A Non-blinded, Randomized Trial Evaluating the Effectiveness of PCI with Drug-eluting Stent Implantation versus CABG

David Park

A. Study Purpose and Rationale

Significant left main coronary artery disease carries grim prognosis. When treated with medical therapy alone, mortality rates at one year and three years are 21% and 50%, respectively. Current recommendations for unprotected left main disease or left main equivalent disease is coronary artery bypass graft surgery (CABG). The success of percutaneous intervention (PCI)-angioplasty was limited by unacceptably high rates of acute thrombosis and restenosis. However, with the development of drug-eluting stents, anti-platelet agents, and improved technique, percutaneous intervention of critical lesions is becoming an ever-closer reality. Here, we propose the use of drug eluting-stents in comparison with CABG for the treatment of left main coronary artery stenosis.

B. Study Design and Statistical Analysis

A two-arm, non-blinded, randomized clinical trial evaluating the effectiveness of PCI with drug-eluting stent implantation compared to the existing standard of care, CABG, for the treatment of left main coronary artery disease. The study team will be composed of interventional cardiologists, cardiothoracic surgeons, and neurologists at 6 participating cardiac centers.

The primary objective is to assess the effectiveness of PCI with drug-eluting stents compared to CABG in preventing a composite of all-cause mortality, nonfatal myocardial infarction, or target lesion revascularization in 2000 subjects over a 2-year trial duration. Secondary outcome will include: i) quality of life at 30 days, 6 months, 1 and 2 years post-procedure; ii) neurocognitive function at 30 days, 1 and 2 years post-procedure; iii) cost-effectiveness analyses including: cost of initial procedure, hospital length of stay, resource utilization, repeat hospitalizations, and repeat revascularization events annually for 2 years post-procedure in each randomized subject.

The proposed sample size provides 80% power to detect realistic differences between the two arms, with $P = 0.05$, using Kaplan-Meier survival curves truncated at the end of the 2 year follow-up period. Randomization will be performed using standard methods to ensure equal allocation to the two treatment groups. Cross-overs will be defined as receiving the alternative therapy within the randomization period. Any subsequent revascularization attempt will be analyzed in the primary endpoint.

All clinical end-point data will be analyzed using the intention to treat principle. The primary composite endpoint will be displayed as survival curves of time to first event from the point of randomization. Survival characteristics of the two groups will be analyzed using the Kaplan-Meier method. In the event of uneven distribution of potential confounding variables, Cox proportional hazards regression will be used to adjust treatment effect to covariates. Normally distributed variables will be expressed as mean and will be compared using the unpaired Student t test. Chi^2 test will be used to compare proportions. All statistical tests will be two tailed. Discrete variables will be expressed as percentages and compared in terms of odds ratio (OR) for stented lesions vs CABG, including 95% confidence intervals calculated by Chi^2 and Fisher's exact test. Statistical significance will be defined as $p<0.05$.

C. Study Procedure

At the time of angiography, the films will be reviewed by an interventional cardiologist and cardiothoracic surgeon to verify that the patient has left main disease >70% and is a candidate for either study procedure. Eligibility will be assessed based on the inclusion/exclusion criteria. Once informed consent is signed, the patient will be randomized. Upon randomization to PCI/stent or CABG, the intervention must be completed within 48hrs.

PCI/stent: Strict adherence to practice guidelines is required for maximal benefit of the PCI/stent procedure. Adjunctive therapy with oral aspirin and clopidogrel should be initiated pre-procedure and continued for a minimum of 1-year. During cardiac catheterization, the patient will be subjected to unfractionated heparin in combination with the GPIIb/IIIa inhibitor, abciximab. The patient should continue with standard post-myocardial infarction medical therapy, including a statin, ACE inhibitor, beta blocker, and aspirin. The treatment goal for patients undergoing PCI/stent is an angiographic objective of <20% residual stenosis and TIMI 3 distal flow.

CABG: Once randomized to CABG, several technical recommendations should be applied. The internal mammary artery (IMA) to the left anterior descending (LAD) is highly recommended in all patients. Another recommendation is epiaortic analysis of the ascending thoracic aorta to rule out ascending aorta atherosclerotic lesions. If epiaortic lesions are noted, an off-pump approach is preferred to minimize neurocognitive deficits. As in PCI/stent, appropriate medical therapy is critical for maximal benefit.

