Cardiac Events in Patients Undergoing Noncardiac Surgery: Shifting the Paradigm from Noninvasive Risk Stratification to Therapy

Paul A. Grayburn, MD, and L. David Hillis, MD

Internists and cardiologists are often asked to estimate the risk for perioperative myocardial infarction or cardiac death in patients being considered for noncardiac surgery. Estimating this risk in an individual patient is difficult and complex. Although noninvasive imaging tests are often used for this purpose, a review of the literature reveals that the positive predictive value of noninvasive imaging tests is uniformly low and that they do not provide information beyond that obtained by assessing simple clinical risk variables. Moreover, no evidence exists that noninvasive imaging tests lead to a therapeutic strategy that reduces the risk for perioperative myocardial infarction or cardiac death. Since the publication of guidelines for preoperative risk stratification by the American College of Cardiology/American Heart Association in 1996 and the American College of Physicians in 1997, three clinical trials have shown that β-blocker therapy reduces the risk for perioperative cardiac events. This paper focuses on the relationship between risk stratification and subsequent therapy to minimize or eliminate risk. In short, the paradigm is shifting from predicting which patient is at high risk for having a perioperative cardiac event to minimizing the likelihood of such an event with specific perioperative pharmacologic therapy.


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Pathophysiology of Perioperative Cardiac Complications

The pathophysiology of perioperative myocardial infarction differs somewhat from that of myocardial infarction occurring in the usual setting. In the latter, rupture of a coronary arterial atherosclerotic plaque leads to platelet aggregation and thrombus formation (11). In contrast, plaque rupture occurs in only about half of perioperative myocardial infarctions (12, 13); the remainder are due to a prolonged imbalance between myocardial oxygen supply and demand in the setting of coronary artery disease. Myocardial oxygen supply may be diminished by anemia or hypotension, whereas oxygen demand may be increased by tachycardia and hypertension resulting from postoperative pain, withdrawal of anesthesia, or shifts in intravascular volume. Perioperative myocardial infarction usually occurs 1 to 4 days after surgery (14–16), when the effects of anesthesia have dissipated and perioperative pain and fluid shifts are occurring.

Issues in Risk Stratification

The goal of risk stratification is to reduce risk (17). First, any test used for preoperative risk stratification must be accurate. It should have a high positive and negative predictive value and should result in a change in risk from the pretest likelihood. Since predictive values depend on event rate, likelihood ratios should be calculated. The likelihood ratio of a positive or negative test result should be greater than 10 or less than 0.2, respectively, because these values indicate a substantial change in risk from the pretest level (2). The test should provide information that adds or is complementary to known risk variables. Second, risk stratification is most helpful when it influences outcome. For example, would a test lead to cancellation of surgery or alternative treatment? Would it mandate therapy to reduce perioperative risk, such as prophylactic coronary revascu-
superior receiver-operating characteristic curve analysis.

Risk-assessment tool must influence outcome
Identifies subgroups in which surgery should be cancelled or treatment changed
Identifies subgroups that do or do not benefit from proven therapy to reduce risk
Risk-assessment tool must have a favorable harms–benefit tradeoff

Risk Stratification by Clinical Variables
Cardiac Risk Index
The original cardiac risk index (18) was described in 1001 patients undergoing general, orthopedic, or urologic procedures. Subsequently, this index was modified and then tested in another clinical setting in blinded fashion in patients undergoing vascular or general surgery (19). Eagle and colleagues (20) proposed a simple clinical risk index that, although widely used, has not been tested prospectively in another clinical setting. Lee and colleagues (21) described the largest and most current scheme of clinical risk assessment, the revised cardiac risk index. After identifying the following six variables in 2893 patients, they tested them in another clinical setting in 1422 patients: high-risk surgical procedure, history of ischemic heart disease (excluding previous coronary revascularization), history of congestive heart failure, history of stroke or transient ischemic attack, preoperative insulin therapy, and preoperative serum creatinine levels greater than 152.5 μmol/L (2.0 mg/dL). By receiver-operating characteristic curve analysis, the revised cardiac risk index was superior to the original and modified cardiac risk indices. We recommend the revised cardiac risk index (Table 2) for clinical risk evaluation because of its simplicity, strength of study design, and superior receiver-operating characteristic curve analysis.

Does Clinical Risk Stratification Satisfy the Critical Elements?
1. Is it accurate? Yes. The receiver-operating characteristic curve area greater than 0.8 indicates that the revised cardiac risk index is accurate in segregating patient risk groups.
2. Does it add to pretest knowledge? Yes.
3. Is the harms–benefit tradeoff favorable? Yes. The revised cardiac risk index is derived inexpensively from the history, physical examination, and serum creatinine level.

