Optimal dual antiplatelet therapy duration for bioresorbable scaffolds: an individual patient data pooled analysis of the ABSORB trials

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KEYWORDS

- adjunctive pharmacotherapy
- bioresorbable scaffolds
- clinical trials
- stent thrombosis

Abstract

Background: Compared with everolimus-eluting metallic stents, the Absorb bioresorbable scaffold (BRS) results in increased rates of myocardial infarction (MI) and scaffold thrombosis (ST) during its three-year bioresorption phase. It is unknown whether prolonged dual antiplatelet therapy (DAPT) duration might decrease the risk of ischaemic events.

Aims: We sought to evaluate the impact of DAPT duration on ischaemic and bleeding outcomes following BRS implantation.

Methods: We conducted an individual patient data pooled analysis from four ABSORB randomised trials and one prospective ABSORB registry. Study endpoints were MI, ST, bleeding, and death up to three-year follow-up. Propensity score-adjusted Cox regression analysis was used to account for baseline differences related to DAPT duration.

Results: The five ABSORB studies included 2,973 patients. DAPT use was 91.7%, 53.2%, and 48.0% at 1, 2, and 3 years, respectively. DAPT use within the first year after BRS implantation was associated with markedly lower risks of MI (adjusted hazard ratio [aHR] 0.17, 95% CI: 0.10-0.32; p<0.0001) and ST (aHR 0.08, 95% CI: 0.03-0.19; p<0.0001). Conversely, DAPT use between 1 and 3 years did not significantly affect the risk of MI (aHR 1.04, 95% CI: 0.70-1.55; p=0.84) or ST (aHR 0.86, 95% CI: 0.42-1.75; p=0.67). DAPT did not have major effects upon bleeding or death in either period.

Conclusions: DAPT use during the first year after BRS implantation was strongly associated with lower risks of ST and MI. However, a benefit of ongoing DAPT use between 1 and 3 years after BRS implantation was not apparent.

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Abbreviations

BRS	bioresorbable scaffold
DAPT	dual antiplatelet therapy
DES	drug-eluting stents
EES	everolimus-eluting stents
HR	hazard ratio
IPD	individual patient data
MI	myocardial infarction
ST	scaffold thrombosis
TLF	target lesion failure

Introduction

First-generation Absorb™ (Abbott Laboratories, Abbott Park, IL, USA) poly-L-lactic acid (PLLA)-based everolimus-eluting bioresorbable scaffolds (BRS) failed to show non-inferiority compared with cobalt-chromium fluoropolymer-based everolimus-eluting stents (EES) due to higher rates of scaffold thrombosis (ST), target vessel-related myocardial infarction (MI), and target lesion revascularisation[1,2]. However, a recently published, individual patient data (IPD) pooled analysis from four ABSORB randomised trials demonstrated that the risk period was confined to the first three years after BRS implantation, the approximate time of PLLA bioresorption. In particular, the incidence of ST with BRS was negligible during follow-up between 3 and 5 years (only one case of ST among 2,161 BRS-treated patients [<0.1%] in this two-year period, compared with a 2.4% ST rate between the time of implant and three-year follow-up)[2]. These data indicate that the period of excess risk for the first-generation Absorb BVS ends at approximately three years.

The use of prolonged dual antiplatelet therapy (DAPT) with metallic drug-eluting stents (DES) has been shown to reduce MI and stent thrombosis rates, at the cost of increased bleeding[3]. Prolonging DAPT after BRS implantation during the three-year risk period may thus mitigate their higher propensity for ischaemic events (ST and MI) during the bioresorption phase. However, the causes of very late ST and MI after BRS are multifactorial, and include novel mechanisms such as intraluminal scaffold dismantling[4]; whether prolonged DAPT is useful to prevent these BRS-related events is unknown.

We therefore sought to evaluate the impact of DAPT duration on ischaemic and bleeding events following BRS implantation up to three-year and five-year follow-up from a large individual patient data pooled analysis of four randomised controlled trials and one prospective registry.

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Methods

PATIENT POPULATION AND INCLUDED STUDIES

We pooled IPD from five prospective studies into a common database, including four randomised controlled trials comparing BRS and EES (ABSORB II, NCT01425281; ABSORB Japan, NCT01844284; ABSORB China, NCT01923740; and ABSORB III, NCT01751906) and one single-arm BRS prospective registry (ABSORB EXTEND, NCT01023789). The principal analysis focused on three-year outcomes, the period of active scaffold bioresorption. A secondary exploratory analysis of five-year outcomes is also provided. This observational analysis followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement **(Supplementary Table 1)**. The main characteristics of these five studies are summarised in **Supplementary Table 2**. In all five studies, aspirin use was required indefinitely; use of a platelet receptor $P2Y_{12}$ inhibitor was required for the first year after BRS implant, after which its administration was optional according to investigator discretion. In all of the studies the patients were queried for their continuous (i.e., daily) DAPT usage during follow-up.

ENDPOINTS AND DEFINITIONS

For the present study we were interested in evaluating the impact of DAPT duration during the high-risk period of the first three years following BRS implantation. We further pre-specified examining outcomes between 0 and 1 year after device implantation (the typical high-risk period for metallic DES, after which event rates are low), and between 1 and 3 years after device implantation, when the greatest hazards for BRS relative to DES were noted[2]. The outcome measures of interest for this study were MI (target vessel-related and non-target vessel-related), ST, bleeding, and all-cause death. Procedural and non-procedural MI were defined using the ABSORB III criteria[1]. ST was defined according to the Academic Research Consortium definite or probable criteria[5]. Bleeding was defined by the GUSTO classification of "life-threatening or severe" (either intracranial haemorrhage or bleeding that causes haemodynamic compromise and requires intervention) or "moderate" (bleeding that requires blood transfusion but does not result in haemodynamic compromise)[6]. All ischaemic events were adjudicated by an independent clinical events committee after review of original source documents. Bleeding events were site-reported and monitored but not adjudicated.

STATISTICAL ANALYSIS

Baseline characteristics are summarised using means and standard deviations for continuous variables, and as numbers and percentages for categorical variables. The principal analyses were performed from the time of BRS implantation up to three years (0-3 years), and between 0-1 year and 1-3 years separately. A secondary analysis was performed considering 3-5 year and 0-5 year events. Analyses were stratified according to DAPT usage. Event rates were estimated with the Kaplan-Meier method, and compared with the log-rank test.

A propensity score-adjusted analysis was used to account for differences in 11 patients and lesion variables that might have affected the decision to use long-term DAPT. The propensity score accounted for age, sex, diabetes, recent smoker (<1 month), acute coronary syndrome (versus stable coronary artery disease), total lesion length, smallest baseline reference vessel diameter, treatment of any calcified lesion, any bifurcation lesion, any lesion in the left main or left anterior descending coronary arteries, and the number of treated lesions. Daily DAPT use was entered into a propensity score-adjusted and

study-level adjusted Cox multivariable model as a time-adjusted covariate, and the effect of permanent DAPT discontinuation (≥2 days, and until last follow-up or time of event) was assessed. The results of this analysis are presented as hazard ratios (HR) and 95% confidence intervals (CI). To examine the change in hazards during the three-year follow-up period further, a flexible parametric propensity score-adjusted survival model was used to estimate the HR and 95% CI for the study outcomes over time. An interaction term between DAPT status and a natural spline of the log of time with two degrees of freedom was included in the model. A p-value <0.05 was considered significant. All statistical analyses were performed with SAS, version 9.4 (SAS Institute, Cary, NC, USA).

