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.

Funding Canadian Institutes of Health Research; Commonwealth Government of Australia's National Health and Medical Research Council; Instituto de Salud Carlos III (Ministerio de Sanidad y Consumo), Spain; British Heart Foundation; AstraZeneca.

Lancet 2008; 371: 1839–47

Published Online May 13, 2008 DOI:10.1016/S0140-6736(08)60601-7

See Comment page 1813

*Members listed at end of paper

Correspondence to: Dr P J Devereaux, McMaster University, Faculty of Health Sciences, Clinical Epidemiology and Biostatistics, Room 2C8, 1200 Main Street West, Hamilton, ON, L8N 3Z5, Canada **philipj@mcmaster.ca**

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

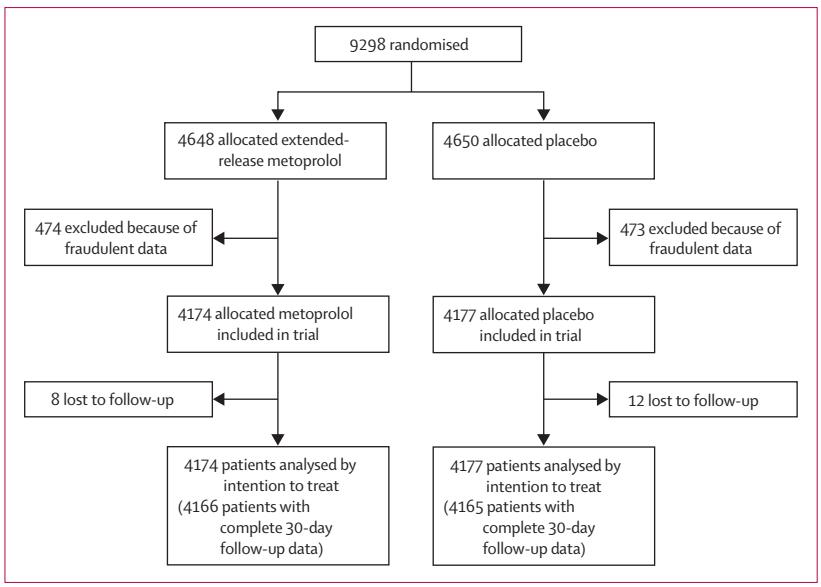

Figure 1: **Trial profile**

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

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,

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

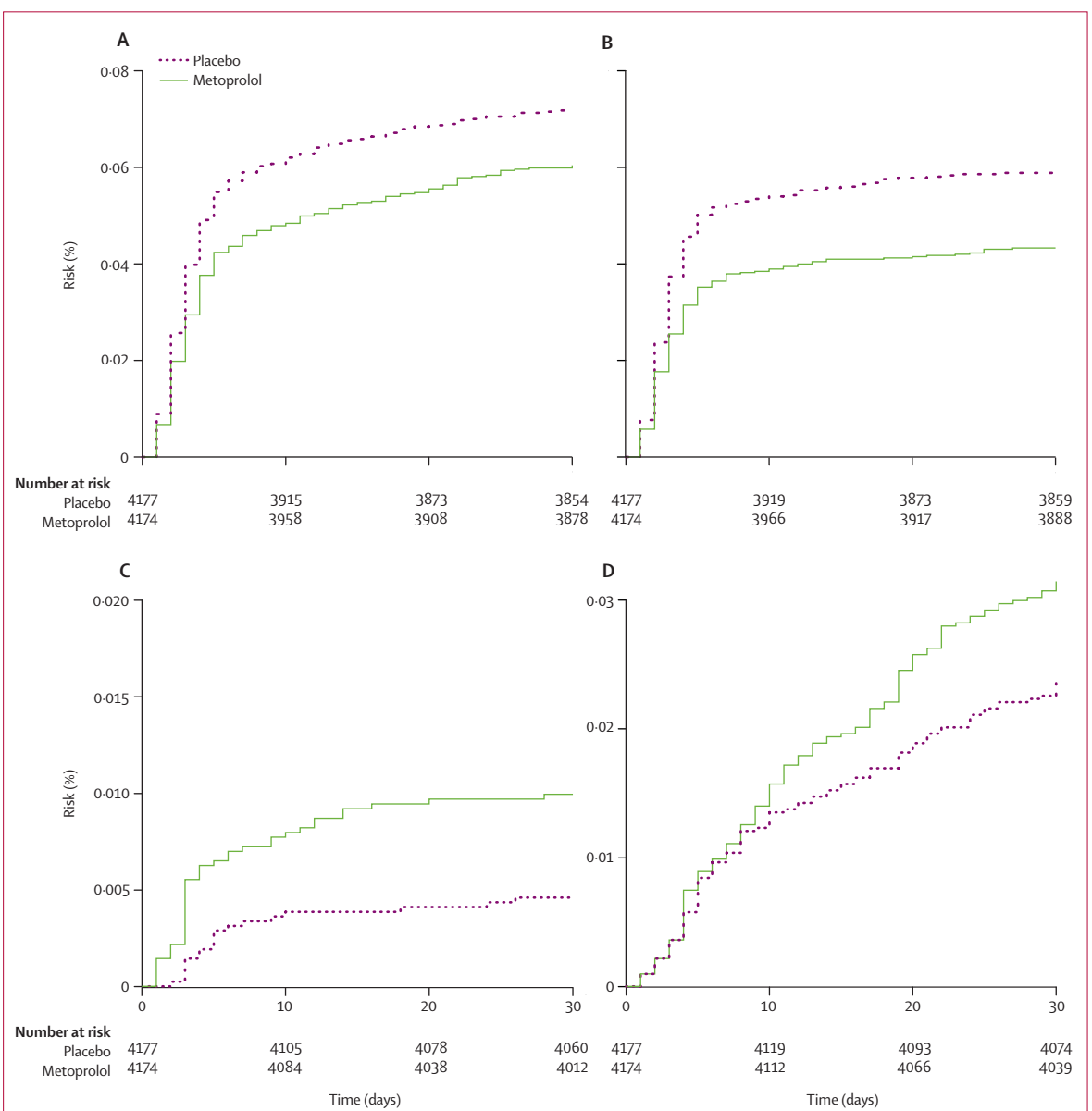

Figure 2: **Kaplan-Meier estimates of the primary outcome (A), myocardial infarction (B), stroke (C), and death (D)**

	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***

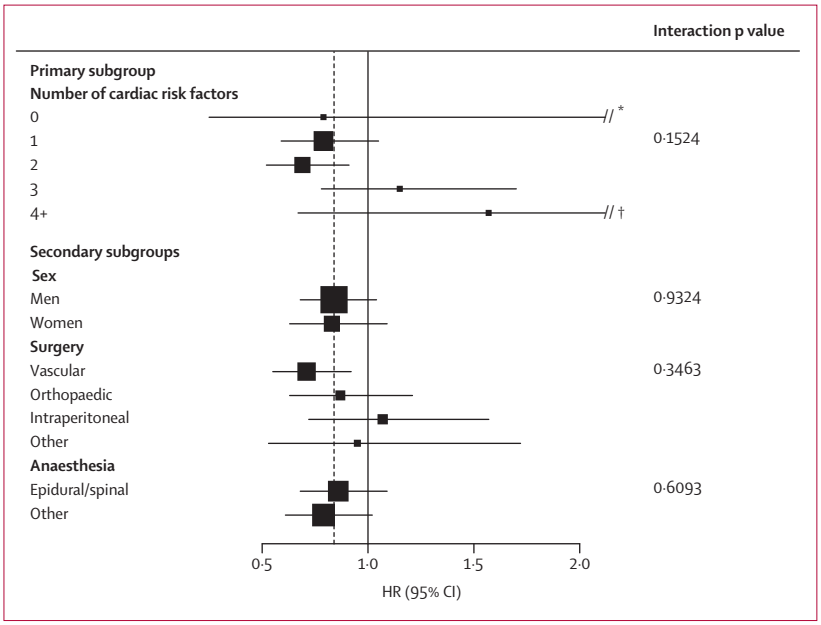

Figure 3: **Subgroup analyses for the primary outcome**
*Upper CI 2·51. †Upper CI 3·69.

