

## Perioperative Beta-blockade: Where do we stand?

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The postoperative period is a hyperadrenergic state with associated increases in heart rate and blood pressure. Beta-blockers attenuate the effects of increased catecholamine levels. Early studies of perioperative beta-blockade using surrogate cardiovascular end points, such as ECG evidence of myocardial ischemia, yielded promising results. In the late 1990s, two influential trials studying perioperative beta-blockade were published. In the first, 200 patients with preexisting coronary artery disease (CAD) or multiple risk factors for it who were scheduled for noncardiac surgery were randomized to receive atenolol or placebo initiated immediately before surgery and continued in the postoperative period.<sup>1</sup> No difference in outcomes was demonstrated in the immediate postoperative period, but the atenolol group had reduced overall mortality and cardiac outcomes over the ensuing two years.<sup>1</sup> This study was criticized for concerns regarding inclusion of patients previously treated with beta-blockers and lack of intention-to-treat analysis. The second trial, the Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress EKG (DECREASE) study, was a small unblinded study comparing perioperative treatment with bisoprolol to usual care in patients with a positive dobutamine stress echocardiogram undergoing major vascular surgery.<sup>2</sup> DECREASE reported a 90% relative risk reduction in the combined endpoint of postoperative cardiac death and nonfatal myocardial infarction (MI). The DECREASE study group published several additional influential perioperative beta-blocker trials; however, the DECREASE trials have been discredited due to major flaws, in-

cluding the fabrication of data.<sup>3,5</sup> (In 2011, Don Poldermans, the lead author of the DECREASE trials, was relieved from his post at Erasmus University in the Netherlands for academic misconduct.)

A number of subsequent studies of perioperative beta-blockade in a variety of patient populations predominantly showed no benefit. The PeriOperative ISchemic Evaluation (POISE) trial, involving 8,000 patients from 190 hospitals in 23 countries, was published in 2008. Patients with CAD or with multiple risk factors for it and undergoing major noncardiac surgery were randomly assigned to receive placebo or high-dose oral and/or intravenous metoprolol succinate immediately before and continued after surgery.<sup>6</sup> The primary composite outcome of cardiovascular death, nonfatal MI, or nonfatal cardiac arrest was decreased by metoprolol succinate. However, this benefit was offset by an increased risk of stroke and all-cause mortality. Subsequent meta-analyses,<sup>7</sup> excluding the DECREASE trials and dominated by the POISE trial, have reported similar findings.

Most recently, a propensity-matched retrospective cohort study using the Veterans Health Administration databases was conducted.<sup>8</sup> Patients “exposed” to beta-blockers (i.e. received beta-blockers on postoperative day 0 or 1) after noncardiac nonvascular surgery were found to have reduced overall mortality and cardiac morbidity without an increased risk of stroke; for uncertain reasons, no difference was observed in vascular surgery patients. Most patients with beta-blocker “exposure” were receiving long-term beta-blocker therapy; however, similar out-

comes were observed when the beta-blocker was initiated within 30 days of surgery. There were insufficient data to assess outcomes when a beta-blocker was started within seven days of surgery.

### “Con” Opinion (Paul B. Cornia)

When I began practicing perioperative medicine 12 years ago, the use of perioperative beta-blockers for prophylactic purposes (i.e., started prior to surgery to reduce the risk of postoperative cardiac events, including death) was fairly common. Beta-blockers are well known to be beneficial in a variety of settings such as acute myocardial infarction and for the first few years after, heart failure with reduced left ventricular ejection fraction, and the treatment of angina. Additionally, beta-blockers have been in clinical use for several decades and are generally well tolerated by patients. The long positive track record of beta-blockers almost certainly aided in the rapid uptake of use in the perioperative setting. In retrospect, however, it remains surprising to me how quickly and widespread this practice became based on the two small studies in the late 1990s.

The recently released American College of Cardiology/American Heart Association Perioperative Guideline<sup>9</sup> contains several class IIb recommendations (i.e. benefit greater than or equal to risk) for prophylactic perioperative beta-blockade, including for patients with intermediate- or high-risk preoperative tests (e.g. cardiac stress tests) or those with at least three points using the Revised Cardiac Risk Index. However, others have argued strongly that prophylactic beta-blockade should not be rec-

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ommended, and I agree with this.<sup>10</sup> Based on the results of the POISE trial, the practice guideline further stipulates that if a beta-blocker is started prior to surgery, it should be done more than one day before surgery (class IIb recommendation) and not on the day of surgery (class III recommendations [harm]).

