

Outcomes of patients treated with ultrathin-strut biodegradable polymer sirolimus-eluting stents versus fluoropolymer-based everolimus-eluting stents: a meta-analysis of randomised trials



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This paper also includes supplementary data published online at: http://www.pcronline.com/eurointervention/135th_issue/35

KEYWORDS

- clinical research
- clinical trials
- drug-eluting stent

Abstract

Aims: The ultrathin-strut biodegradable polymer sirolimus-eluting stent (SES) is a new-generation drug-eluting stent (DES) developed to improve the percutaneous treatment of patients with coronary artery disease. Here, we sought to investigate whether the performance of the ultrathin-strut biodegradable polymer SES is superior to that of the benchmark thin-strut fluoropolymer-based everolimus-eluting stent (EES).

Methods and results: We undertook a study-level meta-analysis of trials in which patients receiving percutaneous coronary intervention (PCI) were randomly assigned to either SES or EES. Primary efficacy and safety outcomes were target lesion revascularisation (TLR) and definite/probable stent thrombosis (ST), respectively. Secondary outcomes were myocardial infarction (MI), death, target lesion failure (TLF) and target vessel failure (TVF). A total of 4,853 patients received a PCI with either SES (n=2,816) or EES (n=2,037) in six trials. After a weighted median follow-up of 12 months, patients treated with SES had a risk of TLR (odds ratio [95% confidence interval]: 1.24 [0.83-1.85], p=0.30), definite/probable ST (0.84 [0.53-1.33], p=0.45) and MI related to the target vessel (0.77 [0.55-1.07], p=0.12) comparable to that of patients treated with EES. We found no significant difference with regard to other secondary outcomes.

Conclusions: At one-year follow-up, the ultrathin-strut biodegradable polymer sirolimus-eluting stent displays a performance comparable to that of the fluoropolymer-based everolimus-eluting stent.

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Abbreviations

DES	drug-eluting stent
EES	everolimus-eluting stent
MI	myocardial infarction
PCI	percutaneous coronary intervention
SES	sirolimus-eluting stent
ST	stent thrombosis
TLR	target lesion revascularisation

Introduction

In the last decade, metallic drug-eluting stent (DES) platforms have evolved towards percutaneous devices with highly compatible antiproliferative drugs and polymers, supported by thinner backbones¹. By virtue of these iterations, percutaneous coronary intervention (PCI) with current-generation metallic DES platforms represents the preferred revascularisation strategy for patients with coronary artery disease (CAD)².

The thin-strut (81 µm) fluoropolymer-based everolimus-eluting stent (EES) (XIENCE; Abbott Vascular, Santa Clara, CA, USA) is regarded as the benchmark contemporary DES. Indeed, this platform has demonstrated favourable vascular response³ and superior clinical performance in direct and indirect comparisons against various drug-eluting and bare metal stents⁴. Notwithstanding this, recent refinements in DES technology have led to innovative coatings and metallic scaffold designs, which have allowed a further reduction of strut thickness while retaining biocompatibility and radial strength⁵. The ultrathin-strut biodegradable polymer sirolimus-eluting stent (SES) (Orsiro; Biotronik, Bülach, Switzerland) has the thinnest struts (60 µm) among contemporary drug-eluting stents⁶. Despite encouraging preclinical data³, a number of recent randomised clinical trials did not consistently display that the performance of SES is superior to that of fluoropolymer-based EES⁷⁻⁹.

Against this background, we performed a study-level meta-analysis to investigate whether the efficacy and safety of the ultrathin-strut biodegradable polymer SES is superior to that of the thin-strut fluoropolymer-based EES.

Methods

SEARCH STRATEGY AND SELECTION CRITERIA

The details of search strategy and selection criteria are presented in **Supplementary Appendix 1** and **Supplementary Appendix 2**.

DATA COLLECTION AND ASSESSMENT OF RISK OF BIAS

Two investigators (S. Cassese and N. Mankarious) independently assessed publications for eligibility at title and/or abstract level, with divergences resolved by a third investigator (M. Joner). Studies that met inclusion criteria were selected for further analysis. Freedom from bias was independently evaluated for each study by the same investigators in accordance with The Cochrane Collaboration method¹⁰. Composite quality scores were not assigned¹¹.

OUTCOME VARIABLES

For this report, the primary efficacy and safety outcomes were target lesion revascularisation (TLR) and definite/probable stent thrombosis (ST), respectively. The main secondary outcome was myocardial infarction (MI). Other secondary outcomes of interest were death, target lesion failure (TLF), the device-oriented composite endpoint including cardiac death, target vessel MI, or ischaemia-driven target lesion revascularisation (ID-TLR), and target vessel failure (TVF), the patient-oriented composite endpoint including cardiac death, target vessel MI, or ischaemia-driven target vessel revascularisation. All endpoints were evaluated in the intention-to-treat population up to 12-month follow-up and according to definitions reported in the original protocols. In case of missing data relevant to the study research question, the principal investigators (for investigator-initiated trials) or the manufacturer (for industry-initiated trials) were contacted directly.

