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ORIGINAL RESEARCH

Ten-Year Clinical Outcomes of Biodegradable Versus Durable Polymer New-Generation Drug-Eluting Stent in Patients With Coronary Artery Disease With and Without Diabetes Mellitus

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BACKGROUND: Extended long-term follow-up data of new-generation drug-eluting stents in patients with diabetes mellitus is scant. The aim of this study is to assess the 10-year clinical outcome of new-generation biodegradable polymer-based sirolimus-eluting stents (Yukon Choice PC) versus permanent polymer-based everolimus-eluting stents (XIENCE) in patients with and without diabetes mellitus.

METHODS AND RESULTS: In a prespecified subgroup analysis, outcomes of patients with or without diabetes mellitus treated with drug-eluting stents were compared. The primary end point of this analysis was major adverse cardiac event, the composite of death, myocardial infarction, or target lesion revascularization. The analysis includes a total of 1951 patients (560 patients with and 1391 patients without diabetes mellitus) randomized to treatment with Yukon Choice PC (n=1299) or Xience (n=652). Regarding the primary end point, at 10 years patients with diabetes mellitus showed significantly higher major adverse cardiac event rates than patients without diabetes mellitus (P<0.001; hazard ratio [HR], 1.41; 95% CI, 1.22–1.63). There was no significant difference between patients treated with Yukon Choice PC versus Xience, neither in the subgroup of patients with (P=0.91; HR, 1.01; 95% CI, 0.79–1.30) nor without diabetes mellitus (P=0.50; HR, 0.94; 95% CI, 0.79–1.21). Rates of definite/probable stent thrombosis were 2.3% in patients with and 1.9% in patients without diabetes mellitus (HR, 1.27; 95% CI, 0.34–2.60; P=0.52), without significant differences between study devices.

CONCLUSIONS: The clinical outcome of patients with diabetes after percutaneous coronary intervention with different new-generation drug-eluting stents is considerably worse than that of patients without diabetes mellitus, with event rates constantly increasing out to 10 years.

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Key Words: biodegradable polymer ■ diabetes mellitus ■ new-generation drug-eluting stent ■ permanent polymer

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CLINICAL PERSPECTIVE

What Is New?

- Treatment of coronary artery disease in patients with diabetes mellitus presents a particular challenge, because it is associated with a more diffuse and complex disease, and consequently suboptimal clinical outcome after percutaneous coronary intervention.
- Since the Xience drug-eluting stent had emerged as a benchmark device in the overall population as well as patients with diabetes mellitus, further device innovations have been aiming at improved biocompatibility and arterial healing, the effects of which are expected to occur over time.
- However, until the present, there is no evidence of superiority of one of these device innovations over another.

What Are the Clinical Implications?

- When compared with a new-generation durable polymer drug-eluting stents, biodegradable polymer drug-eluting stents do not seem to have a clinically meaningful impact on outcomes at 10 years.
- Consistently high clinical event rates after percutaneous coronary intervention in patients with diabetes mellitus, as well as the constant increase out to 10 years, emphasize the particular challenge of patients with diabetes mellitus with coronary artery disease.

Nonstandard Abbreviations and Acronyms

BP-SES	biodegradable polymer-based sirolimus-eluting stent
MACE	major adverse cardiac events
PP-EES	durable polymer-based everolimus-eluting stent
TLR	target lesion revascularization

Treatment of coronary artery disease in patients with diabetes mellitus presents a particular challenge, because it is associated with a more diffuse manifestation, complex disease, and consequently suboptimal clinical outcome after percutaneous coronary intervention (PCI).[1,2] In order to improve the outcome of patients with diabetes mellitus undergoing PCI, extensive research effort has been dedicated to the comparison of coronary stents of different design and generation in the general population of patients with coronary heart disease as well as the specific subgroup of patients with diabetes mellitus. While the new-generation permanent polymer-based everolimus-eluting Xience stent had emerged as benchmark device in this setting,[3] further innovations of strut design and polymer composition have led to a wide range of available drug-eluting stents (DES) at present.

An important part of these device innovations has been focusing on improved polymer biocompatibility, following different strategies to reduce the persistent inflammatory stimulus because of remaining polymer coating after completion of drug release, as indicated by autopsy studies.[4] New-generation polymer coatings had to be more biocompatible if permanent, or at best biodegradable. However, evidence for superiority of one particular polymer strategy over another is still lacking[5] and even with the newest generation of DES, patients with diabetes mellitus still show worse outcome after PCI as compared with patients without diabetes mellitus during short- and mid-term follow-up.[6] Extended long-term data beyond 5 years of randomized trials assessing current-generation DES in patients with and without diabetes mellitus are scant.

To address this issue, we report the 10-year clinical outcomes of the prespecified subgroups of patients with and without diabetes mellitus, randomly assigned to receive a new-generation biodegradable polymer-based sirolimus-eluting stent (BP-SES; Yukon Choice PC) or a new-generation durable polymer-based everolimus-eluting stent (PP-EES; Xience), in the setting of the ISAR-TEST 4 (Intracoronary Stenting, Angiographic Results: Test Efficacy of 3 Limus-Eluting Stents) randomized trial.

METHODS

The data, analytic methods, and study materials will be made available to other researchers for purposes of reproducing the results or replicating the procedure. The data are available from the corresponding author on reasonable request. Between September 2007 and August 2008, patients older than age 18 years with ischemic symptoms or evidence of myocardial ischemia (inducible or spontaneous) in the presence of ≥50% de novo stenosis located in native coronary vessels were enrolled at 2 centers in Munich, Germany, provided that written informed consent by the patient or her/his legally authorized representative for participation in the study was obtained. Patients with a target lesion located in the left main stem or in cardiogenic shock were considered ineligible for the study. Further details of the study population, methods, end points, and results at 10-year follow-up have been previously reported.[7,8] Patients were randomly allocated to receive a new-generation BP-SES (Yukon Choice PC, Translumina, Hechingen, Germany and Translumina Therapeutics, Dehradoon, India), a new-generation PP-EES (Xience, Abbott Vascular,

Abbott Park, IL), or an early-generation permanent polymer-based sirolimus-eluting stent (Cypher; Cordis Corporation, Miami Lakes, FL) in a 2:1:1 allocation. The study cohort of patients treated with early-generation permanent polymer-based sirolimus-eluting stent has been excluded from the current analysis given the limited relevance for daily clinical practice because this stent is no longer commercially available since 2013. Figure S1 shows principal characteristics of the study devices. Detailed descriptions of stent platforms and elution characteristics have been reported elsewhere.[7,9,10] The aim of the current study was to compare outcomes of patients treated with Yukon Choice PC versus Xience after 10-year follow-up with special focus on patients with and without diabetes mellitus.

The primary end point of this analysis was major adverse cardiac event (MACE), the composite of death, myocardial infarction (MI), or target lesion revascularization (TLR). The main secondary end point of interest was the individual components of MACE and definite/probable stent thrombosis. Stent thrombosis was classified according to the Academic Research Consortium criteria.[11] Patients with diabetes mellitus represented a prespecified subgroup of interest according to the trial protocol.

Follow-Up

Patients were systematically evaluated at 1 and 12 months and annually out to 120 months. Extended follow-up was performed in the setting of routine care by either telephone calls or office visit in the 2 participating centers. The trial protocol included planned angiographic follow-up at 6 to 8 months for all patients. The study was conducted in accordance with the provisions of the Declaration of Helsinki and with the International Conference on Harmonization Good Clinical Practices. All patients had given their written informed consent to the trial protocol. Analysis of data from extended follow-up, which was not prespecified within the study protocol, was approved by the institutional ethics committee responsible for the participating centers. Additional written informed consent from patients was waived, because of the routine availability of patient follow-up data. All events were adjudicated and classified by an event adjudication committee blinded to the treatment groups.

Statistical Analysis

Continuous data are presented as mean (±SD) or median (25th–75th percentiles). Categorical data are presented as counts and proportions (%). Unless otherwise stated, differences between groups regarding baseline, angiographic, and procedural data were checked for significance using Student *t* test or Wilcoxon rank sum test (continuous data) or the χ^2 or Fisher exact test where the expected cell value was <5 (categorical variables).

