JACC: CARDIOVASCULAR INTERVENTIONS VOL. 14, NO. 22, 2021

Differential Effects of Newer-Generation Ultrathin-Strut Versus Thicker-Strut Drug-Eluting Stents in Chronic and Acute Coronary Syndromes

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ABSTRACT

OBJECTIVES The authors sought to compare the differential effects of ultrathin-strut and thicker-strut drug-eluting stents (DES) in patients with chronic (CCS) versus acute (ACS) coronary syndromes.

BACKGROUND Newest-generation ultrathin-strut DES reduce target lesion failure (TLF) compared with thicker-strut second-generation DES in patients undergoing percutaneous coronary intervention.

METHODS PubMed, Embase, and Cochrane Central Register of Controlled Trials were searched for randomized controlled trials comparing newer-generation ultrathin-strut (<70 μm) versus thicker-strut (≥70 μm) DES. Patients were divided based on baseline clinical presentation (CCS versus ACS). The primary endpoint was TLF, a composite of cardiac death, target vessel myocardial infarction, or clinically indicated target lesion revascularization (TLR).

RESULTS A total of 22,766 patients from 16 randomized controlled trials were included, of which 9 trials reported TLF rates in ACS patients. At a mean follow-up of 12.2 months, the risk of TLF was lower among patients treated with ultrathin-strut compared with thicker-strut DES (risk ratio [RR]: 0.85; 95% CI: 0.75-0.95; $P = 0.006$). The difference was driven by a lower risk of clinically-indicated TLR (RR: 0.75; 95% CI: 0.63-0.89; $P < 0.001$) among patients treated with ultrathin-strut DES. The treatment effect was consistent between patients presenting with CCS and ACS (relative RR: 0.97; 95% CI: 0.73-1.31; P for interaction = 0.854). In patients with ST-segment elevation myocardial infarction, TLF risk was lower among those treated with ultrathin- compared with thicker-strut DES (RR: 0.74; 95% CI: 0.54-0.99; $P = 0.049$).

CONCLUSIONS Ultrathin-strut DES reduce the risk of TLF compared with thicker-strut second-generation DES in patients undergoing percutaneous coronary intervention, a difference caused by a lower risk of ischemia-driven TLR. The treatment effect was consistent among patients with CCS and ACS. (J Am Coll Cardiol Intv 2021;14:2461–2473) © 2021 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Newer-generation drug-eluting stents (DES) are the current standard of care for patients with chronic (CCS) or acute (ACS) coronary syndromes undergoing percutaneous coronary intervention (PCI) (1). The excellent safety and efficacy profiles of second-generation DES compared with bare-metal stents (2) and early-generation thick-strut DES (3) have, however, largely plateaued

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John Hirshfeld, Jr, MD, served as Guest Editor for this paper.
The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received April 30, 2021; revised manuscript received September 1, 2021, accepted September 3, 2021.

ISSN 1936-8798 https://doi.org/10.1016/j.jcin.2021.09.028

JACC: CARDIOVASCULAR INTERVENTIONS VOL. 14, NO. 22, 2021
NOVEMBER 22, 2021:2461–2473

ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndrome

BP-SES = biodegradable polymer sirolimus-eluting stent(s)

CCS = chronic coronary syndrome

DES = drug-eluting stent(s)

MI = myocardial infarction

PCI = percutaneous coronary intervention

RCT = randomized controlled trial

RR = risk ratio

STEMI = ST-segment elevation myocardial infarction

TLF = target lesion failure

TLR = target lesion revascularization

over recent years, disclosing the need for additional technical refinements in DES designs to further improve clinical outcomes.

Newest-generation DES incorporate ultrathin-strut stent platforms and biodegradable polymers with the potential to mitigate chronic inflammation and arterial injury, accelerate endothelialization, and reduce neointimal proliferation and thrombogenicity compared with second-generation thicker-strut DES. These features may confer particular clinical benefits in the highly prothrombotic and proinflammatory setting of ACS (4), which is associated with delayed vascular healing (5) and results in an increased risk for recurrent stent-related adverse events (6). In a large-scale meta-analysis, newest-generation ultrathin-strut DES were shown to improve 1-year stent-related outcomes compared with contemporary second-generation thicker-strut DES (7), but the analysis did not differentiate clinical outcomes between patients treated for CCS or ACS. Recent evidence indicates that ultrathin-strut biodegradable polymer sirolimus-eluting stents (BP-SES) reduce target lesion failure (TLF) at 1-year follow-up among ACS patients with (8) and without (9) ST-segment elevation myocardial infarction (STEMI) compared with thicker-strut newer-generation DES. We therefore performed a study-level meta-analysis of randomized clinical trials to investigate the potential differential clinical effects of newest-generation ultrathin-strut DES versus thicker-strut second-generation DES in patients with CCS or ACS undergoing percutaneous coronary revascularization.

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METHODS

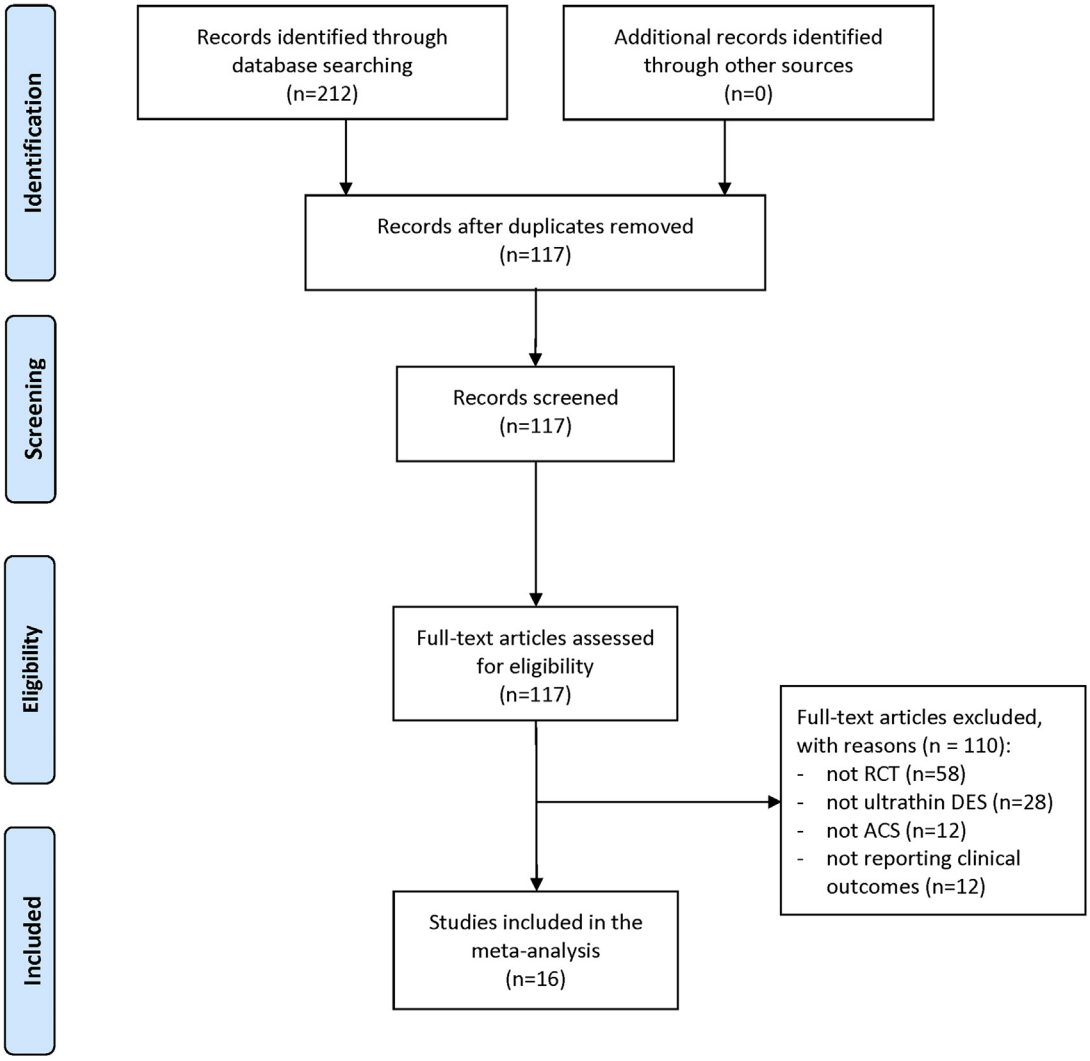
This systematic review and meta-analysis of randomized controlled trials (RCTs) was conducted in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) (10) recommendations. The protocol was registered with PROSPERO (CRD42021226073).