STATISTICAL ANALYSIS

Odds ratio (OR) and 95% confidence intervals (95% CI) were used to compare the outcomes of interest of SES versus EES and pooled using the Mantel-Haenszel fixed-effect model and the DerSimonian and Laird random-effect model. Treatment effect was not assessed in trials in which no events were reported within groups. Heterogeneity between trials was quantified using the I² statistic accompanied by a chi² test: I² values around 25%, 50% and 75% were suggested to indicate low, moderate or high heterogeneity, respectively¹⁰. In addition, we estimated the between-study variance (τ^2). The possibility of small study effects resulting from publication bias or other biases was examined for primary outcomes by means of visual inspection of funnel plots of the ORs of individual trials against their standard errors. An influence analysis, in which meta-analysis estimates are computed omitting one study at a time, was performed for primary outcomes. We used a chi² test for subgroup by treatment interaction for two purposes: as first, to investigate the possible time dependence of the risk of definite/probable and definite ST (early – up to 30 days – versus late – beyond 30 days to 12 months) associated with either SES or EES; as second, to test whether the inclusion of patients with acute MI (yes versus no), the protocol-mandated angiographic surveillance (yes versus no), and the type of sponsorship (industry- versus investigator-initiated) were associated with estimated ORs of primary and main secondary outcomes. By using random-effects meta-regression analysis, we assessed the influence on primary and main secondary outcomes of relevant patient characteristics at baseline (proportion of males, diabetics and acute coronary syndromes). Finally, we determined the power of our random-effects meta-analysis to detect a pre-specified 30% relative risk reduction (RRR) of primary and secondary outcomes with SES conditional on the observed precision of the pooled estimate¹². The 30% RRR threshold was chosen because it approximates the nominal effect size seen in cardiovascular trials that is both clinically meaningful and realistic. This study was reported in compliance with the Preferred Reporting Items for Systematic reviews and

Meta-Analyses (PRISMA) statement (**Supplementary Table 1**)¹³. All analyses were performed in R, version 3.3.2 (R Foundation for Statistical Computing, Vienna, Austria). This study is registered with PROSPERO, number CRD42017078538.

Results

ELIGIBLE STUDIES

Figure 1 shows the flow diagram for the trial selection process. Finally, we selected six trials (five reported with full-length manuscripts^{7-9,14,15} and one reported with a meeting presentation [Saito S., Japan Circulation Society Congress, 2017, Kanazawa, Japan]) in which a total of 4,853 PCI patients were randomly assigned to either SES (n=2,816) or EES (n=2,037). For two out of six trials, the investigators¹⁵ and the manufacturer (Saito S., Japan Circulation Society Congress, 2017, Kanazawa, Japan) agreed to provide unpublished study-level data concerning clinical and angiographic features, as well as clinical outcomes. The main characteristics of the trials included are described in detail in **Supplementary Table 2**. Briefly, patients with obstructive chronic/stable or unstable CAD were randomised to PCI with SES versus EES. Patients assigned to EES received the XIENCE V[®]/XIENCE Prime[®]/XIENCE Xpedition[®] (Abbott Vascular) stent. All but one trial¹⁵ had a multicentre design. Two^{7,8} out of six trials enrolled patients with acute MI. Three studies^{8,14,15} required per protocol a control angiography six to nine months after index PCI: in these trials the percentage of patients with angiographic follow-up data ranged from 74.3% to 85.5%. At the time of index PCI, all patients received loading doses of thienopyridines, as well as aspirin. In all cases, a maintenance dose of aspirin was recommended indefinitely, whilst the length and the type of thienopyridine

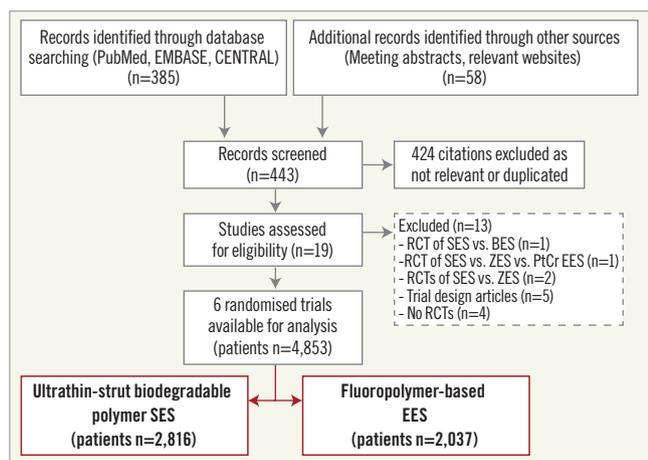


Figure 1. PRISMA flow chart for the trial selection process. BES: biolimus-eluting stent; EES: fluoropolymer-based everolimus-eluting stent; PRISMA: Preferred Reporting Items for Systematic reviews and Meta-Analyses; PtCr EES: platinum-chromium biodegradable polymer everolimus-eluting stent; RCT(s): randomised controlled trial(s); SES: ultrathin-strut biodegradable polymer sirolimus-eluting stent; ZES: zotarolimus-eluting stent

