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Bioresorbable vascular scaffolds versus conventional drug-eluting stents across time: a meta-analysis of randomised controlled trials

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ABSTRACT

Background Bioresorbable vascular scaffolds (BVS) were designed to reduce the rate of late adverse events observed in conventional drug-eluting stents (DES) by dissolving once they have restored lasting patency.

Objectives Compare the safety and efficacy of BVS versus DES in patients receiving percutaneous coronary intervention for coronary artery disease across a complete range of randomised controlled trial (RCT) follow-up intervals.

Methods A systematic review and meta-analysis was performed using Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. MEDLINE, EMBASE and Web of Science were searched from inception through 5 January 2022 for RCTs comparing the clinical outcomes of BVS versus DES. The primary safety outcome was stent/scaffold thrombosis (ST), and the primary efficacy outcome was target lesion failure (TLF: composite of cardiac death, target vessel myocardial infarction (TVMI) and ischaemia-driven target lesion revascularisation (ID-TLR)). Secondary outcomes were patient-oriented composite endpoint (combining all-death, all-MI and all-revascularisation), its individual components and those of TLF. Studies were appraised using Cochrane's Risk of Bias tool and meta-analysis was performed using RevMan V.5.4.

Results 11 919 patients were randomised to receive either BVS (n=6438) or DES (n=5481) across 17 trials (differing follow-up intervals from 3 months to 5 years). BVS demonstrated increased risk of ST across all timepoints (peaking at 2 years with risk ratio (RR): 3.47; 95% CI 1.80 to 6.70; p=0.0002). Similarly, they showed increased risk of TLF (peaking at 3 years, RR: 1.35; 95% CI 1.07 to 1.70; p=0.01) resulting from high rates of TVMI and ID-TLR. Though improvements were observed after device dissolution (5-year follow-up), these were non-significant. All other outcomes were statistically equivalent. Applicability to all BVS is limited by 91% of the BVS group receiving Abbott's Absorb.

Conclusion This meta-analysis demonstrates that current BVS are inferior to contemporary DES throughout the first 5 years at minimum.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Bioresorbable vascular scaffolds (BVS) were designed to replace conventional drug-eluting stents (DES); however, early clinical trials demonstrated increased rates of adverse safety and efficacy outcomes.

WHAT THIS STUDY ADDS

⇒ This meta-analysis of 17 randomised controlled trials comparing BVS to DES shows them to be inferior in safety and efficacy domains at all timepoints out to 5 years. This appears to be driven by an elevated rate of stent thrombosis.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This meta-analysis builds on early research by being the first to compare RCTs of BVS to DES across all available follow-up durations from implantation to 5-year follow-up—facilitating evaluation of BVS across their bioabsorption window. Long-term data, past the point of stent dissolution, would be needed to see if there is any late benefit to be derived from current BVS.

INTRODUCTION

Drug-eluting stents (DES) replaced bare-metal stents (BMS) as the convention for percutaneous coronary intervention (PCI). DES use polymeric coatings to deliver an immunosuppressant (eg, everolimus) that inhibits neointimal hyperplasia and subsequently reduces restenosis.[1] Clinically, this reduces the rate of repeat myocardial infarction (MI) and the need for revascularisation.[2] DES development appears to have reached maturity, with the competing designs (using permanent or bioabsorbable coatings) achieving equivalence in large-scale, long-term clinical trials.[3–5] However, even the contemporary DES have their problems. The permanently retained metallic stent and its polymeric coating cause persistent inflammation—driving neoatherosclerosis, restenosis and late stent thrombosis—while eliminating local vasomotor function.[1] Subsequently, stent-related events (ie, thrombosis, MI and

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Table 1 Full inclusion and exclusion criteria for the systematic review

	Inclusion criteria	Exclusion criteria
Participants	Individuals receiving PCI for coronary artery disease (CAD)	Non-human (animal models or in vitro)
Intervention	BVS (entirely bioabsorbable scaffold)	Conventional permanent DES or BMS
Comparator	DES (permanent stent)	BMS
Outcomes	Reporting at least one of: the primary safety and/or efficacy outcomes (definite/probable ST and TLF)	Non-clinical outcomes (histological, imaging, economic)
Study design	Prospective RCT	Non-RCT (single-arm, registries)
Publications	Published full-text articles	Reviews, conference abstracts, posters, letters, case reports
Language	English	Other languages

BVS, bioresorbable vascular scaffolds; DES, drug-eluting stents; PCI, percutaneous coronary intervention; RCT, randomised controlled trial; ST, stent/scaffold thrombosis; TLF, target lesion failure.

restenosis requiring repeat revascularisation) continue to accrue at a rate of around 2% per year after the first year, with no evident plateau—that is to say, remaining a risk for life.[6]

A potential solution to this lies with bioresorbable vascular scaffolds (BVS). The premise being that these devices provide adequate structural support to the target artery while it remodels, before completely dissolving to return normal vascular function and negate the late adverse events described above. Abbott Vascular's Absorb BVS was the first device of this kind to gain regulatory approval and is currently the most extensively studied. As detailed in table 3, Absorb is an all polymer, everolimus-eluting BVS with an indicated time to total dissolution of around 2 years.[7] Despite its early promise,[7 8] the GHOST-EU registry and BVS-EXAMINATION study soon demonstrated an increased risk of early stent/scaffold thrombosis (ST) in the Absorb BVS groups.[9 10] A review of seven randomised controlled trials (RCTs) comparing the midterm clinical outcomes of Absorb BVS versus DES by Cassese *et al* went on to confirm that the BVS carried a significantly increased risk of adverse safety and efficacy outcomes over the first 2 years (namely ST and target lesion failure (TLF)—discussed ahead).[11]

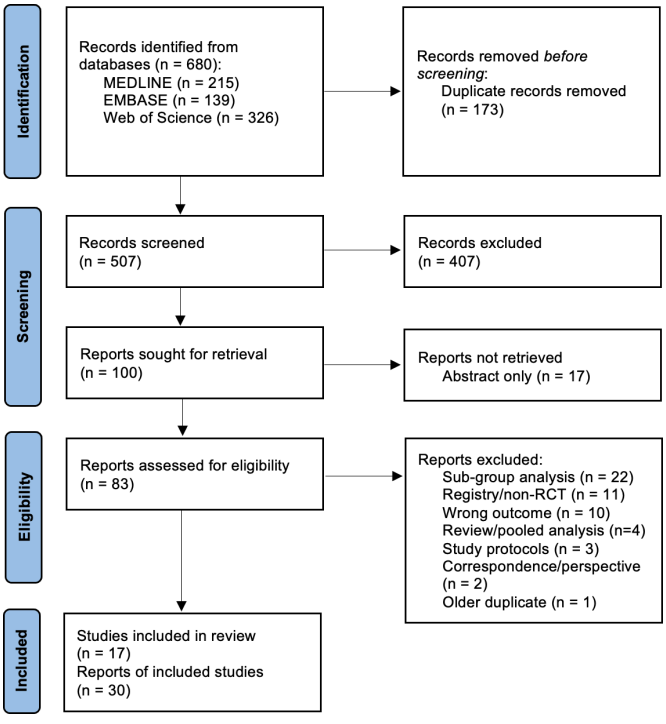

Figure 1 Preferred Reporting Items for Systematic Reviews and Meta- Analyses flow diagram reporting search strategy and study selection. Searches completed in parallel on 5 January 2022. RCT, randomised controlled trial.

