Perioperative β blockade: where do we go from here?

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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

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 multimodal 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.

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

1 POISE Study Group. Effect of extended-release metoprolol succinate in patients undergoing non-cardiac surgery (POISE trial): a randomised controlled trial. *Lancet* 2008; published online May 13. DOI:10.1016/S0140-6736(08)60601-7.
2 Fleisher LA, Beckman JA, Brown KA, et al. ACC/AHA 2007 Guidelines on perioperative cardiovascular evaluation and care for noncardiac surgery: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to revise the 2002 guidelines on perioperative cardiovascular evaluation for noncardiac surgery) developed in collaboration with the American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Rhythm Society, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, and Society for Vascular Surgery. *J Am Coll Cardiol* 2007; **50:** 1707–32.
3 Leapfrog Group. http://www.leapfroggroup.org (accessed May 6, 2008).
4 Cruickshank JM. Beta-blockers continue to surprise us. *Eur Heart J* 2000; **21:** 354–64.
5 MERIT-HF Study Group. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). *Lancet* 1999; **353:** 2001–07.
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9 Poldermans D, Hoeks S, Feringa H. Preoperative risk assessment and risk reduction prior to surgery. *J Am Coll Cardiol* (in press).
10 Smith SC, Jr., Allen J, Blair SN, et al. AHA/ACC guidelines for secondary prevention for patients with coronary and other atherosclerotic vascular disease: 2006 update: endorsed by the National Heart, Lung, and Blood Institute. *Circulation* 2006; **113:** 2363–72.

reductions in the important primary outcomes of cardiac death, nonfatal MI, and cardiac arrest (5.8% vs 6.9%; hazard ratio [HR]: 0.83; 95% CI: 0.70–0.99; $P = 0.04$) were essentially counterbalanced by an increase in death (3.1% vs 2.3%; HR: 1.33; $P = 0.03$) and stroke (1.0% vs 0.5%; HR: 2.17; $P = 0.005$). Other beneficial effects included a reduction in atrial fibrillation and the need for myocardial revascularization. A particularly troubling adverse effect was a doubling of the percentage of patients dying from sepsis. Bradycardia and significant hypotension were also more common although, of some assurance, there was no increase in the incidence of acute heart failure.

Early reaction to the POISE study results among perioperative clinicians appears similar to the "shock waves" caused by the initial report of the large scale COMMIT study (45,852 patients) (with formal publication more than a year later), which reevaluated, in one of its treatment arms, the well established, yet poorly validated, practice of aggressive early institution of β-blockade during acute MI (in contrast to the better validated efficacy of "delayed" secondary prevention).[23] This landmark study, coincidentally performed exclusively outside of the United States in China, reported that the benefits of reduced reinfarction with acute β-blockade were nearly counterbalanced by an increased incidence of early cardiogenic shock. The COMMIT study revealed that patients at greatest risk for this serious adverse outcome were already hemodynamically unstable, thus leaving the clinician latitude to treat stable lower risk patients more aggressively should they prefer to. It is important to note that the major result of the COMMIT study does not proscribe β-blocker use "peri acute MI," but does suggest that it should only be instituted orally in lower risk patients after the first 24 h (or later if at all in less stable patients). It is of particular importance to the issue of perioperative β-blockade that adverse safety implications of the COMMIT study regarding aggressive β-blockade are now prominently displayed as Class III Level of Evidence A recommendations in the recently released American College of Cardiology/American Heart Association Guidelines for Management of Patients with ST and Non-ST elevation Myocardial Infarction Practice Guidelines.[24,25]

The preliminary results of the POISE study suggest that delineation of patients at increased risk for adverse outcomes was not detected. This finding is very troublesome for the future of widespread treatment protocols and would likely preclude widespread perioperative β-blockade protocols from a Class 1 type recommendation in subsequent Practice Guidelines. Analysis the results of the POISE study results will clearly have to await publication of the final manuscript. Many issues will be debated: What were the heart rates and blood pressures at key time periods and what dose adjustments occurred? How were MIs detected? Are there center and country level effects with regards to the adverse outcomes that clearly have an established and rapidly growing scientific basis (but was not specifically addressed in the POISE protocol)? Were there genetic or racial effects?[26–29]

Until the full details are known, the discussions will center around the "surrogate outcomes" of arterial blood pressure and heart rate. The hypothesis that low blood pressure or cardiac output might worsen gut translocation and increase risk of sepsis may have been borne out by POISE. The increase in stroke may be related to critical cerebral hypoperfusion from low blood pressure. Critics of POISE will state that the patients were clearly overdosed, whereas its supporters will point out that cardiologists and others have been quite insistent that adequate β-blockade requires aggressive heart rate control as long as the systolic blood pressure is more than 100 mm Hg. It is equally likely that POISE would have been roundly criticized had the heart rates not been aggressively controlled and had found no positive treatment effect. The latest observational and secondary analysis of pilot randomized controlled trial (RCT) data from Dr. Polderman's group continues to strongly support aggressive heart rate control and notably, consideration of arterial blood pressure in these studies is limited solely to its use as a safety end-point only (dosing withheld for a systolic blood pressure <100 mm Hg).[30,31] The critics will propose cutting the existing doses in their protocols by half, or perhaps more, whereas POISE supporters will argue that safe titration is likely not possible, and thus widespread use of a drug that now appears to have a more narrow therapeutic index than previously appreciated should never be considered a standard therapy (nor used as a performance measure for quality of care). The arguments raised here may be similar to the aprotinin controversy, in which a supposedly well established drug, which appeared to have a very beneficial effect on a very important surrogate outcome (blood transfusion) may be less safe than thought, based on outcome results of a much larger clinical trial than previously conducted.[32,33]

Vexing clinical questions remain. POISE apparently enrolled patients who were naïve to β-blockers at the time of study enrollment, many of whom had known CAD. Are the results generalizable to those already receiving such therapy, which in the United States may approach or exceed half of all adult patients in some settings? Critics will point out that withdrawal of β-blockade is exceedingly hazardous, a finding widely, but not universally, supported[34] in the literature.[35–38] Perhaps the biggest issue is how should we manage heart rate and arterial blood pressure? It is in this context that the meta-analysis of Beattie et al. presented in this issue of the journal is of considerable interest.[39]

This meta-analysis examined 10 contemporary (but pre-POISE) RCTs (1997–2006) involving 2176 patients in which some heart rate data were presented, a decidedly controversial aspect of this analysis given lack of continuous longitudinal data in many of these reports.

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Although, in aggregate, perioperative β-blockade was not associated with a reduction in perioperative MI (odds ratio, 0.76; 95% CI: 0.4–1.4), a significant reduction (odds ratio, 0.23; 95% CI: 0.08–0.65) was noted when perioperative β-blockade resulted in "aggressive" heart rate control, based on a somewhat arbitrarily defined threshold of 100 bpm derived from the data presented in the RCTs alone (which coincidentally corresponds to the commonly used clinical threshold promoted by older observational clinical studies of perioperative ischemia). However, hypotension and bradycardia were significantly more common with such control (as noted by POISE) with a weak suggestion of an increase in the incidence of CHF (not noted by POISE). The incidence of stroke in these RCTs was too small to be investigated, in contrast to the much larger POISE trial. Subanalysis of derived variables related to heart rate (e.g., mean, maximum, and variation in heart rate) all supported the statistical association of strong heart rate control with reduction in perioperative MI.

