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Randomized evaluation of vessel preparation with orbital atherectomy prior to drug-eluting stent implantation in severely calcified coronary artery lesions: Design and rationale of the ECLIPSE trial

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Background Severe coronary artery calcification has been associated with stent underexpansion, procedural complications, and increased rates of early and late adverse clinical events in patients undergoing percutaneous coronary intervention. To date, no lesion preparation strategy has been shown to definitively improve outcomes of percutaneous coronary intervention for calcified coronary artery lesions.

Study design and objectives ECLIPSE (NCT03108456) is a prospective, randomized, multicenter trial designed to evaluate two different vessel preparation strategies in severely calcified coronary artery lesions. The routine use of the Diamondback 360 Coronary Orbital Atherectomy System is compared with conventional balloon angioplasty prior to drug-eluting stent implantation. The trial aims to enroll approximately 2000 subjects with a primary clinical endpoint of target vessel failure, defined as the composite of cardiac death, target vessel-related myocardial infarction, or ischemia-driven target vessel revascularization assessed at 1 year. The co-primary endpoint is the acute post-procedural in-stent minimal cross-sectional area as assessed by optical coherence tomography in a 500-subject cohort. Enrollment is anticipated to complete in 2022 with total clinical follow-up planned for 2 years.

Conclusions ECLIPSE is a large-scale, prospective randomized trial powered to demonstrate whether a vessel preparation strategy of routine orbital atherectomy system is superior to conventional balloon angioplasty prior to implantation of drug-eluting stents in severely calcified coronary artery lesions. (Am Heart J 2022;249:1–11.)

Approximately one-third of patients undergoing percutaneous coronary intervention (PCI) have target lesions with moderate or severe calcification.[1-4] Treatment of calcified lesions has been strongly associated with higher rates of myocardial infarction (MI), stent thrombosis, and repeat revascularization after PCI, even with drug-eluting stents (DES), compared with non-calcified lesions.[3,5-8]

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Abbreviation: DES, drug-eluting stents; IVUS, intravascular ultrasound; MACE, major adverse cardiac events; MI, myocardial infarction; MSA, in-stent minimal cross-sectional area; OAS, orbital atherectomy system; OCT, optical coherence tomography; PCI, percutaneous coronary intervention; RVD, reference vessel diameter; STEMI, ST-segment elevation myocardial infarction; TVF, target vessel failure.

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Coronary artery calcification may result in stent delivery failure, structural damage to the polymer or implanted stent, and acute procedural complications including vessel dissection or perforation, no reflow, abrupt vessel closure, and distal embolization.[9-13] Up to 50% of coronary stents deployed in calcified lesions demonstrate asymmetry and/or underexpansion.[14,15] Stent underexpansion is associated with an increased risk of both stent thrombosis and restenosis.[4,16-18]

Although coronary atherectomy is considered an essential tool to facilitate device delivery and modify vessel compliance,[19] atherectomy is used in <5% of all PCI procedures, although with substantial variability between hospitals and operators.[20] This may in part be due to unfamiliarity with the technology, fear of complications, and lack of randomized clinical trial evidence supporting its routine use in severely calcified lesions. In the randomized Rotational Atherectomy Prior to Taxus Stent Treatment for Complex Native Coronary Artery Disease (ROTAXUS) trial (n = 240), routine pre-treatment of complex moderately or severely calcified lesions with high-speed rotational atherectomy compared with balloon angioplasty alone before first-generation paclitaxel-eluting stent implantation provided superior rates of procedural and strategy success[21]; however, late lumen loss and restenosis at 9 months were no different between groups,[9] and no improvement with atherectomy in clinical outcomes at 1-year or 2-year follow-up was present.[20] In the Comparison of Strategies to Prepare Severely Calcified Coronary Lesions (PREPARE-CALC) trial, a strategy of up-front rotational atherectomy was more often successful than a cutting or scoring balloon pre-dilatation strategy in 200 subjects with severely calcified lesions, but again there were no benefits in terms of late lumen loss or target lesion revascularization at 9 months with this approach.[22] Of note, both the ROTAXUS and PREPARE-CALC trials enrolled a small number of patients (240 and 200 patients respectively), and were therefore underpowered to demonstrate whether a routine atherectomy-based lesion preparation strategy for calcified coronary lesions confers a clinically relevant improvement in outcomes. Thus, absent a positive randomized trial, the best method of lesion preparation of calcified coronary artery lesions prior to DES implantation remains uncertain.

Orbital atherectomy

The Diamondback 360 Coronary Orbital Atherectomy System (OAS; Cardiovascular Systems, Inc, St. Paul, MN) has emerged as an effective alternative for lesion preparation of calcified coronary artery lesions. The OAS system consists of a 6 French compatible electronically-driven atherectomy device with a simplified set-up and table actuation. An offset diamond-coated crown is advanced over a dedicated wire (ViperWire Advance, Coronary Guide Wire, Cardiovascular Systems, Inc) and elliptically orbits within the vessel lumen when activated. Differential sanding of calcified tissue as well as lateral pulsatile forces on the vessel wall from the crown leads to plaque modification that facilitates stent delivery and expansion.

