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ACC/AHA PRACTICE GUIDELINES

ACC/AHA 2006 Guideline Update on Perioperative Cardiovascular Evaluation for Noncardiac Surgery: Focused Update on Perioperative Beta-Blocker Therapy

A Report of the American College of Cardiology/ American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2002 Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery)

Developed in Collaboration With the American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Rhythm Society, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, and Society for Vascular Medicine and Biology

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PREAMBLE

The American College of Cardiology/American Heart Association (ACC/AHA) Task Force on Practice Guidelines makes every effort to avoid any actual, potential, or perceived conflict of interest that might arise as a result of an industry relationship or personal interest of the writing committee. Specifically, all members of the writing committee, as well as peer reviewers of the document, were asked to provide disclosure statements of all such relationships that might be perceived as real or potential conflicts of interest. These statements are reviewed by the parent task force, reported orally to all members of the writing committee at each meeting, and updated and reviewed by the writing committee as changes occur. Please see Appendix 1 for author relationships with industry and Appendix 2 for peer reviewer relationships with industry.

These guidelines attempt to define practices that meet the needs of most patients in most circumstances. These guideline recommendations reflect a consensus of expert opinion after a thorough review of the available, current scientific evidence and are intended to improve patient care. If these guidelines are used as the basis for regulatory/payer decisions, the ultimate goal is quality of care and serving the patient's best interests. The ultimate judgment regarding care of a particular patient must be made by the healthcare provider and patient in light of all the circumstances presented by that patient.

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1. INTRODUCTION

1.1. Purpose of the Expedited Update

Since the publication of the previous guidelines on perioperative cardiovascular evaluation for noncardiac surgery in 2002, the issue of perioperative beta blockade for non-cardiac surgery has taken on increased importance. Specifically, the Physicians Consortium for Performance Improvement and the Surgical Care Improvement Project have both identified perioperative beta blockade as a quality measure. Given the importance of these quality measures for both public reporting and eventual pay-for-performance, and the recent series of publications on the subject, it became imperative to update the recommendations related to beta blockade. Therefore, we have chosen to expedite the review of the literature on perioperative beta blockade in order to produce recommendations that can be used in these national quality initiatives. In general, ACC/AHA Class I and III indications for therapy identify potential dimensions of care and processes for performance measurement; however, not all Class I and III guidelines recommendations should be selected for performance measurement (1). Furthermore, Class IIa and Class IIb recommendations are not considered for stand-alone measures.

Please note that the full 2002 Guideline on Perioperative Cardiovascular Evaluation for Noncardiac Surgery is being updated and represents current ACC/AHA policy, with the exception of the text and tables in the perioperative beta-blocker therapy section. This focused update replaces the beta-blocker section in the 2002 Guideline and is considered current ACC/AHA policy until the update of the full guideline is published. Please note that Table 2, "Clinical Predictors of Increased Perioperative Cardiovascular Risk," is currently under review and may be modified as part of the update of the full guideline.

1.2. Organization of Committee and Evidence Review

The Committee to Update the 2002 Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery: Focused Update on Perioperative Beta-Blocker Therapy reviewed the literature relevant to perioperative cardiac evaluation since the last publication of these guidelines in 2002. Literature searches were conducted in PubMed/MEDLINE. Searches were limited to the English language, 2002 through 2006, and human subjects. In addition, related-article searches were conducted in MEDLINE to find further relevant articles. Finally, committee members recommended applicable articles outside the scope of the formal searches.