But perhaps apropos of what appears to be a continuously uncertain atmosphere surrounding perioperative β-blockade, a very recently published meta-analysis by Biccard et al. of the same RCTs (sans one study) reported no such relation.[40] When comparing the methodology of these meta-analyses, it appears that the upper hand with regards to statistical sophistication goes to that of Beattie et al. However, both groups note that the amount of hemodynamic data presented in the RCTs are quite limited. Given an increasing trend to substitute meta-analysis for large-scale clinical research, there is a definite suggestion in the recent literature that the limitations of meta-analysis should be carefully considered before they are used to guide clinical care.[41–43] Nonetheless, it is also clear that well done meta-analyses have shaped medical practice, and one need only look as far as the widespread promotion of β-blockers for secondary prevention post-MI in medical patients to observe this in action.[44]

So *quo vadis* perioperative β-blockade? After a decade have we established what perioperative β-blockade is? Is it simply prevention or attenuation of tachycardia? In this regard, the conflicting meta-analyses of Beattie et al. and Biccard et al. are disappointing.[39,40] Hopefully, the full results of POISE will shed light on this topic, although the constrained data collection (particularly of "surrogate outcomes" which includes hemodynamics) mandated by a "large simple trial" make this unlikely. Will we be able to delineate groups of patients in which efficacy and safety can be assured? Will the trends towards increased use of β-blockers in CAD be counterbalanced or even decrease in response to recent evidence and guideline recommendations against the use of β-blockers as first-line drugs for hypertension (in the absence of a strong suspicion for or documentation of underlying CAD) given evidence that they are inferior to diuretics and angiotensin receptor blockers with regards to stroke and adverse renal outcome reduction?[45,46] What of the increasing number of large observational studies suggesting strong efficacy of statins independent of β-blockers?[47] Do alpha2 agonists have superior efficacy or safety?[48] Will the eagerly awaited DECREASE-IV β-blocker-statin RCT reach supporting or confliction conclusions to POISE?[49] Conflicting meta-analyses aside, clinicians should jointly consider and manage both heart rate and arterial blood pressure (as well as cardiac output which is rarely measured directly), attempting to balance increased left ventricular diastolic perfusion time from a low heart rate while maintaining adequate coronary (and other organ) perfusion pressure. Perhaps, it is as simple as that . . . . but as the POISE study clearly points out, the devil is in the details.

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β-blocker therapy in non-cardiac surgery

The POISE trial (May 31, p 1839)[1] of perioperative β blockade was admirable. However, I wonder whether the noble goal of the trial led to a design that was predictably flawed and that should have been viewed as unethical.

It was foreseeable that use of a controlled-release formulation of metoprolol that resulted in stable 24-h concentrations in plasma[2] might have been problematic in an acute perioperative setting where a patient's physiology can change strikingly in hours. Yet the justification consisted of weak, disconnected pieces of evidence in irrelevant settings. The decision to use this potentially hazardous, long-acting preparation was not evinced to be independent of the study's association with AstraZeneca.

Furthermore, although conceding "there is strong evidence that perioperative β blockers cause hypotension and bradycardia requiring treatment",[2] the arbitrary dose and dosing regimen lacked reference to any physiological or experimental rationale. The quasijustification provided, post-hoc, in the Discussion was not sustainable.

Similarly, no justification was provided for why rigid, uniform, absolute haemodynamic cut-off values for withholding the drug were superior to a regimen which included consideration of an individual patient's preoperative and contemporaneous clinical condition. Did any centres refuse to participate because of these concerns? Was the fact that intention-to-treat analysis underestimates adverse effects[3] considered when the POISE Study Group examined the pretrial literature? In light of these issues, were patients reasonably informed?

The premise that such a rigid, one-size-fits-all regimen could ever "provide a reliable assessment of the effects of β-blocker therapy in patients undergoing non-cardiac surgery"[2] is highly unlikely. We are predictably left in a situation where the next question is: "What about 150 mg then?" The lack of a pretrial, sample-size correction for predictable non-compliance[4] further confuses this issue. If there are too many factors to control to allow individualisation of the drug regimen, the answer is to conceive a more relevant study design.

I declare that I have no conflict of interest.

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1 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.
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The POISE trial[1] is the biggest study to address the role of β-blocker therapy in non-cardiac surgery. Despite the fact that the primary endpoint analysis disclosed a protective effect, there was an increased incidence of stroke and overall mortality in the metoprolol group. The POISE Study Group suggests that the perioperative β-blocker paradigm should now be modified.

However, a cautious analysis of the POISE data could give some clues to the mechanisms underlying these results. The metoprolol group had a higher incidence of clinically significant hypotension that could explain the occurrence of more strokes and deaths. Additional data provided by the POISE Study Group and in the webextra material shows that, in the metoprolol group, clinically significant hypotension occurred in 625 (15%) and bradycardia in 277 (6·6%). Why only 555 of them temporarily discontinued the study drug remains unexplained. Indeed, at least 70 patients continued on metoprolol despite a formal indication to discontinue (temporary or permanent).

The effect of these 70 patients on the secondary endpoints overall mortality (129 patients) and stroke (41 patients) should be clarified. If no conclusive information can be gathered from this analysis, standard clinical practice should be maintained until new data are available.[2]

We declare that we have no conflict of interest.

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The POISE Study Group[1] found that preoperative and perioperative treatment with extended-release metoprolol in patients undergoing non-cardiac surgery could cause harm, with an excess of death and strokes in the treatment group, despite a reduction in myocardial infarction.

It is worth noting that 2·7% of the treatment group had been admitted to hospital for heart failure in the past 3 years and 6·2% had a history of heart failure, but were not taking β blockers. Given what we know about the importance of low starting doses and gradual uptitration of β blockers in this group,[2,3] the administration of high-dose metoprolol to β-blocker-naive patients with heart failure perioperatively could cause substantial harm.

What were the risks in the group of patients with a history of heart failure and do the trial results alter


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if this group is excluded from the analysis?

I declare that I have no conflict of interest.

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Authors' reply

Michael Keane questions our use of a controlled-release formulation of metoprolol. Before POISE, the small perioperative trials that resulted in guidelines recommending perioperative β blockers used long-acting formulations.[1,2] A large perioperative cohort study suggested that the long-acting β blockers were more cardioprotective than the short-acting β blockers.[3] The POISE trial was an investigator-initiated trial that, after extensive peer review, received funding from four national funding bodies. Institutional review boards in 190 centres in 23 countries approved the protocol.

Keane would prefer a more flexible approach to dosing and holding of the study drug. All the previous perioperative β-blocker trials used relatively similar haemodynamic requirements to those used in POISE.[4] Guidelines provided in POISE did not preclude use of clinical judgment. To our knowledge, no centre refused to participate owing to concerns about haemodynamic thresholds for dosing and holding the study drug.

Bruno Caramelli and colleagues note that some of the patients who had clinically significant hypotension or bradycardia did not temporarily discontinue the study drug. They imply that this might explain the negative β-blocker outcomes; however, it does not.

Some of the patients who had clinically significant hypotension or bradycardia had the study drug permanently, rather than temporarily, discontinued. Eight metoprolol patients and 14 placebo patients who had clinically significant hypotension and no temporary or permanent discontinuation of the study drug died (p=0·2008) within the 30-day follow-up period; no strokes occurred in this group of patients. Four metoprolol patients and two placebo patients who had clinically significant bradycardia and no temporary or permanent discontinuation of the study drug died (p=0·4135) within the 30-day follow-up period; no strokes occurred in this group of patients.

Jasper Trevelyan inquires whether there was a subgroup effect among the patients without a history of admission for congestive heart failure within 3 years of randomisation or any history of congestive heart failure for the outcome death and stroke. Such analyses did not show any subgroup effect. The interaction p values were 0·8564 for death and 0·9042 for stroke.

It remains possible that an alternative strategy for perioperative β-blocker administration will retain the benefits shown in POISE (eg, reduction in myocardial infarction) and eliminate the harms (eg, increased death and stroke). Pending the results of a large, well designed trial such as POISE to show such findings, the best evidence suggests that stroke-averse patients undergoing non-cardiac surgery who are concerned about increases in absolute death rates are unlikely to want a β blocker.

SY has received consultancy fees, research grants, and honoraria from AstraZeneca who provided the study drug for the POISE Trial. The remaining authors declare that they have no conflict of interest outside of AstraZeneca providing the study drug for the POISE Trial.

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The POISE trial[1] of perioperative β-blocker therapy reports a reduction in cardiac events at the cost of increased mortality and stroke. The accompanying Comment[2] correctly notes that efficacy of non-surgical β-blocker therapy might not be extrapolable to the surgical setting, where an unpredictable stress response exists.

