Evaluation of Wall *S*hear Stress and Neointimal *He*aling Following Percutaneous Coronary Intervention of *A*ngulated Vessels with *R*esolute® Integrity Zotarolimus Eluting Coronary *Stent* Compared to XIENCE XPEDITION® Everolimus Eluting Coronary Stent (*SHEAR-STENT* Study)

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Protocol

CONFIDENTIAL

NOT FOR DISSEMINATION

Table of Contents

Study Locations

Emory University Hospital (Atlanta, GA), Hospital Clinico San Carlos (Madrid, Spain), Seoul National University College of Medicine (Seoul, S. Korea), Keimyung University Dongsan Medical Center (Daegu, S. Korea), Ulsan University Hospital - University of Ulsan College of Medicine (Dong-gu, S. Korea), Wakayama Medical University (Wakayama, Japan), Kobe University (Kobe, Japan), Clinical Center of Serbia (Belgrade, Serbia), Nanjing Medical University (Nanjing, China), Samsung Medical Center (Seoul, S. Korea), Kyushu Medical Center (Fukuoka, Japan), Teikyo University (Tokyo, Japan), New Tokyo Hospital (Tokyo, Japan), University of Latvia, (Riga, Latvia)

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Evaluation of Wall *S*hear Stress and Neointimal *He*aling Following Percutaneous Coronary Intervention of *A*ngulated Vessels with *R*esolute® Integrity™Zotarolimus Eluting Coronary *Stent* Compared to XIENCE XPEDITION® Everolimus Eluting Coronary Stent (*SHEAR-STENT* Study)

Rationale

After approval of the Resolute Integrity® Zotarolimus drug-eluting stent (R-ZES) in February 2012 by the U.S. Food and Drug Administration, it and the Abbott Vascular's XIENCE XPEDITION® Everolimus drug-eluting stent (X-EES) are expected to be market share leaders. A recent head-to-head trial (Resolute All Comers Trial) comparing these two stents demonstrated non-inferiority of R-ZES to X-ESS for the primary endpoint of target lesion failure at 12 months (8.2% and 8.3%, respectively, $p< 0.001$ for non-inferiority) with a non-significantly higher rate of stent thrombosis of R-ZES compared with X-EES (2.3% vs. 1.5%, respectively; $p = 0.17$)[1]. The non-inferiority of the R-ZES to X-EES has been reconfirmed in real-world patients by the TWENTE Trial[2]**.** While such studies provide significant empirical data on the clinical performance and safety of the new R-ZES compared with X-ESS[1, 3, 4], they do not offer insight into the possible mechanisms relating to early and late stent healing that can drive clinical adverse outcomes.

Although drug-eluting stents (DES) have significantly reduced restenosis rates[5-10], concerns of late stent thrombosis (LST) and timing of re-endothelialization persist[11-13]. Numerous mechanisms have been implicated in the cause for LST, including several aspects of stent design[14-17]. While the elution characteristics of the R-ZES are similar to X-ESS, the BioLinx tri-polymer coating of R-ZES may be more biocompatible than the X-EES polymer and preclinical porcine models have demonstrated reduced inflammatory scores with R-ZES[18]. Furthermore, the altered biomechanical environment post-stenting (e.g., hemodynamics, arterial straightening) can significantly affect the recovery time of endothelial structure and function[16, 19].

The deployment of a stent in an artery significantly affects the near-wall flow patterns, as well as the overall flow patterns in the artery[17, 20-22]. Specifically, the protrusion of the stent strut into the lumen results in flow separation and the formation of recirculation zones or eddy currents both proximal and distal to each stent strut. These non-physiologic flow characteristics near stent struts persist until re-endothelization and neointimal tissue growth occurs. The degree to which the flow patterns are disrupted depends strongly on the stent design.

Computational fluid dynamics (CFD) techniques have been employed to investigate the hemodynamic alterations following stent deployment as they allow for accurate information on flow parameters [e.g., wall shear stress (WSS), velocity, pressure][17, 21, 22]. Duraiswamy and colleagues quantified WSS values near stent struts in four commercially available stents[23]. Results indicated that stent designs whose struts were aligned perpendicular to the flow direction resulted in much lower WSS values and greater flow disturbances than designs that did not have these design characteristics. Furthermore, stent designs whose struts were aligned primarily in the axial direction (i.e., the direction of blood flow) disturb flow the least. Examination of the R-ZES design reveals a continuous wire that is molded into a sinusoidal wave and wrapped in a helical pattern and laser-fused at certain points[24]. This allows significantly more struts to be aligned in the axial direction than the X-EES design.Furthermore, the conformability of the R-ZES may cause less vessel straightening and less plaque prolapse, leading to more physiologic shear stress compared to X-EES. *Thus, we*

hypothesize that R-ZES will result in less disturbed flow and more physiologic WSS at the stent edges compared with the X-EES design and promote more complete tissue coverage within the stent.

Specific Aim:

The aim of this proposal is,in patients undergoing PCI to angulated coronary arteries,to:

1) To calculate*OCT-derived WSSwithin R-ZES and X-EES stents* and relate differences in regional in-stent WSS to neo-intimal tissue coverage assessed by OCT at one year.
2) To calculate*IVUS-derived WSSat the* R-ZES and X-EES *stent edges* and relate differences in regional WSS at stent edges to change in plaque areaat one year.

Hypotheses:

In patients undergoing PCI to angulated coronary arteries:

1) With *a* conformable stent design that is more conducive to physiologic flow characteristics, the R-ZES stent will result in less vessel straightening and less plaque prolapse compared to X-EES. This would result in fewer lowWSS areas within the stent that, in turn, would lead to less neo-intimal tissue coverage.
2) R-ZES will result in less straightening of vessel at the stent edges compared with X-EES, yielding fewerlow WSS segments which, in turn, will result in less plaque area at the stent edges at one year.

