

Drug Eluting Stents Versus Medical Therapy for Vulnerable Plaques Identified by Intravascular Ultrasound

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A. Study Purpose and Rationale

Coronary artery plaques are composed of an atheromatous core covered by a fibrous cap. Rupture of atherosclerotic coronary plaques is a complex event leading to intraluminal thrombus formation and acute coronary syndromes (unstable angina, non-ST elevation myocardial infarction, ST elevation myocardial infarction, and sudden death).¹⁻³ Coronary angiography is limited to providing a luminal silhouette, and luminal stenosis only indirectly suggests plaque rupture and thrombus formation.⁴

Intravascular Ultrasound (IVUS) has identified coronary artery lesions in angiographically normal arteries by allowing characterization of plaque morphology in addition to visualization of the vessel wall⁴. IVUS investigations of non-occlusive lesions before an acute coronary syndrome have later been confirmed to have ruptured during an acute coronary syndrome.^{5,6} Morphologic features associated with future acute coronary syndromes have designated certain plaques as vulnerable. These features include thin fibrous cap, eccentric shape, large echolucent plaque area, and less than 50% stenosis.^{5,6} In addition, vulnerable plaques are more likely to occur in the proximal left anterior descending artery (pLAD) than in other coronary arteries⁷.

These findings suggest that directed intervention upon a vulnerable plaque may prevent future coronary syndromes. The purpose of this investigation is to determine whether drug eluting stent placement over vulnerable plaques imaged by IVUS in acute coronary syndrome patients prevents future acute coronary syndromes compared to medical therapy alone.

B. Study Design and Statistical Analysis

This is a randomized clinical trial involving subjects undergoing intervention upon a single, non pLAD culprit lesion during an acute coronary syndrome. Patients with IVUS identified pLAD vulnerable plaques will be randomized by sealed envelope method to receiving an additional drug eluting stent. Both groups of patients will receive optimal medical therapy directed by their primary cardiologists, who will be blinded to the investigational nature of all pLAD stents placed.

A planned sample size of 700 patients provides 80% statistical power to detect a 50% reduction in recurrent acute coronary syndrome involving the investigational target lesion during the ensuing 24 months. An estimated 10% of patients treated with optimal medical therapy will experience a recurrent acute coronary syndrome due to target plaque rupture. Using Chi squared analysis the number of patients required to determine statistical significance at 80 % power is 338; 12 additional patients will be added to each group to compensate for attrition (i.e. presentation to an outside hospital during an acute coronary event).

The primary measure of outcome will be the incidence of acute coronary syndromes involving the investigational lesion (chi squared analysis). Secondary measures of outcome will include acute coronary syndromes resulting from a separate culprit lesion, procedure related complications associated with additional stent placement, device related complications after stent placement, and mortality related to the investigational lesion (chi squared analysis).

C. Study Procedure

Informed consent will be obtained prior to cardiac catheterization. All patients will be treated and stabilized according to current acute coronary syndrome practice guidelines.^{8,9} All patients will receive aspirin 325 mg and clopidogrel 300 mg prior to intervention, 75 mg clopidogrel daily thereafter for 6

months. Intravenous bivalirudin will be administered during the procedure. Use of IIb/IIIa inhibitors will be left to the discretion of operator. After routine catheterization and intervention upon the culprit lesion is completed, IVUS study of the proximal LAD will be performed. The ultrasound transducer will be advanced distally over guidewire into the LAD and then slowly mechanically retracted at 1 mm/second. Pullback will be interrupted for all significant atherosclerotic lesions. Precise localization will be made by fluoroscopy to identify the transducer probe within the artery. Images will be recorded on VHS videotape and analyzed by the ultrasound system software for percent plaque area, eccentricity, fibrous cap thickness, and intraplaque echolucent area. Criteria for intervention will be confirmed by a third party cardiologist uninvolved with the procedure. Diffusely diseased vessels without an unidentifiable focal lesion will be excluded from investigation. Standard post procedure care measures will be taken.

Following the intervention patients will be followed by a primary cardiologist with standard optimized medical therapy (aspirin, clopidogrel, beta blocker, angiotensin converting enzyme inhibitor, statin). The number and location of stents will be disclosed with blinding to the investigational nature of the pLAD stent. Recurrent cardiac events over the ensuing two years will be monitored; any further required intervention will be performed at Columbia University Medical Center. Repeat IVUS during an acute pLAD coronary event will be left to the discretion of the operator as therapeutic revascularization may take precedence over clinical investigation. Repeat cardiac catheterization during a subsequent event will allow comparison to investigational lesion location from prior angiographic and IVUS studies.

A safety officer will be appointed to perform interim analysis after enrollment and randomization of the first 50 patients to evaluate procedure related complications, device related complications, and incidence of recurrent acute coronary syndromes.

