



Absorb Bioresorbable Scaffold Versus Xience Metallic Stent for Prevention of Restenosis Following Percutaneous Coronary Intervention in Patients at High Risk of Restenosis: Rationale and Design of the COMPARE ABSORB Trial

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ABSTRACT

Background: The advent of bioresorbable vascular scaffolds (BVS) was considered as a potential improvement in percutaneous coronary intervention (PCI) after the groundbreaking development of drug eluting stents (DES). However, the clinical performance, long-term safety and efficacy of BVS in complex coronary lesions remain uncertain. COMPARE ABSORB, a multicenter, single blind, prospective randomized trial, aims to compare the clinical outcomes between the Absorb BVS and Xience everolimus-eluting metallic stent (EES) in patients with coronary artery disease and a high risk of restenosis. **Design:** COMPARE ABSORB is designed to enroll 2100 patients at up to 45 European sites. Enrolled patients will possess high risk for restenosis due to clinical profile or coronary lesion complexity and will undergo elective or emergent PCI. Once included in the study, patients will receive either Absorb BVS or Xience EES. Specific advice on implantation technique including mandatory pre-dilatation, sizing and post-dilatation (PSP), will be used in the Absorb BVS arm. The primary endpoint is target lesion failure (TLF), a device-oriented composite endpoint (cardiac death, target vessel myocardial infarction and clinically-indicated target lesion revascularization). The trial is powered to assess non-inferiority of Absorb BVS compared with Xience EES with a predetermined non-inferiority margin of 4.5% at 1 year after index procedure. The clinical follow-up will continue for 7 years.

Conclusions: The prospective COMPARE ABSORB randomized trial (ClinicalTrials.gov NCT02486068) will help to assess the long-term safety and efficacy of Absorb BVS compared with Xience EES in the treatments of patients with complex coronary artery disease and a high attendant risk of restenosis.

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1. Introduction

The implantation of a bioresorbable scaffold is a transformative approach to the treatment of coronary atherosclerosis, liberating the coronary artery from permanent metallic caging. Theoretically, the vessel wall, is able to remodel and exhibit plaque reduction in response to pharmacological treatment and physiological stimuli, but this can only occur in the absence of a permanent implant [1–3]. In patients with simple lesions, the ABSORB cohort A and B first-in-man trials showed clinical safety up to 5 years with potential late benefits of bioresorbable vascular scaffold (BVS) implantation, such as lumen enlargement, plaque reduction and restoration of vasomotion. These phenomena start to appear from 1 to 2 years after implantation of the BVS in the early phase of bioresorption [4–7]. After the first-in-man studies, Absorb BVS was compared with Xience EES in relatively low-risk lesions and patients in 4 randomized trials: ABSORB II, ABSORB III, ABSORB Japan and ABSORB China, with hard clinical primary endpoints. Although the Absorb BVS met the criteria for non-inferiority compared with Xience EES in the first year after implantation [8], an increased risk of adverse events after 1 year has been reported [9,10]. Subsequently, the all-comers AIDA trial, originally designed to investigate non-inferiority of the Absorb BVS in 2-year target vessel failure rate compared with Xience EES, was stopped early due to safety concerns, with 2-year definite or probable device thrombosis rates significantly higher in the Absorb BVS arm than in the Xience EES arm despite no overall target vessel failure hazard difference [11]. Simultaneously, an individual patient-level pooled meta-analysis of 4 randomized Absorb trials identified that Absorb BVS was associated with a higher 3-year rate of TLF than Xience EES, driven by an increased rate of scaffold thrombosis and target vessel myocardial infarction [12]. Consequently, an ESC-EAPCI task force stated that the current BVS should not preferred to conventional DES in clinical practice [13,14]. Based on these early warning signals, the use of Absorb BVS was restricted to centers participating in clinical studies since May 31, 2017.

