Cardiovascular problems in noncardiac surgery

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Purpose of review

Perioperative cardiac complications remain a major area of concern as our surgical population increases in volume, age and frequency of comorbidity. A variety of strategies can be used to optimize patients and potentially reduce the incidence of these serious complications.

Recent findings

Recent literature suggests a trend towards less invasive testing for detection and quantification of coronary artery disease and greater interest in pharmacologic 'cardioprotection' using β-blockers, statins and other agents targeting heart rate control and other mechanisms (e.g. reducing inflammatory responses). The recent Perioperative Ischemic Evaluation study has substantially altered this approach at least towards widespread application to lower/intermediate risk cohorts. Considerable attention has been focused on ensuring optimal standardized perioperative management of patients with a recent percutaneous coronary intervention, particularly those with an intracoronary stent. Widespread surveillance of postoperative troponin release and increasing recognition of the prognostic potential of elevated preoperative brain natriuretic peptides point towards changing strategies for long-term risk stratification.

Summary

The complexity of a particular patient's physiologic responses to a wide variety of surgical procedures, which are undergoing constant technological refinement generally associated with lesser degrees of invasivity and stress make calculation of patients' perioperative risk very challenging. At the present time, adequate information is available for the clinician to screen patients with high-risk preoperative predictors, delay elective surgery for patients with recent intracoronary stents and continue chronic β-blockade in appropriate patients. New large-scale database and subanalyses of major trials (e.g. Perioperative Ischemic Evaluation and Coronary Artery Revascularization Prophylaxis) should provide additional information to minimize perioperative cardiac risk.

Keywords

β-adrenergic blockade, guidelines, myocardial infarction, natriuretic peptides, postoperative complications, troponins

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Introduction

Prevention and recognition of postoperative cardiac problems following noncardiac surgery is an area of intense clinical and economic interest in the perioperative and critical care environments. Cardiovascular problems occur with the highest frequency in patients with preexisting cardiovascular disease (CVD) and those undergoing major surgical procedures.

Cardiovascular complications following noncardiac surgery [e.g. myocardial infarction (MI), cardiac arrest, congestive heart failure (CHF), unstable angina, unstable cardiac rhythms, hypertensive urgencies/emergencies and ischemic/thrombotic stroke) consume substantial resources, but the social and financial impact has not been systematically quantified. The recently published Perioperative Ischemic Evaluation (POISE) β-blocker randomized clinical trial (RCT) provides a broader perspective, given its scope (>8000 patients from 23 countries) [1••]. A recent prospective cohort analysis indicates a cost of nearly $10 000 per perioperative myocardial ischemic injury (PMII) [2] (Table 1). The incentives and opportunities to intervene perioperatively differ between health systems based on available resources and institutional expertise (e.g. clinical guidelines compliance, electronic medical records, resources such as availability of onsite cardiac catheterization facilities and so on).

Instead of preoperative detection of myocardium at risk due to coronary artery disease (CAD) in the past, the focus has shifted to routine use of 'cardioprotective

Table 1 Incremental cost of a perioperative myocardial ischemic injury event during the index hospital stay in a cohort of 236 high risk patients undergoing major vascular surgery (excluding carotid surgery)

Resource use	No. of days	Unit cost per day (2004 USD)	Total cost (USD)
Participants without a PMII event			
Index hospital days (total)	10	–	13 660
Ward days	6.3	700	4410
ICU days	3.7	2500	9250
Participants with a PMII event			
Index hospital days (total)	16.8	–	23 640
Ward days	10.2	700	7140
ICU days	6.6	2500	16 500
Incremental cost of a PMII event			9980

ICU, intensive care unit; PMII, perioperative myocardial ischemic injury; USD, US dollars Reproduced from [2].