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; I^2=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; I^2=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; I^2=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 benefit 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**

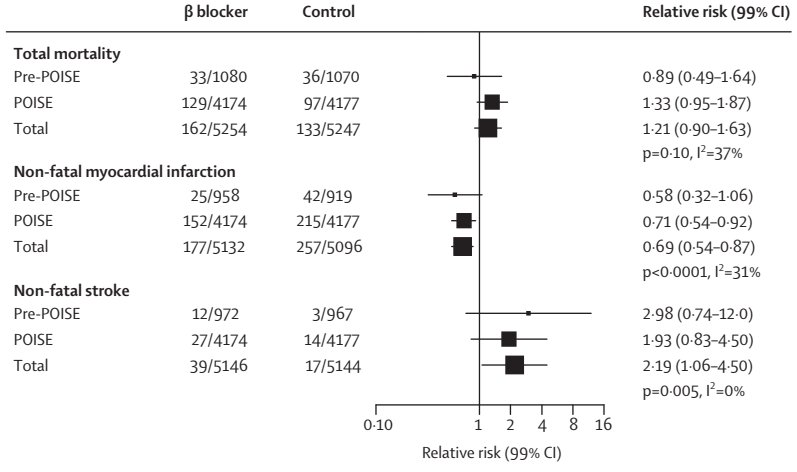

Figure 4: **Meta-analysis of β-blocker trials in patients undergoing non-cardiac surgery**

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.