Design

One hundred twenty six patients from participating US and international study sites *Emory University Hospital (Atlanta, GA), Hospital Clinico San Carlos (Madrid, Spain), Seoul National University College of Medicine (Seoul, S. Korea), Keimyung University Dongsan Medical Center (Daegu, S. Korea), Ulsan University Hospital - University of Ulsan College of Medicine (Dong-gu, S. Korea), Wakayama Medical University (Wakayama, Japan), Kobe University (Kobe, Japan), Clinical Center of Serbia (Belgrade, Serbia), Nanjing Medical University (Nanjing, China), Samsung Medical Center (Seoul, S. Korea), Kyushu Medical Center (Fukuoka, Japan), Teikyo University (Tokyo, Japan), New Tokyo Hospital (Tokyo, Japan), University of Latvia, (Riga, Latvia)*undergoing PCI to angulated coronary vessels will be randomized to stent implantation with either the R-ZES or X-EES in a 1:1 ratio. Allocation of stent types will be blinded to patients. Prior to stent deployment, IVUS and OCT will be performed to assess the baseline plaque composition. After successful stent deployment, post-stent OCT and IVUS will be performed to assess the adequacy of stent deployment. Using OCT, IVUS, and angiographic data, computational fluid models will be performed off-line to measure regional WSS. Patients will then be followed on optimal medical therapy including dual anti-platelet therapy for one year. They will also receive a follow up phone call by study staff at 6 months to assess their clinical status and medication compliance. At 1 year follow-up, patients will return to the cardiac catheterization laboratory for repeat angiography, OCT, and IVUS. Of the total n=630 subjects projected to be enrolled, 80% (n=504) is anticipated to screen fail based on the predefined inclusion criteria. Subsequently we anticipate n=126 subjects to complete baseline evaluation. A 20% drop out rate for the 1-year follow-up invasive evaluation has been considered reducing the total number of subjects completing the follow-up to n=100. Patients will be stratified on the basis of whether they have diabetes or not, as diabetic patients have long been recognized as a complex PCI cohort and associated with an increased risk of major adverse cardiovascular events, including death and myocardial infarction.

Figure 1: Schematic of Study Design. CFD: computational fluid dynamic simulations, IVUS: Intravascular Ultrasound, OCT: Optical Coherence Tomography, PCI: percutaneous coronary intervention, SIHD: stable ischemic heart disease

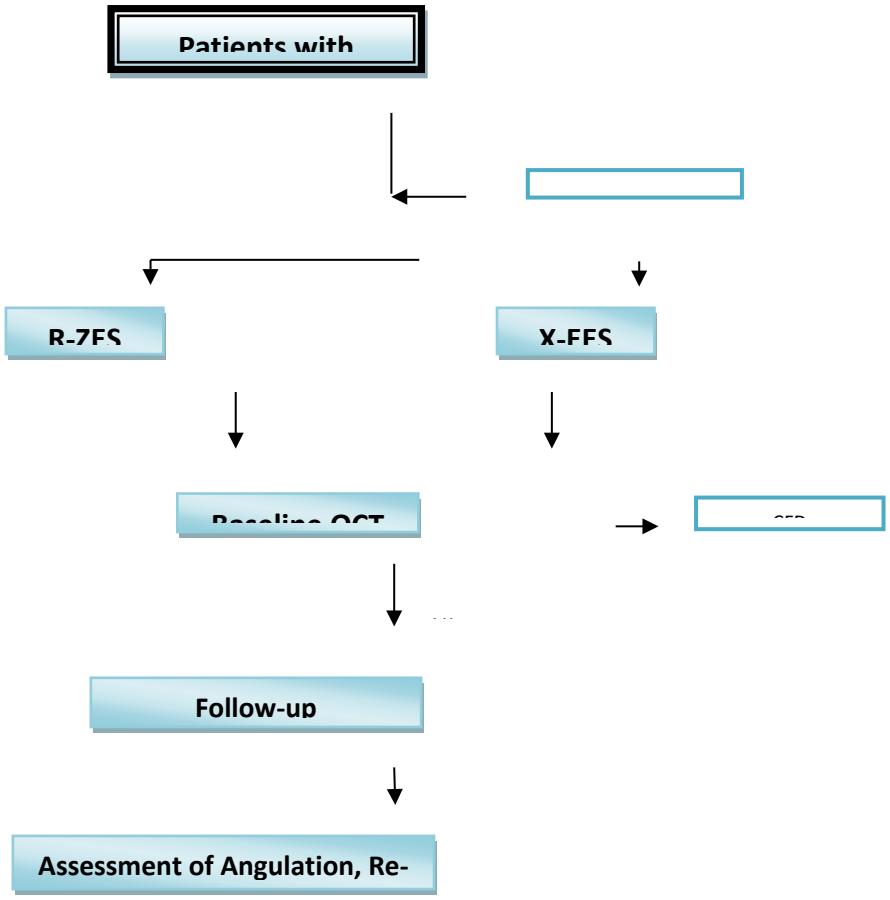
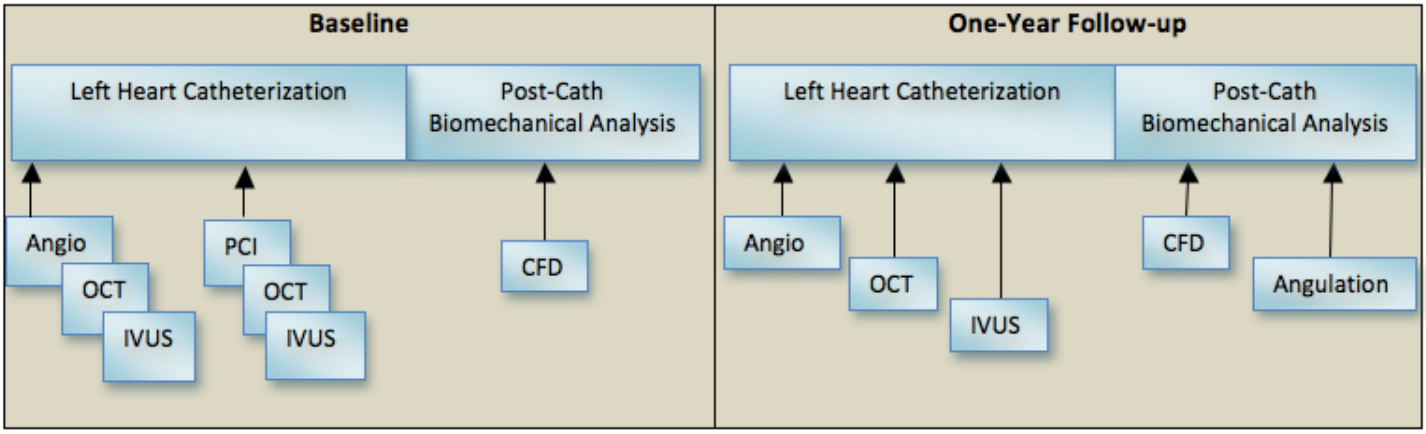


