JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY VOL. 71, NO. 18, 2018

PUBLISHED BY ELSEVIER

Efficacy Over Time With Drug-Eluting Stents in Saphenous Vein Graft Lesions

Roisin Colleran, MB BCH,[a,*] Sebastian Kufner, MD,[a,*] Julinda Mehilli, MD,[b,c] Christian Rosenbeiger, MSc,[a] Stefanie Schüpke, MD,[a,b] Petra Hoppmann, MD,[d] Michael Joner, MD,[a,b] Nader Mankerious, MSc,[a] Massimiliano Fusaro, MD,[a] Salvatore Cassese, MD, PhD,[a] Mohamed Abdel-Wahab, MD,[e] Franz-Josef Neumann, MD,[f] Gert Richardt, MD,[e] Tareq Ibrahim, MD,[d] Heribert Schunkert, MD,[a,b] Karl-Ludwig Laugwitz, MD,[b,d] Adnan Kastrati, MD,[a,b] Robert A. Byrne, MB BCH, PhD,[a,b] for the ISAR-CABG Investigators

ABSTRACT

BACKGROUND In the ISAR-CABG (Is Drug-Eluting-Stenting Associated with Improved Results in Coronary Artery Bypass Grafts?) trial, clinical outcomes at 1 year in patients undergoing treatment of saphenous vein graft lesions were superior with drug-eluting stents (DES) versus bare-metal stents.

OBJECTIVES The authors compared outcomes between treatment groups at 5 years.

METHODS Patients were randomized (1:1:1:3) to receive DES (either permanent-polymer paclitaxel-eluting stents, permanent-polymer sirolimus-eluting stents, or biodegradable-polymer sirolimus-eluting stents) or bare-metal stents. The primary endpoint was the combined incidence of death, myocardial infarction (MI), or target lesion revascularization (TLR). Secondary endpoints were the composite of death or MI and TLR.

RESULTS A total of 610 patients were allocated to treatment with DES (n = 303) or bare-metal stents (n = 307). At 5 years, the primary endpoint occurred in 159 (55.5%) versus 157 (53.6%) patients in the DES and bare-metal stent groups, respectively (hazard ratio [HR]: 0.98; 95% confidence interval [CI]: 0.79 to 1.23; p = 0.89). There was interaction between treatment effect and time ($p_{interaction}$ = 0.005), with a lower event rate in the DES group at 1 year (HR: 0.64; 95% CI: 0.44 to 0.94; p = 0.02) but a numerically higher rate between 1 and 5 years (HR: 1.24; 95% CI: 0.94 to 1.63; p = 0.13). Death or MI occurred in 93 (32.8%) versus 108 (36.6%) patients, respectively (HR: 0.85; 95% CI: 0.64 to 1.12; p = 0.24), without significant interaction between treatment effect and time ($p_{interaction}$ = 0.57). TLR occurred in 84 (33.1%) versus 69 (25.5%) patients in the DES and bare-metal stent groups, respectively (HR: 1.20; 95% CI: 0.87 to 1.64; p = 0.27). There was interaction between treatment effect and time ($p_{interaction}$ <0.001): TLR was significantly lower in the DES group at 1 year (HR: 0.49; 95% CI: 0.28 to 0.86; p = 0.01) but significantly higher thereafter (HR: 2.02; 95% CI: 1.32 to 3.08; p = 0.001).

CONCLUSIONS In patients undergoing treatment of saphenous vein graft lesions, the advantage of DES over bare-metal stents demonstrated at 1 year was lost at 5 years due to higher attrition of efficacy in the DES group. (Efficacy Study of Drug-Eluting and Bare Metal Stents in Bypass Graft Lesions [ISAR-CABG]; NCT00611910) (J Am Coll Cardiol 2018;71:1973–82) © 2018 by the American College of Cardiology Foundation.

Percutaneous coronary intervention (PCI) of saphenous vein grafts (SVG) is common, accounting for 5% to 10% of all PCI procedures (1). In patients with previous coronary artery bypass graft surgery (CABG) requiring revascularization, PCI is preferred over redo CABG in the presence of a patent left internal mammary artery graft because of the risks associated with repeat surgery (2,3). Nonetheless, in

Listen to this manuscript's audio summary by *JACC* Editor-in-Chief Dr. Valentin Fuster.

From the [a]Deutsches Herzzentrum München, Technische Universität München, Munich, Germany; [b]DZHK (German Centre for Cardiovascular Research), partner site Munich Heart Alliance, Munich, Germany; [c]Medizinische Klinik und Poliklinik I, Ludwig-Maximilians-Universität München, Munich, Germany; [d]Klinik und Poliklinik Innere Medizin I, Klinikum rechts der Isar, Technische Universität München, Munich, Germany; [e]Herzzentrum der Segeberger Kliniken, Bad Segeberg, Germany; and the [f]University Heart Center Freiburg/Bad Krozingen, Bad Krozingen, Germany. *Drs.Colleran and Kufner contributed equally to this work. Funded by Deutsches Herzzentrum München. Dr. Mehilli has received lecture fees from Abbott Vascular, Terumo, Edwards Lifesciences, Boston Scientific, and Biotronik; and research grants to the institution from Abbott Vascular and Edwards Lifesciences.

ISSN 0735-1097/$36.00 https://doi.org/10.1016/j.jacc.2018.03.456

ABBREVIATIONS AND ACRONYMS

CABG = coronary artery bypass graft surgery

CI = confidence interval

DES = drug-eluting stent(s)

HR = hazard ratio

MI = myocardial infarction

PCI = percutaneous coronary intervention

PES = paclitaxel-eluting stent(s)

SES = sirolimus-eluting stent(s)

SVG = saphenous vein graft(s)

TLR = target lesion revascularization

the long term, PCI is limited by higher rates of repeat revascularization compared with redo CABG (4,5).

In keeping with findings in native coronary artery disease, randomized studies comparing drug-eluting stents (DES) and bare-metal stents for treatment of SVG lesions have consistently shown favorable results for DES with respect to angiographic and clinical restenosis at short- to medium-term follow-up (6-9). The ISAR-CABG (Is Drug-Eluting-Stenting Associated with Improved Results in Coronary Artery Bypass Grafts?) trial was the largest such trial. The primary analysis at 1 year showed superior clinical outcomes for DES compared with bare-metal stents, driven by significantly lower rates of target lesion revascularization (TLR) in the DES group.

