The POISE Trial: Casting More Doubt on the Benefits of Perioperative β Blockers

Devereaux PJ, Yang H, Yusuf S, et al; POISE Study Group. Effects of extended-release metoprolol succinate in patients undergoing non-cardiac surgery (POISE trial): a randomised controlled trial. Lancet 2008;371:1839–47.

Study Overview

Objective. To evaluate the effects of perioperative β blockers versus placebo.

Design. Prospective, multicenter, randomized, placebo-controlled trial.

Setting and participants. 8351 patients aged ≥ 45 years with or at risk for atherosclerotic disease who were undergoing noncardiac surgery were randomized by computerized phone randomization to either extended-release metoprolol (n = 4174) or placebo (n = 4177). Participants received extended-release metoprolol 100 mg or matching placebo 2 to 4 hours before surgery. The first postoperative dose (100 mg or placebo) was given 6 hours after surgery or sooner if the heart rate was ≥ 80 bpm or systolic blood pressure was ≥ 100 mm Hg. Patients started oral extended-release metoprolol 200 mg or placebo 12 hours after the first postoperative dose and continued the medication daily for 30 days.

Main outcome measures. The primary outcome was a composite of cardiovascular death, nonfatal myocardial infarction (MI), and nonfatal cardiac arrest at 30 days after randomization. Individual secondary outcomes at 30 days included total mortality, cardiovascular death, nonfatal MI, nonfatal cardiac arrest, cardiac revascularization, stroke, congestive heart failure, new clinically significant atrial fibrillation, hypotension, bradycardia, length of hospital stay, length of intensive care unit/cardiac care unit stay, and heart rate at discharge. Participants were analyzed on an intent-to-treat basis.

Main results. Baseline characteristics between the study groups were similar. The majority of patients in both groups had atherosclerotic disease (3444 [83%] in the metoprolol group vs. 3410 [82%] in the placebo group). Fewer patients in the metoprolol group compared with the placebo group reached the primary outcome (5.8% vs. 6.9%; P = 0.039), attributed mostly to fewer MIs in the metoprolol group (4.2% vs. 5.7%; P = 0.0017). Patients in the metoprolol group also required fewer cardiovascular revascularization procedures (0.3% vs. 0.6%) and developed fewer episodes of clinically significant atrial fibrillation (2.2% vs. 2.9%). However, more patients in the metoprolol group died (3.1% vs. 2.3%; P = 0.0317), had strokes (1.0% vs. 0.5%; P = 0.0053), and developed clinically significant hypotension (15% vs. 9.7%) or bradycardia (6.6% vs. 2.4%) as compared with placebo-treated patients. Prespecified subgroup analysis based on revised cardiac risk index score, sex, type of surgery, or type of anesthetic did not show a subgroup effect. Post hoc multivariate analyses suggested that clinically significant hypotension, bradycardia, and stroke caused the increase in death in the metoprolol group.

Conclusion. In patients undergoing noncardiac surgery, prophylactic β blockade significantly decreased the incidence of MI but increased the incidence of death and stroke.

Commentary

The use of β blockers in the perioperative setting gained favor after trials in the 1990s showed a decrease in cardiovascular events [1,2]. However, this benefit was seen in trials limited by small sample sizes and design flaws, including nonstandard dose, route, and timing of medication administration. Subsequent meta-analyses revealed conflicting results, suggesting either a reduction or no difference in cardiovascular events [3,4]. Based on these data, American College of Cardiology (ACC)/American Heart Association (AHA) guidelines recommended perioperative β blockers for high-risk patients with known ischemic heart disease undergoing vascular surgery and for patients already on β blockers prior to surgery [5]. More recent trials have demonstrated no benefit of perioperative β blockers among patients undergoing vascular surgery [6,7] and noncardiac surgery [8].

Since the ACC/AHA guidelines were issued, the PeriOperative ISchemic Evaluation (POISE) trial represents the largest randomized trial investigating the effects of perioperative β blockers. The marginal benefit observed in the primary composite outcome (cardiovascular death, nonfatal MI, and nonfatal cardiac arrest at 30 days after randomization) was essentially due to a reduction of nonfatal MIs in the β-blocker group. However, analysis of secondary outcomes demonstrated no benefit and, in fact, the findings point against the routine use of perioperative β blockers due to the increased incidence of 30-day mortality and stroke in the metoprolol arm.

POISE has its shortcomings. The dose of β blockers administered was high (extended-release metoprolol 200 mg or 15 mg intravenously every 6 hours in patients unable to take oral medications) and dosing was started immediately before surgery. Many of the patients were at relatively low risk for developing cardiovascular events based on the ACC/AHA guidelines and would not have met criteria for receipt of perioperative β blockers, limiting the generalizability of the results. In addition, the risk of death from stroke was not explained by hypotension or other identified risk factors, which taken together only accounted for approximately half the observed increased rate of stroke.

Applications for Clinical Practice

The POISE trial adds to the evidence base questioning the routine use of perioperative β blockers in patients at intermediate risk of cardiovascular events. Although there is no doubt of the survival benefits observed with β blockers for secondary prevention of cardiovascular events, the recommendations of the ACC/AHA guidelines are still the most valid for the perioperative setting: for high-risk patients not already on β blockers, start therapy early (days to weeks prior to surgery), aim for a heart rate in the low 60s bpm, and continue therapy for at least 1 week postoperatively.

—Review by Cindy Mui, MD (New York University School of Medicine, New York, NY) and Nirav R. Shah, MD, MPH

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