The OPTIMIZE randomized trial to assess safety and efficacy of the Svelte IDS and RX Sirolimus-eluting coronary stent Systems for the Treatment of atherosclerotic lesions: Trial design and rationale

Laura Mauri, MD, MSC, [a] Gheorghe Doros, PhD, [b,c] Sunil V. Rao, MD, [d] David J. Cohen, MD MSC, [e] Steven Yakubov, MD, [f] John Lasala, MD, PhD, [g] S. Chiu Wong, MD, [h] James Zidar, MD, [i] and Dean J. Kereiakes, MD [j]

Background Coronary stenting without angioplasty pretreatment (direct stenting) may simplify procedures in appropriate lesions. Direct stenting is facilitated by smaller profile coronary stent platforms. The present study was designed for regulatory approval of a novel drug-eluting coronary stent and incorporates both randomized comparison for non-inferiority to an approved predicate device as well as a nested evaluation of subjects eligible for direct stenting.

Study Design and Objectives Prospective, single-blind, randomized, active-control, multi-center study designed to assess the safety and efficacy of the novel Svelte sirolimus-eluting stent (SES) systems. A total of 1630 subjects with up to 3 target lesions will be randomized 1:1 to the Svelte SES versus either the Xience or Promus everolimus-eluting stents (control). Randomization will be stratified by whether or not a direct stenting strategy is planned by the investigator. The primary endpoint is target lesion failure (TLF) at 12 months post index procedure, defined as cardiac death, target vessel myocardial infarction, or clinically driven target lesion revascularization, and the primary analysis is a non-inferiority test with a non-inferiority margin of 3.58%. Secondary clinical endpoints include individual components of TLF, stent thrombosis and measures of procedural resource utilization including contrast administration, fluoroscopy exposure and procedural resource utilization as well as costs.

Conclusion The OPTMIZE Trial will evaluate the safety, efficacy and clinical value of the novel Svelte SES in subjects with up to 3 lesions, and will provide a comparison of direct stenting between randomized devices. (Am Heart J 2019;216:82-90.)

Drug-eluting stents (DES) are the mainstay of percutaneous coronary revascularization for patients with both stable ischemic heart disease and acute coronary syndromes. Through the evolution in coronary stent design, safer drug-polymer combinations have been identified and smaller profile devices have facilitated the use of radial artery access. Further, a direct stenting strategy (without pre-dilation) may reduce procedural time and resource consumption when compared with the conventional multistep approach.

Conventional percutaneous coronary intervention (PCI) usually includes pre-dilation of the target lesion prior to stent placement. This convention was dictated, in large part, by the physical characteristics of early stents, which were relatively large caliber, inflexible devices that could not be reliably delivered to the target lesions. Additionally, early stents were often hand-crimped onto balloon catheters, with tenuous securement and unreliable stent retention on their delivery systems.[1,2] These features made balloon pre-dilation of the target lesion mandatory for reliable stent delivery. Current generation stents and stent delivery systems may facilitate stent placement without pre-dilation, a strategy known as 'direct stenting'.

Direct stenting is currently employed in approximately 30−40% of PCI procedures,[3,4] and has been compared with conventional stenting (using pre-dilation) in numerous observational[5-11] and randomized studies[12-19] predominantly using bare metal stents (BMS). In select lesions (lower degrees of lesion calcification with minimal vessel tortuosity), high rates of technical and procedural success have been observed.[14-17] Additionally, significant reductions in procedure time, radiation exposure, contrast administration and cost have been realized with comparable 6−12-month clinical outcomes.[8,9,12-19]

From the [a]Harvard Medical School, [b]Baim Institute for Clinical Research, [c]Department of Biostatistics, Boston University, [d]The Duke Clinical Research Institute, [e]Saint Luke's Mid America Heart Institute, Kansas City, MO, [f]OhioHealth Riverside Methodist Hospital, [g]Washington University School of Medicine in St. Louis, [h]Weil Cornell Medicine, [i]University of North Carolina, and [j]The Christ Hospital and Lindner Research Center.
RCT# NCT03190473
Sorin Jakob Brener, MD served as guest editor for this article.
Submitted September 27, 2018; accepted July 5, 2019.
Reprint requests: Dean J. Kereiakes MD FACC FSCAI, The Christ Hospital Heart and Vascular Center, And The Christ Hospital Research Institute, 2123 Auburn Avenue Suite 424, Cincinnati, OH 45219.
E-mail: Lindner@thechristhospital.com
0002-8703

https://doi.org/10.1016/j.ahj.2019.07.003

While PCI with stenting for coronary artery disease is associated with high rates of clinical success and low procedural morbidity, the risks of radiation exposure, contrast use and access site bleeding, as well as overall procedure costs are not negligible. Clinical risks are incrementally higher in subjects with advanced age,[20,21] multi-vessel disease requiring staged procedures, chronic kidney disease[22,23] and peripheral arterial disease,[24,25] and mitigation of these risks is of paramount importance.

Fixed-wire balloon catheters were introduced in the early days of PCI to provide lower profile options particularly for treatment of complex lesions.[26,27] As stent technology evolved, conventional angioplasty balloons were relegated to pre-and post-dilation functions, and guide wire-based stent delivery systems became dominant in context that multiple device exchanges were often necessary.