We submit that, by dosing patients to a predefined fixed target heart rate and blood pressure in the POISE trial, the importance of individual adaptive responses within biological systems and the timeframe required to reset these might have been underestimated. Specifically, the drug was not titrated to achieve an optimum change within the cardiovascular physiology of each patient. The importance of tight

intraoperative haemodynamic control in a relatively homogeneous population, manifesting as improved 30-day mortality, has recently been emphasised.[3]

We speculate whether other factors, intrinsic to the dynamic surgical stress response, also significantly contributed to adverse outcome. Participants in the POISE study were patients with major cardiovascular risk undergoing non-cardiac surgery, and were therefore undoubtedly affected by impaired vascular homoeostasis. The surgical stress response induces a proinflammatory–prothrombotic–antifibrinolytic milieu that might contribute to increased risk of perioperative adverse outcome. Endothelial dysfunction has been reported to predict adverse acute and long-term outcome after vascular surgery,[4] and improved perioperative survival has been attributed to the pleiotropic (anti-inflammatory, endothelial-modulating) effects of statin therapy.[5]

We suggest that individualised tight haemodynamic control and microvascular homoeostasis both significantly contribute to perioperative outcome in non-cardiac surgery, and need to be carefully considered when assessing therapeutic options for these patients.

We declare that we have no conflict of interest.

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POISE trial quality control

As Secretary of the Isfahan Regional Bioethics Committee (IRBC), I would like to provide the following clarifications with regard to webappendix 1 of the POISE trial.[1]

One of the research centres in our region participated in POISE. As highlighted in the webappendix, there was the unfortunate occasion of data falsification in this centre. We were informed of the incident immediately after the fraud came to light. An investigation was launched and the principal investigator and coordinator of POISE were contacted.

Our investigation revealed that a recently graduated doctor who was employed as a research assistant by the POISE Study Group was at the centre of the fraud. We found that inadequate supervision had been given to this person. It was also unfortunate that a previous audit on behalf of the principal investigator and coordinator lacked sufficient rigour to detect the fraud. This was a breach of the 26-item National Ethical Codes for Protection of Research Participants.[2] IRBC issued official academic penalties against the Iranian principal investigator as well as the coordinating research centre.

As a result of the investigation, IRBC asked the university to which the research centre in dispute was affiliated to do an audit of all other projects underway. The audit did not reveal any other major problems and IRBC was assured that the research assistant at the centre of this fraud had not been involved in any other projects at this research centre or anywhere else in the country. On the basis of a request by the research centre to other principal investigators of international studies, audits were done that gave similar results.

Since the occurrence of this incident, IRBC recommended to the chancellor of the university that external audit costs be included in the budget of all studies applying for ethics approval. This has been accepted by the chancellor and implemented.

The Iranian team did its utmost to facilitate the external audit, and the highest levels of executive authorities in the region were engaged in the collaboration.

We at the IRBC will continue to strengthen and review our safeguards to prevent similar events happening in the future, will endeavour to promote principles of good research practice drawn from our rich cultural heritage, and hope that the wrongdoings of a few do not cast a shadow on the commendable activities of the many.

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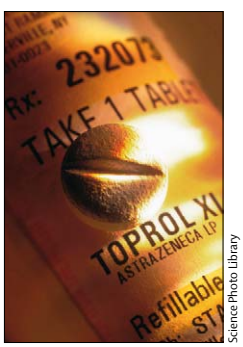
Perioperative β blockade

In their Comment[1] on the POISE trial,[2] Lee Fleisher and Don Poldermans (May 31, p 1813) defend perioperative β blockade in non-cardiac surgery, mostly on the basis of DECREASE,[3] which showed an overall favourable risk/benefit ratio. However, before we accept their conclusion, we should remember that half the highly selected 112 patients in DECREASE had a previous myocardial infarction, up to a third were symptomatic with angina



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pectoris, and all of them had abnormal stress echocardiography. Thus, these patients should have been on a β blocker to begin with, irrespective of their need for surgery. The DECREASE trial was unblinded and hence has a high risk of bias.

Fleisher and Poldermans also argue that the deleterious effect seen in POISE was probably due to the high dose of the β blocker. Indeed, the dose of metoprolol in POISE was eight times the equivalent dose of bisoprolol used in the DECREASE trial. However, in POISE, only 15% of patients on a β blocker developed clinically significant hypotension, whereas this proportion was consistently higher in other trials, up to 85%,[4] even though the doses were lower than those used in POISE.

The double-blind POISE trial, with a sample size 75 times that of the unblinded DECREASE, showed clear harm of perioperative blockade and its results are in accord with the DIPOM trial[5] (relative risk of all-cause mortality 1·33 for POISE and 1·32 for DIPOM). To us this seems sufficient evidence to turn the page. Instead of clinging to old dogma, perioperative guidelines urgently need to be rewritten.

FHM has been a member of speakers' bureaux for Abbott, GlaxoSmithKline, Novartis, Pfizer, AstraZeneca, Bayer, Boehringer Ingelheim, BMS, Forest, Sankyo, and Sanofi; and has received research grants from GlaxoSmithKline, Pfizer, Novartis, and CardioVascular Therapeutics. The other authors declare that they have no conflict of interest.

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Authors' reply

We agree with Sripal Bangalore and colleagues that guidelines for perioperative β blockade should be assessed in terms of recently published trials including POISE[1] and DECREASE-IV.[2] Importantly, Bangalore and colleagues point out that there is a group of patients who "should have been on a β blocker to begin with, irrespective of their need for surgery". We agree that coronary artery disease and left ventricular dysfunction should be treated according to common guidelines, irrespective of the planned surgery.[3] These are also major determinants of adverse postoperative outcome. Additionally, optimum treatment of perioperative cardiac events should not only include β blockers, but also treatment aimed at coronary plaque stabilisation.

There is increasing evidence that continuation of β blockers, statins, and aspirin is essential in patients undergoing non-cardiac surgery.[4] POISE does not address this population of chronic users; high-dose treatment was started only hours before surgery. We therefore believe that there is some period of time before surgery in which β blockers could be titrated to effect in patients with a class I indication for these agents, irrespective of the need for surgery, and that continuation and titration of the β blocker in the perioperative period will be associated with greater benefit than risk. In our experience, such treatment includes low-dose bisoprolol begun at least 7 days before surgery in patients with active ischaemic heart disease.

Given the protocol of the POISE trial, we agree that giving high-dose metoprolol succinate acutely in the perioperative period has greater risk than benefit.

LAF was chair for the ACC/AHA 2007 guidelines on perioperative cardiovascular evaluation and care for non-cardiac surgery. DP has received educational grants from Merck, Novartis, and Pfizer. These companies sponsored symposia during the European Society of Cardiology (ESC) Annual Sessions, which were chaired by DP. DP is chair of the ESC Guidelines committee for preoperative cardiac risk assessment and perioperative cardiac management in non-cardiac surgery.

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WHO's checklist for surgery: don't confine it to the operating room

In your Editorial of July 5,[1] you describe the launch of the *Safe Surgery Saves Lives* campaign by WHO's World Alliance for Patient Safety.[2] The Alliance has developed a surgical safety checklist that is essentially an expanded timeout procedure, including a debriefing. In recent years, this type of procedure has been widely advocated and

Effects of extended-release metoprolol succinate in patients undergoing non-cardiac surgery (POISE trial): a randomised controlled trial

*POISE Study Group**

Summary

Background Trials of β blockers in patients undergoing non-cardiac surgery have reported conflicting results. This randomised controlled trial, done in 190 hospitals in 23 countries, was designed to investigate the effects of perioperative β blockers.

Methods We randomly assigned 8351 patients with, or at risk of, atherosclerotic disease who were undergoing non-cardiac surgery to receive extended-release metoprolol succinate (n=4174) or placebo (n=4177), by a computerised randomisation phone service. Study treatment was started 2–4 h before surgery and continued for 30 days. Patients, health-care providers, data collectors, and outcome adjudicators were masked to treatment allocation. The primary endpoint was a composite of cardiovascular death, non-fatal myocardial infarction, and non-fatal cardiac arrest. Analyses were by intention to treat. This trial is registered with ClinicalTrials.gov, number NCT00182039.

