Practical, Effective Use of Beta Blockers to Improve Perioperative Patient Outcomes

Introduction
Although the science of identifying patients who are at highest risk for perioperative cardiac events (e.g., myocardial infarction [MI], unstable angina, congestive heart failure, and cardiac death) is well developed, the evidence to support how best to care for high-risk patients was, until recently, scanty and conflicting.1,2

The emergence of a literature supporting the efficacy and effectiveness of perioperative beta blockade to reduce the cardiac risks of surgery3–5 has helped to partially resolve the essential conundrum posed by virtually all guidelines addressing the perioperative care of the patient with known coronary disease or substantial risks for atherosclerosis: although preoperative testing algorithms uncover coronary disease, none of them supports preoperative revascularization unless the patient requires this procedure outside of surgery.1,2

Over the past nine years or so, a substantial number of well-designed clinical studies have outlined the potential benefits of perioperative adrenergic blockade. Virtually all of these trials have demonstrated a substantial reduction in risk when applied effectively in appropriate patients. However, a parallel set of published studies indicates how current systems of care are ill equipped to deliver this important new therapy to suitable candidates.6–8

This article outlines the evidence base to support the use of perioperative beta blockers in patients undergoing major noncardiac surgery and describes several potential solutions to the organizational or other possible obstacles to effective implementation.

Perioperative Cardiac Events: Importance of the Problem
Cardiac events are the most common and life-threatening in-hospital complications of surgery, occurring in approximately 5% of all major noncardiac procedures, on average, and in as many as 30% of patients at highest risk.9–12 These complications in themselves may result in death or may begin a cascade of noncardiac complications (such as pneumonia and delirium), which further compound the severity of the initial cardiac event.13

Beginning with the original Goldman Cardiac Risk Index, published in the early 1980s,14 the science of identifying those patients at highest risk has advanced rapidly. Many alternative or modified risk indices have been proposed in the intervening years. Although these vary slightly in their constituent parts, at their core each is essentially a tool for predicting each patient’s underlying risk of coronary atherosclerosis and the ability to withstand the stress of surgery.1,15–19 Because this stress is manifested through physiological parameters (i.e., pulse, blood pressure) that are associated with adrenergic output, early researchers hypothesized that adrenergic blockade would reduce perioperative cardiac events.20–22

Perioperative Adrenergic Blockade
Evidence of Efficacy and Effectiveness
Beginning with a series of small studies in the late 1980s, evidence from a variety of researchers and sites has consistently supported the value of adrenergic blockade for reducing perioperative cardiac risk. The earliest studies in this area of inquiry examined the effectiveness of nonselective beta blockers (e.g., propranolol) in reducing the surrogate outcome of perioperative ischemia, which was known to pose a three-fold to eight-fold higher risk of subsequent cardiac events.9,21,23–26

Strong evidence of the potential of these agents to reduce “hard” clinical outcomes (e.g., mortality, MI) began with the
sennial study by Mangano et al. in 199727 and was further buttressed by results from Poldermans et al. in 199928 and from other observational studies in 2001 and 2002.12,29 As a group, these studies suggest that the use of beta blockers might provide a relative reduction in risk between 30% and 90%. The sole “negative” study, a trial of beta blockers in patients undergoing elective total knee replacement, showed a benefit of similar magnitude (a relative risk reduction of 0.33), although this did not reach statistical significance—largely as a result of low overall event rates in the study population.30 Results from all of these papers were part of a 2003 meta-analysis5 that estimated that the number of patients needed to treat (NNT) to prevent one perioperative cardiac event or death was approximately 30, a figure similar to the 25–50 patients calculated in my 2001 paper.5

Some corresponding literature has also addressed the efficacy of alpha2-adrenergic agents, such as clonidine (Catapres®, Boehringer Ingelheim) or mivazerol. Although the mechanism of action of these agents differs from that of the beta blockers used in the studies described earlier, they provide a similar level of sympatholysis, and the supportive literature is similar in describing their efficacy in reducing perioperative ischemia. Trials with these agents have enrolled more patients (more than 3,000) than have studies of beta blockers, and they appear to have been effective in preventing perioperative MIs and deaths, albeit with a higher number of patients needed to treat (NNT) to prevent one perioperative cardiac event or death was approximately 30, a figure similar to the 25–50 patients calculated in my 2001 paper.5