Fig.2: Flow chart of the SHEAR-STENT Study



Methodology:

1. Angiography and Percutaneous Coronary Intervention

Patients will undergo routineangiography (bi-planar views if available) and stent deployment per standard of care.

2. Angiographic assessment of angulation

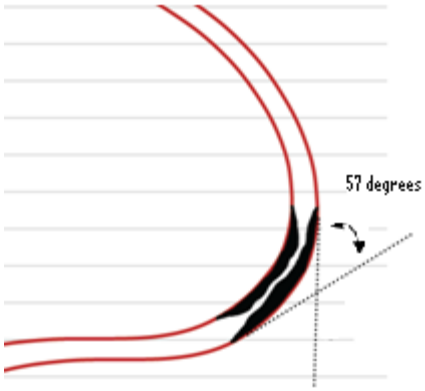


Figure 3: Angulation

Angulation is the angle created by the intersection of two tangential lines at the beginning and end of an index coronary segment with the angiogram frozen in end-diastole. In this study, we define an angulated vessel as one with ≥30degrees bend (Figure 3). When the angulation is clearly >60 degrees, a visual assessment by the investigator will suffice for enrollment. However, for angles <60 degrees the angiographic image is frozen in end diastole in the control room and printed on paper. Subsequently, 2 tangential lines are drawn on the vessel at the proximal and distal edge of the lesion and the intersecting angle measured with a protractor. In cases where the affected artery/stent has more than one curvature (assumes an "S" shape, instead of variations of a "C" shape), the higher degree of angulation will be analyzed. Stents that overlap or are in very close proximity to each other with a gap of less than 5 mm will be assigned to the same coronary lesion.

3. Intravascular Imaging

3.1. Data Acquisition

Optical coherence tomography (OCT) and Intravascular ultrasound (IVUS) will be performed at baseline to assess plaque burden prior to and after stent deployment as well as to evaluate stent expansion and stent apposition. OCT and IVUS will be repeated at one year follow-up to evaluate neo-intimal tissue coverage within the stent and change in plaque area at the stent edges. IVUS analysis will be performed with a motorized pullback at 0.5 mm/s. Following IVUS, OCT will be performed with a commercially available system (C7-XR™ OCT Intravascular Imaging System, St. Jude Medical). The OCT catheter will be positioned distal to the region of interest and automated pullback will be performed at 20 mm/s while the blood is removed by the continuous power injection of iso-osmolar contrast through the guiding catheter.

3.2. Data Analysis

Both stent platforms are FDA approved and clinically utilized in the United States and internationally. This trial is not powered to detect clinical outcome difference between the two stent platforms but rather enhance our understanding of the relationship between biomechanics and stent healing in these angulated vessels. We therefore do not think this trial will be discontinued and hence do not plan to perform an interim analysis.

3.2.1. Intravascular Ultrasound

Offline, manual detection of lumen area, stent area, vessel area(external elastic membrane) and the media-adventitia interface will be performed for each IVUS cross-section from baseline and follow up examinations. Cross sections with rotational distortion artifacts and severe calcifications will be excluded from the analysis. Plaque area and plaque burden will be measured at baseline and follow up for every IVUS cross-section from the pullback run. Baseline and follow-up IVUS cross-sections will be compared, reviewed and co-registered based on a reproducible index side branch atthe distal end of the target segment. Changes in external elastic membrane, lumen area, plaque burden and plaque area, and fourplaque tissue components defined by IVUS-virtual histology(necrotic core, dense calcium, fibrous tissue, and fibrofatty tissue) will be calculated as follow-up values minus baseline values for each IVUS segment. The 5 mm segments proximal and distal to the stent edges will be defined and analyzed with IVUS. Change in plaque area at the stent edges (secondary IVUS endpoint) will be calculated from the change in plaque area in the 5 mm proximal and distal segments as described above.