The safety and efficacy of OAS was evaluated in the single-arm, prospective Evaluate the Safety and Efficacy of OAS in Treating Severely Calcified Coronary Lesions (ORBIT II) study, in which 443 consecutive subjects with *de novo* severely calcified coronary lesions from 49 US sites were treated with OAS prior to stent implantation.[23] The primary efficacy endpoint was procedural success, defined as stent delivery with a residual stenosis of <50% without the occurrence of in-hospital major adverse cardiac events (MACE; a composite of MI, target vessel revascularization, or cardiac death). The primary safety endpoint was MACE at 30 days after the procedure. Both primary endpoints were assessed in comparison to prespecified objective performance goals, and both primary endpoints were met Table I. presents the outcomes from the ORBIT II study through 3-year follow-up.[23-26] On the basis of ORBIT II, the OAS Classic Crown system was approved by the United States Food and Drug Administration in 2013 with an indication to facilitate stent delivery in patients with coronary artery disease who are acceptable candidates for PCI or stenting due to *de novo*, severely calcified coronary artery lesions. OAS recently (January 2021) received CE Mark designation for its commercialization in Europe.

Despite the widely accepted belief that atherectomy enables greater stent expansion (the predominant determinant of restenosis and thrombosis), its infrequent use indicates uncertainty regarding its risk:benefit profile for routine lesion preparation of severely calcified lesions.[20] Table II summarizes the rates of clinical and angiographic outcomes from recent published data according to lesion preparation strategy in calcified lesions in patients without acute coronary syndromes (including balloon angioplasty, orbital atherectomy, rotational atherectomy, and cutting balloon) and stent type.[6,9,21,24,25] From these limited data it is impossible to be certain of the optimal lesion preparation strategy for severely calcified lesions. Given the commonality of calcified disease treated in routine practice, an appropriately powered randomized trial of contemporary lesion preparation strategies in severely calcified coronary artery lesions is thus warranted. Beyond an examination of the clinical impact of an atherectomy-based approach to lesion preparation, an imaging substudy embedded within the randomized trial might additionally inform whether the different mechanisms of balloon angioplasty and atherectomy[27-29] translate to the observed clinical findings.

Design of the ECLIPSE trial

The Evaluation of Treatment Strategies for Severe CaLcIfic Coronary Arteries: Orbital Atherectomy Versus Conventional Angioplasty Technique Prior to Implantation

Table I. ORBIT II major adverse cardiac events rates through 3-year follow-up

	In-hospital[23]	30 Days[23]	1 Year[24]	2 Years[25]	3 Years[26]
Major adverse cardiac events	9.8%	10.4%	16.9%	20.0%	23.5%
Myocardial infarction	9.3%	9.7%	10.6%	10.9%	11.2%
Non-Q-wave	8.6%	8.8%	9.7%	10.0%	10.0%
Q-wave	0.7%	0.9%	0.9%	0.9%	1.2%
TVR	0.7%	1.4%	5.8%	8.1%	10.2%
TLR	0%	0.7%	4.7%	6.2%	7.8%
Cardiac death	0.2%	0.2%	3.2%	4.7%	6.7%

TLR, target lesion revascularization; *TVR*, target vessel revascularization.

of Drug-Eluting StEnts (ECLIPSE) is a prospective, randomized, multicenter trial designed to evaluate a routine up-front vessel preparation strategy with OAS compared with conventional balloon angioplasty prior to DES implantation in severely calcified coronary artery lesions. The ECLIPSE trial is powered to demonstrate differences between groups in the co-primary endpoints of (1) target vessel failure (TVF) at 1 year, and (2) post-procedural in-stent minimal cross-sectional area (MSA) in a subset of patients undergoing optical coherence tomography (OCT) imaging at the conclusion of the PCI procedure. Approximately 2000 subjects will be enrolled from up to 150 sites in the US; approximately 500 subjects will be included in the OCT imaging cohort. The trial is funded by Cardiovascular Systems Inc, with independent angiographic and imaging core laboratories, an independent clinical events adjudication committee, and an independent data safety monitoring board.

Study population. Complete inclusion and exclusion criteria are shown in Table III. In brief, patients with stable ischemic heart disease or acute coronary syndromes (non–ST-segment elevation MI [STEMI] or unstable angina) or stabilized recent STEMI (>48 hours prior to randomization procedure) may be enrolled. Key angiographic inclusion criteria require *de novo* (non-restenotic) native coronary artery target lesion(s) with diameter stenosis ≥70% and <100%, or a stenosis ≥50% and <70% with evidence of ischemia on a stress test or with abnormal invasive physiology. Target lesions must have angiographic or intravascular imaging evidence of severe calcium at the lesion site. Severe angiographic calcification is defined as the presence of radiopacities noted without cardiac motion prior to contrast injection involving both sides of the arterial wall in at least 1 location, with total length of calcium ≥15 mm and extending at least partially into the target lesion. Severe calcification is defined by intravascular ultrasound (IVUS) or OCT as the presence of ≥270° of calcium in at least 1 imaging cross-section.

Key exclusion criteria include prior PCI in the target vessel or its branches within 12 months; unsuccessful or complicated PCI within 30 days, including during the randomization procedure; any cardiac intervention or cardiac surgery planned within 12 months post-randomization procedure except a planned staged PCI as part of the randomized treatment strategy; evidence of heart failure; and relative or absolute contraindication to dual antiplatelet therapy or (for patients with atrial fibrillation) single antiplatelet therapy (P2Y12 inhibitor preferred) with an anticoagulant for at least 6 months after PCI. Angiographic exclusion criteria include target lesions requiring treatment within or through a bypass graft, target lesions with thrombus, severe tortuosity, unprotected left main, aorto-ostial lesion, or true bifurcation with the side branch being severely calcified or requiring treatment. Additionally, while all sites are strongly encouraged to enroll consecutive patients meeting the entry criteria, patients may also be excluded if the investigator does not have equipoise regarding the treatment strategy (ie, in the investigator's opinion the target lesion absolutely requires atherectomy or the target lesion is absolutely contraindicated for atherectomy).

