# Medical therapy to reduce perioperative cardiac complications

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***Preoperative cardiac assessment has become an integral part of contemporary anesthesia practice. Simple clinical markers can identify high-risk patients, but the question of how to reduce cardiac complications among high-risk patients has been controversial. Good quality randomized controlled trials have showed that neither preoperative coronary revascularization nor the placement of pulmonary artery catheters reduces perioperative cardiac complications. On the other hand, there is increasing evidence that medical therapy offers myocardial protection and reduces perioperative cardiac complications. The data supporting these conclusions are reviewed in an evidence-based manner. At present, it is prudent to treat moderate- to high-risk patients undergoing elective surgery with beta-blockers if possible. Because not all patients are candidates for beta-blocker therapy, data regarding the perioperative use of alternative medications to reduce perioperative cardiac complications have been explored and are reviewed.***

***Key words:*** **Beta-blockers, perioperative cardiac complications.**

Each year, approximately 25 million people in the United States undergo noncardiac surgery. Approximately 8 million of these have known cardiac disease, major cardiac risk factors, or are older than 65 years. Therefore, it is not surprising that cardiac complications occur when these patients are subjected to stress during the perioperative period. Current estimates of serious perioperative cardiac morbidity vary between 1% and 10%, depending on the subset of patients and the type of surgical procedure.[1]

Continuous electrocardiographic monitoring with ST segment analysis has provided insight into the pathophysiologic features and frequency of perioperative myocardial ischemia.[2,3] The Perioperative Ischemia Research Group used continuous electrocardiographic monitoring before, during, and after noncardiac operations and found that myocardial ischemia occurred most frequently during the early postoperative period (20% in the preoperative, 25% in the intraoperative, and 41% in the postoperative period).

Postoperative ischemia has been well characterized. Its peak incidence is within 48 hours of surgery, which correlates with the peak incidence of postoperative myocardial infarction (MI). The ischemic episodes are not associated with tachycardia and follow a circadian rhythm, with most ischemia occurring in the early morning hours. Postoperative ischemia is more severe than ischemia detected at other times and is clinically silent more than 90% of the time. Silent postoperative ischemia has been reported to be present for more than 50 minutes before each clinical event.[4-6]

Perioperative myocardial ischemia usually occurs in the presence of fixed severe coronary artery stenoses, which limit oxygen delivery during the stressful perioperative period. A recent study confirmed this by demonstrating that perioperative MIs were preceded by prolonged ST segment depression.[7] Although prolonged stress-induced ischemia accounts for most perioperative infarctions, some are caused by acute thrombosis. Histopathologic analysis of coronary arteries in patients who had fatal perioperative MIs have demonstrated the disruption of unstable coronary plaques within mild to moderately stenosed vessels.[8] Plaque disruption leads to platelet aggregation and subsequent coronary artery thrombosis. The postoperative period is accompanied by activation of neurohumoral pathways, increases in catecholamine levels, reduced levels of endogenous tissue plasminogen activator, and platelet activation, all of which have been postulated to contribute to perioperative myocardial ischemia.

Previous studies have shown that patients at increased risk for perioperative cardiac events can be identified on the basis of simple clinical markers. In addition to the ASA classification, the most commonly used indices are the "Revised Cardiac Index" for general surgical procedures and the "Eagle Clinical Criteria" for major vascular surgery[9,10] (Table 1 and Table 2). Each of these risk stratification strategies has been validated in prospective studies.[11] Because these indices perform so well, a thorough history, physical examination, and electrocardiogram are sufficient to assess perioperative cardiac risk for most patients. Further workup is necessary in certain patients, such as those unable to exercise and those

**Table 1. Revised cardiac index for preoperative risk stratification**[9]

| Risk factor | No. of risk factors | Postoperative cardiac complications* (%) |
|---|---|---|
| High-risk surgery | 0 | 0.4 |
| History of ischemic heart disease | 1 | 0.9 |
| History of congestive heart failure | 2 | 7 |
| History of cerebrovascular disease | >3 | 11 |
| Preoperative treatment with insulin | | |
| Preoperative serum creatinine level >2.0 mg/dL | | |

* Cardiac complications: defined as ventricular fibrillation, acute myocardial infarction, pulmonary edema, complete heart block, cardiac death.

**Table 2. Eagle clinical criteria for preoperative risk stratification for patients undergoing major vascular surgery**[10]

| Risk factor | No. of risk factors | Postoperative cardiac complications* (%) |
|---|---|---|
| Older than 70 y | 0 | 3 |
| Diabetes mellitus | 1-2 | 30 |
| Angina | 1-2 with negative stress test result | 3 |
| Q waves on preoperative electrocardiogram | 1-2 with positive stress test result | 30 |
| Ventricular arrhythmias | >3 | 30 |

* Cardiac complications: defined as ventricular fibrillation, acute myocardial infarction, pulmonary edema, complete heart block, cardiac death.

who cannot provide adequate history. These patients should be considered for further evaluation with a stress test.