Although adverse clinical events have progressively declined from BMS to first and subsequently, second generation durable polymer DES,[28-42] even "best −in −class" second generation DES durable polymers have occasionally been incriminated in development of inflammation, thrombosis and neo-atherosclerosis. In attempt to further improve clinical outcomes, DES with bioresorbable polymers have been developed, which completely resorb following drug elution to leave behind a bare metal scaffold.[43-48]

The Svelte sirolimus-eluting stent (SES)-integrated delivery system (IDS) consists of a balloon expandable, thin (81 micron)-strut cobalt chromium coronary stent which elutes sirolimus from a novel, fully bioresorbable polymer and is pre-mounted on a single lumen, fixed-wire delivery system. The Svelte SES-rapid exchange (RX) consists of the same DES platform pre-mounted on a rapid-exchange delivery system. The Svelte SES-IDS is specifically designed to facilitate direct stenting and radial access PCI. The Svelte SES-IDS system has the smallest caliber crossing profile among currently available DES. The 2.50 and 3.00 mm IDS devices have 0.031 and 0.032 inch crossing profiles respectively. The pharmacokinetics of the Svelte SES has been designed to mimic the drug release of the Cipher (Cordis/Johnson & Johnson) SES and XIENCE (Abbott Vascular) everolimus-eluting stent (EES). The Svelte novel polymer is an amino-acid composition which undergoes enzymatic degradation with complete resorption in approximately 12 months, leaving behind the cobalt chromium stent.

Study design

Objective and design

The objective of the OPTIMIZE Study (ClinicalTrials.gov NCT03190473) is to assess the safety and efficacy of the Svelte SES-IDS and Svelte SES-RX compared with either the Xience or Promus EES (control) in subjects with ≤3 de novo target lesions in ≤2 native coronary artery vessels, with a maximum of 2 lesions in a single vessel.

OPTIMIZE is a prospective, single (patient)-blind, randomized, active-control, multi-center study which will include up to 120 sites in the United States (US), Europe and Japan (with up to one third of the sites outside of the US). A total of 1630 subjects will be randomized in a 1:1 ratio to Svelte SES (IDS or RX) or control DES (Fig. 1). Subjects will be followed through 5 years post index procedure, with clinical follow-up at 30 days, 6 months, 12 months, and annually thereafter through 5 years.

A subgroup of 150 subjects (75 subjects per treatment group) at up to 5 sites in the US and 10 sites in Japan will have angiographic evaluation at 12 months post procedure with the first 60 subjects (30 subjects per treatment group) also having an intravascular ultrasound (IVUS) evaluation.

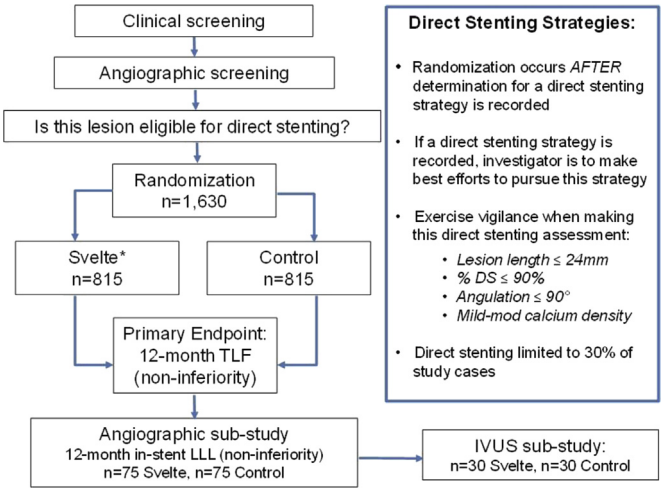
Study Sample

Subjects aged ≥18 years with symptomatic coronary artery disease due to de novo lesions in native coronary arteries with a reference vessel diameter of 2.25−4.0 mm and lesion length of ≤34 mm, who qualify for PCI with stenting, are eligible for enrollment. Up to 3 target lesions in up to 2 separate target vessels are permitted with up to 2 lesions in a single vessel. The target lesions are required to have angiographic evidence of ≥50% and< 100% stenosis with Thrombolysis in Myocardial Infarction (TIMI) flow >1. The target lesion cannot be located in or accessed via a saphenous vein graft or an arterial graft. The target lesion can not be in the left main coronary artery, within 3 mm of the origin of the left anterior descending or left circumflex coronary arteries, or involving a complex bifurcation (e.g. bifurcation lesion requiring treatment with more than 1 stent). Subjects with acute ST-elevation myocardial infarction (STEMI) are excluded; however, clinically and hemodynamically stable STEMI subjects after successful primary PCI with decreasing cardiac enzymes ≥72 hours prior to the index procedure are eligible for enrolment. Clinically and hemodynamically stable non-STEMI subjects with decreasing cardiac enzymes prior to the index procedure are also eligible. Subjects are further screened per the protocol inclusion and exclusion criteria (Table 1) to achieve a total of 1630 randomized subjects from 120 sites in and out of the US. (See Fig. 1).

Devices

The Svelte stent is a thin-strut (81 μm for 3-cell and 84 μm for 4-cell), highly flexible, cobalt chromium (CoCr) alloy (L605) designed to provide flexibility during delivery and vessel conformability following expansion. The Svelte stent has a low crimped profile compared with conventional stents, attaining a cross–sectional area approximately one-half that of currently approved stents.

Figure 1



OPTIMIZE Study Design and Patient Flow.

Polymer-based drug carriers are critical to the safety and efficacy of DES, as they regulate drug elution and may be the cause of lingering and late inflammatory responses. The Svelte carrier is a biocompatible and bioresorbable polyesteramide (PEA); a synthetic amorphous elastomeric random copolymer consisting of amino acid units separated by hydrocarbon diacid and diol spacers (tradename PEA III Ac Bz). The PEA carrier is mixed with sirolimus

(70%/30% wt/wt PEA/sirolimus ratio) and directly applied to the entire stent surface. There are no primer or topcoat layers.

The PEA carrier biodegradation occurs in vitro by surface erosion through enzyme-mediated hydrolysis with minimal change in molecular weight of the non-eroded coating remaining on the substrate. The primary enzymatic chain scission takes place at the ester linkages And provides a more controlled degradation process compared with bulk erosion via hydrolysis. The initial degradation products resulting from the chain scission are typically oligomers containing the original monomeric species. Further enzymatic and hydrolytic degradation of these oligomers produces the naturally occurring amino acid, alcohol and fatty carboxylic acid units which are further converted to common metabolites and removed through typical biological pathways. From the time of stent implantation, drug content is eluted within 60 days and the drug carrier is resorbed within 12 months.

