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# Pivotal Trial to Evaluate the Safety and Efficacy of the Orbital Atherectomy System in Treating De Novo, Severely Calcified Coronary Lesions (ORBIT II)

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**Objectives** The ORBIT II (Evaluate the Safety and Efficacy of OAS in Treating Severely Calcified Coronary Lesions) trial evaluated the safety and efficacy of the coronary Orbital Atherectomy System (OAS) to prepare de novo, severely calcified coronary lesions for stent placement.

**Background** Despite advances in interventional techniques, treatment of calcified coronary lesions remains a challenge. Stent placement in these lesions may result in stent underexpansion, malapposition, and procedural complications.

**Methods** ORBIT II is a prospective, multicenter, nonblinded clinical trial that enrolled 443 consecutive patients with severely calcified coronary lesions at 49 U.S. sites from May 25, 2010, to November 26, 2012. Investigators used the centrifugal action of the OAS diamond-coated crown to modify calcified lesions prior to stent placement.

**Results** The pre-procedure mean minimal lumen diameter of 0.5 mm increased to 2.9 mm after the procedure. The primary safety endpoint was 89.6% freedom from 30-day major adverse cardiac events compared with the performance goal of 83%. The primary efficacy endpoint (residual stenosis <50% post-stent without in-hospital major adverse cardiac events) was 88.9% compared with the performance goal of 82%. Stent delivery occurred successfully in 97.7% of cases with <50% stenosis in 98.6% of subjects. Low rates of in-hospital Q-wave myocardial infarction (0.7%), cardiac death (0.2%), and target vessel revascularization (0.7%) were reported.

**Conclusions** The ORBIT II coronary OAS trial met both the primary safety and efficacy endpoints by significant margins. Preparation of severely calcified plaque with the OAS not only helped facilitate stent delivery, but improved both acute and 30-day clinical outcomes compared with the outcomes of historic control subjects in this difficult-to-treat patient population. (Evaluate the Safety and Efficacy of OAS in Treating Severely Calcified Coronary Lesions [ORBIT II]; NCT01092416) (J Am Coll Cardiol Intv 2014;7:510–8) © 2014 by the American College of Cardiology Foundation

Despite advances in interventional equipment and techniques, effective treatment for patients with severe coronary calcification remains a challenge. Compared with noncalcified lesions, increased coronary arterial calcium deposition leads to a higher incidence of major adverse cardiac events (MACE), in particular the rate of non–Q-wave myocardial infarction (MI) (1). Calcified lesions have been shown to respond poorly to percutaneous coronary intervention (PCI) and are associated with a high frequency of restenosis, target lesion revascularization (TLR) (2), vessel dissection during PCI (3), failure to deliver a stent (4), balloon ruptures (5,6) and undilatable lesions (7,8). Up to 50% of coronary stents deployed in calcified lesions were found to have asymmetric stent expansion (9), potentially increasing the likelihood of stent thrombosis and/or restenosis (10). Attempts to remedy incomplete stent expansion with aggressive high-pressure balloon dilation may result in coronary artery rupture or dissection (11). Thus, severely calcified lesions are typically excluded from most trials.

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Additionally, given the difficulty in treating calcific coronary lesions percutaneously, these patients may be referred for coronary artery bypass surgery. In the SYNTAX (Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery) trial, 32.7% of patients with previous coronary artery bypass surgery were found to have heavily calcified lesions (12).

Coronary calcification is often underappreciated by conventional angiography alone. Mintz et al. (13) studied 1,155 coronary native vessel target lesions (n = 1,117). Calcium was detected by angiography in 38% of lesions (26% moderately, 12% severely calcified), whereas intravascular ultrasound (IVUS) showed 73% of lesions to have calcium deposits, suggesting that coronary calcification is relatively common (13). As IVUS is an underused diagnostic modality, coronary calcification is often underestimated or considered mild or moderate via angiogram, when it may actually be confirmed as severe calcification if IVUS is used.

Factors that lead to coronary calcification, such as diabetes, renal failure, and advanced age are on the rise (14–17). Effective treatment strategies are needed if the growing burden of calcific coronary disease is to be mitigated. Prior to approval by the U.S. Food and Drug Administration (FDA) of the coronary Orbital Atherectomy System (OAS) manufactured by Cardiovascular Systems, Inc. (CSI, St. Paul, Minnesota) on October 21, 2013, the only treatment option available for patients with severely calcified coronary lesions was rotational atherectomy (RA) even though RA is not indicated by the FDA for that population of patients. RA studies indicated improved procedural success in severely calcified lesions; however, its use has not led to a reduction in restenosis (11).

## Methods

**Device description.** The coronary OAS manufactured by CSI is used to facilitate stent delivery in patients with coronary artery disease who are acceptable candidates for percutaneous transluminal coronary angioplasty or stenting due to de novo, severely calcified coronary artery lesions. Two OAS configurations were used in the ORBIT II (Evaluate the Safety and Efficacy of OAS in Treating Severely Calcified Coronary Lesions) study, pneumatic and electric OAS. A detailed discussion of the novel use of centrifugal force and differential sanding employed by the coronary OAS to modify calcified coronary lesions was previously described by Parikh et al. (18–20).