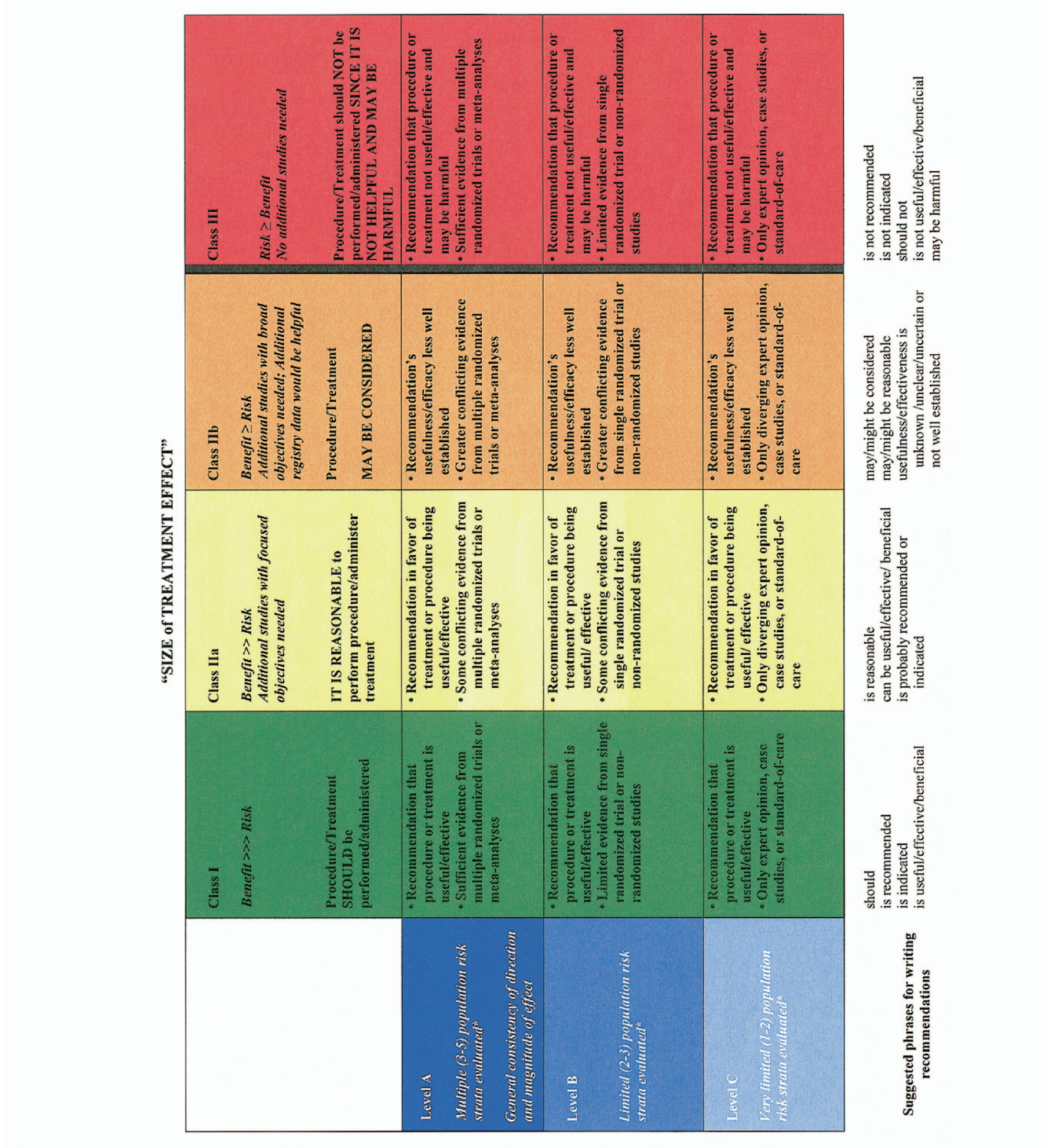
As a result of these searches, 23 published articles and 1 abstract were identified and reviewed by the committee for the expedited update of the Beta-Blocker section. Using evidence-based methodologies developed by the ACC/AHA Task Force on Practice Guidelines, the committee updated the guideline text and recommendations.

These classes summarize the recommendations for procedures or treatments as follows:

- Class I: Conditions for which there is evidence for and/or general agreement that the procedure or treatment is beneficial, useful, and effective.
- Class II: Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure or treatment.
  - Class IIa: Weight of evidence/opinion is in favor of usefulness/efficacy.
  - Class IIb: Usefulness/efficacy is less well established by evidence/opinion.
- Class III: Conditions for which there is evidence and/or general agreement that the procedure/treatment is not useful/effective, and in some cases may be harmful.

In addition, the weight of evidence in support of the recommendation is listed as follows:

- Level of Evidence A: Data derived from multiple, randomized, clinical trials.
- Level of Evidence B: Data derived from a single-randomized trial or non-randomized studies.



*Data available from clinical trials or registries about the usefulness/efficacy in different subpopulations, such as gender, age, history of diabetes, history of prior MI, history of heart failure, and prior aspirin use. A recommendation with Level of Evidence B or C does not imply that the recommendation is weak. Many important clinical questions addressed in the guidelines do not lend themselves to clinical trials. Even though randomized trials are not available, there may be a very clear clinical consensus that a particular test or therapy is useful or effective.

†In 2003, the ACC/AHA Task Force on Practice Guidelines developed a list of suggested phrases to use when writing recommendations. All guideline recommendations have been written in full sentences that express a complete thought, such that a recommendation, even if separated and presented apart from the rest of the document (including headings above sets of recommendations), would still convey the full intent of the recommendation. It is hoped that this will increase readers' comprehension of the guidelines and will allow queries at the individual recommendation level.

Figure 1. Applying classification of recommendations and level of evidence.

Table 1. Recommendations for Perioperative Beta-Blocker Therapy Based on Published Randomized Clinical Trials

	Low Cardiac Patient Risk	Intermediate Cardiac Patient Risk	CHD or High Cardiac Patient Risk
			Patients found to have myocardial ischemia on preoperative testing
Vascular Surgery	Class IIb Level of Evidence: C	Class IIb Level of Evidence: C	Class I* Level of Evidence: B Class IIa† Level of Evidence: B
High-/Intermediate-Risk Surgery	‡	Class IIb Level of Evidence: C	Class IIa Level of Evidence: B
Low-Risk Surgery	‡	‡	‡

*Applies to patients found to have coronary ischemia on preoperative testing. †Applies to patients found to have coronary heart disease. ‡Indicates insufficient data. See text for further discussion.
CHD = coronary heart disease.

