ABSORB II randomized controlled trial. A clinical evaluation to compare the safety, efficacy, and performance of the Absorb everolimus-eluting bioresorbable vascular scaffold system against the XIENCE everolimus-eluting coronary stent system in the treatment of subjects with ischemic heart disease caused by de novo native coronary artery lesions: Rationale and study design

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Background Currently, no data are available on the direct comparison between the Absorb everolimus-eluting bioresorbable vascular scaffold (Absorb BVS) and conventional metallic drug-eluting stents.

Methods The ABSORB II study is a randomized, active-controlled, single-blinded, multicenter clinical trial aiming to compare the second-generation Absorb BVS with the XIENCE everolimus-eluting metallic stent. Approximately 501 subjects will be enrolled on a 2:1 randomization basis (Absorb BVS/XIENCE stent) in approximately 40 investigational sites across Europe and New Zealand. Treated lesions will be up to 2 de novo native coronary artery lesions, each located in different major epicardial vessels, all with an angiographic maximal luminal diameter between 2.25 and 3.8 mm as estimated by online quantitative coronary angiography (QCA) and a lesion length of ≤48 mm. Clinical follow-up is planned at 30 and 180 days and at 1, 2, and 3 years. All subjects will undergo coronary angiography, intravascular ultrasound (IVUS) and IVUS–virtual histology at baseline (pre–device and post–device implantation) and at 2-year angiographic follow-up. The primary end point is superiority of the Absorb BVS vs XIENCE stent in terms of vasomotor reactivity of the treated segment at 2 years, defined as the QCA quantified change in the mean lumen diameter prenitrate and postnitrate administration. The coprimary end point is the noninferiority (reflex to superiority) of the QCA-derived minimum lumen diameter at 2 years postnitrate minus minimum lumen diameter postprocedure postnitrate by QCA. In addition, all subjects allocated to the Absorb BVS group will undergo multislice computed tomography imaging at 3 years.

Conclusions The ABSORB II randomized controlled trial (ClinicalTrials.gov NCT01425281) is designed to compare the safety, efficacy, and performance of Absorb BVS against the XIENCE everolimus-eluting stent in the treatment of de novo native coronary artery lesions. (Am Heart J 2012;164:654-63.)

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The Absorb everolimus-eluting bioresorbable vascular scaffold (Absorb BVS) was developed to provide a novel approach to treat coronary artery lesions with transient vessel support and drug delivery.

Preclinical evaluation in animal model demonstrated substantial polymer degradation at 2-years post–Absorb BVS implantation, with complete disappearance of the Absorb BVS strut implantation "footprint" in the vessel wall within a 4-year period, with no significant inflammatory response associated with BVS implantation at short or long-term follow-up.[1]

The first-generation Absorb BVS was tested in the ABSORB Cohort A Trial and demonstrated promising results with a low clinical event rate at 4-year follow-up.[2] The device was, however, limited by slightly higher late recoil compared with conventional metallic platform stents.[3,4] Improvements in design were therefore introduced in the second-generation Absorb BVS: notably an enhanced mechanical strength, more durable support to the vessel wall, a reduced maximum circular unsupported surface area, and a more uniform strut distribution and drug delivery. The performance of this next-generation Absorb BVS was subsequently investigated in the ABSORB Cohort B Trial[5,6] which reported excellent clinical results up to1-year follow-up.[7]

To date, the treatment of coronary artery disease with the second-generation Absorb BVS has been investigated in a limited number of patients with relatively simple coronary lesion complexity. Furthermore, no randomized comparison between the Absorb BVS and the conventional metallic drug-eluting stent has yet been undertaken.

Therefore, the ABSORB II controlled randomized trial (ClinicalTrials.gov NCT01425281) comparing the metallic everolimus-eluting stent XIENCE with the Absorb BVS will be initiated, and treatment will be expanded to include subjects with small target vessel diameter and long lesion length.

Investigational device

The second-generation Absorb BVS (Abbott Vascular, Santa Clara, CA) is a balloon-expandable device consisting of a polymer backbone of poly-L-lactide (PLLA) coated with a thin layer of a 1:1 mixture of an amorphous matrix of poly-D, L-lactide (PDLLA) polymer and 100 $\mu g/cm^2$ of the antiproliferative drug everolimus. Two platinum markers located at each Absorb BVS edge allow for accurate visualization of the radiolucent Absorb BVS during angiography or other imaging modalities. The PDLLA controls the release of everolimus, 80% of which is eluted within the first 30 days. Both PLLA and PDLLA are fully bioresorbable. The polymers are degraded via hydrolysis of the ester bonds, and the resulting lactate and its oligomers are quickly transformed to pyruvate and metabolized in the Krebs energy cycle. Small particles, less than 2 μm in diameter, have also been shown to be phagocytized and degraded by macrophages.[8] According to preclinical studies, the time for complete bioresorption of the polymer backbone is 2 to 3 years.[1]

Table I. Device sizes to be used in the study according to the maximum lumen diameter (Dmax) by online QCA only