Non-target vessel treatment, PCI of multiple lesions or vessels, and staged procedures. Treatment of 1 or more lesions in a non-target vessel may occur prior to randomization or in the following situations: (1) During the procedure but prior to randomization if all lesions in the non-target vessel procedure are treated successfully and without complications; (2) >24 hours prior to randomization if all lesions in the non-target vessel procedure were treated successfully and without complications; and (3) >30 days prior to randomization regardless of whether any lesions in the non-target vessels were treated successfully and/or without complications (see Supplemental Appendix for more details). PCI of multiple lesions or vessels and staged procedures are allowed but only under specific conditions summarized in Supplemental Appendix Table SI.

OCT substudy. An OCT substudy will be performed in approximately 500 subjects meeting all OCT inclusion/exclusion criteria at qualifying sites to better understand the mechanisms of action of both vessel preparation strategies and their impact on stent expansion, dissections, and malapposition. For the OCT cohort only, patients with estimated glomerular filtration rate <50 mL/min/m^2 are excluded. Pre-treatment OCT is recom-

Table II. Adverse ischemic outcomes with atherectomy use in recent studies of patients without acute coronary syndromes

	ROTAXUS[9,21]		PREPARE-CALC[22]		ADAPT-DES[6]		ORBIT II†[24,25]			
	POBA + 1st-Gen DES (n = 120)	HSRA + 1st-Gen DES (n = 120)	CB/SB + 3rd-Gen DES (n = 100)	HSRA + 3rd-Gen DES (n = 100)	HSRA + 2nd-Gen DES (n = 100)	CB + 2nd-Gen DES (n = 34)	OAS Overall (n = 429)	OAS + BMS (n = 43)	OAS + 1st-Gen DES (n = 74)	OAS + 2nd-Gen DES (n = 312)
1-yr events*										
Target vessel failure‡	24.2%	28.3%	8%	6%	18.0%	8.8%	16.9%	24.3%	10.9%	15.8%
Death	5.0%	5.8%	2%	2%	3.0%	5.9%	4.4%	7.3%	5.5%	2.6%
Cardiac	—	—	1%	1%	1.0%	2.9%	3.2%	2.5%	4.1%	2.0%
Myocardial infarction	6.7%	5.8%	3%	2%	4.1%	0.0 %	10.6%	7.0%	5.4%	11.2%
Target lesion revascularization	11.7%	12.5%	7%	2%	11.2%	0.0%	4.7%	15.3%	1.4%	3.9%
Target vessel revascularization	16.7%	18.3%	8%	3%	14.2%	3.1%	5.8%	15.1%	2.8%	5.2%
2-yr events										
Target vessel failure‡	29.4%	34.3%	-	-	22.1%	25.0%	20.0%	24.3%	15.3%	18.8%
Death	8.3%	7.4%	-	-	6.0%	12.3%	7.9%	7.3%	8.4%	6.6%
Cardiac	—	—	-	-	3.1%	6.0%	4.7%	2.5%	5.6%	3.3%
Myocardial infarction	8.3%	6.5%	-	-	6.2%	3.1%	10.9%	7.0%	5.4%	11.6%
Target lesion revascularization	13.8%	16.7%	-	-	11.2%	3.1%	6.2%	15.3%	4.5%	5.3%
Target vessel revascularization	19.3%	22.2%	-	-	15.2%	14.4%	8.1%	15.1%	5.9%	7.3%

*ROTAXUS and PREPARE-CALC reported outcomes at 9 mo.
†ORBIT II 1- and 2-yr rates were updated at the 3-yr data extract.
‡for ORBIT II, major adverse cardiac event (MACE; cardiac death, myocardial infarction or target vessel revascularization) rate presented.
BMS, bare metal stents; *CB*, cutting balloon; *DES*, drug-eluting stents; *Gen*, generation; *HSRA*, high-speed rotational atherectomy; *OAS*, orbital atherectomy system; *POBA*, plain old balloon angioplasty; *SC*, scoring balloon.

Table III. ECLIPSE inclusion and exclusion criteria

Inclusion criteria

General inclusion criteria

1. Subject is 18 yrs of age or older.
2. Subject presents with: a) stable ischemic heart disease; b) acute coronary syndrome (NSTEMI or unstable angina); or c) stabilized recent STEMI (>48 hrs prior to randomization procedure)
3. Subject has signed written informed consent.

Angiographic inclusion criteria

1. The target lesion(s) is a de novo (non-restenotic) coronary lesion.
2. The target vessel(s) is a native coronary artery with:
   a. A stenosis ≥70% and <100%, or
   b. A stenosis ≥50% and <70% with evidence of ischemia via:
      i. Positive stress test, or
      ii. Fractional flow reserve (FFR) value ≤0.80, or
      iii. Instantaneous wave-free ratio (iFR) value ≤0.90
3. The reference diameter of each target vessel is ≥2.5 mm and ≤4.0 mm at the lesion site.
4. Each target vessel has TIMI flow 2 or 3 at baseline.
5. The target lesion has fluoroscopic, IVUS or OCT evidence of severe calcium at the lesion site defined as:
   • Via angiogram: presence of radiopacities noted without cardiac motion prior to contrast injection involving both sides of the arterial wall in at least one location, with total length of calcium ≥15 mm and extending partially into the target lesion, or
   • Via IVUS or OCT: presence of ≥270° of calcium in at least one cross section.