medications', in particular β-blockers, and most recently statins. There has also been a distinct focus on perioperative care of the patient with a coronary stent(s) [3•,4•]. An increasing number of recent articles have investigated the epidemiology of perioperative cardiovascular complications using large system-wide clinical databases (including the United States Government's Medicare and Department of Veterans Affairs National Surgical Quality Improvement Program which has recently been adopted by the American College of Surgery as the national model for University and private sector institutions) [5•,6•]. This approach avoids the logistical, cost and ethical issues involved in conducting RCTs and provides the distinct advantages for comparative effectiveness research. Finally, the use of cardiovascular biomarkers such as the troponins and most recently, N-terminal pro B-type natriuretic peptide (NT-pro-BNP), in 'defining' perioperative MI (PMI) and as prognostic markers of postoperative (and longer term) outcome has led to more questions and refinement of existing methods. Thus, in the case of troponin I, a better appreciation of the pitfalls associated with variability in the reference ranges for the multiple testing assays in clinical use has led to some degree of uncertainty in the literature, whereas technical improvements in newer assays enabling detection of even lower levels of myocardial injury complicates recent attempts to standardize PMI definitions [7••,8••,9•].

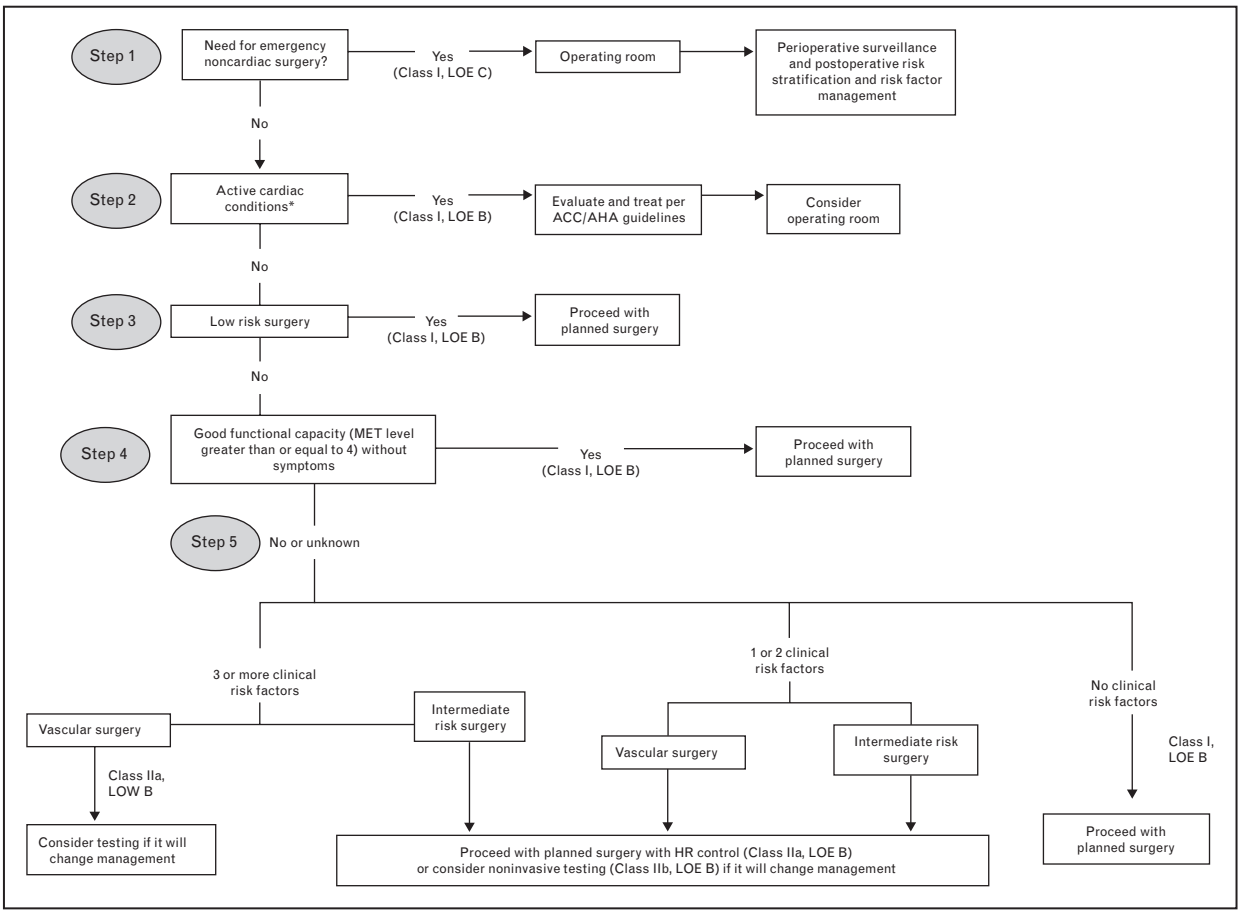
Risk stratification

The most commonly accepted methods for perioperative risk stratification are well described in the American College of Cardiology (ACC)/American Heart Association (AHA) Guidelines for Perioperative Evaluation [10]. The term perioperative is now well accepted instead of the prior literature focus nearly exclusively on preoperative evaluation. Although quite comprehensive in their scope, these guidelines similar to the others under the ACC/AHA 'umbrella' have recently come under criticism for an overemphasis on clinical recommendations based on lower levels of evidence (particularly Class IIb and IIc) or expert opinion alone [11••]. Between the original 1996 and the updated 2007 Perioperative Guidelines, the number of Class I recommendations decreased by 9.3%, whereas Class II recommendations (primarily of the b variety) increased by 88.8%.

The stepwise approach promoted by this guideline is based on determining the acuity and severity of various cardiac risk factors in concert with the perceived risk of the surgical procedure along with the functional activity level of the patient [12] (Fig. 1). Although intuitively sound, it is based on limited evidence and has not been well validated in large patient cohorts. Risk estimates based on combinations of cardiac risk factors have varied in the literature, but the Revised Cardiac Risk Index of Lee *et al.