SEE PAGE 1983

Existing randomized studies of patients who underwent treatment of SVG lesions with DES versus bare-metal stents are limited by small patient sample size and relatively short duration of follow-up. For example, the RRISC (Reduction of Restenosis In Saphenous vein grafts with Cypher) trial included 75 patients with clinical follow-up at a median of 32 months (6,10), and the SOS (Stenting of Saphenous Vein Grafts) trial included 80 patients with clinical follow-up at a median of 35 months (7,11). Against this background, the aim of the current study was to compare long-term clinical outcomes in patients randomized to treatment of SVG lesions with DES or bare-metal stents.

METHODS

PATIENTS AND STUDY DESIGN. The ISAR-CABG trial is a randomized, multicenter, assessor-blinded, open-label, superiority trial. Details of the trial design and primary results were previously reported (8). In brief, patients age >18 years, with symptoms or objective evidence of myocardial ischemia in the presence of ≥50% de novo stenosis of a SVG were eligible for inclusion. Exclusion criteria included cardiogenic shock and malignancies or other comorbid conditions with life expectancy <12 months. Written informed consent was obtained from patients or their legally authorized representative. Patients were enrolled at 4 centers in Germany between November 2007 and February 2010. The study was conducted in accordance with the provisions of the Declaration of Helsinki and with the International Conference on Harmonization Good Clinical Practices. The trial protocol was approved by the ethics committee of each participating center (Online Appendix). Follow-up to 60 months was done as part of clinical routine, and ethics committee approval was received for the study of long-term follow-up data. The trial is reported in line with CONSORT (Consolidated Standards of Reporting Trials) recommendations for reporting of randomized trials and a CONSORT checklist is reported in the online appendix (Online Table 1).

RANDOMIZATION AND MASKING. Patients who met all inclusion criteria and no exclusion criteria were randomized in the order that they qualified. Immediately after the lesion was crossed with a guidewire, patients were randomly allocated (1:1:1:3) to receive either DES (1 of 3 types: permanent-polymer paclitaxel-eluting stents [PES] [Taxus; Boston Scientific, Marlborough, Massachusetts], permanent-polymer sirolimus-eluting stents [SES] [Cypher; Cordis, Johnson & Johnson/Cardinal Health, Milpitas, California], or biodegradable-polymer SES [Yukon; Translumina Therapeutics LLP, New Delhi, India]) or bare-metal stents. The choice of bare-metal stent was at the operator's discretion. In each participating center, allocation to treatment was made by means of sealed, opaque envelopes containing a computer-generated sequence. Randomization was stratified for each participating center. Time zero was defined as the time of randomization, at

Dr. Schüpke has received consulting fees from Bayer Vital; lecture fees from Daiichi-Sankyo; and institutional grants from the German Center for Cardiovascular Research (DZHK). Dr. Joner has received speaker fees from Biotronik, Boston Scientific, AstraZeneca, Coramaze, and OrbusNeich; and research grants from Biotronik and the European Society of Cardiology. Dr. Abdel-Wahab has received proctor fees from Boston Scientific. Dr. Neumann has received speaker honoraria, consultancy fees, and research grants to the institution from Daiichi-Sankyo, AstraZeneca, Sanofi, Bayer, The Medicines Company, Bristol-Myers Squibb, Novartis, Roche, Boston Scientific, Biotronik, Medtronic, Edwards Lifesciences, Pfizer, and Boehringer Ingelheim. Dr. Schunkert has received honoraria from AstraZeneca, Bayer Vital, Merck Sharp & Dohme, Novartis, Servier, Sanofi, Boehringer Ingelheim, Daiichi-Sankyo, Amgen, and Pfizer; and consulting fees from AstraZeneca, Amgen, and Merck Sharp & Dohme. Prof. Laugwitz holds patents related to drug-eluting stent technologies. Dr. Byrne has received lecture fees from B. Braun Melsungen, Biotronik, and Boston Scientific; and grants to the institution from Boston Scientific and HeartFlow. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received November 27, 2017; revised manuscript received February 14, 2018, accepted March 13, 2018.

TABLE 1 Baseline Patient Characteristics According to Treatment Group

	DES Group (n = 303)	BMS Group (n = 307)
Age, yrs	71.4 ± 9.0	71.5 ± 9.3
Female	40 (13)	48 (16)
Diabetes mellitus	111 (37)	107 (35)
Insulin-dependent	39 (13)	34 (11)
Hypertension	216 (71)	223 (73)
Hyperlipidemia	268 (88)	264 (86)
Current smoker	25 (8)	18 (6)
Prior myocardial infarction	170 (56)	168 (55)
Clinical presentation		
Unstable angina pectoris	115 (38)	124 (40)
Stable angina pectoris	188 (62)	183 (60)
No. of diseased coronary vessels		
1 vessel	3 (1)	5 (2)
2 vessels	12 (4)	18 (6)
3 vessels	288 (95)	284 (93)
Saphenous vein graft age, yrs	13.4 ± 5.6	13.7 ± 5.2
Serum creatinine, μmol/l	106.1 ± 62.8	103.4 ± 46.0
Left ventricular ejection fraction, %*	49.2 ± 12.2	49.5 ± 13.8
Multiple treated lesions	69 (22.5)	74 (24.4)

Values are mean ± SD or n (%). There were no significant differences in baseline clinical characteristics between treatment groups ($p > 0.05$ for all comparisons).
*Data were available for 83% of study sample (n = 505).
BMS = bare-metal stent; DES = drug-eluting stent.

