REVIEW

BRIAN HARTE, MD
Clinical Assistant Professor of Medicine, Cleveland Clinic Lerner College of Medicine of Case Western University; Chairman, Department of Hospital Medicine, Cleveland Clinic

AMIR K. JAFFER, MD
Associate Professor of Medicine; Chief, Division of Hospital Medicine, University of Miami Leonard M. Miller School of Medicine, Miami, FL

Perioperative beta-blockers in noncardiac surgery: Evolution of the evidence

ABSTRACT

After studies in the 1990s suggested that beta-blockers offer substantial benefits when given before surgery, several national organizations endorsed the perioperative use of these drugs as a best practice in certain patients. However, subsequent research has cast doubt on whether it is appropriate to use these drugs as widely as suggested by those early studies.

KEY POINTS

Beta-blockers reduce perioperative ischemia, but the benefit may be only in high-risk patients undergoing high-risk surgery. Currently, the best evidence supports their use in two groups: patients undergoing vascular surgery who have known ischemic heart disease or multiple risk factors for it, and patients who are already on beta-blockers.

The Perioperative Ischemic Evaluation (POISE) findings suggest that beta-blockers should be used in the immediate preoperative period only with great caution, after ensuring that the patient is clinically stable and without evidence of infection, hypovolemia, anemia, or other conditions that could make heart-rate titration misleading or use of the drug dangerous.

When feasible, beta-blockers should be started a month before surgery, titrated to a heart rate of 60 beats per minute, and continued for approximately a month. If the drug is then to be discontinued, it should be tapered slowly.

THE PENDULUM of expert opinion is swinging away from routinely recommending beta-blockers to prevent cardiac events in noncardiac surgery patients. We won't be abandoning the perioperative use of beta-blockers altogether, but we will probably be using them more selectively than in the past.

The latest factor driving the trend is the online publication in May 2008 of the results of the Perioperative Ischemic Evaluation (POISE) trial,[1] the largest placebo-controlled trial of perioperative beta-blocker use to date. In brief, in a cohort of patients with atherosclerotic disease or at risk for it who were undergoing noncardiac surgery, fewer patients who received extended-release metoprolol succinate had a myocardial infarction, but more of them died or had a stroke compared with those receiving placebo. (Extended-release metoprolol succinate is available in the United States as Toprol-XL and generically.)

Not so long ago, the pendulum was going the other way. After two small trials in the 1990s concluded that beta-blockers reduced the risk of perioperative cardiac events in selected patients with known or suspected coronary disease,[2,3] their perioperative use was subsequently endorsed by the Leapfrog Group and the Agency for Healthcare Research and Quality. The National Quality Forum included perioperative beta-blockade in its "Safe Practices for Better Healthcare 2006 update,"[4,5] and the Physician Consortium for Performance Improvement and the Surgical Care Improvement Project both listed it as a quality measure.

Since then, this practice has been close-

ly studied, especially as concomitant research has failed to demonstrate that preoperative coronary revascularization improves outcomes, even in the presence of ischemic disease. But evidence has been accumulating that routine use of beta-blockers may not benefit as many patients as was hoped, and may actually cause harm. The 2007 joint American College of Cardiology (ACC) and American Heart Association (AHA) guidelines on perioperative cardiovascular evaluation and care for noncardiac surgery gives its strongest recommendation (class I: benefit clearly outweighs risk) for perioperative beta-blocker use only for patients at high risk: those with known ischemic heart disease undergoing vascular surgery and those who are already on these drugs before surgery.[6]

However, there are still gaps in our knowledge. Perhaps, with proper implementation, we may be able to use beta-blockers to improve outcomes in patients at intermediate risk as well. In this paper, we review the rationale and the evidence for and against perioperative use of beta-blockers and provide practical guidance for internists and hospitalists.