**Abbreviations and Acronyms**

DES = drug-eluting stent(s)
FDA = U.S. Food and Drug Administration
IVUS = intravascular ultrasound
MACE = major adverse cardiac events
MI = myocardial infarction
OAS = Orbital Atherectomy System
PCI = percutaneous coronary intervention
RA = rotational atherectomy
TLR = target lesion revascularization

**Study design and endpoints.** ORBIT II, a prospective, nonrandomized, single arm, multicenter study, was designed to demonstrate: 1) OAS safety in de novo, severely calcified

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coronary lesions; and 2) efficacy of the OAS defined as successful stent delivery and deployment in severely calcified coronary lesions. The ORBIT II trial was conducted in the United States per good clinical practice and the applicable *Code of Federal Regulations* and the study was approved by each institutional review/ethics committee. An angiographic core laboratory (Cleveland Clinic Foundation, Cleveland, Ohio) analyzed the procedural angiograms and reported the minimum lumen diameter and final percentage of residual stenosis used for the primary efficacy endpoint calculation, as well as the presence and type of dissections and perforations.

Men and women, at least 18 years of age, with a clinical indication for coronary intervention, who were found to have a de novo, severely calcified lesion in a native coronary artery on fluoroscopy or IVUS, were enrolled in the study after meeting study selection criteria and providing informed consent. Key study inclusion criteria included: 1) target vessel reference diameter $\geq$2.5 mm and $\leq$4.0 mm with a stenosis $\geq$70% and $<$100% or a stenosis $\geq$50% and $<$70% with evidence of clinical ischemia via positive stress test, or fractional flow reserve value $\leq$0.8, or IVUS minimum lumen area $\leq$4.0 $mm^2$; 2) target lesion length $\leq$40 mm; 3) fluoroscopic or IVUS evidence of severe calcium deposit at the lesion site based on angiographic presence of radio-opacities noted without cardiac motion prior to contrast injection involving both sides of the arterial wall in at least one location, total length of calcium of at least 15 mm and extending partially into the target lesion, or presence of $\geq$270° of calcium at 1 cross section via IVUS. Patients were excluded if any of the following applied: 1) the target vessel had a stent from previous PCI unless the stent was on a different branch than the target lesion and was implanted more than 30 days before with no higher than 30% in stent-restenosis; 2) they had a recent MI, defined as creatine kinase-myocardial band $>1\times$ upper limit of normal within 30 days prior to index procedure; 3) they were diagnosed with chronic renal failure unless under hemodialysis, or had a serum creatinine level $>$2.5 mg/dl; 4) there was evidence of current left ventricular ejection fraction $\leq$25% (where current is defined as the latest left ventricular ejection fraction measurement completed within the last 6 months).

Once the plaque was modified to improve vessel compliance, the investigator was then required to implant the FDA-approved stent(s) according to the manufacturer's instructions for use. Post-OAS/pre-stent and post-stent percutaneous transluminal coronary angioplasty was optional. There were no required/mandated medications in the study. The use of thrombectomy therapy, an embolic protection device, brachytherapy, or a cutting balloon was not allowed. After final treatment, the subjects were required to complete an in-clinic visit at 30 days after the procedure (between 30 and 44 days following OAS treatment).

**Primary endpoint.** The primary safety endpoint was to demonstrate that the OAS is safe when used for stent deployment in de novo, calcified coronary lesions and was measured by a composite of MACE at 30 days after the procedure. MACE was defined as comprising MI, target vessel revascularization, and cardiac death. MI was defined as creatine kinase-myocardial band level $>3\times$ upper limit of normal with or without a new pathologic Q-wave. Target vessel revascularization was defined as repeat revascularization of the target vessel (inclusive of the target lesion) after completion of the index procedure. The primary efficacy endpoint was defined as procedural success defined as stent delivery with a residual stenosis of $<$50% without the occurrence of an in-hospital MACE.

**Secondary endpoint.** The secondary endpoints included angiographic success defined as success in facilitating stent delivery with a residual stenosis $<$50% without severe angiographic complications during the index procedure as well as the rate of individual severe angiographic complications during the index procedure. Severe angiographic complications included severe dissections (types C to F), perforation, persistent slow flow, persistent no reflow, and abrupt closure.

**Statistical analysis.** The primary safety and efficacy endpoints are based on comparisons to pre-specified performance goals based on relevant published reports. Criteria for relevant published reports included: English language availability; calcified lesions with and without pre-treatment with atherectomy; in-hospital or 30-day MACE data; publication later than 2000; and inclusion of $\geq$50 patients. When the endpoint criteria were calculated, only 1 published study (21) of a patient population (severely calcified) matched that of ORBIT II; therefore, papers reporting the presence of calcification within a heterogeneous population were included and adjusted for the approximate percentage of severely calcified lesions. One study segregated the severely calcified lesions (group F patients, $>$270° calcium) from the rest of the population and was used to create the adjustment factor for estimating the proportion of patients with calcified lesions in other studies as well as the adjustment factor for the MACE rate for patients with severely calcified lesions (1). Relevant published data have shown that the 30-day MACE rate ranged from 4.4% to 23.5%, with an adjusted weighted mean MACE rate of 15.5% (1,21–24). Adjustments to the published 30-day MACE rates were done to derive estimates of the rates among a severely calcified lesion population. Weighting of the adjusted rates was then done using the sample sizes of the studies. The ORBIT II performance goal for the 30-day MACE rate was conservatively set at 83%, allowing for some degree of variability due to sampling while still providing adequate power based on expectations on the performance of the OAS system. Based on the published reports, the adjusted weighted mean procedural success rate was determined to be 84%; therefore, a performance goal of 82% as the pre-defined study success criterion for the primary efficacy endpoint was chosen as conservative and clinically relevant (1,21,23–26).