* [13] incorporating only six predictors (ischemic heart disease, CHF, cerebrovascular disease, high-risk surgery, insulin-requiring diabetes and creatinine >2.0 mg/dl) is clearly the 'de-facto' standard, given the ease of scoring and nearly linear gradient of risk with increasing numbers of factors for many surgical procedures. The component variables are now incorporated into the ACC/AHA Guidelines as 'intermediate risk' predictors second only to fairly obvious high-risk predictors indicating an acutely cardiovascularly unstable patient (e.g. unstable coronary syndromes, decompensated heart failure, severe arrhythmias or conduction disorders and severe valvular disease). The increasing use of laparoscopic abdominal procedures, video-assisted thoracoscopy and endovascular aortic procedures appears to have reduced perioperative risk of previously highly stressful procedures substantially, and thus, the ACC/AHA algorithm may not be as robust as originally presented.

In the patient perceived to be at high risk for ischemia, the most commonly used testing modality is now dobutamine stress testing. Beattie *et al.* [14] compared stress echo with thallium imaging techniques in a meta-analysis of 68 studies in 10 049 patients and reported similar sensitivity for prediction of PMI in patients with a moderate-to-large-sized defect (present in 14% of patients) with a likelihood ratio of 8.35 [95% confidence

Figure 1 Cardiac evaluation and care algorithm for noncardiac surgery based on active clinical conditions, known cardiovascular disease, or cardiac risk factors for patients 50 years of age or more



Reproduced from [12].

interval (CI) 5.6–12.5] but better negative predictive ability for a negative study (likelihood ratio 0.23 vs. 0.44). Although a recent expert consensus statement suggests little if any diagnostic advantages of one technique over the other in general populations, stress echo is now recommended due to lower cost and lack of radiation exposure [15•].

A major goal of preoperative evaluation for ischemic potential related to CAD has been directed towards detection of the 'culprit' lesions with high-grade stenoses that may be amenable to preoperative revascularization in hopes of reducing PMI and associated complications [this despite the well documented observation that the vast majority of PMIs are of the non-ST elevation MI (NSTEMI) variety that are potentially more difficult to localize to a particular epicardial lesion]. Intellectually, it is clear that certain lesions are high risk in any situation (high grade left main or equivalents) and usually accorded higher priority than anything but the most emergent surgery. However, the perioperative risk of asymptomatic (or mildly so) one, two or even three-vessel disease has remained very controversial.

