Perioperative beta-blockade, 2008: What does POISE tell us, and was our earlier caution justified?

In the early days of patients presenting for surgery while on beta-blockers, it was customary to stop their administration 2 weeks before elective surgery because of the perceived risk of cardiovascular collapse that could result from blockade of compensatory mechanisms. This view was supported by mostly anecdotal evidence, and seemed illogical as surgery constitutes a high stress situation during which the heart may need to be protected by blockade from the effects of exaggerated sympathetic activity. In 1973, the first detailed haemodynamic study of beta-blockade in surgical patients showed that beta-blockade was compatible with anaesthesia and surgery, reduced the risk of hypertension on laryngoscopy and intubation, and decreased the incidence of both ventricular arrhythmias and myocardial ischaemia.2

Further evidence for protection against perioperative myocardial ischaemia by acute beta-blockade was observed in a number of subsequent studies.3,4 A significant improvement in cardiac outcome at 2 yr after non-cardiac surgery was reported by Mangano and colleagues5 in a randomized controlled trial (RCT) in 1996. In this trial, the event-free survival was 91% for those given atenolol for 1 week post-surgery and 81% for those given a placebo. However, in their analysis, the authors did not include events occurring during hospitalization, and in contrast to the published results, an intention-to-treat analysis does not show long-term mortality benefit.6 Despite the limitations of the data from this trial, the American College of Medicine proposed in 1997 that atenolol should be given before operation to all patients with coronary artery disease or risk factors for that condition.7 Such an approach was indirectly supported by the data available at the time related to the efficacy of beta-blockade in the treatment of acute myocardial infarction, and its secondary prevention, hypertension, and later in the management of patients with cardiac failure.

In 1999, another RCT of patients with reversible ischaemia, on dobutamine echocardiography, presenting for major elective vascular surgery showed a 100% reduction in the incidence of myocardial infarctions and an 80% reduction in cardiac deaths in the patients treated before and after operation with bisoprolol.8 Although there were also limitations in this trial (e.g. it was unblinded and stopped at the first interim analysis, despite only randomizing 112 patients and the presence of 20 events), these data strengthened the case for beta-blockade. Our previous editorial in the British Journal of Anaesthesia expressed enthusiasm for the use of these drugs, but cautioned the reader against injudicious use!9

The American College of Cardiology/American Heart Association (ACC/AHA) guideline of 2002 stated: ‘current studies suggest that appropriately administered beta-blockers reduce perioperative ischaemia and may reduce the risk of myocardial infarction and death in high risk patients’.10 Nevertheless, these guidelines categorized the use of beta-blockers in patients undergoing vascular surgery with ischaemia detected during preoperative testing as a class I recommendation, and they gave a class IIa recommendation to the use of perioperative beta-blocker therapy in patients with preoperative untreated hypertension, known coronary artery disease, or major risk factors for coronary disease.

The acknowledgement of some degree of uncertainty about the efficacy of beta-blockade in surgical patients was appropriate, as some other studies failed to show early or short-term outcome benefits.11,12 When data from these and other studies were combined, early systematic reviews of acute beta-blockade with a meta-analysis of RCTs, based on a relatively small number of patients, showed evidence of cardiac protection.13,14 However, more recent and much larger meta-analyses of their use in non-cardiac,15 and in cardiac and non-cardiac surgery16 indicate only a trend towards protection. The findings from these systematic reviews express uncertainties that are reflected in the 200617 and 200718 ACC/AHA guidelines which state ‘current studies suggest that beta-blockers reduce perioperative ischaemia and may reduce the risk of myocardial infarction and death.
in patients with known coronary artery disease. Nevertheless, these guidelines once again categorized the use of beta-blockers in patients undergoing vascular surgery with ischaemia detected during preoperative testing as a class I recommendation, and they gave a class IIa recommendation to use perioperative beta-blocker therapy in patients undergoing vascular surgery in whom preoperative testing identifies coronary heart disease, patients undergoing vascular or intermediate-risk surgery with the presence of another risk factor.

At the same time, our knowledge about the efficacy of beta-blockers in other settings was starting to change. Beta-blockers were removed as a first-line drug in the management of hypertension based upon data from large trials and meta-analyses demonstrating that calcium channel blockers and ACE inhibitors and angiotensin receptor antagonists were superior in preventing the risk of stroke. Further, the role of beta-blockers in acute myocardial infarction was changed with the publication of the COMMIT trial (a RCT of acute coronary infarction vs placebo in patients with acute myocardial infarction) that showed no impact on 30 day mortality.