3.2.2. Intravascular Optical Coherence Tomography

Offline, manual detection of lumen area and stentarea will be performed for each OCT cross-section from baseline and follow up examinations. Images with artifacts (e.g. blood) or otherwise uninterpretable will be excluded from the analysis. At the strut-level analysis, the struts will be classified either as covered or uncovered (a tissue layer over the endoluminal surface is not visible). *To derive data for the primary study endpoint*, from the follow-up OCT images, the total neo-intimal tissue coverage area will be calculated as: (stent area − lumen area). For secondary analyses, % tissue coverage area will be calculated as: tissue coverage area/stent area × 100; and% tissue coverage volume will be calculated as: tissue coverage volume/stent volume × 100. The tissue coverage symmetry per frame will be analyzed with the following ratio: (maximum tissue coverage thickness per frame – minimum tissue coverage thickness per frame)/maximum tissue coverage thickness per frame. This ratio can have values between 0 and 1. The closer the ratio is to 1 the higher is the asymmetry of the tissue coverage. Strut tissue coverage will be measured through mean tissue coverage thickness, tissue coverage area proportion of tissue coverage area and proportion of uncovered struts. Plaque prolapse will be defined as tissue identified between stent struts extending inside a circular arc connecting adjacent struts.

4. Wall Shear Stress Calculations

Computational fluid dynamic (CFD) simulations to calculate WSS values have been used extensively and validated in our laboratory. Following angiographic, IVUS and OCT acquisition, 3-dimensional (3D) coronary geometries will be reconstructed by determining the location of the OCT transducer during pullback by using the corresponding angiographic projections. The 3D reconstructed catheter core serves as the stem on which to rebuild the 3D geometry. Following image adjustment due to rotation, each frame is aligned perpendicular to the catheter core. Lumen boundary points for each frame will be determined connected by spline curves to connect consecutive images. The geometry is smoothed, meshed, and imported into the commercial solver (Ansys, Inc., Canonsburg, PA), which employs the finite volume method for solving the Navier-Stokes equations. Velocity profiles will be applied at the inlet, traction-free boundary conditions are applied at all outlets, and a no-slip boundary condition ($v = 0$) is applied at the wall. The fluid (blood) is assumed to be an incompressible Newtonian fluid, which is valid under the pulsatile, moderate Reynolds number flow conditions in coronary arteries. WSS values are determined as a function of time in the cardiac cycle and the evaluation is highly reproducible.

Nodal WSS values will be extracted from the area of interest (i.e., lesion/stented region and stent edges) of computational models at pre- and post-stenting. The stented region and 5-millimeter (mm) segments of the proximal and distal edges will be divided into 1- mm segments and WSS values will be spatially and temporally averaged. Low WSS will be defined as <10 Dynes/cm^2. Corresponding regions between the pre-and post-stenting models for a given patient will be examined to assess alterations in WSS following stent implantation. Arterial straightening will be assessed by examination of the OCT-derived coronary reconstructions. Following reconstruction, centerline data will be examined to quantify vessel curvature, average cross-sectional area, maximum/minimum/average lumen diameters, and vessel volume will be calculated.

Patient Selection

Patients planned to be admittedfor coronary angiography and percutaneous coronary artery revascularization procedure should be screened for trial eligibilityby a member of the research team previously trained to the protocol. The investigator or designee will explain the nature and scope of the trial, potential risks and benefits of participation, and answer all questions. Subjects must consent to participate in the study and may withdraw their consent at any time without any penalty or loss of benefit.

Patient Inclusion:

1. Patient must be 30 to 80 years old
2. Severe coronary lesion in a vessel with ≥30^o angulation requiring PCI
3. Lesion treatable by a *single* Resolute Integrity or Onyx or Abbott Xience Xpedition or Sierra coronary drug eluting stent.
4. Patients with stable ischemic heart disease or acute coronary syndrome undergoing clinically PCI.

Patient Exclusion:

1. Inability to provide informed consent prior to randomization
2. Anatomy requiring coronary artery bypass surgery (CABG)
3. History of prior CABG in the territory of the vessel being considered for PCI
4. Heavily calcified lesion requiring rotablation or other debulking or scoring device for successful stent deployment
5. Large thrombus burden on angiography
6. Previously stented vessels.
7. Ostial lesions: lesion located within 5mm of the origin of the LAD, LCx, or RCA
8. Lesions at bifurcations and those that occlude side branches>2.5mm
9. Recent (<72 hours) ST-elevation myocardial infarction (STEMI)
10. Planned surgical procedures in the subsequent 12 months
11. History of hypersensitivity or contraindication to device materials and their degradants, everolimus, zotarolimus, cobalt, chromium, nickel, platinum, tungsten, acrylic and fluoro polymers
12. History of any solid organ transplantation or subject is on a waiting list for any solid organ transplant.
13. Left ventricular ejection fraction < 30%
14. Known allergies to clinically utilized anti-thrombotic or anti-platelet agents
15. Unable to tolerate long term dual anti-platelet therapy
16. Pregnancy or lactation

17. Subject has renal insufficiency as defined as an estimated GFR < 30 ml/min/1.73m^2.
18. Concurrent enrollment in another clinical trial that has not yet completed its primary endpoint

Study Endpoints

Primary Endpoints (Efficacy):

1. In stent mean cross-sectional area of neo-intimal tissue coverageby OCT at follow-up.

Secondary Endpoints:

A. *In-Stent*

1. ***Safety:*** Mean thickness of strut coverage at follow up
2. ***Mechanistic:***
   a. Degree of vascular straightening post-PCI (post PCI angulation -baseline angulation)
   b. Plaque prolapse post-PCI (identified by OCT)
   c. Percent stent area with low WSSpost-PCI (OCT derived)

B. Stent Edge (5 mm proximal and distal to stent)

1. ***Efficacy:***Change in plaque area at follow up
2. ***Mechanistic:***
   a. Degree of vascular straightening post-PCI at the stent edges
   b. Percent area with low WSS at stent edges post-PCI (IVUS derived)

