Author's response to reviews

Title: Composite versus conventional coronary artery bypass grafting strategy for
the anterolateral territory: study protocol for a randomized controlled trial

Authors:

Ariane Drouin (ariane.drouin@umontreal.ca)
Nicolas Noiseux (noiseuxn@videotron.ca)
Carl Chartrand-Lefebvre (carl.chartrand-lefebvre@umontreal.ca)
Gilles Soulez (gilles.soulez@umontreal.ca)
Samer Mansour (s.mansour@umontreal.ca)
Jan-Alexis Tremblay (jan-alexis.tremblay@umontreal.ca)
Fadi Basile (fadi.basile.chum@ssss.gouv.qc.ca)
Ignacio Prieto (ignacio.prieto.chum@ssss.gouv.qc.ca)
Louis-Mathieu Stevens (lm.stevens@umontreal.ca)

Version: 3 Date: 8 August 2013

Author's response to reviews: see over
Montreal, August 7th 2013

Doug Altman, Ph.D.
Curt Furberg M.D., Ph.D.
Jeremy Grimshaw, M.B.Ch.B., Ph.D.
Peter Rothwell, M.D., Ph.D.
Editors-in-Chief Trials
236 Gray's Inn Road
London WC1X 8HB, United Kingdom

Dear Drs. Altman, Furberg, Grimshaw and Rothwell,

The authors thank you and the reviewer for the thoughtful and detailed analysis of our manuscript entitled: Composite versus conventional coronary artery bypass grafting strategy for the anterolateral territory: study protocol for a randomized controlled trial. The article underwent a complete revision taking into account the suggestions. I hope you will find this revision acceptable for publication. We also believe that randomized clinical trials in surgery should be encouraged. This clinical trial presents an innovative alternative to conventional coronary artery bypass graft surgery.

In the following document, each suggestion of the reviewers was answered point-by-point as per the attached Responses to Comments of Reviewers. Also enclosed is the modified manuscript.

I trust you will find everything to be satisfactory; we remain,

With thanks,

Louis-Mathieu Stevens, M.D., Ph.D.
Department of Surgery, Division of Cardiac Surgery
Centre hospitalier de l’Université de Montréal, Hôtel-Dieu Hospital
Phone: 514-890-8131 Fax: 514-412-7231
Email: lm.stevens@umontreal.ca
RESPONSES TO REVIEWER’S COMMENTS

Comment: The first sentence of the abstract should be modified, as it suggests definite evidence on which patients do profit from CABG looking at mortality as an outcome. Also please include a paragraph drawing attention to the controversial issues in both management strategies (re-vascularisation or a conservative approach with drugs) in the BACKGROUND of the manuscript. Keep in mind that of 7 randomized trials conducted 2 decades ago, only 1 found a statistically significant difference in mortality! In addition to that, the advance of medical therapy in ischemic heart disease and heart failure should be discussed.

Response: A 1994 meta-analysis of 7 studies that randomized a total of 2649 patients to medical therapy or CABG showed that CABG offered a survival advantage over medical therapy for patients with left main or 3-vessel disease (Yusuf S et al, *Lancet* 1994). The studies also established that CABG is more effective than medical therapy at relieving angina symptoms. During the past decade, the MASS II trial of patients with multivessel coronary artery disease showed that CABG patients were less likely than those treated with medical therapy to have subsequent MI, need additional revascularisation, or experience cardiac death in the 10 years after randomization (Hueb W. et al., *Circulation* 2010). Advances in medical therapy in ischemic heart disease and heart failure have improved the outcomes of the patients with coronary artery disease undergoing or not coronary revascularisation. In BARI 2D trial of patients with diabetes mellitus, no significant difference of mortality in the cohort of patients randomized to optimal medical therapy plus CABG versus optimal medical therapy alone, but the study was not powered for this endpoint and the study excluded patients with left-main disease and included
few patients with proximal left anterior descending coronary or left ventricular ejection fraction > 50% (Frye RL et al. N Engl J Med 2009). The ISCHEMIA trial is currently underway to determine the best way to manage patients with stable ischemic heart disease. The first sentence of the abstract was modified and the first paragraph of the background was modified to expose the advances with medical therapy and the controversial issues in management strategies.

Comment: Please prospectively include risks scores (at baseline) and the measurement of NT-proBNP in order to be able to better describe your patient population.

Response: Both the STS score and EUROscore II have been prospectively calculated for all patients participating in this trial. Pre-specified sub-analyses will be performed to assess if there is any heterogeneity in the trial’s results among patients with different level of risk. A sentence was added in the text to explicit this point.