Risk Stratification by Diagnostic Testing
For diagnostic testing to be useful in risk stratification, it should provide information that adds or is complementary to that provided by the revised cardiac risk index. Furthermore, diagnostic testing should not lead to unnecessary additional testing or harmful delays in surgery (22–25). Finally, diagnostic testing ideally should lead to proven therapy to reduce risk.

Myocardial Perfusion Imaging
Myocardial perfusion imaging, performed at rest and during vasodilator stress, is widely used. Since many patients referred for vascular surgery cannot ambulate effectively because of claudication, their histories may not provide an accurate assessment of symptoms or functional class. Patients with reversible or fixed perfusion defects probably have coronary artery disease, the main risk factor for perioperative cardiac events. Most patients do not develop chest pain or ST-segment depression during vasodilator stress (26). However, they have impaired vasodilator reserve in areas subtended by a stenosed coronary artery, leading to heterogeneity in radionuclide activity in different segments of myocardium. Thus, perfusion imaging is sensitive for detecting coronary artery disease, not ischemia (27). Table 3 lists large studies of myocardial perfusion imaging in which likelihood ratios could be calculated from the published data (20, 28–37).

Does This Test Satisfy the Critical Elements?
1. Is it accurate? No. The positive likelihood ratio is low. The negative likelihood ratio is good in some studies but poor in others. Two large prospective, blinded studies showed that myocardial perfusion imaging did not provide independent prognostic value beyond clinical risk stratification (34, 39).
2. Does it influence outcome? No published prospective trials have addressed this question.
3. Is the harms–benefit tradeoff favorable? No. Patients with positive test results often are subjected to further testing, increasing the risk of complications.

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Table 1. Critical Elements for Risk Stratification in Patients Undergoing Noncardiac Surgery

| Risk-assessment tool must be accurate |
| Predicts perioperative events (positive likelihood ratio > 10) |
| Predicts absence of perioperative events (negative likelihood ratio < 0.2) |
| Identifies subgroups in which surgery should be cancelled or treatment changed |
| Identifies subgroups that do or do not benefit from proven therapy to reduce risk |
| Risk-assessment tool must have a favorable harms–benefit tradeoff |

Table 2. Major Cardiac Event Rates by the Revised Cardiac Risk Index

<table>
<thead>
<tr>
<th>Class</th>
<th>Events/Patients, n/n</th>
<th>Event Rate (95% CI), %</th>
</tr>
</thead>
<tbody>
<tr>
<td>I (0 risk factors)</td>
<td>2/488</td>
<td>0.4 (0.05–1.5)</td>
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<tr>
<td>II (1 risk factor)</td>
<td>5/567</td>
<td>0.9 (0.3–2.1)</td>
</tr>
<tr>
<td>III (2 risk factors)</td>
<td>17/258</td>
<td>6.6 (3.9–10.3)</td>
</tr>
<tr>
<td>IV (≥3 risk factors)</td>
<td>12/109</td>
<td>11.0 (5.8–18.4)</td>
</tr>
</tbody>
</table>

*Adapted from Lee et al. (21). ROC = receiver-operating characteristic.
P = 0.034 versus original cardiac risk index (ROC curve area, 0.701), modified cardiac risk index (ROC curve area, 0.582), and American Society of Anesthesia Classification (ROC curve area, 0.697). Major cardiac events include myocardial infarction, cardiac arrest, pulmonary edema, and complete heart block. Risk factors are high-risk surgical procedure (intraperitoneal, intrathoracic, or suprainguinal vascular reconstruction), history of ischemic heart disease (excluding previous revascularization), history of congestive heart failure, history of stroke or transient ischemic attack, preoperative insulin therapy, and preoperative serum creatinine levels ≥ 152.5 μmol/L (≥2.0 mg/dL).
other evaluation, such as coronary angiography. Such a strategy is costly and may delay surgery unnecessarily.

**Dobutamine Stress Echocardiography**

Dobutamine stress echocardiography (DSE) allows a physician to evaluate left ventricular regional wall motion at rest and during dobutamine stress. It provides an adrenergic stimulus that is more similar physiologically to the stress of the perioperative period than that provided by vasodilators. Dobutamine stress echocardiography is widely available and portable and does not involve radiation exposure. Since an adequate cardiac workload is not always achieved with dobutamine alone, atropine or handgrip exercise may be used with dobutamine to ensure an adequate increase in heart rate and systemic arterial pressure (38, 39).

