

Clinical outcomes of bioabsorbable polymer sirolimus-eluting stents versus durable polymer everolimus-eluting stents: two-year follow-up of the DESSOLVE III trial



Yuki Katagiri¹, MD; Yoshinobu Onuma², MD, PhD; Philipp Lurz³, MD, PhD; Pawel Buszman⁴, MD, PhD; Jan J. Piek¹, MD, PhD; Joanna J. Wykrzykowska¹, MD, PhD; Taku Asano¹, MD; Norihiro Kogame¹, MD; Kuniaki Takahashi¹, MD; Chun-Chin Chang², MD; Robbert J. de Winter¹, MD, PhD; Patrick W. Serruys^{5*}, MD, PhD; William Wijns⁶, MD, PhD

1. Amsterdam University Medical Centre, Amsterdam, the Netherlands; 2. Thoraxcenter, Erasmus Medical Center, Rotterdam, the Netherlands; 3. Department of Internal Medicine/Cardiology, University of Leipzig-Heart Centre, Leipzig, Germany; 4. Centre for Cardiovascular Research and Development, American Heart of Poland, Katowice, Poland; 5. The National Heart and Lung Institute, Imperial College London, London, United Kingdom; 6. National University of Ireland Galway, The Lambe Institute for Translational Medicine and CURAM, Galway, Ireland

A list of the study collaborators can be found in the Appendix paragraph.

GUEST EDITOR: Alec Vahanian, MD, PhD; Department of Cardiology, Hôpital Bichat-Claude Bernard, and University Paris VII, Paris, France

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KEYWORDS

- ACS/NSTE-ACS
- clinical trials
- drug-eluting stent
- stable angina

Abstract

Aims: The aim of this study was to assess whether the nine months of cytostatic inhibition by crystalline sirolimus has a beneficial effect in the two-year follow-up in an all-comer population undergoing percutaneous coronary intervention.

Methods and results: The DESSOLVE III study (n=1,398) is a prospective, all-comer, multicentre, randomised controlled study (NCT02385279) allocating 703 patients to receive the MiStent drug-eluting stent with a fully absorbable polymer coating containing and embedding a microcrystalline form of sirolimus into the vessel wall, and 695 patients to receive the XIENCE durable polymer everolimus-eluting stent. At two years, the device-oriented composite endpoint (cardiac death, target vessel myocardial infarction [TV-MI], and clinically indicated target lesion revascularisation [TLR]) occurred in 8.7% and 8.6% (p=0.958) of patients, and the patient-oriented composite endpoint (all deaths, all MI, and all revascularisations) was observed in 18.5% and 19.6% (p=0.598) of patients in the MiStent and XIENCE arms, respectively. The frequency of TV-MI and clinically indicated TLR was also comparable for both stent types. The rate of definite/probable stent thrombosis was not different in the two arms (0.9% vs 1.3%, p=0.435).

Conclusions: In an all-comer population, at two-year follow-up, the use of the MiStent sirolimus-eluting bioabsorbable polymer-coated stent was at least as safe and efficacious as the XIENCE durable polymer stent. The MiStent's potential long-term clinical benefit will be further elucidated after five years of follow-up.

*Corresponding author: Cardiovascular Science Division of the NHLI within Imperial College of Science, Technology and Medicine, South Kensington Campus, London, SW7 2AZ, United Kingdom. E-mail: patrick.w.j.c.serruys@gmail.com

Abbreviations

DES	drug-eluting stent
DOCE	device-oriented composite endpoint
EES	everolimus-eluting stent
POCE	patient-oriented composite endpoint
QCA	quantitative coronary angiography
QFR	quantitative flow ratio
SES	sirolimus-eluting stent
ST	stent thrombosis
TLR	target lesion revascularisation
TVR	target vessel revascularisation

Introduction

Permanent polymers on drug-eluting stents (DES) have been linked to late stent thrombosis (ST) and DES failure due to inciting a late inflammatory response¹. Bioabsorbable polymer-based DES were developed to address this limitation. Results have supported their use as safe and efficacious alternatives to permanent polymer DES².

The MiStent[®] sirolimus-eluting absorbable polymer coronary stent system (MiStent SES; Micell Technologies, Durham, NC, USA) combines crystalline sirolimus, polylactide-co-glycolic acid (PLGA) biodegradable polymer and a cobalt-chromium stent platform^{3,4}. The controlled release system of crystalline sirolimus provides the benefit of protection from an initial burst release followed by rapid drug degradation and allows a targeted delivery of the active ingredient into the surrounding tissue with continuous and predictable drug elution throughout the affected artery following stent implantation up to nine months. The theoretical advantage of MiStent is the longer inhibition of neointimal hyperplasia due to the sustained presence of microcrystalline sirolimus, and thinner struts which promote earlier neointimal coverage.

Previously, the DESSOLVE III all-comer randomised trial showed non-inferiority of the MiStent SES as compared to the XIENCE everolimus-eluting stent (EES; Abbott Vascular, Santa Clara, CA, USA) in terms of the device-oriented composite endpoint (DOCE) at 12 months⁵. Considering the fact that the polymer in the MiStent SES disappears at three months while the drug is eluted up to nine months post implantation, longer-term follow-up is needed to confirm the benefit of the early disappearance of the absorbable polymer and late elution of the drug. So far, in the DESSOLVE I single-arm trial (n=30), no patients receiving the MiStent had target lesion failure (TLF) up to five years⁶. In DESSOLVE II (n=184), TLF was not significantly different between the MiStent group and the Endeavor[®] (Medtronic, Minneapolis, MN, USA) group at five years (9.2% vs 8.5%)⁶. However, it is unclear whether this is still the case in an all-comer population at midterm follow-up as there is a potential concern that the longer duration of low-level drug might be associated with a rebound of neointimal hyperplasia once the upregulation of p27 has subsided⁷. Therefore, we aim to present the two-year evaluation after implantation of the MiStent sirolimus-eluting bioabsorbable polymer-coated stent as compared to the XIENCE

durable polymer everolimus-eluting stent in the DESSOLVE III all-comer trial.

Methods

STUDY DESIGN AND POPULATION

The trial design and methods, as well as the study population, have been described in the previous report⁵. In brief, the DESSOLVE III all-comer trial is a prospective, randomised, 1:1 ratio, controlled, single-blind, multicentre study (NCT02385279). Twenty sites in Europe participated in the study and the enrolment period was from March to December 2015. There were minimal inclusion/exclusion criteria. The primary endpoint of the study was a non-inferiority comparison at 12 months of a DOCE (commonly described as TLF, a composite of cardiac death [including death of unknown cause or no information on cause of death], target vessel myocardial infarction [TV-MI]), and clinically indicated target lesion revascularisation [TLR]) of the MiStent SES group as compared to the XIENCE EES group. All patients provided written informed consent to participate in the study, which was approved by the ethics committee of each enrolling site. The study was performed in accordance with the Declaration of Helsinki and Good Clinical Practices (GCP).

Two-year follow-up was planned in the trial protocol. The predefined two-year endpoints are listed in **Supplementary Table 1**. Event adjudication by a clinical events committee (CEC) and additional quantitative coronary angiography (QCA) were performed by Cardialysis (Rotterdam, the Netherlands). For all revascularisations and stent thrombosis events, the angiogram was sent to the angiographic core laboratory, regardless of whether target or non-target vessel (non-TV) revascularisation was performed.

