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ORIGINAL PAPER

Three-year efficacy and safety of new- versus early-generation drug-eluting stents for unprotected left main coronary artery disease insights from the ISAR-LEFT MAIN and ISAR-LEFT MAIN 2 trials

Salvatore Cassese[1] · Sebastian Kufner[1] · Erion Xhepa[1] · Robert A. Byrne[1] · Johanna Kreutzer[1] · Tareq Ibrahim[2] · Klaus Tiroch[3] · Marco Valgimigli[4] · Ralph Tölg[5] · Massimiliano Fusaro[1] · Heribert Schunkert[1,7] · Karl-Ludwig Laugwitz[2,7] · Julinda Mehilli[6,7] · Adnan Kastrati[1,7]

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Abstract

Background In percutaneous coronary intervention (PCI) patients new-generation drug-eluting stent (DES) has reduced adverse events in comparison to early-generation DES. The aim of the current study was to investigate the long-term clinical efficacy and safety of new-generation DES versus early-generation DES for PCI of unprotected left main coronary artery (uLMCA) disease.

Methods The patient-level data from the ISAR-LEFT MAIN and ISAR-LEFT MAIN 2 randomized trials were pooled. The clinical outcomes of PCI patients assigned to new-generation DES (everolimus- or zotarolimus-eluting stent) versus early-generation DES (paclitaxel- or sirolimus-eluting stent) were studied. The primary endpoint was the composite of death, myocardial infarction (MI), target lesion revascularization and stroke (MACCE, major adverse cardiac and cerebrovascular event).

Results In total, 1257 patients were available. At 3 years, the risk of MACCE was comparable between patients assigned to new-generation DES or early-generation DES (28.2 versus 27.5 %, hazard ratio—HR 1.03, 95 % confidence intervals—CI 0.83–1.26; $P = 0.86$). Definite/probable stent thrombosis was low and comparable between new-generation DES and early-generation DES (0.8 versus 1.6 %, HR 0.52, 95 % CI 0.18–1.57; $P = 0.25$); in patients treated with new-generation DES no cases occurred beyond 30 days. Diabetes increased the risk of MACCE in patients treated with new-generation DES but not with early-generation DES ($P_{\text{interaction}} = 0.004$).

Conclusions At 3-year follow-up, a PCI with new-generation DES for uLMCA disease shows comparable efficacy to early-generation DES. Rates of stent thrombosis were low in both groups. Diabetes significantly impacts the risk of MACCE at 3 years in patients treated with new-generation DES for uLMCA disease.

ClinicalTrials.gov Identifiers: NCT00133237; NCT00598637.

Keywords Drug-eluting stent · Everolimus · Left main coronary artery · Paclitaxel · Percutaneous coronary intervention · Sirolimus · Zotarolimus

For the Intracoronary Stenting and Angiographic Results: Drug-Eluting Stents for Unprotected Coronary Left Main Lesions (ISAR-LEFT MAIN) and ISAR-LEFT MAIN 2 Study Investigators.

S. Cassese and S. Kufner contributed equally to this work.

✉ Sebastian Kufner
sebastian.kufner@gmx.de

[1] Deutsches Herzzentrum München, Technische Universität München, Munich, Germany

[2] 1. medizinische Klinik, Klinikum rechts der Isar, Technische Universität München, Lazarettstrasse 36, 80636 Munich, Germany

[3] Department of Cardiology, Helios Klinikum Wuppertal, Universität Witten/Herdecke, Wuppertal, Germany

[4] Department of Cardiology, Bern University Hospital, Bern, Switzerland

[5] Herzzentrum der Segeberger Kliniken Gruppe, Bad Segeberg, Germany

[6] Department of Cardiology, Ludwig-Maximilians-Universität, Munich, Germany

[7] DZHK (German Centre for Cardiovascular Research), Partner Site Munich Heart Alliance, Munich, Germany

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Introduction

Significant unprotected left main coronary artery (uLMCA) disease is reported in nearly 6 % of patients undergoing coronary angiography [1]. Moreover the progressive aging of patients accessing interventional procedures is expected to increase the prevalence of uLMCA disease in the years to come. Percutaneous coronary intervention (PCI) is a valuable option for patients presenting uLMCA disease [2] with proven superiority compared with medical therapy alone [3], and similar survival compared with by-pass surgery [4].

Drug-eluting stents (DES) have significantly improved the outcomes of PCI patients in comparison with bare metal stents [5, 6]. Notwithstanding this, early-generation DES had significant limitations, and late stent failure remained a clinical problem. In particular, late stent thrombosis and restenosis continued to accrue with time, especially in case of challenging patterns of coronary artery disease (CAD), such as those involving uLMCA disease [5–7]. The iterative development of new-generation DES has improved the vascular healing after stent implantation [8]. In this regard, large-scale randomized trials and meta-analyses [9, 10] suggest better outcomes with new-generation DES in comparison to BMS and to early-generation DES, with a benefit accruing with time [11]. In these studies, however, the proportion of patients treated with new-generation DES for uLMCA disease was limited. In addition, no specifically designed randomized trial has evaluated whether new-generation DES are superior to early-generation DES in the cohort of patients suffering from uLMCA disease.