Exclusion criteria

General exclusion criteria

1. History of any cognitive or mental health status that would interfere with trial participation.
2. Participating in or has plans to participate in any other investigational drug or device trial that has not reached its primary endpoint.
3. Subject is a female who is pregnant.
4. Subject is receiving or scheduled to receive chemotherapy within thirty (30) days prior or any time after the randomization procedure.
5. Subject has a life expectancy of ≤12 mo.
6. Any PCI in the target vessel or its branches within 12 mo prior to randomization.
7. Subject has undergone a PCI procedure that is unsuccessful or with complications within 30 days prior to randomization, including during the randomization procedure.
8. Any cardiac intervention or cardiac surgery planned within 12 mo post randomization aside from a potential planned staged PCI as part of the randomized treatment strategy.
9. Subject has major valve disease and underwent intervention within 30 days prior to randomization.
10. Subject has received a heart transplant.
11. Evidence of heart failure by at least one of the following:
    a. Most recent LVEF ≤25%, or
    b. Current heart failure defined as dyspnea at rest (NYHA class IV assessed day of procedure), or
    c. Killip class ≥2 (post STEMI patients)
12. Planned use in the randomized lesion(s) of a bare metal stent (BMS), bioresorbable scaffold (BRS), or non-stent treatment only.
13. Subject has a known sensitivity to contrast media, which cannot be adequately pre-medicated.
14. Subject has a relative or absolute contraindication to dual antiplatelet therapy or (for patients with atrial fibrillation) single antiplatelet therapy (P2Y12 inhibitor preferred) with an anticoagulant for at least 6 mo after PCI.
15. Subject has a history of a stroke or transient ischemic attack (TIA) within six (6) months prior to randomization, or any permanent neurologic deficit.
16. Subject has a history of bleeding diathesis or coagulopathy or intention to refuse blood transfusion if one should become necessary.
17. Subject has evidence of an active infection on the day of the randomization procedure requiring oral or intravenous antibiotics.
18. Subject with known allergy to atherectomy lubricant components including soybean oil, egg yolk phospholipids, glycerin and sodium hydroxide.

OCT cohort exclusion criterion

1. CKD with eGFR <50 mL/min/m^2. These patients may be enrolled in the overall trial population but will not be included in the OCT imaging cohort.

Angiographic exclusion criteria

1. Each target lesion requires treatment within or through an arterial or venous bypass graft.
2. Each target vessel has angiographically visible or suspected thrombus.
3. Each target vessel has severe or excessive tortuosity.

(continued on next page)

Table III. (*continued*)

4. Each target lesion is an unprotected LM lesion, an aorto-ostial lesion (RCA within 3 mm of the aorta), or is within <3 mm of an unprotected LM (ie, proximal LAD or LCX within 3 mm of the LM).
5. Each target lesion is a true bifurcation with a heavily calcified side branch, or if the side branch requires planned stenting or other intervention (eg, atherectomy).

Note: True bifurcation lesions may be enrolled if all criteria below are met:

- Disease extension into the side branch ≤5 mm
- Side branch is not heavily calcified
- Intended treatment of the side branch is provisional balloon only or no treatment

6. Angiographic or imaging evidence of a dissection in the target vessel(s) prior to randomization.
7. All 3 major epicardial coronary arteries require treatment, unless the treatment of 1 or 2 vessels is staged (see planned staged procedure section).
8. Investigator does not have equipoise regarding the treatment strategy (ie, in the investigator's opinion the target lesion absolutely requires atherectomy OR the target lesion is absolutely contraindicated for atherectomy).

BMS, bare metal stent; *BRS*, bioresorbable scaffold; *FFR*, fractional flow reserve; *iFR*, instantaneous wave-free ratio; *IVUS*, intravascular ultrasound; *LAD*, left anterior descending; *LCX*, left circumflex; *LM*, left main; *LVEF*, left ventricle ejection fraction; *NSTEMI*, non–ST-segment elevation myocardial infarction; *OCT*, optical coherence tomography; *PCI*, percutaneous coronary intervention; *STEMI*, ST-segment elevation myocardial infarction; *TIA*, transient ischemic attack.

mended but not mandatory. Following stent implantation and optimization, a final post-stent OCT run must be conducted in all subjects to measure post-stent MSA and assess other OCT parameters. If additional therapies are administered following any OCT run, another final OCT run must be performed and will be used for final endpoint assessments.

Primary endpoints. The ECLIPSE trial is designed and powered to demonstrate differences in the co-primary endpoints of the clinical outcome of TVF at 1 year (in all subjects) and post-procedural MSA (in the OCT cohort).

