Long-term outcome of Sirolimus-eluting versus Uncoated Stents in Small Coronary Arteries: A Multicenter Randomized Trial.

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A. Study Purpose and Rationale

Drug eluting stents (DES) have dramatically changed the practice of interventional cardiology mostly on the basis of clinical trials showing substantial reduction in angiographic and clinical restenosis compared to bare metal stents (BMS). DES cost nearly 3-4 times as much as BMS, but the benefit of reduced need for target vessel revascularization has largely driven the adoption of DES as the device of choice [1]. Of the 1.5 million stents deployed annually, DES make up more than 85%, generating $6 billion a year in sales and thousands of dollars of fees for each procedure performed by the interventional cardiologists implanting them [2]. Recently, however, the true clinical benefit for DES has been called into question. In a critical evaluation of DES, Tung et al found that a substantial portion of target vessel revascularization, the main indication of its use, occurred due to protocol-mandated angiography bias—meaning many BMS treated vessels were revascularized base on angiographical evidence of restenosis alone.

Surrogate outcomes, such as angiographical restenosis or late luminal loss, have failed to consistently translate into clinical benefit [1]. Unlike restenosis, however, stent thrombosis is a potentially life-threatening complication of coronary stents as nearly half of patients presenting with stent thrombosis result in death. Despite the theoretical concern of increased risk of stent thrombosis due to delayed endothelialization in DES, clinical trials have shown similar rates of stent thrombosis of 0.4-0.6% in both groups of stents after 1 year. However, the rate of stent thrombosis in "real world" registries may in fact be 2-3 times higher [3] and some studies have shown a non-significant trend toward increased risk in DES [5]. Most recent meta-analysis data show that while the stent thrombosis rate wanes with time in BMS, it continues to occur at a rate of 0.6% per year in DES for a cumulative rate of 2.9% at 3 years [6]. Whether or not this translates in to increased overall mortality or myocardial infarction is not currently known although preliminary data from ongoing long-term follow up studies show a trend toward increased risk of these hard clinical end points [4].

On September 14, 2006, the FDA issued an alert, stating that recent data suggests "a small but significant increase in the rate of death and myocardial infarction possibly due to stent thrombosis in patients treated with DES." However, due to lack of definitive evidence, FDA maintained that DES remains safe and effective for the currently approved indications for use. However, already some clinicians are recommending limiting DES to selective patients at high risk for restenosis.

One such group of patients is those who require stenting of small coronary arteries. In a secondary analysis of the RAVEL trial, which randomized 238 patients to either sirolimus-eluting stent or bare metal stent in elective PCI, the rate of restenosis at 6 months was inversely proportional to the reference vessel diameter [7]. In the SES-SMART study, again sirolimus-eluting stents were compared to uncoated stents in 257 patients who underwent stenting of small coronary vessels 2.75mm or less in diameter. The results of this trial showed not only a reduction in restenosis rate in the sirolimus stent group as expected, but also a statistically significant reduction in rate of myocardial infarction (7.8% vs 1.6% in Sirolimus group, p=0.04), which was a prespecified secondary end-point [8]. There was also a statistically significant reduction in the combined all-cause mortality and MI in the sirolimus stent group. It is difficult to explain why sirolimus-eluting stents would decrease the rate of myocardial infarction since the mechanisms of restenosis and thrombosis are different. Also, given the increased risk of stent thrombosis in DES long-term, it is not clear whether this potential benefit is sustained over many years. A large randomized comparison of sirolimus-eluting stent and uncoated stent with long-term follow up is

required to truly determine the efficacy of the sirolimus stent in reducing the combined end-point of all cause mortality and myocardial infarction in this subgroup of patients.

B. Study Design and Statistical Analysis

This study is a multi-center, randomized trial to test the hypothesis that the implantation of sirolimus-eluting stent in small coronary arteries (defined as reference vessel diameter of < 2.75 mm) is associated with a reduced 5 year combined mortality and myocardial infarction in comparison with the implantation of uncoated stent. There will be two study groups, one receiving sirolimus-eluting and one receiving an uncoated stent of visually and angiographically identical architecture. The primary outcome will be the percentage of patients in either group reaching a composite endpoint of all-cause mortality and myocardial infarction over 5 years. Secondary outcomes will include all-cause mortality, cardiovascular mortality, myocardial infarction, stent thrombosis, and clinically driven target vessel revascularization (PCI or CABG). No follow up angiographic evaluation will be required.

