

Tips from the Top

Implementation of a Program for Perioperative Cardiac Risk Reduction Therapy (PCRRT) Using Beta Blockers and Clonidine (BBAC)

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Approximately 100,000 of the 400,000 patients per year in the United States who undergo cardiac surgery and 1.5 million of the 30 million who undergo non-cardiac surgery suffer perioperative cardiovascular morbidity resulting in 50,000 myocardial infarctions and 20,000 deaths a year at a cost exceeding \$20 billion annually.^{1,2} Perioperative Cardiac Risk Reduction Therapy (PCRRT) using prophylactic beta blockade administered perioperatively reduces the incidence of perioperative cardiac death between 50 percent and 90 percent in patients at risk who undergo non-cardiac surgery.^{3,4} PCRRT with clonidine, an alpha-2 agonist, reduces the incidence of postoperative mortality 50 percent in patients who undergo non-cardiac surgery.⁵

In 1996, the American Heart Association and the American College of Cardiology published medical guidelines,⁶ and in 2003⁷ they revised them, recommending the perioperative administration of beta blockers to patients who required them in the recent past to control symptoms of angina or to patients with symptomatic arrhythmias or hypertension, as well as to patients at high cardiac risk owing to the finding of ischemia on preoperative testing or to those undergoing vascular surgery. They also recommend that beta blockers be administered to patients with untreated hypertension, known coronary disease, or major risk factors for coronary disease (Class IIa). Alpha-2 agonist therapy is recommended for the same population as a Class IIb recommendation. (For an explanation of the classes in the ACC/AHA Guidelines, see footnote on page 42.)

What is the justification for these recommendations by the American College of Cardiology? Initial efforts at reducing cardiac risk consisted primarily of risk stratification.⁸ However, risk stratification merely identifies fixed risk factors (coronary artery disease, peripheral vascular disease, age, diabetes, smoking, hypercholesterolemia, hypertension); it does not actually reduce risk. In 1990, Mangano et al. identified risk factors common to the previous risk stratification studies but also

identified the additional risk factor of perioperative myocardial ischemia. Myocardial ischemia is unique as a cardiac risk factor because, unlike age or pre-existing medical conditions, it could be modified.¹ Many authors have tried to predict preoperative morbidity and mortality using preoperative testing, but none has been successful at reducing risk through preoperative testing.^{9,10} Moreover, even if a preoperative test were able to predict perioperative morbidity, it is important to ask what could be done to lower that risk? It is important to point out that it does not help simply to tell clinicians that a patient is at high risk. Very few physicians need preoperative testing to identify patients at cardiac risk; the history and physical are adequate to identify patients at risk. If no specific recommendations that are shown to reduce cardiac risk are forthcoming, the preoperative testing is without benefit.

It is worth considering that if preoperative testing suggests an intervention or therapy designed to reduce cardiac risk, that approach must reduce total risk. It is very difficult to add the risk of a procedure (coronary artery bypass graft surgery (CABG) or percutaneous coronary intervention (PCI)) to a second procedure (non-cardiac surgery) and get a lower total risk. The Coronary Artery Revascularization Prophylaxis (CARP) trial definitively demonstrated that risk stratification followed by PCI or coronary artery bypass surgery before elective vascular surgery does not significantly alter short- or long-term outcome.¹¹ On the basis of these data, the strategy of coronary artery revascularization using PCI or CABG before elective vascular surgery among patients with stable cardiac symptoms cannot be recommended.¹¹ Furthermore, PCI prior to non-cardiac surgery may actually increase operative risk. Percutaneous coronary angioplasty with intracoronary stents (PCI) prior to elective surgery has been associated with a 20 percent operative mortality.¹² If clinicians think that prophylactic CABG prior to elective non-cardiac surgery must be beneficial, it is important to note that the MAS-II trial, a randomized trial comparing CABG, PCI, and medical therapy, showed a survival advantage to medical therapy at one year.¹³