- Level of Evidence C: Only consensus opinion of experts, case studies, or standard-of-care.

A recommendation with Level of Evidence B or C does not imply that the recommendation is weak. Many important clinical questions addressed in guidelines do not lend themselves to clinical trials. Although randomized trials are not available, there may be a very clear clinical consensus that a particular test or therapy is useful and effective. The schema for classification of recommendations and level of evidence is summarized in Figure 1, which also illustrates how the grading system provides an estimate of the size of the treatment effect and an estimate of the certainty of the treatment effect.

Please note the use of bold-faced type in the recommendations shows where the intent of the recommendation has changed from the 2002 ACC/AHA Guideline Update on Perioperative Cardiovascular Evaluation for Noncardiac Surgery. The bold-faced type only highlights changes to the recommendations; it does not show changes to supporting text, tables, and figures.

The Committee consisted of acknowledged experts in general cardiology as well as persons with recognized expertise in more specialized areas including anesthesiology, cardiovascular surgery, echocardiography, electrophysiology, interventional cardiology, nuclear cardiology, vascular medicine, and vascular surgery; both academic and private sectors were represented. The following organizations assigned official representatives: the Society for Vascular Medicine and Biology, American Society of Nuclear Cardiology, Heart Rhythm Society, Society for Vascular Surgery, American Society of Echocardiography, Society of Cardiovascular Anesthesiologists, and the Society for Cardiovascular Angiography and Interventions.

This document was reviewed by 2 official reviewers nominated by the ACC; 2 official reviewers nominated by the AHA; 1 official reviewer from the ACC/AHA Task Force on Practice Guidelines as well as reviewers from the Society for Vascular Medicine and Biology, American Society of Nuclear Cardiology, Heart Rhythm Society, American Society of Echocardiography, Society of Cardiovascular Anesthesiologists, and the Society for Cardiovascular Angiography and Interventions; and 20 content reviewers, including members from American College of Cardiology Foundation (ACCF) Cardiac Catheterization Committee, ACCF Peripheral Vascular Disease Committee, ACCF Cardiovascular Clinical Imaging Committee, ACCF Echocardiography Committee, ACCF Clinical Electrophysiology Committee, AHA Council on Cardiopulmonary Perioperative and Critical Care Leadership Committee, AHA Council on Cardiovascular Surgery and Anesthesia Leadership Committee, and the AHA Council on Clinical Cardiology, Electrocardiography, and Arrhythmias Committee.

2. PERIOPERATIVE MEDICAL THERAPY

2.1. Perioperative Beta-Blocker Therapy

Recommendations for Beta-Blocker Medical Therapy (Table 1):

Class I

1. Beta blockers should be continued in patients undergoing surgery who are receiving beta blockers to treat angina, symptomatic arrhythmias, hypertension, **or other ACC/AHA Class I guideline indications.** ***(Level of Evidence: C)***
2. Beta blockers should be given to patients undergoing vascular surgery at high cardiac risk owing to the finding of ischemia on preoperative testing. ***(Level of Evidence: B)***

Class IIa

1. Beta blockers are probably recommended for patients undergoing vascular surgery in whom preoperative assessment identifies coronary heart disease. ***(Level of Evidence: B)***
2. **Beta blockers are probably recommended for patients in whom preoperative assessment for vascular surgery identifies high cardiac risk as defined by the presence of multiple clinical risk factors.*** ***(Level of Evidence: B)***

Table 2. Clinical Predictors of Increased Perioperative Cardiovascular Risk (Myocardial Infarction, Heart Failure, Death)

Major
Unstable coronary syndromes
• Acute or recent MI* with evidence of important ischemic risk by clinical symptoms or noninvasive study
• Unstable or severe† angina (Canadian Class III or IV)‡
Decompensated heart failure
Significant arrhythmias
• High-grade atrioventricular block
• Symptomatic ventricular arrhythmias in the presence of underlying heart disease
• Supraventricular arrhythmias with uncontrolled ventricular rate
Severe valvular disease
Intermediate
Mild angina pectoris (Canadian Class I or II)
Previous MI by history or pathological Q waves
Compensated or prior heart failure
Diabetes mellitus (particularly insulin-dependent)
Renal insufficiency
Minor
Advanced age
Abnormal ECG (left ventricular hypertrophy, left bundle-branch block, ST-T abnormalities)
Rhythm other than sinus (e.g., atrial fibrillation)
Low functional capacity (e.g., inability to climb one flight of stairs with a bag of groceries)
History of stroke
Uncontrolled systemic hypertension

*The American College of Cardiology National Database Library defines *recent MI* as greater than 7 days but less than or equal to 1 month (30 days); acute MI is within 7 days. †May include "stable" angina in patients who are unusually sedentary. ‡Campeau et al. (2).

