Orbital Atherectomy for Treating De Novo Severely Calcified Coronary Narrowing (1-Year Results from the Pivotal ORBIT II Trial)

Philippe Généreux, MD[a,b,c], Arthur C. Lee, MD[d], Christopher Y. Kim, MD[e], Michael Lee, MD[f], Richard Shlofmitz, MD[g], Jeffrey W. Moses, MD[a,b], Gregg W. Stone, MD[a,b], and Jeff W. Chambers, MD[h,*]

Percutaneous coronary intervention of severely calcified lesions has historically been associated with major adverse cardiac event (MACE) rates as high as 30%. In the ORBIT II (Evaluate the Safety and Efficacy of OAS in Treating Severely Calcified Coronary Lesions) trial, treatment of de novo severely calcified lesions with the Diamondback 360° Coronary Orbital Atherectomy System (OAS) resulted in low rates of procedural and 30-day adverse ischemic events. The long-term results from this trial have not been reported. We sought to determine the 1-year outcomes after orbital atherectomy of severely calcified coronary lesions. ORBIT II was a single-arm trial enrolling 443 subjects at 49 US sites with severely calcified lesions usually excluded from randomized trials. OAS utilizes a centrifugal differential sanding mechanism of action for plaque modification prior to stent implantation. After OAS drug-eluting stents were implanted in 88.2% of the patients. The primary safety end point was 30-day MACE, the composite of cardiac death, myocardial infarction, or target vessel revascularization [TVR]. The present analysis reports the 1-year follow-up results from ORBIT II. One-year data were available in 433 of 443 patients (97.7%), with median follow-up time of 16.7 months. The 1-year MACE rate was 16.4%, including cardiac death (3.0%), myocardial infarction (9.7%), and target vessel revascularization (5.9%). The 1-year target lesion revascularization rate was 4.7%, and stent thrombosis occurred in 1 patient (0.2%). Independent predictors of 1-year MACE and target vessel revascularization were diameter stenosis at baseline and the use of bare-metal stents. In patients with severely calcified lesions who underwent percutaneous coronary intervention, the use of OAS was associated with low rates of 1-year adverse ischemic events compared with historical controls. This finding has important clinical implications for the selection of optimum treatment strategies for patients with severely calcified lesions. **(Am J Cardiol 2015;115:1685−1690)**

Despite advances in technology, percutaneous coronary intervention (PCI) of severely calcified coronary lesions remains a challenge. Contemporary studies have shown that the presence of moderate or severe coronary calcification at the target lesion is associated with a substantial increase in death, myocardial infarction (MI), stent thrombosis, and need for revascularization.[1−6] Coronary calcification is frequent, with about 1/3 of the lesions treated by PCI presenting with a substantial amount of calcification angiographically.[1] Current therapeutic options to manage calcified lesions (e.g., cutting/scoring balloons and rotational atherectomy) are associated with a high rate of restenosis and stent failure at long-term follow-up.[5] Recently, the ORBIT II (Evaluate the Safety and Efficacy of OAS in Treating Severely Calcified Coronary Lesions) trial demonstrated favorable procedural and 30-day outcomes with the Diamondback 360° Coronary Orbital Atherectomy System (OAS) (Cardiovascular Systems, Inc., St. Paul, Minnesota) in the treatment of severely calcified lesions, resulting in its Food and Drug Administration (FDA) approval.[7] Whether the beneficial effects of this device seen at 30 days translate into favorable 1-year outcomes is not known. We report the prespecified analysis of the 1-year outcomes from the ORBIT II pivotal trial.

Methods

The design and initial results of ORBIT II have been published previously.[7] In brief, ORBIT II was a prospective, multicenter, nonblinded, single-arm clinical trial that enrolled patients with de novo severely calcified coronary lesions who underwent PCI. Key study inclusion criteria included: (1) target vessel reference diameter ≥2.5 and

[a]Columbia University Medical Center, New York, New York; [b]Cardiovascular Research Foundation, New York, New York; [c]Hôpital du Sacré-Coeur de Montréal, Université de Montréal, Montréal, Québec, Canada; [d]The Cardiac and Vascular Institute, Gainesville, Florida; [e]Utah Cardiology, Layton, Utah; [f]UCLA Medical Center, Los Angeles, California; [g]St. Francis Hospital—The Heart Center, Rosyln, New York; and [h]Metropolitan Heart and Vascular Institute, Mercy Hospital, Minneapolis, Minnesota. Manuscript received January 15, 2015; revised manuscript received and accepted March 10, 2015.

