may be repeated if the first set of pullback images were judged suboptimal in quality.

IVUS Analysis

The IVUS images will be sent to an independent core laboratory and interpreted by an experienced cardiologist blinded to treatment allocation. The methods for the analysis have been previously reported and validated [49]. Briefly, using the aorto-ostial anastomosis as a landmark, the most proximal 40 mm of vein graft will be analyzed. The video images will be digitized and measurements of lumen, intimal hyperplasia, and external elastic lamina areas will be available for each digitized cross section. Intimal hyperplasia volumes will be computed by multiplying the corresponding areas of each of the cross-sections by the distance between slices and by adding the products. For the purpose of this study, the mean plaque area per patient for the 40 mm-analyzed segment will be used for comparison between treatment groups.

Sample Size

The trial will be powered to test the hypothesis that clopidogrel and aspirin should reduce vein graft intimal hyperplasia by 20% compared to aspirin alone at one year following bypass surgery. According to Hozumi et al., at one year, the mean intimal area of angiographically normal saphenous vein grafts is 5.26 mm^2, with a standard deviation of 1.38 mm^2 [50]. Intravascular ultrasound imaging will be performed at follow-up in one vein graft per patient. In order to account for potential angiographic refusals and study withdrawals, approximately 100 patients in total will be required to test the null hypothesis with an α value of 0.05 and a power of 0.90.

Data Collection and Safety Monitoring

Intimal area will be recorded at the time of IVUS one year after CABG. Vein graft patency and stenosis will be assessed by angiography. The incidence of major adverse coronary events and bleeding complications will be documented during postoperative clinic visits at one month, six months and twelve months after surgery. Telephone home assessments every three months will also be used to document events. All serious adverse events will be reported to the ethics committee. The development of serious adverse events that might be attributable to clopidogrel will lead to the termination of the study drug.

Ethics

The study will adhere to the highest research ethics standards of the OHI. This protocol follows the CONSORT guidelines [51] and was approved on July 19, 2005 by the University of Ottawa Heart Institute Human Research Ethics Board.

Statistical Analysis

Vein graft intimal area, the primary outcome of the study, will be compared between the two randomization groups using two-sided Student's t tests. Vein graft patency will be compared using a Fisher's exact test. With respect to the secondary outcomes, continuous data will be compared between the two groups using two-sided Student's t tests, two-sample Wilcoxon rank-sum tests, or ANOVA as appropriate, and a Fisher's exact test will be used for categorical data. In order to assess possible interactions between patient characteristics (such as diabetes) and treatment outcomes, an exploratory analysis using multivariate linear regression will be performed. In the improbable event that all vein grafts are occluded and IVUS cannot be performed in a particular patient undergoing the one-year study, a value of five times the mean intimal area (decided *a priori*) will be assigned for that patient.

Discussion

The CASCADE study is a novel randomized double-blind placebo-controlled trial that will help clarify the controversial issue of antiplatelet therapy following CABG surgery. Specifically, it will answer the questions of whether the addition of clopidogrel to aspirin is safe following cardiac surgery and whether it reduces saphenous vein graft intimal hyperplasia. Although subgroup analyses of previous trials have suggested a benefit of clopidogrel in cardiac surgery patients [39,42,43], no trial to date has specifically focused on the clinical or angiographic outcomes in patients treated with clopidogrel therapy immediately after surgical revascularization. Should the combination of clopidogrel and aspirin reduce the process of vein graft intimal hyperplasia, the CASCADE trial has the potential to redefine modern antiplatelet management of coronary artery bypass patients.

We believe that the strengths of this study are its randomized and blinded design. Patients will be randomized into two treatment groups, and graft selection for IVUS imaging will be randomized within each patient. Blinding will occur for all patients and health care providers, and the IVUS and angiogram images will be interpreted by an external blinded core laboratory. While the process of intimal hyperplasia may be reduced in the trial, the study will not be powered to demonstrate a difference in angiographic patency or freedom from coronary events following CABG. In order to demonstrate a difference in either of these outcomes, a considerably larger sample size and longer follow-up period would be required.

The results of this randomized trial will be generalizable to all patients undergoing standard CABG or OPCAB surgery with saphenous vein. Although the trial enrolment is limited to lower risk patients, it is anticipated that the results will also be applicable to higher risk patients with