Rationale, design, and organization of the *PeriOperative ISchemic Evaluation* (POISE) Trial: A randomized controlled trial of metoprolol versus placebo in patients undergoing noncardiac surgery

The POISE Trial Investigators

Background Noncardiac surgery is associated with significant cardiovascular mortality, morbidity, and cost. Small trials of β-blockers suggest that they may prevent cardiovascular events in patients undergoing noncardiac surgery, but trial results are inconclusive. We have initiated the POISE trial to definitively establish the effects of β-blocker therapy in patients undergoing noncardiac surgery.

Methods The POISE trial is a blinded, randomized, and controlled trial of controlled-release metoprolol versus placebo in 10 000 patients at risk for a perioperative cardiovascular event who are undergoing noncardiac surgery. Patients will receive the study drug 2 to 4 hours before surgery and subsequently for 30 days. The primary outcome is a composite of cardiovascular death, nonfatal myocardial infarction, and nonfatal cardiac arrest at 30 days. Patients will also be followed for events at 1 year.

Results To date, the POISE trial has recruited >6300 patients in 182 centers in 21 countries. Currently, the patients' mean age is 69 years; 63% are males, 43% have a history of coronary artery disease, 43% have a history of peripheral arterial disease, and 30% have diabetes. Most participants have undergone vascular (42%), intraabdominal (23%), or orthopedic (19%) surgery.

Conclusions The POISE trial is a large international trial that will provide a reliable assessment of the effects of β-blocker therapy in patients undergoing noncardiac surgery. (Am Heart J 2006;152:223-30.)

Magnitude of the problem

Worldwide, approximately 500 000 to 900 000 patients per year undergoing noncardiac surgery suffer a perioperative cardiac death, nonfatal myocardial infarction, or nonfatal cardiac arrest.[1] Cardiac complications after noncardiac surgery result in substantial cost because these events prolong hospitalization by a mean of 11 days.[2] Furthermore, perioperative ischemia is an independent predictor of cardiac death and myocardial infarction during the 2 years after surgery.[3,4]

Competing interests: Dr. Salim Yusuf received research grants and honoraria from AstraZeneca, Mississauga, Ontario, Canada, the manufacturer of controlled-release metoprolol.

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Rationale for a perioperative β-blocker trial

Perioperative cardiovascular events are likely mediated through a host of mechanisms, including increases in adrenergic activity, free fatty acid levels, platelet reactivity, plasminogen activator inhibitor I, factor VIII–related antigen levels, and inflammation as well as decreases in antithrombin III levels.[1] β-Blockers reduce adrenergic activity and free fatty acid levels.[5] Therefore, β-blockers may prevent perioperative cardiovascular events. At the same time, it is unlikely that β-blockers would result in a large reduction in risk (ie, a relative risk reduction >35%) because of the number of important pathogenic mechanisms unaffected by β-blockers. Furthermore, there is strong evidence that perioperative β-blockers cause hypotension and bradycardia requiring treatment[6]; in the setting of significant coronary artery disease, these hemodynamic events may lead to myocardial infarction.[1]

Recently, the American College of Cardiology/American Heart Association stated in their practice guidelines for noncardiac surgery that "there are still very few randomized trials of medical interventions before noncardiac

surgery to prevent perioperative cardiac complications, and they do not provide enough data from which to draw firm conclusions or recommendations."[7] Despite this statement, these guidelines and several other authors have recommended that patients receive β-blocker therapy around the time of noncardiac surgery.[7-10]

These recommendations were primarily based on the results of 2 very small trials that claimed benefits from the use of perioperative β-blockers.[11,12] These trials were limited because 1 removed events after randomization; 1 was unblinded and stopped at an interim analysis, which suggested an unexpectedly very large treatment effect; and both had few events.[13] A meta-analysis of all available trials demonstrated that the current perioperative β-blocker evidence is insufficient and inconclusive.[6] Furthermore, 2 recent trials have not demonstrated benefit, calling into question whether β-blockers are of net value in patients undergoing noncardiac surgery.[14,15] Therefore, a large randomized controlled trial (RCT) involving several thousands of patients, in whom a few hundred events would be expected to occur, is necessary to reliably address the value of β-blockers in preventing major perioperative cardiovascular events.