Survival was analyzed according to Kaplan–Meier methods and hazard ratios (HRs) were calculated using Cox proportional hazards model after checking for fulfillment of the proportional hazards assumption by the method of Grambsch and Therneau.[12]

All analyses were by intention-to-treat using all patients randomized in the study. An additional analysis was performed to compare clinical outcomes in the overall study cohort in patients with versus without diabetes mellitus independent of treatment allocation. Statistical analysis was performed by using the R 3.5.1 Statistical Package (R Foundation for Statistical Computing, Vienna, Austria). For all comparisons a 2-sided *P* value <0.05 was considered to indicate statistical significance.

RESULTS

This analysis includes a total of 1951 patients with coronary artery disease randomized to treatment with either Yukon Choice PC (n=1299) or Xience (n=652) new-generation DES in the setting of the randomized Intracoronary Stenting and Angiographic Results: Test Efficacy of 3 Limus-Eluting Stents (ISAR-TEST 4) trial.

Prevalence of diabetes mellitus in the overall study cohort was 28.7% and was comparable in both treatment groups (Yukon Choice PC: 376 patients [28.9%] and Xience: 184 [28.2%], *P*=0.74).

Median follow-up interval of the entire study cohort was 10.66 years (25th–75th percentiles: 9.43–11.37). The last follow-up contact was an office visit in 33.7% and a telephone interview in 66.3% of the patients, respectively. Ten-year clinical follow-up was not available in 356 patients (18.2%) (patients with diabetes mellitus 121 [21.6%] versus patients without diabetes mellitus 235 [16.9%], *P*=0.015).

Baseline patient and lesion characteristics according to diabetic status were well balanced, with few exceptions (Tables 1 and 2). Patients with diabetes mellitus had significantly more often arterial hypertension (77.0% versus 65.3%, *P*<0.001) and 3-vessel coronary artery disease (66.1% versus 55.5%, *P*<0.001) and presented with significantly longer lesions (15.6 versus 14.7 mm, *P*=0.020), smaller minimal lumen diameter before (0.96 versus 1.00 mm, *P*=0.047) as well as after the procedure (2.53 versus 2.60 mm, *P*<0.001), higher mean body mass index (28.5 ± 4.7 versus 26.8 ± 3.9, *P*<0.001), and lower mean left ventricular ejection fraction (51.0 ± 12.7% versus 54.1 ± 10.8%, *P*<0.001). Baseline patient and lesion characteristics according to diabetic status and treatment group are summarized in Table S1. They were well balanced, except 1: Patients without diabetes mellitus treated with Yukon Choice PC

Table 1. Baseline Patient Characteristics in Patient With and Without Diabetes Mellitus

Characteristics	With Diabetes Mellitus	Without Diabetes Mellitus	*P* Value
Patients	(n=560)	(n=1391)	
Age, y, ±SD	67.1 (±10.1)	66.5 (±11.10)	0.23
Male sex	413 (73.8)	1072 (77.1)	0.14
Insulin-dependent diabetes mellitus	168 (30.0)		
Oral antidiabetic medication	286 (51.1)		
Arterial hypertension	431 (77.0)	908 (65.3)	<0.001*
Current smoker	74 (13.2)	229 (16.5)	0.09
Hyperlipidemia	374 (66.8)	917 (65.9)	0.76
Coronary artery disease			<0.001*
1-vessel disease	47 (8.4)	223 (16.0)	
2-vessel disease	143 (25.5)	395 (28.4)	
3-vessel disease	370 (66.1)	772 (55.5)	
Clinical presentation			0.22
ST-segment–elevation myocardial infarction	60 (10.7)	177 (12.7)	
Non–ST-segment–elevation acute coronary syndrome	178 (31.8)	395 (28.4)	
Stable angina	322 (57.5)	819 (58.9)	
Prior myocardial infarction	167 (29.8)	396 (28.8)	0.59
Prior coronary artery bypass grafting	67 (12.0)	131 (9.4)	0.11
Body mass index, ±SD	28.5 (±4.7)	26.8 (±3.9)	<0.001*
Ejection fraction, %, ±SD	51.0 (±12.7)	54.1 (±10.8)	<0.001*

Values are n (%) or mean (±SD) unless otherwise indicated. *P* values are derived from Cox proportional hazard models.
*Indicates statistical significance.

had significantly more often bifurcational lesions than those treated with Xience (26.4% versus 21.7%, *P*=0.03).

Clinical Outcome After PCI of Patients With Versus Without Diabetes Mellitus

Overall clinical outcomes of patients with and without diabetes mellitus are summarized in Table 3. Rates of MACE were significantly higher in patients with diabetes mellitus as compared with patients without diabetes mellitus (56.5% versus 43.5%; *P*<0.001; HR, 1.41; 95% CI, 1.22–1.63). Kaplan–Meier curves for the incidence of MACE are displayed in Figure 1. In patients with diabetes mellitus, rates of all-cause mortality (42.3% versus 27.1%; *P*<0.001; HR, 1.68; 95% CI, 1.41–2.00) as well as cardiac death (27.7% versus 16.4%; *P*<0.001; HR, 1.70; 95% CI, 1.35–2.16) were significantly higher than in patients without diabetes mellitus. Kaplan–Meier curves for all-cause mortality are displayed in

Table 2. Lesion and Procedural Characteristics in Patients With and Without Diabetes Mellitus

Lesion Characteristics	With Diabetes Mellitus	Without Diabetes Mellitus	*P* Value
Lesions	(n=714)	(n=1819)	
Vessel			0.16
LAD	303 (42.4)	822 (45.2)	
LCx	210 (29.4)	467 (25.7)	
RCA	201 (28.2)	530 (29.1)	
Ostial	121 (16.9)	304 (16.7)	0.93
Bifurcational	155 (21.7)	451 (24.8)	0.11
Chronic occlusion	37 (5.2)	88 (4.84)	0.80
Complex (B2/C)	514 (72.0)	1315 (72.3)	0.92
Lesion length, mm,	15.6 (9.1)	14.7 (±8.65)	0.020*
Minimal lumen diameter, mm			
Before procedure	0.96 (±0.46)	1.00 (±0.52)	0.047*
After procedure	2.53 (±0.47)	2.60 (±0.48)	<0.001*
Percent stenosis, %			
Before procedure	65.4 (±14.9)	64.8 (±16.4)	0.38
After procedure	11.9 (±7.24)	11.4 (±6.95)	0.14

Values are n (%) or mean (±SD) unless otherwise indicated. *P* values are derived from Cox proportional hazard models. LAD indicates left anterior descending; LCx, left circumflex artery; and RCA, right coronary artery.
*Indicates statistical significance.

Figure 2. Rates of MI were comparable between patients with and without diabetes mellitus (8.4% versus 7.6%, *P*=0.78; HR, 1.05; 95% CI, 0.72–1.54). Kaplan–Meier curves for the incidence of MI are displayed in Figure 3. Concerning antirestenotic efficacy, the incidence of TLR was significantly higher in patients with diabetes mellitus as compared with patients without diabetes mellitus (23.9% versus 18.0%, *P*=0.007; HR, 1.37; 95% CI, 1.09–1.73). Kaplan-Meier curves for the incidence of TLR are displayed in Figure 4.

Regarding safety outcomes, rates of definite/probable stent thrombosis were comparable in patients with and without diabetes mellitus (2.3% versus 1.9%; *P*=0.52, HR, 1.27; 95% CI, 0.62–2.60). The results concerning rates of stent thrombosis according to diabetic status are detailed in Table 4.

