A sirolimus-eluting bioabsorbable polymer-coated stent (MiStent) versus an everolimus-eluting durable polymer stent (Xience) after percutaneous coronary intervention (DESSOLVE III): a randomised, single-blind, multicentre, non-inferiority, phase 3 trial

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Summary

Background MiStent is a drug-eluting stent with a fully absorbable polymer coating containing and embedding a microcrystalline form of sirolimus into the vessel wall. It was developed to overcome the limitation of current durable polymer drug-eluting stents eluting amorphous sirolimus. The clinical effect of MiStent sirolimus-eluting stent compared with a durable polymer drug-eluting stents has not been investigated in a large randomised trial in an all-comer population.

Methods We did a randomised, single-blind, multicentre, phase 3 study (DESSOLVE III) at 20 hospitals in Germany, France, Netherlands, and Poland. Eligible participants were any patients aged at least 18 years who underwent percutaneous coronary intervention in a lesion and had a reference vessel diameter of 2·50–3·75 mm. We randomly assigned patients (1:1) to implantation of either a sirolimus-eluting bioresorbable polymer stent (MiStent) or an everolimus-eluting durable polymer stent (Xience). Randomisation was done by local investigators via web-based software with random blocks according to centre. The primary endpoint was a non-inferiority comparison of a device-oriented composite endpoint (DOCE)—cardiac death, target-vessel myocardial infarction, or clinically indicated target lesion revascularisation—between the groups at 12 months after the procedure assessed by intention-to-treat. A margin of 4·0% was defined for non-inferiority of the MiStent group compared with the Xience group. All participants were included in the safety analyses. This trial is registered with ClinicalTrials.gov, number NCT02385279.

Findings Between March 20, and Dec 3, 2015, we randomly assigned 1398 patients with 2030 lesions; 703 patients with 1037 lesions were assigned to MiStent, of whom 697 received the index procedure, and 695 patients with 993 lesions were asssigned to Xience, of whom 690 received the index procedure. At 12 months, the primary endpoint had occurred in 40 patients (5·8%) in the sirolimus-eluting stent group and in 45 patients (6·5%) in the everolimus-eluting stent group (absolute difference –0·8% [95% CI –3·3 to 1·8], $p_{non\text{-}inferiority}$=0·0001). Procedural complications occurred in 12 patients (1·7%) in the sirolimus-eluting stent group and ten patients (1·4%) in the everolimus-eluting stent group; no clinical adverse events could be attributed to these dislodgements through a minimum of 12 months of follow-up. The rate of stent thrombosis, a safety indicator, did not differ between groups and was low in both treatment groups.

Interpretation The sirolimus-eluting bioabsorbable polymer stent was non-inferior to the everolimus-eluting durable polymer stent for a device-oriented composite clinical endpoint at 12 months in an all-comer population. MiStent seems a reasonable alternative to other stents in clinical practice.

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Introduction

Several novel stent technologies have been developed to improve early and late clinical outcomes in the treatment of coronary artery disease. The first generation of drug-eluting stents was coated with a permanent polymer, which eluted a drug that inhibited the excessive growth of neointimal tissue. Although drug-eluting stents succeeded in suppressing neointimal hyperplasia,[1,2] the presence of these durable polymers might contribute to complications including delayed vessel healing, hypersensitivity reactions, neoatherosclerosis, and restenosis, with the added risks of repeat intervention, stent thrombosis, acute myocardial infarction, and sudden cardiac death.[3–7] To address the limitations of the first-generation drug-eluting stents, changes were made to three of their components: the change of a metallic

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Research in context

Evidence before this study

We searched PubMed and checked the conference listings for the EuroPCR, European Society of Cardiology, Transcatheter Cardiovascular Therapeutics, and American College of Cardiology for complete reports of randomised trials comparing MiStent, a sirolimus-eluting absorbable polymer coronary stent, with any other drug-eluting stents. We used the search terms "MiStent", and "randomised" for reports published in English up to June 13, 2017. We identified one such trial—the DESSOLVE II randomised controlled trial—in which patients given MiStent had less in-stent late lumen loss at 9 months than patients given a zotarolimus-eluting stent. In a retrospective, patient-matched propensity analysis of pooled data from three clinical trials (DESSOLVE I, DESSOLVE II, and ISAR-TEST-4), significantly less clinically indicated target-lesion revascularisation occurred with the sirolimus-eluting stent compared with the Xience everolimus-eluting durable polymer stent, at 1 year follow-up (1·0% *vs* 6·0%; p=0·05) and 3 years follow-up (2·0% *vs* 8·4%; p=0·05). However, no randomised studies had been published with a clinical primary endpoint.

Added value of this study

This is the first randomised trial with a clinical primary endpoint comparing a sirolimus-eluting absorbable polymer coronary stent with a contemporary durable polymer drug-eluting stent in an allcomer population of patients after percutaneous coronary intervention. The sirolimus-eluting stent was non-inferior to the everolimus-eluting stent for the device-oriented composite endpoint of cardiac death, target vessel myocardial infarction, or clinically indicated target lesion revascularisation at 12 months.

Implications of all the available evidence

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

platform with thin struts, and changes to the coating and drug-elution profile. One of the efforts to improve drug-eluting stent technology was to use temporary bioabsorbable polymers for the coating. Indeed, elimination of the polymer might lower the rates of stent thrombosis at a later phase, as suggested by results from a published comparison with first-generation drug-eluting stents.[8]

A sirolimus-eluting absorbable polymer coronary stent system (MiStent) was developed with the aim to further reduce neointima without compromising endothelial coverage of the thin struts that are expected to reduce injury to the vessel walls. MiStent has a fully absorbable polymer coating containing a microcrystalline form of sirolimus. The bioabsorbable coating disappears in 3 months, but sirolimus persists in the vessel walls for up to 9 months.

