Safety and efficacy of a sirolimus-eluting coronary stent with ultra-thin strut for treatment of atherosclerotic lesions (TALENT): a prospective multicentre randomised controlled trial

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Summary

Background **Supraflex is a sirolimus-eluting stent with a biodegradable polymer coating and ultra-thin struts. We aimed to compare Supraflex with the standard of care, Xience, an everolimus-eluting stent with a durable polymer coating, regarding clinical outcomes with a randomised trial in an all-comer population.**

Methods **We did a prospective, randomised, single-blind, multicentre study (TALENT) across 23 centres in Europe (the Netherlands, Poland, the UK, Spain, Bulgaria, Hungary, and Italy). Eligible participants were aged 18 years or older, had one or more coronary artery stenosis of 50% or greater in a native coronary artery, saphenous venous graft, or arterial bypass conduit, and had a reference vessel diameter of 2·25–4·50 mm. Patients underwent percutaneous coronary intervention in an all-comer manner. We randomly assigned patients (1:1) to implantation of either a sirolimus-eluting stent with a biodegradable polymer coating and ultra-thin struts (Supraflex) or an everolimus-eluting stent with a durable polymer coating (Xience). Randomisation was done by local investigators by use of a web-based software with random blocks according to centre. The primary endpoint was a non-inferiority comparison of a device-oriented composite endpoint—cardiac death, target-vessel myocardial infarction, or clinically indicated target lesion revascularisation—between groups at 12 months after the procedure, assessed in an intention-to-treat population. On assumption of 1-year composite endpoint prevalence of 8·3%, a margin of 4·0% was defined for non-inferiority of the Supraflex group compared with the Xience group. This trial is registered with ClinicalTrials.gov, number NCT 02870140.**

Findings **Between Oct 21, 2016, and July 3, 2017, 1435 patients with 1046 lesions were randomly assigned to Supraflex, of whom 720 received the index procedure, and 715 patients with 1030 lesions were assigned to Xience, all receiving the index procedure. At 12 months, the primary endpoint had occurred in 35 patients (4·9 %) in the Supraflex group and in 37 patients (5·3%) in the Xience group (absolute difference –0·3% [one-sided 95% upper confidence bound 1·6%], $p_{non\text{-}inferiority}$<0·0001). Definite or probable stent thrombosis prevalence, a safety indicator, was low in both groups and did not differ between them.**

Interpretation **The Supraflex stent was non-inferior to the Xience stent for a device-oriented composite clinical endpoint at 12 months in an all-comer population. Supraflex seems a safe and effective alternative drug-eluting stent to other stents in clinical practice.**

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Introduction

The evolution of coronary stent technologies has led to reduced adverse outcomes in patients who undergo percutaneous coronary intervention. These technological developments stem from reductions in strut and polymer thickness, improvements in metal alloys and biocompatibility of coating, and optimisation of the kinetics of drug release. The second generation of drug-eluting stents was introduced with thin struts (80–90 µm), new antiproliferative drugs with better elution profiles, and biocompatible polymers. These new stents had lower rates of restenosis coupled with adequate strut coverage,[1,2] resulting in significantly lower rates of thrombotic complications compared with those of first-generation, drug-eluting stents and bare metal stents.[3,4] Subsequently, biodegradable polymers were developed to disappear after drug release, thereby leaving a bare metal stent-like platform. The efficacy of

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Research in context

Evidence before this study

We searched PubMed and checked the listings of the EuroPCR, European Society of Cardiology, Transcatheter Cardiovascular Therapeutics, and American College of Cardiology conferences for complete reports of clinical studies comparing Supraflex, a sirolimus-eluting coronary stent with biodegradable polymer coating, with any other drug-eluting stents. We used the search terms "Supraflex" AND "all-comers" for reports published in English up to Aug 29, 2018. We identified one multicentre, single-group, observational registry—the FLEX Registry. At 12 months, the primary device-oriented composite endpoint occurred in 36 (3·7%) of 980 patients who received Supraflex implantation. However, this registry, which had site-reported events without central adjudication, was a non-randomised trial.

Added value of this study

To our knowledge, this is the first randomised trial with a clinical primary endpoint comparing Supraflex with a contemporary drug-eluting stent in an all-comer population. The Supraflex stent was non-inferior to Xience, an everolimus-eluting stent with durable polymer coating, for the device-oriented composite endpoint of cardiac death, target-vessel myocardial infarction, or clinically indicated target lesion revascularisation at 12 months. Per-protocol analysis showed a significantly lower clinically indicated target lesion revascularisation in the Supraflex group than in the Xience group.

Implications of all the available evidence

The sirolimus-eluting Supraflex coronary stent with absorbable polymer coating was non-inferior to a currently best-in-class drug-eluting stent at 12 months and further benefits might emerge in long-term follow-up.

drug-eluting stents with biodegradable polymer coating was shown to be non-inferior to that of stents with durable polymer coating in several studies.[5–7] A study[8] published in 2017 showed that a drug-eluting stent with a biodegradable polymer coating and ultra-thin struts was superior to a stent with durable polymer coating, achieving a lower rate of target lesion failure at 12 months than that of the stent with durable coating. Additionally, a meta-analysis[9] published in 2018 showed that drug-eluting stents with ultra-thin struts (strut thickness <70 μm) reduced the incidence of target lesion failure compared with that of contemporary stents with thicker struts. Because clinical outcomes of contemporary stents are reaching a safety plateau, it is probable that cost-effectiveness might influence the decision on which stent to use.

The Supraflex is a sirolimus-eluting coronary stent made with a cobalt chromium alloy that has a biodegradable polymer technology and an ultra-thin strut thickness of 60 μm. With this stent, the drug is released over a short period of 48 days. Provided that clinical outcomes are comparable with market-leading stents, the introduction of Supraflex in the European market will increase competition and might drive down healthcare costs.[10] In the FLEX-Registry,[11] Supraflex showed a low incidence of major adverse cardiac events at 12 months of follow-up (3·7%) and excellent strut coverage at 6 months of follow-up in 995 unselected real-world patients. Although the ultra-thin strut stent with biodegradable polymer might have an important role in patients' outcomes,[7] the Supraflex has not yet been tested in the context of a randomised clinical trial.