Routine use of beta–blockers may not help as many patients as hoped, and may actually cause harm

WHY CARDIAC EVENTS OCCUR AFTER SURGERY

Adverse cardiovascular events such as myocardial infarction and unstable angina are the leading causes of death after surgery.[7] Such events occur in approximately 1% of patients older than 50 years undergoing elective inpatient surgery, but this number may be higher (approximately 5%) in those with known or suspected coronary disease.[8,9] Perioperative cardiac events can also be harbingers of further complications, dramatically increasing hospital length of stay.[10]

Some ischemic events are caused by physiologic derangements involving the balance between inflammatory mediators, sympathetic tone, and oxygen supply and demand that occur under the stress of surgery. Others are more "traditional" in etiology, involving acute plaque rupture, thrombosis, and occlusion. Studies have consistently found a correlation between perioperative ischemia and cardiac events (both in-hospital and long-term) and death.[11–17] Other studies suggest that most perioperative cardiac infarcts are non-Q-wave events,[18] and most events occur within the first few days after surgery, particularly the first 48 hours, when the effects of anesthetics, pain, fluid shifts, and physiologic derangements are greatest.

Factors that may trigger acute occlusion in the perioperative period include abrupt changes in sympathetic tone, increased levels of cortisol and catecholamines, and tissue hypoxia. Other potential triggers activated or increased by the stress of surgery include coagulation factors such as alterations in platelet function; inflammatory factors such as tumor necrosis factor alpha, interleukin 1, interleukin 6, and C-reactive protein; and metabolism of free fatty acids (which contribute to increased oxygen demand as well as endothelial dysfunction).[9,19,20]

A 1996 autopsy study found that 38 (90%) of 42 patients who died of a perioperative infarct had evidence of acute plaque rupture or plaque hemorrhage on coronary sectioning, findings corroborated in another, similar study.[21,22] These studies suggest that multiple causes contribute to perioperative myocardial infarction, and a single strategy may not suffice for prevention.

IF BETA-BLOCKERS PROTECT, HOW DO THEY DO IT?

Beta-blockers have several effects that should, in theory, protect against cardiac events during and after surgery.[23] They reduce cardiac oxygen demand by reducing the force of contraction and the heart rate, and they increase the duration of diastole, when the heart muscle is perfused. They are also antiarrhythmic, and they may limit free radical production, metalloproteinase activity, and myocardial plaque inflammation.[24]

Some researchers have speculated that using beta-blockers long-term may alter intracellular signaling processes, for example decreasing the expression of receptors that receive signals for cell death, which in turn may affect the response to reperfusion cell injury and death. If this is true, there may be an advantage to starting beta-blockers well in advance of surgery.[25]

EARLY CLINICAL EVIDENCE IN FAVOR OF PERIOPERATIVE BETA-BLOCKER USE

Evidence in patients at high risk

Mangano et al,[2] in a study published in 1996, randomized 200 patients with known coronary disease or established risk factors for it who were undergoing noncardiac surgery to receive the beta-blocker atenolol orally and intravenously or placebo in the immediate perioperative period. Fewer patients in the atenolol group died in the first 6 months after hospital discharge (0 vs 8%, $P < .001$), the first year (3% vs 14%, $P = .005$), and the first 2 years (10% vs 21%, $P = .019$). However, there was no difference in short-term outcomes, and the study excluded patients who died in the immediate postoperative period. If these patients had been included in the analysis, the difference in the death rate at 2 years would not have been statistically significant.[26] Other critical findings: more patients in the atenolol group were using angiotensin-converting enzyme inhibitors and beta-blockers when they were discharged, and the placebo group had slightly more patients with prior myocardial infarction or diabetes.[27] (Atenolol is available in the United Sates as Tenormin and generically.)