Findings All 8351 patients were included in analyses; 8331 (99·8%) patients completed the 30-day follow-up. Fewer patients in the metoprolol group than in the placebo group reached the primary endpoint (244 [5·8%] patients in the metoprolol group *vs* 290 [6·9%] in the placebo group; hazard ratio 0·84, 95% CI 0·70–0·99; p=0·0399). Fewer patients in the metoprolol group than in the placebo group had a myocardial infarction (176 [4·2%] *vs* 239 [5·7%] patients; 0·73, 0·60–0·89; p=0·0017). However, there were more deaths in the metoprolol group than in the placebo group (129 [3·1%] *vs* 97 [2·3%] patients; 1·33, 1·03–1·74; p=0·0317). More patients in the metoprolol group than in the placebo group had a stroke (41 [1·0%] *vs* 19 [0·5%] patients; 2·17, 1·26–3·74; p=0·0053).

Interpretation Our results highlight the risk in assuming a perioperative β-blocker regimen has benefit without substantial harm, and the importance and need for large randomised trials in the perioperative setting. Patients are unlikely to accept the risks associated with perioperative extended-release metoprolol.

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Introduction

Worldwide, about 100 million adults undergo non-cardiac surgery every year.[1] Non-cardiac surgery is associated with major cardiovascular complications and over 1 million patients are likely to have such a complication every year.[2]

Non-cardiac surgery causes a rise in catecholamine concentrations that results in an increase in heart rate, blood pressure, and free fatty acid concentrations, which in turn increases myocardial oxygen demand.[2–4] β blockers attenuate the effects of increased catecholamine levels and therefore could prevent perioperative cardiovascular complications.[5,6] Small non-cardiac surgery trials suggested that β blockers might reduce the occurrence of major cardiovascular events,[7,8] although these trials had methodological limitations.[9] Recent, moderate sized randomised controlled trials of perioperative β blockers did not demonstrate benefit.[10,11] A meta-analysis of non-cardiac surgery randomised controlled trials suggested that β blockers might prevent major cardiovascular events but increase the risk of hypotension and bradycardia.[12] To further investigate the effects of perioperative β-blocker therapy, we undertook the PeriOperative ISchemic Evaluation (POISE) trial, a randomised controlled trial comparing the effect of extended-release metoprolol succinate with that of placebo on 30-day risk of major cardiovascular events in patients with, or at risk of, atherosclerotic disease who were undergoing non-cardiac surgery.

Methods

Patients

Recruitment for POISE took place between October, 2002, and July, 2007. Patients were eligible if they were undergoing non-cardiac surgery, were aged 45 years or older, had an expected length of hospital stay of at least 24 h, and fulfilled any one of the following criteria: history of coronary artery disease; peripheral vascular disease; stroke; hospitalisation for congestive heart failure within previous 3 years; undergoing major vascular surgery (ie, vascular surgery except arteriovenous shunt, vein stripping procedures, and carotid endarterectomies); or

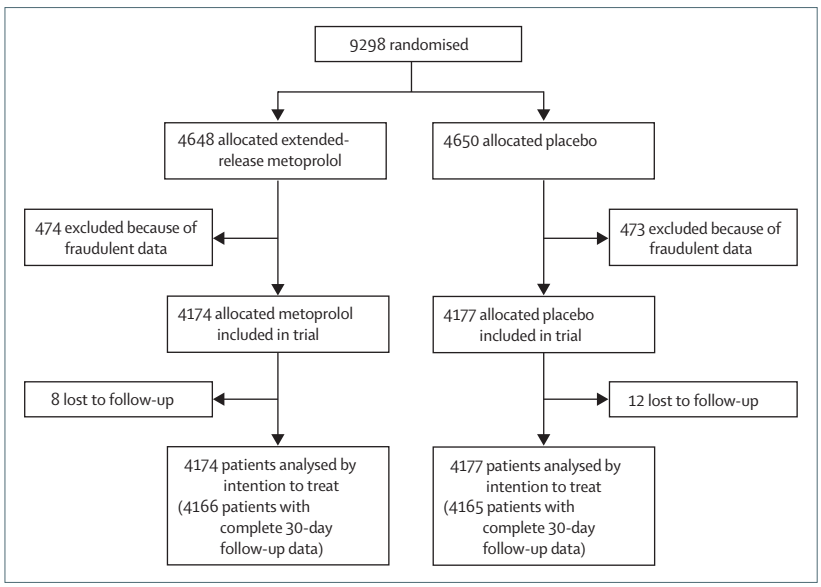

Figure 1: **Trial profile**

any three of seven risk criteria (undergoing intrathoracic or intraperitoneal surgery, history of congestive heart failure, transient ischaemic attack, diabetes, serum creatinine >175 μmol/L, age >70 years, or undergoing emergent or urgent surgery).

Patients meeting any of the following criteria were excluded: heart rate under 50 beats per minute (bpm); second or third degree heart block; asthma; receiving a β blocker or their physician planned to start one perioperatively; prior adverse reaction to a β blocker; coronary artery bypass graft surgery in the preceding 5 years and no cardiac ischaemia since; low-risk surgical procedure (based on individual physician's judgment); on verapamil; or previous enrolment in POISE.

All participating sites obtained ethical approval from institution ethics review boards before recruiting patients. All participants provided written informed consent.

Procedures

Details of the methods of this trial have been published previously.[13] Briefly, after obtaining written informed consent, patients were randomly assigned to treatment group via a 24-h computerised randomisation phone service using block randomisation stratified by centre. Participants, health-care providers, data collectors, and outcome adjudicators were masked to treatment allocation but data analysts were not.

The study regimen was influenced by practicality (eg, starting the study drug 2–4 h before surgery) and trials that showed that extended-release metoprolol 200 mg daily had a more even reduction in exercise heart rate and systolic blood pressure than did atenolol 100 mg daily[14] and better anti-anginal effects than metoprolol 100 mg twice daily.[15] Furthermore, the operations committee reviewed confidential blinded safety data on the first 10 000 patients included in COMMIT (a randomised controlled trial of 45 852 patients with acute myocardial infarction randomised to early intravenous metoprolol and starting on day 2 extended-release metoprolol 200 mg daily *vs* placebo).[16]

In POISE, patients received the first dose of the study drug (ie, oral extended-release metoprolol 100 mg or matching placebo) 2–4 h before surgery. Study drug administration required a heart rate of 50 bpm or more and a systolic blood pressure of 100 mm Hg or greater; these haemodynamics were checked before each administration. If, at any time during the first 6 h after surgery, heart rate was 80 bpm or more and systolic blood pressure was 100 mm Hg or higher, patients received their first postoperative dose (extended-release metoprolol 100 mg or matched placebo) orally. If the study drug was not given during the first 6 h, patients received their first postoperative dose at 6 h after surgery. 12 h after the first postoperative dose, patients started taking oral extended-release metoprolol 200 mg or placebo every day for 30 days. If a patient's heart rate was consistently below 45 bpm or their systolic blood pressure dropped below 100 mm Hg, study drug was withheld until their heart rate or systolic blood pressure recovered; the study drug was then restarted at 100 mg once daily. Patients whose heart rate was consistently 45–49 bpm and systolic blood pressure exceeded 100 mm Hg delayed taking the study drug for 12 h.

Patients who were unable to take medications orally received the study drug by slow or rapid intravenous infusion every 6 h until they could resume oral medications. The slow infusion consisted of 15 mg of the study drug in 25 mL normal saline infused over 60 min; heart rates and blood pressures were checked at 10, 30, and 60 min into the infusion. If a patient's heart rate dropped below 50 bpm or systolic blood pressure dropped to below 100 mm Hg the infusion was stopped and subsequent infusions had 10 mg of study drug. The rapid intravenous infusion consisted of 5 mg of the study drug infused over 2 min and repeated—as long as haemodynamic criteria were met—every 5 min for a total of 15 mg. Investigators were allowed to select either the slow or rapid intravenous infusion for any participant who was unable to take medications orally.