<table>
<thead>
<tr>
<th>Study (Reference)</th>
<th>Surgery</th>
<th>Patients</th>
<th>Death or Myocardial Infarction</th>
<th>Predictive Values</th>
<th>Likelihood Ratios</th>
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<tr>
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<td></td>
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<td>Positive</td>
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<td>Poldermans et al. (40)</td>
<td>Vascular</td>
<td>131</td>
<td>4</td>
<td>14</td>
<td>100</td>
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<tr>
<td>Poldermans et al. (41)</td>
<td>Vascular</td>
<td>300</td>
<td>6</td>
<td>24</td>
<td>100</td>
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<tr>
<td>Das et al. (42)</td>
<td>General</td>
<td>530</td>
<td>6</td>
<td>15</td>
<td>100</td>
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</tr>
<tr>
<td>Boersma et al. (43)</td>
<td>Vascular</td>
<td>1097</td>
<td>3</td>
<td>14</td>
<td>98</td>
</tr>
</tbody>
</table>

**Table 4. Studies of Dobutamine Stress Echocardiography for Risk Stratification**

**Does This Test Satisfy the Critical Elements?**

1. Is it accurate? No. The likelihood ratio of a positive test result is poor. The negative likelihood ratio is good in all but one study. A recent large study (43) showed that DSE did not add incremental value in low- or medium-risk patients (score of 0 to 2 on the revised cardiac risk index).
2. Does it influence outcome? No studies have addressed this prospectively.
3. Is the harms–benefit tradeoff favorable? No. Dobutamine stress echocardiography has a low positive predictive value. Patients with positive test results are often subjected to further evaluation, which may cause an unnecessary delay in noncardiac surgery.

**Coronary Angiography**

Coronary angiography is not recommended for risk stratification in patients undergoing noncardiac surgery (1–3). However, patients considered for noncardiac surgery who have an indication for angiography independent of the planned surgery should undergo angiography, such as those with acute coronary syndromes or angina refractory to medical therapy. The ACC/AHA guidelines also recommend coronary angiography for patients with high-risk results on noninvasive testing.

**Therapies to Reduce the Risk for Perioperative Cardiac Complications**

**Coronary Artery Bypass Grafting**

No randomized, controlled trials have assessed the benefit of coronary artery bypass grafting (CABG) before noncardiac surgery, but patients with previous CABG have low rates of cardiac complications with noncardiac surgery (44–47). Using the Coronary Artery Surgery Study (CASS) registry data, Eagle and colleagues (47) found that patients who underwent major vascular, abdominal, thoracic, or head and neck surgery after previous CABG had fewer perioperative deaths and myocardial infarctions than patients receiving medical therapy. Based on these data, the ACC/AHA and ACP guidelines do not recommend non-
invasive testing for risk stratification in symptom-free patients who have had CABG within 5 years (1, 2).

Coronary artery bypass grafting does not protect an asymptomatic patient from complications of noncardiac surgery. Coronary artery bypass grafting itself confers a risk for death, nonfatal myocardial infarction, stroke, and cognitive dysfunction. Peri-CABG mortality in more than 180,000 Medicare patients (1996 data) was 5.4% (48). The recovery period after CABG causes an obligate delay in planned noncardiac surgery. In two studies of patients with abnormal dipyridamole thallium scans (49, 50), a strategy of coronary angiography and subsequent CABG led to worse outcomes than did noncardiac surgery without preoperative imaging. In short, prophylactic CABG is more likely to harm than benefit most patients undergoing noncardiac surgery. However, if the patient has symptoms or coronary anatomy that mandate CABG independently of planned noncardiac surgery, CABG is indicated.

Percutaneous Coronary Intervention

No randomized, controlled trials have shown that percutaneous coronary intervention is beneficial as prophylactic therapy in patients undergoing noncardiac surgery, and a recent report by Kaluza and colleagues (51) suggests caution in performing noncardiac surgery soon after coronary arterial stenting. Among patients who had noncardiac surgery within 6 weeks of successful stent placement, 20% died, 18% had nonfatal myocardial infarction, and 28% had major bleeding. Percutaneous coronary intervention should be reserved for patients with an acute coronary syndrome or stable angina refractory to medical therapy. If coronary stenting is performed, elective noncardiac surgery should be deferred for 6 weeks or longer.