prescription depended on clinical indication. The adherence to prescribed dual antiplatelet therapy was available for 4,364 patients after 12 months: at this time point 2,067 (80.8%) of 2,558 patients treated with SES and 1,387 (76.7%) of 1,806 patients treated with EES were actually on dual antiplatelet therapy. All interventions were performed in accordance with standard of care including anticoagulation, stent deployment optimisation or use of intravascular imaging techniques, at the operators' discretion or according to protocols. In three trials^{9,14,15} the primary endpoint consisted of angiographic (namely, in-stent late lumen loss) or imaging (namely, neointimal tissue coverage) measures of efficacy. The remaining trials were powered for composite clinical endpoints. Two^{7,14} out of six trials had outcome data beyond 12 months available; however, to ensure a homogeneous observation period across included trials the current report analysed adverse events occurring up to 12 months after index PCI. The definitions of outcomes are reported in **Supplementary Table 3** and the risk of bias among studies is reported in **Supplementary Table 4**.

The baseline characteristics of individuals enrolled are shown in **Table 1**. Patients were more often male, with a median age of 64.6 years (interquartile range, 63.7-66.0) and roughly one third were diabetics. Nearly a fourth of participants presented with ACS at the time of index PCI. Overall, at baseline angiography, treated lesions presented a mean reference vessel diameter of 2.73 mm, a diameter stenosis of 61.6%, and a length of 14.9 mm, and more than half had a complex morphology. Among those randomised, 4,756 patients (98.0%) were available for assessment of outcomes of interest after a weighted median follow-up of 12 months (mean 11.0±2.5).

CLINICAL OUTCOMES

Figure 2 displays a summary of risk estimates as well as the power of the random-effects meta-analysis to detect a 30% RRR of primary and secondary outcomes associated with SES. The details of risk estimates for each study endpoint are presented in **Supplementary Figure 1-Supplementary Figure 3**.

The primary efficacy outcome of TLR occurred in 152 patients (3.2%) (**Supplementary Figure 1A**). Patients treated with SES had a risk of TLR comparable to that observed with EES (3.4% versus 2.9%; OR [95% CI] 1.24 [0.83-1.85], p=0.30; I²=15%). ID-TLR occurred in 131 patients (2.7%). Patients treated with SES had a risk of ID-TLR comparable to that observed with EES (3.0% versus 2.4%; 1.27 [0.83-1.95], p=0.26; I²=15%). Of interest, in those trials^{9,14,15} with protocol-mandated control angiography, the degree of in-stent late lumen loss after a median of nine months [mean 8.0±1.7] was comparable between SES and EES (weighted mean difference [95% CI] -0.00 [-0.06, 0.06], p=0.99; I²=0%; data available for 695 patients).

The primary safety outcome of definite/probable ST occurred in 76 patients (1.6%) (**Supplementary Figure 1B**). Patients treated with SES had a risk of definite/probable ST comparable to that observed with EES (1.3% versus 1.9%; 0.84 [0.53-1.33], p=0.45; I²=0%). The risk of early (0.90 [0.50-1.61], p=0.72; I²=0%) and late (0.73

Table 1. Main characteristics of patients and lesions enrolled among trials included in the study.

Trial	Patients, n	Age, years	Males, %	Diabetes, %	ACS at admission, %	Lesions, n	Diameter stenosis, %	RVD, mm	Length, mm	B2/C, %	Direct stenting, %
BIOFLOW III ⁴	452	63.7 (9.8)	348 (76.9)	128 (28.3)	93/418 (22.2)*	505	66.0 (14.4)	2.76 (0.49)	13.5 (6.2)	132 (26.1)	227 (44.9)
BIOFLOW IV ⁴	579	64.7 (9.6)	426/575 (74.1)	176/575 (30.6)	125/575 (21.7)*	659	65.7 (12.6)	2.76 (0.47)	13.6 (6.2)	224/636 (35.3)	114/659 (17.3)
BIOFLOW V ⁸	1,334	64.5 (10.4)	988 (74.0)	466/1,332 (35.0)	677 (50.8)	1,700	55.6 (13.4)	2.60 (0.55)	13.2 (7.6)	1,189/1,612 (73.7)	46 (2.7)
BIOSENSE ⁷	2,119	66.0 (11.5)	1,634 (77.1)	486 (22.9)	1,131 (53.3)	3,139	N/R	N/R	N/R	N/R	867 (27.6)
ISAR ORSIRO OCT ¹⁵	39	70 (8.8)	24 (61.5)	10 (27.2)	11 (28.2)*	39	61.4 (11.3)	2.98 (0.47)	13.4 (6.6)	12 (30.7) ^o	12 (30.7)
PRISON IV ⁹	330	62.6 (10)	259 (78.4)	65 (19.6)	57 (17.2)	330	60.5 (16.9)	2.59 (1.01)	20.6 (13.4)	330 (100) ^e	0 (0)