DEVICE DESCRIPTION

MISTENT SES

The metallic platform of the MiStent SES is a cobalt-chromium alloy with a thin 64 µm strut thickness. The stent coating (approximately 5 µm thick on the luminal and 15 µm thick on the abluminal stent surfaces)⁴ consists of PLGA loaded with microcrystalline particles of sirolimus. It has been shown that the polymer is fully biodegraded and resorbed within three months post implantation while the drug remains in the tissue surrounding the stent for up to nine months in order to continue to control the growth of neointimal tissue³.

XIENCE EES

The control XIENCE EES is a cobalt-chromium alloy device with a strut thickness of 81 µm and a 7.8 µm thick durable polymer coating. The durable polymer is made of polyvinylidene fluoride-hexafluoropropylene loaded with everolimus.

EXPLORATORY ANALYSES

In an attempt to explain the difference in non-TV revascularisation at two years, *post hoc* paired QCA analyses at baseline (post procedure) and before revascularisation (at the time of event) were performed in lesions with non-TV revascularisation. Quantitative

flow ratio (QFR) was further analysed in revascularised non-TV at baseline and before revascularisation whenever technically feasible (methods and details of the feasibility of QFR analysis are provided in **Supplementary Appendix 1** and **Supplementary Figure 1**).

STATISTICAL ANALYSIS

Details of the statistical analysis are provided in **Supplementary Appendix 2**.

Results

STUDY SUBJECTS

A study flow chart is shown in **Figure 1**. Two-year follow-up information was available in 98.4% (692/703) of patients in the MiStent arm and in 99.1% (689/695) of patients in the XIENCE arm of the initial cohorts. Three patients withdrew consent in the MiStent arm and eight and six patients were lost to follow-up in the MiStent and the XIENCE arms, respectively.

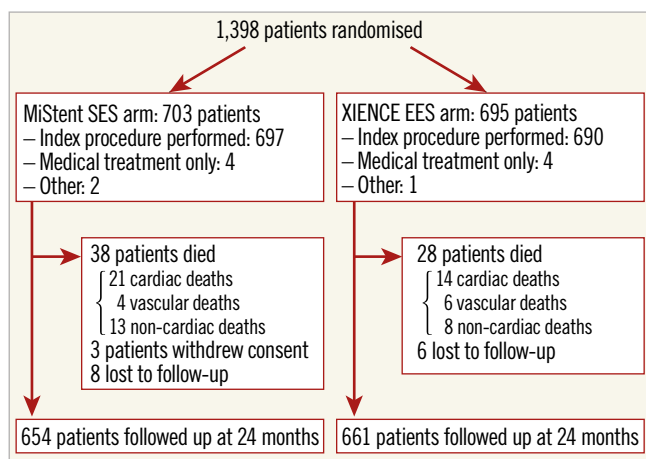


Figure 1. Study flow chart. EES: everolimus-eluting stent; SES: sirolimus-eluting stent

TWO-YEAR CLINICAL ENDPOINTS

Comparisons of clinical endpoints as well as the individual components of the composite endpoints are presented in **Table 1**.

At two-year follow-up, DOCE occurred in 60 (8.7%) patients treated with MiStent and 59 (8.6%) patients treated with XIENCE (difference 0.1%, 95% confidence interval [CI]: -2.9 to 3.1, p=0.958) (**Figure 2A**). Frequencies of all death (38 [5.4%] vs 28 [4.0%], difference 1.4%, 95% CI: -0.8 to 3.6, p=0.220), cardiac death (21 [3.0%] vs 14 [2.0%], difference 1.0%, 95% CI: -0.7 to 2.7, p=0.239), TV-MI (19 [2.7%] vs 16 [2.3%], difference 0.4%, 95% CI: -1.2 to 2.1, p=0.621), and clinically indicated TLR (31 [4.6%] vs 37 [5.4%], difference -0.9%, 95% CI: -3.2 to 1.4, p=0.447) were not significantly different for both stent types (**Figure 2B-Figure 2D**).

The patient-oriented composite endpoint (POCE: defined as all deaths, all MI and all revascularisations) was observed in

Table 1. Clinical outcomes at 24 months after stent implantation (intention-to-treat basis).

Composite outcomes	MiStent SES (n=703)	XIENCE EES (n=695)	Difference (%) (95% CI)	p-value
DOCE/TLF*	8.7 (60)	8.6 (59)	0.1 (-2.9, 3.1)	0.96
POCE ^o	18.5 (129)	19.6 (136)	-1.1 (-5.3, 3.0)	0.60
MACE [‡]	13.2 (92)	13.1 (91)	0.1 (-3.5, 3.6)	0.96
TVF [§]	9.7 (67)	10.8 (74)	-1.1 (-4.3, 2.1)	0.52
Components of composite endpoints				
All-cause death	5.4 (38)	4.0 (28)	1.4 (-0.8, 3.6)	0.22
Cardiac death	3.0 (21)	2.0 (14)	1.0 (-0.7, 2.7)	0.24
Any MI [¶]	3.0 (21)	2.8 (19)	0.3 (-1.5, 2.0)	0.76
Q-wave	0.6 (4)	1.0 (7)	-0.4 (-1.4, 0.5)	0.36
Non-Q-wave	2.5 (17)	1.9 (13)	0.6 (-1.0, 2.1)	0.47
Target vessel MI [¶]	2.7 (19)	2.3 (16)	0.4 (-1.2, 2.1)	0.62
Q-wave	0.6 (4)	0.9 (6)	-0.3 (-1.2, 0.6)	0.52
Non-Q-wave	2.2 (15)	1.6 (11)	0.6 (-0.9, 2.0)	0.44
Non-target vessel MI [¶]	0.3 (2)	0.4 (3)	-0.1 (-0.8, 0.5)	0.66
Q-wave	0.0 (0)	0.1 (1)	-0.1 (-0.4, 0.1)	0.32
Non-Q-wave	0.3 (2)	0.3 (2)	-0.0 (-0.6, 0.6)	1.00
Any revascularisation	12.5 (85)	15.5 (106)	-3.1 (-6.8, 0.6)	0.11
Target lesion revascularisation	5.1 (35)	6.0 (41)	-0.9 (-3.3, 1.6)	0.48
Clinically indicated	4.6 (31)	5.4 (37)	-0.9 (-3.2, 1.4)	0.45
Non-clinically indicated	1.9 (13)	1.8 (12)	0.1 (-1.3, 1.6)	0.83
Target vessel revascularisation	6.9 (47)	8.5 (58)	-1.6 (-4.5, 1.2)	0.27
Clinically indicated	5.9 (40)	7.7 (52)	-1.8 (-4.4, 0.9)	0.19
Non-clinically indicated	2.6 (18)	2.8 (19)	-0.2 (-1.9, 1.6)	0.88
Non-TV revascularisation	7.3 (50)	10.0 (68)	-2.6 (-5.6, 0.3)	0.09
Stent thrombosis				
Definite stent thrombosis	0.6 (4)	1.0 (7)	-0.4 (-1.4, 0.5)	0.36
Acute (0-1 days)	0.0 (0)	0.0 (0)	0.0 (0.0, 0.0)	NA
Subacute (2-30 days)	0.0 (0)	0.1 (1)	-0.1 (-0.4, 0.1)	0.32
Late (31-360 days)	0.4 (3)	0.6 (4)	-0.1 (-0.9, 0.6)	0.71
Very late stent thrombosis (after 360 days) ^a	0.3 (2)	0.3 (2)	0.0 (-0.6, 0.6)	1.00
Definite or probable stent thrombosis	0.9 (6)	1.3 (9)	-0.4 (-1.6, 0.7)	0.44
Acute (0-1 days)	0.0 (0)	0.0 (0)	0.0 (0.0, 0.0)	NA
Subacute (2-30 days)	0.3 (2)	0.3 (2)	-0.0 (-0.6, 0.6)	0.99
Late (31-360 days)	0.4 (3)	0.6 (4)	-0.1 (-0.9, 0.6)	0.71
Very late stent thrombosis (after 360 days) ^a	0.3 (2)	0.4 (3)	-0.1 (-0.8, 0.5)	0.66

