Large Randomized Controlled Trials in Perioperative Cardiovascular Medicine: a Proposal for the Design, Conduct and Efficient Management

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Summary

The number of patients undergoing noncardiac surgery is growing worldwide. To optimally assist patients during the perioperative period, we must improve our knowledge of how to prevent major perioperative cardiovascular events around the time of noncardiac surgery. To achieve this goal there is a need for large randomized controlled trials that can provide reliable and conclusive results in this field. This narrative review describes a proposal for the design, conduct and management of large controlled trials in perioperative cardiovascular medicine.

Introduction

In the last few decades, noncardiac surgery has made substantial advances in the treatment of diseases and improving patients' quality of life[1,2]. As a result, it is estimated that 100 million adults undergo noncardiac surgery worldwide, requiring hospital admission[3]. Noncardiac surgery is associated with significant cardiac morbidity, mortality, and consequent costs[2]. Currently, little is known about how to prevent major cardiovascular events in patients undergoing surgery. The identification of which interventions have a better risk-benefit ratio in patients submitted to non-cardiac surgery will require reliable knowledge derived from large-scale random clinical trials (RCTs).

In this narrative review, we discuss some concepts related to large RCTs in perioperative cardiovascular medicine, including fundamental aspects of trial design and management.

Trial design

The complementary role between systematic reviews and randomized controlled trials

Systematic reviews with meta-analysis are studies in which the "participants" are original published research reports. Systematic reviews have explicit inclusion criteria, comprehensive literature searches, and unbiased data extraction; meta-analyses utilize advanced statistical methods to combine studies results[4]. Before designing a large RCT protocol, conducting (or reviewing if available) a systematic review can provide an overview of the current state of knowledge, event rates, and an estimate of the treatment effect. Additionally, formal methods to determine if the current evidence is reliable and conclusive are available, which can help to determine if there is a need for undertaking a large RCT[4,5].

Trial quality

The most fundamental advance that has made studies more reliable is adequate randomization[6]. The main objective of randomization is to ensure that known and unknown prognostic factors related to the outcomes are well balanced between the treatment groups. If this goal is achieved, then clinicians can attribute any difference in outcomes (provided it was measured in an unbiased way) to the intervention. Another crucial aspect of trial quality is concealment of randomization and this means that individuals randomizing patients are unaware of which treatment group the next patient will be allocated to. Foreknowledge of the next treatment allocation could affect the decision to enter the patient and those allocated to one treatment might then differ systematically from those allocated to another. Thus, it is crucial to implement effective allocation concealment strategies such as central randomization (by automated telephone or internet-based systems) or coded drug packs prepared by an independent pharmacy.[7] Allocation concealment is different from blinding. In RCTs, the term blinding refers to keeping study participants, health care providers, data collectors, outcome adjudicators, or data analysts unaware of the assigned treatment, to ensure that they are not influenced by such knowledge. As opposed to blinding, it is possible to conceal the randomization in every randomized trial, even in a trials comparing surgery with medical therapy. In contrast, blinding relates to what happens after randomization; it is not possible in all trials and seeks to reduce, between groups, differential use of effective cointerventions, reporting of events, encouragement during performance testing, and outcome assessment[6,8,9].

Even in a concealed and blinded RCT, a bias can be introduced by the post-randomization exclusion of certain patients (such as those who are noncompliant with study treatment), especially if the prognosis of those excluded from

Key Words

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one treatment group differs from that of those excluded from another. In order to keep the groups with similar prognosis throughout the trial, the intention-to-treat principle (i.e., all patients are analyzed in the groups to which they were randomized) should guide all analyses[6,8,9].

Another important methodological consideration is whether a trial is interrupted early due to an unexpected large treatment effect based upon a few events. Studies suggest there is substantial risk that such trials overestimate the treatment effect or may suggest an effect when, in fact, there is no effect. As such, trialists and readers of RCTs should beware of trials interrupted early due to benefit with few events[10].

Several publications have provided empirical evidence of the potential impact of methodological quality domains such as allocation concealment, blinding, intention-to-treat analysis, and trials interrupted early due to beneficial results of RCTs[5,6,8-11].