The POISE trial—an overview

The POISE trial is a large RCT designed to determine the impact of perioperative administration of metoprolol on the 30-day risk of major cardiovascular events (ie, cardiovascular death, nonfatal myocardial infarction, and nonfatal cardiac arrest) in at-risk patients (ie, patients with or at risk for atherosclerotic cardiovascular disease) undergoing noncardiac surgery.

In the POISE trial, we evaluate controlled-release oral metoprolol succinate and intravenous metoprolol tartrate, which patients receive when they are unable to take oral medications. Both of these drugs are cardioselective β_1 adrenergic receptor antagonists. The dissolution and absorption properties of controlled-release metoprolol result in stable plasma concentrations with minimum fluctuations over a 24-hour period under fasting and nonfasting conditions.[16,17]

Methods

Trial design

The POISE trial is an RCT of metoprolol versus placebo in patients at risk for a perioperative cardiovascular event who are undergoing noncardiac surgery. Participants, health care providers, data collectors, and outcome adjudicators are blinded to whether patients receive metoprolol or placebo.

Trial population

Investigators will consider patients undergoing elective and urgent/emergent noncardiac surgical procedures for enrollment. Tables I and II present the POISE trial's inclusion and exclusion criteria, respectively.

Table I. Inclusion criteria of the POISE trial

Patients undergoing noncardiac surgery are eligible if they
1. are ≥45 y;
2. have an expected postoperative length of stay ≥24 h for surgical reasons; and
3. fulfill any 1 of the following 6 criteria:
   a. have a history of coronary artery disease as defined by any 1 of the following 6 criteria:
      i. history of angina
      ii. prior myocardial infarction
      iii. prior positive exercise stress test findings
      iv. prior documentation of cardiac ischemia on nuclear or echocardiography stress testing
      v. prior coronary artery angiographic evidence of atherosclerotic stenosis >50% of the vessel diameter
      vi. an electrocardiogram with pathologic Q waves in 2 contiguous leads
   b. have a history of peripheral arterial disease as defined by any 1 of the following 3 criteria:
      i. intermittent claudication that is known or likely caused by atherosclerotic disease
      ii. an ankle/arm SBP ratio ≤0.90 in either leg at rest
      iii. angiographic or Doppler study demonstrating >70% stenosis
   c. have a history of stroke thought to be caused by atherothrombotic disease;
   d. have a history of hospitalization for congestive heart failure within 3 y of randomization;
   e. are undergoing major vascular surgery (ie, vascular surgery excluding arteriovenous shunt, vein stripping procedures, and carotid endarterectomies); or
   f. have any 3 of the following 7 risk factors:
      i. high-risk type of surgery (ie, intrathoracic or intraperitoneal)
      ii. any history of congestive heart failure
      iii. diabetes and currently taking an oral hypoglycemic agent or insulin
      iv. preoperative serum creatinine >175 μmol/L (>2.0 mg/dL)
      v. >70 y
      vi. history of a transient ischemic attack
      vii. emergency/urgent surgery (ie, surgery that must be undertaken within 24 h of acute presentation to hospital)

Randomization

Patients are randomized after providing a written informed consent form via a 24-hour computerized randomization phone service at the Population Health Research Institute, Hamilton Health Sciences, and McMaster University (Hamilton, Ontario, Canada). The computerized randomization process uses block randomization stratified by center. The block size is unknown to study center personnel. Patients are randomized in a 1:1 ratio to receive metoprolol or matching placebo.

