REVIEW

Preoperative Cardiac Risk Stratification 2007: Evolving Evidence, Evolving Strategies

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Dr. Auerbach is supported by a K08 research and training grant (K08 HS11416-02) from the Agency for Healthcare Research and Quality.

Various guidelines and risk indices have optimized cardiac risk stratification, and the emphasis has shifted to reducing perioperative risk. This review is an update on invasive (CABG/PCI) and noninvasive (medical therapy with beta-blockers, alpha-agonists, and statins) strategies to reduce cardiac risk for noncardiac surgery and the controversies surrounding their use. ***Journal of Hospital Medicine*** **2007;2: 174–180.** © *2007 Society of Hospital Medicine.*

KEYWORDS: preoperative care, perioperative, risk assessment, beta-adrenergic blockers, percutaneous coronary intervention, coronary artery bypass, statin.

More than 33 million patients undergo surgery annually in the United States. Approximately 8 million of these patients either have known coronary artery disease or risk factors for it, and an estimated 50,000 patients sustain a perioperative myocardial infarction, with an additional 1 million developing another medical complication. An integrated comprehensive approach is necessary to risk-stratify these patients in an attempt to reduce these complications.

The basic role of risk stratification is to identify those patients at increased risk for complications; however, we are looking for a small number of patients at high risk in a population of relatively low-risk patients. Most surgical patients do well, and further diagnostic testing has a low yield in predicting those likely to have a complication (poor positive predictive value [PPV]). Our goal should be to determine the underlying potential triggers of cardiac complications and institute measures to prevent them. After briefly reviewing pathophysiology, risk indices, and guidelines for preoperative cardiac risk assessment and diagnostic testing, we will focus on risk reduction strategies including prophylactic revascularization (CABG/PCI) and medical therapy.

PATHOPHYSIOLOGY OF PERIOPERATIVE MYOCARDIAL INFARCTION

Perioperative myocardial infarctions result from myocardial ischemia or plaque rupture and coronary thrombosis.[1] Myocardial ischemia may be caused by increased oxygen demand or decreased oxygen delivery. Surgical trauma, anesthesia, pain, hypothermia, and bleeding trigger a stress state. This in turn increases catecholamine release, leading to tachycardia, hypertension, and increased oxygen demand. Anesthesia, hypotension, bleeding, and anemia may produce hypoxia, with subsequently decreased delivery of oxygen. Surgical trauma initiates an inflammatory response, leading to plaque fissuring, and a hypercoagulable state,

DOI 10.1002/jhm.158
Published online in Wiley InterScience (www.interscience.wiley.com).

which can result in acute coronary thrombosis. Perioperative prophylaxis should target these potential triggers.

CARDIAC RISK INDICES AND GUIDELINES

Over the past 3 decades, a number of cardiac risk indices have been published. The older group of indices was most notable for Goldman's original cardiac risk index[2] and Detsky's modification.[3] The newer group consists of the American College of Physicians (ACP) guidelines[4] (now considered outdated), the American College of Cardiology/American Heart Association (ACC/AHA) guidelines (to be updated again in early 2007),[5] and the Lee revised cardiac risk index (RCRI).[6]

The 2002 ACC guidelines[5] outline how to determine the need for additional cardiac (usually noninvasive) testing (NIT): after ascertaining the urgency of surgery, history of revascularization procedures, and previous stress test results (if any), a combination of clinical risk predictors, surgery-specific risk, and patient self-reported exercise capacity should be entered into an algorithm. The guidelines state a shortcut can be used: noninvasive testing should be considered if a patient has any 2 of the following: (1) intermediate clinical risk (stable angina or old MI, compensated heart failure, diabetes mellitus, renal insufficiency), (2) high-risk surgery (aortic or major vascular procedures, prolonged surgery with significant expected blood loss or fluid shifts), or (3) poor exercise capacity ($<$4 METs). Patients with major clinical predictors (unstable coronary syndromes, decompensated heart failure, severe valvular heart disease, or hemodynamically significant arrhythmias) should not undergo elective surgery without further workup or treatment. The ACP guidelines use the Detsky[3] modified CRI and "low-risk variables" to suggest any need for further testing depending on type of surgery (vascular or nonvascular). At times these 2 guidelines offer conflicting recommendations, with the ACC more likely than the ACP to recommend NIT. The RCRI, which was developed prospectively and has been validated, uses 6 predictors of major cardiac complications—high-risk surgery, coronary artery disease, stroke, congestive heart failure, diabetes mellitus requiring insulin, and serum creatinine $>$ 2 mg/dL. Patients with 0 or 1 risk factors are considered at low risk, those with 2 risk factors at moderate risk, and those with 3 or more risk factors at high risk ($\geq$10% complication rate). Although the RCRI does not make recommendations about whether to test, it has been incorporated into a number of algorithms combining risk stratification with recommendations about noninvasive testing as well as use of perioperative beta-blockers.[7–10]

