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Sirolimus-eluting stents with ultrathin struts versus everolimus-eluting stents for patients undergoing percutaneous coronary intervention: final three-year results of the TALENT trial

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KEYWORDS

- clinical trials
- drug-eluting stent
- innovation

Abstract

Background: In the TALENT study, the sirolimus-eluting ultrathin strut Supraflex stent was non-inferior to the XIENCE stent for a device-oriented composite endpoint (DoCE: defined as cardiac death, target vessel myocardial infarction [TV-MI], or clinically indicated target lesion revascularisation [CI-TLR]) at 12 months.

Aims: This study investigated the 3-year outcomes of the TALENT trial and long-term impact of ultrathin drug-eluting stents (DES), compared to the XIENCE everolimus-eluting thin stent.

Methods: The TALENT trial is a prospective, multicentre, randomised all-comers trial comparing the Supraflex sirolimus-eluting stent with the XIENCE everolimus-eluting stent, with planned follow-up for 3 years.

Results: The TALENT trial enrolled 1,435 patients (Supraflex n=720, XIENCE n=715) with 3-year follow-up data available in 97.8% in the Supraflex group, and in 98.9% in the XIENCE group. At 3 years, DoCE occurred in 57 patients (8.1%) in the Supraflex group, and in 66 patients (9.4%) in the XIENCE group (p=0.406). There were no significant between-group differences in rates of cardiac death, TV-MI or CI-TLR. The rates of definite or probable stent thrombosis were low and similar between groups (1.1% vs 1.4%; p=0.640). In a meta-analysis of long-term follow-up (3-5 years), ultrathin strut DES tended to reduce DoCE (relative risk 0.89 [0.79-1.01]; p=0.068), compared to thicker strut DES. The risks for cardiac death and definite or probable stent thrombosis were similar between ultrathin strut DES and thicker strut DES.

Conclusions: At 3-year follow-up, the use of the Supraflex stent was at least as safe and efficacious as the XIENCE stent in an all-comers population. ClinicalTrials.gov: NCT02870140

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Abbreviations

CI	confidence interval
CI-TLR	clinically indicated target lesion revascularisation
DES	drug-eluting stent
DoCE	device-oriented composite endpoint
EES	everolimus-eluting stent
ITT	intention-to-treat
MI	myocardial infarction
PP	per protocol
PoCE	patient-oriented composite endpoint
RR	relative risk
SES	sirolimus-eluting stent
TV	target vessel

Introduction

Stents with thinner struts have been shown to reduce acute thrombogenicity and promote faster endothelialisation, compared to stents with thicker struts[1-3]. One hypothesis behind this is that protruding thicker struts disrupt laminar flow, inducing flow disturbances, which can activate a platelet-signalling procoagulation pathway[1,4]. The physiological benefits and improved fluid dynamics with thinner struts may be partly responsible for the reduced rates of restenosis, stent thrombosis, and myocardial infarction (MI) observed with contemporary second-generation drug eluting stents (DES), which all have strut thicknesses of <100 µm, when compared to first-generation DES, which had strut thicknesses of >132 µm. The development of ultrathin strut stents, with strut thicknesses of <70 µm may further improve event-free survival compared to thin strut DES (second-generation DES).

The Supraflex stent (Sahajanand Medical Technologies) is a sirolimus-eluting stent (SES) with a biodegradable polymeric coating and 60 µm ultrathin struts. In the TALENT study, the Supraflex SES was non-inferior to the XIENCE durable polymer everolimus-eluting stent (EES; Abbot Vascular), for a device-oriented composite endpoint (DoCE) of cardiac death, target vessel myocardial infarction (TV-MI), or clinically indicated target lesion revascularisation (CI-TLR) at 12 months[5,6]. The longer-term outcomes with ultrathin DES are currently limited, and therefore we investigated the final 3-year outcomes after implantation of the Supraflex SES as compared to the XIENCE EES in the TALENT all-comers trial.

Methods

STUDY DESIGN AND POPULATION

The design and 2-year results of the TALENT trial have been reported previously[5-7]. In brief, the TALENT trial is a prospective, multicentre, single-blinded, all-comers, randomised controlled trial, allocating patients in a 1:1 ratio to either the Supraflex SES or XIENCE EES. Twenty-three sites in Europe enrolled patients from October 2016 to July 2017. The primary endpoint of the study was a non-inferiority comparison at 12 months of a DoCE, defined as a composite of cardiac death, TV-MI, and CI-TLR. The composite secondary endpoints were a patient-oriented composite endpoint (PoCE) of all-cause death, any MI, and any revascularisation, and target vessel failure (TVF), a composite of cardiac death, TV-MI, and clinically indicated target vessel revascularisation (CI-TVR). Stent thrombosis – a safety indicator – was defined as per the Academic Research Consortium definition[8]. MI was defined according to the Society for Cardiovascular Angiography and Interventions consensus for periprocedural MI (when occurring 48 hrs or less after the index procedure) or according to the Third Universal Definition for MI[9,10]. Clinical data were adjudicated by an independent clinical event committee, blinded to stent allocation.

Patients with stable coronary artery disease received dual antiplatelet therapy (DAPT) for >6 months after percutaneous coronary intervention (PCI), followed by aspirin monotherapy indefinitely. Patients with acute coronary syndrome received DAPT for >12 months after PCI, followed by aspirin monotherapy indefinitely. The protocol prespecified patient follow-up up to 3 years.

All patients provided written informed consent to participate in the study. The study protocol of the TALENT trial was approved by institutional ethics committees of participating institutions and central regulatory bodies for each country, and was conducted according to the Declaration of Helsinki and Good Clinical Practice.

STUDY STENTS

Supraflex is a new-generation metallic stent consisting of an L605 cobalt-chromium alloy platform with ultrathin struts (60 µm) across all stent diameters, flexible S-link connectors, and a biodegradable polymeric matrix coating. Sirolimus, at a concentration of 1.4 µg/mm², together with the polymeric matrix, is coated on the conformal surface of the stent, with an average coating thickness of 4-5 µm. Seventy percent of the sirolimus is eluted in the first 7 days, with the remainder released over the following 48 days. The polymer gradually degrades over 9-12 months. The crossing profile of the Supraflex is 0.99 mm (the crossing profile of the newest XIENCE Alpine EES is 1.10 mm and of the XIENCE Sierra EES is 0.99 mm).

The control stent used in the study was the XIENCE EES, which has a cobalt chromium alloy platform and a strut thickness of 81 µm. It has an 8 µm thick durable polymer coated with everolimus at a dose of 1 µg/mm², which is completed eluted over 120 days.

META-ANALYSIS

Randomised clinical trials comparing ultrathin strut DES (strut thickness <70 µm) and thicker strut DES (strut thickness ≥81 µm) with at least 3-year outcomes were searched on PubMed, EMBASE, and abstracts and presentations from major cardiovascular meetings between January 2010 and October 2021 **(Supplementary Table 1)**. The meta-analytic summary estimates (relative risk [RR] with 95% confidence interval [CI]) for the ultrathin strut DES versus thicker strut DES in terms of DoCE, its individual components, definite or probable stent thrombosis, and

all-cause death at the time of last available follow-up were evaluated using results reported in intention-to-treat (ITT) analyses. All outcomes were calculated using both the fixed-effects model and the random-effects model of DerSimonian and Laird[11]. This was done to compare the fixed- and random-effects estimates of the intervention as recommended by the Cochrane Collaboration, given that we anticipated some heterogeneity ($I^2>0$). If the estimates are similar, then any small-study effects have little impact on the intervention effect estimate. Heterogeneity was assessed using the I^2 statistic, with $I^2<25\%$ considered low, $I^2\geq25\%$ and $\leq75\%$ considered moderate, and $I^2>75\%$ considered high[12,13]. When heterogeneity was moderate or high, the L'Abbé plot was demonstrated. Publication bias was visually inspected using a funnel plot. Risk of bias was assessed according to the Cochrane Collaboration's tool[14].

STATISTICAL ANALYSIS

All patients in the ITT analysis were analysed according to their assigned treatment group, regardless of the actual treatment received. Patients who were randomised to a treatment group and only received that assigned study stent were included in the per protocol (PP) analysis.

Prespecified subgroup analyses were performed for the primary endpoint, DoCE, with respect to diabetes, ST-segment elevation MI (STEMI), small vessels (≤2.75 mm), multivessel treatment, long lesions (>18 mm), in-stent restenosis, bypass graft, left main treatment, bifurcation treatment, or overlapping stents.

The cumulative event rates were estimated using the Kaplan-Meier method and comparisons of outcomes were performed with the log-rank test. Hazard ratios were calculated using the Cox proportional hazards model. P-values are for the superiority and a two-sided p-value <0.05 was considered statistically significant. Analyses were performed using SAS software, version 9.3 (SAS Institute Inc.) and R version 3.6.0 (R Foundation for Statistical Computing).

Results

STUDY POPULATION

The TALENT trial enrolled 1,435 patients with 2,076 lesions; 720 patients with 1,046 lesions were randomly assigned to Supraflex, and 715 patients with 1,030 lesions to XIENCE **(Figure 1)**. Baseline clinical, angiographic, and procedural characteristics were comparable between the two groups, as previously reported[15]. Three-year follow-up data were available for 97.8% (704/720) of patients in the Supraflex group and for 98.9% (707/715) of patients in the XIENCE group **(Figure 1)**.

CLINICAL OUTCOMES AT 3 YEARS (ITT ANALYSIS)

At 3 years DoCE occurred in 57 patients (8.1%) in the Supraflex group, and in 66 patients (9.4%) in the XIENCE group (difference −1.3% [95% CI: −4.3% to 1.6%]; p=0.406) **(Table 1, Figure 2A)**. There were no significant between-group differences in rates of cardiac death, TV-MI, and CI-TLR **(Table 1, Figure 2B-Figure 2D)**.