In the DESSOLVE I first-in-man trial,[9] patients with the sirolimus-eluting stent showed low and stable in-stent late lumen loss through an 18-month follow-up (median 0·08 mm, range –0·30 to 0·46). In the DESSOLVE II randomised controlled trial,[10] patients given the sirolimus-eluting stent had less in-stent late lumen loss at 9 months than patients given a zotarolimus-eluting stent (mean 0·27 mm [SD 0·46] *vs* 0·58 mm [0·41], p<0·001). In a retrospective, patient-matched propensity analysis of pooled data from three clinical trials[11] (DESSOLVE I, DESSOLVE II, and ISAR-TEST-4), significantly less clinically indicated target-lesion revascularisation occurred with the sirolimus-eluting stent compared with the best-in-class drug-eluting stent Xience, an everolimus-eluting durable polymer stent, at 1 year follow-up (1·0% *vs* 6·0%; p=0·05) and 3 years follow-up (2·0 % *vs* 8·4%; p=0·05). We therefore designed a trial to investigate non-inferiority of clinical outcomes after implantation of the sirolimus-eluting stent compared with the everolimus-eluting stent in a real-world setting.

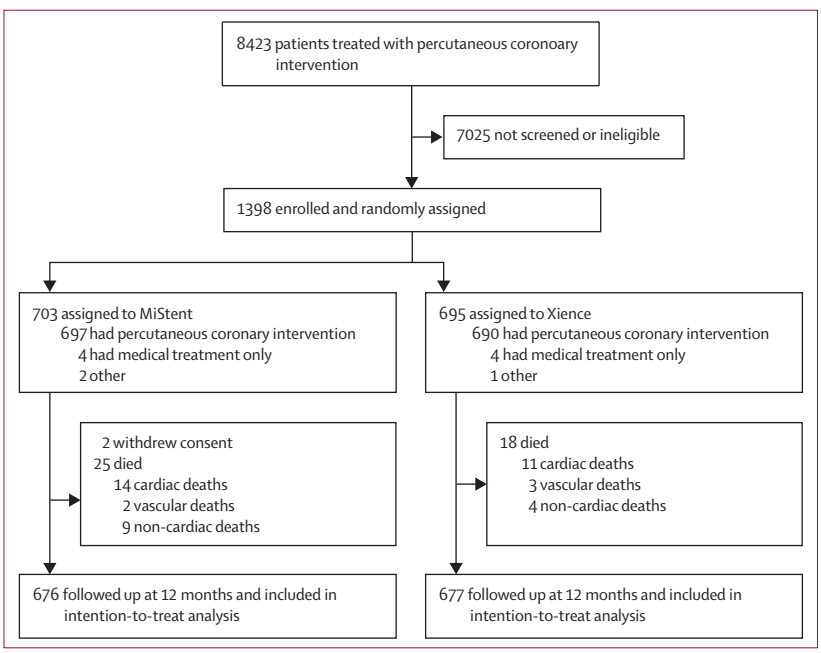

Figure 1: **Trial profile**

Methods

Study design and participants

We did a prospective, randomised, controlled, single-blind, multicentre study at 20 hospitals in Germany, France, Netherlands, and Poland (appendix). The study was approved by the ethics committee of each enrolling site. There were minimal inclusion and exclusion criteria for this study (appendix). Briefly, any patients

	MiStent SES (n=703)	Xience EES (n=695)
Age (years)	66·4 (10·7; n=703)	66·3 (10·7; n=695)
Sex		
Male	494/703 (70%)	513/695 (74%)
Female	209/703 (30%)	182/695 (26%)
Body-mass index (kg/m²)	27·9 (4·4; n=701)	28·1 (4·5; n=694)
Smoking status		
Current	171/644 (27%)	168/636 (26%)
Previous	203/644 (32%)	213/636 (34%)
Never	270/644 (42%)	255/636 (40%)
Diabetes mellitus		
Insulin-dependent	65/700 (9%)	61/689 (9%)
Non-insulin-dependent	121/700 (17%)	126/689 (18%)
No diabetes mellitus	514/700 (73%)	502/689 (73%)
Hypertension	496/694 (72%)	517/686 (75%)
Hypercholesterolaemia	408/671 (61%)	393/655 (60%)
Family history of coronary artery disease	245/628 (39%)	231/605 (38%)
Previous myocardial infarction	190/701 (27%)	192/691 (28%)
Established peripheral vascular disease	65/696 (9%)	72/686 (11%)
Previous PCI	236/701 (34%)	247/693 (36%)
Previous CABG	51/703 (7%)	66/694 (10%)
Heart failure	51/700 (7%)	52/690 (8%)
Renal insufficiency*	47/701 (7%)	46/689 (7%)
Indication		
Stable angina	289/703 (41%)	287/695 (41%)
Unstable angina	162/703 (23%)	166/695 (24%)
Non-ST elevation myocardial infarction	149/703 (21%)	133/695 (19%)
ST-elevation myocardial infarction	103/703 (15%)	109/695 (16%)

Data are mean (SD) or n (%). EES=everolimus-eluting stent. SES=sirolimus-eluting stent. PCI=percutaneous coronary intervention. CABG=coronary artery bypass graft. *Serum creatinine concentration >2·5 mg/dL or creatinine clearance ≤30 mL/min.

Table 1: **Baseline characteristics of the intention-to-treat population**

	MiStent SES (1037 lesions)	Xience EES (993 lesions)
Vessel location		
LAD	430 (41%)	394 (40%)
LCX	271 (26%)	259 (26%)
RCA	314 (30%)	317 (32%)
Left main	16 (2%)	14 (1%)
Bypass graft	6 (<1%)	9 (1%)
Number of lesions treated	1·49 (0·83; n=697)	1·44 (0·78; n=690)
Index PCI undertaken	697 (99%)	690 (99·3%)
Reason PCI not undertaken		
Medical treatment only	4 (<1%)	1 (<1%)
Other	2 (<1%)	4 (<1%)
TIMI flow pre-procedure		
Flow 0	92 (9%)	93 (9%)
Flow 1	36 (3%)	33 (3%)
Flow 2	187 (18%)	155 (16%)
Flow 3	647 (62%)	636 (64%)
Assessment not done	75 (7%)	76 (8%)
Restenotic lesion	31 (3%)	31 (3%)
Small vessel (≤2·75 mm)	422 (41%)	405 (41%)
Long lesion (>18 mm)	583 (56%)	468 (47%)
Bifurcation involved	77 (7%)	69 (7%)
Thrombus aspiration	34 (3%)	44 (4%)
Pre-dilatation	718 (69%)	663 (67%)
Maximum pressure (atm)	13·6 (3·7; n=718)	13·7 (3·5; n=663)
Maximum balloon length (mm)	15·9 (4·0; n=718)	16·3 (4·3; n=663)
Maximum balloon diameter (mm)	2·51 (0·41; n=718)	2·47 (0·40; n=663)
Stent characteristics		
Number of stents used per lesion	1·23 (0·56; n=1037)	1·23 (0·60; n=993)
Total stent length per lesion (mm)	24·2 (12·8; n=1025)	25·0 (14·9; n=983)
Overlapping stents per lesion*	197/897 (22·0%)	199/893 (22·3%)
Stent length per stent (mm)	19·4 (6·2; n=1278)	20·1 (8·1; n=1226)
Stent diameter per stent (mm)	3·03 (0·39; n=1278)	2·99 (0·41; n=1226)
Post-stenting balloon dilatation	450 (43%)	404 (41%)
Maximum pressure (mm)	16·5 (4·0; n=450)	16·7 (3·7; n=404)
Maximum balloon length (mm)	14·2 (4·7; n=450)	14·2 (5·3; n=404)
Maximum balloon diameter (mm)	3·22 (0·54; n=450)	3·17 (0·56; n=404)
TIMI flow post-procedure		
Flow 0	2 (<1%)	3 (<1%)
Flow 1	1 (<1%)	2 (<1%)
Flow 2	13 (1%)	16 (2%)
Flow 3	968 (93%)	913 (92%)
Assessment not done	53 (5%)	59 (6%)