What interventions to test?

Surgery is the ultimate cardiovascular stress test, due to several factors such as surgical trauma, anesthesia and analgesia, intubation and extubation, pain, hypothermia, bleeding, anemia, and fasting[12-15]. These factors can initiate inflammatory, hypercoagulable, stress and hypoxic states, which are associated with perioperative elevations in troponin levels and arterial thrombosis, finally resulting in myocardial infarction (MI) and mortality[16-19]. These multiple triggers and states open the possibility for a variety of potential prophylactic interventions, such as beta-blockers, acetylsalicylic acid (ASA), calcium-channel blockers, alpha-adrenergic blockers, alpha-adrenergic agonists, and statins[2,20-23]. Non-pharmacological intervention such as adequate control of temperature, optimization of hemoglobin levels, type of anesthesia, and strict control of blood glucose levels are potential targets for prophylactic interventions[13-15,24]. Currently, the available evidence from systematic reviews and RCTs are not adequate in terms of validity and size to support the routine use of any of these interventions around the time of noncardiac surgery[23]. Thus, these interventions require testing *versus* placebo or in case of non-pharmacological treatment, against usual management.

What outcomes to measure?

Trials should focus on patient-important outcomes[25,26]. Trials should always measure all-cause mortality. Non-fatal major cardiovascular events such as MI, stroke and cardiac arrest are also relevant. Follow-up should be carried out for at least 30 postoperative days and perhaps even longer (i.e., 6-12 months)[21]. Currently, there are no standard diagnostic criteria for most of these events in patients undergoing noncardiac surgery. The criteria proposed by *Devereaux* for the *POISE Trial Investigators*[2,21] are shown in Table 1 and can be a useful guide for future perioperative trials. One potential advantage of using similar outcome definitions in different trials is to help combine their results in future systematic reviews with meta-analysis of RCTs[5].

Table 1 - Criteria for major perioperative cardiovascular events as proposed by *Devereaux for the POISE Trial Investigators* (Adapted from references 2, 21)

The diagnosis of **perioperative MI** requires any 1 of the following criteria:
• **Criterion 1:** A typical rise in the troponin level or a typical fall in an elevated troponin level detected at its peak after surgery in a patient without a documented alternative explanation for an elevated troponin level (e.g., pulmonary embolism); or a rapid rise and fall in CK-MB, only if troponin measurement is unavailable.* This criterion requires that 1 of the following criteria must also exist: • Ischemic signs or symptoms (e.g., chest, arm or jaw discomfort, shortness of breath, pulmonary edema) • Development of pathological Q waves on an ECG • ECG changes indicative of ischemia • Coronary artery intervention • New or presumed new cardiac wall-motion abnormality on echocardiography, or new or presumed new fixed defect on radionuclide imaging
• **Criterion 2:** Pathological findings of an acute or healing MI
• **Criterion 3:** Development of new pathological Q waves on an ECG if troponin levels were not obtained or were obtained at times that could have missed the clinical event
Cardiovascular death: Is defined as any death with a cardiovascular cause and includes those deaths following a cardiovascular procedure (e.g., percutaneous transluminal coronary angioplasty), cardiac arrest, MI, pulmonary embolus, stroke, hemorrhage, or deaths due to an unknown cause.
Non-cardiovascular death: Is defined as deaths due to a clearly documented non-cardiovascular cause (e.g., trauma, infection, malignancy).
Cardiac arrest: Is defined as a successful resuscitation from either documented or presumed ventricular fibrillation or sustained ventricular tachycardia or asystole.
Stroke: Is defined as the presence of a new focal neurological deficit thought to be vascular in origin, with signs and symptoms lasting more than 24 hours. It is strongly recommended (but not required) that an imaging procedure such as a CT scan or MRI be performed. Stroke will be further classified as definite ischemic, hemorrhagic or uncertain.