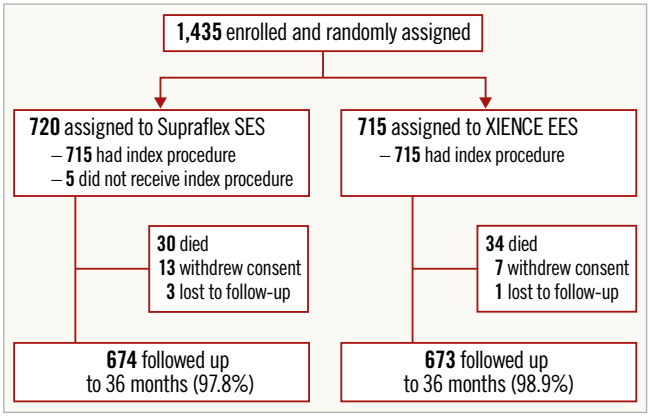


Figure 1. *Study flowchart. EES: everolimus-eluting stent; SES: sirolimus-eluting stent.*

There were also no significant differences in the groups between 1 and 3 years **(Supplementary Figure 1)**. The percentage of patients with DAPT at 6 and 12 months was similar **(Supplementary Table 2)**, and the rates of definite or probable stent thrombosis were low and comparable (Supraflex 1.1% vs XIENCE 1.4%, difference −0.4% [95% CI: −1.5% to 0.7%]; p=0.640) **(Table 1, Figure 2E)**. The rates of other clinical events are presented in **Table 1**. Non-TV revascularisation was significantly lower in the XIENCE group (5.7%), compared to the Supraflex group (8.6%) (difference 2.9% [95% CI: 0.2% to 5.6%]; p=0.035), although these events were not associated with lesions treated with study stents.

PER PROTOCOL (PP) ANALYSIS

In the PP analysis at 3 years DoCE occurred in 43 (6.6%) patients treated with Supraflex and 59 (8.7%) patients treated with XIENCE (difference −2.1% [95% CI: −5.0% to 0.8%], p=0.165) **(Supplementary Table 3, Supplementary Figure 2A)**. The rates of cardiac death, TV-MI and CI-TLR were all numerically lower, but not statistically different with Supraflex compared with XIENCE. Notably the significantly lower rate of CI-TLR observed with Supraflex in the PP analysis at 1-year (1.2% vs 3.1%, difference −1.9% [95% CI: −3.5% to 0.3%], p=0.021)[6] was no longer evident at 3 years (3.6% vs 5.1%, difference −1.5%, [95% CI: −3.7 to 0.7], p=0.192) **(Supplementary Table 3, Supplementary Figure 2B-Supplementary Figure 2D)**. There were no significant differences between stents in rates of non-TV revascularisation (Supraflex 7.8% vs XIENCE 5.8%, difference 2.0% [95% CI: −0.7% to 4.7%], p=0.143).

SUBGROUP ANALYSIS

The treatment effect in DoCE was no different across the prespecified subgroup analyses for diabetes, STEMI, multivessel treatment, long lesions, in-stent restenosis, bypass graft, left main treatment, bifurcation treatment, or overlapping stents, although Supraflex resulted in better outcomes in patients without small vessels treated **(Figure 3)**.

Table 1. Clinical outcomes at 36 months after stent implantation.

Clinical outcomes (ITT)	Supraflex SES (n=720)	XIENCE EES (n=715)	Difference (95% confidence interval)	*p*-value
DoCE	8.1 (57)	9.4 (66)	–1.3 (–4.3-1.6)	0.406
PoCE	18.0 (128)	16.5 (117)	1.5 (–2.5-5.4)	0.424
TVF	9.8 (69)	10.6 (75)	–0.9 (–4.0-2.3)	0.604
Components of composite endpoints				
Death	4.2 (30)	4.8 (34)	–0.6 (–2.7-1.6)	0.619
Cardiac death	1.8 (13)	2.1 (15)	–0.3 (–1.8-1.2)	0.707
MI	5.3 (37)	6.0 (42)	–0.7 (–3.1-1.7)	0.563
Q-wave	0.9 (6)	1.0 (7)	–0.1 (–1.2-0.9)	0.785
Non-Q-wave	4.6 (32)	5.3 (37)	–0.7 (–3.0-1.5)	0.536
TV-MI	3.3 (23)	4.6 (32)	–1.3 (–3.3-0.7)	0.219
Q-wave	0.6 (4)	0.9 (6)	–0.3 (–1.2-0.6)	0.529
Non-Q-wave	2.8 (20)	3.9 (27)	–1.0 (–2.9-0.9)	0.300
Non-TV-MI	2.0 (14)	1.6 (11)	0.4 (–1.0-1.8)	0.545
Q-wave	0.3 (2)	0.1 (1)	0.1 (–0.4-0.6)	0.563
Non-Q-wave	1.7 (12)	1.6 (11)	0.2 (–1.2-1.5)	0.833
All revascularisation	13.3 (93)	11.6 (81)	1.7 (–1.8-5.2)	0.325
TL revascularisation	6.3 (44)	6.3 (44)	–0.0 (–2.5-2.5)	0.993
Clinically indicated	5.0 (35)	5.9 (41)	–0.9 (–3.2-1.5)	0.483
Non-clinically indicated	1.6 (11)	1.4 (10)	0.1 (–1.1-1.4)	0.827
TV revascularisation	8.0 (56)	8.2 (57)	–0.2 (–3.0-2.7)	0.922
Clinically indicated	6.9 (48)	7.6 (53)	–0.7 (–3.4-2.0)	0.603
Non-clinically indicated	1.6 (11)	2.0 (14)	–0.4 (–1.8-1.0)	0.543
Non-TV revascularisation	8.6 (60)	5.7 (40)	2.9 (0.2-5.6)	0.035
Stent thrombosis				
Definite	1.0 (7)	1.3 (9)	–0.3 (–1.4-0.8)	0.620
Definite (very late, >360 days)	0.3 (2)	0.6 (4)	–0.3 (–1.0-0.4)	0.419
Definite or probable	1.1 (8)	1.4 (10)	–0.3 (–1.5-0.9)	0.640
Definite or probable (very late, >360 days)	0.3 (2)	0.6 (4)	–0.3 (–1.0-0.4)	0.419

Data are presented as percentages (numbers). DoCE: device-oriented composite endpoint; ITT: intention-to-treat; MI: myocardial infarction; PoCE: patient-oriented composite endpoint; TL: target lesion; TV: target vessel; TVF: target vessel failure

META-ANALYSIS

Including the TALENT trial, there were 11 randomised trials (15,370 patients) with at least 3-year results comparing outcomes between ultrathin strut DES with thicker strut DES **(Table 2, Supplementary Table 4, Supplementary Figure 3)**. Overall, ultrathin strut DES resulted in an 11% reduction in DoCE compared to thicker strut DES (RR 0.89, 95% CI: 0.79-1.01; p=0.068), although the effect was not statistically significant **(Figure 4)**. Ultrathin strut DES and thicker strut DES had similar risks for definite or probable stent thrombosis and mortality **(Figure 4)**. Moderate heterogeneity was observed for DoCE and death; thus the L'Abbé plots are presented in **Supplementary Figure 4**. The funnel plots and risk of bias are shown in **Supplementary Figure 5** and **Supplementary Table 4**.

In patients with diabetes or small vessels treated, there were no statistically significant differences in DoCE between ultrathin strut DES and the thicker strut DES **(Supplementary Figure 6)**.

Discussion

At 3-year follow-up of the randomised all-comers TALENT trial, there were no significant differences in rates of DoCE, its individual components, or stent thrombosis between patients assigned to the Supraflex or XIENCE groups (**Central illustration**, panel A).

IMPACT OF THE SUPRAFLEX STENT ON REPEAT REVASCULARISATION

At 1-year follow-up in the PP analysis, the Supraflex stent resulted in a significantly lower rate of CI-TLR, compared to XIENCE. At 3-year follow-up, whilst the rate of CI-TLR was still numerically lower with Supraflex, the difference was no longer statistically significant (5.0% vs 5.9%; p=0.483 [ITT analysis]; 3.6% vs 5.1%; p=0.192 [PP analysis]). Longer follow-up and/or a larger sample size are certainly needed to fully examine how this early difference could be more durable.