Similar reviews comparing BVS to DES have been published,[12–14] all citing similar limitations: (1) a limited number of published studies and (2) a focus on a single BVS type (Absorb). Ni *et al* indicated that the observed failure may change as new BVS come to the fore with 'smaller footprints, less thrombogenicity (eg, magnesium), faster reabsorption and advanced mechanical properties'.[14] As such, this review aims to incorporate recent developments and identify the more current consensus on the safety and efficacy of BVS versus DES with respect to clinical outcomes. Further, given that BVS are a transient intervention this study looks to evaluate how this safety and efficacy profile changes with time, with particular interest to the pre-bioabsorption and post-bioabsorption window.

Objective

Compare the safety and efficacy of BVS versus conventional DES in the treatment of coronary artery disease by PCI across all available timepoints, using published data on clinical outcomes from RCTs.

METHODS

This review was designed in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist (presented in online supplemental appendix C). The protocol is registered with PROSPERO, accessible at: www.crd.york.ac.uk/ with

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Table 2 Salient characteristics of the included studies

Study	Trial ID	Centres, n	Patients, n		Stent/scaffold type		Available outcome data (Y/N)		Follow-up durations (months)	Year
			BVS	DES	BVS	DES	Primary safety (ST)	Primary efficacy (TLF)		
ABSORB CHINA[25 26]	NCT01923740	24	241	239	ABSORB BVS	XIENCE EES	Y	Y	12, 36	2018
ABSORB II[27–31]	NCT01425281	46	335	166	ABSORB BVS	XIENCE EES	Y	Y	12, 24, 36, 48, 60	2020
ABSORB III[32–34]	NCT01751906	193	1322	686	ABSORB BVS	XIENCE EES	Y	Y	12, 36, 60	2019
ABSORB IV[35]	NCT02173379	147	1296	1308	ABSORB BVS	XIENCE EES	Y	Y	12	2018
ABSORB JAPAN[36–38]	NCT01844284	38	266	134	ABSORB BVS	XIENCE EES	Y	Y	12, 24, 60	2020
AIDA[39 40]	NCT01858077	5	924	921	ABSORB BVS	XIENCE EES	Y	Y	24, 60	2021
COMPARE-ABSORB[41]	NCT02486068	45	848	822	ABSORB BVS	XIENCE EES	Y	Y	12	2020
COVER-AMI[42]	NCT02890589	1	10	12	ABSORB BVS	Synergy EES	N	Y	3	2019
EVERBIO II[43–45]	NCT01711931	1	80	160	ABSORB BVS	Promus Element EES or Biomatrix Flex BES	Y	Y	9, 24, 60	2021
Hernandez *et al*[46]	–	1	100	100	ABSORB BVS	Synergy EES	Y	N	12	2016
ISAR-ABSORB[47]	NCT01942070	5	173	89	ABSORB BVS	XIENCE EES	Y	Y	12	2019
MAGSTEMI[23]	NCT03234348	11	74	76	Magmaris	Orsiro SES	Y	Y	12	2019
NeoVas[48]	NCT02305485	32	278	282	NeoVas	XIENCE EES	Y	Y	12	2018
PRAGUE-22[22]	ISRCTN89434356	2	25	25	Magmaris	XIENCE EES	Y	Y	12	2021
Seo *et al*[49]	NCT02796157	Multi-	171	170	ABSORB BVS	XIENCE EES	Y	N	12	2020
TROFI-II[50 51]	NCT01986803	8	95	96	ABSORB BVS	XIENCE EES	Y	Y	12, 36	2018
XINSORB[52]	ChiCTR1800014966	17	200	195	XINSORB SES	TIVOLI SES	Y	Y	12	2019

All prospective, non-inferiority, RCTs in adult patients. Published follow-up durations are given with year of latest publication.
BVS, bioresorbable vascular scaffolds; DES, drug-eluting stents; EES, everolimus-eluting stent; RCT, randomised controlled trial; SES, sirolimus-eluting stent; ST, stent/scaffold thrombosis; TLF, target lesion failure.

registration number: CRD42022301449. There was no patient or public involvement in this study.

Eligibility criteria

For a study to be included in the meta-analysis, the outcomes of interest must be extractable as incidence rates on an intention-to-treat (ITT) basis (table 1).

Study outcomes

The primary safety outcome is definite/probable ST (ST). The primary efficacy outcome is TLF, this is the device-oriented composite endpoint of cardiac death, target vessel MI (TVMI) and ischaemia-driven target lesion revascularisation (ID-TLR). Secondary outcomes include: the patient-oriented composite endpoint (POCE; a composite of all-cause mortality, all-MI and all-revascularisation), its individual components, cardiac death, TVMI and ID-TLR. These standardised outcomes have previous been defined by the Academic Research Consortium on coronary device trials.[15] All outcomes are assessed on an ITT basis.

Search and screening strategy

A keyword search was performed across MEDLINE, EMBASE and Web of Science from inception to 5 January 2022, as summarised below (detailed in online supplemental appendix A):

- Coronary Disease OR Myocardial Infarction OR Percutaneous Coronary Intervention
- AND: Bioresorbable Vascular Scaffold OR Bioresorbable Vascular Stent OR Third-Generation Stent
- AND: Drug Eluting Stent OR Everolimus Eluting Stent OR Second-Generation Stent

Duplicates were removed and publications were screened by title and abstract; a second investigator (SZ) independently screened a sample of the publications to ensure agreement. Subsequently, full text articles were retrieved and assessed for eligibility. The reference lists of the included articles were searched for appropriate trials to include. Details of this process are summarised in a PRISMA flowchart (figure 1).

Data collection and analysis

A data extraction table was developed using Cochrane guidance.[16] Two reviewers piloted the data extraction method on a sample of papers in parallel, consensus was established, and the remaining studies were analysed by the main reviewer.

All statistical analysis was completed using RevMan V.5.4 software. The summary statistic used for this study is

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Table 3 Specification of stents used in the included clinical trials

Stent name	Manufacturer	Strut thickness (µm)	Materials	Eluted drug
BVS				
ABSORB BVS	Abbott Vascular	157	PLLA stent, PDLLA coating	Everolimus
MAGMARIS/DREAMS	BIOTRONIK	125	Mg stent, PLLA coating	Sirolimus
NEOVAS	Lepu Medical Technology	170	PLLA, PDLA coating	Sirolimus
XINSORB	Huaan Biotechnology	160	PLLA stent, PDLLA and PLLA coating	Sirolimus
DES				
Biomatrix Flex	Biosensors International	120	SS (316L), PLA coating (bioabsorbable)	Biolimus
Orsiro	BIOTRONIK	60	CoCr stent, PLLA coating (bioabsorbable)	Sirolimus
PROMUS Element	Boston Scientific	81	Pl-Cr stent, PVDF-HFP coating (durable)	Everolimus
SYNERGY	Boston Scientific	74	Pl-Cr stent, PLGA coating (bioabsorbable)	Everolimus
Tivoli	Essen Technology	80	CoCr, PLGA coating (bioabsorbable)	Sirolimus
XIENCE	Abbott Vascular	81	CoCr stent, PVDF-HFP coating (durable)	Everolimus

CoCr, cobalt-chromium; Mg, magnesium alloy; PDLLA, poly-D,L-lactic acid; Pl-Cr, platinum-chromium; PLGA, poly lactic-co-glycolic acid; PLLA, poly-L-lactic acid; PVDF-HFP, poly(vinylidene fluoride-co-hexafluoropropylene); SS, stainless steel.

risk ratio (RR) with 95% CIs, given its proven consistency for dichotomous outcomes and ease of interpretation compared with other methods, for example, OR. In view of the variation in population and procedural characteristics across the included studies, for example, differing clinical indications (stable angina vs STEMI), devices, and preinflation/postinflation protocols, a Mantel-Haenszel random-effects model was used.[16] Model-based sensitivity analysis comparing the consistency of results using fixed-effect models was performed to verify this decision.