DIAGNOSTIC CARDIAC TESTS

Tests should not be done if the results will not alter patient management. If further assessment is indicated based on the ACC/AHA algorithm, other risk indices,[10] or criteria independent of the need for surgery, the physician must decide whether to do a noninvasive (eg, echocardiogram or stress test) or an invasive test (coronary angiography). Unless a patient has independent criteria for angiography or, occasionally, a very high prior probability of significant CAD based on multiple risk factors, noninvasive testing is usually the preferred first step. A resting echocardiogram is potentially useful for providing information about suspected valvular heart disease but is not a consistent predictor of ischemic events.

For ambulatory patients, exercise stress testing is usually preferred over pharmacologic testing; in the perioperative setting, the usefulness of exercise testing is limited by the indications for obtaining stress testing (namely, poor functional status) as well as its main limitation, patient inability to reach 85% of the target heart rate. As a result, pharmacologic stress testing should be the primary modality for patients requiring preoperative risk stratification. Pharmacologic stress testing can be done with nuclear imaging (dipyridamole or adenosine thallium) or echocardiography (dobutamine echocardiography). For the most part, the results are comparable,[11,12] with both having excellent negative predictive values (NPV $>$ 95%) but poor positive predictive values (PPV $<$ 20%); however, dobutamine echocardiography tends to have fewer false positives. Dipyridamole or adenosine testing is relatively contraindicated with bronchospasm and COPD but is preferred over exercise or dobutamine for patients with a left bundle-branch block. Suspected critical aortic stenosis is a contraindication to stress testing. Positive noninvasive findings should result in prophylactic measures, either medical therapy or an invasive procedure.

CORONARY REVASCULARIZATION

Coronary Artery Bypass Grafting

Observational studies have shown that patients with CAD (in the CASS study) treated by coronary artery bypass grafting (CABG) surgery versus had a lower mortality (0.9% vs. 2.4%) and fewer nonfatal

TABLE 1
Summary of Recommendations for Preoperative Risk Stratification

1. Evaluate the patient for *new or unstable* cardiopulmonary symptoms, specifically those that would prompt evaluation in the absence of a potential surgery.
- NEW or UNSTABLE SYMPTOMS AND *ELECTIVE* SURGERY:
  → Pursue additional testing as clinical judgment dictates.
  → Delay in surgery may be appropriate.
- NEW OR UNSTABLE SYMPTOMS AND *EMERGENT/URGENT* SURGERY:
  → Weigh medical risks/benefits of surgery with patient and family, surgeon, and anesthesia.
  → Proceed to surgery with close attention to postoperative monitoring for ischemia.
  → Begin cardioprotective agents whenever appropriate.
- NO NEW SYMPTOMS:
  → Proceed to clinical risk stratification.

2. Use a structured clinical risk stratification rule.
- *Low-risk patients* (0-1 revised cardiac risk index criteria)
  → Proceed to surgery, no need for beta-blockers or additional noninvasive stress testing.
- *Moderate-risk patients* (2 revised cardiac risk index criteria)
  → Assess for functional status and current level of anginal symptoms and/or claudication.
  - Patients who have a history of angina or claudication but no longer have these symptoms because of decreasing functional status (< 4 METS) should be considered for noninvasive stress testing.
  - Patients who have good functional status regardless of history of angina or claudication do not require additional testing and should receive beta-blockers around the time of surgery.
- *High-risk patients* (3 or more revised cardiac risk index criteria)
  → Should probably have noninvasive stress testing prior to surgery.
  → All should be targeted for beta-blocker therapy.

