Comparison of Orbital Versus Rotational Atherectomy Effects On Coronary Microcirculation in Percutaneous Coronary Intervention (PCI)

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Comparison of Orbital versus Rotational Atherectomy Effects On Coronary Microcirculation in Percutaneous Coronary Intervention

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Scientific basis/Rationale: The presence of heavily calcified coronary lesions necessitates the use of ablative devices that aid in successful percutaneous coronary intervention (PCI). However, atherectomy devices generate microparticles that embolize to the distal coronary microcirculation and may compromise myocardial tissue perfusion. We hypothesize that the orbital atherectomy system (OAS), a newer generation atherectomy device, reduces the incidence of microcirculatory compromise as compared to older generation rotational atherectomy (RA) due to differences in the mechanism of athero-ablation.

Two mechanisms that deserve particular attention are the eccentric mounting of the OAS crown and the higher flow rates on the vasodilator flush. Firstly, as opposed to rotational atherectomy where the larger, centrally mounted burr may cause obstruction of flow during the atherectomy, the smaller eccentrically mounted crown in OAS allows continuous perfusion during both atherectomy as well as rest periods. Second, both during rest and atherectomy, the flow rates of vasodilatory flush is higher in OAS compared to RA. Combined, these differences in coronary and vasodilator flush flow could lead to improved perfusion of the distal circulation, particularly during the atherectomy runs when risk of embolization is highest.

The loss of microcirculatory function can be transient, with partial or complete restoration of microcirculatory blood flow, or permanent. As shown in studies of patients with acute coronary syndromes, the loss of microcirculatory function is a critical and independent predictor of myocardial recovery and adverse outcomes.[1] The putative protective effects of OAS on coronary microvasculature may therefore be of major clinical significance and impact.

Central hypothesis: OAS is associated with lower loss of coronary microcirculatory function as compared to RA.

Primary Objectives: To compare the effect of OAS versus RA *on coronary microcirculatory function as measured by saline transit time under basal and hyperemic conditions in patients with clinical indication for PCI in whom atherectomy for optimal PCI is clinically warranted.*

Fractional flow reserve (FFR), coronary flow reserve (CFR) and the index of microcirculatory resistance (IMR) will be the primary physiological indices recorded

Exploratory Objectives: *To compare the incidence of peri-PCI myonecrosis with OAS versus RA,* as assessed by measurement of CK-MB and Troponin I and in a subgroup of 20 myocardial edema and late gadolinium enhancement on cardiac MRI..

Rationale: Lower incidence of microvascular compromise with OAS may be *protective against peri-atherectomy microvascular "plugging" and loss of tissue perfusion*, and thereby may result in a reduction in peri-PCI myocardial necrosis, potentially protecting left ventricular function. In patients undergoing elective PCI, IMR has been shown to

independently predict PCI-related microvascular damage and peri-procedural myonecrosis.

Trial Design: Randomized, prospective, single-center, investigator initiated, study at Columbia University Medical Center (CUMC).

Sample Size: 20

Inclusion Criteria:

1) Age ≥ 18 years
2) Patient with an indication for PCI including:
    i) Angina (stable or unstable),
    ii) Silent ischemia (a visually estimated target lesion diameter stenosis of ≥70%, a positive non-invasive stress test, or FFR ≤0.80 must be present),
    iii) NSTEMI
3) Patients will undergo cardiac catheterization and possible or definite PCI with intent to stent using any non-investigational metallic drug-eluting stent (DES)
4) Signed written informed consent
5) Heavily calcified (severe)lesions necessitating atherectomy.