ECG = electrocardiogram; MI = myocardial infarction.

3. **Beta blockers are probably recommended for patients in whom preoperative assessment identifies coronary heart disease or high cardiac risk as defined by the presence of multiple clinical risk factors* and who are undergoing intermediate- or high-risk procedures as defined in these guidelines.** ***(Level of Evidence: B)***

Class IIb

1. **Beta blockers may be considered for patients who are undergoing intermediate- or high-risk procedures as defined in these guidelines, including vascular surgery, in whom preoperative assessment identifies intermediate cardiac risk as defined by the presence of a single clinical risk factor.*** ***(Level of Evidence: C)***
2. **Beta blockers may be considered in patients undergoing vascular surgery with low cardiac risk (as defined in these guidelines) who are not currently on beta blockers.** ***(Level of Evidence: C)***

Class III

1. Beta blockers should not be given to patients undergoing surgery who have absolute contraindications to beta blockade. *(Level of Evidence: C)*

Please see Table 2, Clinical Predictors of Increased Perioperative Cardiovascular Risk, for an explanation of the clinical risk factors. High cardiac risk includes patients with major and intermediate clinical predictors. Care should be taken in applying recommendations on beta-blocker therapy to patients with decompensated heart failure, nonischemic cardiomyopathy, high-degree AV block, or severe valvular heart disease in the absence of coronary heart disease.

2.1.1. Summary of evidence. Despite several meta-analyses, some reaching conflicting conclusions, there are still very few randomized trials of medical therapy before noncardiac surgery to prevent perioperative cardiac complications. The studies that have been conducted in this area have largely focused on beta-blocker therapy; however, there remain many limitations to the available data. Few studies have compared different beta-blocker agents or characterized their dose effect in the perioperative setting. Even fewer have included a protocol for the titration of therapy to effect (e.g., target heart rate), or examined regimens that include a preoperative trial of beta-blocker therapy. Studies to determine the ideal target population, ideal dose, and route are lacking. In addition, the practical limitations such as how, when, how long, and by whom perioperative beta-blocker therapy is ideally or practically implemented remain unaddressed. Randomized, controlled trials are still needed to explore the observation that there may be some harm associated with beta-blocker therapy in low-risk patients (3). Moreover, there is currently a lack of data regarding which beta blocker to use perioperatively. Some observational data suggest that perioperative death or myocardial infarction (MI) rates may differ when different beta-blockers are given perioperatively (4). In summary, the best approach on how to medically protect patients from cardiovascular complications during noncardiac surgery is still unknown.

Limitations in the Perioperative Beta-Blocker Literature:

- Most trials are inadequately powered.
- Few randomized trials of medical therapy to prevent perioperative major adverse cardiac events have been performed.
- Few randomized trials have examined titration of therapy to effect (e.g., target heart rate).
- Few randomized trials have examined the role of perioperative beta-blocker therapy.
- Studies to determine the role of beta blockers in intermediate- and low-risk populations are lacking.
- Studies to determine the optimal type of beta blockers are lacking.
- No studies have addressed care-delivery mechanisms in the perioperative setting, identifying how, when, and by whom perioperative beta-blocker therapy should be implemented and monitored.

Although many of the randomized, controlled trials of beta-blocker therapy are small, the weight of evidence—especially in aggregate—suggests a benefit to perioperative beta blockade during noncardiac surgery, particularly in high-risk patients. Current studies suggest that beta block-

ers reduce perioperative ischemia and may reduce the risk of MI and death in high-risk patients. Available evidence suggests, but does not definitively prove that, when it is possible, beta blockers should be started several days or weeks before elective surgery, with the dose titrated to achieve a resting heart rate between 50 and 60 beats per min, to assure that the patient is indeed receiving the benefit of beta blockade and should continue during the intraoperative and postoperative period to maintain a heart rate less than 80 beats per min (5). Several prospective, randomized trials are either underway or soon to be presented. These will hopefully shed light on some of the questions regarding perioperative beta-blocker therapy. Per the ACC/AHA Task Force on Practice Guidelines methodology, unpublished data cannot be used to formulate guideline recommendations.

