.[c]
Peri-operative continuation of statins is recommended, favouring statins with a long half-life or extended-release formulation.	I	C	
Pre-operative initiation of statin therapy should be considered in patients undergoing vascular surgery, ideally at least 2 weeks before surgery.	IIa	B	112,113, 115

[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

4.1.3 Nitrates

Nitroglycerine is well known for reversing myocardial ischaemia. The effect of peri-operative intravenous nitroglycerine on peri-operative ischaemia is a matter of debate and no effect has been demonstrated on the incidence of myocardial infarction or cardiac death. Also peri-operative use of nitroglycerine may pose a significant haemodynamic risk to patients, since decreased pre-load may lead to tachycardia and hypotension.

4.1.4 Angiotensin-converting enzyme inhibitors and angiotensin-receptor blockers

Independently of the blood pressure-lowering effect, angiotensin converting enzyme inhibitors (ACEIs) preserve organ function; however, data from an observational study suggested that, *regardless of the prescription of beta-blockers and statins*, ACEIs did not decrease the frequency of 30-day or 1-year death or cardiac complications after major vascular surgery in high-risk patients (revised cardiac index ≥ 3).[110] Despite the lack of specific data on angiotensin-receptor

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blockers (ARBs), the following recommendations apply to ACEIs and ARBs, given their numerous common pharmacological properties.

Additionally, peri-operative use of ACEIs or ARBs carries a risk of severe hypotension under anaesthesia, in particular following induction and concomitant beta-blocker use. Hypotension is less frequent when ACEIs are discontinued the day before surgery. Although this remains debatable, ACEIs withdrawal should be considered 24 hours before surgery when they are prescribed for hypertension. They should be resumed after surgery as soon as blood volume and pressure are stable. The risk of hypotension is at least as high with ARBs as with ACEIs, 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 treatment with ACEIs under close monitoring during the peri-operative period. When LV dysfunction is discovered during pre-operative evaluation in untreated patients in a stable condition, surgery should if possible be postponed, to allow for diagnosis of the underlying cause and the introduction of ACEIs and beta-blockers.

Recommendations on use of ACEIs and ARBs

Recommendations	Class[a]	Level[b]
Continuation of ACEIs or ARBs, under close monitoring, should be considered during non-cardiac surgery in stable patients with heart failure and LV systolic dysfunction.	IIa	C
Initiation of ACEIs or ARBs should be considered at least 1 week before surgery in cardiac-stable patients with heart failure and LV systolic dysfunction.	IIa	C
Transient discontinuation of ACEIs or ARBs before non-cardiac surgery in hypertensive patients should be considered.	IIa	C

ACEI = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; LV = left ventricular.
[a]Class of recommendation.
[b]Level of evidence.

4.1.5 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, which do not act directly on heart rate, and diltiazem or verapamil, which lower the heart rate.

The relevance of randomized trials assessing the peri-operative effect of calcium channel blockers is limited by their small size, lack of risk stratification, and the absence of systematic reporting of cardiac death and myocardial infarction. A meta-analysis pooled 11 randomized trials totalling 1007 patients. All patients underwent non-cardiac surgery under calcium channel blocker treatment. There was a significant reduction in the number of episodes of myocardial ischaemia and supraventricular tachycardia (SVT) in the pooled analyses; however, the decrease in mortality and myocardial infarction reached statistical significance only when both endpoints were combined in a composite of death and/or myocardial infarction (relative risk 0.35; 95% CI 0.08–0.83; $P < 0.02$). Subgroup analyses favoured diltiazem. Another study in 1000 patients undergoing acute or elective aortic aneurysm surgery showed that dihydropyridine use was independently associated with an increased incidence of peri-operative mortality.[119] 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, the continuation or introduction of heart rate-reducing calcium channel blockers may be considered in patients who do not tolerate beta-blockers. Additionally, calcium channel blockers should be continued during non-cardiac surgery in patients with vasospastic angina.

4.1.6 Alpha$_2$ receptor agonists

Alpha$_2$ receptor agonists reduce post-ganglionic noradrenaline output and might therefore reduce the catecholamine surge during surgery. The European Mivazerol trial randomized 1897 patients with IHD who underwent intermediate- or high-risk non-cardiac surgery. Mivazerol did not decrease the incidence of death or myocardial infarction in the whole population; however, there was a reduction of post-operative death or myocardial infarction observed in a sub-population of 904 patients undergoing vascular surgery. The international Peri-Operative ISchemic Evaluation 2 (POISE-2) trial randomized 10 010 patients undergoing non-cardiac surgery to clonidine or placebo. Clonidine did not reduce the rate of death or non-fatal myocardial infarction in general, or in patients undergoing vascular surgery (relative risk 1.08; 95% CI 0.93–1.26; $P = 0.29$). On the other hand, clonidine increased the risk of clinically important hypotension (relative risk 1.32; 95% CI 1.24–1.40; $P < 0.001$) and non-fatal cardiac arrest (relative risk 3.20; 95% CI 1.17–8.73; $P = 0.02$).[120] Therefore, alpha$_2$ receptor agonists should not be administered to patients undergoing non-cardiac surgery.

4.1.7 Diuretics

Diuretics are frequently used in patients with hypertension or heart failure. In general, diuretics for hypertension should be continued to the day of surgery and resumed orally when possible. If blood pressure reduction is required before oral therapy can be continued, other antihypertensive agents may be considered. In heart failure, dosage increase should be considered if symptoms or signs of fluid retention are present. Dosage reduction should be considered in patients with hypovolaemia, hypotension, or electrolyte disturbances. In general, diuretic treatment—if necessary to control heart failure—should be continued to the day of surgery and resumed orally when possible. In the peri-operative period, volume status in patients with heart failure should be monitored carefully and optimized by loop diuretics or fluids.

The possibility of electrolyte disturbance should be considered in any patient receiving diuretics. Hypokalaemia is reported to occur in up to 34% of patients undergoing surgery (mostly non-cardiac). It is well known to significantly increase the risk of ventricular fibrillation and cardiac arrest in cardiac disease. In a study of 688 patients with cardiac disease undergoing non-cardiac surgery, hypokalaemia was independently associated with peri-operative mortality. Importantly, the use of K^+ and Mg^{++}-sparing aldosterone antagonists reduces the risk of mortality in severe heart failure. Special attention should be

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given to patients taking diuretics and patients prone to developing arrhythmias. Any electrolyte disturbance—especially hypokalaemia and hypomagnesaemia—should be corrected in due time before surgery. 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.

4.2 Peri-operative management in patients on anti-platelet agents

4.2.1 Aspirin

Peri-operative evaluation of the impact of aspirin continuation or cessation on serious cardiovascular events or bleeding has disclosed controversial results with, on the one hand, a reduction of intra- and peri-operative stroke—but without influence on myocardial infarction during non-cardiac surgery—and, on the other hand, no statistical significance for the combined endpoint of vascular events. Additionally, concerns of promoting peri-operative haemorrhagic complications have often led to the discontinuation of aspirin in the peri-operative period. A large meta-analysis, including 41 studies in 49 590 patients, which compared peri-procedural withdrawal vs. bleeding risks of aspirin, concluded that the risk of bleeding complications with aspirin therapy was increased by 50%, but that aspirin did not lead to greater severity of bleeding complications.[121] In subjects at risk of—or with proven—IHD, aspirin non-adherence/withdrawal tripled the risk of major adverse cardiac events.

The POISE-2 trial randomized 10 010 patients undergoing non-cardiac surgery to aspirin or placebo.[122] The patients were stratified according to whether they had *not* been taking aspirin before the study (initiation stratum, with 5628 patients) or they were already on an aspirin regimen (continuation stratum, with 4382 patients). In the POISE-2 trial, aspirin was stopped at least three days (but usually seven days) before surgery. Patients less than six weeks after placement of a bare metal coronary stent, or less than one year after placement of a drug-eluting coronary stent, were excluded from the trial and the number of stented patients outside these time intervals was too small to draw firm conclusions as to the risk–benefit ratio. Additionally, only 23% of the study population had known prior CAD and patients undergoing carotid endarterecomy surgery were excluded. Patients started taking aspirin (at a dose of 200 mg) or placebo just before surgery and continued it daily (at a dose of 100 mg) for 30 days in the initiation stratum and for 7 days in the continuation stratum, after which they resumed their regular aspirin regimen. Aspirin did not reduce the rates of death or non-fatal myocardial infarction at 30 days (7.0% in the aspirin group vs. 7.1% in the placebo group; hazard ratio 0.99; 95% CI 0.86–1.15; $P = 0.92$). Major bleeding was more common in the aspirin group than in the placebo group (4.6% vs. 3.8%, respectively; hazard ratio 1.23; 95% CI 1.01–1.49; $P = 0.04$). The primary and secondary outcome results were similar in the two aspirin strata. The trial results do not support routine use of aspirin in patients undergoing non-cardiac surgery, but it is uncertain whether patients with a low peri-operative bleeding risk and a high risk of thrombo-embolic events could benefit from low-dose aspirin. Aspirin should be discontinued if the bleeding risk outweighs the potential cardiovascular benefit.[121,123–125] For patients undergoing spinal surgery or certain neurosurgical or ophthalmological operations, it is recommended that aspirin be discontinued for at least seven days.

In conclusion, the use of low-dose aspirin in patients undergoing non-cardiac surgery should be based on an individual decision, which depends on the peri-operative bleeding risk, weighed against the risk of thrombotic complications.

4.2.2 Dual anti-platelet therapy

Five to twenty-five percent of patients with coronary stents require non-cardiac surgery within 5 years following stent implantation. The prognosis of stent thrombosis appears to be worse than for *de novo* coronary occlusion, and premature cessation of dual anti-platelet therapy (DAPT) in patients with recent coronary stent implantation is the most powerful predictor for stent thrombosis. The consequences of stent thrombosis will vary according to the site of stent deployment, e.g. thrombosis of a left main stem stent is, in most cases, fatal.

The management of anti-platelet therapy, in patients who have undergone recent coronary stent treatment and are scheduled for non-cardiac surgery, should be discussed between the surgeon and the cardiologist, so that the balance between the risk of life-threatening surgical bleeding on anti-platelet therapy—best understood by the surgeon—and the risk of life-threatening stent thrombosis off DAPT—best understood by the cardiologist—can be considered. The 'standard' duration for DAPT after bare-metal stenting (BMS) is different to that for drug-eluting stent (DES) treatment .[126]

To reduce risk of bleeding and transfusion, current Guidelines recommend delaying elective non-cardiac surgery until completion of the full course of DAPT and, whenever possible, performing surgery without discontinuation of aspirin.[74] Patients who have undergone a previous percutaneous coronary intervention (PCI) may be at higher risk of cardiac events during or after subsequent non-cardiac surgery, particularly in cases of unplanned or urgent surgery following coronary stenting. While non-cardiac surgery performed early after balloon angioplasty is not associated with an increased risk of cardiac events,[127] stenting dramatically changes the scenario. Accordingly, mortality rates of up to 20% were reported in relation to peri-operative stent thrombosis when surgery was performed within weeks following coronary stenting and DAPT was discontinued.[128] Therefore, elective surgery should be postponed for a minimum of 4 weeks and ideally for up to 3 months after BMS implantation. Importantly, whenever possible, aspirin should be continued throughout surgery.[129] In 2002, DES were introduced in Europe and became widely accepted as an efficient tool for reducing in-stent re-stenosis; however, the major drawback of the first-generation DES was the need for prolonged DAPT (aspirin plus clopidogrel) for 12 months. A higher risk of non-cardiac surgery early after DES placement has been reported,[126] and a higher risk for major adverse cardiac events has also been shown during the first weeks after non-cardiac surgery in patients with implanted stents.[126,130] But, for the new-generation (second- and third-generation) DES, routine extension of DAPT beyond 6 months is no longer recommended based on currently available data. Observational data from new-generation zotarolimus-eluting and everolimus-eluting stents suggest that even shorter durations of DAPT may be sufficient,[131] and a randomized study showed a similar outcome in patients treated with 3 and 12 months of DAPT after PCI.[132]

In patients undergoing myocardial revascularization for high-risk ACS, DAPT treatment is recommended for 1 year irrespective of stent type. Overall, in patients undergoing non-cardiac surgery after recent ACS or stent implantation, the benefits of early surgery for a specific pathology (e.g. malignant tumours, vascular aneurysm repair) should be balanced against the risk of stent thrombosis and the strategy should be discussed.

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In summary, it is recommended that DAPT be administered for at least 1 month after BMS implantation in stable CAD,[133] for 6 months after new-generation DES implantation,[133] and for up to 1 year in patients after ACS, irrespective of revascularization strategy.[133] Importantly, a minimum of 1 (BMS) to 3 (new-generation DES) months of DAPT might be acceptable, independently of the acuteness of coronary disease, in cases when surgery cannot be delayed for a longer period; however, such surgical procedures should be performed in hospitals where 24/7 catheterization laboratories are available, so as to treat patients immediately in case of peri-operative atherothrombotic events. Independently of the timeframe between DES implantation and surgery, single anti-platelet therapy (preferably with aspirin) should be continued.

In patients needing surgery within a few days, current ESC Guidelines recommend withholding clopidogrel and ticagrelor for five days and prasugrel for seven days prior to surgery unless there is a high risk of thrombosis.[74] In contrast, other guidelines recommend using platelet function tests for optimal timing of surgery, as discussed in a recent publication.[134,135] However, the guidelines do not provide the 'ideal' platelet function assay or a 'bleeding cut-off', and more research in this area is needed.

For patients with a very high risk of stent thrombosis, bridging therapy with intravenous, reversible glycoprotein inhibitors, such as eptifibatide or tirofiban, should be considered. Cangrelor, the new reversible intravenous $P2Y_{12}$-inhibitor, has been shown to provide effective platelet inhibition but is not yet available.[136] The use of low-molecular-weight heparin (LMWH) for bridging in these patients should be avoided. Dual anti-platelet therapy should be resumed as soon as possible after surgery and, if possible, within 48 hours.

4.2.3 Reversal of anti-platelet therapy

For patients receiving anti-platelet therapy, who have excessive or life-threatening peri-operative bleeding, transfusion of platelets is recommended.

4.3 Peri-operative management in patients on anticoagulants

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

4.3.1 Vitamin K antagonists

Patients treated with oral anticoagulant therapy using vitamin K antagonists (VKAs) are subject to an increased risk of peri- and post-procedural bleeding. If the international normalized ratio (INR) is $\leq$1.5, surgery can be performed safely; however, in anticoagulated patients with a high risk of thrombo-embolism—for example, patients with:

- AF with a CHA_2DS_2-VASc [Cardiac failure, Hypertension, Age $\geq$75 (Doubled), Diabetes, Stroke (Doubled) – Vascular disease, Age 65–74 and Sex category (Female)] score of $\geq$4] *or*
- mechanical prosthetic heart valves, newly inserted biological prosthetic heart valves, *or*
- mitral valvular repair (within the past 3 months) *or*
- recent venous thrombo-embolism (within 3 months) *or*
- thrombophilia,

discontinuation of VKAs is hazardous and these patients will need bridging therapy with unfractionated heparin (UFH) or therapeutic-dose LMWH.[69,137] In general, there is better evidence for the efficacy and safety of LMWH, in comparison with UFH, in bridging to surgery.[69,137] LMWH is usually administered subcutaneously and weight-adjusted for once- or twice-daily administration without laboratory monitoring. In patients with a high thrombo-embolic risk, therapeutic doses of LMWH twice daily are recommended, and prophylactic once-daily doses in low-risk patients.[137] The last dose of LMWH should be administered no later than 12 hours before the procedure. Further adjustment of dose is necessary in patients with

Table 6 Pharmacological features of non-vitamin K antagonist oral anticoagulants

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Target	IIa (thrombin)	Xa	Xa	Xa
Application	Oral	Oral	Oral	Oral
Hours to C^{max}	1.25–3	2–4	3–4	1–2
Pro-drug	Yes	No	No	No
Food interactions	No	No	No	No
Bioavailability (%)	6.5	80–100	50	62
Drug interactions	P gp inhibitors or inductors	CYP3a4 inhibitors or inductors P gp inhibitors or inductors	CYP3a4 inhibitors or inductors P gp inhibitors or inductors	P gp inhibitors
Median half-life (hours)	12–14	7-11 (11–13 in the elderly)	12	6-11
Renal clearance (%)	85	33	27	37-50
Dose regimen	b.i.d.	q.d.	b.i.d.	q.d

b.i.d. = *bis in diem* (twice daily); C_{max} = maximum concentration; CYP3a4 = cytochrome P3a4 enzyme; P gP = platelet glycoprotein; q.d. = *quaque die* (once daily).

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moderate-to-high kidney function impairment. It is recommended that VKA treatment be stopped 3–5 days before surgery (depending on the type of VKA), with daily INR measurements, until ≤1.5 is reached, and that LMWH or UFH therapy be started one day after discontinuation of VKA—or later, as soon as the INR is <2.0.

In patients with mechanical prosthetic heart valves, the evidence in favour of intravenous UFH is more solid; thus in some centres these patients are hospitalized and treated with UFH until four hours before surgery, and treatment with UFH is resumed after surgery until the INR is within the therapeutic range.[69] On the day of the procedure, the INR should be checked. 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 patient's haemostatic status, but at least 12 hours after the procedure. VKAs should be resumed on day 1 or 2 after surgery—depending on adequate haemostasis—with the pre-operative maintenance dose plus a boosting 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 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- or minor skin surgery, no change in oral anticoagulation therapy is needed; however, it is wise to keep INR levels in the lower therapeutic range.

4.3.2 Non-vitamin K antagonist oral anticoagulants

In patients treated with the non-VKA direct oral anticoagulants (NOACs) dabigatran (a direct thrombin inhibitor), rivaroxaban, apixaban, or edoxaban (all direct factor Xa inhibitors), all of which have a well-defined 'on' and 'off' action, 'bridging' to surgery is in most cases unnecessary, due to their short biological half-lives (*Table 6*).[138]

An exception to this rule is the patient with high thrombo-embolic risk, whose surgical intervention is delayed for several days. The overall recommendation is to stop NOACs for 2–3 times their respective biological half-lives prior to surgery in surgical interventions with 'normal' bleeding risk, and 4–5 times the biological half-lives before surgery in surgical interventions with high bleeding risk.[139,140] New tests for better quantification of activity levels of the various NOACs are under development. In general, reduced kidney function or moderate-to-high increased bleeding risk should lead to earlier cessation of NOACs. If patients are pre-treated with dabigatran, which has about an 80% renal excretion rate, the individual glomerular filtration rate determines the time of its cessation prior to surgery.[139,141] Kidney function is thus essential for tailoring dabigatran therapy, and earlier cessation is recommended for all NOACs if the bleeding risk is increased.

Because of the fast 'on'-effect of NOACs (in comparison with VKAs), resumption of treatment after surgery should be delayed for 1–2 (in some cases 3–5) days, until post-surgical bleeding tendency is diminished.

4.3.3 Reversal of anticoagulant therapy

4.3.3.1 Vitamin K antagonists

In patients who are receiving VKAs and who require reversal of the anticoagulant effect for an urgent surgical procedure, low-dose (2.5–5.0 mg) intravenous or oral vitamin K is recommended. The effect of vitamin K on INR will first be apparent after 6–12 hours. If more immediate reversal of the anticoagulant effect of VKAs is needed, treatment with fresh-frozen plasma or prothrombin complex concentrate (PCC), is recommended, in addition to low-dose intravenous or oral vitamin K.

In patients receiving UFH and requiring reversal of the anticoagulant effect for an urgent surgical procedure, cessation of therapy is sufficient, because coagulation is usually normal four hours after cessation. When UFH is given subcutaneously, the anticoagulant effect is more prolonged. For immediate reversal, the antidote is protamine sulphate. The dose of protamine sulphate can be calculated by assessment of the amount of heparin received in the previous two hours. (http://www.medicines.org.uk/emc/medicine/10807/spc). The dose of protamine sulphate for reversal of a heparin infusion is 1 U per 1 U of heparin sodium.

In patients who are receiving LMWHs, the anticoagulant effect may be reversed within eight hours of the last dose because of the short half-life. If immediate reversal is required, intravenous

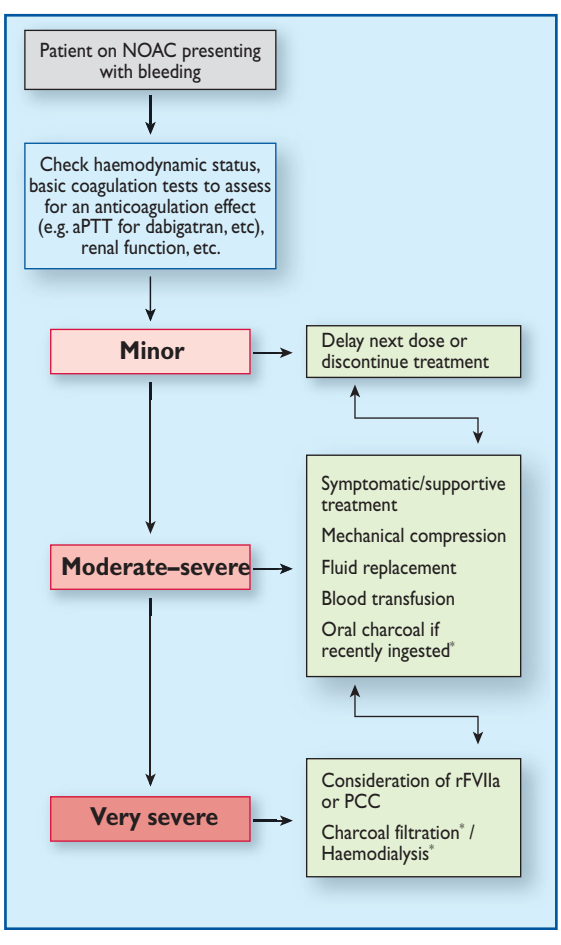

Figure 2 Management of bleeding in patients taking non-vitamin K antagonist direct oral anticoagulants. From Camm *et al.* 2012.[144] *With dabigatran; aPTT = activated partial thromboplastin time; NOAC = non-vitamin K antagonist direct oral anticoagulant; PCC = prothrombin coagulation complex; rFVIIa = activated recombinant factor VII.

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protamine sulphate can be used, but anti-Xa activity is never completely neutralized (maximum 50%).

4.3.3.2 *Non-vitamin K antagonist oral anticoagulants*

When severe bleeding complications occur under the influence of NOACs, symptomatic treatment should be initiated (*Figure 2*) because of the lack of specific antidotes (these are currently under development). Preliminary data have shown a potential benefit for the use of PCC or activated PCC when bleeding occurs under the direct factor Xa inhibitor rivaroxaban, and is also applicable to apixaban[142] and dabigatran,[143] whereas haemodialysis is an effective method for eliminating dabigatran from the circulation but does not help when a direct factor Xa inhibitor has been used (*Figure 2*).

Recommendations on anti-platelet therapy

Recommendations	Class[a]	Level[b]	Ref.[c]
It is recommended that aspirin be continued for 4 weeks after BMS implantation and for 3–12 months after DES implantation, unless the risk of life-threatening surgical bleeding on aspirin is unacceptably high.	I	C	
Continuation of aspirin, in patients previously thus treated, may be considered in the peri-operative period, and should be based on an individual decision that depends on the peri-operative bleeding risk, weighed against the risk of thrombotic complications.	IIb	B	121,122
Discontinuation of aspirin therapy, in patients previously treated with it, should be considered in those in whom haemostasis is anticipated to be difficult to control during surgery.	IIa	B	121,122
Continuation of $P2Y_{12}$ inhibitor treatment should be considered for 4 weeks after BMS implantation and for 3–12 months after DES implantation, unless the risk of life-threatening surgical bleeding on this agent is unacceptably high.	IIa	C	
In patients treated with $P2Y_{12}$ inhibitors, who need to undergo surgery, postponing surgery for at least 5 days after cessation of ticagrelor and clopidogrel—and for 7 days in the case of prasugrel—if clinically feasible, should be considered unless the patient is at high risk of an ischaemic event.	IIa	C	

BMS = bare-metal stent; DES = drug-eluting stent.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

4.4 Revascularization

The role of routine, prophylactic, invasive, coronary diagnostic evaluation and revascularization in reducing coronary risk for non-cardiac surgery remains ill-defined. Indications for pre-operative coronary angiography and revascularization, in patients with known or suspected IHD who are scheduled for major non-cardiac surgery, are similar to those in the non-surgical setting.[74] Control of myocardial ischaemia before surgery is recommended whenever non-cardiac surgery can be safely delayed. There is, however, no indication for routinely searching for the presence of myocardial (silent) ischaemia before non-cardiac surgery.