Both bodies of literature have substantial shortcomings. First, no single study of either agent has had an adequate sample size to definitively determine differences in mortality. Next, both groups of studies have focused on higher-risk surgical procedures (e.g., vascular operations), making it somewhat difficult to extend to lower-risk procedures such as laparoscopic or one-day surgery. Differences between protocols in published studies leave important questions unanswered, such as the following:

- Which patients should be targeted?
- What is the optimal time to begin these agents, and when should they be stopped?
- Which drug should be used?
- How can a practical and effective strategy be implemented at hospitals on the basis of this evidence?

**Gaps in Administering Effective Care**

Although the evidence for the efficacy of perioperative beta blockade has been reasonably strong for almost eight years, this practice has not been widely incorporated into practice. The 1997 American College of Physicians (ACP) guidelines favored using beta blockers “in appropriate patients,” and both the 1997 published version and the 2002 Web update to the American Heart Association/American College of Cardiology (AHA/ACC) perioperative cardiac risk-management guidelines made similar recommendations.1,2 Neither group explicitly specified how the use of beta blockers would influence its other recommendations, such as the need for preoperative testing in moderate-risk to high-risk patients. More recent publications have clarified the recommendations in this regard,4,12,29 but they have not included an adequate quantity of practical tips for implementing effective practices.

In the meantime, an increasing number of studies are describing the gaps between knowledge and practice. One study from a large academic hospital in Massachusetts suggested that fewer than 50% of eligible patients were receiving beta blockers at that site. These authors suggested that improving adherence to evidence-based selection criteria would save between 40 and 70 lives annually.7 A study of vascular surgery patients in the Netherlands suggested that even in this high-risk patient population, fewer than 50% received beta blockers perioperatively.12

More recently, a survey of Canadian anesthesiologists suggested that although most of them believed that adrenergic blockade was effective and safe, fewer than 20% had a policy or guideline for using beta blockers at their site.8

The need to effectively address these known gaps in care—gaps akin to those seen in the underuse of beta blockers and aspirin in medical patients with MI—is clear and is likely to become more acute. The LeapFrog Group, a consortium of health care purchasers that seeks to compel quality change by selecting high-quality providers for its members, has recently added perioperative beta blockade in vascular surgery patients to its list of key indicators.32 Public reporting of surgical outcomes and adverse drug events is also on the horizon, making it even more important for health care systems and hospitals to create an environment in which physicians can provide uniform and effective evidence-based care.

**Knowing the Key Clinical Practices and Local Systems**

To use perioperative adrenergic blockade effectively, all physicians, hospitals, and health care systems should be aware of the key clinical practices associated with these agents. Health care systems and individual providers should also understand the unique local opportunities or challenges that might make implementation more or less difficult.

**Key Clinical Practices**

**Identifying Patients for Perioperative Adrenergic Blockade**

Several published algorithms have suggested strategies for identifying patients who require perioperative beta blockers. In general, these algorithms incorporate clinical factors known to be associated with coronary disease risk (e.g., smoking and hypercholesterolemia), a known history of coronary disease, and the type of surgery being planned. These factors are based on those used in previous studies of perioperative beta blockers as well as on broadly accepted definitions of “at-risk” patients.

I suggest using a combination of minor and major clinical risk factors to identify patients who would be suitable for perioperative adrenergic blockers (Table 1); these factors can be used to select patients and, subsequently, to follow the diagnostic algorithm displayed in Figure 1. Major criteria are based on the revised Cardiac Risk Index, and minor criteria are based on the study entry criteria used by Mangano et al.27 Later steps in the algorithm are based on empirical evidence published by Boersma et al.,12 other authors have suggested sim-
Patients with no major criteria and with less than one minor criterion may proceed to the operating room with no additional workup and no beta blockers.

Patients with three or more major criteria would benefit from beta blockade, but additional risk stratification with noninvasive stress testing (e.g., persantine thallium stress imaging) is necessary before surgery.