Overall numbers (proportions) and mean values (SD) are reported; denominators have been provided when they differ from the total number of patients/lesions. ⁴Saito S., Japan Circulation Society Congress, 2017, Kanazawa, Japan; *refers to unstable angina only; ^orefers to B2 lesions; ^erefers to total coronary occlusions or chronic total occlusions in all cases. ACS: acute coronary syndrome; N/R: not reported; RVD: reference vessel diameter. Official titles and acronyms: BIOFLOW II: BIOTRONIK-Safety and Clinical Performance of the Drug Eluting Orsiro Stent in the Treatment of Subjects With Single de Novo Coronary Artery Lesions - II; BIOFLOW IV: BIOTRONIK-A Prospective, Randomized, Multicenter Study to Assess the Safety and Effectiveness of the Orsiro Sirolimus Eluting Stent in the Treatment of Subjects With up to Two de Novo Coronary Artery Lesions - IV; BIOFLOW V: BIOTRONIK - A Prospective Randomized Multicenter Study to Assess the SaFety and Effectiveness of the Orsiro SiroLimus Eluting Coronary Stent System in the Treatment Of Subjects With up to Three De Novo or Restenotic Coronary Artery Lesions - V; BIOSENSE: A Randomized Comparison of a Sirolimus-eluting Stent With Biodegradable Polymer Versus an Everolimus-eluting Stent With a Durable Polymer for Percutaneous Coronary Revascularization; ISAR ORSIRO OCT: Intracoronary Stenting and Angiographic Results: ORSIRO Stents Versus XIENCE PRIME Stents Assessed by Optical Coherence Tomography; PRISON IV: Hybrid Sirolimus-eluting Stent With Bioresorbable Polymer Versus Everolimus-eluting Stent With Durable Polymer for Total Coronary Occlusions in Native Coronary Arteries.

[0.33-1.61], $p=0.43$; $I^2=0\%$) definite/probable ST was comparable between SES and EES (data available for 4,423 participants). There was no time-dependent risk of definite/probable ST associated with SES versus EES (p for interaction- $p_{int}=0.67$). Definite ST occurred in 25 patients (0.5%). Patients treated with SES had a risk of definite ST comparable to that observed with EES (0.6% versus 0.4%; 1.48 [0.64-3.44], $p=0.36$; $I^2=0\%$). The risk of early (1.75 [0.49-6.25], $p=0.39$; $I^2=0\%$) and late (1.03 [0.09-11.34], $p=0.98$; $I^2=64\%$) definite ST was comparable between SES and EES (data available for 4,421 participants). There was no time-dependent risk of definite ST associated with SES versus EES ($p_{int}=0.70$).

The main secondary outcome of MI occurred in 199 patients (4.2%) (**Supplementary Figure 2**). Patients treated with SES displayed a tendency to lower risk of MI as compared to EES (3.8% versus 4.6%; 0.77 [0.57-1.02], $p=0.07$; $I^2=0\%$). MI related to the target vessel occurred in 166 patients (3.7%, data available for 4,423 participants). Patients treated with SES had a risk of MI related to the target vessel comparable to EES (3.5% versus 4.1%; 0.77 [0.55-1.07], $p=0.12$; $I^2=11\%$).

Death occurred in 92 patients (1.9%, data available for 4,760 individuals). Patients treated with SES had a risk of death similar to that observed with EES (1.8% versus 2.0%; 1.02 [0.67-1.56],

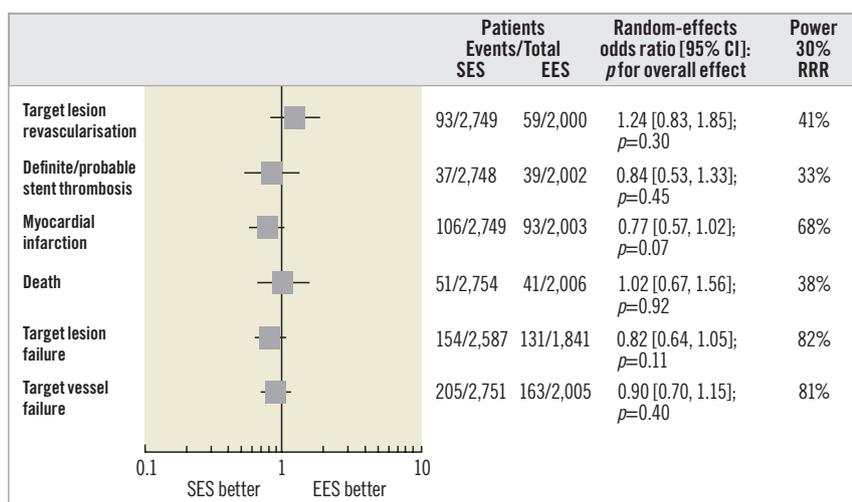


Figure 2. Summary of risk estimates for primary and secondary outcomes for SES versus EES. Plot of random-effects odds ratios associated with SES versus EES. The diamonds indicate the point estimate and the left and the right ends of the lines the 95% confidence intervals (CI). The power of random-effects meta-analysis to detect a pre-specified 30% RRR of primary and secondary outcomes with SES conditional on the observed precision of the pooled estimate is shown in the last column on the right. EES: fluoropolymer-based everolimus-eluting stent; RRR: relative risk reduction; SES: ultrathin-strut biodegradable-polymer sirolimus-eluting stent

p=0.92; I²=0%). Cardiac death occurred in 53 patients (1.1%) (**Supplementary Figure 3A**). Patients treated with SES displayed a risk of cardiac death comparable to that observed with EES (0.9% versus 1.4%; 0.76 [0.44-1.31], p=0.32; I²=0%).