The Svelte SES-IDS system has a 0.014″ (0.36 mm) shapeable, radiopaque wire tip that extends 35 mm beyond the balloon tip, a low-compliant delivery balloon and a proximal shaft compatible with 5 French guiding catheters (≥ 0.056″ / 1.42 mm ID) (Fig. 2). The Svelte SES-RX system is compatible with guide wires of outer diameter 0.014″ (0.36 mm) and 5F guiding catheters (≥ 0.056″ / 1.42 mm ID).

The Svelte DES-IDS and Svelte DES-RX systems are available in diameters 2.50, 3.00 and 3.50 mm and in lengths 8 mm, 13 mm, 18 mm, 23 mm and 28 mm. The Svelte DES-RX is additionally available in 2.25 and 4.00 mm diameters with lengths 8 mm, 13 mm, 18 mm, 23 mm and 28 mm, and in 2.50 mm, 3.00 mm, 3.50 mm and 4.00 mm diameters with lengths 33 mm and 38 mm.

Control DES include any commercially available Xience EES (Abbott Vascular, Santa Clara, California) or Promus EES (Boston Scientific, Marlborough, Massachusetts).

Endpoints

The primary endpoint is target lesion failure (TLF) rate at 12 months post procedure, defined as the composite of all cardiac deaths, target vessel myocardial infarctions (MIs) (Q-wave or non−Q-wave), or clinically driven target lesion revascularizations (TLRs).

Secondary endpoints include device success, lesion success, procedure success, direct stent strategy success, procedure time, intervention time, device time, vascular complications, transfusion, hematoma, contrast volume, fluoroscopy duration, death (cardiac and non-cardiac), target vessel MI, TLR (total and clinically driven), target vessel revascularization (TVR) (total and clinically driven), major adverse cardiac events (MACE), TLF, target vessel failure (TVF), and stent thrombosis according to Academic Research Consortium (ARC) criteria.[49] See Table 2 for complete definitions.

Table 1. Inclusion and exclusion criteria of the OPTIMIZE study.

General Inclusion Criteria

1. Subject is ≥18 years old;
2. Subject (or subject's legal representative) understands the study requirements, the treatment procedures and provides written informed consent before any study-specific tests or procedures are performed;
3. Japan Only: For subject <20 years of age, the subject and the subject's legal representative must provide written informed consent before any study specific tests or procedures are performed;
4. Subject is eligible for PCI;
5. Subject has symptomatic coronary artery disease with objective evidence of ischemia or silent ischemia;
6. Subject has clinical symptoms or ECG changes consistent with non-STEMI), is clinically and hemodynamically stable and has cardiac enzymes documented to be decreasing prior to the study procedure (CK-MB is preferred, but if troponin is assessed, enzymes decreasing, stable or elevated up to 20% over the prior assessment are acceptable);
7. Subject is an acceptable candidate for CABG;
8. Subject agrees to comply with specified follow-up evaluations.

Angiographic Inclusion Criteria (Visual Estimate):

1. Subject has ≤3 de novo target lesions in ≤2 native coronary artery vessels, with
   ≤ 2 lesions in a single vessel, each meeting the angiographic criteria and none of the exclusion criteria;
2. Target lesion(s) must be located in a native coronary artery with RVD ≥ 2.25 mm and ≤ 4.00 mm;
3. Target lesion(s) length must be ≤34 mm (the intention should be to cover the whole lesion with one stent of adequate length);
4. Target lesion(s) must have visually estimated stenosis ≥50% and< 100% with TIMI flow >1 and confirmation by ACC/AHA guideline compliant physiologic assessment. For lesions with visually estimated stenosis ≥50% and ≤ 70%, additional confirmation by ACC/AHA guideline compliant physiologic assessment is required;
5. Coronary anatomy is likely to allow delivery of a study device(s) to the target lesion(s).

General Exclusion Criteria:

1. Subject has clinical symptoms or ECG changes consistent with acute STEMI. Subject may be included if primary PCI for STEMI was successfully completed and subject is clinically and hemodynamically stable with cardiac enzymes documented to be decreasing ≥72 hours prior to the study procedure;
2. Subject has cardiogenic shock, hemodynamic instability requiring inotropic or mechanical circulatory support, intractable ventricular arrhythmia, or ongoing intractable angina;
3. Subject has received an organ transplant or is on a waiting list for an organ transplant;
4. Subject is receiving or is scheduled to receive chemotherapy 30 days before or after the index procedure;
5. Subject requires a planned PCI (including staged procedures) or CABG after the index procedure;
6. Subject was previously treated at any time with intravascular brachytherapy;
7. Subject has a known allergy to contrast (that cannot be adequately premedicated) and/or the study stent systems or protocol-required concomitant medications
   (e.g. platinum, platinum-chromium alloy, stainless steel, sirolimus, everolimus or structurally related compounds, polymer or individual components, all P2Y12 inhibitors or aspirin);
8. Subject has one of the following (as assessed prior to the index procedure):
   a. Other serious medical illness (e.g. cancer, congestive heart failure) with an estimated life expectancy of <24 months;
   b. Current problems with substance abuse (e.g. alcohol, cocaine, heroin, etc.);
   c. Planned procedure that may cause non-compliance with the protocol or confound data interpretation;
9. Subject is receiving chronic (≥ 72 hours) anticoagulation therapy (e.g. heparin, coumadin) for indications other than acute coronary syndrome;
10. Subject has a platelet count <100,000 cells/mm3 or> 700,000 cells/mm3;
11. Subject has a white blood cell count <3000 cells/mm3;
12. Subject has documented or significant liver disease, including laboratory evidence of hepatitis;
13. Subject is on dialysis or has a baseline serum creatinine level> 2.0 mg/dL (177 μmol/L);
14. Subject has a history of bleeding diathesis or coagulopathy or will refuse blood transfusions;
15. Subject has a history of a CVA or TIA within the past 6 months;
16. Subject has an active peptic ulcer or active gastrointestinal bleeding;
17. Subject has severe symptomatic heart failure (i.e. NYHA class IV);
18. Subject intends to participate in another investigational drug or device clinical study within 12 months after the index procedure;
19. Subject has a known intention to procreate within 12 months after the index procedure (a woman of child-bearing potential who is sexually active must agree to use a reliable method of contraception from the time of screening through 12 months after the index procedure);
20. Subject is pregnant or nursing (subject must have a negative pregnancy test within 7 days prior to the index procedure if a woman of child-bearing potential);
21. Subject is participating in another investigational drug or device clinical study;
22. Planned use of cutting balloon or atherectomy (rotational, orbital, laser or other) of the target lesion(s) during the index procedure.