An electrocardiograph (ECG) was recorded 6–12 h postoperatively and on the first, second, and 30th days after surgery. We obtained a measurement of troponin or, if unavailable, a creatine kinase-MB measurement 6–12 h postoperatively and on the first, second, and third days after surgery. These measurements were recorded on the case report forms and forwarded to the POISE project office. All measurements were reviewed centrally. If a patient's biomarkers or cardiac enzymes were raised but a myocardial infarction case report form was not submitted, we asked the centre to review the case to ensure that a myocardial infarction was not missed. Centres were encouraged to obtain more frequent ECGs

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and cardiac biomarkers if they suspected a myocardial infarction.

The prespecified primary outcome was a composite of cardiovascular death, non-fatal myocardial infarction, and non-fatal cardiac arrest at 30 days after randomisation. Individual secondary outcomes at 30 days are shown in webtable 1. Outcome adjudicators—clinicians blinded to treatment allocation—adjudicated whether a death was cardiovascular or non-cardiovascular, and whether a patient had a myocardial infarction, non-fatal cardiac arrest, or stroke; their decisions were used in the statistical analyses.

Monitoring in POISE consisted of central data consistency checks, statistical monitoring, and on-site monitoring. On-site monitoring occurred at all hospitals that recruited 40 or more participants and all sites that stood out on statistical monitoring. For the on-site monitoring, the study statistician randomly selected participants with and without primary outcome events and independent monitors audited their hospital charts and all other supporting documents. The 560 POISE participants for whom on-site monitoring occurred came from 77 hospitals that collectively randomised 85% of all trial participants; 88% of the primary outcomes occurred at these hospitals. On-site monitoring, outside of the special cases reported in webappendix 1, did not indicate any major discrepancies between the submitted data and the audit findings.

Statistical analysis

Assuming an event rate in the control group of 6% for our primary outcome, we calculated that 8000 randomised patients would provide 85% power and 10 000 patients 92% power to detect a relative risk reduction of 25% (two-sided $\alpha=0\cdot05$).[13] We set a goal to randomise 10 000 patients, recognising that we would have adequate power if we randomised 8000 patients.[13] Without knowledge of the trial results and knowing that we had randomised more than 8000 patients and had a higher than predicted event rate, the operations committee decided to terminate recruitment on July 31, 2007, mainly because the remaining study drug expired in September, 2007.

We analysed patients in the treatment group to which they were allocated—ie, on an intention-to-treat basis. Patients lost to follow-up without having the outcome of interest were censored on the last day their outcome status was known. All analyses used Cox proportional hazards models except for new clinically significant atrial fibrillation, cardiac revascularisation, congestive heart failure, clinically significant hypotension, and clinically significant bradycardia, for which we used a χ^2 test.

On the basis of a study that suggested perioperative β-blocker efficacy might vary across baseline risk,[17] we prespecified our primary subgroup analysis on the basis of the revised cardiac risk index scoring system.[18] We also did prespecified secondary subgroup analyses based on sex, type of surgery, and use of an epidural or spinal anaesthetic. For all subgroup analyses, we used Cox proportional hazard models that incorporated tests for interactions, designated to be significant at $p<0\cdot05$.

See Online for webtable 1 and webappendix 1

	Metoprolol group (N=4174)	Placebo group (N=4177)
Age (years)	68·9 (10·5)	69·1 (10·4)
Sex (female)	1549 (37·1%)	1509 (36·1%)
Preoperative heart rate (beats per minute)	77·6 (12·2)	78·1 (12·4)
Preoperative blood pressure (mm Hg)	138·7 (19·9)/78·3 (11·3)	138·7 (19·7)/78·5 (11·3)
Patients fulfilling eligibility criteria		
Coronary artery disease	1805 (43·3%)	1784 (42·7%)
Peripheral arterial disease	1731 (41·5%)	1680 (40·2%)
Stroke thought due to atherothrombotic disease	619 (14·8%)	644 (15·4%)
Hospitalisation for CHF within 3 years of randomisation	112 (2·7%)	108 (2·6%)
Undergoing major vascular surgery	1500 (36·0%)	1485 (35·6%)
Three of seven risk factors	765 (18·3%)	788 (18·9%)
Intrathoracic or intraperitoneal surgery	997 (23·9%)	1026 (24·6%)
Any history of congestive heart failure	260 (6·2%)	239 (5·7%)
Diabetes and currently on an oral hypoglycaemic agent or insulin	1217 (29·2%)	1210 (29·0%)
Preoperative serum creatinine >175 μmol/L	207 (5·0%)	194 (4·6%)
Age >70 years	2106 (50·5%)	2205 (52·8%)
History of a transient ischaemic attack	442 (10·6%)	440 (10·5%)
Emergent/urgent surgery	440 (10·5%)	438 (10·5%)
Other cardiovascular risk factors		
History of hypertension	2635 (63·2%)	2627 (62·9%)
Current smoker	806 (19·3%)	793 (19·0%)
Pre-operative cardiac medications*		
Aspirin	1517 (36·4%)	1494 (35·8%)
Low-molecular weight heparin or intravenous unfractionated heparin	388 (9·3%)	384 (9·2%)
ACE inhibitor or ARB	1849 (44·3%)	1868 (44·7%)
Statin	1335 (32·0%)	1342 (32·1%)
Diuretic	912 (21·9%)	852 (20·4%)
Calcium channel blocker	902 (21·6%)	937 (22·4%)
Surgery		
Vascular	1749 (41·9%)	1716 (41·1%)
Intraperitoneal	887 (21·3%)	928 (22·2%)
Orthopaedic	873 (20·9%)	883 (21·1%)
Other	665 (15·9%)	650 (15·6%)
Anaesthesia/analgesia		
General	1965 (47·1%)	1985 (47·5%)
Spinal	717 (17·2%)	696 (16·7%)
Lumbar epidural	460 (11·0%)	441 (10·6%)
General and thoracic epidural	377 (9·0%)	351 (8·4%)
General and lumbar epidural	140 (3·4%)	155 (3·7%)
Regional anaesthesia	139 (3·3%)	145 (3·5%)
Other	322 (7·7%)	333 (8·0%)

Data are mean (SD) or n (%). ACE=angiotensin-converting enzyme, ARB=angiotensin-receptor blocker. CHF=congestive heart failure. *Any use in 24 h before surgery except for aspirin which only required any use in the 7 days before surgery.

Table 1: **Preoperative characteristics and type of surgery and anaesthesia or analgesia**

	Metoprolol group (N=4174)	Placebo group (N=4177)
Took 100% of study drug	2919 (70%)	3193 (76%)
Took >80% of study drug	3162 (76%)	3255 (78%)
Temporary discontinuation of study drug	752 (18%)	495 (12%)
Due to bradycardia or hypotension	555 (13%)	274 (7%)

Data are n (%).

Table 2: **Adherence to study medication**

	Metoprolol group (n=4174)	Placebo group (n=4177)	Hazard ratio	p value
Cardiovascular death, non-fatal myocardial infarction, or non-fatal cardiac arrest*	244 (5·8%)	290 (6·9%)	0·84 (0·70–0·99)	0·0399
Cardiovascular death	75 (1·8%)	58 (1·4%)	1·30 (0·92–1·83)	0·1368
Non-fatal myocardial infarction	152 (3·6%)	215 (5·1%)	0·70 (0·57–0·86)	0·0008
Non-fatal cardiac arrest	21 (0·5%)	19 (0·5%)	1·11 (0·60–2·06)	0·7436
Total mortality	129 (3·1%)	97 (2·3%)	1·33 (1·03–1·74)	0·0317
Myocardial infarction	176 (4·2%)	239 (5·7%)	0·73 (0·60–0·89)	0·0017
Cardiac revascularisation†	11 (0·3%)	27 (0·6%)	0·41 (0·20–0·82)	0·0123
Stroke	41 (1·0%)	19 (0·5%)	2·17 (1·26–3·74)	0·0053
Non-fatal stroke	27 (0·6%)	14 (0·3%)	1·94 (1·01–3·69)	0·0450
Congestive heart failure†	132 (3·2%)	116 (2·8%)	1·14 (0·89–1·46)	0·3005
New clinically significant atrial fibrillation†	91 (2·2%)	120 (2·9%)	0·76 (0·58–0·99)	0·0435
Clinically significant hypotension†	625 (15·0%)	404 (9·7%)	1·55 (1·38–1·74)	<0·0001
Clinically significant bradycardia†	277 (6·6%)	101 (2·4%)	2·74 (2·19–3·43)	<0·0001
Non-cardiovascular death	54 (1·3%)	39 (0·9%)	1·39 (0·92–2·10)	0·1169

Data are n (%) or hazard ratio or relative risk (95% CI). *Some patients had more than one event. †Relative risks presented, rather than hazard ratios, since we did not collect the actual date patients experienced these events.