DATA SOURCES AND SEARCH STRATEGY. We conducted a systematic literature search of PubMed, Embase, and the Cochrane Central Register of Controlled Trials databases as of September 30, 2020. We focused on peer-reviewed publications of RCTs. Details of the MeSH (Medical Subject Headings) terms used for literature search are provided in Supplemental Table 1. The reference lists of studies, review articles, meta-analyses, and editorials identified were screened for additional eligible studies. There were no language or sample size restrictions.

STUDY SELECTION. We included RCTs that compared newest-generation ultrathin-strut DES with thicker-strut second-generation DES for percutaneous coronary revascularization and reported clinical outcomes. Ultrathin-strut was defined as a strut thickness <70 μm based on a previous study (7). The stent strut thickness cutoffs used to categorize stents in the present analysis were considered as proxies for the totality of recent innovations seen in the most modern metallic DES designs, which include iterations in stent platform geometry, polymer composition, thickness, or distribution, and antiproliferative drug composition or elution kinetics. For the purpose of this meta-analysis, only results at the landmark time point of 1 year were used to ensure a uniform follow-up. Individual reports of the same trial providing outcome data at different follow-up periods were excluded. Observational and unpublished studies were also excluded due to the inherent risk of bias. Three authors (S.D., M.C., and Q.C.) independently performed the literature search, reviewed the identified titles and abstracts, and selected studies for inclusion based on the predefined criteria. Disagreements were resolved by consensus and arbitration by a fourth author (J.F.I.).

DATA EXTRACTION AND RISK OF BIAS ASSESSMENT. Data extraction was individually performed by 3 independent investigators (S.D., M.C., and Q.C.) and verified by a fourth investigator (J.F.I.). The following information was extracted for each individual study: publication and study characteristics (including authors, publication year, journal, study design, recruitment period, follow-up duration, number of patients randomized, and number of patients analyzed for each outcome), patient and lesion characteristics (including age, sex, comorbidities, baseline clinical presentation, relevant angiographic and procedural data), intervention and comparator characteristics (including ultrathin- and thicker-strut DES type), and outcome data (including reported outcome definitions). Three investigators (S.D., M.C., and Q.C) reviewed the studies and assessed the risk of bias for each individual study using the Cochrane Collaboration criteria (11), which includes the following items: allocation sequence generation, allocation concealment, participant, personnel and outcome assessors blinding, completeness of outcome data, and selective outcome reporting. Blinding was considered complete when outcome

FIGURE 1 Study Selection (PRISMA Flow Diagram)



ACS = acute coronary syndrome; DES = drug-eluting stent(s); PRISMA = Preferred Reporting Items for Systematic reviews and Meta-Analyses; RCT = randomized controlled trial.

assessors were blinded. We did not consider patient or performing physician blinding pertinent because of the procedural nature of the interventions. Studies with high or unclear risk for bias were considered at high risk of bias, whereas the remaining studies were considered at low risk for bias.

STUDY ENDPOINTS. The primary endpoint was TLF, a composite of cardiac death, target vessel myocardial infarction (MI), or clinically indicated target lesion revascularization (TLR). Secondary endpoints included individual components of the primary endpoint, and any (definite, probable, or possible) or definite/probable stent thrombosis according to the Academic Research Consortium definition (12). The same definitions as applied by individual trials included were used (Supplemental Table 2). MI was defined as both procedural and/or spontaneous MI (Supplemental Table 2).

STATISTICAL ANALYSIS. We used fixed-effects models with inverse variance weighting (13) to estimate relative risk ratios (RR) and their 95% CIs for individual trials and combined values considering the low-to-moderate level of heterogeneity between studies. In addition, we calculated random-effects estimates for completeness (13). Results were displayed by using forest plots illustrating the relative

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TABLE 1 Baseline Clinical and Procedural Characteristics of Included Trials

Trials (Ref. #)	Year	N	Follow-Up, mo	Ultrathin-Strut DES	Thicker-Strut DES	Mean Age, y	Men, %	Diabetes Mellitus, %	Prior MI, %	ACS, %	Stent Diameter, mm	RVD, mm
BIOSCIENCE (15)	2014	2,119	12	Orsiro	Xience	66.0	77.2	23.0	20.2	53.4	3.0 ± 0.5	NR
BIOFLOW II (16)	2015	452	12	Orsiro	Xience	63.8	76.4	28.4	25.2	0	NR	2.8 ± 0.5
SORT OUT VII (17)	2016	2,525	12	Orsiro	Nobori	65.5	75.2	18.7	17.6	52.7	NR	3.2 ± 0.6
BIO-RESORT (18)	2016	2,342	12	Orsiro	Resolute Integrity	63.9	72.7	18.0	19.5	69.7	NR	2.8 ± 0.6
BIOFLOW V (19)	2017	1,334	12	Orsiro	Xience	64.6	74.0	35.5	26.5	50.5	NR	2.6 ± 0.6
ORIENT (20)	2017	372	12	Orsiro	Resolute Integrity	65.0	71.3	26.1	NR	45.8	3.0 ± 0.5	NR
PRISON IV (21)	2017	330	12	Orsiro	Xience	62.6	78.5	19.7	30.3	17.3	3.2 ± 0.4	3.0 ± 0.7
DESSOLVE III (22)	2018	1,398	12	MiStent	Xience	66.4	72.0	27.0	27.5	59.0	3.0 ± 0.4	NR
meriT-V (23)	2018	256	9	BioMime	Xience	64.5	63.5	22.5	18.4	31.3	3.1 ± 0.4	2.9 ± 0.4
BIONYX (24)	2018	2,488	12	Orsiro	Resolute Onyx	64.0	76.1	20.5	16.1	70.9	NR	2.8 ± 0.6
TALENT (25)	2019	1,435	12	Supraflex	Xience	65.5	76.2	23.4	18.4	58.1	3.0 ± 0.5	NR
BIOSTEMI (8)	2019	1,300	12	Orsiro	Xience	62.7	76.0	12.0	4.0	100	NR	NR
BIOFLOW IV (26)	2019	575	12	Orsiro	Xience	64.6	74.8	30.8	31.1	0	3.0 ± 0.4	2.8 ± 0.5
BIOFLOW VI (27)	2020	440	12	Orsiro	Xience	58.8	68.6	27.9	10.9	78.4	3.2 ± 0.5	NR
SORT OUT IX (28)	2020	3,151	12	Orsiro	BioFreedom	66.3	77.4	19.3	15.0	53.0	NR	3.5 ± 0.6
BIODEGRADE (29)	2020	2,327	18	Orsiro	BioMatrix	63.5	71.9	33.4	5.0	67.4	3.0 ± 0.4	2.5 ± 0.7