Kaplan-Meier analysis with a confidence interval based on Peto's method was used for the primary safety endpoint and an exact binomial confidence interval for procedural success. Descriptive statistics are provided for secondary endpoints.

The ORBIT II sample size was based on the primary safety endpoint. A chi-square test was used to determine the approximate sample size necessary to detect a clinically meaningful change with approximately 80% power and 1-sided alpha-level of 0.025. Adjusting for a 5% rate of attrition and missing data at 30 days after the procedure, it was determined that enrollment of 429 subjects would be required. The overall study sample size was increased to 479 subjects to ensure the inclusion of 100 subjects treated with the electric OAS.

Statistical analyses were performed with either SAS software system (SAS Institute Inc., Cary, North Carolina) or R (R Core Team 2012, R Foundation for Statistical Computing, Vienna, Austria). Patient demographics, medical history, risk factors, pre- and post-procedure lesion characteristics, procedure characteristics, and outcome variables were summarized using descriptive statistics for continuous variables presented as mean ± SE and frequency tables or proportions for discrete variables.

## Results

**Patient demographics and lesion characteristics.** The ORBIT II study population consisted of 443 patients enrolled at 49 sites in the United States. Of the 443 subjects enrolled, 3 subjects were immediately withdrawn from the study (the OAS device was never inserted) because 2 of them no longer met all angiographic criteria following insertion of the study guidewire (ViperWire, CSI, St. Paul, Minnesota) and 1 subject was prepped with a 6-F sheath that did not allow for the introduction of the OAS per the instructions for use. The OAS device was inserted in 440 subjects and crossed the lesion in 432 subjects. In 2 cases, the OAS device was activated but could not cross the lesion. Patient demographics are presented in Table 1. Subjects enrolled in the ORBIT II study demonstrated a high number of risk factors for coronary disease consistent with advanced atherosclerotic disease such as diabetes and previous CABG. Target vessel and lesion characteristics, including angiographic determination of pre-procedure percentage of stenosis are reported in Table 2. Minimum lumen diameter was calculated from the percentage of stenosis and reference vessel diameter in all cases. Vessel calcification (determined by angiography) is reported in Table 2. For the majority of subjects (92%), angiography determined the calcification of the target vessel.

**Procedural results.** Procedural results are listed in Table 3. Table 4 summarizes the overall procedural results using the OAS, and Table 5 summarizes the OAS treatment parameters.

**Table 1. Baseline Characteristics**

| | |
|---|---|
| Average age, yrs, n = 443 | 71.4 |
| Male | 286/443 (64.6) |
| Ethnicity | |
| Caucasian | 389/443 (87.8) |
| Black or African American | 25/443 (5.6) |
| Asian | 9/443 (2.0) |
| Hispanic or Latino | 16/443 (3.6) |
| Native American | 1/443 (0.2) |
| Other | 3/443 (0.7) |
| eGFR, ml/min/1.73 $m^2$, n = 441 | 75.8 |
| History of diabetes mellitus | 160/443 (36.1) |
| History of dyslipidemia | 407/443 (91.9) |
| History of hypertension | 406/443 (91.6) |
| History of angina | 348/443 (78.6) |
| Previous stroke/transient ischemic attack | 39/443 (8.8) |
| Prior MI | 99/443 (22.3) |
| Prior CABG | 65/443 (14.7) |
| Smoker (current or former) | 293/443 (66.1) |

Values are n/N (%) unless otherwise indicated.
CABG = coronary artery bypass graft; eGFR = estimated glomerular filtration rate; MI = myocardial infarction.

**Primary safety endpoint.** The 30-day MACE components are presented in Table 6. At 30 days after the index procedure, MACE occurred in 46 subjects. The null hypothesis was to be rejected in favor of the alternative if the lower 2-sided 95% confidence bound for the MACE-free rate was >83% (Fig. 1). All subjects for whom the guidewire crossed

**Table 2. Vessel and Lesion Characteristics**

| | |
|---|---|
| Target vessel | |
| Left anterior descending artery | 227/440 (51.6) |
| Left circumflex artery | 64/440 (14.5) |
| Left main artery | 10/440 (2.3) |
| Right coronary artery | 132/440 (30.0) |
| Ramus | 7/440 (1.6) |
| ACC/AHA lesion class | |
| Type A | 0/440 (0.0) |
| Type B1 | 114/440 (25.9) |
| Type B2 | 197/440 (44.8) |
| Type C | 129/440 (29.3) |
| Mean lesion length, mm, n = 440 | 18.9 ± 0.4 |
| Mean diameter stenosis, %, n = 440 | 84.4 ± 0.4 |
| Mean reference vessel diameter, mm, n = 440 | 3.1 ± 0.0 |
| Mean minimum lumen diameter, mm, n = 440 | 0.5 ± 0.0 |
| Subjects with calcification determined by angiography only | 405/440 (92.0) |
| Total length of calcium (including segmented), mm | 28.6 ± 0.8 |
| Subjects with calcium visible on both sides of vessel | 405/405 (100) |
| Subjects with calcification determined by IVUS | 35/440 (8.0) |
| Maximum degree of calcium via IVUS | 295.0 ± 6.1 |

Values are n/N (%) or mean ± SE.
ACC = American College of Cardiology; AHA = American Heart Association; IVUS = intravascular ultrasound.

