Clinical Practice

This Journal *feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the authors' clinical recommendations.*

LOWERING CARDIAC RISK IN NONCARDIAC SURGERY

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A 65-year-old man requires resection of an abdominal aortic aneurysm. He has a remote history of myocardial infarction and has rare episodes of angina. Recent coronary-artery angiography revealed stenosis of the left circumflex artery of more than 70 percent. What can be done to minimize this patient's risk of perioperative cardiac complications?

THE CLINICAL PROBLEM

The risk of cardiovascular complications is elevated in many patients who are scheduled to undergo noncardiac surgery. Of the estimated 27 million patients in the United States who are given anesthesia for surgical procedures each year, approximately 8 million have known coronary artery disease or coronary risk factors.[1] An estimated 50,000 patients who are scheduled to undergo noncardiac surgery will have a perioperative myocardial infarction, and an estimated 1 million patients will have a perioperative cardiac complication. The economic burden of these complications is estimated to be $20 billion annually.[1]

Identification of High-Risk Patients

During the 1980s, physicians' ability to identify patients at elevated risk for perioperative cardiac complications increased substantially. Such patients include those with unstable coronary syndromes (e.g., unstable angina and recent myocardial infarction), in whom elective surgery should be delayed until their condition is stabilized. The history and findings on physical examination may identify other conditions that place the patient at high perioperative risk (Table 1) and should lead to further consideration of additional diagnostic procedures. Patients with no cardiac risk factors are generally at very low risk and need no further evaluation or therapy. The occurrence of ischemia on stress testing has a low positive predictive value in such patients and may be associated with more false positive than true positive results.[4] Similarly, asymptomatic patients who have one or more risk factors for coronary disease (e.g., a family history of coronary heart disease, smoking, an elevated cholesterol level, obesity, or inactivity) but who do not have established coronary artery disease have been shown to be at very low risk. An exception is patients with diabetes, particularly long-standing diabetes.

In the case of patients with one or more risk factors, the first issue to consider is how the results of various tests would influence decision making. If a finding of stress-induced myocardial ischemia, clinically significant ventricular or valvular dysfunction, or both might lead to cancellation of elective surgery, coronary revascularization, a change in perioperative monitoring, or the initiation of risk-reducing medical therapy, then the cost and potential inconvenience of testing are justified. If the intended treatment is unlikely to be affected by test results, then testing is rarely justified. The decision to perform further tests is beyond the scope of this review, but the choice of tests was reviewed in a recent Clinical Practice article,[5] and guidelines for testing have also been published.[6,7] We will focus on the evidence that supports the use of perioperative interventions to reduce the risk of coronary complications.

Therapies and Interventions to Reduce Complications

Therapies aimed at reducing the incidence of perioperative cardiac complications fall into three categories: preoperative coronary revascularization, perioperative medical therapy, and intraoperative and postoperative monitoring. Perioperative medical therapies include β-adrenergic–receptor antagonists, α_2-adrenergic agonists, nitrates, and calcium-channel blockers. Other agents, such as aspirin, angiotensin-converting–enzyme inhibitors, and statins, play an important part in the treatment of cardiovascular disease. Although there is no reason to believe that the therapeutic effectiveness of these agents is diminished in patients with cardiovascular disease who undergo noncardiac surgery, their ability to reduce the incidence of perioperative cardiac complications has not been studied specifically. Preoperative coronary revascularization procedures that have been advocated include percutaneous coronary intervention with balloon angioplasty, with or without the placement of coronary stents, and coronary-artery bypass grafting.[6]

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TABLE 1. FACTORS THAT INCREASE THE RISK OF PERIOPERATIVE CARDIAC COMPLICATIONS IN PATIENTS UNDERGOING NONCARDIAC SURGERY AND INDICATIONS FOR THE USE OF PERIOPERATIVE BETA-BLOCKER THERAPY.

RISK FACTOR	ODDS RATIO (95% CI)*	PERIOPERATIVE BETA-BLOCKER INDICATED
Ischemic heart disease†	2.4 (1.3–4.2)	Yes
Congestive heart failure	1.9 (1.1–3.5)	Yes
High-risk surgery‡	2.8 (1.6–4.9)	Uncertain, but probably
Diabetes mellitus (especially insulin-requiring)	3.0 (1.3–7.1)	Yes
Renal insufficiency	3.0 (1.4–6.8)	Uncertain, but probably if renal insufficiency is due to diabetes or vascular disease
Poor functional status§	1.8 (0.9–3.5)	Yes, if poor status is thought to be due to coronary artery disease or heart failure

*Data are from Lee et al.[3] and Reilly et al.[5] CI denotes confidence interval.