Drug administration

The oral study drug preparation consists of 200-mg tablets of controlled-release metoprolol or matching placebo, and the intravenous study drug preparation consists of 5-mg ampules of metoprolol tartrate or matching placebo. Administration of the study drug at each dosing time, except during the first 6 hours after surgery, requires a patient to have a heart rate ≥50 beats/min and a systolic blood pressure (SBP) ≥100 mm Hg.

Figure 1 presents a flowchart of the study drug administration. Two to 4 hours before surgery, patients will take 100 mg

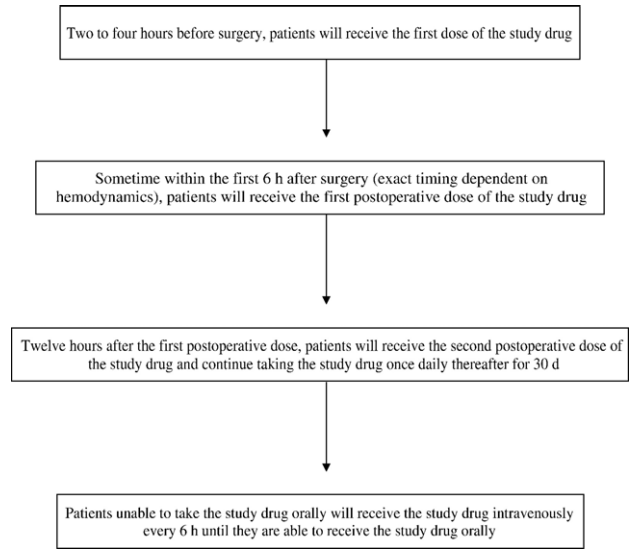
Table II. Exclusion criteria of the POISE trial

Patients are excluded if they

1. have significant bradycardia (heart rate <50 beats/min) or second- or third-degree heart block without a pacemaker;
2. have asthma that has been active within the last decade (ie, a clinical diagnosis of asthma and use of regular inhaled steroids or β agonists at least once per week over the period of 1 m, any time in the last 10 y);
3. have chronic obstructive pulmonary disease with bronchospasm on pulmonary function tests (ie, an increase in FEV1≥12% and of at least 200 mL, 15 min after inhalation of a β_2 agonist);
4. are currently taking a systemic β-blocker or their physician plans to prescribe a systemic β-blocker before the operation or during the first 30 d after the operation;
5. have had a prior adverse reaction to a β-blocker;
6. have had coronary artery bypass graft surgery with complete revascularization in the preceding 5 y and no evidence of cardiac ischemia since the surgery;
7. are undergoing a surgical procedure that the investigator deems to be of low risk (eg, cataract surgery);
8. are currently taking verapamil; or
9. have previously enrolled in the POISE trial

FEV1, Forced expiratory volume in 1 second.

Figure 1



Flowchart of drug administration.

(ie, half a tablet) of the study drug orally. If the patients heart rate is >80 beats/min and their SBP is ≥100 mm Hg during the first 6 hours after surgery, they will take 100 mg of the study drug orally. Patients who do not receive a dose of the study drug during the first 6 hours after surgery will take 100 mg of the study drug orally at 6 hours after surgery. Starting 12 hours after patients receive their first postoperative study drug dose and daily thereafter for 30 days, they will take 200 mg of the study drug orally. If the patients' heart rate is consistently <45 beats/min or their SBP is <100 mm Hg, caregivers will hold the study drug until the patients' heart rate or SBP recovers and will then administer 100 mg of the study drug orally. If the patients' heart rate is consistently between 45 and 49 beats/min and their SBP is ≥100 mm Hg, they will delay taking the study drug for 12 hours.