Data are n (%) or mean (SD). SES=sirolimus-eluting stent. EES=everolimus-eluting stent. LAD=left anterior descending artery. LCX=left circumflex artery. RCA=right coronary artery. PCI=percutaneous coronary intervention. TIMI=thrombolysis in myocardial infarction. *For staged procedures, no information was available about overlapping stents.

Table 2: **Angiographic and procedural characteristics**

aged at least 18 years who underwent percutaneous coronary intervention in a lesion with a reference vessel diameter of 2·50–3·75 mm were included. The range of vessel diameter was determined by the fact that no regulatory data were available at the time of trial design to ensure the feasibility of overexpanding a 3·5 mm stent to more than 3·75 mm. All patients provided written informed consent to participate in the study.

Randomisation and masking

We randomly assigned patients (1:1) to implantation of either or an everolimus-eluting durable polymer stent (Xience). Randomisation was done by local investigators via web-based software with blocks of 24 patients and randomly ordered sub-blocks according to centre. Clinical data were adjudicated by an independent clinical event committee, which was masked to stent allocation along with patients.

Procedures

The metallic platform of MiStent (Micell Technologies, Durham, NC, USA) is a cobalt-chromium alloy with a thin 64 µm strut thickness. The stent coating (approximately 5 µm thick on the luminal surface and 15 µm thick on the abluminal surface)[12] consists of

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See **Online** for appendix

	MiStent SES (n=703)	Xience EES (n=695)	Percentage difference (95% CI)	p value
Primary outcome				
Device-oriented composite endpoint*	5·8% (40)	6·5% (45)	−0·8% (−3·3 to 1·8)	0·57
Separate endpoints for the primary outcome				
Cardiac death	2·0% (14)	1·6% (11)	0·4% (−1·0 to 1·8)	0·55
Target-vessel myocardial infarction†	1·9% (13)	1·9% (13)	0 (−1·4 to 1·4)	0·99
Clinically indicated target-lesion revascularisation	1·9% (13)	3·1% (21)	−1·2% (−2·8 to 0·5)	0·17
Secondary outcomes				
Patient-oriented composite endpoint‡	13·3% (93)	14·6% (101)	−1·2% (−4·9 to 2·4)	0·55
Major adverse cardiac event§	9·3% (65)	9·4% (65)	−0·1% (−3·1 to 3·0)	1·00
Target vessel failure¶	6·5% (45)	7·7% (53)	−1·2% (−3·9 to 1·5)	0·40
Any death	3·6% (25)	2·6% (18)	1·0% (−0·8 to 2·8)	0·29
Cardiac death	2·0% (14)	1·6% (11)	0·4% (−1·0 to 1·8)	0·55
Any myocardial infarction†	2·4% (17)	2·2% (15)	0·3% (−1·3 to 1·9)	0·73
Q wave	0·4% (3)	0·9% (6)	−0·4% (−1·3 to 0·4)	0·31
Non-Q wave	2·0% (14)	1·4% (10)	0·6% (−0·8 to 1·9)	0·42
Target-vessel myocardial infarction†	2·2% (15)	1·9% (13)	0·3% (−1·2 to 1·8)	0·72
Q wave	0·4% (3)	0·7% (5)	−0·3% (−1·1 to 0·5)	0·47
Non-Q wave	1·7% (12)	1·3% (9)	0·4% (−0·9 to 1·7)	0·52
Non-target-vessel myocardial infarction†	0·3% (2)	0·3% (2)	0 (−0·6 to 0·6)	1·00
Q wave	0	0·1% (1)	−0·1% (−0·4 to 0·1)	0·32
Non-Q wave	0·3% (2)	0·1% (1)	0·1% (−0·4 to 0·6)	0·56
Periprocedural myocardial infarction†	1·4% (10)	1·2% (8)	0·3% (−0·9 to 1·5)	0·65
Any revascularisation	8·9% (61)	11·4% (78)	−2·5% (−5·7 to 0·7)	0·14
Target-lesion revascularisation	3·4% (23)	4·1% (28)	−0·7% (−2·8 to 1·3)	0·48
Clinically indicated	2·6% (18)	3·8% (26)	−1·2% (−3·1 to 0·7)	0·22
Non-clinically indicated	1·3% (9)	1·2% (8)	0·1% (−1·0 to 1·3)	0·80
Target-vessel revascularisation	4·7% (32)	5·9% (40)	−1·2% (−3·6 to 1·2)	0·34
Clinically indicated	3·5% (24)	5·0% (34)	−1·5% (−3·6 to 0·7)	0·18
Non-clinically indicated	1·9% (13)	1·9% (13)	0 (−1·5 to 1·4)	0·99
Non-target-vessel revascularisation	5·6% (38)	7·2% (49)	−1·6% (−4·2 to 1·0)	0·23
Thrombosis endpoints				
Definite stent thrombosis	0·4% (3)	0·7% (5)	−0·3% (−1·1 to 0·5)	0·48
Acute (0–1 days)	0	0	0	NA
Sub-acute (2–30 days)	0	0·1% (1)	−0·1% (−0·4 to 0·1)	0·32
Late (31–360 days)	0·4% (3)	0·6% (4)	−0·1% (−0·9 to 0·6)	0·71
Definite or probable stent thrombosis	0·7% (5)	0·9% (6)	−0·1% (−1·1 to 0·8)	0·76
Acute (0–1 days)	0	0	0	NA
Sub-acute (2–30 days)	0·3% (2)	0·3% (2)	−0·0% (−0·6 to 0·6)	0·99
Late (31–360 days)	0·4% (3)	0·6% (4)	−0·1% (−0·9 to 0·6)	0·71

