clinicians believe in the beneficial effects of clopidogrel, the increased risk of bleeding and the lack of data in CABG patients make it impossible to establish definitive recommendations. We therefore propose the Clopidogrel after Surgery for Coronary Artery Disease (CASCADE) study, a randomized, placebo-controlled trial comparing clopidogrel plus aspirin versus aspirin alone in CABG patients revascularized with saphenous vein. The primary aim of this study will be to evaluate the effect of combined antiplatelet therapy on the reduction of SVG intimal hyperplasia one year after CABG, through the assessment of intimal area by intravascular ultrasound (IVUS). Secondary aims will evaluate the safety of clopidogrel administration following CABG with regards to bleeding complications. We hypothesize that the combination of clopidogrel with aspirin will reduce the SVG intimal hyperplasia (intimal area) by 20% one year post-CABG compared to the usual antiplatelet therapy of aspirin alone.

Methods

Study Population and Recruitment Procedure

The study population will include all patients undergoing multi-vessel elective or urgent CABG using at least two saphenous vein grafts at the University of Ottawa Heart Institute (OHI) over the study period (see Table 1 for inclusion and exclusion criteria). Patients undergoing off-pump CABG (OPCAB) will also be eligible for this study, as long as at least two saphenous vein grafts are used. OPCAB is performed in order to avoid the hazards associated with standard CABG, such as cardiopulmonary bypass and aortic cross-clamping, and is carried out at the discretion of the surgeon in patients deemed to be at higher risk of thromboembolic or renal complications during surgery. All CABG patients at the OHI will be triaged pre-operatively, and study eligible patients will be selected and approached by the study nurse to explain the trial and obtain consent.

Description of Intervention and Control

A prospective randomized double-blinded placebo-controlled study will be conducted from November 2005 to November 2007 in order to achieve the study objectives. Patients will be recruited over the first 12 months of the study, and graft evaluation for each patient will occur over the following 12 months (one year after surgery for each patient). Patients will be randomized into an experimental group (receiving clopidogrel) or a control group (placebo). The placebo and clopidogrel medications will be prepared by the Bristol Myers-squibb Sanofi Canada Partnership and appear identical. Medication administration and data collection will be performed in a double-blind manner, such that neither the patient nor the healthcare personnel will be aware of the medication assignment. Recruitment and written consent will be performed prior to surgery. However, patients will not be randomized until after surgery has been completed and clinical stability ensured. Patients that are bleeding excessively after surgery (chest tube output > 200 cc/hr) or those requiring high levels of hemodynamic support (more than 2 inotropes and/or intra-aortic balloon pump) will not be randomized into the study.

After surgery, the study medication will be administered via nasogastric tube when the chest tube drainage has decreased to ≤50 cc/hr for 2 hours. Each patient will receive either clopidogrel 75 mg or placebo, in addition to enteric coated aspirin 162 mg (Figure 1). The study drug and aspirin 162 mg will be repeated orally in the same dose once daily for the duration of one year. Because post-CABG patients are relatively aspirin resistant following surgery, the aspirin dose of 162 mg will ensure adequate platelet inhibition in those patients randomized to aspirin alone. Furthermore, 162 mg falls within the safety window of combining aspirin with clopidogrel [30,40,44].

Allocation Procedure

A stratified random design allocation will be utilized to account for the presence or absence of diabetes, as well as the use or nonuse of cardiopulmonary bypass (standard CABG versus OPCAB). A block randomization technique will ensure an equal distribution of diabetic patients in both arms of the trial and an equal distribution of OPCAB patients. The randomization schedule will be generated using SAS 9.1 software (SAS, Cary, NC). All patients and study personnel will be blinded to the treatment assignment, which will be performed by the hospital pharmacy.

Concomitant Medication and Treatments

Patients will receive concomitant therapies in both groups as recommended by the current American College of Cardiology / American Heart Association guidelines. This will include smoking cessation counseling and the administration of aspirin, beta blockers, angiotensin converting enzyme inhibitors, and lipid lowering medications. Target LDL values will be those recommended as per current guidelines [45-47] and will be assessed during the study follow-up period. Routine peptic ulcer prophylaxis will not be administered in order to fully evaluate gastrointestinal side effects.

Diabetic patients will be eligible for enrollment in this study, regardless of their preoperative need for insulin therapy, and will be allocated equally into both groups through stratified randomization. Diabetic patients will have aggressive perioperative glycemic control, including an intravenous insulin infusion both in the operating room and in the intensive care unit, and a subcutaneous insulin sliding scale while recovering on the surgical ward.