See page 1689 for disclosure information.

*Corresponding author: Tel: 763-236-9112.

E-mail address: J.Chambers@mhvi.com (J.W. Chambers).

http://dx.doi.org/10.1016/j.amjcard.2015.03.009

≤4.0 mm with a stenosis ≥70% and <100% or a stenosis ≥50% and <70% with evidence of clinical ischemia through positive stress test, fractional flow reserve value ≤0.8, or intravascular ultrasound (IVUS) minimum lumen area ≤4.0 mm^2; (2) target lesion length ≤40 mm; and (3) imaging evidence of severe calcium at the lesion site based on the angiographic presence of radio-opacities noted without cardiac motion before contrast injection involving both sides of the arterial wall in at least 1 location, total length of calcium of ≥15 mm and extending partially into the target lesion, or presence of ≥270° of calcium at 1 cross-section through IVUS. Patients were excluded if (1) the target vessel had a stent from a previous PCI unless the stent was on a different branch than the target lesion and was implanted >30 days before with no >30% in-stent restenosis; (2) recent MI (defined as creatine kinase-MB [CK-MB] >1× upper limit of laboratory normal [ULN] within 30 days of the index procedure); and (3) evidence of current left ventricular ejection fraction ≤25%. The ORBIT II trial conformed to ethical guidelines of the Declaration of Helsinki, and study participants provided informed consent.

The coronary OAS uses a diamond-coated eccentric crown that, while rotating over an atherectomy guide wire, expands laterally through centrifugal force (up to a maximum orbit diameter for a given rotational speed) resulting in a differential sanding of coronary calcification. Two OAS configurations were used in the ORBIT II trial, pneumatic OAS and electric OAS, with crown diameter ranging from 1.25 up to 2.00 mm. Detailed description of OAS mechanism of action can be found elsewhere.[8,9] The use of other adjunctive devices, such as thrombectomy, embolic protection devices, brachytherapy, or cutting balloons, was not allowed. Pre- and postprocedure dual antiplatelet therapy was recommended to conform to the American Heart Association/American College of Cardiology/Society for Cardiovascular Angiography and Interventions joint guidelines for PCI.[10]

The primary safety end point of ORBIT II was the rate of 30-day major adverse cardiac events (MACEs) defined as the composite of cardiac death, MI, and target vessel revascularization (TVR). MI was defined as CK-MB >3x ULN with or without new pathologic Q waves. Rate of stent thrombosis was reported and defined according to the Academic Research Consortium definition.[11] All adverse events were adjudicated by an independent clinical events committee. All patients were followed clinically during the index hospitalization, at 30 days and at 1 year.

Continuous variables are summarized as mean ± SD. Survival curves for time-to-event variables were constructed on the basis of all available follow-up data using Kaplan-Meier methods. Multivariable Cox proportional hazards regression was performed to identify independent predictors of 1-year MACE and target vessel revascularization (TVR) (2-sided $\alpha = 0.05$ for significance). The multivariable model was built with candidate variables being selected if of clinical interest and/or satisfying the criterion of $p < 0.2$ in the univariate analysis. Variables included in the final were carefully selected to avoid overfitting and included for MACE: age, previous coronary artery bypass graft surgery, estimated glomerular filtration rate, reference vessel diameter, lesion length, diameter stenosis, and use of bare-metal stents (BMS) versus drug-eluting stents (DES), and for TVR: reference vessel diameter, diameter stenosis, and use of BMS versus DES. All statistical analyses were