		Lesion and Device Sizes	
Device		**Dmax**	**Lesion length**
ABSORB BVS Scaffold diameter	2.5 mm	≥2.25 and ≤3.0 mm	≤48 mm Scaffold length: 18, 28 mm
	3.0 mm	≥2.5 and ≤3.3 mm	≤48 mm Scaffold length: 18, 28 mm
	3.5 mm	≥3.0 and ≤3.8 mm	≤48 mm Scaffold length: 12, 18, 28 mm
XIENCE Stent diameter	2.5 mm	≥2.25 and ≤3.0 mm	≤48 mm Scaffold length: 18, 28 mm
	3.0 mm	≥2.5 and ≤3.3 mm	≤48 mm Scaffold length: 18, 28 mm
	3.5 mm	≥3.0 and ≤3.8 mm	≤48 mm Scaffold length: 12, 18, 28 mm

Control device

The control device to be used in the trial is a CE Marked everolimus eluting coronary stent system from the XIENCE family of stents (manufactured by Advanced Cardiovascular Systems, Inc., a subsidiary of Abbott Vascular, Inc) referred to hereafter as XIENCE stent. The XIENCE stent is a balloon-expandable metallic platform stent manufactured from a flexible cobalt chromium alloy with a multicellular design and coated with a thin nonadhesive, durable, biocompatible acrylic, and fluorinated everolimus-releasing copolymer.

The delivery system to be used in both arms of the trial will use the same principle of operation as other Abbott Vascular Rapid Exchange coronary stent systems and coronary dilation catheters.

Treatment strategy

Quantitative assessment of target vessel diameter by online quantitative coronary angiography (QCA) is required at baseline after nitroglycerin for appropriate Absorb BVS or XIENCE stent size selection. The required range for target vessel diameter is assessed in terms of the online QCA parameters distal Dmax and proximal Dmax, which refer to maximum lumen diameter evaluated before predilatation up to 5 to 10 mm distal and proximal to the boundaries of the lesion length defined by QCA. A 3.5 mm ABSORB BVS or XIENCE should be used when both the proximal and distal mean lumen diameter are

within the upper limit of 3.8 mm and the lower limit of 3.0 mm. 3.0-mm Absorb BVS or XIENCE stent must be used when both the proximal and distal mean lumen diameters are within the upper limit of 3.3 mm and the lower limit of 2.5 mm. A 2.5-mm Absorb BVS or XIENCE stent must be used when both the proximal and the distal mean lumen diameters are within the upper limit of 3.0 mm and the lower limit of 2.25 mm. Both the proximal mean lumen diameter and the distal mean lumen diameter need to be within the upper and lower limits specified for the scaffold/stent size. Overlap will be allowed (Table I).

Dual-antiplatelet therapy

All subjects will receive ≥75 mg of aspirin daily after the index procedure and throughout the length of the clinical investigation. All subjects will be maintained at a minimum of 75 mg of clopidogrel daily or a minimum of 10 mg of prasugrel daily for a minimum of 180 days after the procedure, leading to a dual-antiplatelet therapy for a minimum of 180 days. If a subject develops sensitivity to clopidogrel or prasugrel, they may be switched to ticlopidine according to standard hospital practice.

The antiplatelet therapy can be halted for clinical indications if required; however, it must be resumed as soon as possible per-physician discretion.

Trial design and objective

The ABSORB II randomized controlled trial (RCT) is intended to continue to evaluate the safety and efficacy of the Absorb BVS and to directly compare it to the metallic drug-eluting stent XIENCE stent.

XIENCE stent and Absorb BVS share the same basic MULTI-LINK design, and both devices are similar in terms of drug, drug dose density, and elution profile.

The ABSORB II RCT is a prospective, randomized, active-controlled, single-blinded, parallel 2-arm, multicenter clinical trial. A total of approximately 501 subjects (334 in the Absorb BVS group and 167 in the XIENCE stent group) will be randomized in approximately 40 sites in Europe and New Zealand. The trial protocol allows the treatment of up to 2 de novo native coronary artery lesions, each located in different major epicardial vessels, with a maximal lumen diameter between 2.25 and 3.8 mm as assessed by online QCA and a maximum lesion length of ≤48 mm.

All subjects will be screened per the protocol inclusion and exclusion criteria before enrollment. Subjects will have clinical follow-up at 30 and 180 days and at 1, 2, and 3 years. All subjects will undergo coronary angiography, intravascular ultrasound (IVUS), and IVUS–virtual histology (VH) imaging pre–device and post–device implantation and at 2 years post–index procedure.

Subjects from the Erasmus Medical Centre (MC) Rotterdam, the Netherlands, will also undergo intravascular imaging with near-infrared spectroscopy system (Lipiscan, InfraReDx, Burlington, USA) pre– and post–device implantation and at 2 years post–index procedure.

All subjects allocated to the Absorb BVS arm will undergo multislice computed tomography (MSCT) imaging at 3 years post–index procedure. Subjects will be unblinded after the completion of the 2-year follow-up for the coprimary end points.