Data are percentage (counts), unless otherwise specified. ^aOne patient in the MiStent group had one late definite ST and one very late definite ST. This case was censored at the first ST when counting the total number of ST. *DOCE/TLF was defined as cardiac death, target vessel MI or clinically indicated TLR. ^oPOCE was defined as all-cause death, any MI, or any revascularisation. [‡]MACE was defined as all-cause death, any MI, or any TVR. [§]TVF was defined as cardiac death, target vessel MI, or clinically indicated TVR. [¶]MI was determined on the basis of the extended historical definition. CI: confidence interval; DOCE: device-oriented composite endpoint; EES: everolimus-eluting stent; MACE: major adverse cardiac events; MI: myocardial infarction; NA: not available; POCE: patient-oriented composite endpoint; SES: sirolimus-eluting stent; TLF: target lesion failure; TLR: target lesion revascularisation; TVF: target vessel failure

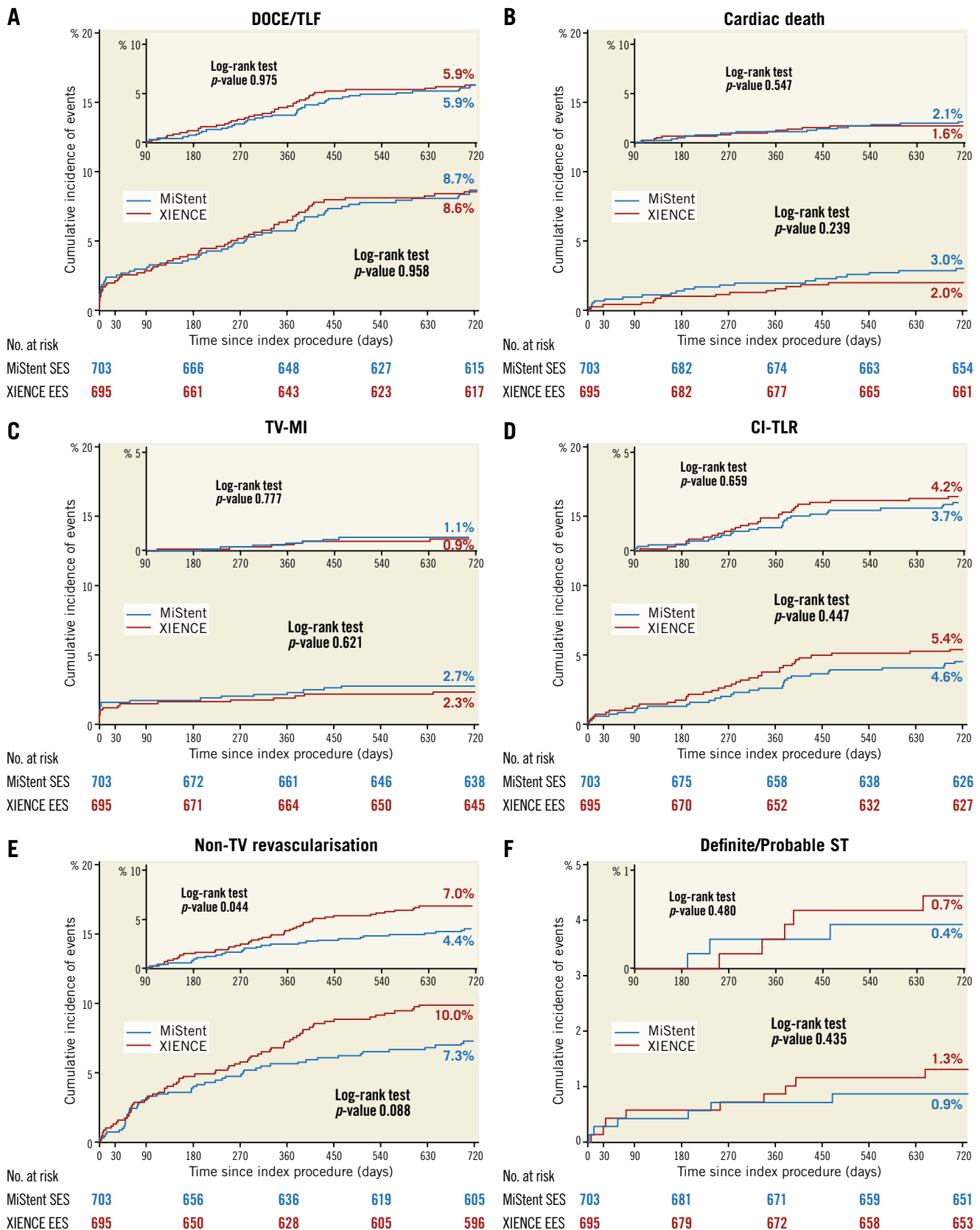


Figure 2. Kaplan-Meier estimates for the device-oriented composite endpoint (DOCE), its components, non-target vessel revascularisation, and stent thrombosis over 720 days of follow-up. Kaplan-Meier curves show the cumulative incidence of DOCE - a composite of cardiac death, target vessel myocardial infarction (TV-MI), or clinically indicated target lesion revascularisation (CI-TLR) (A); cardiac death (B); TV-MI (C); CI-TLR (D); non-target vessel revascularisation (non-TV revascularisation) (E); and definite/probable stent thrombosis (ST) (F).

129 patients (18.5%) and 136 patients (19.6%), respectively, in the MiStent arm and the XIENCE arm (difference -1.1%, 95% CI: -5.3 to 3.0, $p=0.598$) (Figure 3). Any revascularisation at two years tended to be less frequent in the MiStent arm than in the XIENCE arm (85 [12.5%] vs 106 [15.5%], difference -3.1%, 95% CI: -6.8 to 0.6, $p=0.106$), largely driven by a difference in the rate of non-TV revascularisation (50 [7.3%] vs 68 [10.0%], difference -2.6%, 95% CI: -5.6 to 0.3, $p=0.088$) (Figure 2E).

At two years, the rate of definite/probable ST was not different in the MiStent and XIENCE arms (6 [0.9%] vs 9 [1.3%], difference -0.4%, 95% CI: -1.6 to 0.7, $p=0.435$) (Figure 2F).

LANDMARK ANALYSIS AT 90 DAYS

Landmark analyses after 90 days, the time point when the biodegradable polymer of the MiStent was supposed to be completely absorbed, are presented in the upper right corner of each panel of Figure 2. The rate of DOCE, as well as its components

after 90 days, was not significantly different between the two arms. However, the rate of non-TV revascularisation was significantly lower in the MiStent arm after 90 days (29 [4.4%] vs 46 [7.0%], $p=0.044$) (Figure 2E).