Poldermans et al,[3] in a study published in 1999, randomized 112 vascular surgery patients to receive either oral bisoprolol or placebo. These patients were selected from a larger cohort of 1,351 patients on the basis of high-risk clinical features and abnormal results on dobutamine echocardiography. Bisoprolol was started at least 1 week before surgery (range 7–89 days, mean 37 days), and patients were reevaluated before surgery so that the dose could be titrated to a goal heart rate of less than 60 beats per minute. After surgery, the drug was continued for another 30 days. The study was stopped early because the bisoprolol group had a 90% lower rate of nonfatal myocardial infarction and cardiac death at 30 days. Despite the study's limitation (eg, enrolling selected patients and using an unblinded protocol), these compelling findings made a strong case for the use of beta-blockers perioperatively in patients at high risk, ie, those with ischemic heart disease who are undergoing major vascular surgery. (Bisoprolol is available in the United States as Zebeta and generically)

Evidence in patients at intermediate risk

Boersma et al[28] performed a follow-up to the study by Poldermans et al, published in 2001, in which they analyzed characteristics of all 1,351 patients who had been originally considered for enrollment. Using regression analysis, they identified seven clinical risk factors that predicted adverse cardiac events: angina, prior myocardial infarction, congestive heart failure, prior stroke, diabetes, renal failure, and age 70 years or older. Furthermore, for the entire cohort, patients receiving beta-blockers had a lower risk of cardiac complications (0.8%) than those not receiving beta-blockers (2.3%). In particular, the patients at intermediate risk (defined as having one or two risk factors) had a very low event rate regardless of stress test results, provided they were on beta-blockers: their risk of death or myocardial infarction was 0.9%, compared with 3.0% for those not on beta-blockers.

The authors concluded that dobutamine stress testing may not be necessary in patients at intermediate risk if beta-blockers are appropriately prescribed. However, others took issue with their data and conclusions, arguing that there have been so few trials that the data are still inconclusive and inadequate to ascertain the benefit of perioperative beta-blockade, particularly in patients not at high risk.[26,29]

The Revised Cardiac Risk Index. Although the Boersma risk-factor index is not used in general practice, numerous experts[27,20–32] recommend a similar one, the Revised Cardiac Risk Index, devised by Lee et al.[8] This index consists of six risk factors, each of which is worth one point:

- Congestive heart failure, based on history or examination
- Myocardial infarction, symptomatic ischemic heart disease, or a positive stress test
- Renal insufficiency (ie, serum creatinine level > 2 mg/dL)
- History of stroke or transient ischemic attack
- Diabetes requiring insulin
- High-risk surgery (defined as intrathoracic, intra-abdominal, or suprainguinal vascular surgery).

A strong case can be made for perioperative beta–blockers in patients at high risk, but less so for lower–risk patients

Patients with three or more points are considered to be at high risk, and those with one or two points are considered to be at intermediate risk. The ACC/AHA 2007 guidelines[6] use a modified version of this index that considers the issue of surgical risk separately from the other five clinical conditions.

Devereaux et al[33] performed a meta-analysis, published in 2005, of 22 studies of perioperative beta-blockade. They concluded that beta-blockers had no discernable benefit in any outcome measured, including deaths from any cause, deaths from cardiovascular causes, other cardiac events, hypotension, bradycardia, and bronchospasm. However, they based this conclusion on the use of a 99% confidence interval for each relative risk, which they believed was justified because the trials were small and the numbers of events were only moderate. When the outcomes are assessed using the more common 95% confidence interval, benefit was detected in the combined end point of cardiovascular death, nonfatal myocardial infarction, and nonfatal cardiac arrest.

High risk: ≤ 3 points

Intermediate risk: 1–2 points

Low risk: 0 points

Yang et al,[34] **Brady et al,**[35] and **Juul et al**[36] performed three subsequent randomized trials that added to the controversy. Most of the patients in these trials were at intermediate or low risk, and none of the trials found a significant benefit with perioperative beta-blocker use. However, the protocols in these studies were different from the one in the study by Poldermans et al,[3] which had found perioperative beta-blockade to be beneficial. Whereas patients in that earlier study started taking a beta-blocker at least 1 week before surgery (and on average much earlier), had their dose aggressively titrated to a target heart rate, and continued taking it for 30 days afterward, the protocols in the later trials called for the drug to be started within 24 hours before surgery and continued for only a short time afterward.