ACS = acute coronary syndrome; BIODEGRADE = Comparison of Biomatrix and Orsiro Drug Eluting Stent trial; BIOFLOW II = Study of the Orsiro Drug Eluting Stent System; BIOFLOW IV = Prospective, Randomized, Multicenter Study to Assess the Safety and Effectiveness of the Orsiro Sirolimus-eluting Stent; BIOFLOW V = Safety and Effectiveness of the Orsiro Sirolimus Eluting Coronary Stent System in Subjects With Coronary Artery Lesions; BIOFLOW VI = BIOTRONIK Orsiro Pre-Marketing Registration; BIONYX = Bioresorbable Polymer ORSIRO Versus Durable Polymer RESOLUTE ONYX Stents; BIO-RESORT = Comparison of BIOdegradable Polymer and DuRablE Polymer Drug-eluting Stents in an All COmeRs PopulaTion; BIOSCIENCE = Sirolimus-eluting Stents With Biodegradable Polymer Versus an Everolimus-eluting Stents; BIOSTEMI = A Comparison of an Ultrathin Strut Biodegradable Polymer Sirolimus-Eluting Stent With a Durable Polymer Everolimus-Eluting Stent for Patients With Acute ST-Segment Elevation Myocardial Infarction Undergoing Primary Percutaneous Coronary Intervention; DES = drug-eluting stent; DESSOLVE III = Study Comparing the MiStent SES Versus the XIENCE EES Stent; meriT-V = BioMime Vs. Xience Randomised Control Clinical Study; MI = myocardial infarction; NR = not reported; ORIENT = Comparison of the Angiographic Result of the Orsiro Hybrid Stent With Resolute Integrity Stent; PRISON IV = Hybrid Sirolimus-eluting Versus Everolimus-eluting Stents for Total Coronary Occlusions; RVD = reference vessel diameter; SORT OUT IX = BIOFREEDOM Stent Versus ORSIRO Stent; SORT OUT VII = Sirolimus Eluting ORSIRO Stent Versus Biolimus-eluting NOBORI Stent; TALENT = Thin Strut Sirolimus-eluting Stent in All Comers Population vs Everolimus-eluting Stent.

contribution to the summary estimate of individual trials. Heterogeneity between studies was assessed using Higgins and Thompson's I^2 statistic with values ≤25%, between 25% and 75%, and ≥75% considered low, moderate, and high heterogeneity, respectively (14). We performed subgroup analyses according to baseline clinical presentation (CCS versus ACS), DES type (ultrathin-strut versus thicker-strut DES), and type of ultrathin-strut DES used with respect to the primary endpoint of TLF. Sensitivity analyses by leave-one-out were conducted for each individual outcome, thus allowing direct comparisons between ultrathin-strut (<70 μm) and thin-strut (81-91 μm) DES by excluding RCTs with thick-strut (120 μm) second-generation DES comparators. Publication bias was assessed by visual inspection of funnel plots. Statistical analysis was conducted by using R software (R-4.0.2, R Foundation for Statistical Computing).

RESULTS

A total of 22,766 patients from 16 randomized clinical trials who underwent percutaneous coronary revascularization with newest-generation ultrathin-strut DES (n = 11,875) or thicker-strut second-generation DES (n = 10,891) qualified for inclusion (8,15-29) (**Figure 1, Table 1**). The risk of bias assessment for the included trials is detailed in Supplemental Table 3. The mean follow-up was 12.2 ± 1.7 months. TLF rates were available for 18,356 patients, including 10,455 patients (57%) with ACS (ultrathin-strut DES, n = 5,359; thicker-strut DES, n = 5,096) and n = 7,901 (43%) with CCS (ultrathin-strut DES, n = 4,198; thicker-strut DES, n = 3,703). The baseline clinical characteristics of patients enrolled in individual trials are reported in **Table 1**. The dual antiplatelet therapy regimen, recommended duration, and adherence at follow-up are detailed in Supplemental Table 4. Newest-generation ultrathin-strut DES included were Orsiro (Biotronik) (13 trials, n = 10,284), MiStent (Micell Technologies) (1 trial, n = 703), BioMime (Meril Life Sciences) (1 trial, n = 168), and Supraflex (Sahajanand Medical Technologies) (1 trial, n = 720) biodegradable polymer sirolimus-eluting stents. Thicker-strut second-generation DES comparators included Xience (Abbott Vascular) everolimus-eluting stents (10 trials, n = 4,357); Resolute Integrity (2 trials, n = 1,295) and Resolute Onyx (1 trial, n = 1,243) zotarolimus-eluting stents (Medtronic); Nobori (Terumo) (1 trial,

n = 1,264) and BioMatrix (Biosensors) (1 trial, n = 1,160) biolimus-eluting stents; and BioFreedom (1 trial, n = 1,572) biolimus-coated stents (Biosensors). The main characteristics of newer-generation ultrathin-strut and thicker-strut DES evaluated are outlined in **Table 2**. Strut thickness ranged from 60 to 65 μm in the ultrathin-strut DES group, and from 81 to 120 μm in the thicker-strut DES comparator group.

The risk of TLF was lower among patients treated with ultrathin-strut DES as compared with those treated with thicker-strut second-generation DES (RR: 0.85; 95% CI: 0.75-0.95; $P = 0.006$) (**Figure 2**). This reduction represented a difference in risk of −0.8 percentage points (95% CI: −1.3 to −0.2) or a number needed to treat of 130 to prevent 1 TLF event with newest-generation ultrathin-strut DES over a mean 12 months of follow-up (Supplemental Figure 1). There was no heterogeneity ($I^2 = 0\%$), and no publication bias was detected on the funnel plot. No differences in RR were found between trials using Orsiro BP-SES and the other trials ($P = 0.64$) (Supplemental Figure 2). Sensitivity analyses demonstrated consistent results with respect to the risk of TLF after exclusion of trials including thick-strut second-generation DES comparators (17,28,29) (Supplemental Table 5). Differences in TLF were driven by a lower risk of clinically indicated TLR among patients treated with newest-generation ultrathin-strut DES compared with thicker-strut second-generation DES (RR: 0.75; 95% CI: 0.63-0.89; $P < 0.001$) (**Figure 2**). There was moderate heterogeneity ($I^2 = 40\%$), and no publication bias was observed on the funnel plot. No difference in RR was detected between trials using Orsiro BP-SES and the other trials ($P = 0.57$) (Supplemental Figure 3). After exclusion of the SORT OUT IX (28) trial, the pooled RR for clinically indicated TLR was closer to 1 (RR: 0.84; 95% CI: 0.69-1.01; $P = 0.062$) among patients treated with ultrathin-strut DES as compared with those treated with thicker-strut DES (Supplemental Table 6). The risk of cardiac death (RR: 1.10; 95% CI: 0.87-1.39; $P = 0.420$), target vessel MI (RR: 0.86; 95% CI: 0.72-1.04; $P = 0.114$), any stent thrombosis (RR: 1.01; 95% CI: 0.79-1.29; $P = 0.948$), and definite or probable stent thrombosis (RR: 0.95; 95% CI: 0.72-1.24; $P = 0.679$) did not differ between patients treated with ultrathin-strut DES or thicker-strut second-generation DES (**Figure 2**). There were no or low heterogeneities ($I^2 = 0\%$, 0%, 6%, and 0%, respectively), and no publication biases were observed on the funnel plot. No differences in RR were found between trials evaluating the Orsiro BP-SES and remaining studies ($P = 0.25$; 0.79, 0.87, and 0.92, respectively) (Supplemental Figures 4 to 7). After excluding SORT OUT VII (17), SORT OUT IX (28), and BIODEGRADE (29) trials, sensitivity analyses for each individual endpoint were consistent with the main analysis (Supplemental Tables 7 to 10). In addition, there were no differences with regard to the risk of any (RR: 0.91; 95% CI: 0.77-1.07; $P = 0.238$), periprocedural (RR: 0.82; 95% CI: 0.61-1.09; $P = 0.168$) and spontaneous (RR: 0.92; 95% CI: 0.66-1.29; $P = 0.638$) MI between patients treated with ultrathin-strut DES or thicker-strut second-generation DES (Supplemental Figure 8).