Angiographic inclusion criteria:

1) The target lesion must be located in a native coronary artery with visually estimated reference vessel diameter of ≥2.25 mm to ≤4.00 mm.
2) Lesion length between 20 mm and 50mm

General Exclusion Criteria:

1) Estimated creatinine clearance <30 ml/min using Cockcroft-Gault equation, unless the patient is on dialysis;
2) STEMI within 24 hours of initial time of presentation to the first treating hospital, whether at a transfer facility or the study hospital.
3) PCI within 24 hours preceding the study procedure.
4) Cardiogenic shock (defined as persistent hypotension (systolic blood pressure <90 mm/Hg for more than 30 minutes) or requiring pressors or hemodynamic support, including IABP, at time of procedure.
5) Mobitz II second degree or complete heart block
6) Malignant ventricular arrhythmias requiring treatment
7) Pulmonary edema defined as patient with shortness of breath, evidence of volume overload on physical exam, and crepitations on physical exam (>1/3 of lungs) or radiographic interstitial or alveolar pulmonary edema
8) Subject is intubated.
9) Known LVEF <35%.
10) Severe valvular disease (e.g. severe mitral regurgitation or severe aortic stenosis)
11) Patient is participating in any other investigational drug or device clinical trial that has not reached its primary endpoint.
12) Women who are pregnant or breastfeeding (women of child-bearing potential must have a negative pregnancy test within one week before treatment).

Angiographic Exclusion Criteria:

1) Lesion length <20mm
2) Study target lesion in a bypass graft
3) Ostial RCA study target lesion
4) Chronic total occlusion (TIMI flow 0/1) study target lesion
5) Bifurcation study lesion with a planned dual stent strategy
6) In-stent restenosis study target lesion

Procedures:

Physiological indices: Subjects will be randomized on a 1:1 basis to OAS versus RA. In both groups, we will perform sequential physiological interrogation of the coronary vasculature before and immediately after atherectomy and at the end of PCI, utilizing a direct and robust assessment of microvascular function. This will be achieved by measurement of the mean transit time (T_{mn}) of saline using a single pressure-temperature sensor-tipped coronary wire (Certus™ guidewire, St Jude Medical, St Paul, Minnesota). The following parameters will be assessed:

(1) Total coronary flow ($1/T_{mn}$)

With the pressure sensor of the coronary wire acting also as a distal thermistor and the shaft of the wire serving as a proximal thermistor, the mean transit time of saline injected down a coronary artery can be derived from a coronary thermodilution curve. De Bruyne, Pijls and colleagues found a strong correlation between the inverse of T_{mn} and absolute flow[2].

(2) Microvascular resistance ($P_d * T_{mn}$)

Extrapolating from Ohm's law, distal coronary pressure (P_d) divided by the inverse of the hyperemic mean transit time (a correlate to absolute flow), measured simultaneously with the coronary pressure wire, will evaluate microvascular resistance. Under peak hyperemia (achieved by intravenous infusion of adenosine at 140 μg/kg/min) this ratio has been called the IMR[3]. IMR is derived from the assumption that at peak hyperemia the variability of resting vascular tone and hemodynamics will be eliminated, and the *minimum* microvascular resistance will be achieved[3].

(3) Coronary Wedge Pressure (P_w)

In addition to the IMR we will assess the coronary wedge pressure, measured by trapping the pressure transducer on the pressure wire with a proximally inflated balloon. Measurements will be taken immediately following atherectomy and than repeated following administration of adenosine and a 3 minute rest period. The difference between the pre and post adenosine coronary wedge pressure will be indicative of the microcirculatory "plugging" caused by atherectomy.

In addition, we will measure T_{mn} both at rest and at peak hyperemia. If the effects of OAS on the microvasculature are less than RA and the relatively smaller microparticles generated by OAS are more readily "washed out" of the microcirculation with adenosine-induced hyperemia, we expect to see a difference between OAS and RA in T_{mn} and $P_d * T_{mn}$ both with resting and hyperemic (i.e. IMR) indices.

We will also use the data to calculate the coronary flow reserve (CFR) that is an index of total blood flow in coronary bed under peak hyperemia relative to rest as described previously[2].