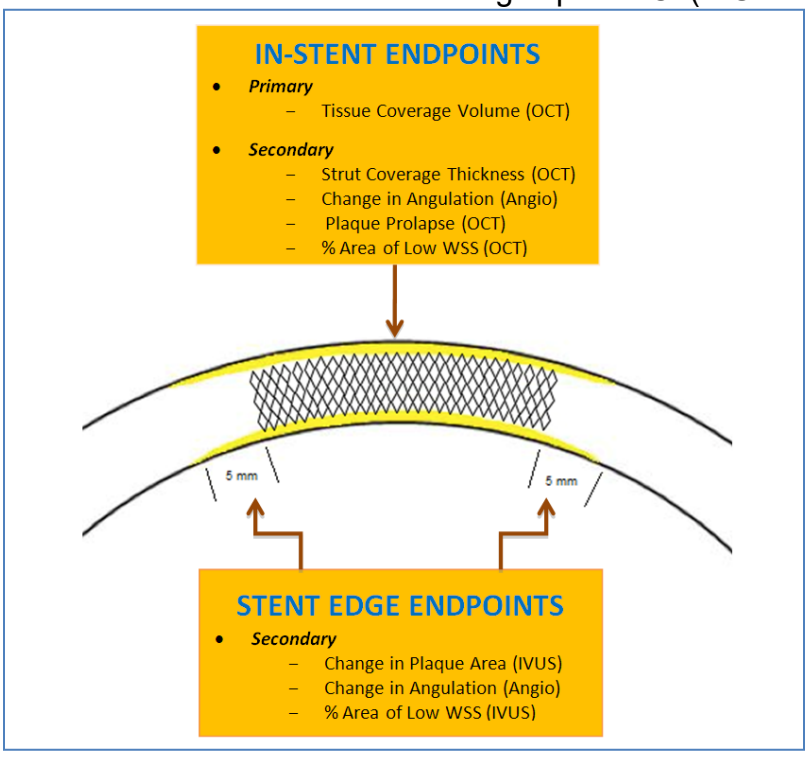


Figure 4: Schema of Study endpoints

Statistics

OCT cross-section frames will be selected from the stented segments at approximately 1 mm intervals for quantitative analysis. Each observed stent strut in each still frame will be classified as either completely or incompletely tissue-covered. Furthermore, in those struts where tissue coverage is observed, tissue coverage area and tissue coverage thickness will be measured. Previously published studies investigating R-ZES and X-EES strut re-endothelialization by OCT in all comers did not show statistically significant differences in neointimal thickness or volume, though the studies did not concentrate on angulated vessels[3, 4].In a sample of 58 patients (30 ZES and 28 EES) with 72 lesions, 107stents, and 23,197 struts, the OCT sub-study of the RESOLUTE All Comers OCTtrial showed the tissue coverage volume of 15.9mm^3±11.6mm^3 for the ZES and 18.7mm^3±14.4mm^3 for EES (p-value=0.27).[3]Power calculations were based on the assumption that at 12 months the tissue coverage volume for ZES was 14.68mm^{3}and EES 22mm^3. Detection of a 20% or more change in primary endpoint between the two groups at a power of 80% and a two-sided alpha level of 0.05 will requires an enrollment of 50 patients per group. Assuming a dropout rate of 20%, we propose to recruit 126 patients.

Continuous variables will be reported as mean and standard deviations (1SD), and a t-test or U-test will be employed depending on whether or not the variables are normally distributed and the standards of deviations are the same.Analysis of variables at the level of patient, treatment arm, and lesion will be performed using multilevel regression models. Chi-square test or Fisher's exact test will be used, as appropriate, to compare categorical variables.

All statistical analyses will be carried out using the Statistical Package for Social Sciences (SPSS) software (SPSS, Inc., Chicago, IL). A two-sided *p*-value of <0.05 will be considered statistically significant.

Duration of study

It is estimated that it will take 1 year to enroll patients and collect baseline data and 1 year for follow-up data collection.

Follow-up

All patients will be followed while in hospital for major adverse events. Total CK, CK-MB and troponin (if available) will be measured 12-24 hours after the procedure. Patients will be contacted by phone at 6 month (±30 days), and undergo follow up cardiac catheterization at 1year (±30 days) after enrolment with the specific assessments as outlined in the follow-up table below. During follow-up patients will be assessed for any major adverse cardiac events (MACE).

Table 1: Follow-Up Schedule

	Baseline	12-24Hr Post Proc.	Discharge	6 month (±30 days)	1 year (±30 days)
	Hosp.	Hosp.	Hosp.	Call	Hosp.
Medical History/Demographics	X				
Cardiac Enzymes (Tn, CK, MB)	X	X			
ECG	X	X	X		
Routine Lab Studies	X	X	X		X
Pregnancy Test	X				X

	Baseline	12-24Hr Post Proc.	Discharge	6 month (±30 days)	1 year (±30 days)
Cardiac Medications	X		X	X	X
Angiogram	X				X
OCT	X				X
IVUS	X				X
Adverse Events		X	X	X	X

Data Management

All documents and data shall be produced and maintained in a way that assures control and traceability. All documents, and subsequent versions, related to a clinical investigation shall be identifiable, traceable and appropriately stored to provide a complete history of the clinical study. The principal investigator shall be responsible for the accuracy, legibility, and security of all clinical study data, documents, and subject records at the investigator's participating medical site. The principal investigator (or an appropriately designated study staff) is responsible for entering the data from source documentation to CRFs.