However, there undoubtedly exists a clear relationship between implantation techniques and observed clinical outcomes, identified both in the GHOST-EU registry [15] and in particular the 4 Cities study [16], where development of a 'BVS-specific' implantation technique significantly reduced scaffold thrombosis rates. A pooled analysis of Absorb trials confirmed that aggressive pre-dilation and optimal post-dilation were independent predictors of freedom from scaffold thrombosis or TLF respectively between 1 and 3 years, suggesting that an optimal PSP (Pre-dilation, Sizing and Post-dilatation) technique was strongly associated with improved Absorb BVS-related outcomes during 3-year follow-up [17].

In previous Absorb trials, as well in the AIDA trial, the "PSP" implantation technique was neither fully developed nor adopted as part of the study design. Whether using optimal "PSP" implantation techniques with the Absorb BVS could reduce adverse events, especially the risk of scaffold thrombosis, in comparison to the Xience EES, requires further examination.

In the era of DES, in-stent restenosis, neoatherosclerosis and late catch-up phenomenon remain unmet needs in the treatment of coronary artery disease, especially for patients presenting with high risk of restenosis. The advent of BVS technology provides the hope of transient vessel support with drug delivery capability, potentially without the limitations of permanent metallic implants [18,19] and freedom from restenosis after complete bioresorption.

2. Study objectives

Knowing that the TLF rate for metallic drug-eluting stents (DES) continues to accumulate over the years and that this linear progression of TLF is more prominent in high risk lesions and patients, it is hypothesized that the use of BVS specifically might be of more benefit on the

long-term in comparison to current metallic DES, especially after complete bioresorption.

Second, the previous mentioned trials (ABSORB II, III, Japan, China and AIDA) all started with an initial conservative implantation technique using smaller sized pre-dilatation balloons, limited use of intravascular imaging for optimal sizing, specifically in smaller vessels and using smaller post-dilatation balloons and with lower post-dilatation pressures. The COMPARE ABSORB trial will benefit from such initial experiences and is one of the first trials with Absorb BVS in which both a specific PSP implantation technique has been implemented in the protocol from the start, and that includes only experienced operators/centers for enrollment. One of the purposes of the current investigation is therefore to prove the short-term equivalence and long-term benefit of the Absorb BVS over Xience EES in patients at high risk of restenosis with complex lesion(s) using up-to-date implantation techniques.

3. Randomization and trial management

The COMPARE ABSORB trial is a prospective, single-blind, with a 1:1 balanced randomization, controlled, multicenter study in 45 European sites. This trial is designed to enroll 2100 patients and it is anticipated that 1050 patients will be treated with the Absorb BVS and 1050 patients will be treated with the Xience EES (Abbott Vascular, Santa Clara, CA). Randomization will be performed via web-based software with random blocks according to center. Randomization will occur after all inclusion criteria are met and no exclusion criteria are present, and as soon as the baseline angiographic assessment confirms that the patient matches enrolment criteria and after the guide-wire has successfully passed the first target lesion. Treatment of non-target lesions during the index procedure was allowed, if this was done successfully and without complication before initial treatment of the first target lesion. All target lesions for each patient treated at the index and staged procedure will receive the same assigned stent type according to randomization. Medical teams responsible for care of the patients during the procedure and their hospital stay were instructed not to tell or write in the procedure report or discharge letter the treatment group to which the patients had been assigned for accurate interpretation of patient-reported outcomes. All data will be entered into a secure web-based data capture system (Clinigrid, Paris, France). An independent clinical research organization (CERC, Massy, France) will monitor the trial by site visits and remote monitoring. Source data verification on informed consent, endpoint related events and follow-up will be performed for 100%. Source verification for base-line data will be performed for 50%. Adverse clinical events will be adjudicated by an independent Clinical Event Committee, and clinical/angiographic data analyzed by an independent angiography core lab and statistical department (Cardialysis, Rotterdam, The Netherlands). For clinical oversight and daily operations of the trial a Steering Committee and Executive Committee, respectively, has been appointed.

An independent Data Safety and Monitoring Board will monitor the individual and collective safety of the patients in the study during enrolment phase and up to 1 year of follow-up (primary endpoint). The patients will be followed through 7 years to assess the clinical status and major clinical events (Fig. 1).

