β-Blockers and Reduction of Cardiac Events in Noncardiac Surgery

Scientific Review

Andrew D. Auerbach, MD, MPH
Lee Goldman, MD

Context Recent studies suggest that perioperatively administered β-blockers may reduce the risk of adverse cardiac events in patients undergoing major noncardiac surgery.

Objective To review the efficacy of perioperative β-blockade in reducing myocardial ischemia, myocardial infarction, and cardiac or all-cause mortality from randomized trials.

Data Sources A MEDLINE and conventional search of English-language articles published since 1980 was performed to gather information related to perioperative cardiac complications and β-blockade. Reference lists from all relevant articles and published recommendations for perioperative cardiac risk management were reviewed to identify additional studies.

Study Selection and Data Extraction Prospective randomized studies (6) were included in the analysis if they discussed the impact of β-blockade on perioperative cardiac ischemia, myocardial infarction, and mortality for patients undergoing major noncardiac surgery. Articles were examined for elements of trial design, treatment protocols, important biases, and major findings. These elements were then qualitatively compared.

Data Synthesis We identified 5 randomized controlled trials: 4 assessed myocardial ischemia and 3 reported myocardial infarction, cardiac, or all-cause mortality. All studies sought to achieve β-blockade before the induction of anesthesia by titrating doses to a target heart rate. Of studies reporting myocardial ischemia, numbers needed to treat were modest (2.5-6.7). Similarly modest numbers needed to treat were observed in studies reporting a significant impact on cardiac or all-cause mortality (3.2-8.3). The most marked effects were seen in patients at high risk; the sole study reporting a nonsignificant result enrolled patients with low baseline risk. As a group, studies of perioperative β-blockade have enrolled relatively few carefully selected patients. In addition, differences in treatment protocols leave questions unanswered regarding optimal duration of therapy.

Conclusions Despite heterogeneity of trials, a growing literature suggests a benefit of β-blockade in preventing perioperative cardiac morbidity. Evidence from these trials can be used to formulate an effective clinical approach while definitive trials are awaited.

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CARDIAC EVENTS SUCH AS MYOcardial infarction or cardiac death are common complications of surgery, occurring in 1% to 5% of unselected patients undergoing noncardiac surgery.[1-6] These events are associated with markedly increased mortality[7,8] and result in higher costs,[6,9] making them the most common reasons for preoperative evaluations.[10-12]

The prevalence of these events and their high mortality have made the prevention of perioperative cardiac events the subject of practice guidelines,[13] position papers,[14] and numerous prediction rules seeking to identify patients at high risk for cardiac complications.[5,7,15-20] Until recently, attempts to reduce the incidence of these complications depended on preoperative assessments of risk followed by clinical recommendations, including the option of postponing or canceling the surgical procedure.[13,14]

The evidence behind guidelines for testing or interventions, whether preoperative, intraoperative, or postoperative, was remarkably weak even as consensus approaches were developed for using treatments up to and including prophylactic coronary artery bypass surgery. Concern exists that preoperative intervention might prove detrimental because it remains unclear whether the benefit in reduced perioperative cardiac events is offset by the risks of revascularization itself.[13,14,21,22] Strategies including percutaneous transluminal angioplasty as the revascular-

See also p 1445.

Author Affiliations: Department of Medicine, University of California–San Francisco.
Corresponding Author and Reprints: Andrew D. Auerbach, MD, MPH, Department of Medicine, Box 0120, University of California–San Francisco, San Francisco, CA 94143-0120 (e-mail: ada@medicine.ucsf.edu).
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ization modality are promising[23]; large prospective trials examining these approaches are under way.

Strong evidence links myocardial ischemia with postoperative cardiac events.[24-28] One study found that postoperative ischemia increased the odds of postoperative myocardial events 21-fold.[29] As a result, medical strategies to reduce perioperative ischemia have been proposed. Studies using intraoperative calcium channel blockers[30,31] or intravenous nitroglycerin[32,33] provided mixed results. In contrast, small observational studies of β-blocking agents were more promising, with several suggesting that β-adrenoreceptor blockade blunted electrocardiographic signs of ischemia.[34-36] Extending this observation, several recent randomized trials have examined the effects of perioperative β-blocker administration on patient outcomes, including perioperative ischemia, myocardial infarction, and mortality. Results of these investigations may describe an important new method of reducing perioperative cardiac risk.