Two randomized trials examined the effect of perioperative beta blockers on cardiac events surrounding surgery. Poldermans et al. (5) examined the effect of bisoprolol on patients undergoing vascular surgery and in patients at high-risk for perioperative cardiac complications scheduled for vascular surgery. Of 846 patients with risk factors for cardiac disease, 173 patients were found to have new regional wall motion abnormalities (RWMA) on dobutamine stress echocardiogram (DSE). Of these patients, 61 were excluded from further study owing to large areas (greater than or equal to 5 segments) of RWMA on DSE or because they were already taking beta blockers. The remaining 112 high-risk patients were randomized to standard care or bisoprolol started at least 7 days preoperatively and titrated to maintain heart rate less than 60 beats per min preoperatively and less than 80 beats per min intraoperatively and postoperatively. The rates of cardiac death (3.4% vs. 17%; $p = 0.02$) and nonfatal MI (0% vs. 17%; p less than or equal to 0.001) were lower for the bisoprolol versus placebo groups, respectively. Importantly, due to the unblinded design and inclusion of only high-risk patients in this study, the results cannot be generalized to all patients undergoing noncardiac surgery.

Boersma et al. (6) subsequently reanalyzed the total cohort of 1,351 consecutive patients considered for enrollment in the aforementioned randomized trial of bisoprolol. Forty-five patients had perioperative cardiac death or nonfatal MI. A total of 83% of patients had fewer than three clinical risk factors. Among this subgroup, patients receiving beta blockers had a lower risk of cardiac complications (0.8% [2 of 263]) than those not receiving beta blockers (2.3% [20 of 855]). In patients with three or more risk factors (17%), those taking beta blockers who had a DSE demonstrating four or fewer segments of new wall-motion abnormalities had a significantly lower incidence of cardiac complications (2.3% [2 of 86]) compared with those not receiving beta-blocker therapy (9.9% [12 of 121]). However, among the small group of patients with more extensive ischemia on DSE (five or more segments), there was no difference in the incidence of cardiac events (4 of 11 for those taking beta blockers versus 5 of 15 for those not taking beta blockers). Therefore, beta-blocker therapy was beneficial in all but the subset of patients with more extensive ischemia. Nevertheless, one must be cautious about inferring a class effect from this observation about bisoprolol and treatment protocol.

The Multicenter Study of Perioperative Ischemia research group (7,8) reported on 200 patients undergoing general surgery randomized to a combination of intravenous and oral atenolol versus placebo for 7 days. Although they found no difference in perioperative MI or death, they reported significantly fewer episodes of ischemia by Holter monitoring (24% vs. 39%; $p = 0.03$) in the atenolol versus placebo groups, respectively. They then followed these patients after discharge and documented fewer deaths in the atenolol group over the subsequent 6 months (1% vs. 10%; p less than 0.001). It is not clear why such a brief course of therapy could exert such a delayed effect, and the study did not control for other medications given either before or after surgery. Angiotensin-converting enzyme inhibitor and beta-blocker use preoperatively differed significantly between the study groups.

Additional studies have examined the use of perioperative beta blockers but are limited in power to detect cardiac events or are not randomized. Stone et al. (9) randomized a group of patients with mild hypertension who underwent predominantly (58%) vascular surgery to oral beta blockers 2 h before surgery or standard care. Control subjects had a higher frequency (28%) of ST-segment depression (on intraoperative monitoring, as reported by the authors) than treated patients (2%). In a nonrandomized study, Pasternack et al. (10) gave oral metoprolol immediately before surgery, followed postoperatively by intravenous metoprolol during abdominal aortic aneurysm repair. Only 3% suffered an acute MI compared with 18% for matched controls. Pasternack et al. (11) subsequently reported fewer episodes of intraoperative ischemia in patients treated with oral metoprolol before peripheral vascular surgery compared with untreated patients. Yeager et al. (12) reported a case-control analysis of their experience with perioperative MI during vascular surgery, comparing 53 index cases of perioperative MI with 106 matched controls. They found a strong association of beta-blocker use with a decreased likelihood of MI (odds ratio = 0.43; $p = 0.01$). Raby et al. (13) demonstrated in 26 vascular surgery patients with documented preoperative ischemia and randomized to a protocol of heart rate suppression with intravenous esmolol compared to standard care that the esmolol group had fewer episodes of ischemia than controls (33% vs. 73%; $p = 0.055$). Zaugg et al. (14) randomized elderly noncardiac surgery patients to preoperative and postoperative atenolol titrated to heart rate and intraoperative atenolol titrated to heart rate or no beta blockers, and detected no episodes of intraoperative myocardial ischemia, electrocardiographic changes consistent with MI, or death in any group. Three (of 19) patients in the no beta-blocker group developed significant elevations of cardiac troponin-I consistent with a perioperative MI compared with 0 (of 40) patients who received one of the atenolol groups. Brady et al. (15) randomized patients undergoing elective vascular surgery to

either metoprolol 50 mg twice per day or placebo, from admission to hospital, until 7 days postoperatively. They found no difference in cardiovascular events, which included MI, unstable angina, ventricular tachycardia, and stroke. This trial may have been underpowered (n = 103) to identify a difference in outcomes, particularly hard outcomes of death and MI. Also, by trial design, therapy was initiated the day before vascular surgery, and it is quite possible that those randomized to metoprolol received incomplete beta blockade in the early perioperative period.