We therefore did a trial to investigate non-inferiority of clinical outcomes after implantation of the Supraflex stent compared with the standard of care for atherosclerotic lesions (Xience, an everolimus-eluting stent with durable polymer coating) in broad patient and lesion scenarios from an all-comer European population.

Methods

Study design and participants

The TALENT trial was a prospective, randomised, controlled, single-blind, multicentre study in an all-comers population across 23 hospitals or specialised centres in Europe (the Netherlands, Poland, the UK, Spain, Bulgaria, Hungary, and Italy). There were few inclusion and exclusion criteria (appendix).[12] Briefly, patients aged at least 18 years, with one or more coronary artery stenosis of 50% or greater in a native coronary artery, saphenous venous graft, or arterial bypass conduit with a reference vessel diameter of 2·25–4·50 mm, who were suitable for coronary stent implantation were eligible for inclusion. Any type of coronary artery lesions and anatomical locations were included. The number of stents, treated lesions, and vessels and the length of lesions was unrestricted. All patients signed informed consent, which was approved by the ethics committee of each enrolling centre.

Randomisation and masking

Patients who met the enrolment criteria were randomly assigned (1:1) to implantation of either the Supraflex or the Xience stent. Randomisation was done by local investigators by use of a web-based software with random blocks according to centre. Clinical data were adjudicated by an independent clinical event committee, which was masked to the type of stent allocated to the patient.

Procedures

The Supraflex is a new generation metallic stent (Sahajanand Medical Technologies, Surat, India) consisting of an L605 cobalt–chromium alloy platform with ultra-thin struts (60 µm) across all stent diameters, highly flexible S-link connectors, and a biodegradable polymeric matrix coating (poly L-lactide, 50:50 mixture poly D,L-lactide-co-glycolide and polyvinyl pyrrolidone). Sirolimus, at a concentration of 1·4 µg/mm² and together with the polymeric matrix, is coated on the conformal surface of the stent. The average thickness of coating ranged from 4 µm to 5 µm. The drug is 70% released within 7 days, and the remainder is released over a period of 48 days.[11] The polymer gradually degrades over 9–12 months. Available stent diameters for this trial were between 2·25 mm and 4·0 mm, and available stent lengths were 8–48 mm. The crossing profile of Supraflex is 0·99 mm, whereas the crossing profile of the newest Xience Alpine is 1·10 mm and of Xience Sierra is 0·99 mm.

The control stent with durable polymer coating, Xience (Abbot Vascular, Santa Clara, CA, USA), is a cobalt–chromium alloy device with a strut thickness of 81 µm and an 8 µm-thick durable polymer coating. This polymer is made of polyvinylidene fluoride–hexafluoropropylene loaded with everolimus.[13] We used only Xience stents with similar diameter and length to those of Supraflex, thus Xience stents up to 48 mm in length and with diameters between 2·25 mm and 4·0 mm were allowed for implantation.

Investigators determined lesion parameters by visual estimation with angiography or online quantitative coronary angiography. Patients with stable coronary artery disease received dual antiplatelet therapy for at least 6 months after percutaneous coronary intervention, followed by aspirin monotherapy indefinitely. Patients with acute coronary syndrome received dual antiplatelet therapy for at least 12 months after percutaneous coronary intervention, followed by aspirin monotherapy indefinitely. For patients with acute coronary syndrome, the order of preference for P2Y12 (P2Y purinoceptor 12) inhibitors was ticagrelor, followed by prasugrel (or clopidogrel), according to local practice and drug availability.

Cardiac biomarkers (creatine kinase, creatine kinase-myocardial band, and troponin I or T) were measured within 24 h before percutaneous coronary intervention and 3–8 h after the procedure (appendix). Patients were followed up by hospital visit at 1 month and 12 months and by phone contact at 6 months to assess clinical status and adverse events. All information was recorded for data collection at each visit.

Outcomes

The primary endpoint of the study was a non-inferiority comparison at 12 months between the Supraflex group and the Xience group regarding a device-oriented composite endpoint of cardiac death, target vessel myocardial infarction, and clinically indicated target lesion revascularisation. The composite secondary endpoints were a patient-oriented composite endpoint of all-cause death, any myocardial infarction, and any revascularisation, a target vessel failure of cardiac death, target vessel myocardial infarction, and clinically indicated target vessel revascularisation. Other secondary endpoints of the study included individual components of composite endpoints and stent thrombosis (appendix).

Definite and probable stent thrombosis, which are safety indicators, were adjudicated according to the definition of the Academic Research Consortium (ARC).[14] Myocardial infarction was defined according to the Society for Cardiovascular Angiography and Interventions consensus for periprocedural myocardial infarction (when occurring 48 h or earlier after the index procedure) or according to the Third Universal Definition for myocardial infarction (when occurring later than 48 h after the index procedure).[15,16] Device success was defined as successful delivery and deployment of (only) the assigned device at the intended target lesion and successful withdrawal of