The primary objective of the ABSORB II RCT is to compare the safety, efficacy, and performance of Absorb BVS against the XIENCE stent in the treatment for subjects with ischemic heart disease caused by de novo native coronary artery lesions.

The ABSORB II RCT is intended to show superiority of Absorb BVS vs XIENCE stent, in terms of the primary end point of vasomotor reactivity as assessed by the change in mean lumen diameter prenitrate and postnitrate and at 2-year invasive follow-up with QCA, and noninferiority (reflex to superiority) in terms of the coprimary end point of minimum lumen diameter (MLD)

Table II. Inclusion criteria

General Inclusion Criteria

- Subject's age must be at least 18 and <85 y
- Subject must agree not to participate in any other clinical investigation for a period of 3 y after the index procedure. This includes clinical trials of medication and invasive procedures. Questionnaire-based studies or other studies that are noninvasive and do not require medication are allowed.
- Subject is able to verbally confirm understanding of risks, benefits, and treatment alternatives of receiving the Absorb BVS and he/she or his/her legally authorized representative provides written informed consent before any clinical investigation-related procedure, as approved by the appropriate ethics committees
- Subject must have evidence of myocardial ischemia (eg, stable or unstable angina, silent ischemia
- Subject must be an acceptable candidate for coronary artery bypass graft surgery
- Subject must agree to undergo all clinical investigation plan-required follow-up visits, exercise testing, blood draw, and adherence to ESC guidelines and completion of quality of life questionnaires and of a subject diary to collect information including but not limited to tobacco use, food intake, daily exercise, and body weights

Angiographic inclusion criteria

- 1 or 2 de novo native lesions each located in a different epicardial vessel
- If 2 treatable lesions meet the eligibility criteria, they must be in separate major epicardial vessels (Left Anterior Descending (LAD) with septal and diagonal branches, Circumflex (CX) with obtuse marginal and/or ramus intermedius branches, and Right Coronary Artery (RCA) and any of its branches).
- Lesion(s) must have a visually estimated diameter stenosis of ≥50% and <100% with a TIMI flow of ≥1.
- Lesion(s) must be located in a native coronary artery with Dmax by online QCA of ≥2.25 and ≤3.8 mm.
- Lesion(s) must be located in a native coronary artery with lesion(s) length by online QCA of ≤48 mm.
- Percutaneous interventions for lesions in a nontarget vessel are allowed if done ≥30 d before or if planned to be done 2 y after the index procedure.
- Percutaneous intervention for lesions in the target vessel is allowed if done >6 mo before or if planned to be done 2 y after the index procedure.

Table III. Exclusion criteria

General exclusion criteria

- Known hypersensitivity or contraindication to aspirin, both heparin and bivalirudin, antiplatelet medication specified for use in the study (clopidogrel and prasugrel and ticlopidine, inclusive), everolimus, PLLA, PDLLA, cobalt, chromium, nickel, tungsten, acrylic and fluoropolymers, or contrast sensitivity that cannot be adequately pre-medicated.
- Subject has a known diagnosis of acute myocardial infarction at any time preceding the index procedure, and relevant cardiac enzymes (according to local standard hospital practice) have not returned within normal limits at the time of procedure.
- Evidence of ongoing acute myocardial infarction in electrocardiogram before procedure
- Subject has current unstable arrhythmias.
- Left ventricular ejection fraction <30%
- Subject has received a heart transplant or any other organ transplant or is on a waiting list for any organ transplant.
- Subject is receiving or scheduled to receive chemotherapy of malignancy within 30 d before or after the procedure.
- Subject is receiving immunosuppressant therapy and/or has known immunosuppressive or autoimmune disease (eg, human immunodeficiency virus, systemic lupus erythematosus, rheumatoid arthritis, severe asthma requiring immunosuppressive medication, etc).
- Subject is receiving chronic anticoagulation therapy that can not be stopped and restarted according to local hospital standard procedures.
- Elective surgery is planned within 2 y after the procedure that will require discontinuing either aspirin, clopidogrel, prasugrel, or ticlopidine.
- Subject has a platelet count <100,000 cells/mm^3 or >700,000 cells/mm^3, a white blood cell count of <3,000 cells/mm^3, or documented or suspected liver disease (including laboratory evidence of hepatitis).
- Known renal insufficiency (eg, estimated Glomerular Filtration Rate (eGFR) <60 mL/min/1.73m^2 or serum creatinine level of >2.5 mg/dL, or subject on dialysis)
- History of bleeding diathesis or coagulopathy or will refuse blood transfusions
- Subject has had a cerebrovascular accident or transient ischemic neurological attack within the past 6 mo.
- Pregnant or nursing subjects and those who plan pregnancy in the period up to 3 y after index procedure (Female subjects of child-bearing potential must have a negative pregnancy test done within 28 d before the index procedure and contraception must be used during participation in this trial.)
- Other medical illness (eg, cancer or congestive heart failure) or known history of substance abuse (alcohol, cocaine, heroin etc) as per physician judgment that may cause noncompliance with the protocol or confound the data interpretation or is associated with a limited life expectancy
- Subject is already participating in another clinical investigation that has not yet reached its primary end point.
- Subject is belonging to a vulnerable population (per investigator's judgment, eg, subordinate hospital staff or sponsor staff) or subject unable to read or write.