Data are percentage (n). SES=sirolimus-eluting stent. EES=everolimus-eluting stent. NA=not applicable.*Cardiac death, target-vessel myocardial infarction, or clinically indicated target-lesion revascularisation. †Determined on the basis of the extended historical definition. ‡All-cause death, any myocardial infarction, or any revascularisation. §All-cause death, any myocardial infarction, or any target-vessel 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**

polylactide–coglycolic acid loaded with microcrystalline particles of sirolimus. The electrostatic coating process results in the deposition of dry-powder crystalline sirolimus onto the stent surface. This is a solvent-free coating process further differentiated by the use of supercritical fluid technology to apply the polymer component.[13] The polymer is fully biodegraded and resorbed within 3 months after implantation but sirolimus remains in the tissue surrounding the stent for up to 9 months to continue to control the growth of neointimal tissue.[14] Available stent diameters for this trial were 2·50, 2·75, 3·00, and 3·50 mm and available stent lengths were 9–30 mm (appendix).

The control everolimus-eluting durable polymer stent (Xience; Abbott Vascular, Santa Clara, CA, USA) is a cobalt–chromium alloy device with 81 µm of strut thickness and a 7·8 µm-thick durable polymer coating. The durable polymer is made of polyvinylidene fluoride-hexafluoropropylene loaded with everolimus.[15] Only everolimus-eluting stents of similar diameter and lengths to those of the sirolimus-eluting stents were used (ie, those up to 30 mm length with diameters between 2·5 mm and 3·5 mm were allowed for implantation; appendix).

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 acute coronary syndrome, the order of preference was ticagrelor, prasugrel (or clopidogrel) according to local practice and drug availability.[16]

Cardiac biomarkers (creatine kinase, creatine kinase-myocardial band, and troponin I or T) were drawn within 24 h before percutaneous coronary intervention and approximately 6 h after the procedure. Patients were followed up by hospital visit at 1 and 12 months and by phone contact at 6 months to assess clinical status and adverse events.

Outcomes

The primary endpoint of the study was a non-inferiority comparison at 12 months of a device-oriented composite endpoint in the sirolimus-eluting stent group compared with the everolimus-eluting stent group. A device-oriented composite primary endpoint was defined as occurrence of either cardiac death, myocardial infarction not clearly attributable to a non-target vessel, or clinically indicated target lesion revascularisation. The main secondary endpoint was a patient-oriented composite endpoint of any death, any myocardial infarction, and any revascularisation. Other secondary endpoints of the study are in the appendix.

Stent thrombosis, a safety indicator, was adjudicated according to the definition from the Academic Research Consortium.[17] Myocardial infarction including periprocedural and spontaneous myocardial infarction was defined according to WHO's extended definition.[18]

Statistical analysis

The trial was powered for testing of non-inferiority for the primary endpoint at 12 months after the procedure.

