FAST BREAKING PAPERS - 2009

February 2009

PDF

Philip J. Devereaux talks with *ScienceWatch.com* and answers a few questions about this month's Fast Breaking Paper in the field of Clinical Medicine.

Article Title: Effects of extended-release metoprolol succinate inpatients undergoing non-cardiac surgery (POISE trial): a randomised controlled trial
Authors: Devereaux, PJ, et al.
Journal: LANCET
Volume: 371
Issue: 9627
Page: 1839-1847
Year: MAY-JUN 2008
* McMaster Univ, Fac Hlth Sci Clin Epidemiol & Biostat, Room 2C8,1200 Main St W, Hamilton, ON L8N 3Z5, Canada.
* McMaster Univ, Fac Hlth Sci Clin Epidemiol & Biostat, Hamilton, ON L8N 3Z5, Canada.
(addresses have been truncated)

SW: Why do you think your paper is highly cited?

During the last few decades, substantial advances in noncardiac surgery (i.e., all surgeries except surgeries performed directly on the heart) have improved disease treatment and patients' quality of life. As a result, the number of patients having noncardiac surgery is growing. Worldwide, over 200 million adults annually undergo major noncardiac surgery.

Noncardiac surgery is associated with major cardiovascular complications (i.e., death due to a cardiovascular cause, nonfatal heart attacks, nonfatal cardiac arrest, and nonfatal stroke). Worldwide, approximately 3-5.4 million adult patients annually suffer a major perioperative cardiovascular complication in the first 30 days after surgery. This is similar to the annual global incidence of new patients acquiring human immunodeficiency virus (HIV), and identifies major perioperative vascular complications as a similarly common major public health problem.

Despite the magnitude of this problem, this is a neglected area; there is not a single established effective and safe intervention to prevent major perioperative cardiovascular complications. The striking absence of prophylactic interventions reflects the paucity of large randomized controlled trials (RCTs) evaluating perioperative interventions.

Considering this background, there are several reasons why PeriOperative ISchemic Evaluation (POISE) is so highly cited. First, POISE is the world's largest randomized controlled trial ever undertaken to assess a potential prophylactic intervention to prevent major perioperative cardiovascular events. POISE evaluated a beta-blocker (a

commonly used drug to treat high blood pressure that also keeps a patient's heart rate down) versus a placebo in 8,351 patients in 190 centers in 23 countries.

Second, for 10 years, guideline committees have recommended giving a beta-blocker to patients undergoing noncardiac surgery based upon physiological arguments (e.g., keeping a patient's heart rate down may protect the heart) and two small randomized trials with substantial methodological limitations that included a total number of patients less than 5% of the number of patients included in POISE.

POISE challenges the appropriateness of the current guidelines, in that POISE demonstrated a perioperative beta-blocker decreases the risk of a heart attack around the time of surgery, but increases the risk of stroke and death. Third, these harmful consequences, unanticipated prior to POISE, highlight the importance and need for large randomized controlled trials in perioperative medicine.

SW: Does it describe a new discovery, methodology, or synthesis of knowledge?

POISE describes a new discovery in that, prior to POISE, it was unknown that starting a patient on a beta-blocker around the time of noncardiac surgery could increase a patient's risk of death or stroke.

SW: Would you summarize the significance of your paper in layman's terms?

POISE suggests that, for every 1,000 patients undergoing noncardiac surgery, a beta-blocker would prevent 15 patients from suffering a heart attack, but it would also result in an excess of eight deaths, with five patients suffering a stroke.

SW: How did you become involved in this research, and were there any problems along the way?

Initially, a small group of anesthesiologists, cardiologists, internists, and surgeons came together and decided to start investing ways to prevent major cardiovascular complications around the time of noncardiac surgery because this represents such a large population problem for which there was very limited research.

We encountered two primary problems in conducting this research. First, POISE almost did not happen because many physicians (primarily based upon the influence of the guidelines that advocated patients should get a beta-blocker around the time of surgery) felt it was unethical to not give a beta-blocker to a patient having surgery. We had to spend a lot of time giving talks and meeting with physicians around the world to review the reality of the perioperative beta-blocker data. We had to point out that the data was not definitive and that we needed a large RCT to ensure that a perioperative beta-blocker was beneficial and safe.