*Note: CK-MB - creatine kinase MB isoenzyme, ECG - electrocardiogram, CT - computed tomography, MRI - magnetic resonance imaging ; *Because CK-MB is both less sensitive and less specific in the perioperative setting when compared with other settings and with troponin levels, it should be used for diagnostic purposes only when troponin levels are not obtainable.*

Use of composite outcomes will enhance statistical power, but investigators should ascertain that the events similarly represent patient-important outcomes. Sometimes the components of composite outcomes are part of the same pathogenic mechanism (e.g., cardiovascular mortality, or non-fatal MI, or non-fatal stroke). In other RCTs, the individual components of the composite outcome may combine efficacy and safety measures (e.g., venous thromboembolism or major bleeding)[25].

Ideally, a blinded event-adjudication committee should evaluate the events, especially in a trial in which the participants, health care providers, or data collectors have not been blinded. The statistical analyses should use the decisions from the outcome adjudicators regarding the presence of events[26].

Reliable assessment of moderate treatment effects

Although there are a few striking examples of treatments for serious disease which really do work extremely well (i.e., the efficacy of penicillin, warfarin therapy in atrial fibrillation) most claims of large treatment effects turn out to be erroneous[27]. For most common serious diseases, all that clinicians can realistically expect are moderate treatment effects (i.e., relative risk reductions between 15 and 30%). A central reason for this is that most disease states are multifactorial in their etiology. Therefore, even when an intervention effectively blocks one or more pathogenic mechanisms, a number of unaffected pathogenic mechanisms will remain; thus, large treatment effects are improbable[11,28]. For a common and potentially fatal medical problem, if a simple, nontoxic, and widely practicable treatment can be shown to reliably reduce patient-important outcomes even if moderately, the potential benefit to the population would be substantial (tens of thousands of major events avoided or delayed each year)[11].

The only way to reliably study such moderate treatment effects is to obtain large amounts of information (which, in general, requires large numbers of patients and, especially, a large number of events). For instance, even by assuming a high rate of perioperative cardiovascular events of 10%, trials need at least 350, and ideally 650, events to convincingly demonstrate a 25% relative risk reduction (Table 2)[29].

Strategies to achieve a large number of patients and events

Easy and flexible inclusion criteria

Investigators can maximize event rates through selective enrollment of moderate and high-risk individuals. Examples of high-risk individuals are: patients with one or more manifestations of atherothrombotic disease (coronary heart disease, ischemic stroke, peripheral artery disease), elderly patients with multiple cardiovascular risk factors, and emergency surgeries. In order to ensure feasible, rapid and large recruitment rates, broad and simple entry criteria, similar to daily clinical practice are required[27]. Investigators can recruit these patients through multiple mechanisms including preoperative assessment clinics, cardiology clinics, internal medicine clinics, emergency rooms, and hospital wards (medical and surgical).

Table 2 - Estimated sample and event sizes in order to reliably detect a 25% relative risk reduction, considering a 10% control group event rate, and a two-tailed alpha of 5% (Adapted from *Yusuf et al*[29]).

Number of Events	Number of Patients	Statistical Power
0-50	< 500	10%
50-150	1.000	10-30%
150-300	3.000	30-70%
350-650	6.000	70-90%
> 650	10.000	>90%

Data collection

To make large-scale recruitment feasible, investigators should streamline trial procedures to impose almost no extra workload on participating clinicians, beyond that required to treat their patients. Case report forms (CRFs) should be brief, including only variables that are really relevant to clinical practice and vital to the trial management. Examples of essential data are center identification, patient identification (and how to keep track of them), confirmation of eligibility criteria, key baseline variables and concomitant interventions that could influence outcomes, the trial events, and compliance. Adverse event reporting should also be limited to critical issues (major and minor bleeding in the case of ASA, pulmonary edema, hypotension and bradycardia requiring treatment in case of beta-blockers, etc.)[11].

Trial conduct and management

The project office (coordinating center)

In a large multicentric trial, the project office is primarily responsible for the development of the trial protocol, the trial manual of operations, the CRFs, organization of the study logistics, development of the randomization scheme, the study database, data internal consistency checks, data analysis, coordination of the study centers, dispatching regular newsletters, and dealing with inquiries and questions that might arise from individual participating hospitals. As noted by Chen et al[11] the project office must be easy to contact, friendly, helpful, knowledgeable, reliable, and efficient. The trial team that works at the project office is usually composed by the principal investigators, the project manager, the trial statisticians, the data managers and data clerks, the trial pharmacists, and, sometimes a trial programmer[7,11,30].

