

Perioperative β blockade: where do we go from here?



The POISE (PeriOperative ISchemic Evaluation) trial reported in today's *Lancet* presents mixed results of the effectiveness of perioperative β -blocker therapy.¹ In the trial, 8351 patients were randomly assigned to either controlled-release oral metoprolol succinate or placebo. The primary endpoint of cardiac death, non-fatal myocardial infarction, or cardiac arrest was reduced in the metoprolol group compared with placebo (5.8% vs 6.9%, hazard ratio 0.84, 95% CI 0.70–0.99, $p=0.04$), driven by a reduction of non-fatal myocardial infarctions. However, these improvements were at the cost of an increased incidence of total mortality and stroke. Stroke was associated with perioperative hypotension, bleeding, atrial fibrillation, and a history of stroke or transient ischaemic attack in patients assigned to receive metoprolol. Data from sites in Iran and Colombia were excluded because of inconsistencies in these regions.

The use of β blockers in the perioperative setting is a subject of importance and debate. One area which is not debated, however, is that patients who have been treated with β blockers for a long time should be continued on their medication throughout the perioperative period.² In the USA, several groups have identified initiation of treatment with perioperative β blockers as a recommended practice and have advocated its adoption as a performance measure of quality of care.³ The POISE study puts that contention into question. However, in the non-surgical setting, β blockers are the cornerstone in the treatment of coronary artery disease, improving survival in patients with angina pectoris, myocardial infarction, peripheral arterial disease, and heart failure.^{4,5} Coronary artery disease and heart failure are the major risk factors of adverse postoperative outcome after non-cardiac surgery.⁶ What is the reason that treatment of the same patients with coronary artery disease by β blockers is associated with different outcomes in the surgical setting?

There are two reasons that might explain these differences: β -blocker treatment regimens differ, and the operative setting has specific haemodynamic regulatory mechanisms. In the POISE study, metoprolol succinate, a long-acting β blocker, was used. The starting dose was 100 mg given orally 2–4 h before surgery, and again 100 mg 0–6 h after surgery. Medication was withheld

if systolic blood pressure dipped below 100 mm Hg or heart rate was below 50 beats per min. So, on the first day of surgery, metoprolol succinate could have been administered at a dose up to 200 mg, 50% of the maximum daily therapeutic dose. In the non-surgical setting, much lower starting doses are recommended. For instance, in patients with New York Heart Association Class II heart failure, 12.5–25 mg a day is started for 2 weeks, and for hypertension the initial dose is 25–100 mg, usually increased at weekly intervals.^{4,5} In the POISE study, the starting dose of metoprolol succinate was 2–8 times the commonly prescribed dose.

By contrast with the fixed higher metoprolol succinate dose regimen of the POISE study, a low-dose bisoprolol regimen was applied in the series of randomised and non-randomised DECREASE (Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echo) trials.^{7,8} In DECREASE, the bisoprolol starting dose was 25% of the maximum daily therapeutic dose in the initial studies and was decreased to 12% in the more recent studies, similar to heart failure patients at least 30 days before surgery. The dose was adjusted immediately before surgery to achieve a heart rate control between 50 and 65 beats per min. The importance of the initiation time of β -blocker therapy before surgery could also be argued by the pathophysiology of a perioperative myocardial infarction. Half of fatalities at autopsy are related to coronary plaque rupture and thrombus formation.⁹ The acute effects of β blockade include the reduction of myocardial oxygen demand by a decrease in heart rate, systolic pressure, and ventricular contractility, which can reduce shear stress at the level of a vulnerable plaque. Otherwise, the suggested effect of β blockers on coronary plaque stabilisation might be related to anti-inflammatory properties and possibly only be noted after protracted use.

The POISE trial supports the results of DECREASE and other trials of long-acting agents in reducing perioperative cardiac events, although with an increased incidence of stroke. As the authors of POISE show, other randomised trials of acute initiating β blockers immediately before surgery also have shown an increased stroke rate. However, contrary to the current protocol, the incidence of perioperative stroke in the low-dose bisoprolol regimen started at least

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Surgery	No clinical risk factors	One or more clinical risk factors	Coronary heart disease or high cardiac risk	Patients currently taking β blocker
Vascular	Class IIb, level of evidence: B*	Class IIa, level of evidence: B	Class I†/ class IIa‡, level of evidence: B	Class I, level of evidence: B
Intermediate risk	..	Class IIb, level of evidence: C	Class IIa, level of evidence: B	Class I, level of evidence: C
Low risk	Class I, level of evidence: C

*Weight of evidence in support of recommendation is listed as follows: Level of evidence A=data derived from multiple randomised clinical trials. Level of evidence B=data derived from single-randomised trial or non-randomised studies. Level of evidence C=only consensus opinion of experts, case studies, or standard-of-care. †Applies to patients found to have coronary ischaemia on preoperative testing. ‡Applies to patients found to have coronary heart disease. Level of evidence according to ACC/AHA. Class I=conditions for which there is evidence for and/or general agreement that procedure or treatment is beneficial, useful, and effective. Class II=conditions for which there is conflicting evidence and/or divergence of opinion about usefulness/efficacy of procedure or treatment. Class IIa=weight of evidence/opinion is in favour of usefulness/efficacy. Class IIb=usefulness/efficacy is less well established by evidence/opinion. Class III=conditions for which there is evidence and/or general agreement that procedure/treatment is not useful/effective, and in some cases might be harmful. Adapted from reference 2.

Table: Recommendations for perioperative β -blocker therapy according to ACC/AHA guidelines

7 days before surgery in the DECREASE trials was 0.4% of 3994 patients, similar to that with placebo therapy. By contrast, 1.0% of patients in the higher-dose metoprolol regimen started the morning of surgery in POISE.

What are the consequences of the POISE results for β -blocker use in daily clinical practice? Based on the pathophysiology discussed above, reduction of perioperative cardiac morbidity will require a multi-modal approach that we believe includes heart rate control. In patients with class I indications for β blockers for secondary prevention of heart disease, therapy is recommended independent of the non-cardiac surgery.^{1,10} The current trial clearly shows that acute administration of higher-dose β -blocker therapy in the perioperative period is associated with greater risk than benefit, but we believe that the protocol used in the DECREASE studies (low-dose long-acting agents titrated to effect at least 7 days in advance) is associated with overall benefit compared to risk.

What do we do for those with indications for perioperative β -blocker therapy (table), but in whom there is insufficient time to appropriately titrate the medication? The over-riding theme is that tachycardia caused by perioperative events, such as bleeding, hypovolaemia, inadequate control of pain, or infection, should not be initially treated with additional β -blocker therapy. The underlying cause of these conditions should be treated first. If tachycardia persists, then we recommend that a β blocker can be used cautiously in high-risk patients with proven or suspected coronary artery disease, preferably supervised in the perioperative setting by physicians who have experience with perioperative haemodynamics, such that hypotension and other haemodynamic aberrations which might

have led to the increased incidence of stroke or septic death are avoided.

*Lee A Fleisher, Don Poldermans

University of Pennsylvania School of Medicine, Philadelphia, PA 19104, USA (LAF); and Department of Surgery, Erasmus Medical Centre, Rotterdam, Netherlands (DP)

Lee.fleisher@uphs.upenn.edu

Our views here are not those of the guideline committees we chair.

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