The main reason for pre-operative myocardial revascularization is the potential prevention of peri-operative myocardial ischaemia that leads to necrosis or electric/haemodynamic instability at the time of surgery. Coronary pathology underlying fatal peri-operative myocardial infarctions revealed that two-thirds of the patients had significant left-main or three-vessel disease.[145] Most of the patients did not exhibit plaque fissuring and only one-third had an intracoronary thrombus. These findings suggest that a substantial proportion of fatal peri-operative myocardial infarctions may have resulted from low-flow, high-demand ischaemia, owing to the stress of the operation in the presence of fixed coronary artery stenoses and therefore amenable to revascularization. In patients who underwent coronary angiography before vascular surgery, a number of non-fatal peri-operative myocardial infarctions occurred as a consequence of plaque rupture in arteries without high-grade stenosis. These results are not surprising, considering the extreme and complex stress situations associated with surgery—such as trauma, inflammation, anaesthesia, intubation, pain, hypothermia, bleeding, anaemia, fasting, and hypercoagulability—which may induce multiple and complex pathophysiological responses.[146]

The Coronary Artery Surgery Study (CASS) database includes almost 25 000 patients with CAD, initially allocated to either coronary artery bypass graft (CABG) surgery or medical management, with a follow-up of >10 years, and 3368 underwent non-cardiac surgery during follow-up.[147] A retrospective analysis of this population suggested that vascular, abdominal, and major head and neck surgeries were associated with a higher risk of peri-operative myocardial infarction and death in the presence of non-revascularized CAD. Furthermore, the study showed that patients who were clinically stable in the years after CABG had a reduced risk of cardiac complications in the event that they required non-cardiac surgery. This protective effect of previous coronary revascularization was more pronounced in patients with triple-vessel CAD and/or depressed LV function, as well as in those undergoing high-risk surgery, and lasted for at least six years; however, the study was performed at a time when medical therapy did not meet current standards. It can be concluded that asymptomatic patients who underwent CABG within the previous six years are relatively protected from myocardial infarction complicating non-cardiac surgery and may undergo non-cardiac surgery without routine pre-operative stress testing. This may not be the recommendation for patients with decreased LV function, as illustrated in a small cohort of 211 patients who underwent non-cardiac surgery within one year of CABG and in whom peri-operative predictors for mortality at one year were: LV ejection fraction (LVEF) <45% ($P < 0.001$), elevated right ventricular systolic pressure

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($P = 0.03$), emergency operation (OR 6.8), need for dialysis ($P = 0.02$) or ventilator support ($P = 0.03$).[148]

As mentioned above, patients who have had a previous PCI may be at higher risk of cardiac events during or after subsequent non-cardiac surgery, particularly in cases of unplanned or urgent surgery following coronary stenting. It is therefore preferable, whenever possible, to postpone elective surgery until 12 months after DES implantation.[149] However, recent data have suggested that, beyond six months following newer-generation DES implantation—and, for some specific DES devices, beyond three months of DES implantation—the peri-operative cardiac event rates may be acceptable.[126,132,150] Independently of the interval between DES implantation and surgery, aspirin should be continued and, in cardiac-stable/asymptomatic patients with recent myocardial infarction treated with stenting, the timing of non-cardiac, non-urgent surgery will in part be dictated by the type of stent implanted.

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

Recommendations	Class[a]	Level[b]	Ref.[c]
It is recommended that, except for high-risk patients, asymptomatic patients who have undergone CABG in the past 6 years be sent for non-urgent, non-cardiac surgery without angiographic evaluation.[d]	I	B	147,148
Consideration should be given to performing non-urgent, non-cardiac surgery in patients with recent BMS implantation after a minimum of 4 weeks and ideally 3 months following the intervention.[d]	IIa	B	129
Consideration should be given to performing non-urgent, non-cardiac surgery in patients who have had recent DES implantation no sooner than 12 months following the intervention. This delay may be reduced to 6 months for the new-generation DES.[d]	IIa	B	149,150
In patients who have had recent balloon angioplasty, surgeons should consider postponing non-cardiac surgery until at least 2 weeks after the intervention.	IIa	B	127,151

BMS = bare-metal stent; CABG = coronary artery bypass graft surgery; DES = drug-eluting stent.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.
[d]Aspirin to be continued throughout peri-operative period.

4.4.1 Prophylactic revascularization in patients with asymptomatic or stable ischaemic heart disease

Giving clear recommendations on prophylactic revascularization in patients with asymptomatic or stable IHD is challenging, as most of the data are derived from retrospective studies and registries.

The Coronary Artery Revascularization Prophylaxis (CARP) trial compared optimal medical therapy with revascularization (CABG or PCI) in patients with stable IHD before major vascular surgery.[152] Of 5859 patients screened at 18 centres of the United States Department of Veterans Affairs, 510 patients were enrolled in a randomized trial. Patients were included, based on increased risk for peri-operative cardiac complications, as assessed by the consultant cardiologist on the basis of a combination of cardiovascular risk factors and the detection of ischaemia on non-invasive testing; 28% of the study patients had three or more clinical risk factors and 49% had two or more variables as defined by the revised cardiac risk index. There was no difference in either mortality or peri-operative myocardial infarction at 2.7 years after commencement of the trial. The results of the CARP study indicated that systematic prophylactic revascularization before vascular surgery does not improve clinical outcomes in stable patients.

A second prospective, randomized trial included 208 patients, selected on the basis of a revised cardiac risk index, who were scheduled for major vascular surgery.[153] Patients were randomly allocated to either a 'selective strategy' in which coronary angiography was performed, based on the results of non-invasive tests, or to a 'systematic strategy', in which patients routinely underwent a pre-operative coronary angiography. While the rate of myocardial revascularization was higher in the systematic strategy group (58.1% vs. 40.1%), the peri-operative, in-hospital, adverse cardiac event rate (defined as mortality, non-fatal myocardial infarction, cerebrovascular accident, heart failure, and need for new cardiac revascularization procedures), although higher in the selective strategy group, was not significantly different from that in the systematic strategy group (11.7% vs. 4.8%; $P = 0.1$). In contrast, the long-term outcome (after 58 $\pm$ 17 months) in terms of survival and freedom from cardiac events was significantly better in the systematic strategy group.

A recent randomized, prospective, controlled trial, focussing on a particular homogeneous subset of non-cardiac surgical interventions (CEA), examined the value of pre-operative coronary angiography and stenting in 426 patients without history of CAD or cardiac symptoms and with normal cardiac ultrasound and electrocardiography results. The patients were randomized to pre-operative coronary angiography and—if needed—revascularization, or to no coronary angiography. The primary combined endpoint was the incidence of any post-operative myocardial ischaemic events combined with the incidence of complications of coronary angiography and stenting. In the angiography group, 68 patients (31%) experienced a significant coronary artery stenosis; 66 of these patients underwent stenting (87% with a DES) and two underwent CABG, with no post-operative events. In the non-angiography group, nine ischaemic events were observed (4.2%; $P = 0.01$). In this particular group of patients, the results suggest a short-term benefit of systematic coronary angiography.[76]

Covering 3949 patients enrolled in 10 studies between the years 1996 and 2006 (nine observational and the CARP randomized trial), a meta-analysis that addressed the value of pre-operative coronary revascularization before non-cardiac surgery revealed no significant difference between coronary revascularization and medical management groups, in terms of post-operative mortality and

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myocardial infarction (OR 0.85; 95% CI 0.48–1.50 and OR 0.95; 95% CI 0.44–2.08, respectively).[154] There were no long-term outcome benefits associated with prophylactic coronary revascularization (OR 0.81; 95% CI 0.40–1.63 for long-term mortality and OR 1.65; 95% CI 0.70–3.86 for late adverse cardiac events); thus, in asymptomatic patients or those with stable CAD, prophylactic coronary angiography—and, if needed, revascularization before non-cardiac surgery—does not confer any beneficial effects as compared with optimal medical management in terms of peri-operative mortality, myocardial infarction, long-term mortality, and adverse cardiac events.

Successful performance of a vascular procedure, without prophylactic revascularization, in a stable coronary patient, does not imply that the patient would not require subsequent revascularization. Despite the lack of extensive scientific data, myocardial revascularization may be recommended in patients presenting with persistent signs of extensive ischaemia before elective non-cardiac surgery similar to non-surgical settings recommended by the ESC Guidelines.[56]

4.4.2 Type of prophylactic revascularization in patients with stable ischaemic heart disease

Occasionally, patients with stable IHD may require elective surgery, which may be postponed for several months and up to a year. There are no solid data to guide a revascularization strategy in such a case. It seems reasonable to propose a cardiovascular work-up according to the ESC Guidelines on stable *angina pectoris*.[56] Revascularization should be considered, in order to improve symptoms and prognosis in patients with obstructive CAD. All patients considered for revascularization should receive optimal medical treatment. The timing of revascularization is critical and depends on the clinical presentation: stable vs. ACS. The type of revascularization, CABG vs. PCI, depends on the extent of CAD and technical feasibility and is discussed in detail in the ESC Guidelines on myocardial revascularization,[74] of which a new edition will be published in 2014. Percutaneous coronary intervention should be performed to improve symptoms in stable symptomatic patients with single or multi-vessel disease, in whom intervention is technically appropriate and procedural risk does not outweigh the potential benefit. The choice between PCI and CABG, often a matter of debate, will depend on several factors: according to the 5-year results of the Synergy between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery (SYNTAX) trial, CABG should remain the standard of care for patients with complex lesions (high or intermediate SYNTAX scores). For patients with less-complex disease (low SYNTAX scores) or left-main coronary disease (low or intermediate SYNTAX scores) PCI is an acceptable alternative.[155] In the presence of minimal symptoms or their absence, these patients may be treated medically. If PCI is performed before non-cardiac surgery, according to the previous edition of these Guidelines, BMS is advocated in order not to delay the surgery; however, if the data from recent trials evaluating newer DES devices are confirmed, this recommendation may no longer be valid and certain new-generation DES may be used in low-risk patients requiring early non-cardiac surgery.[132] If non-cardiac surgery cannot be postponed, CABG should be favoured over BMS-based PCI in patients with a higher risk of re-stenosis (small diameter vessel; long lesions; multiple stents required; left-main trunk lesions) unless the need for a shorter duration of DAPT, using new-generation DES devices, is confirmed.

Recommendations for prophylactic revascularization in stable/asymptomatic patients

Recommendations	Class[a]	Level[b]	Ref.[c]
Performance of myocardial revascularization is recommended according to the applicable guidelines for management in stable coronary artery disease.	I	B	56
Late revascularization after successful non-cardiac surgery should be considered, in accordance with ESC Guidelines on stable coronary artery disease.	I	C	
Prophylactic myocardial revascularization before high-risk surgery may be considered, depending on the extent of a stress-induced perfusion defect.	IIb	B	147
Routine prophylactic myocardial revascularization before low- and intermediate-risk surgery in patients with proven IHD is not recommended.	III	B	152

IHD = ischaemic heart disease.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

4.4.3 Revascularization in patients with non-ST-elevation acute coronary syndrome

No trial has yet investigated the role of prophylactic revascularization in patients with NSTE-ACS requiring non-cardiac surgery; therefore, if the clinical condition requiring non-cardiac surgery is not life-threatening, priority should be given to the management of NSTE-ACS. In such cases, the 2011 ESC Guidelines on the management of NSTE-ACS apply.[73] With regard to the type of coronary revascularization employed in patients later requiring non-cardiac surgery, most undergo PCI. In the rare scenario of NSTE-ACS linked with the need for subsequent early non-cardiac surgery, at the time of PCI, preference should be given either to BMS, in order to avoid delaying surgery beyond 1 and preferably 3 months, or to new-generation DES if data from recent trials confirm non-inferiority.[156,157] In rare cases, balloon angioplasty alone may be a reasonable strategy if a good acute result is expected, because aspirin—rather than dual anti-platelet therapy—may be sufficient.[156]

The value of coronary revascularization for NSTE-ACS, in patients who later require non-cardiac surgery, has been addressed in a retrospective analysis covering 16 478 patients who, between 1999 and 2004, had a myocardial infarction and underwent hip surgery, cholecystectomy, bowel resection, elective AAA repair, or lower extremity amputation in a period of up to three years following the myocardial infarction. This study showed that patients who were revascularized before surgery had an approximately 50% lower rate of re-infarction (5.1% vs. 10.0%; $P < 0.001$) as well as 30-day (5.2% vs. 11.3%; $P < 0.001$) and 1-year mortality (18.3% vs. 35.8%;

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$P < 0.001$) compared with those who were not revascularized. This large sample, representing real-world practice, suggests that patients with a recent myocardial infarction can benefit from pre-operative revascularization.[158]

Recommendations on routine myocardial revascularization in patients with NSTE-ACS

Recommendations	Class[a]	Level[b]	Ref.[c]
If non-cardiac surgery can safely be postponed, it is recommended that patients should be diagnosed and treated in line with the guidelines on NSTE-ACS.	I	A	73,75, 133,158
In the unlikely combination of a life-threatening clinical condition requiring urgent non-cardiac surgery and revascularization for NSTE-ACS, the expert team should discuss, case by case, the priority of surgery.	IIa	C	133
In patients who have undergone non-cardiac surgery, aggressive medical treatment and myocardial revascularization according to the guidelines on NSTE-ACS are recommended following surgery.	I	B	73
If PCI is indicated before semi-urgent surgery, the use of new-generation DES, BMS or even balloon angioplasty is recommended.	I	B	151,156

ACS = acute coronary syndromes; BMS = bare-metal stent; DES = drug-eluting stent; NSTE-ACS = non–ST-elevation acute coronary syndrome; PCI = percutaneous coronary intervention.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

5. Specific diseases

Several specific diseases merit special consideration in terms of cardiovascular pre-operative assessment.

5.1 Chronic heart failure

The diagnosis of heart failure requires the presence of symptoms and signs typical of heart failure and, in addition, evidence of reduced LV function [heart failure with reduced LVEF (HF-REF)] or a non-dilated left ventricle with normal or nearly normal systolic function and relevant structural disease and/or diastolic dysfunction [heart failure with preserved LVEF (HF-PEF)].[159] The prevalence of heart failure in developed countries is 1–2%, but rises to ≥10% among persons ≥70 years of age.[160]

Heart failure is a well-recognized factor for peri-operative and post-operative cardiac events and is an important predictor in several commonly used risk scores.[41–43,161–164] In a large registry analysis of 160 000 Medicare procedures on patients aged ≥65 years, heart failure was present in 18% and was associated with a 63% increased risk of operative mortality and a 51% greater risk of 30-day all-cause re-admission, compared with the CAD group or patient group without heart failure.[163] A reduced LVEF of ≤35% was found to be a strong predictor of post-operative cardiac events following vascular surgery.[165] The prognostic impact of HF-PEF on peri-operative morbidity and mortality is not well defined. One study found no significant differences in events between controlled HF-PEF and HF-REF patients undergoing non-cardiac surgery,[166] whereas another found that only those with severely depressed LVEF (<30%) had increased peri-operative event rates, compared with a group with moderate (LVEF 30–40%) or mildly (LVEF >40, <50%) reduced LV function.[167] Compared with HF-REF patients, HF-PEF patients tend to be older, female, more likely to have hypertension and AF, and less likely to have CAD; generally, their prognoses are also better.[168] In the absence of evidence-based studies, the similar peri-operative management can be recommended in patients with HF-PEF as in patients with HF-REF, with emphasis also on parameters besides LVEF, such as general clinical status, evidence of volume overload, and increased levels of natriuretic peptides.

Transthoracic echocardiography (TTE) is a key element in the pre-operative assessment of patients with known or suspected heart failure. LVEF, as well as LV and atrial volumes should be measured with bi-planar or three-dimensional echocardiography.[169] Assessments of valve function and diastolic function (such as E/e' ratio) are likewise of major importance,[170] as is evaluation of inferior *vena cava* diameter for the determination of volume status and right atrial pressure. Deformation imaging with strain analysis may reveal dysfunction that is not apparent using traditional methods.[170] The information on cardiac structure and function obtained by TTE provides important prognostic information before non-cardiac surgery.[59,171] Thus, routine pre-operative echocardiography should be considered in high-risk surgical populations; however, routine echocardiography is not indicated in every cardiac patient. In a large Canadian cohort study, pre-operative echocardiography was not associated with improved survival or shorter hospital stay following major non-cardiac surgery.[172] In emergency non-cardiac surgery, a pre-operative-focussed TTE examination may significantly alter diagnosis and management.[173] In patients with a poor echocardiographic window, CMR imaging is an excellent method for the evaluation of both cardiac structure and function.[174]

The pre-operative levels of natriuretic peptides (BNP or NT proBNP) are strongly correlated to the prognosis of heart failure and to peri-operative and post-operative morbidity and mortality.[3,175,176] Compared with a pre-operative natriuretic-peptide measurement alone, additional post-operative natriuretic-peptide measurement enhanced risk stratification for the composite outcomes of death or non-fatal myocardial infarction at 30 days and ≥ 180 days after non-cardiac surgery.[55] Thus, the assessment of natriuretic peptides should form part of a routine pre-operative evaluation when cardiac dysfunction is known or suspected.

The best assessment of a patient's overall functional capacity is achieved by performing a cardiopulmonary exercise test (CPX/CPET).[177] Both the cardiac and pulmonary reserve and their interaction can then be evaluated; this is far more accurate than judging the capacity by interview alone. An anaerobic threshold of <11 mL O_2/kg/min has been used as a marker of increased risk.[177]

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Two review papers have assessed the role of CPX as a pre-operative evaluation tool.[178,179] Meta-analyses are difficult, due to heterogeneity in methodology and outcome measures. There are no 'blinded' studies and the CPX results may influence the decision on whether to operate on a patient with a potentially serious disease and prognosis. One of the above papers concludes that paucity of robust data precludes routine adoption of CPX in risk-stratifying patients undergoing major vascular surgery,[178] while the other reports that peak oxygen consumption—and possibly anaerobic threshold—are valid predictors of peri-operative morbidity and mortality in patients undergoing non-cardiopulmonary thoraco-abdominal surgery.[179]

The current ESC Guidelines on acute and chronic heart failure give a strong recommendation for the use of optimal tolerated doses of ACE inhibitors (or ARBs in the case of ACE intolerance), beta-blockers, and aldosterone antagonists as primary treatment strategies in patients with HF-REF, to reduce morbidity and mortality.[159] Digitalis is a third-level drug to be considered in patients treated optimally with recommended drugs.[159] All patients with heart failure, who are scheduled for non-cardiac surgery, should be treated optimally according to these recommendations. Furthermore, HF-REF patients with LVEF $\leq$35% and left bundle branch block with QRS $\geq$120 ms should be evaluated with respect to cardiac resynchronization therapy (CRT) or CRT-defibrillator (CRT-D) therapy before major surgery.[159] Diuretics are recommended in heart failure patients who have signs or symptoms of congestion (see section 4.1.7).[159]

In patients with newly diagnosed severe systolic heart failure, it is recommended that non-urgent surgery be deferred for at least three months to allow a new medical therapy and/or intervention ample time to improve LV function and LV remodelling.[164] Rapid pre-operative initiation of high doses of beta-blockers[78] and/or ACEIs, without adequate time for dose titration, is not recommended. Patients with heart failure should preferably be euvolemic before elective surgery, with stable blood pressure and optimal end-organ perfusion.

Although continuation of ACEIs/ARBs until the day of surgery has been associated with an increased incidence of hypotension,[180] it is in general recommended that all heart-failure medications, such as ACE inhibitors, ARBs, and beta-blockers, be continued and that the patient's haemodynamic status be carefully monitored and give appropriate volume replacement when necessary. In patients considered susceptible to hypotension, transient discontinuation the day before surgery may be considered. Evening dosage of ACEIs/ARBs the day before surgery—and not on the morning of surgery—may be considered in order to avoid hypotension, whereas beta-blockade should be continued if possible. Heart failure medications should be re-instituted post-operatively, as soon as clinical conditions allow. Consider also the possibility of giving the medications via nasogastric tube or bioequivalent intravenous dose. Regarding patients with LV-assist devices, who are scheduled for non-cardiac surgery, they should be evaluated pre-operatively by the centre responsible for implantation and follow-up. Patients with HF-PEF have an increased stiffness of the left ventricle and are susceptible to pulmonary oedema with fluid overload. Adequate peri-operative monitoring, attention to volume status, control of afterload, and adequate diuretic treatment are important considerations for these patients.

Post-operative heart failure may pose diagnostic challenges, as it often presents atypically and may have a different aetiology from the non-surgical setting. The evaluation should include physical examination, ECG, serial biomarker measurements for both ischaemic myocardial damage and natriuretic peptides, 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-operative and immediate post-operative setting. In the period after surgery, fluids given during the operation may be mobilized, causing hypervolaemia and pulmonary congestion. Careful attention to fluid balance is therefore essential.

Once the aetiology of post-operative heart failure has been diagnosed, treatment is similar to the non-surgical setting. Patients who develop heart failure have a significantly increased risk of hospital re-admission after surgical procedures, confirming the need for careful discharge planning and close follow-up, ideally using a multidisciplinary approach.[159]

Recommendations on heart failure

Recommendations	Class[a]	Level[b]	Ref.[c]
It is recommended that patients with established or suspected heart failure, and who are scheduled for non-cardiac intermediate or high-risk surgery, undergo evaluation of LV function with transthoracic echocardiography and/or assessment of natriuretic peptides, unless they have recently been assessed for these.	I	A	55,165, 167,175,176
It is recommended that patients with established heart failure, who are scheduled for intermediate or high-risk non-cardiac surgery, be therapeutically optimized as necessary, using beta-blockers, ACEIs or ARBs, and mineralocorticoid antagonists and diuretics, according to ESC Guidelines for heart failure treatment.	I	A	159
In patients with newly diagnosed heart failure, it is recommended that intermediate- or high-risk surgery be deferred, preferably for at least 3 months after initiation of heart failure therapy, to allow time for therapy up-titration and possible improvement of LV function.	I	C	164
It is recommended that beta blockade be continued in heart failure patients throughout the peri-operative period, whereas ACEIs/ARBs may be omitted on the morning of surgery, taking into consideration the patient's blood pressure. If ACEIs/ARBs are given, it is important to carefully monitor the patient's haemodynamic status and give appropriate volume replacement when necessary.	I	C	
Unless there is adequate time for dose-titration, initiation of high-dose beta-blockade before non-cardiac surgery in patients with heart failure is not recommended.	III	B	

ACEI = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; ESC = European society of cardiology; LV = left ventricular.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

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5.2 Arterial hypertension

In general, the presence of arterial hypertension is a risk factor, but not a very strong independent one for cardiovascular complications in non-cardiac surgery. In a systematic review and meta-analysis of 30 observational studies, pre-operative hypertension was associated with a 35% increase in cardiovascular complications;[181] however, uncontrolled blood pressure is one of the commonest causes of deferred operation.[182] When raised blood pressure is discovered in a pre-operative evaluation, it is advisable to search for target organ damage and evidence of associated cardiovascular pathology (ECG, renal function parameters, and evidence of heart failure), and to initiate therapy to lower the blood pressure to an appropriate level; this is particularly important for those with concomitant risk factors. It is also important to validate the diagnosis by multiple measurements, considering ambulatory monitoring if necessary.[183]

During the induction of anaesthesia, sympathetic activation can cause an increase in blood pressure of 20–30 mm Hg and a heart rate increase of 15–20 bpm in normotensive individuals.[184] This response may be more pronounced in patients with untreated hypertension. As the period of anaesthesia progresses, patients with pre-existing hypertension are more likely to experience lability of intra-operative blood pressure, which may lead to myocardial ischaemia. Avoiding excessive peaks in pressure is important but the hypertensive patient may also be unstable, and profound hypotension—especially when associated with baroreflex-mediated tachycardia—may be equally detrimental. In a study on hypertensive and diabetic patients undergoing non-cardiac surgery, a decrease in blood pressure of >20 mm Hg for >1 hour was found to be a risk factor for complications.[185] It is recommended that peri-operative blood pressure be kept at 70–100% of baseline, avoiding excessive tachycardia. Post-surgical elevation of blood pressure is frequently brought about by anxiety and pain after awakening, and may return to normal after treating these factors.

Common reasons for delaying surgery in patients with hypertension are poorly controlled blood pressure of grade 3 (systolic blood pressure ≥180 mm Hg and/or diastolic blood pressure ≥110 mm Hg), discovery of end-organ damage that has not previously been evaluated or treated, or suspicion of secondary hypertension without properly documented aetiology. In patients with grade 1 or 2 hypertension (systolic blood pressure <180 mm Hg; diastolic blood pressure <110 mm Hg) there is no evidence of benefit from delaying surgery to optimize therapy.[182] In such cases, antihypertensive medications should be continued during the peri-operative period. In patients with grade 3 hypertension, the potential benefits of delaying surgery to optimize the pharmacological therapy should be weighed against the risk of delaying the procedure. In a randomized study, when compared with deferred surgery, immediate blood pressure reduction with nifedipine was associated with similar complication rates but a shorter hospital stay.[186]

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.[183] For more information on peri-operative use of hypertensive medications, see section 4.1.

Recommendations on arterial hypertension

Recommendations	Class[a]	Level[b]	Ref.[c]
It is recommended that patients with a new diagnosis of hypertension pre-operatively be screened for end-organ damage and cardiovascular risk factors.	I	C	
Large peri-operative fluctuations in blood pressure in hypertensive patients should be avoided.	IIa	B	187
Clinicians may consider *not* deferring non-cardiac surgery in patients with grade 1 or 2 hypertension (systolic blood pressure <180 mm Hg; diastolic blood pressure <110 mm Hg).	IIb	B	182

[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

5.3 Valvular heart disease

Patients with VHD are at increased risk of peri-operative cardiovascular complications during non-cardiac surgery.[69] The risk is highly variable, according to the type and severity of VHD and the type of non-cardiac surgery.