Potential collaborative centers

To make a large trial feasible, a network of investigators and research sites are required. Collaborative centers can be identified in various ways, including from previous trials, from personal contacts of principal investigators, from scientific meetings, and from regional hospital directories[7]. Investigators could have different medical backgrounds such as cardiology, internal medicine, surgery (different specialties), and anesthesiology. If the trial design is simple and the data collection is "streamlined", then the study centers should include not only specialized or university hospitals, but also many relatively nonspecialized and non-university general hospitals. While specialists in university hospitals are more likely to have their own research agenda or be involved in other similar studies, nonspecialized general hospitals may have no other way of taking part in medical research, and being involved in large randomized trials organized by specialists in the field is often educational, thus making them very effective collaborators. Unless patient recruitment can be completed fairly rapidly, usually after one or two years, trial recruitment may fall off in some centers. It is, therefore, very important to keep collaborators motivated throughout the whole course of the trial. Newsletters should be prepared regularly. These newsletters can include recruitment

rates (total, per country, and per center), regular updates on study procedures, and recent evidence on the area of perioperative cardiovascular medicine. Additionally, hospitals that are recruiting exceptionally well should be acknowledged in various ways[11].

Investigators' meeting

Investigators' meetings can bring together potential collaborators to discuss and revise the trial protocol, to address frequently asked questions and practical concerns about the trial, and to help speed up or maintain recruitment. It would be sensible to organize national or regional meetings if there are a large number of widely dispersed centers. Linking trial meetings to other national conferences or special symposia to which collaborators are likely to be going anyway is another effective, and possibly cheaper, way to bring together the collaborators regularly[7,11].

Potential barriers for the conduct of important perioperative trials

The bureaucratization of the conduct of clinical trials has made the conduct and expense of large and important academic trials very challenging[7]. Extensive on-site monitoring processes, for example, were created in response to the rare instance of fraud, but have never been empirically shown to really reduce fraud or improve the reliability and methodological quality of trials. In fact, "data-intensive studies" may not only be wasteful, but might interfere by diverting efforts and financial resources from those aspects of the trial that really matter, such as methodological quality, adequate number of patients, and patient-important outcomes. A recent study by *Eisenstein et al*[31] simulated two scenarios regarding large clinical trials in acute coronary syndromes and heart failure. The results suggested that site-related expenses (including site management and payments) represented over 65% of total costs for both trials. Performing sensitivity analyses, the authors also concluded that total costs were reduced by 40% by simultaneously reducing CRFs pages, monitoring visits, and site-payment amounts but maintaining the numbers of patients and sites. These findings suggest that the most efficient way to reduce trial costs and still meet the trial's scientific objectives is to reduce unnecessary management complexity[31].

Trial publication

The success of any trial depends entirely on the wholehearted collaboration and coal-commitment of a large number of investigators, co-investigators, and research coordinators in several sites. For this reason, chief credit for the main study findings should be given not to the trial organizers, but to all those who have collaborated in the study. The final publication of the main results should be in the name of the whole collaborative group[11].

Conclusions and future directions

Current RCTs are too small to provide strong inferences regarding the impact of perioperative interventions on perioperative cardiovascular death, nonfatal myocardial infarction, or cardiac arrest in moderate and high-risk patients undergoing noncardiac surgery. The first large trial in this area, the POISE study, offers hope that a major shift in trial size in this area will occur. Interventions that should be tested using this model include, among others: ASA, calcium-channel blockers, alpha-adrenergic agonists, statins control of temperature, type of anesthesia, and hyperglycemia control. . These trials should include simple procedures with adequate methodology (concealed allocation, blinding, and intention-to-treat analysis). If such trials are large, and the results are both statistically reliable and medically convincing, they may well influence the management of many thousands, or even perhaps millions, of future patients undergoing noncardiac surgery. We hope that researchers interested in the prevention and treatment of major perioperative cardiovascular events find in this narrative review a stimulus to design, conduct, and participate in large trials in this exciting and developing area of knowledge.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

This study is not associated with any graduation program.

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