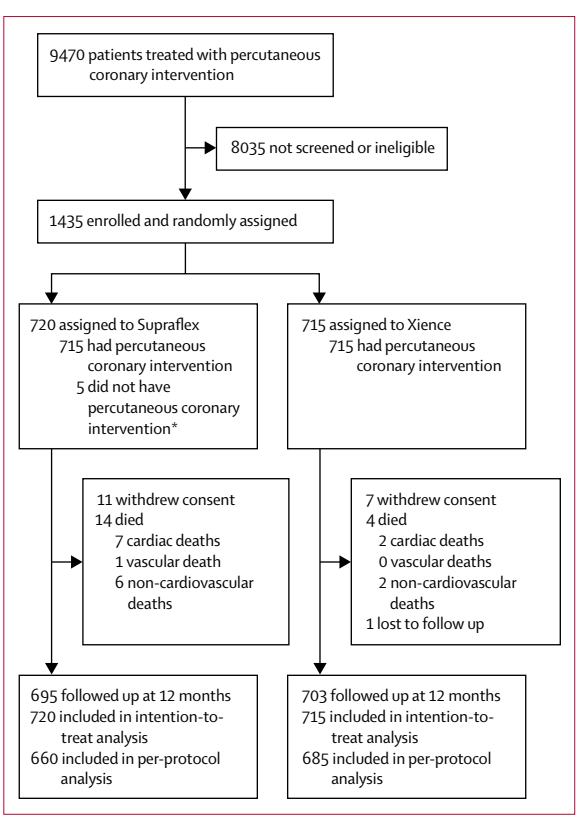

Figure 1: **Study profile**

*Percutaneous intervention was cancelled in two patients on the basis of intravascular ultrasound finding. In one patient, vasospastic stenosis observed during diagnostic angiography was not confirmed at the time of planned coronary intervention; therefore the procedure was not done. One patient was referred after randomisation to surgery because of concomitant mitral regurgitation. One patient did not receive percutaneous intervention because of a randomisation error.

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See Online for appendix

	Supraflex (n=720)	Xience (n=715)
Median age (IQR), years	66 (58–72)	65 (58–72)
Sex		
Men	546 (75·8%)	547 (76·5%)
Women		
Body-mass index (kg/m^2)	28·3 (4·8; n=719)	28·3 (4·6)
Smoking status		
Current	176 (24·5%; n=719)	172 (24·1%)
Previous	286 (39·8%; n=719)	311 (43·5%)
Never	257 (35·7%; n=719)	232 (32·4%)
Diabetes	157 (21·8%)	178 (24·9%)
Insulin-dependent	48 (6·7%)	67 (9·4%)
Non-insulin-dependent	109 (15·1%)	111 (15·5%)
Hypertension	470 (65·3%)	472 (66·1%; n=714)
Hypercholesterolaemia	444 (61·8%; n=718)	428 (60·2%; n=711)
Family history of coronary artery disease	311 (46·3%; n=671)	303 (45·2%; n=671)
Previous myocardial infarction	136 (18·9%)	128 (17·9%)
Established peripheral vascular disease	51 (7·1%)	64 (9·0%)
Previous PCI	175 (24·3%)	153 (21·4%)
Previous CABG	33 (4·6%)	55 (7·7%)
Heart failure	34 (4·7%)	49 (6·9%)
Renal insufficiency*	20 (2·8%)	14 (2·0%)
Indication		
Stable angina	291 (40·4%)	310 (43·4%)
Acute coronary syndrome	429 (59·6%)	405 (56·6%)
Unstable angina	116 (16·1%)	99 (13·8%)
Non-ST elevation myocardial infarction	194 (26·9%)	189 (26·4%)
ST elevation myocardial infarction	119 (16·5%)	117 (16·4%)

Data are mean (SD) or n (%). PCI=percutaneous coronary intervention. CABG=coronary artery bypass graft. *Defined as serum creatinine concentration >2·5 mg/dL or creatinine clearance ≤30 mL/min.

Table 1: **Patient baseline characteristics**

the delivery system with attainment of final in-stent residual stenosis of less than 30% (preferably by online quantitative coronary angiography).

Statistical analysis

The trial was powered for testing of non-inferiority for the primary endpoint at 12 months after the procedure. After reviewing event rates from published data, we expected the composite endpoint prevalences at 12 months for both treatment groups to be 8·3%.[17] A margin of 4% (50% of the expected event rate) was defined for the non-inferiority margin of the Supraflex group compared with the Xience group. On the basis of this margin and a one-sided type I error of 0·05, a total of 1386 patients (693 patients in each group) would have at least 85% power to detect non-inferiority. Accounting for approximately 3% of patients lost to follow-up, we randomly assigned a total of 1435 patients. The primary analyses were based on an intention-to-treat population. For the primary endpoint analysis, we used a standard normal distribution to create a one-sided 95% upper confidence bound for the difference in Kaplan-Meier rates for the device-oriented composite endpoints of the Supraflex group and the Xience group. If the one-sided 95% upper confidence bound was less than or equal to the non-inferiority margin of 4·0%, Supraflex was declared to be non-inferior to Xience. This testing implied a 5·0% one-sided significance level. A secondary analysis of the primary endpoint and all secondary clinical endpoints was done in the per-protocol population, which consisted of patients who had received only the assigned study stent. Continuous variables were presented as mean (SD) and compared with the use of t test. Categorical variables were reported as n (%). Categorical variables with more than two categories were assessed by Mantel-Haenszel rank score test, and dichotomous variables were assessed by Fisher's exact test. Composite endpoints were calculated by use of time-to-first of any of the composite events per patient. Patients started being at risk on the day of index percutaneous coronary intervention or, if no procedure was done, on the day of randomisation. Survival curves were constructed with use of Kaplan-Meier estimates and the log-rank test was used to compare between-group differences. We pre-specified stratified analyses of the primary endpoint at 12 months for subgroups of patients with diabetes, ST-segment elevation myocardial infarction, small vessels (≤2·75 mm), multivessel treatment, long lesions (>18 mm), in-stent restenosis, bypass graft, left main treatment, bifurcation treatment, or overlapping stents. We calculated the interaction p value for the subgroup analysis. Unless otherwise specified, a two-sided p value of less than 0·05 was considered to indicate statistical significance. All statistical analyses were done using SAS software version 9.3. An independent data safety and monitoring board monitored the individual and collective safety of the patients in the study during the enrolment phase. This trial is registered with ClinicalTrials.gov, number NCT 02870140.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report, and did not participate in the decision to submit the manuscript for publication. The executive committee (AZa, RJdW, UK, and PWS) had full access to all the data in the study, and the corresponding authors (YO and PWS) had full responsibility for the decision to submit for publication.