Table 1
Baseline, angiographic, and procedural characteristics

Variable	N = 443
Age (years)	71.4 ± 9.9
Men	286/443 (64.6%)
Smoker (current or former)	293/443 (66.1%)
History of diabetes mellitus	160/443 (36.1%)
History of dyslipidemia	407/443 (91.9%)
History of hypertension	406/443 (91.6%)
Estimated glomerular filtration rate (mL/min/1.73 m^2)	75.8 ± 26.2
Prior stroke/transient ischemic attack	39/443 (8.8%)
Prior myocardial infarction	99/443 (22.3%)
Prior coronary artery bypass graft surgery	65/443 (14.7%)
Target coronary artery	
Left anterior descending	227/440 (51.6%)
Left circumflex	64/440 (14.5%)
Left main	10/440 (2.3%)
Right	132/440 (30.0%)
Ramus	7/440 (1.6%)
Mean lesion length (mm)	18.9 ± 9.0
Mean diameter stenosis (%)	84.4 ± 9.0
Mean reference vessel diameter (mm)	3.1 ± 0.4
American College of Cardiology/American Heart Association lesion type	
Type A	0/440 (0.0%)
Type B1	114/440 (25.9%)
Type B2	197/440 (44.8%)
Type C	129/440 (29.3%)
Subjects with stent implanted	432/440 (98.2%)
Stents implanted per patient	1.3 ± 0.6
Types of stents implanted	
Bare metal stent	64/542 (11.8%)
Drug-eluting stent	478/542 (88.2%)
First-generation drug-eluting stent	94/478 (19.7%)
Second-generation drug-eluting stent	384/478 (80.3%)
Total procedure time (min)*	52.5 ± 29.6
Total fluoroscopy time (min)	18.2 ± 12.3
Total volume of contrast used (mL)	173.9 ± 86.4
Orbital atherectomy system device used (size in mm)	
Pneumatic, 1.25	320/457 (70.0%)
Pneumatic, 1.50	33/457 (7.2%)
Pneumatic, 1.75	2/457 (0.4%)
Pneumatic, 2.00	2/457 (0.4%)
Electric, 1.25	98/457 (21.4%)
Electric, 1.50	2/457 (0.4%)
Orbital atherectomy system device speed(s) used (rpm)	
Low only (80,000)	93/432 (21.5%)
Low and high (80,000/120,000)	317/432 (73.4%)
High only (120,000)	22/432 (5.1%)
Total orbital atherectomy system device run time (seconds)	66.8 ± 45.6
Individual orbital atherectomy system run time (seconds)	19.5 ± 5.7

Values are n/N (%), mean ± standard deviation.

* 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.

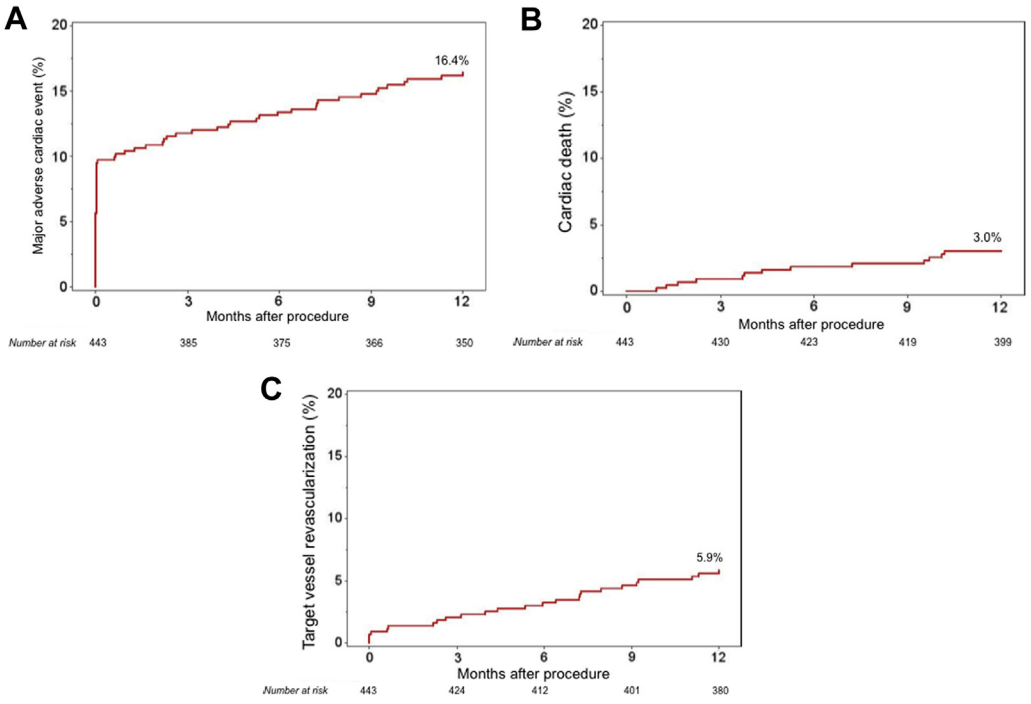

Figure 1. Time-to-event curves through 1 year. Cumulative event rates through 1 year in patients enrolled in the ORBIT II trial—*(A)* MACE, *(B)* cardiac death, and *(C)* TVR.