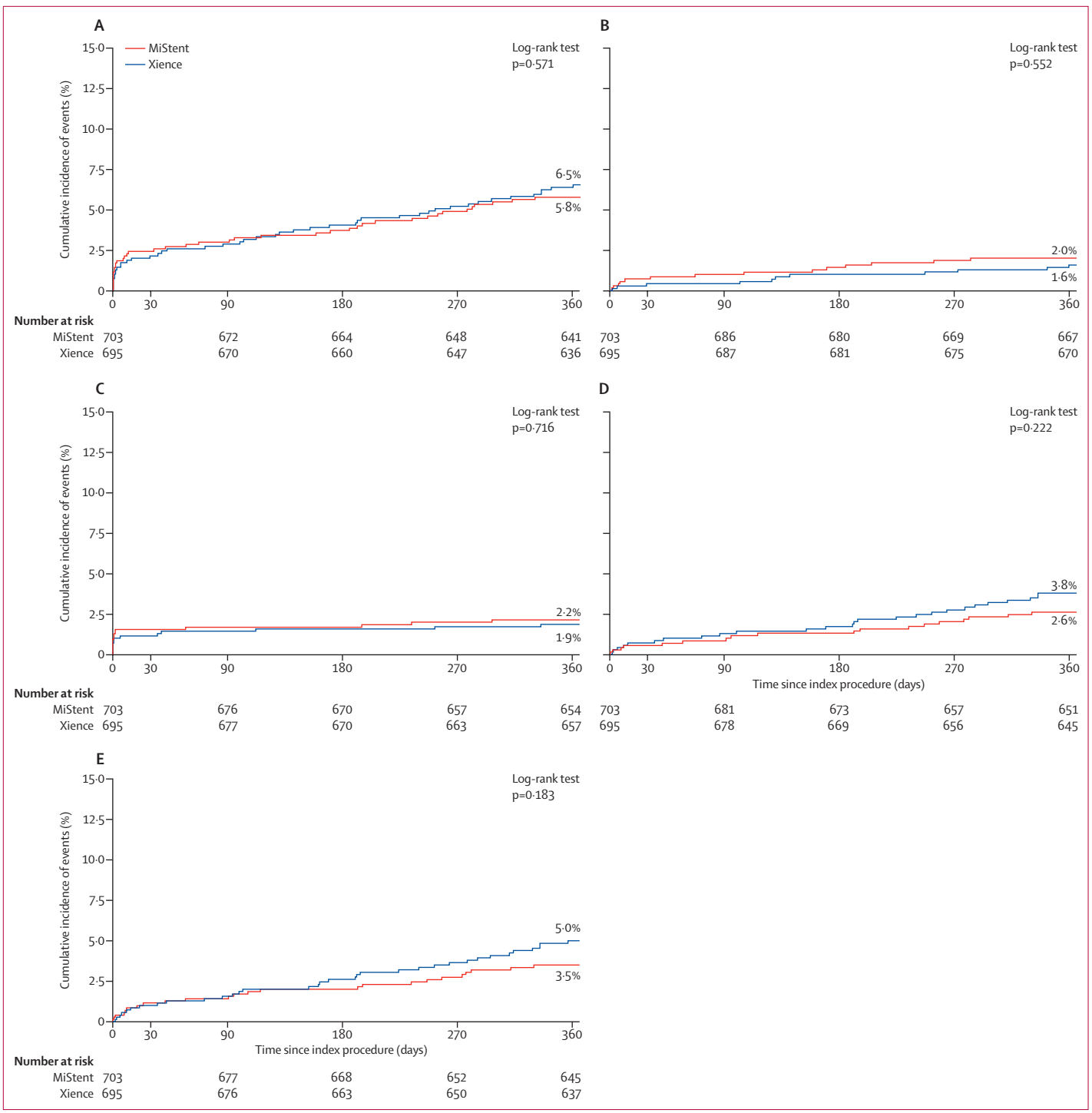

Figure 2: **Estimates for the primary endpoint and its components, and clinically indicated target vessel revascularisation**
Cumulative incidence of (A) the device-oriented composite endpoint or target-lesion failure (the primary endpoint)—a composite of (B) cardiac death, (C) target-vessel myocardial infarction, (D) clinically indicated target-lesion revascularisation. (E) Clinically indicated target vessel revascularisation (CI-TVR), over 360 days of follow-up.

On the basis of event rates from scientific literature,[19] the proportion of patients with the composite endpoint at 12 months for both treatment groups was expected to be 8·3%. A margin of 4·0% was defined for the non-inferiority margin of the sirolimus-eluting stent group compared with the everolimus-eluting stent group. Based on this margin and a one-sided type I error of 0·05, a total of 1364 patients (682 patients in each group)

	MiStent SES (n=653)	Xience EES (n=666)	Percentage difference (95% CI)	p value
Device-oriented composite endpoint*	5·3% (34)	6·1% (40)	−0·8% (−3·3 to 1·7)	0·56
Cardiac death	2·2% (14)	1·7% (11)	0·5% (−1·0 to 2·0)	0·50
Target-vessel myocardial infarction†	2·0% (13)	1·7% (11)	0·3% (−1·1 to 1·8)	0·64
Clinically indicated target-lesion revascularisation	2·2% (14)	3·5% (23)	−1·3% (−3·1 to 0·5)	0·16

Data are percentage (counts). SES=sirolimus-eluting stent. EES=everolimus-eluting stent. *Cardiac death, target-vessel myocardial infarction, or clinically indicated target-lesion revascularisation. †Determined on the basis of the extended historical definition.

Table 4: **Clinical outcomes at 12 months after stent implantation, per-protocol**

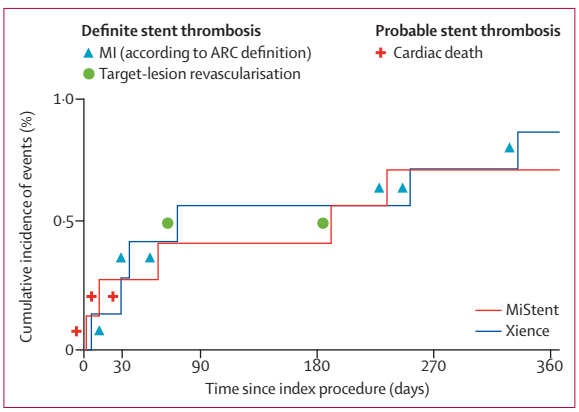

Figure 3: **Cumulative incidence of definite or probable stent thrombosis**
Definite stent thrombosis (myocardial infarction or target-lesion revascularisation; blue and green, or probable stent thrombosis (cardiac death; red) in five patients in the MiStent group and six in the Xience everolimus-eluting stent group, along with the worst hierarchical clinical outcome, over 360 days of follow-up. ARC=Academic Research Consortium.

would have at least 85% power to detect non-inferiority. Accounting for approximately 2% of patients lost to follow-up, a total of 1400 patients were to be randomly assigned. For primary endpoint analysis, using the standard normal distribution, a 90% two-sided CI was created for the intention-to-treat between-group differences in the primary endpoint Kaplan-Meier. If the upper limit of this 90% two-sided CI was less than or equal to the non-inferiority margin of 4·0%, the sirolimus-eluting stent would be considered non-inferior to the everolimus-eluting stent. This testing implied a 5% one-sided significance level.

In patients enrolled at three interventional cardiology centres in Poland, an optical coherence tomography (OCT) substudy was done with specific inclusion and exclusion criteria. Quantitative assessment of the stented coronary segment of the final OCT pullback was done by an independent core laboratory (Cardialysis BV; Rotterdam, Netherlands) using QIvus software (version 3.0). The analysts were masked to the device type and the measurements were based on abluminal stent contour.[20]

The analyses were based on an intention-to-treat patient population. Categorical variables were reported as counts and percentages. 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. Continuous variables were presented as mean (SD) and were compared with the use of *t* test. We used the Kaplan-Meier method to calculate the time to clinical endpoints, and the log-rank test to compare between-group differences. We prespecified stratified analyses of the primary endpoint at 12 months for subgroups of patients with diabetes, ST-segment elevation myocardial infarction, renal insufficiency (ie, serum creatinine >2·5 mg/dL, or creatinine clearance ≤30 mL/min), small vessels (≤2·75 mm), multivessel treatment, long lesions (>18 mm), in-stent restenosis, bypass graft, left main treatment, bifurcation treatment, or overlapping stents. Cox-proportional hazards analysis was done to calculate hazard ratios with 95% CI and p values. 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 enrolment phase. This trial was registered at ClinicalTrials.gov, number NCT02385279.

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 three primary investigators (PWS, RJdW, and WW) had full access to all the data in the study, and the corresponding author (PWS) had final responsibility for the decision to submit for publication.

Results

Between March 20, and Dec 3, 2015, we randomly assigned 1398 patients with 2030 lesions; 703 patients with 1037 lesions were assigned to MiStent, of whom 697 received the index procedure, and 695 patients with 993 lesions were asssigned to Xience, of whom 690 received the index procedure (figure 1). Baseline clinical characteristics were similar in the two study groups (table 1). 414 patients (59%) in the MiStent group and 408 (59%) in the Xience group presented with acute coronary syndrome.