Table 3: **Effects of study treatment on primary and secondary outcomes at 30 days**

The independent external safety, efficacy, and monitoring committee planned to do three unblinded interim analyses and review adverse events after about 2500, 5000, and 7500 patients were randomised. The first two interim analyses were completed but the operations committee and safety, efficacy, and monitoring committee jointly decided to forgo the third because the trial would complete recruitment shortly thereafter. For both interim analyses, the monitoring committee required surpassing of the following thresholds in at least two consecutive analyses 3 months or more apart before making a recommendation to consider stopping the trial: for the primary outcome, four standard deviations, and for an adverse effect on mortality, three standard deviations of the hazard ratio.[19,20] The α-level for the final analyses remained α=0·05 in view of the infrequent interim analyses, their extremely low α levels, and their requirement for confirmation with subsequent analyses.

Statistical analyses were done with SAS version 9.1 for unix. Meta-analyses were done with Rev Man version 4.2.

Role of the funding source

The Population Health Research Institute, Hamilton Health Sciences, and McMaster University, Hamilton, Ontario, Canada coordinated the study, managed the data, and undertook analyses, under the supervision of the operations committee, who designed POISE. None of the funding sources had a role in the trial design, conduct, data collection, analyses, data interpretation, or writing of this manuscript. The sponsors were not involved in developing the analysis plan or in the analysis. The data analysis plan was prespecified by the operations committee, who vouch for the data and analyses. The corresponding author had full access to all data in the trial. The writing committee had final responsibility for the decision to submit for publication.

Results

Figure 1 shows the trial profile. Concern was raised during central data consistency checks about 752 participants at six hospitals in Iran coordinated by one centre and 195 participants associated with one research assistant in three of 11 hospitals in Colombia. On-site auditing of these hospitals and cases indicated that fraudulent activity had occurred. Before the trial was concluded, the operations committee—blinded to the trial results at these hospitals and overall—decided to exclude these data (webappendix 1).

The analyses presented here thus focus on 8351 patients from 190 hospitals in 23 countries (figure 1). The 30-day follow-up was complete for 8331 (99·8%) participants. Table 1 shows the preoperative characteristics, the type of surgery, and anesthaesia or analgesia used in the two groups. Atherosclerotic cardiovascular disease was common: 3444 [83%] patients in the metoprolol group and 3410 [82%] patients in the placebo group had a history of coronary artery disease, peripheral vascular disease, or stroke. During the 30-day follow-up period, we had to unblind patients or health-care providers to nine treatment allocations; in six of these cases unblinding occurred after the patient had experienced a primary outcome or a non-cardiovascular death. Table 2 shows adherence to study medications. Bradycardia or hypotension were the most common reasons for temporary discontinuations.

Significantly fewer participants in the metoprolol group than in the placebo group experienced the primary endpoint (hazard ratio 0·84, 95% CI 0·70–0·99, p=0·0399; table 3). This beneficial effect resulted from fewer myocardial infarctions in the metoprolol group than in the placebo group (0·73, 0·60–0·89, p=0·0017; table 3). Figure 2 shows the Kaplan-Meier estimates for the primary outcome and for myocardial infarction, the curves of which separated during the first few days after surgery.

By contrast, more individuals in the metoprolol group than in the placebo group had a stroke (hazard ratio 2·17, 95% CI 1·26–3·74, p=0·0053; table 3); the Kaplan-Meier estimates started separating on day 1 (figure 2).Of the 60 strokes that occurred in the metoprolol group,

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49 were ischaemic and three were haemorrhagic; the type of stroke was designated uncertain for the remaining eight cases.

More people receiving metoprolol died than did individuals receiving placebo (1·33, 1·03–1·74, p=0·0317; table 3); the Kaplan-Meier estimates started separating on day 10 (figure 2). Webtable 2 shows the causes of death as reported by investigators; the only reported cause of death for which there was a significant difference between groups was sepsis or infection, which was more common among patients allocated to metoprolol.

Fewer patients in the metoprolol group than in the placebo group had a non-fatal myocardial infarction (hazard ratio 0·70, 95% CI 0·57–0·86; p=0·0008; table 3). More patients, however, had a non-fatal stroke in the metoprolol group than in the placebo group (1·94, 1·01–3·69; p=0·0450; table 3). Less than half the patients who had a non-fatal myocardial infarction also had ischaemic symptoms (ie, chest, epigastric, arm, wrist, or jaw discomfort, shortness of breath; 48 [31·6%] patients in the metoprolol group and 82 [38·1%] in the placebo group). Less than a third of patients who had a non-fatal myocardial infarction also had congestive heart failure, coronary revascularisation, or went on to have a non-fatal cardiac arrest (table 4). Most patients who had a non-fatal stroke subsequently required help to perform everyday activities or were incapacitated (table 4).

See Online for webtable 2

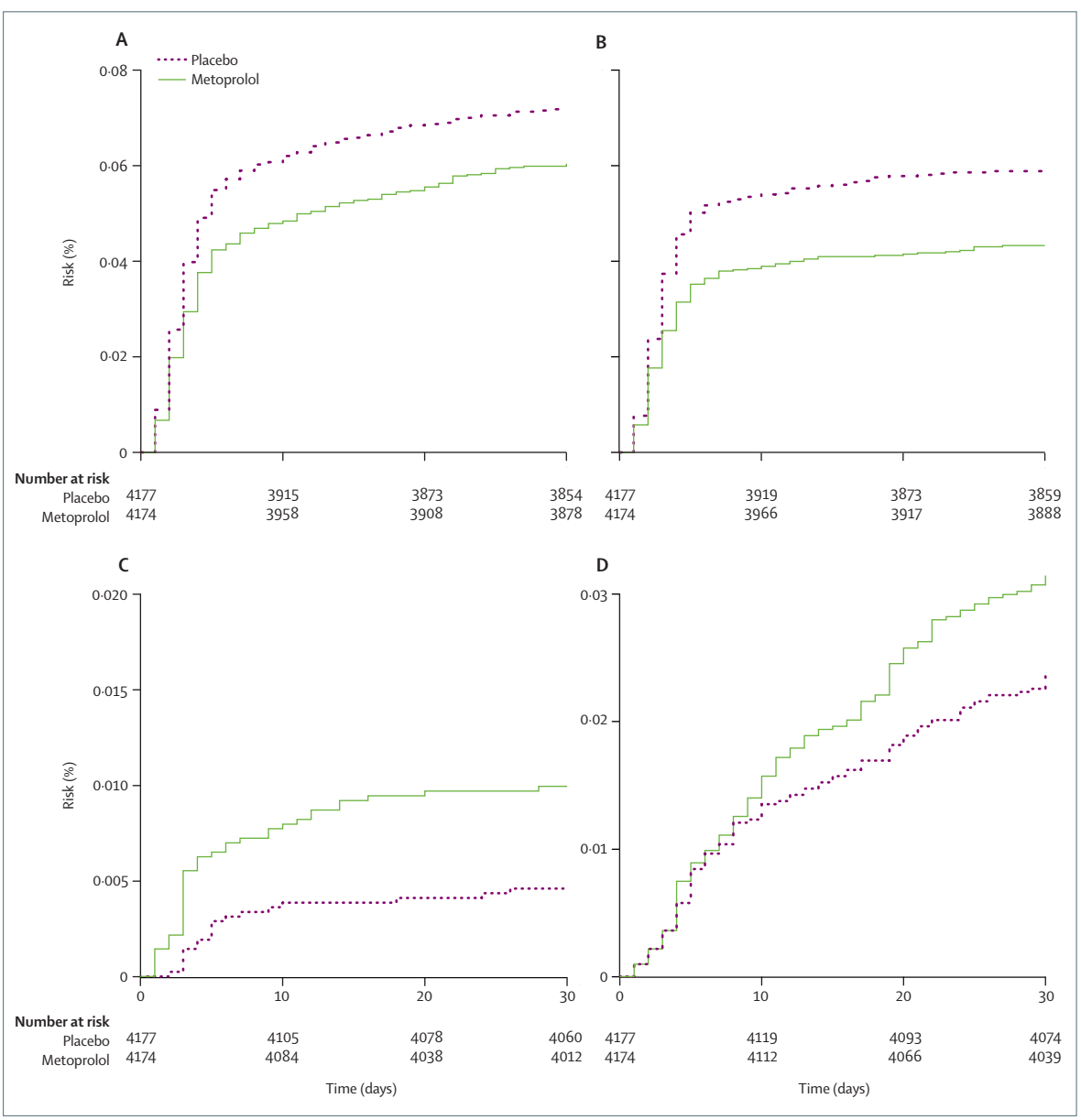

Figure 2: **Kaplan-Meier estimates of the primary outcome (A), myocardial infarction (B), stroke (C), and death (D)**