TVF at 1 year. The primary clinical endpoint of TVF is defined as the composite of cardiac death, target vessel-related MI, or ischemia-driven target vessel revascularization at 1-year follow-up as adjudicated by the clinical events committee. For the principal analysis of the primary endpoint, MI events are adjudicated per the Third Universal Definition of Myocardial Infarction[30] except for Type 4a (post-PCI) and Type 5 (post-coronary artery bypass grafting) MI, both of which will be adjudicated per the Society for Cardiovascular Angiography and Interventions (SCAI) definitions of a clinically relevant MI.[31]

Acute MSA. Acute MSA is defined as the in-stent minimal cross-sectional area as assessed by OCT at the conclusion of the procedure. Post-procedure MSA will be assessed in qualifying OCT substudy patients and analyzed by the independent OCT core laboratory.

Secondary endpoints. *Procedural success.* Procedural success is defined as successful stent delivery with final core laboratory-defined TIMI flow 3 in the target vessel and angiographic in-stent diameter stenosis ≤20% in all treated lesions, and with the absence of stent loss, coronary perforation, or intra-procedural death. Since subjects may have multiple target lesions treated, a subject may have final TIMI flow assessed in several vessels and in-stent diameter stenosis measured in multiple lesions. For the procedural success endpoint, if there are multiple vessels or lesions treated as part of the randomization strategy, all must meet criteria for procedural success.

Strategy success. Strategy success is defined by procedural success without crossover to alternative treatment. For the strategy success endpoint, if there are multiple vessels or lesions treated as part of the randomization strategy, all lesions must meet criteria for strategy success. Additional data collection is summarized in Supplemental Appendix Table SII and will be reported as tertiary endpoints. These include angiographic, clinical, and health economic outcomes data that will contribute to the totality of the risk/benefit profile of the OAS procedure compared with control.

Randomization. Subjects who have signed an institutional review board/ethics committee-approved informed consent form and have met all of the inclusion criteria and none of the exclusion criteria will be randomized 1:1 to routine vessel preparation with OAS or a conventional balloon angioplasty pre-dilatation strategy. In order to ensure that the lesion can be crossed and for patient safety, randomization is performed after the target lesion(s) are successfully wired using a standard guidewire without complications, but before any interventional procedures (eg, angioplasty or atherectomy). Subject randomization will be stratified by site and extent of disease (single lesion or multiple lesions). Subjects with more than 1 severely calcified lesion (or vessel) can be randomized as long as all lesions (or vessels) meet eligibility criteria. All target lesions and vessels will be declared prior to randomization. All lesions will be treated with commercially available DES Figure. summarizes the study flow.

Study procedure and treatment arms. *Orbital atherectomy strategy.* The Diamondback 360 Coronary OAS 1.25 mm Classic Crown will be used for orbital atherectomy. Cutting and scoring balloons are also allowed in the OAS treatment arm, as well as all com-

mercially approved high-pressure balloon angioplasty catheters. However, no other atherectomy devices (ie, rotational or laser) or intravascular lithotripsy are permitted in the OAS treatment arm. Following OAS, balloon pre-dilatation (prior to DES implantation) is mandatory. Use of a non-compliant balloon for balloon pre-dilatation is strongly recommended, sized 1:1 to the reference vessel diameter (RVD), at increasing pressure until full balloon expansion is achieved. If full expansion is not achieved, additional treatment with OAS should be considered followed by repeat pre-dilatation with a non-compliant balloon until full balloon expansion is achieved on angiography. Following stent implantation, a 1:1 post-dilation with a non-compliant balloon at ≥18 atm is mandatory. In the case that the ViperWire Advance (or Flex Tip) coronary guidewire (Cardiovascular Systems, Inc) is unable to cross the lesion (eg, through a microcatheter or as a last resort after inflation of a 1.5 mm balloon), the subject will not be treated with OAS. The subject will be treated according to standard treatment and included in the intent-to-treat population for analysis.

Conventional balloon angioplasty strategy. Cutting and scoring balloons are allowed in this arm, as well as all commercially approved high-pressure balloon angioplasty catheters. No other atherectomy devices (ie, rotational or laser) or intravascular lithotripsy are permitted in the conventional balloon angioplasty treatment arm.

Crossover. Strict criteria for acceptable crossovers in each arm have been pre-specified in the protocol. An acceptable crossover from balloon angioplasty to OAS in the control arm is defined as occurring when: (1) The lesion cannot be crossed despite the use of ≥2 guidewires and ≥2 balloons and the use of a guide extension catheter or other advanced support options; (2) the lesion cannot be dilated despite the use of ≥2 balloons at a minimum of 16 atm and the attempted use of a cutting or scoring balloon at ≥12 atm; or (3) after balloon pre-dilatation, IVUS or OCT demonstrates ≥270° luminal calcification with residual minimal lumen cross-sectional area <3 mm^2 (despite non-compliant balloon dilation at a minimum of 16 atm).

An acceptable crossover from OAS to balloon angioplasty alone in the OAS arm is defined as occurring when the ViperWire Advance (or Flex Tip) cannot be passed distally in the vessel or when OAS will not advance or cross the lesion despite the use of a guide extension catheter or other advanced support options.

Rotational or laser atherectomy and lithotripsy are not permitted in either arm unless the target lesion is refractory to the 2 trial treatment arms (OAS and balloon angioplasty techniques). If used, rotational or laser atherectomy will be considered a crossover. An expert committee will classify crossovers as acceptable or unacceptable, per the definitions above, and review clinical decisions.