Methods

The details of our literature search methods have been described previously.[37] Studies were identified by searching the MEDLINE electronic bibliographic database. The search strategy was performed by using the Medical Subject Heading (MeSH) terms *perioperative care*, *postoperative complications*, *adrenergic antagonists*, *adrenergic β-antagonists*, *myocardial ischemia*, *myocardial infarction*, *mortality*, and *heart disease mortality*. In addition, we searched for key title words related to perioperative cardiac complications and adrenergic blockade and combined the results of these searches with MeSH terms. Reference lists from all relevant articles and published recommendations for perioperative cardiac risk management[13,14,38] were reviewed to identify additional studies.

To account for advances in perioperative medical, surgical, and anesthetic technique, we limited our search to investigations published since 1980. To focus on efficacy, we further limited our search to prospective randomized trials reporting the impact of β-blockade on perioperative cardiac ischemia, myocardial infarction, and mortality.

Because of the recognized difficulties in quality scoring of randomized trials,[39,40] we did not score the quality of trials meeting our inclusion criteria. However, the abstraction forms for each trial did include key elements pertaining to trial design, such as blinding, comparability of the intervention and control groups, completeness of follow-up, and important confounders or biases.

Our search strategy yielded 7 randomized trials of perioperative β-blockade. A randomized trial by Harwood et al[41] was excluded because both groups received β-blockers (ie, there was no control group). Although data from a study by Wallace et al[26] were derived from the study by Mangano et al,[42] the study reported effects of β-blockade on different outcomes (ie, myocardial ischemia) and was included as a subset of the same study in our review.

Thus, this review included 6 publications representing 5 trials studying

Table. Randomized Controlled Trials of the Effectiveness of Perioperative β-Blockade*

Source, y	Study Population and Eligibility	β-Blocker Regimen	Target Heart Rate
Mangano et al,[42] 1996; Wallace et al,[27] 1998	200 Patients undergoing elective noncardiac surgery according to several clinical criteria (see Box 1)	Atenolol, 5-10 mg intravenously 30 min before and after surgery and 50-100 mg/d by mouth throughout the hospital stay (up to 7 days)	55-65/min (doses held if rate <55/min or systolic blood pressure <100 mm Hg or if there was a defined adverse event)
Poldermans et al,[45] 1999	112 Patients with positive test results on dobutamine echocardiography and undergoing elective abdominal aortic or infrainguinal arterial reconstruction	Bisoprolol, 5-10 mg/d by mouth begun an average of 37 days preoperatively and continued for 30 days postoperatively	Intravenous metoprolol to target heart rate if patient not taking by mouth perioperatively; doses held if heart rate <50/min or systolic blood pressure <100 mm Hg
Raby et al,[37] 1999	26 Patients with preoperative ischemia by Holter monitor and undergoing aortic aneurysm repair, infrainguinal arterial bypass, or carotid endarterectomy	Esmolol, intravenous for 48 hours postoperatively	Titrate to heart rate 20% below ischemic threshold but no less than 60/min
Stone et al,[44] 1988	128 Untreated hypertensive (systolic blood pressure, 160-200 mm Hg; diastolic, 90-100 mm Hg) patients undergoing elective surgery	Labetalol, atenolol, oxprenolol; patients randomized to control, labetalol (100 mg by mouth), atenolol (50 mg by mouth), or oxprenolol (20 mg by mouth) given before induction of anesthesia	None described
Urban et al,[43] 2000	120 Patients undergoing elective knee arthroplasty according to the criteria of Mangano et al[42] (Box 1)	Esmolol intravenously within 1 hour after surgery; change to metoprolol the morning of the first postoperative day	<80/min (esmolol); <80/min for 48 hours postoperatively and then continue dose until discharge (metoprolol)

*MI indicates myocardial infarction; NS, not significant.
†All comparisons are presented as β-blocker vs control.

the effectiveness of perioperative β-blockade in reducing perioperative myocardial ischemia and cardiac or all-cause mortality (TABLE).

Study Interventions and Outcomes

Although studies used different agents, doses, and dosing schedules, the general approach in each study was similar: administration of a β-blocker before induction of anesthesia, followed by β-blockade throughout the operation and postoperative period. In all but one study, the dose was titrated to a target heart rate, generally 70/min or lower (Table).

The identified studies reported a range of clinical outcomes: 4 included assessment of myocardial ischemia,[26,36,43,44] and 3 reported myocardial infarction, pulmonary edema, cardiac death, or all-cause mortality.[42,44,45]

Evidence for Effectiveness of β-Blockade in Reducing Perioperative Cardiac Events