Table 2
Clinical outcomes through time

Variable	In-Hospital	30-Day	1-Year
Major adverse cardiac events	43 (9.8)	46 (10.4)	72 (16.4)
Major adverse cardiac events (using myocardial infarction = creatine kinase-MB 10× upper limit of normal)	11 (2.5)	14 (3.2)	43 (9.9)
Death	2 (0.5)	2 (0.5)	19 (4.4)
Cardiac death	1 (0.2)	1 (0.2)	13 (3.0)
Myocardial infarction (creatine kinase-MB 3× upper limit of normal)	41 (9.3)	43 (9.7)	43 (9.7)
Non−Q-wave myocardial infarction	38 (8.6)	39 (8.8)	39 (8.8)
Q-wave myocardial infarction	3 (0.7)	4 (0.9)	4 (0.9)
Myocardial infarction (creatine kinase-MB 10× upper limit of normal)	9 (2.1)	9 (2.0)	9 (2.0)
Target vessel revascularization	3 (0.7)	6 (1.4)	25 (5.9)
Target lesion revascularization	0 (0.0)	3 (0.7)	20 (4.7)
Target vessel revascularization non-target lesion revascularization	3 (0.7)	3 (0.7)	8 (1.9)
Academic Research Consortium definite/probable stent thrombosis	1 (0.2)	1 (0.2)	1 (0.2)

Kaplan-Meier rate estimates; data presented as n (%). In-hospital rates are based on binomial proportions, out of the 440 treated subjects.

Table 3
One-year clinical events according to stent type

Variable	Bare Metal Stent (n=43)	Drug-eluting Stent (n=389)	p Value
Major adverse cardiac events	10 (24.3%)	56 (14.5%)	0.047
Target vessel revascularization	6 (15.1%)	18 (4.7%)	0.01
Target lesion revascularization	6 (15.3%)	13 (3.4%)	0.002
Target vessel revascularization non-target lesion revascularization	2 (5.0%)	6 (1.6%)	0.15

Kaplan-Meier rate estimates. Data presented as n (%). P-value from Cox Proportional hazards model.

performed using SAS, version 9.3 (SAS Institute, Cary, North Carolina).

The ORBIT II trial was funded by Cardiovascular Systems, Inc., and was designed collaboratively by the steering committee and the sponsor. The authors had unrestricted access to the study data, drafted the manuscript, made the decision to submit for publication, and guarantee the integrity and accuracy of its content.

Results

From May 25, 2010, to November 26, 2012, 443 consecutive patients with severely calcified coronary lesions

Table 4
Analysis of independent predictors of 1-year adverse events

Variable	Major Adverse Cardiac Events				Target Vessel Revascularization			
	Unadjusted Hazard Ratio (95% Confidence Interval)	p Value	Adjusted Hazard Ratio (95% Confidence Interval)	p Value	Unadjusted Hazard Ratio (95% Confidence Interval)	p Value	Adjusted Hazard Ratio (95% Confidence Interval)	p Value
Age (per 10 years)	1.02 (0.81, 1.30)	0.84	0.87 (0.67, 1.12)	0.27	0.99 (0.95, 1.02)	0.45		
Diabetes mellitus	1.00 (0.62, 1.61)	0.99			1.01 (0.45, 2.29)	0.98		
Smoker*	0.79 (0.49, 1.27)	0.32			0.64 (0.29, 1.41)	0.27		
Prior myocardial infarction	1.07 (0.62, 1.84)	0.81			1.10 (0.44, 2.75)	0.84		
Prior coronary artery bypass grafting	1,57 (0.89, 2.78)	0.12	1.21 (0.64, 2.29)	0.56	1.46 (0.55, 3.88)	0.45		
Estimated glomerular filtration rate (mL/min/1.73 m^2) (per 10)	0.94 (0.86, 1.03)	0.21	0.95 (0.86, 1.04)	0.26	1.09 (0.95, 1.25)	0.20		
Left ventricular ejection fraction (per 10%)	0.94 (0.74, 1.19)	0.61			1.10 (0.72, 1.69)	0.65		
Reference vessel diameter (mm) baseline	0.64 (0.35, 1.16)	0.14	0.74 (0.40, 1.39)	0.35	0.47 (0.17, 1.33)	0.16	0.37 (0.12, 1.14)	0.08
Narrowing length (mm)	1.02 (1.00, 1.05)	0.09	1.02 (0.99, 1.04)	0.26	1.01 (0.97, 1.06)	0.56		
Diameter stenosis (%)	1.03 (1.00, 1.05)	0.052	1.03 (1.00, 1.06)	0.04	1.05 (1.00, 1.10)	0.04	1.06 (1.00, 1.11)	0.04
Bare metal stent vs drug-eluting stent	1.93 (1.01, 3.68)	0.047	2.33 (1.17, 4.65)	0.02	3.38 (1.34, 8.52)	0.01	4.38 (1.69, 11.35)	0.002
1.25 mm vs >1.25 mm crown	1.24 (0.50, 3.08)	0.64			1.02 (0.24, 4.34)	0.98		

* Current/former smoker versus never smoked.

from 49 US sites were enrolled in the ORBIT II trial. Among them, 432 (97.5%) were actually treated with OAS before stent placement, and 1-year data were available in 433 patients (97.7%) (median follow-up time of 16.7 months). Baseline, angiographic, and procedural characteristics of the study population are listed in Table 1. DES were implanted in most of the lesions treated (88.2% of stents).