Perioperative beta-blocker therapy has been reviewed in several meta-analyses and in a very large cohort population study. Auerbach and Goldman (16) undertook a review of this topic in 2002. They reported on a MEDLINE search and literature review of only five studies. (All five studies are included in Table 3.) They calculated a number needed to treat, on the basis of these studies, of only 2.5 to 6.7 to see improvement in measures of myocardial ischemia, and only 3.2 to 8.3 in studies reporting a significant impact of beta blockers on cardiac or all-cause mortality. They concluded that the literature supports a benefit of beta blockers on cardiac morbidity.

A systematic review of the perioperative medical therapy literature by Stevens et al. (17) for noncardiac surgery included the results of 11 trials using beta blockers for perioperative therapy. These authors concluded that beta-blockers significantly decreased ischemic episodes during and after surgery. Beta blockers significantly reduced the risk of nonfatal MI; however, the results became nonsignificant if the two most positive trials were eliminated. Likewise, the risk of cardiac death was significantly decreased with beta-blocker usage. It should be noted that these authors incorporated studies not considered in other meta-analyses, including studies that were not blinded. Results to be quantified were limited to those in the 30-day perioperative period. The authors also reported a direct relationship between the prevalence of prior MI and the magnitude of risk reduction observed with beta-blocker therapy, suggesting that higher risk confers greater benefit. The number needed to prevent perioperative ischemia was 8 patients, the number needed to prevent MI was 23, and 32 subjects must be treated to prevent cardiac death. These authors point out that, given the observation that high-risk patients seem to receive all the benefit, the target population for beta-blocker therapy is not clear. They also highlighted that schedules of beta-blocker administration varied significantly among the reported studies and the potential for a single large strongly positive study to skew the results of this meta-analysis.

In contrast, Devereaux et al. (18) published their opinion paper on the clinical evidence regarding the use of beta-blocker therapy in patients undergoing noncardiac surgery for the purpose of preventing perioperative cardiac complications. They expressed the opinion that the literature supporting use of beta blockers during noncardiac surgery is modest at best, based on a few small, unblinded studies with a focused patient population. In a review of the literature in 2005, Devereaux et al. (19) discussed 22 studies randomizing 2,437 patients undergoing noncardiac surgery to beta-blocker therapy or placebo. The POBBLE study was not included in this review (14). They found no statistically significant benefit on any of the individual outcomes and a "nominally" statistically significant benefit (relative risk of 0.44 with 95% confidence interval [CI] 0.20 to 0.97, 99% CI 0.16 to 1.24) for the composite outcome of cardiovascular mortality, nonfatal MI, and nonfatal cardiac arrest. The authors felt these data were inadequate to draw conclusions and that a larger, controlled study is indicated before conclusions can be made. This review, however, included a wide variety of studies, patient populations, and beta-blocker regimens. Many of the studies described only a single or double dose of beta blocker preoperatively or at induction of anesthesia. Much of the data, therefore, does not pertain to perioperative beta blockade for the purpose of cardiac risk reduction or focused on a low-risk population. Additionally, the largest studies included—that is, those reported by Miller et al. (20) and preliminary data from Yang et al. (21), which together account for almost as many subjects as all other studies combined—may not have been appropriate to include in this analysis. The first, by Miller et al. (20), was a study of a single intravenous dose of beta blocker for the purpose of blood pressure control during intubation, not reduction of perioperative events. It included follow-up only to the point of discharge from the recovery room. The second, that of Yang et al. (21), has yet to be published and, therefore, has not undergone formal peer review. The studies included in this review also vary widely in length of follow-up.

McGory et al. (22) performed a meta-analysis of six randomized trials of perioperative beta blockade and concluded that therapy was associated with significant reductions in perioperative myocardial ischemia (33% to 15%), MI, cardiac mortality, and long-term cardiac mortality (12% to 2%). These authors used the combined data to derive odds ratios and CIs for several outcomes. For perioperative overall mortality the odds ratio for beta-blocker therapy was 0.52 (95% CI 0.20 to 1.35), and for perioperative cardiac mortality the odds ratio was 0.25 (95% CI 0.07 to 0.87). Neither the POBBLE study nor the unpublished findings included in the Devereaux et al. (19) paper were included, explaining the marked difference in findings from the other meta-analysis.