The Department of Veterans Affairs Coronary Artery Revascularization Prophylaxis (CARP) study, despite enrollment of fewer patients (510 vs. 590 patients) over a longer period of time (4 vs. 3 years) than initially projected, is considered 'the' landmark study [16]. Following exclusion of very high-risk patients (left main disease, ejection fraction less than 20% or severe aortic stenosis), patients scheduled for vascular surgery deemed at risk underwent coronary angiography. Patients considered amenable to revascularization were then randomized to either medical therapy or revascularization [with percutaneous coronary intervention (PCI) performed in 59% and coronary artery bypass grafting (CABG) in 41%]. Similar rates of PMI were detected (12% revascularized vs. 14% medical Rx), and long-term outcome (the primary outcome) at 2.7 years was also similar (23% revascularized vs. 22% medical Rx). This study has been criticized on the basis of the low percentage of patients

with three-vessel disease (35%). A subsequent subanalysis of the revascularized patients revealed that those randomized to CABG had a higher degree of revascularization with fewer PMIs (6.6% CABG vs. 16.8% PCI, $P = 0.02$), suggesting this is a more efficient strategy if employed [17]. However, new advances in PCI since the conduct of CARP and use of drug-eluting stents (DESs) (not used in CARP) must be considered.

A recent single center retrospective review of preoperative testing in 294 Veterans undergoing thoracotomy, in which 63% underwent preoperative testing [of which approximately 50% underwent dobutamine stress echocardiography (DSE)], found abnormal results in 43% tested [18]. Of these, revascularization was performed in four of 40 patients subjected to coronary angiography. No significant differences were reported between those tested and not tested (3.3 vs. 0.9%, $P = 0.29$). This study is difficult to interpret due to limited statistical power and lack of precise risk adjustment or propensity matching techniques.

With widespread implementation of perioperative β-blocker protocols in higher risk patients, the role of preoperative testing, particularly in those with stable CAD is clearly decreasing. More aggressive risk stratification in those without known CAD but who are considered high risk remains very controversial. Poldermans *et al.* [19,20•] maintain that intermediate risk patients (based on moderate stress-induced ischemia) scheduled for vascular surgery, as long as they are adequately treated with β-blockade based on 'tight perioperative heart rate (HR) control' [HR <65 beats/min (bpm)] do not benefit from preoperative testing.

Hammill *et al.* [5•] using Medicare data (2000–2004) investigated associations of CAD and CHF with operative mortality and 30-day all-cause readmission in 1 539 327 patients, the majority of whom underwent orthopedic or general surgery. Eighteen percent of patients had CHF and 34% CAD. CHF patients had significantly worse outcomes than those with or without CAD (hazard ratio 1.63, 95% CI 1.52–1.74 and hazard ratio 1.51, 95% CI 1.45–1.58, respectively). It is notable that 55% of CHF patients had three or more of the Revised Cardiac Risk index factors in contrast to 10% of CAD patients and 1% of comparison patients. This analysis, despite the substantial limitations of relying on the International Classification of Diseases (ICD-9) coding data, is consistent with older clinical literature and points out the importance of careful perioperative management of patients with known CHF.

Kheterpal *et al.* [6•] have combined risk and outcome data from the American College of Surgeons (ACS)-National Surgical Quality Improvement Program (NSQIP) database with intraoperative hemodynamic data from an automated anesthesia record keeper system in 7740 patients undergoing noncardiac surgery (general, vascular and urologic) at a single university center to provide a unique look at the additive predictive ability of such data relative to traditional preoperative clinical risk variable stratification. The primary outcome measures were 'cardiac adverse events' (cardiac arrest, PMI and clinically significant arrhythmia within 30 days). The outcome rate overall was quite low (1.1%) with PMI coded in 25%, cardiac arrest in 43% and arrhythmia in 44%. Seven independent preoperative predictors of cardiac adverse events were found (age ≥68 years, BMI ≥30 kg/m^2, emergent surgery, previous coronary intervention or cardiac surgery, active CHF, cerebrovascular disease and hypertension requiring medication). Considering the intraoperative ACS-NSQIP variables, operative duration of at least 3.8 h and packed red blood cell (PRBC) transfusion of at least one unit were additionally significant. The additive hemodynamic predictors were mean arterial pressure (MAP) less than 50 mmHg, decrease in MAP more than 40% and HR more than 100 bpm. Despite methodological limitations [21•], such approaches represent a new wave of investigation.