Outcomes were evaluated at all available follow-up durations. Grouped analysis of follow-up intervals of ≤12 months and 2, 3 and 5 years was also performed to investigate the relationship between adverse event accrual and the BVS resorption window. Statistical significance is interpreted using $p<0.05$ and non-overlap of 95% CIs. Heterogeneity among trials is estimated using Cochran's Q test and the I^2-statistic (where <25%, 25–50% and >50% represent low, moderate and high heterogeneity, respectively).

Study-based sensitivity analysis was performed by individually omitting each study from the meta-analysis and assessing changes in outcome (in terms of direction of effect and change in magnitude and significance). Small study effects and publication bias was evaluated by visual inspection of funnel plots. Risk of bias in the included studies is evaluated using the Cochrane Risk of Bias Tool (RoB 2).

RESULTS

Study selection and characteristics

A PRISMA flow diagram describing the search strategy is presented in figure 1. The search identified 680 publications for screening; 173 duplicates were removed and a further 407 were excluded at title and abstract review. One hundred full-text articles were reviewed for eligibility, of which, 70 were excluded (reasons given in figure 1). The 30 remaining articles meeting the inclusion criteria report different follow-up durations of 17 individual RCTs—enrolling a total of 11 919 patients for PCI with either BVS (n=6438) or DES (n=5481).

The main characteristics of the 17 included studies are presented in table 2. Salient characteristics of the included studies . The most studied stents were Abbott Vascular's ABSORB BVS (n=5861) and XIENCE DES (n=4631). Details of all included stents are given in table 3. The most common follow-up duration presented is 12 months (14 independent studies), with 5 studies going out to 5 years. Only one follow-up at 48 months was identified (ABSORB II); given the lack of comparators at this interval and that these data are incorporated in to ABSORB II's 60-month follow-up, it was excluded from meta-analysis. Patient and procedural characteristics are presented in online supplemental appendix table 1.

Study quality assessment

Quality assessment of the included RCTs using Cochrane's Risk of Bias (RoB 2) tool is summarised in table 4. Most of the studies were assessed as having a low risk of bias, with four exceptions. Briefly, prepublished protocols/plans for result reporting could not be found for COVER-AMI, PRAGUE-22, Hernandez *et al* and XINSORB, while Hernandez *et al* also did not provide adequate information on their randomisation procedure. It was decided that these concerns alone were not sufficient to exclude these studies from the analysis.

Funnel plots for the primary safety and efficacy outcomes are presented in figure 2; they show no

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Table 4 Quality assessment of studies included for meta-analysis (using Cochrane's RoB2 tool)

	Randomisation process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	Overall bias
ABSORB CHINA	+	+	+	+	+	+
ABSORB II	+	+	+	+	+	+
ABSORB III	+	+	+	+	+	+
ABSORB IV	+	+	+	+	+	+
ABSORB JAPAN	+	+	+	+	+	+
AIDA	+	+	+	+	+	+
COMPARE-ABSORB	+	+	+	+	+	+
COVER-AMI	+	+	+	+	-	-
EVERBIO II	+	+	+	+	+	+
Hernandez *et al*	-	+	+	+	-	-
ISAR-ABSORB	+	+	+	+	+	+
MAGSTEMI	+	+	+	+	+	+
NeoVas	+	+	+	+	+	+
PRAGUE-22	+	+	+	+	-	-
Seo *et al*	+	+	+	+	+	+
TROFI-II	+	+	+	+	+	+
XINSORB	+	+	+	+	-	-

+ Low risk of bias.
- Some concerns.
X High risk of bias.
BVS, bioresorbable vascular scaffolds; DES, drug-eluting stents.

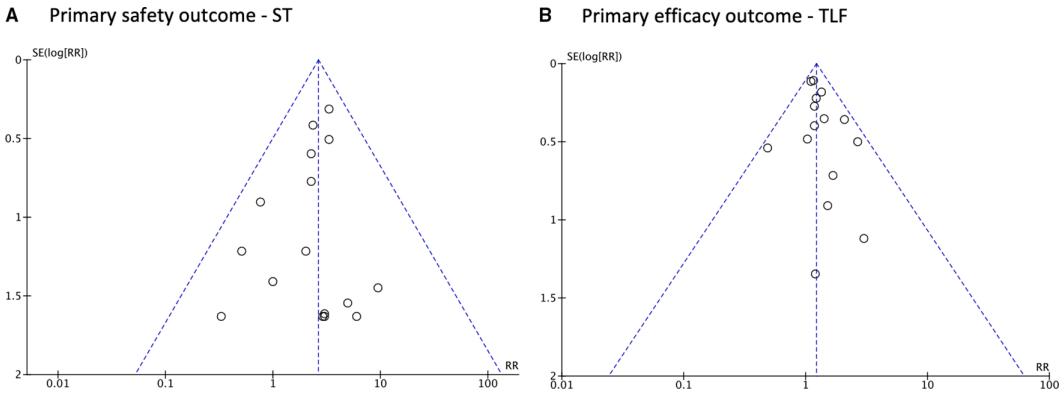

Figure 2 Funnel plot analysis for (A) the primary safety outcome (stent/scaffold thrombosis, ST) and (B) the primary efficacy outcome (target lesion failure, TLF) at latest follow-up. Diagonal lines show pseudo-95% CIs. RR, risk ratio.

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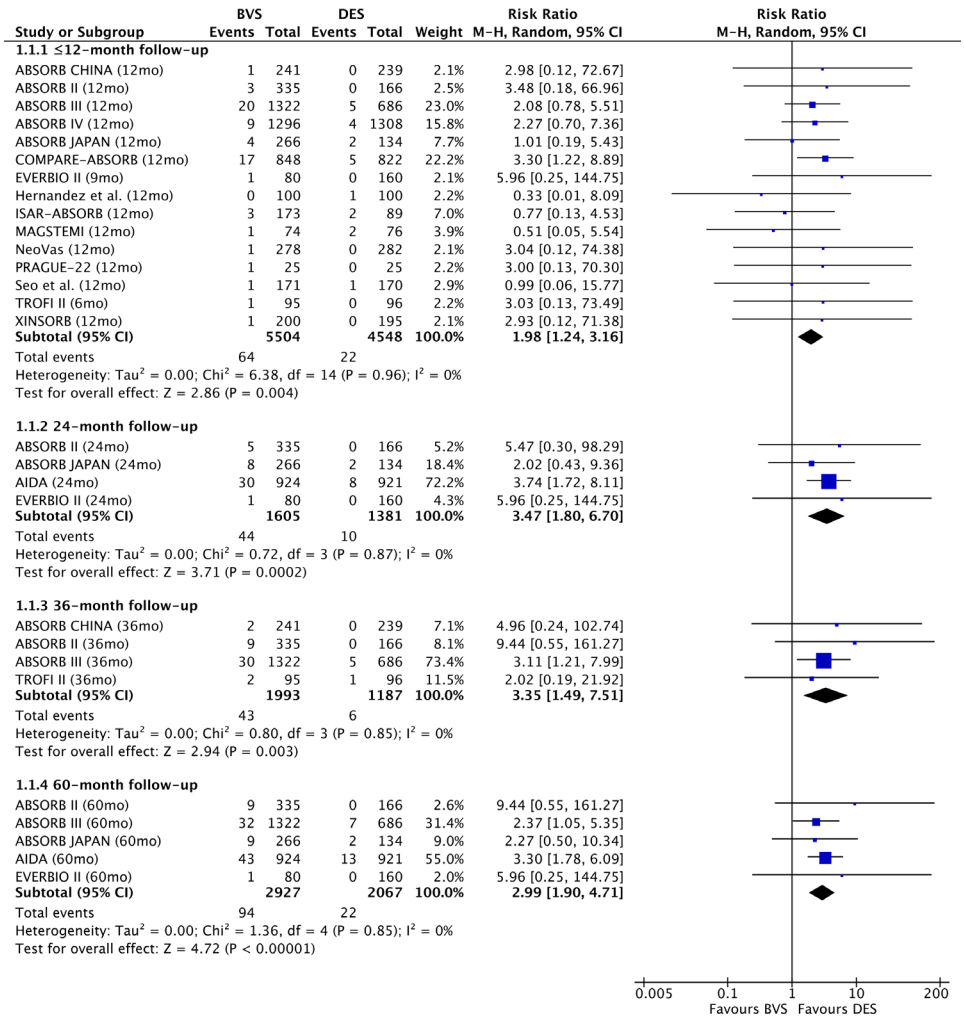