Against this background, we report the long-term efficacy and safety of new-generation DES as compared with early-generation DES 3 years after PCI for uLMCA disease in the setting of the randomized Intracoronary Stenting and Angiographic Results: Drug-Eluting Stents for Unprotected Coronary Left Main Lesions (ISAR-LEFT MAIN) and ISAR-LEFT MAIN 2 trials [12, 13].

Methods

Study population and protocol

Full details of the study population, methods, endpoints and primary analyses of the ISAR-LEFT MAIN and ISAR-LEFT MAIN 2 clinical trials have been reported previously [12, 13]. In brief, both trials included patients with symptomatic CAD receiving PCI with DES for uLMCA lesions. The ISAR-LEFT MAIN trial enrolled 607 patients between July 2005 and June 2007 in two German centers. A total of 302 patients received paclitaxel-eluting stent (PES, Taxus—Boston Scientific, Natick, MA, USA) and 305 patients were assigned to receive sirolimus-eluting stent (SES, Cypher—Cordis, Warren, NJ, USA). In ISAR-LEFT MAIN 2, 650 patients were enrolled in three German and one Italian centers between December 2007 and September 2011. A total of 326 patients were assigned to receive everolimus-eluting stent (EES, Xience V—Abbott Vascular, Santa Clara, CA, USA) and 324 patients to zotarolimus-eluting stent (ZES, Resolute—Medtronic Inc., Santa Rosa, CA, USA). In both trials the primary endpoint was the combined incidence of death, myocardial infarction (MI) and target lesion revascularization (TLR). Inclusion criteria were comparable between studies: patients were suitable for enrollment if they were aged >18 years; had ischemic symptoms or evidence of myocardial ischemia (inducible or spontaneous) in the presence of ≥ 50 % de novo stenosis located in uLMCA; had provided written, informed consent. Patients were considered ineligible for the studies if they: had a ST-segment elevation MI within 48 h of symptom onset; a previous coronary bypass surgery; a planned PCI within 30 days from index revascularization; a planned surgery prompting interruption of antiplatelet treatment within 6 months after enrollment; presented with cardiogenic shock, malignancies or other co-morbid conditions with life expectancy <12 months or that may result in protocol non-compliance; had contraindications or known allergy to antiplatelet therapy, stent components or pregnancy (present, suspected or planned). Patient allocation to each of the treatment groups was in equal proportions. Enrolled patients were pretreated with aspirin (325–500 mg) before PCI. After revascularization aspirin was prescribed indefinitely and thienopyridines for at least 24 months. Other cardioactive drugs were prescribed according to standard practice at the time of enrollment. All patients were evaluated at 30 days, 1 and 3 years by phone contact or office visit. As per original protocol, an angiographic follow-up was scheduled for all patients at 6–9 months.

Endpoints and definitions

The primary endpoint of interest in the current analysis is the composite of death, MI, TLR and stroke (MACCE, major adverse cardiac and cerebrovascular event). Other outcomes of interest are the individual components of the primary endpoint, the composite of death, MI and TLR, and stent thrombosis (ST). Study definitions have been described in detail previously [12, 13].

Statistical analysis

The results of the primary analyses have already been published; [12, 13] this additional analysis is exploratory in nature. Baseline descriptive statistics are presented as median (interquartile range) for continuous variables and as counts or proportions (%) for categorical variables. Differences across groups were checked for significance using analysis of variance for continuous data and Chi-squared test (or Fisher's exact test where the expected cell value was <5) for categorical variables. Survival was analyzed according to Kaplan–Meier methods and hazard ratio (HR) with pertinent 95 % confidence interval (95 % CI) was calculated using Cox proportional hazards methods. Landmark analyses explored the occurrence of MACCE, MI and definite/probable ST up to 30 days and between 30-day and 3-year follow-up. For the current report, summary statistics were derived for comparisons of new-generation DES (including patients assigned to receive EES or ZES) versus early-generation DES (including patients assigned to receive PES or SES). Analysis of the primary outcome was also performed for the comparison new-generation DES versus early-generation DES according to subsets of interest [surgical risk (expressed as EuroSCORE tertiles), CAD complexity (expressed as SYNergy between PCI with TAXUS and cardiac surgery–SYNTAX–scores tertiles), diabetic status and lesion location) and the interaction between treatment effect and these covariates was assessed with Cox proportional hazards models. All endpoints of interest for the current analysis were analyzed on an intention-to-treat basis. Statistical software S-PLUS, version 4.5 (S-PLUS, Insightful Corp, Seattle, WA, USA) was used for analysis.