Results

PATIENTS AND PROCEDURES

The five ABSORB studies included 2,973 patients (3,149 lesions) treated with Absorb BRS at 357 centres in America, Europe, Asia, and Oceania. Three-year follow-up data were available for 2,851/2,973 patients (95.9%). The baseline characteristics of the patients enrolled from each study have been reported previously[2]. Clinical, angiographic, and procedural characteristics across the five studies are presented in **Supplementary Table 3**-**Supplementary Table 5**, respectively. Mean age was 62.4±10.8 years, 73.0% of patients were male, 29.2% had diabetes, 23.3% prior MI, 31.7% prior PCI, and 31.5% presented with an acute coronary syndrome. A single lesion was treated in 94.0% of patients, 60.5% had a type B2/C lesion treated, predilatation was performed in 99.8%, post-dilatation with a non-compliant balloon was performed in 61.6%, and intravascular imaging guidance was used in 21.6%. Device success was achieved in 98.7% of lesions.

DAPT USE DURING FOLLOW-UP

Figure 1 shows data on aspirin, $P2Y_{12}$ inhibitor, and DAPT use at several time points during follow-up. Among $P2Y_{12}$ inhibitors, clopidogrel was used in the majority of patients (82.7%), followed by prasugrel (11.1%) and ticagrelor (6.3%). DAPT was used in 91.7% of patients at 1 year, 53.2% at 2 years, and 48.0% at 3 years. Whereas aspirin was maintained in the vast majority of patients at three-year follow-up (95.3%), there was a sharp drop in $P2Y_{12}$ inhibitor use between one year (93.6%) and subsequent time points, such that at three-year follow-up only 51.1% of patients were still on one of these agents. Longer-term follow-up showed further slight reductions in the use of antiplatelet agents (particularly $P2Y_{12}$ inhibitors), so that at five-year follow-up 39.8% of patients were still on DAPT.

Supplementary Table 6 shows clinical, angiographic, and procedural characteristics according to DAPT status. **Supplementary Table 7** presents data on the timing of DAPT discontinuation. While permanent DAPT discontinuation was uncommon (2.5%) within the first 6 months after implantation, its incidence rose to 16.5% between 6 and 12 months following the index PCI. DAPT was permanently interrupted in 44.5% of the study population between 1 and 2 years, in 51.4% of patients between 2 and 3 years, in 55.2% of patients between 3 and 4 years, and in 59.8% of patients between 4 and 5 years.

ADVERSE EVENTS ACCORDING TO DAPT USE DURING THREE-YEAR FOLLOW-UP

Table 1 presents the Kaplan-Meier estimates of pooled study outcomes. MI, ST, bleeding, and death occurred in 8.2%, 2.3%, 1.8%, and 2.9% of BRS-treated patients, respectively, during the three-year study period. In patients who developed MI or ST off DAPT within 1 year, the median duration from the time of last DAPT discontinuation to the event was 7.5 days, ranging from 0-334 days. In patients who developed MI or ST off DAPT between 1 and 3 years, the median duration from the time of last DAPT discontinuation to the event was median 451 days, ranging from 2-1,032 days.

Table 2 shows the unadjusted relationships between permanent DAPT discontinuation and study outcomes. The **Central illustration** presents the propensity score-adjusted Cox regression analysis for

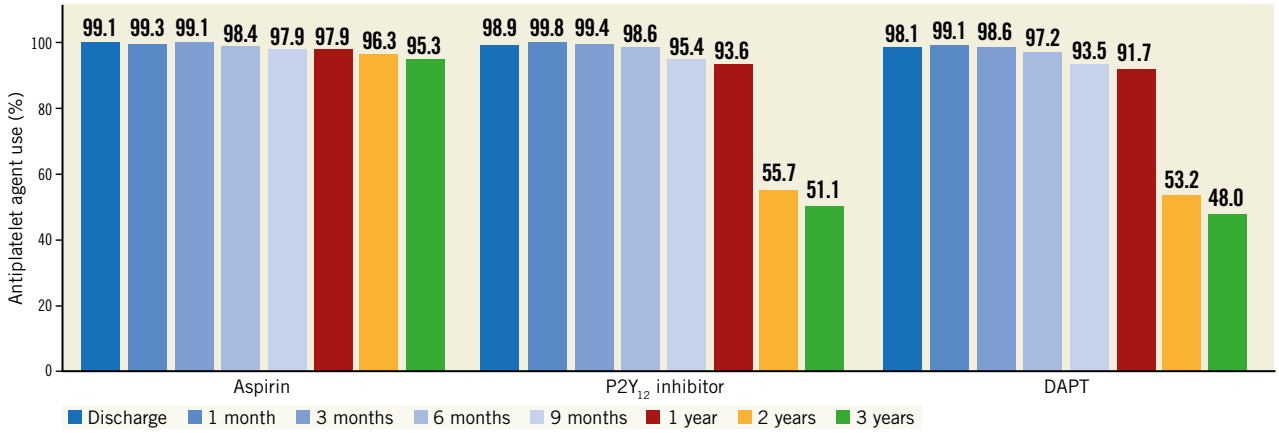


Figure 1. *Aspirin, $P2Y_{12}$ inhibitor, and dual antiplatelet therapy use at different time points during the three-year follow-up. Usage rates of each agent based on the total number of patients alive and on-study at that specific timepoint (i.e., end of interval), and thus the rates are different from those in Supplementary Table 7. DAPT: dual antiplatelet therapy*

Table 1. Kaplan-Meier estimates of pooled ischaemic and bleeding event rates in the five included studies.

Variable		Number of events	Rate	*p*-value (0-1 vs 1-3 years)
Myocardial infarction	0-1 year	150	5.1%	0.01
	1-3 years	102	3.6%	
	0-3 years	238	8.2%	
Scaffold thrombosis	0-1 year	36	1.2%	0.80
	1-3 years	31	1.1%	
	0-3 years	67	2.3%	
Bleeding	0-1 year	25	0.8%	0.15
	1-3 years	29	1.0%	
	0-3 years	53	1.8%	
Death	0-1 year	25	0.8%	<0.0001
	1-3 years	57	2.0%	
	0-3 years	82	2.9%	