Given the failure of standard cardiac risk stratification followed by coronary revascularization to reduce total operative risk, a number of clinical trials of medical therapy have been completed.^{3,14-22} This extensive search for a medical therapy to reduce perioperative myocardial ischemia and cardiac death identified two generic therapies that reduce the risk of perioperative cardiac morbidity and mortality (beta blockers^{3,18,19,23} and clonidine²⁴). Prophylactic beta blocker therapy reduces perioperative mortality 50 percent to 90 percent.^{3,18,19,23} Prophylactic clonidine therapy reduces 30-day mortality seven-fold.²⁴ The cost per life saved is between \$3 and \$600 depending on PO or IV therapy and the risk group. The American Heart Association and American College of Cardiology recognized the profound importance of prophylactic perioperative beta blocker therapy and made it a level I indication in 1996 for patients with known coronary artery disease or known vascular disease (higher risk).

There has been some discussion of how to treat patients at lower risk (those with only risk factors for coronary artery disease). In the VA studies,^{3,14,24} treating patients with

two risk factors (age \geq 65 years, diabetes, hypertension, smoking, cholesterol \geq 240 mg/dl) reduced total operative mortality and improved long-term survival. Other authors agree that higher risk patients should definitely be on beta blockers but are less certain of the benefits in lower risk patients.²⁵⁻²⁷ Lindenauer et al., using epidemiologic analysis at a single hospital, concluded in 2004 that a large percentage of the postoperative myocardial infarctions (MI) might have been prevented if a beta blocker had been administered to all ideal candidates around the time of surgery.²⁸ In a recent article in the *New England Journal of Medicine (NEJM)* using epidemiologic data from 329 hospitals, Lindenauer et al. tempered their earlier recommendations and suggested that perioperative beta blocker therapy is associated with a reduced risk of in-hospital death among high-risk, but not low-risk, patients undergoing major non-cardiac surgery.²⁹ London et al. concluded that evidence for the efficacy of perioperative beta blockers is strong and the established clinical guidelines of the ACC/AHA* should be used to guide the institution and maintenance of perioperative beta blocker therapy in patients at risk.²⁷

Any therapy has risks and benefits. If patients with extremely low cardiac risk are given cardiac medications, the risk of side effects may outweigh the benefits. This statement does not imply that beta blockers should be withheld from patients with cardiac risk; it simply means that perioperative beta blocker therapy should be administered to patients who have significant cardiac risk as defined by prior studies (known coronary artery disease, known peripheral vascular disease, or two risk factors for coronary artery disease: age \geq 60 years, diabetes, hypertension, smoking, cholesterol \geq 240 mg/dl).

Despite the proven effects of PCRRT for the reduction of perioperative mortality, the low cost per life saved, and the adoption by the ACC and AHA in 1996 and the re-issue in 2003^{6,7} of perioperative cardiac risk reduction therapy (PCRRT) using beta blockers or clonidine, actual change in physician behavior towards the use of PCRRT medications has been slow. In a recent survey, 90 percent of anesthesiologists had heard of perioperative beta blockade (PCRRT) and 40 percent had used it.³⁰⁻³² Unfortunately, PCRRT therapy has not been adopted universally for a number of reasons including lack of education about the therapy, lack of knowledge about contraindications to beta blockade, lack of understanding about how to implement an effective PCRRT program,^{31,32} anesthesiologist's hesitation about prescribing an oral medication,³³ lack of feedback about the benefits of adopting PCRRT, and lack of feedback on the risks of not adopting a PCRRT protocol. Anesthesiologists started preoperative beta blockers infrequently even in patients without contraindications.^{33,34} Disturbingly, a significant fraction (30 percent) of high-risk patients with clear indications for perioperative beta blockade are admitted on beta blockers but have them discontinued³⁴ with associated adverse outcomes. These findings suggest that educating anesthesiologists about the perioperative use of beta blockade may increase the use of this therapy proven to reduce perioperative mortality.^{31,33}

In international studies, 90 percent of anesthesiologists were aware of perioperative beta blockade, but unfortunately specific protocols were available in only 10 percent of institutions.³⁰⁻³² To obtain a worldwide 90 percent familiarity with and 40 percent use of the therapy in less than a decade is a phenomenal success for a therapy without any corporate support.³¹ This accomplishment has been achieved through academic detailing, national and international lectures, publications, adoption of the therapy as a standard of care by the ACC and AHA, and through Web-based education such as www.betablockerprotocol.com.