(4) CFR ($T_{mn\ at\ rest}/T_{mn\ at\ hyperemia}$)

The indication for PCI will be based on measurement of FFR, the current standard of practice, which will be determined as:

(5) FFR ($P_d/P_{a\ at\ hyperemia}$)

where P_a is the aortic pressure measured by the guiding catheter at peak hyperemia. PCI is indicated in stenoses with FFR <0.8[5].

T_{mn} under basal condition followed sequentially by IMR, FFR and CFR under maximum hyperemia will be measured at 3 separate time points: 1) pre-atherectomy, 2) immediately post atherectomy and 3) at the end of the PCI.

	Screening	Procedure	Post Procedure	Discharge
Consent	X			
Medical History	X			
Randomization	X			
CK/MB			X^1	
Troponin I			X^1	
Physiological Measurements (FFR)		X^2		

X^1 4-8 hours post procedure; if positive again at 12-18 hours

X^2 Physiological measurements (Total coronary flow, Microvascular resistance, Coronary wedge pressure, Coronary flow reserve and Fractional flow reserve) will be taken before and immediately after atherectomy and at the end of PCI)

Sample Size: A clinically important difference would be 20% reduction in IMR in OAS, equating to an IMR difference of 7 (SD=8, α =0.05 and power=0.80) and requiring a total sample size of 20.

Projected time for completion: 1 year. CUMC has a large volume for PCI with ~ 3000 number of PCIs per year including ~250 procedures requiring atherectomy.

Significance of the results: If OAS is shown to cause lower disruption and loss of coronary microcirculatory function, the use of this atherectomy device may have significant favorable impact on myocardial recovery and function post PCI as compared to RA, potentially leading to prevention of major adverse cardiovascular events.

Preliminary results:

Table 1. Physiological findings*

	OAS (n=6)	RA (n=4)	P
Post-atherectomy			
Coronary Flow (1/s)	1.78±.21	1.41±.62	0.25
Index of microcirculatory resistance (a.u)	21±6	31±7	0.04
Coronary wedge pressure (mmHg)	21±6	27±6	0.15

± standard deviation; *preliminary nonrandomized data.

Risks:

The risks associated with this study will involve the risks of inserting wires into the coronary arteries and with the administration of adenosine. The study protocol calls for an additional intracoronary wire insertion for physiology measurements. The risks include extra flouroscopy time (approximately 10-20 seconds), extra contrast (less than 10 mL), and a <1% risk of coronary artery damage (dissection or perforation). Adenosine is used to measure FFR. The most common adverse effects of adenosine are headache, facial flushing, bronchospasm, and conduction abnormalities. Performance of FFR is generally safe, but does require placement of a wire and catheter in the coronary artery which can rarely cause injury to the artery.

There are no risks for an MRI and few, if any, side effects. The test does not use radiation, and to date, there have been no documented side effects from the radio and magnetic waves it uses. Allergic reactions to the dye are rare. Individuals with claustrophobia may feel uncomfortable in the MRI machine.

Radiation Risk
A small amount of radiation is needed for this research (about ½ millisievert). The extra lifetime risk of dying from cancer due to this radiation may be one in 50,000. The chances of a person dying of cancer with no extra radiation exposure are about one in 4. At such low radiation exposures, scientists disagree about the amount of risk. These estimates are very uncertain. An amount of radiation greater than usual is needed for this research.

Benefits:
Conducting FFR may provide the operator with additional information about the anatomy and physiology of the patients heart and further assistant in the direction of their course of treatment. Future patients will benefit from the knowledge gained from conducting this study.

Alternatives
Patients who do not consent to participate in the research will be treated with whichever device the operator prefers (OAS versus RA) with or without FFR and will not undergo FFR. All other procedures are standard of care.

Safety Monitoring Plan
The PI (Dr. Ali will be responsible for monitoring and patient safety for the full duration of the study. Adverse events will be reviewed and all unanticipated problems will be reported to the IRB in accordance with Columbia University Medical Center IRB Policies and Procedures.

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