TABLE 2 Baseline Lesion and Procedural Characteristics According to Treatment Group

	DES Group (n = 386 Lesions)	BMS Group (n = 385 Lesions)
Recipient vessel		
Left anterior descending coronary artery	123 (32)	118 (31)
Left circumflex coronary artery	134 (35)	140 (36)
Right coronary artery	129 (33)	127 (33)
Stenosis localization		
Aortic anastomosis	60 (16)	71 (18)
Coronary anastomosis	47 (12)	39 (10)
Proximal	101 (26)	90 (23)
Medial	108 (28)	98 (25)
Distal	56 (15)	65 (17)
Diffuse	14 (4)	22 (6)
Degeneration score		
0	139 (36)	130 (34)
1	100 (26)	106 (28)
2	77 (20)	76 (20)
3	70 (18)	73 (19)
TIMI flow before the procedure		
0	20 (5)	20 (5)
1	11 (3)	17 (4)
2	65 (17)	66 (17)
3	290 (75)	282 (73)
TIMI flow after the procedure		
0	1 (<1)	6 (2)
1	0 (0)	3 (1)
2	25 (6)	27 (7)
3	360 (93)	349 (91)
Reference vessel diameter, mm	3.36 ± 0.68	3.38 ± 0.73
Lesion length, mm	15.1 ± 10.2	14.3 ± 9.8
Lesion pre-dilatation	227 (65.0)	232 (63.2)
Diameter stenosis, pre, %	65.3 ± 14.8	64.6 ± 16.1
Balloon diameter, max, mm	3.65 ± 0.64	3.72 ± 0.76
Balloon pressure, max, mm Hg	15.0 ± 3.6	15.3 ± 3.8
Diameter stenosis, post, %	11.4 ± 7.4	10.6 ± 13.1
Length of stented segment, mm	26.8 ± 15.4	27.5 ± 13.4

Values are n (%) or mean ± SD. Quantitative coronary angiography analysis based on in-stent analysis. There were no significant differences in baseline lesion and procedural characteristics between treatment groups ($p > 0.05$ for all comparisons).
TIMI = Thrombolysis In Myocardial Infarction; other abbreviations as in Table 1.

which time point patients were considered enrolled in the study and eligible for the intention-to-treat analysis.

PROCEDURES. Details of the study procedure and periprocedural antithrombotic therapy were reported previously (8). Embolic protection devices were rarely used (4% of lesions). Intravascular imaging was not used during the index procedure or during follow-up. After the intervention, lifelong aspirin and dual antiplatelet therapy for a minimum of 6 months were recommended for all patients, with other cardiac medications according to the judgment of the treating physician. All patients were followed up yearly by phone or office visit ≤60 months.

OUTCOMES. The primary endpoint was the combined incidence of death, myocardial infarction (MI), or TLR at 5 years post-index intervention. Secondary endpoints of interest in the present analysis were the combined incidence of death and MI, TLR, and definite stent thrombosis. MI was defined as previously reported (8). TLR was defined as any repeat percutaneous intervention of the target lesion, or bypass surgery involving the vessel supplied by the target venous graft in the presence of angiographic restenosis (in-segment diameter stenosis ≥50% in quantitative angiography analysis) and either symptoms of ischemia or a positive functional study corresponding to the area served by the target graft, or diameter stenosis of 70% or more at follow-up angiography in the absence of documented clinical or functional ischemia. Definite stent thrombosis was defined according to Academic Research Consortium criteria. Clinical 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 to 75th percentiles). Categorical data are presented as counts or proportions (%). Data distribution was

TABLE 3 Clinical Results at 5 Years According to Treatment Group

	DES Group (n = 303)	BMS Group (n = 307)	Hazard Ratio (95% Confidence Interval)	p Value
Death	78 (27.5)	84 (28.9)	0.94 (0.69–1.28)	0.70
Cardiac death	48 (18.2)	53 (20.1)	0.92 (0.62–1.36)	0.67
Myocardial infarction	22 (8.2)	28 (9.9)	0.76 (0.44–1.36)	0.37
ST-segment elevation myocardial infarction	4 (1.5)	6 (2.0)	0.67 (0.19–2.37)	0.53
Definite stent thrombosis	5 (2.0)	1 (0.4)	5.11 (0.60–44.72)	0.14
Target lesion revascularization	84 (33.1)	69 (25.5)	1.20 (0.87–1.64)	0.27
Repeat PCI	84 (33.1)	67 (24.8)	1.24 (0.90–1.71)	0.19
Repeat coronary artery bypass surgery	0 (0.0)	3 (1.1)	–	0.99
Target vessel revascularization*	100 (39.5)	89 (32.9)	1.09 (0.82–1.45)	0.57
Death or myocardial infarction	93 (32.8)	108 (36.6)	0.85 (0.64–1.12)	0.24
Death, myocardial infarction, target lesion revascularization	159 (55.5)	157 (53.6)	0.98 (0.79–1.23)	0.89

Values are n (%) unless otherwise indicated. Percentages are Kaplan-Meier estimates. *Target vessel revascularization includes all revascularization procedures in the target graft, including target lesion revascularization.
PCI = percutaneous coronary intervention; other abbreviations as in Table 1.

tested for normality using the Kolmogorov-Smirnov test for goodness of fit. For patient-level data, differences between groups were checked for significance using the Student's *t*-test or Wilcoxon rank sum test (continuous data) or the chi-square or Fisher exact test where the expected cell value was <5 (categorical variables). For lesion-level data, differences between groups were checked for significance using generalized estimating equations in order to address intrapatient correlation in patients who underwent multilesion intervention (12). Event rates are shown as Kaplan-Meier estimates. Hazard ratios (HRs), confidence intervals (CIs), and p values were calculated from univariate Cox proportional hazards models or log-rank tests. Statistical analysis was intention-to-treat.

Pre-specified subgroups for assessment of potential treatment differences were defined by age, sex, diabetes status, venous graft age, and degeneration score. The statistical interaction between treatment effect regarding the primary endpoint and each of the baseline characteristics used for subgroup definition was assessed. A 2-sided p value <0.05 was considered to indicate statistical significance. Statistical software S-PLUS, version 4.5 (S-PLUS, Insightful Corp., Seattle, Washington) was used for analysis. Statistical analysis was performed by Dr. Kastrati. The trial is registered at ClinicalTrials.gov (NCT00611910).

RESULTS

In total, 610 patients were enrolled in the study, 303 patients in the DES group (permanent polymer PES [n = 101], permanent polymer SES [n = 101], or biodegradable polymer SES [n = 101]) and 307 patients in the bare-metal stent group. All patients received the allocated stent type. A study flow diagram is shown in Online Figure 1.