Figure 3 Forest plot for the primary safety outcome of stent thrombosis (ST)—grouped by follow-up duration. Diamonds indicate point estimates and extremes of 95% CIs. See online supplemental appendix B figure 3 for corresponding funnel plot. BVS, bioresorbable vascular scaffolds; DES, drug-eluting stents.

significant interference from small-study effects and the relative symmetry suggests limited publication bias.

There was no evidence of significant heterogeneity in the included studies across the outcomes of interest. Sensitivity analysis across each outcome did not demonstrate significant deviation due to any one included study—including the four with identified bias concerns. Results remain consistent when checked using a fixed-effects model.

Study outcomes

Primary safety outcome: ST

Excluding COVER-AMI, all studies reported the primary safety outcome of definite/probable ST. As demonstrated in figure 3, patient enrolled to the BVS group have a statistically significant increased risk of ST across all time-points. This appears to peak with a relative risk of 3.47 (95% CI 1.80 to 6.70; p=0.0002; I^2=0%) at 24-month follow-up and decrease over the proceeding intervals to 2.99 at 60 months (95% CI 1.90 to 4.71; p≤0.00001; I^2=0%), however, this is not statistically significant. At latest follow-up (online supplemental appendix figure 2), this outcome occurred in 2.05% of BVS versus 0.69% of DES patients (RR: 2.56; 95% CI 1.79 to 3.66; p≤0.00001; I^2=0%).

Subgroup analysis of early (0–30 days), late (31 days to 1 year) and very late ST (VLST; 1 year onwards) was performed exclusively on studies that provided extractable data for all three of these time points. BVS exhibit an increased risk of ST across the described intervals, the relative risk appears to peak in the late phase (31 days to 1 year), though there is no significant difference between the intervals (figure 4).

Primary efficacy outcome: TLF

Excluding Hernandez *et al* and Seo *et al*, all other studies report the primary efficacy outcome of TLF. As demonstrated in figure 5, patients with BVS have a significantly increased risk of TLF at all time-points. While remaining inferior throughout, the extent of inferiority (in terms of RR) appears to decrease between 36-month and 60-month follow-up (from RR=1.33 to RR=1.18), though this drop is not statistically significant (overlapping 95% CI 1.07 to 1.70 and 95% CI 1.02 to 1.37, respectively).

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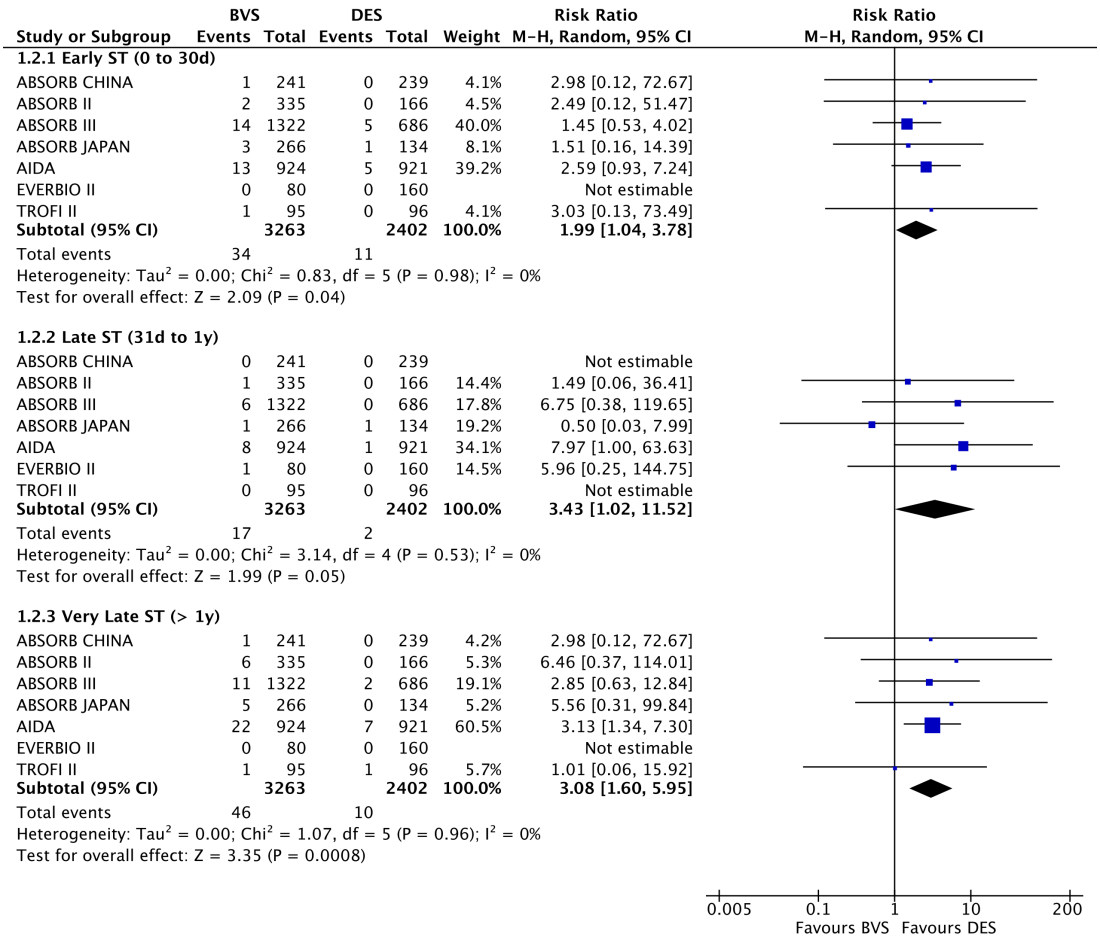

Figure 4 Forest plot for stent thrombosis at early (0–30 days), late (31 days to 1-year) and very late intervals (after 1 year). BVS, bioresorbable vascular scaffolds; DES, drug-eluting stents.

At latest follow-up (online supplemental figure 4), TLF occurred in 9.73% of BVS versus 7.45% of DES patients (RR: 1.21; 95% CI 1.07 to 1.37; p=0.002; I^2=0%).

Secondary outcomes

Patient-oriented composite endpoint

All studies excluding Hernandez *et al* and Seo *et al* reported POCE or provided adequate information to reliably calculate it. While RRs favoured DES at all time points, overlapping CIs failed to grant this true significance. At latest available follow-up for all studies, POCE occurred in 17.64% of BVS versus 14.78% of DES patients (RR: 1.10; 95% CI 1.01 to 1.19; p=0.03; I^2=0%; see online supplemental appendix B, figure 6).

