2009 ACCF/AHA Focused Update on Perioperative Beta Blockade

A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines

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, Society for Vascular Medicine, and Society for Vascular Surgery

2009 WRITING GROUP TO REVIEW NEW EVIDENCE AND UPDATE THE 2007 GUIDELINES ON PERIOPERATIVE CARDIOVASCULAR EVALUATION AND CARE FOR NONCARDIAC SURGERY

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Preamble

A primary challenge in the development of clinical practice guidelines is keeping pace with the stream of new data on which recommendations are based. In an effort to respond more quickly to new evidence, the American College of Cardiology Foundation/American Heart Association (ACCF/AHA) Task Force on Practice Guidelines has created a "focused update" process to revise the existing guideline recommendations that are affected by the evolving data or opinion. Prior to the initiation of this focused approach, periodic updates and revisions of existing guidelines required up to 3 years to complete. Now, however, new evidence will be reviewed in an ongoing fashion to respond more efficiently to important science and treatment trends that could have a major impact on patient outcomes and quality of care. Evidence will be reviewed at least twice a year, and updates will be initiated on an as-needed basis as quickly as possible, while maintaining the rigorous methodology that the ACCF and AHA have developed during their 25 years of partnership.

These updated guideline recommendations reflect a consensus of expert opinion after a thorough review primarily of late-breaking clinical trials identified through a broad-based vetting process as being important to the relevant patient population, as well as of other new data deemed to have an impact on patient care (see Section 1.1., Methodology and Evidence Review, for details regarding this focused update). This focused update is not intended to represent an update based on a full literature review from the date of the previous guideline publication. Specific criteria/considerations for inclusion of new data include the following:

- publication in a peer-reviewed journal;
- large, randomized, placebo-controlled trial(s);
- nonrandomized data deemed important on the basis of results impacting current safety and efficacy assumptions;
- strength/weakness of research methodology and findings;
- likelihood of additional studies influencing current findings;
- impact on current performance measure(s) and/or likelihood of need to develop new performance measure(s);
- requests and requirements for review and update from the practice community, key stakeholders, and other sources free of relationships with industry or other potential bias;
- number of previous trials showing consistent results; and
- need for consistency with a new guideline or guideline revision.

In analyzing the data and developing updated recommendations and supporting text, the focused update writing group used evidence-based methodologies developed by the ACCF/AHA Task Force on Practice Guidelines, which are described elsewhere.[1]

The schema for class of recommendation and level of evidence is summarized in Table 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. Note that 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 may not be available, there may be a very clear clinical consensus that a particular test or therapy is

Table 1. Applying Classification of Recommendations and Level of Evidence

ESTIMATE OF CERTAINTY (PRECISION) OF TREATMENT EFFECT ↓ / SIZE OF TREATMENT EFFECT →	CLASS I *Benefit >>> Risk* Procedure/Treatment **SHOULD** be performed/ administered	CLASS IIa *Benefit >> Risk* *Additional studies with focused objectives needed* **IT IS REASONABLE** to perform procedure/administer treatment	CLASS IIb *Benefit ≥ Risk* *Additional studies with broad objectives needed; additional registry data would be helpful* Procedure/Treatment **MAY BE CONSIDERED**	CLASS III *Risk ≥ Benefit* Procedure/Treatment should **NOT** be performed/administered **SINCE IT IS NOT HELPFUL AND MAY BE HARMFUL**
LEVEL A Multiple populations evaluated* Data derived from multiple randomized clinical trials or meta-analyses	■ Recommendation that procedure or treatment is useful/effective ■ Sufficient evidence from multiple randomized trials or meta-analyses	■ Recommendation in favor of treatment or procedure being useful/effective ■ Some conflicting evidence from multiple randomized trials or meta-analyses	■ Recommendation's usefulness/efficacy less well established ■ Greater conflicting evidence from multiple randomized trials or meta-analyses	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Sufficient evidence from multiple randomized trials or meta-analyses
LEVEL B Limited populations evaluated* Data derived from a single randomized trial or nonrandomized studies	■ Recommendation that procedure or treatment is useful/effective ■ Evidence from single randomized trial or nonrandomized studies	■ Recommendation in favor of treatment or procedure being useful/effective ■ Some conflicting evidence from single randomized trial or nonrandomized studies	■ Recommendation's usefulness/efficacy less well established ■ Greater conflicting evidence from single randomized trial or nonrandomized studies	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Evidence from single randomized trial or nonrandomized studies
LEVEL C Very limited populations evaluated* Only consensus opinion of experts, case studies, or standard of care	■ Recommendation that procedure or treatment is useful/effective ■ Only expert opinion, case studies, or standard of care	■ Recommendation in favor of treatment or procedure being useful/effective ■ Only diverging expert opinion, case studies, or standard of care	■ Recommendation's usefulness/efficacy less well established ■ Only diverging expert opinion, case studies, or standard of care	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Only expert opinion, case studies, or standard of care
Suggested phrases for writing recommendations†	should is recommended is indicated is useful/effective/beneficial	is reasonable can be useful/effective/beneficial is probably recommended or indicated	may/might be considered may/might be reasonable usefulness/effectiveness is unknown/unclear/uncertain or not well established	is not recommended is not indicated should not is not useful/effective/beneficial may be harmful

*Data available from clinical trials or registries about the usefulness/efficacy in different subpopulations, such as sex, age, history of diabetes, history of prior myocardial infarction, 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 ACCF/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.

useful and effective. Both the class of recommendation and level of evidence listed in the focused updates are based on consideration of the evidence reviewed in previous iterations of the guideline and in the focused update. Of note, the implications of older studies that have informed recommendations but have not been repeated in contemporary settings are considered carefully.

The ACCF/AHA practice guidelines address patient populations (and healthcare providers) residing in North America. As such, drugs that are not currently available in North America are discussed in the text without a specific class of recommendation. For studies performed in large numbers of subjects outside of North America, each writing committee reviews the potential impact of different practice patterns and patient populations on the treatment effect and on the relevance to the ACCF/AHA target population to determine whether the findings should inform a specific recommendation.

The ACCF/AHA practice guidelines are intended to assist healthcare providers in clinical decision making by describing a range of generally acceptable approaches for the diagnosis, management, and prevention of specific diseases or conditions. The guidelines attempt to define practices that meet the needs of most patients in most circumstances. 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. Thus, there are circumstances in which deviations from these guidelines may be appropriate. Clinical decision making should consider the quality and availability of expertise in the area where care is

provided. These guidelines may be used as the basis for regulatory or payer decisions, but the ultimate goal is quality of care and serving the patient's best interests.

Prescribed courses of treatment in accordance with these recommendations are only effective if they are followed by the patient. Because lack of patient adherence may adversely affect treatment outcomes, healthcare providers should make every effort to engage the patient in active participation with prescribed treatment.

The ACCF/AHA Task Force on Practice Guidelines makes every effort to avoid actual, potential, or perceived conflicts of interest that may arise as a result of industry relationships or personal interests among the writing committee. Specifically, all members of the writing committee, as well as peer reviewers of the document, are asked to disclose all such relationships pertaining to the trials and other evidence under consideration (see Appendixes 1 and 2). Final recommendations were balloted to all writing committee members. Writing committee members with relevant relationships with industry were required to recuse themselves from voting on that recommendation. Previous writing committee members who did not participate are not listed as authors of this focused update.

With the exception of the recommendations presented here, the full-text guideline remains current. Only the recommendations from the affected section(s) of the full-text guideline are included in this focused update. For easy reference, all recommendations from any section of a guideline impacted by a change are presented with notation as to whether they remain current, are new, or have been modified. When evidence impacts recommendations in more than 1 set of guidelines, those guidelines are updated concurrently.

The recommendations in this focused update will be considered current until they are superseded by another focused update or the full-text guidelines are revised. This focused update is published in the November 24, 2009, issues of the *Journal of the American College of Cardiology* and *Circulation* as an update to the full-text guideline, and a revised version of the 2007 full-text guideline that incorporates the focused update has also been e-published in these issues and is available on the respective Web sites.[2] For easy reference, this online-only version denotes sections that have been updated.

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1. Introduction

1.1. Methodology and Evidence Review

Late-breaking clinical trials presented at the 2008 annual scientific meetings of the ACCF, AHA, and European Society of Cardiology, as well as selected other data through June 2009, were reviewed by the standing guideline writing committee along with the parent task force and other experts to identify those trials and other key data that may impact guideline recommendations. On the basis of the criteria/considerations noted previously, recent trial data and other clinical information were considered important enough to prompt a focused update of the "ACC/AHA 2007 Guidelines on Perioperative Cardiovascular Evaluation and Care for Noncardiac Surgery".[3] This update addresses predominantly the prophylactic use of beta blockers perioperatively to minimize cardiac risk, but it does not cover other legitimate uses of beta blockers (e.g., as an adjunct in anesthetic regimens, for intraoperative control of heart rate or blood pressure, or to achieve heart rate control in common perioperative arrhythmias such as atrial fibrillation).

When considering the new data for this focused update, the writing group faced the task of weighing evidence from studies enrolling large numbers of subjects outside North America. While noting that practice patterns and the rigor applied to data collection, as well as the genetic make-up of subjects, may influence the observed magnitude of a treatment's effect, the writing group believed the data were relevant to formulation of recommendations for perioperative management in North America. The reasons for this decision include the following: 1) The use of detailed protocol-driven management strategies likely reduced treatment variability among sites; and 2) it may be impractical to expect that the thousands of patients undergoing noncardiac surgery who are needed to meet the estimated sample size for contemporary clinical trials would be enrolled exclusively at North American sites.

To provide clinicians with a comprehensive set of data, whenever possible, the exact event rates in various treatment arms of clinical trials are presented to permit calculation of the absolute risk difference and number needed to treat (NNT) or harm. The relative treatment effects are described either as odds ratio (OR), relative risk (RR), or hazard ratio (HR), depending on the format in the original publication.

Consult the full-text version or executive summary of the "ACC/AHA 2007 Guidelines on Perioperative Cardiovascular Evaluation and Care for Noncardiac Surgery"[3] for policy on clinical areas not covered by the focused update. Individual recommendations updated in this focused update will be incorporated into future revisions and/or updates of the full-text guidelines.

