Clinical Outcomes of Biodegradable Polymer Drug-Eluting Stents for Percutaneous Coronary Intervention: An Updated Meta-analysis of Randomized Controlled Trials

Address for correspondence:
Cheuk-Man Yu, MD
Division of Cardiology
Department of Medicine and
Therapeutics
Prince of Wales Hospital, The Chinese
University of Hong Kong
Shatin, N.T., Hong Kong.
cmYu@cuhk.edu.hk

Joey S.W. Kwong, PhD; Cheuk-Man Yu, MD, FRCP, FRACP

Institute of Vascular Medicine, Li Ka Shing Institute of Health Sciences, S.H. Ho Cardiovascular Disease and Stroke Centre, Heart Education And Research Training (HEART) Centre, and Division of Cardiology, Department of Medicine and Therapeutics, Prince of Wales Hospital, The Chinese University of Hong Kong, Shatin, Hong Kong

ABSTRACT

Biodegradable polymer drug-eluting stents (DES) are innovative concepts in the era of percutaneous coronary intervention. We systematically reviewed the latest randomized evidence on the efficacy and safety of biodegradable polymer DES as compared to durable polymer DES. MEDLINE, Embase, and the Cochrane database were searched in August 2013 for eligible randomized controlled trials (RCTs) comparing biodegradable polymer DES with durable polymer DES. Clinical outcomes of interest were mortality, myocardial infarction (MI), target lesion revascularization (TLR), target vessel revascularization (TVR), and stent thrombosis. A total of 20 RCTs randomizing 20 021 participants were included, of whom 11 045 were allocated to biodegradable polymer DES and 8976 to durable polymer DES. Treatment of biodegradable polymer DES was not associated with a significant reduction of any of the clinical outcomes (all-cause mortality, odds ratio [OR]: 0.94, 95% confidence interval [CI]: 0.80 to 1.10, $P = 0.42$; cardiovascular mortality, OR: 0.97, 95% CI: 0.79 to 1.19, $P = 0.74$; MI, OR: 1.07, 95% CI: 0.91 to 1.26, $P = 0.41$; TLR, OR: 0.87, 95% CI: 0.69 to 1.08, $P = 0.20$; TVR, OR: 1.05, 95% CI: 0.85 to 1.28, $P = 0.67$; definite/probable stent thrombosis, OR: 0.80, 95% CI: 0.59 to 1.07, $P = 0.14$). Current randomized data indicate that clinical efficacy and safety profiles of biodegradable polymer DES are comparable to those of durable polymer DES. Findings from large-scale studies with rigorous methodology and long follow-up duration are needed.

Introduction

The ongoing quest for innovative stent design for percutaneous coronary intervention (PCI) led us to the era of drug-eluting stents (DES) with biodegradable polymer coatings, which offer the antirestenotic benefits of traditional DES in the immediate vessel healing stage without any durable polymer-related complications such as polymer delamination, arterial inflammation, and delayed vascular healing, thereby providing the long-term safety benefits of a bare-metal stent (BMS) after the polymer coatings degrade.^{1–4} Existing meta-analyses of randomized trials investigating the efficacy and safety of biodegradable polymer DES vs durable polymer DES are available.^{5,6} However, due to different study inclusion criteria they came to conflicting conclusions. With the recent availability of

further randomized data, we consequently conducted the current meta-analysis to systematically review the latest evidence on the clinical efficacy and safety of biodegradable polymer DES vs durable polymer DES.

Methods

Literature Search

We searched MEDLINE, Embase, and the Cochrane Central Register of Controlled Trials (CENTRAL) in August 2013 to identify eligible randomized controlled trials (RCTs) comparing all types of biodegradable polymer DES with durable polymer DES in patients undergoing PCI. No restrictions were imposed on patient or lesion type, follow-up duration, sample size, language, or publication status. Keywords included (biodegradable or bioabsorbable or bioresorbable), (stent or scaffold), and (coronary or vascular). Reference lists of retrieved records and relevant reviews were also screened. Studies were selected by both authors independently, and disagreements were resolved by discussion.

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Additional Supporting Information may be found in the online version of this article.

Data Extraction and Study Quality Assessment

Primary outcomes were: (1) mortality (all-cause and cardiovascular), (2) myocardial infarction (MI), (3) target lesion revascularization (TLR), (4) target vessel revascularization (TVR), and (5) stent thrombosis. Secondary outcomes were angiographic measures including late lumen loss, minimal lumen diameter, diameter stenosis, and binary restenosis. Definitions of outcomes used in individual studies were accepted. Stent thrombosis was defined according to the Academic Research Consortium (ARC).⁷ Clinical and angiographic outcomes within 1 year as well as those obtained at longer (>1 year) follow-up were evaluated; data available at the longest follow-up were extracted for each study for data analysis. Data were extracted independently by the 2 authors, and disagreements were resolved by discussion. We used the Cochrane Collaboration's tool for assessing risk of bias to assess methodological quality of the included trials.⁸

Statistical Analysis

A Mantel-Haenszel random-effects model was used to analyze dichotomous and continuous data as odds ratios (ORs) and mean differences (MDs), respectively, with 95% confidence intervals (CIs). Results were considered to be statistically significant at $P < 0.05$. We explored statistical heterogeneity across studies using the I^2 statistic and χ^2 test ($P < 0.10$ for statistical significance).⁸ Prespecified subgroup analyses included follow-up durations, type of biodegradable polymer DES, and dosage regimens. Potential publication bias was assessed using funnel plots for the primary clinical outcomes. Statistical analysis was performed using the Review Manager 5.2 software (The Nordic Cochrane Centre, the Cochrane Collaboration, Copenhagen, Denmark).