Despite worldwide recognition of the therapy, it is not utilized in all patients at risk. Epidemiologic analysis of experience with perioperative care demonstrated in one hospital that 97 percent of the patients who developed postoperative MI could have been identified as being at increased risk for cardiac complications, and 81 percent appeared to be ideal perioperative beta blocker candidates.²⁸ Treatment with a beta blocker before infarction was associated with an odds ratio of in-hospital mortality of 0.19 (95 percent confidence interval, 0.04-0.87). This finding represents an 81 percent reduction in the risk of death.^{28,35} A large percentage of the postoperative MIs could have been prevented if a beta blocker had been administered to all ideal candidates around the time of surgery. Use of beta blockers before infarction reduces overall mortality, even among patients who go on to develop this complication.²⁸ Recently we demonstrated in a prospective randomized clinical trial that PCRRT with clonidine, an alpha-2 agonist, also reduces 30-day and two-year mortality.²⁴ This trial provides a second-line agent for patients who have a specific contraindication to beta blockers. Clonidine reduces the release of epinephrine and norepinephrine²⁴ while beta blockers block the end organ effect.¹⁴

The reductions in mortality with perioperative cardiac risk reduction therapy can be most dramatic when a protocol is in place to guide PCRRT.³⁶ In 1998, at the Veterans Affairs Medical Center San Francisco we instituted a Perioperative Cardiac Risk Reduction Therapy (PCRRT) program in patients undergoing non-cardiac surgery. In reviewing our National Surgical Quality Improvement Program (NSQIP) data for the years since instituting that policy, we have seen a statistically significant low outlier for 30-day mortality for major non-cardiac surgery for five of the last six years. Prior to the PCRRT program our five-year average observed-to-expected ratio was 1.0.

* The ACC/AHA classifications of evidence used in this report to summarize the indication for a particular therapy or treatment are as follows:

1. Class I: Conditions for which there is evidence and/or general agreement that a given procedure/therapy is useful and effective.
2. Class II: Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of performing the procedure/therapy.
3. Class IIa: Weight of evidence/opinion is in favor of usefulness/efficacy.
4. Class IIb: Usefulness/efficacy is less well established by evidence/opinion.
5. Class III: Conditions for which there is evidence and/or general agreement that a procedure/therapy is not useful/effective and in some cases may be harmful.

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Prospective randomized clinical trials have clearly demonstrated that PCRRT reduces operative^{4,24} and long-term mortality.^{3,19,24} Epidemiologic analysis supports the use of PCRRT in patients with cardiac risk.^{28,29}

The American College of Cardiology and the American Heart Association have stated that perioperative beta blocker therapy for patients with elevated risk is a Class I indication. The consensus of medical experts^{3,14,18,19,24-29} suggests that perioperative beta blockers reduce operative mortality in patients with cardiac risk. The prospective, randomized, clinical trials^{3,14,18,19,24} and the epidemiologic analyses support the use of perioperative beta blockers.^{28,29} It is time to consider implementing a program at your hospital to ensure the use of perioperative beta blockade in all patients with known coronary artery disease, peripheral vascular disease, or two risk factors. A PCRRT program can reduce surgical mortality and reduce patient care costs.