All death

All studies excluding Hernandez *et al* and Seo *et al* provided mortality outcomes. Mortality rates were lower for BVS versus DES across 24-month, 36-month and 60-month follow-ups, but higher in the 12-month and under group. None of which reached statistical significance. See online supplemental figure 8.

Cardiac death

All studies provided incidence of cardiac death. The same relationship described for all-death above was observed for the outcome of cardiac death. See online supplemental figure 9.

All MI

All studies provided incidence of MI. Significantly increased rates of MI occurred in BVS versus DES groups across all follow-up durations (10.49% vs 7.26% at 60 month follow-up; RR: 1.39; 95% CI 1.15 to 1.67; p=0.0007), with no significant difference in rate between each group. See online supplemental figure 10.

Target vessel MI

Excluding Hernandez *et al*, Seo *et al*, MAGSTEMI and ABSORB II at 48 and 60 months, incidence of TVMI was reported for all other studies. The BVS group showed increased rates of TVMI across all follow-up durations compared with DES, this reached significance in the ≤12, 24 and 60-month groups (for the latter: 8.49% vs 5.26%; RR: 1.48; 95% CI 1.18 to 1.86; p=0.0008). See online supplemental figure 11.

All revascularisation

All studies but Seo *et al* reported incidence of revascularisation. This was similar between BVS and DES at all follow-up durations. See online supplemental figure 12.

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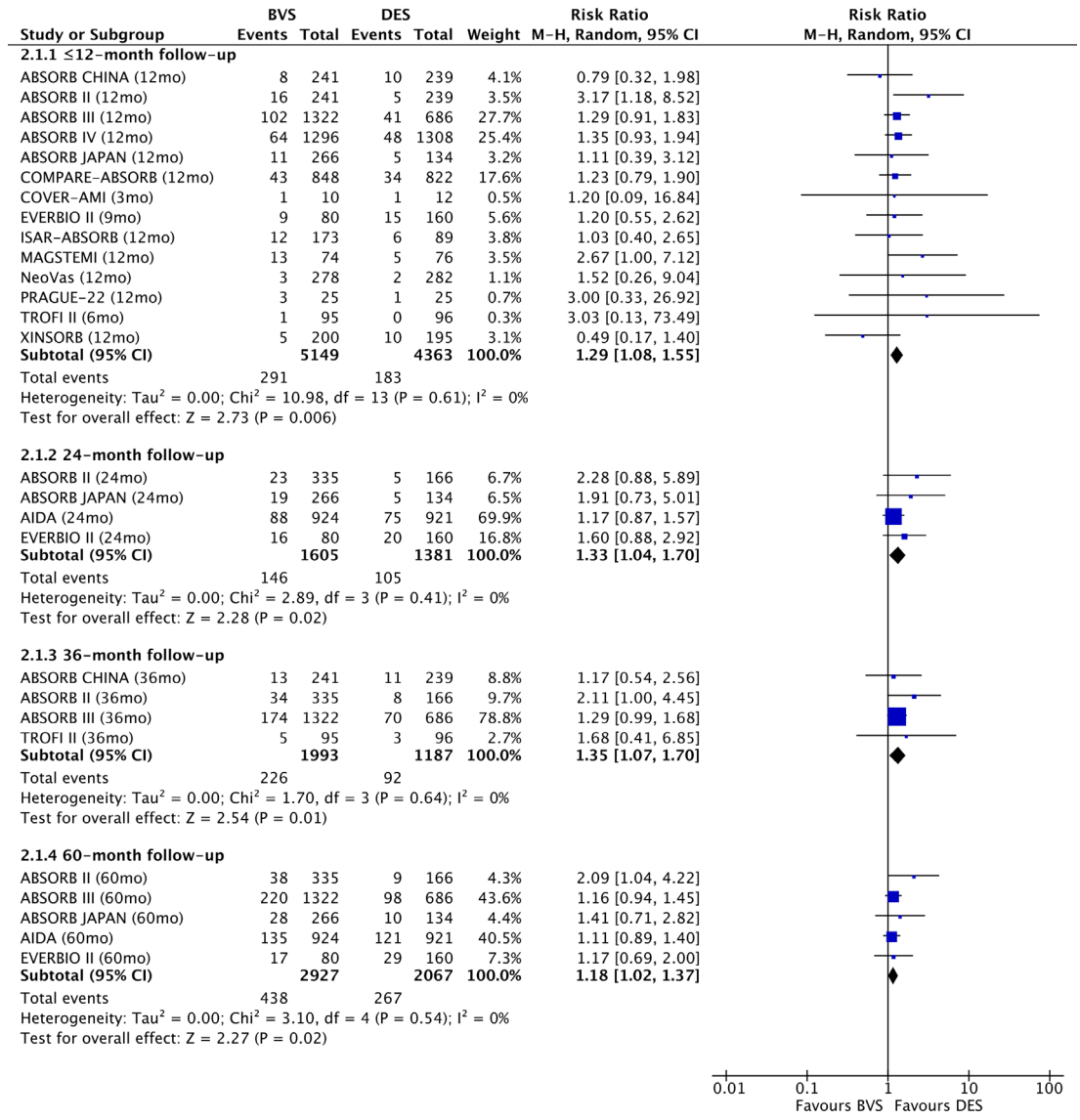

Figure 5 Forest plot for the primary efficacy outcome of target lesion failure (TLF)—grouped by follow-up duration. See Figure 5, Appendix B for corresponding funnel plot. BVS, bioresorbable vascular scaffolds; DES, drug-eluting stents.

Ischaemia-driven target lesion reintervention

All studies but Hernandez *et al* and ISAR-ABSORB provided incidence of ID-TLR. The BVS group showed increased rates of ID-TLR at each follow-up duration, but this only reached significance at 24 and 60 months (for the latter: 9.09% vs 7.11%; RR: 1.36; 95% CI 1.11 to 1.65; p=0.003). online supplemental figure 13.

Summarising the significant findings, BVS was found to be inferior to DES in terms of ST, TLF, ID-TLR, TVMI and all-MI, but not POCE, all-death, cardiac death or all-revascularisation. Table 5 provides a summary of all finding.

DISCUSSION

The main findings of this meta-analysis of 17 RCTs comparing BVS with DES across all available follow-up durations (grouped to ≤12 months and 2, 3, and 5 years) are as follow: First, BVS are inferior to DES at all timepoints with respect to the primary safety (ST) and efficacy outcomes (TLF). Second, the increased risk of ST is significant (3.47-fold greater at 2 years), starts early (the first 30 days) and remains durable throughout 5 years of follow-up (2.99-fold greater risk at 5 years). Third, the increased risk of TLF (1.18-fold higher at 5 years) appears to be driven primarily by elevated rates of TVMI and ID-TLR. Finally, the more generalised secondary outcomes (POCE, all-death, cardiac death and all-revascularisation) are statistically equivalent between groups across all time points—confirming that it is local, device-specific failings driving the inferiority of BVS.

It is important to note that while there is an increased relative risk of ST in BVS versus DES, the incidence of this complication is low (2.05% and 0.69% at latest follow-up, respectively), and its overall clinical relevance is ultimately limited, with equivocal all-cause mortality and revascularisation rates observed across all time points.