Data entered on CRFs will be reviewed and verified by the authorized principal investigator and promptly submitted to the Primary Site. Any alteration of the data shall be made by only authorized personnel. The investigator designee will submit data through the REDCap electronic data capture system managed by the Primary Site. Copies of required source documents will be scanned and uploaded to the REDCap electronic data capture system in a timely manner where the data will be reviewed by the primary site. Subject's information must be de-identified prior to uploading documents on REDCap. Any queries or clarifications requested by the Primary Site will be resolved through a documented data clarification process.

Recording Data

The REDCap electronic database system will be utilized for this study. REDCap provides a HIPPA-compliant, encrypted, backed-up place to store the data and allows online data entry from multiple sites, including international sites. Access to the database is limited to certain investigators and designees at the study site. Procedures for verification, validation, and securing of electronic clinical data will be maintained by the Primary Site under separate cover.

The data reported by the investigator or designee on the CRFs shall be derived from sourcedocuments and be consistent with the source documents, any discrepancies shall be explained inwriting. The informed consent form shall be signed and dated by the principal investigator or his/her authorizeddesignee(s).Electronic CRFs should be entered into REDCap in a timely fashion. All imaging data (such as coronary angiography, IVUS and OCT) will be recorded on a compatible compact disk (CD-ROM or DVD) and shipped to the Primary Site. A copy of the OCT data will also be shipped to the OCT Core Laboratory (Case Western Reserve University).

Source Documents

Source documents shall be created and maintained by the investigation site team throughout theclinical study. All findings in this clinical study must be documented as source data, andtherefore can be verified (and audited). Source documentation may be paper or electronic, and isdefined as the first time the data appears and may include for example; all clinical records,hospital records, surgery

reports, autopsy reports, and any other material that contains originalinformation used for clinical study data collection or adverse event reporting.The Primary Site representative or site investigator is responsible for verifying the CRFs throughout the study toverify adherence to the protocol as well as completeness, accuracy, and consistency of the data derived from each site.The Primary Site or representative must have access to the source documentation and other studyrelated records to verify the entries on the CRFs.

Confidentiality of Data

All subject information collected during the course of this study will be kept strictly confidentialaccording to applicable country-specific laws and regulations. All data and informationconcerning subjects and their participation in this study are considered confidential. All public reporting of the results ofthe study will eliminate identifiable references to the subjects. Information on paper will be keptin secured locations. Electronic information will be kept on password-protected computers.

Personal data, including medical and health information, will be processed both by computer andmanually, during and after the study, and its affiliates, its designated third party dataprocessors, the IRB, the institution conducting the study, the investigators and otherhealthcare personnel involved in the study for the purposes of this study. Subject data will not contain details of study subject identity. The datawill be stored on a secure server and backed up routinely. All records and reports required by orprepared in connection with this study shall be maintained by the institution and the investigators
in a secure location for a minimum period of 15 years post approval or longer as may beotherwise required by local law. Personal data will be key-coded to prevent subjectidentification, except by the institution, investigators and other healthcare personnel involved inthe study, if necessary for the purpose of the study, for regulatory inspections, and to complywith EUH reporting obligations.

Any information about subjects that leaves the institution conducting the study will be modifiedto remove certain information that could identify the subject (e.g., subject's name, age on the dayof enrollment, address, and hospital number) and only be identifiable by a study ID code. Studydata published in medical journals and/or presented at scientificconferences will not allow the identification of study subjects.

Data and Document Retention

The principal investigators shall maintain the clinical study data and documentsas required by applicable regulatory requirement(s). They shalltake measures to prevent accidental or premature destruction of these documents. The principalinvestigator may transfer custody of records to another person/party anddocument the transfer at the study site or at the Primary Site facility.

Amendment to Study Forms

The study forms shall be amended by the Primary Site as needed throughout the clinical study, andjustification documented and maintained. The amendments shall be notified to, or approved by, the IRBifrequired. The version number and date of amendments shall be documented.

Deviations from Clinical Study Plan

Investigators are not allowed to deviate from the protocol except when necessary to protect the life orphysical well-being of a subject in an emergency. Prior approval by the Primary Site is expected in those situations in which the investigator anticipates, contemplates or makes a conscious decision to departfrom procedures specified in the clinical investigational plan. Prior approval is generally notexpected in situations where unforeseen circumstances are beyond the investigator's control, but isstill considered a deviation (e.g. a clinical investigation subject who fails to attend a scheduledfollow-up visit, a clinical study subject too ill to perform a protocol-required test).

To obtainapproval, the investigator must call or email and discuss the potential deviation with the Primary Site Principal Investigator or designee prior to initiating any changes. A Protocol Deviation CRF will be completed for eachprotocol deviation. When relevant, the ethics committeesor the appropriateregulatory bodies will be informed of protocol deviations.Primary Site will review and monitor investigator compliance and determine if there is a need forcorrective action based on the severity and/or trends in non-compliance.

Investigator shall notify Primary Site promptly, and the reviewing IRBwithin 5 working days where appropriate of the following:

1. A deviation to protect the life or physical well-being of a subject in an emergency and;
2. Failure to obtain an informed consent.

Investigators or the designee must notify Primary Siteas soon as possible by calling the clinicalstudy manager or designee and complete the clinical study deviation case report form.The investigator is required to adhere to local IRB or regulatoryrequirements procedures for reporting other deviations.

Monitoring and Reporting

Each site's evaluation will be carried out by though centralized monitoring by hired research staff at the Primary Site. Processes to ensure site record keeping, data entry, and reporting are well-defined to ensure timely access to clinical trial data and supporting documentation. Various modes of communication (e.g., teleconferences, videoconferencing, email) will be used for specific study time points (e.g., study initiation) and activities (e.g., to discuss findings of a monitor's eCRF review, training of new site staff). The sites will regularly upload study documents via the electronic data capture which will be remotely verified. An onsite visit could be warranted if concerns regarding noncompliance or major safety issues arise.