Inconsistencies in the summated results of small perioperative beta-blocker RCTs were one of the main reasons behind the setting up of a large multinational RCT of beta-blockade versus placebo in patients at risk of perioperative cardiac events: the PeriOperative Ischemia Study Evaluation (POISE trial). Enrolment started in 2002 and lasted until July 2007. Its results were published recently in the Lancet. The total number of patients enrolled was 8351 from 190 hospitals in 23 countries. Four thousand one hundred and seventy-four patients received the study drug, metoprolol succinate extended-release (with the goal of 200 mg daily but down-titrated for hypotension or bradycardia to 100 mg daily). The drug or placebo was started 2-4 h before surgery and was continued for 30 days. The primary outcomes were cardiovascular death, non-fatal myocardial infarction, and non-fatal cardiac arrest. Secondary outcomes included total mortality, stroke, myocardial infarction, coronary revascularization, atrial fibrillation, congestive heart failure, hypotension, and bradycardia.

The 30 day results showed a significant reduction in all myocardial infarction [176 (4.2%) in the metoprolol group vs 239 (5.7%) in the placebo group], a reduced need for coronary revascularization, and a reduction in the number of patients developing atrial fibrillation. In contrast, there was a significant increase in total mortality [129 (3.1%) metoprolol group vs 97 (2.3%) placebo group], stroke [41 (1%) metoprolol group vs 19 (0.5%) placebo group], and clinically significant hypotension and bradycardia.

The frequent occurrence of hypotension may explain the excess strokes, as the aetiology of the 60 observed strokes was ischaemic in 47, haemorrhagic in three, and uncertain in another eight. Interestingly, despite the decreased incidence of new atrial fibrillation in the metoprolol group and atrial fibrillation influencing the occurrence of the 30 day risk of stroke, there was still an overall increase in the stroke rate among the metoprolol patients.

The POISE results suggest that for every 1000 patients with a similar risk profile undergoing non-cardiac surgery, metoprolol will prevent 15 patients from suffering a myocardial infarction, three from undergoing coronary revascularization, and seven from developing new significant atrial fibrillation. However, on the adverse side, the POISE results also suggest that metoprolol will cause an excess of eight patients to die and five to suffer a stroke for every 1000 treated with a perioperative beta-blocker.

The study, therefore, does not support the widespread introduction of perioperative beta-blockers in all patients at risk because of coronary disease as had been proposed 11 yr previously. Further data analysis may reveal that some groups of patients benefit from beta-blockade without the increased risk of all-cause mortality and stroke. However, such analyses will probably relate to small samples and hence be underpowered and should be only viewed as hypothesis generating.

Is it possible to obtain benefit from perioperative beta-blockade and at the same time avoid the risks?

First, the trial design dictated that the study drug was started only a few hours before surgery; this may have increased the risk of perioperative hypotension and bradycardia. Moreover, some of the protective effects of beta-blockade may take longer than a few hours to develop, especially their anti-inflammatory effects. In the study showing the most marked protective effect, beta-blockade was initiated a week before surgery. In the POISE study, metoprolol extended-release was given as 100 mg b.d. This drug regimen raises two issues: was the dose (200 mg daily) too high (explaining the high incidence of hypotension); or are the findings a drug-specific rather than a class effect? This seems unlikely, given that previous meta-analyses of beta-blockade have encompassed a variety of drugs and dosages and demonstrated that clinically significant hypotension was caused by a variety of beta-blockers at varying doses. However, a recent study examining mortality after myocardial infarction in patients receiving long-term secondary prevention treatment with beta-blockers found a higher mortality in patients receiving metoprolol compared with those treated with atenolol or acebutolol. The authors offer no explanation for their findings, but this may raise a question over the choice of metoprolol in the POISE study.