A cohort study by Lindenauer et al. (23) reviewed records from over 700,000 patients undergoing noncardiac surgery at 329 hospitals in the United States. Participant hospitals in this cohort study were members of a consortium database measuring quality and health care use. These authors evaluated all noncardiac surgical cases, and compared those who received beta blockers within the first 2 days of hospitalization with those who did not receive beta blockers during the first 2 hospital days. The authors used propensity score matching techniques in an attempt to reduce bias. These authors found

Table 3. Randomized Trials of Perioperative Prophylactic Beta Blockers and Cardiac Morbidity

Author, Year (Ref.)	Procedure	n	Control	Drug	Ischemia*		MI		Death	
					Control	Drug	Control	Drug	Control	Drug
Stone, 1988 (9)	Noncardiac Mild hypertension	128	Placebo	Labetalol Atenolol Olprenolol PO preoperatively	11/39 (28%)	2/89† (2%)	0/39 (0)	0/89 (0)		
Poldermans, 1999 (5)	Vascular	112	Unblinded	5 to 10 mg PO bisoprolol			9/53 (17%)	0/59† (0)	9/53 (17%)	2/59† (3%)
Raby, 1999 (13)	Vascular	26	Placebo	IV esmolol	8/11 (73%)	5/15† (33%)				
Wallace, 1998 (8) Mangano, 1996 (7)	Noncardiac	200	Placebo	10 to 20 mg IV or 50 to 100 mg PO atenolol	39/101 (39%)	24/99† (24%)			(at 6 months) 10/101 (10%)	1/99† (1%)
Zaugg, 1999 (14)	Noncardiac	63 (59 analyzed)	No perioperative beta blockers	Atenolol targeted to maintain HR either 1) pre- and postoperatively or 2) intraoperatively	0/20 (0%)	0/43 (0%)	3/19 (16%)	0/40 (0%)		
Urban, 2000 (25)	Noncardiac	107	Placebo	IV esmolol on the day of surgery, followed by metoprolol starting at 25 mg PO BID and increased to maintain a HR less than 80 beats/min, and continued for the next 48 h	8/55 (15%)	3/52 (6%)	3/55 (5%)	1/52 (2%)		
Brady, 2005 (15)	Vascular	103	Placebo	50 mg PO metoprolol twice daily preoperatively until 7 days post surgery	4/44 (9%)	5/53 (9%)	5/44 (11%)	3/53 (6%)	1/44 (2%)	3/53 (6%)

*Myocardial ischemia. †p less than 0.05 for drug versus control.
BID = twice per day; HR = heart rate; IV = intravenous; MI = myocardial infarction; PO = by mouth.

that for a revised cardiac risk index score (24) of three or more (based on the presence of history of ischemic heart disease, cerebrovascular disease, renal insufficiency, diabetes mellitus, or a patient undergoing high-risk surgery), patients who received beta blockers were significantly less likely to die in hospital. This was not true for those with a revised risk index of 2, l, or 0. Those with a risk index of 0 were more likely to die in hospital if given a beta blocker on Day 1 or Day 2 of hospitalization. This study is retrospective and not randomized and, therefore, is subject to potential bias. This is particularly true in terms of reporting bias, as the documentation was based entirely on administrative data sets, using arbitrary definitions of "on" or "off" perioperative beta blockers, based solely on hospital day of use. Nonetheless, there appears to be an association between improved outcomes and the use of beta blockers in clinically high-risk patients.

Finally, one recent observational cohort study examined the question of which beta blocker may be best for perioperative medical therapy. Redelmeier et al. (4) reviewed administrative data related to elective surgery in Ontario, Canada, and documented perioperative beta-blocker usage from April 1992 to April 2002 (10 years). They limited their analysis to patients over the age of 65 years, who were receiving either atenolol or metoprolol before and after surgery and identified 37,151 subjects. A total of 1,038 suffered either a perioperative MI or death, and the rate of MI or death was significantly lower among those patients receiving atenolol versus metoprolol (2.5% vs. 3.2%, p less than 0.001). This difference persisted even after adjusting for demographic, clinical, and surgical factors. The inclusion of other long-acting beta blockers in the analysis yielded an identical risk reduction. These data suggest that long-acting beta blockade (when therapy is initiated before surgery) may be superior to short-acting beta blockade. These observations await clinical trial evaluation.

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APPENDIX 1. Author Relationships With Industry for the ACC/AHA Guideline Update on Perioperative Cardiovascular Evaluation for Noncardiac Surgery: Focused Update on Perioperative Beta-Blocker Therapy

Committee Member	Consultant	Research Grant	Scientific Advisory Board	Speakers' Bureau	Other
Joshua A. Beckman, MD	• Bristol-Myers Squibb	None	• Sanofi-Aventis	• Bristol-Myers Squibb • Merck • Eli Lilly • Sanofi-Aventis	None
Kenneth A. Brown, MD	None	None	None	None	None
Hugh Calkins, MD	None	None	None	None	None
Elliott Chaikof, MD	None	None	None	None	None
Kirsten E. Fleischmann, MD, MPH	None	None	None	None	• Pfizer (QI/CME Initiatives)
Lee A. Fleisher, MD	None	None	None	None	None
William K. Freeman, MD	None	None	None	None	None
James B. Froehlich, MD, MPH	• Pfizer	None	• Sanofi-Aventis	• Sanofi-Aventis • Otsuka • Pfizer • Merck	None
Edward K. Kasper, MD	None	None	None	None	None
Judy R. Kersten, MD	• Abbott Laboratories	• Abbott Laboratories	None	• Abbott Laboratories	
Barbara Riegel, DNSc, RN	None	None	None	None	None
John F. Robb, MD	None	None	None	None	None