Baseline clinical characteristics were similar for both treatment groups (Table 1). There were no significant differences in baseline lesion or procedural characteristics between groups (Table 2). The majority of patients were on statin therapy at hospital discharge: 270 of 293 (92.2%) versus 245 of 265 (92.5%); p = 0.89. A total of 438 (72%) patients underwent planned follow-up angiography at 6 to 8 months post-procedure. Clinical follow-up at 5 years was complete in all but 50 (8.1%) patients, with no significant difference between treatment groups (p = 0.28). Median follow-up duration in patients with incomplete follow-up was 1.1 (0.7 to 2.6) years. Clinical outcomes at 5-year follow-up are shown in Table 3.

PRIMARY ENDPOINT. At 5 years, the primary endpoint occurred in 159 (55.5%) patients in the DES group and 157 (53.6%) patients in the bare-metal stent group (HR: 0.98; 95% CI: 0.79 to 1.23; p = 0.89) (Figure 1A). A significant interaction between treatment effect and time was observed ($p_{interaction}$ = 0.005). Landmark analysis showed a lower rate of the primary endpoint in the DES group compared with the bare-metal stent group at 1 year (HR: 0.64; 95% CI: 0.44 to 0.94; p = 0.02) but a numerically higher rate in the DES group between 1 and 5 years (HR: 1.24; 95% CI: 0.94 to 1.63; p = 0.13). There was no significant difference in outcomes between patients randomized to treatment with each of the 3 different DES types with respect to the primary endpoint (Table 4).

In the pre-specified patient subgroups (defined by age >73.2 or ≤73.2 years, male or female, diabetic or nondiabetic, SVG age >13 or ≤13 years, and SVG degeneration score >1 or ≤1), there was no interaction with treatment effect with respect to the primary endpoint ($p_{interaction}$ >0.13 in all cases).

SECONDARY ENDPOINTS. The composite of death and MI occurred in 93 (32.8%) versus 108 (36.6%) patients (HR: 0.85; 95% CI: 0.64 to 1.12; p = 0.24) at 5 years (Figure 1B). No significant interaction between treatment effect and time was observed ($p_{interaction}$ = 0.57). Landmark analysis showed comparable rates of death or MI in the DES and bare-metal stent groups at 1 year (HR: 0.74; 95% CI: 0.44 to 1.25; p = 0.27) and between 1 and 5 years (HR: 0.89; 95% CI: 0.64 to 1.24; p = 0.49).

At 5 years, TLR occurred in 84 (33.1%) patients in the DES group and 69 (25.5%) patients in the

bare-metal stent group (HR: 1.20; 95% CI: 0.87 to 1.64; p = 0.27) (Figure 2A). A significant interaction between treatment effect and time was observed ($p_{interaction}$ <0.001). Landmark analysis showed lower TLR rates in the DES group at 1 year (HR: 0.49; 95% CI: 0.28 to 0.86; p = 0.01) but higher rates between 1 and 5 years (HR: 2.02; 95% CI: 1.32 to 3.08; p = 0.001) (Figure 2B).

There was no difference between treatment groups in the clinical presentation of patients who underwent TLR: presentation was with acute coronary syndrome in 51 (33.3%) patients, with stable angina in 94 (61.4%) patients, and 8 (5.2%) patients were asymptomatic (p = 0.52). The angiographic morphology of restenotic lesions in patients who underwent TLR was diffuse in 89 (58.9%) and focal in 62 (41.1%); 137 (90.7%) were within the stented area and 14 (9.3%) in the 5-mm segment proximal or distal to the stent, with no difference between the groups (p = 0.40 and p = 0.66, respectively). Forty-nine (32.0%) patients underwent multiple TLR procedures throughout the follow-up period, with no difference between the treatment groups (p = 0.47).

Eighty-four (13.8%) patients underwent TVR that did not involve the target lesion, with no difference between the treatment groups (p = 0.34); of these 20 patients underwent multiple TVR procedures that did not involve the target lesion during the follow-up period, with no difference between the groups (p = 0.29).

SVG occlusion was found in 63 (10.3%) patients within the follow-up period: 32 were managed conservatively, with no difference between the groups (p = 0.72). Of those who underwent revascularization, 17 were treated by TLR and 14 by PCI of the native vessel supplied by the target SVG.

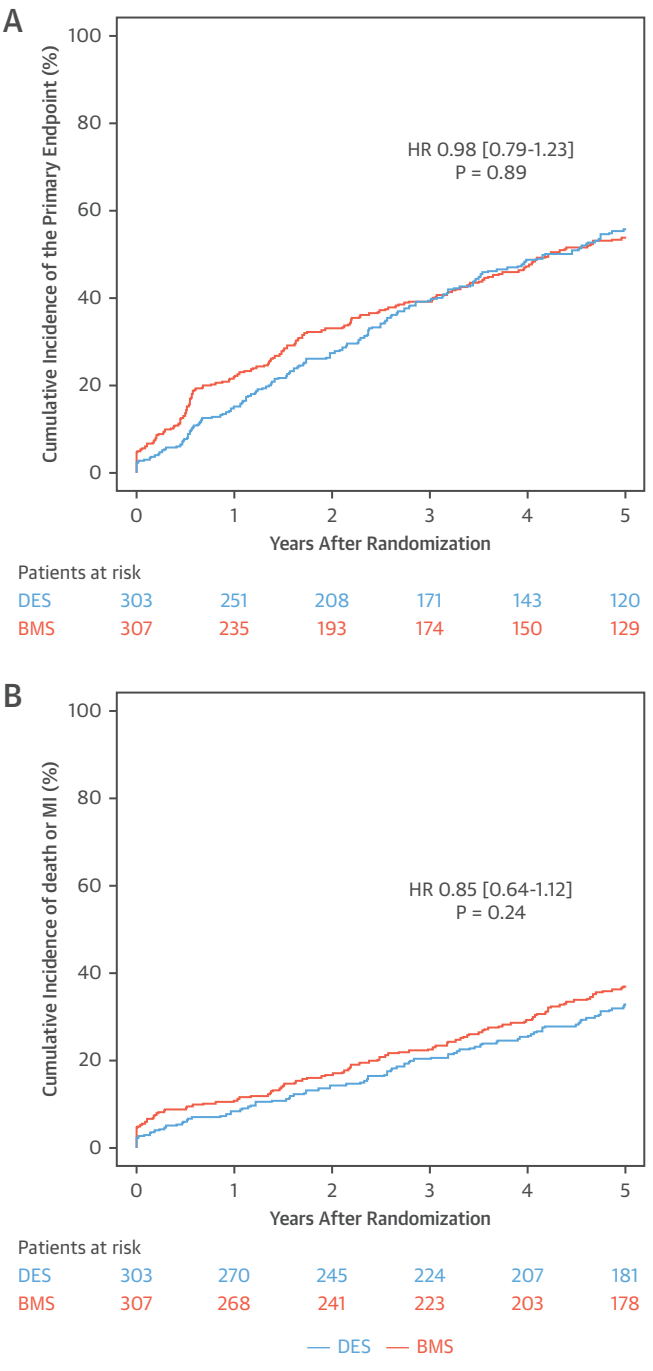
Definite stent thrombosis occurred in 5 (2.0%) versus 1 (0.4%) patient in the DES and bare-metal stent groups, respectively (HR: 5.11; 95% CI: 0.60 to 44.72; p = 0.14).