At 1 year, the primary composite end point of MACE occurred in 16.4% of patients, with cardiac death occurring in 3.0%, MI in 9.7%, and TVR in 5.9% of patients (Figure 1, Table 2). The target lesion revascularization (TLR) rate was 4.7%, and only 1 (0.2%) stent thrombosis occurred within 1 year (Table 2). When using the SCAI definition of periprocedural MI (CK-MB $\geq$10$\times$ ULN without new Q waves or $\geq$5$\times$ ULN with new Q waves),[12] the 1-year MI and MACE rates were 2.0% and 9.9%, respectively. Table 3 lists the rates of 1-year adverse clinical events stratified by stent type. Use of BMS was associated with a significantly higher rate of MACE, TVR, and TLR at 1 year.

Independent predictors of 1-year MACE and TVR are summarized in Table 4. After multivariable analysis, diameter stenosis and the use of BMS emerged as independent predictors of MACE and TVR.

Discussion

The present study describes the long-term impact of treatment of severely calcified lesions using the novel and recently FDA-approved OAS. The main findings of the present study extend the favorable procedural and 30-day results previously reported[7] and demonstrate a relatively low rate of 1-year adverse ischemic events after treatment of this complex and high-risk cohort with OAS.

PCI of calcified lesions have been shown to be associated with a worse prognoses compared with lesions with no calcification.[1–3,5,6] Coronary calcification often leads to difficulty in delivering coronary devices, may damage the drug polymer and stent platform,[13] and limit full stent expansion, resulting in suboptimal procedural results and an increased risk of subsequent ischemic adverse events. Appropriate lesion preparation remains crucial to ensure optimal angiographic and clinical outcomes. However, despite improving procedural success and acute gain, the Rotational Atherectomy Prior to Taxus Stent Treatment for Complex Native Coronary Artery Disease (ROTAXUS) trial failed to demonstrate any clinical benefit of rotational atherectomy compared with standard balloon predilation for preparation of calcified lesions before DES implantation in regard to 9-month TVR (16.7% vs 18.3%, p = 0.73), TLR (11.7% vs 12.5%, p = 0.85), and MACE rates (defined as a composite of death, MI, and TVR; 24.2% vs 28.3%, p = 0.46).[14] In contrast, the results with OAS in the present study are encouraging, with lower rates of TVR (5.9%), TLR (4.7%), and cumulative MACE (16.7%) at 1 year compared with historical controls, despite using a more stringent definition of severe coronary calcification as an enrolling criterion. Indeed, >90% of the treated lesions in the ORBIT II trial were considered severely calcified compared with ~50% of the lesions enrolled in ROTAXUS.[14] Similarly, our results compared favorably with the recently published large pooled analysis from the Acute Catheterization and Urgent Intervention Triage Strategy and Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction trials, showing TLR and MACE rates in patients with severe coronary calcification who underwent PCI being 8.7% and 19.9%, respectively.[1] That being said, ORBIT II was a single-arm trial with no direct comparator, and conclusions from indirect comparisons with different studies (including different patient populations, different stent types, etc.) should be considered hypothesis generating.

Given the angiographic complexity and high-risk profile of the ORBIT II population, the 1-year stent thrombosis rate is surprisingly low and compares favorably with previous

studies.[15−17] Indeed, only 1 case (0.2%) of stent thrombosis occurred (at day 0, postprocedure). This finding is notable and may represent one of the most beneficial effects of OAS as an optimal tool in lesion preparation for severely calcified lesions. Angiographic lesion complexity and calcification have been identified as independent predictors of stent thrombosis,[1,18−20] with stent underexpansion being the most likely causal common denominator.[21−23] Although our findings are encouraging given the complexity of the lesions treated in ORBIT II, the relatively small number of patients enrolled in our study and the lack of a control arm preclude definitive conclusions regarding the utility of OAS to prevent stent thrombosis.