**Table 3. Overall Procedural Results**

| | |
|---|---|
| Subjects treated with pre-OAS balloon dilations | 8/440 (1.8) |
| Subjects treated with post-OAS/pre-stent balloon dilations | 181/440 (41.1) |
| Maximum inflation pressure, atm, n = 180 | 12.1 ± 0.3 |
| Mean post-OAS balloon angioplasty residual stenosis, %, n = 179 | 42.4 ± 1.5 |
| Subjects with stent placed | 432/440 (98.2) |
| Post-OAS stents used per subject, n = 432 | 1.3 ± 0.0 |
| Types of stents used in study | |
| BMS | 62/542 (11.4) |
| Covered | 2/542 (0.4) |
| DES | 478/542 (88.2) |
| Maximum deployment pressure, atm, n = 430 | 13.8 ± 0.2 |
| Post-stent residual stenosis, %, n = 431 | 5.8 ± 0.6 |
| Subjects treated with post-stent balloon angioplasty | 227/440 (51.6) |
| Mean post-stent balloon angioplasty residual stenosis, %, n = 223 | 1.1 ± 0.2 |

Values are n/N (%) or mean ± SE.
BMS = bare-metal stent(s); DES = drug-eluting stent(s); OAS = Orbital Atherectomy System.

the lesion have been included in the primary safety endpoint analysis (n = 443). As shown in Figure 1, the observed freedom from 30-day MACE was 89.6%, with a 2-sided confidence interval of 86.7% to 92.5%. Greater than the pre-defined performance goal of 83%, this lower bound of 86.7% indicates the goal was met successfully.

**Primary efficacy endpoint.** Successful stent delivery and <50% residual stenosis occurred in 97.7% and 98.6% of subjects, respectively. In-hospital MACE occurred in 43 subjects (9.8%), and the individual components of in-hospital MACE are presented in Table 6. The null hypothesis was to be rejected in favor of the alternative if the lower 2-sided 95% confidence bound for the primary efficacy rate was greater than the performance goal of 82% (Fig. 2). Only subjects treated by the OAS (the guidewire crossed the lesion and OAS device was inserted) have been included in the primary efficacy endpoint analysis (n = 440). As presented in Figure 2, the observed rate of procedural success was 88.9% with a 2-sided confidence interval of 85.5% to 91.6%. Greater than the pre-defined performance goal of 82%, this lower bound of 85.5% indicates the goal was met successfully.

**Table 4. Final Overall Procedural Results**

| | |
|---|---|
| Total procedure time, min,* n = 439 | 52.5 ± 1.4 |
| Total fluoroscopy time, min, n = 436 | 18.2 ± 0.6 |
| Total volume of contrast used, ml, n = 438 | 173.9 ± 4.1 |
| Final procedure minimum lumen diameter,† mm, n = 425 | 2.9 ± 0.0 |
| Final procedure stenosis,† %, n = 439 | 4.7 ± 0.7 |

Values are mean ± SE. *Total procedure time defined as the time from when the first guide catheter was placed in the access site to the time the last guide catheter was removed from the access site. †Minimum lumen diameter and final procedure stenosis were assessed by the angiographic core laboratory.

**Table 5. OAS Treatment Parameters**

| | |
|---|---|
| Subjects where OAS device was inserted, n | 440 |
| Subjects treated with OAS device, n | 432 |
| OAS device used | |
| Pneumatic, 1.25 mm | 320/457 (70.0) |
| Pneumatic, 1.50 mm | 33/457 (7.2) |
| Pneumatic, 1.75 mm | 2/457 (0.4) |
| Pneumatic, 2.00 mm | 2/457 (0.4) |
| Electric, 1.25 mm | 98/457 (21.4) |
| Electric, 1.50 mm | 2/457 (0.4) |
| OAS devices used per subject, n = 432 | 1.1 ± 0.0 |
| OAS device speed(s) used, revolutions/min | |
| Low only, 80,000 | 93/432 (21.5) |
| Low and high, 80,000 and 120,000 | 317/432 (73.4) |
| High only, 120,000 | 22/432 (5.1) |
| Total OAS device run time, s, n = 431 | 66.8 ± 2.2 |
| Average individual OAS run time, s, n = 430 | 19.5 ± 0.3 |
| Post-OAS residual stenosis, %, n = 432 | 58.7 ± 0.8 |

Values are n/N (%) or mean ± SE unless otherwise indicated.
OAS = Orbital Atherectomy System.