Results

Description of Studies

We identified 1408 records from our literature search; of these, 45 full-text reports were retrieved for further assessment (see Supporting Figure 1 in the online version of this article).⁹ Twenty studies randomizing 20 021 participants were included in this meta-analysis.^{10–41} A total of 11 045 participants were allocated to biodegradable polymer DES and 8976 to durable polymer DES. Four studies had an “all-comer” design, without imposing any restrictions on lesion characteristics (type, number, location); the remaining included studies' angiographic eligibility criteria were de novo lesions with $\geq 50\%$ diameter stenosis, lesion length < 30 mm, and a reference vessel diameter ranging from 2.25 to 4.0 mm (Table 1). The majority of participants were male (64%–91%), had stable/unstable angina pectoris, with a mean age between 56 to 70 years (Table 1). The type of biodegradable polymer DES used in the intervention groups included biolimus-eluting stents (BES) (8 studies; $n = 6034$), everolimus-eluting stents (EES) (1 study; $n = 193$), paclitaxel-eluting stents (PES) (2 studies; $n = 1030$), and sirolimus-eluting stents (SES) (9 studies; $n = 3788$), with stainless steel and polylactic acid being the most common metal scaffold

and biodegradable polymer, respectively, in the design of the study interventions (see Supporting Table S1 in the online version of this article). The type of durable polymer DES used in the comparison arms consisted of EES (7 studies; $n = 3620$), PES (5 studies; $n = 1022$), and SES (9 studies; $n = 4334$). Angiographic end points were measured at 6 to 9 months, whereas clinical follow-up varied more greatly, ranging from 4 months (PILOT [Polymer Degrading-Sirolimus Eluting-Coronary Stent Trial])³⁷ to 5 years (the LEADERS [Limus Eluted From A Durable Versus ERodable Stent Coating] trial).²⁷ Methodological quality among the included studies was good (see Supporting Table S2 and Supporting Figure 2 in online version of this article). All the included studies were identified as RCTs, with most being conducted in multiple study centers. Methods of randomization were clearly described in all but 5 studies and were deemed adequate (eg, computer-generated sequence generation, use of central telephone allocation system). Double blinding was not applied in any of the included studies. However, although most studies were either open-label or single-blind studies, we concluded that the overall validity of the trial findings would remain unaffected, because our outcomes of interest are clinical end points and are objective and clearly defined.

Data Analysis

Clinical Outcomes: All-cause deaths were reported in 361 of 11 045 (3.27%) participants randomized to biodegradable polymer DES and in 359 of 8976 (4.00%) participants to durable polymer DES. No significant difference was observed between groups (OR: 0.94, 95% CI: 0.80 to 1.10; $P = 0.42$) (Figure 1A). Analysis of cardiovascular mortality showed similar results between the biodegradable polymer DES and the durable polymer DES arms (1.99% vs 2.36%; OR: 0.97, 95% CI: 0.79 to 1.19; $P = 0.74$) (Figure 1B).

MI occurred in 356 of 11 045 (3.22%) participants allocated to the biodegradable polymer DES and in 284 of 8976 (3.16%) participants allocated to the durable polymer DES. Meta-analysis showed no significant difference between groups (OR: 1.07, 95% CI: 0.91 to 1.26; $P = 0.41$) (Figure 2).

TLR was performed in 462 of 8376 (5.52%) participants randomized to biodegradable polymer DES and in 470 of 7199 (6.53%) participants to durable polymer DES. There was no significant difference between groups (OR: 0.87, 95% CI: 0.69 to 1.08; $P = 0.20$) (Figure 3A). Incidence of TVR was also similar between the biodegradable polymer DES and the durable polymer DES groups (6.05% vs 6.52%; OR: 1.05, 95% CI: 0.85 to 1.28; $P = 0.67$) (Figure 3B).

Stent thrombosis was reported in 186 of 11 045 (1.68%) participants who received biodegradable polymer DES and in 186 of 8976 (2.07%) participants who received durable polymer DES. No significant difference was observed between groups (OR: 0.90, 95% CI: 0.73 to 1.12; $P = 0.36$) (Figure 4A). Stratified analysis of definite or probable stent thrombosis revealed similar findings between the biodegradable polymer DES and the durable polymer DES groups (0.90% vs 1.19%; OR: 0.80, 95% CI: 0.59 to 1.07; $P = 0.14$) (Figure 4B).

