EDITORIAL

Should physicians initiate β-blocker therapy in patients undergoing non-cardiac surgery?

Insights from the POISE trial

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A recent study published in *Lancet* used surgical data from 56 countries around the world to determine that globally there are over 230 million major surgical procedures undertaken annually.[1] Given that cardiac and pediatric surgery only account for a minority of major surgical cases, it suggests that over 200 million adults undergo major noncardiac surgery annually, and several million of these patients will suffer a major perioperative cardiovascular event (i.e., cardiovascular death, nonfatal myocardial infarction, nonfatal cardiac arrest, or nonfatal stroke).[2] Despite the magnitude of this public health problem, there has existed a paucity of adequately powered randomized controlled trials (RCTs) that have evaluated interventions that may lower the risk of a major cardiovascular event around the time of noncardiac surgery.[2]

Patients undergoing major noncardiac surgery experience high physiological stress marked by a rise in catecholamines that result in an increase in heart rate and hence myocardial oxygen demand.[3,4] Several studies have shown an association between tachycardia and perioperative cardiac ischemia.[5-7] The increase in perioperative catecholamine levels also results in an increase in free fatty acids levels, which further increasing oxygen demand because free fatty acids require aerobic metabolism.[8] Additionally, free fatty acids can damage myocardial cell membranes and can precipitate serious arrythmias.

β-blockers attenuate the effects of increased catecholamine levels, and this provided the physiological rationale that starting in the 1980s led authors to propose β-blockers as a potential preventive intervention for major perioperative cardiovascular complications.[7,9] Paradoxically, in the early 1970s β-blockers were stopped days before surgery as it was perceived that they could inhibit compensatory cardiovascular mechanisms and thus predispose patients to serious cardiovascular outcomes.[10] In the 1990s 2 small RCTs[11,12] (312 patients in total) with concerning methodological limitations (i.e., unblinded, stopped early for unexpectedly large treatment effect in the setting of very few events, and failure to use the intention-to-treat principle)[13], suggested that β-blockers given around the time of noncardiac surgery could prevent major cardiovascular events. More recently, 2 moderate sized perioperative β-blocker RCTs (1417 patients in total), which avoided the biases of the prior small RCTs, did not show a benefit with perioperative β-blockers.[14,15] Despite the limitations of the data, over a decade ago guideline committees started recommending perioperative β-blockers[16], and even with the recent moderate sized RCTs demonstrating no benefit to perioperative β-blockade, guideline committees have continued to recommend that physicians give β-blockers to patients undergoing noncardiac surgery.[17]

Recently, we were part of a large international group that completed and published the first large perioperative β-blocker RCT. This trial was called the POISE (Perioperative Ischemic Evaluation) trial, and it was an RCT comparing the effect of extended-release metoprolol succinate (metoprolol CR) with that of placebo on the 30-day risk of major cardiovascular events in patients with, or at risk of, atherosclerotic disease who were undergoing noncardiac surgery.[18] In POISE randomisation was conducted by a computerised

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randomisation service that was available for investigators to phone 24-hours a day. Patients, health-care providers, data collectors, and outcome adjudicators were blinded to treatment allocation. POISE included 8351 patients from 190 hospitals in 23 countries, and 8331 patients (99.8%) completed the 30-day follow-up. Analyses followed the intention-to-treat principle.

The dosing regimen in POISE was designed so that patients could get 200 mg of the study drug (i.e., metoprolol CR or matching placebo) during the first 24 hours.[18] Patients received 100 mg 2–4 hours prior to surgery and then 6 hours after surgery another 100 mg. Patients thereafter received 200 mg of the study drug daily for 30 days. If a patient's heart rate was below 45 beats per minute (bpm) or their systolic blood pressure (SBP) <100 mmHg, their study drug was withheld until their heart rate or SBP recovered and then they restarted the study drug at 100 mg orally once a day. Patients whose heart rate was 45–49 bpm and SBP >100 mmHg delayed taking the study drug for 12 hours.

At the 30-day follow-up 244 (5.8%) of the metoprolol patients and 290 (6.9%) of the placebo patients suffered the primary outcome – a composite of cardiovascular death, nonfatal myocardial infarction, and nonfatal cardiac arrest (hazard ratio [HR] for the metoprolol group, 0.84; 95% CI 0.70–0.99, p = 0.04).[19] This benefit was due to a reduction in myocardial infarction (176 [4.2%] in the metoprolol group compared to 239 [5.7%] in the placebo group; HR 0.73, 95% CI 0.60–0.89, p = 0.002). Mortality, however, was higher in the metoprolol group (129 [3.1%] patients) compared to the placebo group (97 [2.3%] patients) (HR 1.33, 95% CI 1.03–1.74, p = 0.03). More patients also suffered a stroke in the metoprolol group than in the placebo group (41 [1.0%] vs. 19 [0.5%], HR 2.17, 95% CI 1.26–3.74, p = 0.005).