Clinical outcomes with regard to TLF in the subgroups of patients with CCS and ACS were reported in 11 (n = 7,901) and 9 (n = 10,455) trials, respectively. The risk of TLF was lower among patients with ACS treated with newest-generation ultrathin-strut DES as compared with those treated with thicker-strut second-generation DES (RR: 0.85; 95% CI: 0.71-1.01; $P = 0.064$) (**Central Illustration**). Among patients with CCS, there was no statistically significant difference in the risk of TLF between patients treated with ultrathin-strut DES or thicker-strut second-generation DES (RR: 0.87; 95% CI: 0.72-1.05; $P = 0.145$) (**Central Illustration**). Overall, there was no interaction between treatment effect (ultrathin-strut DES versus thicker-strut DES) and clinical presentation (CCS vs ACS) with regard to the risk of TLF (relative RR: 0.97; 95% CI: 0.73-1.31; $P = 0.854$) (Supplemental Figure 9). There were no or low heterogenicities ($I^2 = 0\%$ and 16%, respectively), and no publication biases were observed on the funnel plot in both CCS and ACS patient subgroups. No differences in RR were found between trials evaluating the Orsiro BP-SES and other studies ($P = 0.83$ in both CCS and ACS subgroups) (Supplemental Figures 10 and 11). Sensitivity analyses demonstrated consistent results with respect to the risk of TLF among patients with CCS and ACS after exclusion of trials including a 120-μm thick-strut DES comparator (17,28,29) (Supplemental Tables 11 and 12).

Among patients with STEMI, TLF rates were reported in 7 trials (n = 3,671). The TLF risk was lower among patients with STEMI treated with newest-generation ultrathin-strut DES compared with those treated with thicker-strut second-generation DES (RR: 0.74; 95% CI: 0.54-0.99; $P = 0.049$) (Supplemental Figure 12). There was no heterogeneity ($I^2 = 0\%$), and no publication bias was observed on the funnel plot. No differences in RR were found between trials using Orsiro BP-SES and other trials ($P = 0.88$) (Supplemental Figure 13). Sensitivity

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TABLE 2 Characteristics of Stents Used in Included Trials

	ORSIRO	SUPRAFLEX	MiStent	BioMime	XIENCE
Platform material	Cobalt chromium	Cobalt chromium	Cobalt chromium	Cobalt chromium	Cobalt chromium
Strut thickness	60 μm	60 μm	64 μm	65 μm	81 μm
	Ultrathin-strut	Ultrathin-strut	Ultrathin-strut	Ultrathin-strut	Thin-strut
Passive coating	Silicon carbide	-	-	-	-
Polymer coating	PLLA	PLLA, PDLLA, PLGA, PVP	PLGA	PLLA and PLGA	PBMA, PVDF-HFP
	Biodegradable	Biodegradable	Biodegradable	Biodegradable	Durable
Polymer degradation time	12-24 mo	9-12 mo	3 mo	6-9 mo	-
Polymer thickness	Abluminal 7.5 μm Luminal 3.5 μm	4-5 μm	Abluminal 15 μm Luminal 5 μm	Abluminal 2 μm Luminal 2 μm	7.6 μm
Antiproliferative drug	Sirolimus	Sirolimus	Sirolimus	Sirolimus	Everolimus

PBMA = poly-n-butyl methacrylate; PDLLA = Poly-d,l-lactic acid; PHMA = polyhexyl methacrylate; PLA = polylactic acid; PLGA = polylactide-coglycolic acid; PLLA = poly-L-lactic acid; PVA = polyvinyl acetate; PVDF-HFP = polyvinylidene fluoride-*co-hexafluoropropylene*; PVP = polyvinylpyrrolidone.

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analyses showed consistent results with regard to the risk of TLF after excluding the SORT OUT VII (17), SORT OUT IX (28), and BIODEGRADE (29) trials (Supplemental Table 13).

DISCUSSION

In the present systematic review and meta-analysis of 16 randomized clinical trials including 22,766 patients, newest-generation ultrathin-strut DES were associated with a lower risk of TLF compared with thicker-strut second-generation DES, a difference driven by a lower risk of clinically indicated TLR among patients treated with ultrathin-strut DES as compared with those treated with contemporary thicker-strut DES. The treatment effect was consistent among patients with CCS or ACS. To the best of our knowledge, the present is the first analysis suggesting differential clinical outcomes between ultrathin-strut DES and thicker-strut second-generation DES in patients with ACS versus CCS.

The outstanding clinical performance of second-generation polymer-based DES compared with bare-metal stents and early-generation DES have largely plateaued over the past decade, hence resulting in persistent long-term device-related adverse outcomes (30). Newer-generation DES combining ultrathin-strut stent platforms with biodegradable polymer coatings represent the most recent technological refinement in metallic DES design. Biodegradable polymers have potential to mitigate chronic inflammatory responses (31) and hypersensitivity reactions (32) induced by permanent polymer coatings, but biodegradable polymer DES have, however, consistently failed to provide superior clinical outcomes compared with their second-generation polymer-based counterparts (33). Thinner struts improve stent conformability and deliverability, decrease flow disturbance and endothelial shear stress (4,34), and reduce thrombogenicity (4) compared with thicker-strut stent platforms, all of which have the potential to limit stent-related vascular injury and inflammation, and facilitate early arterial healing. The present meta-analysis demonstrates that these properties may translate into differential clinical outcomes with a 16% lower risk of TLF among all-comer patients treated with newest-generation ultrathin-strut DES as compared with those treated with contemporary thicker-strut second-generation DES. This risk reduction translates into a number of 130 patients to treat with ultrathin-strut DES compared with thicker-strut second-generation DES to prevent 1 TLF event over a mean 12-month follow-up. The reduction in TLF was primarily caused by a 25% lower risk of clinically indicated TLR with newest-generation ultrathin-strut DES compared with thicker-strut second-generation DES. Notably, no differences were found between ultrathin-strut DES and thicker-strut second-generation DES with regard to the risk of cardiac death, target vessel MI, or stent thrombosis, confirming the excellent safety profile of the latest newer-generation DES designs. Although reductions in TLF and ischemia-driven TLR with ultrathin-strut DES were mainly driven by studies evaluating the Orsiro BP-SES, the clinical differences were consistent irrespective of the type of ultrathin-strut DES used and after excluding trials with a 120-μm thick-strut DES comparator. Our findings are consistent