Patients who are unable to take medications orally will receive the study drug by slow or rapid intravenous infusion every 6 hours until they are able to receive the study drug orally. The slow intravenous infusion consists of 15 mg of the study drug in 25 mL of normal saline infused over a 60-minute period, and patients will have their heart rate and blood pressure checked 10, 30, and 60 minutes after starting the infusion. If the patients' heart rate is <50 beats/min or their SBP is <100 mm Hg, the infusion is stopped and subsequent infusions will consist of 10 mg of the study drug in 25 mL of normal saline infused over a 60-minute period.

The rapid intravenous infusion will consist of 5 mg of the study drug infused over 2 minutes. Patients will receive the rapid intravenous infusion every 5 minutes, for a total of 15 mg, as long as their vital signs fulfill the standard heart rate and SBP requirements before each dosing.

If patients develop congestive heart failure, significant first-degree heart block, second- or third-degree heart block, or bronchospasm, they will have their study medication withheld until the attending physician decides that it is safe for them to restart intake of the study drug. Patients restarting intake of the study drug after any of these problems will receive the study drug at 100 mg orally.

Medical management, including any drug therapy, is at the discretion of the treating physician. All treating physicians are encouraged not to prescribe β-blocker therapy on the day of surgery or during the initial 30 days after surgery.

Patient follow-up

Short-term follow-up. Patients will have an electrocardiogram recorded 6 to 12 hours postoperatively and on the 1st, 2nd, and 30th days after surgery. They will have troponin or creatine kinase–MB, when troponin is not available, drawn 6 to 12 hours postoperatively and on the 1st, 2nd, and 3rd days after surgery. Research personnel will follow patients in the hospital and record the occurrence of any primary or secondary outcome. Research personnel will contact patients at 30 days and record the occurrence of any primary or secondary outcome.

Long-term follow-up. We will undertake a long-term follow-up (minimum of 1 year) for all patients. In Canada, the Canadian Institute for Health Information and Statistics Canada will provide the long-term follow-up data on nonfatal outcomes and mortality, respectively. In other countries without a national health administrative database, study personnel will contact patients by phone at 1 year after surgery.

Trial outcomes

The primary outcome of the POISE trial is a composite outcome of cardiovascular death, nonfatal myocardial infarction, and nonfatal cardiac arrest at 30 days after randomization. Secondary outcomes at 30 days include total mortality, cardiovascular death, myocardial infarction, nonfatal cardiac arrest, cardiac revascularization (ie, coronary artery bypass

graft surgery or percutaneous coronary intervention), congestive heart failure, clinically significant atrial fibrillation, rehospitalization for cardiac reasons, clinically significant bradycardia, clinically significant hypotension, stroke, length of hospital stay, and length of intensive care unit/cardiac care unit stay. For the long-term follow-up, we will evaluate total mortality, cardiovascular death, nonfatal myocardial infarction, nonfatal cardiac arrest, cardiac revascularization, and stroke. Appendix A presents our outcome definitions.

Outcome adjudication

A committee of clinicians who are blinded to the treatment allocation will adjudicate the following outcomes: subclassification of death, myocardial infarction, nonfatal cardiac arrest, and stroke. We will use the decisions from the Adjudication Committee for all statistical analyses involving these outcomes.

Statistical considerations

Sample size

Several large studies using multivariate analysis have demonstrated that patients with coronary artery disease are at high risk for a perioperative cardiovascular event.[8] Most recently, Gilbert et al[18] prospectively evaluated 2035 patients undergoing noncardiac surgery and found that patients with angina and an expected length of hospital stay >24 hours had a 6.6% event rate of the composite outcome of perioperative cardiac death and nonfatal myocardial infarction (data courtesy of Dr Gilbert).

Patients undergoing major vascular surgery are at high risk for perioperative cardiovascular events.[7] In the MaVS trial, patients undergoing vascular surgery had an 8.8% event rate of the composite outcome of perioperative cardiac death, nonfatal myocardial infarction, and nonfatal cardiac arrest.[14] Because of the strong correlation between peripheral vascular disease and coronary artery disease, patients with a history of peripheral vascular disease undergoing other noncardiac surgeries also have a high risk for perioperative cardiovascular events.[7]

Several large studies have identified congestive heart failure as an independent predictor of perioperative cardiac outcomes.[8] Most patients with a history of congestive heart failure have underlying coronary artery disease,[19] as do patients with a history of atherothrombotic stroke.