4. Patient population

Patients aged 18–75 years with symptomatic ischemic heart disease and presence of high-risk features for restenosis due to clinical profile or coronary lesion complexity and who are scheduled to undergo elective or emergent PCI are potential candidates to participate in this study. Subjects participating in the study must meet at least one of the inclusion criteria: medically treated diabetes, or multivessel disease with >1 de-novo target lesions and/or presence of at least one complex target lesion. Subjects who meet any of the exclusion criteria are not allowed

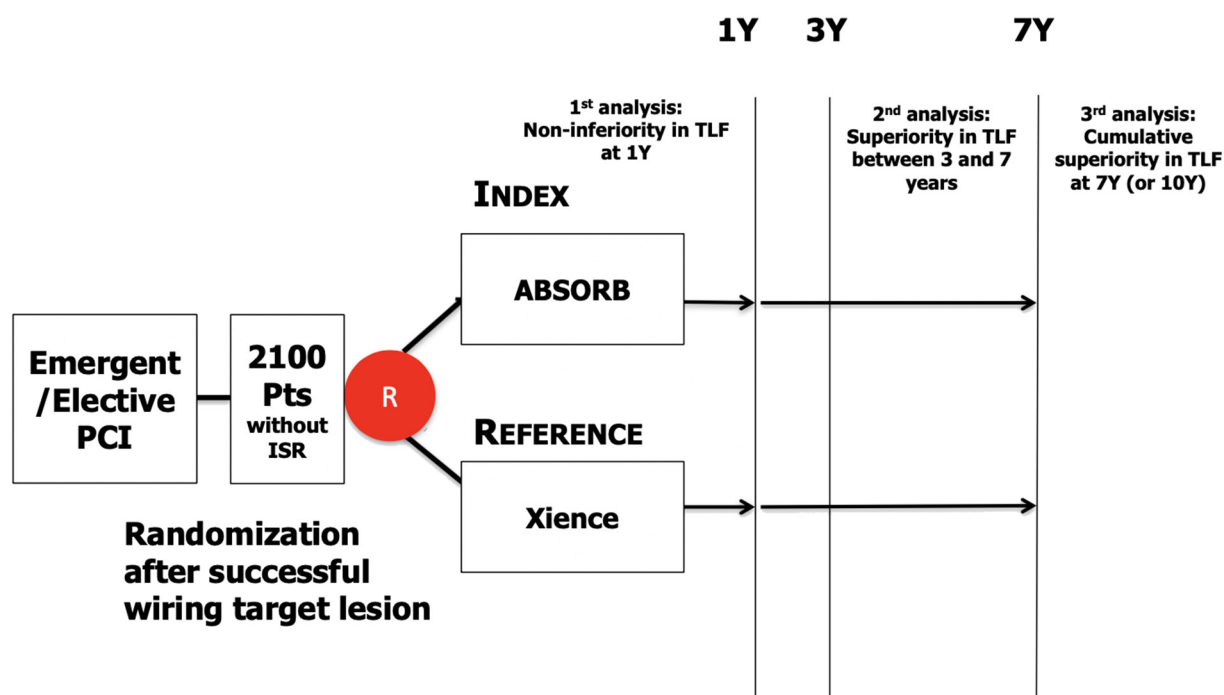


Fig. 1. COMPARE ABSORB study design diagram.

to enter the study. Inclusion and exclusion criteria are listed in Tables 1 and 2, respectively.

5. Patient information and informed consent

Prior to study start, investigators will obtain written IRB/Ethics Committee approval for the study and the patient information/informed consent form. Only patients with signed or witnessed oral consent during primary PCI can be included. In case of witnessed oral consent, written consent will be obtained after the initial procedure. Study patients will be assured that they may withdraw from the study at any time and for any reason with prejudicing medical care.

6. Study endpoints

The study primary endpoint is target lesion failure (TLF), defined as a composite of cardiac death, myocardial infarction (MI) in target vessel

Table 1
Inclusion criteria.