Angiographic Exclusion Criteria (visual estimate):

1. Subject has a planned treatment of >3 lesions;
2. Subject has a planned treatment of >2 major epicardial vessels;
3. Subject has a planned treatment of a single lesion with >1 stent;
4. Subject has 2 target lesions in the same vessel that are separated by <15 mm;
5. Subject's target lesion(s) is located in the left main artery;
6. Subject's target lesion(s) is located within 3 mm of the origin of the LAD or LCX coronary arteries;
7. Subject's target lesion(s) is located within a SVG or arterial graft;

(continued on next page)

8. Subject's target lesion(s) will be accessed via SVG or arterial graft;
9. Subject has a target lesion(s) with TIMI flow 0 (total occlusion) or TIMI flow 1 prior to guide wire crossing;
10. Subject's target lesion(s) involves a complex bifurcation (e.g. bifurcation lesion requiring treatment with more than 1 stent);
11. Subject's target lesion(s) is restenotic from previous stent implantation or a study stent would overlap with a previously implanted stent;
12. Subject has unprotected left main coronary artery disease (> 50% diameter stenosis);
13. Subject has been treated with any type of PCI (i.e. balloon angioplasty, stent, cutting balloon or atherectomy) 24 hours prior to the index procedure;
14. Subject has thrombus or possible thrombus present in the target vessel.

ACC, American College of Cardiology; *AHA*, American Heart Association; *CABG*, coronary artery bypass graft; *CK-MB*, creatine kinase myocardial band; *CVA*, cardiovascular accident; *ECG*, electrocardiogram; *LAD*, left anterior descending; *LCX*, left circumflex; *NYHA*, New York Heart Association; *PCI*, percutaneous coronary intervention; *RVD*, reference vessel diameter; *STEMI*, ST elevation myocardial infarction; *SVG*, saphenous vein graft; *TIA*, transient ischemic attack; *TIMI*, thrombolysis in myocardial infarction.

Angiographic and IVUS Sub-study Endpoints

The primary angiographic endpoint is in-stent late lumen loss (LLL) at 12 months post-procedure. Secondary angiographic and IVUS endpoints at 12 months include in-segment LLL, minimum lumen diameter (MLD), % diameter stenosis, binary restenosis, % volume obstruction and incomplete apposition. Independent core laboratories will assess all angiographic and IVUS data.

Randomization

Eligible subjects will be randomized in a 1:1 ratio to undergo percutaneous coronary revascularization with either the Svelte SES-IDS or Svelte SES-RX (investigational group) or the Xience EES or Promus EES (control group). Prior to randomization, the investigator will declare the planned stenting strategy (i.e., direct stenting or pre-dilation). Randomization will be stratified based on the stenting strategy.

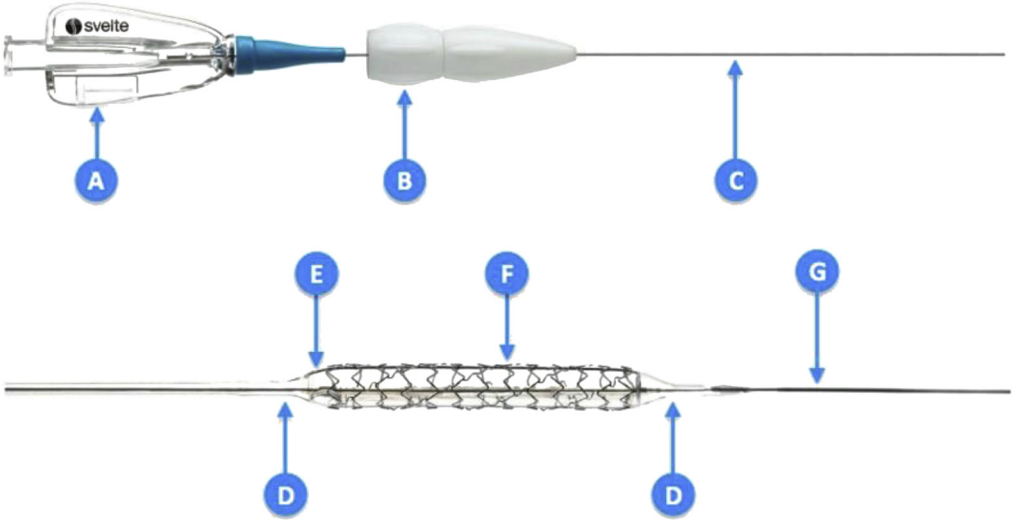
Direct Stenting versus Pre-dilation

All lesions must be treated with the same stenting strategy; i.e., if one lesion is not eligible for direct stenting, then all target lesions in that patient must be treated using a pre-dilation approach. Lesions eligible for direct stenting are those up to 24 mm in length with diameter stenosis ≤90%, angulation ≤90° and mild to moderate calcium density. Moderate-to-severely calcified and highly stenosed (> 90%) lesions in tortuous vessels (angulation >90°) are not considered appropriate for direct stenting.