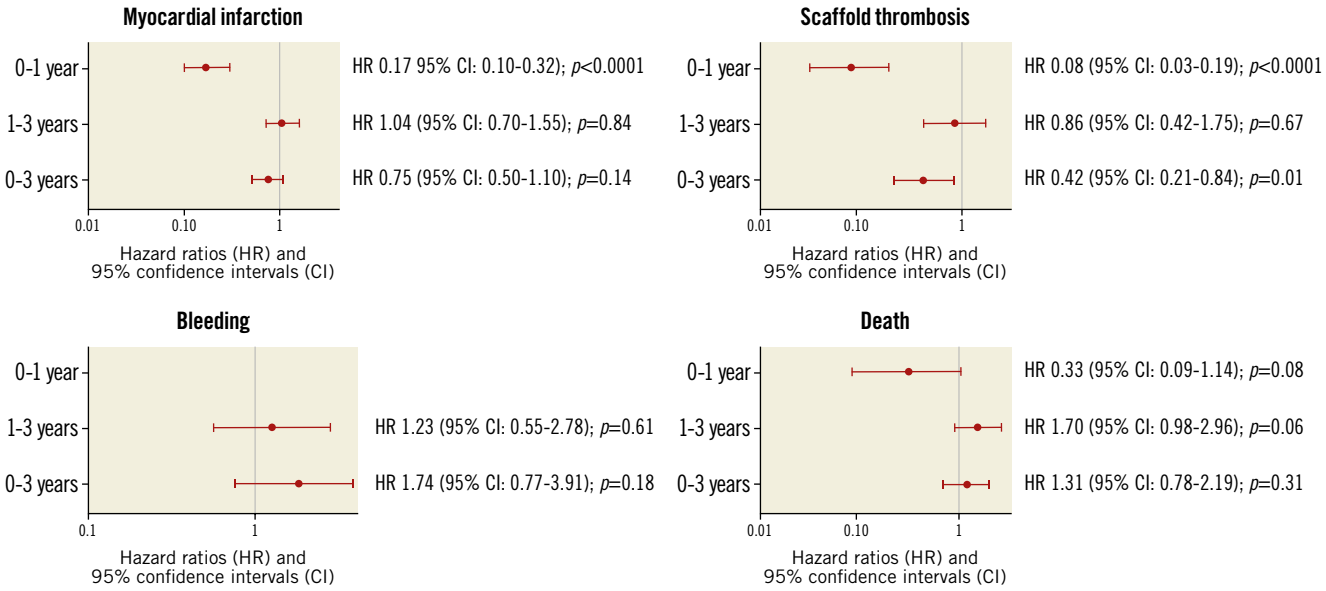
Landmark analysis: patients can have events (except death) in both time periods (0-1 year and 1-3 years), which explains why the sum of the numbers of events (and incidence rates) for the two periods can be greater than the total between 0 and 3 years.

the impact of daily DAPT status on outcomes. During the entire three-year period, DAPT use was associated with a non-significant effect on MI (HR 0.75, 95% CI: 0.50-1.10; p=0.14) but was strongly associated with reduced ST (HR 0.42, 95% CI: 0.21-0.84; p=0.01). However, these effects varied markedly between 0 and 1 year, and 1 and 3 years. During the first year after BRS implantation, use of DAPT was associated with a markedly reduced risk of MI (HR 0.17, 95% CI: 0.10-0.32; p<0.0001) and ST (HR 0.08, 95% CI: 0.03-0.19; p<0.0001). Conversely, DAPT use was not protective against MI (HR 1.04, 95% CI: 0.70-1.55; p=0.84) or ST (HR 0.86, 95% CI: 0.42-1.75; p=0.67) between 1 and 3 years. DAPT use had a weak and non-significant effect on bleeding throughout the study period. Finally, while DAPT use tended to confer protection from death within the first year after BRS implantation (HR 0.33, 95% CI: 0.09-1.14; p=0.08), this relationship tended to be reversed between 1 and 3 years (HR 1.70, 95% CI: 0.98-2.96; p=0.06), resulting in an overall neutral effect when considering the three-year follow-up as a whole (HR 1.31, 95% CI: 0.78-2.19; p=0.31).

By spline analysis **(Figure 2)**, the adjusted HR for the association between DAPT use and MI was markedly low (<0.10) in the two months following BRS implantation, and later rose to stabilise at an HR of ~1.0 at 12 months, remaining constant until the end of the three-year follow-up. The upper bound of the 95% CI crossed 1.0 at approximately 4 months; after this time point the association between DAPT use and MI was non-significant. The unadjusted HR for ST was also very low (<0.10) until ~5 months after BRS implantation, and thereafter increased, stabilising at an HR of ~0.50 at 12 months up to the end of follow-up. The upper bound of the 95% CI approximated 1.0 at 12 months and beyond. Spline analysis indicated a small but non-significant risk of DAPT use for bleeding throughout the three-year study period. The findings for all-cause death also demonstrated non-significant associations throughout follow-up, although the HR tended to be below 1.0 for the first 6-8 months and above 1.0 thereafter.

FIVE-YEAR OUTCOMES ANALYSIS

Our secondary analysis explored the impact of DAPT usage beyond three-year follow-up. Between 3 and 5 years, low event rates were observed for the outcomes of MI (2.0%), ST (0.1%),



Central illustration. *Propensity score-adjusted Cox regression analysis showing the impact of dual antiplatelet therapy on study outcomes. Analysis of the effect of permanent DAPT discontinuation on study outcomes. Estimates for the 0 to 1-year effect of DAPT on bleeding could not be calculated because of the low number of events.*

Table 2. Unadjusted pooled adverse event rates occurring in patients with versus without permanent dual antiplatelet therapy discontinuation.

Variable		No permanent discontinuation	Permanent discontinuation*	HR (95% CI) for no permanent discontinuation	*p*-value¶
Myocardial infarction	0-1 year	4.8% (117/2,472)	6.6% (33/498)	0.61 (0.41-0.91)	0.08
	1-3 years	5.2% (71/1,431)	2.1% (31/1,480)	2.33 (1.49-3.57)	<0.0001
	0-3 years	10.9% (157/1,493)	5.6% (81/1,477)	1.85 (1.39-2.44)	<0.0001
Scaffold thrombosis	0-1 year	1.1% (27/2,481)	1.9% (9/489)	0.47 (0.21-1.05)	0.17
	1-3 years	1.4% (18/1,427)	0.9% (13/1,484)	1.56 (0.76-3.23)	0.28
	0-3 years	2.8% (40/1,475)	1.9% (27/1,495)	1.49 (0.91-2.44)	0.08
Bleeding	0-1 year	0.8% (20/2,491)	0.6% (3/479)	0.69 (0.20-2.38)	0.68
	1-3 years	1.2% (17/1,443)	0.6% (9/1,468)	1.43 (0.63-3.23)	0.09
	0-3 years	2.1% (30/1,491)	1.3% (19/1,479)	1.15 (0.64-2.04)	0.09
Death	0-1 year	0.8% (19/2,487)	1.2% (6/483)	0.56 (0.21-1.47)	0.30
	1-3 years	3.4% (46/1,447)	0.8% (11/1,464)	4.55 (2.27-8.33)	<0.0001
	0-3 years	3.6% (51/1,482)	2.2% (31/1,488)	1.61 (1.02-2.56)	0.02

Note: 16.2% of patients had permanent dual antiplatelet therapy (DAPT) discontinuation between 0 and 1 year, and 50.7% of patients had permanent DAPT discontinuation between 1 and 3 years. *≥2 days and until last follow-up or time of event. ¶*p*-values by log-rank test and hazard ratios by Cox regression. CI: confidence interval; HR: hazard ratio

and bleeding (1.2%), while death was observed in 3.5% of patients overall. The 0-5 year estimates of the study endpoints were 9.9%, 2.5%, 3.1%, and 6.2%, respectively.