SUBGROUP ANALYSIS

The treatment effect in DOCE was not different across the stratified analyses for diabetes, acute coronary syndrome (ACS), ST-elevation myocardial infarction (STEMI), gender, renal insufficiency, small vessel, long lesion, bifurcation, left main, bypass lesion, restenotic lesion, multivessel, and overlapping stent (Figure 4).

Discussion

The first report of the two-year follow-up of a randomised comparison between MiStent and XIENCE in an all-comer setting showed that the rate of DOCE at two years was not significantly

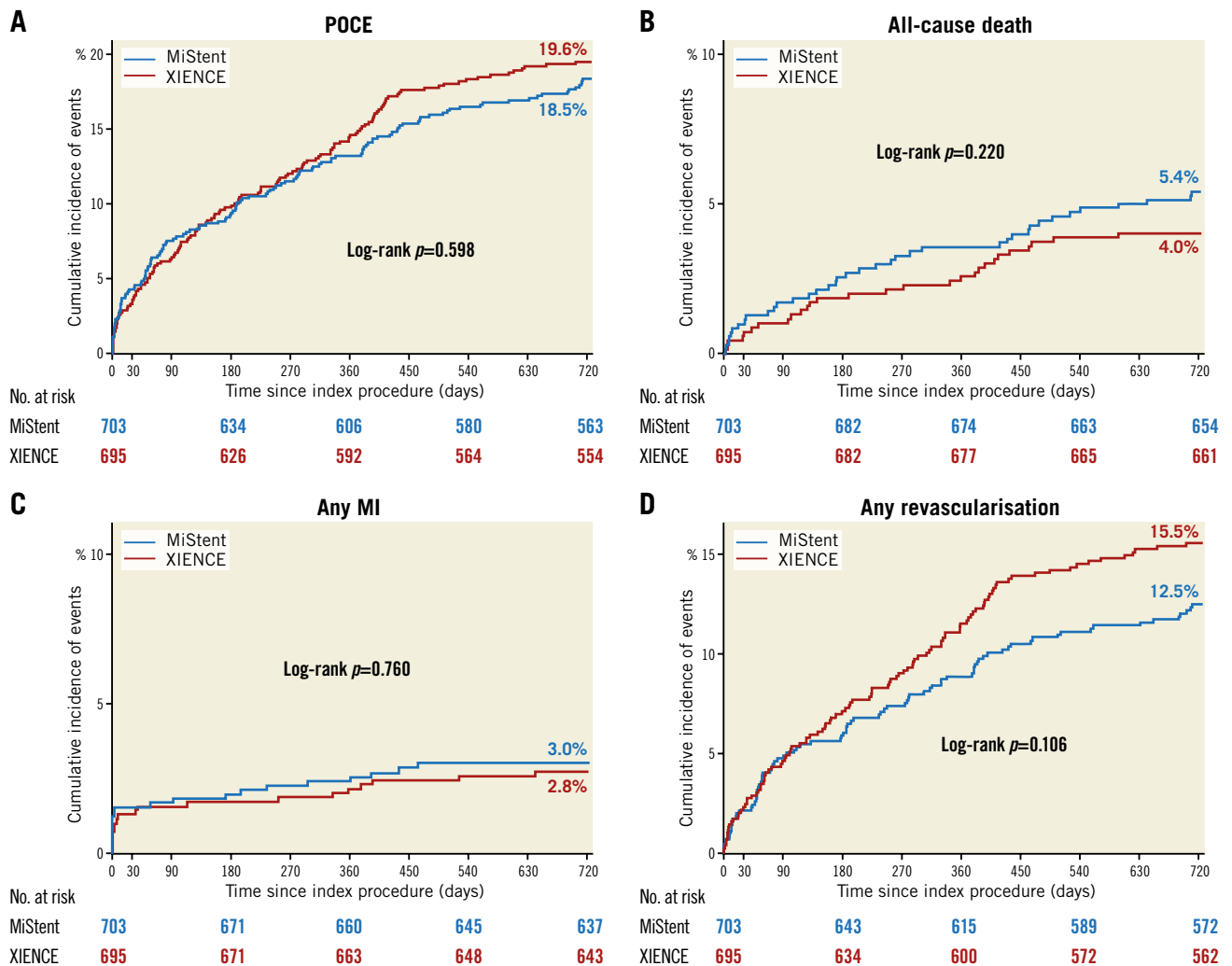


Figure 3. Kaplan-Meier estimates for the patient-oriented composite endpoint (POCE) and its components over 720 days of follow-up. Kaplan-Meier curves show the cumulative incidence of POCE - a composite of all-cause death, any myocardial infarction (any MI), or any revascularisation (A); all-cause death (B); any MI (C); and any revascularisation (D).