3. Order and interpret noninvasive stress test results.
- Persantine (or adenosine) thallium or MIBI, or dobutamine echocardiography have similar test characteristics. Choose whichever test is most readily available and most accurate at your institution.
- Most patients referred for noninvasive tests will require perioperative beta blockers.
- Positive tests should be interpreted with caution before pursuing revascularization. Clinical symptoms during the test and the amount of myocardium at risk may help to identify patients with anatomic or functional triple-vessel or left-main disease who would benefit from revascularization (the latter of whom would not have qualified for CARP).
- Normal noninvasive stress tests have very good negative predictive value and are reassuring even for patients who have high-risk clinical profiles.

4. Special considerations.
- Patients with coronary artery disease as the sole risk factor
  → Require beta-blockers long-term, and should receive them during surgery.
  Should have functional status assessed according to suggestions above.
- Patients with abnormal systolic murmurs
  → Pursue echocardiography in patients with a history consistent with potential aortic stenosis (eg, syncope, exertional chest pain), those with late-peaking systolic murmurs that have a high specificity for aortic stenosis (eg, murmurs that obscure the second heart sound and/or are associated with decreased *parvus et tardus* peripheral arterial pulses).[42]
- Statins
  → As yet, there is no role for routine prophylactic use of statins in the perioperative setting, although observational evidence is accumulating; however, we recommend that patients currently taking statins continuing taking them perioperatively.

myocardial infarctions (0.7% vs. 1.1%) than patients treated with medical therapy who underwent noncardiac surgery months or years later.[13] This protective effect of CABG lasted approximately 4-6 years; however, there was no benefit for low-risk noncardiac procedures. Furthermore, the risk of perioperative mortality (3%) and morbidity associated with the CABG itself was not taken into account, which would have negated its potential benefit.

Percutaneous Coronary Intervention

Several reports suggested that a previous percutaneous coronary intervention (PCI) was also associated with a lower risk of perioperative mortality and nonfatal myocardial infarction (MI) compared to historical controls. Early studies suggested that noncardiac surgery could be performed as early as 7-10 days after balloon angioplasty (BA). As bare-metal stents gradually replaced BA, subsequent reports highlighted the increased risk of noncardiac surgery within 2 weeks[14] and then within 4-6 weeks[15] after stenting. This was primarily because of in-stent thrombosis associated with premature discontinuation of dual antiplatelet therapy or increased major bleeding if this therapy was continued. The current recommendation is to wait at least

4-6 weeks after inserting a bare-metal stent and to discontinue clopidogrel ± aspirin at least 5 days before surgery. A recent review from the Mayo Clinic[16] found BA to be reasonably safe if patients require surgery soon after cardiac intervention (after 2 weeks).

More recently drug-eluting stents (DESs) have become the standard; however, the recommendations for antiplatelet therapy (in the absence of surgery) are for a minimum of 2-3 months after sirolimus-coated stents and at least 6 months after stents with paclitaxel. There has been very little in the published literature on patients undergoing noncardiac surgery after drug-eluting stents. A small retrospective review suggested that patients whose DES had been placed a median of 260 days before surgery had few cardiac events in the perioperative period.[17] The recommendations of a French task force did not provide strong guidance, probably because of a lack of evidence.[18] The only prospective study of stenting and noncardiac surgery involved continuing antiplatelet therapy (or stopping it less than 3 days before surgery) and using unfractionated heparin or enoxaparin in 103 patients. Despite this therapy, 5 patients died, 12 had myocardial infarctions, 22 had elevation of troponin, but only 4 had major bleeding. Patients with stenting less than 35 days before surgery were at the greatest risk.[19] In view of these findings, if noncardiac surgery must be performed within 2 months and the patient is appropriate for PCI, balloon angioplasty or a bare-metal stent is preferred over DES implantation. If a patient has a DES in place (particularly if it has been fewer than 6 months since implantation) and requires noncardiac surgery, the optimal approach would be to continue at least one if not both antiplatelet agents through surgery; if this is not possible, "bridging" therapy with intravenous IIB/IIIA receptor blockers has been a suggested approach.[10]