To analyze the likelihood of publication bias, funnel plots were constructed for the primary clinical outcomes. None

Table 1. Characteristics of Included Studies

Study	No.	Intervention	Comparator	Population	Mean Age, y	Male, %	Prior PCI, %	Follow-up
COMPARE II (2013) ¹⁰	2707	BP-BES (Nobori)	EES (Xience V or Prime)	All-comer; eligible for PCI; RVD 2.0–4.0 mm; no restrictions on number or length or location of lesions	BP-BES: 63.0 ± 11.1, EES: 62.7 ± 11.0	BP-BES: 74.4, EES: 74.3	BP-BES: 17.8, EES: 17.0	Clinical: 12 months
COSTAR II (2008) ^{11,12}	1675	BP-PES (CoStar)	PES (Taxus)	De novo single lesion (length <30 mm), >50% but <99% stenosis, in 1–3 epicardial arteries; RVD 2.5–3.5 mm	BP-PES: 63.5 ± 10.8, PES: 63.7 ± 10.6	BP-PES: 73.1, PES: 71.1	BP-PES: 33.5, PES: 32.7	Clinical: 8 months, angiographic: 9 months
EVOLUTION (2012) ¹³	1909	BP-SES (EXCEL)	SES (Cypher Select)	Stable angina, ACS or silent ischemia; ≥1 de novo stenosis (lesion length ≤29 mm) ≥50% in native arteries; RVD 2.5–3.75 mm	BP-SES: 63.3 ± 10.43, SES: 62.1 ± 11.00	BP-SES: 67.7, SES: 73.0	BP-SES: 10.2, SES: 8.1	Clinical: 12 months
EVOLVE (2013) ^{14,15}	291	BP-EES (SYNERGY; SYNERGY Half Dose)	EES (PROMUS Element)	Symptomatic CAD or silent ischemia; a de novo lesion (length ≤28 mm) >50% stenosis; in a native vessel; RVD 2.25–3.5 mm	BP-EES (full dose): 64.9 ± 11.0, BP-EES (half dose): 62.9 ± 10.2, EES: 62.1 ± 10.0	BP-EES (full dose): 69.9, BP-EES (half dose): 69.7, EES: 79.6	BP-EES (full dose): 33.3, BP-EES (half dose): 38.4, EES: 32.7	Clinical: 2 years, angiographic: 6 months
ISAR-TEST 3 (2009) ^{16,17}	404	BP-SES	SES (Cypher)	Ischemic symptoms or myocardial ischemia; ≥50% de novo stenosis in native vessels	BP-SES: 66.5 ± 11.6, SES: 65.0 ± 10.7	BP-SES: 78.2, SES: 81.7	?	Clinical: 2 years, angiographic: 6–8 months
ISAR-TEST 4 (2011) ^{18–21}	2603	BP-SES	EES (Xience) or SES (Cypher)	Ischemic symptoms or myocardial ischemia; ≥50% de novo stenosis in native vessels	BP-SES: 66.7 ± 10.7, EES/SES: 66.8 ± 11.1	BP-SES: 75.3, EES/SES: 76.8	?	Clinical: 3 years, angiographic: 6–8 months
LEADERS (2013) ^{22–27}	1707	BP-BES (BioMatrix Flex)	SES (Cypher Select)	All-comer; symptomatic CAD; ≥1 lesion with ≥50% stenosis; RVD 2.25–3.5 mm; no limit on number of lesions or lesion length	BP-BES: 64.6 ± 10.8, SES: 64.5 ± 10.7	BP-BES: 75.0, SES: 74.6	BP-BES: 36.4, SES: 36.7	Clinical: 5 years, angiographic: 9 months