APPENDIX 2. External Peer Reviewer Relationships With Industry for the ACC/AHA Guideline Update on Perioperative Cardiovascular Evaluation for Noncardiac Surgery: Focused Update on Perioperative Beta-Blocker Therapy*

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Dr. Peter Alagona	• Official Reviewer–Board of Trustees (BOT)	None	None	None	None	None
Dr. Joseph Alpert	• Official Reviewer–AHA Reviewer	None	None	None	None	None
Dr. Vincent Carr	• Official Reviewer–Board of Governors (BOG)	None	None	None	None	None
Dr. Ray Gibbons	• Official Reviewer–AHA Reviewer	• Radiant Medical • Boston Scientific • Boehringer Ingelheim • Spectranetrics • KAI Pharmaceuticals • TargeGen • TherOx • King Pharmaceuticals	None	None	• Hawaii Biotech • Cardiovascular Clinical Studies (WOMEN study, TIMI 37 A) • Consumers Union	None
Dr. Bruce Lytle	• Official Reviewer–ACCF/AHA Task Force Practice Guidelines	None	None	• Johnson & Johnson	None	None
Dr. Susan Begelman	• Organizational Reviewer–Society for Vascular Medicine and Biology (SVMB)	None	• Bristol-Myers Squibb • Sanofi-Aventis • GlaxoSmithKline	None	• Bristol-Myers Squibb • Sanofi-Aventis • GlaxoSmithKline	None

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Dr. Simon Body	• Organizational Reviewer–Society of Cardiovascular Anesthesiologists (SCA) • Content Reviewer–AHA Council on Cardiopulmonary, Perioperative and Critical care	None	None	None	None	None
Dr. Bengt Herweg	• Organizational Reviewer–Heart Rhythm Society (HRS)	None	None	None	None	None
Dr. Scott Kinlay	• Organizational Reviewer–Society for Vascular Medicine and Biology (SVMB)	• Pfizer	• Pfizer • Merck	None	• Pfizer	None
Dr. Richard Page	• Organizational Reviewer–Heart Rhythm Society (HRS) • Content Reviewer-ACCF Clinical Electrophysiology Committee • Content Reviewer–AHA Council on Clinical Cardiology Electrocardiography and Arrhythmias Committee	None	None	None	• Procter and Gamble Pharmaceuticals	None
Dr. Mark Turco	• Organizational Reviewer–Society for Cardiovascular Angiography and Interventions (SCAI)	None	• Boston Scientific Corp. • Medtronic	None	• Boston Scientific Corp. • Medtronic	None
Dr. Neil Weissman	• Organizational Reviewer–American Society of Echocardiography (ASE)	• Edwards Life Sciences • Carbomedics • Wyeth • Bristol-Myers Squibb Medical Imaging • Cook Corp. • Boston Scientific • Arbor Surgical • Arena Pharmaceutical • Mitsubishi	None	None	• Wyeth • Pfizer • Bristol-Myers Squibb Medical Imaging • Boston Scientific	None
Dr. Kim Williams	• Organizational Reviewer–American Society of Nuclear Cardiology (ASNC) • Content Reviewer–ACCF Cardiovascular Clinical Imaging Committee	• Bristol-Myers Squibb • CV Therapeutics	• GE Healthcare • Astellas Pharma	None	• GE Healthcare	• King Pharmaceuticals (Expert Reader)
Dr. Mazen Abu-Fadel	• Content Reviewer–ACCF Cardiac Catheterization Committee	None	None	None	None	None
Dr. Ralph Bolman	• Content Reviewer–AHA Council on Cardiovascular Surgery and Anesthesia	None	None	None	None	None

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Dr. Jose Diez	• Content Reviewer–ACCF Cardiac Catheterization Committee	None	None	None	None	None
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Dr. Leonard Dreifus	• Content Reviewer–ACCF Clinical Electrophysiology Committee	None	None	None	• Merck	None
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Dr. Smadar Kort	• Content Reviewer–ACCF Echocardiography Committee	None	None	None	None	None
Dr. Peter Kowey	• Content Reviewer–ACCF Clinical Electrophysiology Committee	None	None	None	None	None
Dr. Fred Krainin	• Content Reviewer–ACCF Cardiac Catheterization Committee	None	None	• Boston Scientific • Johnson & Johnson • Medtronic	None	None
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Dr. Carlos Ruiz	• Content Reviewer–ACCF Cardiac Catheterization Committee	None	None	None	None	None
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