β-Adrenergic Blockade

Since publication of the ACC/AHA and ACP guidelines on risk stratification for noncardiac surgery, two randomized, controlled trials and one large nonrandomized report have shown that β-blocker therapy reduces perioperative cardiac complications. Mangano and colleagues (52) performed a randomized, double-blind, placebo-controlled trial of atenolol in 200 patients with known coronary artery disease or risk factors for atherosclerosis who underwent noncardiac surgery. No perioperative deaths occurred in patients given atenolol, and only one death was reported in patients receiving placebo. However, by 6 months, eight deaths had occurred in patients given placebo and none in patients given atenolol (P < 0.001). This difference was sustained for the 2-year follow-up period.

Poldermans and colleagues’ study (53), 112 patients with one or more clinical risk factors and ischemia by DSE scheduled to undergo abdominal aortic aneurysm repair or infrainguinal arterial reconstruction were randomly assigned to placebo or bisoprolol. The study was terminated early when the investigators noted that bisoprolol markedly reduced perioperative mortality (17% vs. 3.4%; P = 0.02) and myocardial infarction (17% vs. 0%; P < 0.001).

Subsequently, Boersma and colleagues (43) calculated the odds ratios for perioperative death and myocardial infarction using clinical variables, the revised cardiac risk index, DSE, and β-blocker therapy in 1351 patients screened by Poldermans and colleagues (53). Dobutamine stress echocardiography was performed in 1097 patients, and β-blockers were given to 360 patients. The incidence of nonfatal myocardial infarction or death was 3.3%. Among the 83% of patients found to be at low or intermediate risk by the revised cardiac risk index (0 to 2 risk factors), cardiac complications occurred in fewer than 2% of patients taking β-blockers, irrespective of DSE results. In contrast, DSE provided additional, complementary information in patients with 3 or more risk factors: Among patients receiving β-blockers, the event rate was 2% in those without ischemia by DSE and 11% if DSE showed ischemia.

In summary, β-blockade reduces the incidence of perioperative cardiac complications in patients at low, intermediate, and high risk, as defined by the revised cardiac risk index. It is effective even in patients with inducible ischemia by DSE. Finally, β-blockers are inexpensive. Questions remain about β-blockade in patients having noncardiac surgery. First, patients with severe left ventricular systolic dysfunction were excluded from previous studies. It is unclear how these patients should be managed. Second, the optional duration of β-blocker therapy is uncertain. Third, it is unclear whether the observed benefit of atenolol or bisoprolol is unique to these agents or similar for all β-blockers.

Other Medical Therapies

A few studies have examined nitroglycerin or calcium-channel blockers in patients undergoing noncardiac surgery. The results are inconclusive. Aspirin reduces morbidity and mortality in patients with acute coronary syndromes (54), but no data exist on its use perioperatively. Its potential benefits must be balanced against the increased risk for bleeding. Similarly, no studies have assessed the effect of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors or angiotensin-converting enzyme inhibitors on the incidence of perioperative cardiac events.

PROPOSED CLINICAL ALGORITHM FOR PREOPERATIVE RISK STRATIFICATION

On the basis of the above considerations, preoperative risk stratification can be simplified so that the following questions are addressed (Figure). First, has the patient had coronary revascularization within 5 years without recurrent symptoms? If “yes,” the patient may have surgery, since risk for perioperative myocardial infarction or death is very low. Second, would cardiac catheterization and revascularization be chosen irrespective of the proposed noncardiac surgery? If “yes,” the urgency of the noncardiac surgery must be weighed against the urgency of coronary angiography and revascularization. If the surgery is elective and the need for revascularization is pressing, angiography or revascularization should be done and noncardiac surgery
should be deferred. If “no,” and the patient has none of the revised cardiac risk index variables, noncardiac surgery can be done without delay. If the patient has one or two risk variables, β-blockade should be initiated perioperatively. If β-blockade is contraindicated, surgery can be done without it, since the risk in these patients is only minimally increased. If the patient has three or more risk variables, β-blockade should be initiated perioperatively. If β-blockade is contraindicated or the surgical risk is deemed excessive, canceling or deferring the surgery should be considered. In such patients, DSE may be helpful since perioperative risk is low in patients without ischemia and high in patients with ischemia (43).

CONCLUSIONS

Risk stratification in patients scheduled for noncardiac surgery remains an important issue. The era of routine noninvasive testing has ended; myocardial perfusion imaging and DSE add little to the clinically defined risk index in most patients. Coronary angiography and revascularization should be performed in patients who require these procedures independently of planned noncardiac surgery. Patients considered at risk for myocardial infarction or cardiac death during noncardiac surgery should receive a β-blocker to reduce the risk for perioperative cardiac events.

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