EuroIntervention 2014;10-online publish-ahead-of-print November 2014

Five-year outcomes from a trial of three limus-eluting stents with different polymer coatings in patients with coronary artery disease: final results from the ISAR-TEST 4 randomised trial

Sebastian Kufner[1]*, MD; Robert A. Byrne[1], MB, BCh, PhD; Marco Valeskini[1]; Stefanie Schulz[1], MD; Tareq Ibrahim[2], MD; Petra Hoppmann[2], MD; Simon Schneider[2], MD; Karl-Ludwig Laugwitz[2,3], MD; Heribert Schunkert[1,3], MD; Adnan Kastrati[1,3], MD; for the Intracoronary Stenting and Angiographic Results: Test Efficacy of 3 Limus-Eluting Stents (ISAR-TEST 4) Investigators

1. Deutsches Herzzentrum München, Technische Universität, Munich, Germany; 2. 1. Medizinische Klinik, Klinikum rechts der Isar, Technische Universität, Munich, Germany; 3. DZHK (German Centre for Cardiovascular Research), partner site Munich Heart Alliance, Munich, Germany

KEYWORDS

- biodegradable polymer
- drug-eluting stent
- everolimus
- long-term outcome
- permanent polymer
- sirolimus

Abstract

Aims: Both biodegradable polymer sirolimus-eluting stents and permanent polymer everolimus-eluting stents offer potential for enhanced late outcomes in comparison with earlier-generation permanent polymer sirolimus-eluting stents. However, long-term comparative efficacy data among these devices remain a scientific gap. We aimed to compare the efficacy and safety of biodegradable polymer sirolimus-eluting stents (Yukon Choice PC) versus permanent polymer everolimus-eluting stents (XIENCE) versus permanent polymer sirolimus-eluting stents (CYPHER) at five-year follow-up.

Methods and results: Overall, 2,603 patients were randomised to treatment with the Yukon Choice PC (n=1,299), XIENCE (n=652) or CYPHER (n=652) stents. The primary endpoint was the device-oriented composite of cardiac death, target vessel-related myocardial infarction (MI), or target lesion revascularisation (TLR). The main secondary endpoint was definite/probable stent thrombosis (ST). Follow-up was performed up to five years. Concerning the primary endpoint, there was no significant difference between Yukon Choice PC and XIENCE stents (20.5% vs. 19.5%, HR=1.04, 95% CI: 0.84-1.29; p=0.71) or between CYPHER and XIENCE stents (23.5% vs. 19.5%, HR=1.21, 95% CI: 0.95-1.53; p=0.12). In terms of safety, rates of ST were similar with both Yukon Choice PC and XIENCE (1.2% vs. 1.4%; HR=0.83, 95% CI: 0.37-1.91; p=0.67) but numerically higher with CYPHER as compared to XIENCE (2.4% vs. 1.4%, HR=1.67, 95% CI: 0.73-3.82; p=0.22).

Conclusions: Biodegradable polymer Yukon Choice PC and permanent polymer XIENCE stents showed comparable clinical outcomes at five years. Permanent polymer CYPHER stents showed numerically higher rates of device-related adverse events. Trials registration: ClinicalTrials.gov (identifier: NCT00598676).

**Corresponding author: ISARESEARCH Centre, Deutsches Herzzentrum, Lazarettstrasse 36, 80636 Munich, Germany. E-mail: kufners@dhm.mhn.de*

SUBMITTED ON 22/04/2014 - REVISION RECEIVED ON 1st 14/06/2014 / 2nd 22/07/2014 - ACCEPTED ON 25/07/2014

DOI: 10.4244/EIJY14M11_02

Introduction

The development of drug-eluting stents (DES) represented a significant victory in the battle against coronary restenosis[1,2]. However, the improvement in efficacy with early-generation DES occurred at the collateral cost of a delay in healing of the stented arterial segment[3]. This condition underlies a spectrum of clinical events including late stent thrombosis, late luminal loss creep and in-stent neoatherosclerosis[4,5]. Although undoubtedly multifactorial in origin, inflammatory reaction to permanent polymer coatings seems to play a central role[6].

Both biodegradable polymer sirolimus-eluting stents (Yukon Choice PC; Translumina GmbH, Hechingen, Germany and Dehradun, India) and permanent polymer everolimus-eluting stents (XIENCE; Abbott Vascular, Abbott Park, IL, USA) offer potential for enhanced late outcomes in comparison with early-generation permanent polymer DES. Preclinical data with these devices show evidence of improved vascular healing[7,8]. Moreover, in relation to biodegradable polymer DES, long-term data from clinical trials have shown improvement in late outcomes versus early-generation DES[9,10]. On the other hand, long-term follow-up data with the XIENCE stent remain scant and direct comparison of five-year outcomes versus biodegradable polymer DES is an important scientific gap.

In the present analysis, we report the final five-year outcomes from patients enrolled in the Intracoronary Stenting and Angiographic Results: Test Efficacy of Three Limus-Eluting STents (ISAR-TEST 4) trial and randomly allocated to treatment with Yukon Choice PC, XIENCE or permanent polymer sirolimus-eluting stents (CYPHER).

Methods

Between September 2007 and August 2008, patients were enrolled at two centres in Munich, Germany. The primary study comparison was between outcomes of patients treated with biodegradable polymer versus permanent polymer DES. Full details of the study population, methods, endpoints and primary analysis have been previously reported[11]. In brief, patients were randomly allocated to receive biodegradable polymer sirolimus-eluting stents (Yukon Choice PC) or permanent polymer DES (either everolimus-eluting [XIENCE] or sirolimus-eluting stents [CYPHER; Cordis Corporation, Miami Lakes, FL, USA]) in a 2:1:1 allocation. Description of stent platforms and elution characteristics are reported elsewhere[11-13]. The aim of the current study was to compare outcomes of patients treated with Yukon Choice PC versus XIENCE and CYPHER versus XIENCE stents after five years of clinical follow-up.