TABLE 2 Continued

RESOLUTE ONYX	RESOLUTE INTEGRITY	NOBORI	BIOMATRIX	BIOFREEDOM
Cobalt chromium, platinum iridium core	Cobalt chromium	Stainless steel	Stainless steel	Stainless steel
81 μm	91 μm	120 μm	120 μm	120 μm
Thin-strut	Thin-strut	Thick-strut	Thick-strut	Thick-strut
-	-	-	-	-
PBMA, PHMA, PVP, PVA	PBMA, PHMA, PVP, PVA	PLLA	PLA	-
Durable	Durable	Biodegradable	Biodegradable	Polymer-Free
-	-	6-9 mo	6-9 mo	-
5-6 μm	6 μm	Abluminal 10 μm	Abluminal	-
Zotarolimus	Zotarolimus	Biolimus A9	Biolimus A9	Biolimus A9

with a previous meta-analysis of 10 randomized clinical trials including 11,658 patients (7) indicating a reduction in TLF among patients treated with ultrathin-strut DES compared with thicker-strut second-generation DES. Unlike our results, the difference in TLF was mainly driven by a lower risk of target vessel MI with ultrathin-strut DES compared with thicker-strut second-generation DES, whereas no differences were found with respect to ischemia-driven TLR (7). Several reasons may account for this difference. First, the larger number of studies and patients included in the present meta-analysis increases statistical power to detect, or refute, differences with regard to individual components of TLF with low event rates. Second, the inclusion of recent large-scale all-comer randomized clinical trials with a high proportion of ACS patients combined with differing MI definitions used in individual studies may challenge the early determination of target vessel myocardial re-infarction among ACS patients with positive baseline cardiac biomarkers (35). Our findings indicating lower TLR rates with the use of ultrathin-strut DES are, however, consistent with a recent analysis from a large, real-world, nationwide registry, which demonstrated lower rates of TLR with newest-generation ultrathin-strut BP-SES compared with contemporary newer-generation DES at 2 years of follow-up (36).

In comparison with CCS, ACS confers an increased long-term risk for stent-related adverse events (6) due to an enhanced prothrombotic and inflammatory response after DES implantation (4), which results in delayed arterial healing at the culprit site (5). Recent studies suggest that the effects of ultrathin-strut SES designs with respect to device-oriented clinical outcomes may be potentiated in ACS patients compared with second-generation thicker-strut DES (8,9). In the present analysis, we found that newest-generation ultrathin-strut DES reduce the risk of TLF compared with thicker-strut second-generation drug-eluting stent irrespective of the patient baseline clinical presentation. There was, however, a signal suggesting a 15% lower risk of TLF in ACS patients treated with ultrathin-strut DES as compared with those treated with thicker-strut newer-generation DES. In addition, we found a 26% reduction in TLF risk among patients with STEMI who underwent primary PCI with ultrathin-strut DES compared with thicker-strut second-generation DES. These findings are consistent with the results of 2 recent studies including patients with ACS. In the BIOFLOW V (Safety and Effectiveness of the Orsiro Sirolimus Eluting Coronary Stent System in Subjects With Coronary Artery Lesions) randomized trial, 1-year TLF rates were lower among ACS patients treated with newest-generation ultrathin-strut DES compared with thin-strut second-generation DES, but the study excluded highest-risk patients with STEMI (9). In the first head-to-head randomized comparison of 2 newer-generation DES in patients undergoing primary PCI for STEMI, ultrathin-strut DES were recently found superior to thin-strut second-generation DES with regard to TLF at 1 year of follow-up, a difference caused by a lower risk of ischemia-driven TLR in patients treated with ultrathin-strut DES. Although the treatment effect was consistent irrespective of the type of ultrathin-strut DES used in the present analysis, the reduction in TLF risk among ACS patients treated with ultrathin-strut DES was mainly observed in trials investigating the Orsiro BP-SES. Ultrathin-strut DES evaluated in the present meta-analysis share similar metallic stent platform strut thickness and the use of biodegradable

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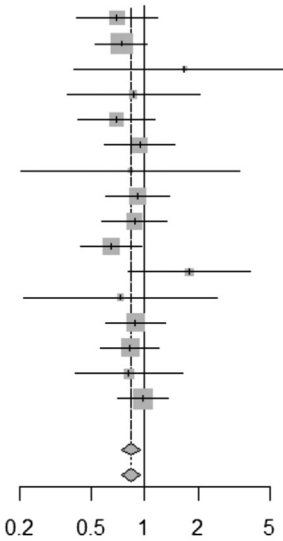
FIGURE 2 Clinical Outcomes With Newer-Generation Ultrathin-Strut Versus Thicker-Strut DES

A

Study	ultrathin-strut Events	ultrathin-strut Total	thin-strut Events	thin-strut Total	RR	95%-CI	Weight (fixed)	Weight (random)
BIODEGRADE, 2020	24	1167	34	1160	0.702	[0.419; 1.176]	6.1%	5.3%
SORT OUT IX, 2020	59	1579	79	1572	0.744	[0.535; 1.034]	14.1%	13.0%
BIOFLOW VI, 2020	5	220	3	220	1.667	[0.403; 6.889]	0.5%	0.7%
BIOFLOW IV, 2019	14	385	8	190	0.864	[0.369; 2.023]	1.9%	2.0%
BIOSTEMI, 2019	25	649	36	651	0.697	[0.423; 1.147]	6.4%	5.7%
TALENT, 2019	35	720	37	715	0.939	[0.599; 1.474]	6.6%	7.0%
meriT-V, 2018	5	168	3	84	0.833	[0.204; 3.404]	0.7%	0.7%
BIONYX, 2018	44	1245	48	1243	0.915	[0.613; 1.367]	8.5%	8.8%
DESSOLVE III, 2018	40	703	45	695	0.879	[0.582; 1.328]	8.0%	8.3%
BIOFLOW V, 2017	52	833	41	427	0.650	[0.439; 0.963]	9.6%	9.2%
PRISON IV, 2017	16	165	9	165	1.778	[0.809; 3.908]	1.6%	2.3%
ORIENT, 2017	6	250	4	122	0.732	[0.210; 2.546]	1.0%	0.9%
BIORESORT, 2016	47	1169	53	1173	0.890	[0.606; 1.307]	9.4%	9.6%
SORT OUT VII, 2016	48	1261	58	1264	0.830	[0.570; 1.206]	10.3%	10.1%
BIOFLOW II, 2015	19	298	12	154	0.818	[0.408; 1.641]	2.8%	2.9%
BIOSCIENCE, 2014	69	1063	70	1056	0.979	[0.710; 1.350]	12.5%	13.7%
Fixed effect model		**11875**		**10891**	**0.846**	**[0.751; 0.952]**	**100.0%**	**--**
Random effects model					**0.844**	**[0.750; 0.951]**	**--**	**100.0%**