Clinical Outcome After Treatment With Yukon Choice PC Versus Xience in Patients With Versus Without Diabetes Mellitus

Regarding the primary end point MACE, there was no significant difference between patients treated with Yukon Choice PC or Xience new-generation DES, neither in the subgroup of patients with diabetes mellitus (*P*=0.91; HR, 1.01; 95% CI, 0.79–1.30) nor in the subgroup of patients without diabetes mellitus (*P*=0.50; HR, 0.94; 95% CI, 0.79–1.21) (Table S2). Corresponding

Table 3. Clinical Outcomes Out to 10 years in Patients With and Without Diabetes Mellitus

Event	With Diabetes Mellitus(n=560)	Without Diabetes Mellitus (n=1391)	Hazard Ratio	*P* Value
Major adverse cardiac events	286 (56.5)	568 (43.5)	1.41 (1.23–1.63)	<0.001*
Death	206 (42.3)	347 (27.1)	1.68 (1.41–2.00)	<0.001*
Cardiac death	112 (27.7)	189 (16.4)	1.70 (1.35–2.16)	<0.001*
Myocardial infarction	38 (8.4)	95 (7.6)	1.05 (0.72–1.54)	0.78
Target lesion revascularization	109 (23.9)	219 (18.0)	1.37 (1.09–1.73)	0.007*

Data are shown as number (Kaplan–Meier estimates as percentages), hazard ratios are derived from Cox proportional hazard models, and *P* values are derived from Cox proportional hazard models.
*Indicates statistical significance.

Kaplan–Meier curves for the incidence of MACE are displayed in Figure S2. Mortality rates at 10 years were comparable between the treatment groups in both patients with diabetes mellitus (Yukon Choice PC 42.0% versus Xience 42.9%; *P*=0.95; HR, 1.01; 95% CI, 0.75–1.35) and patients without diabetes mellitus (Yukon Choice PC 27.9% versus Xience 25.7%; *P*=0.49; HR, 0.92; 95% CI, 0.74–1.16) (Figure S3). Regarding the incidence of MI at 10 years, there was no significant difference between Yukon Choice PC and Xience in patients with diabetes mellitus (Yukon Choice PC 8.5% versus Xience 8.1%; *P*=0.85, HR, 0.94; 95% CI, 0.47–1.86) and patients without diabetes mellitus (Yukon Choice PC 7.5% versus Xience 7.9%; *P*=0.82, HR, 1.05; 95% CI, 0.69–1.60) (Figure S4). Both treatment groups showed comparable rates of TLR at 10 years in patients with diabetes mellitus (Yukon Choice PC 24.5% versus Xience 22.7%; *P*=0.82; HR, 0.96; 95%

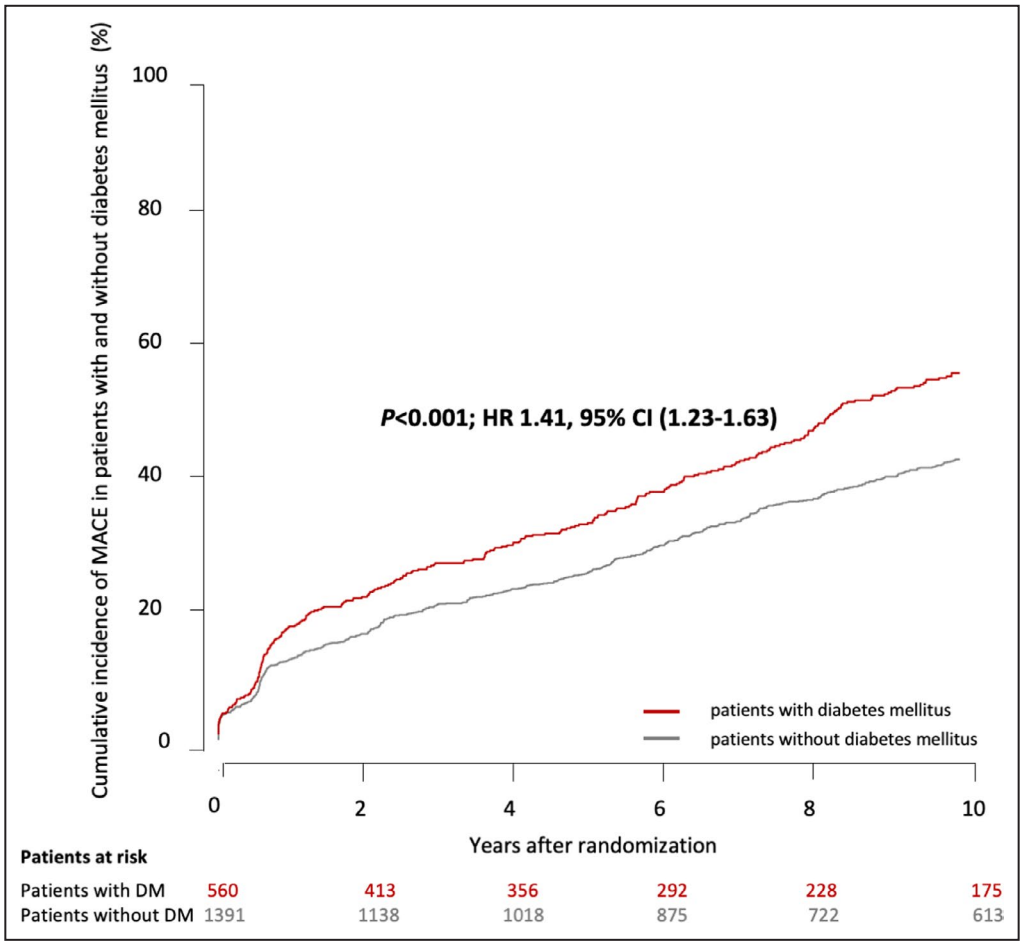

Figure 1. Comparison of cumulative incidence of major adverse cardiac events in patients with vs without diabetes mellitus.
DM indicates diabetes mellitus; HR, hazard ratio; and MACE, major adverse cardiac events.

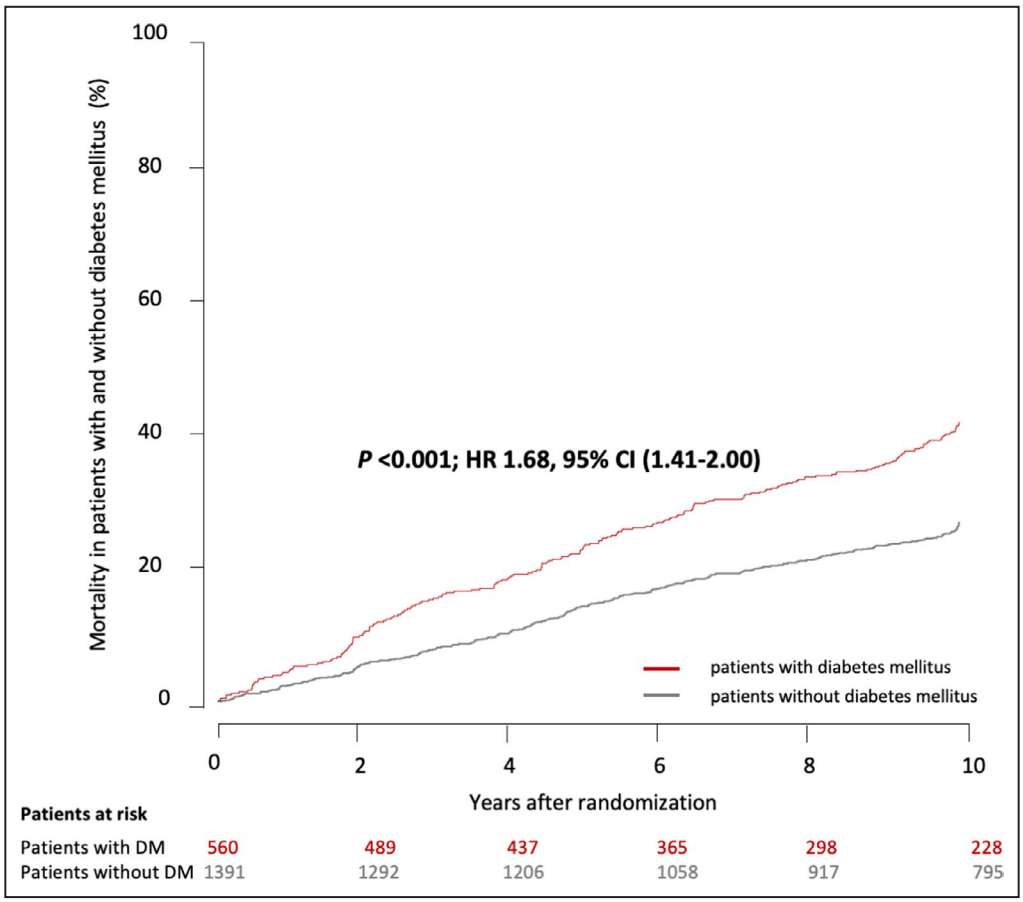

Figure 2. Comparison of all-cause mortality in patients with vs without diabetes mellitus.
DM indicates diabetes mellitus; and HR, hazard ratio.