1.2. Organization of Committee and Relationships With Industry and Other Entities

For this focused update, all members of the 2007 Perioperative Guideline Writing Committee were invited to participate; those who agreed (referred to as the 2009 Focused Update Writing Group) were required to disclose all relationships with industry and other entities relevant to the data under consideration. Each recommendation required a confidential vote by the writing group members before and after external review of the document. Any writing group member with a relationship with industry relevant to the recommendation was recused from voting on that recommendation. The committee included representatives from the American Society of Echocardiography

(ASE), Heart Rhythm Society (HRS), Society of Cardiovascular Anesthesiologists (SCA), Society for Cardiac Angiography and Interventions (SCAI), Society for Vascular Medicine (SVM), and Society for Vascular Surgery (SVS).

1.3. Document Review and Approval

This document was reviewed by 2 official reviewers nominated by the ACCF and 2 official reviewers nominated by the AHA, as well as 2 reviewers each from the ASE, American Society of Nuclear Cardiology, HRS, SCA, SCAI, SVM, and the SVS, and 8 individual content reviewers from the ACCF Cardiac Catheterization Committee and the ACCF Interventional Council. All information on reviewer relationships with industry was collected and distributed to the writing group and is published in this document (Appendix 2).

This document was approved for publication by the governing bodies of the ACCF and the AHA and endorsed by the ASE, American Society of Nuclear Cardiology, HRS, SCA, SCAI, SVM, and the SVS.

7. Perioperative Therapy

7.2. Perioperative Medical Therapy

7.2.1. Recommendations for Perioperative Beta-Blocker Therapy (Table 2)

The issue of perioperative beta-blocker therapy was last addressed by this committee in the "ACC/AHA 2007 Guidelines on Perioperative Cardiovascular Evaluation and Care for Noncardiac Surgery".[3] As outlined in that document, preoperative beta-blocker therapy should be considered in the context of a full evaluation of each patient's clinical and surgical risk, including identification of active cardiac conditions that require intensive management and may result in delay or cancellation of surgery unless the surgery is emergent Table 3. Clinical risk factors for perioperative cardiovascular complications, as used in our current recommendations, are unchanged from the prior document and include the following:

- history of ischemic heart disease;
- history of compensated or prior heart failure;
- history of cerebrovascular disease;
- diabetes mellitus; and
- renal insufficiency (defined in the Revised Cardiac Risk Index as a preoperative serum creatinine of more than 2 mg/dL).[9]

The surgery-specific cardiac risk of noncardiac surgery (Table 4 also remains relevant, with an important caveat being that limited data are available to guide beta-blocker use in the presence of newer techniques (e.g., percutaneous or endovascular vascular procedures) that may be associated with lower short-term risk.

The prior document outlined conflicting evidence regarding the efficacy of beta blockers in reducing perioperative cardiac events, as well as limitations in the evidence base. These included the relatively small number of randomized trials on this issue and the dearth of studies comparing different beta-blocker agents or providing data to determine the ideal target population, duration of preoperative titration, and route of administration. In addition, practical concerns, such as how, when, how long, and by whom perioperative beta-blocker therapy should ideally or practically be prescribed, remained unaddressed. We advocated for randomized controlled trials to explore the observation that there may be some harm associated with beta-blocker therapy in low-risk patients.[7] Moreover, there was a lack of data regarding which beta blocker to use perioperatively. In summary, the best approach on how to reduce cardiovascular complications medically during noncardiac surgery was still unknown. Limitations in the perioperative beta-blocker literature included the following:

- Most trials were inadequately powered.
- Few randomized trials of medical therapy to prevent perioperative major adverse cardiac events had been performed.
- Few randomized trials had examined the role of perioperative beta-blocker therapy, and there was particularly a lack of trials that focused on high-risk patients.
- Studies to determine the role of beta blockers in intermediate- and low-risk populations were lacking.
- Studies to determine the optimal type, dose, timing, duration, and titration of beta blockers were lacking.
- No studies addressed care-delivery mechanisms in the perioperative setting, identifying how, when, and by whom perioperative beta-blocker therapy should be prescribed and monitored.

In addition, as outlined above, there is a paucity of information to help guide beta-blocker use in the setting of shifts in surgical techniques away from traditional open procedures that require general anesthesia and toward less invasive endovascular or percutaneous techniques, which may not require general anesthesia.

Since that guideline was published, important additional information on some but not all of these issues has been provided by the POISE (PeriOperative ISchemic Evaluation) trial,[8] a large, randomized, controlled trial of fixed higher-dose, extended-release metoprolol started the day of surgery in more than 8000 patients undergoing noncardiac surgery, which prompted this focused update on the subject of perioperative beta-blocker therapy. This study, which will be discussed in detail in Section 7.2.1.1, confirmed a reduction in primary cardiac events such as cardiovascular death, myocardial infarction (MI), and cardiac arrest with perioperative beta-blocker therapy. However, that benefit was offset by an increased risk of stroke and total mortality, which suggests that routine administration of high-dose beta blockers in the absence of dose titration is not useful and may be harmful to beta-blocker–naïve patients undergoing surgery.

Current studies suggest that beta blockers reduce perioperative ischemia and may reduce the risk of MI and cardiovascular death in high-risk patients. However, routine administration of higher-dose long-acting metoprolol in beta-blocker–naïve patients on the day of surgery and in the absence of dose titration is associated with an overall increase in mortality. How should clinicians reconcile these conflicting data? Importantly, the POISE results[8] do not address continuation of beta blockers in patients undergoing surgery

Table 2. Updates to Section 7.2.1. Recommendations for Perioperative Beta-Blocker Therapy

2007 Perioperative Guideline Recommendations	2009 Perioperative Focused Update Recommendations	Comments
	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)*	1. Beta blockers should be continued in patients undergoing surgery who are receiving beta blockers for treatment of conditions with ACCF/AHA Class I guideline indications for the drugs. *(Level of Evidence: C)*	2007 recommendation remains current in 2009 update with revised wording.
2. Beta blockers should be given to patients undergoing vascular surgery who are at high cardiac risk owing to the finding of ischemia on preoperative testing. *(Level of Evidence: B)*		Deleted/combined recommendation (class of recommendation changed from I to IIa for patients with cardiac ischemia on preoperative testing).
	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)*	1. Beta blockers titrated to heart rate and blood pressure are probably recommended for patients undergoing vascular surgery who are at high cardiac risk owing to coronary artery disease or the finding of cardiac ischemia on preoperative testing.[4,5] *(Level of Evidence: B)*	Modified/combined recommendation (wording revised and class of recommendation changed from I to IIa for patients with cardiac ischemia on preoperative testing).
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 more than 1 clinical risk factor.* *(Level of Evidence: B)*	2. Beta blockers titrated to heart rate and blood pressure are reasonable for patients in whom preoperative assessment for vascular surgery identifies high cardiac risk, as defined by the presence of more than 1 clinical risk factor.* *(Level of Evidence: C)*	Modified recommendation (level of evidence changed from B to C).
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 more than 1 clinical risk factor,* who are undergoing intermediate-risk or vascular surgery. *(Level of Evidence: B)*	3. Beta blockers titrated to heart rate and blood pressure are reasonable for patients in whom preoperative assessment identifies coronary artery disease or high cardiac risk, as defined by the presence of more than 1 clinical risk factor,* who are undergoing intermediate-risk surgery.[6] *(Level of Evidence: B)*	2007 recommendation remains current in 2009 update with revised wording.
	Class IIb	
1. The usefulness of beta blockers is uncertain for patients who are undergoing either intermediate-risk procedures or vascular surgery, in whom preoperative assessment identifies a single clinical risk factor.* *(Level of Evidence: C)*	1. The usefulness of beta blockers is uncertain for patients who are undergoing either intermediate-risk procedures or vascular surgery in whom preoperative assessment identifies a single clinical risk factor in the absence of coronary artery disease.* *(Level of Evidence: C)*	2007 recommendation remains current in 2009 update with revised wording.
2. The usefulness of beta blockers is uncertain in patients undergoing vascular surgery with no clinical risk factors who are not currently taking beta blockers. *(Level of Evidence: B)*	2. The usefulness of beta blockers is uncertain in patients undergoing vascular surgery with no clinical risk factors* who are not currently taking beta blockers.[7] *(Level of Evidence: B)*	2007 recommendation remains current in 2009 update.
	Class III	
1. Beta blockers should not be given to patients undergoing surgery who have absolute contraindications to beta blockade. *(Level of Evidence: C)*	1. Beta blockers should not be given to patients undergoing surgery who have absolute contraindications to beta blockade. *(Level of Evidence: C)*	2007 recommendation remains current in 2009 update.
	2. Routine administration of high-dose beta blockers in the absence of dose titration is not useful and may be harmful to patients not currently taking beta blockers who are undergoing noncardiac surgery.[8] (*Level of Evidence: B)*	New recommendation

*Clinical risk factors include history of ischemic heart disease, history of compensated or prior heart failure, history of cerebrovascular disease, diabetes mellitus, and renal insufficiency (defined in the Revised Cardiac Risk Index as a preoperative serum creatinine of >2 mg/dL).[9]

ACC indicates American College of Cardiology; and AHA, American Heart Association.

Table 3. Active Cardiac Conditions for Which the Patient Should Undergo Evaluation and Treatment Before Noncardiac Surgery (Class I, Level of Evidence: B)*

Condition	Examples
Unstable coronary syndromes	Unstable or severe angina† (CCS class III or IV)‡ Recent MI§
Decompensated HF (NYHA functional class IV; worsening or new-onset HF)	
Significant arrhythmias	High-grade atrioventricular block Mobitz II atrioventricular block Third-degree atrioventricular heart block Symptomatic ventricular arrhythmias Supraventricular arrhythmias (including atrial fibrillation) with uncontrolled ventricular rate (heart rate >100 bpm at rest) Symptomatic bradycardia Newly recognized ventricular tachycardia
Severe valvular disease	Severe aortic stenosis (mean pressure gradient >40 mm Hg, aortic valve area <1.0 cm^2, or symptomatic) Symptomatic mitral stenosis (progressive dyspnea on exertion, exertional presyncope, or HF) or MVA <1.5 cm^2

bpm indicates beats per minute; CCS, Canadian Cardiovascular Society; HF, heart failure; MI, myocardial infarction; MVA, mitral valve area; and NYHA, New York Heart Association.

*The presence of 1 or more of these conditions mandates intensive management and may result in delay or cancellation of surgery unless the surgery is emergent.[3]

†According to Campeau.[10]

‡May include "stable" angina in patients who are unusually sedentary.