Of 4 studies reporting the effect of β-blockers on perioperative ischemia, all but 1 found a statistically significant reduction in ischemia among treated patients. Wallace et al,[26] in a subset analysis of data from Mangano et al,[46] reported less frequent perioperative myocardial ischemia in atenolol-treated patients. Stone et al[43] suggested a similar effect of β-blockade on Holter monitor–documented myocardial ischemia. However, the authors did not report the types of procedures included in their sample, nor did they statistically compare baseline patient characteristics, leaving their conclusions open to debate. Raby et al[36] also found a significant beneficial effect of β-blockade by using a continuous infusion of esmolol in high-risk patients undergoing vascular surgery. Although Urban et al[44] also found a reduction in perioperative ischemia, this difference failed to reach statistical significance. These findings may be explained in part by differences in the cardiac risk of this cohort, who were undergoing elective total knee replacement. In studies finding a statistical difference, rates of ischemia were between 28% and 73% in controls compared with the 15% rate of ischemia observed in this control group. In addition, the target heart rate of 80/min used in this study was substantially higher than that in other studies, suggesting that inadequate adrenergic blockade may have played a role in their findings.

Of studies reporting cardiac events and cardiac mortality, 2 reported significant improvement in patient outcomes because of β-blockade. In a study of male veterans at risk for coronary disease (BOX 1) and undergoing major noncardiac surgery, Mangano et al[42] observed no difference in in-hospital mortality caused by β-blockade. However, they observed a relative reduction in all-cause mortality of nearly 55% at 2 years. This difference, which appeared within the first 8 months of follow-up, was ascribed to a marked reduction in cardiac events in the first year of therapy (67% reduction at year 1, 48% at year 2). Patients in the β-blocker group had less coronary disease at study entry, were receiving angiotensin-converting enzyme inhibitors more frequently, and were less likely to have

Findings (Postoperative Ischemia/Other)	Number Needed to Treat	Adverse Events†	Comments
No differences in in-hospital cardiac or mortality outcomes. All-cause mortality at 2 years: 9% vs 21% (P = .02); cardiac death at 2 years: 4% vs 12% (P = .03); postoperative ischemia: 24% vs 39% (P = .03)	All-cause mortality at 2 years, 8.3; ischemia, 6.7	Intraoperative bradycardia more common with atenolol (38% vs 15%; P<.001) but no difference in need for treatment. No increase in third-degree heart block, hypotension, bronchospasm, or congestive heart failure	Included patients taking β-blockers long-term, most of whom (19% vs 8%) were in the β-blocker group
Reduced incidence of perioperative cardiac death and nonfatal MI. Cardiac death: 3.4% vs 17% (P = .02); nonfatal MI: 0% vs 17% (P<.001)	Cardiac death or nonfatal MI, 3.2	No exacerbations of peripheral vascular disease	Excluded patients taking β-blockers long-term
Postoperative myocardial ischemia: 33% vs 73% (P<.05)	2.5	No patient had β-blocker therapy suspended because of unacceptable adverse events	Physicians prescribe postoperative β-blockers more often in control groups (82% vs 13%; P<.05)
Postoperative MI: 2/89 (2%) vs 11/39 (28%) untreated (P<.001)	3.8	21 Patients taking β-blockers had bradycardia and half required atropine; no bradycardia in control patients	Patients had similar baseline characteristics, but these were not statistically compared. No description of surgeries performed
Postoperative ischemia: 6% vs 15% (NS); postoperative MI: 2% vs 6% (NS)	Not calculated	None noted	Included patients with long-term β-blocker use (30% in each treatment arm)

Box 1. Eligibility Criteria for Use of Perioperative β-Blockers

Minor Clinical Criteria (Adapted From Mangano et al[42])

Use β-blockers in patients meeting any 2 of the following criteria:
- Aged 65 years or older
- Hypertension
- Current smoker
- Serum cholesterol concentration at least 240 mg/dL (6.2 mmol/L)
- Diabetes mellitus not requiring insulin therapy

Revised Cardiac Risk Index Criteria[5]*

Use β-blockers in patients meeting any of the following criteria:

High-risk surgical procedure, defined as intraperitoneal, intrathoracic, or suprainguinal vascular procedure

Ischemic heart disease, defined as the following:
- History of myocardial infarction
- History of or current angina
- Use of sublingual nitroglycerine
- Positive exercise test results
- Q waves on electrocardiogram
- Patients who have undergone percutaneous transluminal coronary angioplasty or coronary artery bypass graft surgery and who have chest pain presumed to be of ischemic origin

Cerebrovascular disease, defined as the following:
- History of transient ischemic attack
- History of cerebrovascular accident

Diabetes mellitus requiring insulin therapy

Chronic renal insufficiency, defined as a baseline creatinine level of at least 2.0 mg/dL (177 μmol/L)

*Suggested by Boersma et al.[60] Congestive heart failure is also an element in the Revised Cardiac Risk Index but is not an indication for perioperative β-blockade.