The primary outcome of the ISAR-TEST 4 study was a device-oriented composite of cardiac death, myocardial infarction (MI) related to the target vessel, or revascularisation related to the target lesion (TLR). The main secondary endpoint was definite/probable stent thrombosis. Stent thrombosis was classified according to the Academic Research Consortium (ARC) criteria[14]. Patients were systematically evaluated at one, 12, 24, 36 and 60 months by telephone call or office visit. 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 (25^{th}-75^{th} percentiles). Categorical data are presented as counts and proportions (%). Unless otherwise stated, differences between groups were checked for significance, using Tukey's multiple comparison test (continuous data) and chi-squared or Fisher's exact test (categorical variables). Survival was analysed according to Kaplan-Meier methods and hazard ratios were calculated using Cox proportional hazards methods. The proportional hazards assumption was checked by the method of Grambsch and Therneau[15] and was fulfilled in all cases in which we used Cox proportional hazards models. Analysis of the primary outcome was also performed for pre-specified subsets of interest, and interaction between treatment effect and these covariates was assessed with Cox proportional hazards models. All analyses were by intention-to-treat using all patients randomised in the study, regardless of the treatment actually received. Statistical software S-PLUS, version 4.5 (S-PLUS; Insightful Corp., Seattle, WA, USA) was used for analysis.

Results

A total of 2,603 patients were randomised to receive either Yukon Choice PC (n=1,299), XIENCE (n=652) or CYPHER (n=652) stents. Study flow chart and treatment allocation are shown in **Figure 1**. Baseline patient and lesion characteristics were well balanced across all groups **(Table 1)**. Five-year follow-up was complete in all but 229 patients (8.8%), and three-year follow-up was complete in all but 110 patients (4.2%).

YUKON CHOICE PC VERSUS XIENCE: FIVE-YEAR CLINICAL FOLLOW-UP

The results of follow-up are summarised in **Table 2** and the landmark analysis from one to five years is shown in **Table 3**. At five years, the incidence of the primary endpoint was not significantly different between Yukon Choice PC and XIENCE stents (20.5% vs. 19.5%, respectively, hazard ratio [HR]=1.04, 95% CI: 0.84-1.29; p=0.71) **(Figure 2A)**. The incidence of the primary endpoint

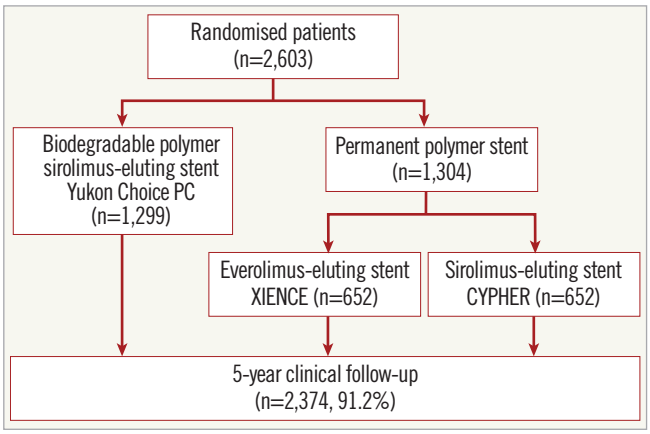

Figure 1. *ISAR-TEST 4 study flow chart. Participant flow through the study.*

Table 1. Yukon Choice PC versus XIENCE and CYPHER versus XIENCE: characteristics of patients and lesions at baseline.

		Yukon Choice PC	*p*-value	XIENCE	*p*-value	CYPHER
Patients		**n=1,299**		**n=652**		**n=652**
Age, yrs		66.7±11.1	0.99	66.7±10.3	0.99	66.8±11.1
Male sex, no. (%)		978 (75.3)	0.20	507 (77.8)	0.43	495 (75.8)
Diabetes mellitus, no. (%) Insulin-dependent		376 (28.9) 108 (8.3)	0.70 0.55	184 (28.2) 60 (9.2)	0.58 0.85	193 (29.6) 62 (9.5)
Arterial hypertension, no. (%)		897 (69.1)	0.55	442 (67.8)	0.86	439 (67.3)
Hyperlipidaemia, no. (%)		868 (66.8)	0.43	423 (64.9)	>0.99	423 (64.9)
Current smoker, no. (%)		202 (15.6)	0.91	101 (15.5)	0.33	114 (17.5)
Prior myocardial infarction, no. (%)		372 (28.6)	0.85	191 (29.3)	0.58	182 (27.9)
Prior coronary artery bypass grafting, no. (%)		129 (9.9)	0.66	69 (10.6)	0.40	60 (9.2)
Clinical presentation, no. (%)	STEMI*	167 (12.9)	0.16	70 (10.7)	0.99	70 (10.7)
	NSTE¶-acute coronary syndrome	374 (28.8)	0.42	199 (30.5)	0.25	180 (27.6)
	Stable angina	758 (58.4)	0.85	383 (58.7)	0.28	402 (61.7)
Ejection fraction, %		53.1±11.9	0.87	53.4±11.7	0.88	53.8±12.1
Multilesion intervention, no. (%)		375 (28.9)	0.80	174 (26.7)	0.61	166 (25.6)
1-vessel disease, no. (%)		175 (13.5)	0.55	95 (14.6)	0.33	83 (12.7)
2-vessel disease, no. (%)		357 (27.5)	0.84	182 (27.9)	0.67	189 (29.0)
3-vessel disease, no. (%)		767(60.1)	0.62	375 (59.1)	0.78	380 (58.3)
Multivessel disease, no. (%)		1,124 (86.5)	0.55	557 (85.4)	0.33	557 (87.3)
Lesions		**n=1,683**		**n=850**		**n=839**
Target vessel location, no. (%)	Left anterior descending artery	753 (44.7)	0.36	372 (43.8)	0.57	376 (44.8)
	Left circumflex artery	454 (27.0)	0.79	223 (26.2)	0.86	230 (27.4)
	Right coronary artery	476 (28.3)	0.19	255 (30.0)	0.48	233 (27.8)
Chronic total occlusion, no. (%)		89 (5.3)	0.31	36 (4.2)	0.16	50 (6.0)
Bifurcation, no. (%)		421 (25.0)	0.06	185 (21.8)	0.36	198 (23.6)
Ostial, no. (%)		267 (15.9)	0.09	158 (18.6)	0.48	146 (17.4)
Complex morphology (B2/C), no. (%)		1,225 (72.8)	0.36	604 (71.1)	0.36	614 (73.2)
Lesion length, mm		14.8±8.8	0.56	15.2±8.9	0.65	14.8±8.2
Vessel size, mm		2.79±0.52	0.88	2.80±0.45	0.97	2.80±0.48
Minimum lumen diameter, mm	Before procedure	0.98±0.51	0.93	0.99±0.49	0.77	0.97±0.51
	Post procedure	2.58±0.50	0.74	2.59±0.44	0.99	2.59±0.45
Percent stenosis, %	Before procedure	65.0±16.0	0.97	64.8±16.0	0.79	65.4±16.1
	Post procedure, in-stent	11.4±7.4	0.27	11.8±6.3	0.004	10.8±6.2
	Post procedure, in-segment	23.2±11.7	0.75	23.6±11.4	0.89	23.3±10.8