	Metoprolol group	Placebo group
Non-fatal myocardial infarction	152	215
Congestive heart failure†	30 (20%)	30 (14%)
Non-fatal cardiac arrest	7 (5%)	3 (1%)
Cardiac revascularisation†	9 (6%)	19 (9%)
Non-fatal stroke‡	27	14
Full recovery	4 (15%)	3 (21%)
Persistent symptoms but no functional limitation	4 (15%)	1 (7%)
Functional impairment but patient can manage independently	4 (15%)	1 (7%)
Patient requires help to do everyday activities	8(30%)	9 (64%)
Patient incapacitated	7 (26%)	0 (0%)

*If still alive 30 days after randomisation. †Actual date patients had these events not collection, therefore we cannot state with certainty if these events preceded the non-fatal myocardial infarction. ‡Outcome at 7 days or discharge, whichever was earlier, after stroke onset.

Table 4: **Outcomes for patients with a non-fatal myocardial infarction and non-fatal stroke***

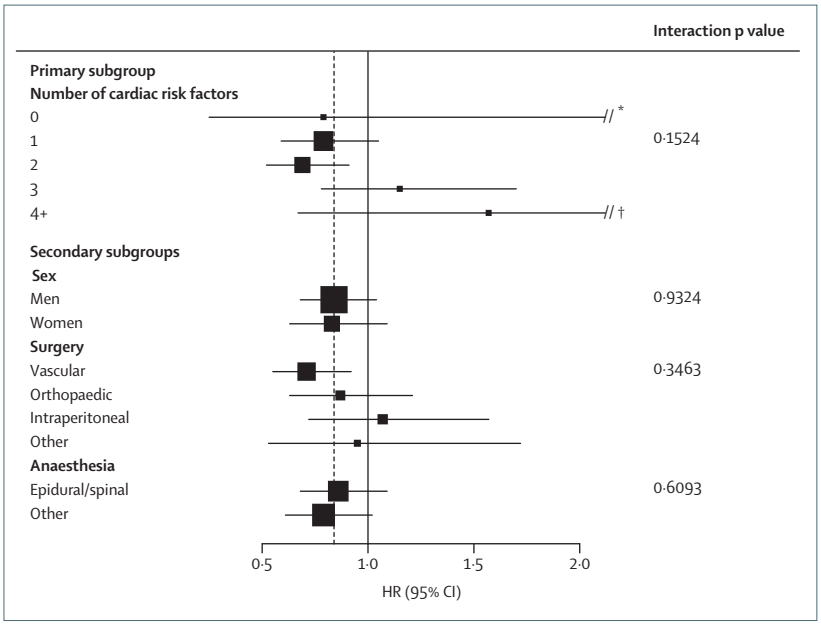

Figure 3: **Subgroup analyses for the primary outcome**
*Upper CI 2·51. †Upper CI 3·69.

See Online for webappendix 2

Fewer individuals in the metoprolol group had cardiac revascularisation or developed new clinically significant atrial fibrillation than did those in the placebo group, but more receiving metoprolol had clinically significant hypotension and bradycardia (table 3).

Median length of hospital stay was 8 (IQR 4–14) days in the metoprolol group and 8 (4–15) days in the placebo group (p=0·4046). The number of nights spent in an intensive or cardiac care unit was much the same in the two groups (0 nights: 71·1% in the metoprolol group *vs* 71·4% in the placebo group; 1–2 nights: 18·7% *vs* 18·4%; 3 nights or more: 10·2% *vs* 10·1%). At hospital discharge, participants who had received metoprolol had a lower mean heart rate than did placebo patients (71·6 [SD 12·0] *vs* 78·6 [11·8] bpm; p<0·0001); and patients in the metoprolol group had a lower mean systolic and diastolic blood pressure than did those in the placebo group (129·0 [18·9]/72·0 [11·1] *vs* 131·1 [18·2]/74·2 [11·1] mm Hg; p<0·0001 for both systolic and diastolic).

See Online for webtable 3

Figure 3 shows the results of our prespecified subgroup analyses and indicates consistency of effects. Although not planned, based on our findings related to mortality, myocardial infarction, and stroke, we repeated the subgroups analyses in figure 3 for these individual outcomes and also assessed whether there was a subgroup effect based on region (ie, Asia; Europe, Australia, New Zealand; North America; South America), whether on-site monitoring occurred, and based on the presence of atherosclerotic cardiovascular disease. None of these analyses showed a subgroup effect (data not shown). Our subgroup analyses were underpowered to detect the modest differences in subgroup effects that one might expect to detect if there was a true subgroup effect. Post-hoc multivariable analyses to investigate how extended release metoprolol could have increased the risk of death and stroke are shown in table 5 and webappendix 2. Clinically significant hypotension had the largest population attributable risk for death and the largest intraoperative or postoperative risk for stroke.

Discussion

These data indicate that although perioperative extended-release metoprolol reduced the risk of myocardial infarction, cardiac revascularisation, and clinically significant atrial fibrillation 30 days after randomisation compared with placebo, the drug also resulted in a significant excess risk of death, stroke, and clinically significant hypotension and bradycardia.

Although the exclusion of a number of randomised patients from our analyses because of fraudulent activities could be seen as a limitation, our on-site monitoring assessed the hospitals that collectively contributed 88% of the primary outcomes, and showed that the trial was rigorously done in all these hospitals. Further, subgroup analyses suggest there were no differences in effects across hospitals on the basis of whether or not on-site monitoring occurred. One should also note that all questionable data were excluded from all analyses, without knowledge of the results, when evidence of fraud was found. We disclosed this information to our external safety, efficacy, and monitoring committee and to all relevant authorities.

We did a number of meta-analyses of trials of perioperative β blockers including events within a 30-day follow-up period. In a meta-analysis of eight trials, including POISE,[6,8,10,11,21–23] β blockers did not show a significant effect on death (figure 4, webtable 3), but there was moderate heterogeneity that was explained by one

trial with few events and an extreme result that led to early stopping.[8] Exclusion of this trial from the meta-analysis suggests that the risk of death increases with β blockers (relative risk 1·29, 95% CI 1·02–1·62; p=0·03; I²=0%). By contrast, a meta-analysis of the nine trials, again including POISE, in which at least one patient had a non-fatal myocardial infarction[8,10,11,22,24–27] suggests that β blockers reduce the risk of this outcome, but there was substantial heterogeneity. Analysis of the six trials, including POISE, that were blinded and not stopped early for an unexpected large treatment effect with few events resulted in essentially the same estimate of effect but no heterogeneity (0·73, 0·60–0·88; p=0·001; I²=0%).[10,11,22,24,25] Patients in POISE and five other trials had a non-fatal stroke within a 30-day follow-up period.[6,10,11,22,23] Meta-analysis of these trials indicates that perioperative β blockers increase the risk of non-fatal stroke (2·19, 1·26–3·78; p=0·005; I²=0%).