Investigators are required to keep records on all relevant observations, including records concerning adverse effects (whether anticipated or unanticipated. All adverse events and technical observations will be captured on an adverse event CRF. It is the responsibility of the investigator to assess the subject for adverse events and capture the required adverse event information on a CRF. Adverse events will be reported from time of procedure until completion of follow-up. The investigator must also notify the responsible IRB regarding new and significant safety information and any event identified by Primary Sitethat requires expedited reporting as serious, unexpected, and related to the clinical study device.

The general procedure for reporting any adverse event is as follows:
1. If an adverse event occurs, complete the Adverse Event CRF.
2. The Adverse Event CRF must be signed and dated by the investigator.

For Serious Adverse Event and all Unanticipated Adverse Device Effects, the investigator isrequired to document and report to the Primary Site without undue delay, but not longer than 48 hours from first knowledge of event. The investigator must notify the IRB, if appropriate,in accordance with national and local laws and regulations.

Emergency Contact

In the event that emergent reporting of an adverse event to the Primary Site is necessary, clinical siteswill complete a CRF through the electronic database. Once submitted, notification will be sent electronically to the Primary Site and the CRF will be immediately available for review.

Publications

The results of this clinical study will be submitted for publication following study completion anddata analysis.

Suspension or Premature Termination of the Clinical Study

The Primary Site may suspend or prematurely terminate either a clinical study in an individual site or theentire clinical study for significant and documented reasons.A principal investigator, IRB or regulatory authority maysuspend or prematurely terminate participation in a clinical study at the study sites for which they areresponsible.If suspicion of an unacceptable risk to subjects arises during the clinical study, or when so instructedby the IRB or regulatory authority, the Primary Site shallsuspend the clinical study while the risk is assessed. The Primary Site shall terminate the clinical study ifan unacceptable risk is confirmed.

The Primary Site shall consider terminating or suspending the participation of a particular study site orinvestigator in the clinical study if monitoring or auditing identifies serious or repeated deviations onthe part of an investigator.If suspension or study termination occurs, the terminating party shall justify its decision and providewritten notice of termination in accordance with the study agreement. The principal investigator andthe Primary Site shall keep each other informed of any communication received from IRB or regulatory authority.If, for any reason, the Primary Site suspends or prematurely terminates the study at an individual studysite, the Primary Site shall inform the responsible regulatory authority, as appropriate, and ensure that theIRB are notified, either by the principal investigator or by thePrimary Site. If the suspension or premature termination was in the interest of safety, the Primary Site shallinform all other principal investigators.If suspension or premature termination occurs, the Primary Site shall remain responsible for providingresources to fulfill the obligations and existing agreements for following up thesubjects enrolled in the clinical study, and the principal investigator or authorized designee shallpromptly inform the enrolled subjects at his/her study site, if appropriate.

Resuming the Clinical Study after Temporary Suspension

When the Primary Site concludes an analysis of the reason(s) for the suspension, implements thenecessary corrective actions, and decides to lift the temporary suspension, the Primary Site shall inform the principal investigators, IRB or regulatory authority,where appropriate, and the regulatory authority of the rationale, providing them with the relevantdata supporting this decision.Concurrence shall be obtained from the, IRB or regulatoryauthority where appropriate, before the clinical study

resumes.If subjects have been informed of the suspension, the principal investigator or authorizeddesignee shall inform them of the reasons for resumption.