## Risk-reduction strategies

The aforementioned approaches can identify patients at increased risk for postoperative cardiac complications. Once a patient is determined to be at high risk, risk-reduction strategies should be considered. The options for reducing risk include coronary revascularization with coronary artery bypass grafting (CABG), percutaneous coronary intervention (PCI), and medical therapy. There recently have been several well-conducted clinical trials indicating that medical therapy provides myocardial protection and should be our therapy of choice to reduce perioperative cardiac events.

## Coronary revascularization

The question of preoperative coronary revascularization for high-risk patients is often raised. Coronary artery bypass grafting specifically to decrease postoperative complications should be considered differently from a CABG performed for indications with known survival benefit. There is no question that CABG should be performed before elective noncardiac surgery in patients who have independent indications for coronary revascularization.

The role of preoperative coronary revascularization in patients being evaluated for noncardiac surgery has been controversial for several decades. Recent studies have begun to clarify this issue. One study involved patients who participated in a trial comparing CABG and PCI and later required noncardiac surgery.[12] Among the 934 participants of this study, 501 subsequently required noncardiac surgery with a median interval between coronary revascularization and noncardiac surgery of 29 months. The rates of cardiac complications after noncardiac surgery were similar in patients who had undergone CABG or PCI for approximately 4 years. After 4 years, the risks of noncardiac surgery began to increase in both groups. From this study, we are able to conclude that prior coronary revascularization may be protective for a period of 4 years, and, in this setting, CABG and PCI are equivalent. This study did not provide information regarding the relative risk reductions of preoperative coronary revascularization vs medical therapy.[12]

This question was addressed recently by a landmark multicenter study.[13] Patients with clinically significant but stable coronary artery disease who were undergoing elective major vascular surgery were

assigned randomly to undergo preoperative coronary revascularization (PCI or CABG, 258 patients) or perioperative medical therapy alone (252 patients). There were 4 deaths related to the preoperative revascularization procedure, 2 each in the CABG and PCI groups. After elective vascular surgery, there were no significant differences in perioperative death (3% in both groups), perioperative MI (8% in both groups), or length of stay in the intensive care unit (2 days) between patients who underwent preoperative coronary revascularization and patients who received medical therapy. At a median follow-up of 2.7 years, there was no difference in mortality between the 2 groups (22% in both groups). It is important to keep in mind the exclusion criteria for this study when considering the implications of these results. Patients were enrolled only if they had stable coronary symptoms and were excluded if they had at least 50% stenosis of the left main coronary artery, a left ventricular ejection fraction of less than 20%, or severe aortic stenosis. Even given these limitations, this study was methodologically sound and provides good evidence that there is no benefit from prophylactic preoperative revascularization to prevent cardiac complications among a high-risk population.[13]

A recent study addressed the question of preoperative coronary angioplasty specifically.[14] This study demonstrated that patients who underwent preoperative angioplasty had the same incidence of postoperative cardiac complications as those who did not.[14] Other studies have reported that preoperative coronary artery stenting is associated with increased perioperative cardiac morbidity and mortality.[15,16] Thus, prophylactic revascularization before elective surgery does not reduce perioperative cardiac complications and should not be recommended unless revascularization is otherwise indicated independent of the need for noncardiac surgery.

## Medical therapy

• *Beta-blockers.* There is increasing evidence that aggressive medical therapy can provide myocardial protection and decrease perioperative cardiac complications. In the first randomized controlled trial of perioperative beta-blockers, 200 patients with or at risk for coronary artery disease undergoing noncardiac surgery were randomized to receive placebo or intravenous atenolol 30 minutes before surgery and intravenous or oral atenolol for the duration of the hospital stay.[17] Although there was no difference in short-term mortality, the atenolol group had a 40% decrease in postoperative myocardial ischemia and a significant survival advantage at 2 years. In addition to these primary endpoints, diabetic patients receiving atenolol had a 4-fold reduction in risk compared with diabetic patients receiving placebo.[17,18]

In another study, 112 high-risk vascular surgery patients were randomized to receive perioperative bisoprolol or standard perioperative care. The fact that these were all high-risk patients undergoing high-risk surgery resulted in an increased incidence of cardiac complications and increased statistical power. An independent safety committee halted the study early because a striking benefit was demonstrated in the bisoprolol group. Perioperative death occurred in 3.4% of patients in the bisoprolol group and 17% of patients in the standard care group, whereas nonfatal MI did not occur in the bisoprolol group but occurred in 17% of the standard care group. These combined primary endpoints occurred in 3.4% of patients in the bisoprolol group and 34% of patients in the standard care group.[19] These studies are methodologically sound and provide good evidence that perioperative beta-blockers reduce short- and long-term cardiac complications.