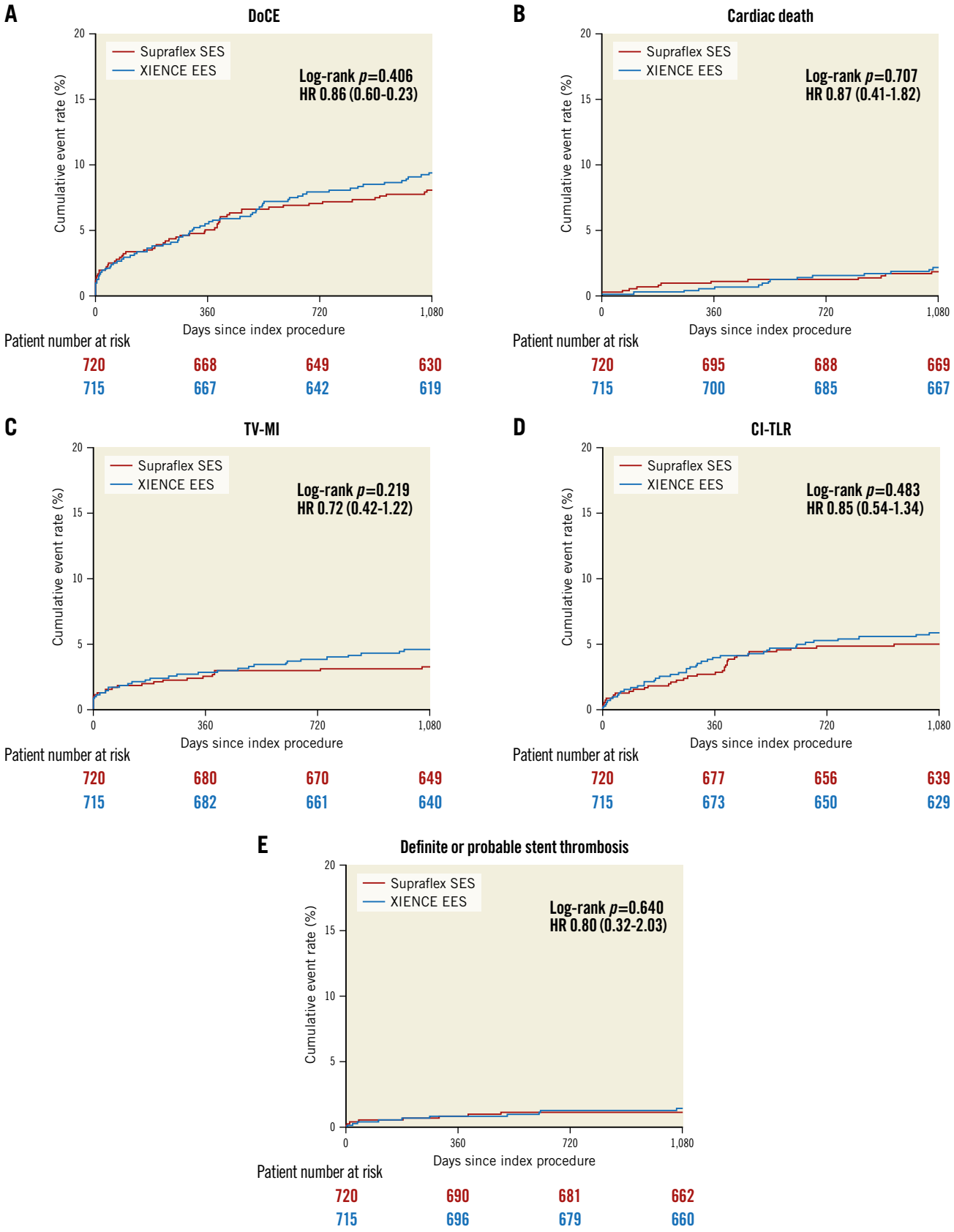


Figure 2. *Kaplan-Meier estimates for the device-oriented composite endpoint (DoCE) and its components at 3 years (intention-to-treat [ITT] basis). A) DoCE, B) cardiac death, C) target vessel myocardial infarction (TV-MI), D) clinically indicated target lesion revascularisation (CI-TLR), and E) definite or probable stent thrombosis. HR: hazard ratio.*

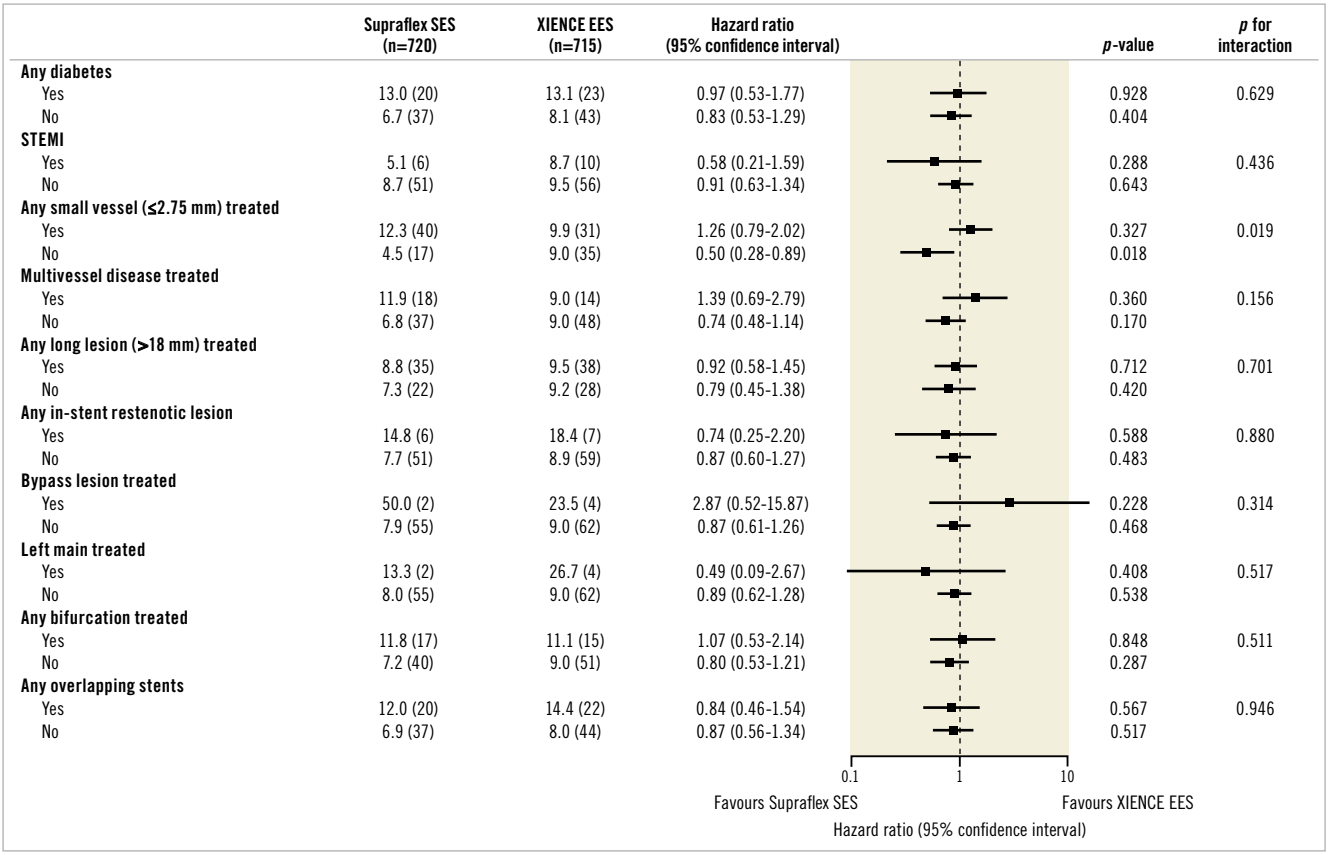


Figure 3. *Subgroup analysis for DoCE (ITT basis). DoCE: device-oriented composite endpoint; ITT: intention-to-treat; STEMI: ST-elevation myocardial infarction*

IMPACT OF ULTRATHIN STRUT POLYMERS

A meta-analysis of 10 randomised trials including 11,658 patients by Bangalore et al demonstrated that at 1-year ultrathin strut DES (Orsiro, MiStent, and BioMime) resulted in a 16% RR reduction in DoCE (RR 0.84, 95% CI: 0.72-0.99), compared to second-generation DES with thicker struts (XIENCE, Resolute, and Nobori)[16]. Recently, another meta-analysis at a mean follow-up of 2.5 years demonstrated that ultrathin strut DES reduced the risk of DoCE (RR 0.85, 95% CI:

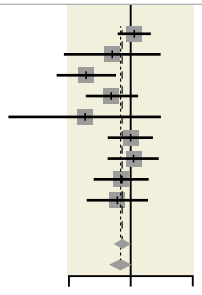
Table 2. Clinical randomised trials for a meta-analysis.

Study	Publi-cation	Follow-up	Comparisons	Population	Number of patients	DoCE	Cardiac death	TV-MI	CI-TLR	Definite or probable stent thrombosis
BIOSCIENCE[18]	2018	5 years	Orsiro vs XIENCE	All-comers	1,063 vs 1,056	20.2% vs 18.8%	8.6% vs 7.5%	6.3% vs 7.1%	10.8% vs 10.0%	6.3% vs 7.7%
BIOFLOW II[19]	2018	5 years	Orsiro vs XIENCE	All-comers	298 vs 154	10.4% vs 12.7%	1.7% vs 2.8%	3.4% vs 3.3%	6.3% vs 6.7%	0.0% vs 0.7%
BIOFLOW IV	2019	4 years	Orsiro vs XIENCE	All-comers	385 vs 190	NA	NA	NA	NA	0.8% vs 0.0%
BIOFLOW V[20]	2020	3 years	Orsiro vs XIENCE	Non-all-comers	884 vs 450	8.2% vs 13.6%	1.1% vs 1.2%	5.0% vs 9.2%	3.2% vs 6.7%	0.5% vs 1.5%
BIO-RESORT[21]	2019	3 years	Orsiro vs Resolute Integrity	All-comers	1,169 vs 1,173	6.7% vs 8.3%	2.1% vs 2.3%	3.0% vs 3.5%	2.9% vs 3.8%	1.1% vs 0.9%
PRISON-IV[22]	2019	3 years	Orsiro vs XIENCE	Chronic total occlusion	165 vs 165	NA	1.2% vs 1.8%	NA	NA	NA
ORIENT[23]	2020	3 years	Orsiro vs Resolute Integrity	All-comers	250 vs 122	4.7% vs 7.8%	0.8% vs 2.6%	NA	3.8% vs 5.2%	0.0% vs 1.6%
SORT OUT VII[24]	2020	3 years	Orsiro vs Nobori	All-comers	1,261 vs 1,264	9.0% vs 9.1%*	3.0% vs 2.6%	3.1% vs 2.9%*	5.2% vs 5.9%	1.5% vs 2.1%
BIONYX[25]	2021	3 years	Orsiro vs Resolute Onyx	All-comers	1,245 vs 1,243	7.5% vs 7.2%	1.9% vs 1.1%	3.1% vs 3.2%	4.6% vs 4.7%	1.2% vs 0.6%
DESSOLVE III[26]	2020	3 years	MiStent vs XIENCE	All-comers	703 vs 695	10.5% vs 11.5%*	3.9% vs 3.8%	3.2% vs 2.5%*	5.2% vs 6.5%	1.2% vs 1.5%
TALENT	2021	3 years	Supraflex vs XIENCE	All-comers	720 vs 715	8.1% vs 9.4%	1.8% vs 2.1%	3.3% vs 4.6%	5.0% vs 5.9%	1.1% vs 1.4%

*In the SORT OUT VII and DESSOLVE III trials, myocardial infarction (MI) not clearly attributable to a non-target vessel was used, instead of TV-MI. CI-TLR: clinically indicated target lesion revascularisation; TV-MI: target-vessel myocardial infarction