There was no significant difference between the 3 DES types with respect to any secondary endpoint (Table 4).

DISCUSSION

The current analysis is important as it represents long-term follow-up of the largest randomized trial to date comparing DES and bare-metal stents for the treatment of SVG lesions. The main finding is that in patients with SVG lesions treated by PCI, the advantage of DES over bare-metal stents with respect to clinical outcomes observed at 1 year was

FIGURE 1 Kaplan-Meier Curves of the Primary Endpoint and of Death or MI at 5 Years



(A) Kaplan-Meier curves showing cumulative incidence of the primary endpoint (composite of death, MI, or target-lesion revascularization). **(B)** Kaplan-Meier curves showing cumulative incidence of death or myocardial infarction at 5 years. BMS = bare-metal stent; DES = drug-eluting stent; HR = hazard ratio; MI = myocardial infarction.

TABLE 4 Clinical Results at 5 Years According to DES Type

	Permanent Polymer PES (n = 101)	Permanent Polymer SES (n = 101)	Biodegradable Polymer SES (n = 101)	p Value
Death	20 (21.2)	26 (27.4)	32 (34.0)	0.16
Cardiac death	12 (13.4)	15 (17.0)	21 (24.5)	0.19
Myocardial infarction	9 (9.9)	7 (8.0)	6 (6.6)	0.76
Definite stent thrombosis	1 (1.1)	3 (3.9)	1 (1.1)	0.45
Target lesion revascularization	27 (31.3)	33 (38.4)	24 (29.7)	0.33
Death or myocardial infarction	27 (28.5)	30 (31.5)	36 (38.0)	0.37
Death, myocardial infarction, target lesion revascularization	47 (49.2)	56 (58.6)	56 (58.9)	0.37

Values are n (%). Percentages are Kaplan-Meier estimates.
DES = drug-eluting stent; PES = paclitaxel-eluting stent; SES = sirolimus-eluting stent.

no longer apparent at 5 years, with comparable event rates in both treatment groups at this juncture. This observation was driven by late catch up in TLR rates in the DES group: although at 1 year, the incidence of TLR in the DES group was less than one-half that in the bare-metal stent group, between 1 and 5 years, the rate was more than twice that in the bare-metal stent group (**Central Illustration**). Moreover, observations appeared consistent irrespective of the DES type used.

Systematic long-term follow-up of randomized trials of coronary devices is an important element of device evaluation. Both device approval and clinical practice are often informed by the primary results of randomized trials, frequently assessed at 12 months post-intervention. Although treatment effects at longer-term follow-up are often consistent with primary results, in some instances, important differences are seen. For example, in 2 device trials in recent years, the advantage demonstrated for one device over another with respect to the primary endpoint was lost at longer-term follow-up (13–16). Moreover, safety concerns or advantages related to certain devices may only become apparent during long-term follow-up, after the primary results have been reported (17–19).

There is a paucity of randomized data regarding long-term outcomes of DES versus bare-metal stents for the treatment of SVG lesions. Other published randomized trials examining this question are small with limited duration of follow-up (9–11). At primary analysis, the 75-patient RRISC trial and the 80-patient SOS trial both showed lower angiographic restenosis with DES compared with bare-metal stents at 6 and 12 months, respectively; this translated into lower rates of repeat revascularization at 6 and 18 months, respectively (6,7). More recently, the BASKET-SAVAGE (Basel Kosten Effektivitäts Trial-SAphenous Venous Graft Angioplasty Using Glycoprotein 2b/3a Receptor Inhibitors and Drug-Eluting Stents) trial, which was terminated early after enrolment of 173 patients, also showed improved clinical outcomes at 1 year with DES, mainly driven by lower rates of repeat revascularization (9).

However, at longer-term follow-up, some differences in comparative efficacy were seen. Although follow-up of the SOS trial demonstrated persistently lower repeat revascularization rates in the DES group at a median of 35 months (11), the DELAYED RRISC (Death and Events at Long-term follow-up AnalYsis: Extended Duration of the Reduction of Restenosis In Saphenous vein grafts with Cypher stent) trial showed some evidence of late “catch up” in repeat revascularization in the DES group, resulting in loss of the early efficacy advantage of DES at 32 months (10). In addition, for reasons that are unclear, late all-cause mortality was significantly higher in the SES group in comparison with the bare-metal stent group. The reason for the discordance with respect to late antirestenotic efficacy between these 2 trials is not known, though these results should be interpreted with caution, due to the modest number of included patients. Moreover, although durability of the efficacy advantage for DES over bare-metal stents was reported at 3 years in the BASKET-SAVAGE trial, only one-third of patients completed follow-up to 3 years (9).

Results of the DIVA (Drug-Eluting Stents vs Bare-metal stents In Saphenous Vein Graft Angioplasty) trial with median follow-up of 2.7 years were recently presented (20). Although no difference in clinical outcomes between DES and bare-metal stents was reported at 12 months, in keeping with findings in our study, higher attrition of efficacy of DES was observed during longer-term follow-up.