Revascularization Versus No Revascularization: the CARP Trial

The only randomized controlled study to compare invasive and noninvasive strategies was the Coronary Artery Revascularization Prophylaxis (CARP) trial.[20] More than 5800 patients with stable cardiac symptoms scheduled for elective nonvascular surgery in VA hospitals were screened, approximately 20% underwent coronary angiography, and 510 patients (9% of the original group) were randomized to PCI/CABG or no revascularization. Revascularization was associated with 1.7% mortality and a 5.8% nonfatal MI rate, and an additional 4% died after successful revascularization while awaiting vascular surgery. Short-term outcomes were similar in both the revascularization and no revascularization groups (3% 30-day mortality and 8%-12% perioperative nonfatal MI). The primary outcome, long-term mortality, also did not differ between the groups (22% vs. 23%) after an average follow-up of 2.7 years. The investigators concluded on the basis of this data that prophylactic revascularization could not be recommended for patients with stable CAD undergoing elective vascular surgery. Of note is that both groups of patients in the CARP trial were given intensive medical therapy, with 84% on beta-blockers, 54% on statins, 51% on ACE inhibitors, and 73% on aspirin, which may have made it difficult to show any significant benefit of revascularization. Other limitations of that study are that it was underpowered to detect a short-term benefit and excluded patients with unstable or more severe cardiac symptoms or disease (left main disease, aortic stenosis, and severe left ventricular dysfunction). In any case, the results of this support the ACC guidelines, which state that prophylactic revascularization is *rarely necessary* just to get the patient through surgery.

If the goal of risk stratification is to determine which patients are at increased risk and if revascularization fails to lower that risk, various medical therapies, including beta-blockers, alpha-agonists, and statins, should be considered as risk-reduction strategies.

PHARMACOLOGIC STRATEGIES

Cardioprotection with Adrenergic Modulation and Statin Therapy

Support for adrenergic modulation (with beta-blockers and alpha-agonists) to prevent postoperative cardiac complications has been the subject of a number of reviews, including our own.[7,8,21] Initial enthusiasm[22,23] has been tempered, however, as evidence has evolved.

The results of a randomized trial published in abstract form[24] showed no significant difference in rates of a combined end point of mortality, myocardial infarction, heart failure, and ventricular arrhythmia 30 days after vascular surgery of 500 patients randomized to metoprolol or placebo. Furthermore, in a randomized trial of 107 aortic surgery patients with no history of coronary disease, metoprolol started on admission and contin-

ued for 7 days did not significantly reduce cardiac events.[25] In addition, a well-designed meta-analysis suggested that there are too few data to definitively determine whether perioperative beta-blockade is efficacious.[26] Finally, the results of a rigorously analyzed observational trial using administrative data from nearly 700,000 patients suggested that perioperative beta-blockade was protective (reduced mortality) only in higher-risk patients (eg, RCRI $\geq$ 2 points). In those at lower risk, beta blockade was associated with a higher risk of complications, even if the lower-risk patients had only 1 risk factor of either diabetes or coronary disease.[27]

Trials of alpha adrenergic agonists have also been summarized in at least 2 meta-analyses. One of these meta-analyses reported alpha-2 agonists reduced mortality by nearly half and reduced postoperative myocardial infarction by a third in vascular patients, but had no benefit in others.[28] Another meta-analysis calculated that 83 patients needed to be treated with alpha-agonists to prevent one cardiac event,[29] a number higher than that for beta-blockers.

Data on the effectiveness of statins is accumulating. The results of 5 observational trials[30-34] and 1 randomized study[35] suggest that patients receiving statin therapy at the time of surgery (and afterward) have a lower risk of having a cardiac event and lower mortality, with relative reductions in risk between 80%[30] and 30%.[32] In the 1 randomized trial, of 100 vascular surgery patients, 20 mg/day of atorvastatin was begun 1 month before surgery and continued for 45 days,[35] with beta-blockers included "per protocol." This protocol reduced the combined outcome of cardiac mortality, myocardial infarction, stroke, or unstable angina, but the overall number of events was very small (4 patients vs. 13 patients, $P = .03$). However, no patient required discontinuation of the drug because of side effects.