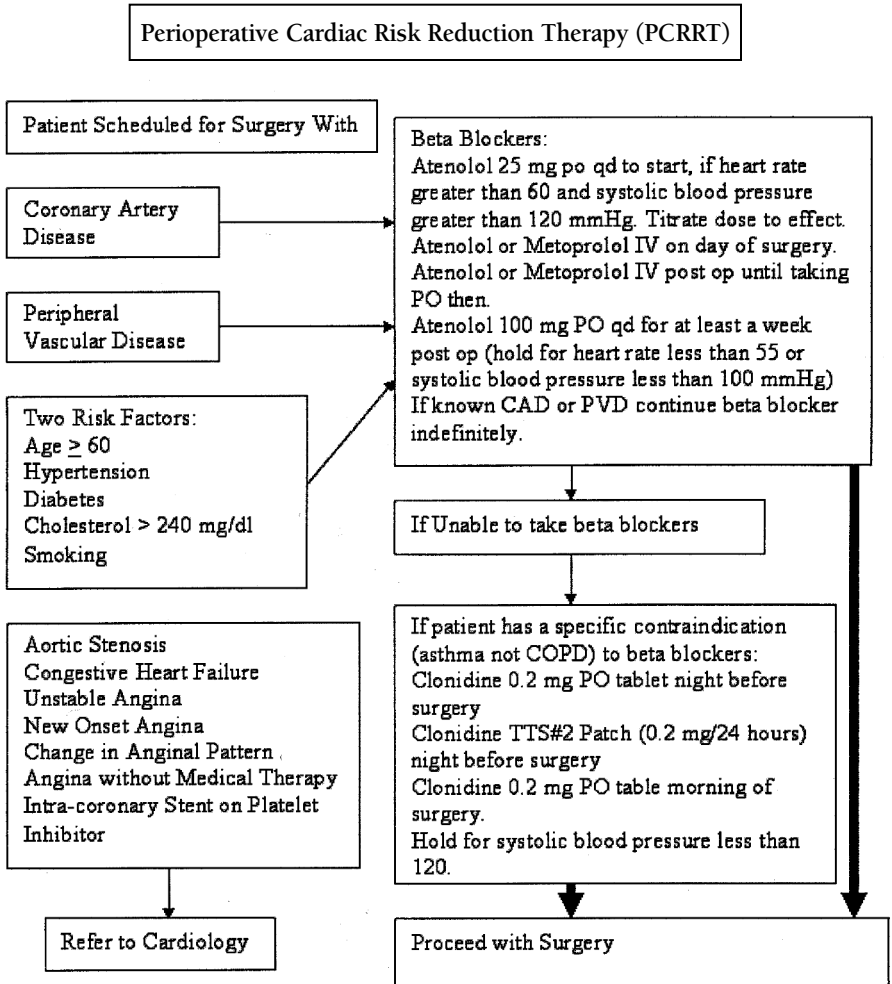
General Guidelines for the Adoption of Perioperative Anti-Ischemic Prophylaxis. It is difficult to make a protocol for other hospitals because systems work in different ways. However, there are a few basic rules that should be followed. These recommendations are based on five articles which clearly demonstrate the efficacy of the technique in the prevention of perioperative mortality.¹⁻⁵ Obtain information on PCRRT at www.betablockerprotocol.com.

1. All patients who either have coronary artery disease (CAD), peripheral vascular disease (PVD), or two risk factors for coronary artery disease (age >60, cigarette smoking, diabetes, hypertension, cholesterol >240 mg/dl) should be on perioperative beta blockade unless they have a specific intolerance to beta blockers. Patients with renal failure or renal insufficiency may also benefit from therapy.
2. If a patient has an absolute contraindication to perioperative beta blockers, clonidine may be used as an alternative. Clonidine should be administered as follows.
 - a. Clonidine 0.2 mg PO on the night before surgery as well as a Clonidine TTS#2 (0.2 mg/24 hours) Patch. Hold the tablet for systolic blood pressure less than 120 mmHg.
 - b. Clonidine 0.2 mg PO on morning of surgery.
 - c. Leave the patch on for a week.
3. Beta blockade should be started as soon as the patient is identified as having CAD, PVD, or risk factors. If the surgeon identifies the patients as having risk, the surgeon should start the medication. If the anesthesia preop clinic identifies the patient, it should be started in the preop clinic. If the patient is not identified until the morning of surgery, intravenous atenolol or metoprolol should be used. (See 5.d. below) If the drug is started prior to the day of surgery, then atenolol 25 mg PO QD is an appropriate starting dose.
4. Beta blockade should be continued until at least 30 days postoperatively.