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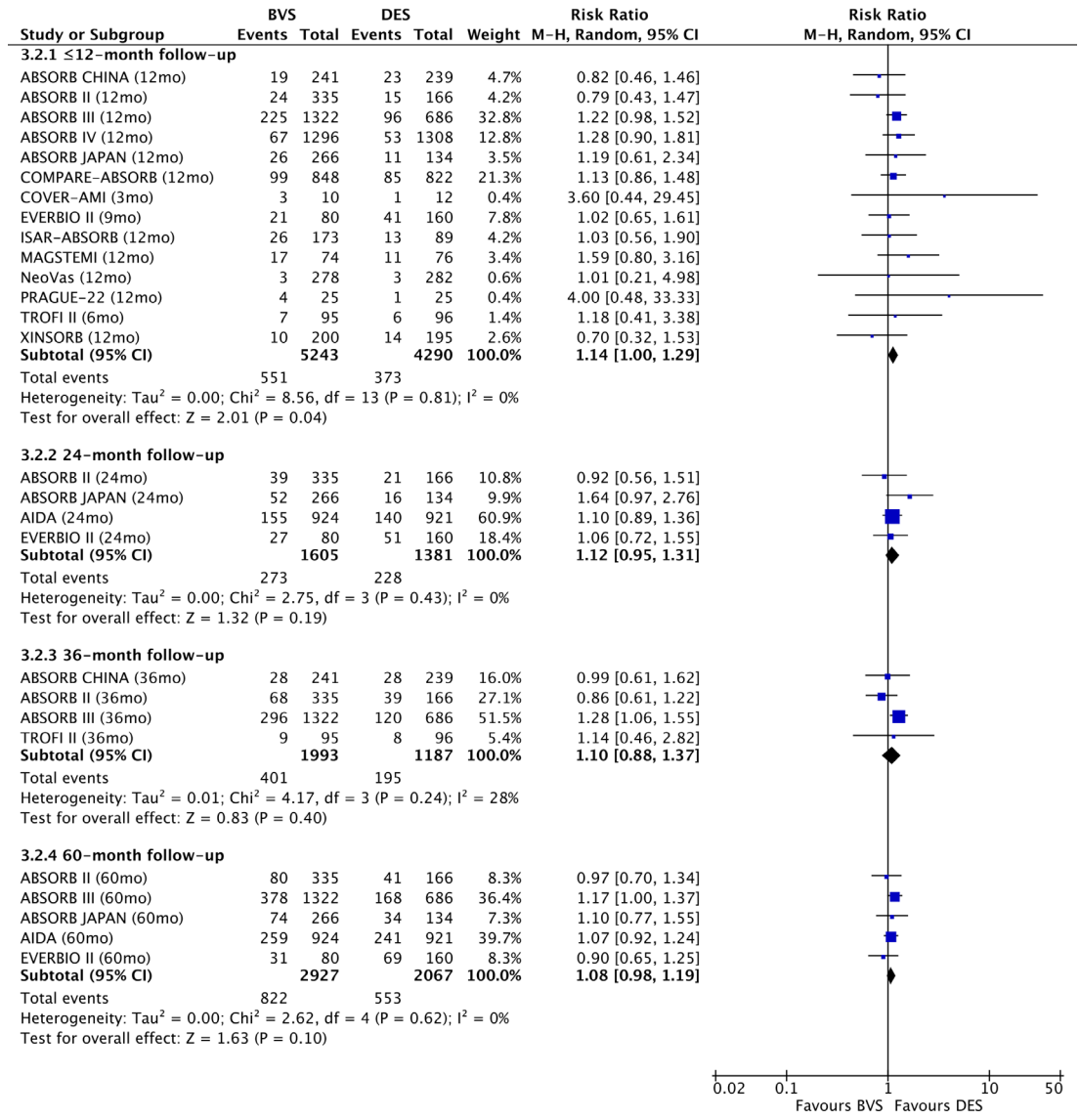

Figure 6 Forest plot for the patient-oriented composite endpoint—grouped by follow-up. See Appendix B, Figure 7 for corresponding funnel plot. BVS, bioresorbable vascular scaffolds; DES, drug-eluting stents.

The low heterogeneity demonstrated throughout this meta-analysis supports conclusions that the elevated adverse outcome rates are attributed directly to the use of BVS versus DES, rather than any inter-study differences. Our findings are in agreement with previous reviews of outcomes at early and interim follow-up durations.[13 17] For example, in their exclusive analysis of Absorb BVS trials at 2-year follow-up, Cassese *et al*[11] demonstrated a similar threefold increased risk of ST accompanied by an increased risk of TLF due to high relative TVMI and ID-TLR rates—as depicted above. Thus, confirming that BVS are at least inferior to DES as solid stents—prior to their complete bio-absorption at around 2 years.[7]

But conceptually, the value of BVS is their promise of a reduction in the late events that plague conventional DES by disappearing once they have fulfilled their purpose of restoring patency to the target artery. To a limited extent, this review supports this premise. Here, both primary outcomes demonstrate a relative plateau in event accumulation for BVS after their dissolution window—with drops in the relative risk between 3-year and 5-year follow-ups, although non-significant with overlapping 95% CIs. However, even if this relationship were to achieve significance at later intervals—which is not unreasonable to suggest, given the adverse event accrual rate of 2% per year for permanent metallic stents[6]—the high initial adverse event rates could continue to render BVS both clinically and economically unfavourable.

Given the particularly high relative risk of ST, and the fact that it can mechanistically drive TLF via TVMI and ID-TLR, it presents as the obvious target for investigation. Cuculi and colleagues studied the causes of ST in BVS using quantitative coronary angiography and optical coherence tomography.[18] They describe a biphasic model, where early ST results from inadequate antithrombotic therapy and poor implantation technique (scaffold undersizing and underexpansion); and late/VLST is associated with peri-strut low-intensity areas (indicative of

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Table 5 Summary of meta-analysis findings relating to key clinical outcomes (grouped by follow-up duration)

Outcome	Follow-up duration			
	≤12 months	24 months	36 months	60 months
Primary safety: definite/probable-ST	✗	✗	✗	✗
Primary efficacy: TLF	✗	✗	✗	✗
POCE	-	-	-	-
All-death	-	-	-	-
Cardiac death	-	-	-	-
All-MI	✗	✗	✗	✗
TVMI	✗	✗	-	✗
All-revascularisation	-	-	-	-
ID-TLR	-	✗	-	✗

Based on risk ratio and significance interpreted using 95% CIs and p<0.05.
+ BVS superior to DES.
- Equivalent.
✗ BVS inferior to DES.
BVS, bioresorbable vascular scaffolds; DES, drug-eluting stents; ID-TLR, ischaemia-driven target lesion revascularisation; MI, myocardial infarction; POCE, patient-oriented composite endpoint; TLF, target lesion failure; TVMI, target vessel myocardial infarction.

inflammation), neovascularisation and scaffold discontinuity. This biphasic relationship may explain the late spike in relative risk of ST which we observe in the BVS group between 31 days and 1 year (see the Primary safety outcome: ST section).

Possible underlying causes of the above observations have previously been discussed[1] and may be grouped as device and operator driven. Device-related failings include their thicker strut profile—table 3 shows this to be around double that of DES across the included studies. This is required to achieve adequate radial strength from the dissolvable material, a factor which would decrease non-linearly as stents dissolve. Strut thickness is known to increase rates of ST clinically,[19] where the increased surface area and changes to haemodynamics at the micro-level are widely discussed to be thrombogenic.[20] Novel metallic BVS with thinner struts and reduced thrombogenicity may address this going forwards,[21] though they present mixed results in the Prague-22[22] and MAGSTEMI[23] trials evaluated in this study. Operator related failings include suboptimal PCI technique. This was investigated by Puricel *et al*, who subsequently described an optimised BVS-specific implantation strategy (involving specific sizing and predilation and postdilation parameters) that effectively reduced ST rates from 3.3% to 1% at 1 year.[24] Clearly there are numerous opportunities for improving outcomes.