Overall, lesion characteristics were comparable except for long lesions (>18 mm) being more frequent in the sirolimus-eluting stent group than in the everolimus-eluting stent group (table 2). Mean stent length and diameter per stent was slightly shorter and larger in the sirolimus-eluting stent group, but these variables per lesion, and the number of stents used, did not differ between groups. The device success analysis indicated ten (0·8%) dislodgments of the sirolimus-eluting stent,

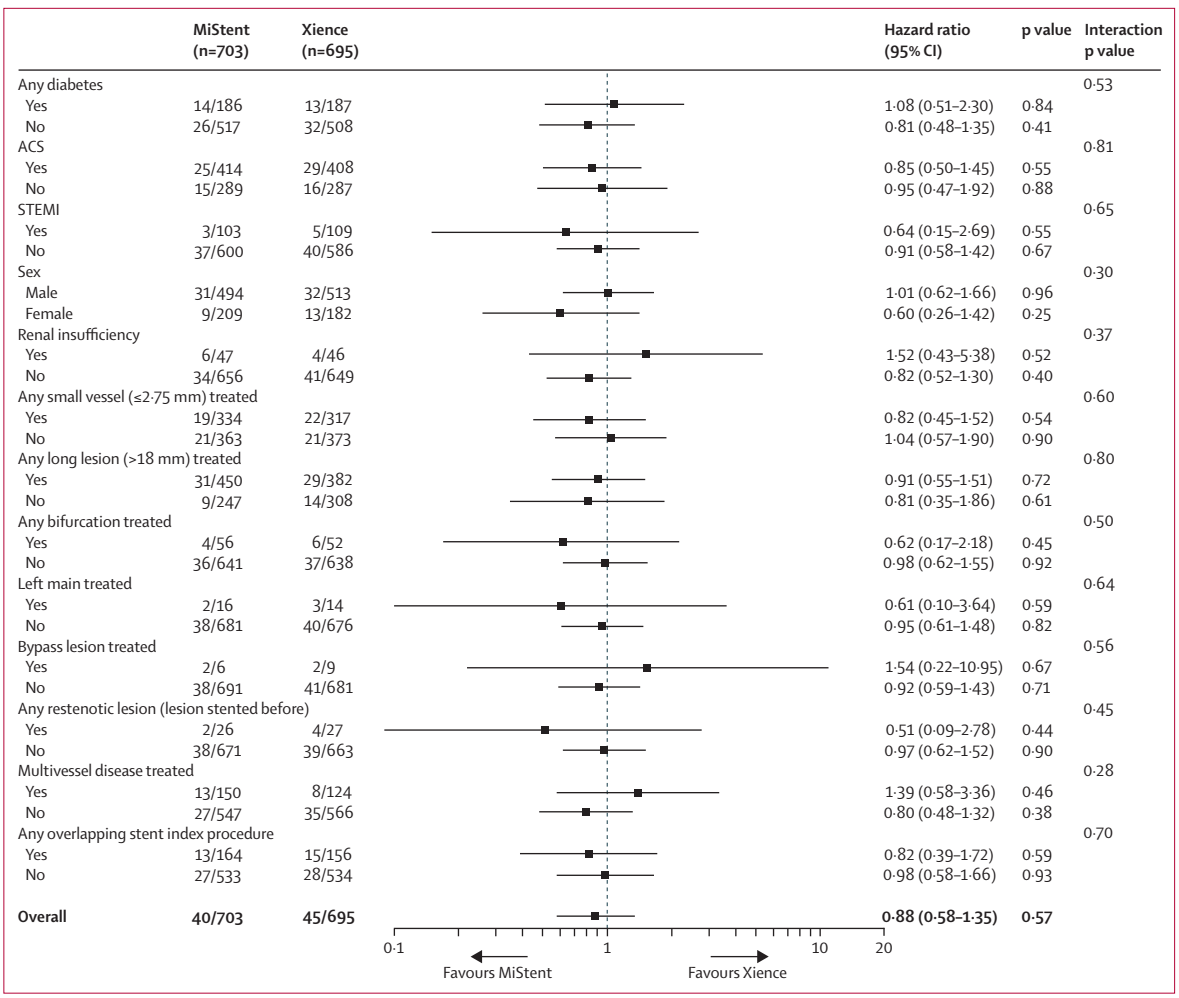

Figure 4: **Stratified analyses of the device-oriented composite primary endpoint at 12 months**
Data are hazard ratios (95% CI) and p values across subgroups from Cox-proportional hazards analysis. Renal insufficiency was defined as a serum creatinine concentration >2·5 mg/dL or creatinine clearance ≤30 mL/min. ACS=acute coronary syndrome. STEMI=ST-segment elevation myocardial infarction.

mainly in complex and calcified lesions (appendix), whereas no dislodgement was noted in the everolimus-eluting stent group. Procedural success occurred in 691 (98·3%) of 703 patients in the sirolimus-eluting stent group and 685 (98·6%) of 695 patients in the everolimus-eluting stent group (p=0·69). No clinical adverse events could be attributed to these dislodgments through a minimum of 12 months of follow up.

The primary device-oriented composite endpoint occurred in 40 patients (5·8%) in the sirolimus-eluting stent group and in 45 patients (6·5%) in the everolimus-eluting stent group (table 3, figure 2). Non-inferiority of the sirolimus-eluting stent compared with the everolimus-eluting stent was shown, with an absolute difference of –0·8% and upper limit of the two-sided 90% CI of 1·4% ($p_{non\text{-}inferiority}$=0·0001, $p_{superiority}$=0·571). Frequency of cardiac death, target vessel myocardial infarction, and clinically-indicated target lesion revascularisation was similar for both stent types (table 3, figure 2). There were no between-group differences for the patient-oriented composite endpoint, and the per-protocol analysis of the primary endpoint also showed no difference between the groups (table 4).

At 12 months, definite and probable stent thrombosis did not differ between groups (table 3, figure 3). The primary endpoint also did not differ between groups across the stratified analyses for the patient subgroups (figure 4).