Using published data from existing risk indices for predicting perioperative cardiovascular events,[1] we anticipate that patients with any 3 of 7 risk factors (high-risk type of surgery [ie, intrathoracic or intraperitoneal], emergency/urgent surgery, any history of congestive heart failure, history of a transient ischemic attack, diabetes and currently taking an oral hypoglycemic agent or insulin therapy, preoperative serum creatinine >175 μmol/L [>2.0 mg/dL], or >70 years) will have a perioperative rate of cardiovascular death, nonfatal myocardial infarction, or nonfatal cardiac arrest of at least 5.3% during their hospitalization.

We expect that 6% of the control group in the POISE trial will suffer the primary outcome within 30 days, based on a screening study and the eligibility criteria that the patients randomized to date have fulfilled. Table III presents the power to detect relative risk reductions of 25% and 30% based on sample sizes of 6000, 8000, and 10 000 patients with an α level of .05 (2 sided). Our goal is to randomize 10 000 patients; however, even with smaller sample sizes, we have adequate power to detect plausible and clinically relevant relative risk reductions.

Data analysis

We will use the intention-to-treat principle for all our analyses.

Main analysis

We will present the time to the first occurrence of one of the components of the primary outcome using the Kaplan-Meier estimator. We will use a log-rank statistic to compare the rate of occurrence of the primary outcome between the 2 groups. Using a Cox proportional hazards model, we will calculate the hazard ratio and its associated 95% CI. We will infer statistical significance if the computed P value is <.05.

Secondary analyses. We will use the log-rank statistic to compare the occurrence rate of each binary secondary outcome. We will compare the length of hospital stay and the length of intensive care unit/cardiac care unit stay using an unpaired t test or a nonparametric test if the data are far from normally distributed. The Cox proportional hazards model will provide the basis for subgroup analyses (ie, patients with diabetes, renal failure, coronary artery disease, hypertension, congestive heart failure, cerebrovascular disease, or peripheral vascular disease; patients who receive epidural or spinal anesthesia; men and women; types of surgeries; effects among patients at different ages; and effects based on the number of inclusion criteria fulfilled); in addition, we will infer a subgroup effect if the interaction term of treatment and subgroup is statistically significant.

Interim analyses. The independent External Safety and Efficacy Monitoring Committee (ESEMC) will ensure patient safety, review interim analyses, provide feedback to the Operations Committee, and ensure that the study adheres to the highest ethical standards. Three interim efficacy analyses will occur when 25%, 50%, and 75% of the 30-day primary outcome data are available. The ESEMC will use the modified Haybittle-Peto rule of 4 standard deviations for analyses in the first half of the study and 3 standard deviations for all analyses in the second half.[20,21] The ESEMC will only consider a finding in favor of treatment significant if these predefined boundaries are exceeded in at least 2 consecutive analyses, ≥3 months apart. The

Table III. Power calculations for 30-d follow-up

Primary study outcome: cardiac death, nonfatal myocardial infarction, or nonfatal cardiac arrest at 30 d			Power based on various sample sizes (2-sided α = .05)		
Control event rate (%)	**Treatment event rate (%)**	**Relative risk reduction (%)**	**N = 6000 (%)**	**N = 8000 (%)**	**N = 10000 (%)**
6	4.5	25	74	85	92
6	4.2	30	89	96	98
5.5	4.1	25	72	83	91
5.5	3.9	30	83	92	97

Table IV. Baseline characteristics (n = 6385)