Supplementary Table 8 shows event rates as well as unadjusted and adjusted risks of the study endpoint in patients with versus without permanent DAPT discontinuation at 3-5 years and for the totality of follow-up (0-5 years). Event rates at 3-5 years in the permanent discontinuation group were very low (0-0.2%) for all endpoints, which led to unstable risk estimates. Considering the 0-5 year follow-up period in its entirety, there were no differences in the adjusted risks of MI, ST, bleeding or death between groups.

Supplementary Figure 1 shows the spline analysis including longer-term follow-up (up to five years). The findings extend those seen in the principal three-year analysis, with no significant adjusted differences between patients on versus off DAPT between 3 and 5 years. Of note, the spline model could not be fitted for the outcome of ST, as this event occurred in only 0.1% of patients in this period.

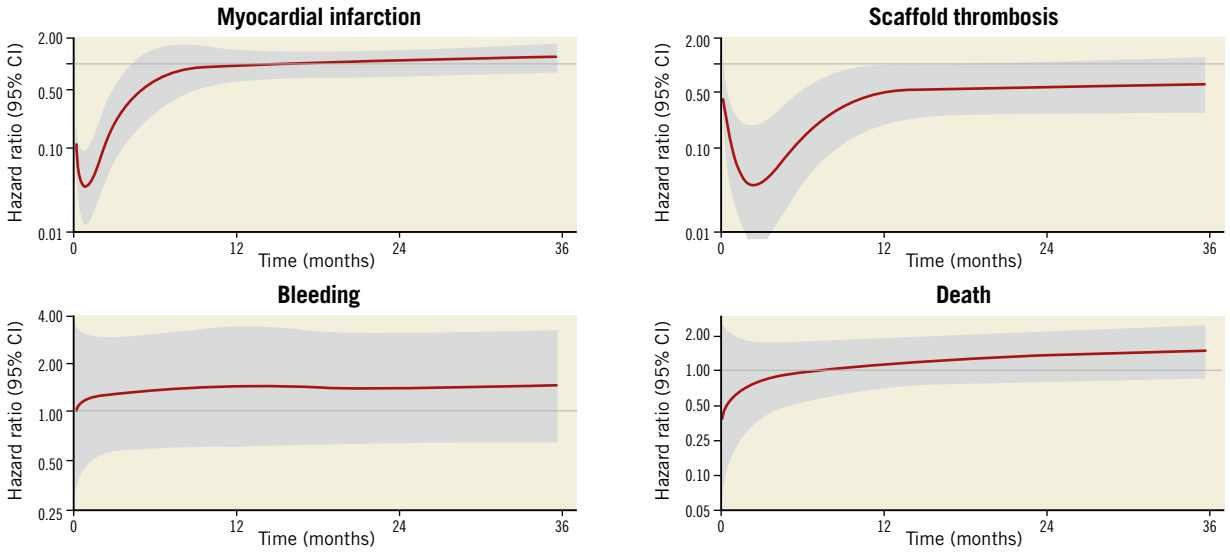


Figure 2. *Spline analysis demonstrating the time-varying association of the hazard for study outcomes depending on dual antiplatelet therapy status during the three-year follow-up period. This analysis evaluates the effect of permanent dual antiplatelet therapy discontinuation on study outcomes. The solid red line represents the adjusted hazard ratio, while the grey shadow represents the 95% confidence interval. Analyses are covariate-adjusted for all outcomes, except for scaffold thrombosis which is unadjusted, as the adjusted spline model for scaffold thrombosis would not successfully converge due to the low number of events. CI: confidence interval*

Discussion

The major findings from the present large-scale Absorb BRS IPD pooled analysis are: 1) while DAPT use was high (>90%) during the first year after BRS implantation, half or less of the study population remained on both aspirin and a $P2Y_{12}$ inhibitor between 1 and 5 years; 2) permanent DAPT discontinuation during the first year after Absorb BRS implantation was associated with markedly higher adjusted risks of MI and ST; 3) conversely, DAPT discontinuation was not associated with increased ischaemic events between 1 and 3 years after BRS implantation (the period of active scaffold bioresorption), nor between 3 and 5 years (the period after complete scaffold bioresorption when event rates are low); and 4) DAPT use did not have effects on bleeding or all-cause death throughout the three-year study period.

Current guidelines recommend DAPT use for 6 months after metallic DES implantation in most patients with stable coronary artery disease, and for 12 months in most patients with acute coronary syndromes[7]. The rationale for these recommendations is that in prior studies the incremental bleeding risks from prolonging DAPT beyond these periods were greater than the additional ischaemic protection that was afforded. Whether these same recommendations are appropriate after BRS implantation is unknown and necessitates re-consideration of the relative risks of ischaemia versus bleeding over time with these novel devices. In this regard, the first-generation Absorb BRS compared with contemporary metallic DES has a larger footprint (strut thickness 157 µm) which may lead to greater platelet activation and delayed endothelialisation, incomplete support of the vessel wall during healing and scaffold resorption, and the development of scaffold discontinuities during the bulk resorption process with the potential for late intraluminal scaffold dismantling, all of which would be expected to prolong the ischaemic risk period[4,8]. In an IPD pooled analysis from the ABSORB II, ABSORB III, ABSORB China and ABSORB Japan randomised trials, treatment with Absorb BRS compared with EES was associated with higher rates of target lesion failure (TLF, 14.9% vs 11.6%; HR 1.26, 95% CI: 1.03-1.54) up to five-year follow-up[2]. However, the period of excess risk was limited to the first 3 years; between 3 and 5 years the rates of TLF were similar with BRS and EES. Moreover, device thrombosis was observed in 2.4% of BRS-treated patients versus 0.6% of EES-treated patients between 0 and 3 years (HR 3.86, 95% CI: 1.75-8.50), compared with 0.1% of BRS-treated patients versus 0.3% of EES-treated patients between 3 and 5 years (HR 0.44, 95% CI: 0.07-2.70). Significant time-dependent interactions were present for device use and these endpoints, indicating that the period of excess risk for the first-generation Absorb BVS ends when bioresorption is complete at ~3 years. Our principal analysis therefore assessed the impact of DAPT on adverse events after BRS for up to three years in the present study.

Prior studies examining the potential utility of prolonged DAPT after BRS have been limited to a modest number of patients and reported conflicting outcomes. Felix et al[9] analysed 685 BRS-treated patients without early ST who took DAPT for >6 months. The ST incidence density was 0.26 versus 1.77 per 100 patient-years between 6 and 18 months after BRS implantation in patients on versus off DAPT, respectively, but rose to 6.57 per 100 patient-years within the first month after DAPT discontinuation. Of interest, all four cases of very late ST (>1 year after implantation) occurred in patients who had recently discontinued DAPT, and no case of very late ST occurred in patients who continued DAPT for >18 months. Similarly, in an early report from the ABSORB EXTEND registry[10], 2 of the 4 ST cases were related to either premature DAPT termination or resistance to clopidogrel (all 4 ST events occurred during the first year after implantation). Likewise, among 810 Absorb BRS-treated patients in the Swedish SCAAR registry[11], 6/11 patients who suffered ST within two years were non-adherent to DAPT, and all these events occurred within the first month following DAPT termination. All three very late ST events were observed in patients off DAPT, although there was no temporal relationship between DAPT discontinuation and ST in this period.