Given the problems with the DECREASE trials, these results should be excluded from clinical decision making. Presently, the best available randomized controlled trial (RCT) data (i.e. POISE) show increased mortality and stroke with prophylactic perioperative beta-blockade. As part of the recently released ACC/AHA clinical practice guidelines, an independent scientific review of perioperative beta-blocker RCT data was conducted. Among the RCTs included, non-fatal MI was reduced; however, stroke and overall mortality were increased. Importantly, the results were qualitatively unchanged even when the POISE trial was excluded. All trials (excluding DECREASE) initiated beta-blockade at least one day prior to surgery.

So where do we stand? It is critical to bear in mind the context of this discussion—that is, perioperative therapy (beta-blockade) purely for *prophylactic* purposes. It is essential that the benefit of a prophylactic treatment clearly outweighs the risk. The available evidence shows real harm (i.e. increased overall mortality and stroke) when beta-blockers are started at least one day prior to surgery. Concerns about the dosing regimen used in the POISE trial (i.e. high dose and started immediately prior to surgery) have led many to question the results. I agree with the conclusion of the ACC scientific review that “multicenter RCTs are

needed to address this knowledge gap.” Until we have data that confirm that an alternative regimen of prophylactic perioperative beta-blockade started prior to surgery (e.g. started days to weeks prior to surgery, possibly with dose titration) is both safe and effective, I do not believe that it should be recommended.

**“Pro Opinion” (Clifford D. Packer)**

There is ample evidence that perioperative beta-blockers reduce rates of MI and cardiac mortality in high-risk patients. The physiologic plausibility of the benefit is clear—beta-blockers reduce catecholamine levels, heart rate, and myocardial oxygen demand and have been shown to reduce rates of troponin leak and ECG evidence of ischemia in the perioperative period.<sup>11</sup> Most of the perioperative beta-blocker trials, including POISE, have shown substantial reductions in both fatal MI and non-fatal cardiac complications. There are two major quandaries, however, that have led to uncertainty about the utility of perioperative beta-blockers: the Poldermans scandal and the findings of increased stroke risk and increased overall mortality in the POISE trial.

POISE is by far the largest prospective beta-blocker trial, and therefore it profoundly affects the meta-analysis results described above. Unfortunately, POISE is a seriously flawed study. In an elderly cohort of patients (average age 69), 100 mg extended-release metoprolol was given two to four hours before surgery, with no titration period. Subjects were then given an additional 100 mg in the first six hours after surgery if their heart rate was greater than 80 and systolic blood pressure

greater than 100; then an additional 200 mg was given 12 hours after the first postoperative dose, followed by 200 mg daily. Many patients, therefore, received 200 to 400 mg of extended-release metoprolol in the first 24 hours. Not surprisingly, substantially more patients in the treatment group had hypotension, bradycardia, and ischemic stroke than in the placebo group. “Our post-hoc analysis,” the authors concluded, “suggests that clinically significant hypotension, bradycardia, and stroke explain how B-blockers increased the risk of death in this trial.” This is true as far as it goes; what the POISE trial proved is that excessive doses of perioperative beta-blockers given without a titration period can lead to bad outcomes. This is a classic overtreatment effect. We know that bradycardia and hypotension are bad in the perioperative period. The question is, “Would a prospective trial with low initial dosing and careful dose titration over more than one week (so that bradycardia and hypotension were avoided or minimized) reduce both cardiac and overall mortality?”

Based on all available evidence, I think the answer is likely to be yes, at least for high-risk patients with revised cardiac risk index (RCRI) scores of two or more. Two large well-constructed retrospective studies by Lindenauer et al.<sup>12</sup> and London et al.<sup>8</sup> show remarkably similar overall mortality benefits for patients with risk scores of two or more, with the benefit increasing as the RCRI score rises, which supports the concept of a strong protective physiologic effect. London et al. also showed that long-term beta-blocker use was associated with lower rates

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of adverse outcomes than with initiation of treatment within a week or less, supporting the importance of a titration effect.

Beware of pendulum swings in medicine. Sometimes we abandon useful treatments too quickly on the basis of flawed or limited evidence. I conclude, POISE and Poldermans notwithstanding, that the preponderance of the evidence still supports the careful use of perioperative beta-blockers for high-risk patients. A well-designed prospective trial, with low starting doses and a sufficient titration period, would hopefully settle the question.

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