5.3.1 Patient evaluation

Echocardiography should be performed on any prospective non-cardiac surgery patient with known or suspected VHD, in order to assess its severity and consequences. This is particularly relevant in the presence of a cardiac murmur. In the presence of severe VHD, it is recommended that a clinical and echocardiographic evaluation be performed and, if necessary, treated before non-cardiac surgery. As for the general evaluation of a patient with VHD, the key issues are to assess the severity of VHD, the symptoms and their relationship to VHD, and the estimated risks of valvular intervention and of cardiac complications according to the type of non-cardiac surgery. The usual classification of non-cardiac surgery, using the three risk groups defined in *Table 3*, should also be used in patients with VHD.

5.3.2 Aortic stenosis

Aortic stenosis is the most common VHD in Europe, particularly among the elderly. Severe aortic stenosis is defined according to an integrative approach taking into account valve area (<1.0 cm^2 or 0.6 cm^2/m^2 body surface area, except in obese patients), and flow-dependent indices (maximum jet velocity 4 m/sec and mean aortic pressure gradient ≥40 mm Hg).

Severe aortic stenosis constitutes a well-established risk factor for peri-operative mortality and myocardial infarction. In the case of urgent non-cardiac surgery in patients with severe aortic stenosis, such procedures should be performed under more invasive haemodynamic monitoring, avoiding rapid changes in volume status and

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heart rhythm as far as possible. In the case of elective non-cardiac surgery, the presence of symptoms is essential for decision-making.[69]

In symptomatic patients, aortic valve replacement should be considered before elective surgery.[69] In patients who are not candidates for valve replacement, due either to high risks associated with serious comorbidities or refusal to undergo the operation, non-cardiac surgery should be performed only if is essential. In patients at high risk or contra-indicated for aortic valve replacement, balloon aortic valvuloplasty or, preferably, transcatheter aortic valve implantation (TAVI) may be a reasonable therapeutic option before surgery.[69] The choice between balloon aortic valvuloplasty and TAVI should take into account the impact of non-cardiac disease on life expectancy and the degree of urgency of the non-cardiac surgery.

In asymptomatic patients, non-cardiac surgery of low to intermediate risk can be performed safely;[188] If possible, the absence of symptoms should be confirmed by exercise testing. If high-risk surgery is planned, further clinical assessment is necessary to assess the risk of aortic valve replacement. In those at high risk for aortic valve replacement, elective surgery under more invasive haemodynamic monitoring should be performed only if strictly necessary. In the remaining patients, aortic valve replacement should be considered as the initial procedure.[69]

5.3.3 Mitral stenosis

Non-cardiac surgery can be performed with relatively low levels of risk in patients with non-significant mitral stenosis (valve area >1.5 cm^2) and in asymptomatic patients with significant mitral stenosis (valve area <1.5 cm^2) and systolic pulmonary artery pressure <50 mm Hg. Pre-operative surgical correction of mitral stenosis in these patients is not indicated. Control of heart rate is essential to avoid tachycardia, which may cause pulmonary oedema. Attentive control of fluid overload is also important. Development of AF may cause serious clinical deterioration. With the high risk of embolism, anticoagulation control is important.[69,189] In asymptomatic patients with significant mitral stenosis and systolic pulmonary artery pressure >50 mm Hg, 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.[69,189]

5.3.4 Primary aortic regurgitation and mitral regurgitation

Non-significant aortic regurgitation and mitral regurgitation do not independently increase the risk of cardiovascular complications during non-cardiac surgery. In asymptomatic patients with severe aortic or mitral regurgitation and preserved LV function, non-cardiac surgery can be performed without additional risk. Symptomatic patients—and those who are asymptomatic with severely impaired LVEF ($<30\%$)—are at high risk of cardiovascular complications, and non-cardiac surgery should be performed only if necessary.[69] Patients with severe aortic or mitral regurgitation and heart failure may benefit from optimization of pharmacological therapy to produce maximal haemodynamic stabilization before undergoing high-risk surgery (see section 5.1).

5.3.5 Secondary mitral regurgitation

Secondary mitral regurgitation is due to LV remodelling that causes a distortion of the subvalvular apparatus on a structurally normal valve. In the case of non-cardiac surgery, these patients should undergo peri-operative evaluation and management according to the recommendations for LV systolic dysfunction and, if secondary mitral regurgitation is due to IHD, those for IHD. Because secondary mitral regurgitation is variable according to loading conditions, particular attention should be paid to the assessment of volume status and heart rhythm during the peri-operative period.

5.3.6 Patients with prosthetic valve(s)

Patients who have undergone previous surgical correction of VHD and have a prosthetic valve can undergo non-cardiac surgery without additional risk, provided that there is no evidence of valve or ventricular dysfunction. In current practice, the main problem is the need for a modification of the anticoagulation regimen in patients in the peri-operative period, with oral anticoagulants being temporarily replaced by UFH or LMWH at therapeutic doses (see section 4.3).

5.3.7 Prophylaxis of infective endocarditis

Indications for antibiotic prophylaxis are limited to high-risk patients undergoing dental care; however, non-specific prophylaxis remains recommended in all patients at intermediate or high risk of infective endocarditis. This is of particular importance in the field of non-cardiac surgery, given the increasing burden of healthcare-related infective endocarditis. Prophylaxis of infective endocarditis is discussed in detail in specific ESC guidelines.[190]

Recommendations on VHD

Recommendations	Class[a]	Level[b]	Ref.[c]
Clinical and echocardiographic evaluation is recommended in all patients with known or suspected VHD, who are scheduled for elective intermediate or high-risk non-cardiac surgery.	I	C	
Aortic valve replacement is recommended in symptomatic patients with severe aortic stenosis, who are scheduled for elective non-cardiac surgery, provided that they are not at high risk of an adverse outcome from for valvular surgery.	I	B	69
Aortic valve replacement should be considered in asymptomatic patients with severe aortic stenosis, who are scheduled for elective high-risk non-cardiac surgery, provided that they are not at high risk of an adverse outcome from for valvular surgery.	IIa	C	
Elective low or intermediate-risk non-cardiac surgery should be considered in asymptomatic patients with severe aortic stenosis if there has been no previous intervention on the aortic valve.	IIa	C	

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Recommendations	Class[a]	Level[b]	Ref.[c]
In symptomatic patients with severe aortic stenosis who are scheduled for elective non-cardiac surgery, TAVI or balloon aortic valvuloplasty should be considered by the expert team if they are at high risk of an adverse outcome from for valvular surgery.	IIa	C	
Elective non-cardiac surgery should be considered in patients with severe valvular regurgitation, who do not have severe heart failure or LV dysfunction.	IIa	C	
Percutaneous mitral commissurotomy should be considered in patients with severe mitral stenosis, who have symptoms of pulmonary hypertension and are scheduled for elective intermediate- or high-risk non-cardiac surgery.	IIa	C	

LV = left ventricular; TAVI = transcatheter aortic valve implantation; VHD = valvular heart disease.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

5.4 Arrhythmias

Cardiac arrhythmias are a significant cause of morbidity and mortality in the peri-operative period. Although the mechanisms for arrhythmias in patients with structural heart disease are reasonably well-defined, the modulating influence of transient physiological imbalance in patients undergoing surgery is less certain. Before surgery, patients with a history of arrhythmias should be reviewed by a cardiologist. Arrhythmias such as AF and ventricular tachycardia often indicate underlying structural heart disease; therefore the discovery of such pre-operative arrhythmias should lead to evaluation, including echocardiography, before surgery.*

5.4.1 New-onset ventricular arrhythmias in the pre-operative period

Ventricular arrhythmias, including ventricular premature beats (VPBs) and ventricular tachycardia (VT) are particularly common in high-risk patients. Monomorphic VT may result from myocardial scarring, and polymorphic VT is a common result of acute myocardial ischaemia. Pre-operative detection of these arrhythmias should therefore lead to evaluation including methods such as echocardiography, coronary angiography (with revascularization) and, in selected cases, invasive electrophysiological study, as appropriate.

Treatment steps for VPBs include identifying and correcting the reversible causes (e.g. hypoxia, hypokalemia and hypomagnesaemia). There is no evidence that VPBs or non-sustained VTs alone are associated with a worse prognosis or that suppressive therapy is beneficial.

The American College of Cardiology/American Heart Association/ESC Guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death recommend that, regardless of the cause, sustained monomorphic VT with haemodynamic compromise must be treated promptly with electric cardioversion. Intravenous amiodarone can be used for initial treatment of patients with stable sustained monomorphic VT, to prevent recurrences.[191]

Immediate defibrillation is required to terminate ventricular fibrillation and sustained polymorphic VT. Beta-blockers are useful in patients with recurrent sustained polymorphic VT, especially if ischaemia is suspected or cannot be excluded. Amiodarone is reasonable for patients with recurrent sustained polymorphic VT in the absence of long QT syndrome.[191] Torsades de pointes (TdP) may occur and the withdrawal of any offending drugs and correction of electrolyte abnormalities are recommended. Management with magnesium sulphate should be considered for patients with TdP and long QT syndrome.[192] Beta-blockade, combined with temporary pacing, is suggested in patients with TdP and sinus bradycardia. Isoproterenol is recommended in patients with recurrent, pause-dependent TdP, who do not have congenital long QT syndrome.[191]

If the diagnosis is unclear, wide-QRS tachycardia should be presumed to be VT until proven otherwise. Calcium channel blockers, such as verapamil and diltiazem, should not be used in patients to terminate wide-QRS-complex tachycardia of unknown origin, especially in patients with a history of myocardial dysfunction.[191]

5.4.2 Management of supraventricular arrhythmias and atrial fibrillation in the pre-operative period

Supraventricular arrhythmias and AF are more common than ventricular arrhythmias in the peri-operative period. The aetiology of these arrhythmias is multifactorial. Sympathetic activity, as the primary autonomic mechanism, can be responsible for triggering AF.

While initiating specific drug therapy, possible aggravating factors such as respiratory failure or electrolyte imbalance should also be corrected. No medication is recommended to suppress supraventricular premature beats. Vagal manoeuvres may terminate SVT in some cases; they usually respond well to treatment with adenosine. In cases with incessant or commonly recurring SVT in the peri-operative setting, where prophylactic treatment is needed, beta-blockers, calcium channel blockers, or amiodarone treatment can be used. In rare cases (and taking into account the urgency and nature of planned surgery), pre-operative catheter ablation of the arrhythmia substrate may be considered, e.g. for patients with Wolff-Parkinson-White syndrome and pre-excited AF.

The objective in managing peri-operative AF is usually ventricular rate control. As recommended in the ESC Guidelines for management of AF, beta-blockers and calcium channel blockers (verapamil, diltiazem) are the drugs of choice for rate control.[144] Amiodarone can be used as a first-line drug in patients with heart failure, since digoxin is frequently ineffective in high adrenergic states such as surgery. Beta-blockers have been shown to accelerate the conversion of AF to sinus rhythm in the intensive care unit (ICU) after non-cardiac surgery.[193] Anticoagulation must be based on the individual clinical situation.

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5.4.3 Peri-operative bradyarrhythmias

Peri-operative bradyarrhythmias usually respond well to short-term pharmacological therapy; temporary cardiac pacing is rarely required**.** Prophylactic pacing before non-cardiac surgery is not commonly indicated. Pre-operative establishment of temporary or permanent cardiac pacing may be appropriate for patients with complete heart block or symptomatic asystolic episodes. The indications for temporary pacemakers during the peri-operative period are generally the same as those for permanent pacemakers**.** Asymptomatic bifascicular block, with or without first-degree atrioventricular block, is not an indication for temporary pacing; however, the availability of an external pacemaker for transcutaneous pacing is appropriate.

5.4.4 Peri-operative management of patients with pacemaker/implantable cardioverter defibrillator

Patients with a permanent pacemaker can safely undergo surgery if appopriate precautions are taken.[194] The use of unipolar electrocautery represents a significant risk, as the electrical stimulus from electrocautery may inhibit 'demand' pacemakers, or may reprogram the pacemaker. These problems can be avoided or minimized by using bipolar electrocautery, correct positioning the ground plate for the electrical circuit. Keeping the electrocautery device away from the pacemaker, giving only brief bursts, and using the lowest possible amplitude may also decrease the interference. The pacemaker should be set in an asynchronous or non-sensing mode in patients who are pacemaker-dependent. This is most easily done in the operating room by placing a magnet on the skin over the pacemaker. Patients whose underlying rhythm is unreliable should have pacemaker interrogation after surgery, to ensure appropriate programming and sensing-pacing thresholds.

Interference with the function of implantable cardioverter defibrillators (ICD) can also occur during non-cardiac surgery, as a result of the electrical current generated by electrocautery. The ICD should be turned off during surgery and switched on in the recovery phase before discharge to the ward. The defibrillator function of an ICD can be temporarily deactivated by placing a magnet on the skin over the ICD. While the device is deactivated, an external defibrillator should be immediately available.

Recommendations for ventricular arrhythmias

Recommendations	Class[a]	Level[b]
Continuation of oral anti-arrhythmic drugs before surgery is recommended.	I	C
Anti-arrhythmic drugs are recommended for patients with sustained VT, depending on the patient's characteristics.	I	C
Anti-arrhythmic drugs are not recommended for patients with VPBs.	III	C

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

Recommendations on supraventricular arrhythmias

Recommendations	Class[a]	Level[b]
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 haemodynamically stable patients is recommended.	I	C

SVT = supraventricular tachycardia.
[a]Class of recommendation.
[b]Level of evidence.

Recommendations on bradyarrhythmias and pacemakers

Recommendations	Class[a]	Level[b]
The indications for temporary pacemakers during the peri-operative period are generally the same as those for permanent pacemakers.	I	C
It is recommended that the hospital nominate a person who is responsible for programming of the implanted arrhythmia devices before and after surgery.	I	C
Patients with ICDs, whose devices have been pre-operatively deactivated, should be on continuous cardiac monitor throughout the period of deactivation. External defibrillation equipment should be readily available.	I	C
Patients who have asymptomatic bifascicular or trifascicular block are not recommended for routine management with a peri-operative temporary pacing wire.	III	C

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

5.5 Renal disease

Impaired renal function is associated with a significantly increased risk of CVD and is an independent risk factor for adverse post-operative cardiovascular outcomes, including myocardial infarction, stroke, and progression of heart failure. The development of acute kidney injury (AKI) after major surgery reduces long-term survival in patients with normal baseline renal function.[195] Risk factors for the development of post-operative AKI following non-cardiac surgery have been identified and include age >56 years, male sex, active cardiac failure,

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Table 7 Summary of definitions of acute kidney injury

Urine output (common to all)	KDIGO stage[198,199] Serum creatinine		AKIN stage Serum creatinine		RIFLE class Serum creatinine or GFR	
<0.5 mL/kg/h for 6 h	Stage 1	Increase of 1.5–1.9 times baseline or ≥27 μmol/L (≥0.3 mg/dL) increase	Stage 1	Increase to >150–200% (1.5–2-fold) from baseline or ≥27 μmol/L (≥0.3 mg/dL) increase	Risk	Increase in serum creatinine ×1.5 or GFR decrease >25%
<0.5 mL/kg/h for 12 h	Stage 2	Increase of 2–2.9 times baseline	Stage 2	Increase to >200–300% (>2–3-fold) from baseline	Injury	Increase in serum creatinine ×2 or GFR decreased >50%
<0.3 mL/kg/h for 24 h or anuria for 12h	Stage 3	Increase of >3 times baseline or increase in serum creatinine to ≥354 μmol/L (≥4 mg/dL) or initiation of RRT	Stage 3	Increase to >300% (>3-fold) from baseline or ≥354 μmol/L (≥4 mg/dL) with an acute increase of >44 μmol/L (>0.5 mg/dL) or initiation of RRT	Failure	Increase in serum creatinine ×3 or serum creatinine ≥354 μmol/L (>4 mg/dL) with an acute rise ≥44 μmol/L (>0.5 mg/dL) or GFR decreased >75%
					ESRD	ESRD >3 months

AKI = acute kidney injury; AKIN = Acute Kidney Injury Network; ESRD = end-stage renal disease; GFR = glomerular filtration rate; KDIGO = Kidney Disease: Improving Global Outcomes; RIFLE = Risk, Injury, Failure, Loss, End-stage renal disease; RRT = renal replacement therapy.

presence of ascites, hypertension, emergency surgery, intraperitoneal surgery, pre-operative creatinine elevation, and *diabetes mellitus*. Patients with ≥6 of these factors have a 10% incidence of AKI, and a hazard ratio of 46 as compared with those with <3 risk factors.[196] Further, the relationship between chronic kidney disease (CKD) and cardiovascular morbidity/mortality is independent of hypertension and diabetes.

Chronic kidney disease is defined as impaired kidney function or raised proteinuria, confirmed on two or more occasions at least three months apart. Here, the estimated glomerular filtration rate (eGFR) should be calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula, which uses sex, age, ethnic origin, and serum creatinine concentration. Additionally, proteinuria should be assessed using the urinary albumin–creatinine ratio. Chronic kidney disease is thus classified into six stages of eGFR and three stages of proteinuria.[197] A comparison of the most recent definitions of AKI is shown in *Table 7*.

Renal function can be calculated routinely using the Cockcroft-Gault formula, or an eGFR calculated from serum creatinine using the Modification of Diet in Renal Disease (MDRD) study or the CKD-EPI equations. The use of newer biomarkers in the diagnosis of AKI is still under investigation. Normal GFR values are 100–130 mL/min/1.73 m^2 in young men, and 90–120 mL/min/1.73 m^2 in young women, and vary depending on age, sex, and body size. A cut-off GFR value of <60 mL/min/1.73 m^2 correlates significantly with major cardiovascular adverse events. Identification of patients at risk of peri-operative worsening of renal function is important, in order to initiate supportive measures such as maintenance of adequate intravascular volume for renal perfusion and use of vasopressors.[198]

Susceptibility to developing AKI after exposure to a specific insult has been identified according to a number of observational studies.[199] The most frequent causes for AKI in hospitalized cardiac patients relate to the combination of a low cardiac output/high venous pressure, and/or the administration of iodinated contrast media during diagnostic and interventional vascular procedures. Contrast-induced AKI (CI-AKI) is defined as a rise of serum creatinine of 44 μmol/L (0.5 mg/dL) or a 25% relative rise from baseline at 48 hours (or 5–10% at 12 hours) following contrast administration. It occurs in up to 15% of patients with chronic renal dysfunction who are undergoing radiographic procedures.[200] Although most cases of CI-AKI are self-limiting, with renal function returning to normal within 7 days of the procedure, these patients occasionally (in 0.5–12% of cases) develop overt renal failure, associated with increased morbidity and mortality. In some, severe renal impairment necessitates renal-replacement therapy and can lead to permanent renal injury. The pathogenesis of CI-AKI is multifactorial, and is thought to include a decrease in glomerular filtration and renal hypoperfusion, together with renal medullary ischaemia, direct tubular toxicity via reactive oxygen species, and direct cellular toxicity from the contrast agent.

A number of risk factor scoring systems exist for predicting CI-AKI. These include the urgency of the procedure, baseline renal function, diabetes, and contrast volume. A range of strategies has been proposed to prevent CI-AKI, including minimizing the volume of contrast medium administered, use of less-nephrotoxic contrast agents, provision of prophylactic renal-replacement therapy, patient hydration, and use of pharmacological agents to counteract the nephrotoxicity of contrast agents.[198]

The relationship between the volume of contrast agent administered and the development of CI-AKI is well known, and exceeding the maximum contrast dose (contrast volume/eGFR) is

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strongly associated with the development of CI-AKI. The impact of the osmolality of contrast agent on nephrotoxicity has been evaluated in a number of randomized controlled trials, with dissimilar results; however, based on a number of meta-analyses, the use of low osmolar contrast media (LOCM) or iso-osmolar contrast media (IOCM) is recommended in patients with mild, moderate, or severe CKD, who are undergoing contrast-enhanced radiography. Numerous studies have addressed the use of renal-replacement therapies to prevent CI-AKI.[201] Although renal-replacement therapy has a favourable effect, in terms of reducing CI-AKI (relative risk 0.19; $P < 0.001$) in patients with stage 4 or 5 CKD, haemodialysis has been found to be non-beneficial (and potentially harmful) for the prevention of CI-AKI in those with baseline CKD stage ≤ 3.

Recommendations on renal function

Recommendations	Class[a]	Level[b]	Ref.[c]
Patients undergoing contrast-enhanced radiographic procedures			
Patients should be assessed for risk of CI-AKI.	IIa	C	
Prevention of contrast-induced nephropathy in patients with moderate or moderate-to-severe CKD			
Hydration with normal saline is recommended before administration of contrast medium.	I	A	198
Use of LOCM or IOMC is recommended.	I	A	198
It is recommended that the volume of contrast media be minimized.	I	B	198
Hydration with sodium bicarbonate should be considered before administration of contrast medium.	IIa	A	202
Short-term high-dose statin therapy should be considered.	IIa	B	203
Patients with severe CKD			
In patients with stage 4 or 5 CKD, prophylactic haemofiltration may be considered before complex intervention or high-risk surgery.	IIb	B	201
In patients with stage ≤3 CKD, prophylactic haemodialysis is not recommended.	III	B	201

CI-AKI = contrast-induced acute kidney injury; CKD = chronic kidney disease; GFR = glomerular filtration rate; IOMC = iso-osmolar contrast medium; LOCM = low-osmolar contrast medium.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

Pre-procedural hydration with intravenous isotonic fluids is the most effective method of reducing the risk of CI-AKI.[198] Normal saline or isotonic sodium bicarbonate (1.26%) may be used and peripherally administered, with the advantage that it requires only one hour of pre-treatment and may therefore present the preferred option in patients scheduled for urgent or outpatient procedures.[202] N-acetyl cysteine may be considered for prophylaxis of CI-AKI, given its low cost and toxicity profile; however, the evidence for its benefit remains inconclusive. A number of small studies undertaking alkalinization of urine using a range of agents (bicarbonate, sodium/potassium citrate, acetazolamide) have shown a reduction in the incidence of contrast-induced nephropathy; recent information suggesting the use of high-dose statins in preventing CI-AKI is promising.[203] Although there are theoretical benefits from the use of loop diuretics in early or established AKI, these have not been supported by data in studies, and diuretics are therefore not recommended for the prevention or treatment of AKI.[198]

5.6 Cerebrovascular disease

The majority of the literature on peri-operative stroke focuses on cardiac surgery, with an event rate ranging from 2–10%, according to the type of operation.[204] With respect to non-cardiac surgery, peri-operative stroke has been reported in 0.08–0.7% of patients undergoing general surgery, in 0.2–0.9% of patients requiring orthopaedic surgery, in 0.6–0.9% of lung operations, and in 0.8–3.0% of surgeries involving the peripheral vasculature.[204,205] The associated mortality ranges from 18–26%.[204,205] A more recent analysis on 523 059 patients undergoing non-cardiac surgery reported a lower incidence of peri-operative stroke (0.1%).[206] The occurrence of this adverse event was associated with a 700% increase in peri-operative mortality, corresponding to an absolute risk increase exceeding 20%. Multivariate analysis identified age, history of myocardial infarction within 6 months prior to surgery, acute renal failure, history of stroke, history of TIA, dialysis, hypertension, chronic obstructive pulmonary disease (COPD), and current tobacco use as independent predictors of peri-operative stroke, while high body mass index was found to be protective.[206]

Peri-operative strokes are mainly ischaemic and cardioembolic and AF is often the underlying leading condition. Triggers include the withdrawal of anticoagulation and the hypercoagulable state related to surgery. Additional aetiologies include atheroembolism, originating from the aorta or the supra-aortic vessels, and local atherothrombosis in the presence of intracranial small-vessel disease. Hypoperfusion—related to peri-operative arterial hypotension and/or severe stenosis of the cervicocranial vessels—is an unusual cause of peri-operative stroke.[207] Rarely, peri-operative stroke may be due to air, fat, or paradoxical embolisms.

In an attempt to attenuate the risk of peri-operative stroke, antiplatelet/anticoagulant treatments should be continued whenever possible throughout the peri-operative period. Alternatively, the period of drug withdrawal should be kept as short as possible while weighting thrombo-embolic and haemorrhagic risks (see sections 4.2 and 4.3). Adequate selection of the anaesthetic technique

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(regional vs. neuraxial vs. general anaesthesia), prevention and treatment of AF, euglycaemic control (avoiding both hyperglycaemia and hypoglycaemia), as well as meticulous peri-operative blood pressure control, may all contribute to reducing the risk of peri-operative stroke.