Characteristic	Value
Age [y, mean (SD)]	69 (10)
Sex (% female)	37
Preoperative heart rate [beats/min, mean (SD)]	77 (12)
Preoperative SBP [mm HG, mean (SD)]	138 (20)
Patients fulfilling eligibility criteria (%)	
Coronary artery disease	43
Peripheral arterial disease	43
Stroke thought to be caused by atherothrombotic disease	15
Hospitalization for congestive heart failure within 3 y of randomization	3
Undergoing major vascular surgery	34
3 of 7 risk factors	19
Intrathoracic or intraperitoneal surgery	29
Any history of congestive heart failure	6
Diabetes and currently taking an oral hypoglycemic agent or insulin	30
Preoperative serum creatinine >175 μmol/L (>2.0 mg/dL)	5
>70 y	50
History of a transient ischemic attack	11
Emergent/urgent surgery	9
Patients with other cardiovascular risk factors (%)	
History of hypertension	63
Current smoker	19
Former smoker	37

Table V. Types of surgery and anesthesia/analgesia (n = 6385)

	Patients (%)
Type of surgery	
Vascular	42
Intraabdominal	23
Orthopedic	19
Head and neck	2
Thoracic	2
Gynecologic	2
Other	9
Type of anesthesia/analgesia	
General	54
Neuraxial anesthesia	
Lumbar epidural	9
Spinal	14
Combined spinal epidural	3
Epigeneral anesthesia	
General and thoracic epidural	9
General and lumbar epidural	3
Regional anesthesia	3
Other combination	5

corresponding critical χ^2 values are 16.0 (ie, α = .0001) for the first 2 planned analyses and 12.25 (α = .00047) for the third analysis. The α level for the final analysis will be the conventional α level of .05 given the infrequent interim analyses, their extremely low α levels, and the requirement for confirmation with subsequent analyses.

If the intervention surpasses the modified Haybittle-Peto rule, then the ESEMC will advise the Operations Committee of the finding. The ESEMC will also consider the consistency of the secondary end points and subgroups and any relevant external information when considering a recommendation to stop the trial.

The ESEMC will also monitor the study to assess if there is an adverse impact of metoprolol on mortality. For these analyses, an excess in mortality of 3 standard deviations in the first half and 2.6 standard deviations in the second half would trigger discussions about stopping the trial for harm.

Trial organization and funding

The Population Health Research Institute is the coordinating center for this study worldwide and is primarily responsible for the development of the trial protocol, organization of the trial, development of the randomization scheme, the study database, data consistency checks, data analysis, and coordination of the study centers. The trial structure includes the following groups: the Operations Committee, coordinating center, national coordinators, the Adjudication Committee, the ESEMC, and the investigators. Appendix B lists the group members.

Grants from the Canadian Institutes of Health Research, the Commonwealth Government of Australia's National Health and Medical Research Council, and the British Heart Foundation provide the funds for the POISE trial. AstraZeneca (Mississauga, Ontario, Canada) has

provided the study drug and funding for drug labeling, packaging, and shipping.

Current status of the trial

The POISE trial is currently recruiting patients in 182 centers within 21 countries and has randomized >6300 patients as of March 2006. Tables IV and V present baseline characteristics of the sample and types of surgery as well as anesthesia/analgesia, respectively. These data demonstrate that after randomizing approximately two thirds of the sample, the patients' mean age is 69 years, 63% of them are males, 43% of them have a history of coronary artery disease, 43% of them have a history of peripheral arterial disease, and 30% of them have diabetes. The most common types of surgery are vascular (42%), intraabdominal (23%), and orthopedic (19%); approximately two thirds of the patients have received a general anesthetic. After the first and second interim analyses, the ESEMC members were unanimous in recommending that the POISE trial continue.

Discussion

Patients undergoing noncardiac surgery frequently suffer major perioperative cardiovascular events. Despite the magnitude of the problem, there has been a paucity of large trials evaluating the benefits and harms of perioperative interventions. There exist encouraging but inconclusive preliminary evidence suggesting that β-blockers may prevent perioperative cardiovascular events.