Table 1. Continued

Study	No.	Intervention	Comparator	Population	Mean Age, y	Male, %	Prior PCI, %	Follow-up
Li et al (2010) ²⁸	228	BP-SES (EXCEL)	SES (Cypher Select)	STEMI; de novo lesions; RVD 2.5–3.5 mm	BP-SES: 60.1 ± 11.9, SES: 59.7 ± 10.8	BP-SES: 77.2, SES: 73.5	BP-SES: 4.4, SES: 1.8	Clinical: 12 months, angiographic: 9 months
NEVO RES-I (2013) ^{29,30}	394	BP-SES (NEVO)	PES (Taxus Liberté)	Stable/unstable angina or silent ischemia; single >50% and <100% de novo lesions (length ≤28 mm) in a native artery; RVD 2.5–3.5 mm	BP-SES: 63.0 ± 10.0, PES: 59.7 ± 10.8	BP-SES: 78, PES: 74	BP-SES: 34, PES: 25	Clinical: 2 years, angiographic: 6 months
NEXT (2013) ³¹	3235	BP-BES (Nobori)	EES (Xience)	Underwent PCI; without any exclusion criteria	BP-BES: 69.1 ± 9.8, EES: 69.3 ± 9.8	BP-BES: 77, EES: 77	N/A	Clinical: 12 months, angiographic: 8 months
Nobori 1 Phase 1 (2007) ³²	120	BP-BES (Nobori)	PES (Taxus Express)	Ischemic heart disease; de novo lesions (length ≥5 mm and ≤25 mm) in up to 2 native arteries; RVD 2.5–3.5 mm	BP-BES: 65 ± 11, PES: 63 ± 11	BP-BES: 69, PES: 66	BP-BES: 19, PES: 9	Clinical: 270 days, angiographic: 9 months
Nobori 1 Phase 2 (2009) ³³	243	BP-BES (Nobori)	PES (Taxus Liberté)	Stable/unstable angina or ischemia; de novo lesions (length ≥5 mm and ≤25 mm) in up to 2 native arteries; RVD 2.5–3.5 mm	BP-BES: 62.7, PES: 63.2	BP-BES: 74.5, PES: 68.9	BP-BES: 20.3, PES: 21.1	Clinical: 300 days, angiographic: 9 months
Nobori Japan (2012) ³⁴	335	BP-BES (Nobori)	SES (Cypher)	Stable/unstable angina or ischemia; up to de novo lesions (length ≤30 mm) in different epicardial vessels; >50% stenosis; RVD 2.5–3.5 mm;	BP-BES: 67.1 ± 10.3, SES: 67.7 ± 9.3	BP-BES: 71.6, SES: 72.0	BP-BES: 32.5, SES: 38.6	Clinical: 9 months, angiographic: 8 months

Table 1. Continued

Study	No.	Intervention	Comparator	Population	Mean Age, y	Male, %	Prior PCI, %	Follow-up
NOYA 1 (2012) ³⁵	300	BP-SES (NOYA)	SES (FIREBIRDS 2)	Maximum 2 de novo lesions (length ≤ 30 mm) in native arteries; RVD 2.25–4.0 mm	BP-SES: 56.6 $\pm$ 10.2, SES: 56.7 $\pm$ 9.2	BP-SES: 66.7, SES: 72.0	BP-SES: 8.0, SES: 9.3	Clinical: 2 years, angiographic: 9 months
OCTDESI (2010) ³⁶	60	BP-PES (JACTAX High Dose; JACTAX Low Dose)	PES (Taxus Liberté)	A de novo lesion (length ≤ 25 mm) in a native artery; $\geq 70\%$ stenosis; RVD 2.75–3.5 mm	BP-PES (high dose): 64.1 $\pm$ 8.7, BP-PES (low dose): 66.0 $\pm$ 6.6, PES: 63.1 $\pm$ 8.2	BP-PES (high dose): 75.0, BP-PES (low dose): 90.5, PES: 78.9	BP-PES (high dose): 40.0, BP-PES (low dose): 9.5, PES: 42.1	Clinical: 1 year, angiographic: 6 months
PILOT (2013) ³⁷	20	BP-SES (ITRIX)	EES (Xience)	Angina and/or ischemia; presence of a de novo lesion with $\geq 50\%$ stenosis	BP-SES: 59.4 $\pm$ 13.2, EES: 65.8 $\pm$ 9.8	BP-SES: 90.9, EES: 88.9	BP-SES: 36.4, EES: 22.2	Clinical: 4 months
Seppatham et al (2011) ³⁸	200	BP-BES (BioMatrix)	EES (Xience V)	Stable angina or ACS; at least 1 de novo lesion with $\geq 50\%$ stenosis; RVD 2.25–3.5 mm	BP-BES: 60.6 $\pm$ 9.1, EES: 62.4 $\pm$ 10.2	BP-BES: 66, EES: 64	?	Clinical: 1 year
SORT OUT V (2013) ³⁹	2468	BP-BES (Nobori)	SES (Cypher Select)	All-comer; chronic stable CAD or ACS; at least 1 lesion with $\geq 50\%$ stenosis; no restrictions on number or length of lesions	BP-BES: 65.0 $\pm$ 10.6, SES: 65.2 $\pm$ 10.3	BP-BES: 74.6, SES: 75.1	BP-BES: 17.3, SES: 16.5	Clinical: 12 months
TARGET I (2013) ⁴⁰	460	BP-SES (FIREHAWK)	EES (Xience V)	Single de novo lesions (length ≤ 24 mm); $\geq 70\%$ stenosis; RVD 2.5–4.0 mm	BP-SES: 58.7 $\pm$ 9.4, EES: 59.6 $\pm$ 9.4	BP-SES: 69.2, EES: 68.4	BP-SES: 4.8, EES: 5.6	Clinical: 12 months, angiographic: 9 months
Zhang et al (2013) ⁴¹	662	BP-SES (EXCEL)	SES (Partner)	Stable or unstable angina; acute MI	BP-SES: 67.5 $\pm$ 9.8, SES: 65.9 $\pm$ 11.1	BP-SES: 69.2, EES: 68.5	BP-SES: 8.8, EES: 11.84	Clinical: 2 years