β-blocker use discontinued postoperatively, perhaps biasing results in favor of the treatment group.[47,48] However, adjustment for these differences in multivariable models did not alter their findings.[46] Although acknowledging the limitations of their results in terms of generalizability to other patient populations and sites, the authors favored broader use of β-blockade in clinical trials.

Poldermans et al[45] found an even greater benefit of β-blockade among high-risk patients. These investigators enrolled patients who were to undergo vascular surgery and had myocardial ischemia documented by dobutamine echocardiography, with an estimated rate of major perioperative cardiac events of 28%. The entire patient cohort had experienced a 90% reduction in cardiac death or nonfatal myocardial infarction by 30 days. Follow-up care did not include additional therapy (ie, cardiac catheterization or revascularization), raising concerns that the research algorithm did not realistically reflect clinical practice.[49,50] However, if the true rate of events in β-blocker–treated patients is low (the point estimate from this small study was 3.4%), the risks associated with revascularization[51] may outweigh any incremental benefit.

In contrast to the previous 2 studies, the study by Urban et al[44] found no significant difference in rates of in-hospital myocardial infarction. It is likely that these investigators' ability to detect a difference was limited in part by the relatively small sample size and shorter length of follow-up. This study also included a large proportion of patients (30% in each group) who had been receiving β-blockers preoperatively; such patients were variably excluded from other trials. Patients who are β-blocker naive may have a different response to perioperative β-blockers, or long-term use of these agents may represent a confounding factor incompletely accounted for in other studies of perioperative β-blockade.

Differences in absolute magnitude of benefit can be ascribed in part to the cardiac risks of the patients enrolled (reflected in event rates in the control groups), with the greatest absolute benefits seen in patients at highest risk. That is, assuming a fixed relative benefit of β-blockade, the absolute differences in rates of adverse events will vary according to the baseline risk of the patients treated. For patients at extremely high risk, such as those enrolled by Poldermans et al,[45] the absolute reduction in risk was 30%, resulting in a number needed to treat of slightly more than 3. In contrast, Mangano et al[42] observed an 8% absolute risk reduction, suggesting that 9 patients would require therapy to reduce mortality at 2 years. Although not statistically significant, the 4% absolute reduction in risk (2% in treated patients vs 6% in control patients) observed by Urban et al[44] would result in a much larger number needed to treat, despite an approximately 33% reduction in risk.

Adverse Effects of Perioperative β-Blockade

Stone et al[43] reported high rates of bradycardia (21 of 89 patients) in β-blocker–treated patients, half of whom required atropine therapy. Adverse events related to the use of β-blockers in other reviewed studies were similarly infrequent. For example, 38% of β-blocker–treated subjects, compared with 15% of control subjects, had bradycardia intraoperatively, but other postoperative adverse events were rare and did not require discontinuation of the medication.[42] Similar rates of adverse effects have been noted in studies examining β-blockade in patients undergoing cardiac surgery.[41,52,53] One study examining the use of propranolol in patients undergoing thoracotomy for pneumonectomy suggested that patients receiving this nonselective β-blocker had

more frequent postoperative bradycardia (25% vs 4%; $P=.018$) and hypotension (49% vs 20%; $P=.003$); higher incidence of pulmonary edema (16% vs 8%; $P=.45$) was not statistically significant.[54]

The use of perioperative β-blockade in patients who had not been receiving β-blockers long-term may also pose an additional risk in that withdrawal of β-blockers may lead to adrenergic hypersensitivity and possibly worsen outcomes. A recent prospective observational study noted that patients who were not receiving β-blockers long-term but who discontinued perioperative use immediately after surgery had a markedly increased risk for postoperative myocardial infarction.[55] This effect was not observed in randomized trials of β-blockade that used shorter treatment regimens[36,43] and needs to be confirmed by larger studies. Alternatively, confusion about the use of β-blockade or discontinuity in postoperative care may lead to β-blockers' being inappropriately discontinued during hospitalization or afterward. Discontinuing β-blocker use in patients who have a longstanding indication for adrenergic blockade may lead to adverse outcomes perioperatively[56] or worsened patient survival.[57-59]

Clinical Questions

Which Patients Should Receive β-Blockers Perioperatively? Studies of perioperative β-blockade have been performed largely in selected patient populations with a risk of perioperative cardiac events that is higher, on average, than that of the general population of surgical patients. Thus, physicians must seek data from studies that included patients most akin to those they treat in practice. Although it has significant limitations, the study by Mangano et al[46] is the only one to enroll a reasonably broad spectrum of surgical patients. Thus, its criteria may represent a reasonable means of identifying patients who would benefit from β-blockade (Box 1), largely by excluding low-risk patients. This approach has been incorporated into the American College of Physicians guidelines.[14]

A recent observational study of patients undergoing vascular surgery suggested a clinical approach to the use of β-blockade. In this study, adjusted relative risk of postoperative cardiac events among patients receiving β-blockers was 0.3 (95% confidence interval [CI], 0.1-0.7) across strata of the Revised Cardiac Risk Index (Box 1),[60] an effect size similar to that seen in randomized trials. However, lowest-risk patients who had no Revised Cardiac Risk Index criteria received little benefit in absolute terms from β-blockers, while those at highest risk (3 or more criteria) remained at substantial risk even if treated with β-blockers. As an observational trial, these findings may be subject to confounding factors not accounted for in multivariable analyses and may not be generalizable to other groups.