D. Medical Device

Drug-eluting stents (DES) are among the newest arsenals employed by interventional cardiologists to counter in-stent restenosis. One such FDA-approved DES uses rapamycin, which indirectly inhibits the cell cycle. The clinical effect is inhibition of neointimal hyperplasia by suppressing vascular smooth muscle cell proliferation and migration. The SIRIUS study was a randomized, double-blinded phase III clinical trial comparing rapamycin-coated versus uncoated stents. The results for in-stent restenosis in coated vs uncoated stents were 3.2% vs. 35.4% respectively; $p<0.001$.

E. Study Questionnaire

Standard quality of life questionnaires will be implemented detailing the patients' perception of their over-all health and functional status before and after therapy. Immediate (30 days), intermediate (6 months), and long-term (1&2 years) quality of life assessments will be made.

a. Neurocognitive testing

A serious and common complication of CABG is post-operative cognitive dystfunction POCD). This condition is thought to be a consequence of atherosclerotic showering from aortic manipulation during surgery. A well-described neurocognitive battery will be used to assess praxis, memory, attention, executive functions, verbal function, and reading ability. This battery will be performed at preset time points to compare subtle differences in neurocognitive function between the two interventions.

F. Study Subjects

The study population will consist of patients demonstrating the following characteristics: typical angina pectoris and documented myocardial ischemia and newly diagnosed left main artery stenosis (a reduction of luminal diameter of > 70%). Exclusion criteria are myocardial infarction within 6 months, prior CABG, prior stent, previous stroke within 6 months, contraindication to anticoagulation and/or antiplatelet therapy, and anatomical contraindications (ostial lesions, major branch points at the target lesion, total occlusion, or severe tortuosity). Once enrolled and randomized, comparisons between the two study populations will be examined to ensure equal distribution of covariates including age, sex, race,

presence of diabetes, heart disease, congestive heart failure, peripheral vascular disease, dementia, chronic renal insufficiency, and other comorbid conditions. The patients will then compared to a national registry to applicability of the study to the general population.

G. Recruitment of Subjects

Subject recruitment will be conducted at the six participating clinical centers and affiliate hospitals. Invitations to the study will be disseminated to cardiologists with inclusion criteria defined. At the discretion of the primary care physician and cardiologist, the patient can enroll in the study at a participating center. Pregnant women and children will be excluded from the study for safety concerns. All participating centers will undergo cultural sensitivity training, provide day care, and be available on weekends to ensure compliance and improve yield.

H. Confidentiality of Study Data

Patient confidentiality will be in strict adherence with HIPA regulations. All patient information will under password restriction or in locked cabinets and rooms. All patient information will be recorded in the patients' medical records and treated as such.

I. Potential Conflict of Interest

As both investigational arms of the study have opposing goals of therapy, this study is safe guarded against potential conflict of interest. All cases must be reviewed by both an interventional cardiologist and a cardiothoracic surgeon at all time points during the trial.

a. Potential Risks

i. PCI with DES implantation

Stents are permanent foreign bodies implanted intra-arterially. Early, rare complications of stent implantation are thrombosis, stent migration, embolization, and arterial dissection/rupture. Stent thrombosis has been characterized and effective strategies for minimizing this complication are well documented. Proper technique by an experienced operator and treatment with anti-platelet medication have been shown to decrease the incidence of thrombosis. Stents that have migrated or embolized can be retrieved with endovascular snares.

ii. CABG Surgery Risks

Coronary artery bypass surgery is the revascularization strategy of choice in left main coronary artery disease. In most patients, 30-day risk of death, MI, and stroke should not exceed 5-7%. Other well-documented post-operative risks include bleeding requiring transfusion, reoperation, wound infection, and pulmonary embolization.

b. Potential Benefits

Currently, CABG remains the treatment of choice for revascularization of left main coronary artery disease. Early studies with drug eluting stents demonstrate excellent preliminary data in in-stent restenosis studies. If left main stenting proves a viable alternative to CABG, patients would avoid general anesthesia, sternotomy, and other post-operative complications.

J. Radiation or Radioactive Substances

Patients undergoing percutaneous coronary intervention will be subjected to radiation requiring approval the Joint Radiation Safety Committee (JRSC).