Inclusion criteria
Patients aged 18–75 years with at least one of the following:
1. High-risk characteristics for restenosis
• Medically treated diabetes (oral medication or insulin) and/or multivessel disease of which more than one <i>de-novo</i> target lesion to be treated with the study scaffold/stent
2. Complex target lesion
Single <i>de-novo</i> target lesion satisfying at least one of the following:
• Lesion length > 28 mm
• Small vessels: Target lesion reference vessel diameter $\geq$ 2.5 mm and $\leq$ 2.75 mm
• Lesion with pre-existing total occlusion (pre-procedural TIMI = 0)
• Bifurcation with single stent strategy

Table 2
Exclusion criteria.

Exclusion criteria
1. Age < 18 years, or > 75 years
2. Patients incapable of giving informed consent
3. Patients under judicial protection, tutorship or curatorship
4. Known comorbidities which make patients unable to complete 7 years of follow-up
5. Female of childbearing potential (and last menstruation within the last 12 months), who did not undergo tubal ligation, ovariectomy or hysterectomy
6. Pregnant woman
7. Breastfeeding woman
8. Known intolerance to aspirin, heparin, PLLA, everolimus, contrast material
9. Cardiogenic Shock (Killip >2)
10. PCI with implantation of stents/scaffolds within previous 30 days.
11. Active bleeding or coagulopathy
12. Subject is currently participating in another clinical trial that has not yet completed its primary endpoint
13. Renal insufficiency (GFR <45 ml/min)
14. Life expectancy <7 years
15. Known non-adherence to dual antiplatelet therapy
16. Patients on oral anticoagulation therapy (including novel oral anticoagulant such as dabigatran, rivaroxaban, apixaban and edoxaban)
17. Known Impaired left ventricular function (left ventricular ejection fraction <30%).
18. Patients at high bleeding risk who are not suitable for long-term DAPT.
19. Following lesion characteristics:
o Target lesion with reference vessel diameter (RVD) < 2.50 mm and > 4 mm
o STEMI with RVD of >3.5 mm of the culprit target lesion
o Target lesion with in-stent/scaffold thrombosis
o Graft lesions as target lesions
o Lesion involving left main trunk
o Severe tortuosity of target vessel
o Aorto-ostial lesion(s)
o In-scaffold/in-stent restenosis
o Bifurcation target lesion with intended 2 stent/scaffold strategy
20. Non-target lesion and target lesion in the same epicardial coronary artery (right coronary artery, left circumflex artery or left anterior descending artery)

territory and clinically-indicated target lesion revascularization. Society for Cardiovascular Angiography and Interventions (SCAI) consensus definition will be used to adjudicate peri-procedural MI occurring within 48 h after the index procedure, while the Third Universal definition will be used for spontaneous MI [20,21].

7. Study hypotheses

The following hypotheses will be tested in this study, with the primary hypotheses tested hierarchically.

A. Primary hypotheses

- Hypothesis I (short term) Absorb BVS is non-inferior to Xience EES in terms of TLF at 1 year.
- Hypothesis II (long term) Absorb BVS is superior to Xience EES in terms of TLF between 3 and 7 years (in a landmark analysis after 3 years)
- Additional hypothesis (long term) Absorb BVS is superior to Xience EES in terms of cumulative TLF rate at 7 years

B. Secondary hypothesis

Absorb BVS is superior to Xience EES in terms of cumulative incidence of angina at 1 year.

In case non-inferiority of hypothesis I is not met, hypothesis II and the additional hypotheses will be descriptively analyzed. Hypothesis II represents the proof of concept of fewer events after bioresorption of a bioresorbable scaffold compared with metallic DES.

8. Sample size calculation

Detailed information regarding sample size calculations and non-inferiority margins for the primary hypothesis are as follows (Other details are provided in Appendix):

9. Primary Hypothesis I

From review of previous randomized trials [22], the 1-year TLF rate for Xience EES is estimated at 8.5%. Hypothesis I (non-inferiority at 1 year) will be tested with a non-inferiority boundary of 4.5%. The required sample size is $2 \times 808 = 1616$ patients for non-inferiority testing at 1 year with a power of 90% ($\alpha = 0.05$, two sided).