Perioperative management of the patient with a coronary stent

Perioperative management of patients with a recent PCI procedure is controversial and complex. Although the risk of subacute (within 30 days of implantation) and late stent thrombosis is significantly greater with DES (related to their much slower rate of stent endothelialization), the issue is more complex. The type, length and number of stents, their location and vessel size, proximity to vessel bifurcation and patient-related variables all modify the risk. Diabetic patients are particularly predisposed to late complications. Many DES stents have been used for 'off-label' indications (e.g. more complex coronary anatomy than the approved indications), and it is likely that such patients are at higher perioperative risk.

Since 2006, several guidelines were published including a multispecialty guideline under the AHA/ACC umbrella addressing the duration of antiplatelet therapy and the hazards of premature discontinuation [22]. The guideline emphasizes the absolute need to continue dual therapy for a minimum of 4–6 weeks following bare metal stent (BMS) and at least 1 year following DES and the need for communication between clinicians (including choice of stent if the patient is known to require major surgery within 1 year). The importance of dual antiplatelet therapy perioperatively, wherever possible, or at least perioperative aspirin (with rapid reinstitution of thienopyridine therapy) is emphasized. The ACC/AHA Perioperative Evaluation Guidelines group (reporting in 2006)

support this, and the American Society of Anesthesiologists Committee has issued a Practice Alert reiterating these recommendations [10,23•].

RCTs in this setting are hampered by logistics and ethics, and large observational analyses are the best available evidence. An analysis of patients undergoing noncardiac surgery with either a prior BMS (899 patients over a 15-year period) or DES (520 patients over a 3-year period) is the largest cohort yet published [24••,25••]. In patients with BMS, adverse cardiac events decreased with increasing time of stent implantation relative to surgery (10.5% within 30 days vs. 2.8% after 90 days). In contrast with DES, the lower rate after 1 year (3.3%) was not significantly different from rates observed earlier (6.4% at 0–90 days, 5.7% at 91–180 days and 5.9% at 181–365 days). Subanalyses of adverse event predictors in DES patients should be interpreted with caution due to small number of events. Emergency surgery was the strongest predictor (odds ratio 4.4, 95% CI 1.55–12.7, $P = 0.006$) with advanced age and shock at time of PCI, and previous history of MI patients with thienopyridine use within less than 7 days before had increased complication rate compared with those discontinuing within 7–30 days, and perioperative antiplatelet treatment was not associated with need of transfusions. Hence, large-scale registries for retrospective analyses of low frequency, but potentially fatal, events are clearly needed.

Perioperative pharmacologic cardioprotection: β-blockers, statins, α-2 agonists and antiplatelet agents

Perioperative pharmacologic cardioprotection, currently focusing on β-blockers, is particularly controversial due to the POISE study [1••]. In this multinational trial of over 8000 patients, 'intensive' β-blockade started shortly before surgery was associated with a reduction in myocardial ischemia (primarily nonfatal PMI detected primarily by troponin release) but a higher mortality (with death due to sepsis as a primary difference) as well as a doubling of the stroke rate (Fig. 2) The major criticism of this trial is the dose and speed of the perioperative β-blockade. This particular protocol reflects the rampant clinical enthusiasm generated by early small studies. The markedly different pharmacokinetics between extended release metoprolol succinate and the shorter acting metoprolol tartrate may also have contributed [26].