TLF occurred in 285 patients (6.4%, data available for 4,428 participants) (**Supplementary Figure 3B**). Patients treated with SES had a risk of TLF comparable to that of EES (5.9% versus 7.1%; 0.82 [0.64-1.05], p=0.11; I²=0%).

TVF occurred in 368 patients (7.7%) (**Supplementary Figure 3C**). Patients treated with SES displayed a risk of TVF comparable to that of EES (7.4% versus 8.1%; 0.90 [0.70-1.15], p=0.40; I²=18%).

SMALL STUDY EFFECTS, INFLUENCE AND SENSITIVITY ANALYSES

By visual inspection, funnel plots for primary efficacy and safety outcomes revealed no evidence for small study effects (**Supplementary Figure 4A, Supplementary Figure 5A**). The influence analysis demonstrated that no single study significantly altered the direction of the summary ORs for primary outcomes (**Supplementary Figure 4B, Supplementary Figure 5B**). The subgroup by treatment interaction analysis for primary and main secondary outcomes is reported in **Figure 3**: the inclusion of patients with acute MI (p_{int}≥0.45), the angiographic surveillance (p_{int}≥0.82) and the sponsorship (p_{int}≥0.14) did not affect the risk estimates for TLR and definite/probable ST. The risk estimate for MI was independent from angiographic surveillance (p_{int}=0.49) and sponsorship (p_{int}=0.52). In contrast, SES was associated with a lower risk of MI as compared to EES across trials enrolling patients with acute MI (0.71 [0.52-0.98], p=0.039, p_{int}=0.042). The meta-regression analysis found that the treatment effect regarding TLR (p=0.47, 0.11 and 0.49), definite/probable ST (p=0.88, 0.99

and 0.49) and MI (p=0.20, 0.13 and 0.36) was not significantly affected by the baseline proportion of males, diabetics and acute coronary syndromes, respectively.

Discussion

This meta-analysis investigated the outcomes of PCI patients treated with either ultrathin-strut biodegradable polymer SES or thin-strut fluoropolymer-based EES. At one-year follow-up as compared to EES, SES showed similar overall efficacy and safety. The tendency towards lower risk of MI associated with SES versus EES and the modification of treatment effect with respect to this outcome in trials enrolling patients with acute MI require further investigation.

The ultrathin-strut, biodegradable polymer SES investigated in the present study consists of a cobalt-chromium scaffold (strut thickness 60 µm for stent diameters up to 3.0 mm and 80 µm for stent diameters >3.0 mm) coated with a fully biodegradable dual polymer. This coating is composed of a thin layer of amorphous, hydrogen-rich, silicon carbide, which is in contact with the stent surface, and an asymmetric circumferential layer containing a matrix of poly-L-lactic acid (PLLA) loaded with the antiproliferative drug sirolimus (1.4 µg/mm² of stent surface). Of note, the PLLA has the slowest degradation kinetic among biodegradable polymers, enabling a more controlled release of antiproliferative drug from the stent surface⁶. In this meta-analysis we investigated the aggregate data from six randomised trials with ≈5,000 PCI patients allocated to either ultrathin-strut, biodegradable polymer SES or the best-in-class thin-strut fluoropolymer-based EES. In contrast with other meta-analyses^{4,16,17}, we analysed the totality of aggregate data from randomised trials comparing SES versus EES, by including unpublished data relevant to the study research question.