5. The optimal time to start beta blockade is at the time of identification of the risk. This process should be multitiered to avoid missing patients. The culture must change for the maximal number of patients to be treated. We use the following approach.
 - a. The surgeon starts the patient on a beta blocker if they have CAD, PVD, or two risk factors. Atenolol 25 mg PO QD is an appropriate starting dose.
 - b. If a medical or cardiology consult is requested by surgery, the most common advice is to start a beta blocker.
 - c. The anesthesia preop clinic checks to see if the patients at risk are on a beta blocker. If the patient is not adequately blocked, the dose is increased.
 - d. On the day of surgery the anesthesia providers may increase the dose or treat with intravenous beta blockers. Intravenous metoprolol in 5 mg boluses is used. Standard dose is 10 mg IV (hold for heart rate less than 50 or systolic blood pressure less than 100 mmHg). Intraoperative doses are used as needed. The patient is also re-dosed in the PACU post op as needed.
 - e. The patient remains on the drug post-operatively for 30 days. If the patient is NPO, the patient receives intravenous atenolol (10 mg IV Q12 hours) or metoprolol (5 mg IV Q6 hours). Hold for systolic blood pressure less than 100 mmHg and/or heart rate less than 50 beats per minute. If the patient is taking PO medications, the patient receives atenolol 100 mg PO QD if the heart rate is greater than 65 and the systolic blood pressure is greater than 100 mmHg. If the heart rate is between 55 and 65, the dose is 50 mg. There is a hold order for heart rate less than 50 or systolic blood pressure less than 100 mmHg. At the SF VA, we do not require a “monitored” (EKG) bed. We have a nursing administration protocol which allows nurses to administer patients on a regular med-surg unit. If the systolic blood pressure is greater than 100 mmHg and the heart rate is greater than 55 beats per minute, the drug is infused. *[Note: The doses of metoprolol and atenolol are similar, the interval between succeeding doses being shorter for metoprolol because of its shorter half-life. For example, metoprolol 5 mg IV Q6 hours is equivalent to atenolol 10 mg IV Q12 hours.]*
 - f. The patient remains on the drug for at least 30 days postoperatively.
 - g. Many patients should remain on the drug for life (known CAD, known PVD, hypertension).
6. Preoperative testing should be used as needed. If a patient is identified with new onset angina, unstable angina, a change in the anginal pattern or congestive failure, then the further risk stratification is appropriate. If the patient is stable with known CAD, PVD or two risk factors for CAD, then they should be placed on a beta blocker.
7. Care should be taken with patients who are in congestive heart failure (CHF), aortic stenosis, intra-coronary stents on platelet inhibitors or renal failure. All patients who have CHF should be evaluated by cardiology for the initiation of

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beta blocker therapy. Beta blocker therapy has been shown in multiple studies to reduce the risk of death from CHF. Many patients with CHF are profoundly improved by beta blockade. Patients with aortic stenosis should be evaluated by cardiology and beta blockade initiated with cardiology supervision. Patients with intra-coronary stents on platelet inhibitors should be seen by cardiology. **WARNING:** Discontinuation of platelet inhibitors in patients with intra-coronary stents can be lethal. Patients with renal failure should be treated with agents, but special attention is needed.



Information on implementing a PCRRT program can be obtained at www.betablockerprotocol.com.