Results

Between Oct 21, 2016 and July 3, 2017, we randomly assigned 1435 patients with a total of 2076 lesions to

either the Supraflex group (720 patients with 1046 lesions) or the Xience group (715 patients with 1030 lesions; figure 1). Five patients in the Supraflex group did not undergo percutaneous coronary intervention. 11 patients (1·5%) in the Supraflex group and seven patients (1·0%) in the Xience group withdrew consent within 12 months of the procedure. Baseline clinical characteristics were similar in the two study groups (table 1). 429 patients (59·6%) in the Supraflex group and 405 (56·6%) in the Xience group presented with acute coronary syndrome. To enable a timely report of the primary endpoint, the steering committee decided to encourage patients who were randomly assigned between June 3 and July 3, 2017 (last month of enrolment) to undergo the 1-year follow-up visit before 360 days had passed, with a minimum of 330 days after the index procedure. 720 patients from the Supraflex group and 715 from the Xience group were included in the intention-to-treat population.

Overall, lesion characteristics were similar between the two groups (table 2). Mean pre-dilatation balloon diameter was larger in the Supraflex group than in the Xience group. Mean stent length and diameter per stent were similar between groups. The number of stents used was not different between both groups. Mean post-dilatation balloon length was greater in the Xience group than in the Supraflex group. The device success proportion was analysed in 2000 lesions in which investigators attempted to implant the allocated stent. The detailed reasons for not using the allocated stent are provided in the appendix. The device success proportion per lesion in both groups was high, but there was significant difference between the Supraflex and the Xience group (973 [97·6%] of 997 lesions *vs* 998 [99·5%] of 1003; difference –1·9%, 95% CI –3·0 to –0·9; p=0·0003; appendix). This difference was mainly driven by increased crossover to non-allocated stent in the Supraflex group compared with that in the Xience group. There were no differences in the residual in-stent stenosis of 30% or greater between groups. This difference in device success did not affect in-hospital patient outcomes (in-hospital device-oriented composite endpoint 11 [1·5%] of 720 patients *vs* 10 [1·4%] of 715; difference 0·1%, 95% CI –1·2 to 1·5; p=0·837).

The primary device-oriented composite endpoint occurred in 35 (4·9%) of 720 patients in the Supraflex group and in 37 (5·3%) of 715 in the Xience group (table 3, figure 2A). Non-inferiority of the Supraflex stent compared with the Xience stent was shown, with an absolute difference of –0·3% and one-sided 95% upper confidence bound of 1·6% ($p_{non\text{-}inferiority}$ <0·0001, $p_{superiority}$=0·801). The frequencies of cardiac death, target vessel myocardial infarction, and clinically indicated target lesion revascularisation were similar for both stent types (table 3, figure 2). The details of cardiac deaths are described in the appendix. Results of the device-oriented composite endpoint from the per-protocol analysis, including 1345 patients, also showed non-inferiority of Supraflex compared with Xience (23 [3·5%] of 660 patients in the Supraflex group *vs* 30 [4·4%] of 685 in the Xience group; difference –0·9%, 95% CI –3·0 to 1·2; $p_{non\text{-}inferiority}$ <0·0001, $p_{superiority}$=0·41), with a significantly lower clinically indicated target

	Supraflex (1046 lesions)	Xience (1030 lesions)
Vessel location		
LAD	468 (44·7%)	432 (41·9%)
LCX	220 (21·0%)	237 (23·0%)
RCA	338 (32·3%)	328 (31·8%)
Left main	15 (1·4%)	16 (1·6%)
Bypass graft	5 (0·5%)	17 (1·7%)
Number of lesions treated per patient	1·45 (0·77; n=720)	1·44 (0·74; n=715)
Total stent length per patient (mm)	37·2 (27·4; n=709)	37·2 (27·0; n=710)
Index PCI undertaken	715 (99·3%; n=720)	715 (100%; n=715)
Reason PCI not undertaken		
Medical treatment only	3 (0·4%; n=720)	0
Other	2 (0·3%; n=720)	0
TIMI flow pre-procedure		
Flow 0	143 (13·7%)	112 (10·9%)
Flow 1	40 (3·8%)	42 (4·1%)
Flow 2	66 (6·3%)	84 (8·2%)
Flow 3	758 (72·5%)	744 (72·2%)
Assessment not done	39 (3·7%)	48 (4·7%)
Restenotic lesion	44 (4·2%)	42 (4·1%)
Small vessel (≤2·75 mm)	420 (40·2%)	414 (40·2%)
Long lesion (>18 mm)	518 (49·7%; n=1042)	511 (49·6%)
Bifurcation involved	167 (16·0%)	157 (15·2%)
Thrombus aspiration	40 (3·8%)	39 (3·8%)
Pre-dilatation	807 (77·2%)	782 (75·9%)
Maximum pressure (atm)	13·6 (4·3; n=801)	13·5 (4·1; n=777)
Maximum balloon length (mm)	15·75 (4·77; n=805)	15·40 (4·50; n=782)
Maximum balloon diameter (mm)	2·52 (0·43; n=805)	2·46 (0·43; n=782)
Stent characteristics		
Number of stents used per lesion	1·2 (0·5; n=1046)	1·2 (0·5; n=1030)
Total stent length per lesion (mm)	25·7 (14·5; n=1028)	26·0 (14·5; n=1015)
Overlapping stents per lesion	221 (21·1%)	201 (19·5%)
Stent length per stent (mm)	21·3 (8·3; n=1239)	21·8 (8·8; n=1208)
Stent diameter per stent (mm)	3·0 (0·5; n=1239)	3·0 (0·5; n=1208)
Post-stenting balloon dilatation	544 (52·0%)	538 (52·2%)
Maximum pressure (atm)	17·1 (4·3; n=543)	17·5 (3·9; n=532)
Maximum balloon length (mm)	13·79 (4·83; n=544)	14·39 (4·88; n=537)
Maximum balloon diameter (mm)	3·30 (0·58; n=544)	3·29 (0·60; n=538)
TIMI flow post-procedure		
Flow 0	7 (0·7%)	1 (0·1%)
Flow 1	2 (0·2%)	3 (0·3%)
Flow 2	11 (1·1%)	9 (0·9%)
Flow 3	995 (95·1%)	975 (94·7%)
Assessment not done	31 (3·0%)	42 (4·1%)

(Table 2 continues on next page)