There is limited data on long term outcome of patients treated with drug eluting stents. Based on unpublished data from the RAVEL study at 5 year follow up [4] a primary event rate of 11% can be reasonably expected over 5 years in the uncoated stent group. The effect of sirolimus-eluting stent on the primary outcome is not likely to be as high as that seen in the relatively small SES-SMART trial, given that the relative risk reduction in MI alone was 79% [8]. Rather, this study will be powered to detect a difference in 20% in the rates of the primary outcome as this will provide a good indication of clinical significance as well as a manageable enrollment number.

Since the primary outcome is a categorical variable, power was calculated for a chi-squared test. With an expected event rate of 11% in the uncoated stent group and a relative risk reduction of 20% in the sirolimus stent group, the study will need to enroll 2983 patients in each group to have a two-sided alpha error of 0.05 and beta error of 0.20.

A high-volume cardiac catheterization center could be expected to enroll 400 patients over a period of 2 years, so there will be 15 involved sites. Patients will be randomized by means of sealed randomization envelopes supplied to each clinical center from the study coordinating center. Randomization will be done by site and treatment group in blocks of ten, ensuring a 1:1 ratio of assigned treatments. Operators (including treating physicians and study investigators) and patients will be blinded to treatment assignments.

An independent data safety monitoring board will evaluate study data after two years from the date of first patient enrollment. Study will be discontinued if a statistically significant difference with p value of less than 0.01 in the primary outcome is observed between the two treatment groups.

C. Study Procedure

Prior to randomization, a study investigator will meet with each patient to obtain written consent. Patients will be given ASA, clopidogrel, and heparin in accordance with currently accepted standard of care. The use of glycoprotein IIb/IIIa receptor antagonists will be at the discretion of the investigator. Online quantitative coronary angiography confirming vessel diameter will be performed before randomization. Stent implantation will follow the standard interventional techniques. Patients will be followed at 30 days and then yearly for evaluation to monitor the interim development of primary and secondary end points. The decision to perform repeat angiography was at the discretion of the blinded investigator.

D. Study Drugs

Not applicable.

E. Medical Device

The sirolimus-eluting stents (Cypher balloon-expandable stent; Cordis, Miami Lakes, Fla) has a 5 micrometer coating consisting of a blend of 33% sirolimus and 67% non-erodable polymer. The drug-polymer matrix contains 140 microgram sirolimus per cm-squared surface area. A drug-free polymer layer on top of the drug-polymer matrix serves as a diffusion barrier to prolong drug release; around 80% of sirolimus is released within 30 days of implantation. The bare-metal control stent will be of identical visual and radiographical architecture (BxSonic balloon-expandable stent; Cordis). The diameters for both types of stents are 2.25, 2.50, and 2.75 mm, and lengths are 8, 13, 18, 23, 28, and 33 mm.

Both stents are commercially available and widely used. The safety and efficacy of each stent has been well documented in previous clinical trials and will not be elaborated upon here.

F. Study Questionnaires

Not applicable.

G. Study Subjects

Study patients must be aged 18 years or older undergoing percutaneous coronary intervention regardless of indication. Patients must have a single, previously untreated 50% to 99% target lesion in a native coronary artery 2.75mm in diameter or less. If a patient has a multi-vessel disease, the other lesions must be greater than 2.75mm in diameter and in a different coronary vessel. Stenting of all non-randomized lesions will be performed with an uncoated stent.

Exclusion criteria were severe calcifications or thrombus containing lesions, intervention on restenotic lesion, and known allergies to ASA, clopidogrel, heparin, contrast agents, or sirolimus.

H. Recruitment of Subjects

Subjects will be recruited at 15 high-volume cardiac catheterization centers. Subjects will be identified by their interventional cardiologists and referred to the study. A study investigator will then meet with each patient to obtain written informed consent.

I. Confidentiality of Study Data

Each patient data will be encoded using a unique code. Data will be stored in a secure location and password protected with access granted only to investigators.

J. Location of Study

CPMC and 14 other high-volume cardiac catheterization centers

K. Potential Risks

Patients may have an increased rate of target vessel revascularization procedure as prior clinical trials have shown increased rate of restenosis leading to a high use of this intervention. Also, for those patients with multi-vessel lesions, all of the non-randomized lesions will be stented with BMS since new evidence show likely increased risk of overall mortality and MI in

patients receiving DES for arteries > 2.75mm in diameter. However, this is not yet proven definitely.

L. Potential Benefits

Patients may or may not have any benefit from this study. There is potential benefit of increased medical attention received by closer follow up.

M. Alternate Therapies

Not applicable

N. Compensation to Subjects

There will be no compensation of participation in this study.

O. Costs to Subjects

Subjects will have no additional cost for participating in the study.

P. Minors as Research Subjects

Not applicable

Q. Radiation or Radioactive Substances

Not applicable

R. References

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