"When our methods of data monitoring detected these cases of fraud, the POISE Operations Committee, with the support of the Data Safety and Monitoring Committee (DSMB), the primary funder of POISE (the Canadian Institutes of Health Research [CIHR]), and the ethics committee at McMaster University decided to exclude all the patients associated with fraud."

Second, we discovered fraud in centers participating in Iran and also with a study coordinator who participated in Colombia. We employed three methods of data monitoring in POISE that included: 1. central data consistency checks that evaluated the consistency of center data as it was submitted; 2. statistical monitoring evaluating data across centers to see if any centers stood out; and 3. on-site monitoring.

When our methods of data monitoring detected these cases of fraud, the POISE Operations Committee, with the support of the Data Safety and Monitoring Committee (DSMB), the primary funder of POISE (the Canadian Institutes of Health Research [CIHR]), and the ethics committee at McMaster University decided to exclude all the patients associated with fraud.

SW: Where do you see your research leading in the future?

We are initiating the POISE-2 pilot and have submitted a grant to fund the main POISE-2 Trial. POISE-2 will build upon the results in POISE-1 in that we want to find a way to obtain the benefits we demonstrated with perioperative beta-blockers (i.e., reduction in heart attacks) but avoid the harms we demonstrated (i.e., increased risk of death and stroke). The negative effects demonstrated in POISE-1 appeared to have occurred through a perioperative beta-blocker causing significant low blood pressure around the time of surgery.

In POISE-2 we will evaluate a drug (i.e., clonidine, an alpha-2 agonist) that can help to keep a patient's heart rate down, similar to a beta-blocker but, based upon some research we have undertaken, may have less significant reductions in blood pressure. These physiological changes encourage us that clonidine around the time of noncardiac surgery may prevent heart attacks without increasing the risk of

stroke or death, but we will require a large randomized controlled trial to compare clonidine versus a placebo, in order to have confidence in the effect of this drug. In POISE-2, we will also study the effects of ASA (aspirin) versus placebo around the time of surgery.

Based on findings in POISE-1, we have also initiated the world's largest international prospective cohort study evaluating major cardiovascular complications around the time of noncardiac surgery. This study is called the VISION Study and will include 40,000 patients. We have recruited over 8,000 patients in the first 18 months and are on track to complete this study in the next two years. VISION is addressing many questions, including what proportion of heart attacks physicians may avoid missing around the time of surgery through monitoring of a simple and relatively inexpensive blood test, i.e., Troponin T (TnT).

SW: Do you foresee any social or political implications for your research?

POISE has another take-away message that goes beyond perioperative beta-blockers. Guidelines have recommended perioperative beta-blockers for over a decade. Even if only 10% of physicians acted on the guideline recommendations throughout the last decade (several studies suggest that 30% of physicians prescribed a perioperative beta-blocker to their at-risk patients), 100 million patients would have received a beta-blocker around the time of surgery.

If the results of POISE are widely applicable, throughout the last decade 800,000 patients would have died prematurely and 500,000 patients would have suffered a stroke because they were given a beta-blocker around the time of surgery. This highlights the risk in assuming a perioperative beta-blocker regimen has benefit without substantial harm, the importance and need for large randomized trials in the surgical setting, and the risk in guidelines making recommendations based upon weak evidence.

P. J. Devereaux, M.D., Ph.D.
Assistant Professor
Department of Clinical Epidemiology and Biostatistics
Joint Member, Department of Medicine (Cardiology)
McMaster University
Ontario, Canada

KEYWORDS: PERIOPERATIVE BETA-BLOCKADE; ACUTE MYOCARDIAL-INFARCTION; HIGH-RISK PATIENTS; VASCULAR-SURGERY; MULTICENTER TRIAL; CLINICAL-TRIALS; CARDIAC EVENTS; ISCHEMIA; PLACEBO; MORTALITY.

PDF

back to top

2009 : February 2009 - Fast Breaking Papers : Philip J. Devereaux

Scientific Home | About Scientific | Site Search | Site Map