Lindenauer et al,[37] in a retrospective study published in 2005, found that fewer surgical patients who received beta-blockers in the hospital died in the hospital. The researchers used an administrative database of more than 780,000 patients who underwent noncardiac surgery, and they used propensity-score matching to compare the postoperative mortality rates of patients who received beta-blockers and a matched group in the same large cohort who did not. Beta-blockers were associated with a lower morality rate in patients in whom the Revised Cardiac Risk Index score was 3 or greater. However, although there was a trend toward a lower rate with beta-blocker use in patients whose score was 2 (ie, at intermediate risk), the difference was not statistically significant, and patients with a score of 0 or 1 saw no benefit and were possibly harmed.

The authors admitted that their study had a number of limitations, including a retrospective design and the use of an administrative database for information regarding risk index conditions and comorbidities. In addition, because they assumed that any patient who received a beta-blocker on the first 2 hospital days was receiving appropriate perioperative treatment, they may have incorrectly estimated the number of patients who actually received these drugs as a risk-reduction strategy. For instance, some patients at low risk could have received beta-blockers for treatment of a specific event, which would be reflected as an increase in event rates for this group. They also had no data on what medications the patients received before they were hospitalized or whether the dose was titrated effectively. The study excluded all patients with congestive heart failure and chronic obstructive pulmonary disease, who may be candidates for beta-blockers in actual practice. In fact, a recent observational study in patients with severe left ventricular dysfunction suggested that these drugs substantially reduced the incidence of death in the short term and the long term.[38] Finally, half the surgeries were nonelective, which makes extrapolation of their risk profile by the Revised Cardiac Risk Index difficult, since Lee et al excluded patients undergoing emergency surgery from the cohorts from which they derived and validated their index criteria.

Nevertheless, the authors concluded that patients at intermediate risk derive no benefit from perioperative beta-blocker use, and that the odds ratio for death was actually higher in patients with no risk factors who received a beta-blocker.

DOES PERIOPERATIVE BETA-BLOCKER USE CAUSE HARM?

The published data on whether perioperative beta-blocker use harms patients are conflicting and up to now have been limited.

Stone et al[39] reported a substantial incidence of bradycardia requiring atropine in patients treated with a single dose of a beta-blocker preoperatively, but the complications were not clearly characterized.

The Perioperative Beta-Blockade trial.[35] Significantly more patients given short-acting metoprolol had intraoperative falls in blood pressure and heart rate, and more required inotropic support during surgery, although the treating anesthesiologists refused to be blinded in that study. (Short-acting metoprolol is available in the United States as Lopressor and generically.)

Devereaux et al,[33] in their meta-analysis, found a higher risk of bradycardia requiring treatment (but not a higher risk of hypotension) in beta-blocker users in nine studies, including the study by Stone et al and the Perioperative Beta-Blockade trial (relative risk 2.27, 95% confidence interval 1.36–3.80).

Conversely, at least three other studies found no difference in rates of intraoperative events.[36,40,41] There are few data on the incidence of other complications such as perioperative pulmonary edema and bronchospasm.

POISE: THE FIRST LARGE RANDOMIZED TRIAL

In May 2008, results were published from POISE, the first large randomized controlled trial of perioperative beta-blockade.[1] An impressive 8,351 patients—most of them at intermediate risk—were randomized to receive extended-release metoprolol succinate or placebo starting just before surgery and continuing for 30 days afterward.

Although the incidence of the primary composite end point (cardiovascular death, nonfatal myocardial infarction, and nonfatal cardiac arrest) was lower at 30 days in the metoprolol group than in the placebo group (5.8% vs 6.9%, hazard ratio 0.83, $P = .04$), other findings were worrisome: more metoprolol recipients died of any cause (3.1% vs 2.3%, $P = .03$) or had a stroke (1.0% vs 0.5%, $P = .005$). The major contributor to the higher mortality rate in this group appears to have been sepsis.