§The American College of Cardiology National Database Library defines recent MI as >7 days but ≤1 month (within 30 days).

who are receiving beta blockers for ACCF/AHA Class I guideline indications; therefore, this continues to be a Class I recommendation for beta-blocker therapy in the present focused update. In addition, available evidence suggests but does not definitively prove that when possible and where indicated, beta blockers should be started days to weeks before elective surgery. The dose should be titrated perioperatively to achieve adequate heart rate control to increase the likelihood that the patient will receive the benefit of beta blockade, while seeking to minimize the considerable risks of hypotension and bradycardia seen in POISE (see Section 7.2.1.4). Titrated rate control with beta blockers should continue during the intraoperative and postoperative period, if possible, to maintain a heart rate of 60 to 80 bpm in the absence of hypotension, because this regimen has demonstrated efficacy.[5,11] However, routine administration of high-dose beta blockers in the absence of dose titration for patients undergoing noncardiac surgery is not useful, may be harmful, and cannot be advocated, which results in a new Class III recommendation for this practice. The committee continues to advocate for additional studies to address remaining issues regarding the safety and efficacy of beta-blocker therapy as outlined above.

Table 4. Cardiac Risk* Stratification for Noncardiac Surgical Procedures

Risk Stratification	Procedure Examples
Vascular (reported cardiac risk often >5%)	Aortic and other major vascular surgery Peripheral vascular surgery
Intermediate (reported cardiac risk generally 1% to 5%)	Intraperitoneal and intrathoracic surgery Carotid endarterectomy Head and neck surgery Orthopedic surgery Prostate surgery
Low† (reported cardiac risk generally <1%)	Endoscopic procedures Superficial procedure Cataract surgery Breast surgery Ambulatory surgery

*Combined incidence of cardiac death and nonfatal myocardial infarction.

†These procedures do not generally require further preoperative cardiac testing.[3]

7.2.1.1. Evidence on Efficacy of Beta-Blocker Therapy. Studies reviewed that provide primary data regarding the efficacy and safety of beta-blocker therapy in noncardiac surgery are summarized in Appendix 3. A more detailed discussion of these studies and of systematic reviews and meta-analyses incorporating these data is provided in the sections that follow. Several 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 who were scheduled for vascular surgery. Of 846 patients with risk factors for cardiac disease, 173 were found to have new regional wall-motion abnormalities with stress on dobutamine stress echocardiography. Of these patients, 61 were excluded from further study owing to large areas (5 or more segments) of regional wall-motion abnormalities on dobutamine stress echocardiography 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 before surgery and titrated to maintain heart rate less than 60 bpm preoperatively and less than 80 bpm intraoperatively and postoperatively. The rates of cardiac death (3.4% versus 17%; p=0.02) and nonfatal MI (0% versus 17%; p≤0.001) were lower for the bisoprolol groups than for the placebo groups, respectively. Importantly, owing to the unblinded design and the inclusion of only high-risk patients in this study, the results cannot be generalized to all patients undergoing noncardiac surgery.

Boersma et al[4] subsequently reanalyzed the total cohort of 1351 consecutive patients considered for enrollment in the aforementioned randomized trial of bisoprolol. Forty-five patients had perioperative cardiac death or nonfatal MI. Eighty-three percent of the 1351 patients had fewer than 3 clinical risk factors, and in this subgroup, patients taking beta blockers had a lower risk of cardiac complications (0.8% [2 of 263]) than those not taking beta blockers (2.3% [20 of 855]). In patients with 3 or more risk factors (17%), those taking beta blockers who had a dobutamine stress echocardi-

ography examination that demonstrated 4 or fewer segments of new wall-motion abnormalities had a significantly lower incidence of cardiac complications (2.3% [2 of 86]) than those not receiving beta-blocker therapy (9.9% [12 of 121]). However, among the small group of patients with more extensive ischemia on dobutamine stress echocardiography (5 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.

Mangano et al[12] reported on 200 patients undergoing general surgery who were randomized to a combination of intravenous and oral atenolol versus placebo for 7 days. Although they found no difference in in-hospital perioperative deaths (4 of 99 versus 2 of 101) or MI, they reported significantly fewer episodes of ischemia by Holter monitoring in the atenolol group than in the placebo group (24% versus 39%, respectively; $p=0.03$). They then conducted follow-up on these patients after discharge and documented fewer deaths in the atenolol group over the subsequent 6 months (1% versus 10%; $p<0.001$). Overall, 13 of 99 patients in the atenolol group and 23 of 101 patients in the placebo group died when both in-hospital and postdischarge events were considered. It is unclear 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. Use of angiotensin-converting enzyme inhibitors and beta blockers postoperatively differed significantly between the study groups.

More recent randomized trials have examined beta blockade for the prevention of perioperative cardiac complications during noncardiac surgery. Juul et al[13] randomized 921 subjects with diabetes mellitus who were undergoing a range of noncardiac operations to either 100 mg of extended-release metoprolol or placebo in the DIPOM (DIabetic POstoperative Mortality and morbidity) study. There was no significant difference in the primary composite outcome of time to all-cause mortality, MI, unstable angina, or congestive heart failure (CHF) (21% versus 20%) in patients randomized to higher-dose metoprolol versus placebo. Among those randomized, an equal number of deaths (16%) were observed in both groups. MI rates were not reported separately. Yang et al[14] reported a study of 496 subjects undergoing major vascular surgery who were randomized to dose-adjusted metoprolol or placebo. Exclusions in that study included those already taking a beta blocker. They reported similar MI rates (7.7% versus 8.4%; $p=0.87$) and death rates (0% versus 1.6%) at 30 days in the beta-blocker and placebo groups, respectively. These were not noninferiority analyses but rather simply negative study results. Most importantly for the purposes of these guidelines, the patients included in the studies by Juul et al[13] and Yang et al[14] were patients with diabetes in 1 study and patients undergoing major vascular surgery in the other, who undoubtedly represent a heterogeneous risk group without documented coronary artery disease.

Additional studies have examined the use of perioperative beta blockers but have used surrogate end points such as electrocardiographic ST changes, were not randomized, did not use general anesthesia, or had limited power to detect differences in cardiac events. Stone et al[15] randomized a group of patients with mild hypertension who underwent predominantly (58%) vascular surgery either to oral beta blockers 2 hours before surgery or to 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[16] gave oral metoprolol immediately before abdominal aortic aneurysm repair surgery, followed postoperatively by intravenous metoprolol. Only 3% of patients experienced an acute MI compared with 18% for matched control subjects. Pasternack et al[17] subsequently reported fewer episodes of intraoperative ischemia in patients treated with oral metoprolol before peripheral vascular surgery than in untreated patients. Yeager et al[18] reported a case-control analysis of their experience with perioperative MI during vascular surgery, comparing 53 index cases of perioperative MI with 106 matched control subjects. They found a strong association of beta-blocker use with a decreased likelihood of MI (OR 0.43; $p=0.01$). In 26 vascular surgery patients with documented preoperative ischemia who were randomized to a protocol of heart rate suppression with intravenous esmolol compared with standard care, Raby et al[19] demonstrated that the esmolol group had fewer episodes of ischemia than control subjects (33% versus 73%; $p=0.055$).

Zaugg et al[20] randomized elderly noncardiac surgery patients to preoperative and postoperative atenolol titrated to heart rate, 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 none of 40 patients who received 1 of the atenolol regimens. In a follow-up study, Zaugg et al[21] randomized 219 patients undergoing spinal, rather than general, anesthesia to bisoprolol or placebo. The composite outcome of cardiovascular mortality, nonfatal MI, unstable angina, CHF, and cerebrovascular event was not significantly different over the 1-year follow-up period. Interestingly, adrenergic-receptor genotype was associated with outcome in this study, which raises the possibility that genetic heterogeneity may be another important determinant of outcome. Brady et al[22] randomized patients undergoing elective vascular surgery to either metoprolol 50 mg twice a day or placebo, from admission to the hospital until 7 days after surgery. 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 also been reviewed in several meta-analyses and in a very large cohort population study before publication of the recent POISE trial.[8] Auerbach and Goldman[23] undertook a review of this topic in 2002. They reported on a MEDLINE search and literature review of 5 studies (all 5 studies are included in Table 12 in the full-text guideline[3]). They calculated an NNT on the basis of these studies of 2.5 to 6.7 to see improvement in measures of myocardial ischemia and 3.2 to 8.3 in studies that reported 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 and mortality.

A systematic review of the perioperative medical therapy literature by Stevens et al[24] 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 2 most positive trials were eliminated. Likewise, the risk of cardiac death was significantly decreased with beta-blocker usage. 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, which suggests that higher risk confers greater benefit. The NNT to prevent perioperative ischemia was 8 subjects, the NNT to prevent MI was 23, and 32 patients had to be treated to prevent cardiac death. These authors pointed out that given the observation that high-risk patients appeared 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 they acknowledged the potential for a single, large, strongly positive study to skew the results of this meta-analysis.[24]

In contrast, Devereaux et al[25] 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 the use of beta blockers during noncardiac surgery is modest at best and is based on a few small, unblinded studies with a focused patient population. In a review of the literature in 2005, Devereaux et al[26] discussed 22 studies that randomized 2437 patients undergoing noncardiac surgery to beta-blocker therapy or placebo. The POBBLE (PeriOperative Beta-BLockadE) study[22] was not included in this review. They found no statistically significant benefit with regard to any of the individual outcomes and a "nominally" statistically significant benefit (RR 0.44, 99% confidence interval [CI] 0.16 to 1.24) for the composite outcome of cardiovascular mortality, nonfatal MI, and nonfatal cardiac arrest. The authors believed that these data were inadequate to draw conclusions without a larger, controlled study. 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 blockers preoperatively or at induction of anesthesia. Many of the data, therefore, do not pertain to perioperative beta blockade for the purpose of cardiac risk reduction or are focused on a low-risk population. Additionally, the largest studies included, those reported by Miller et al[27] and preliminary data from Yang et al,[14] which together account for almost as many subjects as all the other studies combined, may not have been appropriate to include in this analysis. The first, by Miller et al,[27] 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 was Yang et al,[14] an abstract of a paper that has now been published. The studies included in this review also varied widely in length of follow-up.

McGory et al[28] performed a meta-analysis of 6 randomized trials of perioperative beta blockade and concluded that therapy was associated with significant reductions in perioperative myocardial ischemia (from 33% to 15%), MI, cardiac mortality, and long-term cardiac mortality (from 12% to 2%). These authors used the combined data to derive ORs and CIs for several outcomes. For perioperative overall mortality, the OR for beta-blocker therapy was 0.52 (95% CI 0.20 to 1.35), and for perioperative cardiac mortality, the OR was 0.25 (95% CI 0.07 to 0.87). Neither the POBBLE[22] study nor the unpublished findings included in Devereaux et al's article were included, which explains the marked difference in findings from the other meta-analysis.