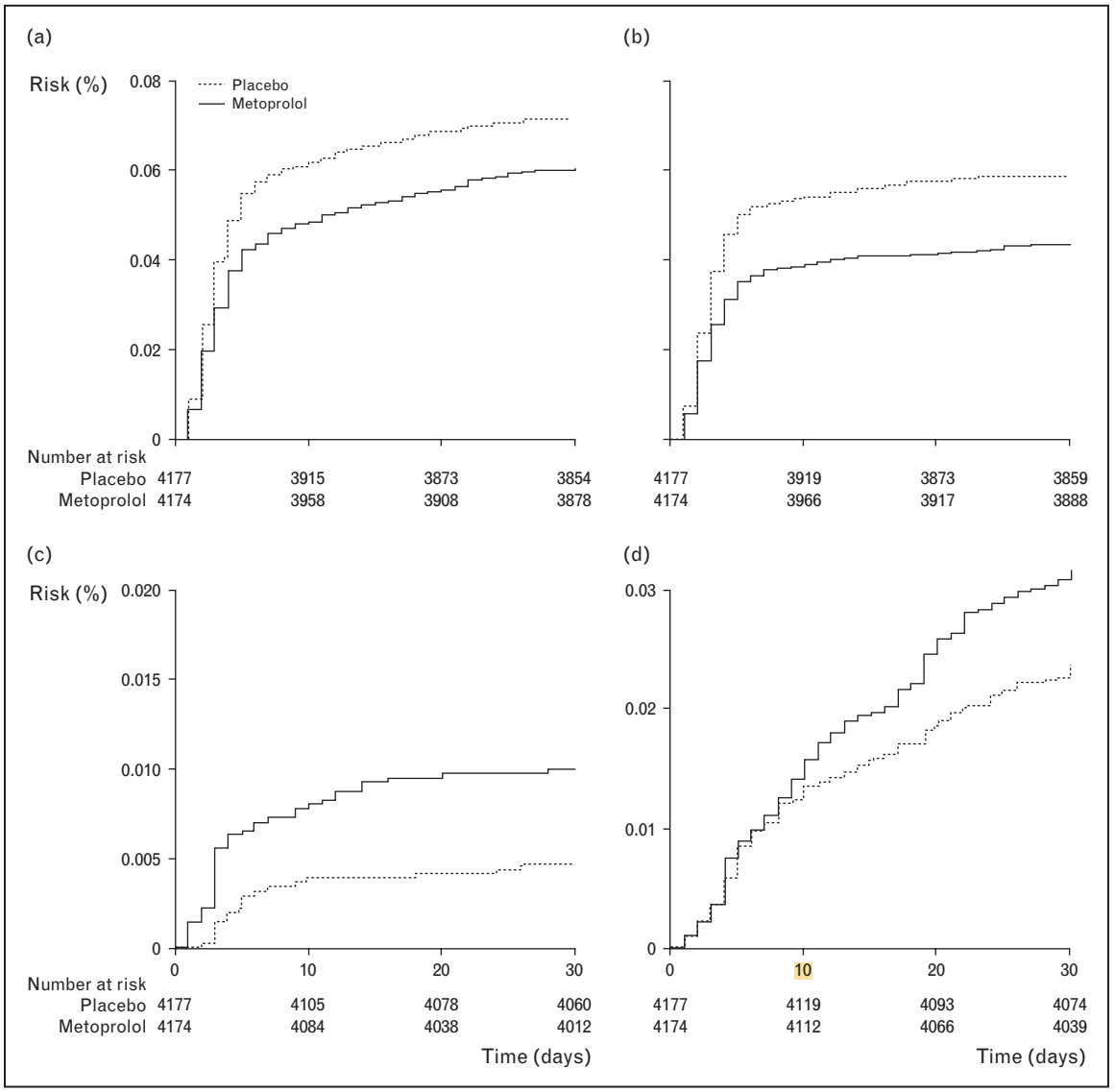
The results of prior trials of perioperative β-blockade have been decidedly mixed and performed in highly variable cohorts. In the highly screened cohort of vascular surgery patients with easily inducible ischemia of Poldermans *et al.* [27] bisoprolol, used to reduce resting HR preoperatively and continued for at least 30 days postoperatively, was associated with a 90% reduction in cardiac mortality perioperatively. In the other extreme, the Veterans Affairs mixed cohort of CAD or risk factor in only patients undergoing either vascular or nonvascular surgery, a short-term protocol starting immediately prior to surgery and lasting for a maximum of 7 days postoperatively, had no difference perioperatively but may have reduced mortality at 6–9 months. The caveat is the exclusion of perioperative deaths, which were higher in the treated group from the subsequent analysis [27,28]. A trial of over 900 diabetic patients with metoprolol succinate for 7 days reported neither short nor long-term outcome difference between groups [29]. Even meta-analyses (with eight now reported) reach varying conclusions depending on which studies are included and how the data are handled [30–34,35••,36•,37•].