Follow-up. Follow-up visits will be performed at 30 days, 90 days, 1 year, and 2 years post-randomized procedure, and may be conducted by phone or office visit. Pre- and post-procedure pharmacotherapy (eg, antithrombin and antiplatelet agent use, statins, etc.) are per standard of care and are left to the discretion of the operator but should not vary by treatment arm.

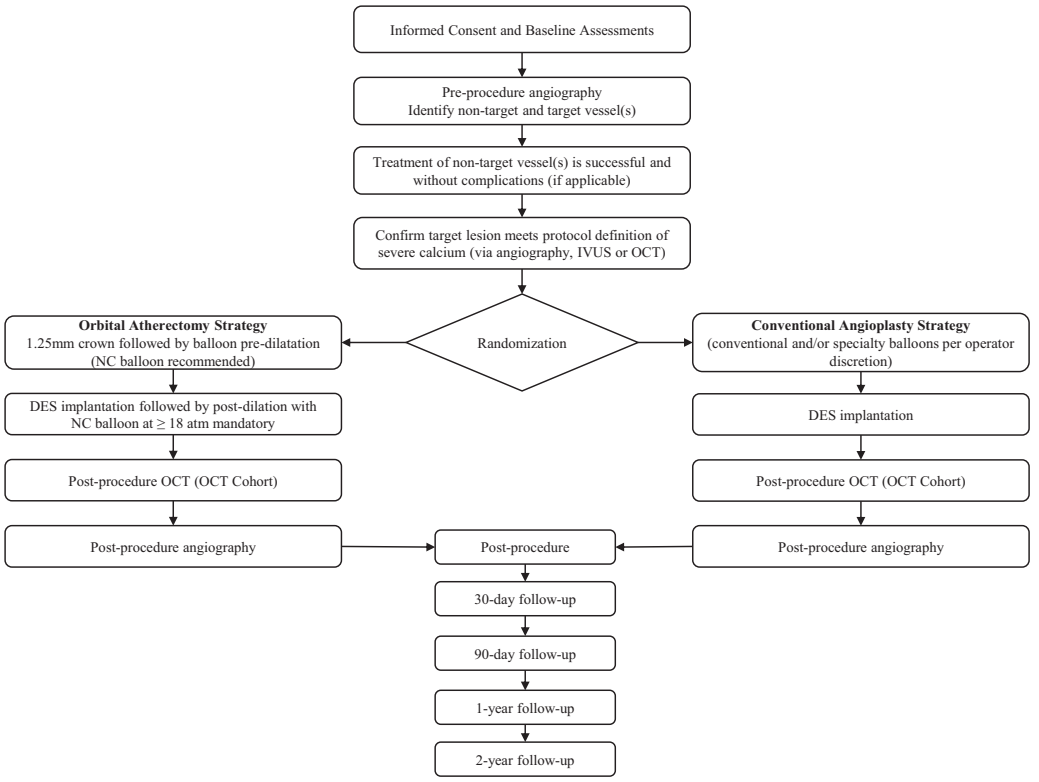
Statistical considerations

Sample size calculations and assumptions. Given that there are 2 co-primary endpoints, alpha will be shared between these 2 outcomes to control type I error. The trial will be considered successful if either co-primary endpoint is met. Based on sample size calculations (Table IV), the TVF endpoint requires the greatest number of subjects (1808); therefore, the overall sample size is based on this number. Enrollment of 1989 subjects is required to ensure that endpoint data are available for 1808 randomized subjects with severely calcified lesions after accounting for an attrition and missing data rate at 1 year of up to 10%. Additional subjects may be enrolled as needed to account for any data loss due to enrollment of subjects who did not meet criteria for severe calcium as determined by the core lab. The principal analyses for both co-primary endpoints as well as the secondary and tertiary endpoints will be performed in the intent-to-treat population. Sensitivity analyses will be performed in per-protocol, modified per-protocol, and as-treated populations.

Co-primary endpoint of TVF. The primary clinical hypothesis is that TVF at 1-year follow-up will be superior after lesion preparation of severely calcified lesions with OAS compared with the conventional balloon angioplasty prior to DES implantation. As shown in Table IV, 1808 evaluable samples provide 90% power to demonstrate a reduction in the 1-year rate of TVF from 14% with control to 9% with OAS (a 36% relative reduction) with a 2-sided type I error rate of 0.04. TVF occurring up to 1-year post-randomization will be evaluated using the 2-sided Wald test for binomial proportions.

Co-primary endpoint of acute MSA. The primary imaging hypothesis is that the MSA as assessed by OCT at the end of the procedure (after DES implantation) will be superior after lesion preparation with OAS compared with conventional balloon angioplasty. The primary analysis of OCT-measured post-procedure MSA will be performed in the pre-specified OCT cohort. As shown in Table IV, 376 evaluable samples provide 90% power to demonstrate a 1 mm^2 difference in the post-procedure MSA between groups with a standard deviation of 2.5 mm^2 and a 2-sided type I error rate of 0.01. The superiority of OAS to balloon angioplasty will be analyzed using a 1-way linear mixed model. This analysis accounts for clustering effect of multiple lesions per subject and will include the treatment as a fixed effect and subject as a

Figure 1



ECLIPSE Trial Flow Chart. *DES*, drug-eluting stent; *IVUS*, intravascular ultrasound; *NC*, non-compliant; *OCT*, optical coherence tomography.