Patients with an intermediate risk (those with one or two major criteria) should be assessed for their functional status level if they have a history of coronary artery disease (CAD) or peripheral vascular disease (PVD). They should also be evaluated for their ability to perform activities requiring four or more metabolic equivalent tasks (METS), such as walking up two flights of steps, according to the AHA/ACC guidelines.

Patients with poor functional status and PVD/CAD should be referred for noninvasive testing. If their noninvasive test results are normal or negative, these patients can safely proceed to surgery.

If the noninvasive test suggests a myocardium at risk, preoperative catheterization and the possibility of revascularization should be carefully considered. In this situation, both the AHA/ACC and the ACP guidelines suggest that patients would not benefit from revascularization unless they would have required it without the surgery.

Results from the Poldermans study, in which patients with known active ischemia underwent surgery with beta blockade, may be comforting to physicians caring for the highest-risk patients.

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Table 1

**Patient Selection Criteria for Perioperative Beta Blockers**

<table>
<thead>
<tr>
<th>Minor Criteria</th>
<th>Major Criteria</th>
</tr>
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<tbody>
<tr>
<td>Age &gt; 65 years</td>
<td>History of MI, angina, or any revascularization, Q waves on ECG, current or past use of nitroglycerine</td>
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<tr>
<td>Current smoking</td>
<td>History of transient ischemic attack or cerebrovascular accident</td>
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<tr>
<td>Hypercholesterolemia</td>
<td>Diabetes‡</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Vascular surgery planned for arteries of chest, abdomen, or pelvis</td>
</tr>
<tr>
<td></td>
<td>Creatinine &gt; 2 mg/dl</td>
</tr>
</tbody>
</table>

† Data from Lee TH, Marcantonio ER, Mangione CM, et al. *Circulation* 1999;100(10):1043–1049.43
‡ Insulin-dependent or non–insulin-dependent diabetes. ECG = electrocardiogram.
risk patients, but revascularization might still be appropriate in some high-risk patients, such as those with left main coronary artery disease. Even when beta blockers are used, taking care of the highest-risk patients will continue to necessitate careful clinical thought, clear communication with anesthesiologists and surgical colleagues, and frank discussions with patients about the surgical risks and benefits.

Patients at Risk Who Should Not Receive Beta Blockers

Two specific groups of patients, both of whom are at substantially elevated risk for cardiac complications, should not routinely take beta blockers at the time of surgery. In both groups, physicians should focus primarily on the patient’s ability to handle fluid loads and to maintain cardiac output and, secondarily, on improving myocardial perfusion by using beta blockers.

The first group includes patients with congestive heart failure, caused by depressed ejection fraction and systolic dysfunction. Beta-blocker therapy improves long-term survival in these patients, but it should not be started in the perioperative period as part of routine practice. Instead, patients should begin therapy far enough in advance so that they are clinically stable before surgery, or these agents should be deferred until after patients are stable postoperatively.

Patients with physiologically significant aortic valvular disease should also be treated differently. Aortic stenosis is an underrecognized and important cardiac risk factor, however, the use of beta blockers in patients with significant flow restriction should not be undertaken without close monitoring. Although it is unclear which of these patients need invasive intraoperative monitoring, which ones need valve replacement or valvuloplasty preoperatively, and which ones need something else entirely, it stands to reason that the indiscriminate use of beta blockers in these patients would not represent optimal care.

Choice of Agent

As described earlier, there is ample evidence to support the idea that alpha2 agents and beta blockers do benefit patients undergoing surgery—a reality that has the potential to force clinicians to decide about the agent of choice for their patients.

Although clonidine offers substantial advantages in terms of ease of dosing in patients who cannot take oral medications (e.g., a transdermal patch can be substituted), there are at least two compelling practical arguments for choosing beta blockers in these patients. The duration of therapy after surgery is still open to debate. The induction (pre-anesthesia) administration of adrenergic blockers is a crucial step in effective clinical practice, but how long they should be given beforehand is still an unanswered question. In another Mangano study, beta blockers were initiated in the pre-anesthesia holding area; other authors began giving agents as long as an average of one month beforehand. Although it seems sensible to try to develop an approach in which agents are started as far in advance as possible, with the intent of giving physicians the opportunity to titrate agents to an effective heart rate before surgery, last-minute identification and administration even on the day of surgery are likely to be effective as well.