	Supraflex (1046 lesions)	Xience (1030 lesions)
(Continued from previous page)		
Any periprocedural complication	48 (6·7%; n=715)	40 (5·6%; n=715)
Dissection	20 (2·8%; n=715)	16 (2·2%; n=715)
Occlusion	7 (1·0%; n=715)	9 (1·3%; n=715)
Coronary spasm	0 (0·0%; n=715)	0 (0·0%; n=715)
Coronary embolism	3 (0·4%; n=715)	2 (0·3%; n=715)
Coronary perforation	3 (0·4%; n=715)	2 (0·3%; n=715)
Thrombi at stented site	1 (0·1%; n=715)	1 (0·1%; n=715)
Other	17 (2·4%; n=715)	14 (2·0%; n=715)

Data are n (%) or mean (SD). LAD=left anterior descending artery. LCX=left circumflex artery. RCA=right coronary artery. PCI=percutaneous coronary intervention. TIMI=thrombolysis in myocardial infarction.

Table 2: **Angiographic and procedural characteristics**

lesion revascularisation in the Supraflex group (8 [1·2%] patients in Supraflex *vs* 21 [3·1%] in Xience; difference –1·9%, –3·5 to –0·3; p=0·021; appendix).

At 12 months, definite or probable stent thrombosis did not differ between groups (table 3). In the Supraflex group, there were two unexplained and unwitnessed deaths attributed to possible stent thrombosis according to ARC-1 definition. Frequency of any stent thrombosis (definite, probable, or possible) also did not differ between groups (table 3).

The patient-oriented composite endpoint was similar between the Supraflex group and the Xience group (table 3). There were 18 all-cause deaths in the trial and, as described previously, cardiac death was not statistically different between groups (table 3). Seven deaths in the Supraflex group were related to non-cardiac conditions (eg, cancer, sepsis, and pneumonia), compared with two deaths in the Xience group. The treatment effect of Supraflex against Xience was consistent across subgroups, except for patients with small vessels (≤2·75 mm; figure 3). In the per-protocol analysis of our study (appendix), Supraflex showed a 20% relative risk reduction in device-oriented composite endpoint at 1 year, mainly driven by a 61% reduction in clinically indicated target lesion revascularisation.

The proportion of patients on dual antiplatelet therapy did not differ between the two groups at 6 and 12 months (626 [89·9%] of 696 patients in the Supraflex group *vs* 642 [91·3%] of 703 in the Xience group, p=0·376 at 6 months, and 552 [80·2%] of 688 in the Supraflex group *vs* 575 [81·8%] of 703 in the Xience group, p=0·458 at 12 months).

Discussion

In the TALENT study, we showed that Supraflex, a sirolimus-eluting coronary stent with biodegradable polymer coating and ultra-thin struts, was non-inferior to the standard of care, an everolimus-eluting stent with durable polymer coating, for a device-oriented composite endpoint of cardiac death, target-vessel myocardial infarction, or clinically indicated target lesion revascularisation at 12 months, in an all-comer European population.

Although device success was high in our study, we found a significant difference that favoured Xience over Supraflex (appendix). This difference was mainly due to a crossover to the comparator that has been on the market for over a decade and with which the investigators are very familiar. When resistance in crossing a lesion was found, some investigators (in seven of 23 centres) tended to quickly crossover to a familiar stent technology. Despite the slight difference in device success proportions between the groups, the success proportions of Supraflex are similar or even superior to other drug-eluting stents in all-comer trials (appendix).[17–19] For instance, device success proportion in the TARGET all-comer trial[18] was 92·4% in the FIREHAWK group and 94·8% in the Xience group, whereas in the BIOFLOW V trial,[8] a non-all-comer trial, it was 98% in the Orsiro group and 97% in the Xience group.

Supraflex, in line with current generation drug-eluting stents with a biodegradable polymer coating and an ultra-thin strut thickness (60 µm), was designed to overcome the limitations of the second-generation drug-eluting stents with durable polymer coating, which have been reported with 2–3% annual increased rate for the device-oriented composite endpoint 1 year after the procedure.[20] By contrast with the Orsiro stent, all Supraflex stents have the same strut thickness, irrespective of their diameter (from 2·00 mm to 4·50 mm). In our study, visual assessment or quantitative coronary angiography online by the operator showed absence of recoil, supporting findings already documented in a previous study.[21] Regarding the MiStent stent, there is a fundamental difference between the drug release kinetics of MiStent and Supraflex. Drug release is completed in 48 days, with a burst elution of 70% within the first 7 days, with the Supraflex stent, whereas MiStent has no drug release within the first 3 days and its polymer is fully biodegraded and resorbed within 3 months after implantation, but microcrystalline sirolimus is impacted and embedded in the vessel wall, acting as a tissue reservoir for 270 days. The arterial sirolimus concentrations still reach more than 2 ng/mg at 270 days. Additionally, the clinical outcome of Supraflex in our study is similar to Orsiro and MiStent in their pivotal trials (appendix).[5,6,8,22]

A meta-analysis[9] published in 2018, of ten randomised trials including 11 658 patients, compared the performance of three drug-eluting stents with ultra-thin struts (Orsiro, MiStent, and BioMime) with that of three second-generation drug-eluting stents with thicker struts (Xience, Resolute, and Nobori). The results showed that newer generation stents with ultra-thin struts were associated with a 16% relative risk