Table IV. Sample size parameters and justification

Endpoint	N	N (with 10% attrition)	Control arm	Test arm	Standard deviation	Type I error	Power	Test
Target vessel failure	1808	1989	14%	9%	—	4%	90%	2-sided binomial proportions
MSA	376	414	4.5 mm^2	5.5 mm^2	2.5 mm^2	1%	90%	2-sided *t* test
Procedural success	870	—	85%	92%	—	5%	90%	2-sided binomial proportions

MSA, in-stent minimal cross-sectional area.

random effect. For the primary analysis no missing data will be replaced. As a sensitivity analysis, missing post-procedure MSA data will be imputed through multiple imputations using the Markov chain Monte Carlo algorithm based on pre-specified baseline covariates.[32,33]

Secondary powered endpoint: Procedural success. Procedural success will be analyzed on a subject level. As shown in Table IV, 870 subjects would provide 90% power to demonstrate an improvement in power from 85% with control to 92% with OAS with a 2-sided Type I error rate of 0.05.

Adaptive design. When the trial has enrolled 700 (~35%) patients and these patients have reached their 1-year follow-up visit and their reported events have been adjudicated, the conditional power for 1-year TVF will be calculated using the same method used for the original power calculations with assumptions based on the collected data. Depending on the conditional power, an unblinded statistician independent of trial leadership may recommend a sample size re-estimation based on the adaptive sample size re-estimation methodology described by Mehta and Pocock.[34] Enrolling 700 patients (n_1) out of a planned total 2000 (n_2), and allowing a maximum possible enrollment of 4000 patients (n_{max}), the ratio of interim patients divided by planned final patients is (n_1/n_2=0.35), allowable patients divided by final planned patients is (n_{max}/n_2 = 2.0), and our promising zone, given a 90% conditional power, starts at ~37% and ends at 90%. This can be verified in Table I of Mehta and Pocock.[34] If at the interim data look, the conditional power falls below 37% or above 90%, then the trial will not enroll additional subjects beyond the

planned 2000 subjects. If the conditional power is between 37% and 90%, sample size will be re-estimated by the unblinded statistician to restore 90% power using assumptions based on the observed data up to that point. Recommendations regarding resizing the trial based on this analysis (without revealing any of the unblinded data) will be provided to the sponsor and steering committee who may elect to accept or reject them.

Subgroup analyses. Subgroup analyses will be performed for the co-primary endpoints in the following subgroups: OCT cohort and non-OCT cohorts; age (<65 years of age versus ≥65); sex; diabetes; baseline chronic kidney disease; clinical presentation (biomarker-positive acute coronary syndromes or recent STEMI versus other); target lesion length of longest lesion (<20 mm, 20-30 mm, >30 mm); single versus multiple lesions treated; smallest RVD (≥ median RVD versus < median RVD and categorized as ≤2.5 mm, >2.5-3.0 mm, >3.0 mm); tortuosity of any treated lesion (none versus moderate or severe); angulation of any treated lesion (>45° versus ≤45°); access site (femoral versus radial); angiographic core laboratory calcium severity; OCT core laboratory calcium severity, arc of calcium, and maximal calcium thickness; and selection of ViperWire Advance with Flex Tip versus ViperWire Advance. The consistency of the relative risks in the treatment versus the control arm across each subgroup pair will be evaluated by interaction testing; formal hypothesis testing for each subgroup will not be performed.

Potential study limitations and mitigation

Although ECLIPSE represents the largest prospective randomized evaluation to date of an atherectomy device in severely calcified coronary lesions, several limitations of the current trial should be acknowledged:

Calcium severity, clinical equipoise, and crossover

The ECLIPSE trial was designed to enroll severely calcified lesions, those in which adequate vessel preparation might be the most beneficial. To ethically randomize such subjects, an investigator must enroll lesions for which true clinical equipoise is present with regard to both treatment strategies. Selective enrollment might skew inclusion to less severe calcification, potentially mitigating the benefits of OAS compared with a conventional balloon-based approach. To mitigate this concern site selection included assessment of each potential center's attitudes toward atherectomy use in severely calcified lesions, with only those sites chosen where the participating operators had equipoise to allow randomization of nearly all consecutive eligible patients. In addition, active monitoring of the severity of coronary calcium is ongoing within the trial as adjudicated by the angiographic and OCT core laboratories. Sites that enroll lesions not meeting the study definition of severe calcification are put on hold for re-training and will be dropped if proper patient selection cannot be subsequently demonstrated. However, patients enrolled without severe calcium will be included in the intent-to-treat analyses.

Excessive crossover rates between the randomized groups might also bias the findings toward the null hypothesis of no difference between arms. As described above, the study protocol pre-specifies strict criteria for acceptable crossovers in an attempt to keep overall rates of crossover low while still permitting safe treatment of study subjects. All crossover cases are actively reviewed by an independent study committee providing feedback to sites. Sites with unacceptable crossovers may also be put on hold for re-training.

Use of intravascular imaging and generalizability of results

Consistent with conventional clinical practice at the time of trial design, the primary criteria for enrollment of angiographically severe calcified lesions is based upon angiographically determined calcium. Although intravascular imaging-based calcium assessment is included as part of the enrollment criteria, it is expected that the majority of patients will be enrolled based upon angiography alone. Since the trial's design and inception, there has been increasing awareness and use of imaging-guided strategies to inform and direct plaque modification strategies, and the extent to which this may impact the trial results is unknown.