Angiographic exclusion criteria

- Target lesion that prevents adequate (residual stenosis at target lesion(s) is ≤40% by visual assessment) coronary predilatation.
- Target lesion in left main trunk
- Aorto-ostial target lesion (within 3 mm of the aorta junction)
- Target lesion located within 2 mm of the origin of the LAD or LCX
- Target lesion located distal to a diseased (vessel irregularity per angiogram and >20% stenosed lesion) arterial or saphenous vein graft
- Target lesion involving a bifurcation lesion with side branch ≥2 mm in diameter, or with a side branch <2 mm in diameter requiring guide-wire protection or dilatation
- Total occlusion (TIMI flow 0), before wire crossing
- Excessive tortuosity (2 or more 45° angles) or extreme angulation (≥90°) proximal to or within the target lesion
- Restenotic from previous intervention
- Heavy calcification proximal to or within the target lesion
- Target lesion involves myocardial bridge.
- Target vessel contains thrombus as indicated in the angiographic images.
- Additionally clinically significant lesion(s) (≥40% diameter stenosis by visual assessment) for which PCI may be required <2 y after the index procedure.
- Subject has received brachytherapy in any epicardial vessel (including side branches).
- Subject has a high probability that a procedure other than predilatation and study device implantation and (if necessary) postdilatation will be required at the time of index procedure for treatment of the target vessel

at 2 years postnitrate minus MLD postprocedure postnitrate by QCA.

All invasive procedures may be deferred to 3 years, depending on the results of the ABSORB Cohort B Trial.

This trial will be conducted in accordance with the Clinical Investigational Plan, the Declaration of Helsinki, ISO 14155 standards, and the appropriate local legislation(s). The conduct of the trial will be approved by the appropriate ethics committee of the respective clinical site and as specified by local regulations.

Patient selection

Subjects enrolled into the clinical trial will be male or female derived from the general interventional cardiology population. The clinical trial will randomize up to approximately 501 subjects. Subjects meeting the general inclusion and exclusion criteria (Tables II and III) will be asked to sign an informed consent form. Nonroutine laboratory assessments specific to the clinical investigation will not be performed before an informed consent form has been signed.

Screening failures will be captured on a paper-screening log.

After successful predilatation of the first target lesion, subject ID, randomization number, and treatment arm will be assigned by a central allocation service (interactive voice/interactive Web-based randomization service).

Subjects will be randomized in a 2:1 ratio to Absorb BVS vs XIENCE stent. Randomization will be further stratified by diabetes mellitus status and number of planned target lesions.