	Supraflex (n=720)	Xience (n=715)	Difference, % (95% CI)	p value
Primary outcome				
Device-oriented composite endpoint*	35 (4·9%)	37 (5·3%)	−0·3% (−2·6 to 2·0)	0·801†
Separate endpoints for the primary outcome				
Cardiac death	7 (1·0%)	2 (0·3%)	0·7% (−0·1 to 1·5)	0·097
Target-vessel myocardial infarction‡	18 (2·5%)	20 (2·8%)	−0·3% (−2·0 to 1·4)	0·734
Clinically indicated target lesion revascularisation	19 (2·7%)	28 (4·0%)	−1·3% (−3·2 to 0·6)	0·183
Secondary outcomes				
Patient-oriented composite endpoint§	70 (9·9%)	61 (8·7%)	1·2% (−1·8 to 4·3)	0·434
Target-vessel failure¶	38 (5·4%)	43 (6·1%)	−0·8% (−3·2 to 1·7)	0·565
Any death	14 (2·0%)	4 (0·6%)	1·4% (0·3 to 2·6)	0·019
Cardiac death	7 (1·0%)	2 (0·3%)	0·7% (−0·1 to 1·5)	0·097
Any myocardial infarction‡	22 (3·1%)	26 (3·7%)	−0·6% (−2·5 to 1·3)	0·551
Q wave	3 (0·4%)	3 (0·4%)	0·0% (−0·7 to 0·7)	0·996
Non-Q wave	19 (2·7%)	24 (3·4%)	−0·7% (−2·5 to 1·1)	0·435
Target-vessel myocardial infarction‡	18 (2·5%)	20 (2·8%)	−0·3% (−2·0 to 1·4)	0·734
Q wave	2 (0·3%)	3 (0·4%)	−0·1% (−0·8 to 0·5)	0·651
Non-Q wave	16 (2·3%)	18 (2·6%)	−0·3% (−1·9 to 1·3)	0·721
Non-target-vessel myocardial infarction‡	4 (0·6%)	6 (0·9%)	−0·3% (−1·2 to 0·6)	0·523
Q wave	1 (0·1%)	0 (0·0%)	0·1% (−0·1 to 0·4)	0·317
Non-Q wave	3 (0·4%)	6 (0·9%)	−0·4% (−1·3 to 0·4)	0·314
Periprocedural myocardial infarction‡	5 (0·7%)	6 (0·8%)	−0·1% (−1·0 to 0·8)	0·755
Any revascularisation	51 (7·3%)	52 (7·4%)	−0·2% (−2·9 to 2·6)	0·914
Target lesion revascularisation	25 (3·5%)	30 (4·3%)	−0·7% (−2·8 to 1·3)	0·494
Clinically indicated	19 (2·7%)	28 (4·0%)	−1·3% (−3·2 to 0·6)	0·183
Non-clinically indicated	7 (1·0%)	6 (0·8%)	0·1% (−0·9 to 1·1)	0·788
Target vessel revascularisation	29 (4·1%)	38 (5·4%)	−1·3% (−3·6 to 0·9)	0·263
Clinically indicated	23 (3·3%)	35 (5·0%)	−1·7% (−3·8 to 0·3)	0·109
Non-clinically indicated	7 (1·0%)	10 (1·4%)	−0·4% (−1·6 to 0·7)	0·459
Non-target vessel revascularisation	33 (4·7%)	21 (3·0%)	1·7% (−0·3 to 3·7)	0·098
Thrombosis endpoints				
Definite stent thrombosis	5 (0·7%)	5 (0·7%)	0·0% (−0·9 to 0·9)	0·996
Acute (0–1 days)	1 (0·1%)	0 (0·0%)	0·1% (−0·1 to 0·4)	0·319
Subacute (2–30 days)	1 (0·1%)	2 (0·3%)	−0·1% (−0·6 to 0·3)	0·562
Late (31–360 days)	3 (0·4%)	3 (0·4%)	0·0% (−0·7 to 0·7)	0·997
Definite or probable stent thrombosis	6 (0·8%)	6 (0·9%)	0·0% (−1·0 to 1·0)	0·996
Acute (0–1 days)	1 (0·1%)	0 (0·0%)	0·1% (−0·1 to 0·4)	0·319
Subacute (2–30 days)	2 (0·3%)	2 (0·3%)	0·0% (−0·6 to 0·5)	0·998
Late (31–360 days)	3 (0·4%)	4 (0·6%)	−0·1% (−0·9 to 0·6)	0·701
Possible stent thrombosis	2 (0·3%)	0 (0·0%)	0·3% (−0·1 to 0·7)	0·159
Any stent thrombosis	8 (1·1%)	6 (0·9%)	0·3% (−0·8 to 1·3)	0·597

Data are n (%). *Cardiac death, target-vessel myocardial infarction, or clinically indicated target lesion revascularisation. †p value for non-inferiority was <0·0001; one-sided 95% upper confidence bound was 1·6%. ‡Determined on the basis of the Society for Cardiovascular Angiography and Interventions 2013 definition within 48 h post procedure or the third universal definition after 48 h post procedure. §All-cause death, any myocardial infarction, or any revascularisation. ¶Cardiac death, target-vessel myocardial infarction, or clinically indicated target vessel revascularisation.

Table 3: **Clinical outcomes at 12 months after stent implantation, by intention to treat**

reduction in device-oriented composite endpoint at 1 year. Additionally, in that meta-analysis, ultra-thin strut stents had numerically, but not significantly, lower prevalences of stent thrombosis.[9] One theoretical disadvantage of thicker struts compared with ultra-thin struts is that thick, protruding struts disrupt the laminar flow and induce flow disturbance, which could further activate a platelet-signalling procoagulation pathway.[23,24] Whether the benefit of drug-eluting stents with thin struts could improve clinical outcomes remains to be assessed by studies with longer follow-up periods.

Supraflex has both thinner total thickness (strut plus coating is 68–70 μm) and shorter duration of drug