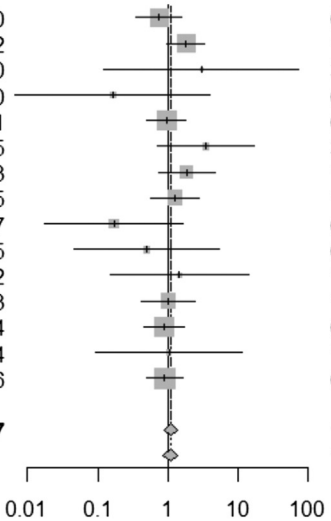
Heterogeneity: $I^2 = 0\%$, $p = 0.88$
Test for overall effect (fixed effect): $z = -2.77$ ($p = 0.006$)



B

Study	ultrathin-strut Events	ultrathin-strut Total	thin-strut Events	thin-strut Total	RR	95%-CI	Weight (fixed)	Weight (random)
BIODEGRADE, 2020	12	1167	16	1160	0.746	[0.354; 1.569]	12.1%	10.3%
SORT OUT IX, 2020	29	1579	16	1572	1.804	[0.984; 3.309]	12.1%	15.5%
BIOFLOW VI, 2020	1	220	0	220	3.000	[0.123; 73.242]	0.4%	0.6%
BIOFLOW IV, 2019	0	385	1	190	0.165	[0.007; 4.024]	1.5%	0.6%
BIOSTEMI, 2019	18	649	19	651	0.950	[0.503; 1.794]	14.3%	14.1%
TALENT, 2019	7	720	2	715	3.476	[0.725; 16.674]	1.5%	2.3%
BIONYX, 2018	13	1245	7	1243	1.854	[0.742; 4.632]	5.3%	6.8%
DESSOLVE III, 2018	14	703	11	695	1.258	[0.575; 2.752]	8.4%	9.3%
BIOFLOW V, 2017	1	833	3	427	0.171	[0.018; 1.638]	3.0%	1.1%
PRISON IV, 2017	1	165	2	165	0.500	[0.046; 5.461]	1.5%	1.0%
ORIENT, 2017	3	250	1	122	1.464	[0.154; 13.929]	1.0%	1.1%
BIORESORT, 2016	10	1169	10	1173	1.003	[0.419; 2.402]	7.5%	7.5%
SORT OUT VII, 2016	16	1261	18	1264	0.891	[0.456; 1.739]	13.6%	12.8%
BIOFLOW II, 2015	2	298	1	154	1.034	[0.094; 11.309]	1.0%	1.0%
BIOSCIENCE, 2014	20	1063	22	1056	0.903	[0.496; 1.645]	16.7%	15.9%
Fixed effect model		**11707**		**10807**	**1.101**	**[0.872; 1.390]**	**100.0%**	**--**
Random effects model					**1.094**	**[0.862; 1.390]**	**--**	**100.0%**

Heterogeneity: $I^2 = 0\%$, $p = 0.53$
Test for overall effect (fixed effect): $z = 0.81$ ($p = 0.420$)



(A) Target lesion failure; **(B)** cardiac death; **(C)** target vessel myocardial infarction; **(D)** clinically indicated target lesion revascularization. BIODEGRADE = Comparison of Biomatrix and Orsiro Drug Eluting Stent; BIOFLOW II = Study of the Orsiro Drug Eluting Stent System; BIOFLOW IV = Prospective, Randomized, Multicenter Study to Assess the Safety and Effectiveness of the Orsiro Sirolimus-eluting Stent; BIOFLOW V = Safety and Effectiveness of the Orsiro Sirolimus Eluting Coronary Stent System in Subjects With Coronary Artery Lesions; BIOFLOW VI = BIOTRONIK Orsiro Pre-Marketing Registration; BIONYX = Bioresorbable Polymer ORSIRO Versus Durable Polymer RESOLUTE ONYX Stents; BIO-RESORT = Comparison of BIOdegradable Polymer and DuRablE Polymer Drug-eluting Stents in an All COmeRs PopulaTion; BIOSCIENCE = Sirolimus-eluting Stents With Biodegradable Polymer Versus an Everolimus-eluting Stents; BIOSTEMI = A Comparison of an Ultrathin Strut Biodegradable Polymer Sirolimus-Eluting Stent With a Durable Polymer Everolimus-Eluting Stent for Patients With Acute ST-Segment Elevation Myocardial Infarction Undergoing Primary Percutaneous Coronary Intervention; DES = drug-eluting stents; DESSOLVE III = Study Comparing the MiStent SES Versus the XIENCE EES Stent; meriT-V = BioMime Vs. Xience Randomised Control Clinical Study; ORIENT = Comparison of the Angiographic Result of the Orsiro Hybrid Stent With Resolute Integrity Stent; PRISON IV = Hybrid Sirolimus-eluting Versus Everolimus-eluting Stents for Total Coronary Occlusions; RR = risk ratio; SORT OUT IX = BIOFREEDOM Stent Versus ORSIRO Stent; SORT OUT VII = Sirolimus Eluting ORSIRO Stent Versus Biolimus-eluting NOBORI Stent; TALENT = Thin Strut Sirolimus-eluting Stent in All Comers Population vs Everolimus-eluting Stent.

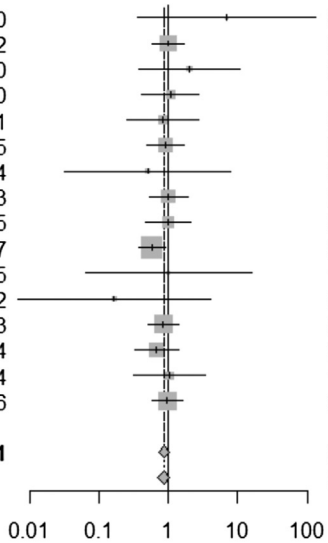
Continued on the next page

FIGURE 2 Continued

C

Study	ultrathin-strut Events	ultrathin-strut Total	thin-strut Events	thin-strut Total	RR	95%-CI	Weight (fixed)	Weight (random)
BIODEGRADE, 2020	3	1167	0	1160	6.958	[0.360; 134.555]	0.2%	0.4%
SORT OUT IX, 2020	26	1579	26	1572	0.996	[0.581; 1.707]	11.3%	12.1%
BIOFLOW VI, 2020	4	220	2	220	2.000	[0.370; 10.807]	0.9%	1.2%
BIOFLOW IV, 2019	13	385	6	190	1.069	[0.413; 2.769]	3.5%	3.9%
BIOSTEMI, 2019	5	649	6	651	0.836	[0.256; 2.725]	2.6%	2.5%
TALENT, 2019	18	720	20	715	0.894	[0.477; 1.675]	8.7%	8.9%
meriT-V, 2018	1	168	1	84	0.500	[0.032; 7.895]	0.6%	0.5%
BIONYX, 2018	18	1245	18	1243	0.998	[0.522; 1.910]	7.8%	8.4%
DESSOLVE III, 2018	13	703	13	695	0.989	[0.462; 2.117]	5.7%	6.1%
BIOFLOW V, 2017	39	833	35	427	0.571	[0.367; 0.888]	20.1%	18.1%
PRISON IV, 2017	1	165	1	165	1.000	[0.063; 15.854]	0.4%	0.5%
ORIENT, 2017	0	250	1	122	0.163	[0.007; 3.972]	0.9%	0.3%
BIORESORT, 2016	26	1169	31	1173	0.842	[0.503; 1.408]	13.5%	13.3%
SORT OUT VII, 2016	12	1261	18	1264	0.668	[0.323; 1.381]	7.8%	6.7%
BIOFLOW II, 2015	8	298	4	154	1.034	[0.316; 3.378]	2.3%	2.5%
BIOSCIENCE, 2014	30	1063	31	1056	0.961	[0.586; 1.577]	13.5%	14.4%
Fixed effect model		**11875**		**10891**	**0.861**	**[0.715; 1.037]**	**100.0%**	**--**
Random effects model					**0.850**	**[0.704; 1.025]**	**--**	**100.0%**