†Ischemic heart disease includes angina and prior myocardial infarction.

‡High-risk surgery includes intraperitoneal, intrathoracic, and suprainguinal vascular procedures.

§Poor functional status is defined as the inability to walk four blocks or climb two flights of stairs.

STRATEGIES AND EVIDENCE

In addressing the evidence that supports the use of therapies to improve cardiac outcomes after noncardiac surgery, it is important to identify the end point of interest. Because clinical studies require large numbers of patients to have the power to demonstrate differences in the rates of myocardial infarction or death, many studies have been designed to detect differences in the rates of myocardial ischemia, since this condition is common in patients with cardiovascular disease, particularly those undergoing major vascular surgery, and its presence appears to predict subsequent myocardial infarction. Many such studies have demonstrated reductions in the rate of myocardial ischemia with medications that suppress postoperative pain, as well as with beta-blockers and α_2-adrenergic agonists. Although studies assessing the effects of surgical or percutaneous coronary revascularization on the risks of perioperative myocardial infarction, death from cardiac causes, or both are far more compelling, they are unfortunately rare.

Monitoring

In studies of patients without active coronary artery disease who were scheduled to undergo major vascular surgery, there was no difference in important cardiovascular outcomes between patients who were randomly assigned to undergo perioperative monitoring with use of a pulmonary-artery catheter and those assigned to be monitored with use of a central venous catheter.[8-10] No randomized trials have addressed the value of postoperative monitoring in an intensive care unit, but the analysis of administrative data bases in conjunction with the assessment of patterns of practice suggests that the presence of a dedicated intensivist who makes daily rounds improves patient outcomes.[11] Therefore, this is the only approach to monitoring for which there is evidence showing that it improves the outcome in patients who are undergoing major vascular surgery.

Medical Treatment

Beta-Blockers

The ability of beta-blockers to reduce the perioperative risk of cardiac complications has been widely studied. The first randomized, placebo-controlled study involved the perioperative use of atenolol in 200 high-risk patients who were scheduled to undergo noncardiac surgery.[12] Atenolol was administered intravenously or orally beginning two days preoperatively and continuing for seven days postoperatively. The incidence of perioperative ischemia was significantly lower in the atenolol group than in the placebo group.[13] There was no difference in the incidence of perioperative myocardial infarction or death from cardiac causes, but the rate of event-free survival at six months was higher in the atenolol group. Several risk factors and medications were not equally distributed in the two groups, however, since the placebo group had more high-risk factors than the atenolol group.

More recently, Poldermans and colleagues studied the perioperative use of bisoprolol in elective major vascular surgery.[14] This medication was started at least 7 days preoperatively — with adjustment of the dose to achieve a resting heart rate of no more than 60 beats per minute — and was continued for 30 days postoperatively. The study was confined to patients who had at least one cardiac risk factor (a history of congestive heart failure, prior myocardial infarction, diabetes, angina pectoris, heart failure, an age of more than 70 years, or poor functional status) and evidence of inducible myocardial ischemia on dobutamine echocardiography. Patients with extensive regional wall-motion abnormalities were excluded. Bisoprolol was associated with a reduction of approximately 91 percent in the perioperative risk of myocardial infarction or death from cardiac causes in this high-risk population. Because of the selection criteria used in this trial, the efficacy of bisoprolol in the group at highest risk, those in whom coronary revascularization or modification would be considered or for whom the surgical procedure might ultimately be cancelled, cannot be determined. However, the rate of events in the standard-care group (34 percent) suggests that all but the patients at highest risk were enrolled in the trial.

α_2-Adrenergic Agonists

The effect of α_2-adrenergic agonists has also been studied in the perioperative period. Several small, randomized studies comparing clonidine with placebo failed to demonstrate that clonidine reduced the rates of myocardial infarction and death from cardiac causes.[15,16] Mivazerol, an intravenous α_2-adrenergic agonist administered by continuous infusion, was compared with placebo in a cohort of 2801 patients who were known to have coronary disease or risk factors for it and who underwent major vascular or orthopedic procedures. Mivazerol was found to have no overall effect on the rates of cardiac complications.[17] However, in the predefined subgroup of patients with known coronary artery disease who underwent major vascular surgery, mivazerol was associated with a significantly lower incidence of myocardial infarction and death from cardiac causes.