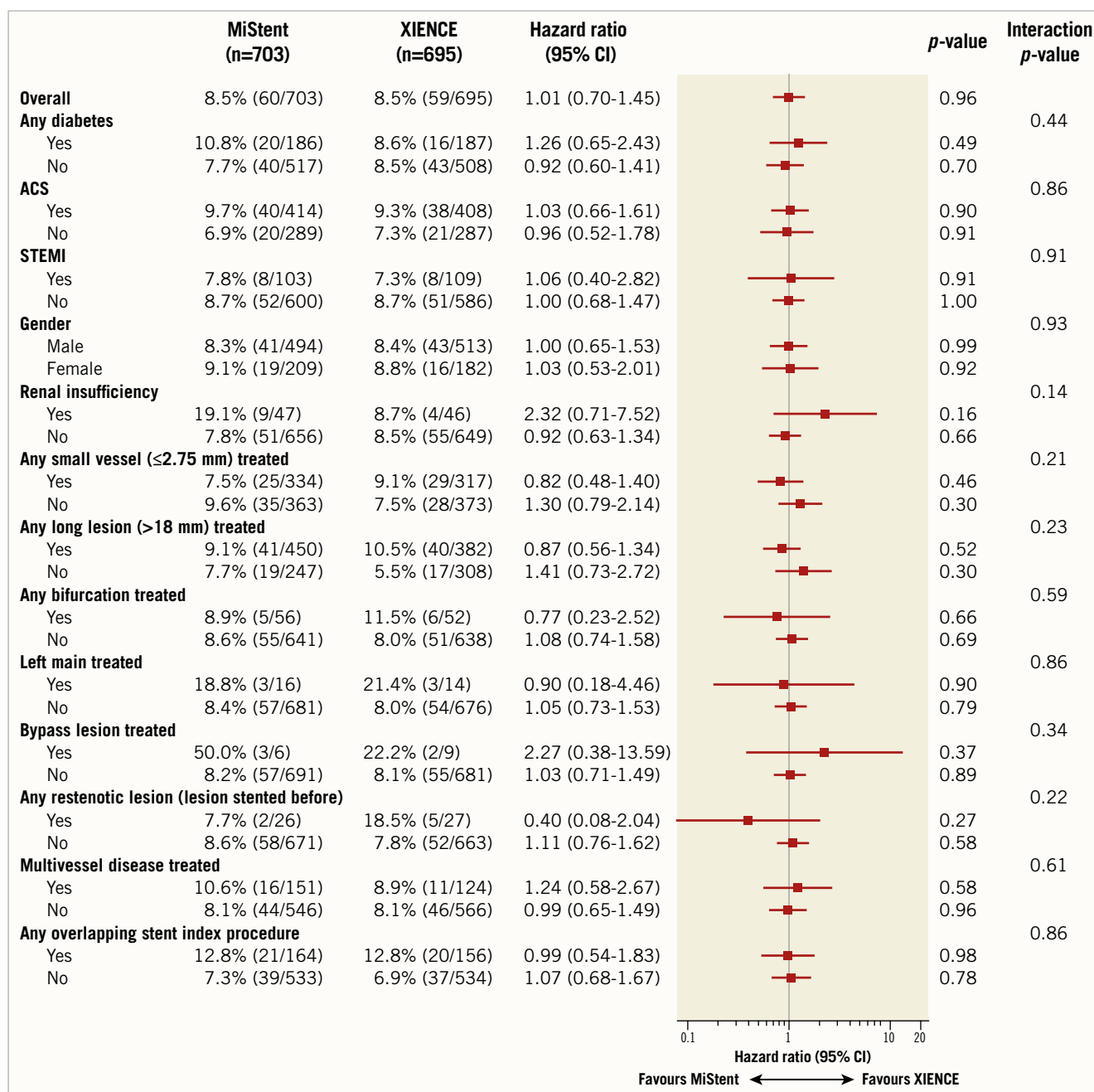


Figure 4. Stratified analyses of the device-oriented composite endpoint at 24 months across subgroups. Hazard ratio with 95% CI and p-value results were from Cox proportional hazards analysis. Renal insufficiency is defined as serum creatinine >2.5 mg/dL or creatinine clearance ≤30 mL/min. ACS: acute coronary syndrome; CI: confidence interval; STEMI: ST-segment elevation myocardial infarction

different in the two groups and was low. The rate of very late stent thrombosis did not differ between groups and was low in both treatment arms. The efficacy and safety of the MiStent is further supported by a recent meta-analysis showing that newer-generation ultra-thin strut DES (60–65 μm), including the MiStent, were associated with a 16% reduction in TLF driven by less MI with lower rates of any stent thrombosis⁸.

In the present study, no significant differences were documented between the two treatment groups in the individual components

of the primary endpoint as well as the secondary clinical endpoints, except for non-TV revascularisation after 90 days, the rate of which was lower in the MiStent arm than in the XIENCE arm.

CAUSE OF DEATH

All-cause death occurred in 5.4% (38) in the MiStent arm and 4.0% (28) in the XIENCE arm (HR 1.36, 95% CI: 0.83-2.21, p=0.22). This difference came mainly from the difference in cardiac death (3.0% [21] vs 2.0% [14], p=0.24), although the differences in both

all-cause death and cardiac death were not statistically significant. Since cardiac death includes unexplained death, it would be difficult to elaborate further on the exact cause of the differences in cardiac death. The differences were less in vascular death (0.6% [4] vs 0.9% [6], in the MiStent and XIENCE arms, respectively [$p=0.53$]) and non-cardiovascular death (1.9% [13] vs 1.2% [8], in the MiStent and XIENCE arms, respectively [$p=0.27$]).

COMPARISON WITH OTHER STUDIES

So far, several randomised controlled trials comparing biodegradable polymer (BP)-DES and durable polymer (DP)-DES have been reported (LEADERS, BIOSCIENCE, EVOLVE II, CENTURY II)⁹⁻¹². However, overall results do not suggest superiority of BP-DES.

The subgroup analysis in the present study showed that DOCE rates were not significantly different across the predefined patient subsets. In contrast, the BIOSCIENCE trial comparing Orsiro BP-SES (Biotronik, Berlin, Germany) and XIENCE DP-EES showed that the Orsiro BP-SES had a significantly lower rate of DOCE at two years in STEMI patients (5.4% vs 10.8%; risk ratio [RR]: 0.48, 95% CI: 0.23 to 0.99; $p=0.043$), with a significant interaction p -value compared with patients without STEMI (RR: 1.15, 95% CI: 0.86 to 1.53; $p=0.86$; p for interaction=0.026). Previously, two-year clinical outcomes were compared in a large population acute myocardial infarction (AMI) registry ($n=3,559$)¹³, including biolimus-eluting stents (the BioMatrix Flex™ stent; Biosensors, Morges, Switzerland, or the Nobori® stent; Terumo Corporation, Tokyo, Japan) as BP-DES. The two-year MACE rate was 10.7% and 9.9% ($p=0.679$) and the incidence of ST was 0.8% vs 0.9% ($p=1.0$) in the BP-DES group and second-generation DP-DES group, respectively. These results suggest at least similar efficacy of BP-DES and DP-DES in AMI patients.

The observed rate of the primary endpoint in XIENCE at two years (8.6%) was almost identical to the expected one-year rate of DOCE (8.0%) in a sample size calculation based on the XIENCE arm of the RESOLUTE All Comers trial, which was published in 2010. In the two-year report of the RESOLUTE All Comers trial¹⁴, the rate of DOCE was 10.7%, the rate of cardiac death was 2.2%, the rate of TV-MI was 4.5%, and the rate of ischaemia-driven TLR was 5.1% in the XIENCE arm. The difference in DOCE between the XIENCE arm in the DESSOLVE III trial and that in the RESOLUTE All Comers trial was mainly driven by the difference in TV-MI. Although both trials were based on the World Health Organization (WHO) (extended) definition of MI, periprocedural MI occurred in 1.2% of patients in the XIENCE arm in DESSOLVE III and 3.1% of patients in the XIENCE arm in the RESOLUTE All Comers trial¹⁵. In DESSOLVE III, cardiac enzyme sampling after the index procedure was available in 92.3%, 94.2%, and 93.1% in CK-MB, troponin, and CK, respectively⁵, whereas 92.5% had an analysable data set for either biomarker in RESOLUTE All Comers. Thus, potential underreporting of periprocedural MI should be excluded. Regarding difference in baseline characteristics, the XIENCE arm of DESSOLVE III had more patients presenting with stable angina (41%) than that of the

RESOLUTE All Comers trial (36%). Notably, there are several differences in the protocols of the two trials: 1) only XIENCE V was used in the RESOLUTE All Comers trial, whereas XIENCE V®, XIENCE PRIME®, or XIENCE Xpedition® (all Abbott Vascular) was allowed in the DESSOLVE III trial (**Supplementary Table 2**); 2) only clopidogrel was used as P2Y₁₂ inhibitor in the RESOLUTE All Comers trial, while ticagrelor and prasugrel were also available and preferred in case of ACS in the DESSOLVE III trial. In addition, as there has been accumulating evidence showing benefit of a physiology approach to define the appropriateness of revascularisation based on the presence of ischaemia^{16,17}, as compared to the era when the RESOLUTE All Comers trial was conducted, frequent use of physiological assessment might have contributed to better outcome in the DESSOLVE III trial, although none of the information regarding physiology assessment was captured in the electronic case report form (eCRF) of the trial. Although it is not to be expected that all consecutive patients will be included in an all-comer trial¹⁸, it is important to note that we were only able to enrol 1,398 (16.6%) patients out of 8,423 patients treated with PCI during the study period in the enrolling sites⁵, whereas the Thoraxcenter in the Erasmus MC (Rotterdam, the Netherlands) reported that 579 patients (48%) were actually included out of 1,242 consecutive PCI patients treated during the inclusion period of the LEADERS and RESOLUTE All Comers trials¹⁸. This raises the question as to whether we enrolled a similar population to other all-comer trials, which may explain the observed low DOCE and TV-MI rates.

EXPLORATORY QFR ANALYSES AND INSIGHTS INTO OBSERVED DIFFERENCE IN NON-TV REVASCULARISATION (Supplementary Appendix 3, Supplementary Table 3, Supplementary Figure 2-Supplementary Figure 4).