More recently, Wiesbauer et al[29] published a systematic review of randomized trials through 2005 of perioperative beta-blocker use in both cardiac and noncardiac surgery. The authors concluded that beta blockers reduced perioperative arrhythmias and myocardial ischemia, but they were unable to show an effect on mortality or perioperative MI. A cohort study by Lindenauer et al[7] reviewed administrative records from more than 600 000 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 of care and healthcare 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. The authors used propensity–score-matching techniques in an attempt to reduce confounding and selection bias. These authors found that for a Revised Cardiac Risk Index score[9] of 3 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 while in the hospital. This was not true for those with a Revised Cardiac Risk Index of 2, l, or 0. Those with a risk index of 0 were more likely to die in the hospital if given a beta blocker on day 1 or day 2 of hospitalization. This study was retrospective and not randomized and is therefore subject to potential bias. This is particularly true in terms of reporting bias, because the documentation was based entirely on administrative data sets, with arbitrary definitions of "on" or "off" perioperative beta blockers that were 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, whereas lower-risk patients had worse outcomes, which raises concerns regarding the routine use of beta blockers perioperatively in lower-risk patients.

One observational cohort study examined the question of which beta blocker may be best for perioperative medical therapy. Redelmeier et al[30] retrospectively reviewed prescription records and administrative data related to elective surgery in Ontario, Canada, from April 1992 to April 2002. They limited their analysis to patients older than 65 years of age who were receiving prescriptions for either atenolol or short-acting metoprolol before and after surgery (although actual beta-blocker use perioperatively was not ascertained) and identified 37 151 subjects. A total of 1038 either had a perioperative MI or died, and the rate of MI or death was significantly lower among those patients receiving atenolol than among those given metoprolol (2.5% versus 3.2%; $p<0.001$). This difference persisted even after adjustment for demographic, clinical, and surgical factors. The inclusion of other long-acting beta blockers in the analysis yielded an identical risk reduction. Although limited by several methodological issues, these data suggest that long-acting beta blockade (when therapy is initiated before surgery) might be superior to short-acting beta blockade, but clinical trial evaluation is awaited to confirm this.

7.2.1.1.1. Recent Data Regarding Perioperative Beta-Blocker Therapy (New Section). Since the publication of the 2007 update, the POISE trial investigators have published the results of their study.[8] Patients were randomly assigned to receive extended-release metoprolol succinate or placebo starting 2 to 4 hours before surgery and continued for 30 days with a primary end point of a composite of cardiovascular death, nonfatal MI, and nonfatal cardiac arrest. Patients were eligible if they were undergoing noncardiac surgery, were 45 years or older, had an expected length of hospital stay of at least 24 hours, and fulfilled any 1 of the following criteria: history of coronary artery disease; peripheral vascular disease; stroke; hospitalization for CHF within previous 3 years; undergoing major vascular surgery; or any 3 of 7 risk criteria (undergoing intrathoracic or intraperitoneal surgery, history of CHF, transient ischemic attack, diabetes mellitus, serum creatinine more than 175 micromoles/L, age older than 70 years, or undergoing emergency or urgent surgery). Patients who were previously receiving a beta blocker or who had coronary artery bypass graft surgery in the preceding 5 years and no cardiac ischemia since that time were excluded. Patients received the first dose of the study drug (metoprolol succinate 100 mg or *placebo*) 2 to 4 hours before surgery. Drug administration in the study required a heart rate of 50 bpm or higher and a systolic blood pressure of 100 mm Hg or greater; these parameters were checked before each administration. If at any time during the first 6 hours after surgery heart rate was 80 bpm or more and systolic blood pressure was 100 mm Hg or higher, patients received their first postoperative dose (extended-release metoprolol 100 mg or matched placebo) orally. If the study drug was not given during the first 6 hours, patients received their first postoperative dose at 6 hours after surgery. Twelve hours after the first postoperative dose, patients started taking oral extended-release metoprolol 200 mg or placebo every day for 30 days. If a patient's heart rate was consistently below 45 bpm or their systolic blood pressure dropped below 100 mm Hg, study drug was withheld until their heart rate or systolic blood pressure recovered; the study drug was then restarted at 100 mg once daily. Patients whose heart rate was consistently 45 to 49 bpm and whose systolic blood pressure exceeded 100 mm Hg delayed taking the study drug for 12 hours. Patients who were unable to take medications orally received the study drug by intravenous infusion (slow infusion of 15 mg of study drug over 60 minutes or rapid infusion of 5 mg over 2 minutes every 5 minutes up to a total of 15 mg as long as hemodynamic criteria were met) until they could resume oral medications.

The final analysis included 8351 patients from 190 hospitals in 23 countries. Several hundred more participants were excluded because of fraudulent activity at their sites. A total of 8331 patients (99.8%) completed the 30-day follow-up. Fewer patients in the metoprolol group than in the placebo group reached the primary end point of cardiovascular death, nonfatal MI, and nonfatal cardiac arrest (244 [5.8%] in the metoprolol group versus 290 [6.9%] in the placebo group; HR 0.84, 95% CI 0.70 to 0.99; $p=0.0399$). Fewer patients in the metoprolol group than in the placebo group had an MI (176 [4.2%] versus 239 [5.7%]; HR 0.73, 95% CI 0.60 to 0.89; $p=0.0017$). However, more people receiving metoprolol died than did individuals receiving placebo (HR 1.33, 95% CI 1.03 to 1.74; $p=0.0317$); the Kaplan-Meier mortality estimates started separating on day 10. The only reported cause of death for which there was a significant difference between groups was sepsis or infection, which was more common among patients allocated to metoprolol. More patients in the metoprolol group than in the placebo group had a stroke (41 [1.0%] versus 19 [0.5%] patients; HR 2.17, 95% CI 1.26 to 3.74; $p=0.0053$). Most patients who had a nonfatal stroke subsequently required help to perform everyday activities or were incapacitated. Multiple predefined subgroup analyses were performed, although the study was underpowered to detect modest differences in subgroup effects. The cohort that developed clinically significant hypotension had the largest population-attributable risk for death and the largest intraoperative or postoperative risk for stroke. In the wake of POISE, a meta-analysis of trials investigating the use of beta blockers around the time of noncardiac surgery and incorporating the POISE results was published.[31] The authors found that beta blockers were associated with a significant reduction in nonfatal MI (OR 0.65) and ischemia (OR 0.36) at the expense of an increased risk of stroke (OR 2.01), as well as bradycardia and hypotension. As the largest of the included trials by far, these results are largely driven by the POISE results. The results point to a need to understand more fully the causes for the increased risk of stroke and death seen in POISE and their relation to the potential hemodynamic effects of beta blockade. Because of limitations inherent in meta-analysis, these analyses could not be adjusted for type and duration or dosage of beta blockers used in treatment protocols.

Several nonrandomized studies have also been published. Kaafarani et al[32] published a retrospective, single-center experience assessing outcomes in those who received beta blockers perioperatively (n=238) compared with a control group (n=408) that did not. In this study, unlike POISE, beta-blocker use was associated with an increased risk of MI at 30 days (2.94% versus 0.74%; p=0.03) and death (2.52% versus 0.25%; p=0.007), and patients who died had significantly higher preoperative heart rates, but these data are difficult to interpret in light of methodological limitations. Matyal et al[33] analyzed retrospective data from 960 patients (594 men, 366 women) undergoing primarily infrainguinal vascular surgery. They reported that use of beta blockers was associated with a lower risk of adverse outcome (including MI, CHF, death, significant arrhythmia, and renal failure) in men (12.6% versus 18.9%; p=0.04) but not in women (17.8% versus 13.7%; p=0.37), which raises the question of sex difference in response to perioperative beta blockade.

Finally, the results of a large (n=1066), randomized, controlled trial of bisoprolol and fluvastatin use in intermediate-risk patients undergoing noncardiac surgery (DECREASE IV) were presented at the 2008 American Heart Association Annual Scientific Sessions and were published recently.[6] Patients were enrolled who were at least 40 years of age, were scheduled for elective noncardiac surgery, and had an estimated risk of perioperative death and MI of 1% to 6%. Exclusion criteria included the use of beta blockers; a contraindication for beta blocker use; the use of statins before randomization; a contraindication for statin use; unstable coronary heart disease or evidence of 3-vessel disease or left main disease; elevated cholesterol according to the National Cholesterol Consensus; emergency surgery; inability or unwillingness to provide written informed consent; and previous participation in the same trial. Participants were randomized according to an open-label, factorial design to 1) beta-blocker therapy (bisoprolol), 2) statin (fluvastatin XL 80 mg daily), 3) a combination of a beta blocker and a statin (bisoprolol and fluvastatin), or 4) neither a beta blocker nor a statin (control group). By design, study medication could be started up to the day of surgery (median 34 days before the procedure, interquartile range 21 to 53 days) and was to be continued until 30 days after surgery. The starting dose of bisoprolol was 2.5 mg orally per day if resting heart rate was higher than 50 bpm. During hospitalization, resting heart rate was evaluated on a daily basis, and drug dose was modified in steps of 1.25 or 2.5 mg per day, up to a maximum dose of 10 mg, aiming for a heart rate of 50 to 70 bpm. The primary efficacy end point was a composite of cardiac death and nonfatal MI until 30 days after surgery. The study was terminated early owing to slow enrollment linked to widespread use of 1 or both types of medications in the population screened. Patient characteristics were as follows: median age 64 years; 60% male; 11% with diabetes mellitus; 6% with angina pectoris; 5% with prior MI; and 4% with prior stroke. The most common types of surgery were general (39%), urological (19%), orthopedic (16%), and ear-nose-throat (12%). Patients randomized to bisoprolol (n=533) had a lower incidence of perioperative cardiac death and nonfatal MI than those who did not receive bisoprolol (2.1% versus 6.0% events; HR 0.34, 95% CI 0.17 to 0.67; p=0.002). Ischemic stroke occurred in 7 patients (0.7%), of whom 4 (0.8%) were randomized to bisoprolol treatment and 3 (0.6%) were randomized to the group that did not receive bisoprolol (p=0.68). In total, 3 patients (0.6%) randomized to bisoprolol reached 1 other beta–blocker-related safety end point (heart failure, clinically significant bradycardia, or hypotension) compared with 2 patients (0.4%) in the group that did not receive bisoprolol (p=0.65). The authors also reported a stroke rate of 0.4% in all the DECREASE studies combined, with no difference between treatment groups.