POISE Study Group

Writing group: P J Devereaux, Homer Yang, Salim Yusuf, Gordon Guyatt, Kate Leslie, Juan Carlos Villar, Denis Xavier, Susan Chrolavicius, Launi Greenspan, Janice Pogue, Prem Pais, Lisheng Liu, Shouchun Xu, German Málaga, Alvaro Avezum, Matthew Chan, Victor M Montori, Mike Jacka, Peter Choi.
Operations committee: P J Devereaux, H Yang, S Yusuf, G Guyatt.
Steering committee: P J Devereaux, H Yang, S Yusuf, G Guyatt, S Chrolavicius, J Pogue, K Leslie, J C Villar, D Xavier, L Greenspan, L Lisheng, S Xu, G Málaga, A Avezum, M Jacka, P Choi.
Events adjudication committee: G Guyatt, O Berwanger, M Chan, D Chauret, N Faroughi, G Fodor, K Gilbert, R J Hudson, C Held, P Ibarra, A Kashfi, M Keltai, M Laine, L Lanthier, V M Montori, A Panju.
Population Health Research Institute (PHRI) project office: L Gallacher, L Greenspan, M Lawrence, A Mead, T Rodrigues.
External safety and efficacy and monitoring committee: G Dagenais, D Cheng, E Lowenstein, R S Roberts.
National coordinating centres: Argentina—Hospital Italiano de Buenos Aires; *Australia/New Zealand/Hong Kong/Singapore/Malaysia*—Royal Melbourne Hospital; *Brazil*—Dante Pazzanese Institue of Cardiology; *China*—Beijing Hypertension League Institute; *Colombia*—Universidad Autónoma de Bucamaranga; *Central America*—International Health Central American Institute; *Ecuador*—Universidad San Francisco de Quito; *Finland*—Turku University Hospital; *Hungary*—Hungarian Institute of Cardiology; *India*—St John's Medical College; *Mexico*—Centro Medico Nacional Siglo XXI; *Norway*—Ulleval Universitetssykehus; *Peru*—Hospital Nacional Cayetano Heredia; *Spain*—Centro Cochrane Iberoamericano-CIBERESP (Hospital de Sant Pau); *Sweden*—Karolinska Hospital; *Thailand*—Monash University; *United Kingdom*—University of Oxford.
National Coordinators: Argentina—A Ciapponi, M Garcia Dieguez; *Australia/New Zealand/Hong Kong/Singapore/Malaysia*—K Leslie; *Brazil*—A Avezum, O Berwanger; *Canada*—R J Hudson, M Jacka, T Schricker, B Warriner; *China:* L Liu, S Xu; *Colombia:* J C Villar; *Central America*—M Tristan, Y Baidel, A Salazar; *Ecuador:* M Espinel, J Carlos Zevallos; *Finland*—K Leino; *Hungary*—M Keltai, J Faller; *India*—P Pais, D Xavier; *Mexico*—S Islas Andrade; *Norway*—J Raeder; *Peru*—G Málaga; *Spain*—P Alonso-Coello, G Urrutia; *Sweden*—P Gannedahl; *Thailand*—A Phrommintikul; *UK*—P Foëx, J Giles, J Sear; *USA*—L Goldman.
Investigators who enrolled the 8351 participants: Argentina (25)—R A Caccavo, A Ferrari, L N Nicolosi, F Sierra, P Tesolin; *Australia (700)*—S Barratt, D Beilby, S Bolsin, D Boyd, S Bugler, L Cope, J Douglas, S Fatovich, J Grant, R Halliwell, R K Kerridge, K Leslie, J Love, S March, T J McCulloch, P S Myles, M Paech, P Peyton, C Poole, S Poustie, M Priestly, M Reeves, S Wallace, B Weitkamp, D Wolfers; *Brazil (286)*—M Baptista, A C do Amara Baruzzi, C Blacher, L C Bodanese, D Campos de Albuquerque, J P Esteves, O R França Neto, L E Guiselli Gallina, N M Izukawa, F C Kallas, J F Kerr Saraiva, J A Marin-Neto, L Nigro Maia, P H Penha Rosateli, R Rabello, T Schammass Ducatti; *Canada (3548)*—R Aggarwala, E Argibay-Poliquin, N Badner, C Baer, W S Beattie, M Bednarowski, H A Bertozzi, G Boisvenu, A Boulton, D Brunet, G L Bryson, J Burlingham, J Campeau, D Chauret, P Choi, D Cook, D R Cook, P Cossette, M Crossan, B Davies, P J Devereaux, J DeWolfe, G Doig, P Duffy, M S Eng, S Finlay, A Finlayson, J Gallacher, W Ghali, K Gilbert, D Hughes, L Hunter, M J Jacka, C Kamra, M Khurana, C Kinsella, L Lanthier, T W R Lee, M Lovell, C MacDonald, P MacDonald, M Marquis, J Marti, R Martinek, R N Merchant, J Misterski, R Mizera, R Moor, J Morin, M O'Reilly, J Ostrander, J L Parlow, J Paul, S Pettit, D Pilon, G Pruneau, S Rammohan, T Schricker, S Sivakumaran, L Sonnema, S Stoger, C Thompson, D Tod, S Toner, M Turabian, D Twist, C Urbanowicz, J M van Vlymen, B Warriner, D N Wijeysundera, D T Wong, H Yang, K Zarnke; *China (857)*—J Chang, K K Chen, W Chen, W Z Chen, J Y Cui, L L Deng, X L Ge, W J Hu, H Y Li, X S Li, Z Li, H L Liu, L H Liu, X Liu, X Y Liu, Y D Liu, B N Lv, F X Ren, X X Suo, L Tang, H Wang, Q Y Wang, G W G Wei, S B Wu, X M Wu, Z D Wu, R Xiao, Y F Xu, X Xu, Z X Zan, L Zhang, W H Zhang, S H Zhao, W D Zhao, Y C Zou, M Z Zuo; *Colombia (671)*—R Agonh, S Alvarez, M Arrieta, J G Barrera, L E Cáceres, W Cañón, H Castellanos, M S Chaparro, A Chaves, J Chona, E Duarte, H F Garcia, C Guevara, P Ibarra, J Manrique, L X Martinez, L Mateus, S B Parra, L F Pava, P E Perafán, R Plata, G W Rangel, M Rojas, M F Romero, T Romero, J Ruiz, G F Torres; *Cuba (12)*—J A Mellada Herrera, E Palomino Cabrera; *Equador (16)*—H Caballero, M Sanchez Velez; *El Salvador (34)*—T Cruz, V Rodriguez; *Finland (41):* M Hynynen, K Leino; *Hong Kong (192)*—M T V Chan, G Y S Choi, T Gin, S C Yu; *Hungary (39)*—K Darvas, L Entz, Z Hajdu, G Keleti, A Nagy, S Peter, J Regoly-Merei; *India (777)*—V Abraham, L Afzal, S Agarwal, R Babu Panwar, A Bharani, N Chidambaram, S Desai, K R Girija, R Gupta, S Gurusan Kaur, K K Haridas, N Jerry, P Kerkar, K Kilpadi, P P Mohanan, S Naik, A G Narayana Swamy, R Parakh, S K Paul, R Pinjala, V Raja Panwar, P Rajendra Kumar, V A Rama Raju, P Ramakrishna, P V Ramana, M Ramanathan, T Ramani Devi, E K Ramdas, J K Saraf, A Sigamani, R Singh, O P Srivastava, K R Suresh, A Swami, S Varma, F Xavier, A Yadav; *Malaysia (139)*—M Y Bahari Noor,