Compared to these prior reports, the present study was substantially larger, included patients across diverse geographic, ethnic, and practice-related spectra, and utilised multivariable analysis to isolate the potential role of DAPT in preventing adverse ischaemic events after Absorb BRS implantation. This analysis demonstrated that DAPT discontinuation during the first year after BRS implantation was strongly related to the occurrence of MI and ST. Conversely (and to our surprise), no clear beneficial effect of prolonged DAPT was apparent between 1 and 3 years after BRS implantation. Prolonged DAPT was associated with a non-significant risk of increased bleeding and a neutral effect on three-year mortality, although in this regard we cannot exclude a beneficial DAPT effect on survival within the first year and slight harm thereafter.

Several possible explanations may underlie the absence of benefit of continued DAPT use after one year in BRS-treated patients. First, in most cases endothelialisation of Absorb BVS is largely complete by 6 months[12]. After 12 months, the struts of adequately implanted (i.e., correctly sized, well-expanded and well-apposed) BRS are completely covered with neointima and thus less vulnerable to platelet adhesion. The very late risk of ischaemic events may thus be evidenced primarily in scaffolds which were not adequately implanted, and are thus prone to intraluminal scaffold dismantling[4]. In this regard, the greatest risk factor for TLF and ST after BRS implantation is in very small vessels, a risk which is confined to the first year[8]. Second, the individual studies comprising the pooled analysis enrolled mostly low-to-intermediate complexity lesions treated in our analysis: mean lesion length was only 13 mm, and the prevalence of overlapping scaffolds, bifurcation intervention, and moderate/severe calcification was low. Prolonged DAPT might have been associated with lower ischaemic events between 1 and 3 years, had a clinically higher risk or angiographically more complex patient population been studied. It may also be that the novel mechanisms related to very late ST and MI after BRS implantation are either platelet reactivity-independent, or conversely would require even more potent inhibition

to prevent. As the vast majority of the study cohort was treated with clopidogrel, we are unable to assess this possibility. Finally, the lack of benefit of prolonged DAPT between 3 and 5 years following device implantation is probably explained by the low event rate after complete scaffold bioresorption, as previously reported[3].

In our analysis, prolonged DAPT use had no significant relationship with bleeding. Bleeding, defined as GUSTO moderate or severe in the present study, was relatively infrequent in the current patient population from which many high bleeding risk patients were excluded. Although it is unlikely that bleeding events so defined would have been missed, we cannot exclude under-reporting of some episodes of less severe bleeding that did not require medical attention. The occurrence of such events would probably have demonstrated a relationship with prolonged DAPT, as seen in prior studies[3].

Similarly, our adjusted analysis on the impact of prolonged DAPT on death was inconclusive. While DAPT usage tended to be associated with a lower risk of death in the first year (probably due to its salutary effects in preventing ST and MI), a non-significant negative association with prolonged DAPT use and survival was observed between 1 and 3 years. Prior studies have observed this phenomenon and correlated the late excess mortality risk directly to bleeding-related deaths[13].

Limitations

First, as a non-randomised analysis, the results from the present study should be considered hypothesis-generating, as we cannot exclude the presence of unmeasured confounders. The occurrence of adverse ischaemic or bleeding events may also have dictated DAPT usage patterns, potentially affecting subsequent outcomes. Second, the specific reasons for DAPT discontinuation were not collected. Third, bleeding events from the component studies were not adjudicated by a clinical events committee. Fourth, the effect of DAPT use in the multivariable models was analysed according to its use the day before an adverse event. Sudden changes in DAPT usage were not accounted for, although few patients between 1 and 3 years had an MI or ST within 1 or 2 days after DAPT discontinuation. Fifth, DAPT utilisation was assessed from patient interview and, although these data were prospectively collected during regular follow-up visits, this is subject to imprecision in recall between visits[14]. Sixth, follow-up was not available in all patients, although the proportion of subjects lost to follow-up was low and unlikely to impact on overall study findings. Finally, the present results apply to the first-generation Absorb BVS, although the concepts outlined herein may be generalisable to other BRS prior to and after the time of their complete bioresorption.

Conclusions and clinical implications

In the present large-scale IPD analysis, DAPT use was strongly associated with a lower risk of MI and ST during the first year after Absorb BRS implantation. However, prolonged DAPT use had an uncertain risk/benefit profile between 1 and 3 years, and its continued use was not associated with a decrease in the risk of ischaemic outcomes in this period. The impact of prolonged DAPT use on bleeding and its net effect on mortality were neutral. No significant relationships between DAPT usage and adverse ischaemic or bleeding events were present between 3 and 5 years after device implantation, the time period after complete scaffold bioresorption when event rates are low. Randomised controlled trials are warranted to evaluate the risk/benefit profile of prolonged DAPT following implantation of novel BRS platforms, especially those with thinner struts or different bioresorption rates.

Impact on daily practice

Dual antiplatelet therapy use during the first year after bioresorbable scaffold implantation was strongly associated with lower risks of scaffold thrombosis and myocardial infarction. However, a benefit of prolonged dual antiplatelet therapy use between 1 and 3 years after bioresorbable scaffold implantation was not apparent, as it did not significantly affect the risk of either outcome. Dual antiplatelet therapy did not have major effects upon bleeding or death in any period during follow-up.

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Conflict of interest statement

L. Azzalini has received honoraria from Teleflex, Abiomed, Philips, Asahi Intecc, Abbott Vascular, and Cardiovascular Systems, Inc. S. Ellis reports consulting fees/support for a meeting relating to the ABSORB study, and being a consultant for Medtronic and Biotronix. D.J. Kereiakes reports being a consultant for Boston Scientific, Sino Medical Sciences Technologies, Svelte Medical, and Elixir Medical. T. Kimura has received research support/honoraria from Abbott Vascular. R. Gao has received research support from Medtronic, MicroPort, and Lifetech Scientific. B. Chevalier reports receiving consultant fees/research grants from Abbott Vascular, being a consultant for Biotronik, Colibri, Medtronic, and Terumo, and being a shareholder of the Cardiovascular European Research Center (CERC). P.W. Serruys reports being a consultant for Biosensors, Sinomed, Balton Sp, Philips/Volcano, Xeltis, Novartis, Meril Life, and HeartFlow, and participation on the board of PROSPECT ABSORB. G. Stone reports payments to the institution from Abbott for biostatistics, clinical events committee and core laboratory work on the clinical trials and for support to attend meetings, speaker honoraria from Cook, being a consultant to Valfix, TherOx, Vascular Dynamics, Robocath, HeartFlow, Gore, Ablative Solutions, Miracor, Neovasc, V-Wave, Abiomed, Ancora, MAIA Pharmaceuticals, Vectorious, Reva, Occlutech, CoreFlow, Matrizyme, Shockwave, and Cardiomech, holding equity/options from Ancora, Qool Therapeutics, Cagent,

Applied Therapeutics, the Biostar family of funds, SpectraWave, Orchestra Biomed, Aria, Cardiac Success, Valfix, and Medfocus, and other financial or non-financial interests (Mount Sinai Hospital). Mount Sinai Hospital receives grants from Abbott for research. The other authors have no conflicts of interest to declare.

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Supplementary data

Supplementary Table 1. STROBE Statement – Checklist of items that should be included in reports of cohort studies.