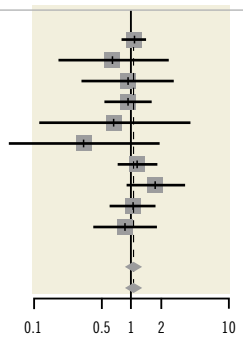
A DoCE

Sent	Study	Publication	Follow-up	Ultrathin Events	Ultrathin Number	Thicker Events	Thicker Number	Risk ratio (95% CI)	Weight (fixed)	Weight (random)
Orsiro	BIOSCIENCE	2018	5 years	198	1,063	189	1,056	1.04 (0.87-1.25)	25.3%	21.4%
	BIOFLOW II	2018	5 years	30	298	19	154	0.82 (0.48-1.40)	3.3%	4.5%
	BIOFLOW V	2020	3 years	70	884	59	450	0.60 (0.44-0.84)	10.4%	10.3%
	BIO-RESORT	2019	3 years	77	1,169	96	1,173	0.80 (0.60-1.07)	12.8%	12.4%
	ORIENT	2020	3 years	11	250	9	122	0.60 (0.25-1.40)	1.6%	2.0%
	SORT OUT VII	2020	3 years	114	1,261	115	1,264	0.99 (0.78-1.27)	15.3%	15.2%
	BIONYX	2021	3 years	91	1,245	88	1,243	1.03 (0.78-1.37)	11.8%	12.8%
MiStent	DESSOLVE III	2020	3 years	72	703	79	695	0.90 (0.67-1.22)	10.6%	11.6%
Supraflex	TALENT	2021	3 years	57	720	66	715	0.86 (0.61-1.20)	8.8%	9.8%
	Fixed effect model				7,593		6,872	0.91 (0.83-1.004)	100.00%	
	Random effects model							0.89 (0.79-1.01)		100.00%
	Heterogeneity: I^2=23%, p=0.18									



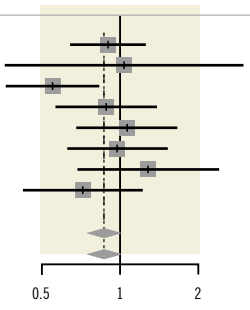
B Cardiac death

Sent	Study	Publication	Follow-up	Ultrathin Events	Ultrathin Number	Thicker Events	Thicker Number	Risk ratio (95% CI)	Weight (fixed)	Weight (random)
Orsiro	BIOSCIENCE	2018	5 years	81	1,063	76	1,056	1.06 (0.78-1.43)	36.6%	38.3%
	BIOFLOW II	2018	5 years	5	298	4	154	0.65 (0.18-2.37)	2.5%	2.1%
	BIOFLOW V	2020	3 years	9	884	5	450	0.92 (0.31-2.72)	3.2%	2.9%
	BIO-RESORT	2019	3 years	24	1,169	26	1,173	0.93 (0.54-1.60)	12.5%	11.5%
	PRISON IV	2019	3 years	2	165	3	165	0.67 (0.11-3.94)	1.4%	1.1%
	ORIENT	2020	3 years	2	250	3	122	0.33 (0.06-1.92)	1.9%	1.1%
	SORT OUT VII	2020	3 years	38	1,261	33	1,264	1.15 (0.73-1.83)	15.8%	16.4%
	BIONYX	2021	3 years	23	1,245	13	1,243	1.77 (0.90-3.47)	6.2%	7.6%
MiStent	DESSOLVE III	2020	3 years	27	703	26	695	1.03 (0.61-1.74)	12.6%	12.5%
Supraflex	TALENT	2021	3 years	13	720	15	715	0.86 (0.41-1.80)	7.2%	6.4%
	Fixed effect model				7,758		7,037	1.05 (0.87-1.26)	100.00%	
	Random effects model							1.05 (0.87-1.26)		100.00%
	Heterogeneity: I^2=0%, p=0.79									



C TV-MI

Sent	Study	Publication	Follow-up	Ultrathin Events	Ultrathin Number	Thicker Events	Thicker Number	Risk ratio (95% CI)	Weight (fixed)	Weight (random)
Orsiro	BIOSCIENCE	2018	5 years	62	1,063	69	1,056	0.89 (0.64-1.24)	23.4%	22.1%
	BIOFLOW II	2018	5 years	10	298	5	154	1.03 (0.36-2.97)	2.2%	2.8%
	BIOFLOW V	2020	3 years	44	884	41	450	0.55 (0.36-0.82)	18.4%	15.8%
	BIO-RESORT	2019	3 years	35	1,169	40	1,173	0.88 (0.56-1.37)	13.5%	13.7%
	SORT OUT VII	2020	3 years	39	1,261	37	1,264	1.06 (0.68-1.65)	12.5%	13.8%
	BIONYX	2021	3 years	38	1,245	39	1,243	0.97 (0.63-1.51)	13.2%	14.0%
MiStent	DESSOLVE III	2020	3 years	22	703	17	695	1.28 (0.69-2.39)	5.8%	7.5%
Supraflex	TALENT	2021	3 years	23	720	32	715	0.71 (0.42-1.21)	10.9%	10.3%
	Fixed effect model				7,343		6,750	0.86 (0.73-1.02)	100.00%	
	Random effects model							0.86 (0.72-1.03)		100.00%
	Heterogeneity: I^2=13%, p=0.33									



D CI-TLR

Sent	Study	Publication	Follow-up	Ultrathin Events	Ultrathin Number	Thicker Events	Thicker Number	Risk ratio (95% CI)	Weight (fixed)	Weight (random)
Orsiro	BIOSCIENCE	2018	5 years	103	1,063	97	1,056	1.05 (0.81-1.37)	23.5%	26.7%
	BIOFLOW II	2018	5 years	18	298	10	154	0.93 (0.44-1.97)	3.2%	3.3%
	BIOFLOW V	2020	3 years	27	884	28	450	0.49 (0.29-0.82)	8.9%	7.0%
	BIO-RESORT	2019	3 years	33	1,169	43	1,173	0.77 (0.49-1.20)	10.3%	9.3%
	ORIENT	2020	3 years	9	250	6	122	0.73 (0.27-2.01)	1.9%	1.8%
	SORT OUT VII	2020	3 years	66	1,261	74	1,264	0.89 (0.65-1.23)	17.8%	17.9%
	BIONYX	2021	3 years	55	1,245	57	1,243	0.96 (0.67-1.38)	13.7%	14.2%
MiStent	DESSOLVE III	2020	3 years	35	703	44	695	0.78 (0.51-1.21)	10.7%	10.0%
Supraflex	TALENT	2021	3 years	35	720	41	715	0.85 (0.55-1.31)	9.9%	9.7%
	Fixed effect model				7,593		6,872	0.87 (0.76-1.001)	100.00%	
	Random effects model							0.88 (0.76-1.003)		100.00%
	Heterogeneity: I^2=0%, p=0.46									

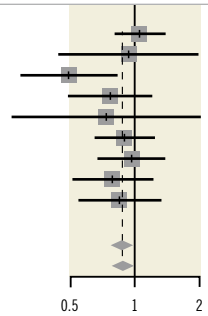
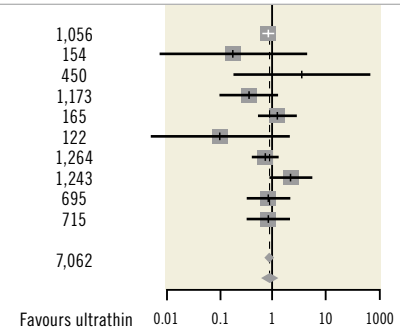


Figure 4. *Long-term outcomes of ultrathin strut DES vs thicker strut DES. A) DoCE, B) cardiac death, C) TV-MI, D) CI-TLR, E) definite or probable stent thrombosis, and F) death. In the BIOFLOW V trial, DoCE was defined as cardiovascular death, TV-MI, or ischaemia-driven TLR. In the SORT OUT VII and DESSOLVE III trials, MI not clearly attributable to a non-target vessel was used instead of TV-MI. CI: confidence interval; CI-TLR: clinically indicated target lesion revascularisation; DoCE: device-oriented composite endpoint; TV-MI: target-vessel myocardial infarction*

E **Definite or probable stent thrombosis**

Sent	Study	Publication	Follow-up	Ultrathin Events	Ultrathin Number	Thicker Events	Thicker Number	Risk ratio (95% CI)	Weight (fixed)	Weight (random)
Orsiro	BIOSCIENCE	2018	5 years	62	1,063	76	1,056	0.81 (0.59-1.12)	49.4%	34.5%
	BIOFLOW II	2018	5 years	0	298	1	154	0.17 (0.01-4.21)	1.3%	0.9%
	BIOFLOW IV	2020	3 years	3	884	0	450	3.46 (0.18-66.63)	0.4%	1.0%
	BIOFLOW V	2019	3 years	4	1,169	6	1,173	0.34 (0.10-1.20)	5.2%	5.3%
	BIO-RESORT	2019	3 years	12	165	10	165	1.20 (0.52-2.78)	6.5%	10.8%
	ORIENT	2020	3 years	0	250	2	122	0.10 (0.00-2.02)	2.2%	1.0%
	SORT OUT VII	2020	3 years	19	1,261	27	1,264	0.71 (0.39-1.26)	17.5%	18.5%
	BIONYX	2021	3 years	15	1,245	7	1,243	2.14 (0.88-5.23)	4.5%	9.7%
MiStent	DESSOLVE III	2020	3 years	8	703	10	695	0.79 (0.31-1.99)	6.5%	9.1%
Supraflex	TALENT	2021	3 years	8	720	10	715	0.79 (0.32-2.00)	6.5%	9.1%
	Fixed effect model				7,978		7,062	0.84 (0.67-1.05)	100.00%	
	Random effects model							0.84 (0.62-1.15)		100.00%
	Heterogeneity: I^2=19%, p=0.27									