D. Study Drugs

N/A

E. Medical Device

Both FDA approved drug eluting stents (Sirolimus "Cypher" Stent: Cordis Corporation/Johnson & Johnson, Warren, New Jersey; Paclitaxel "Taxus" Stent: Boston Scientific Corporation, Boston, Massachusetts) will be available for treatment of the culprit lesion. One or two stents of the assigned type will be used to treat the culprit lesion. A single stent will be deployed across the investigational lesion in the pLAD.

Investigational lesion characterization will be performed using an Intravascular Ultrasound Transducer (30 MHz, 3.5 F Sonicatch or 3.2F Ultracross, Boston Scientific Corporation, Boston, Massachusetts) and accompanying software systems.

F. Study Questionnaire

N/A

G. Study Subjects

Inclusion Criteria:

1. Age 35-75
2. No previous coronary intervention or cardiac surgery
3. Acute coronary syndrome requiring cardiac catheterization
4. Single vessel, non proximal LAD culprit lesion
5. Successful drug eluting stent deployment over culprit lesion

6. IVUS documented proximal LAD target lesion characterized by insignificant stenosis (<50%), thin fibrous cap (<0.7mm), eccentric morphology, and presence of an echolucent zone representing lipid rich core

Exclusion Criteria:

1. Prior coronary angiography or stent placement
2. Prior cardiac surgery
3. Congestive heart failure
4. Proximal LAD culprit lesion
5. Diffuse proximal LAD disease
6. Triple vessel coronary artery disease
7. Left main coronary artery disease
8. Cardiogenic shock
9. Intraaortic Balloon Placement
10. Complicated culprit lesion intervention

H. Recruitment of Subjects

Informed consent will be obtained from patients presenting with acute coronary syndromes prior to cardiac catheterization. Risks and benefits of the investigation will be explained as detailed in Sections L and M.

I. Confidentiality of Study Data

All medical records will be protected by HIPAA compliant confidentiality practices.

J. Potential Conflict of Interest

N/A

K. Location of the Study

All interventional procedures will be performed at the Interventional Cardiology Laboratory, Columbia University Medical Center.

L. Potential Risks

Placement of an additional stent by standard interventional procedures confers the risk of vessel dissection, stent migration, and in-stent restenosis. Stent placement may not be as effective in preventing future events as optimal medical therapy alone. Alternatively, optimal medical therapy alone may not be as effective as stent placement for preventing future events.

M. Potential Benefits

Patients with stented investigational lesions may benefit from fewer future acute coronary syndromes than patients in the optimal medical therapy arm. Alternatively, optimal medical therapy may reduce future coronary events.

N. Alternative Therapies

N/A

O. Compensation to Subjects

N/A

P. Costs to Subjects

N/A

Q. Minors as Research Subjects

N/A

R. Radiation or Radioactive Substances

Joint Radiation Safety Committee (JRSC) approved fluoroscopy will be utilized according to standard coronary angiography procedures.

S. References

1. Davies MJ, Thomas AC. Plaque fissuring-the cause of acute myocardial infarction, sudden ischemic death, and crescendo angina. *Br Heart J* 1985; 53: 363-73.
2. Fuster V, Stein B, Ambrose JA, et al. Atherosclerotic plaque rupture and thrombosis: evolving concepts. *Circulation* 1990; 82 (suppl 11): 47-59.
3. Fuster V, Badimon L, Badimon JJ, et al. The pathogenesis of coronary disease and the acute coronary syndromes, *N Engl J Med* 1992; 3 26: 242-3 18.
4. Ge J, Erbel R, Gerber T, et al. Intravascular Ultrasound imaging of angiographically normal coronary arteries: a prospective study in vivo. *Br Heart J* 1994; 71: 572-8.
5. Ge J, Chirillo J, Schwedtmann G, et al. Screening of ruptured plaques in patients with coronary artery disease by intravascular ultrasound. *Heart* 1999; 81: 621-627.
6. Yamagishi M, Terashima M, Awano K, et al. Morphology of vulnerable coronary plaque: insights from follow-up of patients examined by intravascular ultrasound before an acute coronary syndrome. *JAm Coll Cardiol* 1999; 35: 106-111.
7. Virmani R, Burke AP, Kolodgie FB, Farb A. Vulnerable plaque: the pathology of unstable coronary lesions. *JInterv Cardiol* 2002; 15: 439-46.
8. American College of Cardiology Foundation, American Heart Association. ACC/AHA guidelines for the management of patients with unstable angina and non-ST elevation myocardial infarction. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Bethesda (MD): American College of Cardiology Foundation (ACCF); 2002 Mar. 95 p.
9. Management of Acute Myocardial Infarction in Patients Presenting with ST Segment Elevation. European Society of Cardiology - Medical Specialty Society. 1996 (revised 2003).