J Hassan, N S Hian, I Pilus, C Y Wang; *Mexico (16)*—S Islas-Andrade, J M Mora Martinez, R Orta Flores, H E Tamez Perez; *New Zealand (186)*—B Chan, D McAllister-Sim, T Vinnell, S Walker, Y Young; *Norway (17)*—V Aasbø, J Mellin-Olsen, J Raeder; *Peru (446)*—R Aguirre, M Aphang-Lam, B Arrunategui, L Baca, R Botazzi Alvarez, D Calmett, E Coloma, G Malaga, D Ponce de Leon, J G E Rojas Pareja, A M Sihuayro Ancco, A Soto Tarazona, G Tupayachi; *Singapore (1)*—R P Kelly; *Spain (200)*—C Alvarez Zurro, G Blanc Saizar, P Cruz Pardos, M de Nadal Clanchet, C Fernandez Riveira, M Martiez Borja, A Mases Fernández, V Moral Garcia, L Toran Garcia, B Unceta-Barrenechea Orue; *Sweden (68)*—R Hörnquist, J Malmstedt, J Rosell, L Vimláti; *Thailand (39)*—S Kuanprasert, K Rerkkasem; *UK (41)*—P Foëx, J Giles, G Howard-Alpe, J Sear.

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.

Acknowledgments

Funding for this study was received from the Canadian Institutes of Health Research, the Commonwealth Government of Australia's National Health and Medical Research Council, the Instituto de Salud Carlos III (Ministerio de Sanidad y Consumo) in Spain, the British Heart Foundation, and AstraZeneca, who provided the study drug and funding for drug labelling, packaging, and shipping and helped support the cost of some national POISE investigator meetings. We thank G Sobhi, M Biljan, and the BBSA, DIPOM, MaVS, and POBBLE investigators who provided data for the meta-analyses.

References

1 Mangano D. Peri-operative cardiovascular morbidity: new developments. *Ballieres Clin Anaesthesiol* 1999; **13:** 335–48.

2 Devereaux PJ, Goldman L, Cook DJ, Gilbert K, Leslie K, Guyatt GH. Perioperative cardiac events in patients undergoing noncardiac surgery: a review of the magnitude of the problem, the pathophysiology of the events and methods to estimate and communicate risk. *CMAJ* 2005; **173:** 627–34.

3 Sametz W, Metzler H, Gries M, et al. Perioperative catecholamine changes in cardiac risk patients. *Eur J Clin Invest* 1999; **29:** 582–87.

4 Parker SD, Breslow MJ, Frank SM, et al. Catecholamine and cortisol responses to lower extremity revascularization: correlation with outcome variables. *Crit Care Med* 1995; **23:** 1954–61.

5 Stone JG, Foex P, Sear JW, Johnson LL, Khambatta HJ, Triner L. Risk of myocardial ischaemia during anaesthesia in treated and untreated hypertensive patients. *Br J Anaesth* 1988; **61:** 675–79.

6 Wallace A, Layug B, Tateo I, et al. Prophylactic atenolol reduces postoperative myocardial ischemia. *Anesthesiology* 1998; **88:** 7–17.

7 Mangano DT, Layug EL, Wallace A, Tateo I. Effect of atenolol on mortality and cardiovascular morbidity after noncardiac surgery. *N Engl J Med* 1996; **335:** 1713–20.

8 Poldermans D, Boersma E, Bax JJ, et al. The effect of bisoprolol on perioperative mortality and myocardial infarction in high-risk patients undergoing vascular surgery. *N Engl J Med* 1999; **341:** 1789–94.

9 Devereaux PJ, Yusuf S, Yang H, Choi PT, Guyatt GH. Are the recommendations to use perioperative beta-blocker therapy in patients undergoing noncardiac surgery based on reliable evidence? *CMAJ* 2004; **171:** 245–47.

10 Yang H, Raymer K, Butler R, Parlow J, Roberts R. The effects of perioperative beta-blockade: results of the Metoprolol after Vascular Surgery (MaVS) study, a randomized controlled trial. *Am Heart J* 2006; **152:** 983–90.

11 Juul AB, Wetterslev J, Gluud C, et al. Effect of perioperative beta blockade in patients with diabetes undergoing major non-cardiac surgery: randomised placebo controlled, blinded multicentre trial. *BMJ* 2006; **332:** 1482.

12 Devereaux PJ, Beattie WS, Choi PT, et al. How strong is the evidence for the use of perioperative beta blockers in non-cardiac surgery? Systematic review and meta-analysis of randomised controlled trials. *BMJ* 2005; **331:** 313–21.