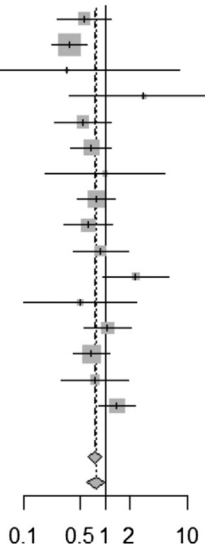
Heterogeneity: I^2 = 0%, p = 0.88
Test for overall effect (fixed effect): z = -1.58 (p = 0.114)



D

Study	ultrathin-strut Events	ultrathin-strut Total	thin-strut Events	thin-strut Total	RR	95%-CI	Weight (fixed)	Weight (random)
BIODEGRADE, 2020	10	1167	18	1160	0.552	[0.256; 1.191]	6.3%	6.5%
SORT OUT IX, 2020	20	1579	55	1572	0.362	[0.218; 0.601]	19.2%	10.1%
BIOFLOW VI, 2020	0	220	1	220	0.333	[0.014; 8.138]	0.5%	0.6%
BIOFLOW IV, 2019	6	385	1	190	2.961	[0.359; 24.420]	0.5%	1.3%
BIOSTEMI, 2019	9	649	17	651	0.531	[0.238; 1.183]	5.9%	6.2%
TALENT, 2019	19	720	28	715	0.674	[0.380; 1.195]	9.8%	9.1%
meriT-V, 2018	4	168	2	84	1.000	[0.187; 5.350]	0.9%	1.9%
BIONYX, 2018	24	1245	31	1243	0.773	[0.456; 1.309]	10.8%	9.8%
DESSOLVE III, 2018	13	703	21	695	0.612	[0.309; 1.212]	7.3%	7.5%
BIOFLOW V, 2017	17	833	10	427	0.871	[0.403; 1.886]	4.6%	6.5%
PRISON IV, 2017	14	165	6	165	2.333	[0.919; 5.924]	2.1%	5.0%
ORIENT, 2017	3	250	3	122	0.488	[0.100; 2.383]	1.4%	2.1%
BIORESORT, 2016	18	1169	17	1173	1.062	[0.550; 2.051]	5.9%	7.9%
SORT OUT VII, 2016	25	1261	37	1264	0.677	[0.410; 1.118]	12.9%	10.2%
BIOFLOW II, 2015	10	298	7	154	0.738	[0.287; 1.901]	3.2%	4.9%
BIOSCIENCE, 2014	35	1063	25	1056	1.391	[0.838; 2.307]	8.7%	10.2%
Fixed effect model		**11875**		**10891**	**0.745**	**[0.626; 0.887]**	**100.0%**	**--**
Random effects model					**0.763**	**[0.596; 0.978]**	**--**	**100.0%**

Heterogeneity: I^2 = 40%, p = 0.05
Test for overall effect (fixed effect): z = -3.30 (p < 0.001)



polymers, but they differ with respect to other components or properties of DES design, such as stent platform geometry, polymer composition, distribution or degradation time, and eluted antiproliferative drug kinetics, as well as stent conformability and deliverability, all of which have potential to impact on clinical outcomes in patients with ACS. The differences in TLF risk among ACS patients treated with ultrathin-strut DES compared with those treated with thicker-strut second-generation DES were consistent in sensitivity analyses which excluded studies with 120-μm thick-strut biodegradable or polymer-free

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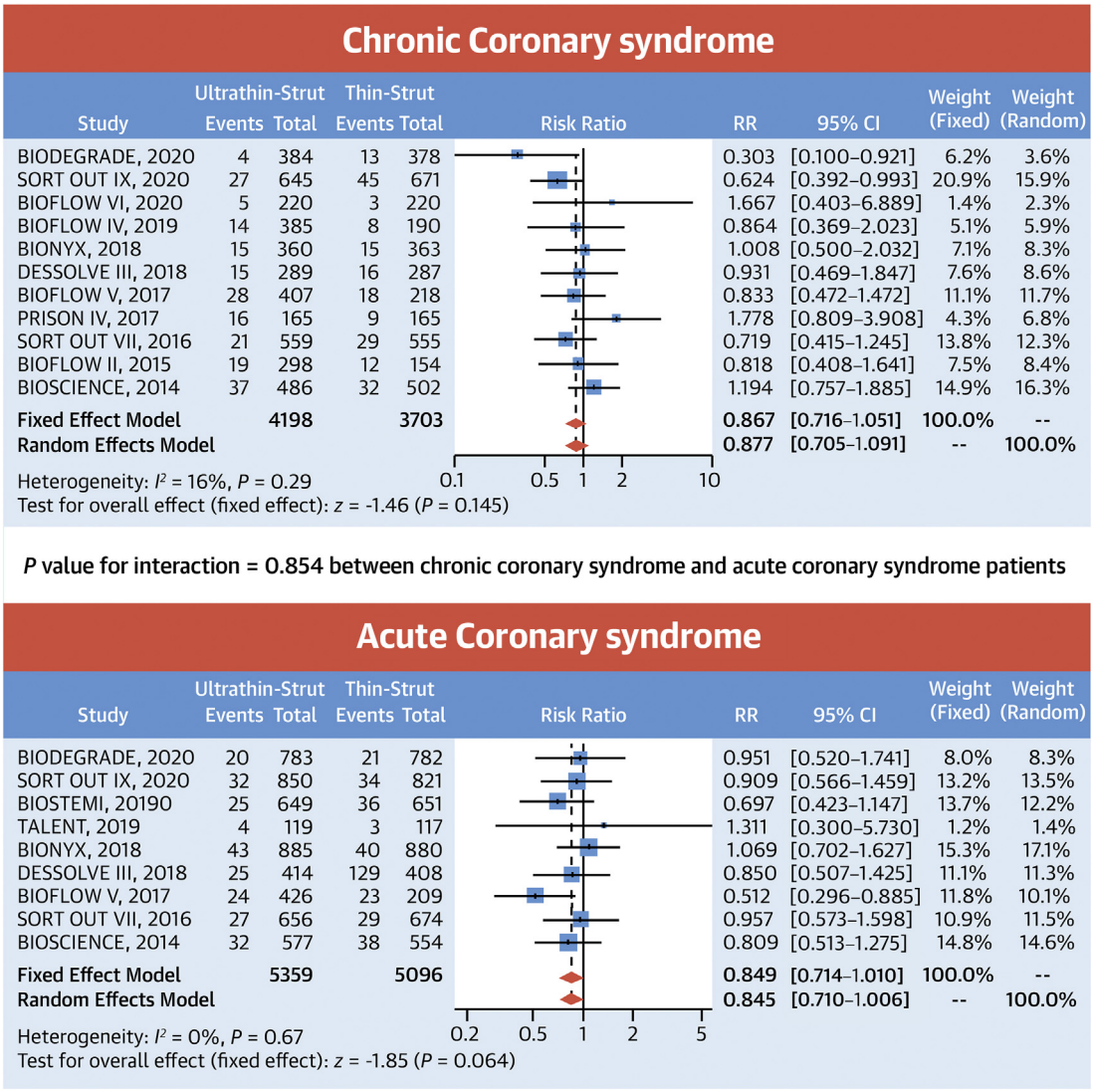
CENTRAL ILLUSTRATION Target Lesion Failure With Ultrathin-Strut Versus Thicker-Strut Drug-Eluting Stents in Patients With Chronic Versus Acute Coronary Syndromes



Iglesias, J.F. et al. J Am Coll Cardiol Intv. 2021;14(22):2461–2473.