10. Statistics

All clinical data will be analyzed according to the intention-to-treat principle. For primary endpoint analysis, the hypothesis I (non-inferiority in TLF at 1 year) will be tested using the standard normal distribution and a two-sided 95% confidence interval for the difference in the target lesion failure Kaplan-Meier rates of the Absorb BVS and Xience EES groups. The follow-up of patients that have withdrawn informed consent, that are lost to follow-up, or that have died of a non-cardiovascular cause, will be censored at the data of the last contact. The null-hypotheses of inferiority of the Absorb BVS (relative to the Xience EES) will be rejected if the 95%-CI excludes the value of 4.5%. Hypothesis II (superiority of the Absorb BVS between 3 and 7 years) will be tested by comparing the post-landmark Kaplan-Meier curves to 7 years with the log-rank test. Binomial variables will be evaluated with Fisher's exact probability tests. Continuous variables will be tested with a two-sample *t*-test or with the Mann-Whitney *U* test when data are not normally distributed. The full data analytic methods are documented in the Statistical Analysis Plan.

11. Study devices

The investigational device to be used in this trial is the Absorb BVS. Absorb BVS is composed of a poly-L-lactic acid (PLLA) backbone, coated with a matrix composed of the drug everolimus and poly-D, L-lactic acid (PDLLA) in a 1:1 ratio. Approximately 80% of the drug is eluted within 28 days. Both PLLA and PDLLA are fully bioresorbable, with PDLLA expected to be totally bioresorbed by the body in 9 months and PLLA in 36 months. Preclinical testing suggests that neither PDLLA nor PLLA remain in the body after the specified period. Absorb BVS is manufactured by Abbott Cardiovascular Systems, Inc., a subsidiary of Abbott Vascular, Inc. and received CE-mark approval in January 2011.

The control device is the Xience family everolimus eluting coronary stent, which is also manufactured by Abbott Cardiovascular Systems, Inc., a subsidiary of Abbott Vascular, Inc. and received CE-mark approval in 2007. The control device is considered to be the current standard for DES given its documented clinical performance and safety.

12. Index and staged procedures

To assess the eligibility of the subject according to the inclusion criteria, the target vessel diameter and the lesion characteristics must be visually evaluated before randomization. Because of the limited available size matrix of the Absorb BVS, the reference vessel diameter of the target lesion(s) should be ≥ 2.50 mm and ≤ 4 mm. In case the vessel size is estimated to be ≤ 2.75 mm or lower by visual assessment, quantitative vessel sizing by QCA, IVUS or OCT is mandatory to ascertain that the reference vessel size is ≥ 2.50 mm in order to exclude small vessels with documented increased TLF and scaffold thrombosis rates. When randomized to the Absorb BVS arm, pre-dilatation of the target lesions is mandatory with a balloon of equal size to the reference vessel diameter (ratio 1:1). Usage of non-compliant balloon is recommended. The Absorb BVS must be deployed slowly in 2 atm increments every 5 s, per Instructions for Use. Post-scaffold high-pressure (≥ 16 atm) dilatation is strongly recommended in all cases, with nominal diameter of the post-dilatation balloon of the same size, or ≤ 0.5 mm larger as the implanted scaffold. For long target lesions, abutting/overlapping of two scaffolds is allowed and the overlapped segment should be a maximum of 1.5 mm. Bifurcation lesions are recommended to be treated with a provisional single scaffold strategy, although fenestration of a side branch may be performed with a ≤ 2.5 mm balloon [23]; two-scaffold strategies with Absorb BVS are not allowed in this trial. Deployment of Xience EES should be performed according to Instructions for Use (IFU). Post-dilatation for subjects treated with Xience EES will be done according to the IFU and operators' discretion.