The effectiveness of β-blockade in patients at high risk because of aortic stenosis or unstable or severe cardiovascular symptoms is unknown. It is likely that patients with severe cardiac symptoms caused by angina pectoris would benefit from β-blockade, but these patients have not been studied directly. The safety and effectiveness of new preoperative β-blockade in patients with a depressed ejection fraction is also unknown, since these patients were not included in randomized trials. β-Blockade has not been studied in patients undergoing regional anesthesia or conscious sedation. In addition, no study to date has directly examined the use of β-blockade in patients who have poor functional status and might otherwise be referred for additional noninvasive testing.[8,13,14,61] Patients who are at risk because of high-grade conduction system disease have an absolute contraindication to β-blockade and require different management strategies.

The effectiveness of β-blockade in terms of costs or outcomes in patients at low risk is unclear. Results from Boersma et al[60] suggest that β-blockade provides little additional benefit in patients with no clinical risk factors. Thus, it seems likely that patients who are undergoing low-risk procedures (eg, those undergoing same-day or outpatient surgery or ophthalmic surgery) and have no or minimal cardiac risk factors may be as likely to experience adverse effects from β-blockers as to experience a cardioprotective benefit.

β-Blockade may have additional beneficial effects for elderly patients. In one study, patients who received β-blockers were extubated more quickly, required less medication for pain, and were more alert sooner after surgery.[62] Although the unblinded nature of this study leaves its findings open to debate, the possibility of additional benefits is tantalizing and worthy of further investigation.

Which β-Blocking Agent Should Be Used? All studies showing benefit of β-blockade on mortality and myocardial ischemia have used β_1-selective agents. Nonselective agents such as propranolol, although likely to have a similar impact on myocardial oxygen demand if titrated appropriately, are more likely to produce adverse pulmonary effects[63,64] and in fact caused more bronchospasm in one study of perioperative propranolol.[54]

No evidence suggests an advantage of any particular β_1-selective β-blocker. Studies to date have used several agents, suggesting that the efficacy of β-blockade is class rather than drug dependent. Blocking or blunting adrenergic responses is the key pathophysiologic step connecting β-blockers to improved outcomes, and evidence suggests that physicians may choose any medication that meets this physiologic goal.

Patients who are receiving long-term β-blocker therapy need not begin taking one of the drugs used in published studies instead. Evidence from Mangano et al[42] and Urban et al[44] support using additional intravenous agents, whether an additional dose of the patient's long-term medication or another β-blocker, immediately perioperatively, but no evidence supports exchanging one agent for another.

Are Other Adrenergic Blocking Agents Effective? Selective sympatholytics (α_2) may also improve patient outcomes. Clonidine has been suggested to

lower blood pressure, heart rate, and norepinephrine levels in patients undergoing surgery, factors considered key in preventing myocardial ischemia.[65,66] In fact, one study of 297 patients undergoing vascular surgery suggested that clonidine-treated patients had fewer episodes of ischemia.[67] In a recent study, mivazerol, an α_2-agonist that reduces postganglionic noradrenaline availability and spinal efferent sympathetic output, reduced the incidence of perioperative ischemia.[68] A subsequent large randomized trial of 1897 patients undergoing noncardiac surgery produced mixed results, however.[69] In the whole cohort, mivazerol had no statistically significant effect on all-cause mortality or myocardial infarction, but cardiac mortality was reduced by half (relative risk of events among treated patients, 0.50; 95% CI, 0.25-0.96). In planned subgroup analyses, a more marked impact was observed among patients undergoing vascular surgery, where the relative risk of postoperative myocardial infarction and death among treated patients was 0.67 (95% CI, 0.45-0.98), and the relative risk for cardiac death was 0.32 (95% CI, 0.12-0.76).[69] Although mivazerol is not available in the United States, findings from this study support the central role of adrenergic blockade in preventing cardiac events.

No data to date suggest that α_1-selective blocking agents provide any benefit to patients perioperatively, and use of these agents alone is not supported by current evidence. Patients receiving α_1 blockers long-term would likely benefit from the addition of β-blocking agents perioperatively.