If any of the target lesions is considered to be not appropriate for direct stenting and/or the operator decides that pre-dilation is the preferred strategy, the Svelte SES-RX should be used.

If a subject is randomized to the control DES group, the operator will follow the approved instructions for use (IFU) supplied with the control DES utilized. The IFU for

Figure 2



Svelte EES — "Stent-on-a-Wire" Integrated Delivery System (IDS) Components.

Table 2. Secondary Endpoints Definitions.

Endpoint	Definition
Device success	Attainment of <30% residual stenosis of the target lesion using the assigned study stent only
Lesion success	Attainment of <30% residual stenosis of the target lesion using any stent or interventional device
Procedure success	Lesion success without occurrence of in-hospital MACE
Direct stent strategy success	Attainment of <30% residual stenosis of the target lesion without pre-dilation if the operator had originally chosen to proceed using a direct stent approach
Procedure time	Time from placement of the introducer sheath to removal of all interventional and diagnostic devices
Intervention time	Time from insertion to removal of the guiding catheter
Device time	Time from exiting of the guide wire tip through the guiding catheter to its retrieval back into the guiding catheter following stent placement
MACE	Composite of all-cause death, target vessel MI, and clinically driven TLR
TLF	Composite of cardiac death, target vessel MI (Q-wave or non−Q-wave MI) and clinically driven TLR
TVF	Composite of cardiac death, target vessel MI (Q-wave or non−Q-wave MI) and clinically driven TVR

MACE, Major adverse cardiac events; *MI*, myocardial infarction; *TLF*, target lesion failure; *TVF*, target vessel failure; *TLR*, target lesion revascularization; *TVR*, target vessel revascularization.

the Promus EES recommends pre-dilation prior to stent deployment, whereas the IFU for the Xience EES recommends pre-dilation as optional depending on subject and lesion characteristics. Promus and Xience are both indicated for pre-dilation prior to deployment in Japan.

Antiplatelet therapy

All subjects will receive 100−300 mg aspirin within 24 hours prior to the procedure and continue on 75−162 mg aspirin daily indefinitely post procedure. Subjects will also receive a loading dose of 600 mg clopidogrel (300 mg in Japan) within 24 hours prior to the procedure or within 1 hour after the procedure. Loading doses of 60 mg prasugrel (20 mg in Japan), 180 mg ticagrelor, or 500 mg ticlopidine within 2 hours of procedure can be used in place of clopidogrel. Post–procedure, dual antiplatelet therapy (DAPT) should be in accordance with local or national guidelines. Enoxaparin is not recommended for periprocedural anticoagulation.

Statistical considerations

Sample size determination

The sample size was calculated based on a non-inferiority design, with the study intending to show non-inferiority of the Svelte SES compared with the Xience or Promus EES in the primary efficacy endpoint of 12-month TLF.

The null hypothesis is that the Svelte SES will have a primary endpoint rate equal to or exceeding that of the combined control group of Xience and Promus EES by the non-inferiority margin or more. Based on the 12-month TLF rate observed for the PROMUS EES in the EVOLVE II study,[50] we assumed a true 12-month TLF rate of 6.5% in both treatment groups and an absolute non-inferiority margin of 3.58% (55% relative non-inferiority margin) with a one-sided alpha of 0.025. A total of 1548 subjects (774 in each treatment group) will have 80% power to reject the null hypothesis in favor of the alternative under these assumptions. A total of 1630 subjects will be randomized to account for 5% loss to follow-up.

The angiographic sub-study was designed to show non-inferiority of the Svelte SES compared with the Xience or Promus EES in the primary angiographic endpoint of 12-month in-stent LLL. Assuming an in-stent LLL non-inferiority margin of 0.20 mm (consistent with recently reported DES studies[51,52]), standard deviation of +/−0.34, with a one-sided alpha of 0.05, a sample size of 128 subjects (64 in each treatment group) will have power of 95% to demonstrate non-inferiority at 12 months follow-up. A total of 150 subjects will be included in the angiographic sub-study to account for 15% loss to follow-up.

Analysis populations

The primary analysis of the primary endpoint will be carried out on the intention-to-treat (ITT) population (all subjects who signed the written informed consent and were randomized). A secondary analysis will be performed on the per-protocol population (all randomized subjects who received only the assigned study stent and were deemed eligible per the protocol selection criteria). Analyses of secondary endpoints will be carried out on these 2 populations. Pre-specified subgroup analyses include direct stenting/balloon pre-dilation strategy, radial/femoral access, age> 75/≤75 years, women/men, subjects with/without diabetes, vessel diameter > median value/≤median value, and lesion length > median value/≤median value. For these subgroup analyses, treatment group difference (Svelte SES minus Xience/Promus EES) in the primary endpoint rate and the 2-sided 95% credible interval of the difference will be presented within each subgroup. A test of interaction will be performed to formally assess heterogeneity of treatment effect on the primary endpoint across subgroups. A similar analysis to assess treatment group differences in the primary

endpoint rate will be performed comparing Svelte IDS and Rx systems.

Missing data

The primary endpoint of 12-month TLF will be tested first on subjects with available data only, i.e., subjects experiencing the primary endpoint or subjects with at least 330 days of follow-up post index procedure. To assess the effect of missing data, several supportive sensitivity analyses will be carried out.

First, missing primary endpoint data due to premature withdrawal will be imputed using multiple imputation approach. The outcome will be imputed given treatment group and relevant baseline covariates, including age, gender, diabetes, and lesion length. Second, a tipping point analysis will be conducted. Third, a sensitivity analysis will be carried out using Cox regression. In this analysis, study discontinuation before an event will be treated as a censored observation at the time of dropout.