CI, 0.64–1.43) and in patients without diabetes mellitus (Yukon Choice PC 18.8% versus Xience 16.5%; *P*=0.49; HR, 0.43; 95% CI, 0.67–1.19) (Figure S5).

There was no significant difference regarding rates of definite/probable stent thrombosis between the treatment groups in patients with diabetes mellitus (Yukon Choice PC 2.2% versus Xience 2.7%; *P*=0.81, HR, 0.86; 95% CI, 0.25–2.94) and patients without diabetes mellitus (Yukon Choice PC 1.6% versus Xience 2.4%; *P*=0.32, HR, 0.66; 95% CI, 0.29–1.49). Results regarding safety outcomes are displayed in Table S3.

DISCUSSION

The present analysis represents the first report of long-term data out to 10 years, comparing new-generation DES with different polymer strategies (permanent and biodegradable) in patients with and without diabetes mellitus.

The main findings of the present study are the following: First, overall clinical event-rates were significantly higher in patients with diabetes mellitus as compared with patients without diabetes mellitus. Second, at 10 years there was no difference concerning clinical event rates in patients treated with Yukon Choice PC versus Xience, in neither of the prespecified subgroups of patients with and without diabetes mellitus. Third, although both stent types showed favorable safety profiles concerning thrombotic events in patients with and without diabetes mellitus, TLR rates in patients with diabetes mellitus remain considerable.

Clinical Outcome After PCI of Patients With Versus Without Diabetes Mellitus

Worse outcome after PCI of patients with diabetes mellitus compared with patients without diabetes mellitus is a consistent finding throughout clinical trials.[2] Yet again, however, the evidence base tapers out with longer follow-up duration. In our analysis, the 10-year rate of the primary composite end point was significantly higher in patients with diabetes mellitus as compared with patients without diabetes mellitus. These findings are driven by significantly increased relative risk of death (68%), cardiac death (70%), and TLR (37%) in patients with diabetes mellitus. Furthermore,

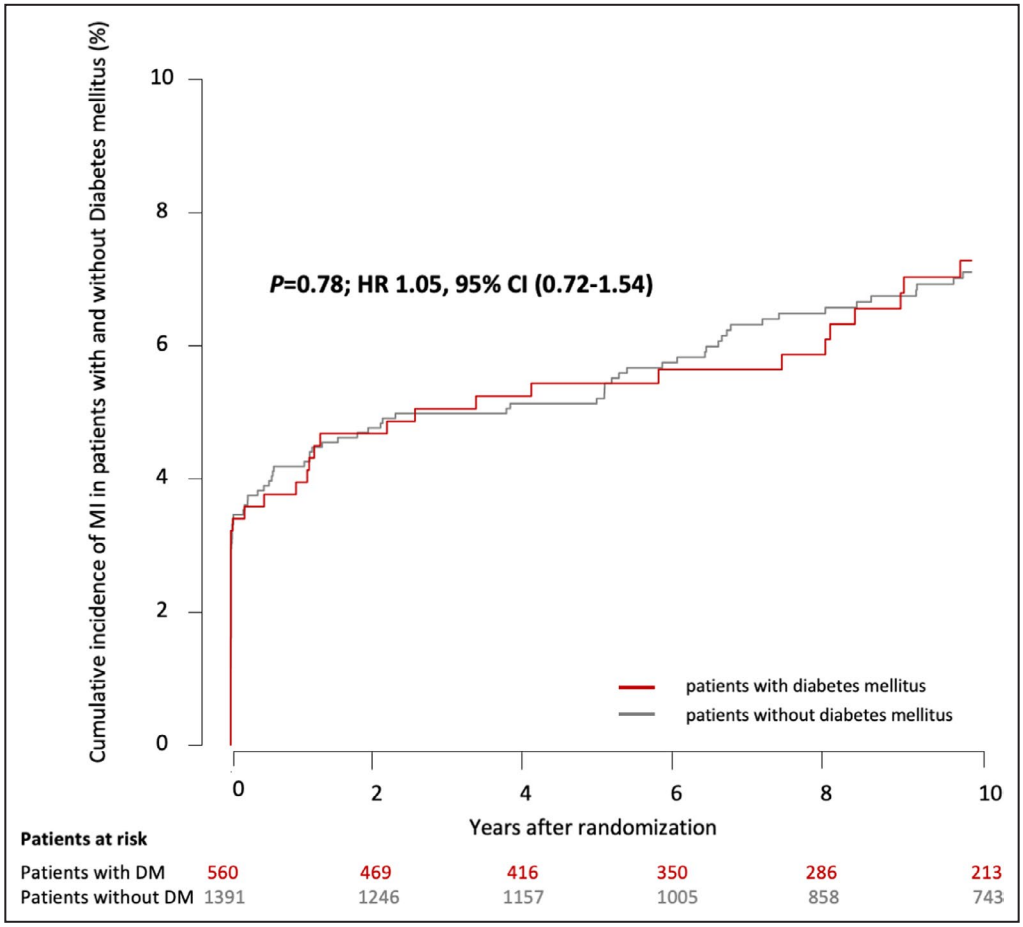

Figure 3. Comparison of cumulative incidence of myocardial infarction in patients with vs without diabetes mellitus.
DM indicates diabetes mellitus; HR, hazard ratio; and MI, myocardial infarction.

while the difference of TLR rates between patients with and without diabetes mellitus seems to plateau after an initial sharp increase at the time of protocol-mandated angiographic follow-up—a known phenomenon in trials with protocol-mandated follow-up angiography[13]—mortality and cardiac mortality rates continue to diverge at a constant rate out to 10 years.

This shift from rather device-specific to more patient-related events, because of disease progression beyond the initial target site, can be observed in many coronary stent trials with long-term follow-up.[14] Of note, overall event-rates in this trial are higher than in previous trials with 10-year follow-up, reporting all-cause mortality rates ranging from 24% to 27% for the overall cohort as well as patients without diabetes mellitus[15–17] and 30% to 40% for patients with diabetes mellitus.[16,18] A potential explanation for this finding as well as for the predominance of patient- over device-specific events 10 years after PCI are the higher mean age and baseline risk of the population enrolled in the ISAR-TEST 4 trial. The finding of a relatively high incidence of cardiac death seems to contrast with previous reports, which indicated that mortality during long-term follow-up after PCI is mainly driven by noncardiac death.[19] However, it might reflect the persistently high cardiovascular risk that patients with diabetes mellitus and symptomatic coronary artery disease—a large proportion having had acute coronary syndrome—are exposed to. Interestingly, despite significant differences in cardiac mortality rates, rates of MI and thrombotic events did not differ between patients with and without diabetes mellitus. A possible explanation for this counterintuitive finding is silent MIs in patients with diabetes mellitus because of autonomic neuropathy. In addition, a recently published large cohort study with a median follow-up duration of 7 years did not show an increased rate of MI in patients with diabetes mellitus and absence of obstructive coronary artery disease as compared with the general population.[20] Finally, although TLR rates remain high in patients with diabetes mellitus, rates of stent thrombosis out