Table 1. Continued

Study (Year)	Clinical Presentation				Lesion Characteristics			
	Stable Angina, %	Unstable Angina, %	STEMI, %	NSTEMI, %	ACC/AHA Lesion Class, %	Lesion Length, mm	RVD, mm	Moderate/Severe Calcification, %
COMPARE II (2013) ¹⁰	BP-BES: 38.9, EES: 38.9	BP-BES: 10.8, EES: 9.7	BP-BES: 20.7, EES: 21.6	BP-BES: 26.4, EES: 26.5	B2 — BP-BES: 33.3, EES: 32.4	BP-BES: 16.8 ± 9.8, EES: 17.7 ± 10.6	BP-BES: 2.9 ± 0.5, EES: 2.9 ± 0.5	BP-BES: 31.8, EES: 28.1
COSTAR II (2008) ^{11,12}	?	BP-PES: 29.4, PES: 32.1	?	?	B2/C — BP-PES: 58.9, PES: 61.5	BP-PES: 15.4 ± 6.5, PES: 15.1 ± 6.5	BP-PES: 2.77 ± 0.47, PES: 2.75 ± 0.48	BP-PES: 25.8, PES: 25.3
EVOLUTION (2012) ¹³	BP-SES: 24.05, SES: 24.18	BP-SES: 66.51, SES: 67.46	?	?	B — BP-SES: 43.47, SES: 46.54	?	?	?
EVOLVE (2013) ^{14,15}	?	BP-EES (full dose): 22.6, BP-EES (half dose): 30.6, EES: 21.1	?	?	B2/C — BP-EES (full dose): 56.0, BP-EES (half dose): 69.7, EES: 62.2	BP-EES (full dose): 13.41 ± 6.29, BP-EES (half dose): 13.55 ± 5.76, EES: 14.62 ± 5.81	BP-EES (full dose): 2.60 ± 0.45, BP-EES (half dose): 2.65 ± 0.40, EES: 2.53 ± 0.41	?
ISAR-TEST 3 (2009) ^{16,17}	?	BP-SES: 31.7, SES: 29.2	?	?	?	BP-SES: 13.9 ± 7.2, SES: 14.6 ± 7.0	BP-SES: 2.74 ± 0.52, SES: 2.75 ± 0.51	?
ISAR-TEST 4 (2011) ^{18–21}	BP-SES: 58.4, EES/SES: 60.2	BP-SES: 28.8, EES/SES: 29.1	?	?	?	BP-SES: 14.8 ± 8.6, EES/SES: 15.0 ± 8.8	BP-SES: 2.79 ± 0.47, EES/SES: 2.80 ± 0.52	?
LEADERS (2013) ^{22–27}	BP-BES: 45.2, SES: 44.4	BP-BES: 22.2, SES: 21.2	BP-BES: 15.8, SES: 16.5	BP-BES: 16.9, SES: 18.0	?	?	BP-BES: 2.60 ± 0.61, SES: 2.60 ± 0.57	Severe BP-BES: 13.1, SES: 14.2
Li et al (2010) ²⁸	?	?	?	?	?	?	BP-SES: 3.03 ± 0.44, SES: 3.05 ± 0.45	?
NEVO RES-I (2013) ^{29,30}	?	?	?	?	B2 — BP-SES: 32, PES: 39	BP-SES: 13.8 ± 6.6, PES: 13.7 ± 6.1	BP-SES: 2.64 ± 0.41, PES: 2.68 ± 0.43	BP-SES: 22, PES: 29
NEXT (2013) ³¹	Stable CAD, BP-BES: 83, EES: 84	BP-BES: 12, EES: 11	?	?	?	BP-BES: 19.5 ± 12.8, EES: 19.3 ± 13.1	BP-BES: 2.62 ± 0.6, EES: 2.61 ± 0.57	BP-BES: 22, EES: 20
Nobori 1 Phase 1 (2007) ³²	?	BP-BES: 15, PES: 29	?	?	B2/C — BP-BES: 56, PES: 69	BP-BES: 11.35 ± 4.51, PES: 11.03 ± 4.75	BP-BES: 2.70 ± 0.44, PES: 2.71 ± 0.52	?
Nobori 1 Phase 2 (2009) ³³	?	BP-BES: 29.4, PES: 25.6	?	?	A/B1 — BP-BES: 50.6, PES: 55.1	BP-BES: 10.56, PES: 10.84	BP-BES: 2.72, PES: 2.73	?