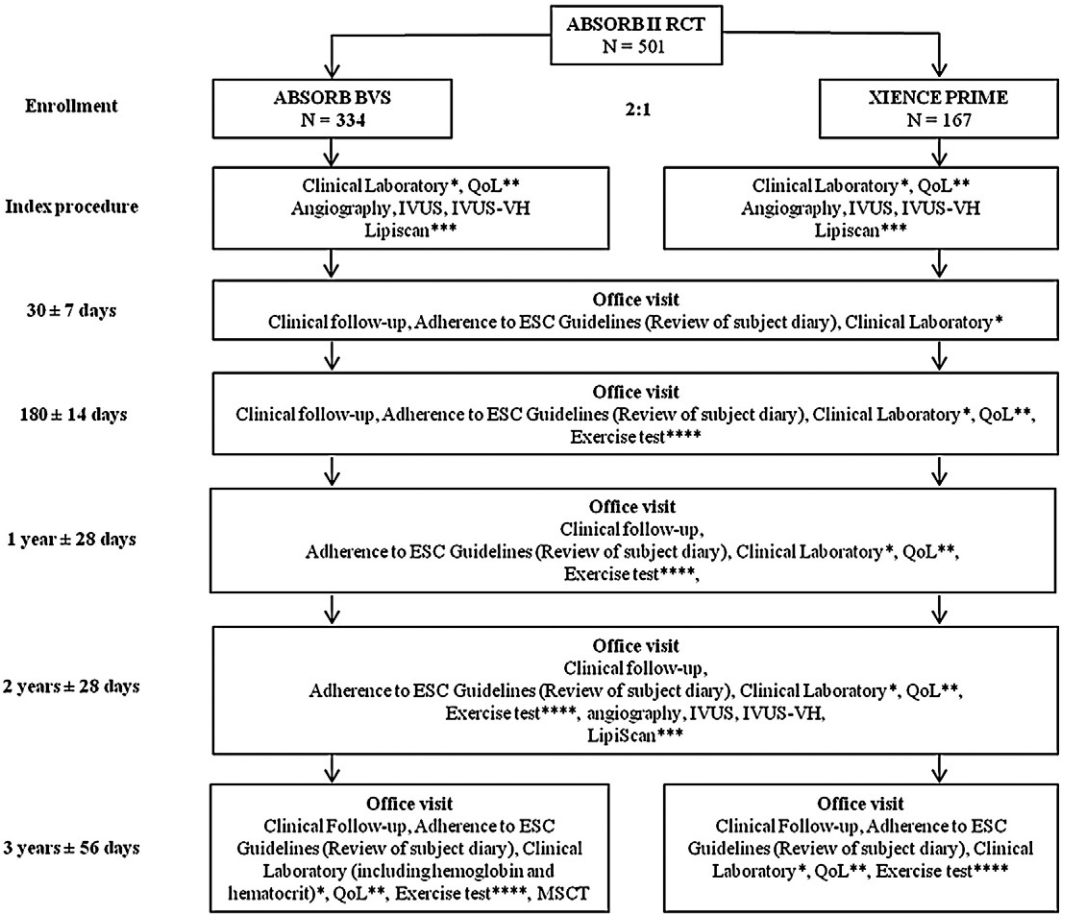
Follow-up schedule

Subjects will be observed for a 3-year period post–index procedure with clinical and invasive imaging follow-up (Figure).

Clinical follow-up

Clinical visit follow-up including blood sampling will be performed in all patients at 30 and 180 days and at 1, 2, and 3 years postprocedure. A central laboratory will be used for

Figure



Clinical investigation flowchart. *Clinical Laboratory: blood sample (to be obtained before exercise testing) to aid in the adjustment of medical treatment and adherence to ESC guidelines. **QoL: quality of life using the SAQ, the SF-12 Health Survey, and the EuroQoL EQ-5D Health Survey. This information will be collected at the indicated time points. ***Lipiscan analysis will be done at the Erasmus MC only. ****Exercise test to be done before any required imaging procedure and after blood draws. The office imaging visit at 2 years (including exercise testing, coronary angiogram, IVUS, IVUS-VH, Lipiscan, SF12, EuroQoL EQ-5D, and SAQ) may be changed to 3 years, depending on cohort B 2-year imaging data. In that case, the 2 year imaging visit would be replaced by an office visit where exercise testing, SF12, EuroQoL EQ-5D, SAQ, adherence to ESC guidelines per protocol medication, concomitant medication, and adverse events would be reviewed.

blood analysis of troponin, creatine kinase, creatine kinase MB, fasting total cholesterol, fasting low-density lipoprotein cholesterol, fasting high-density lipoprotein cholesterol, fasting triglycerides, hemoglobin A1c, and fasting blood glucose levels. These blood samples for central laboratory will be obtained before or at the time of the procedure; the results will not be reviewed at the procedure time.

Local analyses may be performed in parallel to any blood results that are relevant for appropriate protocol compliance, subject care, and treatment optimization.

Exercise testing will be required at 180 days and at 1, 2, and 3 years postprocedure, to be performed before any required imaging procedure and after blood sampling. Exercise tests will be performed at each investigational site according to local clinical practice.

All patients and treating physicians will be asked to adhere to the European Society of Cardiology (ESC) Guidelines[9] in terms of tobacco usage, exercise, healthy food intake, maintaining an adequate weight (body mass index) and waist circumference, achieving target blood lipid levels, and blood pressure control. These parameters will be evaluated at preprocedure, 30 and 180 days, and at 1, 2, and 3 years postprocedure.

Quality of life questionnaires will be undertaken in the ABSORB II RCT to provide a complementary evaluation of the effectiveness of the Absorb BVS system. The questionnaires will be collected at preimplantation, at 180-day, and at 1, 2, and 3-year follow-up and will include both the overall health status, assessed using the SF-12 Health Survey[10] and the EuroQoL EQ-5D survey[11] and

Table IV. Clinical angiographic and imaging end points.

Clinical end points
- Acute success
  - Device success (lesion based analysis)
  - Procedural success (subject based analysis)
- Clinical end point (at 30- and 180-d and at 1, 2, and 3-y follow-up)
  - Component
    - death (cardiac, vascular, noncardiovascular)
    - Myocardial infarction (MI: Q wave Myocardial Infarction (QMI) QMI and Non Q wave Myocardial Infarction NQMI)
    - Target lesion revascularization (TLR)
      - Clinically indicated TLR (CI-TLR)
      - Not clinically indicated TLR (NCI-TLR)
    - TVR
      - Clinically indicated TVR (CI-TVR)
      - Not clinically indicated TVR (NCI-TVR)
    - Non–target vessel revascularization (NTVR)
      - Clinically indicated NTVR (CI-NTVR)
      - Not clinically indicated NTVR (NCI-NTVR)
    - All coronary revascularization
  - Composite end points
    - Death/All MI
    - Cardiac death/TV-MI/CI-TLR (target lesion failure) (device-oriented end point)
    - Cardiac death/all MI/CI-TLR (major adverse cardiac events)
    - Cardiac death/all MI/CI-TVR (target vessel failure)
    - Death/All MI/all revascularization (subject-oriented end point)
  - Scaffold/Stent thrombosis
    - Timing (acute, subacute, late, and very late)
    - Evidence (definite, probable, and possible)

Quality of life (QoL)–related end points
- Health status will be assessed using the SF-12 Health Survey and the EuroQoL EQ-5D at preimplantation, at 180-d, and at 1-, 2-, and 3-y follow-up.
- Disease-specific QoL will be assessed using the SAQ at preimplantation, at 180-d, and at 1-, 2-, and 3-y follow-up.