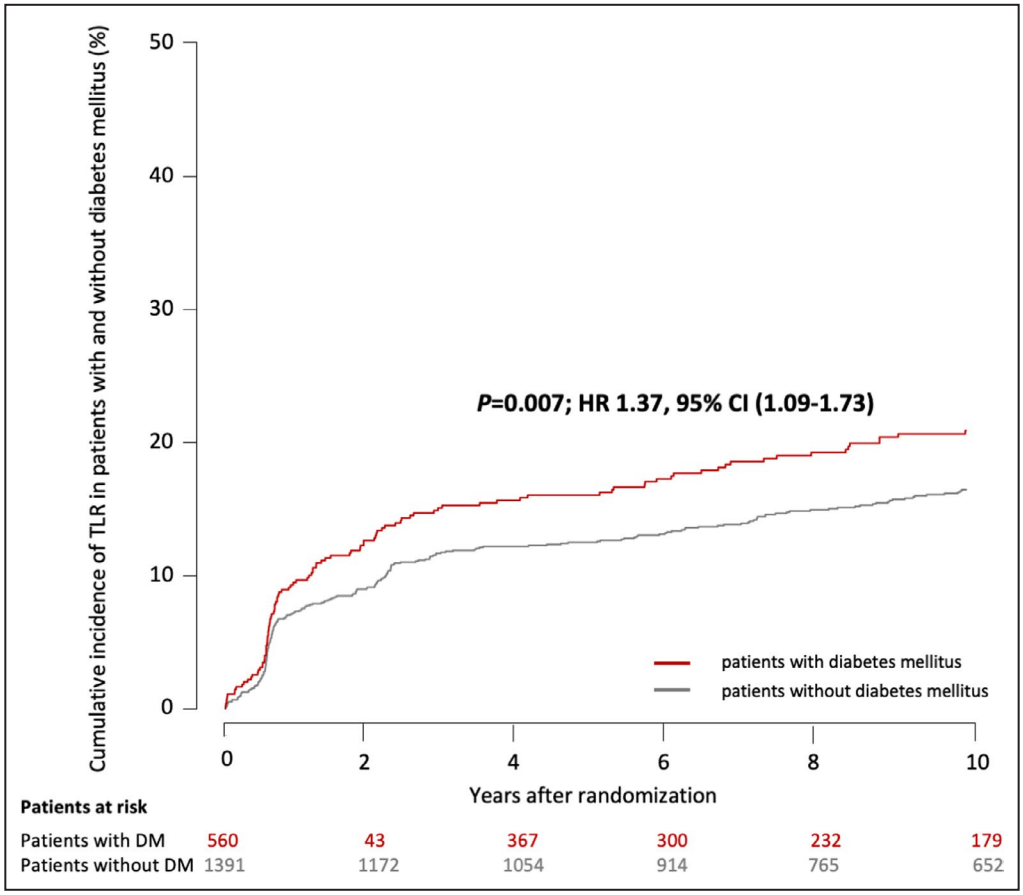

Figure 4. Comparison of cumulative incidence of target lesion revascularization in patients with vs without diabetes mellitus.
DM indicates diabetes mellitus; HR, hazard ratio; and TLR, target lesion revascularization.

to 10 years with new-generation DES are very low, both in patients with and patients without diabetes mellitus.

Given the all-comer design of the present study, our data may add further valuable insights on extended long-term outcome after PCI with new-generation DES in patients with and without diabetes mellitus, especially considering the paucity of data in this particular field. Consistently high all-cause and cardiac mortality rates after PCI in patients with diabetes mellitus as well as the constant increase out to 10 years, emphasize the particular challenge that patients with diabetes mellitus with coronary artery disease represent. Although myocardial revascularization and thus measures to optimize respective devices remains an important part of the management of coronary artery disease in patients with diabetes mellitus, guideline-driven secondary prevention measures should always complement these efforts. Notwithstanding, implementation of these measures still seems to be suboptimal in both clinical trials and everyday clinical practice.[21,22] Along these lines, recent years have added new and promising options to the armamentarium of medical treatment, one of

Table 4. Definite and Probable Stent Thrombosis Out to 10 Y in Patients With and Without Diabetes Mellitus

Event	With Diabetes (n=560)	Without Diabetes (n=1391)	Hazard Ratio	*P* Value
Definite/probable stent thrombosis	11 (2.3)	23 (1.9)	1.27 (0.62–2.60)	0.52
Definite stent thrombosis	7 (1.5)	10 (0.8)	1.84 (0.70–4.83)	0.22
Probable stent thrombosis	4 (0.9)	13 (1.1)	0.82 (0.27–2.52)	0.82

Data are shown as number (Kaplan–Meier estimates as percentages), hazard ratios are derived from Cox proportional hazard models, and *P* values are derived from Cox proportional hazard models.

which even demonstrated the capacity to reduce MACE in patients with diabetes mellitus and established cardiovascular disease.[23]

Clinical Outcome After Treatment With Yukon Choice PC Versus Xience in Patients With Versus Without Diabetes Mellitus

The results in the prespecified subgroup of patients with and without diabetes mellitus are broadly in line with the findings of the overall cohort, reporting similar safety and efficacy of biodegradable and permanent polymer-based new-generation DES at 10 years.[24] Therefore, when compared with a new-generation durable polymer, degradable polymer does not seem to have clinically meaningful impact on outcomes out to 10 years, neither in patients with nor without diabetes mellitus. This is in accordance with the results of other randomized trials comparing new-generation DES with different polymer coatings, failing to show clear evidence of superiority of 1 device over another. The BIOSCIENCE (Ultrathin Strut Biodegradable Polymer Sirolimus-Eluting Stent Versus Durable Polymer Everolimus-Eluting Stent for Percutaneous Coronary Revascularization) trial compared an ultrathin-strut BP-SES to benchmark PP-EES, revealing similar rates of target-lesion failure out to 5 years in patients with diabetes mellitus in both DES groups.[25] In line, in the COMPARE II (Abluminal biodegradable polymer biolimus-eluting stent versus durable polymer everolimus-eluting stent) trial, MACE in patients with diabetes mellitus randomized to a biodegradable-polymer biolimus-eluting stent or benchmark PP-EES occurred at similar rates (biodegradable-polymer biolimus-eluting stent versus PP-EES, 22.2% versus 17.2%, P=0.34).[26] The BIOFLOW-II (Study of the Orsiro Drug Eluting Stent System) trial, comparing BP-SES to benchmark PP-EES out to 5 years with more patient selection criteria, also reported comparable target-lesion failure rates with both BP-SES and PP-EES. However, in this post hoc analysis of 128 patients with diabetes mellitus, patients treated with biodegradable-polymer DES had counterintuitively numerically higher TLR rates (13.5% versus 4.5%; P=0.138) along with lower cardiac deaths rates (1.3% versus 6.9%; P=0.089) and significantly lower stent thrombosis rates (0% versus 6.9%; P=0.039).[27] Of note, follow-up of these trials was limited to a maximum of 5 years.

The present analysis provides the first randomized long-term data comparing new-generation DES with biodegradable versus permanent polymer in patients with and without diabetes mellitus, with clinical follow-up out to 10 years. On the basis of these data, the hypothesis of a so far elusive, very late benefit of biodegradable polymer in the subgroup of patients with diabetes mellitus might not have to be entirely refuted. However, it needs to be acknowledged that whatever effect might be attributable to stent polymer degradability, it does not seem to be pronounced enough to cause outcome differences between otherwise dissimilar new-generation DES. The DES investigated in this and other trials did not only differ in drug-carrying polymer coating, but also regarding stent backbone strut thickness and antiproliferative drug type. Consequently, possible effects of different polymer characteristics could be blurred by counteracting effects. Newer-generation biodegradable-polymer DES have replaced stainless steel backbones by thin strut cobalt chrome alloys (BIOSCIENCE, BIOFLOW-II). Long-term follow-up data are warranted to assess the potential benefit of these devices in the subgroup of patients with diabetes mellitus.