Other Agents

There have been two randomized, placebo-controlled trials of prophylactic nitroglycerin[18,19] and one such trial of prophylactic diltiazem, a calcium-channel antagonist.[20] All three studies were too small to have the power to detect differences in the incidence of cardiac events.

Coronary Revascularization

Percutaneous Revascularization

There have been no randomized trials of preoperative coronary revascularization, but the results of several retrospective cohort studies have been published. Percutaneous transluminal coronary angioplasty (PTCA), primarily with the use of a balloon, has been studied in three cohorts of patients who were undergoing noncardiac surgery.[21-23] The indication for PTCA was not well described but most likely included the need to relieve symptomatic angina or to reduce the perioperative risk of ischemia identified by noninvasive testing. All three cohorts had a low incidence of cardiac complications after noncardiac surgery, but no comparison groups were included.

A more recent study used an administrative data base of patients who were undergoing surgery in Washington State. As compared with patients who did not undergo PTCA preoperatively, those who did undergo the procedure had a lower incidence of perioperative cardiac complications.[24] The benefit of revascularization was most apparent in the group that underwent PTCA at least 90 days before undergoing noncardiac surgery. In contrast, when the revascularization was performed less than 90 days before noncardiac surgery, PTCA was not associated with an improved outcome. This finding suggests that PTCA should not be used solely as a means of reducing perioperative risk.

The placement of coronary stents presents unique challenges because of the risk of coronary thrombosis and bleeding during the initial recovery phase. In a cohort of 40 patients who received stents within 30 days before noncardiac surgery,[25] all 8 deaths and 7 myocardial infarctions, as well as 8 of 11 bleeding episodes, occurred in patients who had undergone surgery within 14 days after stent placement. The complications appeared to be related to serious bleeding resulting from postprocedural anticoagulant therapy or to coronary thrombosis in those who did not receive antithrombotic therapy after stenting. These results suggest that it is prudent to wait at least two weeks, and preferably four weeks, after coronary stenting to perform noncardiac surgery in order to allow complete coronary healing and a full course of antiplatelet therapy to be given. Post-stenting therapy currently includes a combination of aspirin and clopidogrel for four weeks, followed by aspirin for an indefinite period.

Coronary-Artery Bypass Grafting

Coronary-artery bypass grafting has also been advocated as a means of reducing the incidence of perioperative cardiac complications. In the absence of data from randomized trials, evidence suggesting a potential protective effect of preoperative coronary-artery bypass grafting comes from follow-up studies of randomized trials comparing medical and surgical therapy for coronary artery disease. The largest study to date included 3368 noncardiac operations performed within a 10-year period among patients assigned to medical therapy or coronary-artery bypass grafting in the Coronary Artery Surgery Study.[26] Prior successful coronary-artery bypass grafting was protective among patients who underwent high-risk noncardiac surgery (abdominal, thoracic, vascular, or orthopedic surgery).[26] The perioperative mortality rate was nearly 50 percent lower in the group of patients who had undergone coronary-artery bypass grafting than in those who received medical therapy (3.3 percent vs. 1.7 percent, $P \leq 0.05$). There was no difference in the outcome of low-risk procedures such as breast and urologic surgery.

We used data on Medicare claims to assess 30-day and 1-year mortality after noncardiac surgery according to the use of cardiac testing and coronary interventions such as coronary-artery bypass grafting and percutaneous coronary revascularizations with angioplasty, stenting, or both within the year before noncardiac surgery.[27] Preoperative revascularization significantly reduced the one-year mortality rate for patients undergoing aortic surgery but had no effect on the mortality rate for those undergoing infrainguinal surgery. Although the possibility of selection bias cannot be excluded, these findings support the hypothesis that preoperative testing and bypass surgery, when indicated, may reduce the risk of cardiac complications after noncardiac surgery.

Lastly, a recent analysis of the Bypass Angioplasty Revascularization Investigation evaluated the incidence of postoperative cardiac complications after noncardiac surgery among patients with multivessel coronary disease who were randomly assigned to undergo percutaneous coronary revascularization or coronary-artery bypass grafting for severe angina.[28] At an average of 29 months after coronary revascularization, both groups had similar, low rates of postoperative myocardial infarction or death from cardiac causes (1.6 percent in each group of 250 patients). These data suggest that prior successful coronary revascularization, when accompanied by careful follow-up and therapy for subsequent coronary symptoms or signs, is associated with a low rate of cardiac events after noncardiac surgery.