Patients undergoing non-cardiac surgery should be questioned about previous neurological symptoms, and those with symptoms suggestive of TIA or stroke in the preceding 6 months should undergo pre-operative neurological consultation as well as neurovascular and brain imaging, where appropriate. In the absence of dedicated studies addressing this issue, the criteria for carotid revascularization described in the 2011 ESC Guidelines on the diagnosis and treatment of peripheral artery disease should also guide the management of patients with carotid disease, who are undergoing non-cardiac surgery.[19] In patients with symptomatic carotid disease (i.e. with a stroke or TIA affecting the corresponding vascular territory in the preceding 6 months), carotid revascularization should performed first and non-cardiac surgery postponed.

Owing to the increasing average age of the population, an increasing number of patients referred for non-cardiac surgery may have associated asymptomatic carotid artery disease. According to a meta-analysis of studies covering a total of 4573 patients with PAD, the rates of asymptomatic carotid stenosis >50% and >70% were 25% and 14%, respectively.[208] Carotid imaging, while not indicated routinely in patients undergoing non-cardiac surgery, may be considered before vascular surgery, due to the high prevalence of carotid artery disease in this patient group.

The question as to whether patients with severe asymptomatic carotid occlusive disease, who are undergoing elective major non-cardiac surgery, require pre-operative carotid revascularization remains a matter of debate. Importantly, the purpose of carotid revascularization in this setting is more the long-term prevention of stroke than peri-operative stroke reduction; therefore, if carotid revascularization is indicated, this may be performed before or after the planned non-cardiac surgery. Independently of the revascularization strategy, patients with carotid artery stenosis benefit from aggressive cardiovascular risk-factor modification to prevent peri-operative myocardial ischaemia. Accordingly, patients with carotid artery disease suffer a high incidence of CAD. In a prospective investigation in 390 patients undergoing elective carotid artery revascularization, systematic coronary angiography showed the presence of one-, two-, and three-vessel disease, and left main coronary stenoses in 17%, 15%, 22%, and 7% of patients, respectively.[209] Consequently, statins should be continued; whenever possible aspirin and beta-blockers should not be withdrawn, and blood pressure should be carefully controlled (see sections 4.1 and 5.2).

Apart from TIA or stroke, transient or even permanent changes in mental status may occur following non-cardiac surgery, including spatio-temporal disorientation, memory loss, hallucinations, anxiety or depression. These findings may especially be encountered in patients with known cognitive impairment. The underlying mechanisms, often elusive, may include surgery-induced systemic inflammation and cerebral hypoperfusion.

Recommendations on patients with suspected or established carotid artery disease

Recommendations	Class[a]	Level[b]
Pre-operative carotid artery and cerebral imaging are recommended in patients with a history of TIA or stroke in the preceding 6 months.	I	C
Pre-operative, routine carotid artery imaging may be considered in patients undergoing vascular surgery.	IIb	C
Whenever possible, continuation of anti-platelet and statin therapies should be considered throughout the peri-operative phase in patients with carotid artery disease.	IIa	C
For patients with carotid artery disease undergoing non-cardiac surgery, the same indications for carotid revascularization should apply as for the general population.	IIa	C
Pre-operative routine carotid artery imaging is not recommended in patients undergoing non-vascular surgery.	III	C

TIA = transient ischaemic attack.
[a]Class of recommendation.
[b]Level of evidence.

5.7 Peripheral artery disease

Patients with PAD (defined as an ankle–brachial ratio of <0.9, or previously revascularized with surgery or percutaneous transluminal angioplasty) usually have advanced atherosclerotic disease affecting most vascular beds in varying degrees and have a worse prognosis than patients without PAD.[210,211] Even in patients without known CAD, peripheral artery surgery is associated with an increased incidence of peri-operative acute myocardial infarction.[212] Peripheral artery disease is thus an established risk factor for non-cardiac surgery and it is reasonable to assess the presence of IHD from the patient's history and routine clinical examinations and tests; however, it is not recommended to routinely perform exercise or imaging test to detect cardiac ischaemia in PAD patients without clinical symptoms, unless the patient has more than two of the clinical risk factors detailed in *Table 4*. In a randomized trial, prophylactic coronary revascularization before major vascular surgery in stable PAD patients did not reduce the incidence of major clinical endpoints.[152] However, patients with severely reduced LV function or left main disease were excluded.

All patients with PAD should be treated with statins and platelet inhibitors according to guidelines.[211] Blood pressure control and lifestyle measures should be attended to, as recommended in the ESC Guidelines on cardiovascular prevention.[210] It is not recommended that beta-blocker therapy be routinely initiated pre-operatively unless there are other indications, such as heart failure or ischaemic coronary disease (see section 4.1).

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Recommendation on PAD

Recommendation	Class[a]	Level[b]
Patients with PAD should be clinically assessed for ischaemic heart disease and, if more than two clinical risk factors (*Table 4*) are present, they should be considered for pre-operative stress or imaging testing.	IIa	C

PAD = peripheral artery disease.
[a]Class of recommendation.
[b]Level of evidence.

5.8 Pulmonary disease

The co-existence of pulmonary disease in patients undergoing non-cardiac surgery may increase the operative risk. 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 peri-operative risk, but the most common effect is to increase the risk of post-operative pulmonary complications. These complications are in part a consequence of the development of atelectasis during general anaesthesia; however, factors that result in post-operative hypoventilation, reduced tidal volumes, and impaired lung expansion may cause persistent lung collapse and increase the risk of respiratory infection. These complications occur particularly after abdominal or thoracic surgery, and the risk seems to be increased in smokers. Certain respiratory conditions are associated with cardiovascular pathology and may require special cardiac risk assessment and management, in addition to dealing with pulmonary disease *per se*. Three such conditions are COPD, obesity hypoventilation syndrome (OHS), and pulmonary artery hypertension (PAH).

COPD is characterized by airflow obstruction that is usually progressive, not fully reversible, and does not change markedly over several months. The disease is predominantly caused by smoking and is well-recognized as a major cause of morbidity and mortality.[213] The prevalence of COPD in Europe is 4–10% of adults, therefore up to one patient in ten undergoing non-cardiac surgery may have COPD. *Cor pulmonale* with associated right-heart failure may be a direct complication of severe COPD; however, COPD is also associated with an increased risk of CAD. COPD is a risk factor for IHD and sudden death by unknown mechanisms, although there are several shared risk factors for both types of disease (smoking, diabetes, hypertension, systemic inflammation, increased plasma fibrinogen). Epidemiological evidence suggests that reduced forced expiratory volume in 1 second (FEV_1) is a marker for cardiovascular mortality, independent of age, gender, and smoking history, with a 30% increase in cardiovascular mortality and 20% increase in non-fatal coronary events for every 10% decrease in FEV_1.[213] Although patients with COPD have an increased risk of CVD, there is no evidence that COPD is related to a higher risk of peri-operative cardiac complications. Post-operative pulmonary complications result in significant mortality and morbidity, however. Pre-operative evaluation, using specific post-operative pulmonary complication tools, can be used to stratify patients at risk and allow optimal pre-operative and peri-operative management.[214]

In patients with COPD who are having non-cardiac surgery, the pre-operative treatment goals are to optimize pulmonary function and minimize post-operative respiratory complications; this includes using the pre-operative period for education, including possible cessation of smoking (>2 months before surgery), instruction in chest physiotherapy and lung expansion manoeuvres, muscular endurance training, and re-nutrition if required. Beta-adrenergic agonists and anticholinergic agents should be continued until the day of surgery in all symptomatic COPD patients with bronchial hyper-reactivity. In some cases, short-term systemic/inhaled steroids may be considered. Any associated ventricular failure should be managed accordingly. Where there is active pulmonary infection, appropriate antibiotics should be administered for at least 10 days and, if possible, surgery should be delayed.[215]

OHS is defined as the triad of obesity, daytime hypoventilation, and sleep-disordered breathing. Although distinct from simple obesity and sleep apnoea, it is estimated that 90% patients with OHS also have obstructive sleep apnoea. The prevalence of OHS is 0.15–3% of adults, and 7–22% in patients undergoing bariatric surgery.[216] Obesity and obstructive sleep apnoea are associated with a number of comorbidities including CAD, heart failure, stroke, and metabolic syndrome. OHS is associated with even higher morbidity, including heart failure (and obesity-related cardiomyopathy), *angina pectoris*, pulmonary hypertension (30–88%) and *cor pulmonale*, and increased peri-operative mortality.[216] Pre-operatively, the presence of a high body mass index and apnoea–hypopnea index should alert the physician to screen for OHS, including the use of screening questionnaires, peripheral oxygen saturations, and serum bicarbonate levels. Patients at high risk of OHS who are undergoing major surgery should be referred for additional specialist investigation for sleep disordered breathing and pulmonary hypertension, with pre-operative initiation of appropriate positive airway pressure therapy, and planning of peri-operative techniques (anaesthetic and surgical) and post-operative positive airway pressure management within an appropriate monitored environment.[216]

Pulmonary hypertension is a haemodynamic and pathophysiological condition, defined as an increase in mean pulmonary arterial pressure >25 mm Hg at rest, as assessed by right heart catheterization, and can be found in multiple clinical conditions.[217] Pulmonary artery hypertension (PAH) is a clinical condition, characterized by the presence of pre-capillary pulmonary hypertension in the absence of other causes, such as pulmonary hypertension due to lung diseases, chronic thrombo-embolic pulmonary hypertension, or other rare diseases. Pulmonary artery hypertension includes different forms that share a similar clinical picture and virtually identical pathological changes of the lung microcirculation.[217] From surveys and population studies, the prevalence of PAH is reported to be between 15–150 cases per million adults, with approximately 50% of cases being idiopathic. The prevalence is thus low and consequently the condition is uncommon in surgical practice. Pulmonary artery hypertension is associated with increased post-operative complications, including right ventricular failure, myocardial ischaemia, and post-operative hypoxia and, in patients undergoing cardiopulmonary bypass surgery, a mean pre-operative pulmonary artery pressure >30 mm Hg is an independent predictor of mortality. In patients with pulmonary hypertension undergoing non-cardiac surgery, outcome predictors include New York Heart Association functional Class >III, intermediate to high-risk surgery, right ventricular

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dysfunction, and long duration of anaesthesia. This condition has an associated peri-operative cardiopulmonary complication rate of 38%, and mortality of 7%.[218,219] The initial approach after diagnosing PAH is the adoption of general measures and supportive therapy, and referral to an expert centre for initiation of advanced pulmonary hypertensive therapies. Owing to the potential for anaesthesia and surgery to be complicated by acute right heart failure and pulmonary hypertensive crisis, surgical interventions in patients with PAH should be avoided unless absolutely necessary. Ideally, patients with PAH who are undergoing surgery should have an optimized treatment regimen before any surgical intervention, and be managed in a centre with appropriate expertise. Interventions for high-risk patients should be planned by the multidisciplinary pulmonary hypertension team. Patients receiving PAH-specific therapy must not have drugs withheld for the pre-operative fasting state, and may require temporary conversion to intravenous and/or nebulized treatment until they are able to reliably absorb via the enteral route. As the highest mortality is in the post-operative period, it is recommended that facilities for appropriate monitoring should be available, and monitoring continued for at least 24 hours. In case of progression of right heart failure in the post-operative period, it is recommended that the diuretic dose should be optimized and, if necessary, inotropic support with dobutamine be initiated. Starting new, specific PAH drug therapy in the peri-operative period has not been established. In the case of severe right heart failure that is not responsive to supportive therapy, the temporary administration of pulmonary vasodilators (inhaled and/or intravenous) may be considered, under the guidance of a physician experienced in PAH.

Recommendations on PAH and pulmonary diseases

Recommendations	Class[a]	Level[b]	Ref.[c]
It is recommended that patients with severe PAH, who are undergoing elective surgery, be managed in a centre with appropriate expertise.	I	C	217
It is recommended that interventions for high-risk patients with PAH be planned by the multidisciplinary pulmonary hypertension team.	I	C	217, 220
It is recommended that patients with PAH have an optimized treatment regimen before any non-emergency surgical intervention.	I	C	217
It is recommended that patients receiving PAH-specific treatment continue this in the pre-, peri-, and post-operative period without interruption.	I	C	217
It is recommended that monitoring of patients with PAH continue for at least 24 hours in the post-operative period.	I	C	
In the case of progression of right heart failure in the post-operative period of patients with PAH, it is recommended that the diuretic dose be optimized and, if necessary, intravenous vasoactive drugs be initiated under the guidance of a physician experienced in the management of PAH.	I	C	217, 221
In patients with COPD, smoking cessation (>2 months before surgery) is recommended before undertaking surgery.	I	C	
In the case of severe right heart failure that is not responsive to supportive therapy, the temporary administration of pulmonary vasodilators (inhaled and/or intravenous) is recommended, under the guidance of a physician experienced in PAH.	I	C	217
In patients at high risk of OHS additional specialist investigation before major elective surgery should be considered.	IIa	C	216

PAH = pulmonary artery hypertension; OHS = obesity hypoventilation syndrome.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

5.9 Congenital heart disease

Children, adolescents and adults with congenital heart disease are generally regarded as being at increased risk when undergoing non-cardiac surgery but this risk will vary enormously, according to the degree of associated heart failure, pulmonary hypertension, arrhythmias, and shunting of blood—with or without associated oxygen desaturation and by the complexity of the underlying condition.[222] A thorough understanding of the underlying congenital heart disease, including anatomy, physiology, and identification of risk factors, is vital before surgery. When the defect is simple, the circulation physiologically normal and the patient well compensated, the risk may be quite low; however, complicated patients with congenital heart disease should only undergo non-cardiac surgery after thorough evaluation by a multidisciplinary team in a specialized centre. Prophylaxis for endocarditis should be initiated according to the ESC Guidelines on congenital heart disease and infective endocarditis.[190,222]

Recommendation on patients with congenital heart disease

Recommendation	Class[a]	Level[b]
It is recommended that, patients with complex congenital heart disease be referred for additional specialist investigation before undergoing elective non-cardiac surgery, if feasible.	I	C

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

6. Peri-operative monitoring

6.1 Electrocardiography

Continuous ECG monitoring is recommended for all patients undergoing anaesthesia. The patient should be connected to the ECG

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monitor before induction of anaesthesia or institution of a regional block. The duration of ST-segment changes correlates positively with the incidence of peri-operative myocardial infarction; [223] therefore, when ST-segment changes occur, the clinician should assume that myocardial ischaemia is present if the patient has a history of pre-existing cardiac disease or is undergoing surgery.

It is not clear, however, whether ECG monitoring is sufficiently sensitive to identify patients with myocardial ischaemia. In addition, ECG monitoring is of limited value in patients who have intraventricular conduction defects and ventricular paced rhythms. In one study, Holter recordings were used as the reference standard for detection of intra-operative ischaemia and the ST-trending monitors were found to have overall sensitivity of 74% and specificity of 73%.[224]

The choice and configuration of the leads used for monitoring may influence the ability to detect significant ST-segment changes. Although V5 has for many years been regarded as the best choice for the detection of intra-operative ischaemia, one study found that V4 was more sensitive and appropriate than V5 for detecting prolonged post-operative ischaemia and infarction.[225]

As many ischaemic events are dynamic and may not always be detected by the same lead, reliance on a single lead for monitoring results in a greater risk of failing to detect an ischaemic event. With the use of selected lead combinations, more ischaemic events can be precisely diagnosed in the intra-operative setting. In one study, although the best sensitivity was obtained with V5 (75%), followed by V4 (61%), combining leads V4 and V5 increased the sensitivity to 90%. When the leads II, V4 and V5 were used simultaneously, the sensitivity was greater than 95%.[225,226] In another study, in which two or more pre-cordial leads were used, the sensitivity of ECG monitoring was greater than 95% for detection of peri-operative ischaemia and infarction.[225] It was also shown that ECG monitoring with fewer leads (as few as three) has lower sensitivity than monitoring with 12 leads and there is a statistically significant association, independent of peri-operative troponin values, between peri-operative ischaemia on a 12-lead ECG and long-term mortality.[227,228] Thus, 12-lead ECG monitoring is recommended especially in high-risk patients, although correct positioning of 12 leads is not feasible in high abdominal and thoracic surgery.

Recommendations on ECG monitoring

Recommendations	Class[a]	Level[b]	Ref.[c]
Peri-operative ECG monitoring is recommended for all patients undergoing surgery.	I	C	
Selected lead combinations should be considered for better detection of ischaemia in the operating room.	IIa	B	225, 226
When feasible, twelve-lead ECG monitoring should be considered for high-risk patients undergoing surgery.	IIa	B	227, 228

ECG = electrocardiogram.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

6.2 Transoesophageal echocardiography

Transoesophageal echocardiography (TOE) has frequently been used as a monitoring tool during cardiac surgery. TOE has several advantages. 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 oesophageal or gastric diseases. Specific training of users is essential to avoid inaccurate interpretation.

Myocardial ischaemia can be identified by abnormalities in regional wall motion and thickening. The agreement between intra-operative TOE and ECG is rather weak.[229] 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, 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.[229] They were more common in patients submitted to aortic vascular surgery. Episodes were poorly correlated with post-operative cardiac complications.[229]

For the purpose of identifying patients at high risk of peri-operative ischaemic outcomes, routine monitoring for myocardial ischaemia with TOE or 12-lead ECG during non-cardiac surgery is of little more clinical value than pre-operative clinical data and intra-operative monitoring using a 12-lead ECG.[230]

TOE is recommended if acute and severe haemodynamic instability or life-threatening abnormalities develop during or after surgery.[231] It is a useful technique in the context of hypotension during non-cardiac surgery. In a prospective study including 42 adults, TOE was performed before any other haemodynamic monitoring when severe hypotension developed. It was useful for determining the cause of severe hypotension, hypovolaemia, low ejection fraction, severe embolism, myocardial ischaemia, cardiac tamponade, or dynamic LV outflow tract obstruction.[232] The value of TOE for systematic haemodynamic monitoring in patients at risk is more controversial. 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. Secondary mitral regurgitation is usually reduced during general anaesthesia; on the other hand, primary mitral regurgitation can increase. In the setting of severe mitral regurgitation, the LVEF overestimates LV function and other parameters may be more accurate, such as myocardial deformation obtained by two-dimensional speckle tracking. More validation is needed before this method can be used routinely in this setting. In patients with severe aortic stenosis, appropriate pre-load is important during surgery. Monitoring of LV end-diastolic volume with TOE may be more accurate than by pulmonary capillary pressure. An appropriate heart rate is crucial in patients with mitral stenosis and aortic regurgitation: a sufficient

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diastolic period in the former and an appropriate—not long—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 artery pressures in mitral stenosis, and changes in LV volumes and indices of LV function in aortic regurgitation.

Recommendations on intra-operative and/or peri-operative TOE for detection of myocardial ischaemia

Recommendations	Class[a]	Level[b]	Ref.[c]
The use of TOE should be considered in patients who develop ST-segment changes on intra-operative or peri-operative ECG monitoring.	IIa	C	230
The use of TOE may be considered in patients at high risk of developing myocardial ischaemia, who undergo high-risk non-cardiac surgery.	IIb	C	230

ECG = electrocardiogram; TOE = transoesophageal echocardiography.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

Recommendations on intra-operative and/or peri-operative TOE in patients with or at risk of haemodynamic instability

Recommendations	Class[a]	Level[b]	Ref.[c]
TOE is recommended when acute sustained severe haemodynamic disturbances develop during surgery or in the peri-operative period.	I	C	235
TOE monitoring may be considered in patients at increased risk of significant haemodynamic disturbances during and after high-risk non-cardiac surgery.	IIb	C	
TOE monitoring may be considered in patients who present severe valvular lesions during high-risk non-cardiac surgery procedures accompanied by significant haemodynamic stresses.	IIb	C	

TOE = transoesophageal echocardiography.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

Transoesophageal Doppler (TOD) (without echocardiography) can be also used to monitor cardiac output. A government-sponsored systematic review performed in the USA concluded that a strong level of evidence existed to support the usefulness of TOD in reducing the rate of major complications and the length of hospital stay after major surgery.[233] A similar conclusion was drawn in a separate review commissioned by the UK's National Health Service (NHS) Centre for Evidence-based Purchasing, performed in three NHS hospitals, with 626 patients being assessed before- and 621 patients after implementation of an intra-operative TOD-guided fluid optimization strategy. The findings of the NHS review showed a 67% decrease in intra-operative mortality, a 4-day reduction in mean duration of post-operative hospital stay, a 23% reduction in the need for central venous catheter insertion, a 33% decrease in complication rates, and a 25% reduction in re-operation rate.[234]

6.3 Right heart catheterization

Despite more than 30 years' experience with the pulmonary artery catheter (PAC) and right heart catheterization, little evidence exists in the medical literature to demonstrate a survival benefit associated with PAC in peri-operative patients. A case-control analysis, carried out in a subset of patients from a large observational study who underwent PAC placement, and who were matched with a similar number of patients who did not undergo right heart catheterization, demonstrated a higher incidence of post-operative heart failure and non-cardiac events than the control group.[236]

Similarly, a Cochrane review of 12 randomized, controlled clinical trials studying the impact of PAC in a large spectrum of patients—including patients who were undergoing surgery or who were admitted to the ICU with advanced heart failure, acute respiratory distress syndrome, or sepsis—failed to demonstrate a difference in mortality and length of hospital stay, suggesting that PAC does not provide information that is not otherwise available to select a treatment plan.[237]

Routine PAC and right heart monitoring is therefore not recommended in patients during non-cardiac surgery. The use of other non-invasive peri-operative cardiac output monitoring techniques (including TOE with Doppler monitoring) to optimize cardiac output and fluid therapy in high-risk patients undergoing non-cardiac surgery, seems to be associated with reduction in length of stay and complications,[238] yet convincing data on hard end-points are still lacking.

6.4 Disturbed glucose metabolism

Diabetes mellitus is the most common metabolic disorder in Europe, with a prevalence of 6.4% in 2010, which is predicted to increase to 7.7% by 2030.[239] Type 2 diabetes accounts for >90% of cases, and is expected to increase, probably due to the obesity epidemic in children and young adults. The condition promotes atherosclerosis, endothelial dysfunction, activation of platelets, and synthesis of pro-inflammatory cytokines. According to the World Health Organization, approximately 50% of patients with type 2 diabetes die of CVD. It is well established that surgery in patients with diabetes is associated with longer hospital stay, greater use of healthcare resources, and higher peri-operative mortality. Elevated levels of glycosylated haemoglobin (HbA_{1c})—a marker of poor glycaemic control—are associated with worse outcomes in surgical and critical care patients.[240] Further, surgical stress increases the prothrombotic state, which may present a particular issue in patients with diabetes; thus diabetes is an important risk factor for peri-operative cardiac complications and death. Critical illness is also characterized by dysglycaemia, which may develop in the absence of previously diagnosed diabetes, and has repeatedly been

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identified as an important risk factor for morbidity and mortality.[240] More recently, the emphasis has shifted from diabetes to hyperglycaemia, where new-onset hyperglycaemia (compared with hyperglycaemia in known diabetics) may hold a much higher risk of adverse outcome.[240,241] 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. Oxidative stress (a major cause of macrovascular disease) is triggered by swings in blood glucose, more than by sustained and persistent hyperglycaemia. Minimization of the degree of glucose variability may be cardioprotective, and mortality may correlate more closely with blood glucose variability than mean blood glucose *per se*.[240,241]

A significant number of surgical patients will have previously undiagnosed pre-diabetes, and are at increased risk of unrecognised peri-operative hyperglycaemia and the attendant adverse outcomes. Although there is no evidence that screening low- or moderate-risk adults for diabetes improves outcomes, it may reduce complications in high-risk adults. Screening patients using a validated risk calculator (e.g. FINDRISC) can identify high or very high-risk adults; this can be followed up by screening every 3–5 years with HbA_{1C}.[242,243] In patients with diabetes, pre-operative or pre-procedural assessment should be undertaken to identify and optimize comorbidities, and determine the peri-procedural diabetes management strategy. For non-cardiac surgery patients without known diabetes, evidence for strict blood glucose control is derived largely from studies in critically ill patients, and is disputed.[240,241] Early randomized controlled trials of intensive insulin therapy maintaining strict glycaemic control showed morbidity benefits in medical patients in ICUs, and reduced mortality and morbidity in surgical patients in ICUs. Subsequent studies, however, found a reduction in mortality in those whose blood glucose control was less strict [7.8–10 mmol/L (140–180 mg/dL)] than in those in whom it was tightly controlled [4.5–6 mmol/L (81–108 mg/dL)], as well as fewer incidents of severe hypoglycaemia. Subsequent meta-analyses have demonstrated no reduction in 90-day mortality with intensive blood glucose control but a five- to six-fold incidence of hypoglycaemia.[240,241] Several suggestions have been put forward to explain the differences in outcome between these studies, including enteral vs. parenteral feeding, the target for insulin initiation, compliance with therapy, accuracy of glucose measurements, mechanism or site of insulin infusion, type of protocol used, and the nurse's level of experience. In addition, there is disagreement on the timing of the initiation of insulin therapy: tight intra-operative glucose control may provide benefit but appears to be difficult and, thus far, studies have mainly been undertaken in patients undergoing cardiac surgery.