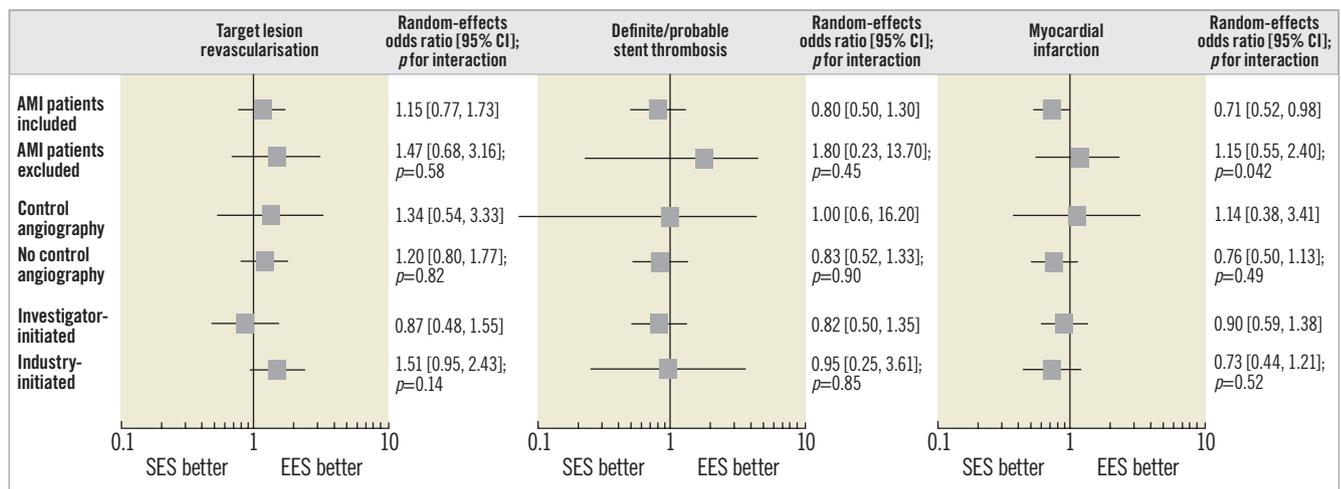


Figure 3. Summary of risk estimates for primary and main secondary outcomes for SES versus EES. Plot of random-effects odds ratios associated with SES versus EES according to subgroups of interest. The diamonds indicate the point estimate and the left and the right ends of the lines the 95% confidence intervals (CI); p-values for interaction are from chi² test. AMI: acute myocardial infarction; EES: fluoropolymer-based everolimus-eluting stent; SES: ultrathin-strut biodegradable polymer sirolimus-eluting stent

Firstly, in this meta-analysis patients treated with SES showed a risk of TLR at one-year follow-up comparable to that of patients assigned to EES. This result lends support to the comparable angiographic performance of SES and EES observed in our analysis and confirms the favourable efficacy profile of SES observed in broadly inclusive patient populations¹⁸. However, the data accumulated have little statistical power to rule out any clinically relevant benefit in terms of TLR associated with SES.

Secondly, we found comparable risk of ST after PCI with SES versus EES without time dependence of risk estimation. This study confirms once more the excellent safety profile of contemporary high-performance DES, with an overall rate of definite ST at 12 months of 0.5% across nearly 5,000 patients, including those presenting with acute MI and highly complex coronary anatomies (such as chronic total occlusions). However, the available sample size remains insufficient to address a measurable advantage of SES versus EES with respect to this endpoint. In addition, despite the fact that longer follow-up is instrumental in unravelling whether SES are safer than EES after complete degradation of the polymer, available outcome data beyond 12 months do not support a lower risk of thrombotic events in patient cohorts receiving a PCI therapy with SES against EES¹⁹.

Thirdly, this analysis refutes the recent hypothesis that the ultrathin-strut biodegradable polymer SES lowers the risk of TLF by virtue of fewer MI events as compared to EES⁸. Indeed, despite the fact that in our analysis the risk of MI trended lower with SES as compared to EES, the risk of MI related to the target vessel and TLF was comparable between treatment groups. Preclinical data found both DES platforms under investigation to be associated with low thrombogenicity and accelerated endothelialisation owing to their thin-strut design and biocompatible carriers^{3,20,21}. Although the coating formulation of SES aims to reduce further the interaction of metal components with the vessel wall⁶, a potential lower risk of MI with SES as compared to EES has yet to be demonstrated. Moreover, the lack of complete details regarding the types of MI event (periprocedural versus spontaneous) and the exploratory nature of subgroup analyses performed in this report prevent full disclosure of the variation of treatment effect for this outcome in patients with acute MI, for which we observed a significant interaction. For this reason, the proof of superior performance of SES versus EES in patients with acute MI remains to be studied²².

Study limitations

A number of limitations inherent to the present study should be acknowledged. First, this meta-analysis was based on aggregate data: an individual patient-data meta-analysis remains necessary to investigate a variation of treatment effect across different subgroups of patients, such as those presenting with acute MI. Second, the median follow-up of one year prevents investigating whether SES performs better than EES beyond the time of complete resorption of the polymer. Third, this study has insufficient statistical power to investigate the comparative efficacy of

SES and EES with respect to outcomes other than MI, TLF and TVF. Fourth, the protocol-mandated surveillance angiography in three trials^{9,14,15} may have magnified differences in the absolute proportion of revascularisations across groups, though we found no interaction between treatment effect and control angiography. Finally, the assessment of publication bias was based on a limited number of trials, limiting the performance of this assessment.

Conclusions

At one-year follow-up, clinical outcomes of PCI patients treated with an ultrathin-strut biodegradable polymer sirolimus-eluting stent were broadly comparable to those of patients treated with a thin-strut fluoropolymer-based everolimus-eluting stent.

Impact on daily practice

The ultrathin-strut biodegradable polymer sirolimus-eluting stent is a new-generation drug-eluting stent developed to improve the percutaneous treatment of patients with coronary artery disease. In this meta-analysis of aggregate data from six randomised trials with circa 5,000 patients the ultrathin-strut biodegradable polymer sirolimus-eluting stent displayed a performance broadly comparable to that of the benchmark fluoropolymer-based everolimus-eluting stent at one-year follow-up. Any potential benefit associated with the ultrathin-strut biodegradable polymer sirolimus-eluting stent should be explored in more complex cohorts of patients and with a clinical follow-up beyond one year.