The POISE trial is a large RCT designed to determine if metoprolol can prevent major perioperative cardiovascular events in patients undergoing noncardiac surgery. To date, the POISE trial has randomized >6300 patients. Regardless of the results, the POISE trial will have important implications. If the POISE trial demonstrates no effect on major perioperative cardiovascular events, then it would allow physicians to avoid unnecessary patient risks and decrease costs. If the POISE trial demonstrates a positive effect, then it will have substantial clinical impact on preventing major perioperative cardiovascular events.

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Appendix A

Outcome definitions

Outcome	Definition
Subclassification of death	*Cardiovascular death* is defined as any death with a cardiovascular cause and includes those deaths after a cardiovascular procedure (eg, percutaneous coronary intervention), cardiac arrest, myocardial infarction, pulmonary embolus, stroke, and hemorrhage or deaths due to an unknown cause. *Noncardiovascular death* is defined as any death owing to a clearly documented noncardiovascular cause (eg, trauma, infection, malignancy).
Myocardial infarction	The diagnosis requires one of the following: 1. A typical increase of troponin *or* a typical decrease of an elevated troponin *or* a rapid increase and decrease of creatine kinase (CK)–MB. An increased troponin value (ie, higher than the decision limit for myocardial infarction) is a measurement exceeding the threshold at which the coefficient of variation equals 10%. An increased CK-MB value (ie, higher than the decision limit for myocardial infarction) is one that exceeds the 99th percentile for CK-MB values in a reference control group. One of the following must also exist for the diagnosis of myocardial infarction: a. ischemic symptoms (eg, chest, epigastric, arm, wrist, or jaw discomfort *or* shortness of breath) b. development of pathologic Q waves on the electrocardiogram (Q-wave changes must be present in any 2 contiguous leads and be ≥1 mm in depth; further Q waves in leads I, II, aVL, aVF, V4, V5, and V6 must be ≥30 milliseconds) c. electrocardiogram changes indicative of ischemia (new or presumed new ST-segment elevation or depression in at least 2 contiguous leads *or* new or presumed new symmetrical inversion of T waves ≥1 mm in at least 2 contiguous leads) d. coronary artery intervention (eg, percutaneous coronary intervention) e. new or presumed new cardiac wall motion abnormality on echocardiographic imaging or a new or presumed new fixed defect on radionuclide imaging 2. Pathologic findings of an acute myocardial infarction
Nonfatal cardiac arrest	The diagnosis requires a successful resuscitation from either documented or presumed ventricular fibrillation, sustained ventricular tachycardia, or asystole
Congestive heart failure	The diagnosis requires both clinical (ie, any of the following signs: elevated jugular venous pressure, respiratory rales, crepitations, or presence of S_3) and radiographic (eg, vascular redistribution, interstitial pulmonary edema, or frank alveolar pulmonary edema) evidence
Clinically significant atrial fibrillation	Atrial fibrillation that results in angina, congestive heart failure, or symptomatic hypotension or that requires treatment with a rate-controlling drug, antiarrhythmic drug, or electric cardioversion
Rehospitalization for cardiac reasons	Rehospitalization for congestive heart failure, ischemic symptoms with ST or T-wave changes on an electrocardiogram, arrhythmia, or heart block
Clinically significant bradycardia	Bradycardia requiring a temporary pacemaker, sympathomimetic agent, atropine, or study drug discontinuation
Clinically significant hypotension	An SBP <90 mm Hg requiring fluid resuscitation, intraaortic balloon pump, an inotropic agent, or study drug discontinuation
Stroke	A new focal neurologic deficit thought to be vascular in origin with signs and symptoms lasting >24 hours

Appendix B

Trial organization

Operations Committee

P.J. Devereaux (co-principal investigator), H. Yang (co-principal investigator), G. Guyatt, P. Choi, and S. Yusuf (chairperson)

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