Proponents and opponents of perioperative β-blockade have vigorously argued their positions in recent editorials [38••,39•–41•]. Patients with known CAD taking β-blockers chronically who do not become hemodynamically unstable (especially in association with low cardiac output or severe hypovolemia) clearly should be maintained on them perioperatively. Patients who have (recognized) impaired ventricular function and have not been previously exposed should probably not be started on them acutely perioperatively unless the dosing is very low and the hemodynamics demonstrate adequate cardiac output. The greatest controversy is its use in patients with risk factors for CAD [e.g. diabetes, peripheral artery disease (PAD), CVD, hypertension, older age and so on], many of whom are not adequately screened for adequacy of ventricular function. Even the pharmacogenomic makeup [42] and other factors (particularly preoperative anemia and the ability of stroke volume to increase in response to decreasing oxygen supply independent of HR response and so on) influence outcome and may not be adequately considered in current evidence-based recommendations.

The responses to the POISE study are still evolving [38••,39•]. At the time of this writing, the ACC/AHA Guidelines group was still crafting updated recommendations. Longer term follow-up of the POISE cohort (only 30-day outcome has been reported) is also critical, given that even low levels of perioperative troponin spillage have been associated with impaired long-term outcome (see below). Whether or not the 1-year mortality in the treated POISE group outweighs the higher perioperative death and disability from stroke remains to be seen. The results resemble the increased short-term mortality in acute MI with early metoprolol succinate [Clopidogrel and Metoprolol in MI Trial (COMMIT) study] [43]. The controversy raised by the POISE study remains, despite several recent small trials [44•–48•].

Other potential cardioprotectants include nondihydropyridine calcium entry blockers (e.g. verapamil and

Figure 2



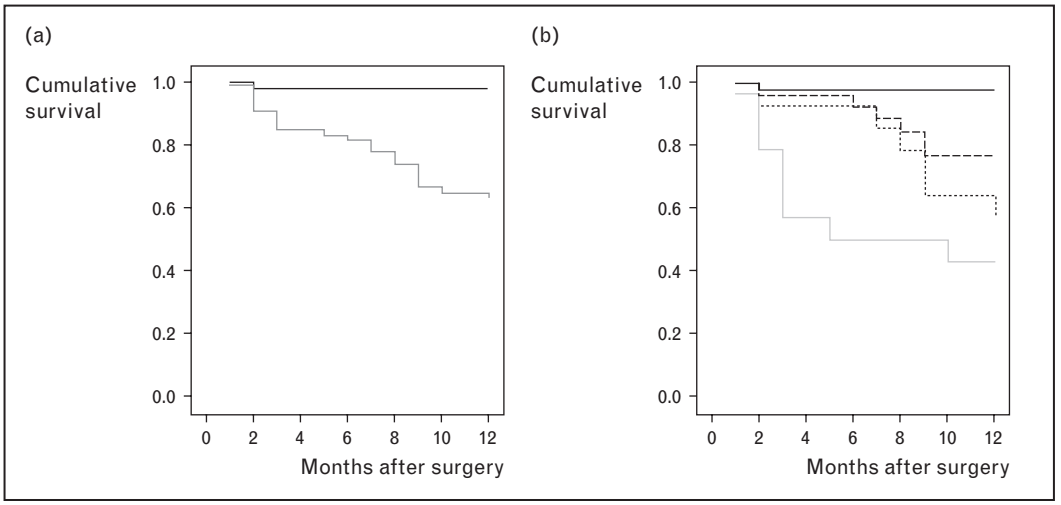
Kaplan–Meier estimates of the primary outcome (a), myocardial infarction (b), stroke (c), and death (d) in the POISE study. The peak incidence of ischemic myocardial events and stroke occurred substantially earlier than mortality. Reproduced from [1••].

diltiazem), α-2 agonists (e.g. clonidine and dexmedetomidine), statins, antiplatelet agents (aspirin) and, on the horizon, 'pure bradycardic' agents such as the I(f) channel inhibitors (e.g. ivrabidine) [49,50•,51•–53•,54••]. Although all of these have strong physiologic rationale for perioperative application, all have very limited RCT data at this point.