LIMITATIONS

Our study has several limitations. First, since the present analysis is a post hoc analysis, results need to be interpreted with caution. Second, although this analysis is the first to report clinical follow-up out to 10 years of a randomized comparison of 2 new-generation DES with different polymer characteristics in patients with and without diabetes mellitus, the trial was not specifically powered for a comparison of clinical outcomes between patients with versus without diabetes mellitus treated with Yukon Choice PC versus Xience. Third, future trials investigating different DES in patients with diabetes mellitus should add optimal medical therapy to the investigational plan as well as monitor therapy adherence.

CONCLUSIONS

The clinical outcome of patients with diabetes mellitus after PCI with new-generation DES is considerably worse than that of patients without diabetes mellitus, with event rates constantly increasing out to 10 years. New-generation DES with biodegradable or permanent polymer show consistently comparable clinical event-rates at 10 years, irrespective of diabetic status. However, alongside strict implementation of secondary prevention measures, efforts to develop tailored stent designs considering the pathophysiological particularities of patients with diabetes mellitus and obstructive coronary artery disease still seem promising and should therefore continue.

APPENDIX

ISAR-Test 4 (Intracoronary Stenting and Angiographic Results: Test Efficacy of 3 Limus-Eluting Stents)

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Supplementary Material

Tables S1–S3
Figures S1–S5

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Supplemental Material

Table S1. Baseline Patient and Lesion Characteristics in Patient with and without Diabetes mellitus, by Treatment group.

	Patients with diabetes mellitus			Patients without diabetes mellitus		
Characteristics	**Yukon Choice PC**	**Xience**	***p* Value**	**Yukon Choice PC**	**Xience**	***p* Value**
Patients	(n=376)	(n=184)		(n=923)	(n=468)	
Age, y, ±SD	66.9 (±10.4)	67.6 (±9.50)	0.44	66.5 (±11.3)	66.4 (±10.6)	0.82
Male sex	274 (72.9)	139 (75.5)	0.57	704 (76.3)	368 (78.6)	0.36
Insulin dependent diabetes	108 (28.7)	60 (32.6)				
Oral antidiabetic medication	196 (52.1)	90 (48.9)				
Arterial hypertension	295 (78.5)	136 (73.9)	0.27	602 (65.2)	306 (65.4)	>0.99
Current smoker	50 (13.3)	24 (13.0)	>0.99	152 (16.5)	77 (16.5)	>0.99
Hyperlipidemia	257 (68.4)	117 (63.6)	0.30	611 (66.2)	306 (65.4)	0.81
Coronary artery disease			0.56			0.67
1-vessel disease	29 (7.7)	18 (9.8)		146 (15.8)	77 (16.5)	
2-vessel disease	100 (26.6)	43 (23.4)		257 (27.8)	139 (29.7)	
3-vessel disease	247 (65.7)	123 (66.8)		520 (56.3)	252 (53.8)	
Clinical presentation			0.73			0.27
ST-segment elevation myocardial infarction	42 (11.2)	18 (9.8)		125 (13.5)	52 (11.1)	
Non-ST-segment elevation acute coronary syndrome	122 (32.4)	56 (30.4)		252 (27.3)	143 (30.6)	
Stable angina	212 (56.4)	110 (59.8)		546 (59.2)	273 (58.3)	
Prior myocardial infarction	112 (29.8)	55 (29.9)	>0.99	260 (28.2)	136 (29.1)	0.78
Prior coronary artery bypass grafting	48 (12.8)	19 (10.3)	0.49	81 (8.8)	50 (10.7)	0.29
Body Mass Index	28.3 (±4.8)	29.0 (±4.6)	0.12	26,7 (±3.9)	27,1 (±4.1)	0.10
Ejection fraction, %	51.1 (±12.4)	50.7 (±13.4)	0.76	53,9 (±10.8)	54,4 (±10.9)	0.42
Lesions	(n=473)	(n=241)		(n=1210)	(n=609)	
Vessel			0.29			0.24
LAD	191 (40.4)	112 (46.5		562 (46.4)	260 (42.7)	
LCx	145 (30.7)	65 (27.0)		309 (25.5)	158 (25.9)	
RCA	137 (29.0)	64 (26.6)		339 (28.0)	191 (31.4)	
Ostial	74 (15.6)	47 (19.5)	0.23	193 (16.0)	111 (18.2)	0.25
Bifurcational	102 (21.6)	53 (22.0)	0.97	319 (26.4)	132 (21.7)	**0.03**
Chronic occlusion	25 (5.29)	12 (4.98)	>0.99	64 (5.3)	24 (3.9)	0.25
Complex (B2/C)	343 (72.5)	171 (71.0)	0.73	882 (72.9)	433 (71.1)	0.45
Lesion length, mm,	15.5 (±9.29)	15.7 (±8.82)	0.77	14.5 (±8.52)	15.0 (±8.91)	0.32
Minimal Lumen Diameter, mm						
Before Procedure	0.94 (±0.45)	0.99 (±0.46)	0.11	1.00 (±0.52)	0.99 (±0.51)	0.65
After Procedure	2.52 (±0.48)	2.55 (±0.44)	0.42	2.60 (±0.50)	2.61 (±0.43)	0.69
Percent stenosis, %						

Before Procedure	65.8 (±15.1)	64.5 (±14.4)	0.26	64.7 (±16.3)	65.0 (±16.6)	0.71
After Procedure	11.7 (±7.76)	12.2 (±6.12)	0.36	11.3 (±7.22)	11.7 (±6.37)	0.20

Values are n (%) or mean (±SD) unless otherwise indicated. P values are derived from Cox proportional hazard models. Bold font indicates statistical significance.

Table S2. Clinical Outcomes Out to 10 years in Patients with and without Diabetes mellitus, Hazard Ratios, by Treatment group.

Event	Yukon Choice PC	Xience	HR (95% CI)	*p* Value
With Diabetes	n=376	n=184		
MACE	191 (46.2)	95 (47.8)	1.01 (0.79-1.30)	0.91
All cause death	138 (42.0)	68 (42.9)	1.01 (0.75-1.35)	0.95
Cardiac death	76 (27.3)	36 (28.4)	0.97 (0.65-1.44)	0.88
Myocardial infarction	26 (8.5)	12 (8.1)	0.94 (0.47-1.86)	0.85
TLR	74 (24.5)	35 (22.7)	0.96 (0.64-1.43)	0.82
Without Diabetes	n=923	n=468		
MACE	384 (44.5)	184 (41.7)	0.94 (0.79-1.21)	0.50
All cause death	236 (27.9)	111 (25.7)	0.92 (0.74-1.16)	0.49
Cardiac death	130 (17.2)	59 (14.8)	0.89 (0.65-1.20)	0.44
Myocardial infarction	62 (7.5)	33 (7.9)	1.05 (0.69-1.60)	0.82
TLR	151 (18.8)	68 (16.5)	0.89 (0.67-1.19)	0.43

Data are shown as number (Kaplan–Meier estimates as percentages), hazard ratios are derived from Cox proportional hazard models, and P values are derived from Cox proportional hazard models.

Table S3. Definite and Probable Stent Thrombosis Out to 10 years in Patients with and without Diabetes mellitus, Hazard Ratios, by Treatment group.