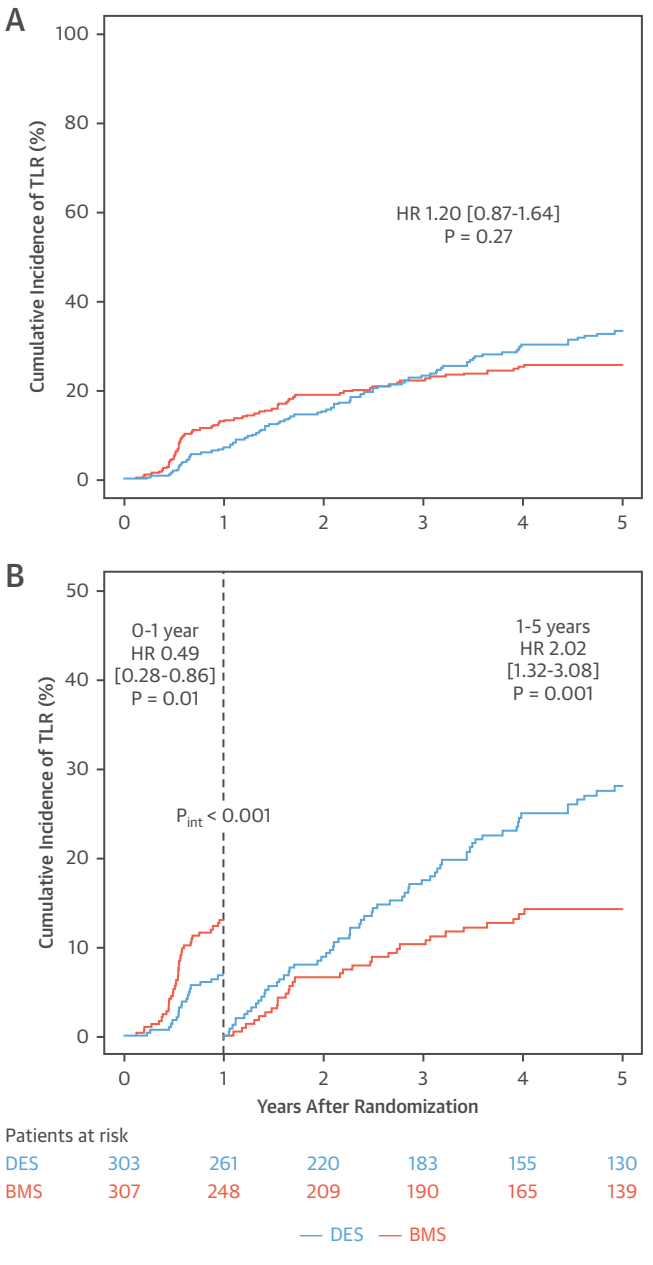
Late catch up in repeat revascularization after DES implantation in native coronary vessels has been described during long-term follow-up of a number of randomized trials. In the SIRTAX LATE (Sirolimus-Eluting Versus Paclitaxel-Eluting Stents for Coronary Revascularization LATE) study, the advantage of SES over PES with respect to major adverse cardiac events and TLR demonstrated at 1 year was lost at 5 years on account of higher late TLR rates in the SES group between 1 and 5 years (16). The SORT-OUT III (Randomized Clinical Comparison of the Endeavor

and the Cypher Coronary Stents in Non-selected Angina Pectoris Patients) trial reported a similar phenomenon, with the superiority of SES over zotarolimus-eluting stents at 1 year in terms of major adverse cardiac events and TLR no longer evident at 5 years due to late catch up in TLR in the SES group (14). Likewise, in the PROTECT (Randomized Study Comparing Endeavor With Cypher Stents) trial, the TLR advantage demonstrated for SES over zotarolimus-eluting stents at 1 and 3 years was no longer present at 4 years due to differential TLR rates between treatment groups after 1 year (19).

The observation of late catch up in TLR is in keeping with findings from preclinical and human imaging studies. In animal models, late catch up in neointimal growth has been demonstrated in DES, but not in bare-metal stent controls (21,22). Angiographic surveillance studies in man have shown late catch up in angiographic restenosis—also termed late luminal creep—in DES. Although studies of patients with serial angiographic follow-up show that neointimal formation peaks 6 months after bare-metal stenting (23), in the case of DES, this process is temporally right-shifted and remains a dynamic ongoing process out to 2 or even 5 years (16,24). In addition, the formation of in-stent neoatherosclerosis may be more accelerated in DES as compared with bare-metal stents (25). Nevertheless, randomized trials enrolling patients with predominantly native vessel disease have shown sustained clinical advantage with DES over bare-metal stents out to 5 to 6 years (26–28) (**Central Illustration**).

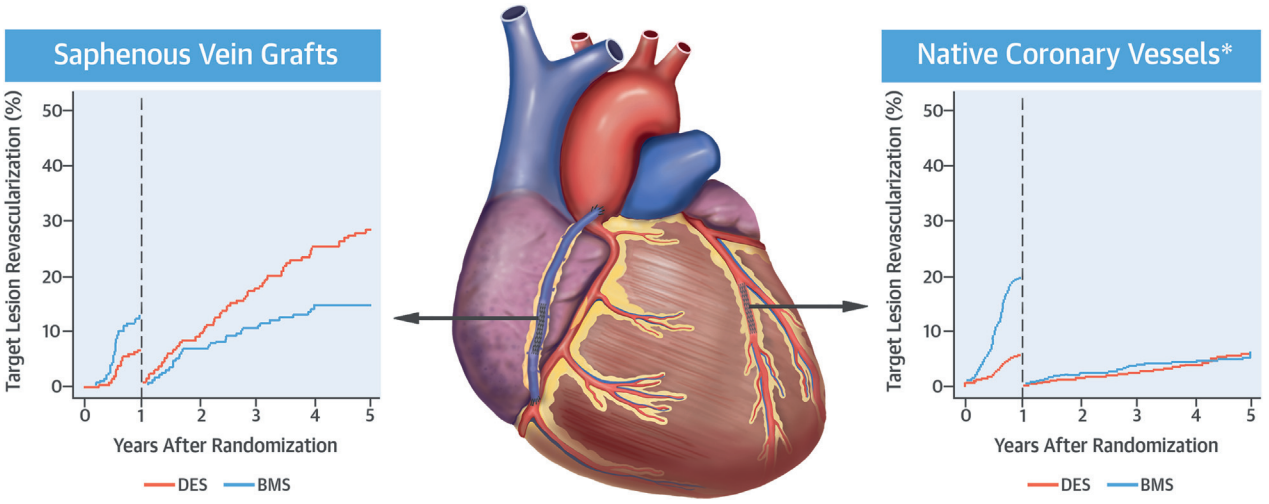
The difference in underlying pathological substrates between SVGs and native arteries may be an important consideration. First, the atherosclerotic process in SVGs is accelerated compared with native coronary arteries. Autopsy studies have shown that in the first year after implantation, the SVG wall becomes thickened by neointimal growth, likely due to exposure to arterial pressure 10-fold higher than venous pressure (29). Second, similar to observations in native coronary arteries, delayed vessel healing is observed with greater frequency in SVGs treated with DES compared with bare-metal stents. However, this seems to be exaggerated in SVGs compared with native coronary arteries (27). This is possibly explained by the differences in the pathology of the underlying plaques: SVGs plaques are typically fibroatheromata with large necrotic cores, and stenting of such lesions generally results in strut penetration of necrotic core. In the case of DES, this contributes to delayed vessel healing, possibly due to longer retention of lipophilic drug (29). It is possible that delayed healing in the DES group may have contributed to the late catch up in TLR observed in the current study. Finally, the