Given these study results, there is a tendency to view effective perioperative beta blockade as providing sufficient cardioprotection to preclude preoperative risk stratification and preoperative cardiac testing. To further elucidate this issue, another recent study looked at the interaction of preoperative stress testing (dobutamine stress echocardiography) and perioperative beta-blockers.[20] This study showed for the first time that low-risk patients, in addition to high-risk patients, undergoing vascular surgery benefited from beta-blocker administration. Similar benefits were seen among patients who were taking beta-blockers long-term and in those who started receiving these medications just before surgery. Unfortunately, this study identified a small group of patients for whom beta-blockers were not protective. Patient's with stress echocardiogram showing widespread severe ischemia (>5 new abnormal segments) had cardiac complication rates that were not reduced beta-blocker administration compared with similar patients who did not receive beta-blockers.[20] Whether we can intervene to effectively decrease perioperative cardiac complications among this very high-risk group and how to identify this group in a cost-effective manner remain under study.

To summarize the effectiveness of perioperative beta-blockers, a recent meta-analysis was performed and concluded that beta-blockers decrease perioperative ischemia and perioperative cardiac death. The primary adverse effect was bradycardia, which required treatment in a minority of patients. The authors cal-

culated a favorable number needed to treat between 2 and 8. It was recommended that all patients at increased risk for cardiac complications undergoing noncardiac surgery be given beta-blockers.[21,22] Some authors, however, express caution regarding the enthusiasm with which we embrace perioperative beta-blocker therapy. They caution that none of the trials to date have included large numbers of patients and that the beneficial effects reported to date seem implausibly large.[23] These investigators are currently attempting to enroll 10,000 patients in a randomized trial of perioperative beta-blockers to definitively establish the degree of benefit and the potential risks associated with perioperative beta-blocker therapy.

At this point, it seems reasonable to treat high-risk patients with perioperative beta-blockers, recognizing the limitations of the current data. Starting beta-blocker therapy 1 to 2 weeks before elective surgery and then continuing them during the postoperative period may be more practical than introducing new medications just before surgery. Questions that remain to be answered with future research include the degree of benefit conferred by beta-blockers, whether all beta-blockers are equally efficacious, and what the optimal dosing schedules are; we also need to further stratify which patients will benefit most from these medications.

## Other medical therapies

• *Nitroglycerin and calcium channel blockers.* Not all patients can tolerate beta-blockers, particularly those with a history of asthma, bronchospasm, bradycardia, or cardiac conduction abnormalities. Thus, there has been interest in other agents that may attenuate the stress response to surgery. The prophylactic use of nitroglycerin has not been shown to decrease perioperative myocardial ischemia or postoperative cardiac complications.[24,25] Calcium channel blockers are widely prescribed and have been studied in the perioperative setting. The studies to date have enrolled small numbers of patients, have different endpoints, and have yielded conflicting results. Two recent meta-analyses have pooled these data and came to disparate conclusions, one finding benefit, the other finding no benefit of calcium channel blockers in the perioperative setting.[25,26] Large-scale randomized trials are necessary to determine the usefulness of calcium channel blockers in this setting.

• *Clonidine.* The centrally acting $\alpha_2$ agonist, clonidine, has been shown to reduce hypertension, tachycardia, and norepinephrine release associated with surgical stress. There have been several small studies in which clonidine has been used in an attempt to decrease perioperative cardiac complications. When the data from these studies were pooled in a meta-analysis, there were trends toward decreased incidence of postoperative MI and death among patients taking clonidine, but these trends did not reach statistical significance.[27]

A more recent trial, however, showed beneficial effects of clonidine. This was a prospective, double-blind trial in which 190 patients with known coronary artery disease or more than 2 coronary risk factors were randomized to perioperative clonidine or placebo. Oral and transdermal clonidine were started on the night before surgery and continued for 4 days. The clonidine group had a significant reduction of perioperative myocardial ischemia. At 30 days, there was a nonsignificant trend toward fewer deaths in the clonidine group, but at 2 years, mortality was reduced significantly in the clonidine group (15% vs 29%).[28] Larger studies clearly are necessary to confirm this benefit and to determine the magnitude of benefit compared with beta-blocker therapy. Until then, prophylactic clonidine may be an alternative for high-risk patients who are unable to take beta-blockers.