When Should β-Blocker Use Be Started Preoperatively and When Should It Be Discontinued? Although questions remain regarding the optimal dosing schedule for perioperative β-blocker therapy, investigations showing a positive effect sought to achieve sympatholysis before induction of anesthesia. Thus, physicians should try to begin therapy early enough so that doses can be titrated appropriately. The time required to meet this goal may vary, depending on the agent, the route of administration, or patient factors, but it is clear that a physiologic dose of β-blocker must be administered for any positive impact to be appreciated. For example, intravenous atenolol, as used by Mangano et al,[42] may be administered and titrated to a physiologic dose in the preanesthesia holding area or even the operating room. Physicians who choose to begin β-blocker therapy orally may require additional lead time for patients to reach the target heart rate. In fact, patients in Poldermans' study[45] began oral therapy 1 month before surgery, on average, with titration of the dose performed at a visit 1 week after initiation of bisoprolol.

Postoperatively, most protocols extended beyond the first postoperative day and even up to 1 month after surgery. Nonrandomized data from Shammash et al[55] and previous case reports suggest the hazards of discontinuation of β-blockers immediately postoperatively. A recent study suggested that, among vascular surgery patients who had not been receiving β-blockers long-term, continuing β-blockade up to 3 years after surgery reduced cardiac mortality.[70] Although tantalizing, these results are based on a small number of patients (n=112) with a high burden of cardiovascular illness and need to be reproduced in larger, less selected cohorts.

The safest conclusion to be drawn from current studies is that β-blocker use should begin before surgery, even up to a month before the procedure, with titration of the dose taking place as an outpatient procedure and up to the induction of anesthesia. Therapy should be continued at least through hospitalization, and longer if adequate medical follow-up can be arranged postoperatively. Close follow-up is particularly important in the care of patients who were not receiving β-blockers long-term before surgery so that the drug dose can be tapered if long-term use is not indicated. Follow-up is also imperative for patients receiving β-blockers for medical reasons so that continuity in their medication is maintained.

Ample evidence suggests that long-term β-blocker therapy is underused in patients with definitive indications.[71-77] Thus, the perioperative period may represent an opportunity to begin β-blocker therapy in appropriate patients, such as those with a history of myocardial infarction.

Long-term use of β-blockade for patients with heart failure has been clearly shown to improve patient mortality,[78] and these patients might also be identified perioperatively. However, guidelines for administration of these agents in patients with heart failure require close monitoring,[79] and the doses administered are usually far lower and not titrated to heart rate. β-Blockade in these patients, therefore, should not be routinely started for prophylaxis perioperatively.

In Which Patients Should Additional Cardiac Risk Stratification Be Pursued? Data describing the effectiveness of β-blockade, especially the results of the study by Poldermans et al,[45] have made some authors wonder whether risk stratification is still necessary.[49] However, β-blockers alone may not reduce the risk of postoperative cardiac events below thresholds suggested in the American College of Physicians[14] or American Heart Association/American College of Cardiology risk stratification guidelines.[13] In the study by Boersma et al,[60] patients who were in the highest risk strata (5 or more points according to the Revised Cardiac Risk Index of Lee et al)[5] and received β-blockers continued to have an estimated cardiac event rate of 14%; these authors suggested that patients with more than 3 clinical predictors (3.4% rate of postoperative cardiac events) be referred for additional risk stratification using noninvasive testing. Thus, although β-blockade may increase the threshold at which physicians refer patients for additional testing, the era of risk stratification is not over.