Angiographic end points
- In-segment Late Loss (LL) LL postnitrate at 2) y
- Proximal LL (proximal defined as within 5 mm of tissue proximal to scaffold/stent placement) postnitrate at 2 y
- Distal LL (distal defined as within 5 mm of tissue distal to scaffold/stent placement) postnitrate at 2 y
- In-scaffold/in-stent, in-segment, proximal and distal MLD postnitrate postprocedure and at 2 y
- In-scaffold/in-stent, in-segment, proximal and distal % diameter stenosis (DS) postnitrate postprocedure and at 2 y
- In-scaffold/in-stent, in-segment, proximal and distal angiographic binary restenosis rate postnitrate at 2 y
- In-scaffold/in-stent net gain (being the change in MLD between 2 y vs preimplantation) postnitrate
- Change in mean and minimal lumen diameters at 2-y follow-up from prenitrate to postnitrate by angiography
- In-scaffold/in-stent %DS at 2 y prenitrate and postnitrate by angiography
- Conformability assessed by change in curvature and angulation between preprocedure, postprocedure, and follow-up

IVUS end points
- Minimal lumen area (MLA) by IVUS postnitrate at 2 y
- Percentage of patients with late gain (IVUS MLA postprocedure postnitrate < IVUS MLA 2-y follow-up postnitrate) without IVUS malapposition
- Change of total plaque (tissue between lumen and external elastic membrane) within scaffold/stent by IVUS postnitrate between postimplantation and 2 y
- Mean/Minimal vessel diameter/area/volume preprocedure, postprocedure, and at 2 y
- Mean/Minimal scaffold/stent diameter/area/volume preprocedure, postprocedure, and (if analyzable) at 2 y
- Mean/Minimal lumen diameter/area/volume preprocedure, postprocedure, and at 2 y, including change in MLA between postprocedure and follow-up
- Plaque behind metallic stent area/volume postprocedure and at 2 y
- Plaque behind polymeric scaffold area/volume postprocedure and at 2 y (if analyzable)
- Mean/maximal neointima hyperplasia in the metallic stent area/volume/percentage at 2 y
- Mean/maximal neointima hyperplasia in the polymeric scaffold area/volume/percentage at 2 y (if analyzable)
- Incomplete apposition (postimplantation), persisting incomplete apposition, late acquired incomplete apposition, and resolved incomplete apposition at 2 y (if analyzable)
- Total plaque area/volume preprocedure, postprocedure, and at 2 y, including change in total plaque between preprocedure and follow-up

IVUS-VH end points
- Dense calcium volume, area, percentage, preprocedure, postprocedure, and at 2 y
- Necrotic core volume, area, percentage, preprocedure, postprocedure, and at 2 y
- Fibrofatty volume, area, percentage, preprocedure, postprocedure, and at 2 y
- Fibrous volume, area, percentage, preprocedure, postprocedure, and at 2 y

Near-infrared spectroscopy end point (substudy in Erasmus MC)
- Change in lipid core burden index from preimplantation to postimplantation and 2-y follow-up

MSCT end points (subjects in the Absorb BVS arm only)
The following MSCT end points will be examined in the Absorb BVS arm only:
- Descriptive analysis of vascular and scaffold morphology at 3 y
- Measurement of lumen area and diameter (minimum, maximum, mean), % DS, and % area stenosis at 3 y

disease-specific quality of life, assessed using the Seattle Angina Questionnaire (SAQ).[12]

Intravascular imaging follow-up

Angiography. All subjects will undergo coronary angiography at pre–device and post–device implantation and at 2-year follow-up.

Grey Scale IVUS-VH. Both IVUS and IVUS-VH assessments will be performed in all patients after coronary angiography, at preimplantation, postimplantation and at 2-year follow-up. Preprocedural IVUS and IVUS-VH will be performed before predilatation of each target lesion. If not technically feasible (ie, the IVUS catheter cannot cross the lesion), predilatation with a small balloon dilatation catheter is allowed for IVUS catheter access. Both IVUS and IVUS-VH are intended for documentary purposes only and not for vessel sizing; thus, this will not have an impact on inclusion/exclusion decision-making processes. In case of 2 target lesions, preprocedural IVUS and IVUS-VH will be

performed for the second lesion after the treatment of the first lesion.

Near-infrared spectroscopy (Lipiscan). A near-infrared spectroscopy substudy will take place in Erasmus MC only. Analyses will be performed at pre– and post–device implantation and at 2-year follow-up. Near-infrared spectroscopy assessment will be performed after IVUS and IVUS-VH at each time point.

All invasive imaging procedures at 2 years may be deferred to 3 years, depending on the results of the ABSORB Cohort B 2-year imaging follow-up data.