HOW SHOULD I INCORPORATE EVIDENCE INTO PRACTICE?

Target Patients Most Likely to Benefit

Recent trends in evidence increasingly support the idea that lower-risk subgroups (such as those with the "minor criteria" employed by Mangano) may not benefit from perioperative beta-blockers and that only higher-risk subgroups should be targeted. This general approach was recommended in recent guidelines from the AHA-ACC,[36] as well as in an extensive review of perioperative cardiac risk management.[10] The strongest recommendations were to continue beta-blockers in patients already on them and to give them to patients scheduled for vascular surgery who had ischemia on a stress test. The ACC also stated that beta-blockers were probably recommended for patients with known CAD or high cardiac risk scheduled for intermediate- to high-risk surgery. Recommendations for other groups were weaker or lacked sufficient evidence.[36] At this point, it seems prudent to target high-risk patients (RCRI $\geq$ 2), as well as those who would require beta-blockers or statin therapy regardless (eg, patients with known coronary artery disease). There are no data to suggest that dose titration of statins is required before surgery.

Be Aware of How Harm Might Be Produced

Notwithstanding its limitations, results from the recent observational trial from Lindenauer raise important questions about the effectiveness of beta-blockers in practice. That is, are beta-blockers safe and effective when used in surgical patients outside the tightly controlled setting of a randomized trial? It is apparent how titrating beta-blockers to a target heart rate without careful clinical assessment (as occurred in most RCTs) might lead to beta-blockers being used to treat tachycardia related to hypovolemia, pain, anemia, bleeding, or early sepsis. Interestingly, beta-blockers may be associated with higher risk in other settings as well,[37] so potential harm in the perioperative period are not completely surprising.

Use a Protocol That Sticks as Close to the Evidence as Possible

To stay as close as possible to what the evidence shows for the use of beta-blockers, this drug should be started early enough to allow dose titration and continued for at least 7 days and optimally 30 days after surgery (indefinitely, if a patient requires it long term), working to ensure that patients are physiologically beta-blocked (eg, heart rate 55-65) for as much of the time that they are being treated as possible. Two recent studies demonstrated the importance of tight heart rate control[38,39]—higher doses of beta-blockers and tight heart rate control were associated with reduced perioperative myocardial ischemia and troponin T release, which might obviate the need for preoperative cardiac testing in intermediate-risk patients undergoing vascular surgery. A recent placebo-controlled, randomized trial[40] suggested that a simple strategy of 4

days of transdermal and oral clonidine reduced perioperative ischemia and mortality. Although this approach is very useful for patients who cannot take pills by mouth, it would necessitate a switch to beta-blockers for patients who need them long term. In addition, use of clonidine may be associated with a higher risk of withdrawal than cardioselective beta-blockers. No prospective trials have compared beta-blockers and alpha-2 agonists. Both produce hypotension and bradycardia, improve pain control, and rarely produce adverse pulmonary effects.[41] At the least, consultants should be clear in their recommendations about the start and stop dates for beta-blockers and should ensure a smooth outpatient transition of patients for whom long-term statin or beta-blocker therapy is needed.

Be Ready to Adjust Your Practice as the Evidence Continues to Evolve

Far too few patients have been randomized to beta-blockers, adrenergic modulation, or statin therapy to date to provide a reasonable estimate of their effects on mortality. As a result, although it seems likely that some subgroups benefit from one or more of these therapies, the degree of risk required—and an optimal dosing schedule—remains a subject of intense debate. The results of perioperative trials of adrenergic modulators have consistently provided evidence supporting their use in other patient populations, but larger studies may not confirm a beneficial effect. Ongoing Canadian (POISE) and European trials (DECREASE IV) should address sample size limitations and provide information critical for clinicians caring for patients in this era of rapidly evolving evidence.

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Received 21 July 2006; revision received 11 November 2006; accepted 25 November 2006.

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