Estimates of target lesion failure (TLF) risk among patients with chronic (CCS) versus acute (ACS) coronary syndromes treated with newest-generation ultrathin-strut drug-eluting stents (DES) or thicker-strut second-generation DES. Ultrathin-strut DES reduce the risk of TLF at a mean 12 months of follow-up compared with thicker-strut second-generation DES, and the treatment effect is consistent among patients with CCS or ACS. BIODEGRADE = Comparison of Biomatrix and Orsiro Drug Eluting Stent; BIOFLOW II = Study of the Orsiro Drug Eluting Stent System; BIOFLOW IV = Prospective, Randomized, Multicenter Study to Assess the Safety and Effectiveness of the Orsiro Sirolimus-eluting Stent; BIOFLOW V = Safety and Effectiveness of the Orsiro Sirolimus Eluting Coronary Stent System in Subjects With Coronary Artery Lesions; BIOFLOW VI = BIOTRONIK Orsiro Pre-Marketing Registration; BIONYX = Bioresorbable Polymer ORSIRO Versus Durable Polymer RESOLUTE ONYX Stents; BIO-RESORT = Comparison of BIOdegradable Polymer and DuRablE Polymer Drug-eluting Stents in an All COmeRs PopulaTion; BIOSCIENCE = Sirolimus-eluting Stents With Biodegradable Polymer Versus an Everolimus-eluting Stents; BIOSTEMI = A Comparison of an Ultrathin Strut Biodegradable Polymer Sirolimus-Eluting Stent With a Durable Polymer Everolimus-Eluting Stent for Patients With Acute ST-Segment Elevation Myocardial Infarction Undergoing Primary Percutaneous Coronary Intervention; DESSOLVE III = Study Comparing the MiStent SES Versus the XIENCE EES Stent; meriT-V = BioMime Vs. Xience Randomised Control Clinical Study; ORIENT = Comparison of the Angiographic Result of the Orsiro Hybrid Stent With Resolute Integrity Stent; PRISON IV = Hybrid Sirolimus-eluting Versus Everolimus-eluting Stents for Total Coronary Occlusions; RR = risk ratio; SORT OUT IX = BIOFREEDOM Stent Versus ORSIRO Stent; SORT OUT VII = Sirolimus Eluting ORSIRO Stent Versus Biolimus-eluting NOBORI Stent; TALENT = Thin Strut Sirolimus-eluting Stent in All Comers Population vs Everolimus-eluting Stent.

DES comparators. These findings are in line with previous evidence (7) indicating that even minimal reductions in strut thickness by 20-30 μm may suffice to translate into differential stent-related outcomes between newer-generation DES in routine clinical practice.

STUDY LIMITATIONS. First, as with any meta-analysis, our analysis shares the limitations of the individual studies included. Second, we did not have access to individual patient data from the included trials. A study-level meta-analysis precludes multivariable and subgroup analyses to account for differences in baseline characteristics between DES groups. In addition, the present analysis does not take into consideration the differences in strut thickness according to the Orsiro BP-SES stent diameter; the Orsiro BP-SES features a 60-μm ultrathin-strut stent platform for stent diameters ≤3.0 mm, whereas strut thickness for stent sizes ≥3.5 mm (80 μm) is similar to that of thicker-strut second-generation DES comparators. However, mean reference vessel diameters in the included trials do not exceed 3.5 mm and are ≤3.0 mm with standard deviations between 0.4 and 0.7 mm in most studies (**Table 1**), suggesting that Orsiro BP-SES ≥3.5-mm stent sizes were likely used in a minority of patients included in the present analysis. Third, stent strut thickness cutoffs used to categorize DES in this meta-analysis are only proxies for all recent iterations in modern metallic DES designs, which also include the use of biodegradable polymers and sirolimus-analogue antiproliferative agents with controlled drug release seen in other newer-generation thin-, but not ultrathin-, strut DES. Fourth, due to the open-label design of randomized clinical trials included, operators were unblinded when using newer-generation ultrathin-strut DES, thus potentially introducing a confounder with regard to vessel preparation modalities and intravascular imaging guidance between DES treatment groups. Finally, the follow-up was limited to 1 year, and additional studies with longer-term follow-up are needed to confirm these findings and to determine the long-term clinical benefits of ultrathin-strut DES, particularly among patients with ACS.

CONCLUSIONS

In a meta-analysis of randomized controlled trials, newest-generation ultrathin-strut DES were associated with a lower 1-year risk of TLF compared with thicker-strut second-generation DES, a difference driven by a lower risk of clinically indicated TLR. The treatment effect was consistent among patients with CCS or ACS.

ACKNOWLEDGMENTS The authors thank Antoine Poncet and Christophe Combescure for their statistical support.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

Statistical support was provided by the Clinical Research Center, University of Geneva, and Geneva University Hospitals. Dr Iglesias has received research grants to the institution from Abbott Vascular, AstraZeneca, Biotronik, and Philips Volcano, outside the submitted work; has received speaker fees from AstraZeneca, Biotronik, Medtronic, Novartis, Philips Volcano, and Terumo, outside the submitted work; and has received and consultancy fees from Biotronik, Cardinal Health, Corflow Therapeutics, Medtronic, and Terumo, outside the submitted work. Dr Degrauwe has received institutional research grants from Abbott Vascular; has received institutional research grants, educational grants, and personal fees from Biotronik. Dr Roffi has received institutional research grants from Terumo, Boston Scientific, Medtronic, Abbott Vascular, and Biotronik outside the submitted work. Dr Pilgrim has received institutional research grants from Biotronik, Boston Scientific, and Edwards Lifesciences; has received speaker fees from Biotronik and Boston Scientific; and has received consultancy fees for HighLife SAS outside the submitted work. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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PERSPECTIVES

WHAT IS KNOWN? Newest-generation ultrathin-strut drug-eluting stents improve stent-related outcomes compared with second-generation thicker-strut drug-eluting stents in patients undergoing percutaneous coronary revascularization. Whether the treatment effect is consistent among patients undergoing percutaneous coronary intervention for chronic or acute coronary syndrome remains uncertain.

WHAT IS NEW? In a meta-analysis of 16 randomized controlled trials including 22,766 patients, newest-generation ultrathin-strut drug-eluting stents were found to reduce the risk of target lesion failure compared with thicker-strut second-generation drug-eluting stent at 1-year follow-up, irrespective of the patient baseline clinical presentation.

WHAT IS NEXT? Longer-term follow-up of existing randomized clinical trials are needed to determine whether the superiority of newest-generation ultrathin-strut drug-eluting stents with respect to stent-related endpoints may translate into improved patient-oriented clinical outcomes.

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KEY WORDS acute coronary syndrome, drug-eluting stent(s), percutaneous coronary intervention, ultrathin-strut

APPENDIX For supplemental figures and tables, please see the online version of this paper.