How beta-blockers might promote death by sepsis is unclear. The authors offered two possible explanations: perhaps beta-blocker-induced hypotension predisposes patients to infection and sepsis, or perhaps the slower heart rate and lower force of contraction induced by beta-blockers could mask normal responses to systemic infection, which in turn could delay recognition and treatment or impede the normal immune response. These mechanisms, like others, are speculative.

The risks of other adverse outcomes such as bradycardia and hypotension were substantially higher in the metoprolol group. The authors also pointed out that most of the patients who suffered nonfatal strokes were subsequently disabled or incapacitated, while most of those who suffered nonfatal cardiac events did not progress to further cardiac problems.

This new study has not yet been rigorously debated, but it will likely come under scrutiny for its dosing regimen (extended-release metoprolol succinate 100 mg or placebo 2–4 hours before surgery; another 100 mg or placebo 6 hours after surgery or sooner if the heart rate was 80 beats per minute or more and the systolic blood pressure 100 mm Hg or higher; and then 200 mg or placebo 12 hours after the second dose and every 24 hours thereafter for 30 days). This was fairly aggressive, especially for patients who have never received a beta-blocker before. In contrast, the protocol for the Perioperative Beta-Blockade trial called for only 25 to 50 mg of short-acting metoprolol twice a day. Another criticism is that the medication was started only a few hours before surgery, although there is no current standard practice for either the dose or when the treatment should be started. The population had a fairly high rate of cerebrovascular disease (perhaps predisposing to stroke whenever blood pressure dropped), and 10% of patients were undergoing urgent or emergency surgery, which carries a higher risk of morbidity.

POISE results: Fewer myocardial infarctions but more deaths and strokes in patients on extended-release metoprolol succinate

ANY ROLE FOR BETA-BLOCKERS IN THOSE AT INTERMEDIATE RISK?

Thus, in the past decade, the appropriate perioperative use of beta-blockers, which, after the findings by Mangano et al and Poldermans et al, were seen as potentially beneficial for any patient at risk of coronary disease, with little suggestion of harm, has become more clearly defined, and the risks are more evident. The most compelling evidence in favor of using them comes from patients with ischemic heart disease undergoing vascular surgery; the 2007 ACC/AHA guidelines recommend that this group be offered beta-blockers in the absence of a contraindication (class I recommendation: benefit clearly outweighs risk).[6] The guidelines also point out that these drugs should be continued in patients already taking them for cardiac indications before surgery, because ischemia may be precipitated if a beta-blocker is abruptly discontinued.[42,43]

Additionally, the guidelines recommend considering beta-blockers for vascular surgery patients at high cardiac risk (with a Revised Cardiac Risk Index score of 3 or more), even if they are not known to have ischemic heart disease. This is a class IIa recommendation (the benefit outweighs the risk, but more studies are required).

To help patients at intermediate risk, we may need to see them up to 1 month before surgery

The guidelines also recommend that beta-blockers be considered for patients who have a score of 0 if they are undergoing vascular surgery (class IIb recommendation) or a score of 1 if they are undergoing vascular surgery (class IIa recommendation) or intermediate-risk surgery (class IIb recommendation). However, in view of the POISE results, these recommendations need to be carefully scrutinized.

These data notwithstanding, beta-blockers still might be beneficial in perioperative patients at intermediate risk.

Start beta-blockers sooner?

To help patients at intermediate risk (such as those with diabetes without known heart disease), we may need to do what Poldermans et al did[3]: instead of seeing patients only once a day or two before surgery, we may need to do the preoperative assessment as much as a month before and, if necessary, start a beta-blocker at a low dose, titrate it to a goal heart rate, and follow the patient closely up until surgery and afterward.