Supplementary Table 2. Major characteristics of the five included studies.

Supplementary Table 3. Clinical characteristics of the five included studies.

Supplementary Table 4. Angiographic characteristics of the five included studies.

Supplementary Table 5. Procedural characteristics of the five included studies.

Supplementary Table 6. Salient clinical, angiographic, and procedural characteristics according to dual antiplatelet discontinuation.

Supplementary Table 7. Any dual antiplatelet therapy discontinuation in 2,973 BRS-treated patients.

Supplementary Table 8. Pooled adverse event rates and unadjusted and adjusted risks occurring in patients with versus without permanent dual antiplatelet therapy (DAPT) discontinuation during 3-5-year and 0-5-year follow-up.

Supplementary Figure 1. Spline analysis demonstrating the time-varying association of the hazard for study outcomes depending on dual antiplatelet therapy (DAPT) status during the five-year follow-up period.

The supplementary data are published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-21-00263

Supplementary data

Supplementary Table 1. STROBE Statement—Checklist of items that should be included in reports of cohort studies.

	Item No	Recommendation	Reported
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	X
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	X
Objectives	3	State specific objectives, including any prespecified hypotheses	X
Methods			
Study design	4	Present key elements of study design early in the paper	X
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	X
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (*b*) For matched studies, give matching criteria and number of exposed and unexposed	X
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	X
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	X
Bias	9	Describe any efforts to address potential sources of bias	X
Study size	10	Explain how the study size was arrived at	X
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	X
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding (*b*) Describe any methods used to examine subgroups and interactions (*c*) Explain how missing data were addressed (*d*) If applicable, explain how loss to follow-up was addressed (*e*) Describe any sensitivity analyses	a. X b. X c. N/A d. N?A e. N/A

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	X
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	X X
Outcome data	15*	Report numbers of outcome events or summary measures over time	X

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	X
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	X
Discussion			
Key results	18	Summarise key results with reference to study objectives	X
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	X
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	X
Generalisability	21	Discuss the generalisability (external validity) of the study results	X
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	X

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org

Supplementary Table 2. Major characteristics of the five included studies. Adapted with permission from [3].

Variable	ABSORB II	ABSORB Japan	ABSORB China	ABSORB III	ABSORB EXTEND
ClinicalTrials.gov identifier	NCT01425281	NCT01844284	NCT01923740	NCT01751906	NCT01023789
Type of study	Randomised	Randomised	Randomised	Randomised	Observational
Masking	Single blind	Single blind	Open label	Single blind	Open label
Number of centres	46	38	24	193	56
Number of patients	501	400	480[a]	2,008	812
- Assigned to BRS	335	266	241	1,322	812
- Assigned to EES	166	134	239	686	N/A
Number of lesions allowed	2	2	2	2	2
Number of vessels allowed[b]	2	2	2	2	2
Target lesion reference vessel diameter (mm)	2.25-3.8 by online QCA	2.5-3.75 by online QCA or visual assessment	2.5-3.75 by online QCA or visual assessment	2.5-3.75 by visual assessment	2.0-3.8 by visual assessment
Maximum target lesion length (mm)	48	24	24	24	28
Device overlap allowed	Yes	For bail-out only	For bail-out only	For bail-out only	Yes
Routine angiographic follow-up	At 3 years	At 13 months	At 1 year	No	No
Primary endpoint	Angiographic vasomotion at 3 years	TLF at 1 year	Angiographic in-segment late loss at 1 year	TLF at 1 year	Not specified
Total duration of follow-up (years)	5	5	5	5	3

[a] A total of 5 patients (3 randomised to BVS and 2 randomised to EES) withdrew consent immediately after enrolment and were deregistered. These patients are not included in the study population.
[b] Maximum one lesion per vessel.
BRS: bioresorbable scaffold; EES: everolimus-eluting stent; QCA: quantitative coronary analysis; TLF: target lesion failure

Supplementary Table 3. Clinical characteristics of the five included studies.

Variable	ABSORB II (n=335)	ABSORB Japan (n=266)	ABSORB China (n=238)	ABSORB III (n=1322)	ABSORB EXTEND (n=812)	Overall (n=2,973)
Age (years)	61.5±10.0	67.2±9.4	57.2±11.4	63.5±10.6	61.1±10.8	62.4±10.8
Men	253 (75.5%)	210 (78.9%)	171 (71.8%)	934 (70.7%)	603 (74.3%)	2,171 (73.0%)
Body mass index (kg/m^2)	27.9±4.1	24.0±3.0	25.2±3.4	30.6±6.2	27.2±4.4	28.4±5.6
Diabetes	80 (23.9%)	96 (36.1%)	61 (25.6%)	416 (31.5%)	216 (26.6%)	869 (29.2%)
Insulin-dependent	22 (6.6%)	24 (9.0%)	23 (9.7%)	138 (10.5%)	37 (4.6%)	244 (8.2%)
Dyslipidaemia	252 (75.2%)	218 (82.0%)	102 (42.9%)	1,140 (86.2%)	584 (71.9%)	2,296 (77.2%)
Hypertension	231 (69.0%)	208 (78.2%)	140 (58.8%)	1,122 (84.9%)	580 (71.4%)	2,281 (76.7%)
Current smoker	79 (23.6%)	53 (19.9%)	78 (32.8%)	281 (21.3%)	188 (23.2%)	679 (22.8%)
Prior myocardial infarction	93 (28.0%)	42 (16.0%)	40 (16.8%)	282 (21.5%)	230 (28.5%)	687 (23.3%)
Prior PCI	117 (34.9%)	94 (35.3%)	24 (10.1%)	482 (36.5%)	224 (27.6%)	941 (31.7%)
Prior CABG	7 (2.1%)	5 (1.9%)	0	57 (4.3%)	14 (1.7%)	83 (2.8%)
Creatinine clearance (ml/min)	98.2±32.3	N/A	97.0±32.2	105.5±79.4	N/A	103.2±68.9
Advanced chronic kidney disease*	N/A	N/A	2 (0.8%)	143 (10.8%)	8 (1.0%)	153 (6.5%)
Evidence of ischaemia at presentation						
None	0	0	1 (0.4%)	28 (2.1%)	54 (6.7%)	83 (2.8%)
Stable angina	214 (63.9%)	170 (63.9%)	53 (22.3%)	757 (57.3%)	461 (56.8%)	1,655 (55.7%)
Unstable angina	68 (20.3%)	26 (9.8%)	156 (65.5%)	355 (26.9%)	215 (26.5%)	820 (27.6%)
Silent ischaemia	42 (12.5%)	70 (26.3%)	6 (2.5%)	132 (10.0%)	49 (6.0%)	299 (10.1%)
Acute myocardial infarction	11 (3.3%)	0	18 (7.6%)	37 (2.8%)	33 (4.1%)	99 (3.3%)
Post-myocardial infarction angina	0	0	4 (1.7%)	12 (0.9%)	0	16 (0.7%)
Stable ischaemic heart disease	256 (76.4%)	240 (90.2%)	60 (25.2%)	917 (69.4%)	564 (69.5%)	2,037 (68.5%)
Acute coronary syndrome	79 (23.6%)	26 (9.8%)	178 (74.8%)	404 (30.6%)	248 (30.5%)	935 (31.5%)

*Estimated glomerular filtration rate <30 ml/min/1.73 m^2 or dialysis at the time of screening.
CABG: coronary artery bypass graft; PCI: percutaneous coronary intervention

Supplementary Table 4. Angiographic characteristics of the five included studies.