For the angiographic sub-study, missing primary endpoint (12-month in-stent LLL) data will be imputed using multiple imputation approach, where the outcome is also imputed based on treatment group, age, gender, diabetes, and lesion length.

Study administration and management

The local Institutional Review Board or Ethics Committee at each participating institution must approve the study, and all subjects must provide written informed consent prior to enrollment. Funding is provided by Svelte.

NAMSA clinical research organization maintains the complete study database and the Baim Institute for Clinical Research will perform all key analyses.

Independent angiographic and IVUS core laboratories will review all angiograms and IVUS images to evaluate lesion and procedural characteristics.

A Clinical Events Committee (CEC) will develop specific criteria for the categorization of clinical events and clinical endpoints in the trial. The CEC will meet regularly to review and adjudicate potential study endpoint events including deaths. All members of the CEC will be blinded to randomized treatment groups.

An independent Data Safety Monitoring Board (DSMB) composed of 4 members (3 physicians from the fields of cardiology and interventional cardiology and 1 biostatistician), will review aggregate and individual subject data related to safety, data integrity, and overall conduct of the trial on a periodic basis. The DSMB may make recommendations to the study sponsor as a result of its monitoring activities.

Discussion

The OPTIMIZE study is a randomized controlled trial designed to assess the safety and efficacy of the SVELTE SES as compared with control DES (Xience and Promus) in subjects with up to 3 target lesions. The primary objective of the study is to compare the SVELTE bioresorbable polymer SES with a durable polymer EES in terms of non-inferiority on the clinical endpoint of TLF to 12 months. The primary endpoint of TLF is a device oriented composite endpoint that combines both safety and efficacy components and has precedence for evaluation of DES.[49] A non-inferiority delta of 55% is similar to that used in recent studies of DES.[50]

While the non-inferiority randomized trial design is similar to recent DES regulatory approval trials, several unique features of the OPTIMIZE trial design deserve note. First, sites likely to be comfortable with radial artery catheterization and direct stenting were encouraged to participate. Second, smaller sized guiding catheters are allowed compared to prior studies (5F instead of 6F minimum). Third, a prespecified direct stent cohort (up to 30% of total trial enrollment) will be analyzed to evaluate for consistency of the treatment effect within this cohort. This is the first US regulatory approval trial to assess a strategy of direct stenting between 2 randomly assigned devices. Finally, catheterization laboratory resource utilization and total costs for the procedures will be compared, as well as procedure time and contrast exposure, in order to evaluate the potential salutary impact of the reduced crossing profile for the study stents. The OPTIMIZE trial design leverages recent trends in PCI practice including the transition from femoral to radial access approach. Radial access for PCI is associated with decreased bleeding and resource use,[53] and in high-risk acute coronary syndrome patients, decreased mortality.[54] Data from the ACC-NCDR CathPCI registry show that the use of transradial PCI has increased significantly over time such that the contemporary rate in US practice is approximately 40%.[55]

The OPTIMIZE study will provide randomized trial data that reflect contemporary coronary interventional practice and will assess the potential benefits of a lower profile device on clinical and catheterization laboratory technique and outcomes.

Acknowledgments

Funding for this clinical research was provided in its entirety by Svelte Medical Systems, Inc., New Jersey, USA.

Tal Regev Beinart, MD, aided in the writing and editing of this manuscript; she was compensated by the Baim Institute for Clinical Research.

Conflicts of Interest

Dr. Mauri reports grants to institution from Amgen, Abbott, Boston Scientific, Boehringer Ingelheim, Biotronik, Corvia, and Recor; and consulting fees from Amgen, Corvia, Recor, and Boehringer Ingelheim.

Dr. Doros reports consultancy from Pfizer, Sarepta, Novartis, Softworld, and Lipocine.

Dr. Rao reports grants to institution from Svelte.

Dr. Cohen reports research grants to institution from Svelte, Medtronic, Boston Scientific, and Abbott Vascular.

Dr. Yakubov reports grants to institution from Svelte, Boston Scientific, Medtronic, and Abbott Vascular.

Dr. Lasala reports consulting fees from Abiomed, and WL. Gore and Associates; speakers bureau for Abiomed, St. Jude Medical/Abbott, Boston Scientific, Astrazeneca, and Edwards, shareholdings from Abiomed, and advisory board membership for Abiomed and Boston Scientific.

Dr. Wong reports grants to institution from Abbott Vascular, Boston Scientific, Biotronik, and Medtronic.

Dr. Zidar reports consulting fees for advisory boards from Abbott Vascular, Medtronic and Siemens; and research grants to institution from Svelte, SinoMed, Boston Scientific, and Abbott Vascular.

Dr. Kereiakes reports consulting fees from Boston Scientific, Sino Med, Svelte, and Micell.