Key limitations

Conclusions regarding BVS versus DES are limited in general applicability, given that 91% of the BVS population studied received *Abbott's Absorb*. Further, a lack of access to the raw data meant it was not possible to statistically analyse the effect that important patient, lesion and procedural characteristics had on the observed outcome.

CONCLUSIONS

This meta-analysis demonstrates that current BVS are inferior to contemporary DES throughout the first 5 years at minimum, increasing patients' risk of serious adverse events (ST and MI) and the need for reintervention of the target lesion during this time. This appears to be applicable to the use of PCI for silent ischaemia through to full STEMI. However, this may change with the implementation of improved implantation strategies, better antiplatelet therapies, progressions in scaffold design and the availability of later follow-up data from more recent trials. These remain important areas for future research, remembering that BVS are compared with contemporary DES like Abbott's Xience, whose gold-standard safety and efficacy profiles follow extensive iterative development.

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Contributors EJ-S was responsible for the planning, conduct and reporting of this study. SZ assisted with screening articles, trialling data extraction methods and report editing. PB guided and critically reviewed the work and is the guarantor of this work.

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REFERENCES

1 Byrne RA, Stone GW, Ormiston J, *et al*. Coronary balloon angioplasty, stents, and scaffolds. *Lancet* 2017;390:781–92.
2 Bønaa KH, Mannsverk J, Wiseth R, *et al*. Drug-eluting or bare-metal stents for coronary artery disease. *N Engl J Med* 2016;375:1242–52.
3 Iqbal J, Serruys PW, Silber S. Comparison of Zotarolimus- and everolimus-eluting coronary stents. *Circulation: Cardiovascular Interventions* 2015;8:e002230.
4 Vlachojannis GJ, Smits PC, Hofma SH, *et al*. Biodegradable Polymer Biolimus-Eluting Stents Versus Durable Polymer Everolimus-Eluting Stents in Patients With Coronary Artery Disease: Final 5-Year Report From the COMPARE II Trial (Abluminal Biodegradable Polymer Biolimus-Eluting Stent Versus Durable Polymer Everolimus-Eluting Stent). *JACC Cardiovasc Interv* 2017;10:1215–21.
5 Kereiakes DJ, Windecker S, Jobe RL, *et al*. Clinical outcomes following implantation of Thin-Strut, bioabsorbable polymer-coated, everolimus-eluting synergy stents. *Circ Cardiovasc Interv* 2019;12:e008152.
6 Madhavan MV, Kirtane AJ, Redfors B, *et al*. Stent-Related Adverse Events >1 Year After Percutaneous Coronary Intervention. *J Am Coll Cardiol* 2020;75:590–604.
7 Onuma Y, Serruys PW. Bioresorbable scaffold. *Circulation* 2011;123:779–97.
8 Serruys PW, Ormiston JA, Onuma Y, *et al*. A bioabsorbable everolimus-eluting coronary stent system (ABSORB): 2-year outcomes and results from multiple imaging methods. *Lancet* 2009;373:897–910.
9 Capodanno D, Gori T, Nef H, *et al*. Percutaneous coronary intervention with everolimus-eluting bioresorbable vascular scaffolds in routine clinical practice: early and midterm outcomes from the European multicentre GHOST-EU registry. *EuroIntervention* 2015;10:1144–53.
10 Brugaletta S, Gori T, Low AF, *et al*. Absorb bioresorbable vascular scaffold versus everolimus-eluting metallic stent in ST-segment elevation myocardial infarction: 1-year results of a propensity score matching comparison: the BVS-EXAMINATION study (bioresorbable vascular scaffold-a clinical evaluation of everolimus eluting coronary stents in the treatment of patients with ST-segment elevation myocardial infarction). *JACC Cardiovasc Interv* 2015;8:189–97.
11 Cassese S, Byrne RA, Jüni P, *et al*. Midterm clinical outcomes with everolimus-eluting bioresorbable scaffolds versus everolimus-eluting metallic stents for percutaneous coronary interventions: a meta-analysis of randomised trials. *EuroIntervention* 2018;13:1565–73.
12 Elias J, van Dongen IM, Kraak RP, *et al*. Mid-term and long-term safety and efficacy of bioresorbable vascular scaffolds versus metallic everolimus-eluting stents in coronary artery disease: A weighted meta-analysis of seven randomised controlled trials including 5577 patients. *Neth Heart J* 2017;25:429–38.
13 Sorrentino S, Giustino G, Mehran R, *et al*. Everolimus-Eluting Bioresorbable scaffolds versus everolimus-eluting metallic stents. *J Am Coll Cardiol* 2017;69:3055–66.
14 Ni L, Chen H, Luo Z, *et al*. Bioresorbable vascular stents and drug-eluting stents in treatment of coronary heart disease: a meta-analysis. *J Cardiothorac Surg* 2020;15:26.
15 Garcia-Garcia HM, McFadden EP, Farb A, *et al*. Standardized end point definitions for coronary intervention trials: the academic research Consortium-2 consensus document. *Circulation* 2018;137:2635–50.
16 Higgins J, Thomas J, Chandler J. *Cochrane Handbook for systematic reviews of interventions*. Cochrane, 2021. www.training.cochrane.org/handbook
17 Ali ZA, Serruys PW, Kimura T, *et al*. 2-year outcomes with the absorb bioresorbable scaffold for treatment of coronary artery disease: a systematic review and meta-analysis of seven randomised trials with an individual patient data substudy. *Lancet* 2017;390:760–72.
18 Cuculi F, Puricel S, Jamshidi P, *et al*. Optical coherence tomography findings in Bioresorbable vascular scaffolds thrombosis. *Circ Cardiovasc Interv* 2015;8:e002518.
19 Iantorno M, Lipinski MJ, Garcia-Garcia HM, *et al*. Meta-Analysis of the impact of strut thickness on outcomes in patients with drug-eluting stents in a coronary artery. *Am J Cardiol* 2018;122:1652–60.
20 Foin N, Lee RD, Torii R, *et al*. Impact of stent strut design in metallic stents and biodegradable scaffolds. *Int J Cardiol* 2014;177:800–8.
21 Waksman R, Lipinski MJ, Acampado E. Comparison of acute thrombogenicity for metallic and polymeric bioabsorbable scaffolds. *Circulation: Cardiovascular Interventions* 2017;10:e004762.
22 Tousek P, Lazarak T, Varvarovsky I, *et al*. Comparison of a Bioresorbable, Magnesium-Based sirolimus-eluting stent with a permanent, everolimus-eluting metallic stent for treating patients with acute coronary syndrome: the PRAGUE-22 study. *Cardiovascular Drugs And Therapy*.
23 Sabaté M, Alfonso F, Cequier A, *et al*. Magnesium-Based resorbable scaffold versus permanent metallic sirolimus-eluting stent in patients with ST-segment elevation myocardial infarction: the MAGSTEMI randomized clinical trial. *Circulation* 2019;140:1904–16.
24 Puricel S, Cuculi F, Weissner M, *et al*. Bioresorbable coronary scaffold thrombosis: multicenter comprehensive analysis of clinical presentation, mechanisms, and predictors. *J Am Coll Cardiol* 2016;67:921–31.
25 Gao R, Yang Y, Han Y, *et al*. Bioresorbable vascular scaffolds versus metallic stents in patients with coronary artery disease: ABSORB China trial. *J Am Coll Cardiol* 2015;66:2298–309.
26 Xu B, Yang Y, Han Y, *et al*. Comparison of everolimus-eluting bioresorbable vascular scaffolds and metallic stents: three-year clinical outcomes from the absorb China randomised trial. *EuroIntervention* 2018;14:e554–61.
27 Serruys PW, Chevalier B, Dudek D, *et al*. A bioresorbable everolimus-eluting scaffold versus a metallic everolimus-eluting stent for ischaemic heart disease caused by de-novo native coronary artery lesions (ABSORB II): an interim 1-year analysis of clinical and procedural secondary outcomes from a randomised controlled trial. *Lancet* 2015;385:43–54.
28 Chevalier B, Onuma Y, van Boven AJ, *et al*. Randomised comparison of a bioresorbable everolimus-eluting scaffold with a metallic everolimus-eluting stent for ischaemic heart disease caused by de novo native coronary artery lesions: the 2-year clinical outcomes of the ABSORB II trial. *EuroIntervention* 2016;12:1102–7.
29 Serruys PW, Chevalier B, Sotomi Y, *et al*. Comparison of an everolimus-eluting bioresorbable scaffold with an everolimus-eluting metallic stent for the treatment of coronary artery stenosis (ABSORB II): a 3 year, randomised, controlled, single-blind, multicentre clinical trial. *Lancet* 2016;388:2479–91.
30 Chevalier B, Cequier A, Dudek D, *et al*. Four-year follow-up of the randomised comparison between an everolimus-eluting bioresorbable scaffold and an everolimus-eluting metallic stent for the treatment of coronary artery stenosis (ABSORB II trial). *EuroIntervention* 2018;13:1561–4.
31 Onuma Y, Chevalier B, Ono M, *et al*. Bioresorbable scaffolds versus everolimus-eluting metallic stents: five-year clinical outcomes of the randomised ABSORB II trial. *EuroIntervention* 2020;16:e938–41.
32 Ellis SG, Kereiakes DJ, Metzger DC, *et al*. Everolimus-Eluting Bioresorbable scaffolds for coronary artery disease. *N Engl J Med* 2015;373:1905–15.
33 Kereiakes DJ, Ellis SG, Metzger C, *et al*. 3-Year Clinical Outcomes With Everolimus-Eluting Bioresorbable Coronary Scaffolds: The ABSORB III Trial. *J Am Coll Cardiol* 2017;70:2852–62.