¶NSTE-acute coronary syndrome: non-ST-segment elevation acute coronary syndrome; *STEMI: ST-segment elevation myocardial infarction

between one and five years was comparable and low in both groups: 8.1% with Yukon Choice PC vs. 6.9% with XIENCE stents (HR=1.17, 95% CI: 0.80-1.72; p=0.42) **(Figure 3A)**. The comparability between the two study devices regarding the primary endpoint was observed across pre-specified subgroups of age, sex, diabetes status and vessel size as well as myocardial infarction at presentation with no significant interaction **(Figure 4A)**.

Regarding safety outcomes, definite/probable stent thrombosis was low in both groups: 1.2% with Yukon Choice PC vs. 1.4% with XIENCE stents (HR=0.83, 95% CI: 0.37-1.91; p=0.67) **(Figure 2B)**. Full results of stent thrombosis adjudication are presented in **Table 2**. The incidence of definite/probable stent thrombosis between one and five years was comparable and low in both groups: two events (0.2%) with Yukon Choice PC and no event with XIENCE (p=0.89) **(Figure 3B)**. The composite of cardiac death or MI related to the target vessel was also similar in both groups at five years **(Figure 2C)** as well as between one and five years **(Table 3)**. Regarding antirestenotic efficacy, TLR at five years was also similar in both groups **(Figure 2D)** with comparable rates in both groups between one and five years **(Table 3)**.

CYPHER VERSUS XIENCE: FIVE-YEAR CLINICAL FOLLOW-UP

At five years, the incidence of the primary endpoint was not significantly different between CYPHER and XIENCE stents (23.5% vs. 19.5%, respectively, HR=1.21, 95% CI: 0.95-1.53; p=0.12) **(Figure 2A)**. The incidence of the primary endpoint between one

Table 2. Yukon Choice PC versus XIENCE and CYPHER versus XIENCE: clinical outcomes up to 5 years*.

		Yukon Choice PC	Hazard ratio (95% CI) Yukon Choice PC vs. XIENCE	*p*-value	XIENCE	Hazard ratio (95% CI) CYPHER vs. XIENCE	*p*-value	CYPHER
Patients		**1,299**			**652**			**652**
All-cause death		182 (14.7)	0.99 (0.77-1.27)	0.95	92 (14.8)	1.22 (0.92-1.61)	0.16	111 (17.9)
Cardiac death		64 (5.2)	0.97 (0.64-1.48)	0.89	33 (5.2)	1.22 (0.77-1.93)	0.40	40 (6.5)
Myocardial infarction		70 (5.5)	1.10 (0.72-1.67)	0.67	32 (5.0)	0.89 (0.70-1.81)	0.62	36 (5.8)
Target vessel myocardial infarction		59 (4.6)	1.14 (0.72-1.81)	0.58	26 (4.1)	1.23 (0.73-2.07)	0.43	32 (5.1)
Cardiac death or target vessel myocardial infarction		113 (8.9)	0.99 (0.72-1.37)	0.97	57 (8.9)	1.15 (0.80-1.63)	0.46	65 (10.4)
Target lesion revascularisation		170 (13.9)	1.11 (0.85-1.45)	0.46	77 (12.6)	1.29 (0.95-1.73)	0.10	97 (15.9)
Death, myocardial infarction or target lesion revascularisation		362 (28.6)	1.01 (0.84-1.21)	0.93	180 (28.4)	1.18 (0.97-1.44)	0.10	208 (33.1)
Cardiac death, target vessel myocardial infarction or target lesion revascularisation		258 (20.5)	1.04 (0.84-1.29)	0.71	124 (19.5)	1.21 (0.95-1.53)	0.12	147 (23.5)
Stent thrombosis	Definite	9 (0.7)	1.13 (0.35-3.66)	0.84	4 (0.6)	2.76 (0.88-8.66)	0.08	11 (1.8)
	Probable	6 (0.5)	0.60 (0.18-1.97)	0.40	5 (0.8)	0.80 (0.22-2.99)	0.74	4 (0.7)
	Possible	14 (1.0)	1.40 (0.51-3.90)	0.52	5 (0.8)	2.82 (1.02-7.84)	0.05	14 (2.4)
	Definite or probable	15 (1.2)	0.83 (0.37-1.91)	0.67	9 (1.4)	1.67 (0.73-3.82)	0.22	15 (2.4)
Early stent thrombosis	Definite	5 (0.4)	1.25 (0.24-6.44)	0.79	2 (0.3)	1.50 (0.25-8.90)	0.66	3 (0.5)
	Probable	2 (0.2)	0.25 (0.05-1.37)	0.11	4 (0.6)	0.25 (0.03-2.23)	0.21	1 (0.1)
	Definite or probable	7 (0.5)	0.58 (0.20-1.74)	0.33	6(0.9)	0.66 (0.19-2.40)	0.53	4 (0.6)
Late stent thrombosis	Definite	8 (0.6)	1.00 (0.30-3.33)	0.99	4 (0.6)	2.00 (0.60-6.65)	0.26	8 (1.3)
	Probable	5 (0.4)	0.50 (0.14-1.73)	0.27	5 (0.8)	0.40 (0.08-2.06)	0.27	2 (0.3)
	Definite or probable	13 (1.0)	0.72 (0.31-1.69)	0.50	9 (1.4)	1.11 (0.45-2.74)	0.82	10 (1.6)
Very late stent thrombosis	Definite	1 (0.8)	n.a.	0.75	0 (0.0)	n.a.	0.25	3 (0.5)
	Probable	1 (0.7)	n.a.	0.75	0 (0.0)	n.a.	0.49	2 (0.3)
	Definite or probable	2 (0.2)	n.a.	0.89	0 (0.0)	n.a.	0.06	5 (0.9)