AREAS OF UNCERTAINTY

There are currently no published randomized trials that can be used to determine the true efficacy of pre-

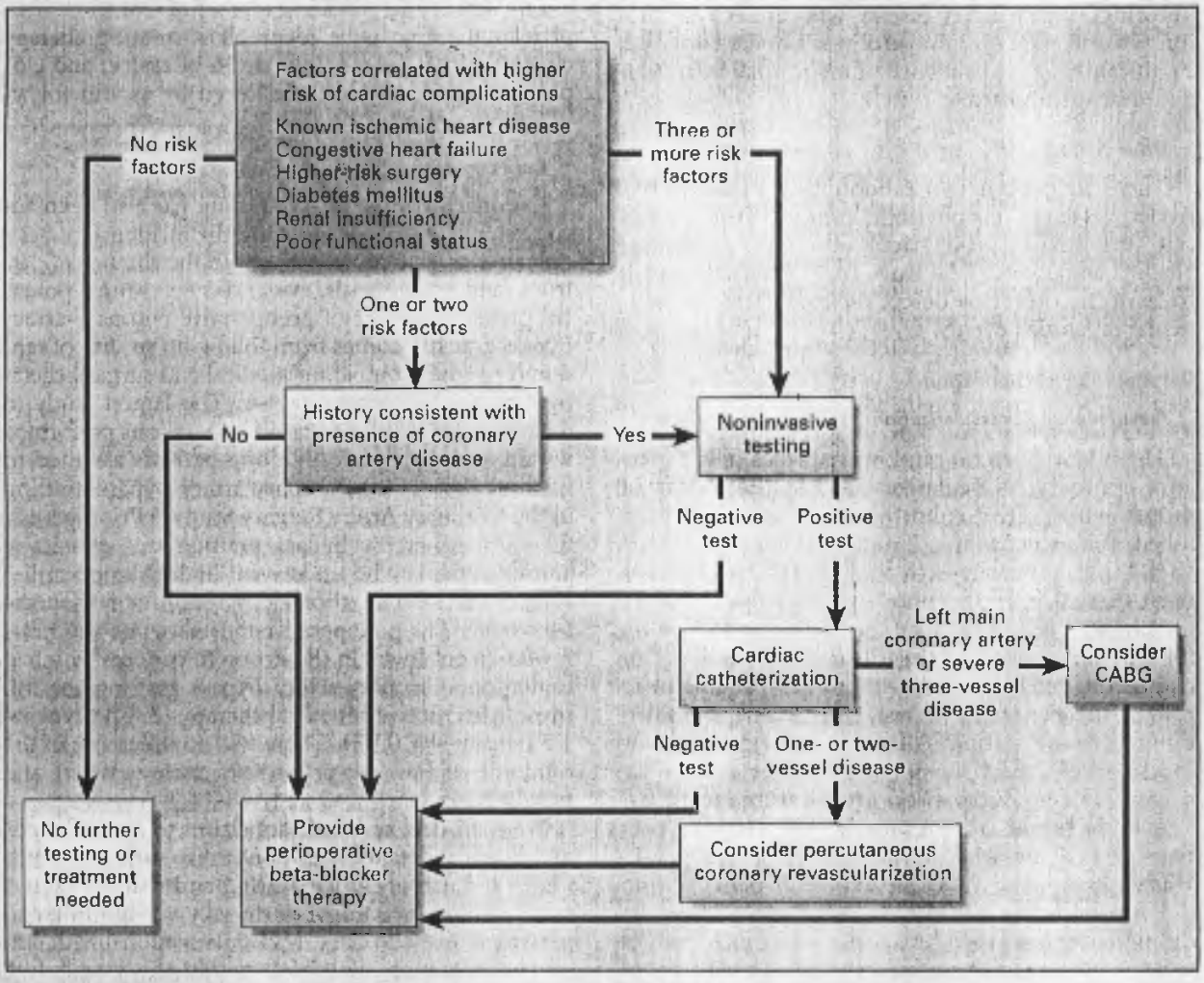

Figure 1. Strategy for Assessing the Risk of Perioperative Coronary Complications in Patients Scheduled to Undergo Noncardiac Surgery.