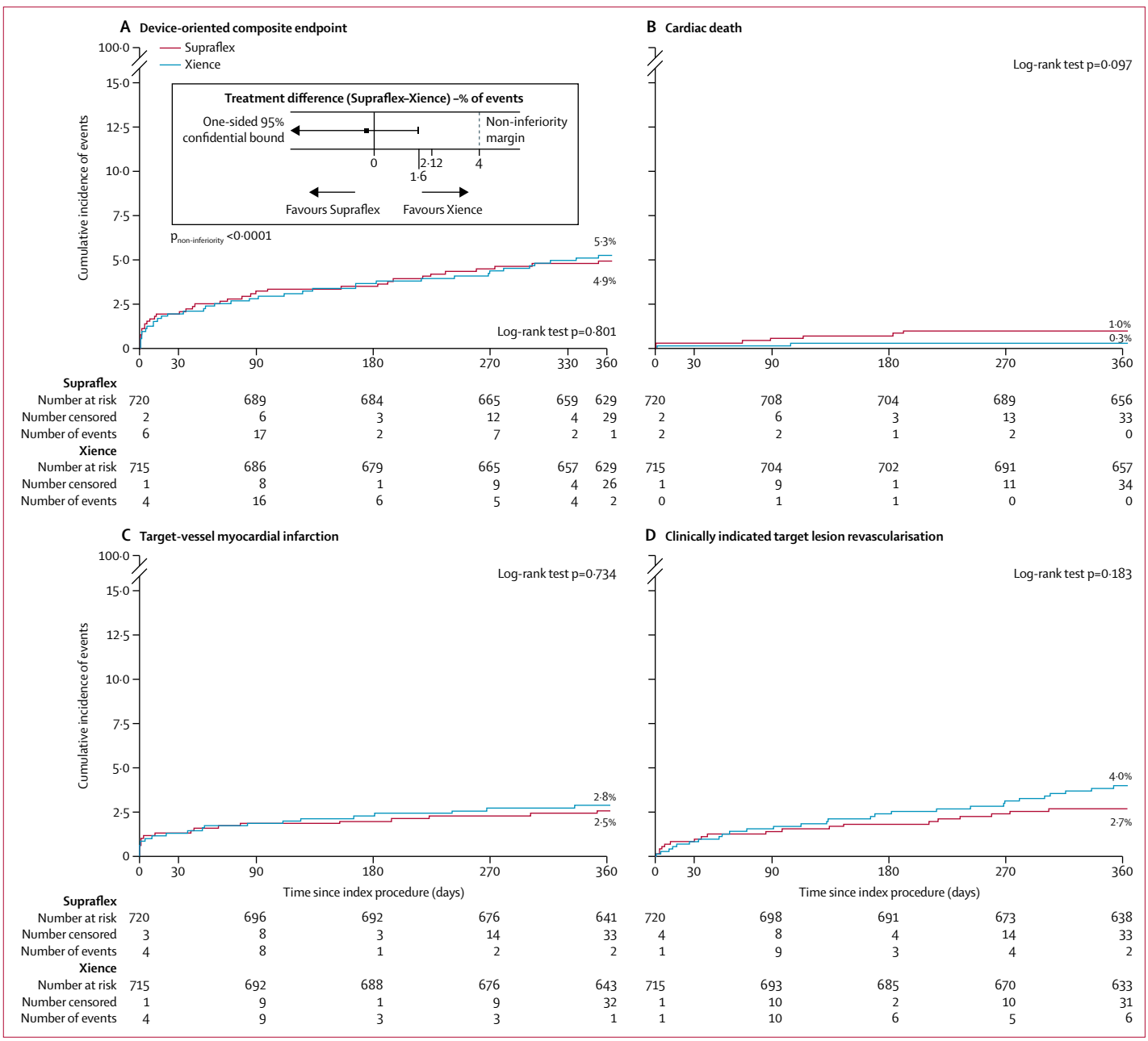

Figure 2: **Kaplan-Meier plot for primary endpoint and its components over 360 days of follow-up**
Kaplan-Meier curves show the cumulative incidence of device-oriented composite endpoint (primary endpoint; A) and of its components: cardiac death (B), target-vessel myocardial infarction (C), and clinically indicated target lesion revascularisation (D).

release (48 days) than those of Xience. In an optical coherence tomography subanalysis in the FLEX registry,[11] Supraflex showed excellent strut coverage of 98·1% at 6 months, whereas strut coverage of Xience was 94·1% in a previous study.[25] Moreover, Supraflex had a favourable healing score in the FLEX registry, which might be attributed to its ultra-thin strut thickness and shorter duration of drug release. The early healing process of Supraflex might allow shorter duration of dual antiplatelet therapy, although further study is needed to assess this.

Our study had some limitations. The observed device-oriented composite endpoint in the control group was lower than the estimated event rate in the sample size calculation. This was mainly due to lower prevalence of target vessel myocardial infarction in the Xience group than in the referenced trial, RESOLUTE.[17] This difference might be caused by different definitions of periprocedural