It is strongly recommended that all lesions in the target vessel are treated in the same procedure, except in patients presenting with ST elevation myocardial infarction (STEMI). In STEMI patients, it is highly recommended that non-culprit lesions are treated at a staged procedure unless clinically indicated. Staged procedures are allowed but should be completed within 6 weeks and mentioned at the index procedure. All lesions should be treated with the assigned type of stent or scaffold. Moreover, all the staged procedures should be declared at the time of or after the index procedure. Treatment of non-target lesions may be performed during the same PCI procedure before randomization. However, patients can be randomized only after all such lesions have been successfully treated without complication. In case of a non-successful or complicated non-target lesion treatment the patient may not be enrolled into the trial. Only after a minimum of 30 days post treatment of such non-target lesions may the patient undergo index treatment of the target lesion (s) and be enrolled into the trial. In this case, pre-procedural cardiac biomarkers should have returned to normal and it should be checked that the patient still fulfils inclusion criteria.

13. Dual antiplatelet therapy

In the Absorb BVS-treated group, patients presenting with acute coronary syndrome (ACS), patients will continue dual antiplatelet therapy (DAPT) with prasugrel or ticagrelor (clopidogrel if neither available) for a minimum of 12 months; after this period, DAPT may be continued to 36 months, except in patients who are at high bleeding risk. For non-ACS presentations, DAPT should be continued for a minimum of 6 months, again continuing to 36 months when bleeding risk permits.

In the Xience EES group, patients should continue DAPT for a minimum of 12 months with prasugrel or ticagrelor (clopidogrel if both not available) for ACS presentations, and for a minimum of 6 months in patients with stable angina. Prolonged DAPT may be prescribed, considering the bleeding and thrombo-ischemic risk of individual patients.

14. Clinical follow-up

Hospital visits are planned at 1, 6- and 12-month post-procedure, at which time assessments of anginal status, cardiovascular drug use and any serious adverse events will be made. Annual phone contacts are then scheduled up to 7 years.

Detailed Quality of Life (EQ5D) and Seattle Angina Questionnaires will be recorded (SAQ) at 30, 180- and 360-day post-procedure and at the time of any recurrent event. Chest pain symptoms potentially related to angina will be assessed using a dedicated structured questionnaire at 1, 6 and 12 months and at intermittent events. In addition, major costs related to diagnostic workups or therapies triggered by symptoms of chest pain will be collected in the first year. After 12 months, major costs related to treatment and target vessel failure will be collected. The cost-effectiveness of the two treatment arms related to chest pain or angina will be assessed at 12 months using unit costs in 5 countries.

15. Safety monitoring by data safety monitoring board

The Data Safety Monitoring Board (DSMB) will monitor the safety of subjects and/or efficacy of treatments throughout the subject enrolment and on an ongoing basis. The composition, guiding policies, and operating procedures governing the DSMB are described in a separate DSMB charter. Based on safety data, the DSMB may recommend the Steering Committee to modify or stop the clinical trial/investigation. All final decisions regarding clinical trial/investigation modifications, however, rest with the Steering Committee.

16. Adjudication of events

Events will be adjudicated by the clinical event committee (CEC), which is comprised of qualified physicians who are *not* investigators in the trial. The CEC will be responsible for adjudicating all serious adverse events (SAE). The composition, guiding policies, and operating procedures governing the CEC are described in a separate CEC manual of operations.

17. Enrolment status and updated protocol

The enrolment of COMPARE ABSORB trial started in September 2015. In the original protocol, primary hypothesis I was a non-inferiority end-point comparing Absorb BVS with Xience EES in terms of TLF at 1 year. Primary hypothesis II was the superiority of Absorb BVS over Xience EES in TLF between 1 and 5 years, based on the assumption that the event rate will continue to increase in the Xience EES arm but will downswing or remain constant in the Absorb BVS arm after 1 year. However, during the enrolment of patients in COMPARE ABSORB, follow-up results of early Absorb trials have shown that the event rate continued to increase in Absorb BVS-treated patients from 1 to 3 years, and that the scaffolds appeared to still be present in imaged coronary arteries, implying that Absorb BVS were not completely absorbed as had been expected. In addition, the