*Data shown as number (percentage as Kaplan-Meier estimate). Hazard ratios (95% CI) derived from Cox proportional hazard models (unadjusted); *p*-values from log-rank testing.

Table 3. Yukon Choice PC versus XIENCE and CYPHER versus XIENCE: landmark analysis clinical outcomes 1 to 5 years*.

		Yukon Choice PC	Hazard ratio (95% CI) Yukon Choice PC vs. XIENCE	*p*-value	XIENCE	Hazard ratio (95% CI) CYPHER vs. XIENCE	*p*-value	CYPHER
Patients		**1,299**			**652**			**652**
All-cause death		122 (10.5)	0.97 (0.72-1.32)	0.86	63 (10.8)	1.27 (0.91-1.77)	0.16	79 (13.6)
Cardiac death		29 (2.5)	1.12 (0.58-2.15)	0.74	13 (2.2)	1.48 (0.73-2.99)	0.28	19 (3.3)
Myocardial infarction		15 (1.3)	1.25 (0.49-3.23)	0.64	6 (1.1)	1.52 (0.54-4.26)	0.43	9 (1.6)
Target vessel myocardial infarction		6 (0.5)	0.75 (0.21-2.67)	0.66	4 (0.7)	2.02 (0.61-6.71)	0.25	8 (1.4)
Cardiac death or target vessel myocardial infarction		32 (2.9)	0.99 (0.72-1.37)	0.99	16 (2.8)	1.64 (0.88-3.07)	0.12	26 (4.7)
Target lesion revascularisation		65 (6.0)	1.21 (0.78-1.90)	0.40	27 (5.0)	1.23 (0.74-2.05)	0.43	32 (6.1)
Death, myocardial infarction or target lesion revascularisation		168 (16.0)	1.02 (0.79-1.33)	0.87	83 (15.8)	1.27 (0.95-1.70)	0.11	180 (19.7)
Cardiac death, target vessel myocardial infarction or target lesion revascularisation		86 (8.1)	1.17 (0.80-1.72)	0.42	37 (6.9)	1.44 (0.94-2.19)	0.09	51 (10)
Stent thrombosis	Definite	1 (0.8)		0.75	0 (0.0)		0.25	3 (0.5)
	Probable	1 (0.7)		0.75	0 (0.0)		0.49	2 (0.3)
	Possible	8 (0.7)	2.01 (0.43-9.46)	0.38	3 (0.3)	5.05 (1.11-23.05)	0.04	10 (1.8)
	Definite or probable	2 (0.2)		0.89	0 (0.0)		0.06	5 (0.9)

Data shown as number (percentage as Kaplan-Meier estimate). Hazard ratios (95% CI) derived from Cox proportional hazard models (unadjusted); *p*-values from log-rank testing