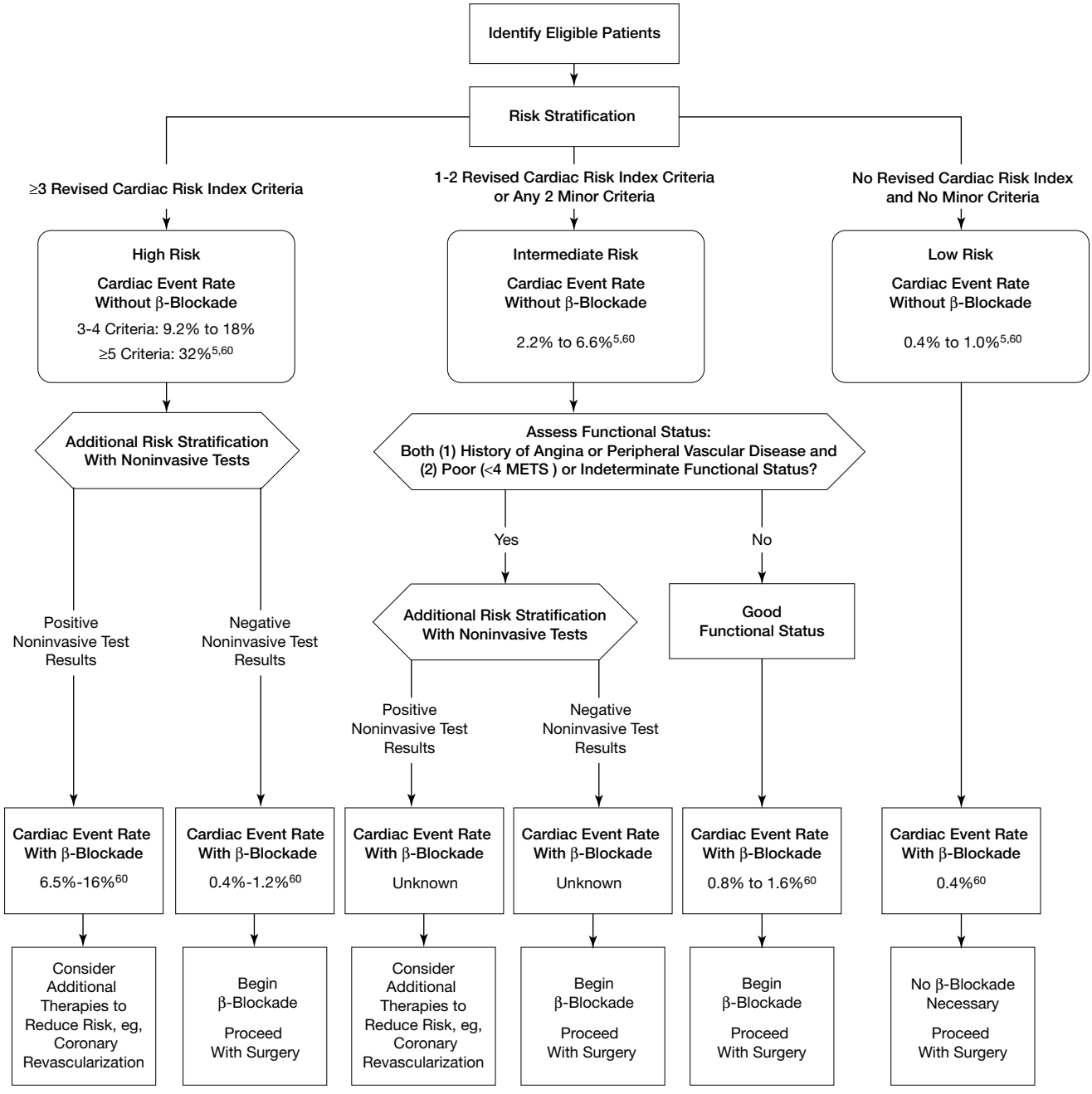
Perioperative β-Blockade: A Suggested Algorithm

Although the literature to date has gaps and areas of uncertainty, there is ample evidence to suggest a clinical approach to the patient undergoing elec-

tive surgery. We have synthesized the results of our literature review into a clinical algorithm (FIGURE), a set of patient selection criteria (Box 1), and a list of suggested medications, routes, and dosages (BOX 2).

As in the era before β-blockers, the initial approach to the patient should include risk stratification according to

Figure. Perioperative β-Blockers: Patient Selection and Preoperative Risk Stratification



Revised Cardiac Risk Index criteria[5] and minor clinical criteria adapted from Mangano et al[42] are listed in Table 2. Revised Cardiac Risk Index criteria exclude patients with congestive heart failure because the safety and efficacy of perioperative β-blockers has not been proven in these patients. Cardiac event rates with and without β-blockade are ranges based on rates from Lee et al[5] for cardiovascular complications observed in the validation set (those in the derivation set were somewhat lower) and on estimates from Boersma et al.[60] Options for noninvasive testing for further risk stratification include dipyramidole thallium scintigraphy, stress echocardiography, exercise electrocardiography, or cardiac catheterization in appropriate patients. Examples of activities that expend about 4 METS (metabolic equivalent tasks) include climbing 1 flight of stairs, being able to walk on level ground at 4 mph, or being able to climb a short hill without difficulty.