At 6 months, OCT was done in a subgroup of 53 patients (25 patients and 25 lesions in the sirolimus-eluting stent group, and 28 patients and 30 lesions in the everolimus-eluting stent group) (table 5). The analysis revealed that mean neointimal hyperplastic volume obstruction, and neointimal hyperplasia volume and area were lower in the sirolimus-eluting stent group. There were no between-group differences in terms of malapposition area, and nearly all struts in both groups were completely covered.

	MiStent SES (25 patients, 25 lesions)	Xience EES (28 patients, 30 lesions)	Difference (95% CI)	p value
Lumen area (mm²)	5·79 (1·47)	5·94 (1·80)	−0·15 (−1·05 to 0·75)	0·74
Minimal lumen area (mm²)	4·61 (1·21)	4·27 (1·59)	0·34 (−0·44 to 1·12)	0·39
Stent area (mm²)	6·64 (1·61)	7·14 (1·91)	−0·51 (−1·47 to 0·46)	0·30
Minimal stent area (mm²)	5·61 (1·39)	5·73 (1·58)	−0·13 (−0·94 to 0·69)	0·76
Neointimal thickness on top of the struts (μm)	74·9 (30·3)	90·0 (41·1)	−15·1 (−35·0 to 48·0)	0·13
Neointimal hyperplasia area (mm²)	0·98 (0·29)	1·31 (0·46)	−0·33 (−0·54 to −0·12)	0·0022
Neointimal hyperplasia volume (mm³)	19·6 (9·8)	32·6 (25·9)	−13·0 (−24·0 to −2·0)	0·0150
Neointimal hyperplasia volume obstruction (%)	15·0% (4·1)	18·9% (6·2)	−3·9 (−6·8 to −0·9)	0·0081
Malapposition area (mm²)	0·05 (0·17)	0·04 (0·10)	0·01 (−0·06 to 0·08)	0·81
Number of struts analysed	189·7 (56·7)	232·9 (102·4)	NA	NA
Malapposed struts (%)	1·1% (2·8)	0·8% (2·0)	0·4 (−0·9 to 1·7)	0·58
Covered struts (%)	99·9% (0·4)	99·8% (0·7)	0·0 (−0·3 to 0·3)	0·89
Covered well-apposed struts (%)	98·6% (2·8)	98·6% (2·6)	0·0 (−1·4 to 1·5)	0·99
Covered malapposed struts (%)	1·1% (2·8)	0·8% (2·0)	0·4 (−0·9 to 1·7)	0·58
Covered side-branch struts (%)	0·1% (0·3)	0·5% (1·3)	−0·4 (−0·9 to 0·2)	0·17
Uncovered struts (%)	0·1% (0·4)	0·2% (0·7)	−0·0 (−0·3 to 0·3)	0·89
Uncovered well-apposed struts (%)	0·1% (0·3)	0	0·1 (−0·0 to 0·2)	0·33
Uncovered malapposed struts (%)	0	0	0	NA
Uncovered side-branch struts (%)	0·1% (0·3)	0·2% (0·7)	−0·1 (−0·4 to 0·2)	0·57

Data are mean (SD) or mean percentage (SD). SES=sirolimus-eluting stent. EES=everolimus-eluting stent. NA=not applicable.

Table 5: **6-month optical coherence tomography results**

Discussion

In this large-scale, allcomer, multicentre, single-blind, randomised trial, a sirolimus-eluting bioabsorbable polymer-coated stent was non-inferior to an everolimus-eluting durable polymer stent for a device-oriented composite endpoint of cardiac death, target-vessel myocardial infarction, or clinically indicated target-lesion revascularisation at 12 months. No differences occurred between the two treatment groups in the individual components of the primary endpoint, or in any of the secondary clinical endpoints. Stent thrombosis, a safety indicator, did not differ between groups and was low in both treatment arms.

Outcomes with the sirolimus-eluting stent matched the outcomes of the best-in-class durable polymer everolimus-eluting stent in this all-comer population, in which 59% patients presented with acute coronary syndrome. The everolimus-eluting stent Xience has been shown to reduce all-cause mortality, myocardial infarction, ischaemia-driven target lesion revascularisation, stent thrombosis, and target lesion failure, compared with first-generation paclitaxel-eluting stents,[21] and to reduce stent thrombosis compared with first-generation sirolimus-eluting stents.[22] Overall rates of clinically indicated repeat revascularisation of the target lesion were low and showed no significant between-group differences. These findings are consistent with a previous all-comer trial comparing Xience and Resolute drug-eluting stents.[19]

Previous randomised trials comparing biodegradable polymer with durable polymer drug-eluting stents do not suggest superiority of biodegradable polymer drug-eluting stents (LEADERS, BIOSCIENCE, EVOLVE II, and CENTURY II);[23–26] and polymer, antiproliferative drug, the pharmacokinetic release profile, platform, and strut thickness all vary across these bioresorbable polymer stents (appendix). For example, the polymer of Orsiro is Poly-L-Lactidde, which degrades over 7 months with 3-month drug release, whereas the polymer of MiStent degrades faster (3 months) with longer drug release (9 months).

Overall rates for definite or probable stent thrombosis were low (<1% at 12 months). There was no difference in either form of stent thrombosis between the groups. Long-term follow-up is needed to confirm the benefit of early disappearance of absorbable polymer and late elution of the drug on stent thrombosis with the sirolimus-eluting stent, as was the case in the LEADERS all-comer trial.[23] In this trial, the biodegradable polymer biolimus-eluting stent was associated with a significant reduction in very late definite stent thrombosis from 1 to 5 years as compared to durable polymer sirolimus-eluting stent,[8] although the rates for stent thrombosis were not statistically different in the primary report at 9 months.[23]

In the 6-month OCT substudy of the DESSOLVE III, the mean neointimal volume obstruction was significantly lower and neointimal hyperplasia volume and area were significantly smaller in the sirolimus-eluting stent group compared with the everolimus-eluting stent. These results suggest stronger neointimal suppression with the sirolimus-eluting stent, which at 12 months was not yet translated into clinical outcomes but might become relevant at a longer follow-up. Of note, the Kaplan-Meier curves of clinically indicated target lesion revascularisation and target-vessel revascularisation diverged after 120 days (figure 2), which is concomitant with early elimination of the polymer and the favourable neointimal suppression results of the DESSOLVE I, II, and OCT substudy. Those results are in line with serial (6 and 12, 6 and 24 months) assessments of the angiographic late lumen loss after implantation of the Xience, which showed a progressive increase of late loss from 0·12 mm to 0·24 mm and from 0·17 mm to 0·33 mm, respectively.[27,28]