Variable	ABSORB II (n=335)	ABSORB Japan (n=266)	ABSORB China (n=238)	ABSORB III (n=1322)	ABSORB EXTEND (n=812)	Overall (n=2,973)
Number of diseased vessels	1.19±0.45	N/A	1.55±0.78	1.37±0.60	1.25±0.63	1.33±0.62
Number of lesions treated	1.09±0.28	1.03±0.18	1.05±0.23	1.05±0.21	1.08±0.27	1.06±0.24
One	306 (91.3%)	257 (96.6%)	225 (94.5%)	1,257 (95.1%)	750 (92.4%)	2,795 (94.0%)
Two	29 (8.7%)	9 (3.4%)	13 (5.5%)	64 (4.8%)	62 (7.6%)	177 (6.0%)
Treated vessel						
Right coronary	95 (26.1%)	85 (30.9%)	63 (25.1%)	404 (29.2%)	250 (28.6%)	897 (28.5%)
Left anterior descending	163 (44.8%)	127 (46.2%)	139 (55.4%)	617 (44.5%)	395 (45.2%)	1,441 (45.8%)
Circumflex	106 (29.1%)	63 (22.9%)	49 (19.5%)	363 (26.2%)	228 (26.1%)	809 (25.7%)
Left main	0	0	0	1 (0.1%)	1 (0.1%)	2 (0.1%)
Baseline quantitative coronary analysis						
Reference vessel diameter (mm)	2.59±0.38	2.71±0.45	2.81±0.44	2.67±0.45	2.65±0.39	2.67±0.43
Minimal luminal diameter (mm)	1.07±0.32	0.96±0.33	0.98±0.40	0.92±0.37	1.11±0.32	1.00±0.36
Diameter stenosis (%)	58.6±11.1	64.5±11.1	65.3±12.9	65.2±12.5	58.0±10.6	62.4±12.2
Lesion length (mm)	13.8±6.5	13.4±5.3	14.1±5.1	12.6±5.4	12.3±5.3	12.9±5.5
Lesion characteristics						
Thrombus	5 (1.4%)	0	0	3 (0.2%)	14 (1.6%)	22 (0.7%)
Tortuosity (moderate/severe)	34 (9.4%)	23 (8.4%)	6 (2.4%)	40 (2.9%)	N/A	103 (4.5%)
Angulation >45°	9 (2.5%)	33 (12.0%)	18 (7.2%)	166 (12.0%)	N/A	226 (9.9%)
Calcification (moderate/severe)	46 (12.7%)	76 (27.7%)	44 (17.5%)	457 (33.1%)	121 (13.9%)	744 (23.7%)
Ulceration	N/A	11 (4.0%)	6 (2.4%)	37 (2.7%)	N/A	54/1,905 (2.8%)
Aneurysm	N/A	2 (0.7%)	1 (0.4%)	36 (2.6%)	N/A	39/1,905 (2.0%)
Bifurcation	0	100 (36.4%)	126 (50.2%)	508 (36.7%)	48 (5.5%)	782 (24.9%)
Type B2/C lesion	165 (45.5%)	208 (75.6%)	188 (74.9%)	949 (68.7%)	386 (44.7%)	1,896 (60.5%)

Supplementary Table 5. Procedural characteristics of the five included studies.

Variable	ABSORB II (n=335)	ABSORB Japan (n=266)	ABSORB China (n=238)	ABSORB III (n=1,322)	ABSORB EXTEND (n=812)	Overall (n=2,973)
Intravascular imaging guidance	325 (97.0%)	40 (15.0%)	0	146 (11.2%)	12 (4.3%)	523 (21.6%)
Predilatation	364 (100.0%)	275 (100.0%)	250 (99.6%)	1,383 (99.9%)	870 (99.7%)	3,142 (99.8%)
Maximum predilatation balloon diameter (mm)	2.6±0.4	2.8±0.4	2.8±0.4	2.9±0.4	2.6±0.3	2.7±0.4
Maximum predilatation balloon pressure (atm)	8.0±0.0	N/A	N/A	12.1±3.4	12.7±3.4	11.7±3.5
Post-dilatation with non-compliant balloon	221 (60.7%)	176 (64.0%)	154 (61.4%)	788 (57.0%)	599 (68.7%)	1,938 (61.6%)
Maximum post-dilatation balloon diameter (mm)	3.15±0.34	3.18±0.44	3.29±0.43	3.22±0.45	3.12±0.24	3.18±0.39
Maximum post-dilatation balloon pressure (atm)	15.4±3.4	15.5±4.1	16.8±3.8	15.6±3.3	16.7±3.5	16.0±3.6
Total scaffold length per lesion (mm)	24.1±10.8	20.2±5.8	22.8±6.7	20.5±7.2	22.0±7.0	21.5±7.6
Overlapping scaffolds	N/A	N/A	N/A	N/A	115 (14.2%)	115 (14.2%)
Post-PCI quantitative coronary analysis						
In-scaffold						
Acute gain (mm)	1.15±0.38	1.47±0.40	1.51±0.46	1.45±0.45	1.17±0.34	1.34±0.44
Minimal luminal diameter (mm)	2.22±0.33	2.42±0.37	2.48±0.39	2.37±0.40	2.28±0.31	2.34±0.37
Diameter stenosis (%)	15.8±6.5	11.6±7.5	12.2±7.5	11.6±8.8	15.3±6.3	13.2±7.9
In-segment						
Acute gain (mm)	0.99±0.40	1.25±0.41	1.32±0.47	1.23±0.46	0.99±0.36	1.14±0.44
Minimal luminal diameter (mm)	2.06±0.37	2.20±0.39	2.30±0.40	2.15±0.41	2.10±0.33	2.14±0.39
Diameter stenosis (%)	20.1±7.7	20.0±6.7	19.0±6.8	20.0±7.9	20.0±7.0	19.9±7.5
Device success	N/A	271 (98.9%)	245 (98.0%)	N/A	861 (98.9%)	1,377 (98.7%)

PCI: percutaneous coronary intervention

Supplementary Table 6. Salient clinical, angiographic, and procedural characteristics according to dual antiplatelet discontinuation.