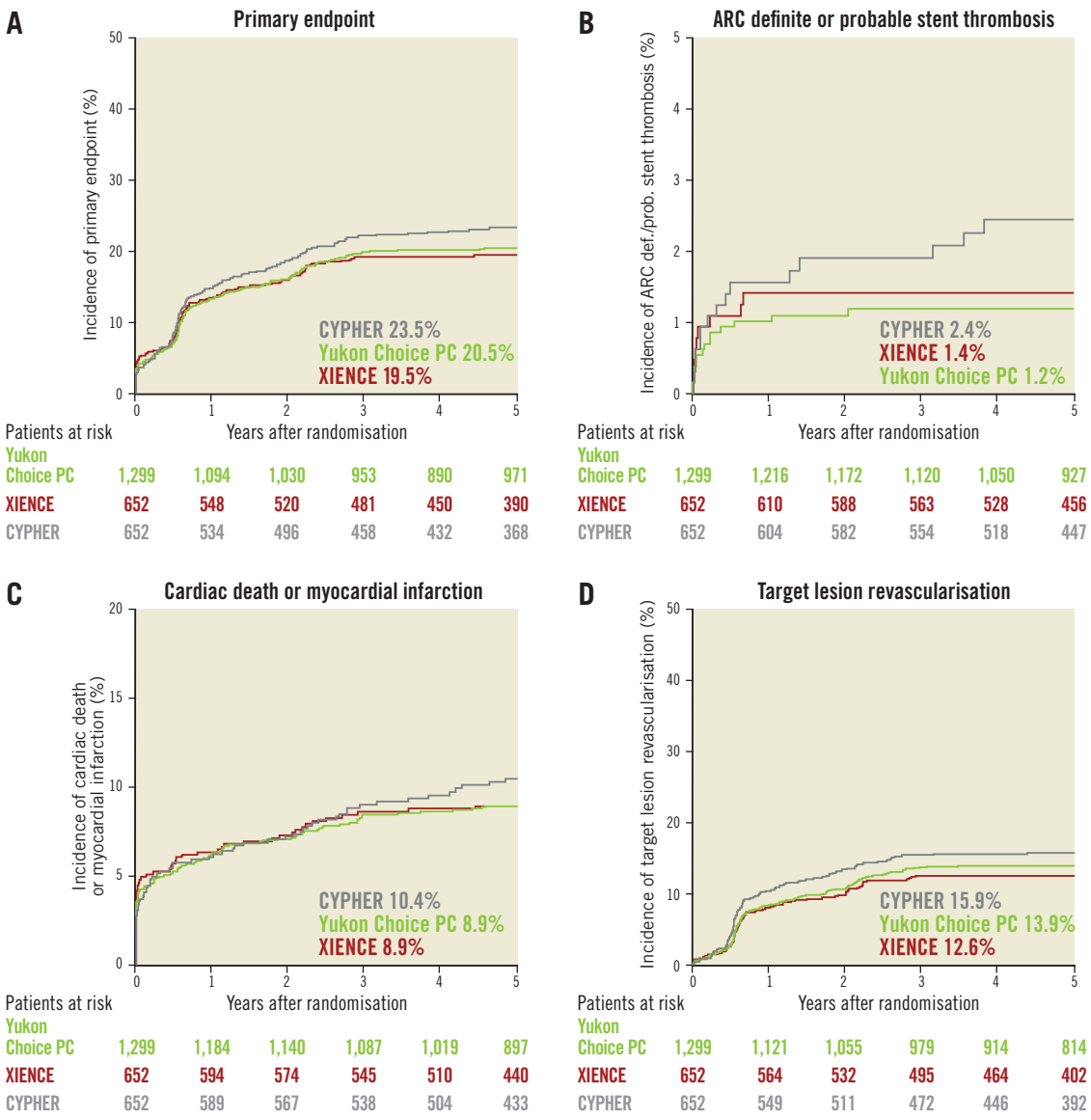

Figure 2. *Comparison of outcomes in patients treated with Yukon Choice PC versus XIENCE versus CYPHER. Kaplan-Meier curves for primary endpoint (A), definite/probable stent thrombosis (B), composite of cardiac death and myocardial infarction related to the target vessel (C), and target lesion revascularisation (D).*

and five years was numerically higher in the CYPHER group (10.0%) as compared to the XIENCE group (6.9%) (HR=1.44, 95% CI: 0.94-2.19; p=0.09) **(Figure 3A)**. The comparability between the two study devices regarding the primary endpoint was observed across all subgroups with no significant interaction **(Figure 4B)**.

Regarding safety outcomes, definite/probable stent thrombosis was numerically higher in the CYPHER (2.4%) as compared to the XIENCE group (1.4%) (HR=1.67, 95% CI: 0.73-3.82; p=0.22) **(Figure 2B)**. The incidence of definite/probable stent thrombosis between one and five years was numerically higher in the CYPHER group (five events, 0.9%) as compared with the XIENCE group (no event) (p=0.06) **(Figure 3B)**. The composite of cardiac death or MI related to the target vessel was comparable in both groups at five years **(Figure 2C)** though was numerically higher with CYPHER as compared with XIENCE between one and five years **(Table 3)**. Regarding antirestenotic efficacy, TLR at five years was numerically higher in the CYPHER as compared with the XIENCE group **(Figure 2D)** though the incidence of TLR between one and five years was comparable in both groups **(Table 3)**.

Discussion

The current manuscript represents the first report of long-term randomised trial data comparing treatment with XIENCE versus Yukon Choice PC and CYPHER stents. The major findings of this study are the following. (i) Both Yukon Choice PC and XIENCE stents are associated with similar clinical outcomes at five years in terms of efficacy and safety, with low rates of device-related events between one and five years. Moreover, although this study was not

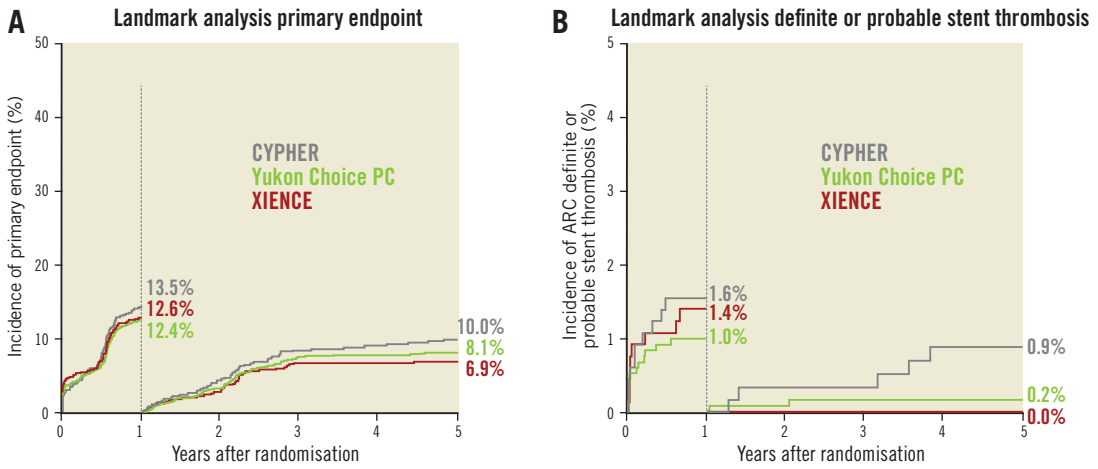

Figure 3. *Landmark analysis from one to five years: comparison of outcomes in patients treated with Yukon Choice PC versus XIENCE versus CYPHER. Kaplan-Meier curves for primary endpoint (A), and definite/probable stent thrombosis (B).*

powered to detect differences in the incidence of stent thrombosis, the incidence of this endpoint was low and similar in both groups. (ii) Both CYPHER and XIENCE stents are associated with similar clinical outcomes at five years. Although not statistically significant, the incidence of stent thrombosis was numerically higher with CYPHER stents, especially between one and five years.