References

1. Schatz RA, Baim DS, Leon M, et al. Clinical experience with the Palmaz-Schatz coronary stent. Initial results of a multicenter study. Circulation 1991;83(1):148-61.
2. Barbato E, Marco J, Wijns W. Direct stenting. Eur Heart J 2003; 24(5):394-403.
3. Beohar N, Davidson CJ, Kip KE, et al. Outcomes and complications associated with off-label and untested use of drug-eluting stents. JAMA 2007;297(18):1992-2000.
4. Ormiston JA, Mahmud E, Turco MA, et al. Direct stenting with the TAXUS Liberte drug-eluting stent: results from the Taxus Atlas Direct Stent Study. JACC Cardiovasc Interv 2008;1(2):150-60.
5. Figulla HR, Mudra H, Reifart N, et al. Direct coronary stenting without predilatation: a new therapeutic approach with a special balloon catheter design. Cathet Cardiovasc Diagn 1998;43(3): 245-52 discussion 253.
6. Hamon M, Richardeau Y, Lécluse E, et al. Direct coronary stenting without balloon predilation in acute coronary syndromes. Am Heart J 1999;138(1 Pt 1):55-9.
7. Pentousis D, Guérin Y, Funck F, et al. Direct stent implantation without predilatation using the MultiLink stent. Am J Cardiol 1998;82(12): 1437-40.
8. Wilson SH, Berger PB, Mathew V, et al. Immediate and late outcomes after direct stent implantation without balloon predilation. J Am Coll Cardiol 2000;35(4):937-43.
9. Briguori C, Sheiban I, De Gregorio J, et al. Direct coronary stenting without predilation. J Am Coll Cardiol 1999;34(7):1910-5.
10. Danzi GB, Capuano C, Fiocca L, et al. Stent implantation without predilation in patients with a single, noncalcified coronary artery lesion. Am J Cardiol 1999;84(10):1250-3 A8.
11. de la Torre Hernandez JM, Gomez I, Rodriguez-Entem F, et al. Evaluation of direct stent implantation without predilatation by intravascular ultrasound. Am J Cardiol 2000;85(8):1028-30 A8.
12. IJsselmuiden AJ, Serruys PW, Scholte A, et al. Direct coronary stent implantation does not reduce the incidence of in-stent restenosis or major adverse cardiac events: six month results of a randomized trial. Eur Heart J 2003;24(5):421-9.
13. Serruys PW, IJsselmuiden S. Hout Bv, et al. Direct stenting with the Bx VELOCITY balloon-expandable stent mounted on the Raptor rapid exchange delivery system versus predilatation in a European randomized Trial: the VELVET trial. Int J Cardiovasc Intervent 2003; 5(1):17-26.
14. Brueck M, Scheinert D, Wortmann A, et al. Direct coronary stenting versus predilatation followed by stent placement. Am J Cardiol 2002; 90(11):1187-92.
15. Martinez-Elbal L, Ruiz-Nodar JM, Zueco J, et al. Direct coronary stenting versus stenting with balloon pre-dilation: immediate and follow-up results of a multicentre, prospective, randomized study. The DISCO trial. DIrect Stenting of COronary Arteries. Eur Heart J 2002;23(8):633-40.
16. Burzotta F, Trani C, Prati F, et al. Comparison of outcomes (early and six- month) of direct stenting with conventional stenting (a meta-analysis of ten randomized trials). Am J Cardiol 2003;91(7): 790-6.
17. Baim DS, Flatley M, Caputo R, et al. Comparison of PRE-dilatation vs direct stenting in coronary treatment using the Medtronic AVE S670 Coronary Stent System (the PREDICT trial). Am J Cardiol 2001; 88(12):1364-9.
18. Dawkins KD, Chevalier B, Suttorp MJ, et al. Effectiveness of "direct" stenting without balloon predilatation (from the Multilink Tetra Randomised European Direct Stent Study [TRENDS]). Am J Cardiol 2006;97(3):316-21.
19. Carrie D, Khalifé K, Citron B, et al. Comparison of direct coronary stenting with and without balloon predilatation in patients with stable angina pectoris. BET (Benefit Evaluation of Direct Coronary Stenting) Study Group. Am J Cardiol 2001;87(6):693-8.
20. Cohen HA, Williams DO, Holmes Jr DR, et al. Impact of age on procedural and 1-year outcome in percutaneous transluminal coronary angioplasty: a report from the NHLBI Dynamic Registry. Am Heart J 2003;146(3):513-9.
21. Feldman DN, Gade CL, Slotwiner AJ, et al. Comparison of outcomes of percutaneous coronary interventions in patients of three age groups (<60, 60 to 80, and >80 years) (from the New York State Angioplasty Registry). Am J Cardiol 2006;98(10):1334-9.
22. McCullough P. Outcomes of contrast-induced nephropathy: experience in patients undergoing cardiovascular intervention. Catheter Cardiovasc Interv 2006;67(3):335-43.
23. Naidu SS, Selzer F, Jacobs A, et al. Renal insufficiency is an independent predictor of mortality after percutaneous coronary intervention. Am J Cardiol 2003;92(10):1160-4.
24. Shaw RE, Anderson HV, Brindis RG, et al. Development of a risk adjustment mortality model using the American College of Cardiology-National Cardiovascular Data Registry (ACC-NCDR) experience: 1998-2000. J Am Coll Cardiol 2002;39(7): 1104-12.
25. Wu C, Hannan EL, Walford G, et al. A risk score to predict in-hospital mortality for percutaneous coronary interventions. J Am Coll Cardiol 2006;47(3):654-60.
26. O'Neill BJ, Feldman RL, Palmer SL, et al. Comparison of fixed-wire and over-the-wire balloon dilatation systems for percutaneous transluminal coronary angioplasty. Am J Cardiol 1994;73(2): 113-6.
27. Thomas ES, Williams DO, Neiderman AL, et al. Efficacy of a new angioplasty catheter for severely narrowed coronary lesions. J Am Coll Cardiol 1988;12(3):694-702.
28. Kastrati A, Williams DO, Neiderman AL, et al. Predictive factors of restenosis after coronary implantation of sirolimus- or paclitaxel-eluting stents. Circulation 2006;113(19):2293-300.