FIGURE 2 Kaplan-Meier Curves of TLR



(A) Kaplan-Meier curves showing cumulative incidence of TLR at 5 years. **(B)** Kaplan-Meier curves with landmark analysis showing cumulative incidence of TLR at 1 year and between 1 and 5 years. TLR = target lesion revascularization; other abbreviations as in **Figure 1**.

CENTRAL ILLUSTRATION **Drug-Eluting Stents Versus Bare-Metal Stents in Saphenous Vein Graft and Native Coronary Lesions: 5-Year Follow-Up**



Colleran, R. et al. J Am Coll Cardiol. 2018;71(18):1973–82.

Kaplan-Meier curves showing differential durability of efficacy of DES versus BMS in vein grafts and native coronary vessels at 1 year and between 1 and 5 years. *The data regarding native coronary vessels are adapted from Kastrati A, Mehilli J, Pache J, et al. Analysis of 14 trials comparing sirolimus-eluting stents with bare-metal stents. N Engl J Med 2007;356:1030–39. BMS = bare-metal stent; DES = drug-eluting stent; SVG = saphenous vein graft.

development of DES and determination of drug dosage was based on observations from implantation in arterial vessels in non-clinical and early human studies.

STUDY LIMITATIONS. A number of important limitations must be taken into account when interpreting the results of this study. First, this is a secondary, non-pre-specified analysis of a randomized trial. Thus, findings are hypothesis-generating. Second, in two-thirds of patients in the DES group, early-generation DES—devices no longer in clinical use—were used. However, the findings observed seemed consistent in both early- and newer-generation DES treatment groups. Moreover, although the newer-generation biodegradable polymer DES investigated is not available for use in the United States, prior clinical trial data shows outcomes comparable to those of Food and Drug Administration-approved newer-generation DES (30,31), and the findings of this study are concordant with findings in the DIVA trial in which predominantly new-generation, Food and Drug Administration-approved DES were used (20), Third, routine surveillance angiography at 6- to 8-month follow-up, which was mandated by the trial protocol, may have elevated rates of TLR in the first year after PCI beyond what might have been observed in the setting of clinical follow-up alone. Finally, information on compliance with medications including dual antiplatelet therapy was not captured. In summary, these data provide a good rationale for, but are no substitute for, a prospective study with new-generation DES versus bare-metal stents and planned long-term follow-up.

CONCLUSIONS

In patients undergoing PCI of SVG lesions, safety outcomes for DES and bare-metal stents remained comparable at long-term follow-up. However, the efficacy advantage of DES over bare-metal stents demonstrated at 1 year was lost at 5-year follow-up due to higher attrition in the DES group.

ADDRESS FOR CORRESPONDENCE: Dr. Robert A. Byrne, Deutsches Herzzentrum München, Technische Universität München, Lazarettstrasse 36, 80636 Munich, Germany. E-mail: byrne@dhm.mhn.de.

PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: Compared with bare-metal stents, DES provide superior patency for treatment of aortocoronary SVG lesions at 1 year but this advantage dissipates over 5 years.

TRANSLATIONAL OUTLOOK: Randomized trials with long-term follow-up are needed to compare the durability of newer-generation DES with bare-metal stents in SVG disease.

REFERENCES

1. Brilakis ES, Wang TY, Rao SV, et al. Frequency and predictors of drug-eluting stent use in saphenous vein bypass graft percutaneous coronary interventions: a report from the American College of Cardiology National Cardiovascular Data CathPCI registry. J Am Coll Cardiol Intv 2010;3:1068–73.

2. Windecker S, Kolh P, Alfonso F, et al. 2014 ESC/EACTS guidelines on myocardial revascularization: the Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J 2014;35:2541–619.

3. Patel MR, Calhoon JH, Dehmer GJ, et al. ACC/AATS/AHA/ASE/ASNC/SCAI/SCCT/STS 2017 appropriate use criteria for coronary revascularization in patients with stable ischemic heart disease: a report of the American College of Cardiology Appropriate Use Criteria Task Force, American Association for Thoracic Surgery, American Heart Association, American Society of Echocardiography, American Society of Nuclear Cardiology, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Computed Tomography, and Society of Thoracic Surgeons. J Am Coll Cardiol 2017;69:2212–41.

4. Morrison DA, Sethi G, Sacks J, et al. Percutaneous coronary intervention versus repeat bypass surgery for patients with medically refractory myocardial ischemia: AWESOME randomized trial and registry experience with post-CABG patients. J Am Coll Cardiol 2002;40:1951–4.

5. Harskamp RE, Beijk MA, Damman P, et al. Clinical outcome after surgical or percutaneous revascularization in coronary bypass graft failure. J Cardiovasc Med (Hagerstown) 2013;14:438–45.

6. Vermeersch P, Agostoni P, Verheye S, et al. Randomized double-blind comparison of sirolimus-eluting stent versus bare-metal stent implantation in diseased saphenous vein grafts: six-month angiographic, intravascular ultrasound, and clinical follow-up of the RRISC trial. J Am Coll Cardiol 2006;48:2423–31.