This research demonstrated a cardioprotective effect of perioperative beta-blocker use in the intermediate-risk group, without an increased incidence of perioperative stroke or mortality, although power for these end points was limited. Importantly, beta blockers were generally started well in advance of surgery and were titrated to heart rate starting at a low dose.[6]

7.2.1.2. Titration of Beta Blockers. Beta-blocker therapy is commonly used to reduce adverse cardiac events in conditions such as MI and CHF. Titration of the dose is a well-recognized part of using this class of medication. For example, the "ACC/AHA 2007 Guidelines for the Management of Patients With Unstable Angina/Non–ST-Elevation Myocardial Infarction"[34] and the "ACC/AHA Guidelines for the Management of Patients With ST-Elevation Myocardial Infarction"[35] recommend dose titration of beta blockers to a goal heart rate of 50 to 60 bpm. Titration to goal heart rate in this case is associated with more benefit than the fixed-dose application of the medication alone. Cucherat[36] evaluated 17 trials of beta blockers in patients with MI that reported change in heart rate, showing that each 10-bpm reduction in the heart rate is estimated to reduce the RR of cardiac death by 30%. In patients with MI, the use of fixed, higher-dose therapy was associated with increases in cardiogenic shock that offset reductions in reinfarction and ventricular fibrillation.[37] In CHF, the "ACC/AHA 2005 Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult"[38] also suggested that beta blockers should be titrated up to high-dose therapy in patients who could tolerate these doses. Recent data suggest that high-dose therapy, in patients who tolerate the dose, reduces event rates more than low-dose therapy.[5]

Similarly, in the management of perioperative patients, fixed-dose beta-blocker administration has not shown sufficient benefit to warrant routine use. POISE, as the largest trial to date, and the only trial with enough power to confirm a null result, makes this clear. Several potential problems can arise from a fixed-dose management strategy. First, fixed-dose strategies cannot account for the variability in response to medications within a population and may provide doses that are inadequate for some patients, adequate for some, and clearly too much for others, as evidenced by increased hypotension and bradycardia. Second, long-acting oral medications may not provide the flexibility required for the dynamic postoperative clinical condition. Third, fixed-dose regimens presuppose a constant requirement for beta blockade in the postoperative setting. Small physiological trials have made clear that sympathetic nervous system tone in-

creases after operation and returns to baseline within 4 to 5 days,[39] which suggests variation in the required dose within individual patients.

In contrast to the fixed-dose studies, beta-blocker dose titration may provide benefit in high-risk patients. Feringa et al[40] performed an observational cohort study of 272 vascular surgery patients. The beta-blocker dose was converted to a percentage of the maximum recommended therapeutic dose. In multivariable analysis, higher beta-blocker doses (per 10% increase) were significantly associated with a lower incidence of myocardial ischemia (HR 0.62, 95% CI 0.51 to 0.75), troponin T release (HR 0.63, 95% CI 0.49 to 0.80), and long-term mortality (HR 0.86, 95% CI 0.76 to 0.97). Higher heart rates during electrocardiographic monitoring (per 10-bpm increase) were significantly associated with an increased incidence of myocardial ischemia (HR 2.49, 95% CI 1.79 to 3.48), troponin T release (HR 1.53, 95% CI 1.16 to 2.03), and long-term mortality (HR 1.42, 95% CI 1.14 to 1.76). An absolute mean perioperative heart rate lower than 70 bpm was associated with the best outcome.

Poldermans et al[11] randomly assigned 770 intermediate-risk patients to cardiac stress testing (n=386) or no testing (n=384). All patients received beta blockers, and the beta-blocker dose was adjusted preoperatively to achieve a resting heart rate of 60 to 65 bpm. In patients with ischemia, physicians aimed to control heart rate below the ischemic threshold. Patients assigned to no testing had a similar incidence of the cardiac events as those assigned to testing. Patients with a heart rate lower than 65 bpm had lower risk than the remaining patients (1.3% versus 5.2%; OR 0.24, 95% CI 0.09 to 0.66; p=0.003). The authors concluded that cardiac testing can safely be omitted in intermediate-risk patients, provided that beta blockers aimed at tight heart rate control are prescribed. The importance of heart rate control in reducing perioperative myocardial ischemia is further supported by a study by Raby et al.[19]

Meta-analyses addressing this subject have had mixed results. Beattie et al[41] identified 10 trials enrolling 2176 subjects. Trials associated with an estimated maximal heart rate of lower than 100 bpm showed cardioprotection for MI (OR 0.23, 95% CI 0.08 to 0.65; p=0.005), whereas those with higher maximal heart rates did not (OR 1.17, 95% CI 0.79 to 1.80; p=0.43). Biccard et al[42] identified 8 studies of perioperative beta blockade around the time of noncardiac surgery and found no correlation between heart rate and cardiac complications at 30 days, although postoperative heart rate was not a primary end point in these studies. Overall, available evidence suggests that beta blockers, if used, should be appropriately titrated throughout the preoperative, intraoperative, and postoperative period to achieve effective heart rate control while avoiding frank hypotension and bradycardia.

7.2.1.3. Withdrawal of Beta Blockers. Beta-blocker withdrawal has been associated with an increased risk of MI and chest pain. Psaty et al[43] showed that hypertensive patients who stopped taking their beta blockers had a transient 4-fold increase in the RR of first events associated with coronary heart disease (RR 4.5, 95% CI 1.1 to 18.5). More recently, Teichert et al[44] showed that selective beta-blocker discontinuation resulted in a higher risk of MI in the first 30 days (RR 2.70, 95% CI 1.06 to 6.89) and between 30 and 180 days (RR 2.44, 95% CI 1.07 to 5.59) after cessation, although older data from Croft et al[45] suggest the short-term risk of discontinuation during MI is modest and does not result in a significant increase in infarct size or worsened in-hospital outcomes.

Concerns regarding the discontinuation of beta-blocker therapy in the perioperative period have existed for several decades.[46] Shammash et al[47] retrospectively studied a total of 140 patients who received beta blockers preoperatively. Mortality in the 8 patients who had beta blockers discontinued postoperatively (50%) was significantly greater than in the 132 patients in whom beta blockers were continued (1.5%; OR 65.0; p<0.001). Hoeks et al[48] studied 711 consecutive peripheral vascular surgery patients. After adjustment for potential confounders and the propensity of its use, continuous beta-blocker use remained significantly associated with a lower 1-year mortality than among nonusers (HR 0.4, 95% CI 0.2 to 0.7). In contrast, beta-blocker withdrawal was associated with an increased risk of 1-year mortality compared with nonusers (HR 2.7, 95% CI 1.2 to 5.9).

Thus, although data are limited, perioperative beta-blocker withdrawal should be avoided unless necessary. As noted in the recommendations, continuation of beta-blocker therapy in the perioperative period is a Class I indication, and accumulating evidence suggests that titration to maintain effective heart rate control while avoiding frank hypotension and bradycardia should be the goal.

7.2.1.4. Risks and Caveats (New Section). Perioperative beta blockade is associated with risk. All of the previously discussed studies have incorporated lower limits of heart rate and blood pressure with regard to holding or discontinuing the study medication. In the POISE trial, the oral study medication was held if the heart rate was consistently below 45 bpm or the systolic blood pressure was below 100 mm Hg.[8] If a patient's heart rate was consistently 45 to 49 bpm, there was a delay of 12 hours in administering the study drug. If the patient was on an intravenous infusion, the study medication was held if the patient's heart rate dropped below 50 bpm or systolic blood pressure dropped to below 100 mm Hg. Similarly, Poldermans et al[5] held beta-blocker medication if the heart rate was lower than 50 bpm or the systolic blood pressure was lower than 100 mm Hg. Several meta-analyses have examined the rates of bradycardia and hypotension. Stevens et al[24] reported an OR of 3.76 (95% CI 2.45 to 5.77; number needed to harm=6) for bradycardia, although the definition of bradycardia varied from study to study. In the more recent meta-analysis, the risk ratio for postoperative bradycardia was 2.22 (95% CI 1.50 to 3.29), and the risk ratio for bradycardia that required treatment was 2.34 (95% CI 1.62 to 3.37).[49] Postoperative hypotension was also significant, with a risk ratio of 1.29 (95% CI 1.10 to 1.51). Beattie et al[41] analyzed 10 randomized trials with 2176 patients and found that perioperative beta blockade was associated with an increased incidence of bradycardia (OR 3.49, 95% CI 2.4 to 5.9) and CHF (OR 1.68, 95% CI 1.00 to 2.8). Importantly, administration of beta blockers did not reliably decrease HRs

in all patients. In the POISE trial,[8] the HR in the metoprolol group for clinically significant hypotension was 1.55 (95% CI 1.38 to 1.74), and the HR for clinically significant bradycardia was 2.74 (95% CI 2.19 to 3.43); in addition, clinically significant hypotension was associated with an adjusted OR of death and stroke of 4.97 (95% CI 3.62 to 6.81), whereas clinically significant bradycardia was associated with an adjusted OR for death and stroke of 2.13 (95% CI 1.37 to 3.12). Given the association between hypotension or bradycardia and morbidity or mortality from the POISE trial, the hemodynamic effects of perioperative beta blockade must be incorporated and considered in any beta-blocker protocol, with the goal of avoidance of bradycardia and hypotension. The association of death due to sepsis and beta-blocker use in POISE also suggests that a thorough search for alternative causes of tachycardia, such as infection, is important. Indeed, patients with persistent tachycardia may have alternative causes, such as sepsis, hypovolemia, pulmonary embolism, and anemia that would warrant short-term down titration or even discontinuation of beta-blocker therapy. Available evidence therefore supports an ongoing examination and reexamination of the indication and contraindications to beta-blocker therapy throughout the postoperative period.

7.2.1.5. Summary (New Section). This focused update incorporates important new information regarding the risks and benefits of perioperative beta blockade, as well as expert consensus. In this update, a Class I indication for perioperative beta-blocker use exists for continuation of a beta blocker in patients already taking the drug. In addition, several Class IIa recommendations exist for patients with inducible ischemia, coronary artery disease, or multiple clinical risk factors who are undergoing vascular (i.e., high-risk) surgery and for patients with coronary artery disease or multiple clinical risk factors who are undergoing intermediate-risk surgery. Initiation of therapy, particularly in lower-risk groups, requires careful consideration of the risk:benefit ratio for an individual patient. Initiation well before a planned procedure with careful titration perioperatively to achieve adequate heart rate control while avoiding frank bradycardia or hypotension is also suggested. In light of the POISE results, routine administration of perioperative beta blockers, particularly in higher fixed-dose regimens begun on the day of surgery, cannot be advocated. Ongoing and future studies in this area should continue to address limitations in our evidence base on this subject and provide further guidance regarding this important topic.