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34 Kereiakes DJ, Ellis SG, Metzger DC, *et al*. Clinical outcomes before and after complete everolimus-eluting Bioresorbable scaffold resorption: five-year follow-up from the absorb III trial. *Circulation* 2019;140:1895–903.
35 Stone GW, Ellis SG, Gori T, *et al*. Blinded outcomes and angina assessment of coronary bioresorbable scaffolds: 30-day and 1-year results from the absorb IV randomised trial. *Lancet* 2018;392:1530–40.
36 Kimura T, Kozuma K, Tanabe K, *et al*. A randomized trial evaluating everolimus-eluting absorb bioresorbable scaffolds vs. everolimus-eluting metallic stents in patients with coronary artery disease: absorb Japan. *Eur Heart J* 2015;36:3332–42.
37 Onuma Y, Sotomi Y, Shiomi H, *et al*. Two-Year clinical, angiographic, and serial optical coherence tomographic follow-up after implantation of an everolimus-eluting bioresorbable scaffold and an everolimus-eluting metallic stent: insights from the randomised ABSORB Japan trial. *EuroIntervention* 2016;12:1090–101.
38 Kozuma K, Tanabe K, Hamazaki Y, *et al*. Long-Term Outcomes of Absorb Bioresorbable Vascular Scaffold vs. Everolimus-Eluting Metallic Stent - A Randomized Comparison Through 5 Years in Japan. *Circ J* 2020;84:733–41.
39 Tijssen RYG, Kraak RP, Hofma SH, *et al*. Complete two-year follow-up with formal non-inferiority testing on primary outcomes of the AIDA trial comparing the absorb bioresorbable scaffold with the XIENCE drug-eluting metallic stent in routine PCI. *EuroIntervention* 2018;14:e426–33.
40 Kerkmeijer LSM, Renkens MPL, Tijssen RYG, *et al*. Long-Term clinical outcomes of everolimus-eluting bioresorbable scaffolds versus everolimus-eluting stents: final five-year results of the AIDA randomised clinical trial. *EuroIntervention* 2022;17:1340–7.
41 Smits PC, Chang CC, Chevalier B, *et al*. Bioresorbable vascular scaffold versus metallic drug-eluting stent in patients at high risk of restenosis: the COMPARE-ABSORB randomised clinical trial. *EuroIntervention* 2020;16:645–53.
42 Lhermusier T, Ohayon P, Boudou N, *et al*. Re-endothelialisation after synergy stent and absorb bioresorbable vascular scaffold implantation in acute myocardial infarction: COVER-AMI study. *Trials* 2019;20:210.
43 Puricel S, Arroyo D, Corpataux N, *et al*. Comparison of everolimus- and biolimus-eluting coronary stents with everolimus-eluting bioresorbable vascular scaffolds. *J Am Coll Cardiol* 2015;65:791–801.
44 Arroyo D, Gendre G, Schukraft S, *et al*. Comparison of everolimus- and biolimus-eluting coronary stents with everolimus-eluting bioresorbable vascular scaffolds: two-year clinical outcomes of the EVERBIO II trial. *Int J Cardiol* 2017;243:121–5.
45 Schukraft S, Arroyo D, Togni M, *et al*. Five-Year angiographic, OCT and clinical outcomes of a randomized comparison of everolimus and biolimus-eluting coronary stents with everolimus-eluting bioresorbable vascular scaffolds. *Catheter Cardiovasc Interv* 2022;99:523-532.
46 de la Torre Hernandez JM, Garcia Camarero T, Lee D-H, *et al*. Procedural resources utilization and clinical outcomes with bioresorbable everolimus-eluting scaffolds and Pt-Cr everolimus-eluting stent with resorbable abluminal polymer in clinical practice. A randomized trial. *Catheter Cardiovasc Interv* 2017;90:E25–30.
47 Byrne RA, Alfonso F, Schneider S, *et al*. Prospective, randomized trial of bioresorbable scaffolds vs. everolimus-eluting stents in patients undergoing coronary stenting for myocardial infarction: the intracoronary scaffold assessment a randomized evaluation of absorb in myocardial infarction (ISAR-Absorb MI) trial. *Eur Heart J* 2019;40:167–76.
48 Han Y, Xu B, Fu G, *et al*. A Randomized Trial Comparing the NeoVas Sirolimus-Eluting Bioresorbable Scaffold and Metallic Everolimus-Eluting Stents. *JACC Cardiovasc Interv* 2018;11:260–72.
49 Seo J, Ahn J-M, Hong S-J, *et al*. Bioresorbable vascular scaffolds versus drug-eluting stents for diffuse long coronary Narrowings. *Am J Cardiol* 2020;125:1624–30.
50 Sabaté M, Windecker S, Iñiguez A, *et al*. Everolimus-Eluting bioresorbable stent vs. durable polymer everolimus-eluting metallic stent in patients with ST-segment elevation myocardial infarction: results of the randomized ABSORB ST-segment elevation myocardial infarction-TROFI II trial. *Eur Heart J* 2016;37:229–40.
51 Katagiri Y, Onuma Y, Asano T, *et al*. Three-year follow-up of the randomised comparison between an everolimus-eluting bioresorbable scaffold and a durable polymer everolimus-eluting metallic stent in patients with ST-segment elevation myocardial infarction (TROFI II trial). *EuroIntervention* 2018;14:e1224–6.
52 Wu Y, Shen L, Yin J, *et al*. Twelve-month angiographic and clinical outcomes of the XINSORB bioresorbable sirolimus-eluting scaffold and a metallic stent in patients with coronary artery disease. *Int J Cardiol* 2019;293:61–6.

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