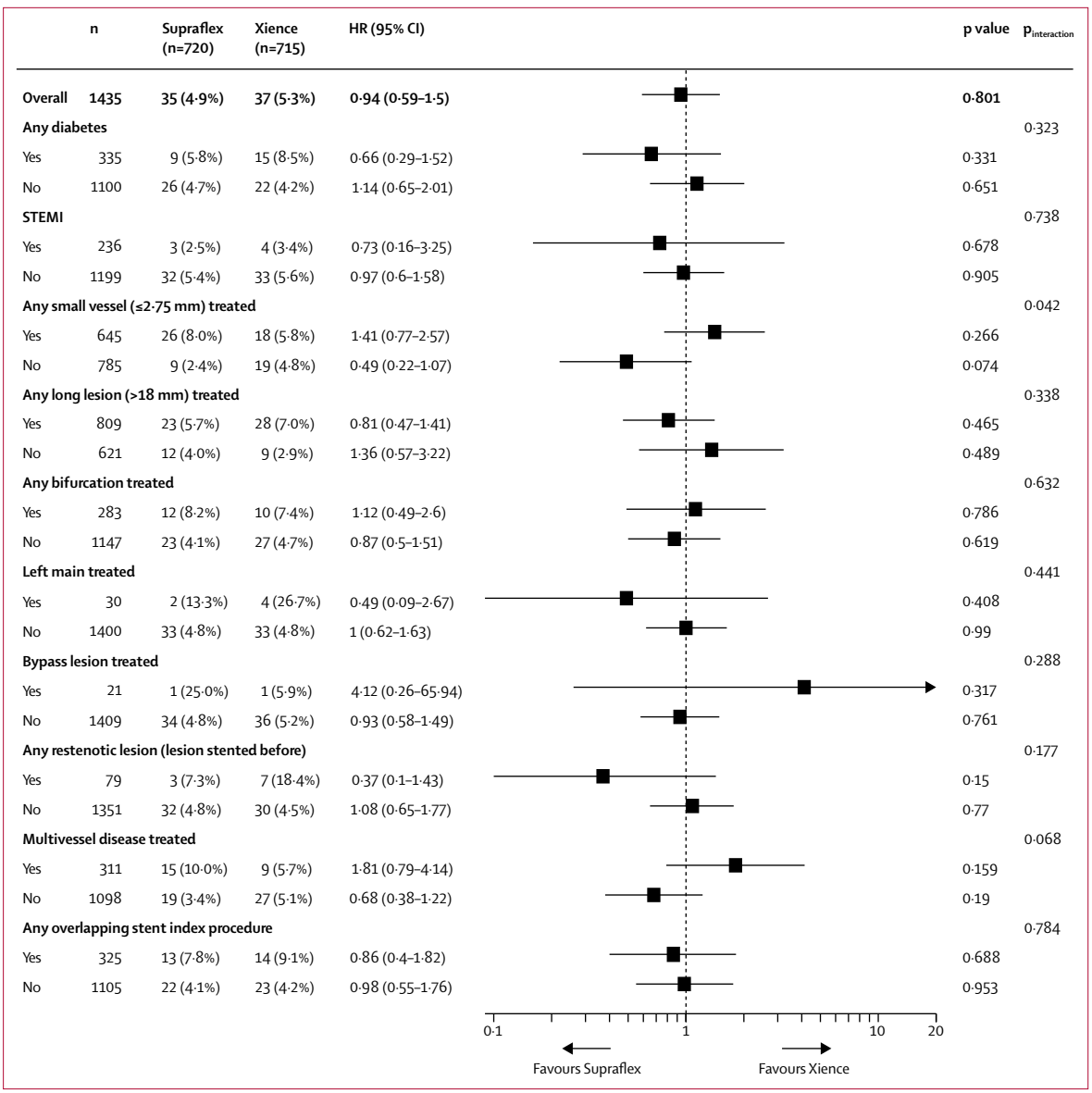

Figure 3: **Stratified analyses of the device-oriented composite endpoint at 12 months across subgroups**
Hazard ratio (HR) with 95% CI and p value results were from Cox proportional hazards analysis. STEMI=ST-segment elevation myocardial infarction.

myocardial infarction. In the TALENT study, the Society for Cardiovascular Angiography and Interventions consensus, which is more clinically relevant in terms of prognosis, was adopted for defining periprocedural myocardial infarction.[15]

The predefined non-inferiority margin might be considered, in retrospect, to be too wide. The original non-inferiority margin of 4·0% was determined as half of the device-oriented clinical endpoint prevalence of 8·3% in the Xience group of the RESOLUTE trial.[17] However, with a post-hoc non-inferiority margin of 2·1%, which corresponds to a hazard ratio of 1·4 based on the observed device-oriented composite endpoint prevalence in the Xience group, non-inferiority would still be met (post-hoc $p_{non\text{-}inferiority}$=0·019).

Although the trial was not powered for all-cause mortality, we found a significant difference in all-cause death between the two groups. The all-cause mortality (0·6%) of the TALENT trial was lower than that observed in the other all-comer trials, such as TARGET,[18] BIOSCIENCE,[6] TWENTE,[26] and RESOLUTE[17] (2·2–2·8%), suggesting the play of chance (appendix).

This 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.

1-year follow-up visits were done up to 30 days earlier than 360 days in 55 patients, although the effect of this early follow-up on primary endpoint measurement would be minimal with the Kaplan-Meier method. Finally, our report was limited to a short follow-up of 12 months. The protocol specifies that the follow-up of patients will continue for up to 3 years to assess the long-term benefits of biodegradable polymer coating (NCT02870140).

In conclusion, the Supraflex sirolimus-eluting stent with biodegradable polymer coating and ultra-thin strut was non-inferior to the Xience everolimus-eluting stent with durable polymer coating for a device oriented composite clinical endpoint at 12 months in an all-comer population.

Contributors

AZa, RJdW, UK, YO, and PWS contributed to the conception and design of the study. PT, SH, AZu, PCS, JP, RMor, ACh, IP, ACe, NKu, AH, AI, IU, AS, RJG, SW, GT, AM, BM, ACo, and SI contributed to data collection. AZa, RJdW, NKo, CCC, RMod, ES, OS, UK, YO, and PWS analysed and interpreted the data. NKo, CCC, RMod, YO, and PWS drafted the report, which was critically revised for important intellectual content by AZa, RJdW, UK, YO, and PWS. All authors approved the final version of the report.

Declaration of interests

AZa reports speaker fees from SMT and speaker and consulting fees from Abbott Vascular. ES received institutional grants from European Cardiovascular Research Institute during the conduct of the study. SH reports unrestricted research grant to institution by Abbott Vascular. PCS reports grants and personal fees from Abbott Vascular, St Jude Medical, and personal fees from Terumo and AstraZeneca, during the conduct of the study. NKu reports grants from DalCor Pharmaceuticals, Hamilton Health Sciences Corporation, Population Health Research Institute, and Bayer, and personal fees from Pfizer and AstraZeneca, outside the submitted work. SW reports grants and personal fees from Abbott Vascular, outside the submitted work. AM reports grants from Cardialysis, during the conduct of the study. BM reports grants from Abbott Vascular, Medtronic, Biotronik, and Boston Scientific, outside the submitted work. YO is a member of the Advisory Board of Abbott Vascular. PWS reports personal fees from Abbot Laboratories, AstraZeneca, Biotronik, Cardialysis, GLG Research, Medtronic, Sino Medical Sciences Technology, Société Europa Digital Publishing, Stentys France, Svelte Medical Systems, Philips/Volcano, St Jude Medical, Qualimed, and Xeltis, outside the submitted work. All other authors declare no competing interests.

Data sharing

All data, including study participant data, data dictionary, statistical analysis plan, and informed consent, will not be shared. The protocol is available online.

For the **study protocol** see https://clinicaltrials.gov/ct2/show/NCT02870140

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