29. Windecker S, Remondino A, Eberli FR, et al. Sirolimus-eluting and paclitaxel-eluting stents for coronary revascularization. N Engl J Med 2005;353(7):653-62.
30. Dibra A, Kastrati A, Mehilli J, et al. Paclitaxel-eluting or sirolimus-eluting stents to prevent restenosis in diabetic patients. N Engl J Med 2005;353(7):663-70.
31. Kastrati A, Mehilli J, von Beckerath N, et al. Sirolimus-eluting stent or paclitaxel-eluting stent vs balloon angioplasty for prevention of recurrences in patients with coronary in-stent restenosis: a randomized controlled trial. JAMA 2005;293(2):165-71.
32. Park KH, Park SW, Hong MK, et al. Comparison of the effectiveness of sirolimus- and paclitaxel-eluting stents for small coronary artery lesions. Catheter Cardiovasc Interv 2006;67(4):589-94.
33. Wessely R, Schömig A, Kastrati A. Sirolimus and Paclitaxel on polymer-based drug-eluting stents: similar but different. J Am Coll Cardiol 2006;47(4):708-14.
34. Elezi S, Dibra A, Mehilli J, et al. Vessel size and outcome after coronary drug-eluting stent placement: results from a large cohort of patients treated with sirolimus- or paclitaxel-eluting stents. J Am Coll Cardiol 2006;48(7):1304-9.
35. Strauss BH. All drug-eluting stents are equal, but some drug-eluting stents are more equal than others. J Am Coll Cardiol 2006;48(7):1310-1.
36. Tanimoto S, Daemen J, Tsuchida K, et al. Two-year clinical outcome after coronary stenting of small vessels using 2.25-mm sirolimus- and paclitaxel-eluting stents: insight into the RESEARCH and T-SEARCH registries. Catheter Cardiovasc Interv 2007;69(1):94-103.
37. Mehilli J, Byrne RA, Tiroch K, et al. Randomized trial of paclitaxel- and sirolimus-eluting stents in small coronary vessels. Eur Heart J 2006;27(3):260-6.
38. Petronio AS, De Carlo M, Branchitta G, et al. Randomized comparison of sirolimus and paclitaxel drug-eluting stents for long lesions in the left anterior descending artery: an intravascular ultrasound study. J Am Coll Cardiol 2007;49(5):539-46.
39. Saia F, Piovaccari G, Manari A, et al. Clinical outcomes for sirolimus-eluting stents and polymer-coated paclitaxel-eluting stents in daily practice: results from a large multicenter registry. J Am Coll Cardiol 2006;48(7):1312-8.
40. Stone GW, Rizvi A, Sudhir K, et al. Randomized comparison of everolimus-eluting and paclitaxel-eluting stents: two-year clinical follow-up from the Clinical Evaluation of the Xience V Everolimus Eluting Coronary Stent System in the Treatment of Patients with de novo Native Coronary Artery Lesions (SPIRIT) III trial. Circulation 2009;119(5):680-6.
41. Kelbaek H, Kløvgaard L, Helqvist S, et al. The Stenting Coronary Arteries in Non-stress/benestent Disease (SCANDSTENT) trial. J Am Coll Cardiol 2006;47(2):449-55.
42. Marroquin OC, Selzer F, Mulukutla SR, et al. A comparison of bare-metal and drug-eluting stents for off-label indications. N Engl J Med 2008;358(4):342-52.
43. Van Der Giessen WJ, Van Beusekom HM. New drug-eluting stents with biodegradable polymers. Minerva Cardioangiol 2011;59(1):31-8.
44. Garg S, Serruys PW. Coronary stents: looking forward. J Am Coll Cardiol 2010;56(10 Suppl):S43-78.
45. Byrne RA, Kastrati A, Kufner S, et al. Randomized, non-inferiority trial of three limus agent-eluting stents with different polymer coatings: the Intracoronary Stenting and Angiographic Results: Test Efficacy of 3 Limus-Eluting Stents (ISAR-TEST-4) Trial. Eur Heart J 2009;30(20):2441-9.
46. Lee SH, Szinai I, Carpenter K, et al. In-vivo biocompatibility evaluation of stents coated with a new biodegradable elastomeric and functional polymer. Coron Artery Dis 2002;13(4):237-41.
47. DeFife KM, Grako K, Cruz-Aranda G, et al. Poly(ester amide) co-polymers promote blood and tissue compatibility. J Biomater Sci Polym Ed 2009;20(11):1495-511.
48. Horwitz JA, Shum KM, Bodle JC, et al. Biological performance of biodegradable amino acid-based poly(ester amide)s: Endothelial cell adhesion and inflammation in vitro. J Biomed Mater Res A 2010;95(2):371-80.
49. Cutlip DE, Windecker S, Mehran R, et al. Clinical end points in coronary stent trials: a case for standardized definitions. Circulation 2007;115(17):2344-51.
50. Kereiakes DJ, Meredith IT, Windecker S, et al . Efficacy and safety of a novel bioabsorbable polymer-coated, everolimus-eluting coronary stent: the EVOLVE II Randomized Trial. Circ Cardiovasc Interv 2015;8(4); pii: e002372. https://doi.org/10.1161/CIRCINTERVENTIONS.114.002372.
51. Meredith IT, Verheye S, Dubois CL, et al. Primary endpoint results of the EVOLVE trial: a randomized evaluation of a novel bioabsorbable polymer-coated, everolimus-eluting coronary stent. J Am Coll Cardiol 2012;59(15):1362-70.
52. Kandzari DE, Smits PC, Love MP, et al. Randomized Comparison of Ridaforolimus- and Zotarolimus-Eluting Coronary Stents in Patients With Coronary Artery Disease: Primary Results From the BIONICS Trial (BioNIR Ridaforolimus-Eluting Coronary Stent System in Coronary Stenosis). Circulation 2017;136(14):1304-14.
53. Amin AP, Patterson M, House JA, et al. Costs Associated With Access Site and Same-Day Discharge Among Medicare Beneficiaries Undergoing Percutaneous Coronary Intervention: An Evaluation of the Current Percutaneous Coronary Intervention Care Pathways in the United States. JACC Cardiovasc Interv 2017;10(4):342-51.
54. Ando G, Capodanno D. Radial Versus Femoral Access in Invasively Managed Patients With Acute Coronary Syndrome: A Systematic Review and Meta-analysis. Ann Intern Med 2015;163(12):932-40.
55. Rao SV, Dharma S. 25 Years of Transradial Intervention: Looking Back and Anticipating What Is Ahead. JACC Cardiovasc Interv 2017;10(22):2266-8.