F **Death**

Sent	Study	Publication	Follow-up	Ultrathin Events	Ultrathin Number	Thicker Events	Thicker Number	Risk ratio (95% CI)	Weight (fixed)	Weight (random)
Orsiro	BIOSCIENCE	2018	5 years	139	1,063	105	1,056	1.32 (1.04-1.67)	25.1%	19.8%
	BIOFLOW II	2018	5 years	14	298	14	154	0.52 (0.25-1.06)	4.4%	4.9%
	BIOFLOW IV	2020	3 years	26	884	17	450	0.78 (0.43-1.42)	5.4%	6.6%
	BIO-RESORT	2019	3 years	53	1,169	57	1,173	0.93 (0.65-1.34)	13.6%	13.2%
	PRISON IV	2019	3 years	4	165	8	165	0.50 (0.15-1.63)	1.9%	2.0%
	ORIENT	2020	3 years	9	250	4	122	1.10 (0.34-3.49)	1.3%	2.1%
	SORT OUT VII	2020	3 years	88	1,261	74	1,264	1.19 (0.88-1.61)	17.6%	16.3%
	BIONYX	2021	3 years	67	1,245	45	1,243	1.49 (1.03-2.15)	10.7%	10.0%
MiStent	DESSOLVE III	2020	3 years	55	703	49	695	1.11 (0.77-1.61)	11.8%	12.9%
Supraflex	TALENT	2021	3 years	30	720	34	715	0.88 (0.54-1.42)	8.1%	9.2%
	Fixed effect model				7,758		7,037	1.12 (0.98-1.27)	100.00%	
	Random effects model							1.07 (0.90-1.27)		100.00%
	Heterogeneity: I^2=35%, p=0.13									

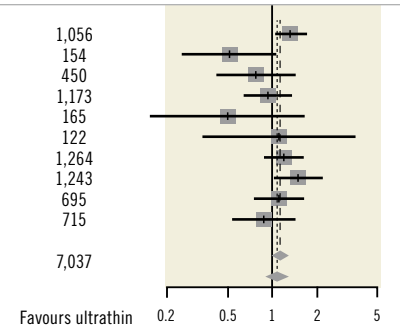
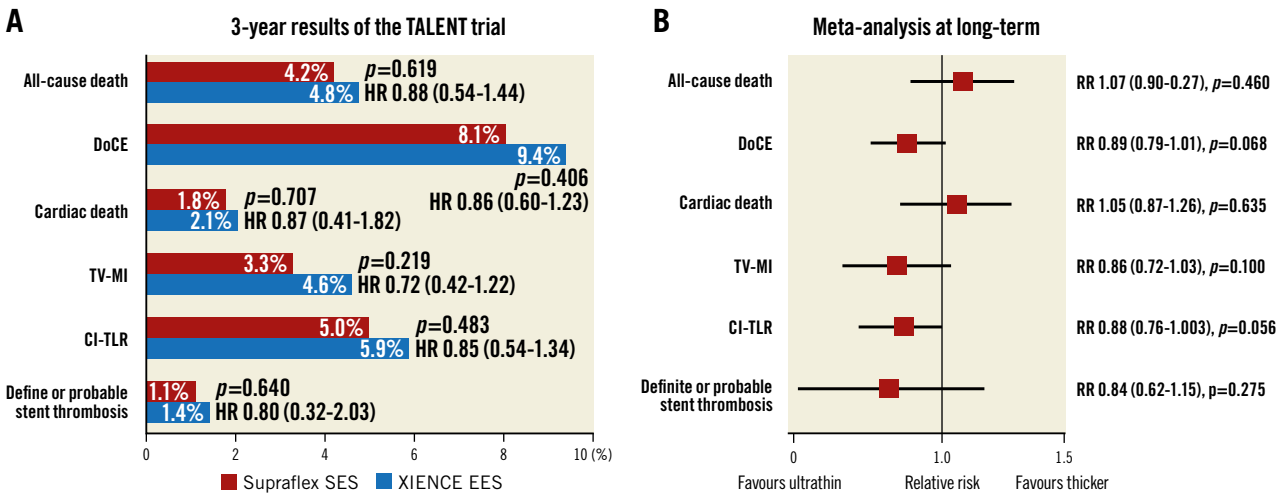


Figure 4. (cont'd) *Long-term outcomes of ultrathin strut DES vs thicker strut DES. A) DoCE, B) cardiac death, C) TV-MI, D) CI-TLR, E) definite or probable stent thrombosis, and F) death. In the BIOFLOW V trial, DoCE was defined as cardiovascular death, TV-MI, or ischaemia-driven TLR. In the SORT OUT VII and DESSOLVE III trials, MI not clearly attributable to a non-target vessel was used instead of TV-MI. CI: confidence interval; CI-TLR: clinically indicated target lesion revascularisation; DoCE: device-oriented composite endpoint; TV-MI: target vessel myocardial infarction*

EuroIntervention

CENTRAL **ILLUSTRATION** **Results of the TALENT trial and a long-term meta-analysis.**



A) Three-year results of the TALENT trial. B) Long-term (3-5 years) results of a meta-analysis. CI: confidence interval; CI-TLR: clinically indicated target lesion revascularisation; EES: everolimus-eluting stent; DoCE: device-oriented composite endpoint; HR: hazard ratio; RR: relative risk; SES: sirolimus-eluting stent; TV-MI: target vessel myocardial infarction

0.76-0.96), driven by less CI-TLR (RR 0.75, 95% CI: 0.62-0.92) compared with second-generation DES with thicker struts, with similar risks of cardiac death and all-cause death[17].

In the TALENT trial, the ultrathin strut Supraflex stent reduced DoCE at 1 year by 6%, compared to the thin strut XIENCE stent in the ITT analysis[6]. The effect of the ultrathin strut Supraflex stent was retained at 3 years with 14% risk reductions in DoCE, although the effect was not statistically significant.

To date, long-term follow-up data with at least 3-year results of ultrathin strut stents (strut thickness <70 µm) versus thicker strut stents (strut thickness ≥81 µm) are available in the BIOSCIENCE[18], BIOFLOW II[19], BIOFLOW V[20], BIO-RESORT[21], PRISON-IV[22], ORIENT[23], SORT OUT VII[24], BIONYX[25] (Orsiro), DESOLVE III[26] (MiStent), and TALENT (Supraflex) randomised trials. The 4-year results of BIOFLOW-IV have not been published, but have been presented at TCT by Slagboom et al. [TCT-43 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 2 *De Novo* Coronary Artery Lesions –BIOFLOW IV: 4-Year Clinical Results. *J Am Coll Cardiol*. 2019;74:B43]. The characteristics of these ultrathin strut stents are shown in **Table 3**[16,27,28].

Our updated meta-analysis of these trials, including results from the current study, demonstrates the safety of ultrathin strut DES compared to thicker strut DES at a minimum of 3 years of follow-up (**Central illustration**, panel B). Although moderate heterogeneity was observed between studies and the difference was not statistically significant, ultrathin strut DES reduced DocE by 11%, compared to thicker strut DES (RR 0.89, 95% CI: 0.79-1.01; p=0.068). The risks for cardiac death and definite or probable stent thrombosis were similar between ultrathin strut DES and thicker strut DES. Theoretically, thinner struts could have some advantages, such as: less stent-induced vessel injury and subsequent inflammation; faster re-endothelialisation; and less flow disturbance and fewer areas of low shear stress behind struts, resulting in reduced thrombogenicity[1-4,29]. The stent strut thickness of Orsiro is 80 µm for stent diameters ≥3.5 mm, which is similar to the stent strut thickness of XIENCE (81 µm for all sizes) and Resolute Onyx (81 µm for stent diameters ≤4.0 mm). The patients treated with Orsiro with a stent diameter ≥3.5 mm may dilute the impact of stent strut thickness. In the BIOSCIENCE trial, 244 patients (23.0%) were treated with stents ≥3.5 mm in the Orsiro group. Thus, the meta-analysis may underestimate the impact of stent strut thickness, and the analysis using individual patient data is mandatory to investigate the impact of ultrathin strut DES precisely.

COMPARISON BETWEEN NEWER-GENERATION ULTRATHIN STRUT DES

There are notable differences in stent profiles amongst the ultrathin strut Orsiro, MiStent, and Supraflex DES. The Supraflex and MiStent DES have a fixed strut thickness of 60 and 64 µm, respectively, irrespective of the stent diameter, which is at variance with the Orsiro stent, which has a strut thickness of 60 µm for stents 2.25 to 3.0 mm in diameter and 80 µm for stents with a diameter of 3.5 to 4.0 mm. Moreover, whilst these ultrathin strut stents all have biodegradable polymers and elute sirolimus, there are fundamental differences in their drug release kinetics. In the Supraflex stent, 70% of the sirolimus is eluted in the first 7 days during an initial burst, followed by sustained release which is completed by day 48; the polymer gradually degrades over 9-12 months. In the MiStent, no drug release occurs in the first 3 days, and whilst the polymer is fully biodegraded and resorbed within 3 months of implantation, microcrystalline sirolimus is impacted and embedded in the vessel wall, acting as a tissue reservoir for 270 days, such that arterial concentrations of sirolimus still reach more than 2 ng/ml at day 270. In the Orsiro stent, sirolimus is slowly released over 12-14 weeks, whilst its polymer completely degrades within 12-24 months. Although the rate of DoCE at 3 years with the MiStent in the all-comers DESSOLVE III trial was 10.2% (72 patients out of 703 patients, Kaplan-Meier estimated rate 10.5%), the rate of DoCE at 3 years was lower in the all-comers population treated with the Supraflex stent (57 patients

Table 3. Characteristics of stents.