Timing of Therapy

The pre-induction (pre-anesthesia) administration of adrenergic blockers is a crucial step in effective clinical practice, but how long they should be given beforehand is still an unanswered question. In another Mangano study, beta blockers were initiated in the pre-anesthesia holding area; other authors began giving agents as long as an average of one month beforehand. Although it seems sensible to try to develop an approach in which agents are started as far in advance as possible, with the intent of giving physicians the opportunity to titrate agents to an effective heart rate before surgery, last-minute identification and administration even on the day of surgery are likely to be effective as well.
apy, treatment for up to 30 days probably provides maximal protective benefit.

**Achieving Pharmacological Sympatholysis**
Although the point can be made briefly, one of the most crucial practices in effective use of perioperative beta blockers is that they be titrated in such a way that a target heart rate is achieved. In the studies reviewed in this article, the target heart rates differed slightly among study protocols, but they were generally less than 70 beats per minute. In fact, the lack of aggressive dose titration might have played a part in the sole “negative” study mentioned earlier. Although it is a simple clinical concept—how to achieve adequate heart rates from the beginning to the end of therapy—substantial consideration is needed in the implementation phase of a perioperative beta-blocker protocol.

**A Sample Protocol**
Table 2 presents a suggested protocol for perioperative beta blockade with metoprolol. Patients who are not taking chronic beta-blocker therapy should begin metoprolol as soon as they are considered eligible. For patients who are taking beta blockers, pulse measurements should be performed to assess the adequacy of beta blockade.

Postoperatively, attention should be paid to patients’ pulse and blood pressure so that doses can be titrated upward or downward as required. Patients who cannot take oral medications can be given intravenous (IV) metoprolol, whether or not they are using beta blockers chronically.

As patients begin to take oral medications, overlapping doses of IV and oral medications can be used to ensure a smooth transition.

Finally, all patients should be assessed for their long-term needs for beta blockade at the time of discharge from the hospital.

**Local Systems**
**Implementation Pearls**
In the end, “the rubber meets the road” during the implementation of any quality initiative. Although many studies have described the broad principles of quality improvement in the inpatient setting, it is important to point out “systems” issues that make implementation of perioperative beta-blockade guidelines or protocols unique. The specific approach taken at various hospitals will differ somewhat, but some common issues and possible solutions are presented next.

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**Table 2  Perioperative Beta Blockade: Suggested Regimen**

<table>
<thead>
<tr>
<th>Pre-hospitalization period (outpatient), or immediately following admission to hospital</th>
<th><strong>Patients not receiving chronic beta-blocker therapy</strong></th>
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<tbody>
<tr>
<td></td>
<td>• Give metoprolol (Toprol-XL®; AstraZeneca) 25–100 mg PO b.i.d.</td>
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<td></td>
<td>• Begin as outpatient, up to 30 days prior to surgery</td>
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<td></td>
<td>• Titrate new or pre-existing beta blocker to heart rate of 65 bpm or lower.</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Immediate preoperative period (in pre-anesthesia holding area)</th>
<th><strong>All patients:</strong> Give metoprolol 5 mg IV every 10 minutes to reach target heart rate before induction of anesthesia, if needed</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patients not taking oral medications who are hemodynamically stable</strong></td>
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<tr>
<td></td>
<td>• Give metoprolol 5 mg IV every 15 minutes up to 15 mg, titrate to heart rate of 65 bpm, repeat every six hours. Bedside (e.g., defibrillator) monitors can be used if local policy requires continuous ECG monitoring during IV infusions of metoprolol.</td>
</tr>
<tr>
<td></td>
<td>• Consider clonidine patch if unable to administer IV metoprolol.</td>
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<td></td>
<td><em>ICU patients with potential hemodynamic instability caused by recent blood loss or prolonged surgery</em></td>
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<td></td>
<td>• Give esmolol 500 mcg/kg IV load over one minute, then infuse 50–200 mcg/kg per minute to target heart rate.</td>
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<tr>
<td></td>
<td>• May also use IV metoprolol per floor protocol.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>In-hospital period and transition to oral medications</th>
<th><strong>Patients switching from IV medications</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Overlap first PO dose of metoprolol or chronic agent with IV metoprolol to maintain target heart rate.</td>
</tr>
<tr>
<td><strong>Patients taking oral medications</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Resume preoperative beta blocker at previous dose; titrate to target heart rate.</td>
</tr>
<tr>
<td></td>
<td>• Metoprolol IV can be used to titrate heart rate as PO dose is adjusted.a</td>
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<table>
<thead>
<tr>
<th>Post-hospitalization period (outpatient)</th>
<th></th>
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<tbody>
<tr>
<td></td>
<td>• Continue preoperative beta blocker to 30 days postoperatively, a and taper.</td>
</tr>
<tr>
<td></td>
<td>• Continue beta-blocker lifelong therapy in patients with a history of myocardial infarction, angina, or previously unrecognized hypertension.</td>
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</tbody>
</table>