The importance of heart-rate control was illustrated in a recent cohort study of perioperative beta-blockers in vascular surgery patients,[44] in which higher beta-blocker doses, carefully monitored, were associated with less ischemia and cardiac enzyme release. In addition, long-term mortality rates were lower in patients with lower heart rates. And Poldermans et al[45] recently performed a study in more than 700 intermediate-risk patients who were divided into two groups, one that underwent preoperative stress testing and one that did not. Beta-blockers were given to both groups, and doses were titrated to a goal heart rate of less than 65. The patients with optimally controlled heart rates had the lowest event rates.

However, the logistics of such a program would be challenging. For the most part, internists and hospitalists involved in perioperative assessment do not control the timing of referral or surgery, and adjustments cannot be made for patients whose preoperative clinic visit falls only a few days before surgery. Instituting a second or third visit to assess the efficacy of beta-blockade burdens the patient and may not be practical.

Are all beta-blockers equivalent?

An additional factor is the choice of agent. While the most significant studies of perioperative beta-blockade have used beta-1 receptor-selective agents (ie, metoprolol, atenolol, and bisoprolol), there is no prospective evidence that any particular agent is superior. However, a recent retrospective analysis of elderly surgical patients did suggest that longer-acting beta-blockers may be preferable: patients who had been on atenolol in the year before surgery had a 20% lower risk of postoperative myocardial infarction or death than those who had been on short-acting metoprolol, with no difference in noncardiac outcomes.[46]

REFERENCES

1. **POISE Study Group.** Effect of extended-release metoprolol succinate in patients undergoing non-cardiac surgery (POISE trial): a randomised controlled trial. Lancet 2008; published online May 13. DOI:10.1016/S0140-6736(08)60601-7.
2. **Mangano DT, Layug EL, Wallace A, Tateo I.** Effect of atenolol on mortality