Biomarkers: troponins and N-terminal pro B-type natriuretic peptide

Widespread use of sensitive and specific biomarkers continues to influence medical practice on many fronts including definition and broadening of our etiologic framework of MI, shifting emphasis in a larger percentage of patients away from the ECG and clinical signs and symptoms than previously [7••,55•]. This is of particular interest in the perioperative (and critical care) environments. The ECG changes consistent with subendocardial ischemia are significantly more common in high-risk patients undergoing major surgery. Thus, most (70–75%) PMIs in the noncardiac setting are of the type 2 variety (using the new clinical classification for MI). Although many PMIs present with changes in clinical status (e.g. worsening or new heart failure, increased or new ventricular arrhythmias, and so on), 'surveillance' studies/strategies clearly pick what appears to be totally asymptomatic elevations of troponin.

Figure 3



(a) Kaplan–Meier survival curve of all patients divided into whether troponin was elevated postoperatively. Group 1, no troponin rise (troponin ≤0.03 μg/l), Group 2, troponin rise (troponin ≥0.04 μg/l) was significantly different at 1 year of the follow-up ($P < 0.0001$). (b) Kaplan–Meier survival curve of all patients divided into their postoperative peak troponin. Group 1, no troponin rise (troponin ≤0.03); Group 2, troponin 0.04–0.1 μg/l; Group 3, troponin >0.1–0.3 μg/l; Group 4, troponin >0.3 μg/l. Groups 2, 3, and 4 had significantly worse 1-year survival compared with Group 1 by the log-rank test ($P = 0.0034$, <0.0001, <0.0001, <0.0001, respectively) with associated hazards ratios of 9, 19, and 29, respectively compared with Group 1. (—) No troponin rise, (—) troponin rise; (--) troponin 0.04–0.1, (···) troponin >0.1–0.3, (—·—) troponin >0.3. Reproduced from [57•].

Lopez-Jimenez *et al.* [56] were the first to report the association of impaired 6-month to 1-year outcome with elevation of troponin T [but not creatine kinase (CK)-MB] following noncardiac surgery. A number of subsequent studies have confirmed this observation. Chong *et al.* [57•] reported that 53% of 102 older patients undergoing emergency orthopedic surgery (primarily hip fracture) sustained troponin I elevation (one year all cause mortality was 37 vs. 2.1% for those without troponin spillage) (Fig. 3). A recent subanalysis of the CARP trial demonstrated PMI based on tropinin I more than the 99th percentile reference in 26.5% of patients with no significant differences between revascularized and nonrevascularized patients [58•].

A number of recent studies have reported use of perioperative natriuretic peptides (particularly NT-pro-BNP) in predicting early and long-term cardiac outcomes in noncardiac surgery [59•]. At the present time, the focus is nearly exclusively on vascular surgery. A recent meta-analysis of seven prospective observational studies and 623 patients revealed an association between elevated natriuretic peptides and adverse both short and longer term outcomes. Two subsequent cohort studies [60•,61•] have reported similar findings.

A newly launched observational cohort study by POISE-associated investigators with partial funding from a biomarker manufacturer [Vascular Events in Noncardiac Surgery Patients Cohort Evaluation Study (VISION) clinicaltrials.gov identifier NCT00512109] is aimed at assessing the impact of cardiac events and biomarker elevations in a projected cohort of 40 000 patients (troponin T measured serially in all and NT-pro-BNP in approximately 25%) on 30-day and 1-year outcomes.

Conclusion

Prevention of postoperative cardiovascular morbidity and mortality requires an integrated approach to preoperative risk stratification, perioperative risk reduction with pharmacologic adjuncts where appropriate or feasible and postoperative monitoring for overt or subclinical complications. Patients with recently placed coronary stents, particularly those with DES, are at particular risk for postoperative complications related to in-stent thrombosis and require expert management and communication between care providers. The POISE study results not only calls into question the safety of wide-scale implementation of an aggressive β-blocking regimen, but also makes it clear that proper patient selection and hemodynamic management strategies are likely key variables in ensuring optimal results. Other agents, particularly statins, maybe of value, but adequate clinical data are not yet available to make strong evidence-based recommendations. The role of various biomarkers, such as preoperative NT-pro-BNP and postoperative troponin I and T in predicting short and long-term complications, is intriguing but opens up many questions as to whether specific interventions independent of the patient's baseline chronic risk can alter outcome.

References and recommended reading

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- • of special interest
- •• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 373–374).

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