Several reasons could underlie the favorable long-term results seen in the present study. OAS uses a principle of off-axis centrifugal force, with the orbital motion diameter being proportional to the applied speed. This orbital movement results in sanding of the entire calcified wall and might allow for greater blood flow (nonocclusive) with less heat generation and thermal injury during the procedure compared with a potentially more aggressive and occlusive atherectomy approach.[24,25] Additional imaging and mechanistic studies are required to determine the extent to which the unique mechanism of OAS contributes to the favorable outcomes observed in the present study.

Approximately 12% of the ORBIT II population underwent PCI of the target lesion with BMS during the index procedure. Not surprisingly, adverse ischemic event were higher in patients with BMS compared with DES, and the use of BMS was identified as an independent predictor of MACE and TVR. Reported previously,[26] this finding reiterates the dismal outcomes of BMS compared with DES when used in highly complex (i.e., heavily calcified) lesions. This finding also underlines the even more favorable results of lesion preparation using OAS, especially if only DES (specifically second generation) were used.[27]

ORBIT II has important strengths. It is the first and largest prospective, multicenter trial including only patients with severe coronary calcification using strict angiographic enrolling criteria in the contemporary era of DES and potent antithrombotic agents. Indeed, ORBIT II enrolled patients typically excluded from standard clinical trials and still demonstrated outcomes comparable with trials excluding such patients. An independent angiographic core laboratory and independent clinical events committee reviewed and adjudicated all angiograms and adverse events. However, some limitations should be acknowledged. First, ORBIT II was a single-arm trial, with no control group. Therefore, extrapolation of the superiority of the OAS device compared with the standard strategy for treatment of severely calcified lesions could not be done. That being said, given that no device was FDA approved for treatment of calcified lesions at the time of conception of the trial, design of a head-to-head trial was deemed not necessary by the FDA. Second, adjunctive intracoronary imaging such as IVUS or optical coherence tomography was not mandated per protocol. Additional data from these imaging techniques would have been highly informative and could have provided insights on the therapeutic mechanisms and effects of OAS.[28,29] Third, 49 sites randomized 443 patients, with a mean of ∼8 patients enrolled per site. Because the OAS device was a novel therapeutic tool and most of the investigators had no previous experience with this device, learning curve issues must be considered, and improved outcomes may be expected with increased operator experience.

Acknowledgment: The authors thank the ORBIT II investigators. The authors thank Brad J. Martinsen, PhD, and Ann Behrens, BS, of Cardiovascular Systems, Inc., and Dominic P. Francese, MPH, for their support in manuscript preparation.

Disclosures

The ORBIT II trial was funded by Cardiovascular Systems, Inc. Dr. Généreux: Consulting fees from Cardiovascular Systems, Inc., and speaker fees from Abbott Vascular; Drs Chambers, Arthur Lee, Kim, Shlofmitz, and Lee: consulting fees from Cardiovascular Systems, Inc (*ClinicalTrials.gov* identifier: NCT01092416). The other authors have no relevant disclosures related to this study.

1. Genereux P, Madhavan MV, Mintz GS, Maehara A, Palmerini T, Lasalle L, Xu K, McAndrew T, Kirtane A, Lansky AJ, Brener SJ, Mehran R, Stone GW. 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;63:1845−1854.
2. Bangalore S, Vlachos HA, Selzer F, Wilensky RL, Kip KE, Williams DO, Faxon DP. Percutaneous coronary intervention of moderate to severe calcified coronary lesions: insights from the National Heart, Lung, and Blood Institute Dynamic Registry. *Catheter Cardiovasc Interv* 2011;77:22−28.
3. Bourantas CV, Zhang YJ, Garg S, Iqbal J, Valgimigli M, Windecker S, Mohr FW, Silber S, Vries T, Onuma Y, Garcia-Garcia HM, Morel MA, Serruys PW. Prognostic implications of coronary calcification in patients with obstructive coronary artery disease treated by percutaneous coronary intervention: a patient-level pooled analysis of 7 contemporary stent trials. *Heart* 2014;100:1158−1164.
4. Xu Y, Mintz GS, Tam A, McPherson JA, Iniguez A, Fajadet J, Fahy M, Weisz G, De Bruyne B, Serruys PW, Stone GW, Maehara A. Prevalence, distribution, predictors, and outcomes of patients with calcified nodules in native coronary arteries: a 3-vessel intravascular ultrasound analysis from Providing Regional Observations to Study Predictors of Events in the Coronary Tree (PROSPECT). *Circulation* 2012;126:537−545.
5. Madhavan MV, Tarigopula M, Mintz GS, Maehara A, Stone GW, Genereux P. Coronary artery calcification: pathogenesis and prognostic implications. *J Am Coll Cardiol* 2014;63:1703−1714.
6. Moussa I, Ellis SG, Jones M, Kereiakes DJ, McMartin D, Rutherford B, Mehran R, Collins M, Leon MB, Popma JJ, Russell ME, Stone GW. Impact of coronary culprit lesion calcium in patients undergoing paclitaxel-eluting stent implantation (a TAXUS-IV substudy). *Am J Cardiol* 2005;96:1242−1247.
7. Chambers JW, Feldman RL, Himmelstein SI, Bhatheja R, Villa AE, Strickman NE, Shlofmitz RA, Dulas DD, Arab D, Khanna PK, Lee AC, Ghali MG, Shah RR, Davis TP, Kim CY, Tai Z, Patel KC, Puma JA, Makam P, Bertolet BD, Nseir GY. Pivotal trial to evaluate the safety and efficacy of the orbital atherectomy system in treating de novo, severely calcified coronary lesions (ORBIT II). *JACC Cardiovasc Interv* 2014;7:510−518.
8. 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;81:1134−1139.