**Secondary endpoints.** Angiographic success was achieved in 91.4% (405 of 443) of subjects and severe angiographic complications occurred at a rate of 7.2% (32 of 443 subjects). Angiographic success results were similar for the pneumatic and electric OAS versions of the device, with rates of 91.0% (312 of 343) and 93.0% (93 of 100), respectively. The rate of severe angiographic complications was similar for the pneumatic and electric OAS devices with a nominally lower rate for the electric OAS (5.0% vs. 7.9% for pneumatic OAS). Some subjects may have failed >1 component of the angiographic success criteria, and, therefore, the categories are not mutually exclusive. Severe angiographic complications are listed in Table 7.

## Discussion

Coronary lesions with severe (or heavy) calcification are classified as complex lesions and are known to carry lower success rates and higher complication rates following PCI

**Table 6. Cumulative MACE Rates**

| | In-Hospital | 30-Day Follow-Up |
|---|---|---|
| MACE rate | 9.8 | 10.4 |
| Cardiac death | 0.2 | 0.2 |
| Non–Q-wave MI | 8.6 | 8.8 |
| Q-wave MI | 0.7 | 0.9 |
| TVR | 0.7 | 1.4 |

Values are %.
MACE = major adverse cardiac events; MI = myocardial infarction; TVR = target vessel revascularization.

**Table 7. Severe Angiographic Complications**

| | Pre OAS Device | Post OAS Device | Post Balloon/Stent | Unknown | Final |
|---|---|---|---|---|---|
| Severe dissection (type C, D, E, and F) | 0.2 | 2.3 | 0.9 | 0.0 | 15/443 (3.4) |
| Perforation | 0.0 | 0.9 | 0.9 | 0.0 | 8/443 (1.8) |
| Persistent slow flow | 0.2 | 0.2 | 0.5 | 0.0 | 4/443 (0.9) |
| Persistent no reflow | 0.0 | 0.0 | 0.0 | 0.0 | 0/443 (0.0) |
| Abrupt closure | 0.2 | 0.9 | 0.2 | 0.5 | 8/443 (1.8) |

Values are % or n/N (%).
OAS = Orbital Atherectomy System.

than do noncalcified or mildly calcified lesions (1,3,6,21,27). Severe calcium also poses technical challenges during PCI, resulting in stent underexpansion, malapposition, or the inability to place a stent (1,4). Extensive calcium may damage the polymer coating of drug-eluting stents (DES) (28,29) and, therefore, contribute to the ineffectiveness of DES when implanted into such lesions (30). As a result, calcification has been an exclusion criterion for almost all large-scale PCI studies, and there were no FDA-approved percutaneous treatments specifically for patients with severely calcified coronary lesions prior to the FDA approval of the OAS device. ORBIT II met its primary safety and efficacy study endpoints as a lesion preparation tool prior to stent placement in this patient population.

The ORBIT II trial is the largest series to date reporting exclusively on patients with severely calcified lesions. The ORBIT II trial found a high rate of successful stent delivery (97.7%) and residual stenosis <50% (98.6%) with a low angiographic complication rate. The incidence of slow flow and no reflow were notably very low, occurring in <1% of patients. This is in contrast to Japanese RA studies showing a range of 0% to 18% (31–34). The ORBIT II dissection (types C to F) rates for post-OAS device and final were 2.3% and 3.4%, respectively. A review of the published reports found 7 studies using RA that reported types C to F dissection rates ranging from 2.1% to 8.4% (32,35–40). The ORBIT II trial had among the lowest rates for this complication. Similarly, abrupt closure occurred in 0.9%

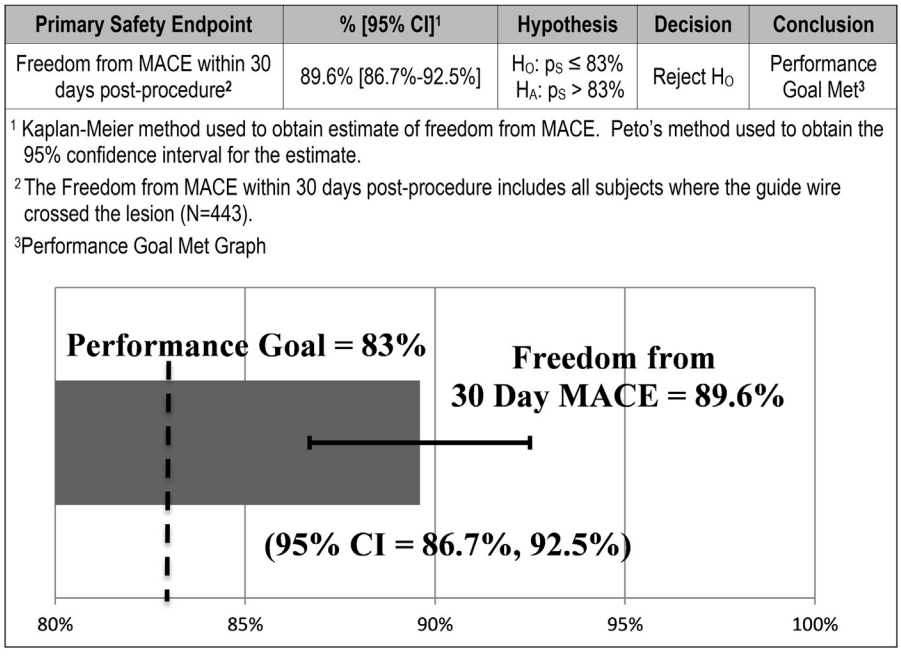


**Figure 1. Primary Safety Endpoint**

The observed freedom from 30-day major adverse cardiac event (MACE) was 89.6%, with a 2-sided confidence interval (CI) of 86.7% to 92.5%. Greater than the pre-defined performance goal of 83%, this lower bound of 86.7% indicates the goal was met successfully. $H_A$ = alternative hypothesis; $H_o$ = null hypothesis; $p_s$ = probability of freedom from MACE within 30 days post procedure.