Staff

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KEY WORDS: ACCF/AHA practice guidelines ■ focused update ■ perioperative beta blockade ■ perioperative care ■ beta blocker ■ preoperative assessment ■ preoperative evaluation

Appendix 1. Author Relationships With Industry and Other Entities—2009 ACCF/AHA Focused Update on Perioperative Beta Blockade

Writing Group Member	Consultant	Speaker	Ownership/ Partnership/ Principal	Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
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Dr Hugh Calkins	None	None	None	None	None	None
Dr Lee A. Fleisher	None	None	None	None	None	None
Dr William K. Freeman	None	None	None	None	None	None
Dr James B. Froehlich	• Pfizer • Sanofi-aventis	• Merck/Schering-Plough • Otsuka • Pfizer • Sanofi-aventis	None	• Blue Cross Blue Shield of Michigan • Gore • Novartis • Sanofi-aventis	None	None
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Dr John F. Robb	None	None	None	None	None	None
Dr R. James Valentine	None	None	None	None	None	None

This table represents the relationships of committee members with industry and other entities that were reported by authors to be relevant to this document. These relationships were reviewed and updated in conjunction with all meetings and/or conference calls of the writing committee during the document development process. The table does not necessarily reflect relationships with industry at the time of publication. A person is deemed to have a significant interest in a business if the interest represents ownership of 5% or more of the voting stock or share of the business entity or ownership of $10 000 or more of the fair market value of the business entity, or if funds received by the person from the business entity exceed 5% of the person's gross income for the previous year. A relationship is considered to be modest if it is less than significant under the preceding definition. Relationships in this table are modest unless otherwise noted.

*Indicates significant relationship.

Appendix 2. Reviewer Relationships With Industry and Other Entities—2009 ACCF/AHA Focused Update on Perioperative Beta Blockade

Peer Reviewer	Representation	Consultant	Speaker	Ownership/ Partnership/ Principal	Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Dr Jeffrey Cavendish	Official Reviewer—ACCF Board of Governors	None	• Bristol-Myers Squibb/Sanofi-aventis • Novartis • Pfizer	None	None	None	None
Dr Jerold Levy	Official Reviewer—American Heart Association	• Baxter • Cubist • Dyax • The Medicines Co. • Novo • Organon	• GlaxoSmithKline • The Medicines Co.	None	• Eli Lilly*	None	None
Dr Robert A. Guyton	Official Reviewer—ACCF/AHA Task Force on Practice Guidelines	• Medtronic	None	None	None	None	None
Dr Rick Nishimura	Official Reviewer—ACCF Board of Trustees	None	None	None	None	None	None
Dr Thomas Ryan	Official Reviewer—American Heart Association	• Phillips	None	None	None	None	None
Dr Herbert Aronow	Organizational Reviewer—Society for Vascular Medicine	• Pfizer	• Sanofi-aventis • Pfizer	None	None	None	None
Dr Mina K. Chung	Organizational Reviewer—Heart Rhythm Society	None	None	None	None	None	None
Dr Mylan Cohen	Organizational Reviewer—American Society of Nuclear Cardiology	• Astellas	• Astellas	None	None	None	None
Dr John Ellis	Organizational Reviewer—Society of Cardiovascular Anesthesiologists	• Baxter*	• Baxter* • The Medicines Co.	None	None	None	None
Dr Robert Hamilton	Organizational Reviewer—Heart Rhythm Society	None	None	None	None	None	None
Dr Thomas Holly	Organizational Reviewer—American Society of Nuclear Cardiology	None	• Astellas	None	• Astellas	None	None
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Appendix 2. Continued

Peer Reviewer	Representation	Consultant	Speaker	Ownership/ Partnership/ Principal	Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Dr Martin G. Keane	Organizational Reviewer—American Society of Echocardiography	• Pfizer	None	None	• Edwards Scientific	None	• Petroff & Associates, plaintiff
Dr Lois Killewich	Organizational Reviewer—Society for Vascular Surgery	None	None	None	None	None	None
Dr Smadar Kort	Organizational Reviewer—American Society of Echocardiography	None	None	None	None	None	None
Dr Martin London	Organizational Reviewer—Society of Cardiovascular Anesthesiologists	None	None	None	None	None	None
Dr Sriharis Naidu	Organizational Reviewer—Society for Cardiovascular Angiography and Interventions	None	None	None	None	None	None
Dr Todd Rasmussen	Organizational Reviewer—Society for Vascular Surgery	None	• Bristol-Myers Squibb	None	None	None	None
Dr Yung Wei-Chi	Organizational Reviewer—Society for Vascular Medicine	None	None	• Pfizer	None	None	None
Dr Theodore A. Bass	Content Reviewer—ACCF Interventional Council	None	None	None	None	None	None
Dr Mark A. Creager	Content Reviewer—ACCF/AHA Task Force on Practice Guidelines	• BioMarin • Genzyme • Sanofi-aventis • Sigma Tau • Vascutek	None	None	• Merck • Sanofi-aventis	None	None
Dr Kim Eagle	Content Reviewer	• NHLBI* • Sanofi-aventis*	None	None	• Gore* • Sanofi-aventis	None	• Defense witness, Yasbeck v. Providence St. Joseph Medical Center, et al.
Dr Gabriel Gregoratos	Content Reviewer	None	None	None	None	None	None

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Appendix 2. Continued

Peer Reviewer	Representation	Consultant	Speaker	Ownership/ Partnership/ Principal	Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Dr David L. Holmes	Content Reviewer—ACCF Interventional Council	None	None	None	None	None	None
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Dr Frederick G. Kushner	Content Reviewer—ACCF/AHA Task Force on Practice Guidelines	None	None	None	• AstraZeneca • Atherogenics • Novartis • Pfizer	None	None
Dr Debrata Mukherjee	Content Reviewer—ACCF Cardiac Catheterization Committee	None	None	None	None	None	
Dr Richard L. Page	Content Reviewer—ACCF/AHA Task Force on Practice Guidelines	None	None	None	None	None	None
Dr Christopher L. White	Content Reviewer—ACCF Interventional Council	• Baxter	None	None	• Boston Scientific	None	None

ACC indicates American College of Cardiology; ACCF, American College of Cardiology Foundation; AHA, American Heart Association; NCDR ICD Registry, National Cardiovascular Data Registry for implantable cardioverter defibrillators, and NHLBI, National Heart, Lung, and Blood Institute.

This table represents the relevant relationships with industry and other entities that were disclosed at the time of peer review. It does not necessarily reflect relationships with industry at the time of publication. A person is deemed to have a significant interest in a business if the interest represents ownership of 5% or more of the voting stock or share of the business entity or ownership of $10 000 or more of the fair market value of the business entity, or if funds received by the person from the business entity exceed 5% of the person's gross income for the previous year. A relationship is considered to be modest if it is less than significant under the preceding definition. Relationships in this table are modest unless otherwise noted. Names are listed in alphabetical order within each category of review.

*Significant (>$10 000) relationship.

Appendix 3. Perioperative Beta Blockade in Noncardiac Surgery Studies: Summary Table

Study	Year of Publication	Trial Type	No. of Patients	Patient Population	Primary End Point	Analysis: HR, RR, OR, NNT	95% CI and/or p	Results
Mangano et al[12]	1996	RCT	200	Patients with or at risk for CAD undergoing noncardiac surgery	"Overall mortality after discharge from the hospital was significantly lower among the atenolol-treated patients than among those who were given placebo over the 6 months following hospital discharge."	0 versus 8%	p<0.001	The authors concluded, "The principal effect was a reduction in deaths from cardiac causes during the first 6 to 8 months. Combined cardiovascular outcomes were similarly reduced among the atenolol-treated patients; event-free survival throughout the 2-year study period was 68% in the placebo group and 83% in the atenolol group; p=0.008."
					Over the first year	3% versus 14%	p=0.005	
					Over 2 years	10% versus 21%	p=0.019	
Wallace et al[50]	1998	RCT	200	Patients with, or at risk for, CAD	"The incidence of myocardial ischemia on Days 0–2 was significantly reduced in the atenolol group (atenolol, 17 of 99 patients; placebo, 34 of 101 patients)."		p=0.008	The authors concluded, "Perioperative administration of atenolol for 1 week to patients at high risk for CAD significantly reduces the incidence of postoperative myocardial ischemia. Reductions in perioperative myocardial ischemia are associated with reductions in the risk for death at 2 years."
					"The incidence of myocardial ischemia on Days 0–7 was significantly reduced in the atenolol group (atenolol, 24 of 99 patients; placebo, 39 of 101 patients)."		p=0.029	
					"Patients with episodes of myocardial ischemia were more likely to die in the next 2 years."		p=0.025	
Poldermans et al[5]	1999	Randomized multicenter trial	112	Major vascular surgery	"The primary study end point of death due to cardiac causes or nonfatal MI occurred in 2 patients in the bisoprolol group (3.4%) and 18 in the standard-care group (34%)."		p<0.001	The authors concluded, "Bisoprolol reduces the perioperative incidence of death from cardiac causes and nonfatal MI in high-risk patients who are undergoing major vascular surgery."
					"Two patients in the bisoprolol group died of cardiac causes (3.4%) compared with 9 in the standard-care group (17%)."		p=0.02	

(*Continued*)

Appendix 3. Continued

Study	Year of Publication	Trial Type	No. of Patients	Patient Population	Primary End Point	Analysis: HR, RR, OR, NNT	95% CI and/or p	Results
					"Nonfatal MI occurred in 9 patients given standard care only (17%) and in none of those given standard care plus bisoprolol."		p<0.001	
Zaugg et al[20]	1999	RCT	63	Elderly, noncardiac surgery patients. Group I, no atenolol; Group II, preoperative and postoperative atenolol; Group III, intraoperative atenolol.	"Hormonal markers of the stress response (neuropeptide Y, epinephrine, norepinephrine, cortisol, and adrenocorticotropic hormone) were evaluated preoperatively and for 72 hours after surgery."	Perioperative beta blockade did not significantly alter the hormonal stress response.		The authors concluded, "Beta-blockade does not reduce the neuroendocrine stress response, suggesting that this mechanism is not responsible for the previously reported improved cardiovascular outcome. However, it confers several advantages, including decreased analgesic requirements, faster recovery from anesthesia, and improved hemodynamic stability. The release of cardiac troponin I suggests the occurrence of perioperative myocardial damage in this elderly population, which appears to be independent of the neuroendocrine stress response."
					The beta-blocked patients "received less fentanyl intraoperatively (27.7%, p<0.0001), experienced faster early recovery, had lower pain scores, and required less analgesia in the postanesthesia care unit. Cardiac troponin I release was detected in 8 of 19, 4 of 20, and 5 of 20 patients in Groups I, II, and III, respectively (p=not significant)." "Three patients in Group I had cardiac troponin I levels consistent with MI."		p<0.0001	