Biodegradable polymer DES are an intuitively attractive technology, combining the acute beneficial effects of polymer coating – control of drug-release kinetics[16] and possible reduction in acute thrombogenicity[17] – with the long-term benefit of uncoated bare metal stents. Randomised control trial data show generally comparable one-year results versus high efficacy early and new-generation permanent polymer stents at 12 months[11,18-21]. In fact, the demonstration of comparable efficacy against standard DES is an important first step in the proof-of-concept chain of investigation. The next step is the evaluation of potential benefit late (>12 months) after device implantation. For this reason, long-term follow-up of clinical trials with this technology is important. The three-year results of ISAR-TEST 4 showed similar clinical outcomes with biodegradable polymer and permanent polymer DES[22]. Final five-year results from the LEADERS trial showed durable long-term efficacy with a trend towards lower rates of stent thrombosis compared with the CYPHER stent[9]. Moreover, pooled long-term follow-up of three randomised trials showed a significant reduction in stent thrombosis with biodegradable polymer DES versus the CYPHER stent driven by a statistically significant and probably clinically important 78% reduction in stent thrombosis events between years one and four[10].

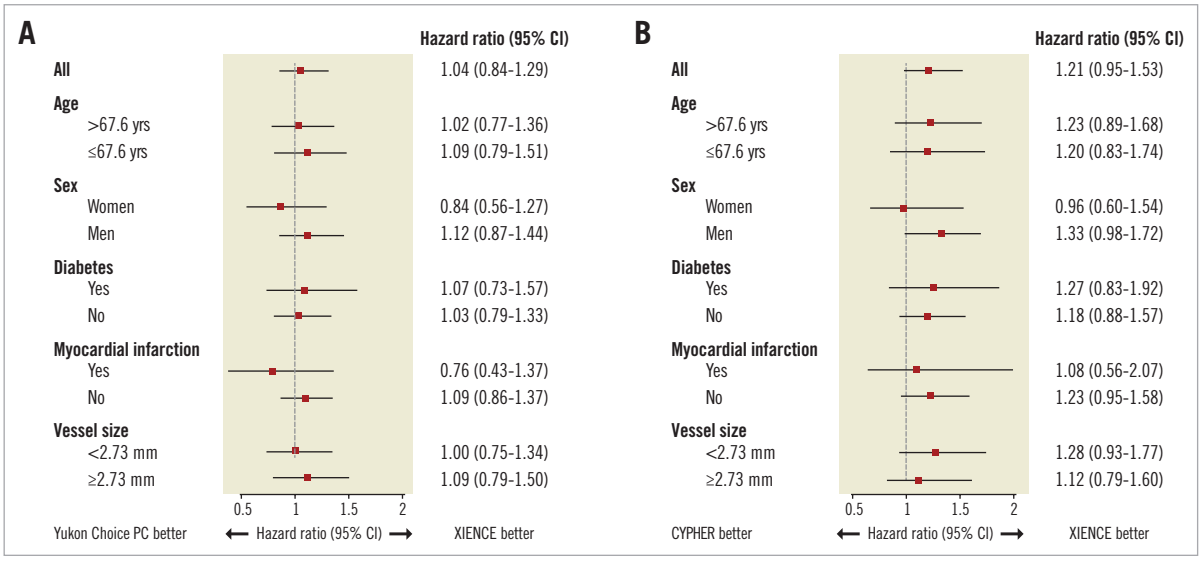

Figure 4. *Comparison of incidence of primary endpoint according to pre-specified subgroups. Subgroup analysis in patients treated with Yukon Choice PC versus XIENCE (A), and CYPHER versus XIENCE (B).*

A limitation of available long-term follow-up data with biodegradable polymer DES is that the early-generation CYPHER stent was the comparator stent[9,10]. However, newer-generation stents such as the XIENCE stent were shown to be more effective and safer than early-generation stents in a number of large-scale registries[23,24]. Moreover, meta-analyses of direct comparison clinical trials also demonstrated some evidence of improved clinical outcomes with the XIENCE stent when compared with the CYPHER stent[25]. These findings are in line with preclinical data showing improved vascular healing with XIENCE stents[7,26]. In this respect, in the present analysis we focused initially on the comparison between patients treated with Yukon Choice PC and XIENCE stents. In addition, however, although the sirolimus-eluting CYPHER stent is no longer in routine clinical use, comparison of five-year outcomes between the widely used XIENCE stent and this benchmark early-generation stent remains an important scientific issue.

The principal findings of the current report are that device-related events were low and comparable with both Yukon Choice PC and XIENCE stents up to five years. The low incidence of events with biodegradable polymer at five years is in line with the late performance observed in other reports[9,10]. These results should be confirmed by long-term follow-up of randomised trials recently reporting primary outcome results[19-21]. Indeed, recently reported results from the NEXT trial showed comparable clinical outcomes between newer biodegradable polymer stents and the XIENCE stent up to two years[26]. In addition, the low incidence of events with the XIENCE stent is important, as this is the first report of five-year follow-up from a large-scale randomised trial with this stent. These data build on the favourable efficacy and safety profile of the device during short- to medium-term follow-up and confirm that this stent should be a benchmark for evaluation of emerging stent technologies.

On the other hand, although not statistically significant, the higher incidence of device-oriented endpoints with the sirolimus-eluting CYPHER stent lends further support to concerns about delayed vascular healing and late adverse events with this stent. Although certainly not powered to detect differences in the incidence of stent thrombosis, the numerically higher rate of stent thrombosis between one and five years with this stent is notable and consistent with prior reports[9].