| Primary Efficacy Endpoint | n/N[1] | % [95% CI][2] | Hypothesis | Decision | Conclusion |
|---|---|---|---|---|---|
| Procedural Success | 391/440 | 88.9% [85.5%-91.6%] | $H_O$: $p_S \leq 82\%$<br>$H_A$: $p_S > 82\%$ | Reject $H_O$ | Performance Goal Met[3] |

[1] n/N is the number of subjects meeting the primary efficacy endpoint over the number of subjects with study guide wire crossing the lesion and OAS device inserted.

[2] Clopper-Pearson Exact two-sided 95% confidence interval.

[3] Performance Goal Met Graph

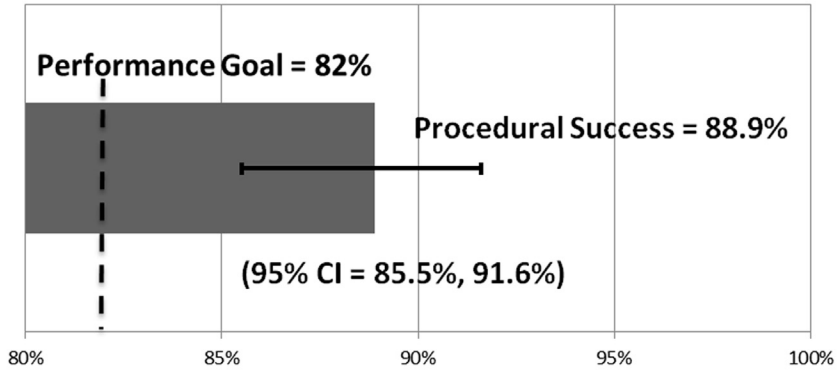


**Figure 2. Primary Efficacy Endpoint**

The observed rate of procedural success was 88.9%, with a 2-sided confidence interval of 85.5% to 91.6%. Greater than the pre-defined performance goal of 82%, this lower bound of 85.5% indicates the goal was met successfully. OAS = Orbital Atherectomy System; $p_s$ = probability of procedural success; other abbreviations as in Figure 1.

(post-OAS device) and 1.8% (final) of patients in the current study compared with rates from 1% to 4% in 6 studies that reported abrupt closure during RA (34–37,40,41). Perforations occurred in 0.9% (post-OAS device) and 1.8% (final) of patients compared with 0.4% to 2.5% in the 10 RA studies reporting on this complication (4,32,34–37,39–42). The post-OAS device perforation rate is at the low end of the previously reported range and the final ORBIT II perforation rate is within the range.

ORBIT II reported much lower in-hospital rates of non–Q-wave and Q-wave MI at 8.6% (38 of 440) and 0.7% (3 of 440), respectively, than did previous studies evaluating coronary calcified lesions. For example, Mosseri et al. (1) evaluated the effect of coronary calcification on non–Q-wave MI in patients treated with RA and bare-metal stents. They demonstrated significant increases in non–Q-wave MI rates corresponding to the increase of calcium arc via IVUS: 20.9% (>270° of calcium group) compared with 8.0% (0° to 90° of calcium group). Clavijo et al. (21), among the very few trials that studied severely calcified lesions treated with DES with and without RA, found a non–Q-wave MI (creatine kinase-myocardial band elevation >3× upper limit of normal) rate of 19.8% in the RA+DES group and a 25.8% rate in the DES-only group. They also reported an in-hospital Q-wave MI rate for RA+DES group at 1.3%.

There are only a few previous studies that reported TLR and death rates for patients with severely calcified coronary arteries. Mosseri et al. (1) reported an in-hospital TLR rate and death rate of 1.6% each. Clavijo et al. (21) reported a 30-day TLR rate of 1.3% and a death rate of 2.6% for the RA+DES group. In contrast, the ORBIT II study reported a lower in-hospital TLR rate of 0.7% and a much lower cardiac death rate of 0.2%.

**Study limitations.** This study lacked a control arm. Even though coronary atherectomy is a known technology with several products already approved by the FDA, none of these were previously indicated for severely calcified coronary arteries and, therefore, could not be used as a control. This was mitigated by comparison to historical control subjects documented in published reports. Although this is a significant limitation, it is important to note that the ORBIT II study was a prospective, multicentered, core lab adjudicated trial that was successful in exceeding its primary endpoints by a significant margin in a difficult-to-treat patient population that is typically excluded from clinical trials.