	Orsiro	MiStent	Supraflex	XIENCE	Resolute Integrity	Resolute Onyx	Nobori
Platform material	Cobalt chromium	Cobalt chromium	Cobalt chromium	Cobalt chromium	Cobalt chromium	Cobalt chromium, platinum-iridium core wire	Stainless steel
Strut thickness	60/80 µm*	64 µm	60 µm	81 µm	91 µm	81/91 µm**	120 µm
Polymer thickness	7.4 µm abluminal 3.5 µm luminal	15 µm abluminal 5 µm luminal	4-5 µm abluminal 4-5 µm luminal	7.6 µm for both sides	5.3 µm for both sides	5.6 µm for both sides	10 µm abluminal
Polymer coating	Biodegradable	Biodegradable	Biodegradable	Durable	Durable	Durable	Biodegradable
Biodegradation of polymer	12-24 months	3 months	9-12 months	NA	NA	NA	6-9 months
Drug eluted	Sirolimus	Sirolimus	Sirolimus	Everolimus	Zotarolimus	Zotarolimus	Biolimus A9
Drug dose	1.4 µg/mm^2	2.4 µg/mm^2	1.4 µg/mm^2	100 µg/cm^2	1.6 µg/mm^2	1.6 µg/mm^2	15.6 µg/mm^2
Drug release	3 months	9 months	48 days	4 months	6 months	6 months	30 days

*60 µm for stents ≤3.0 mm and 80 µm for stents ≥3.5 mm; **81 µm for stents ≤4.0 mm and 91 µm for stents ≥4.5 mm

[7.9%; Kaplan-Meier estimated rate 8.1%] out of 720 patients in the TALENT trial) **(Table 2)**. The rate of DoCE at 3 years in the all-comers population treated with Orsiro was available in the BIO-RESORT, ORIENT, SORT OUT VII, and BIONYX trials, and was 7.5% (293 patients out of 3,925 patients).

Limitations

The TALENT trial was single-blinded, although the effect of this approach on event reporting is minimal because of the adjudication by an independent blinded clinical event committee. The study did not have adequate statistical power for any individual endpoints due to its relatively small sample size.

In terms of meta-analysis, the definition of DoCE was not the same in each trial (e.g., TV-MI or MI not clearly attributable to a non-target vessel, etc). The definition of MI was not consistent across trials (e.g., SCAI definition, universal definition of myocardial infarction, WHO's extended definition, criteria of cardiac biomarkers, etc). Furthermore, long-term results of DoCE were not available for the BIOFLOW-IV and PRISON IV trials. Longer-term follow-up and large-scale individual data are necessary to investigate long-term benefits of ultrathin strut DES.

Conclusions

In the present final report of the TALENT trial, the use of the Supraflex ultrathin strut stent was at least as safe and efficacious as the XIENCE stent at 3 years in an all-comers population.

Impact on daily practice

The Supraflex ultrathin strut stent was at least as safe and efficacious as the XIENCE stent at 3 years in an all-comers population. In a meta-analysis of long-term follow-up (3-5 years), ultrathin strut DES were also as safe and efficacious as thicker strut DES. Ultrathin strut DES can be considered for PCI.

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Role of the Funder/Sponsor

The study funders had no role in trial design, data collection, analysis, interpretation of the data, preparation, approval, or making a decision to submit the manuscript or publication.

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Conflict of interest statement

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Supplementary data

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The supplementary data are published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-21-00766

Supplementary data

Supplementary Table 1. Search syntax.

Database	Search term
PubMed	Filter: 2010-2021 (“ultra-thin”[Title/Abstract] OR “ultrathin”[Title/Abstract] OR “very thin”[Title/Abstract] OR “Orsiro”[Title/Abstract] OR “Mistent”[Title/Abstract] OR “Supraflex”[Title/Abstract] OR “Supralimus”[Title/Abstract] OR “BioMime”[Title/Abstract]) AND (“DES”[Title/Abstract] OR “stents”[Title/Abstract] OR “stent”[Title/Abstract])
EMBASE	ultra thin':ab,ti OR ultrathin:ab,ti OR 'very thin':ab,ti OR orsiro:ab,ti OR mistent:ab,ti OR supraflex:ab,ti OR supralimus:ab,ti OR biomime:ab,ti) AND ('des':ab,ti OR 'stent':ab,ti OR 'stents':ab,ti) AND [randomized controlled trial]/lim AND [2010-2021]/py

Supplementary Table 2. Patients with DAPT.

		Supraflex SES (n=720)	XIENCE EES (n=715)	Difference (95% confidence interval)	p-value
6 months	Patients with stable CAD	85.8% (242/282)	86.5% (262/303)	-0.7% (-6.3%, 5.0%)	0.905
	Patients with ACS	90.1% (372/413)	92.2% (367/398)	-2.1% (-6.0%, 1.8%)	0.324
12 months	Patients with stable CAD	83.7% (231/276)	85.1% (257/302)	-1.4% (-7.3%, 4.5%)	0.648
	Patients with ACS	79.7% (325/408)	81.2% (320/394)	-1.6% (-7.1%, 3.9%)	0.594

ACS: acute coronary syndrome; CAD: coronary artery disease; DAPT: dual antiplatelet therapy

Supplementary Table 3. Clinical outcomes at 36 months after stent implantation (per protocol [PP] basis).

Clinical outcomes (PP)	Supraflex SES (n=660)	XIENCE EES (n=685)	Difference (95% confidence interval)	p-value
DoCE	6.6% (43)	8.7% (59)	-2.1% (-5.0%,0.8%)	0.165
PoCE	16.5% (107)	15.5% (105)	1.0% (-3.0%,4.9%)	0.588
TVF	8.4% (54)	9.9% (67)	-1.6% (-4.7%,1.5%)	0.336
Components of composite endpoints				
Death	4.2% (27)	4.6% (31)	-0.4% (-2.6%,1.8%)	0.728
Cardiac death	1.9% (12)	2.2% (15)	-0.4% (-1.9%,1.1%)	0.649
MI	5.1% (33)	5.8% (39)	-0.7% (-3.1%,1.8%)	0.596
Q-wave	0.8% (5)	0.9% (6)	-0.1% (-1.1%,0.9%)	0.825
Non-Q-wave	4.5% (29)	5.1% (34)	-0.5% (-2.9%,1.8%)	0.644
TV-MI	2.9% (19)	4.6% (31)	-1.7% (-3.7%,0.4%)	0.119
Q-wave	0.5% (3)	0.9% (6)	-0.4% (-1.3%,0.5%)	0.353
Non-Q-wave	2.6% (17)	3.9% (26)	-1.2% (-3.1%,0.7%)	0.214
Non-TV-MI	2.2% (14)	1.4% (9)	0.9% (-0.6%,2.3%)	0.243
Q-wave	0.3% (2)	0.0% (0)	0.3% (-0.1%,0.8%)	0.147
Non-Q-wave	1.9% (12)	1.4% (9)	0.5% (-0.8%,1.9%)	0.441
All revascularisation	11.9% (76)	10.7% (72)	1.1% (-2.3%,4.6%)	0.502
TL revascularisation	4.8% (31)	5.4% (36)	-0.5% (-2.9%,1.9%)	0.677
clinically indicated	3.6% (23)	5.1% (34)	-1.5% (-3.7%,0.7%)	0.192
non-clinically indicated	1.6% (10)	1.0% (7)	0.5% (-0.7%,1.7%)	0.407
TV revascularisation	6.6% (42)	7.2% (48)	-0.6% (-3.3%,2.1%)	0.675
clinically indicated	5.5% (35)	6.7% (45)	-1.2% (-3.8%,1.3%)	0.346

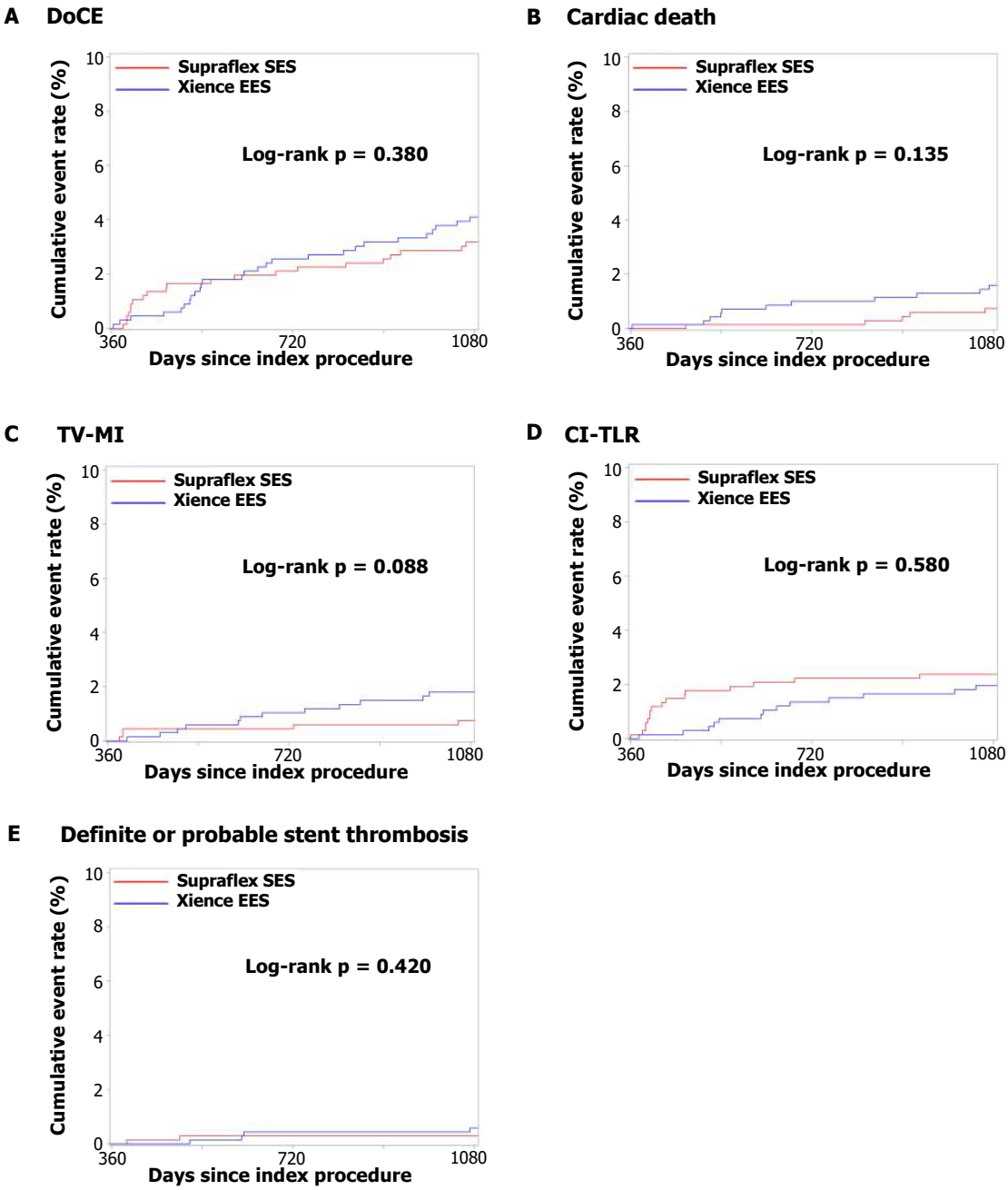
non-clinically indicated	1.6% (10)	1.5% (10)	0.1% (-1.3%,1.4%)	0.915
Non-TV revascularisation	7.8% (50)	5.8% (39)	2.0% (-0.7%,4.7%)	0.143
Stent thrombosis				
Definite	0.8% (5)	1.2% (8)	-0.4% (-1.5%,0.7%)	0.455
Definite (very late, >360 days)	0.3% (2)	0.5% (3)	-0.1% (-0.8%,0.5%)	0.699
Definite or probable	0.9% (6)	1.3% (9)	-0.4% (-1.5%,0.7%)	0.495
Definite or probable (very late, >360 days)	0.3% (2)	0.5% (3)	-0.1% (-0.8%,0.5%)	0.699