Limitations

Further long-term follow-up data are necessary to demonstrate the implications of biodegradable polymer as compared to durable polymer. The omission of events occurring earlier than the landmark was among the recognised limitations of landmark analysis. The study did not have adequate power to undertake a statistical comparison for any itemised endpoints due to the relatively small sample size. Indication (i.e., clinically driven or non-clinically driven) of non-TV revascularisation was not adjudicated by the CEC. The *post hoc* hypothesis-generating QFR analysis in non-TV had low feasibility due to the absence of a pre-specified angiographic acquisition protocol.

Conclusions

In an all-comer population, use of the MiStent sirolimus-eluting bioabsorbable polymer-coated stent was related to sustained efficacy and safety at two-year follow-up, as compared to the XIENCE durable polymer stent. The MiStent's potential long-term clinical benefit will be further elucidated up to a total of five years of follow-up.

Impact on daily practice

In an all-comer population, use of the MiStent sirolimus-eluting bioabsorbable polymer-coated stent was related to sustained efficacy and safety at two-year follow-up, as compared to the XIENCE everolimus-eluting durable polymer stent. This study adds a promising option of a drug-eluting stent to the armamentarium to be used in our daily practice. It remains to be elucidated whether the MiStent has a beneficial effect at the planned medium-term follow-up up to five years.

Appendix. Study collaborators

Gillian A.J. Jessurun, MD, PhD; *Department of Cardiology, Treant Zorggroep, Emmen, the Netherlands.* Karel T. Koch, MD, PhD; *Amsterdam University Medical Centre, Amsterdam, the Netherlands.* Roland P.T. Troquay, MD; *VieCuri Medical Centre for Northern Limburg, Venlo, the Netherlands.* Bas J.B. Hamer, MD; *Meander Medisch Centrum, Amersfoort, the Netherlands.* Ton Oude Ophuis, MD, PhD; *Department of Cardiology, Canisius Wilhelmina Ziekenhuis, Nijmegen, the Netherlands.* Krzysztof P. Milewski, MD, PhD; *Oddzial Kardiologii Inwazyjnej, Elektrofizjologii i Elektrostymulacji PAKS, American Heart of Poland S.A., Tychy, Poland.* Sjoerd H. Hofma, MD, PhD; *Medisch Centrum Leeuwarden, Leeuwarden, the Netherlands.*

Guest Editor

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Conflict of interest statement

Y. Onuma, J.J. Piek, and P.W. Serruys have served as members of the advisory board of Abbott Vascular. S.H. Hofma declares an unrestricted research grant to the institution by Abbott. W. Wijns has received speaker fees from Abbott Vascular, Biotronik, MicroPort, and Terumo; he is a scientific advisor for Rede Optimus Research and a co-founder of Argonauts, an innovation accelerator. The other authors have no conflicts of interest to declare. The Guest Editor is a consultant for Edwards Lifesciences.

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Supplementary data

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Supplementary data

Supplementary Appendix 1. Quantitative flow ratio calculation

In patients with revascularisation in a non-target vessel, quantitative flow ratio (QFR) post procedure and pre-revascularisation were assessed as a *post hoc* study, using validated software (QAngio XA 3D 1.1.16.6; Medis medical imaging systems BV, Leiden, the Netherlands), which received CE (Conformité Européenne) marking certification for clinical usage in April 2017. Details regarding the QFR calculation method have been reported elsewhere^{19,20}. Briefly, the QFR calculation was based on the 3D-QCA reconstructed from two angiographic projections with angles $\geq 25^\circ$ apart and volumetric flow rate calculated by using contrast bolus frame count. The 3D-QCA reconstruction and measurements were performed as described previously²¹. The rate of volumetric flow was assessed with frame count based on the TIMI frame counting method²². In the current study, QFR value was computed by using projections without pharmacologically induced hyperaemia (contrast-flow QFR) for the analysis¹⁹. The QFR analysis was performed at the distal point of the target vessel (vessel QFR). The distal point was placed at least distal of the last lesion as long as the lumen diameter was more than 2 mm.

Supplementary Appendix 2. Statistical analysis

All the analyses were performed on an intention-to-treat basis. Continuous variables are presented as mean and standard deviation and were compared using a two-sample t-test, or as median and interquartile range (IQR) and compared using the Mann-Whitney U test, as appropriate. The categorical variables were summarised in frequencies and percentages and compared using the Fisher's exact test. Time-to-event variables are presented as Kaplan-Meier curves and compared using the log-rank test. Post hoc landmark analyses were performed after 90 days, the time point when the biodegradable polymer of the MiStent was expected to be completely absorbed. Hazard ratios were calculated using the Cox proportional hazards model. Unless otherwise specified, a two-sided p-value of less than 0.05 was considered to indicate statistical significance. All statistical analyses were performed using SAS software, version 9.3 (SAS Institute Inc., Cary, NC, USA).

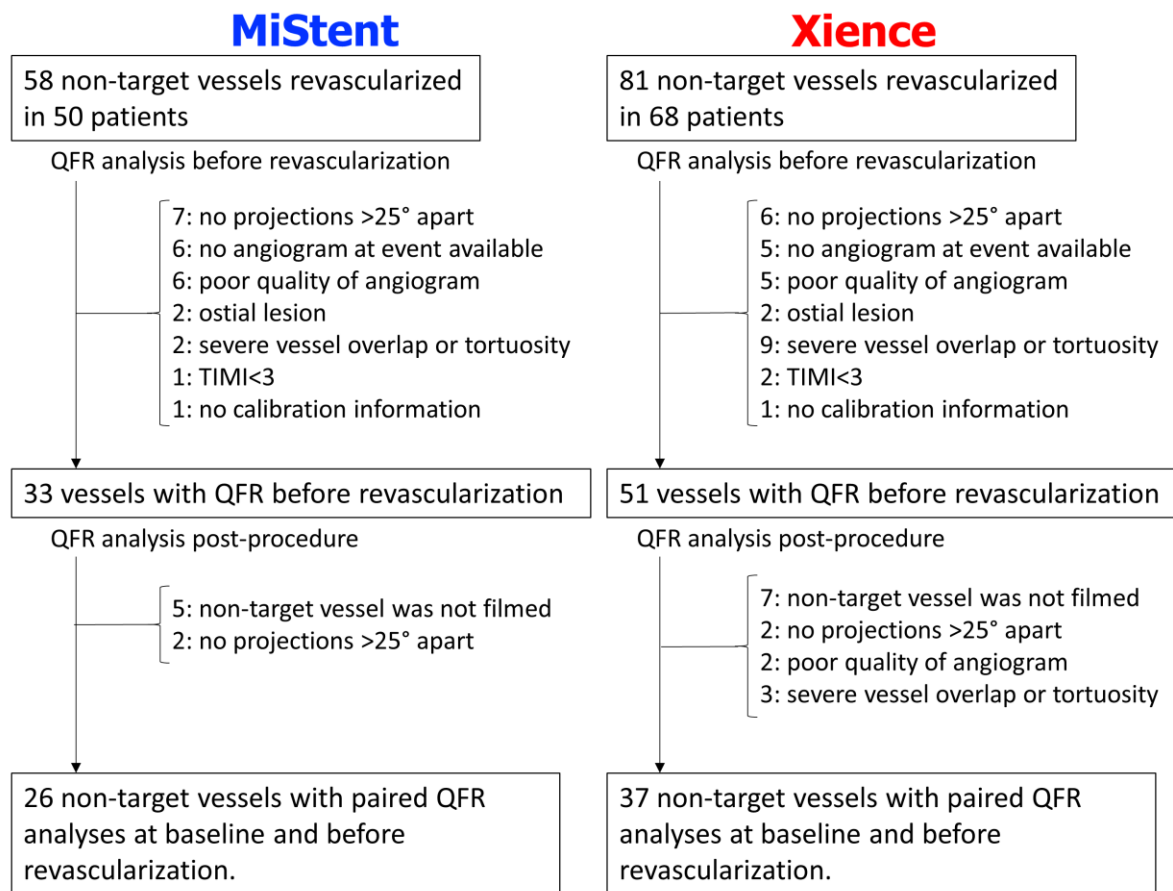
Supplementary Appendix 3. Exploratory QFR analyses and insights into observed difference in non-TV revascularisation

