Chapter 17. Use of Beta Blockers To Prevent Perioperative Cardiac Events: Brief Update Review

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Introduction

Myocardial infarction and cardiovascular death are the most common complications of major non-cardiac surgery; thus, they have long been a focus of preoperative evaluations and a target of perioperative management strategies. Based on strong evidence linking myocardial ischemia with postoperative myocardial events and preliminary evidence that beta-blockade blunts electrocardiographic signs of ischemia, clinical researchers in the late 1990s began examining the effects of perioperative beta-blocker administration on patient outcomes. The 2001 report1 reviewed the evidence up to that point regarding the effectiveness, safety, and cost-effectiveness of this intervention. Based on the results from several well-designed clinical trials, the authors concluded that use of beta-blockers in the perioperative period was associated with significant reductions in patient cardiac morbidity and mortality. However, as of publication of that report, many questions remained regarding the optimal type of beta-blocker, the patients most likely to benefit, and the safest and most effective dosing regimen.

What Have We Learned About the Use of Beta Blockers To Reduce the Risk of Perioperative Cardiac Events?

Since the publication of “Making Health Care Safer” in 2001, new studies have called for a re-examination of the initial enthusiasm for the use of beta blockers to reduce perioperative cardiac events. Two systematic reviews with meta-analysis and one large randomized controlled trial (RCT) have been influential. The first systematic review/meta-analysis was published in 2005 by Devereaux and colleagues.2 This review, which scored 10 out of 11 relevant AMSTAR domains, included 22 trials encompassing 2,437 patients. The point estimates of effect favored patients treated with beta blockers for nearly all outcomes, but the 95% confidence intervals for these estimates were not statistically significant. The exception was the composite outcome of “major peri-operative cardiovascular events,” which included cardiovascular death, non-fatal myocardial infarction, and non-fatal cardiac arrest, where the results significantly favored treatment (pooled relative risk 0.44, 95% CI 0.20 to 0.97). Conversely, pooled estimates of the risk for three adverse effects (congestive heart failure, hypotension needing treatment, and bradycardia needing treatment), all indicated the potential for harm, with pooled relative risks of 1.27 to 2.27, the latter being for bradycardia needing treatment and being statistically significant (95% CI 1.53 to 3.36). This review concluded that the evidence supporting the use of beta blockers in this situation was “encouraging but too unreliable to allow definitive conclusions to be drawn.”

The large RCT was the POISE (perioperative ischemic evaluation) study, published in 2008.3 In this study, 8,351 patients 45 years of age or older who were undergoing non-cardiac surgery, and had either known vascular disease or strong risk factors were randomized to receive 100 mg of oral extended-release metoprolol 2 to 4 hours before surgery, followed by 200 mg every day for 30 days (patients unable to take oral medications received the comparable dose intravenously). The primary outcome was a composite of cardiovascular death, non-fatal...
myocardial infarction, and non-fatal cardiac arrest (in other words, the exact composite outcome with the statistically significant effect in the earlier meta-analysis). Indeed, at 30 days, patients receiving metoprolol had a hazard ratio (HR) for the primary outcome of 0.84 (95% CI 0.70 to 0.99), due primarily to fewer myocardial infarctions. However, patients treated with metoprolol had a statistically significantly greater risk of stroke (HR 2.17, 95% CI 1.26 to 3.74), and, even more alarmingly, a greater risk of all-cause death (HR 1.33, 95% CI 1.03 to 1.74). The authors of POISE concluded that the perioperative use of beta-blockers has both benefits and risks. For example they calculated that for every 1,000 patients undergoing noncardiac surgery, the use of extended-release metoprolol would prevent 15 patients from having a myocardial infarction and three from undergoing cardiac revascularization, but that there would be eight extra deaths and five extra strokes. Based on these differences in benefits and harms, and on the potential for patients to place different values on these outcomes, the authors of POISE concluded that authors of current guidelines advocating the use of beta blockers “should reconsider their recommendations.”

The later systematic review/meta-analysis was published in 2008, and included the POISE results. This review, which scored 11 out of 11 relevant domains in AMSTAR, included 33 trials, now encompassing 12,306 patients. Recalling that POISE contributed more than 8,000 patients alone, in most of the pooled analyses the POISE results contribute 75 percent or greater weight to the pooled result. Unsurprisingly, the meta-analysis found statistically significant benefits for treatment for the outcomes of non-fatal myocardial infarction and myocardial ischemia, nonsignificant results for all other potential benefits, and statistically significant adverse effects for nonfatal stroke (pooled odds ratio[OR] of 2.16), perioperative bradycardia requiring treatment (pooled OR of 2.74), and perioperative hypotension requiring treatment (pooled OR 1.62). The effect on mortality was adverse, but did not reach statistical significance (pooled OR 1.20, 95% CI 0.95 to 1.51). The authors of this review concluded that “evidence does not support the use of beta blocker therapy for the prevention of perioperative clinical outcomes in patients having non-cardiac surgery.”

Conclusions and Comment

Evidence that has emerged since the 2001 publication of “Making Health Care Safer” indicates that perioperative beta blockers have mixed benefits and harms and should not be considered a patient safety practice for all patients. An observational study of more than 600,000 patients suggests that perioperative beta blockers may have more benefit in high risk than in low risk patients. An observational study of more than 600,000 patients who underwent major noncardiac surgery, which did not did not find any evidence of benefit on in-hospital mortality for perioperative beta blockade (adjusted odds ratio = 0.99), did find a suggestion of possible benefit in the subgroup of patients at higher risk of death due to the presence of comorbidities (diabetes, renal insufficiency, ischemic heart disease, cerebrovascular disease) or receipt of high-risk surgery (ref 5). If these suggestive findings are confirmed in subsequent randomized clinical trials the use of peroperative beta blockers could yet be shown to have benefits exceeding risks for certain subgroups of patients, but this question remains a topic for clinical research. Moreover, randomized clinical trials may yet show this intervention to have benefits exceeding risks for some subgroups of patients undergoing noncardiac surgery, but this question remains a topic for clinical research. A summary table is below (Table 1).
**Table 1, Chapter 17. Summary table**

<table>
<thead>
<tr>
<th>Scope of the Problem Targeted by the PSP (Frequency/Severity)</th>
<th>Strength of Evidence for Effectiveness of the PSPs</th>
<th>Evidence or Potential for Harmful Unintended Consequences</th>
<th>Estimate of Cost</th>
<th>Implementation Issues: How Much do We Know?/How Hard Is it?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common/High</td>
<td>High evidence we know harms may equal or exceed benefits</td>
<td>High (death, stroke, hypotension and bradycardia)</td>
<td>Low</td>
<td>N/A</td>
</tr>
</tbody>
</table>

**References**