The British National Formulary 2008 recommends the following doses of metoprolol: hypertension 100–200 mg daily (maximum 400 mg); angina 50–100 mg b.d./t.d.s., and arrhythmias 50 mg t.d.s. (maximum 300 mg). The dose of metoprolol used in the POISE study is, therefore, in keeping with doses used in current practice. Moreover, for a similar...
modified release form of metoprolol, the dose suggested for hypertension and angina is 200 mg daily increased to 400 mg if necessary. The statement in the editorial from Fleisher and Poldermans published in the *Lancet* that the dose of metoprolol was two to eight times the commonly prescribed dose is therefore surprising, and only applies fully in the case of beta-blockade in the treatment of heart failure where, indeed, initial doses are much lower, but this is not relevant to POISE as it was not a heart failure trial.

Secondly, although there were defined limits of heart rate for temporarily withholding the study drug (if the heart rate is \( \leq 50 \text{ beats min}^{-1} \)), there were no upper limits of heart rate to increase the dosage. The value of tight postoperative heart rate control on morbidity and mortality had been observed in other studies and more recently in a meta-analysis. Yet, the role of strict control of heart rate is not unquestioned, and may only be achieved at the cost of other adverse effects (e.g. hypotension). Multivariable analysis of strokes within the POISE study confirms a significant association with clinically significant hypotension.

Thirdly, the admission criteria to POISE may have been too broad, allowing patients with relatively low cardiac risk to be enrolled. This is unlikely, however, as separate analyses did not demonstrate any subgroup effect based upon baseline risk.

Fourthly, recent studies have shown that genetic heterogeneity of the beta-adrenocceptor may influence cardiac outcomes in patients undergoing non-cardiac surgery. Examination for the association of adverse outcomes to particular genetic polymorphisms was not investigated in the POISE study, but clearly future studies might include assessment of the benefits of beta-blockers in high-risk genotype groups.

**What are the take home messages with regard to perioperative beta-blockade after POISE?**

First, POISE showed evidence of cardiac protection. This included a reduction of myocardial infarction (although many of the diagnoses were made in asymptomatic patients based on either ECG or enzyme changes) with few resulting in the development of congestive cardiac failure, the need for emergency revascularization, or non-fatal cardiac arrest.

Secondly, however, the incidence of stroke and their resulting patient disability was increased in the treatment group and all-cause mortality.

Thirdly, on the basis of observational studies, it is recommended that patients already on beta-blockers be maintained on their medication throughout the perioperative period. This recommendation stands, as POISE only studied the effects on outcome of acute perioperative beta-blockade. Although chronic beta-blockade may not offer the expected cardiac protection, the withdrawal of beta-blockers is associated with a significant increase in the risk of adverse cardiac outcomes. The need to increase the dose of beta-blocker to maintain tight heart rate control throughout the perioperative period should be considered, with careful titration of dose to effect. For high-risk patients, this may necessitate the postoperative admission of the patient to an HDU or ITU to monitor drug administration. There will also be need for the development of protocols to which clinicians must adhere; to date, there are no RCTs to support this approach.

Fourthly, in patients with proven, or at high-risk of, coronary heart disease, it is appropriate that they receive beta-blockers for their long-term outcome benefits, irrespective of any impending surgery.

Fifthly, in patients where coronary heart disease is only recognized at the time of admission for elective surgery, the results of the POISE trial would suggest it inappropriate to start beta-blockade at that time. If beta-blockers are indicated for intercurrent medical conditions, then these medications should be started well before rather than at the time of surgery. It should also be recognized that beta-blockers are no longer regarded as first-line treatment in arterial hypertension unless it is associated with coronary heart disease.

Since 1973, there have been several U-turns in respect of beta-blockade, from stopping them before elective surgery to maintenance of treatment. In 1997, beta-blockers were recommended for all patients at risk of coronary disease. This recommendation is no longer tenable. Similarly, from being first-line treatment of hypertension for three decades, beta-blockers are now only considered essential for patients with hypertension and coronary artery disease.

The POISE study highlights the increased risks of stroke and all-cause mortality associated with the perioperative administration of beta-blocking drugs. Other strategies need therefore to be examined as ways of providing cardiac protection. Perioperative beta-blockade should only be prescribed on an individual patient basis after due consideration has been given to their possible benefits and hazards.

**Declaration of interest**

All authors were involved in the collection of data for the POISE trial; however, none took part in the data analysis or writing of the paper.

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Appendix

Readers should be aware that approximately 10% of the recruited patients were excluded from analysis because of fraudulent data at one centre.

References

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