Multislice computed tomography (MSCT). A MSCT scan is mandatory for all subjects in the Absorb BVS arm at 3-year follow-up.

End points

Primary end points and rationale

The coprimary end points of the clinical trial are as follows: (1) vasomotion assessed by change in mean lumen diameter between prenitrate and postnitrate at 2 years by QCA (superiority) and (2) MLD at 2 years postnitrate minus MLD postprocedure postnitrate by QCA (noninferiority, reflex to superiority) (Table IV).

Secondary clinical and imaging end points are reported in Table IV.

Statistical considerations

Sample size calculations and assumptions. The sample size calculation is based on the first coprimary end point (superiority for vasomotion assessed by change in mean lumen diameter between prenitrate and postnitrate at 2 years by QCA). The following assumptions were considered: (1) 2-tailed superiority *t* test, (2) $\alpha = 0.05$, (3) power = 90%, (4) randomization ratio 2:1 (Absorb BVS/XIENCE stent), (5) based on previous vasomotion data at 2 years after BVS implantation,[13] the true change in mean lumen diameter between prenitrate and postnitrate at 2-year follow-up is assumed to be 0.07 mm for Absorb BVS and 0 mm for XIENCE stent), and (6) the standard deviation is assumed to be 0.20 mm.

Based on the above assumptions, 260 lesions in the Absorb BVS arm and 130 lesions in the XIENCE stent arm will be required for the study. The attrition rate observed in ABSORB Cohort A and SPIRIT II at 2 years was 24%; we expect an additional loss of 5% for unmatched prenitrate and postnitrate and about 10% of patients with dual lesions. Therefore, approximately 501 subjects will be randomized in ABSORB II, with approximately 334 in the Absorb BVS arm and 167 in the XIENCE stent arm.

Considering the 390 lesions available for QCA assessments, the study has more than 89% power to detect noninferiority in the second coprimary end point of MLD at 2 years postnitrate minus MLD postprocedure postnitrate by QCA (assuming the true means are equal in both groups with a standard deviation of 0.45 mm and a noninferiority margin (δ) of 0.14 mm).

The power calculations were performed using PASS 11 (NCSS,LLC, Kaysville, Utah, USA).

Coprimary end points analysis. The coprimary end points will be analyzed for the intent-to-treat population, on a lesion basis. For the end point of vasomotion assessed by change in mean lumen diameter between prenitrate and postnitrate at 2 years by QCA, the comparison will be tested using a 2-sided *t* test at the 0.05 significance level. For the end point of MLD at 2 years postnitrate minus MLD postprocedure postnitrate by QCA, noninferiority will be tested using a 1-sided asymptotic test at the 0.05 significance level, considering the noninferiority margin of 0.14 mm. If noninferiority is met with higher value in the Absorb BVS arm, then superiority will be tested using a 2-sided *t* test at the 0.05 significance level. If the normality assumption is untenable, nonparametric tests may be considered. For the trial to be successful, the criteria for superiority should be met for the coprimary end point of vasomotion and the criteria for noninferiority should be met for the coprimary end point of MLD at 2 years postnitrate minus MLD postprocedure postnitrate. In addition, as a secondary analysis, the coprimary end points will be analyzed on the per-treatment-evaluable population.

Secondary end point analyses. Analyses of other secondary end points will be descriptive and will be performed on both the intent-to-treat and per-treatment-evaluable populations. For binary variables such as target vessel failure, target lesion revascularization, and clinical procedure success, counts, percentages, and exact 95% confidence intervals using Clopper-Pearson method will be calculated. For continuous variables such as diameter stenosis, means, standard deviations, and 95% confidence intervals for the mean using the Gaussian approximation will be calculated.

Study management

The ABSORB II trial is funded by Abbott Vascular. The Data Safety Monitoring Board will monitor the safety of subjects and/or efficacy throughout the subject enrollment and on an ongoing basis. The Clinical Events Committee will comprise qualified physicians who are not investigators in the trial. The Clinical Events Committee will be responsible for adjudicating all major adverse cardiac event–related end points. Central laboratory cardiac enzymes values will be used for event adjudication (in case central laboratory values would not be available, the local laboratory results will be used). Imaging acquisitions will be evaluated by an independent core laboratory (Cardialysis, Rotterdam, the Netherlands).

Discussion

The introduction in the last decade of drug-eluting coronary stents marked an important progress in the

field of coronary artery disease treatment. The inhibition of neointimal growth by locally delivering antiproliferative drugs translated into a reduction in intrastent restenosis lowering the need for repeated revascularizations.[14,15]

However, metallic stent placement is not devoid of important long-term limitations. The metallic implant results in a permanent caging of the vessel, preventing late lumen enlargement, jailing side branches, precluding noninvasive imaging, and further surgical revascularization of stented segments.[16] Moreover, despite the beneficial effect of neointimal inhibition, the antiproliferative drug elution has been shown to interfere with the vascular healing processes, thus providing the background for phenomena such as delayed strut coverage and persistent or acquired malapposition, implicated in causing late and very late stent thrombosis.[17,18]

Given this background, the new everolimus-eluting bioresorbable vascular scaffolds have been introduced in the attempt to overcome the previously mentioned limitations and, in the ABSORB II trial, will be compared with the current standard of metal drug-eluting stent.