The correlation of poor surgical outcome with high HbA_{1c} suggests that screening patients and improving glycaemic control before surgery may be beneficial. Although recommendations for peri-operative management of impaired glucose metabolism are extrapolated largely from the critical care literature, general consensus is that interventions in the acutely unwell or stressed patient should be directed towards minimizing fluctuations in blood glucose concentration whilst avoiding hypoglycaemia and hyperglycaemia. In the ICU setting, insulin infusion should be used to control hyperglycaemia, with the trigger for instigating intravenous insulin therapy set at 10.0 mmol/L (180 mg/dL) and relative trigger at 8.3 mmol/L (150 mg/dL). Although there is a lack of agreement on target glucose range,targets below 6.1 mmol/L (110 mg/dL) are not recommended.[240,241]

Recommendations on blood glucose control

Recommendations	Class[a]	Level[b]	Ref.[c]
Post-operative prevention of hyperglycaemia [targeting levels at least <10.0 mmol/L (180 mg/dL)] by intravenous insulin therapy is recommended in adults after high-risk surgery that requires admission to the intensive care unit.	I	B	240, 241
In patients at high surgical risk, clinicians should consider screening for elevated HbA_{1c} before major surgery and improving pre-operative glucose control.	IIa	C	
Intra-operative prevention of hyperglycaemia with insulin may be considered.	IIb	C	
Post-operative targets <6.1 mmol/L (110 mg/dL) are not recommended.	III	A	240, 241

HbA_{1c} = glycosylated haemoglobin.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

6.5 Anaemia

Anaemia can contribute to myocardial ischaemia, particularly in patients with CAD. In emergency surgery, transfusion may be needed and should be given according to clinical needs. In elective surgery, a symptom-guided approach is recommended as no scientific evidence is available to support other strategies.

7. Anaesthesia

The optimal peri-operative course for high-risk cardiovascular patients should be based on close co-operation between cardiologists, surgeons, pulmonologists, and anaesthesiologists. Pre-operative risk assessment and pre-operative optimization of cardiac disease should be performed as a team exercise. Guidelines on pre-operative evaluation of the adult patient undergoing non-cardiac surgery have previously been published by the European Society of Anaesthesiology.[244] The present edition focuses on patients with cardiovascular risk factors and diseases and also takes into account more recent developments, as well as peri-operative management of patients at increased cardiovascular risk.

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7.1 Intra-operative anaesthetic management

Most anaesthetic techniques reduce sympathetic tone, leading to a decrease in venous return due to increased compliance of the venous system, vasodilatation and, finally, decreased blood pressure; thus, anaesthesiological management must ensure proper maintenance of organ flow and perfusion pressure. Recent evidence suggests that there is no universal 'target blood pressure value' to define intra-operative arterial hypotension, but percentage decreases >20% in mean arterial pressure, or mean arterial pressure values <60 mm Hg for cumulative durations of >30 minutes, are associated with a statistically significant increase in the risk of post-operative complications that include myocardial infarction, stroke, and death.[104,245,246] Similarly, increased duration (>30 minutes) of deep anaesthesia (bispectral index scale values <45) was statistically associated with an increased risk of post-operative complications.[246] Efforts should be made to prevent intra-operative arterial hypotension and inadequately deep anaesthesia.

The choice of the anaesthetic agent has been considered to be of little importance in terms of patient outcome, provided that vital functions are adequately supported. There is conflicting evidence, stemming from cardiac surgery, over whether a specific anaesthetic agent is superior in patients with cardiac disease, with the suggestion that volatile anaesthetic agents offer better cardioprotection than intravenous agents. A meta-analysis published in 2013, combining standard and Bayesian approaches on studies performed in adult cardiac surgery patients, concluded that inhaled anaesthesia, as opposed to total intravenous anaesthesia, was associated with a 50% decrease in mortality (from 2.6% in the total intravenous anaesthesia arm to 1.3% in the inhaled anaesthetics arm); the Bayesian meta-analysis concluded that mortality was the lowest when sevoflurane was used as the anaesthetic agent.[247] Comparable data relating to non-cardiac surgery are scarce. One small study observed a lower incidence of major cardiac events in vascular surgery patients anaesthetized with a volatile agent than with an intravenous anaesthetic,[248] but two other studies in non-cardiac surgery patients observed no difference in outcome.[249,250] However, the overall incidence of peri-operative adverse events was too low to be able to address the relationship between choice of anaesthetic agent and patient outcome.[251]

7.2 Neuraxial techniques

Spinal or epidural (globally known as neuraxial) anaesthesia also induces sympathetic blockade. When reaching the thoracic dermatome level 4, a reduction in cardiac sympathetic drive may occur, with subsequent reduction in myocardial contractility, heart rate, and change in cardiac loading conditions. The benefit of neuraxial anaesthesia vs. general anaesthesia is much debated in the literature, with proponents of a beneficial effect of neuraxial anaesthesia and proponents of the lack of effect on criteria such as mortality or severe morbidity (myocardial infarction, other cardiac complications, pulmonary embolism, pulmonary complications, etc.). The same debate applies to patients with CVDs who must undergo non-cardiac surgery. Given the continuing debate on this subject we have estimated that neuraxial anaesthesia and analgesia may be considered for the management of patients with cardiovascular risk factors or diseases.

One meta-analysis reported significantly improved survival and reduced incidence of post-operative thrombo-embolic, cardiac, and pulmonary complications using neuraxial blockade, compared with general anaesthesia.[252] An analysis of a large cohort of patients undergoing colon resection also suggested improved survival with epidural analgesia.[253] Randomized studies and a meta-analysis of several randomized clinical trials in non-cardiac surgery patients, comparing outcomes with regional and general anaesthetic techniques, have shown some evidence of improved outcome and reduced post-operative morbidity with regional anesthesia.[254–256] A recent retrospective analysis, published in 2013, of nearly 400 000 patients undergoing total hip or knee arthroplasty, observed a significantly lower incidence of major morbidity and mortality in patients receiving neuraxial anaesthesia.[257] The most recent meta-analysis stated that, when epidurals or spinals were used to replace general anaesthesia (but not when used to reduce the quantity of drugs required to provide general anaesthesia), there was a significant, 29% decrease in the risk of dying during surgery.[10] In both situations there was a significant decrease in the risk of pneumonia (55% when replacing general anaesthesia and 30% when decreasing the requirements of drugs used for general anaesthesia). In both situations, neuraxial anaesthesia failed to decrease the risk of myocardial infarction. In another recent meta-analysis that targeted patients undergoing lower-limb revascularization (a category of patients with risk factors for CVD), there was no difference in mortality, myocardial infarction, or lower-limb amputation between patients allocated to neuraxial anaesthesia vs. general anesthesia.[258] Nevertheless, neuraxial anaesthesia was associated with a significantly lower risk of pneumonia.[258] Both meta-analyses were based on relatively small numbers of studies (with a high risk of bias) and patients, and did not specifically target patients with documented cardiac disease. Although there are no studies specifically analysing the changes in outcome related to neuraxial anaesthetic techniques in patients with cardiac disease, the use of this technique may be considered in patients who do not have a contra-indication after estimation of risk–benefit ratio. Cardiac patients are often on various types of drugs that interfere with coagulation and care should be taken to ensure sufficient coagulation ability when neuraxial blocks are applied.[259] Furthermore, combination of general anaesthesia with thoracic epidural anaesthesia has been shown to statistically increase the risk of arterial hypotension.[260]

7.3 Peri-operative goal-directed therapy

There is accumulating evidence underlining the advantages of goal-directed fluid therapy in non–cardiac-surgery patients. Goal-directed therapy aims to optimize cardiovascular performance, in order to achieve normal or even supranormal oxygen delivery to tissues, by optimizing pre-load and inotropic function using predefined haemodynamic targets. In contrast to clinical signs or arterial pressure-orientated standard therapy, goal-directed therapy is based on flow or fluid responsiveness of haemodynamic variables, such as stroke volume, response to fluid challenges, stroke volume or pulse pressure variation, or similar cardiac output optimization. Although goal-directed therapy was initially based on the use of a pulmonary artery catheter, less-invasive techniques have been developed, such as oesophageal Doppler and transpulmonary dilution techniques, as well as advanced pressure waveform analysis. Early

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goal-directed fluid therapy—in the right patient cohort and with a clearly defined protocol—has been shown to decrease post-operative mortality and morbidity.[261,262] The mortality benefit of goal-directed fluid therapy was most pronounced in patients with an extremely high risk of death (>20%). All high-risk patients undergoing major surgery had a benefit from goal-directed fluid therapy in terms of complications.[263] A meta-analysis published in 2014 demonstrated that, in patients with CVDs, goal-directed therapy decreased major morbidity without any increase in adverse cardiovascular events.[264]

7.4 Risk stratification after surgery

Several recent studies have demonstrated that it is possible to stratify the risk of post-operative complications and mortality with a simple surgical 'Apgar' score.[265] This post-event stratification might allow redirecting patients to higher intensity units or selected post-operative measurements of natriuretic peptides and troponin.[3,266]

7.5 Early diagnosis of post-operative complications

Several recent publications have demonstrated that differences between hospitals, in terms of post-operative mortality, are not due to the incidence of complications but to the way in which they are managed.[267] These results suggest that early identification of post-operative complications, allied to aggressive management, could decrease post-operative morbidity and mortality. Several recent meta-analyses have demonstrated that increased post-operative troponin and BNP concentrations after non-cardiac surgery were associated with a significantly increased risk of mortality.[55,266,268] The prospective Vascular Events In Noncardiac Surgery Patients Cohort Evaluation (VISION) trial confirmed the results of these meta-analyses.[3] Taken together, these results indicate that early troponin measurement in selected patients could trigger therapeutic consequences. A non-randomized trial demonstrated that a bundle of interventions aimed at promoting homeostasis was associated with a significantly decreased incidence of post-operative troponin elevation and decreased morbidity.[269] Pre-operatively and post-operatively, patients who could most benefit from BNP or high-sensitivity troponin measurements are those with METs ≤4 or with a revised cardiac risk index value >1 for vascular surgery and >2 for non-vascular surgery. Post-operatively, patients with a surgical Apgar score <7 should also be monitored with BNP or high-sensitivity troponin measurements, in order to detect complications early, independently of their revised cardiac risk index values.

7.6 Post-operative pain management

Severe post-operative pain, reported in 5–10% of patients, increases sympathetic drive and delays recovery.[270,271] Neuroaxial analgesia with local anaesthetics, *or* opioids and/or alpha2-agonists, *and* intravenous opioids, alone or in combination with non-steroidal anti-inflammatory drugs, seem to be the most effective regimens. The benefit of invasive (neuraxial) analgesic techniques should be weighed against potential dangers; this is especially important when considering the use of neuraxial blockade in patients on chronic antithrombotic therapy, due to the increased risk of developing a neuraxial haematoma. A meta-analysis published in 2013, which analysed the impact of epidural analgesia vs. systemic analgesia, concluded that epidural analgesia was associated with a significant, 40% decrease in mortality and a significant decrease in the risk of AF, SVT, deep-vein thrombosis, respiratory depression, atelectasis, pneumonia, ileus, and post-operative nausea and vomiting, and also improved recovery of bowel function, but significantly increased the risk of arterial hypotension, pruritus, urinary retention, and motor blockade.[272]

The transition from acute, post-operative pain to chronic, post-surgical pain is an unfortunate consequence of surgery that adversely impacts the patient's quality of life. The prevalence of chronic post-surgical pain differs in various types of surgery. Limited data suggest that local or regional analgesia, gabapentin or pregabaline, or intravenous lidocaine, might have a preventive effect against persistent post-surgical pain and could be used in a high-risk population.[273]

Recommendations on anaesthesia

Recommendations	Class[a]	Level[b]	Ref.[c]
Patients with high cardiac and surgical risk should be considered for goal-directed therapy.	IIa	B	261–264
The measurement of natriuretic peptides and high-sensitivity troponin after surgery may be considered in high-risk patients to improve risk stratification.	IIb	B	3,55,266, 268,272
Neuraxial anaesthesia (alone), in the absence of contra-indications and after estimation of the risk–benefit ratio, reduces the risk of peri-operative mortality and morbidity compared with general anaesthesia and may be considered.	IIb	B	10,252–257
Avoiding arterial hypotension (mean arterial pressure <60 mm Hg) for prolonged cumulative periods (>30 minutes) may be considered.	IIb	B	104,245,246
Neuraxial analgesia, in the absence of contra-indications, may be considered to provide post-operative analgesia.	IIb	B	272
Avoiding non-steroidal anti-inflammatory drugs (especially cyclo-oxygenase-2 inhibitors) as the first-line analgesics in patients with IHD or stroke may be considered.	IIb	B	279

IHD = ischaemic heart disease
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

Patient-controlled analgesia is an alternative for post-operative pain relief. Meta-analyses of controlled, randomized trials have

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shown that patient-controlled analgesia has some advantages, with regard to patient satisfaction, over nurse-controlled or on-demand analgesia. No difference has been demonstrated with regard to morbidity or final outcome. Patient-controlled analgesia is an adequate alternative in patients not suited to regional anaesthesia. Routines for follow-up and documentation of effects should be in place.[270,274–276]

Non-steroidal anti-inflammatory drugs and cyclo-oxygenase-2 inhibitors have the potential for promoting heart and renal failure, as well as thrombo-embolic events, and should be avoided in patients with myocardial ischaemia or diffuse atherosclerosis. Recently, an increased risk of cardiovascular events associated with diclofenac was detected, specifically in a high-risk population.[277] Cyclo-oxygenase-2 inhibitors cause less gastrointestinal ulceration and bronchospasm than cyclo-oxygenase-1 inhibitors. The final value of these drugs in the treatment of post-operative pain in cardiac patients undergoing non-cardiac surgery has not been defined. These drugs should be avoided in cases of renal and heart failure, or in patients who are elderly, on diuretics, or those with unstable haemodynamics.[278]

8. Gaps in evidence

The Task Force has identified several major gaps in the available evidence:

- There is lack of data on how non-cardiac risk factors (frailty, extreme low or high body mass index, anaemia, immune status) interact with cardiovascular risk factors and how they impact on the outcomes of non-cardiac surgery.
- There is a need for risk scores that can predict mortality from non-cardiac causes.
- Interventional or outcome studies need to be performed, that take into consideration increased pre-operative or post-operative high-sensitivity troponin, BNP, and other biomarkers.
- Areas of uncertainty remain in terms of the optimal type, dose, and duration of peri-operative beta-blocker therapy in patients undergoing high-risk non-cardiac surgery.
- It remains unknown whether or not patients at intermediate surgical risk derive benefit from peri-operative beta-blocker therapy.
- Areas of uncertainty remain in terms of the potential benefit of the introduction of statins in patients undergoing high-risk surgery.
- Interventional or outcome studies need to be performed on the prevention or correction of haemodynamic abnormalities or low bispectral index values that are statistically associated with worse outcome.
- Information is lacking on the effects of patient status, operating team size or skills, and the invasiveness of procedures, on outcomes following non-cardiac surgery and these will require investigations in large, procedure-specific, randomized, multicentre studies.

9. Summary

Figure 3 presents, in algorithmic form, an evidence-based, stepwise approach for determining which patients benefit from cardiac testing, coronary artery revascularization, and cardiovascular therapy before surgery. For each step, the Committee has included the level of the recommendations and the strength of evidence in the accompanying *Table 8*.

Step 1. The urgency of the surgical procedure should be assessed. In urgent cases, patient- or surgery-specific factors dictate the strategy and do not allow further cardiac testing or treatment. In these cases, the consultant provides recommendations on peri-operative medical management, surveillance for cardiac events, and continuation of chronic cardiovascular medical therapy.

Step 2. If the patient is unstable, this condition should be clarified and treated appropriately before surgery. Examples are unstable coronary syndromes, decompensated heart failure, severe arrhythmias, and symptomatic valvular disease. Stabilization 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 by a multidisciplinary expert team, including all peri-operative care physicians, because interventions might have implications for anaesthesiological and surgical care. For example, the initiation of dual anti-platelet therapy after coronary artery stent placement might complicate locoregional anaesthesia or specific surgical procedures. Depending on the outcome of this discussion, patients may *either* proceed for coronary artery intervention, namely CABG, balloon angioplasty, or stent placement, with the initiation of dual anti-platelet therapy if the index surgical procedure can be delayed, *or* proceed directly for operation with optimal medical therapy if delay is incompatible.

Step 3. In cardiac-stable patients, determine the risk of the surgical procedure (*Table 3*). If the estimated 30-day cardiac risk of the procedure in cardiac stable patients is low (<1%), it is unlikely that test results will influence management and it would be appropriate to proceed with the planned surgical procedure. The physician can identify risk factors and provide recommendations on lifestyle and medical therapy to improve long-term outcome, as outlined in *Table 8*. Initiation of a beta-blocker regimen may be considered prior to surgery in patients with known IHD or myocardial ischaemia. Treatment should ideally be initiated between 30 days and a minimum of 2 days before surgery and should be continued post-operatively. Beta-blockade should be started with a low dose, slowly up-titrated and tailored to achieve a resting heart rate of between 60 and 70 bpm with systolic blood pressure >100 mm Hg. In patients with heart failure and systolic LV dysfunction, indicated by LVEF <40%, ACEIs (or ARBs in patients intolerant of ACEIs) should be considered before surgery. In patients undergoing vascular surgery, initiation of statin therapy should be considered. Discontinuation of aspirin should be considered in those patients in whom haemostasis is difficult to control during surgery.

Step 4. Consider the functional capacity of the patient. If an asymptomatic or cardiac-stable patient has moderate or good functional capacity (>4 METs), peri-operative 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. The recommendations for medication are the same as in Step 3.

Step 5. In patients with a moderate or poor functional capacity, consider the risk of the surgical procedure, as outlined in *Table 3*. Patients scheduled for intermediate-risk surgery can proceed for surgery. In addition to the suggestions above, in patients with one or more clinical risk factors (*Table 4*), a pre-operative baseline ECG is recommended to monitor changes during the surgical procedure.

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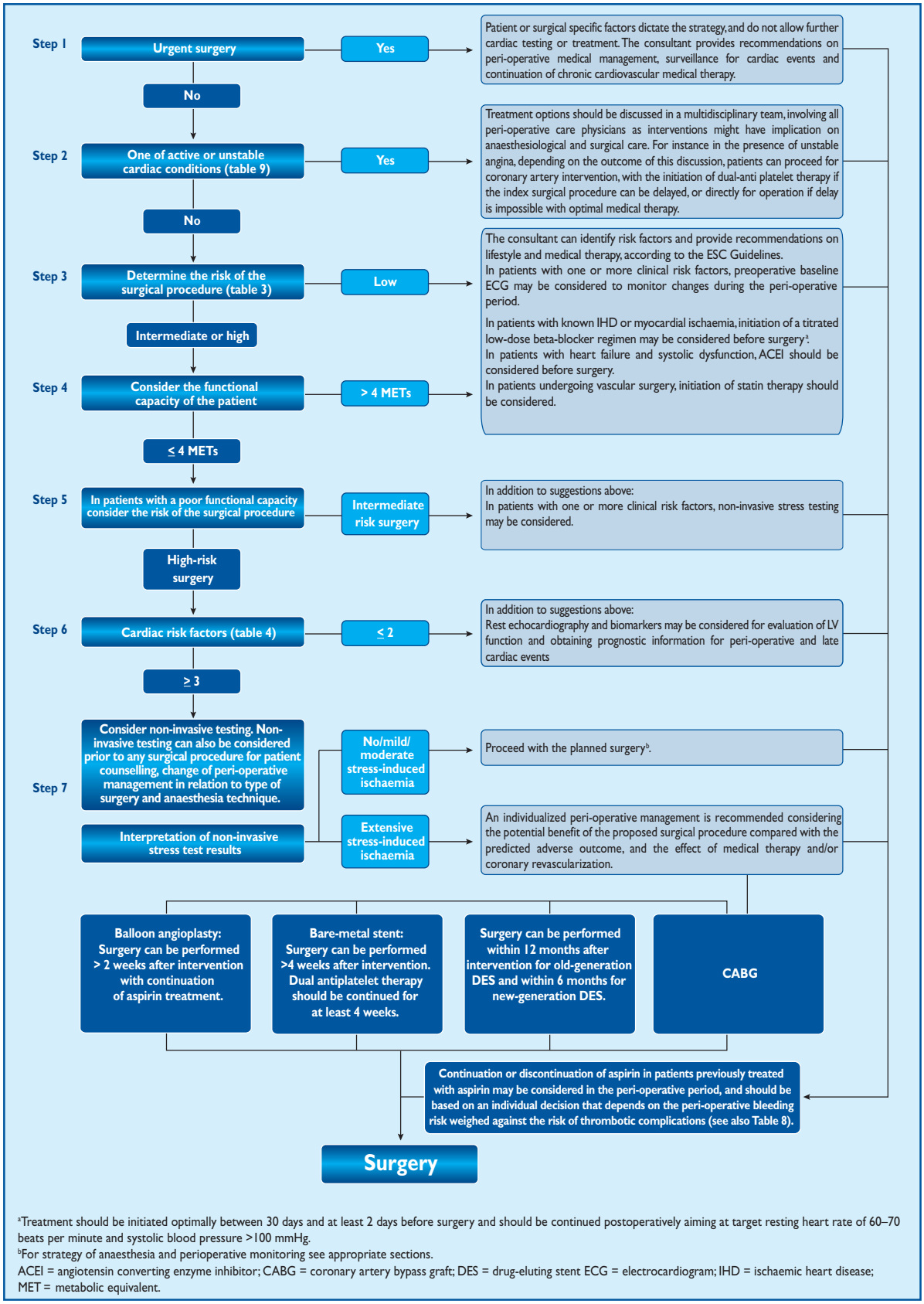

Figure 3 Summary of pre-operative cardiac risk evaluation and perioperative management.

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Table 8 Summary of pre-operative cardiac risk evaluation and peri-operative management

Step	Urgency	Cardiac condition	Type of surgery[a]	Functional capacity	Number of clinical risk factors[b]	ECG	LV echo[c]	Imaging Stress Testing[d]	BNP and TnT[c]	ß-Blockers[e,f]	ACE-inhibitors[e]	Aspirin[e]	Statins[e]	Coronary Revascularisation
1	Urgent surgery	Stable					III C	III C		I B (continuation)	IIa C[h] (continuation)	IIb B (continuation)	I C (continuation)	III C
2	Urgent surgery	Unstable[g]												IIa C
	Elective surgery	Unstable[g]				I C[g]	I C[g]	III C	IIb B					I A
3	Elective surgery	Stable	Low risk (< 1%)		None	III C	III C	III C	III C	III B	IIa C[h]	I C[m]	IIa B[j]	III B
					≥ 1	IIb C	III C	III C		IIb B[i]	IIa C[h]	I C[m]	IIa B[j]	III B
4	Elective surgery	Stable	Intermediate (1–5%) or high risk (>5%)	Excellent or good			III C	III C	III C	IIb B[i]	IIa C[h]	I C[m]	IIa B[j]	III B
5	Elective surgery	Stable	Intermediate risk (1–5 %)	Poor	None	IIb C	III C[k]		III C[k]	IIb B[i]	IIa C[h]	I C[m]	IIa B[j]	III B
					≥ 1	I C	III C[k]	IIb C		IIb B[i]	IIa C[h]	I C[m]	IIa B[j]	III B
6	Elective surgery	Stable	High risk (>5 %)	Poor	1–2	I C	IIb C[k]	IIb C	IIb B[i,k]	IIb B[i,j]	IIa C[h]	I C[m]	IIa B[j]	IIb B
					≥ 3	I C	IIb C[k]	I C	IIb B[k]	IIb B[i,j]	IIa C[h]	I C[m]	IIa B[j]	IIb B

ACE = angiotensin converting enzyme; BNP = brain natriuretic peptide; ECG = electrocardiogram; IHD = ischaemic heart disease; LV = left ventricular. Hatched areas: treatment options should be considered by a multidisciplinary Expert Team.

[a]Type of surgery (*Table 3*): risk of myocardial infarction and cardiac death within 30 days of surgery.

[b]Clinical risk factors presented in *Table 4*.

[c]In patients without signs and symptoms of cardiac disease or ECG abnormalities.

[d]Non-invasive testing, not only for revascularization, but also for patient counselling, change of peri-operative management in relation to type of surgery, and anaesthesia technique.

[e]Initiation of medical therapy, but in the case of emergency surgery, continuation of current medical therapy.

[f]Treatment should be initiated ideally less than 30 days and at least 2 days before surgery and should be continued post-operatively, aiming at a target heart rate of 60–70 beats per minute and systolic blood pressure >100 mm Hg.

[g]Unstable cardiac conditions presented in *Table 9*. Recommendations are based on current guidelines, recommending assessment of LV function and ECG in these conditions.

[h]In the presence of heart failure and systolic LV dysfunction (treatment should be initiated at least 1 week before surgery).

[i]In patients with known IHD or myocardial ischaemia.

[j]In patients undergoing vascular surgery.

[k]Evaluation of LV function with echocardiography and assessment of BNP are recommended in patients with established or suspected HF before intermediate- or high-risk surgery in patients with established or suspected HF (I A).

[l]In the presence of American Society of Anesthesiologists class ≥3 or revised cardiac risk index ≥2.

[m]Aspirin should be continued after stent implantation (for 4 weeks after BMS and 3–12 months after DES implantation).