Data are presented as percentage (number).

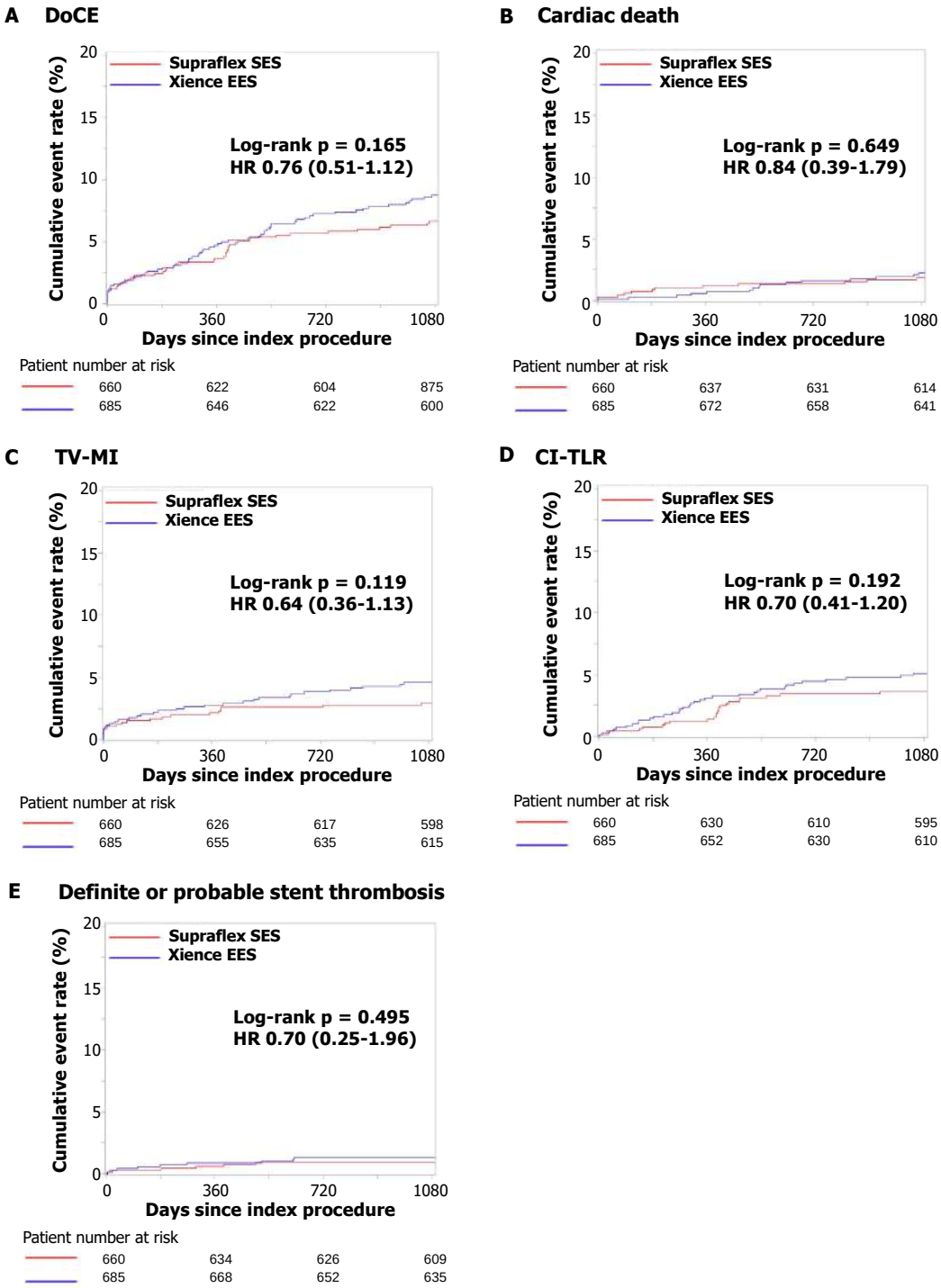
DoCE: device-oriented composite endpoint; MI: myocardial infarction; PoCE: patient-oriented composite endpoint; TL: target lesion; TV: target-vessel; TVF: target vessel failure

Supplementary Table 4. Risk of bias.

	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting
BIOSCIENCE	Low	Low	High	Low	Low	Low
BIOFLOW II	Low	Low	High	Low	Low	Low
BIOFLOW IV	Low	Low	High	High	Low	High
BIOFLOW V	Low	Low	High	Low	Low	Low
BIO-RESORT	Low	Low	Low	Low	Low	Low
PRISON-IV	Low	Low	Low	Low	Low	High
ORIENT	Low	Low	High	Low	Low	Low
SORT OUT VII	Low	Low	High	Low	Low	Low
BIONYX	Low	Low	Low	Low	Low	Low
DESSOLVE III	Low	Low	Low	Low	Low	Low
TALENT	Low	Low	Low	Low	Low	Low

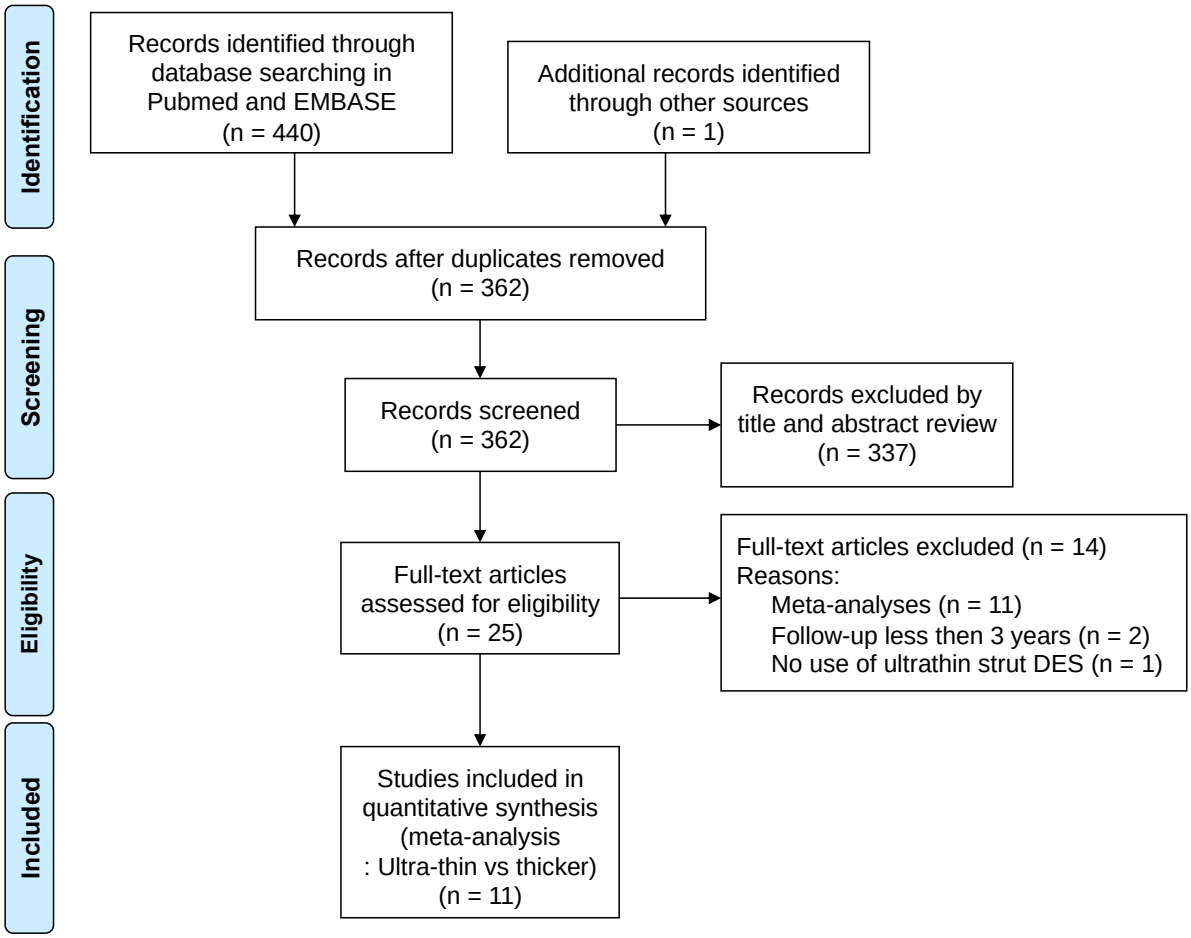


Supplementary Figure 1. Kaplan-Meier estimates for the device-oriented composite endpoint (DoCE) and its components between 1 and 3 years (intention-to-treat [ITT] basis). (A) DoCE, (B) cardiac death, (C) target vessel myocardial infarction (TV-MI), (D) clinical indicated target lesion revascularisation (CI-TLR), and (E) definite or probable stent thrombosis.