Event	Yukon Choice PC	Xience	HR (95% CI)	*p* Value
With Diabetes	n=376	n=184		
Definite stent thrombosis	5 (1.6)	2 (1.1)	1.23 (0.24-6.36)	0.80
Probable stent thrombosis	2 (0.6)	2 (1.5)	0.49 (0.07-3.46)	0.48
Definite/probable stent thrombosis	7 (2.2)	4 (2.7)	0.86 (0.25-2.94)	0.81
Without Diabetes	n=923	n=468		
Definite stent thrombosis	7 (0.9)	3 (0.7)	1.19 (0.31-4.55)	0.80
Probable stent thrombosis	6 (0.8)	7 (1.7)	0.44 (0.15-1.30)	0.14
Definite/probable stent thrombosis	13 (1.6)	10 (2.4)	0.66 (0.29-1.49)	0.32

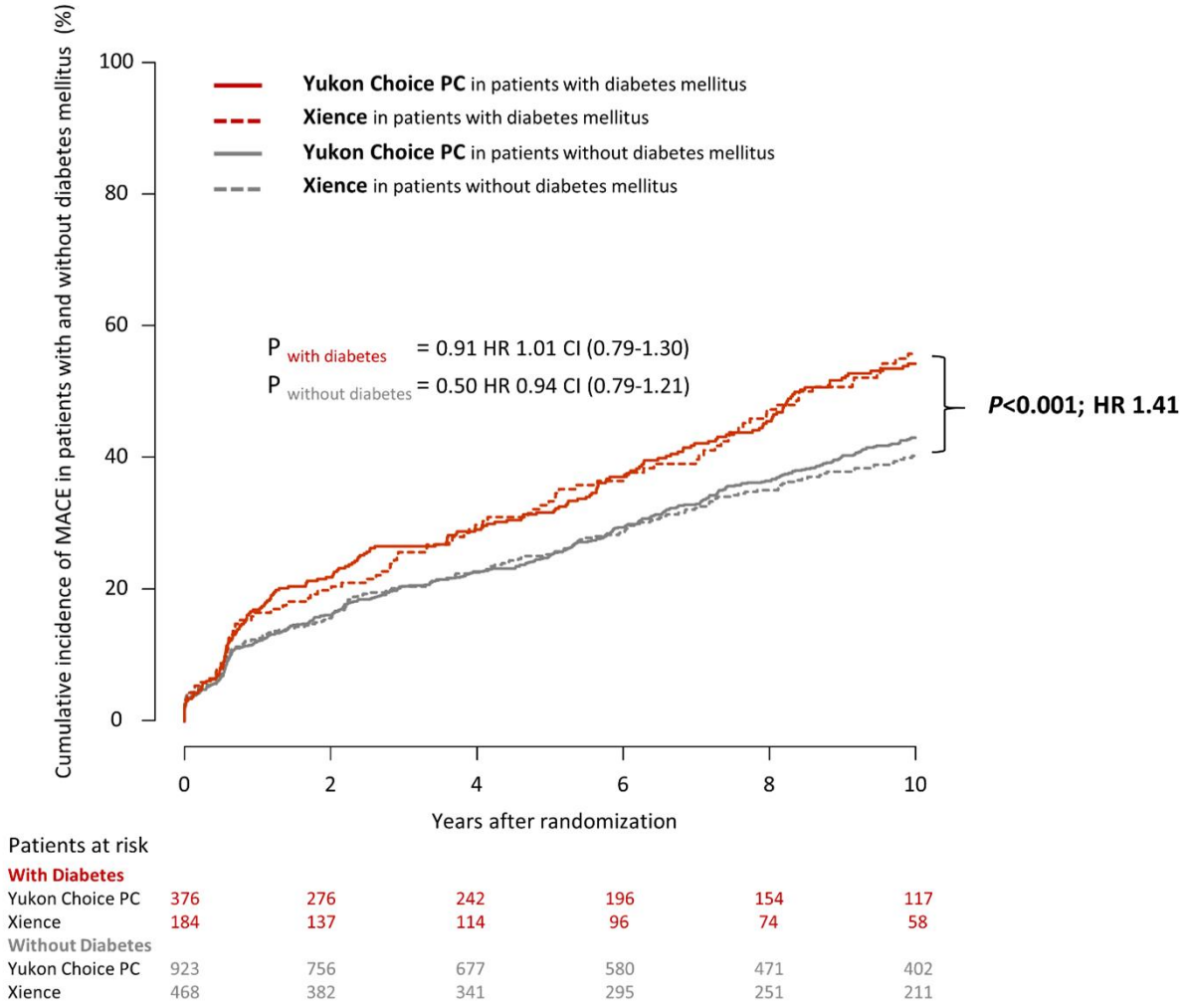
Data are shown as number (Kaplan–Meier estimates as percentages), hazard ratios are derived from Cox proportional hazard models, and P values are derived from Cox proportional hazard models.

Figure S1. Principal characteristics of the study devices.

polymer	permanent	biodegradable
name	Xience	Yukon Choice PC
drug	everolimus	sirolimus
Shape & polymer distribution		
Strut thickness	81 µm	87 µm
Backbone	CoCr/PlCr	316L SS

CoCr indicates cobalt-chromium; PlCr, platinum-chromium; SS, stainless steel

Figure S2 Comparison of cumulative incidence of major adverse cardiac events in patients with vs. without diabetes mellitus treated with Yukon Choice PC vs. Xience DES.

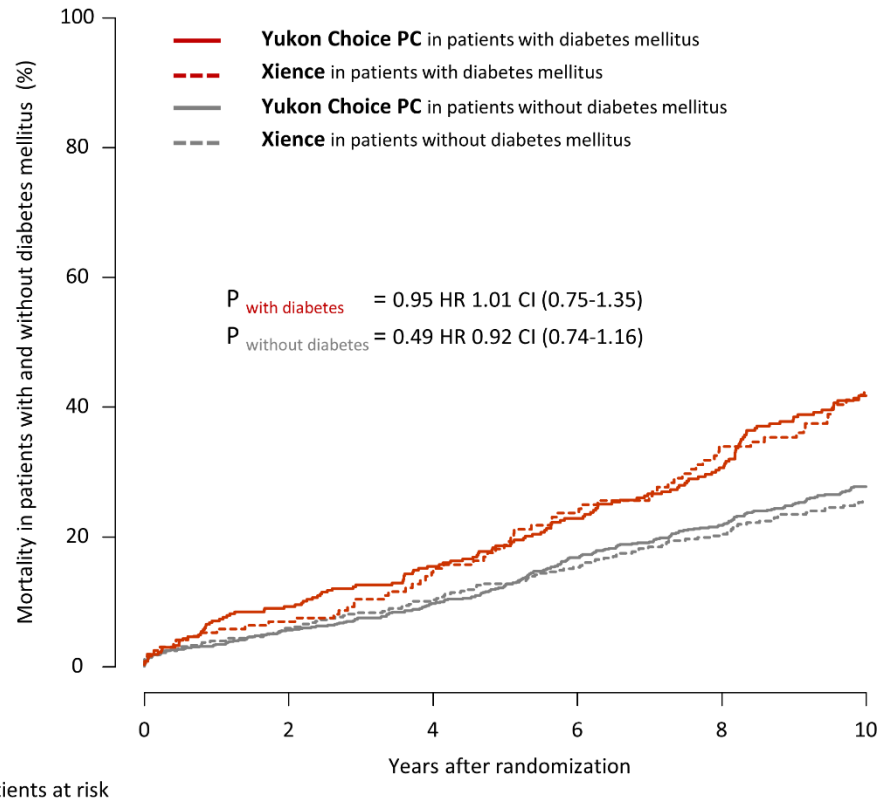


Patients at risk

With Diabetes						
Yukon Choice PC	376	276	242	196	154	117
Xience	184	137	114	96	74	58
Without Diabetes						
Yukon Choice PC	923	756	677	580	471	402
Xience	468	382	341	295	251	211