Step 6. In patients scheduled for high-risk surgery, consider non-invasive testing in patients with more than two clinical risk factors (*Table 4*). Non-invasive testing can also be considered before any surgical procedure for patient counselling, or change of peri-operative management in relation to type of surgery and anaesthesia technique. Risk factors can be identified and medical therapy optimized as in Step 3.

Step 7. Interpretation of non-invasive stress test results: patients without stress-induced ischaemia—or with mild-to-moderate ischaemia suggestive of one- or two-vessel disease—can proceed to the planned surgical procedure. In patients with extensive stress-induced ischaemia (as assessed by non-invasive testing), individualized peri-operative management is recommended, taking into consideration the potential benefit of the proposed surgical procedure, weighed against 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 anti-platelet therapy will interfere with the planned surgical procedure (see sections 4.2 and 4.4).

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Table 9 Unstable cardiac conditions

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

[a]Myocardial infarction within past 30 days, according to the universal definition[49]

10. Appendix

ESC National Cardiac Societies actively involved in the review process of the 2014 ESC/ESA Guidelines on non-cardiac surgery: cardiovascular assessment and management

Austria, Austrian Society of Cardiology, Bernhard Metzler – **Azerbaijan**, Azerbaijan Society of Cardiology, Rahima Gabulova – **Belarus**, Belorussian Scientific Society of Cardiologists, Alena Kurlianskaya – **Belgium**, Belgian Society of Cardiology, Marc J Claeys – **Bosnia and Herzegovina**, Association of Cardiologists of Bosnia & Herzegovina, Ibrahim Terzić – **Bulgaria**, Bulgarian Society of Cardiology, Assen Goudev – **Cyprus**, Cyprus Society of Cardiology, Petros Agathangelou – **Czech Republic**, Czech Society of Cardiology, Hana Skalicka – **Denmark**, Danish Society of Cardiology, Lone Due Vestergaard – **Estonia**, Estonian Society of Cardiology, Margus Viigimaa – **Finland**, Finnish Cardiac Society, Kai Lindgren – **France**, French Society of Cardiology, Gérald Vanzetto – **Georgia**, Georgian Society of Cardiology, Zurab Pagava – **Germany**, German Cardiac Society, Malte Kelm – **Greece**, Hellenic Cardiological Society, Costas Thomopoulos – **Hungary**, Hungarian Society of Cardiology, Robert Gabor Kiss – **Iceland**, Icelandic Society of Cardiology, Karl Andersen – **Israel**, Israel Heart Society, Zvi Vered – **Italy**, Italian Federation of Cardiology, Francesco Romeo – **Kyrgyzstan**, Kyrgyz Society of Cardiology, Erkin Mirrakhimov – **Latvia**, Latvian Society of Cardiology, Gustavs Latkovskis – **Lebanon**, Lebanese Society of Cardiology, Georges Saade – **Libya**, Libyan Cardiac Society, Hisham A. Ben Lamin – **Lithuania**, Lithuanian Society of Cardiology, Germanas Marinskis – **Malta**, Maltese Cardiac Society, Mark Sammut – **Poland**, Polish Cardiac Society, Janina Stepinska – **Portugal**, Portuguese Society of Cardiology, João Manuel Pereira Coutinho – **Romania**, Romanian Society of Cardiology, Ioan Mircea Coman – **Russia**, Russian Society of Cardiology, Dmitry Duplyakov – **Serbia**, Cardiology Society of Serbia, Marina Deljanin Ilic – **Slovakia**, Slovak Society of Cardiology, Juraj Dúbrava – **Spain**, Spanish Society of Cardiology, Vicente Bertomeu – **Sweden**, Swedish Society of Cardiology, Christina Christersson – **The Former Yugoslav Republic of Macedonia**, Macedonian FYR Society of Cardiology, Marija Vavlukis – **Tunisia**, Tunisian Society of Cardiology and Cardio-Vascular Surgery, Abdallah Mahdhaoui – **Turkey**, Turkish Society of Cardiology, Dilek Ural – **Ukraine**, Ukrainian Association of Cardiology, Alexander Parkhomenko – **United Kingdom**, British Cardiovascular Society, Andrew Archbold.

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CME questions for this article are available at: European Heart Journal http://www.oxforde-learning.com/eurheartj and European Society of Cardiology http://www.escardio.org/guidelines.

References

1. Weiser TG, Regenbogen SE, Thompson KD, Haynes AB, Lipsitz SR, Berry WR *et al.* An estimation of the global volume of surgery: a modelling strategy based on available data. *Lancet* 2008;**372**:139–144.
2. Haynes AB, Weiser TG, Berry WR, Lipsitz SR, Breizat AH, Dellinger EP *et al.* A surgical safety checklist to reduce morbidity and mortality in a global population. *N Engl J Med* 2009;**360**:491–499.
3. Devereaux PJ, Chan MT, Alonso-Coello P, Walsh M, Berwanger O, Villar JC *et al.* Association between post-operative troponin levels and 30-day mortality among patients undergoing noncardiac surgery. *JAMA* 2012;**307**:2295–2304.
4. Naughton C, Feneck RO. The impact of age on 6-month survival in patients with cardiovascular risk factors undergoing elective non-cardiac surgery. *Int J Clin Pract* 2007;**61**:768–776.
5. Mangano DT. Peri-operative medicine: NHLBI working group deliberations and recommendations. *J Cardiothorac Vasc Anesth* 2004;**18**:1–6.
6. Ferguson TB, Hammill BG, Peterson ED, DeLong ER, Grover FL. A decade of change: Risk profiles and outcomes for isolated coronary artery bypass grafting procedures, 1990–1999: A report from the STS National Database Committee and the Duke Clinical Research Institute. *Ann Thorac Surg* 2002;**73**:480–489.
7. Carroll K, Majeed A, Firth C, Gray J. Prevalence and management of coronary heart disease in primary care: population-based cross-sectional study using a disease register. *J Public Health Med* 2003;**25**:29–35.
8. Fletcher HR, Milhoan LH, Evans K, Austin PN. Patients with aortic stenosis: who should undergo noncardiac surgery in a rural hospital? *J Perianesth Nurs* 2013;**28**:368–376.
9. Wirthlin DJ, Cambria RP. Surgery-specific considerations in the cardiac patient undergoing noncardiac surgery. *Prog Cardiovasc Dis* 1998;**40**:453–468.
10. Guay J, Choi P, Suresh S, Albert N, Kopp S, Pace NL. Neuraxial blockade for the prevention of post-operative mortality and major morbidity: an overview of Cochrane systematic reviews. *Cochrane Database Syst Rev* 2014;**1**:CD010108.
11. Glance LG, Lustik SJ, Hannan EL, Osler TM, Mukamel DB, Qian F *et al.* The Surgical Mortality Probability Model: derivation and validation of a simple risk prediction rule for noncardiac surgery. *Ann Surg* 2012;**255**:696–702.
12. Wang CL, Qu G, Xu HW. The short- and long-term outcomes of laparoscopic vs. open surgery for colorectal cancer: a meta-analysis. *Int J Colorectal Dis* 2014.
13. Rosenmüller MH, Thorén Örnberg M, Myrnäs T, Lundberg O, Nilsson E, Haapamäki MM. Expertise-based randomized clinical trial of laparoscopic vs. small-incision open cholecystectomy. *Br J Surg* 2013;**100**:886–894.
14. Bauer SM, Cayne NS, Veith FJ. New developments in the pre-operative evaluation and peri-operative management of coronary artery disease in patients undergoing vascular surgery. *J Vasc Surg* 2010;**51**:242–251.
15. Brown LC, Powell JT, Thompson SG, Epstein DM, Sculpher MJ, Greenhalgh RM. The UK EndoVascular Aneurysm Repair (EVAR) trials: randomised trials of EVAR vs. standard therapy. *Health Technol Assess* 2012;**16**:1–218.

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16. Stather PW, Sidloff D, Dattani N, Choke E, Bown MJ, Sayers RD. Systematic review and meta-analysis of the early and late outcomes of open and endovascular repair of abdominal aortic aneurysm. *Br J Surg* 2013;**100**:863–872.
17. Paravastu SC, Jayarajasingam R, Cottam R, Palfreyman SJ, Michaels JA, Thomas SM. Endovascular repair of abdominal aortic aneurysm. *Cochrane Database Syst Rev* 2014;**1**:CD004178.
18. Antoniou GA, Chalmers N, Georgiadis GS, Lazarides MK, Antoniou SA, Serracino-Inglott F *et al.* A meta-analysis of endovascular vs. surgical reconstruction of femoropopliteal arterial disease. *J Vasc Surg* 2013;**57**:242–253.
19. Tendera M, Aboyans V, Bartelink ML, Baumgartner I, Clement D, Collet JP *et al.* ESC Guidelines on the diagnosis and treatment of peripheral artery diseases: Document covering atherosclerotic disease of extracranial carotid and vertebral, mesenteric, renal, upper and lower extremity arteries: the Task Force on the Diagnosis and Treatment of Peripheral Artery Diseases of the European Society of Cardiology (ESC). *Eur Heart J* 2011;**32**:2851–2906.
20. Liu ZJ, Fu WG, Guo ZY, Shen LG, Shi ZY, Li JH. Updated systematic review and meta-analysis of randomized clinical trials comparing carotid artery stenting and carotid endarterectomy in the treatment of carotid stenosis. *Ann Vasc Surg* 2012; **26**:576–590.
21. Cutlip DE, Pinto DS. Extracranial carotid disease revascularization. *Circulation* 2012; **126**:2636–2644.
22. Naylor AR. Time to rethink management strategies in asymptomatic carotid artery disease. *Nat Rev Cardiol* 2012;**9**:116–124.
23. Nallamothu BK, Gurm HS, Ting HH, Goodney PP, Rogers MA, Curtis JP *et al.* Operator experience and carotid stenting outcomes in Medicare beneficiaries. *JAMA* 2011;**306**:1338–1343.
24. Holte K, Kehlet H. Post-operative ileus: a preventable event. *Br J Surg* 2000;**87**: 1480–1493.
25. Popescu WM, Bell R, Duffy AJ, Katz KH, Perrino AC. A pilot study of patients with clinically severe obesity undergoing laparoscopic surgery: evidence for impaired cardiac performance. *J Cardiothorac Vasc Anesth* 2011;**25**:943–949.
26. Lestar M, Gunnarsson L, Lagerstrand L, Wiklund P, Odeberg-Wernerman S. Hemodynamic perturbations during robot-assisted laparoscopic radical prostatectomy in 45° Trendelenburg position. *Anesth Analg* 2011;**113**:1069–1075.
27. Hirvonen EA, Nuutinen LS, Kauko M. Hemodynamic changes due to Trendelenburg positioning and pneumoperitoneum during laparoscopic hysterectomy. *Acta Anaesthesiol Scand* 1995;**39**:949–955.
28. Nguyen NT, Wolfe BM. The physiologic effects of pneumoperitoneum in the morbidly obese. *Annals of Surgery* 2005;**241**:219–226.
29. Keus F, Gooszen HG, van Laarhoven CJ. Open, small-incision, or laparoscopic cholecystectomy for patients with symptomatic cholecystolithiasis. An overview of Cochrane Hepato-Biliary Group reviews. *Cochrane Database Syst Rev* 2010:CD008318.
30. Mamidanna R, Burns EM, Bottle A, Aylin P, Stonell C, Hanna GB *et al.* Reduced risk of medical morbidity and mortality in patients selected for laparoscopic colorectal resection in England: a population-based study. *Arch Surg* 2012;**147**:219–227.
31. Cirocchi R, Farinella E, Trastulli S, Sciannameo F, Audisio RA. Elective sigmoid colectomy for diverticular disease. Laparoscopic vs. open surgery: a systematic review. *Colorectal Dis* 2012;**14**:671–683.
32. Murr MM, Martin T, Haines K, Torrella T, Dragotti R, Kandil A *et al.* A state-wide review of contemporary outcomes of gastric bypass in Florida: does provider volume impact outcomes? *Ann Surg* 2007;**245**:699–706.
33. Grailey K, Markar SR, Karthikesalingam A, Aboud R, Ziprin P, Faiz O. Laparoscopic vs. open colorectal resection in the elderly population. *Surg Endosc* 2013;**27**:19–30.
34. Cao C, Manganas C, Ang SC, Peeceeyen S, Yan TD. Video-assisted thoracic surgery vs. open thoracotomy for non-small cell lung cancer: a meta-analysis of propensity score-matched patients. *Interact Cardiovasc Thorac Surg* 2013;**16**:244–249.
35. De Martino RR, Brooke BS, Robinson W, Schanzer A, Indes JE, Wallaert JB *et al.* Designation as "unfit for open repair" is associated with poor outcomes after endovascular aortic aneurysm repair. *Circ Cardiovasc Qual Outcomes* 2013;**6**:575–581.
36. Hlatky MA, Boineau RE, Higginbotham MB, Lee KL, Mark DB, Califf RM *et al.* A brief self-administered questionnaire to determine functional capacity (the Duke Activity Status Index). *Am J Cardiol* 1989;**64**:651–654.
37. Fletcher GF, Balady GJ, Amsterdam EA, Chaitman B, Eckel R, Fleg J *et al.* Exercise standards for testing and training: A statement for healthcare professionals from the American Heart Association. *Circulation* 2001;**104**:1694–1740.
38. Biccard BM. Relationship between the inability to climb two flights of stairs and outcome after major non-cardiac surgery: implications for the pre-operative assessment of functional capacity. *Anaesthesia* 2005;**60**:588–593.
39. Wiklund RA, Stein HD, Rosenbaum SH. Activities of daily living and cardiovascular complications following elective, noncardiac surgery. *Yale J Biol Med* 2001;**74**: 75–87.
40. Morris CK, Ueshima K, Kawaguchi T, Hideg A, Froelicher VF. The prognostic value of exercise capacity: a review of the literature. *Am Heart J* 1991;**122**:1423–1431.
41. Goldman L, Caldera DL, Nussbaum SR, Southwick FS, Krogstad D, Murray B *et al.* Multifactorial index of cardiac risk in noncardiac surgical procedures. *N Engl J Med* 1977;**297**:845–850.
42. Detsky AS, Abrams HB, Forbath N, Scott JG, Hilliard JR. Cardiac assessment for patients undergoing noncardiac surgery. A multifactorial clinical risk index. *Arch Intern Med* 1986;**146**:2131–2134.
43. Lee TH, Marcantonio ER, Mangione CM, Thomas EJ, Polanczyk CA, Cook EF *et al.* Derivation and prospective validation of a simple index for prediction of cardiac risk of major noncardiac surgery. *Circulation* 1999;**100**:1043–1049.
44. Gupta PK, Gupta H, Sundaram A, Kaushik M, Fang X, Miller WJ *et al.* Development and validation of a risk calculator for prediction of cardiac risk after surgery. *Circulation* 2011;**124**:381–387.
45. Ford MK, Beattie WS, Wijeysundera DN. Systematic review: prediction of perioperative cardiac complications and mortality by the revised cardiac risk index. *Ann Intern Med* 2010;**152**:26–35.
46. Maisel AS, Bhalla V, Braunwald E. Cardiac biomarkers: a contemporary status report. *Nat Clin Pract Cardiovasc Med* 2006;**3**:24–34.
47. Priebe HJ. Peri-operative myocardial infarction: aetiology and prevention. *Br J Anaesth* 2005;**95**:3–19.
48. Weber M, Luchner A, Seeberger M, Manfred S, Mueller C, Liebetrau C *et al.* Incremental value of high-sensitive troponin T in addition to the revised cardiac index for peri-operative risk stratification in non-cardiac surgery. *Eur Heart J* 2013;**34**: 853–862.
49. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD *et al.* Third universal definition of myocardial infarction. *Eur Heart J* 2012;**33**:2551–2567.
50. Wang TJ, Larson MG, Levy D, Benjamin EJ, Leip EP, Omland T *et al.* Plasma natriuretic peptide levels and the risk of cardiovascular events and death. *N Engl J Med* 2004; **350**:655–663.
51. Dernellis J, Panaretou M. Assessment of cardiac risk before non-cardiac surgery: brain natriuretic peptide in 1590 patients. *Heart* 2006;**92**:1645–1650.
52. Rodseth RN, Padayachee L, Biccard BM. A meta-analysis of the utility of preoperative brain natriuretic peptide in predicting early and intermediate-term mortality and major adverse cardiac events in vascular surgical patients. *Anaesthesia* 2008;**63**:1226–1233.
53. Karthikeyan G, Moncur RA, Levine O, Heels-Ansdell D, Chan MT, Alonso-Coello P *et al.* Is a pre-operative brain natriuretic peptide or N-terminal pro-B-type natriuretic peptide measurement an independent predictor of adverse cardiovascular outcomes within 30 days of noncardiac surgery? A systematic review and meta-analysis of observational studies. *J Am Coll Cardiol* 2009;**54**:1599–1606.
54. Moonesinghe SR, Mythen MG, Das P, Rowan KM, Grocott MP. Risk stratification tools for predicting morbidity and mortality in adult patients undergoing major surgery: qualitative systematic review. *Anesthesiology* 2013;**119**:959–981.
55. Rodseth RN, Biccard BM, Le Manach Y, Sessler DI, Lurati Buse GA, Thabane L *et al.* The prognostic value of pre-operative and post-operative B-type natriuretic peptides in patients undergoing noncardiac surgery: B-type natriuretic Peptide and N-terminal fragment of pro-B-type natriuretic Peptide: a systematic review and individual patient data meta-analysis. *J Am Coll Cardiol* 2014;**63**:170–180.
56. Montalescot G, Sechtem U, Achenbach S, Andreotti F, Arden C, Budaj A *et al.* 2013 ESC guidelines on the management of stable coronary artery disease: The Task Force on the management of stable coronary artery disease of the European Society of Cardiology. Eur Heart J *2013*;**34**:2949–3003.
57. Jeger RV, Probst C, Arsenic R, Lippuner T, Pfisterer ME, Seeberger MD *et al.* Long-term prognostic value of the pre-operative 12-lead electrocardiogram before major noncardiac surgery in coronary artery disease. *Am Heart J* 2006;**151**: 508–513.
58. Halm EA, Browner WS, Tubau JF, Tateo IM, Mangano DT. Echocardiography for assessing cardiac risk in patients having noncardiac surgery. Study of Peri-operative Ischemia Research Group. *Ann Intern Med* 1996;**125**:433–441.
59. Rohde LE, Polanczyk CA, Goldman L, Cook EF, Lee RT, Lee TH. Usefulness of transthoracic echocardiography as a tool for risk stratification of patients undergoing major noncardiac surgery. *Am J Cardiol* 2001;**87**:505–509.
60. Etchells E, Meade M, Tomlinson G, Cook D. Semi-quantitative dipyridamole myocardial stress perfusion imaging for cardiac risk assessment before noncardiac vascular surgery: A metaanalysis. *J Vasc Surg* 2002;**36**:534–540.
61. Shaw LJ, Eagle KA, Gersh BJ, Miller DD. Meta-analysis of intravenous dipyridamole-thallium-201 imaging (1985 to 1994) and dobutamine echocardiography (1991 to 1994) for risk stratification before vascular surgery. *J Am Coll Cardiol* 1996;**27**: 787–798.
62. Sicari R, Nihoyannopoulos P, Evangelista A, Kasprzak J, Lancellotti P, Poldermans D *et al.* Stress Echocardiography Expert Consensus Statement: Executive Summary: European Association of Echocardiography (EAE) (a registered branch of the ESC). *Eur Heart J* 2009;**30**:278–289.
63. Das MK, Pellikka PA, Mahoney DW, Roger VL, Oh JK, McCully RB *et al.* Assessment of cardiac risk before nonvascular surgery: dobutamine stress echocardiography in 530 patients. *J Am Coll Cardiol* 2000;**35**:1647–1653.