The decision whether to perform noninvasive testing is based on the presence of clinical risk factors, the patient's functional status, and the type of surgery scheduled. If the result of a noninvasive test is abnormal, the decision whether to perform cardiac catheterization is based on several features. The likelihood of left main coronary artery disease or severe three-vessel disease is much higher and cardiac catheterization should be considered more strongly if ischemia is provoked at a low level of stress or persists during stress testing, if there is severe ST-segment depression, if large areas of the myocardium appear to be at risk, or if ischemia is demonstrated in a patient known to have left ventricular dysfunction at rest. Coronary-artery bypass grafting (CABG) and percutaneous coronary revascularization should be performed only if justified independently of the need for noncardiac surgery. Data are from Boersma et al.[4] and Eagle et al.[29]

operative coronary revascularization. Although there is strong evidence to support the use of beta-blocker therapy in patients undergoing major vascular surgery, given the recognized efficacy of beta-blockers for coronary artery disease and heart failure, the exact timing of therapy and the appropriate patient population remain uncertain. Specifically, the appropriate strategy is unknown for the many patients who present for evaluation the day before surgery and who have never taken beta-blockers. In addition, it is not known whether perioperative beta-blockade reduces morbidity and mortality among the patients at the highest risk (those with diffuse coronary disease) who undergo nonvascular surgery. It is also unclear which patients would benefit from α_2-adrenergic agonists and whether any such benefits would be additive to those of beta-blockers.

GUIDELINES

Two sets of guidelines from national societies address the issue of interventions to reduce the incidence of perioperative cardiac complications of noncardiac surgery.[6,7] The guidelines of the American College of Cardiology–American Heart Association were first issued in 1996[6] and are currently being updated. The guidelines of the American College of Physicians support the use of preoperative testing and coronary therapies in high-risk patients who are undergoing major vascular surgery.[7] An addendum suggests that all high-risk patients should also receive perioperative beta-blocker therapy.

These guidelines[6,7] and numerous reviews conclude that coronary-artery bypass grafting or percutaneous coronary revascularization should be limited to patients who have a clearly defined need for the procedure that is independent of the need for noncardiac surgery.[29] This category includes patients who have poorly controlled angina pectoris despite maximal medical therapy and patients with one of several high-risk coronary characteristics: clinically significant stenosis (>50 percent) of the left main coronary artery, severe two- or three-vessel coronary artery disease (>70 percent stenosis) with involvement of the proximal left anterior descending coronary artery, easily induced myocardial ischemia on preoperative stress testing, and left ventricular systolic dysfunction at rest (Fig. 1).

CONCLUSIONS AND RECOMMENDATIONS

On the basis of the available evidence, we believe that, in the absence of contraindications, beta-blocker therapy should be given to all patients at high risk for coronary events who are scheduled to undergo noncardiac surgery, such as the patient described in the clinical vignette. High-risk patients are those with a history of one or more of the following: myocardial infarction, angina, heart failure, and diabetes, especially if the proposed surgery is itself associated with an elevated risk, as is the case for vascular, thoracic, and major abdominal procedures (Fig. 1). In addition, beta-blockers are reasonable for patients with new or inadequately controlled hypertension who are about to undergo noncardiac surgery. Similarly, we favor their judicious use in patients with renal insufficiency that is thought to be due to diabetes, hypertension, or both, although no randomized clinical trials have tested their effects in this high-risk cohort.

Ideally, beta-blocker therapy should be initiated several days or weeks preoperatively so that the dose can be adjusted to achieve a resting heart rate of no more than 60 beats per minute. We prefer to use shorter-acting beta-selective agents such as metoprolol (25 to 50 mg twice daily), so that the dose can be adjusted over a period of several days. If therapy with a short-acting agent has not been started before the day of surgery, the best route of preoperative delivery may be oral, with intraoperative intravenous titration of the dose and oral administration postoperatively.

Of the other medical therapies available, α_2-adrenergic agonists appear to hold the most promise for use in vascular surgery, although their routine use cannot be supported on the basis of current information. We would consider using such agents in high-risk patients who are scheduled to undergo vascular surgery for whom the use of beta-blockers is contraindicated. The use of calcium-channel blockers and nitrates should be limited to patients in whom these agents have been required to control angina or ischemic symptoms such as shortness of breath in the past and patients in whom perioperative myocardial ischemia develops (particularly in the presence of effective beta-blockade). In high-risk patients scheduled to undergo noncardiac surgery, coronary-artery bypass grafting and percutaneous coronary revascularization are appropriate if they are indicated independently of the need for noncardiac surgery.

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