9. Bhatt P, Parikh P, Patel A, Chag M, Chandarana A, Parikh R, Parikh K. Orbital atherectomy system in treating calcified coronary lesions: 3-year follow-up in first human use study (ORBIT I trial). *Cardiovasc Revasc Med* 2014;15:204−208.
10. Levine GN, Bates ER, Blankenship JC, Bailey SR, Bittl JA, Cercek B, Chambers CE, Ellis SG, Guyton RA, Hollenberg SM, Khot UN, Lange RA, Mauri L, Mehran R, Moussa ID, Mukherjee D, Nallamothu BK, Ting HH; American College of Cardiology Foundation; American Heart Association Task Force on Practice Guidelines; Society for Cardiovascular Angiography and Interventions. 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−e122.
11. Cutlip DE, Windecker S, Mehran R, Boam A, Cohen DJ, van Es GA, Steg PG, Morel MA, Mauri L, Vranckx P, McFadden E, Lansky A, Hamon M, Krucoff MW, Serruys PW; Academic Research Consortium. Clinical end points in coronary stent trials: a case for standardized definitions. *Circulation* 2007;115:2344−2351.
12. Moussa ID, Klein LW, Shah B, Mehran R, Mack MJ, Brilakis ES, Reilly JP, Zoghbi G, Holper E, Stone GW. Consideration of a new definition of clinically relevant myocardial infarction after coronary revascularization: an expert consensus document from the Society for Cardiovascular Angiography and Interventions (SCAI). *J Am Coll Cardiol* 2013;62:1563−1570.
13. Kuriyama N, Kobayashi Y, Yamaguchi M, Shibata Y. Usefulness of rotational atherectomy in preventing polymer damage of everolimus-eluting stent in calcified coronary artery. *JACC Cardiovasc Interv* 2011;4:588−589.
14. Abdel-Wahab M, Richardt G, Joachim Buttner H, Toelg R, Geist V, Meinertz T, Schofer J, King L, Neumann FJ, Khattab AA. 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. *JACC Cardiovasc Interv* 2013;6:10−19.
15. Raber L, Magro M, Stefanini GG, Kalesan B, van Domburg RT, Onuma Y, Wenaweser P, Daemen J, Meier B, Juni P, Serruys PW, Windecker S. Very late coronary stent thrombosis of a newer-generation everolimus-eluting stent compared with early-generation drug-eluting stents: a prospective cohort study. *Circulation* 2012;125:1110−1121.
16. Palmerini T, Biondi-Zoccai G, Della Riva D, Mariani A, Sabate M, Smits PC, Kaiser C, D'Ascenzo F, Frati G, Mancone M, Genereux P, Stone GW. Clinical outcomes with bioabsorbable polymer- versus durable polymer-based drug-eluting and bare-metal stents: evidence from a comprehensive network meta-analysis. *J Am Coll Cardiol* 2014;63:299−307.
17. Palmerini T, Biondi-Zoccai G, Della Riva D, Stettler C, Sangiorgi D, D'Ascenzo F, Kimura T, Briguori C, Sabate M, Kim HS, De Waha A, Kedhi E, Smits PC, Kaiser C, Sardella G, Marullo A, Kirtane AJ, Leon MB, Stone GW. Stent thrombosis with drug-eluting and bare-metal stents: evidence from a comprehensive network meta-analysis. *Lancet* 2012;379:1393−1402.
18. Waksman R, Kirtane AJ, Torguson R, Cohen DJ, Ryan T, Raber L, Applegate R, Waxman S, Gordon P, Kaneshige K, Leon MB; DESERT Investigators. Correlates and outcomes of late and very late drug-eluting stent thrombosis: results from DESERT (International Drug-Eluting Stent Event Registry of Thrombosis). *JACC Cardiovasc Interv* 2014;7:1093−1102.