(*Continued*)

Appendix 3. Continued

Study	Year of Publication	Trial Type	No. of Patients	Patient Population	Primary End Point	Analysis: HR, RR, OR, NNT	95% CI and/or p	Results
Raby et al[19]	1999	RCT	26	High-risk vascular surgery patients	"Ischemia persisted in the postoperative period in 8 (73%) of 11 placebo patients but only 5 (33%) of 15 esmolol patients."		p<0.05	The authors' data suggest that "patient-specific, strict heart rate control aiming for a predefined target based on individual preoperative ischemic threshold was associated with a significant reduction and frequent elimination of postoperative myocardial ischemia among high-risk patients and provides a rationale for a larger trial to examine this strategy's effect on cardiac risk."
Brady et al[22]	2005	Double-blind RCT	103	Patients without previous MI who had infrarenal vascular surgery	"Cardiovascular events occurred in 15 (34%) and 17 (32%) patients in the placebo and metoprolol groups, respectively."	Unadjusted RR 0.94	0.53 to 1.66	The authors concluded, "Myocardial ischemia was evident in a high proportion (one-third) of the patients after surgery. A pragmatic regimen of perioperative beta-blockade with metoprolol did not seem to reduce 30-day cardiovascular events, but it did decrease the time from surgery to discharge."
						Adjusted RR 0.87	0.48 to 1.55	
					"Time from operation to discharge was reduced from a median of 12 days (95% CI 9–19 days) in the placebo group to 10 days (95% CI 8–12 days) in the metoprolol group."	Adjusted HR 1.71	1.09 to 2.66; p<0.02	
Juul et al[13]	2006	RCT	921	Patients who have diabetes >39 years of age scheduled for major noncardiac surgery	"The composite primary outcome measure was time to all-cause mortality, acute MI, unstable angina, or CHF."			The authors concluded, "Perioperative metoprolol did not significantly affect mortality and cardiac morbidity in these patients with diabetes. CI, however, were wide, and the issue needs reassessment."

(*Continued*)

Appendix 3. Continued

Study	Year of Publication	Trial Type	No. of Patients	Patient Population	Primary End Point	Analysis: HR, RR, OR, NNT	95% CI and/or p	Results
					"The primary outcome occurred in 99 (21%) of 462 patients in the metoprolol group and 93 (20%) of 459 patients in the placebo group during a median follow-up of 18 months (range 6–30 months)."	HR 1.06	0.80 to 1.41	
					"All-cause mortality was 16% (74 of 462 patients) in the metoprolol group and 16% (72 of 459 patients) in the placebo group."	HR 1.03	0.74 to 1.42	
Poldermans et al[11]	2006	RCT	1476	Patients undergoing elective open abdominal aortic or infrainguinal arterial reconstruction	"Patients assigned to no testing had a similar incidence of the primary end point as those assigned to testing (1.8% versus 2.3%)."	OR 0.78	0.28 to 2.1; p=0.62	The authors concluded, "Cardiac testing can safely be omitted in intermediate-risk patients, provided that beta blockers aiming at tight [heart rate] control are prescribed."
					"Regardless of allocated strategy, patients with a heart rate <65 bpm had lower risk than the remaining patients (1.3% versus 5.2%)."	OR 0.24	0.09 to 0.66; p=0.003	
Yang et al[14]	2006	RCT	496	Abdominal aortic surgery and infrainguinal or axillofemoral revascularizations	Primary outcome was postoperative 30-day composite incidence of nonfatal MI, unstable angina, new CHF, new atrial or ventricular dysrhythmia requiring treatment, or cardiac death.			The authors concluded, "Metoprolol was not effective in reducing the 30-day and 6-month postoperative cardiac event rates. Prophylactic use of perioperative beta blockers in all vascular patients is not indicated."
					"Primary outcome events at 30 days occurred in 25 patients (10.2%) versus 30 (12.0%) in the metoprolol and placebo groups, respectively."	RR reduction 15.3%	−38.3% to 48.2%; p=0.57	
					Observed effects at 6 months were not significantly different.	RR reduction 6.2%	−58.4% to 43.8%; p=0.81	
					Intraoperative bradycardia requiring treatment was more frequent in the metoprolol group (53 of 246 versus 19 of 250 patients).		p=0.00001	
					Intraoperative hypotension requiring treatment was more frequent in the metoprolol group (114 of 246 versus 84 of 250 patients).		p=0.0045	

(*Continued*)

Appendix 3. Continued

Study	Year of Publication	Trial Type	No. of Patients	Patient Population	Primary End Point	Analysis: HR, RR, OR, NNT	95% CI and/or p	Results
Zaugg et al[21]	2007	Double-blind, placebo-controlled, multicenter trial	219	Patients undergoing surgery with spinal block	"One-year composite outcome included cardiovascular mortality, nonfatal MI, unstable angina, CHF, and cerebrovascular insult."			The authors concluded, "Perioperative bisoprolol therapy did not affect cardiovascular outcome in these elderly at-risk patients undergoing surgery with spinal block."
					"The primary outcome occurred in 25 patients (22.7%) in the bisoprolol group and 24 (22.0%) in the placebo group during the 1-year follow-up."	HR 0.97	0.55 to 1.69; p=0.90	
					"Carriers of at least 1 Gly allele of the beta-1-adrenergic receptor polymorphism *Arg389Gly* showed a higher number of adverse events than Arg-homozygous subjects (32.4% versus 18.7%)."	HR 1.87	1.04 to 3.35; p=0.04	
Devereaux et al[8]	2008	RCT	8331	Patients undergoing noncardiac surgery	"The primary end point was a composite of cardiovascular death, nonfatal MI, and nonfatal cardiac arrest. Fewer patients in the metoprolol group than in the placebo group reached the primary end point (244 [5.8%] patients in the metoprolol group versus 290 [6.9%] in the placebo group)."	HR 0.84	0.70 to 0.99; p=0.0399	The authors concluded their "results highlight the risk in assuming a perioperative beta blockerregimen has benefit without substantial harm, and the importance and need for large randomizedtrials in the perioperative setting. Patients are unlikely to accept the risks associated with perioperative extended-release metoprolol."
					"Fewer patients in the metoprolol group than in the placebo group had an MI (176 [4.2%] versus 239 [5.7%] patients)."	HR 0.73	0.60 to 0.89; p=0.0017	
					"More deaths occurred in the metoprolol group than in the placebo group (129 [3.1%] versus 97 [2.3%] patients)."	HR 1.33	1.03 to 1.74; p=0.0317	
					"More patients in the metoprolol group than in the placebo group had a stroke (41 [1.0%] versus 19 [0.5%] patients)."	HR 2.17	1.26 to 3.74; p=0.0053	

(*Continued*)

Appendix 3. Continued

Study	Year of Publication	Trial Type	No. of Patients	Patient Population	Primary End Point	Analysis: HR, RR, OR, NNT	95% CI and/or p	Results
Dunkelgrun et al[6]	2009	RCT	1066	Intermediate-risk patients undergoing noncardiovascular surgery	The primary end point was the composite of perioperative cardiac death and nonfatal MI.			The authors concluded, "In intermediate-risk surgicalpatients, bisoprolol was associated with a significant reduction of 30-day cardiac complications,while fluvastatin showed a trend for improved outcome."
					"Patients randomized to bisoprolol (n=533) had a lower incidence of the primary end point than those randomized to bisoprolol-control therapy (2.1% versus 6.0% events)."	HR 0.34	0.17 to 0.67; p=0.002	
					"The beneficial effects of bisoprolol were not modified by fluvastatin. Patients randomized to fluvastatin experienced a lower incidence of the primary efficacy end point than those randomized to fluvastatin-control therapy (3.2% versus 4.9% events)."	HR 0.65	0.35 to 1.10; p=0.17	
Nonrandomized Studies								
Pasternack et al[16]	1987		83	Patients scheduled for abdominal aortic aneurysm surgery	Group 1 was treated with oral metoprolol immediately before surgery and with intravenous metoprolol during the postoperative period. Group 2, who did not receive metoprolol, served as a control.			The authors concluded that their "data demonstrate that beta blockade with metoprolol is effective in controlling systolic blood pressure and heart rate both intraoperatively and postoperatively in patients undergoing repair of AAA and can significantly reduce the incidence of perioperative MI and arrhythmias."
					"In Group 1, only 1 patient (3%) had an acute MI. In contrast, 9 Group 2 patients (18%) had perioperative MI.		p<0.05	
					Only 4 Group 1 patients (12.5%) developed significant cardiac arrhythmias as opposed to 29 Group 2 patients (56.9%)."		p<0.001	

(*Continued*)

Appendix 3. Continued

Study	Year of Publication	Trial Type	No. of Patients	Patient Population	Primary End Point	Analysis: HR, RR, OR, NNT	95% CI and/or p	Results
Pasternack et al[17]	1989	Clinical trial	48	Peripheral vascular surgery patients	"Patients treated with oral metoprolol had significantly less intraoperative silent ischemia with respect to relative duration and frequency of episodes, a significantly lower intraoperative heart rate, and less intraoperative silent myocardial ischemia in terms of total absolute duration."			The authors concluded, "These results suggest that beta-adrenergic activation may play a major role in the pathogenesis of silent myocardial ischemia during peripheral vascular surgery."
Yeager et al[18]	1995	Case-control study	159	Vascular surgery	"Beta blockers were used less frequently in patients with perioperative MI than in control patients without perioperative MI (30% versus 50%)."		p=0.01	The authors concluded, "Beta blockade is associated with a decreased incidence of perioperative MI in patients undergoing vascular surgery. Prophylactic perioperative use of beta-blockers may decrease perioperative MI in patients requiring major vascular surgery."
					"Overall, beta blockade was associated with a 50% reduction in perioperative MI."		p=0.03	
Boersma et al[4]	2001	Cohort study	1351	Of patients undergoing major vascular surgery, 611 patients (45%) had a Lee risk index of 1; 509 (38%) had an index of 2; and 231 (17%) had an index of ≥3 points (all patients underwent high-risk surgery and thus had a risk index ≥1 point).	Cardiac death or nonfatal MI within 30 days after surgery was the main outcome measure, compared by clinical characteristics, DSE results, and beta blocker use.			The authors concluded the "additional predictive value of DSE is limited in clinically low-risk patients receiving beta blockers. In clinical practice, DSE may be avoided in a large number of patients who can proceed safely for surgery without delay. In clinically intermediate- and high-risk patients receiving beta blockers, DSE may help identify those in whom surgery can still be performed and those in whom cardiac revascularization should be considered."