Box 2. Perioperative β-Blockers: Agents and Regimens

Prehospitalization (Outpatients) or Immediately Following Admission to Hospital

Not taking β-blockers long-term
- Atenolol, 50-100 mg, perioperatively every day[42] or bisoprolol, 5-10 mg, perioperatively every day[45]
- Begin as outpatient up to 30 days before surgery
- Titrate to heart rate of ≤65/min

Taking β-blockers long-term
- Continue long-term therapy
- Titrate heart rate to ≤65/min, if needed

Immediate Postoperative Period (ie, in Preanesthesia Holding Area)

Atenolol, 5-10 mg, intravenously to reach target heart rate before introduction of anesthesia, if needed,[42] whether β-blockers are taken long-term or not

Immediate Postoperative Period and Transition to Oral Medications, Whether β-Blockers Are Taken Long-term or Not

Patient not taking oral medications and hemodynamically stable
- Atenolol, 5-10 mg, intravenously twice daily to target heart rate[42]

Patient unstable, eg, high bleeding risk or in the intensive care unit
- Esmolol, 500 μg/kg, intravenously for 1 minute and then infusion of 50-200 μg/kg per minute to target heart rate[37,43]

Patient taking oral medications
- Resume perioperative β-blocker use at previous dose; titrate as necessary to target heart rate
- Overlap first oral dose with continued intravenous agents to maintain target heart rate, if necessary

clinical criteria. As described, there are numerous risk stratification strategies available to physicians, many of which have published information regarding test characteristics and accuracy. There is little reason to suspect that other risk indices could not be used similarly, but only 1 study has explicitly reported the use of any risk-stratification method in the context of β-blocker use.[60] This study used the Revised Cardiac Risk Index of Lee et al[5] to identify high-, intermediate-, and low-risk groups and suggested a strategy for further testing or use of β-blockers. The criteria of Mangano et al[42] provide an alternative approach to choosing patients, largely by excluding patients at lowest risk, but do not identify patients who require further risk stratification alone.

The first step in risk stratification is to identify patients who are at lowest risk (those whose estimated risk for perioperative cardiac events is less than 1% without β-blockers) and those at highest risk (those whose estimated risk is higher than 10%). Using β-blockers in patients at low risk (0 Revised Cardiac Risk Index criteria and none of the cardiac risk factors in Mangano et al[42]; Box 1) imparts little absolute benefit, and surgery can proceed without addition of this medication. In contrast, patients at highest risk (3 or more Revised Cardiac Risk Index criteria) require additional risk stratification using noninvasive or invasive testing. Although the study by Boersma et al[60] used dobutamine echocardiography to identify highest-risk patients, other noninvasive testing and even coronary angiography may be substituted according to published guidelines.[13] As described, the utility of preoperative revascularization remains unclear, except in patients with an indication for these procedures in the absence of the planned surgical procedure. We recommend noninvasive testing only in higher-risk patients and in moderate-risk patients whose exercise capacity cannot be determined by history, a much narrower use of testing than recommended by some[80] but consistent with the recommendations of others.[13,14]

Patients who are at high risk and have negative noninvasive testing results and those at intermediate risk (1-2 Revised Cardiac Risk Index criteria) should begin taking a β-blocker if not taking one long-term (Box 2). Optimally, medications should be started before hospitalization and, if possible, as long as 30 days before surgery. This period, used in the study by Poldermans et al,[45] will allow for adequate titration of the medication to the target heart rate. Patients receiving β-blockers long-term should have their dose evaluated and adjusted appropriately as outpatients. Dose titration up to induction of anesthesia may be performed with intravenous atenolol[38] in all patients.

Postoperatively, oral β-blocker use should be restarted as soon as possible, with intravenous atenolol[42] used for stable patients who are unable to take medications orally. Patients who are unstable should receive a short-acting intravenous β-blocker such as esmolol until they are able to tolerate longer-acting oral medications. The transition to oral medications should overlap with intravenous medications to maintain a target heart rate. Oral β-blocker use should be continued at least through hospitalization and up to 1 month postoperatively, when a gradual reduction in the dose can be initiated in patients without an indication for long-term therapy. As mentioned, the postoperative visit may also represent an opportunity to begin long-term β-blocker therapy in appropriate patients.

Conclusions

Results from several well-designed clinical trials suggest that use of β-blockers perioperatively is associated with significant reductions in cardiac morbidity and mortality. However, as a group, studies that support their use are

relatively small, with a total enrollment of fewer than 700 patients. In addition, these studies often included patients who were selected and not consecutively recruited, making generalizability of their results difficult. No randomized study to date has compared the impact of β-blockade in an unselected population of patients undergoing surgery, so there is little direct evidence describing the impact of β-blockers in average patients, such as those who have stable coronary disease and are undergoing elective surgery. β-Blocker therapy may reduce the need for additional tests and revascularization procedures,[8] further reducing costs of care, but wider use of this therapy will be better supported if findings from existing studies are replicated in large randomized trials. Studies are also required to answer questions regarding optimal duration of therapy, identify populations of patients in which β-blocker use is cost-effective, and allow for development of new perioperative risk-management algorithms that reflect the impact of β-blockers on patient outcomes.

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