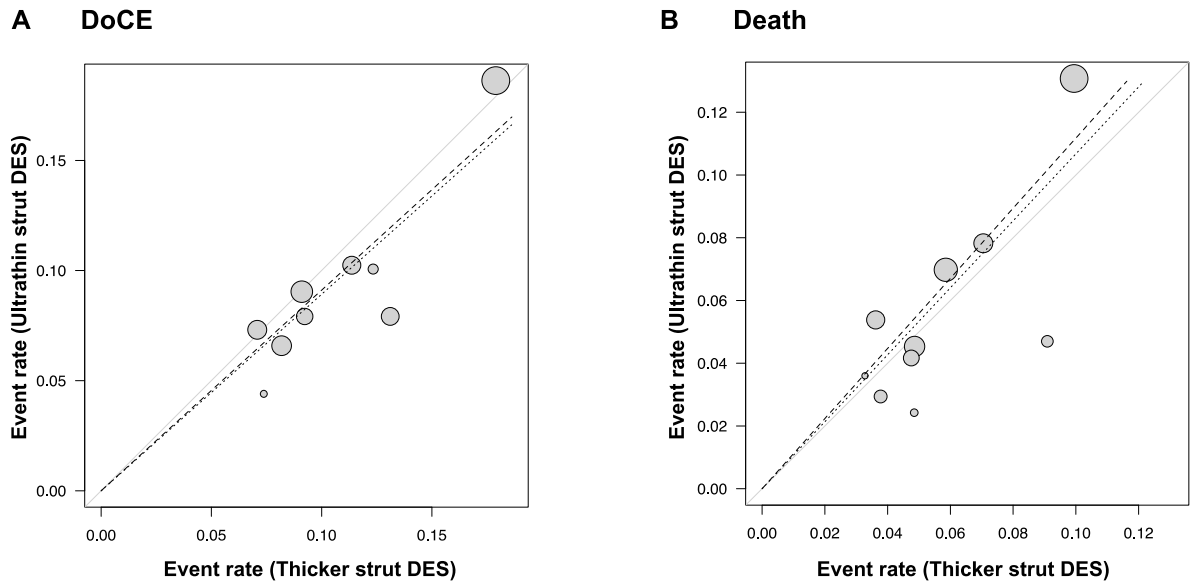


Supplementary Figure 2. Kaplan-Meier estimates for the DOCE and its components at 3 years (per protocol [PP] basis).

(A) DoCE, (B) cardiac death, (C) TV-MI, (D) CI-TLR, and (E) definite or probable stent thrombosis. HR: hazard ratio

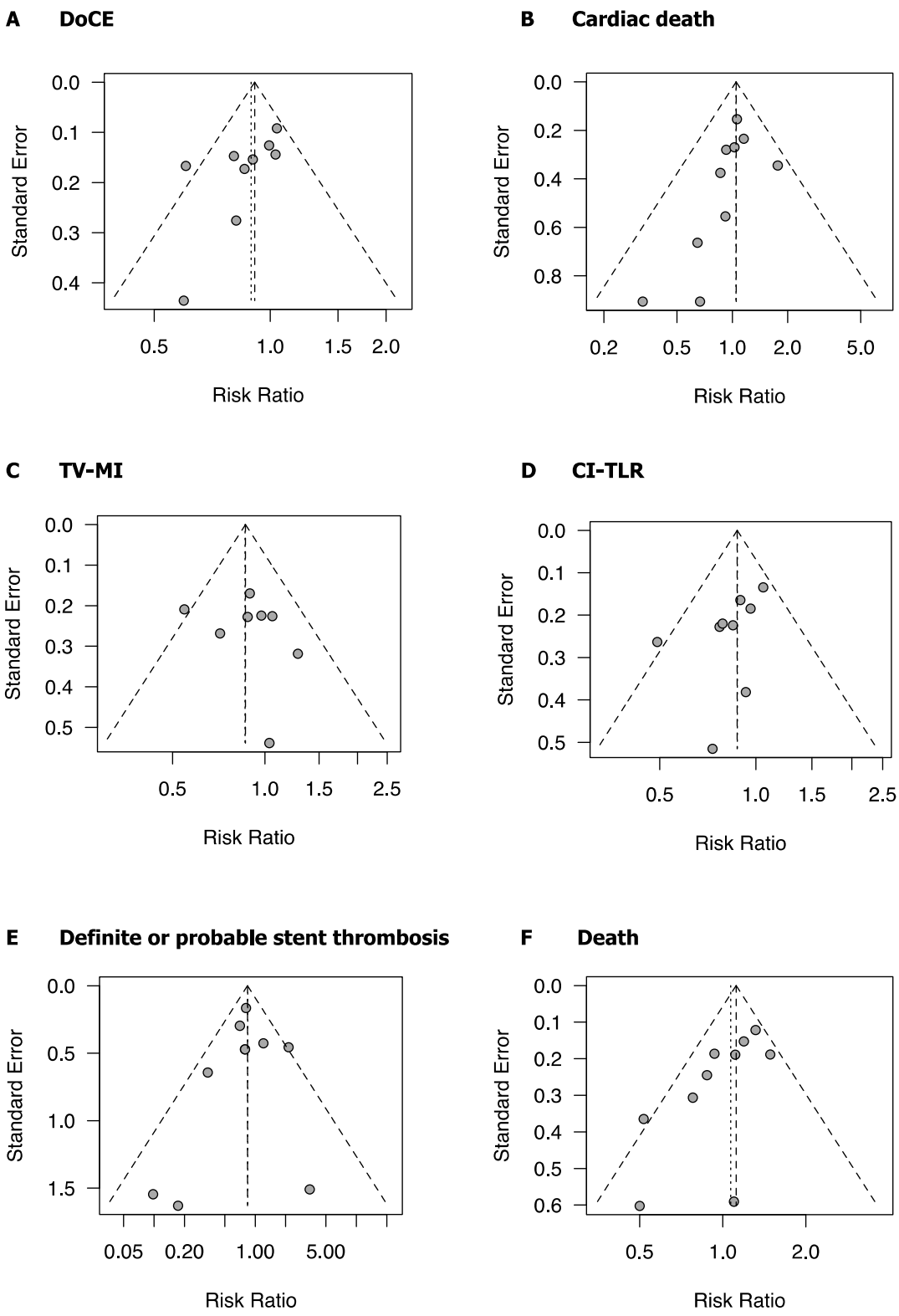


Supplementary Figure 3. Flow chart for randomised control trials included in the meta-analysis.

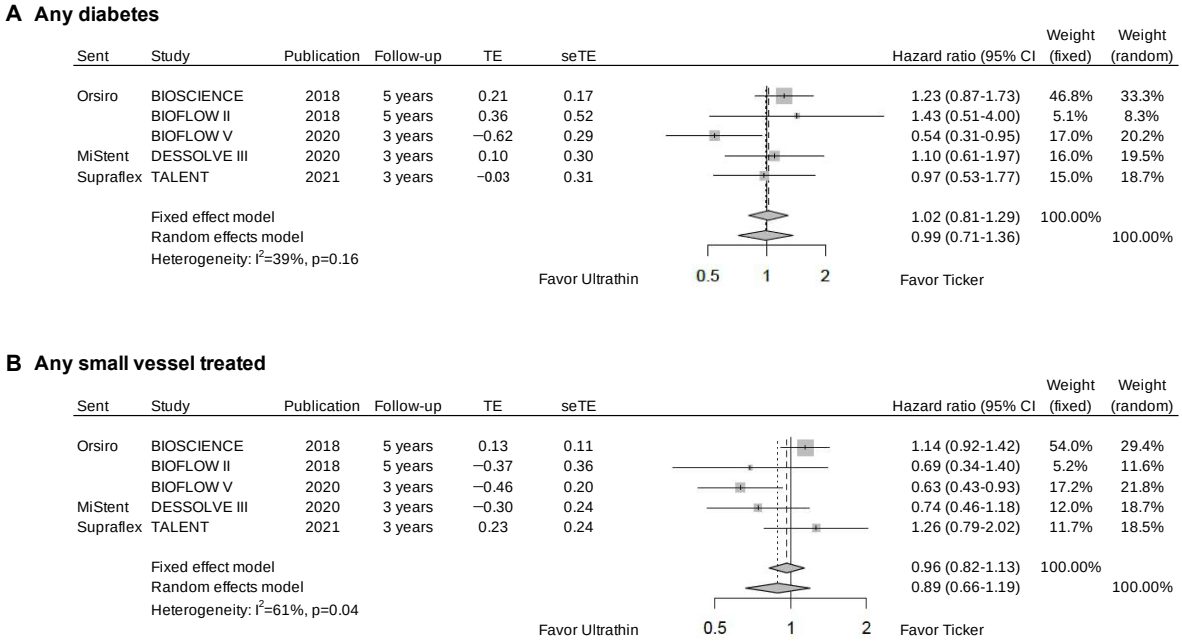


Supplementary Figure 4. L'Abbé plots for the meta-analysis comparing ultrathin strut DES and thicker strut DES.

(A) DoCE, and (B) death. DES: drug-eluting stent



Supplementary Figure 5. Funnel plots for long-term meta-analysis.
(A) DoCE, (B) cardiac death, (C) TV-MI, (D) CI-TLR, (E) definite or probable stent thrombosis, and (F) death.



Supplementary Figure 6. Long-term outcomes of ultrathin strut DES vs thicker strut DES in patients with diabetes and small vessel treated.

Long-term meta-analysis in patients with (A) diabetes, and (B) small vessel treated.