Table 1. Continued

Study (Year)	Clinical Presentation			Lesion Characteristics		
	Stable Angina, %	Unstable Angina, %	STEMI, %	NSTEMI, %	ACC/AHA Lesion Class, %	Moderate/Severe Calcification, %
Nobori Japan (2012) ³⁴	?	BP-BES: 16.5, SES: 11.4	?	?	B2/C – BP-BES: 69.7, SES: 62.0	BP-BES: 2.68 ± 0.57, SES: 2.68 ± 0.54
NOYA 1 (2012) ³⁵	?	BP-SES: 39.2, SES: 51.1	?	?	B2/C – BP-SES: 47.0, SES: 41.7	BP-SES: 2.82 ± 0.52, SES: 2.82 ± 0.60
OCTDESI (2010) ³⁶	?	BP-PES (high dose): 30.0, BP-PES (low dose): 23.8, PES: 21.1	?	?	?	BP-PES (high dose): 2.71 ± 0.32, BP-PES (low dose): 2.88 ± 0.31, PES: 2.76 ± 0.38
PILOT (2013) ³⁷	BP-SES: 81.8, EES: 87.5	BP-SES: 18.2, EES: 12.5	—	—	B2/C – BP-SES: 27.3, EES: 44.4	BP-SES: 2.86 ± 0.27, EES: 2.99 ± 0.59
Seppaham et al (2011) ³⁸	BP-BES: 24, EES: 34	BP-BES: 28, EES: 29	BP-BES: 42, EES: 28	BP-BES: 6, EES: 9	?	BP-BES: 2.97 ± 0.22, EES: 2.96 ± 0.29
SORT OUT V (2013) ³⁹	BP-BES: 49.5, SES: 48.1	Unstable angina or NSTEMI, BP-BES: 30.3, SES: 31.0; STEMI, BP-BES: 18.3, SES: 18.3			C – BP-BES: 38.6, SES: 37.0	BP-BES: 3.2 (3.0–3.5), SES: 3.3 (3.0–3.6)
TARGET I (2013) ⁴⁰	BP-SES: 24.2, EES: 24.2	BP-SES: 71.4, EES: 71.9	—	—	?	BP-SES: 2.87 ± 0.47, EES: 2.90 ± 0.50
Zhang et al (2013) ⁴¹	BP-SES: 24.93, SES: 12.15	BP-SES: 51.32, SES: 71.65	BP-SES: 17.01, SES: 24.30	BP-SES: 1.17, SES: 4.98	B2/C – BP-SES: 69.51, SES: 66.34	BP-SES: 3.26 ± 2.40, SES: 3.13 ± 0.45

Abbreviations: ACC, American College of Cardiology; ACS, acute coronary syndromes; AHA, American Heart Association; BES, biolimus-eluting stent; BP, biodegradable polymer; CAD, coronary artery disease; EES, everolimus-eluting stent; MI, myocardial infarction; NSTEMI, non-ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; PES, paclitaxel-eluting stent; RVD, reference vessel diameter; SES, sirolimus-eluting stent; STEMI, ST-segment elevation myocardial infarction; ?, not stated.

Figure 1. Forest plot of (A) all-cause and (B) cardiovascular mortality. Abbreviations: CI, confidence interval; M-H, Mantel-Haenszel.

of the analyses demonstrated a skewed distribution pattern, suggesting a lack of publication bias among our included studies.

Angiographic Outcomes: A total of 13 studies measured late lumen loss at angiographic follow-up. Compared to durable polymer DES, biodegradable polymer DES led to a significant reduction of in-stent (MD: -0.05 , 95% CI: -0.09 to -0.02 ; $P = 0.004$) and in-segment (MD: -0.04 , 95% CI: -0.06 to -0.01 ; $P = 0.004$) late lumen loss. Substantial statistical heterogeneity was observed in the analysis of in-stent late lumen loss ($I^2 = 75\%$; $P < 0.00001$)

(see Supporting Figure S3 in the online version of this article).

Analysis of minimal lumen diameter included data from 11 studies. Biodegradable polymer DES significantly increased in-stent (MD: 0.08 , 95% CI: 0.03 to 0.14 ; $P = 0.002$) and in-segment (MD: 0.06 , 95% CI: 0.02 to 0.10 ; $P = 0.001$) minimal lumen diameter when compared to durable polymer DES, with moderate statistical heterogeneity observed in the analysis of in-segment minimal lumen diameter ($I^2 = 64\%$; $P = 0.002$) (see Supporting Figure S4 in the online version of this article).

Figure 2. Forest plot of myocardial infarction. Abbreviations: CI, confidence interval; M-H, Mantel-Haenszel.

The same 11 RCTs reported findings on diameter stenosis. Compared to durable polymer DES, treatment of biodegradable polymer DES was associated with significant reduction in diameter stenosis (in-stent, MD: -2.27 , 95% CI: -4.02 to -0.52 ; $P = 0.01$; in-segment, MD: -1.97 , 95% CI: -3.14 to -0.81 ; $P = 0.0009$), with moderate to substantial statistical heterogeneity in both the in-stent ($I^2 = 81\%$; $P < 0.00001$) and in-segment ($I^2 = 53\%$; $P = 0.02$) analyses (see Supporting Figure S5 in the online version of this article).

In-stent binary restenosis was reported in 12 studies. There was no significant difference between the biodegradable polymer DES and durable polymer DES groups (OR: 0.68, 95% CI: 0.25 to 1.83; $P = 0.44$). Analysis of in-segment binary restenosis included data from 13 studies and also demonstrated a lack of significant difference between groups (OR: 0.83, 95% CI: 0.50 to 1.39; $P = 0.49$) (see Supporting Figure S6 in the online version of this article).