19. Yadav M, Genereux P, Palmerini T, Caixeta A, Madhavan MV, Xu K, Brener SJ, Mehran R, Stone GW. SYNTAX score and the risk of stent thrombosis after percutaneous coronary intervention in patients with non-ST-segment elevation acute coronary syndromes: an ACUITY Trial Substudy. *Catheter Cardiovasc Interv* 2015;85:1−10.
20. Palmerini T, Calabro P, Piscione F, De Servi S, Cattaneo M, Maffeo D, Toso A, Bartorelli A, Palmieri C, De Carlo M, Capodanno D, Barozzi C, Tomasi L, Della Riva D, Mariani A, Taglieri N, Reggiani LB, Bianchi R, De Rosa R, Mariani M, Podda G, Genereux P, Stone GW, Angiolillo DJ. Impact of gene polymorphisms, platelet reactivity, and the SYNTAX score on 1-year clinical outcomes in patients with non-ST-segment elevation acute coronary syndrome undergoing percutaneous coronary intervention: the GEPRESS study. *JACC Cardiovasc Interv* 2014;7:1117−1127.
21. Armstrong EJ, Kwa AT, Yeo KK, Mahmud E, Javed U, Patel M, Shunk KA, MacGregor JS, Low RI, Rogers JH. Angiographically confirmed stent thrombosis in contemporary practice: insights from intravascular ultrasound. *Catheter Cardiovasc Interv* 2013;81:782−790.
22. Doi H, Maehara A, Mintz GS, Yu A, Wang H, Mandinov L, Popma JJ, Ellis SG, Grube E, Dawkins KD, Weissman NJ, Turco MA, Ormiston JA, Stone GW. Impact of post-intervention minimal stent area on 9-month follow-up patency of paclitaxel-eluting stents: an integrated intravascular ultrasound analysis from the TAXUS IV, V, and VI and TAXUS ATLAS Workhorse, Long Lesion, and Direct Stent Trials. *JACC Cardiovasc Interv* 2009;2:1269−1275.
23. Mintz GS, Douek P, Pichard AD, Kent KM, Satler LF, Popma JJ, Leon MB. Target lesion calcification in coronary artery disease: an intravascular ultrasound study. *J Am Coll Cardiol* 1992;20:1149−1155.
24. Reisman M, Shuman BJ, Harms V. Analysis of heat generation during rotational atherectomy using different operational techniques. *Cathet Cardiovasc Diagn* 1998;44:453−455.
25. Reisman M, Shuman BJ, Dillard D, Fei R, Misser KH, Gordon LS, Harms V. Analysis of low-speed rotational atherectomy for the reduction of platelet aggregation. *Cathet Cardiovasc Diagn* 1998;45:208−214.
26. Zhang BC, Wang C, Li WH, Li DY. Clinical outcome of drug-eluting versus bare metal stents in patients with calcified coronary lesions: a meta-analysis. *Intern Med J* 2015;45:203−211.
27. Onuma Y, Tanimoto S, Ruygrok P, Neuzner J, Piek JJ, Seth A, Schofer JJ, Richardt G, Wiemer M, Carrie D, Thuesen L, Dorange C, Miquel-Hebert K, Veldhof S, Serruys PW. 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;76:634−642.
28. Jang JS, Song YJ, Kang W, Jin HY, Seo JS, Yang TH, Kim DK, Cho KI, Kim BH, Park YH, Je HG, Kim DS. Intravascular ultrasound-guided implantation of drug-eluting stents to improve outcome: a meta-analysis. *JACC Cardiovasc Interv* 2014;7:233−243.
29. Tellez A, Dattilo R, Mustapha JA, Gongora CA, Hyon CM, Palmieri T, Rousselle S, Kaluza GL, Granada JF. Biological effect of orbital atherectomy and adjunctive paclitaxel-coated balloon therapy on vascular healing and drug retention: early experimental insights into the familial hypercholesterolaemic swine model of femoral artery stenosis. *EuroIntervention* 2014;10:1002−1008.