(*Continued*)

Appendix 3. Continued

Study	Year of Publication	Trial Type	No. of Patients	Patient Population	Primary End Point	Analysis: HR, RR, OR, NNT	95% CI and/or p	Results
					Among the 83% of patients with <3 clinical risk factors, 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]), and DSE had minimal additional prognostic value. In patients with ≥3 risk factors (17%), DSE provided additional prognostic information; patients without stress-induced ischemia had a much lower risk of events than those with stress-induced ischemia (among those receiving beta blockers, 2.0% [1 of 50] versus 10.6% [5 of 47]). Patients with limited stress-induced ischemia (1-4 segments) experienced fewer cardiac events (2.8% [1 of 36]) than those with more extensive ischemia (≥5 segments, 36% [4 of 11]).			
					"Patients who did not undergo DSE (i.e., patients without clinical cardiac risk factors) and those without NWMAs during DSE had a significantly lower cardiac death or MI rate than patients with NWMAs during DSE (0.4% and 1.6% versus 13.5%, respectively)."		p<0.001	
					"In the 222 patients with NWMAs, 67% received beta blockers, with 4.7% having a perioperative cardiac event versus 31.5% of those not receiving beta blockers."	Mantel-Haenszel test 0.1	0.1 to 0.3	
			222		Univariable relation between DSE results and perioperative cardiac death or MI: NWMA (DSE summary).	OR 39.5	5.3 to 292; p<0.001	
					"Multivariable model: After correction for differences in clinical characteristics, patients receiving beta blockers were still at significantly lower risk for the composite end point than those who were not."	Adjusted OR 0.3	0.1 to 0.7	

(*Continued*)

Appendix 3. Continued

Study	Year of Publication	Trial Type	No. of Patients	Patient Population	Primary End Point	Analysis: HR, RR, OR, NNT	95% CI and/or p	Results
					"DSE results (especially the presence or absence of NWMAs) were the most important determinants of perioperative cardiac outcome. In connection with both clinical data and DSE results, beta-blocker therapy was again associated with a significantly reduced risk of the composite end point. The protective effect of beta-blocker therapy was observed in long-term users and in patients who received bisoprolol as part of the DECREASE study (OR 0.1, 95% CI 0.0 to 0.4)."	OR 0.1	0.0 to 0.3	
					"The incidence of the composite end point in patients with a Lee index of 1, 2, or ≥3 points was 1.3%, 3.1%, and 9.1%, respectively."		p<0.001	
Shammash et al[47]	2001		140	Major vascular surgical procedures	"Mortality in the 8 patients who had beta blockers discontinued postoperatively (50%) was significantly greater than mortality (1.5%) in 132 patients who continued taking beta blockers."	OR 65.0	p<0.001	The authors concluded, "Discontinuing beta blockers immediately after vascular surgery may increase the risk of postoperative cardiovascular morbidity and mortality."
					"Beta-blocker discontinuation also was associated with increased cardiovascular mortality (0% versus 29%)."		p=0.005	
					"Beta-blocker discontinuation also was associated with increased postoperative MI."	OR 17.7	p=0.003	
Lindenauer et al[7]	2005	Retrospective cohort study	663 635	Patients ≥18 years of age who underwent major noncardiac surgery	"Among the 580 665 patients with an RCRI score of 0 or 1, treatment was associated with no benefit and possible harm."	Adjusted OR 1.09	1.01 to 1.19	The authors concluded, "Perioperative beta-blocker therapy is associated with a reduced risk of in-hospital death among high-risk, but not low-risk, patients undergoing major noncardiac surgery. Patient safety may be enhanced by increasing the use of beta-blockers in high-risk patients."
					RCRI score 2	Adjusted OR 0.88	0.80 to 0.98	

(*Continued*)

Appendix 3. Continued

Study	Year of Publication	Trial Type	No. of Patients	Patient Population	Primary End Point	Analysis: HR, RR, OR, NNT	95% CI and/or p	Results
					RCRI score 3	Adjusted OR 0.71	0.63 to 0.80	
					RCRI score ≥4	Adjusted OR 0.58	0.50 to 0.67	
Redelmeier et al[30]	2005	Retrospective cohort study	37 151	Patients >65 years of age who were admitted for elective surgery, without symptomatic coronary disease	1038 patients experienced an MI or died, at a rate that was significantly lower for patients receiving atenolol than for those receiving metoprolol (2.5% versus 3.2%).		p<0.001	The authors concluded, "Patients receiving metoprolol do not have as low a perioperative cardiac risk as patients receiving atenolol, in accord with possible acute withdrawal after missed doses."
Feringa et al[40]	2006	Observational cohort study	272	Vascular surgery	"In multivariate analysis, higher beta-blocker doses (per 10% increase) were significantly associated with a lower incidence of myocardial ischemia."	HR 0.62	0.51 to 0.75	The authors concluded, "This study showed that higher doses of beta blockers and tight heart rate control are associated with reduced perioperative myocardial ischemia and troponin T release and improved long-term outcome in vascular surgery patients."
					Troponin T release	HR 0.63	0.49 to 0.80	
					Long-term mortality	HR 0.86	0.76 to 0.97	
					"Higher heart rates during electrocardiographic monitoring (per 10-bpm increase) were significantly associated with an increased incidence of myocardial ischemia."	HR 2.49	1.79 to 3.48	
					Troponin T release	HR 1.53	1.16 to 2.03	
					Long-term mortality	HR 1.42	1.14 to 1.76	
Hoeks et al[48]	2006	Prospective survey	711	Peripheral vascular surgery patients	"After adjustment for potential confounders and the propensity of its use, continuous beta-blocker use remained significantly associated with a lower 1-year mortality compared with nonusers."	HR 0.4	0.2 to 0.7	The authors concluded that this "study demonstrated an under-use of beta blockers in vascular surgery patients, even in high-risk patients. Perioperative beta-blocker use was independently associated with a lower risk of 1-year mortality compared to non-use, while perioperative withdrawal of beta-blocker therapy was associated with a higher 1-year mortality."

(*Continued*)

Appendix 3. Continued

Study	Year of Publication	Trial Type	No. of Patients	Patient Population	Primary End Point	Analysis: HR, RR, OR, NNT	95% CI and/or p	Results
					"In contrast, beta-blocker withdrawal was associated with an increased risk of 1-year mortality compared with nonusers."	HR 2.7	1.2 to 5.9	
Kaafarani et al[32]	2008	Retrospective cohort study	646	All patients who underwent various noncardiac surgical procedures	"Patients at all levels of cardiac risk who received beta blockers had lower preoperative and intraoperative heart rates."			The authors concluded, "Among patients at all levels of cardiac risk undergoing noncardiac surgery, administration of beta blockers should achieve adequate heart rate control and should be carefully monitored in patients who are not at high cardiac risk."
					The beta-blocker group had higher rates of 30-day MI (2.94% versus 0.74%) than the control group.		p=0.03	
					The beta-blocker group had higher 30-day mortality (2.52% versus 0.25%) than the control group.		p=0.007	
					Patients in the beta-blocker group who died perioperatively had significantly higher preoperative heart rate (86 versus 70 bpm).		p=0.03	
Matyal et al[33]	2008	Retrospective	960	Vascular surgery (primarily infrainguinal)	"Adverse outcome was defined as MI, new-onset CHF, significant arrhythmias, renal failure, or death. The incidence of adverse outcomes was lower when beta blockers were administered in men (12.6% versus 18.9%)."		p=0.04	The authors concluded, "Women did not benefit from perioperative beta-blockade. Women at high risk appeared to have a worse outcome because of a higher incidence of CHF."
					"The incidence of adverse outcomes was not lower in women (17.8% versus 13.7%)."		p=0.37	
					"Among beta-blocker–naïve subjects, men had significant reductions in MI and renal failure, whereas women did not have a reduction in the incidence of any outcome."			
					"After risk stratification, the high-risk women who received beta blockade had a statistically worse outcome (36.8% versus 5.9%) because of an increased incidence of CHF."		p=0.02	

AAA indicates abdominal aortic aneurysm; bpm, beats per minute; CAD, coronary artery disease; CHF, congestive heart failure; CI, confidence interval; DSE, dobutamine stress echocardiography; HR, hazard ratio; MI, myocardial infarction; n, number; NNT, number needed to treat; NWMA, new wall-motion abnormality; OR, odds ratio; RCRI, Revised Cardiac Risk Index; RCT, randomized controlled trial; and RR, relative risk.

2009 ACCF/AHA Focused Update on Perioperative Beta Blockade: A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines

2009 WRITING GROUP TO REVIEW NEW EVIDENCE AND UPDATE THE 2007 GUIDELINES ON PERIOPERATIVE CARDIOVASCULAR EVALUATION AND CARE FOR NONCARDIAC SURGERY, Kirsten E. Fleischmann, Joshua A. Beckman, Christopher E. Buller, Hugh Calkins, Lee A. Fleisher, William K. Freeman, James B. Froehlich, Edward K. Kasper, Judy R. Kersten, John F. Robb and R. James Valentine

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Addendum

In the article by Fleischmann et al, "2009 ACCF/AHA Focused Update on Perioperative Beta Blockade," which published ahead of print November 2, 2009, and appeared in the November 24, 2009, issue of the journal (*Circulation.* 2009;120:2123–2151), a clarification is needed.

Upon findings of scientific misconduct involving Professor Don Poldermans from Erasmus University, whose work was cited in the article, the ACCF/AHA Task Force on Practice Guidelines requested that the 2009 ACCF/AHA Writing Committee review communications from the leadership of Erasmus University (http://www.erasmusmc.nl/corp_home/corp_news-center/2011/2011-11/ontslag.hoogleraar/?lang=en), including the reported conclusions of its investigative committee. The ACCF/AHA Writing Committee concluded that recommendations for care in the 2009 article remain valid. The ACCF/AHA Task Force on Practice Guidelines will continue to monitor the situation and inform readers if additional findings warrant revised recommendations.

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