Subgroup Analyses

Subgroup analyses were pursued to explore if the clinical and angiographic effects as demonstrated in the overall analyses would be affected by the different sources of clinical heterogeneity of our included studies (see Supporting Table S3 in the online version of this article). For clinical outcomes, findings obtained from the subgroup analyses of biodegradable BES, PES, and SES were similar to those of the overall analyses. For angiographic outcomes, we found that the significant benefits demonstrated in the overall analyses on late lumen loss, minimal lumen diameter, and diameter stenosis were mirrored by only the biodegradable polymer BES (in-stent late lumen loss, MD: -0.07 , 95% CI: -0.14 to 0.00 , $P = 0.05$, $I^2 = 79\%$; in-segment late lumen loss, MD: -0.06 , 95% CI: -0.09 to -0.02 , $P = 0.0004$, I^2 nonsignificant; in-stent minimal lumen diameter, MD: 0.11,

95% CI: 0.06 to 0.17, $P < 0.0001$, I^2 nonsignificant; in-segment minimal lumen diameter, MD: 0.10, 95% CI: 0.06 to 0.15, $P < 0.00001$, I^2 nonsignificant; in-stent diameter stenosis, MD: -2.73 , 95% CI: -4.90 to -0.57 , $P = 0.01$, $I^2 = 71\%$; in-segment diameter stenosis, MD: -2.41 , 95% CI: -3.69 to -1.13 , $P = 0.0002$, I^2 nonsignificant). Results of the analyses of biodegradable polymer PES and SES were similar to those of the overall analyses. Clinical and angiographic analyses of biodegradable polymer EES were inconclusive, because there was only 1 included study (EVOLVE [A Prospective Randomized Multicenter Single-Blind Non-inferiority Trial to Assess the Safety and Performance of the Evolution Everolimus-Eluting Monorail Coronary Stent System [Evolution Stent System] for the Treatment of a De Novo Atherosclerotic Lesion]). Similarly, the different clinical follow-up durations among the included studies did not have a substantial effect on the clinical end points.

Discussion

Our meta-analysis of 20 randomized studies shows that biodegradable polymer DES have no apparent clinical advantages compared to durable polymer DES. They were found to lead to significant improvement in late loss, minimal lumen diameter, and diameter restenosis, with moderate to substantial statistical heterogeneity across studies. Subgroup analysis revealed that a biodegradable polymer BES was the only device type that sustained the beneficial effects on the aforementioned angiographic outcomes as demonstrated in the overall analyses, and the efficacy and safety profiles of the biodegradable polymer DES were found to be independent of dose or follow-up duration.

A common feature of meta-analysis is the existence of clinical heterogeneity and its implications for research. The design of biodegradable polymer DES varies greatly with

Figure 3. Forest plot of (A) target lesion revascularization and (B) target vessel revascularization. Abbreviations: CI, confidence interval; M-H, Mantel-Haenszel.

different modifications of the 3 components: type of metal scaffold, type and properties of polymer coating (eg, polymer degradation time), and type and dosage of antiproliferative drug. Individual and combinatory properties of these components are critical in determining the success of the stent device, and yet contribute to a high degree of clinical heterogeneity among studies investigating these devices. In regard to the stent platform, stainless steel remains the commonly used metal alloy (see Supporting Table S1 in the online version of this article). However, cobalt chromium or platinum chromium platforms are increasingly used due to their improved radial strength and greater radiopacity, which allow for the engineering of thinner stent struts with a reduced risk of angiographic and clinical restenosis.^{2,42} For biodegradable polymer coatings,

polylactic acid, poly(lactic-co-glycolic acid) and poly(D,L-lactide) polymers are common biodegradable polymers with therapeutic uses.⁴ Polymer degradation time varies between different biodegradable polymer DES, and the breakdown process could be affected by biological environmental factors as well as physical factors such as the thickness of the polymer coating used in the DES devices. In addition, although all stent polymers ultimately break down to carbon dioxide and water, early polymer degradation steps create an acidic environment, and the potential complications in response to the breakdown process remain to be fully investigated for each type of DES system. In addition, numerous antiproliferative drugs are available, ranging from the first-generation paclitaxel and sirolimus to the newer Biolimus A9 (Biosensors Interventional Technologies Pte

(A)

(B)

Figure 4. Forest plot of (A) overall and (B) definite/probable stent thrombosis. Abbreviations: CI, confidence interval; M-H, Mantel-Haenszel.