Post hoc paired QCA analysis in lesions with non-target vessel revascularisation is tabulated in **Supplementary Table 3**. At baseline, minimum lumen diameter (MLD) was significantly larger in MiStent than in XIENCE (1.61 ± 0.62 vs 1.37 ± 0.59 mm, $p=0.048$), while diameter stenosis (DS) was comparable between the two arms. Before the revascularisation event, neither MLD nor DS was statistically different between the two devices.

QFR before non-target vessel revascularisation was comparable in the two arms (0.84 [IQR 0.76, 0.91] vs 0.81 [IQR 0.68, 0.89], $p=0.384$) (**Supplementary Figure 2**). In vessels with paired QFR at baseline and before revascularisation, the number of vessels with QFR at baseline ≤ 0.8 was 26.9% (7/26) in the MiStent arm and 24.3% (9/37) in the XIENCE arm ($p=0.816$), whereas those with QFR before revascularisation ≤ 0.8 were 46.2% (12/26) in the MiStent arm and 48.6% (18/37) in the XIENCE arm ($p=0.845$) (**Supplementary Figure 3**). The number of lesions treated at baseline (1.49 ± 0.83 in the MiStent arm and 1.44 ± 0.78 in the XIENCE arm, $p=0.10$) and the number of stents implanted per patient at baseline (1.82 ± 1.20 in the MiStent arm and 1.76 ± 1.13 in the XIENCE arm, $p=0.39$) were not significantly different. The Venn diagram (**Supplementary Figure 4**) shows that a considerable proportion (23.7%) of the non-TV revascularisation was accompanied by clinically indicated TVR.

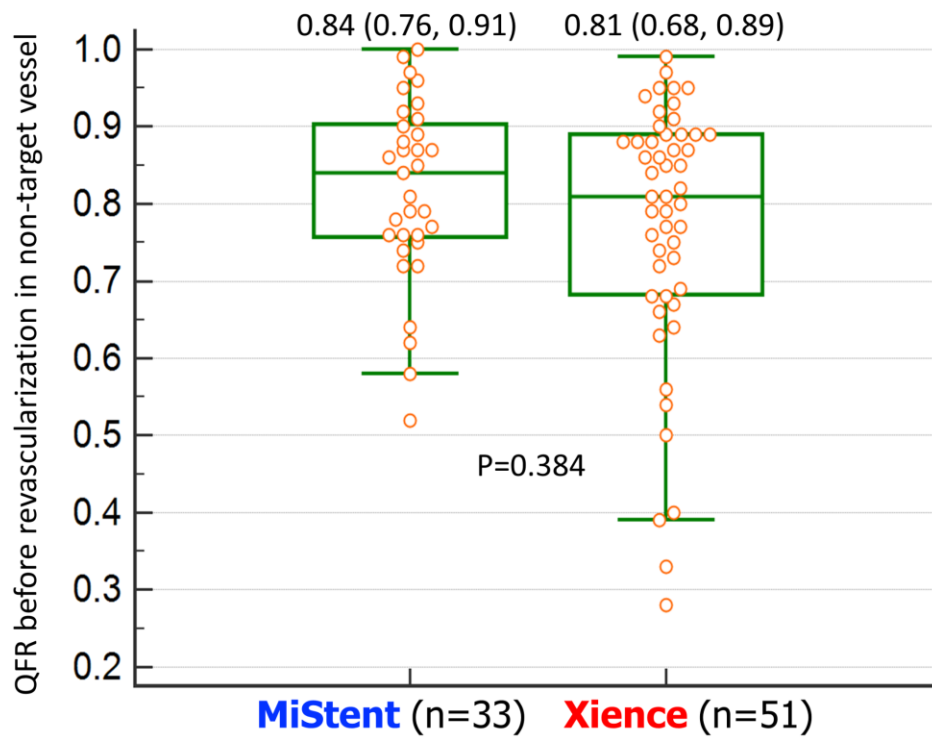
These analyses seem to exclude the potential for overtreatment or undertreatment of non-TV at baseline. Basically, lack of angiography mandated by protocol precludes the bias caused by the artificial increase of revascularisation triggered by angiography. However, the fact that a considerable proportion of the non-TV revascularisation was accompanied by clinically indicated TVR suggests that the differences in non-TV revascularisation between groups could represent an indirect oculostenotic reflex at the occasion of clinically indicated angiography.

Supplementary Figure 1. Feasibility of QFR analysis in revascularised non-target vessels.



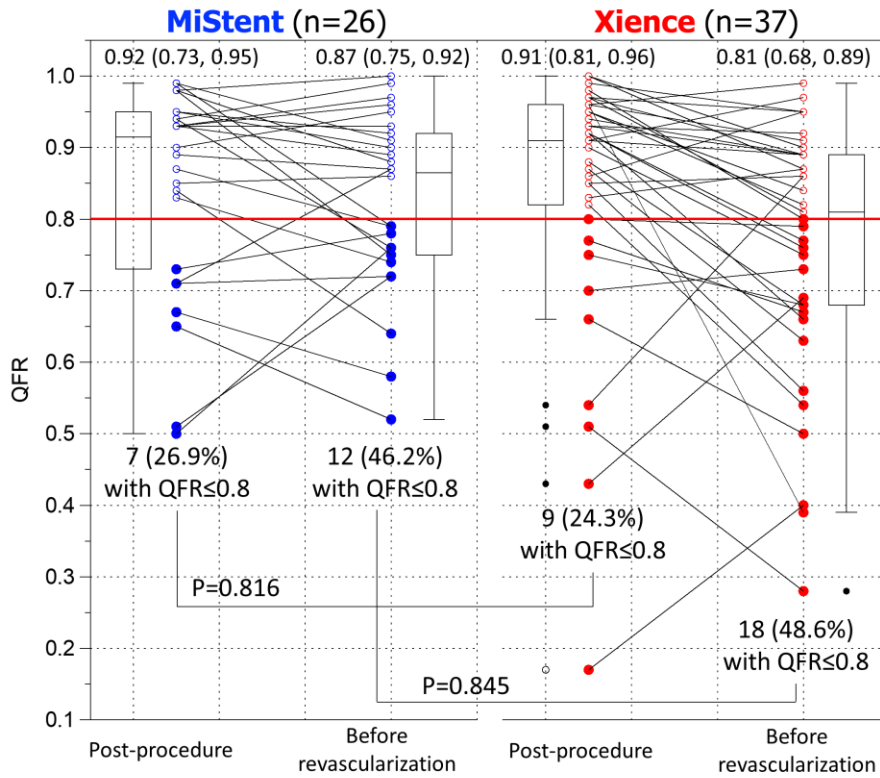
QFR: quantitative flow ratio; TIMI: Thrombolysis In Myocardial Infarction

Supplementary Figure 2. QFR before revascularisation in non-target vessels.