We initially viewed the POISE findings of an increased risk of perioperative stroke and death from a perioperative β-blocker as surprising. However, when we updated our meta-analysis[20] the results of the 7 high-quality trials were consistent in demonstrating a higher risk of death with perioperative β-blocker therapy (relative risk [RR] 1.29, 95% CI 1.02–1.62, p = 0.03, $I^2 = 0\%$)[19]. Likewise, our updated meta-analysis of the 6 high-quality trials that reported a perioperative nonfatal stroke demonstrated a consistent finding of a higher risk of a nonfatal stroke with perioperative β-blocker therapy (RR 2.16, 95% CI 1.26–3.78, p = 0.005, $I^2 = 0\%$). The same was also true for the outcome of nonfatal myocardial infarction in that the prior trials demonstrated the same result as POISE when we included the 6 high-quality trials in an updated meta-analysis; this meta-analysis demonstrated that perioperative β-blocker therapy prevented nonfatal myocardial infarctions (RR 0.73, 95% CI 0.60–0.88, p = 0.01, $I^2 = 0\%$). Therefore, the POISE results for death, stroke, and myocardial infarction are consistent with the prior high-quality trials. The only reason the signal of perioperative β-blockers increasing the risk of death and stroke was not obvious prior to POISE was that the former trials were too small to demonstrate statistically significant results; however, their results were suggesting the same signal as POISE.

The POISE data offer insights into how perioperative β-blockers can increase the risk of death and stroke.[20] In POISE more patients experienced clinically significant hypotension (i.e., a SBP <90 mmHg that someone had to do something about) in the metoprolol group than in the placebo group (625 [15.0%] vs. 404 [9.7%], HR 1.55, 95% CI 1.38–1.74, p <0.0001). Similarly, in POISE more patients experienced clinically significant bradycardia (i.e., bradycardia that required a temporary pacemaker, sympathomimetic agent, atropine, or study drug discontinuation) in the metoprolol group than in the placebo group (277 [6.6%] vs. 101 [2.4%], HR 2.74, 95% CI, 2.19–3.43, p <0.0001). We undertook *post hoc* multivariable analyses and determined population attributable risks (PARs), which represent the proportion of all outcomes attributable to the relevant risk factor if causality were proven. Clinically significant hypotension had the largest PAR (37.3%) for death and the largest intraoperative/postoperative PAR (14.7%) for stroke. Further, perioperative stroke had a PAR of 8.0% and clinically significant bradycardia had a PAR of 7.9% for the outcome death. Therefore, perioperative clinically significant hypotension, bradycardia, and stroke, which perioperative β-blockers caused, potentially account for over 50% of the deaths demonstrated in POISE, and this explains how β-blockers increase a patient's risk of death around the time of noncardiac surgery. Although clinically significant hypotension was an important predictor of perioperative stroke our analysis explains less than half of the strokes. It is possible that more hypotension occured that was clinically relevant but did not fulfill our definition even though it may have accounted for more of the strokes. The increase in clinically significant hypotension demonstrated in POISE was also demonstrated in our previous meta-analysis that included varying doses or other perioperative β-blockers (RR 1.27, 95% CI 1.04–1.56).[20]

The POISE results suggest that for every 1000 patients undergoing noncardiac surgery with a similar risk profile metoprolol CR would prevent 15 patients from suffering a myocardial infarction, three from undergoing a cardiac revascularisation procedure, and seven from developing new clinically significant atrial fibrillation.[20] The POISE trial also suggests that perioperative metoprolol CR would result in an excess of eight deaths, five patients suffering a stroke, 53 experiencing clinically significant hypotension, and 42 experiencing clinically significant bradycardia for every 1000 treated.

Although no patient would want to suffer a perioperative myocardial infarction, we suspect that

patients would place more weight on avoiding an increased risk of death and stroke. Current perioperative guidelines that recommend β-blocker therapy to patients undergoing non-cardiac surgery should reconsider their recommendations in light of these findings.

POISE is the first large perioperative cardiovascular outcome trial, and it demonstrates the risk in assuming a perioperative β-blocker regimen has benefit without substantial harm. In POISE one in every 15 patients who participated suffered a cardiovascular death, nonfatal myocardial infarction, nonfatal cardiac arrest, or nonfatal stroke within the first 30-days. This burden of negative cardiovascular outcomes highlights the importance and need for large randomised trials in the perioperative setting to identify interventions to reduce major perioperative cardiovascular events.

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