Limitations

The current report has some important limitations. First, the primary design of the ISAR-TEST 4 trial was a non-inferiority comparison of biodegradable versus permanent polymer DES at 12 months. Accordingly, additional comparisons at five years are *post hoc*. Second, the trial was not specifically powered for a comparison between Yukon Choice PC versus XIENCE and CYPHER versus XIENCE stents. Although overall event rates were comparable in all groups, comparisons must be interpreted with caution. Third, in terms of the comparison between biodegradable polymer and permanent polymer stents, caution must be exercised in directly attributing any observed outcome differences to the polymer coatings alone, as the stent platforms studied also differ in relation to stent backbone and drug type and dose. Fourth, this study was not powered for the detection of differences according to stent thrombosis. Fifth, the study protocol included angiographic follow-up, and the influence of planned invasive surveillance on the individual components of the primary endpoint should be considered. Sixth, although both treatment groups received the same recommendation for duration of treatment after stenting, complete data relating to compliance or actual duration of dual antiplatelet therapy received were not available.

Conclusions

Biodegradable polymer Yukon Choice PC and permanent polymer XIENCE stents showed comparable clinical outcomes at five years. On the other hand, permanent polymer CYPHER stents showed numerically higher rates of device-related adverse events driven primarily by higher incidences of device-oriented endpoints between one and five years.

Impact on daily practice

Both new-generation biodegradable polymer sirolimus-eluting stents and permanent polymer everolimus-eluting stents offer potential for enhanced late outcomes in comparison with earlier-generation drug-eluting stents. The five-year data from ISAR-TEST 4 build on the favourable efficacy and safety profile of both newer-generation devices during short- to medium-term follow-up and confirms their comparable safety and efficacy during long-term follow-up. The incidence of stent thrombosis events observed with both devices at five years was low, lending further support to the favourable late safety profile of newer-generation DES.

Conflict of interest statement

A. Kastrati holds a patent related to biodegradable polymer coating, and reports having received lecture fees from Abbott, Biosensors and Biotronik. R. Byrne reports having received lecture fees from Biotronik. The other authors have no conflicts of interest to declare.

References

1. Byrne RA, Sarafoff N, Kastrati A, Schömig A. Drug-eluting stents in percutaneous coronary intervention: a benefit-risk assessment. *Drug Saf.* 2009;32:749-70.

2. Stefanini GG, Holmes DR Jr. Drug-eluting coronary-artery stents. *N Engl J Med.* 2013;368:254-65.

3. Joner M, Finn AV, Farb A, Mont EK, Kolodgie FD, Ladich E, Kutys R, Skorija K, Gold HK, Virmani R. Pathology of drug-eluting stents in humans: delayed healing and late thrombotic risk. *J Am Coll Cardiol.* 2006;48:193-202.

4. Byrne RA, Iijima R, Mehilli J, Pinieck S, Bruskina O, Schömig A, Kastrati A. Durability of antirestenotic efficacy in drug-eluting stents with and without permanent polymer. *JACC Cardiovasc Interv.* 2009;2:291-9.

5. Nakazawa G, Otsuka F, Nakano M, Vorpahl M, Yazdani SK, Ladich E, Kolodgie FD, Finn AV, Virmani R. The pathology of neoatherosclerosis in human coronary implants bare-metal and drug-eluting stents. *J Am Coll Cardiol.* 2011;57:1314-22.

6. Byrne RA, Joner M, Kastrati A. Polymer coatings and delayed arterial healing following drug-eluting stent implantation. *Minerva Cardioangiol.* 2009;57:567-84.

7. Joner M, Nakazawa G, Finn AV, Quee SC, Coleman L, Acampado E, Wilson PS, Skorija K, Cheng Q, Xu X, Gold HK, Kolodgie FD, Virmani R. Endothelial cell recovery between comparator polymer-based drug-eluting stents. *J Am Coll Cardiol.* 2008;52:333-42.

8. Steigerwald K, Merl S, Kastrati A, Wieczorek A, Vorpahl M, Mannhold R, Vogeser M, Hausleiter J, Joner M, Schömig A, Wessely R. The pre-clinical assessment of rapamycin-eluting, durable polymer-free stent coating concepts. *Biomaterials.* 2009;30:632-7.

9. Serruys PW, Farooq V, Kalesan B, de Vries T, Buszman P, Linke A, Ischinger T, Klauss V, Eberli F, Wijns W, Morice MC, Di Mario C, Corti R, Antoni D, Sohn HY, Eerdmans P, Rademaker-Havinga T, van Es GA, Meier B, Jüni P, Windecker S. Improved safety and reduction in stent thrombosis associated with biodegradable polymer-based biolimus-eluting stents versus durable polymer-based sirolimus-eluting stents in patients with coronary artery disease: final 5-year report of the LEADERS (Limus Eluted from A Durable versus ERodable Stent coating) randomized, noninferiority trial. *JACC Cardiovasc Interv.* 2013;6:777-89.

10. Stefanini GG, Byrne RA, Serruys PW, de Waha A, Meier B, Massberg S, Jüni P, Schömig A, Windecker S, Kastrati A. Biodegradable polymer drug-eluting stents reduce the risk of stent thrombosis at 4 years in patients undergoing percutaneous coronary intervention: a pooled analysis of individual patient data from the ISAR-TEST 3, ISAR-TEST 4, and LEADERS randomized trials. *Eur Heart J.* 2012;33:1214-22.

11. Byrne RA, Kastrati A, Kufner S, Massberg S, Birkmeier KA, Laugwitz KL, Schulz S, Pache J, Fusaro M, Seyfarth M, Schömig A, Mehilli J; Intracoronary Stenting and Angiographic Results: Test Efficacy of 3 Limus-Eluting Stents (ISAR-TEST-4) Investigators. Randomized, non-inferiority trial of three limus agent-eluting stents with different polymer coatings: the Intracoronary Stenting and Angiographic Results: Test Efficacy of 3 Limus-Eluting Stents (ISAR-TEST-4) Trial. *Eur Heart J.* 2009;30:2441-9.

12. Beijk MA, Piek JJ. XIENCE V everolimus-eluting coronary stent system: a novel second generation drug-eluting stent. *Expert Rev Med Devices.* 2007;4:11-21.