The amino terminal pro B-type natriuretic peptide (NT-proBNP) is used as an aid in the diagnosis and assessment of severity of congestive heart failure. It is also used for the risk stratification of patients with acute coronary syndromes (Bibbins-Domingo K et al., JAMA 2007; Fitzgerald RL et al., Am. Heart J. 2005). NT-proBNP levels predict clinical events in primary care patients at risk with hypertension, diabetes, clinically suspected heart failure (HF), history of coronary artery disease or myocardial infarction (Adlbrecht C et al. Eur J Prev Cardiol. 2012). In our institution, NT-proBNP is measured and followed in patients with severe congestive heart failure, but it is not measured in patients with coronary artery disease without congestive heart failure. It would have been interesting to assess the prognostic value of the NT-proBNP in this trial including patients with no severe congestive heart failure and left ventricular ejection
fraction > 30% (see trial’s exclusion criteria). However, since 49 patients are already enrolled in the trial since July 2012, we do not believe that it is warranted to add this laboratory value for the other patients. NT-proBNP may be more useful in trials dealing with patients with severe congestive failure, such as the STITCH trail.

**Comment:** What is your SOP concerning anti-platelet therapy (ASS, Prasugrel, Ticagrelor)? Please include a statement on this in your METHODS.

**Response:** Our standards of procedures concerning anti-platelet therapy (aspirin, prasugrel and ticagrelor) are now specified in the text. For all patients, aspirin therapy is not stopped before surgery. In stable patients, clopidogrel and ticagrelor are stopped 5 days preoperatively and prasugrel is stopped 7 days preoperatively. In patients with unstable angina not responding to medical treatment, surgery can be performed earlier, accepting a higher risk of bleeding. Type of antiplatelet agent used preoperatively and postoperatively as well as the time of antiplatelet agent discontinuation is prospectively collected in the patient CRF.

**Comment:** You state that the lower risk of stroke may be an advantage of your technique. As you do perform CT scans on your patients for evaluation of the anastomoses, why not include a cranial CT to increase sensitivity to detect strokes (which may be clinically inapparent)?

**Response:** This is a very interesting comment. Unfortunately, some of the potential advantages of the composite strategy cannot be assessed in this trial as all patients undergo surgery using cardiopulmonary bypass (on-pump). One of the potential advantages of the new technique is to
be able to perform the surgery on the beating heart (off-pump) without having to mobilize or clamp the ascending aorta (“no touch” technique) if the patient only require coronary artery bypass grafts on the anterolateral territory (or with an additional graft using an in situ right internal mammary artery). It is believed that most strokes occurring after cardiac surgery are caused by manipulations on the ascending aorta (canulation and clamping). Therefore, we believe there will be no difference in the incidence of stroke between the two groups since the manipulations required on the ascending aorta for cardiopulmonary bypass are the same. The incidence of stroke is prospectively collected in the patient CRF but does not constitute one of the trial’s endpoint. In this trial, most patients undergo an epiaortic ultrasound before aortic canulation to assess the grade of atherosclerotic disease. In patients with severe aortic atherosclerotic disease, the patients are not randomized in the trial and the surgery is performed on a beating heart. This point was clarified in the METHODS section.

Comment: You state that your technique is easier to perform. If this also means faster, it should be stated in the protocol to prospectively assess the operative time.

Response: The new technique is surgically less challenging, but the operative time is about the same for both strategies, especially if the surgery is performed with cardiopulmonary bypass in both groups. Cardiopulmonary bypass, cross-clamp and operative times are prospectively recorded in the patient CRF and these times will be compared between groups. The text was modified to clarify this point.

Comment: The use of an online randomization system is preferred to randomization with envelopes.
Response: We agree that an online randomization system is preferable in the setting of a multi-institutional trial. However, for this single centre trial, we believe that a randomization performed using an opaque sealed envelope drew by the research coordinator does not affect the trial quality because this person is in no instance involved in surgical decisions. All envelopes were prepared before the first patient was randomized for the trial. Sets of envelopes in block of 4, 6 or 8 were prepared for each surgeon.

Comment: Editorial requests: 1) Please ensure the title conforms to journal style for study protocol articles. The title should follow the format ?__________: study protocol for a randomized controlled trial.? 

Response: The manuscript was modified as requested to “Composite versus conventional coronary artery bypass grafting strategy for the anterolateral territory: study protocol for a randomized controlled trial”. The “Running Head” (AMI-PONT trial) was kept but could be removed if it does not conform with The Journal style.