Data are median (interquartile range). QFR: quantitative flow ratio

Supplementary Figure 3. Serial change of QFR post procedure and before revascularisation in non-target vessels.

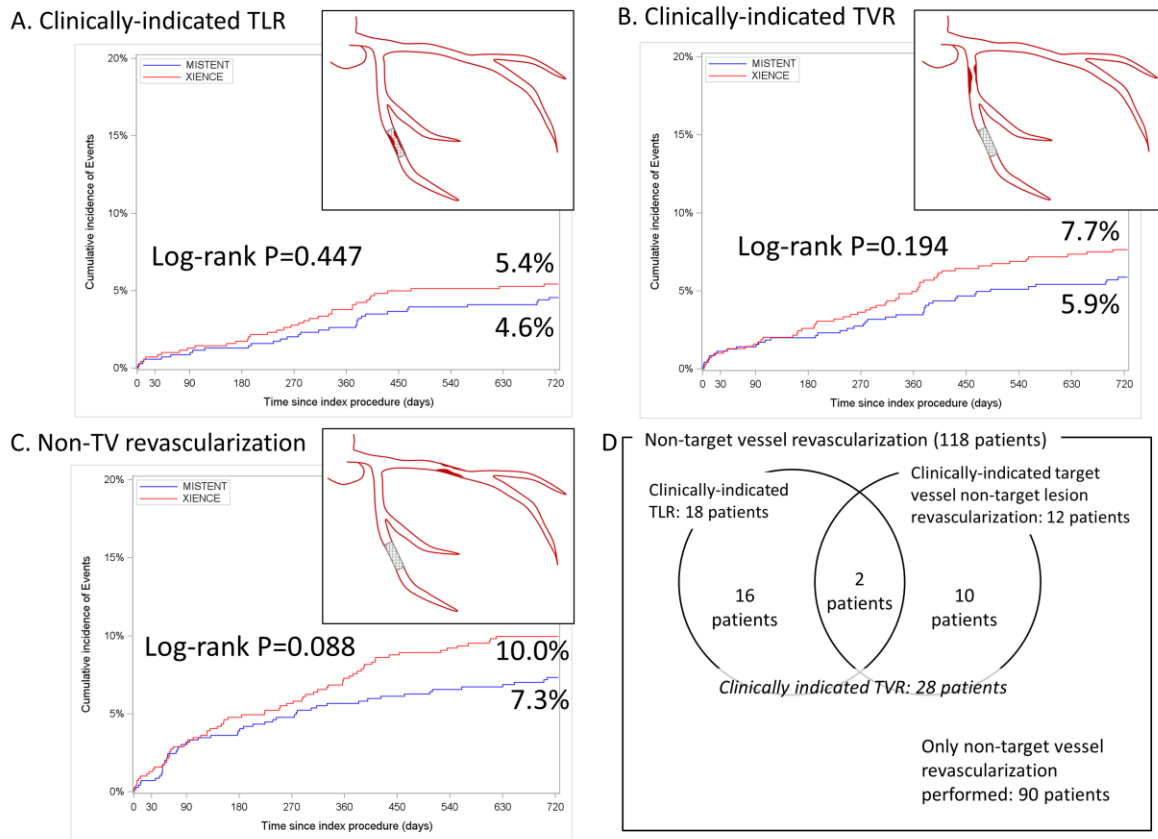


Filled circles indicate $QFR \leq 0.8$. Data are median (interquartile range) or count (percentage).

P-values were by Fisher's exact test.

QFR: quantitative flow ratio

Supplementary Figure 4. Impact of target vessel revascularisation on non-target vessel revascularisation.



Kaplan-Meier curves for clinically indicated TLR (A), clinically indicated TVR (B), and non-target vessel revascularisation (C). Of 118 patients who underwent non-target vessel revascularisation, concomitant clinically indicated target vessel revascularisation was performed in 28 patients (23.7%) (D, Venn diagram). Clinically indicated target vessel revascularisation could serve as an angiographic follow-up of a non-target vessel, which could amplify a non-significant difference of target vessel revascularisation, translating into a larger difference in non-target vessel revascularisation.

TLR: target lesion revascularisation; TV: target vessel; TVR: target vessel revascularisation

Supplementary Table 1. Predefined secondary endpoints at 2 years.

1. Composite endpoint
Patient-oriented composite endpoint (POCE) defined as all-cause death, any myocardial infarction (MI), or any revascularisation
Major adverse cardiac events (MACE) defined as all-cause death, any MI, or any TVR
Target vessel failure (TVF) defined as cardiac death, target vessel (TV)-MI, or clinically indicated target vessel revascularisation (TVR)
DOCE/TLF defined as cardiac death, TV-MI or clinically indicated target lesion revascularisation (TLR) (for all follow-up/visits other than 12 months)
2. Mortality
All death
Cardiac death
Non-cardiac death (vascular and non-cardiovascular)
3. Myocardial infarction
All MI
TV-MI
Non-TV-MI
4. Revascularisation
Target lesion revascularisation (TLR) (any, clinically indicated TLR, non-clinically indicated TLR)
Target vessel revascularisation (TVR) (any, clinically indicated TVR, non-clinically indicated TVR)
Non-TV revascularisation
Any revascularisation

5. Stent thrombosis (ST) rates according to ARC classification

ST - early (acute, subacute), late, very late

ST - definite, probable, possible

ST - definite/probable

Supplementary Table 2. Specifications of different iterations of XIENCE stent system*.

Iteration	Polymer	Drug	Stent design	Catheter
XIENCE V®	Fluoropolymer	Everolimus (1 µg/mm ²)	MULTI-LINK VISION®	XIENCE V® SDS
XIENCE PRIME®	↓	↓	MULTI-LINK 8®	XIENCE PRIME® SDS
XIENCE Xpedition®	↓	↓	↓	XIENCE Xpedition® SDS

* Hermiller JB. From Xience V to Prime to Xpedition: Stent Design Evolution and Clinical Trial Results (SPIRIT and Others). Presented at TCT 2013, San Francisco, CA, USA.

SDS: stent delivery system

Supplementary Table 3. Paired quantitative coronary angiography analysis in lesions with non-target vessel revascularisation.

	MiStent (n=41*)	XIENCE (n=65†)	<i>p</i> -value
Minimum lumen diameter			
At baseline (mm)	1.61±0.62	1.37±0.59	0.048
Before revascularisation (mm)	1.36±0.61	1.23±0.54	0.255
P-value between baseline and before revascularisation	0.001	0.002	
Late loss >0 mm	30 (73.2%)	39 (60.0%)	0.166
Diameter stenosis			
At baseline (%)	44.2±12.1	48.5±18.3	0.195
Before revascularisation (%)	48.4±17.9	51.8±18.2	0.337
P-value between baseline and before revascularisation	0.106	0.071	
Increase in %DS	25 (61.0%)	34 (52.3%)	0.382

*Among 61 non-target vessel lesions revascularised in 50 patients in the MiStent arm, 20 lesions were missing angiogram either post procedure or at the event.

†Among 88 non-target vessel lesions revascularised in 68 patients in the XIENCE arm, 23 lesions were missing angiogram either post procedure or at the event.