MACE indicates major adverse cardiac events

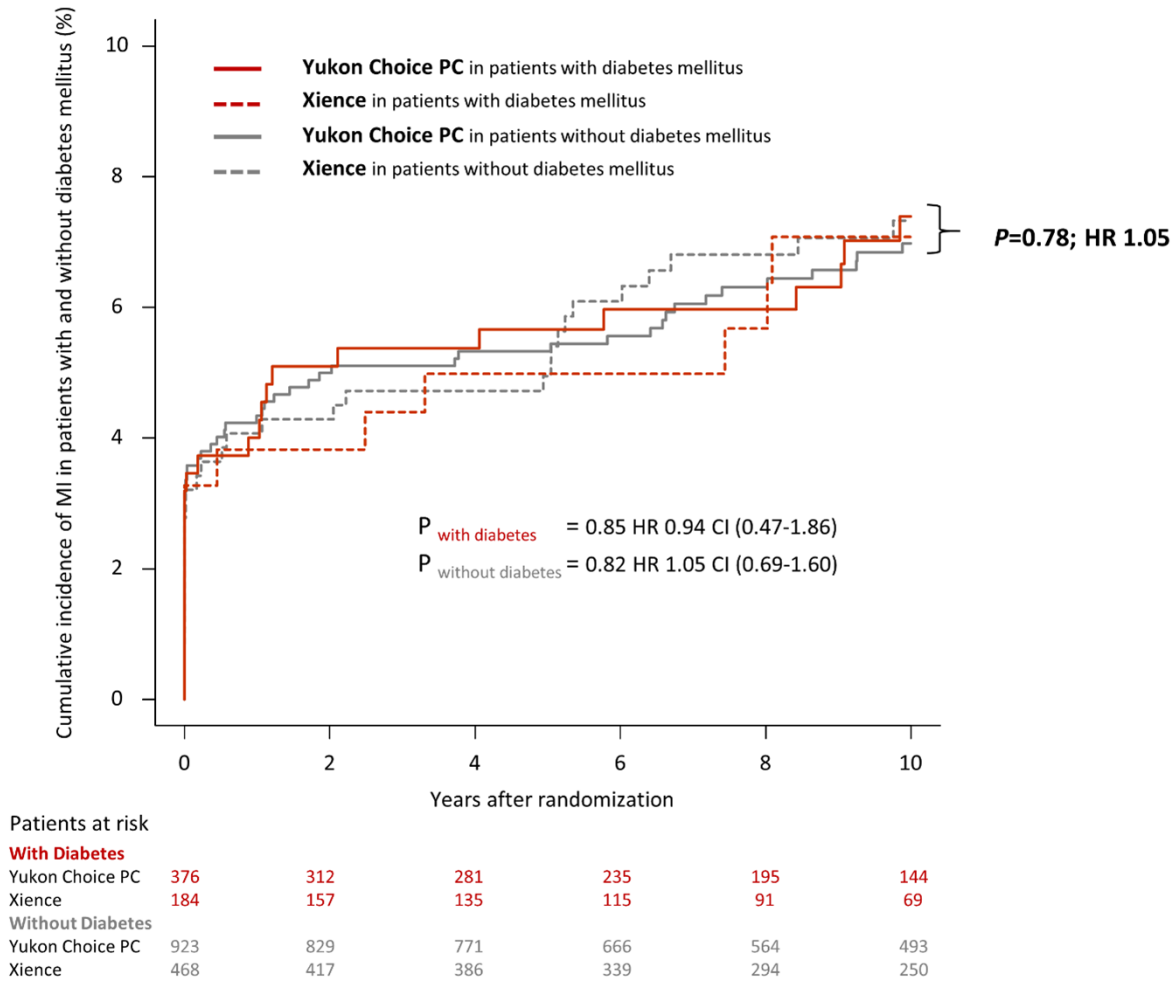
Figure S3. Comparison of all-cause mortality in patients with vs. without diabetes mellitus treated with Yukon Choice PC vs. Xience DES.



Patients at risk

With Diabetes						
Yukon Choice PC	376	326	294	246	204	155
Xience	184	163	143	119	94	73
Without Diabetes						
Yukon Choice PC	923	861	804	699	602	528
Xience	468	431	402	359	315	267

Figure S4. Comparison of cumulative incidence of myocardial infarction in patients with vs. without diabetes mellitus treated with Yukon Choice PC vs. Xience DES.

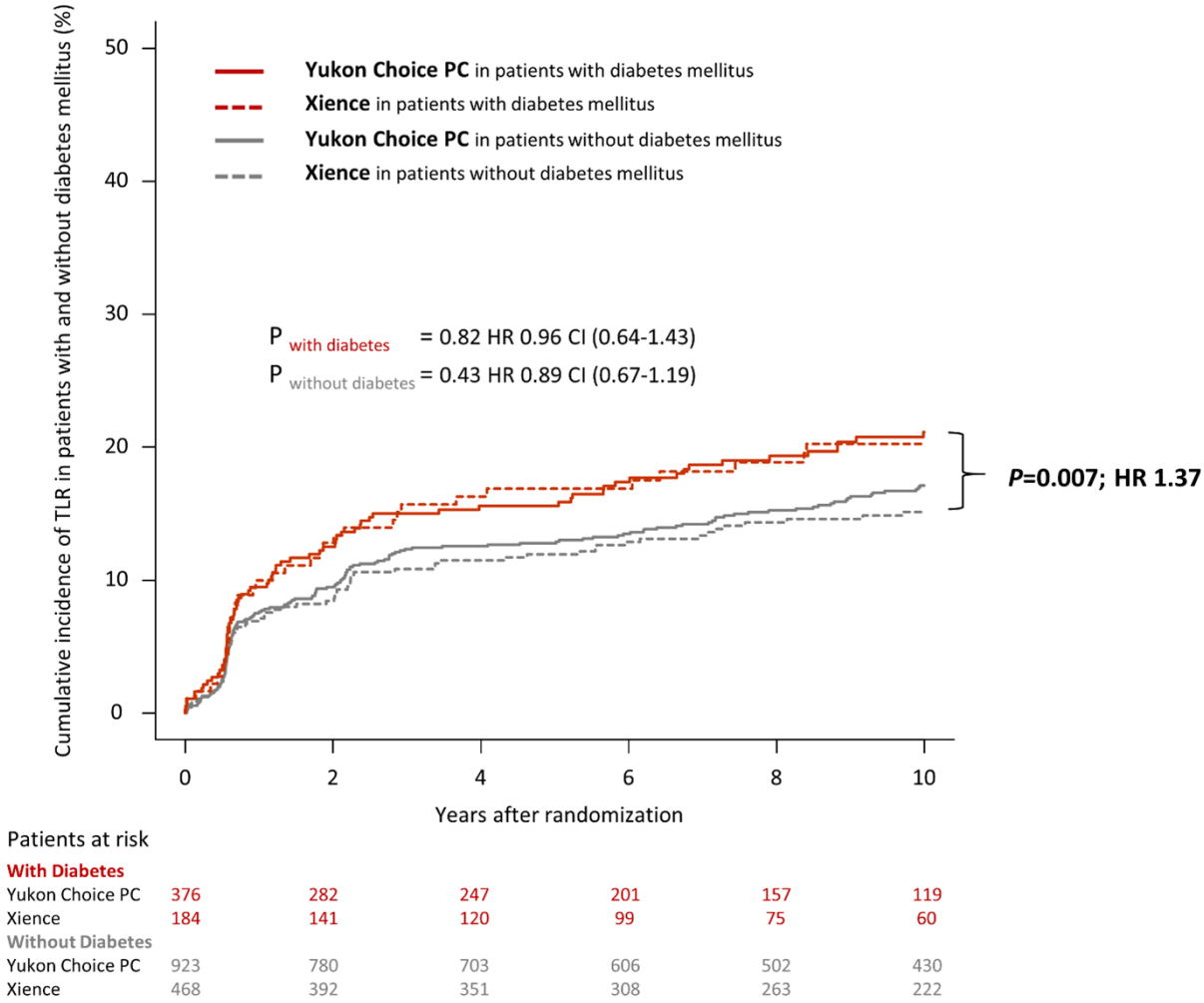


Patients at risk

With Diabetes						
Yukon Choice PC	376	312	281	235	195	144
Xience	184	157	135	115	91	69
Without Diabetes						
Yukon Choice PC	923	829	771	666	564	493
Xience	468	417	386	339	294	250

MI indicates myocardial infarction

Figure S5. Comparison of cumulative incidence of target lesion revascularization in patients with vs. without diabetes mellitus treated with Yukon Choice PC vs. Xience DES.



Patients at risk

With Diabetes						
Yukon Choice PC	376	282	247	201	157	119
Xience	184	141	120	99	75	60
Without Diabetes						
Yukon Choice PC	923	780	703	606	502	430
Xience	468	392	351	308	263	222

TLR indicates target lesion revascularization