## Conclusions

Preparation of severely calcified plaque with OAS not only helped facilitate stent delivery, but also improved both acute

and 30-day clinical outcomes when compared with historic control subjects in this difficult-to-treat patient population. The primary safety endpoint was 89.6% freedom from 30-day MACE compared with its performance goal of 83%. The primary efficacy endpoint (residual stenosis <50% post-stent without in-hospital MACE) was 88.9% compared with the performance goal of 82%. Stent delivery occurred successfully in 97.7% and <50% stenosis in 98.6% of subjects. The OAS is a technology that appears to address the unmet medical need to treat patients with severely calcified coronary lesions. Using the OAS as a lesion preparation tool prior to stent deployment may offer patients with severely calcified coronary lesions a new treatment option.

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## REFERENCES

1. Mosseri M, Satler LF, Pichard AD, Waksman R. Impact of vessel calcification on outcomes after coronary stenting. Cardiovasc Revasc Med 2005;6:147–53.
2. Onuma Y, Tanimoto S, Ruygrok P, et al. Efficacy of everolimus eluting stent implantation in patients with calcified coronary culprit lesions: two-year angiographic and three-year clinical results from the SPIRIT II study. Catheter Cardiovasc Interv 2010;76:634–42.
3. Fitzgerald PJ, Ports TA, Yock PG. Contribution of localized calcium deposits to dissection after angioplasty: an observational study using intravascular ultrasound. Circulation 1992;86:64–70.
4. Abdel-Wahab M, Richardt G, Joachim Büttner H, et al. High-speed rotational atherectomy before paclitaxel-eluting stent implantation in complex calcified coronary lesions: the randomized ROTAXUS (Rotational Atherectomy Prior to Taxus Stent Treatment for Complex Native Coronary Artery Disease) trial. J Am Coll Cardiol Intv 2013;6:10–9.
5. Kahn JK, Hartzler GO. Balloon rupture due to lesion morphology during coronary angioplasty. Cathet Cardiovasc Diagn 1990;21:89–91.
6. Gilutz H, Weinstein JM, Ilia R. Repeated balloon rupture during coronary stenting due to a calcified lesion: an intravascular ultrasound study. Catheter Cardiovasc Interv 2000;50:212–4.
7. Cavusoglu E, Kini AS, Marmur JD, Sharma SK. Current status of rotational atherectomy. Catheter Cardiovasc Interv 2004;62:485–98.
8. Schlüter M, Cosgrave J, Tübler T, Melzi G, Colombo A, Schofer J. Rotational atherectomy to enable sirolimus-eluting stent implantation in calcified, nondilatable de novo coronary artery lesions. Vasc Dis Manage 2007;4:63–9.
9. Moussa I, Di Mario C, Moses J, et al. Coronary stenting after rotational atherectomy in calcified and complex lesions: angiographic and clinical follow-up results. Circulation 1997;96:128–36.
10. Benezet J, Diaz de la Llera LS, Cubero JM, Villa M, Fernandez-Quero M, Sánchez-González A. Drug-eluting stents following rotational atherectomy for heavily calcified coronary lesions: long-term clinical outcomes. J Invasive Cardiol 2011;23:28–32.
11. Levine GN, Bates ER, Blankenship JC, et al. 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. J Am Coll Cardiol 2011;58:e44–122.
12. Serruys PW, Morice MC, Kappetein AP, et al. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. N Engl J Med 2009;360:961–72.
13. Mintz GS, Popma JJ, Pichard AD, et al. Patterns of calcification in coronary artery disease: a statistical analysis of intravascular ultrasound and coronary angiography in 1155 lesions. Circulation 1995;91:1959–65.
14. Guzman RJ. Clinical, cellular, and molecular aspects of arterial calcification. J Vasc Surg 2007;45 Suppl A:A57–63.
15. Centers for Disease Control and Prevention. Trends in aging—United States and worldwide. MMWR Morb Mortal Wkly Rep 2003;52:101–4, 106.
16. Centers for Disease Control and Prevention. Increasing prevalence of diagnosed diabetes—United States and Puerto Rico, 1995–2010. MMWR Morb Mortal Wkly Rep 2012;61:918–21.
17. Collins AJ, Foley RN, Herzog C, et al. US Renal Data System 2012 Annual Data Report. Am J Kidney Dis 2013;61 Suppl 1:A7, e1–476.
18. Parikh K, Chandra P, Choksi N, Khanna P, Chambers J. Safety and feasibility of orbital atherectomy for the treatment of calcified coronary lesions: the ORBIT I trial. Catheter Cardiovasc Interv 2013;81:1134–9.
19. Parikh K, Parikh R, Patel A, Chag M. Two Year Follow Up Data of Orbital Atherectomy System for the Treatment of De Novo Calcified Coronary Lesions - A Single Center Experience. J Am Coll Cardiol 2011;58:B174.
20. Parikh K, Seth A, Baxi H, et al. First in man assessment of Orbital Atherectomy System in treating de novo calcified coronary lesions (ORBIT I) (abstr). J Am Coll Cardiol 2009;53:A20.
21. Clavijo LC, Steinberg DH, Torguson R, et al. Sirolimus-eluting stents and calcified coronary lesions: clinical outcomes of patients treated with and without rotational atherectomy. Catheter Cardiovasc Interv 2006;68:873–8.
22. Dill T, Dietz U, Hamm CW, et al. A randomized comparison of balloon angioplasty versus rotational atherectomy in complex coronary lesions (COBRA study). Eur Heart J 2000;21:1759–66.
23. Safian RD, Feldman T, Muller DW, et al. Coronary angioplasty and Rotablator atherectomy trial (CARAT): immediate and late results of a prospective multicenter randomized trial. Catheter Cardiovasc Interv 2001;53:213–20.
24. Doshi SN, Kini A, Kim MC, et al. A comparative study of rotational atherectomy in acute and stable coronary syndromes in the modern era. Am J Cardiol 2003;92:1404–8.
25. Rubartelli P, Niccoli L, Alberti A, et al. Coronary rotational atherectomy in current practice: acute and mid-term results in high- and low-volume centers. Catheter Cardiovasc Interv 2004;61:463–71.
26. Dietz U, Rupprecht HJ, Ekinci O, et al. Angiographic analysis of immediate and long-term results of PTCR vs. PTCA in complex lesions (COBRA study). Catheter Cardiovasc Interv 2001;53:359–67.
27. Genereux P, Madhavan MV, Mintz GS, et al. Ischemic outcomes after coronary intervention of calcified vessels in acute coronary syndromes: pooled analysis from the HORIZONS-AMI (Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction) and ACUITY (Acute Catheterization and Urgent Intervention Triage Strategy) trials. J Am Coll Cardiol 2014;63:1845–54.
28. Pinto DS, Stone GW, Ellis SG, et al., for the TAXUS-IV Investigators. Impact of routine angiographic follow-up on the clinical benefits of paclitaxel-eluting stents: results from the TAXUS-IV trial. J Am Coll Cardiol 2006;48:32–6.
29. Serruys PW, van Hout B, Bonnier H, et al. Randomised comparison of implantation of heparin-coated stents with balloon angioplasty in selected patients with coronary artery disease (Benestent II). Lancet 1998;352:673–81.