results of ABSORB III and AIDA showed that patients treated with Absorb BVS experienced a significantly higher definite or probable stent/scaffold thrombosis rate than Xience EES arm. Because of this safety concern, the Steering Committee decided to discontinue patient enrolment on 31st August 2017. At that time, the trial already enrolled 1670 patients to examine the primary hypothesis I. According to the 5-year follow-up data from Absorb cohort B, the curve of major adverse cardiovascular events (MACE) appears flat from 3 years and afterwards, and therefore, the long-term benefit of the Absorb BVS could be exhibited at such prolonged timepoints. Therefore, the timing of landmark analysis of the primary hypothesis II was revised to between 3 and 7 years, instead of between 1 and 5 years. This trial still has 80% power to show the superiority of Absorb BVS over Xience EES even if relative risk ratio from 3 to 7 years of Absorb BVS against Xience EES is 0.65. This change is in line with the recent protocol revisions of the ABSORB III and IV trials (NCT02173379).

The other major change in the COMPARE ABSORB protocol is the inclusion criteria for small vessels: initially, the protocol allowed inclusion of target vessels with reference diameter equal to 2.25 mm. However, because of the safety issue in the small vessel subset raised in the Absorb BVS arm of the ABSORB III trial, the Steering Committee decided to exclude target lesions with reference vessel diameter <2.5 mm. In the meantime, results from the ABSORB II and AIDA trials demonstrated that there was a maintained risk of scaffold thrombosis in Absorb BVS arm, especially between 1 and 3 years, and it was therefore suggested that use of extended DAPT regimes in patients treated with Absorb BVS up to 3 years could be justified on an individual patient basis. Although there is limited evidence to support extended DAPT treatment after Absorb BVS implantation, the Steering Committee decided to inform enrolled patients about the type of device they received and prolong the DAPT use up to 3 years on an empirical basis.

For the metallic stent arm, the DAPT study demonstrated that extended DAPT therapy up to 30 months, as compared with aspirin therapy alone, significantly reduced risks of stent thrombosis and major adverse cardiovascular and cerebrovascular events but was associated with an increased risk of bleeding [24]. The PEGASUS-TIMI 54 trial [25] evaluated long-term therapy with ticagrelor in addition to aspirin, in patients with a history of spontaneous MI occurring 1 to 3 years prior to randomization and concluded that ticagrelor significantly reduced the risk of MACE compared with placebo. Recently, a meta-analysis showed that DAPT beyond 1 year among stabilized high-risk patients with prior MI decreased ischemic events, but increased major bleeding [26]. In light of such study results, the ACC/AHA focused update on DAPT recommended that DAPT for longer than 6 months after implantation of a DES may be reasonable for patients with stable ischemic heart disease who are not at high risk of bleeding and who tolerated DAPT without bleeding complications (Class IIb recommendation) [27].

18. Limitations

In our study design, SCAI consensus was adopted to adjudicate periprocedural MI which is more clinically relevant in terms of prognosis. This definition of periprocedural MI is different from that of the reference trial, the RESOLUTE-AC [22]. Although the expected impact of this difference is limited [28], it could be a potential risk for underestimation of the event rate.

19. Conclusions and perspective

The COMPARE ABSORB trial is the only prospective randomized head-to-head comparison of Absorb BVS with best-in-class metallic EES in high risk patient/lesion subsets, reflective of everyday PCI practice. The study also incorporates a recommendation for best-practice implantation technique ('PSP') in the study protocol. These factors make this study unique and scientifically important in furthering our understanding of use of a BVS platform in routine PCI.

Although there is no scientific evidence that prolonged DAPT use will reduce the risk of scaffold thrombosis to date, the COMPARE ABSORB trial also aims to evaluate the effectiveness and safety of extended DAPT duration up to 3 years after Absorb BVS implantation.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.carrev.2019.04.013>.

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