References

1. Serruys PW, Silber S, Garg S, van Geuns RJ, Richardt G, Buszman PE, Kelbaek H, van Boven AJ, Hofma SH, Linke A, Klauss V, Wijns W, Macaya C, Garot P, DiMario C, Manoharan G, Kornowski R, Ischinger T, Bartorelli A, Ronden J, Bressers M, Gobbens P, Negoita M, van Leeuwen F, Windecker S. Comparison of zotarolimus-eluting and everolimus-eluting coronary stents. *N Engl J Med*. 2010;363:136-146
2. von Birgelen C, Basalus MW, Tandjung K, van Houwelingen KG, Stoel MG, Louwerenburg JH, Linssen GC, Said SA, Kleijne MA, Sen H, Lowik MM, van der Palen J, Verhorst PM, de Man FH. A randomized controlled trial in second-generation zotarolimus-eluting resolute stents versus everolimus-eluting Xience Xpedition stents in real-world patients: The twente trial. *J Am Coll Cardiol*. 2012;59:1350-1361
3. Gutierrez-Chico JL, van Geuns RJ, Regar E, van der Giessen WJ, Kelbaek H, Saunamaki K, Escaned J, Gonzalo N, di Mario C, Borgia F, Nuesch E, Garcia-Garcia HM, Silber S, Windecker S, Serruys PW. Tissue coverage of a hydrophilic polymer-coated zotarolimus-eluting stent vs. A fluoropolymer-coated everolimus-eluting stent at 13-month follow-up: An optical coherence tomography substudy from the resolute all comers trial. *Eur Heart J*. 2011;32:2454-2463
4. Kim JS, Kim BK, Jang IK, Shin DH, Ko YG, Choi D, Hong MK, Cho YK, Nam CW, Hur SH, Choi JH, Song YB, Hahn JY, Choi SH, Gwon HC, Jang Y. Comparison of neointimal coverage between zotarolimus-eluting stent and everolimus-eluting stent using optical coherence tomography (cover oct). *Am Heart J*. 2012;163:601-607
5. Kirtane AJ, Gupta A, Iyengar S, Moses JW, Leon MB, Applegate R, Brodie B, Hannan E, Harjai K, Jensen LO, Park SJ, Perry R, Racz M, Saia F, Tu JV, Waksman R, Lansky AJ, Mehran R, Stone GW. Safety and efficacy of drug-eluting and bare metal stents: Comprehensive meta-analysis of randomized trials and observational studies. *Circulation*. 2009;119:3198-3206
6. Tu JV, Bowen J, Chiu M, Ko DT, Austin PC, He Y, Hopkins R, Tarride JE, Blackhouse G, Lazzam C, Cohen EA, Goeree R. Effectiveness and safety of drug-eluting stents in ontario. *N Engl J Med*. 2007;357:1393-1402
7. Stone GW, Lansky AJ, Pocock SJ, Gersh BJ, Dangas G, Wong SC, Witzenbichler B, Guagliumi G, Peruga JZ, Brodie BR, Dudek D, Mockel M, Ochala A, Kellock A, Parise H, Mehran R. Paclitaxel-eluting stents versus bare-metal stents in acute myocardial infarction. *N Engl J Med*. 2009;360:1946-1959
8. Stone GW, Ellis SG, O'Shaughnessy CD, Martin SL, Satler L, McGarry T, Turco MA, Kereiakes DJ, Kelley L, Popma JJ, Russell ME. Paclitaxel-eluting stents vs vascular brachytherapy for in-stent restenosis within bare-metal stents: The taxus v isr randomized trial. *JAMA*. 2006;295:1253-1263
9. James SK, Stenestrand U, Lindback J, Carlsson J, Schersten F, Nilsson T, Wallentin L, Lagerqvist B. Long-term safety and efficacy of drug-eluting versus bare-metal stents in sweden. *N Engl J Med*. 2009;360:1933-1945
10. Kelbaek H, Thuesen L, Helqvist S, Clemmensen P, Klovgaard L, Kaltoft A, Andersen B, Thuesen H, Engstrom T, Botker HE, Saunamaki K, Krusell LR, Jorgensen E, Hansen HH, Christiansen EH, Ravkilde J, Kober L, Kofoed KF, Terkelsen CJ, Lassen JF. Drug-eluting versus bare metal stents in patients with st-segment-elevation myocardial infarction: Eight-month follow-up in the drug elution and distal protection in acute myocardial infarction (dedication) trial. *Circulation*. 2008;118:1155-1162
11. Pilgrim T, Windecker S. Drug-eluting stent thrombosis. *Minerva Cardioangiol*. 2009;57:611-620
12. Kalesan B, Pilgrim T, Heinimann K, Raber L, Stefanini GG, Valgimigli M, da Costa BR, Mach F, Luscher TF, Meier B, Windecker S, Juni P. Comparison of drug-eluting stents with bare metal stents in patients with st-segment elevation myocardial infarction. *Eur Heart J*. 2012;33:977-987

13. Virmani R, Kolodgie FD, Farb A. Drug-eluting stents: Are they really safe? *Am Heart Hosp J*. 2004;2:85-88
14. Yutani C, Imakita M, Ishibashi-Ueda H, Tsukamoto Y, Nishida N, Ikeda Y. Coronary atherosclerosis and interventions: Pathological sequences and restenosis. *Pathol Int*. 1999;49:273-290
15. Centemero MP, Stadler JR. Stent thrombosis: An overview. *Expert Rev Cardiovasc Ther*. 2012;10:599-615
16. Pant S, Bressloff NW, Forrester AI, Curzen N. The influence of strut-connectors in stented vessels: A comparison of pulsatile flow through five coronary stents. *Ann Biomed Eng*. 2010;38:1893-1907
17. LaDisa JF, Jr., Olson LE, Douglas HA, Warltier DC, Kersten JR, Pagel PS. Alterations in regional vascular geometry produced by theoretical stent implantation influence distributions of wall shear stress: Analysis of a curved coronary artery using 3d computational fluid dynamics modeling. *Biomed Eng Online*. 2006;5:40
18. Nakazawa G, Finn AV, John MC, Kolodgie FD, Virmani R. The significance of preclinical evaluation of sirolimus-, paclitaxel-, and zotarolimus-eluting stents. *Am J Cardiol*. 2007;100:36M-44M
19. Timmins LH, Miller MW, Clubb FJ, Jr., Moore JE, Jr. Increased artery wall stress post-stenting leads to greater intimal thickening. *Lab Invest*. 2011;91:955-967
20. Agostini F, Iannone MA, Mazzucco R, Cionini F, Baccaglioni N, Lettieri C, Belfanti D, Tomasi L, Izzo A, Ferrari MR, Brunazzi MC, Zanini R. Coronary flow velocity pattern assessed by transthoracic doppler echocardiography predicts adverse clinical events and myocardial recovery after successful primary angioplasty. *J Cardiovasc Med (Hagerstown)*. 2006;7:753-760
21. Chen MC, Lu PC, Chen JS, Hwang NH. Computational hemodynamics of an implanted coronary stent based on three-dimensional cine angiography reconstruction. *ASAIO J*. 2005;51:313-320
22. LaDisa JF, Jr., Guler I, Olson LE, Hettrick DA, Kersten JR, Warltier DC, Pagel PS. Three-dimensional computational fluid dynamics modeling of alterations in coronary wall shear stress produced by stent implantation. *Ann Biomed Eng*. 2003;31:972-980
23. Duraiswamy N, Schoephoerster RT, Moore JE, Jr. Comparison of near-wall hemodynamic parameters in stented artery models. *J Biomech Eng*. 2009;131:061006
24. Medtronic resolute integrity™ drug-eluting stent obtains fda approval for treating coronary artery disease2012;2012