30. Khattab AA, Otto A, Hochadel M, Toelg R, Geist V, Richardt G. Drug-eluting stents versus bare metal stents following rotational atherectomy for heavily calcified coronary lesions: late angiographic and clinical follow-up results. J Interv Cardiol 2007;20:100–6.
31. Sakakura K, Ako J, Wada H, et al. Comparison of frequency of complications with on-label versus off-label use of rotational atherectomy. Am J Cardiol 2012;110:498–501.
32. Furuichi S, Tobaru T, Asano R, et al. Rotational atherectomy followed by cutting-balloon plaque modification for drug-eluting stent implantation in calcified coronary lesions. J Invasive Cardiol 2012;24:191–5.
33. Tsuchikane E, Suzuki T, Asakura Y, et al., for the DOCTORS Investigators. Debulking of chronic coronary total occlusions with rotational or directional atherectomy before stenting: final results of DOCTORS study. Int J Cardiol 2008;125:397–403.
34. Tsubokawa A, Ueda K, Sakamoto H, Iwase T, Tamaki S. Acute and long-term outcomes of rotational atherectomy in small (<3.0 mm) coronary arteries. J Interv Cardiol 2003;16:315–22.
35. Bersin RM, Cedarholm JC, Kowalchuk GJ, Fitzgerald PJ. Long-term clinical follow-up of patients treated with the coronary Rotablator: a single-center experience. Catheter Cardiovasc Interv 1999;46:399–405.
36. Brown DL, George CJ, Steenkiste AR, et al. High-speed rotational atherectomy of human coronary stenoses: acute and one-year outcomes from the New Approaches to Coronary Intervention (NACI) registry. Am J Cardiol 1997;80:60K–7K.
37. García de Lara J, Pinar E, Ramón Gimeno J, et al. Percutaneous coronary intervention in heavily calcified lesions using rotational atherectomy and paclitaxel-eluting stents: outcomes at one year. Rev Esp Cardiol 2010;63:107–10.
38. Henneke KH, Regar E, König A, et al. Impact of target lesion calcification on coronary stent expansion after rotational atherectomy. Am Heart J 1999;137:93–9.
39. Levin TN, Holloway S, Feldman T. Acute and late clinical outcome after rotational atherectomy for complex coronary disease. Cathet Cardiovasc Diagn 1998;45:122–30.
40. Mauri L, Reisman M, Buchbinder M, et al. Comparison of rotational atherectomy with conventional balloon angioplasty in the prevention of restenosis of small coronary arteries: results of the Dilatation vs Ablation Revascularization Trial Targeting Restenosis (DART). Am Heart 2003;145:847–54.
41. Reisman M, Harms V, Whitlow P, Feldman T, Fortuna R, Buchbinder M. Comparison of early and recent results with rotational atherectomy. J Am Coll Cardiol 1997;29:353–7.
42. Rathore S, Matsuo H, Terashima M, et al. Rotational atherectomy for fibro-calcific coronary artery disease in drug eluting stent era: procedural outcomes and angiographic follow-up results. Catheter Cardiovasc Interv 2010;75:919–27.

**Key Words:** atherectomy ■ calcification ■ cardiovascular intervention ■ clinical trial ■ coronary.