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b.i.d. = twice daily; bpm = beats per minute; ECG = electrocardiography; ICU = intensive-care unit; IV = intravenously; P = orally.

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P&T® June 2004 • Vol. 29 No. 6
1. **Know your systems.** At the outset, you must work hard to understand how patients get from home to their surgeon and the anesthesiologist’s office to the hospital, and back home. Do you have multiple preoperative clinics? Do you have several clinical sites where operations are performed? Do you have a large referral-based patient population?

2. **Know your personnel.** Because surgical patients are often seen by multiple physicians (e.g., surgeons, anesthesiologists, and internists) during a single hospitalization, it is essential to identify interested and motivated personnel from each of these physician groups. Similarly, you might enroll help from nursing, pharmacist, or nurse-practitioner groups who care for surgical patients throughout the hospital. The group should be kept as small as possible, but it should be broad-based, motivated, and composed of thought leaders and clinical practice leaders.

3. **Keep your eye on the ball.** Recognize the key clinical practices in perioperative beta blockade. Remember, the goals of your program are to improve care and to make the system work more efficiently. To this end, avoid systems that cause “double documentation” (e.g., documenting heart rate on the vital signs flow sheet and on the dose-titration sheet) or that add to the workload without subtracting from the workload elsewhere (e.g., a discharge prescription for beta blockers preprinted on the initial order set).

4. **Find the common pathway that all patients must take to get to the operating room.** This pathway should be the focus of your efforts to identify patients who need perioperative beta blockade and patients who should begin therapy. If the hospital has a single preoperative clinic, make your strongest effort there. If you have multiple preoperative clinics or providers, consider beginning your beta-blocker protocol in the pre-anesthesia area on the day of surgery.

5. **Maintain continuity of beta blockade during hospitalization.** After patients have begun the beta-blocker protocol, ensure that they continue it during hospitalization. This is particularly crucial on the day of the operation, when patients make the transition from home to the pre-anesthesia area, and to the operating room, to the postanesthesia area, and to their hospital beds; each of these transitions is a potential “dropped handoff.” A single order set for all patients that is not altered and that follows the patient across the phases of care may achieve this goal in hospitals without computer order-entry systems.

6. **Maintain continuity of beta blockade beyond hospitalization.** Some nuances of this step will depend on how long you choose to treat patients who are not taking beta blockers for their lifetime; at its core, however, an approach that effectively continues beta blockade either for 30 days or for a lifetime needs to develop a system that accurately discriminates between these two groups of patients. This goal might be achieved by specifying patients’ “stop dates” in the order set mentioned earlier, with an additional category for patients who are already on long-term therapy (or in whom long-term therapy is judged to be appropriate at the outset).

7. **Protocolize dose titration.** Ensuring that patients’ heart rates are in a target range is essential; how to do this in practice depends entirely on the local system. In my teaching hospital, this responsibility is falling to the house officers, who are using a preprinted suggested dose-titration algorithm. At other sites, nurses, pharmacists, physician’s assistants, or nurse-practitioners assume this responsibility.