Because the results of other trials with different doses or alternate β blockers are consistent with POISE, the effects of this group of drugs are unlikely to differ across different dosing regimens. Nonetheless, another β blocker or dosing regimen could possibly achieve different results. Our results highlight the risk in assuming a perioperative β-blocker regimen has benefi t without substantial harm before the availability of a large randomised controlled trial establishing such findings.

Our results suggest that for every 1000 patients with a similar risk profile undergoing non-cardiac surgery, extended-release metoprolol would prevent 15 patients from having a myocardial infarction, three from undergoing cardiac revascularisation, and seven from developing new clinically significant atrial fibrillation. The results also suggest that extended-release metoprolol would result in an excess of eight deaths, five patients having a stroke, 53 experiencing clinically significant hypotension, and 42 experiencing clinically significant bradycardia for every 1000 treated.

Our post-hoc multivariate analyses suggest that clinically significant hypotension, bradycardia, and stroke explain how β blockers increased the risk of death in this trial. Sepsis or infection was the only cause of death that was significantly more common among patients in the metoprolol group than in those in the placebo group. The hypotension that β blockers caused could have predisposed patients to developing nosocomial infection.[28,29] The prevention of tachycardia seen with β blockers could delay the recognition of sepsis and infection, therefore delaying treatment, which might increase the risk of death. Furthermore, patients receiving β-blocker therapy who develop sepsis or infection might not have the capacity to mount the required haemodynamic response to sustain life or allow adequate delivery of antibiotics to tissue. The same mechanism might explain how β blockers had no effect on 30-day mortality but significantly increased death due to shock in the COMMIT trial.[16]

	Adjusted odds ratio (95% CI)	Frequency of risk factor n (%)	PAR* (95% CI)
Death			
Preoperative independent predictors			
No use of statin in 24 h before surgery	1·73 (1·22–2·46)	5674 (67·9%)	33·7% (18·3–53·6)
Age ≥70 years	1·65 (1·20–2·26)	4387 (52·5%)	29·3% (16·2–47·0)
Emergent/urgent surgery	3·71 (2·68–5·14)	878 (10·5%)	24·4% (18·0–32·2)
Serum creatinine >175 μmol/L	2·67 (1·75–4·08)	401 (4·8%)	9·5% (5·4–16·0)
History of congestive heart failure	1·76 (1·14–2·72)	535 (6·4%)	6·0% (2·5–13·6)
Use of low-molecular-weight heparin in 24 h before surgery	1·74 (1·14–2·68)	556 (6·7%)	5·9% (2·4–13·8)
Intraoperative and postoperative predictors			
Clinically significant hypotension	4·97 (3·62–6·81)	1029 (12·3%)	37·3% (29·5–45·8)
Myocardial infarction without ischaemic symptoms	3·45 (2·20–5·41)	271 (3·3%)	10·6% (6·4–17·0)
Significant bleeding	1·67 (1·14–2·44)	553 (6·6%)	9·4% (4·3–19·5)
Stroke	18·97 (9·93–36·25)	60 (0·7%)	8·0% (5·0–12·5)
Clinically significant bradycardia	2·13 (1·37–3·32)	351 (4·2%)	7·9% (3·9–15·3)
Myocardial infarction with ischaemic symptoms	3·31 (1·78–6·15)	144 (1·7%)	4·2% (1·9–9·2)
Total explained	..	..	85·5% (78·8–90·4)
Stroke			
Preoperative independent predictors			
History of stroke or transient ischaemic attack	2·80 (1·66–4·73)	1759 (21·1%)	30·5% (17·1–48·2)
Use of clopidogrel or ticlopidine in 24 h before surgery	3·12 (1·43–6·77)	330 (4·0%)	9·1% (3·2–23·2)
Intraoperative and postoperative predictors			
Clinically significant hypotension	2·14 (1·15–3·96)	1029 (12·3%)	14·7% (5·2–35·4)
Significant bleeding	2·18 (1·06–4·49)	553 (6·6%)	10·1% (3·0–28·5)
New clinically significant atrial fibrillation	3·51 (1·45–8·52)	200 (2·4%)	6·9% (2·1–20·4)
Total explained	..	..	51·8% (37·1–66·2)

PAR=population attributable risk. *Proportion of all outcomes attributable to the relevant risk factor if causality were proven. We calculated PAR from a multivariate logisitic regression analysis and PAR estimates were calculated with IRAP (US National Cancer Institute, 2002).[1]

Table 5: **Independent predictors of death and stroke and their associated population attributable risks**

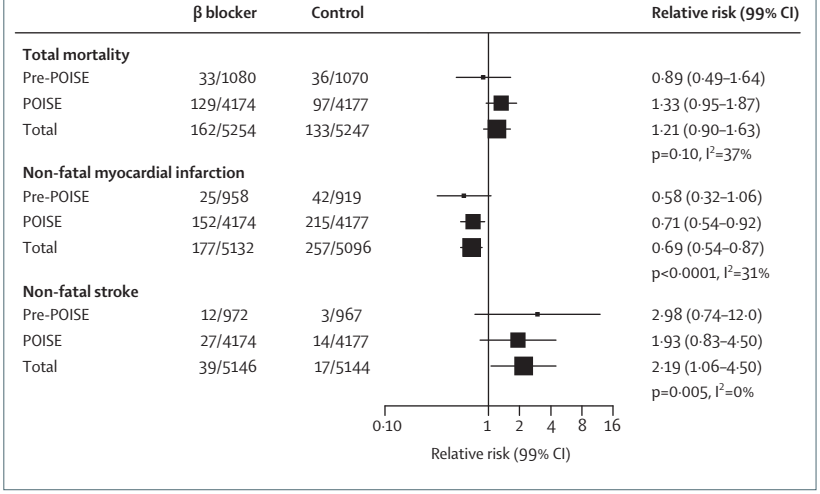

Figure 4: **Meta-analysis of β-blocker trials in patients undergoing non-cardiac surgery**

The results of POISE and of our meta-analysis provide evidence that perioperative β blockers prevent non-fatal myocardial infarctions but increase the risk of non-fatal stroke. The consistency of the myocardial infarction and stroke results in the meta-analyses increases the plausibility of these findings. Our post-hoc multivariate analyses suggest that hypotension is a potential mechanism through which β blockers could increase the risk of stroke; however, identified risk factors explain only half of the strokes.

After 7 days, or at hospital discharge, most patients who had a non-fatal stroke were left requiring help to do everyday activities or were incapacitated. By contrast, few patients who had a non-fatal myocardial infarction had ischaemic symptoms, probably because most myocardial infarctions occurred during the first few days after surgery when patients were receiving analgesic medication.[30] Furthermore, only a few patients who had a non-fatal myocardial infarction also had congestive heart failure, non-fatal cardiac arrest, or cardiac revascularisation.

For every 15 patients who participated in POISE, one had a cardiovascular death, non-fatal myocardial infarction, non-fatal cardiac arrest, or non-fatal stroke at 30-day follow-up. In view of the large numbers of individuals undergoing surgery and the high risk of cardiovascular complications, more large trials are needed urgently. The results of this trial suggest that the addition of perioperative extended-release metoprolol has potential benefits and risks. Patients who would place three times more value on avoiding a perioperative stroke than on avoiding a myocardial infarction, or who are unwilling to accept a probable increase in mortality, are unlikely to want perioperative extended-release metoprolol. Current perioperative guidelines that recommend β-blocker therapy to patients undergoing non-cardiac surgery should reconsider their recommendations in light of these findings.

Contributors

PJD, HY, SY, KL, JCV, SC, LG, JP, LL, PP, SX, GM, AA, MC, VMM, MJ, and PC contributed to the design of the study, and the collection and interpretation of the data. GG contributed to the design of the study. DX contributed to the collection and interpretation of the data. PJD wrote the first draft of the manuscript. All authors provided critical revisions to the manuscript before seeing and approving its final version.

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Conflict of interest statement

SY has received consultancy fees, research grants and honoraria from AstraZeneca, who provided the study drug for the POISE trial. JCV received honoraria to present the POISE protocol at a Colombian AstraZeneca advisory board meeting. The remaining members of the writing committee have no conflict of interest to declare, besides AstraZeneca providing the study drug for the POISE trial.

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