13. Sousa JE, Costa MA, Abizaid A, Abizaid AS, Feres F, Pinto IM, Seixas AC, Staico R, Mattos LA, Sousa AG, Falotico R, Jaeger J, Popma JJ, Serruys PW. Lack of neointimal proliferation after implantation of sirolimus-coated stents in human coronary arteries: a quantitative coronary angiography and three-dimensional intravascular ultrasound study. *Circulation*. 2001;103:192-5.

14. Cutlip DE, Windecker S, Mehran R, Boam A, Cohen DJ, van Es GA, Steg PG, Morel MA, Mauri L, Vranckx P, McFadden E, Lansky A, Hamon M, Krucoff MW, Serruys PW; Academic Research Consortium. Clinical end points in coronary stent trials: a case for standardized definitions. *Circulation*. 2007;115:2344-51.

15. Grambsch PM, Therneau TM. Proportional hazards tests and diagnostics based on weighted residuals. *Biometrika.* 1994;81:515-26.

16. Mehilli J, Byrne RA, Wieczorek A, Iijima R, Schulz S, Bruskina O, Pache J, Wessely R, Schömig A, Kastrati A; Intracoronary Stenting and Angiographic Restenosis Investigators--Test Efficacy of Rapamycin-eluting Stents with Different Polymer Coating Strategies (ISAR-TEST-3). Randomized trial of three rapamycin-eluting stents with different coating strategies for the reduction of coronary restenosis. *Eur Heart J.* 2008;29:1975-82.

17. Kolandaivelu K, Swaminathan R, Gibson WJ, Kolachalama VB, Nguyen-Ehrenreich KL, Giddings VL, Coleman L, Wong GK, Edelman ER. Stent thrombogenicity early in high-risk interventional settings is driven by stent design and deployment and protected by polymer-drug coatings. *Circulation*. 2011;123:1400-9.

18. Windecker S, Serruys PW, Wandel S, Buszman P, Trznadel S, Linke A, Lenk K, Ischinger T, Klauss V, Eberli F, Corti R, Wijns W, Morice MC, di Mario C, Davies S, van Geuns RJ, Eerdmans P, van Es GA, Meier B, Jüni P. Biolimus-eluting stent with biodegradable polymer versus sirolimus-eluting stent with durable polymer for coronary revascularisation (LEADERS): a randomised non-inferiority trial. *Lancet.* 2008;372:1163-73.

19. Smits PC, Hofma S, Togni M, Vazquez N, Valdes M, Voudris V, Slagboom T, Goy JJ, Vuillomenet A, Serra A, Nouche RT, den Heijer P, van der Ent M. Abluminal biodegradable polymer biolimus-eluting stent versus durable polymer everolimus-eluting stent (COMPARE II): a randomised, controlled, non-inferiority trial. *Lancet.* 2013;381:651-60.

20. Natsuaki M, Kozuma K, Morimoto T, Kadota K, Muramatsu T, Nakagawa Y, Akasaka T, Igarashi K, Tanabe K, Morino Y, Ishikawa T, Nishikawa H, Awata M, Abe M, Okada H, Takatsu Y, Ogata N, Kimura K, Urasawa K, Tarutani Y, Shiode N, Kimura T; NEXT Investigators. Biodegradable polymer biolimus-eluting stent versus durable polymer everolimus-eluting stent: a randomized, controlled, noninferiority trial. *J Am Coll Cardiol.* 2013;62:181-90.

21. Christiansen EH, Jensen LO, Thayssen P, Tilsted HH, Krusell LR, Hansen KN, Kaltoft A, Maeng M, Kristensen SD, Botker HE, Terkelsen CJ, Villadsen AB, Ravkilde J, Aaroe J, Madsen M, Thuesen L, Lassen JF; Scandinavian Organization for Randomized Trials with Clinical Outcome (SORT OUT) V investigators. Biolimus-eluting biodegradable polymer-coated stent versus durable polymer-coated sirolimus-eluting stent in unselected patients receiving percutaneous coronary intervention (SORT OUT V): a randomised non-inferiority trial. *Lancet.* 2013;381:661-9.

22. Byrne RA, Kastrati A, Massberg S, Wieczorek A, Laugwitz KL, Hadamitzky M, Schulz S, Pache J, Fusaro M, Hausleiter J, Schömig A, Mehilli J; ISAR-TEST 4 Investigators. Biodegradable polymer versus permanent polymer drug-eluting stents and everolimus- versus sirolimus-eluting stents in patients

with coronary artery disease: 3-year outcomes from a randomized clinical trial. *J Am Coll Cardiol.* 2011;58:1325-31.

23. Tada T, Byrne RA, Simunovic I, King LA, Cassese S, Joner M, Fusaro M, Schneider S, Schulz S, Ibrahim T, Ott I, Massberg S, Laugwitz KL, Kastrati A. Risk of stent thrombosis among bare-metal stents, first-generation drug-eluting stents, and second-generation drug-eluting stents: results from a registry of 18,334 patients. *JACC Cardiovasc Interv.* 2013;6:1267-74.

24. Cassese S, Byrne RA, Tada T, Pinieck S, Joner M, Ibrahim T, King LA, Fusaro M, Laugwitz KL, Kastrati A. Incidence and predictors of restenosis after coronary stenting in 10 004 patients with surveillance angiography. *Heart.* 2014;100:153-9.

25. de Waha A, Cassese S, Park DW, Burzotta F, Byrne RA, Tada T, King LA, Park SJ, Schömig A, Kastrati A. Everolimus-eluting versus sirolimus-eluting stents: an updated meta-analysis of randomized trials. *Clin Res Cardiol.* 2012;101:461-7.

26. Natsuaki M, Kozuma K, Morimoto T, Shiomi H, Kimura T. Two-year outcome of a randomized trial comparing second-generation drug-eluting stents using biodegradable or durable polymer. *JAMA.* 2014;311:2125-7.