7. Brilakis ES, Lichtenwalter C, de Lemos JA, et al. A randomized controlled trial of a paclitaxel-eluting stent versus a similar bare-metal stent in saphenous vein graft lesions the SOS (Stenting of Saphenous Vein Grafts) trial. J Am Coll Cardiol 2009;53:919–28.

8. Mehilli J, Pache J, Abdel-Wahab M, et al. Drug-eluting versus bare-metal stents in saphenous vein graft lesions (ISAR-CABG): a randomised controlled superiority trial. Lancet 2011;378:1071–8.

9. Jeger RV. Drug-eluting vs. bare metal stents in saphenous vein grafts: the prospective randomized BASKET-SAVAGE trial. Paper presented at: European Society of Cardiology Congress; August 30, 2016; Rome, Italy.

10. Vermeersch P, Agostoni P, Verheye S, et al. Increased late mortality after sirolimus-eluting stents versus bare-metal stents in diseased saphenous vein grafts: results from the randomized DELAYED RRISC trial. J Am Coll Cardiol 2007;50:261–7.

11. Brilakis ES, Lichtenwalter C, Abdel-karim AR, et al. Continued benefit from paclitaxel-eluting compared with bare-metal stent implantation in saphenous vein graft lesions during long-term follow-up of the SOS (Stenting of Saphenous Vein Grafts) trial. J Am Coll Cardiol Intv 2011;4:176–82.

12. Zeger SL, Liang KY. Longitudinal data analysis for discrete and continuous outcomes. Biometrics 1986;42:121–30.

13. Rasmussen K, Maeng M, Kaltoft A, et al. Efficacy and safety of zotarolimus-eluting and sirolimus-eluting coronary stents in routine clinical care (SORT OUT III): a randomised controlled superiority trial. Lancet 2010;375:1090–9.

14. Maeng M, Tilsted HH, Jensen LO, et al. Differential clinical outcomes after 1 year versus 5 years in a randomised comparison of zotarolimus-eluting and sirolimus-eluting coronary stents (the SORT OUT III study): a multicentre, open-label, randomised superiority trial. Lancet 2014;383:2047–56.

15. Windecker S, Remondino A, Eberli FR, et al. Sirolimus-eluting and paclitaxel-eluting stents for coronary revascularization. N Engl J Med 2005;353:653–62.

16. Raber L, Wohlwend L, Wigger M, et al. Five-year clinical and angiographic outcomes of a randomized comparison of sirolimus-eluting and paclitaxel-eluting stents: results of the Sirolimus-Eluting Versus Paclitaxel-Eluting Stents for Coronary Revascularization LATE trial. Circulation 2011;123:2819–28.

17. Stefanini GG, Kalesan B, Serruys PW, et al. Long-term clinical outcomes of biodegradable polymer biolimus-eluting stents versus durable polymer sirolimus-eluting stents in patients with coronary artery disease (LEADERS): 4 year follow-up of a randomised non-inferiority trial. Lancet 2011;378:1940–8.

18. Jensen LO, Thayssen P, Christiansen EH, et al. 2-year patient-related versus stent-related outcomes: the SORT OUT IV (Scandinavian Organization for Randomized Trials With Clinical Outcome IV) trial. J Am Coll Cardiol 2012;60:1140–7.

19. Wijns W, Steg PG, Mauri L, et al. Endeavour zotarolimus-eluting stent reduces stent thrombosis and improves clinical outcomes compared with cypher sirolimus-eluting stent: 4-year results of the PROTECT randomized trial. Eur Heart J 2014;35:2812–20.

20. Brilakis ES. Drug-Eluting Stents vs Bare Metal Stents In Saphenous Vein Graft Angioplasty (DIVA). Paper presented at: European Society of Cardiology Congress; August 26, 2017; Barcelona, Spain.

21. Carter AJ, Aggarwal M, Kopia GA, et al. Long-term effects of polymer-based, slow-release, sirolimus-eluting stents in a porcine coronary model. Cardiovasc Res 2004;63:617–24.

22. Wilson GJ, Polovick JE, Huibregtse BA, Poff BC. Overlapping paclitaxel-eluting stents: long-term effects in a porcine coronary artery model. Cardiovasc Res 2007;76:361–72.

23. Kimura T, Yokoi H, Nakagawa Y, et al. Three-year follow-up after implantation of metallic coronary-artery stents. N Engl J Med 1996;334:561–6.

24. Byrne RA, Iijima R, Mehilli J, et al. Durability of antirestenotic efficacy in drug-eluting stents with and without permanent polymer. J Am Coll Cardiol Intv 2009;2:291–9.

25. Otsuka F, Byrne RA, Yahagi K, et al. Neoatherosclerosis: overview of histopathologic findings and implications for intravascular imaging assessment. Eur Heart J 2015;36:2147–59.

26. Weisz G, Leon MB, Holmes DR Jr., et al. Five-year follow-up after sirolimus-eluting stent implantation results of the SIRIUS (Sirolimus-Eluting Stent in De-Novo Native Coronary Lesions) trial. J Am Coll Cardiol 2009;53:1488–97.

27. Ellis SG, Stone GW, Cox DA, et al. Long-term safety and efficacy with paclitaxel-eluting stents: 5-year final results of the TAXUS IV clinical trial (TAXUS IV-SR: Treatment of De Novo Coronary Disease Using a Single Paclitaxel-Eluting Stent). J Am Coll Cardiol Intv 2009;2:1248–59.

28. Bonaa KH, Mannsverk J, Wiseth R, et al. Drug-eluting or bare-metal stents for coronary

artery disease. N Engl J Med 2016;375:1242–52.

29. Yazdani SK, Farb A, Nakano M, et al. Pathology of drug-eluting versus bare-metal stents in saphenous vein bypass graft lesions. J Am Coll Cardiol Intv 2012;5:666–74.

30. Kufner S, Byrne RA, Valeskini M, et al. 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. EuroIntervention 2016;11:1372–9.

31. Stefanini GG, Byrne RA, Serruys PW, et al. 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.

KEY WORDS bare-metal stent, drug-eluting stent, long-term follow-up, randomized trial, repeat revascularization, saphenous vein graft

APPENDIX For the trial protocol as well as a supplemental figure and table, please see the online version of this paper.