Guest Editors

This paper was guest edited by Antonio Colombo, MD, FACC, FESC, FSCAI; Department of Interventional Cardiology, EMO GVM Centro Cuore Columbus, Milan, Italy, and Alec Vahanian, MD, PhD; Department of Cardiology, Hôpital Bichat-Claude Bernard, and University Paris VII, Paris, France.

Conflict of interest statement

R.A. Byrne reports receiving lecture fees from B. Braun Melsungen AG, Biotronik and Boston Scientific, and research grants to the institution from Boston Scientific and HeartFlow, outside the submitted work. N. Mankarious is the recipient of a research fellowship grant funded by the European Association of Percutaneous Cardiovascular Interventions (EAPCI). A. Kastrati reports holding patents related to drug-eluting stent technology, outside the submitted work. M. Joner reports receiving personal fees from OrbusNeich, grants and personal fees from Biotronik, personal fees from coramaze, personal fees from AstraZeneca, and personal fees from Bristol-Myers-Squibb, outside the submitted work. The other authors have no conflicts of interest to declare. The Guest Editor A. Vahanian is a consultant for Edwards Lifesciences. The Guest Editor A. Colombo has no conflicts of interest to declare.

References

1. Byrne RA, Stone GW, Ormiston J, Kastrati A. Coronary balloon angioplasty, stents, and scaffolds. *Lancet*. 2017;390:781-92.
2. Byrne RA, Joner M, Kastrati A. Stent thrombosis and restenosis: what have we learned and where are we going? The Andreas Grüntzig Lecture ESC 2014. *Eur Heart J*. 2015;36:3320-31.
3. Otsuka F, Cheng Q, Yahagi K, Acampado E, Sheehy A, Yazdani SK, Sakakura K, Euller K, Perkins LEL, Kolodgie FD, Virmani R, Joner M. Acute Thrombogenicity of a Durable Polymer Everolimus-Eluting Stent Relative to Contemporary Drug-Eluting Stents With Biodegradable Polymer Coatings Assessed Ex Vivo in a Swine Shunt Model. *JACC Cardiovasc Interv*. 2015;8:1248-60.
4. Kang SH, Chae IH, Park JJ, Lee HS, Kang DY, Hwang SS, Youn TJ, Kim HS. Stent Thrombosis With Drug-Eluting Stents and Bioresorbable Scaffolds: Evidence From a Network Meta-Analysis of 147 Trials. *JACC Cardiovasc Interv*. 2016;9:1203-12.
5. Rizas KD, Mehili J. Stent Polymers: Do They Make a Difference? *Circ Cardiovasc Interv*. 2016 Jun;9(6).
6. Iglesias JF, Roffi M, Degrauwe S, Secco GG, Aminian A, Windecker S, Pilgrim T. Orsiro cobalt-chromium sirolimus-eluting stent: present and future perspectives. *Exp Rev Med Devices*. 2017;14:773-88.
7. Pilgrim T, Heg D, Roffi M, Tuller D, Muller O, Vuillienet A, Cook S, Weilenmann D, Kaiser C, Jamshidi P, Fahrni T, Moschovitis A, Noble S, Eberli FR, Wenaweser P, Juni P, Windecker S. Ultrathin strut biodegradable polymer sirolimus-eluting stent versus durable polymer everolimus-eluting stent for percutaneous coronary revascularisation (BIO-SCIENCE): a randomised, single-blind, non-inferiority trial. *Lancet*. 2014;384:2111-22.
8. Kandzari DE, Mauri L, Koolen JJ, Massaro JM, Doros G, Garcia-Garcia HM, Bennett J, Roguin A, Gharib EG, Cutlip DE, Waksman R; BIOFLOW V Investigators. Ultrathin, bioresorbable polymer sirolimus-eluting stents versus thin, durable polymer everolimus-eluting stents in patients undergoing coronary revascularisation (BIOFLOW V): a randomised trial. *Lancet*. 2017;390:1843-52.
9. Teeuwen K, van der Schaaf RJ, Adriaenssens T, Koolen JJ, Smits PC, Henriques JP, Vermeersch PH, Tjon Joe Gin RM, Scholzel BE, Kelder JC, Tijssen JG, Agostoni P, Suttorp MJ. Randomized Multicenter Trial Investigating Angiographic Outcomes of Hybrid Sirolimus-Eluting Stents With Biodegradable Polymer Compared With Everolimus-Eluting Stents With Durable Polymer in Chronic Total Occlusions: The PRISON IV Trial. *JACC Cardiovasc Interv*. 2017;10:133-43.
10. Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, Savovic J, Schulz KF, Weeks L, Sterne JA; Cochrane Bias Methods Group; Cochrane Statistical Methods Group. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ*. 2011;343:d5928.
11. Jüni P, Witschi A, Bloch R, Egger M. The hazards of scoring the quality of clinical trials for meta-analysis. *JAMA*. 1999;282:1054-60.
12. Turner RM, Bird SM, Higgins JP. The impact of study size on meta-analyses: examination of underpowered studies in Cochrane reviews. *PLoS One*. 2013;8:e59202.
13. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med*. 2009;151:264-9.
14. Windecker S, Haude M, Neumann FJ, Stangl K, Witzensbichler B, Slagboom T, Sabate M, Goicolea J, Barragan P, Cook S, Piot C, Richardt G, Merkely B, Schneider H, Bilger J, Erne P, Waksman R, Zaugg S, Juni P and Lefevre T. Comparison of a novel biodegradable polymer sirolimus-eluting stent with a durable polymer everolimus-eluting stent: results of the randomized BIOFLOW-II trial. *Circ Cardiovasc Interv*. 2015;8:e001441.
15. Koppa T, Tada T, Xhepa E, Kufner S, Byrne RA, Ibrahim T, Laugwitz KL, Kastrati A, Joner M. Randomised comparison of vascular response to biodegradable polymer sirolimus eluting and permanent polymer everolimus eluting stents: An optical coherence tomography study. *Int J Cardiol*. 2018;258:42-9.
16. El-Hayek G, Bangalore S, Casso Dominguez A, Devireddy C, Jaber W, Kumar G, Mavromatis K, Tamis-Holland J, Samady H. Meta-Analysis of Randomized Clinical Trials Comparing Biodegradable Polymer Drug-Eluting Stent to Second-Generation Durable Polymer Drug-Eluting Stents. *JACC Cardiovasc Interv*. 2017;10:462-73.
17. Lipinski MJ, Forrestal BJ, Iantorno M, Torguson R, Waksman R. A comparison of the ultrathin Orsiro Hybrid sirolimus-eluting stent with contemporary drug-eluting stents: A meta-analysis of randomized controlled trials. *Cardiovasc Revasc Med*. 2018;19:5-11.
18. von Birgelen C, Kok MM, van der Heijden LC, Danse PW, Schotborgh CE, Scholte M, Gin RMTJ, Somi S, van Houwelingen KG, Stoel MG, de Man FHF, Louwerenburg JHW, Hartmann M, Zocca P, Linssen GCM, van der Palen J, Doggen CJM, Löwik MM. Very thin strut biodegradable polymer everolimus-eluting and sirolimus-eluting stents versus durable polymer zotarolimus-eluting stents in allcomers with coronary artery disease (BIO-RESORT): a three-arm, randomised, non-inferiority trial. *Lancet*. 2016;388:2607-17.
19. Zbinden R, Piccolo R, Heg D, Roffi M, Kurz DJ, Muller O, Vuillienet A, Cook S, Weilenmann D, Kaiser C, Jamshidi P, Franzone A, Eberli F, Juni P, Windecker S and Pilgrim T. Ultrathin Strut Biodegradable Polymer Sirolimus-Eluting Stent Versus Durable-Polymer Everolimus-Eluting Stent for Percutaneous Coronary Revascularization: 2-Year Results of the BIO-SCIENCE Trial. *J Am Heart Assoc*. 2016;5:e003255.
20. Secco GG, Mattesini A, Fattori R, Parisi R, Castriota F, Vercellino M, Dall'Ara G, Uguccioni L, Marinucci L, De Luca G, Marino PN, Pistis G, Di Mario C. Time-related changes in neointimal tissue coverage of a novel Sirolimus eluting stent: Serial observations with optical coherence tomography. *Cardiovasc Revasc Med*. 2016;17:38-43.
21. Koppa T, Wittchow E, Byrne RA, Bayer G, Diener T, Joner M. Permanent and biodegradable polymer coatings in the absence of antiproliferative drugs in a porcine model of coronary artery stenting. *EuroIntervention*. 2016;11:1020-6.
22. Iglesias JF, Muller O, Zaugg S, Roffi M, Kurz DJ, Vuillienet A, Weilenmann D, Kaiser C, Tapponnier M, Heg D, Valgimigli M, Eeckhout E, Jüni P, Windecker S, Pilgrim T.

A comparison of an ultrathin strut biodegradable polymer sirolimus-eluting stent with a durable polymer everolimus-eluting stent for patients with acute stsegment elevation myocardial infarction undergoing primary percutaneous coronary intervention: rationale and design of the BIOSTEMI trial. *EuroIntervention*. 2017 Dec 5. [Epub ahead of print].

Supplementary data

Supplementary Appendix 1. Search strategy and selection criteria.

Supplementary Appendix 2. Search strategy: PubMed.

Supplementary Table 1. PRISMA checklist.

Supplementary Table 2. Main characteristics of trials included in the study.

Supplementary Table 3. Definitions of clinical outcomes according to protocols of trials included in the study.

Supplementary Table 4. Assessment of risk of bias.

Supplementary Figure 1. Risk estimates of primary outcomes for SES versus EES.

Supplementary Figure 2. Risk estimates of main secondary outcome for SES versus EES.

Supplementary Figure 3. Risk estimates of other secondary outcomes for SES versus EES.

Supplementary Figure 4. Funnel plot and influence analysis for target lesion revascularisation.

Supplementary Figure 5. Funnel plot and influence analysis for definite/probable stent thrombosis.

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