Dislodgment during stent implantation occurred in ten patients in the sirolimus-eluting stent group, but this did not result in clinical events (appendix) All dislodgments occurred during stent retrieval after failing to cross a highly calcified or tortuous lesion. Micell, the manufacturer of MiStent has pursued several product changes to try to reduce the incidence of failure to cross or dislodgments. The first change was implementation of a modified crimping process, which generally increases stent securement and reduces the stent

crossing profile. The second change was qualification of a next-generation balloon catheter with lower balloon profile and improved catheter shaft, which is expected to be more kink-resistant. Initial bench testing indicates a further increase in stent securement and decrease in the stent crossing profile for the sirolimus-eluting stent on this catheter. To date, the incidence of failure to cross or dislodgement in commercial distribution for MiStent is 0·06%, and the dislodgement rate of Xience and Synergy are 0·07% and 0·24%, respectively, according to the Manufacturer and User Facility Device Experience of the US Food and Drug Administration (data on file).

In a report of long-term results from the DESSOLVE I and II trials at 5 years, the sirolimus-eluting stent showed low rates of target lesion revasularisation across DESSOLVE I (0·0%) and DESSOLVE II (3·4%; unpublished data). No stent thrombosis was reported with the sirolimus-eluting stent through 5 years in the DESSOLVE I trial. In DESSOLVE II, definite or probable stent thrombosis occurred in no patients with the sirolimus-eluting stent and 1·7% with Endeavor ZES through 5 years (p=0·331). Although the individual trials were not powered for comparison of clinical endpoints, the results are encouraging, suggesting the long-term efficacy and safety of the sirolimus-eluting stent.

The theoretical advantage of MiStent is the longer inhibition of neointimal hyperplasia due to sustained presence of microcrystallised sirolimus with thinner struts. The device could be used for a lesion with high risk of restenosis. However, this needs to be demonstrated in a future study.

The observed rates of the primary endpoint were lower than the assumed rate in the sample size calculation in both arms. The difference was mainly due to lower rate of target vessel myocardial infarction in the current trial than in the referenced trial, RESOLUTE allcomers (2·2% in the MiStent arm, 1·9% in the Xience arm in the current trial, and 4·1% in the Xience arm in RESOLUTE allcomers). The original non-inferiority margin of 4·0% was determined as half of the observed TLF rate of 8·3% in the Xience arm in the RESOLUTE allcomers. If we apply this relative non-inferiority margin to the current observation, the (post hoc) non-inferiority margin would be 3·0% (approximately half the TLF rate in the control group: 6·5%). However, even under this condition, non-inferiority was still met with this post-hoc non-inferiority margin (post hoc $P_{non\text{-}inferiority}$=0·0018).

Adjudication of ECG was not done by core lab, but based on reports from investigators. However, the high level of compliance in collecting periprocedural biomarkers should exclude potential under-reporting (appendix). Follow-up angiography providing objective evidence of difference in neointimal hyperplasia was not required by protocol; however, this lack of mandated angiography precludes the bias caused by the artificial increase of revascularisation triggered by angiography. Angiograms were reviewed and analysed by quantitative coronary angiography by core lab only in case of event before adjudication by the clinical event committee.

The study did not have adequate power to demonstrate superiority in any itemised endpoints of the composite endpoints, including clinically indicated target lesion revascularisation and target-vessel revascularisation. Our trial was limited to a short follow-up of 12 months, which is 3 months after the end of drug elution. Longer duration of low level drug might be associated with a rebound of neointimal hyperplasia once the upregulation of p27 was eliminated.[29] Protocol therefore specifies that the follow-up of patients will continue up to 3 years. (NCT02385279)

In conclusion, the sirolimus-eluting bioabsorbable polymer-coated stent was non-inferior to the everolimus-eluting durable polymer stent for target lesion failure at 12 months in an all-comer population. At 12 months, non-inferiority in terms of efficacy and safety were shown, with OCT results showing stronger neointimal suppression by the sirolimus-eluting stent. Whether the 9 months cytostatic inhibition could have a beneficial effect in the medium-term follow-up of 3 years as planned in the trial remains to be assessed.

Contributors

RJdW, WW, PWS, and YO contributed to the conception and design of the study. PL, PB, GAJJ, KTK, RPTT, BJBH, TOO, KPM, JW, RW, GC, SHH, SL, AZ, DF, MK, PG, EKA, MN, and MWF contributed to data collection. YK, PWS, RJdW, WW, TA, and YO analysed and interpreted the data. YK, TA, YO, and PWS drafted the report, which was critically revised for important intellectual content by RJdW and WW. All authors approved the final version of the report.

Declaration of interests

GC reports grants to the institution from Fondation coeur et recherche, Daiichi, personal fees from Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Biotronik, Bristol Myers Squibb, Eli Lilly, Europa, personal fees from MSD, Pfizer, Sanofi, The Medecines Company, grants and personal fees from Medtronic, and non-financial support from Boston. SHH reports unrestricted research grant to institution by Abbott. DF reports personal fees from AstraZeneca, B Braun, Novartis, and Biotronik. MN reports grants by the Deutsche Forschungsgemeinschaft through the Sonderforschungsbereich Transregio 19 Inflammatory Cardiomyopathy (SFB TR19 and TP B2), and by the University Hospital Giessen and Marburg Foundation Grant T cell functionality (UKGM 10/2009). MN has been a consultant to the Institute for Cardiac Diagnosis and Therapy GmbH, Berlin, from 2004–08, and has received honoraria for presentations or participated in advisory boards for AstraZeneca, Bayer, Fresenius, Miltenyi Biotech, Novartis, Pfizer, and Zoll. YO is a member of the Advisory Board of Abbott Vascular. WW reports grants to previous institutions from Abbott, Micell, Stentys, and Medtronic, and consultancy fees from Abbott, Biotronik, and MicroPort. He is a shareholder and non-executive board member of Argonauts Partners and Genae. PWS reports consultant fees from Abbott, AstraZeneca, Biotronik, Cardialysis, GLG Research, Medtronic, Sinomedical Sciences Technology, Société Europa Digital Publishing, Stentys France, Svelte Medical Systems, Volcano, St Jude Medical, and Qualimed. All other authors declare no competing interests.

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