Variable	Permanent discontinuation (n=2,139)	No permanent discontinuation (n=830)	Overall (n=2,969)	*p*-value
Age (years)	62.9±10.7	61.2±10.9	62.5±10.8	<0.0001
Men	1,541 (72.0%)	628 (75.7%)	2,169 (73.1%)	0.05
Diabetes	603 (28.2%)	266 (32.0%)	869 (29.3%)	0.04
Current smoker	443 (20.7%)	234 (28.2%)	677 (22.8%)	<0.0001
Prior myocardial infarction	426 (20.0%)	262 (31.8%)	688 (23.3%)	<0.0001
Prior PCI	626 (29.3%)	359 (43.3%)	985 (33.2%)	<0.0001
Acute coronary syndrome	659 (30.8%)	275 (33.2%)	934 (31.5%)	0.21
Number of diseased vessels	1.32±0.61	1.33±0.64	1.33±0.62	0.97
Number of treated lesions	1.06±0.24	1.06±0.24	1.06±0.24	0.93
Total lesion length (mm)*	12.9±5.5	12.6±5.4	12.9±5.5	0.16
Reference vessel diameter (mm)*	2.68±0.43	2.65±0.43	2.67±0.43	0.07
Calcification (moderate/severe)*	559 (24.8%)	183 (20.9%)	742 (23.7%)	0.07
Bifurcation lesion*	569 (25.1%)	212 (24.3%)	781 (24.9%)	0.61
Left main or left anterior descending artery treated*	560 (24.7%)	250 (28.4%)	810 (25.8%)	0.04
Intravascular imaging guidance	412 (23.1%)	110 (17.4%)	522 (21.6%)	0.003
Device success*	2,442 (99.3%)	956 (99.1%)	3,398 (99.2%)	0.55

* per lesion.

Supplementary Table 7. Any dual antiplatelet therapy discontinuation in 2,973 BRS-treated patients.

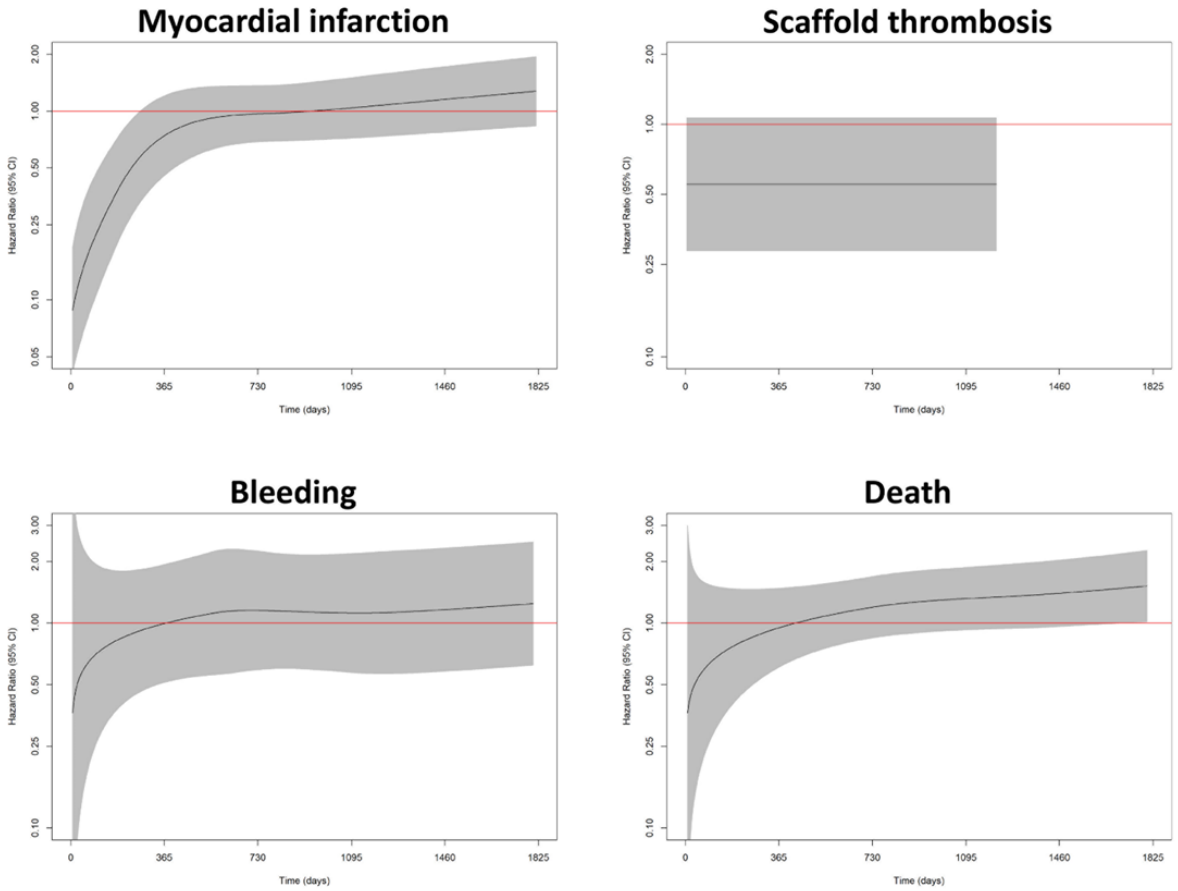
Interval	>24 hours	≥7 days	Permanently
0-1 year	678/2,970 (22.8%)	630/2,970 (21.2%)	482/2,970 (16.2%)
0-6 months	187/2,970 (6.3%)	145/2,970 (4.9%)	73/2,970 (2.5%)
6 months-1 year	610/2,937 (20.8%)	586/2,937 (20.0%)	479/2,937 (16.3%)
1-3 years	1,661/2,911 (57.1%)	1,640/2,911 (56.3%)	1,475/2,911 (50.7%)
1-2 years	1,490/2,911 (51.2%)	1,474/2,911 (50.6%)	1,311/2,911 (45.0%)
2-3 years	1,576/2,840 (55.5%)	1,566/2,840 (55.1%)	1,454/2,840 (51.2%)
0-3 years	1,742/2,970 (58.7%)	1,699/2,970 (57.2%)	1,484/2,970 (50.0%)

Note: the denominators represent the number of patients alive and on-study at the start of each interval.

Supplementary Table 8. Pooled adverse event rates and unadjusted and adjusted risks occurring in patients with versus without permanent dual antiplatelet therapy (DAPT) discontinuation during 3-5-year and 0-5-year follow-up.

Variable	No permanent discontinuation	Permanent discontinuation*	Unadjusted HR (95% CI)	*p*-value	Adjusted HR (95% CI)	*p*-value
Myocardial infarction						
3-5 years	4.8%	0.2%	24.59 (5.85-103.34)	<0.0001	1.08 (0.56-2.07)	0.82
0-5 years	14.0%	6.8%	2.06 (1.60-2.65)	<0.0001	0.84 (0.59-1.18)	0.31
Scaffold thrombosis						
3-5 years	0.1%	0.1%	1.93 (0.10-36.05)	0.78	N/A	N/A
0-5 years	3.3%	1.8%	1.98 (1.21-3.23)	0.005	0.60 (0.31-1.16)	0.13
Bleeding						
3-5 years	2.7%	0.0%	N/A	<0.0001	1.08 (0.40-2.94)	0.87
0-5 years	3.5%	2.2%	1.37 (0.84-2.24)	0.04	1.23 (0.64-2.36)	0.53
Death						
3-5 years	8.0%	0.2%	47.43 (11.52-195.2)	<0.0001	1.08 (0.66-1.77)	0.75
0-5 years	8.2%	4.8%	1.58 (1.13-2.20)	0.0008	1.31 (0.92-1.87)	0.14

CI: confidence interval; HR: hazard ratio



Supplementary Figure 1. Spline analysis demonstrating the time-varying association of the hazard for study outcomes depending on dual antiplatelet therapy (DAPT) status during the 5-year follow-up period.
Note: the model could not be fitted for scaffold thrombosis due to the very low event rate beyond 3 years.