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64. Raux M, Godet G, Isnard R, Mergoni P, Goarin JP, Bertrand M *et al.* Low negative predictive value of dobutamine stress echocardiography before abdominal aortic surgery. *Br J Anaesth* 2006;**97**:770–776.
65. Labib SB, Goldstein M, Kinnunen PM, Schick EC. Cardiac events in patients with negative maximal vs. negative submaximal dobutamine echocardiograms undergoing noncardiac surgery: importance of resting wall motion abnormalities. *J Am Coll Cardiol* 2004;**44**:82–87.
66. Nandalur KR, Dwamena BA, Choudhri AF, Nandalur MR, Carlos RC. Diagnostic performance of stress cardiac magnetic resonance imaging in the detection of coronary artery disease: A meta-analysis. *J Am Coll Cardiol* 2007;**50**:1343–1353.
67. Schwitter J, Wacker CM, Wilke N, Al-Saadi N, Sauer E, Huettle K *et al.* MR-IMPACT II: Magnetic Resonance Imaging for Myocardial Perfusion Assessment in Coronary artery disease Trial: perfusion-cardiac magnetic resonance vs. single-photon emission computed tomography for the detection of coronary artery disease: a comparative multicentre, multivendor trial. *Eur Heart J* 2013;**34**:775–781.
68. Rerkpattanapipat P, Morgan TM, Neagle CM, Link KM, Hamilton CA, Hundley WG. Assessment of pre-operative cardiac risk with magnetic resonance imaging. *Am J Cardiol* 2002;**90**:416–419.
69. Vahanian A, Alfieri O, Andreotti F, Antunes MJ, Baron-Esquivias G, Baumgartner H *et al.* Guidelines on the management of valvular heart disease (version 2012): The Joint Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J* 2012;**33**:2451–2496.
70. Knuuti J, Bengel F, Bax JJ, Kaufmann PA, Le Guludec D, Perrone Filardi P *et al.* Risks and benefits of cardiac imaging: an analysis of risks related to imaging for coronary artery disease. *Eur Heart J* 2013; **35**:633–638.
71. Schein OD, Katz J, Bass EB, Tielsch JM, Lubomski LH, Feldman MA *et al.* The value of routine pre-operative medical testing before cataract surgery. Study of Medical Testing for Cataract Surgery. *N Engl J Med* 2000;**342**:168–175.
72. Patel MR, Bailey SR, Bonow RO, Chambers CE, Chan PS, Dehmer GJ *et al.* ACCF/SCAI/AATS/AHA/ASE/ASNC/HFSA/HRS/SCCM/SCCT/SCMR/STS 2012 appropriate use criteria for diagnostic catheterization: a report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, Society for Cardiovascular Angiography and Interventions, American Association for Thoracic Surgery, American Heart Association, American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Failure Society of America, Heart Rhythm Society, Society of Critical Care Medicine, Society of Cardiovascular Computed Tomography, Society for Cardiovascular Magnetic Resonance, and Society of Thoracic Surgeons. *J Am Coll Cardiol* 2012;**59**:1995–2027.
73. Hamm CW, Bassand JP, Agewall S, Bax J, Boersma E, Bueno H *et al.* ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: The Task Force for the management of acute coronary syndromes (ACS) in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J* 2011;**32**: 2999–3054.
74. Wijns W, Kolh P, Danchin N, Di Mario C, Falk V, Folliguet T *et al.* Guidelines on myocardial revascularization. *Eur Heart J* 2010;**31**:2501–2555.
75. Steg PG, James SK, Atar D, Badano LP, Blömstrom-Lundqvist C, Borger MA *et al.* ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. *Eur Heart J* 2012;**33**:2569–2619.
76. Illuminati G, Ricco JB, Greco C, Mangieri E, Calio' F, Ceccanei G *et al.* Systematic pre-operative coronary angiography and stenting improves post-operative results of carotid endarterectomy in patients with asymptomatic coronary artery disease: a randomised controlled trial. *Eur J Vasc Endovasc Surg* 2010;**39**: 139–145.
77. Lüscher TF, Gersh B, Landmesser U, Ruschitzka F. Is the panic about beta-blockers in peri-operative care justified? *Eur Heart J* 2014. epub ahead of print.
78. Devereaux PJ, Yang H, Yusuf S, Guyatt G, Leslie K, Villar JC *et al.* Effects of extended-release metoprolol succinate in patients undergoing non-cardiac surgery (POISE trial): a randomised controlled trial. *Lancet* 2008;**371**:1839–1847.
79. Zaugg M, Bestmann L, Wacker J, Lucchinetti E, Boltres A, Schulz C *et al.* Adrenergic receptor genotype but not peri-operative bisoprolol therapy may determine cardiovascular outcome in at-risk patients undergoing surgery with spinal block: The Swiss Beta Blocker in Spinal Anesthesia (BBSA) study: A double-blinded, placebo-controlled, multicenter trial with 1-year follow-up. *Anesthesiology* 2007;**107**:33–44.
80. Yang H, Raymer K, Butler R, Parlow J, Roberts R. The effects of peri-operative beta-blockade: Results of the Metoprolol after Vascular Surgery (MaVS) study, a randomized controlled trial. *Am Heart J* 2006;**152**:983–990.
81. Juul AB, Grp DT. Effect of peri-operative beta blockade in patients with diabetes undergoing major non-cardiac surgery: randomised placebo controlled, blinded multicentre trial. *BMJ* 2006;**332**:1482–1485.
82. Brady AR, Gibbs JS, Greenhalgh RM, Powell JT, Sydes MR. Peri-operative beta-blockade (POBBLE) for patients undergoing infrarenal vascular surgery: results of a randomized double-blind controlled trial. *J Vasc Surg* 2005;**41**:602–609.
83. Mangano DT, Layug EL, Wallace A, Tateo I. Effect of atenolol on mortality and cardiovascular morbidity after noncardiac surgery. Multicenter Study of Peri-operative Ischemia Research Group. *New Engl J Med* 1996;**335**:1713–1720.
84. Alonso-Coello P, Paniagua P, Mizera R, Devereaux PJ. Should physicians initiate beta-blocker therapy in patients undergoing non-cardiac surgery? Insights from the POISE trial. *Pol Arch Med Wewn* 2008;**118**:616–618.
85. Bouri S, Shun-Shin MJ, Cole GD, Mayet J, Francis DP. Meta-analysis of secure randomised controlled trials of beta-blockade to prevent peri-operative death in non-cardiac surgery. *Heart* 2014;**100**:456–464.
86. Angeli F, Verdecchia P, Karthikeyan G, Mazzotta G, Gentile G, Reboldi G. β-Blockers reduce mortality in patients undergoing high-risk non-cardiac surgery. *Am J Cardiovasc Drugs* 2010;**10**:247–259.
87. Devereaux PJ, Beattie WS, Choi PT, Badner NH, Guyatt GH, Villar JC *et al.* How strong is the evidence for the use of peri-operative beta blockers in non-cardiac surgery? Systematic review and meta-analysis of randomised controlled trials. *BMJ (Clinical research ed)* 2005;**331**:313–321.
88. McGory ML, Maggard MA, Ko CY. A meta-analysis of peri-operative beta blockade: what is the actual risk reduction? *Surgery* 2005;**138**:171–179.
89. Stevens RD, Burri H, Tramer MR. Pharmacologic myocardial protection in patients undergoing noncardiac surgery: a quantitative systematic review. *Anesth analg* 2003; **97**:623–633.
90. Wiesbauer F, Schlager O, Domanovits H, Wildner B, Maurer G, Muellner M *et al.* Peri-operative beta-blockers for preventing surgery-related mortality and morbidity: a systematic review and meta-analysis. *Anesth analg* 2007;**104**:27–41.
91. Auerbach AD, Goldman L. β-Blockers and reduction of cardiac events in noncardiac surgery: scientific review. *JAMA* 2002;**287**:1435–1444.
92. Bangalore S, Wetterslev J, Pranesh S, Sawhney S, Gluud C, Messerli FH. Peri-operative beta blockers in patients having non-cardiac surgery: a meta-analysis. *Lancet* 2008;**372**:1962–1976.
93. Leibowitz AB. Can meta-analysis of the current literature help determine if peri-operative beta-blockers improve outcome of high-risk patients undergoing noncardiac surgery? *J Cardiothorac Vasc Anesth* 2010;**24**:217–218.
94. Beattie WS, Wijeysundera DN, Karkouti K, McCluskey S, Tait G. Does tight heart rate control improve beta-blocker efficacy? An updated analysis of the noncardiac surgical randomized trials. *Anesth Analg* 2008;**106**:1039–1048.
95. Lindenauer PK, Pekow P, Wang KJ, Mamidi DK, Gutierrez B, Benjamin EM. Peri-operative beta-blocker therapy and mortality after major noncardiac surgery. *N Engl J Med* 2005;**353**:349–361.
96. Shammash JB, Trost JC, Gold JM, Berlin JA, Golden MA, Kimmel SE. Peri-operative beta-blocker withdrawal and mortality in vascular surgical patients. *Am Heart J* 2001;**141**:148–153.
97. London MJ, Hur K, Schwartz GG, Henderson WG. Association of peri-operative beta-blockade with mortality and cardiovascular morbidity following major noncardiac surgery. *JAMA* 2013;**309**:1704–1713.
98. Wallace AW, Au S, Cason BA. Association of the pattern of use of peri-operative beta-blockade and post-operative mortality. *Anesthesiology* 2010;**113**:794–805.
99. Kwon S, Thompson R, Florence M, Maier R, McIntyre L, Rogers T *et al.* β-blocker continuation after noncardiac surgery: a report from the surgical care and outcomes assessment program. *Arch Surg* 2012;**147**:467–473.
100. Wallace AW, Au S, Cason BA. Peri-operative beta-blockade: atenolol is associated with reduced mortality when compared with metoprolol. *Anesthesiology* 2011;**114**: 824–836.
101. Redelmeier D, Scales D, Kopp A. β-blockers for elective surgery in elderly patients: population based, retrospective cohort study. *BMJ (Clinical research ed)* 2005;**331**: 932.
102. Ashes C, Judelman S, Wijeysundera DN, Tait G, Mazer CD, Hare GM *et al.* Selective β1-Antagonism with Bisoprolol Is Associated with Fewer Post-operative Strokes than Atenolol or Metoprolol: A Single-center Cohort Study of 44,092 Consecutive Patients. *Anesthesiology* 2013;**119**:777–787.
103. Ellenberger C, Tait G, Beattie WS. Chronic beta blockade is associated with a better outcome after elective noncardiac surgery than acute beta blockade: a single-center propensity-matched cohort study. *Anesthesiology* 2011;**114**: 817–823.
104. Walsh M, Devereaux PJ, Garg AX, Kurz A, Turan A, Rodseth RN *et al.* Relationship between intra-operative mean arterial pressure and clinical outcomes after noncardiac surgery: toward an empirical definition of hypotension. *Anesthesiology* 2013;**119**:507–515.
105. Andersson C, Mérie C, Jørgensen M, Gislason GH, Torp-Pedersen C, Overgaard C *et al.* Association of β-Blocker Therapy With Risks of Adverse Cardiovascular Events and Deaths in Patients With Ischemic Heart Disease Undergoing Noncardiac Surgery: A Danish Nationwide Cohort Study. *JAMA Intern Med* 2014;**174**: 336–344.
106. Wallace A, Layug B, Tateo I, Li J, Hollenberg M, Browner W *et al.* Prophylactic atenolol reduces post-operative myocardial ischemia. McSPI Research Group. *Anesthesiology* 1998;**88**:7–17.

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107. Lindenauer PK, Pekow P, Wang K, Gutierrez B, Benjamin EM. Lipid-lowering therapy and in-hospital mortality following major noncardiac surgery. *JAMA* 2004;**291**:2092–2099.
108. Hindler K, Shaw AD, Samuels J, Fulton S, Collard CD, Riedel B. Improved postoperative outcomes associated with pre-operative statin therapy. *Anesthesiology* 2006;**105**:1260–1272;quiz 1289–1290.
109. Desai H, Aronow WS, Ahn C, Gandhi K, Amin H, Lai HM *et al.* Incidence of perioperative myocardial infarction and of 2-year mortality in 577 elderly patients undergoing noncardiac vascular surgery treated with and without statins. *Arch Gerontol Geriatr* 2010;**51**:149–151.
110. Lau WC, Froehlich JB, Jewell ES, Montgomery DG, Eng KM, Shields TA *et al.* Impact of adding aspirin to Beta-blocker and statin in high-risk patients undergoing major vascular surgery. *Ann Vasc Surg* 2013;**27**:537–545.
111. Durazzo AE, Machado FS, Ikeoka DT, De Bernoche C, Monachini MC, Puech-Leao P *et al.* Reduction in cardiovascular events after vascular surgery with atorvastatin: a randomized trial. *J Vasc Surg* 2004;**39**:967–975;discussion 975–966.
112. Chopra V, Wesorick DH, Sussman JB, Greene T, Rogers M, Froehlich JB *et al.* Effect of peri-operative statins on death, myocardial infarction, atrial fibrillation, and length of stay: a systematic review and meta-analysis. *Arch Surg* 2012;**147**:181–189.
113. Winchester DE, Wen X, Xie L, Bavry AA. Evidence of pre-procedural statin therapy a meta-analysis of randomized trials. *J Am Coll Cardiol* 2010;**56**:1099–1109.
114. Le Manach Y, Ibanez Esteves C, Bertrand M, Goarin JP, Fleron MH, Coriat P *et al.* Impact of pre-operative statin therapy on adverse post-operative outcomes in patients undergoing vascular surgery. *Anesthesiology* 2011;**114**:98–104.
115. Sanders RD, Nicholson A, Lewis SR, Smith AF, Alderson P. Peri-operative statin therapy for improving outcomes during and after noncardiac vascular surgery. *Cochrane database syst rev* 2013;**7**:CD009971.
116. McNally MM, Agle SC, Parker FM, Bogey WM, Powell CS, Stoner MC. Preoperative statin therapy is associated with improved outcomes and resource utilization in patients undergoing aortic aneurysm repair. *J Vasc Surg* 2010;**51**:1390–1396.
117. Verzini F, De Rango P, Parlani G, Giordano G, Caso V, Cieri E *et al.* Effects of statins on early and late results of carotid stenting. *J Vasc Surg* 2011;**53**:71–79;discussion 79.
118. Le Manach Y, Godet G, Coriat P, Martinon C, Bertrand M, Fleron MH *et al.* The impact of post-operative discontinuation or continuation of chronic statin therapy on cardiac outcome after major vascular surgery. *Anesth Analg* 2007;**104**:1326–1333.
119. Kertai MD, Westerhout CM, Varga KS, Acsady G, Gal J. Dihydropiridine calcium-channel blockers and peri-operative mortality in aortic aneurysm surgery. *Br J Anaesthesia* 2008;**101**:458–465.
120. Devereaux PJ, Sessler DI, Leslie K, Kurz A, Mrkobrada M, Alonso-Coello P *et al.* Clonidine in patients undergoing noncardiac surgery. *N Engl J Med* 2014;**370**:1504–1513.
121. Burger W, Chemnitius JM, Kneissl GD, Rucker G. Low-dose aspirin for secondary cardiovascular prevention: cardiovascular risks after its peri-operative withdrawal vs. bleeding risks with its continuation: review and meta-analysis. *J Int Med* 2005;**257**:399–414.
122. Devereaux PJ, Mrkobrada M, Sessler DI, Leslie K, Alonso-Coello P, Kurz A *et al.* Aspirin in patients undergoing noncardiac surgery. *N Engl J Med* 2014;**370**:1494–1503.
123. Patrono C, Andreotti F, Arnesen H, Badimon L, Baigent C, Collet JP *et al.* Anti-platelet agents for the treatment and prevention of atherothrombosis. *Eur Heart J* 2011;**32**:2922–2932.
124. Korte W, Cattaneo M, Chassot PG, Eichinger S, von Heymann C, Hofmann N *et al.* Peri-operative management of anti-platelet therapy in patients with coronary artery disease: joint position paper by members of the working group on Peri-operative Haemostasis of the Society on Thrombosis and Haemostasis Research (GTH), the working group on Peri-operative Coagulation of the Austrian Society for Anesthesiology, Resuscitation and Intensive Care (ÖGARI) and the Working Group Thrombosis of the European Society for Cardiology (ESC). *Thromb Haemost* 2011;**105**:743–749.
125. Sun JC, Whitlock R, Cheng J, Eikelboom JW, Thabane L, Crowther MA *et al.* The effect of pre-operative aspirin on bleeding, transfusion, myocardial infarction, and mortality in coronary artery bypass surgery: a systematic review of randomized and observational studies. *Eur Heart J* 2008;**29**:1057–1071.
126. Hawn MT, Graham LA, Richman JS, Itani KM, Henderson WG, Maddox TM. Risk of major adverse cardiac events following noncardiac surgery in patients with coronary stents. *JAMA* 2013;**310**:1462–1472.
127. Huber KC, Evans MA, Bresnahan JF, Gibbons RJ, Holmes DR. Outcome of noncardiac operations in patients with severe coronary-artery disease successfully treated pre-operatively with coronary angioplasty. *Mayo Clin Proc* 1992;**67**:15–21.
128. Kaluza GL, Joseph J, Lee JR, Raizner ME, Raizner AE. Catastrophic outcomes of noncardiac surgery soon after coronary stenting. *J Am Coll Cardiol* 2000;**35**:1288–1294.
129. Nuttall GA, Brown MJ, Stombaugh JW, Michon PB, Hathaway MF, Lindeen KC *et al.* Time and cardiac risk of surgery after bare-metal stent percutaneous coronary intervention. *Anesthesiology* 2008;**109**:588–595.
130. Berger PB, Kleiman NS, Pencina MJ, Hsieh WH, Steinhubl SR, Jeremias A *et al.* Frequency of major noncardiac surgery and subsequent adverse events in the year after drug-eluting stent placement results from the EVENT (Evaluation of Drug-Eluting Stents and Ischemic Events) Registry. *JACC Cardiovasc Interv* 2010;**3**:920–927.
131. Baber U, Mehran R, Sharma SK, Brar S, Yu J, Suh JW *et al.* Impact of the everolimus-eluting stent on stent thrombosis: a meta-analysis of 13 randomized trials. *J Am Coll Cardiol* 2011;**58**:1569–1577.
132. Feres F, Costa RA, Abizaid A, Leon MB, Marin-Neto JA, Botelho RV *et al.* Three vs. twelve months of dual anti-platelet therapy after zotarolimus-eluting stents: the OPTIMIZE randomized trial. *JAMA* 2013;**310**:2510–2522.
133. Wijns W, Kolh P, Danchin N, Di Mario C, Falk V, Folliguet T *et al.* Guidelines on myocardial revascularization: The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J* 2010;**31**:2501–2555.
134. Ferraris VA, Saha SP, Oestreich JH, Song HK, Rosengart T, Reece TB *et al.* 2012 update to the Society of Thoracic Surgeons guideline on use of anti-platelet drugs in patients having cardiac and noncardiac operations. Ann Thorac Surg *2012*;**94**:1761–1781.
135. Mahla E, Suarez TA, Bliden KP, Rehak P, Metzler H, Sequeira AJ *et al.* Platelet function measurement-based strategy to reduce bleeding and waiting time in clopidogrel-treated patients undergoing coronary artery bypass graft surgery: the timing based on platelet function strategy to reduce clopidogrel-associated bleeding related to CABG (TARGET-CABG) study. *Circ Cardiovasc Interv* 2012;**5**:261–269.
136. Angiolillo DJ, Firstenberg MS, Price MJ, Tummala PE, Hutyra M, Welsby IJ *et al.* Bridging anti-platelet therapy with cangrelor in patients undergoing cardiac surgery: a randomized controlled trial. *JAMA* 2012;**307**:265–274.
137. Pengo V, Cucchini U, Denas G, Erba N, Guazzaloca G, La Rosa L *et al.* Standardized Low-Molecular-Weight Heparin Bridging Regimen in Outpatients on Oral Anticoagulants Undergoing Invasive Procedure or Surgery An Inception Cohort Management Study. *Circulation* 2009;**119**:2920–2927.
138. Huber K, Connolly SJ, Kher A, Christory F, Dan GA, Hatala R *et al.* Practical use of dabigatran etexilate for stroke prevention in atrial fibrillation. *Int J Clin Pract* 2013;**67**:516–526.
139. De Caterina R, Husted S, Wallentin L, Andreotti F, Arnesen H, Bachmann F *et al.* New oral anticoagulants in atrial fibrillation and acute coronary syndromes: ESC Working Group on Thrombosis-Task Force on Anticoagulants in Heart Disease position paper. *J Am Coll Cardiol* 2012;**59**:1413–1425.
140. Heidbuchel H, Verhamme P, Alings M, Antz M, Hacke W, Oldgren J *et al.* European Heart Rhythm Association Practical Guide on the use of new oral anticoagulants in patients with non-valvular atrial fibrillation. *Europace* 2013;**15**:625–651.
141. Weitz JI, Quinlan DJ, Eikelboom JW. Periprocedural management and approach to bleeding in patients taking dabigatran. *Circulation* 2012;**126**:2428–2432.
142. Eerenberg ES, Kamphuisen PW, Sijpkens MK, Meijers JC, Buller HR, Levi M. Reversal of rivaroxaban and dabigatran by prothrombin complex concentrate: a randomized, placebo-controlled, crossover study in healthy subjects. *Circulation* 2011;**124**:1573–1579.
143. Díaz MQ, Borobia AM, Núñez MA, Virto AM, Fabra S, Casado MS *et al.* Use of prothrombin complex concentrates for urgent reversal of dabigatran in the Emergency Department. *Haematologica* 2013;**98**:e143–e144.
144. Camm AJ, Lip GY, De Caterina R, Savelieva I, Atar D, Hohnloser SH *et al.* 2012 focussed update of the ESC Guidelines for the management of atrial fibrillation: an update of the 2010 ESC Guidelines for the management of atrial fibrillation. Developed with the special contribution of the European Heart Rhythm Association. *Eur Heart J* 2012;**33**:2719–2747.
145. Dawood MM, Gutpa DK, Southern J, Walia A, Atkinson JB, Eagle KA. Pathology of fatal peri-operative myocardial infarction: implications regarding pathophysiology and prevention. *Int J Cardiol* 1996;**57**:37–44.
146. Devereaux PJ, Goldman L, Cook DJ, Gilbert K, Leslie K, Guyatt GH. Peri-operative cardiac events in patients undergoing noncardiac surgery: a review of the magnitude of the problem, the pathophysiology of the events and methods to estimate and communicate risk. *CMAJ* 2005;**173**:627–634.
147. Eagle KA, Rihal CS, Mickel MC, Holmes DR, Foster ED, Gersh BJ. Cardiac risk of noncardiac surgery: Influence of coronary disease and type of surgery in 3368 operations. *Circulation* 1997;**96**:1882–1887.
148. Mookadam F, Carpenter SD, Thota VR, Cha S, Jiamsripong P, Alharthi MS *et al.* Risk of adverse events after coronary artery bypass graft and subsequent noncardiac surgery. *Future Cardiol* 2011;**7**:69–75.
149. Assali A, Vaknin-Assa H, Lev E, Bental T, Ben-Dor I, Teplitsky I *et al.* The risk of cardiac complications following noncardiac surgery in patients with drug eluting stents implanted at least six months before surgery. *Catheter Cardiovasc Interv* 2009;**74**:837–843.

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150. Wijeysundera DN, Wijeysundera HC, Yun L, Wąsowicz M, Beattie WS, Velianou JL *et al.* Risk of elective major noncardiac surgery after coronary stent insertion: a population-based study. *Circulation* 2012;**126**:1355–1362.
151. Brilakis ES, Orford JL, Fasseas P, Wilson SH, Melby S, Lennon RJ *et al.* Outcome of patients undergoing balloon angioplasty in the two months prior to noncardiac surgery. *Am J Cardiol* 2005;**96**:512–514.
152. McFalls EO, Ward HB, Moritz TE, Goldman S, Krupski WC, Littooy F *et al.* Coronary-artery revascularization before elective major vascular surgery. *New Engl J Med* 2004;**351**:2795–2804.
153. Monaco M, Stassano P, Di Tommaso L, Pepino P, Giordano A, Pinna GB *et al.* Systematic strategy of prophylactic coronary angiography improves long-term outcome after major vascular surgery in medium- to high-risk patients: a prospective, randomized study. *J Am Coll Cardiol* 2009;**54**:989–996.
154. Wong EY, Lawrence HP, Wong DT. The effects of prophylactic coronary revascularization or medical management on patient outcomes after noncardiac surgery: a meta-analysis. *Can J Anaesth* 2007;**54**:705–717.
155. Mohr FW, Morice MC, Kappetein AP, Feldman TE, Ståhle E, Colombo A *et al.* Coronary artery bypass graft surgery vs. percutaneous coronary intervention in patients with three-vessel disease and left main coronary disease: 5-year follow-up of the randomised, clinical SYNTAX trial. *Lancet* 2013;**381**:629–638.
156. Matteau A, Mauri L. Optimal timing of noncardiac surgery after stents. *Circulation* 2012;**126**:1322–1324.
157. Bangalore S, Kumar S, Fusaro M, Amoroso N, Attubato MJ, Feit F *et al.* Short- and long-term outcomes with drug-eluting and bare-metal coronary stents: a mixed-treatment comparison analysis of 117 762 patient-years of follow-up from randomized trials. *Circulation* 2012;**125**:2873–2891.
158. Livhits M, Gibbons MM, de Virgilio C, O'Connell JB, Leonardi MJ, Ko CY *et al.* Coronary revascularization after myocardial infarction can reduce risks of noncardiac surgery. *J Am Coll Surg* 2011;**212**:1018–1026.
159. McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Böhm M, Dickstein K *et al.* ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail* 2012;**14**:803–869.
160. Mosterd A, Hoes AW. Clinical epidemiology of heart failure. *Heart* 2007;**93**:1137–1146.
161. Sabaté S, Mases A, Guilera N, Canet J, Castillo J, Orrego C *et al.* Incidence and predictors of major peri-operative adverse cardiac and cerebrovascular events in non-cardiac surgery. *Br J Anaesth* 2011;**107**:879–890.
162. Pannell LM, Reyes EM, Underwood SR. Cardiac risk assessment before non-cardiac surgery. *Eur Heart J Cardiovasc Imaging* 2013;**14**:316–322.
163. Hammill BG, Curtis LH, Bennett-Guerrero E, O'Connor CM, Jollis JG, Schulman KA *et al.* Impact of heart failure on patients undergoing major noncardiac surgery. *Anesthesiology* 2008;**108**:559–567.
164. Upshaw J, Kiernan MS. Pre-operative cardiac risk assessment for noncardiac surgery in patients with heart failure. *Curr Heart Fail Rep* 2013;**10**:147–156.
165. Kazmers A, Cerqueira MD, Zierler RE. Peri-operative and late outcome in patients with left ventricular ejection fraction of 35% or less who require major vascular surgery. *J Vasc Surg* 1988;**8**:307–315.
166. Xu-Cai YO, Brotman DJ, Phillips CO, Michota FA, Tang WH, Whinney CM *et al.* Outcomes of patients with stable heart failure undergoing elective noncardiac surgery. *Mayo Clin Proc* 2008;**83**:280–288.
167. Healy KO, Waksmonski CA, Altman RK, Stetson PD, Reyentovich A, Maurer MS. Peri-operative outcome and long-term mortality for heart failure patients undergoing intermediate- and high-risk noncardiac surgery: impact of left ventricular ejection fraction. *Congest Heart Fail* 2010;**16**:45–49.
168. Meta-analysis global group in chronic heart failure (MAGGIC). The survival of patients with heart failure with preserved or reduced left ventricular ejection fraction: an individual patient data meta-analysis. *Eur Heart J* 2012;**33**:1750–1757.
169. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA *et al.* Recommendations for chamber quantification. *Eur J Echocardiogr* 2006;**7**:79–108.
170. Mor-Avi V, Lang RM, Badano LP, Belohlavek M, Cardim NM, Derumeaux G *et al.* Current and evolving echocardiographic techniques for the quantitative evaluation of cardiac mechanics: ASE/EAE consensus statement on methodology and indications endorsed by the Japanese Society of Echocardiography. *Eur J Echocardiogr* 2011;**12**:167–205.
171. Cowie B. Focussed transthoracic echocardiography predicts peri-operative cardiovascular morbidity. *J Cardiothorac Vasc Anesth* 2012;**26**:989–993.
172. Wijeysundera DN, Beattie WS, Karkouti K, Neuman MD, Austin PC, Laupacis A. Association of echocardiography before major elective non-cardiac surgery with post-operative survival and length of hospital stay: population based cohort study. *BMJ* 2011;**342**:d3695.
173. Canty DJ, Royse CF, Kilpatrick D, Bowyer A, Royse AG. The impact on cardiac diagnosis and mortality of focussed transthoracic echocardiography in hip fracture surgery patients with increased risk of cardiac disease: a retrospective cohort study. *Anaesthesia* 2012;**67**:1202–1209.
174. Raman SV, Simonetti OP. The CMR examination in heart failure. *Heart Fail Clin* 2009;**5**:283–300.
175. Biccard BM, Lurati Buse GA, Burkhart C, Cuthbertson BH, Filipovic M, Gibson SC *et al.* The influence of clinical risk factors on pre-operative B-type natriuretic peptide risk stratification of vascular surgical patients. *Anaesthesia* 2012;**67**:55–59.
176. Rajagopalan S, Croal BL, Reeve J, Bachoo P, Brittenden J. N-terminal pro-B-type natriuretic peptide is an independent predictor of all-cause mortality and MACE after major vascular surgery in medium-term follow-up. *Eur J Vasc Endovasc Surg* 2011;**41**:657–662.
177. Guazzi M, Adams V, Conraads V, Halle M, Mezzani A, Vanhees L *et al.* EACPR/AHA Joint Scientific Statement. Clinical recommendations for cardiopulmonary exercise testing data assessment in specific patient populations. *Eur Heart J* 2012;**33**:2917–2927.
178. Young EL, Karthikesalingam A, Huddart S, Pearse RM, Hinchliffe RJ, Loftus IM *et al.* A systematic review of the role of cardiopulmonary exercise testing in vascular surgery. *Eur J Vasc Endovasc Surg* 2012;**44**:64–71.
179. Smith TB, Stonell C, Purkayastha S, Paraskevas P. Cardiopulmonary exercise testing as a risk assessment method in non cardio-pulmonary surgery: a systematic review. *Anaesthesia* 2009;**64**:883–893.
180. Rosenman DJ, McDonald FS, Ebbert JO, Erwin PJ, LaBella M, Montori VM. Clinical consequences of withholding vs. administering renin-angiotensin-aldosterone system antagonists in the pre-operative period. *J Hosp Med* 2008;**3**:319–325.
181. Howell SJ, Sear JW, Foëx P. Hypertension, hypertensive heart disease and peri-operative cardiac risk. *Br J Anaesth* 2004;**92**:570–583.
182. Casadei B, Abuzeid H. Is there a strong rationale for deferring elective surgery in patients with poorly controlled hypertension? *J Hypertens* 2005;**23**:19–22.
183. Mancia G, Fagard R, Narkiewicz K, Redon J, Zanchetti A, Böhm M *et al.* 2013 ESH/ESC guidelines for the management of arterial hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *Eur Heart J* 2013;**34**:2159–2219.
184. Kihara S, Brimacombe J, Yaguchi Y, Watanabe S, Taguchi N, Komatsuzaki T. Hemodynamic responses among three tracheal intubation devices in normotensive and hypertensive patients. *Anesth Analg* 2003;**96**:890–895, table of contents.
185. Charlson ME, MacKenzie CR, Gold JP, Ales KL, Topkins M, Shires GT. Intra-operative blood pressure. What patterns identify patients at risk for post-operative complications? *Ann Surg* 1990;**212**:567–580.
186. Weksler N, Klein M, Szendro G, Rozentsveig V, Schily M, Brill S *et al.* The dilemma of immediate pre-operative hypertension: To treat and operate, or to postpone surgery? *Journal of Clinical Anesthesia* 2003;**15**:179–183.
187. Goldman L, Caldera DL. Risks of general anesthesia and elective operation in the hypertensive patient. *Anesthesiology* 1979;**50**:285–292.
188. Calleja AM, Dommaraju S, Gaddam R, Cha S, Khandheria BK, Chaliki HP. Cardiac risk in patients aged >75 years with asymptomatic, severe aortic stenosis undergoing noncardiac surgery. *Am J Cardiol* 2010;**105**:1159–1163.
189. Fleisher LA, Beckman JA, Brown KA, Calkins H, Chaikof EL, Fleischmann KE *et al.* ACC/AHA 2007 guidelines on peri-operative cardiovascular evaluation and care for noncardiac surgery: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines on Peri-operative Cardiovascular Evaluation for Noncardiac Surgery) developed in collaboration with the American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Rhythm Society, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, and Society for Vascular Surgery. *J Am Coll Cardiol* 2007;**50**:e159–e241.
190. Habib G, Hoen B, Tornos P, Thuny F, Prendergast B, Vilacosta I *et al.* Guidelines on the prevention, diagnosis, and treatment of infective endocarditis (new version 2009): the Task Force on the Prevention, Diagnosis, and Treatment of Infective Endocarditis of the European Society of Cardiology (ESC). Endorsed by the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and the International Society of Chemotherapy (ISC) for Infection and Cancer. *Eur Heart J* 2009;**30**:2369–2413.
191. Zipes DP, Camm AJ, Borggrefe M, Buxton AE, Chaitman B, Fromer M *et al.* ACC/AHA/ESC 2006 guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: executive summary: A report of the American College of Cardiology/American Heart Association Task Force and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Develop Guidelines for Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death) Developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. *Eur Heart J* 2006;**27**:2099–2140.
192. Drew BJ, Ackerman MJ, Funk M, Gibler WB, Kligfield P, Menon V *et al.* Prevention of torsade de pointes in hospital settings: a scientific statement from the American