13 Devereaux PJ, Yang H, Guyatt GH, et al. Rationale, design, and organization of the PeriOperative ISchemic Evaluation (POISE) trial: a randomized controlled trial of metoprolol versus placebo in patients undergoing noncardiac surgery. *Am Heart J* 2006; **152:** 223–30.

14 Blomqvist I, Westergren G, Sandberg A, Jonsson UE, Lundborg P. Pharmacokinetics and pharmacodynamics of controlled-release metoprolol: a comparison with atenolol. *Eur J Clin Pharmacol* 1988; **33** (suppl)**:** S19–24.

15 Egstrup K, Gundersen T, Harkonen R, Karlsson E, Lundgren B. The antianginal efficacy and tolerability of controlled-release metoprolol once daily: a comparison with conventional metoprolol tablets twice daily. *Eur J Clin Pharmacol* 1988; **33** (suppl)**:** S45–49.

16 Chen ZM, Pan HC, Chen YP, et al. Early intravenous then oral metoprolol in 45 852 patients with acute myocardial infarction: randomised placebo-controlled trial. *Lancet* 2005; **366:** 1622–32.

17 Lindenauer PK, Pekow P, Wang K, Mamidi DK, Gutierrez B, Benjamin EM. Perioperative beta-blocker therapy and mortality after major noncardiac surgery. *N Engl J Med* 2005; **353:** 349–61.

18 Lee TH, Marcantonio ER, Mangione CM, et al. Derivation and prospective validation of a simple index for prediction of cardiac risk of major noncardiac surgery. *Circulation* 1999; **100:** 1043–49.

19 Haybittle JL. Repeated assessment of results in clinical trials of cancer treatment. *Br J Radiol* 1971; **44:** 793–97.

20 Peto R, Pike MC, Armitage P, et al. Design and analysis of randomized clinical trials requiring prolonged observation of each patient. I. Introduction and design. *Br J Cancer* 1976; **34:** 585–612.

21 Bayliff CD, Massel DR, Inculet RI, et al. Propranolol for the prevention of postoperative arrhythmias in general thoracic surgery. *Ann Thorac Surg* 1999; **67:** 182–86.

22 Brady AR, Gibbs JS, Greenhalgh RM, Powell JT, Sydes MR. Perioperative beta-blockade (POBBLE) for patients undergoing infrarenal vascular surgery: results of a randomized double-blind controlled trial. *J Vasc Surg* 2005; **41:** 602–09.

23 Zaugg M, Bestmann L, Wacker J, et al. Adrenergic receptor genotype but not perioperative bisoprolol therapy may determine cardiovascular outcome in at-risk patients undergoing surgery with spinal block: the Swiss Beta Blocker in Spinal Anesthesia (BBSA) study: a double-blinded, placebo-controlled, multicenter trial with 1-year follow-up. *Anesthesiology* 2007; **107:** 33–44.

24 Jakobsen CJ, Bille S, Ahlburg P, Rybro L, Pedersen KD, Rasmussen B. Preoperative metoprolol improves cardiovascular stability and reduces oxygen consumption after thoracotomy. *Acta Anaesthesiol Scand* 1997; **41:** 1324–30.

25 Raby KE, Brull SJ, Timimi F, et al. The effect of heart rate control on myocardial ischemia among high-risk patients after vascular surgery. *Anesth Analg* 1999; **88:** 477–82.

26 Zaugg M, Tagliente T, Lucchinetti E, et al. Beneficial effects from beta-adrenergic blockade in elderly patients undergoing noncardiac surgery. *Anesthesiology* 1999; **91:** 1674–86.

27 Urban MK, Markowitz SM, Gordon MA, Urquhart BL, Kligfield P. Postoperative prophylactic administration of beta-adrenergic blockers in patients at risk for myocardial ischemia. *Anesth Analg* 2000; **90:** 1257–61.

28 Kohsaka S, Menon V, Lowe AM, et al. Systemic inflammatory response syndrome after acute myocardial infarction complicated by cardiogenic shock. *Arch Intern Med* 2005; **165:** 1643–50.

29 Moore FA. The role of the gastrointestinal tract in postinjury multiple organ failure. *Am J Surg* 1999; **178:** 449–53.

30 Devereaux PJ, Goldman L, Yusuf S, Gilbert K, Leslie K, Guyatt GH. Surveillance and prevention of major perioperative ischemic cardiac events in patients undergoing noncardiac surgery: a review. *CMAJ* 2005; **173:** 779–88.