## Conclusion

Although the effectiveness of perioperative beta blockers appears almost beyond question, numerous aspects of how to use current evidence in practice remain to be fully elucidated. To answer some of these questions, we can amalgamate evidence from the studies themselves; for others, we must use methods provided by the many years of evidence supporting the use of beta blockers in other settings.

The greatest challenge for hospitals and health care systems is how to implement guidelines that ensure that all patients are treated appropriately. Knowing your sites and systems well, and tailoring your guidelines so that the key clinical practices are addressed completely, can greatly facilitate the success of your efforts.

## References


13. Fleischmann KE, Goldman L, Young B, Lee TH. Association between cardiac and noncardiac complications in patients under-

Disclosure
Dr. Auerbach has no financial relationships to disclose.
Continuing Education for Physicians and Pharmacists

ACPE Program #079-999-04-018-H01
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TOPIC: Practical, Effective Use of Beta Blockers to Improve Perioperative Patient Outcomes

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4. According to this article, patients who should receive beta blockers at the time of surgery are those:
   a. with congestive heart failure caused by depressed ejection fraction and systolic dysfunction.
   b. who have physiologically significant aortic valvular disease.
   c. with a history of coronary disease.
   d. all of the above

5. According to this article, which of the following recommendations is incorrect in regard to prescribing perioperative beta blockers?
   a. diabetes
   b. vascular surgery that is planned for the arteries of the chest, abdomen, or pelvis
   c. age older than 65 years
   d. a creatine value greater than 2 mg/dl

6. Regarding the timing of beta-blocker therapy, the article suggests all of the following except:
   a. Pre-induction administration of adrenergic blockers is a crucial step in effective clinical practice.
   b. Immediate administration must be avoided because there is no evidence that it will work.
   c. It makes good clinical sense to try to develop an approach in which beta-blocker therapy will begin as far in advance as possible.
   d. "Last-minute" administration of an agent, even on the day of surgery, is likely to be effective.

7. Regarding the duration of therapy with beta blockers, which of the following is not suggested in regard to perioperative beta blockade?
   a. The duration of therapy after surgery is a relatively open question.
   b. Longer treatment with beta blockers may extend the protective benefit of adrenergic blockade.
   c. For patients who do not require lifelong beta-blocker therapy, treatment for up to 30 days is likely to provide maximal protective benefit.
   d. all of the above

8. Which of the following is not true regarding beta blockade during and after hospitalization?
   a. Patients who are not able to take oral medications can be given an IV beta blocker whether or not they are currently taking beta blockers.
   b. Maintain continuity of beta blockade during hospitalization.
   c. During the transition from oral to IV therapy, do not overlap the first PO dose of metoprolol or chronic agent with IV metoprolol in order to maintain the target heart rate.
   d. Continue beta blockers for life in patients with a history of myocardial infarction, angina, or previously unrecognized hypertension.

9. Which of the following is incorrect in regard to beta blockade during and after hospitalization?
   a. Patients who are not able to take oral medications can be given an IV beta blocker whether or not they are currently taking beta blockers.
   b. Maintain continuity of beta blockade during hospitalization.
   c. During the transition from oral to IV therapy, do not overlap the first PO dose of metoprolol or chronic agent with IV metoprolol in order to maintain the target heart rate.
   d. Continue beta blockers for life in patients with a history of myocardial infarction, angina, or previously unrecognized hypertension.

10. Which of the following is not a major criterion for prescribing perioperative beta blockers?
    a. diabetes
    b. vascular surgery that is planned for the arteries of the chest, abdomen, or pelvis
    c. age older than 65 years
    d. a creatine value greater than 2 mg/dl
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Date of publication: June 2004
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Authors: Andrew D. Auerbach, MD, MPH
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2. a [ ] b [ ] c [ ] d [ ] 7. a [ ] b [ ] c [ ] d [ ]
3. a [ ] b [ ] c [ ] d [ ] 8. a [ ] b [ ] c [ ] d [ ]
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