In randomized OCT substudy patients, post-procedural OCT might lead operators to perform additional treatments, thereby optimizing results compared with non-OCT patients and potentially narrowing stent expansion and other parameters between the 2 strategies. While a limitation, such practice represents appropriate responses to OCT-guided stent implantation and is allowed, with a final OCT reassessment made after completion of any additional treatments. Further, the relative outcomes of the OCT and non-OCT cohorts will be examined.

Finally, the ECLIPSE trial compares OAS with a conventional balloon-based approach for vessel preparation of severely calcified lesions prior to contemporary DES implantation. Direct comparison with other techniques such as rotational atherectomy, laser atherectomy, or intravascular lithotripsy is not possible within this study. Nor will the results be generalizable to moderately calcified lesions.

Impact of the COVID-19 pandemic

The first patient was randomized in the ECLIPSE trial on March 27, 2017. In early 2020, with just over two-thirds of the anticipated number of subjects enrolled, the COVID-19 pandemic struck, with dramatic effects on

clinical research programs. In order to preserve personal protective equipment and to limit hospital and research personnel and catheterization laboratory staff exposure, the trial steering committee and study sponsor recommended suspending enrollment in the ECLIPSE trial on March 20, 2020. All follow-up visits were transitioned to phone/telehealth, and a remote site monitoring program was initiated. Several additional fields were added to the trial case report forms in order to capture antecedent COVID-19 infections. After several months of observation, the trial was cautiously re-initiated at selected sites in October 2020, but continued modifications have been made to study processes, and patients enrolled in the trial as well as study teams have no doubt been affected by the pandemic. Despite a randomized study design, which fortunately should balance pandemic-related effects across trial arms, the impact of the pandemic upon enrollment, follow-up, and outcomes (eg, if a patient were to have severe COVID-19–related illness) is yet to be determined.

Summary

ECLIPSE is a large-scale, prospective, randomized trial powered that is evaluating whether vessel preparation with OAS is superior to conventional balloon angioplasty for the treatment of severely calcified coronary artery lesions prior to implantation of contemporary DES. The ECLIPSE trial is designed and powered to demonstrate differences in the co-primary endpoints of post-procedural MSA as assessed by OCT and TVF at 1 year. With 2000 patients randomized and undergoing 2-year follow-up, the ECLIPSE trial will provide robust evidence to guide the interventional management of patients with severely calcified coronary artery lesions.

Conflict of interest

Dr Généreux: Speaker fee – Abiomed, Edwards Lifesciences, Medtronic; Shockwave, Teleflex, consultant – Abbott Vascular, Abiomed, Boston Scientific, Cardiovascular System Inc, Cordis, Edwards Lifesciences, iRythm, Medtronic, Opsens, Pi-Cardia, Saranas, Siemens Healthcare, SIG.NUM, Soundbite Medical Solutions Inc. Teleflex; 4C Medical, Equity/options – Pi-Cardia, Puzzle Medical, Saranas, SIG.NUM, Soundbite Medical. Dr Kirtane: Institutional funding to Columbia University and/or Cardiovascular Research Foundation from Medtronic, Boston Scientific, Abbott Vascular, Abiomed, CSI, CathWorks, Siemens, Philips, ReCor Medical. In addition to research grants, institutional funding includes fees paid to Columbia University and/or Cardiovascular Research Foundation for speaking engagements and/or consulting. Personal: Consulting – Neurotronic; travel expenses/meals from Medtronic, Boston Scientific, Abbott Vascular, Abiomed, CSI, CathWorks, Siemens, Philips, ReCor Medical, Chiesi, OpSens, Zoll, and Regeneron. Dr Kandzari: Institutional research/grant support – Abbott Vascular, Biotronik, Boston Scientific, Cardiovascular Systems, Medtronic, Teleflex; personal consulting honoraria – Cardiovascular Systems, Medtronic. Dr Armstrong: Consultant for Abbott Vascular, Boston Scientific, Cardiovascular Systems Inc, Intact Vascular, Gore, Medtronic, Philips, and Shockwave. Dr Krucoff: Consulting/speaker fee: Abbott Vascular, Biosensors, Boston Scientific, Cardiovascular System Inc, Medtronic, OrbusNeich, SMT, Terumo; Research grants: Abbott Vascular, Biosensors, Boston Scientific, Cardiovascular System Inc, Medtronic, OrbusNeich, SMT, Terumo, Cook, Gore. Dr Lerew: Employee – Cardiovascular Systems, Inc. Dr Ali: Institutional research grants to Columbia University – Abbott, Cardiovascular Systems Inc; consultant – Amgen, AstraZeneca, Boston Scientific.; equity – Shockwave. Dr Maehara: Grant support and consultant - Abbott Vascular and Boston Scientific. Dr O'Neill: Consultant - Edwards Lifesciences, Abbott, and Boston Scientific. Dr Stone: Speaker or other honoraria from Cook and Terumo; Consultant to Valfix, TherOx, Vascular Dynamics, Robocath, HeartFlow, Gore, Ablative Solutions, Miracor, Neovasc, V-Wave, Abiomed, Ancora, MAIA Pharmaceuticals, Vectorious, Reva, Matrizyme, Cardiomech, Elucid Bio, Occlutech; Equity/options from Ancora, Cagent, Applied Therapeutics, Biostar family of funds, SpectraWave, Orchestra Biomed, Aria, Cardiac Success, MedFocus family of funds, Valfix. Other authors: None.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ahj.2022.03.003.

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