Ltd, Singapore), everolimus, and zotarolimus. Their optimal dosage and the corresponding local adverse effects should be clearly defined to allow for effective device selection. We conducted subgroup analyses by the type of drug eluted and found that biodegradable polymer BES was the only group that confirmed the significant angiographic improvement as observed in the overall analyses. Future meta-analyses with further randomized data could consider refining the approach of subgroup analysis by exploring the effects of biodegradable polymer DES of similar design in the context of design components (metallic platform, polymer coating, antiproliferative drug) and the influence of other sources

of heterogeneity, such as strut thickness, properties of polymer coating, and dosage of antiproliferative drug. It is also worth highlighting that the biodegradable polymer DES used in our included studies were assessed in different study populations. Although the majority of participants had de novo lesions of similar length and size, their clinical presentation at time of enrollment varied from stable angina to acute coronary syndromes of unstable angina, ST-segment elevation myocardial infarction, and non-ST-segment elevation myocardial infarction (Table 1). It is certainly of high clinical relevance and interest to further investigate the applicability of these biodegradable

devices as compared to the widely used second-generation DES in patients with different clinical conditions (stable vs unstable angina) and different lesion characteristics such as lesions with severe calcifications, short (length <20 mm) or small (reference vessel diameter <2.25 mm). Further randomized evidence exploring the efficacy and safety of biodegradable polymer DES as compared to the first- as well as second-generation DES is required before we are able to come to the most robust conclusions on which subsets of patients would benefit most from these newer devices. Findings from ongoing studies including STACCATO (Stent sTrut Apposition and Coverage in Coronary ArTeries: an Optical Coherence Tomography (OCT) Study) (BioMatrix [Biosensors Interventional Technologies Pte Ltd, Singapore] vs Xience V [Abbott Vascular, Abbott Laboratories, Abbott Park, Illinois, USA]) and ISAR-TEST 6 (Intracoronary Stenting and Angiographic Results: Test Efficacy of Biodegradable and Permanent Limus-Eluting Stents-6) (Nobori [Terumo Corporation, Tokyo, Japan] vs Xience V) are of substantial value and their publication is eagerly anticipated. PCI represents a huge market in interventional cardiology, and the economic impact of using newer devices should be acknowledged.⁴³ Subsequent efforts in investigating the cost-effectiveness of biodegradable polymer DES are also warranted.

The concept of replacing the permanent polymer coating with a coating that degrades over time, leaving what is essentially a BMS, could be the answer to resolving the frustrating safety issues of the traditional DES with durable polymer. Whether this new technology will lead to improved long-term efficacy and safety outcomes requires statistically robust data from adequately powered trials conducted over a sufficient period of time. The main clinical outcome of interest is whether biodegradable polymer DES are associated with reduced incidence of stent thrombosis. The standardized definitions of stent trials issued by the ARC are in place to assure consistency of trial reporting and facilitate evaluation of efficacy and safety of coronary stents in clinical studies.⁷ Furthermore, amid concerns that late stent thrombosis may be associated with increased death and MI,^{44,45} it would be relevant to explore if biodegradable polymer DES are effective in reducing the incidence of late and very late stent thrombosis. However, although we were able to analyze overall stent thrombosis, not all of the included studies provided information stratified by certainty (definitive, probable, or possible) or timing (late or very late stent thrombosis). We thus urge trial investigators to uniformly report stent thrombosis according to the ARC definitions in future studies. Moreover, causes of stent thrombosis are multifactorial, and careful assessment of outcome measures is warranted to establish the precise mechanisms of biodegradable polymer DES-associated stent thrombosis.⁴⁶ However, over half of our included studies followed their participants to 1 year only. We propose that future randomized studies should be designed with a longer follow-up period to establish long-term clinical effects of biodegradable polymer DES; angiographic follow-up should be coordinated according to the device-specific polymer degradation timeline to monitor the occurrence of any local complications and other potential adverse events arising throughout the entire polymer breakdown process.

Our meta-analysis is limited by the fundamental clinical heterogeneity in terms of baseline characteristics such as type of device tested, follow-up duration, and sample size. Although funnel plots indicated a lack of publication bias, and our systematic literature search was designed to identify abstracts as well as full-text trial reports, we acknowledge the fact that studies of null or negative findings are often unpublished, and their impact might be hindered by published studies, which are relatively more positive in nature. Therefore, a meta-analysis based on published trial-level data should be regarded as exploratory and does not fully represent the real-world practice. We also acknowledge the observed moderate to substantial statistical heterogeneity in the overall analyses of the secondary angiographic outcomes. Although subgroup analyses by type of biodegradable polymer DES reduced the level of statistical heterogeneity, results of the angiographic analyses should be interpreted with caution. Care should also be exercised when interpreting results of biodegradable polymer DES and PES due to the small number of included studies. Nevertheless, by using a comprehensive search strategy, our meta-analysis is the largest and most up-to-date meta-analysis published thus far, with a total of 20 RCTs and data from 20 021 participants, and our results extend to a wide range of biodegradable polymer DES as well as durable polymer DES.

Conclusion

Biodegradable polymer DES demonstrated comparable clinical efficacy and safety as compared to the durable polymer DES. The varied structural designs, biodegradability, and biocompatibility of the polymer coating, and pharmacological properties of the antiproliferative agents, make exploring clinical differences among the available biodegradable polymer DES difficult. The sheer variety of devices poses a double-edged sword by providing clinicians with a wide array of choices but increase the challenge in decision-making during the device-selection process. Comparative studies involving biodegradable polymer DES of similar design could be useful in obtaining accurate effect estimates. Furthermore, coronary stent trials should be designed with uniformly defined end points and sufficient follow-up duration to assure statistical robustness and clinical relevance.

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