• *Statins.* There has been increasing recognition that a variety of other mechanisms other than increased adrenergic activity contribute to perioperative cardiac complications. At the same time, there has been increased interest in statins and their benefits beyond lowering cholesterol. It appears that they have a variety of effects that stabilize potentially vulnerable coronary plaques. In nonoperative settings, statins have been associated with decreased in-hospital deaths in patients with acute coronary syndromes and periprocedural MI following PCI. To date, there are several large observational studies suggesting a strong association between perioperative statin use and decreased cardiac complications after noncardiac surgery.[29-31]

There is 1 randomized prospective trial using statins in an attempt to reduce cardiac complications after elective vascular surgery in which 100 patients were randomized to 20 mg of atorvastatin per day or placebo for 45 days perioperatively.[32] Patients had vascular surgery at a mean of 31 days after the start of the study medication. Patients taking atorvastatin had a lower risk for the composite endpoint of cardiovascular events (cardiac death, nonfatal MI, unstable angina, or ischemic stroke) than did patients randomized to placebo. There were no significant differences among the individual components of the composite endpoint between the 2 groups.[32] Approximately half of the patients in both groups received beta-blockers perioperatively. The sample was not large enough for subset analysis to determine whether the beneficial

**Table 3. Perioperative beta-blocker administration***

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|---|
| **Atenolol**[17] |
| 30 mins before anesthesia induction |
| 5 mg IV over 5 minutes; repeat dose after 10 min if no exclusions |
| Postoperative administration |
| NPO, atenolol, 5 mg IV every 12 h |
| PO, 50-100 mg daily |
| Exclusions: hold any dose if heart rate < 55 beats per min, systolic blood pressure < 100, third-degree heart block, physical examination evidence of congestive heart failure or bronchospasm |
| **Bisoprolol**[19] |
| Start at least 1 wk before surgery |
| 5 mg PO daily; if after 1 wk heart rate > 60 beats per min, increase to 10 mg daily |
| Medication given on morning of surgery |
| Postoperative administration |
| NPO, IV metoprolol titrated to a heart rate of < 80 beats per min |
| PO, same outpatient dose |

* IV indicates intravenous; NPO, nothing by mouth; and PO, by mouth.

effects of atorvastatin were influenced by beta-blocker administration or other factors. Once again, larger randomized controlled trials are necessary to confirm this benefit and to determine the degree of benefit. Other questions that remain unanswered include how long to treat with a statin preoperatively and how long to continue the medicine postoperatively.

## Pulmonary artery catheters

The value of pulmonary artery catheters in high-risk surgical patients has been controversial. Early uncontrolled studies reported benefit compared with historical control subjects.[33] A small prospective study involving 89 patients undergoing vascular surgery reported decreased mortality and decreased early graft thrombosis in patients who had their hemodynamic status optimized with a pulmonary artery catheter compared with those who did not.[34] A subsequent observational study of 221 patients reported that perioperative pulmonary artery catheterization did not improve outcomes and was associated with prolonged hospitalization.[35]

A rigorous, randomized controlled trial on the use of pulmonary artery catheters was published recently.[36] In this study, 1,994 high-risk patients (older than 60 years or ASA class III or IV) undergoing urgent or elective noncardiac surgery were randomized to receive a pulmonary artery catheter or usual care. The authors used a predefined protocol and physiologic goals for patients receiving a pulmonary artery catheter. There were no differences in in-hospital mortality or mortality at 1 year between the invasively monitored group and the standard care group. Similarly, there were no differences between groups for a variety of secondary endpoints, including MI, congestive heart failure, arrhythmias, and catheter-related complications.[36] This large randomized controlled trial, together with observational studies, establishes that the use of pulmonary artery catheters does not decrease perioperative morbidity or mortality and should not be recommended as a risk-reduction strategy for high-risk surgical patients.

## Conclusion

The evaluation of cardiac risk before surgical procedures has become an integral part of contemporary anesthesia practice. Although there is agreement that clinical markers can identify high-risk patients, the approach to risk reduction has been controversial. Good data are becoming available to help guide clinical decision making. There is no evidence that preoperative coronary revascularization, with CABG or PCI, offers risk-reduction benefit. Data from randomized controlled trials regarding medical therapies look very promising. Beta-blockers decrease perioperative myocardial ischemia and decrease cardiac complications among patients undergoing high-risk surgery. Although several trials have confirmed these results, definitive large-scale trials are lacking. At present, it seems prudent to treat high-risk patients without contraindications with beta-blockers during the perioperative period (Table 3). For patients who cannot tolerate beta-blockers, perioperative calcium channel blockers and clonidine may offer some degree of cardioprotection. Treatment with a statin perioperatively also seems to be beneficial and may be considered in high-risk patients. Whether adding a statin to beta-blockers or other drugs in this setting further reduces risk is unclear and deserves further study. The use of pulmonary artery catheters does not decrease perioperative complications in high-risk patients and should not be recommended for routine use.

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