Vasomotion plays an important role in the regulation of coronary blood flow, ensuring the maintenance of an appropriate coronary flow pressure, and impaired vasomotor activity of coronary vessels has been shown to be associated with an increased risk of future cardiovascular events.[19–21] Restoration of vasomotor activity is therefore desirable after percutaneous revascularization and is a suitable end point for the evaluation of coronary artery disease treatment with drug-eluting stents/scaffolds in randomized trials.

Minimum lumen diameter at 2 years minus postprocedural MLD is a measurement of neointimal hyperplasia and therefore a mechanistic measurement of procedural-related hemodynamic narrowing; theoretically and clinically correlated with binary restenosis and target vessel revascularization (TVR).[22-24] Consequently, the MLD at 2 years minus the postimplantation MLD at baseline is considered a suitable end point for evaluation of the performance of drug-eluting stents/scaffolds in the present randomized trial.

In addition to the theoretical advantages, namely, the possibility for further surgical revascularization and a potential reduction in events such as late scaffold thrombosis after the complete scaffold bioresorption,[16] the implantation of the Absorb BVS has previously been demonstrated not to preclude the noninvasive imaging of the treated arteries at any stage of patient follow-up,[13,25] and the restoration of coronary vasomotion was observed to return after 1 year post–scaffold implantation.[7] Moreover, the Absorb BVS placement has been associated with the formation of a neointimal layer that may potentially represent a de novo circumferential plaque thick cap, after scaffold bioresorption, with the potential function of plaque stabilization.[26]

From a physiological perspective, complete scaffold bioresorption exposes the vessel wall to the cyclical strain of blood pulsatility. Previous studies have suggested that the mechanical stimuli induced by a pulsatile blood flow increase the release of nitric oxide and prostacyclin[27] and is associated with a reduction of monocyte adhesion, providing a fundamental atheroprotective effect.[28–31]

Biomechanical stimuli also modulate endothelial cell morphology, proliferation, apoptosis,[32,33] elongation and realignment,[34] extracellular matrix production,[35] and inflammatory signals.[36]

Pulsatile flow and its mechanical action on vessel wall are associated with a down-regulation of NADPH oxidase activity, present in the endothelium, vascular smooth muscle cells, fibroblasts, and monocytes,[37,38] with a consequent reduction in reactive oxygen species formation.[39,40]

Previous reports have demonstrated that reactive oxygen species such as superoxide and hydrogen peroxide inactivates nitric oxide and provokes the formation of oxidants that induces both low-density lipoprotein oxidation and expression of monocyte chemoattractant proteins on endothelial cells with subsequent monocyte binding and transendothelial migration, which are both fundamental processes in atherogenesis.[41–44]

The restoration of the beneficial cyclical strain[7,45] and the consequent reduction in reactive oxygen species formation may therefore have an impact on both endothelium-dependent vasodilation and atherogenesis.

In addition, the previously mentioned phenomena will take place in a microenvironment treated with the mammalian target of rapamycin (mTOR) inhibitor everolimus. The protein mTOR is a key serine-threonine kinase playing a central role in the regulation of cell growth, proliferation, and survival. On a molecular level, everolimus forms a complex with the cytoplasmic protein FKBP-12[46]; this complex binds to mTOR and inhibits its signaling function, thus inhibiting growth factor–stimulated proliferation of vascular smooth muscle cells, which is triggered by injury to endothelial cells and leads to neointima formation.[47]

In the new scenario of a coronary vessel free of metallic caging, the concomitant scaffold drug elution at early stages,[48] medical therapy,[49–51] and changes in lifestyle[52,53] may all play a key additional role to facilitate phenomena such as plaque regression, expansive remodeling, and late luminal enlargement.

An analysis of vasoreactivity in scaffolded segments at 12- and 24-month follow-up with both endothelial-dependent and endothelial-independent agents has been recently reported, showing that endothelial dysfunction in those regions is correlated to the amount of plaque burden and necrotic core content.[54]

These data support the hypothesis that an improvement of plaque composition and plaque burden could have a beneficial impact also on post–scaffolding vasomotion resembling the behavior of native nonstented segments.

Consequently, in the ABSORB II RCT, special attention will be paid to the adherence to guidelines for the prevention of cardiovascular disease.[9] Patients enrolled will be observed regarding their lifestyle habits and compliance to medical treatment, and efforts will be made to aid subjects in following recommendations by notifying any nonsatisfactory result in collaboration with their treating physician(s).

In conclusion, the present trial will provide a randomized direct comparison between the everolimus-eluting bioresorbable vascular scaffold and the everolimus-eluting metallic stent but also aims to present a new approach to coronary artery disease treatment that integrates transient mechanical revascularization, drug elution, medical treatment, and lifestyle changes into a single strategy to restore coronary blood flow and vessel physiology.

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