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Heart Association and the American College of Cardiology Foundation. *J Am Coll Cardiol* 2010;**55**:934–947.
193. Balser JR, Martinez EA, Winters BD, Perdue PW, Clarke AW, Huang WZ *et al.* beta-adrenergic blockade accelerates conversion of post-operative supraventricular tachyarrhythmias. *Anesthesiology* 1998;**89**:1052–1059.
194. Healey JS, Merchant R, Simpson C, Tang T, Beardsall M, Tung S *et al.* Canadian Cardiovascular Society/Canadian Anesthesiologists' Society/Canadian Heart Rhythm Society joint position statement on the peri-operative management of patients with implanted pacemakers, defibrillators, and neurostimulating devices. *Can J Cardiol* 2012;**28**:141–151.
195. Bihorac A, Yavas S, Subbiah S, Hobson CE, Schold JD, Gabrielli A *et al.* Long-term risk of mortality and acute kidney injury during hospitalization after major surgery. *Ann Surg* 2009;**249**:851–858.
196. Kheterpal S, Tremper KK, Heung M, Rosenberg AL, Englesbe M, Shanks AM *et al.* Development and validation of an acute kidney injury risk index for patients undergoing general surgery: results from a national data set. *Anesthesiology* 2009;**110**:505–515.
197. Earley A, Miskulin D, Lamb EJ, Levey AS, Uhlig K. Estimating equations for glomerular filtration rate in the era of creatinine standardization: a systematic review. *Ann Intern Med* 2012;**156**:785–795.
198. KDIGO Clinical Practice Guideline for Acute Kidney Injury. In: Kidney Int Suppl., 2012:**2**(suppl.2):1–138.
199. Kellum JA, Lameire N, Group ftKAGW. Diagnosis, evaluation, and management of acute kidney injury: a KDIGO summary (Part 1). *Crit Care* 2013;**17**:204.
200. McCullough PA, Soman SS. Contrast-induced nephropathy. *Crit Care Clin* 2005;**21**:261–80.
201. Cruz DN, Goh CY, Marenzi G, Corradi V, Ronco C, Perazella MA. Renal replacement therapies for prevention of radiocontrast-induced nephropathy: a systematic review. *Am J Med* 2012;**125**:p66–78.e3.
202. Jang JS, Jin HY, Seo JS, Yang TH, Kim DK, Kim TH *et al.* Sodium bicarbonate therapy for the prevention of contrast-induced acute kidney injury—a systematic review and meta-analysis. *Circ J* 2012;**76**:2255–2265.
203. Leoncini M, Toso A, Maioli M, Tropeano F, Villani S, Bellandi F. Early high-dose rosuvastatin for Contrast-Induced Nephropathy Prevention in Acute Coronary Syndrome. Results from Protective effect of Rosuvastatin and Anti-platelet Therapy On contrast-induced acute kidney injury and myocardial damage in patients with Acute Coronary Syndrome (PRATO-ACS Study). *J Am Coll Cardiol* 2013.
204. Selim M. Peri-operative stroke. *N Engl J Med* 2007;**356**:706–713.
205. Macellari F, Paciaroni M, Agnelli G, Caso V. Peri-operative stroke risk in nonvascular surgery. *Cerebrovasc Dis* 2012;**34**:175–181.
206. Mashour GA, Shanks AM, Kheterpal S. Peri-operative stroke and associated mortality after noncardiac, nonneurologic surgery. *Anesthesiology* 2011;**114**:1289–1296.
207. Ng JL, Chan MT, Gelb AW. Peri-operative stroke in noncardiac, nonneurosurgical surgery. *Anesthesiology* 2011;**115**:879–890.
208. Ahmed B, Al-Khaffaf H. Prevalence of significant asymptomatic carotid artery disease in patients with peripheral vascular disease: a meta-analysis. *Eur J Vasc Endovasc Surg* 2009;**37**:262–271.
209. Hofmann R, Kypta A, Steinwender C, Kerschner K, Grund M, Leisch F. Coronary angiography in patients undergoing carotid artery stenting shows a high incidence of significant coronary artery disease. *Heart* 2005;**91**:1438–1441.
210. Perk J, De Backer G, Gohlke H, Graham I, Reiner Z, Verschuren M *et al.* European Guidelines on cardiovascular disease prevention in clinical practice (version 2012). The Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts). *Eur Heart J* 2012;**33**:1635–1701.
211. Tendera M, Aboyans V, Bartelink ML, Baumgartner I, Clément D, Collet JP *et al.* ESC Guidelines on the diagnosis and treatment of peripheral artery diseases: Document covering atherosclerotic disease of extracranial carotid and vertebral, mesenteric, renal, upper and lower extremity arteries: the Task Force on the Diagnosis and Treatment of Peripheral Artery Diseases of the European Society of Cardiology (ESC). *Eur Heart J* 2011;**32**:2851–2906.
212. Ashton CM, Petersen NJ, Wray NP, Kiefe CI, Dunn JK, Wu L *et al.* The incidence of peri-operative myocardial infarction in men undergoing noncardiac surgery. *Ann Intern Med* 1993;**118**:504–510.
213. Sin DD, Wu LL, Man SFP. The relationship between reduced lung function and cardiovascular mortality: A population-based study and a systematic review of the literature. *Chest* 2005;**127**:1952–1959.
214. Canet J, Gallart L, Gomar C, Paluzie G, Vallès J, Castillo J *et al.* Prediction of post-operative pulmonary complications in a population-based surgical cohort. *Anesthesiology* 2010;**113**:1338–1350.
215. Edrich T, Sadovnikoff N. Anesthesia for patients with severe chronic obstructive pulmonary disease. *Curr Opin Anaesthesiol* 2010;**23**:18–24.
216. Chau EH, Lam D, Wong J, Mokhlesi B, Chung F. Obesity hypoventilation syndrome: a review of epidemiology, pathophysiology, and peri-operative considerations. *Anesthesiology* 2012;**117**:188–205.
217. Galiè N, Hoeper MM, Humbert M, Torbicki A, Vachiery JL, Barbera JA *et al.* Guidelines for the diagnosis and treatment of pulmonary hypertension: the Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS), endorsed by the International Society of Heart and Lung Transplantation (ISHLT). *Eur Heart J* 2009;**30**:2493–2537.
218. Ramakrishna G, Sprung J, Ravi BS, Chandrasekaran K, McGoon MD. Impact of pulmonary hypertension on the outcomes of noncardiac surgery. *J Am Coll Cardiol* 2005;**45**:1691–1699.
219. Kaw R, Pasupuleti V, Deshpande A, Hamieh T, Walker E, Minai OA. Pulmonary hypertension: an important predictor of outcomes in patients undergoing noncardiac surgery. *Respir Med* 2011;**105**:619–624.
220. Gille J, Seyfarth HJ, Gerlach S, Malcharek M, Czeslick E, Sablotzki A. Peri-operative anesthesiological management of patients with pulmonary hypertension. *Anesthesiol Res Pract* 2012;**2012**:356982.
221. Price LC, Wort SJ, Finney SJ, Marino PS, Brett SJ. Pulmonary vascular and right ventricular dysfunction in adult critical care: current and emerging options for management: a systematic literature review. *Crit Care* 2010;**14**:R169.
222. Baumgartner H, Bonhoeffer P, De Groot NM, de Haan F, Deanfield JE, Galie N *et al.* ESC Guidelines for the management of grown-up congenital heart disease (new version 2010). *Eur Heart J* 2010;**31**:2915–2957.
223. Landesberg G, Luria MH, Cotev S, Eidelman LA, Anner H, Mosseri M *et al.* Importance of long-duration post-operative ST-segment depression in cardiac morbidity after vascular surgery. *Lancet* 1993;**341**:715–719.
224. Leung JM, Voskanian A, Bellows WH, Pastor D. Automated electrocardiograph ST segment trending monitors: Accuracy in detecting myocardial ischemia. *Anesth Analg* 1998;**87**:4–10.
225. Landesberg G, Mosseri M, Wolf Y, Vesselov Y, Weissman C. Peri-operative myocardial ischemia and infarction: Identification by continuous 12-lead electrocardiogram with online ST-segment monitoring. *Anesthesiology* 2002;**96**:264–270.
226. London MJ, Hollenberg M, Wong MG, Levenson L, Tubau JF, Browner W *et al.* Intraoperative myocardial ischemia: localization by continuous 12-lead electrocardiography. *Anesthesiology* 1988;**69**:232–241.
227. Martinez EA, Kim LJ, Faraday N, Rosenfeld B, Bass EB, Perler BA *et al.* Sensitivity of routine intensive care unit surveillance for detecting myocardial ischemia. *Crit Care Med* 2003;**31**:2302–2308.
228. Landesberg G, Shatz V, Akopnik I, Wolf YG, Mayer M, Berlatzky Y *et al.* Association of cardiac troponin, CK-MB, and post-operative myocardial ischemia with long-term survival after major vascular surgery. *J Am Coll Cardiol* 2003;**42**:1547–1554.
229. London MJ, Tubau JF, Wong MG, Layug E, Hollenberg M, Krupski WC *et al.* The "natural history" of segmental wall motion abnormalities in patients undergoing noncardiac surgery. S.P.I. Research Group. *Anesthesiology* 1990;**73**:644–655.
230. Eisenberg MJ, London MJ, Leung JM, Browner WS, Hollenberg M, Tubau JF *et al.* Monitoring for myocardial ischemia during noncardiac surgery. A technology assessment of transesophageal echocardiography and 12-lead electrocardiography. The Study of Peri-operative Ischemia Research Group. *JAMA* 1992;**268**:210–216.
231. Thys DM, Abel M, Bollen BA, Cahalan MK, Curling P, Dean RJ *et al.* Practice guidelines for peri-operative transesophageal echocardiography: A report by the American Society of Anesthesiologists and the Society of Cardiovascular Anesthesiologists Task Force on Transesophageal Echocardiography. *Anesthesiology* 1996;**84**:986–1006.
232. Schulmeyer C, Farías J, Rajdl E, de La Maza J, Labbé M. Utility of transesophageal echocardiography during severe hypotension in non-cardiac surgery. *Rev Bras Anestesiol* 2010;**60**:513–521.
233. Agency of Healthcare Research and Quality (AHRQ) Technology Assessment Program: Oesophageal Doppler ultrasound-based cardiac output monitoring for real-time therapeutic management of hospitalized patient. MD, USA: Agency of Healthcare Research and Quality, 2007.
234. NHS Technology Adoption Centre How to why to guides, Doppler guided intra-operative fluid management. Manchester, UK: How to why to guides, Doppler guided intra-operative fluid management, 2010.
235. Practice guidelines for peri-operative transesophageal echocardiography. An updated report by the American Society of Anesthesiologists and the Society of Cardiovascular Anesthesiologists Task Force on Transesophageal Echocardiography. *Anesthesiology* 2010;**112**:1084–1096.
236. Polanczyk CA, Rohde LE, Goldman L, Cook EF, Thomas EJ, Marcantonio ER *et al.* Right heart catheterization and cardiac complications in patients undergoing noncardiac surgery: An observational study. *JAMA* 2001;**286**:309–314.
237. Rajaram SS, Desai NK, Kalra A, Gajera M, Cavanaugh SK, Brampton W *et al.* Pulmonary artery catheters for adult patients in intensive care. *Cochrane Database Syst Rev* 2013;**2**:CD003408.

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238. Gan TJ, Soppitt A, Maroof M, el-Moalem H, Robertson KM, Moretti E *et al.* Goal-directed intra-operative fluid administration reduces length of hospital stay after major surgery. *Anesthesiology* 2002;**97**:820–826.
239. *IDF Diabetes Atlas, 6th edn.* Brussels, Belgium: International Diabetes Federation, 2013.
240. Marik PE, Preiser JC. Toward understanding tight glycemic control in the ICU: a systematic review and metaanalysis. *Chest* 2010;**137**:544–551.
241. Jacobi J, Bircher N, Krinsley J, Agus M, Braithwaite SS, Deutschman C *et al.* Guidelines for the use of an insulin infusion for the management of hyperglycemia in critically ill patients. *Crit Care Med* 2012;**40**:3251–3276.
242. Rydén L, Grant PJ, Anker SD, Berne C, Cosentino F, Danchin N *et al.* ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD: the Task Force on diabetes, pre-diabetes, and cardiovascular diseases of the European Society of Cardiology (ESC) and developed in collaboration with the European Association for the Study of Diabetes (EASD). *Eur Heart J* 2013; **34**:3035–3087.
243. Pottie K, Jaramillo A, Lewin G, Dickinson J, Bell N, Brauer P *et al.* Recommendations on screening for type 2 diabetes in adults. *CMAJ* 2012;**184**:1687–1696.
244. De Hert S, Imberger G, Carlisle J, Diemunsch P, Fritsch G, Moppett I *et al.* Preoperative evaluation of the adult patient undergoing non-cardiac surgery: guidelines from the European Society of Anaesthesiology. *Eur J Anaesthesiol* 2011; **28**:684–722.
245. Bijker JB, Persoon S, Peelen LM, Moons KG, Kalkman CJ, Kappelle LJ *et al.* Intraoperative hypotension and peri-operative ischemic stroke after general surgery: a nested case-control study. *Anesthesiology* 2012;**116**:658–664.
246. Sessler DI, Sigl JC, Kelley SD, Chamoun NG, Manberg PJ, Saager L *et al.* Hospital stay and mortality are increased in patients having a "triple low" of low blood pressure, low bispectral index, and low minimum alveolar concentration of volatile anesthesia. *Anesthesiology* 2012;**116**:1195–1203.
247. Landoni G, Greco T, Biondi-Zoccai G, Nigro Neto C, Febres D, Pintaudi M *et al.* Anaesthetic drugs and survival: a Bayesian network meta-analysis of randomized trials in cardiac surgery. *Br J Anaesth* 2013;**111**:886–896.
248. Van der Linden PJ, Dierick A, Wilmin S, Bellens B, De Hert SG. A randomized controlled trial comparing an intra-operative goal-directed strategy with routine clinical practice in patients undergoing peripheral arterial surgery. *Eur J Anaesthesiol* 2010;**27**:788–793.
249. Zangrillo A, Testa V, Aldrovandi V, Tuoro A, Casiraghi G, Cavenago F *et al.* Volatile agents for cardiac protection in noncardiac surgery: a randomized controlled study. *J Cardiothorac Vasc Anesth* 2011;**25**:902–907.
250. Lurati Buse GA, Schumacher P, Seeberger E, Studer W, Schuman RM, Fassl J *et al.* Randomized comparison of sevoflurane vs. propofol to reduce peri-operative myocardial ischemia in patients undergoing noncardiac surgery. *Circulation* 2012; **126**:2696–2704.
251. De Hert SG. Cardioprotection by volatile anesthetics: what about noncardiac surgery? *J Cardiothorac Vasc Anesth* 2011;**25**:899–901.
252. Rodgers A, Walker N, Schug S, McKee A, Kehlet H, van Zundert A *et al.* Reduction of post-operative mortality and morbidity with epidural or spinal anaesthesia: results from overview of randomised trials. *BMJ* 2000;**321**: 1493–1497.
253. Wu CL, Rowlingson AJ, Herbert R, Richman JM, Andrews RAF, Fleisher LA. Correlation of post-operative epidural analgesia on morbidity and mortality after colectomy in Medicare patients. *J Clin Anesth* 2006;**18**:594–599.
254. Bode RH, Lewis KP, Zarich SW, Pierce ET, Roberts M, Kowalchuk GJ *et al.* Cardiac outcome after peripheral vascular surgery: Comparison of general and regional anesthesia. *Anesthesiology* 1996;**84**:3–13.
255. Mauermann WJ, Shilling AM, Zuo Z. A comparison of neuraxial block vs. general anesthesia for elective total hip replacement: A meta-analysis. *Anesth Analg* 2006; **103**:1018–1025.
256. Rigg JRA, Jamrozik K, Myles PS, Silbert BS, Peyton PJ, Parsons RW *et al.* Epidural anaesthesia and analgesia and outcome of major surgery: a randomised trial. *Lancet* 2002;**359**:1276–1282.
257. Memtsoudis SG, Sun X, Chiu YL, Stundner O, Liu SS, Banerjee S *et al.* Peri-operative comparative effectiveness of anesthetic technique in orthopedic patients. *Anesthesiology* 2013;**118**:1046–1058.
258. Barbosa FT, Jucá MJ, Castro AA, Cavalcante JC. Neuraxial anaesthesia for lower-limb revascularization. *Cochrane Database Syst Rev* 2013;**7**:CD007083.
259. Gogarten W, Vandermeulen E, Van Aken H, Kozek S, Llau JV, Samama CM *et al.* Regional anaesthesia and antithrombotic agents: recommendations of the European Society of Anaesthesiology. *Eur J Anaesthesiol* 2010;**27**:999–1015.
260. Leslie K, Myles P, Devereaux P, Williamson E, Rao-Melancini P, Forbes A *et al.* Neuraxial block, death and serious cardiovascular morbidity in the POISE trial. *Br J Anaesth* 2013;**111**:382–390.
261. Hamilton MA, Cecconi M, Rhodes A. A systematic review and meta-analysis on the use of preemptive hemodynamic intervention to improve post-operative outcomes in moderate and high-risk surgical patients. *Anesth Analg* 2011;**112**: 1392–1402.
262. Grocott MP, Dushianthan A, Hamilton MA, Mythen MG, Harrison D, Rowan K *et al.* Peri-operative increase in global blood flow to explicit defined goals and outcomes following surgery. *Cochrane Database Syst Rev* 2012;**11**:CD004082.
263. Cecconi M, Corredor C, Arulkumaran N, Abuella G, Ball J, Grounds RM *et al.* Clinical review: Goal-directed therapy-what is the evidence in surgical patients? The effect on different risk groups. *Crit Care* 2013;**17**:209.
264. Arulkumaran N, Corredor C, Hamilton MA, Ball J, Grounds RM, Rhodes A *et al.* Cardiac complications associated with goal-directed therapy in high-risk surgical patients: a meta-analysis. *Br J Anaesth* 2014;**112**:648–659.
265. Haynes AB, Regenbogen SE, Weiser TG, Lipsitz SR, Dziekan G, Berry WR *et al.* Surgical outcome measurement for a global patient population: validation of the Surgical Apgar Score in 8 countries. *Surgery* 2011;**149**:519–524.
266. Rodseth RN, Biccard BM, Chu R, Lurati Buse GA, Thabane L, Bakhai A *et al.* Post-operative B-type natriuretic peptide for prediction of major cardiac events in patients undergoing noncardiac surgery: systematic review and individual patient meta-analysis. *Anesthesiology* 2013;**119**:270–283.
267. Ghaferi AA, Birkmeyer JD, Dimick JB. Variation in hospital mortality associated with inpatient surgery. *N Engl J Med* 2009;**361**:1368–1375.
268. Levy M, Heels-Ansdell D, Hiralal R, Bhandari M, Guyatt G, Yusuf S *et al.* Prognostic value of troponin and creatine kinase muscle and brain isoenzyme measurement after noncardiac surgery: a systematic review and meta-analysis. *Anesthesiology* 2011;**114**:796–806.
269. Ausset S, Auroy Y, Verret C, Benhamou D, Vest P, Cirodde A *et al.* Quality of post-operative care after major orthopedic surgery is correlated with both long-term cardiovascular outcome and troponin Ic elevation. *Anesthesiology* 2010;**113**: 529–540.
270. Liu SS, Wu CL. The effect of analgesic technique on post-operative patient-reported outcomes including analgesia: A systematic review. *Anesth Analg* 2007; **105**:789–808.
271. White PF, Kehlet H. Post-operative pain management and patient outcome: Time to return to work! *Anesth Analg* 2007;**104**:487–489.
272. Pöpping DM, Elia N, Van Aken HK, Marret E, Schug SA, Kranke P *et al.* Impact of Epidural Analgesia on Mortality and Morbidity After Surgery: Systematic Review and Meta-analysis of Randomized Controlled Trials. *Ann Surg* 2013.
273. Clarke H, Bonin RP, Orser BA, Englesakis M, Wijeysundera DN, Katz J. The prevention of chronic postsurgical pain using gabapentin and pregabalin: a combined systematic review and meta-analysis. *Anesth Analg* 2012;**115**:428–442.
274. Dolin SJ, Cashman JN, Bland JM. Effectiveness of acute post-operative pain management: I. Evidence from published data. *Br J Anaesth* 2002;**89**:409–423.
275. Jørgensen H, Wetterslev J, Møiniche S, Dahl JB. Epidural local anaesthetics vs. opioid-based analgesic regimens on post-operative gastrointestinal paralysis, PONV and pain after abdominal surgery. *Cochrane Database Syst Rev* 2000:CD001893.
276. Block BM, Liu SS, Rowlingson AJ, Cowan AR, Cowan JA, Wu CL. Efficacy of post-operative epidural analgesia: A meta-analysis. *JAMA* 2003;**290**:2455–2463.
277. Bhala N, Emberson J, Merhi A, Abramson S, Arber N, Baron JA *et al.* Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: meta-analyses of individual participant data from randomised trials. *Lancet* 2013;**382**: 769–779.
278. Schug SA, Manopas A. Update on the role of non-opioids for post-operative pain treatment. *Best Pract Res Clin Anaesthesiol* 2007;**21**:15–30.
279. Varas-Lorenzo C, Riera-Guardia N, Calingaert B, Castellsague J, Salvo F Nicotra F *et al.* Myocardial infarction and individual nonsteroidal anti-inflammatory drugs meta-analysis of observational studies. *Pharmacoepidemiol Drug Saf* 2013.

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