and cardiovascular morbidity after noncardiac surgery. Multicenter Study of Perioperative Ischemia Research Group. N Engl J Med 1996; 335:1713–1720.
3. **Poldermans D, Boersma E, Bax JJ, et al.** The effect of bisoprolol on perioperative mortality and myocardial infarction in high-risk patients undergoing vascular surgery. Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography Study Group. N Engl J Med 1999; 341:1789–1794.
4. **Shojania KG, Duncan BW, McDonald KM, Wachter RM, Markowitz AJ.** Making health care safer: a critical analysis of patient safety practices. Evid Rep Technol Assess (Summ) 2001; (43):i–x, 1–668.
5. **National Quality Forum.** Safe Practices for Better Healthcare—2006 update. Washington, DC: National Quality Forum, 2006.
6. **Fleisher LA, Beckman JA, Brown KA, et al.** ACC/AHA 2007 guidelines on perioperative cardiovascular evaluation and care for noncardiac surgery: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery). Circulation 2007; 116:1971–1996.
7. **Mangano DT.** Perioperative cardiac morbidity. Anesthesiology 1990; 72:153–184.
8. **Lee TH, Marcantonio ER, Mangione CM, et al.** Derivation and prospective validation of a simple index for prediction of cardiac risk of major noncardiac surgery. Circulation 1999; 100:1043–1049.
9. **Devereaux PJ, Goldman L, Cook DJ, Gilbert K, Leslie K, Guyatt GH.** Perioperative cardiac events in patients undergoing noncardiac surgery: a review of the magnitude of the problem, the pathophysiology of the events and methods to estimate and communicate risk. Can Med Assoc J 2005; 173:627–634.
10. **Fleischmann KE, Goldman L, Young B, Lee TH.** Association between cardiac and noncardiac complications in patients undergoing noncardiac surgery: outcomes and effects on length of stay. Am J Med 2003; 115:515–520.
11. **Landesberg G, Luria MH, Cotev S, et al.** Importance of long-duration postoperative ST-segment depression in cardiac morbidity after vascular surgery. Lancet 1993; 341:715–719.
12. **Mangano DT, Browner WS, Hollenberg M, London MJ, Tubau JF, Tateo IM.** Association of perioperative myocardial ischemia with cardiac morbidity and mortality in men undergoing noncardiac surgery. The Study of Perioperative Ischemia Research Group. N Engl J Med 1990; 323:1781–1788.
13. **Raby KE, Goldman L, Creager MA, et al.** Correlation between preoperative ischemia and major cardiac events after peripheral vascular surgery. N Engl J Med 1989; 321:1296–1300.
14. **Landesberg G, Mosseri M, Zahger D, et al.** Myocardial infarction after vascular surgery: the role of prolonged stress-induced, ST depression-type ischemia. J Am Coll Cardiol 2001; 37:1839–1845.
15. **Mangano DT, Browner WS, Hollenberg M, Li J, Tateo IM.** Long-term cardiac prognosis following noncardiac surgery. The Study of Perioperative Ischemia Research Group. JAMA 1992; 268:233–239.
16. **Kim LJ, Martinez EA, Faraday N, et al.** Cardiac troponin I predicts short-term mortality in vascular surgery patients. Circulation 2002; 106:2366–2371.
17. **Landesberg G, Shatz V, Akopnik I, et al.** Association of cardiac troponin, CK-MB, and postoperative myocardial ischemia with long-term survival after major vascular surgery. J Am Coll Cardiol 2003; 42:1547–1554.
18. **Badner NH, Knill RL, Brown JE, Novick TV, Gelb AW.** Myocardial infarction after noncardiac surgery. Anesthesiology 1998; 88:572–578.
19. **Priebe HJ.** Triggers of perioperative myocardial ischaemia and infarction. Br J Anaesth 2004; 93:9–20.
20. **Zaugg M, Schaub MC, Foex P.** Myocardial injury and its prevention in the perioperative setting. Br J Anaesth 2004; 93:21–33.
21. **Dawood MM, Gutpa DK, Southern J, Walia A, Atkinson JB, Eagle KA.** Pathology of fatal perioperative myocardial infarction: implications regarding pathophysiology and prevention. Int J Cardiol 1996; 57:37–44.
22. **Cohen MC, Aretz TH.** Histological analysis of coronary artery lesions in fatal postoperative myocardial infarction. Cardiovasc Pathol 1999; 8:133–139.
23. **London MJ, Zaugg M, Schaub MC, Spahn DR.** Perioperative beta-adrenergic receptor blockade: physiologic foundations and clinical controversies. Anesthesiology 2004; 100:170–175.
24. **Yeager MP, Fillinger MP, Hettleman BD, Hartman GS.** Perioperative beta-blockade and late cardiac outcomes: a complementary hypothesis. J Cardiothorac Vasc Anesth 2005; 19:237–241.
25. **Zaugg M, Schaub MC, Pasch T, Spahn DR.** Modulation of beta-adrenergic receptor subtype activities in perioperative medicine: mechanisms and sites of action. Br J Anaesth 2002; 88:101–123.
26. **Devereaux PJ, Yusuf S, Yang H, Choi PT, Guyatt GH.** Are the recommendations to use perioperative beta-blocker therapy in patients undergoing noncardiac surgery based on reliable evidence? Can Med Assoc J 2004; 171:245–247.
27. **Eagle KA, Froehlich JB.** Reducing cardiovascular risk in patients undergoing noncardiac surgery. N Engl J Med 1996; 335:1761–1763.
28. **Boersma E, Poldermans D, Bax JJ, et al.** Predictors of cardiac events after major vascular surgery: role of clinical characteristics, dobutamine echocardiography, and beta-blocker therapy. JAMA 2001; 285:1865–1873.
29. **Stevens RD, Burri H, Tramer MR.** Pharmacologic myocardial protection in patients undergoing noncardiac surgery: a quantitative systematic review. Anesth Analg 2003; 97:623–633.
30. **Goldman L.** Assessing and reducing cardiac risks of noncardiac surgery. Am J Med 2001; 110:320–323.
31. **Wesorick DH, Eagle KA.** The preoperative cardiovascular evaluation of the intermediate-risk patient: new data, changing strategies. Am J Med 2005; 118:1413.
32. **Auerbach AD, Goldman L.** Beta-blockers and reduction of cardiac events in noncardiac surgery: scientific review. JAMA 2002; 287:1435–1444.
33. **Devereaux PJ, Beattie WS, Choi PT, et al.** How strong is the evidence for the use of perioperative beta blockers in non-cardiac surgery? Systematic review and meta–analysis of randomized controlled trials. BMJ 2005; 331:313–321.
34. **Yang H, Raymer K, Butler R, Parlow JL, Roberts RS.** Metoprolol after vascular surgery (MaVS). Can J Anaesth 2004; 51(suppl 1):A7.
35. **Brady AR, Gibbs JS, Greenhalgh RM, Powell JT, Sydes MR.** Perioperative beta-blockade (POBBLE) for patients undergoing infrarenal vascular surgery: results of a randomized double-blind controlled trial. J Vasc Surg 2005; 41:602–609.
36. **Juul AB, Wetterslev J, Gluud C, et al.** Effect of perioperative β blockade in patients with diabetes undergoing major non-cardiac surgery: randomised placebo controlled, blinded multicentre trial. BMJ 2006; 332:1482.
37. **Lindenauer PK, Pekow P, Wang K, Mamidi DK, Gutierrez B, Benjamin EM.** Perioperative beta-blocker therapy and mortality after major noncardiac surgery. N Engl J Med 2005; 353:349–361.
38. **Feringa HH, Bax JJ, Schouten O, et al.** Beta-blockers improve in-hospital and long-term survival in patients with severe left ventricular dysfunction undergoing major vascular surgery. Eur J Vasc Endovasc Surg 2005; 31:351–358.
39. **Stone JG, Foex P, Sear JW, Johnson LL, Khambatta HJ, Triner L.** Myocardial ischemia in untreated hypertensive patients: effect of a single small oral dose of a beta-adrenergic blocking agent. Anesthesiology 1988; 68:495–500.
40. **Zaugg M, Tagliente T, Lucchinetti E, et al.** Beneficial effects from beta-adrenergic blockade in elderly patients undergoing noncardiac surgery. Anesthesiology 1999; 91:1674–1686.
41. **Wallace A, Layug B, Tateo I, et al.** Prophylactic atenolol reduces postoperative myocardial ischemia. McSPI Research Group. Anesthesiology 1998; 88:7–17.
42. **Psaty BM, Koepsell TD, Wagner EH, LoGerfo JP, Inui TS.** The relative risk of incident coronary heart disease associated with recently stopping the use of beta-blockers. JAMA 1990; 263:1653–1657.
43. **Shammash JB, Trost JC, Gold JM, Berlin JA, Golden MA, Kimmel SE.** Perioperative beta-blocker withdrawal and mortality in vascular surgical patients. Am Heart J 2001; 141:148–153.
44. **Feringa HHH, Bax JJ, Boersma E, et al.** High-dose beta-blockers and tight heart rate control reduce myocardial ischemia and troponin T release in vascular surgery patients. Circulation 2006; 114(suppl 1):I-344–I-349.
45. **Poldermans D, Bax JJ, Schouten O, et al.** Should major vascular surgery be delayed because of preoperative cardiac testing in intermediate-risk patients receiving beta-blocker therapy with tight heart rate control? J Am Coll Cardiol 2006; 48:964–969.
46. **Redelmeier D, Scales D, Kopp A.** Beta blockers for elective surgery in elderly patients: population based, retrospective cohort study. BMJ 2005; 331:932.

ADDRESS: *Brian Harte, MD, Department of Hospital Medicine, S70, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH 44195; e-mail harteb@ccf.org.*