Results

A total of 1257 patients were included in the present analysis: 650 patients were treated with new-generation DES, and 607 patients were treated with early-generation DES (Fig. 1).

Baseline clinical characteristics are described in the Table 1. Briefly, both treatment groups included approximately 30 % diabetics, and a similar number of cases presenting with acute coronary syndrome at the time of index PCI. The group assigned to receive new-generation DES had a higher proportion of active smokers and malignant diseases, had a higher proportion of high-risk surgical candidates (as defined by European System for Cardiac Operative Risk Evaluation scores), and included more patients with reduced left ventricular ejection fraction at baseline as compared to the group assigned to early-generation DES.

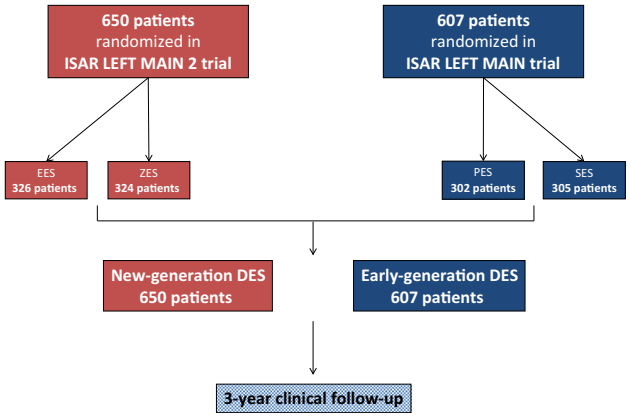

Fig. 1 Flow chart of the study. *ISAR-LEFT MAIN* Intracoronary Stenting and Angiographic Results: Drug-Eluting Stents for Unprotected Coronary Left Main Lesions, *EES* everolimus-eluting stent, *ZES* zotarolimus-eluting stent, *PES* paclitaxel-eluting stent, *SES* sirolimus-eluting stent, *DES* drug-eluting stent

Baseline angiographic and procedural characteristics are presented in the Table 2. Patients treated with new-generation DES had a smaller uLMCA diameter at baseline, a lower proportion of occluded right coronary arteries, a higher proportion of lesions involving the distal uLMCA (with more often trifurcation morphology), and presented higher SYNTAX scores as compared to patients treated with early-generation DES. Patients assigned to receive new-generation DES were predominantly treated with a single-stent "crossover" technique.

Clinical outcomes

Concerning clinical outcomes of patients with uLMCA disease treated with EES versus ZES, 3 years after PCI there was no difference in terms of death ($P = 0.70$), MI ($P = 0.80$), TLR ($P = 0.12$), or stroke ($P = 0.20$). Similarly, patients treated with SES versus PES showed no difference in terms of death ($P = 0.94$), MI ($P = 0.70$), TLR ($P = 0.24$), or stroke ($P = 0.27$) at 3-year follow-up.

At 3 years MACCE had occurred in 179 cases (28.2 %) with new-generation DES and 167 cases (27.5 %) with early-generation DES without significant difference between groups (HR 1.02, 95 % CI 0.83–1.26; $P = 0.86$; Fig. 2). After adjustment for differences in baseline clinical and anatomical characteristics as well as technical features, the 3-year probability of MACCE remained comparable between groups (adjusted HR 0.90, 95 % CI 0.72–1.13; $P = 0.37$). The risk of MACCE within 30 days (2.7 versus 5.3 %, HR 0.49, 95 % CI 0.27–0.88; $P = 0.01$) was lower in patients assigned to receive new-generation DES versus early-generation DES. This difference was due to a significant lower risk of MI within 30 days in patients assigned to receive new-generation DES. Indeed, eight

Table 1 Baseline clinical characteristics

	New-generation DES, $n = 650$	Early-generation DES, $n = 607$	P value
Age, years	70.2 (63.0–77.2)	69.2 (63.0–75.7)	0.16
Female	162 (25)	139 (23)	0.40
Hypertension	449 (69)	419 (69)	0.98
Hypercholesterolemia	470 (72)	466 (77)	0.07
Diabetes mellitus	185 (28)	176 (29)	0.83
Insulin	61 (9)	54 (9)	0.76
Active smoker	91 (14)	61 (10)	0.03
BMI, kg/m^2	27.1 (24.7–29.6)	26.2 (24.2–28.6)	0.001
Creatinine, mg/dl	1 (0.8–1.1)	1 (0.8–1.2)	0.96
ACS at admission	231 (36)	247 (41)	0.06
History of prior MI	197 (30)	161 (27)	0.14
History of prior PCI	343 (53)	292 (48)	0.10
LVEF	56 (43–60)	58 (46–62)	0.04
Malignancies	148 (23)	61 (10)	<0.001
Parsonnet score	10 (5–21)	10 (5–19)	0.16
EuroSCORE	5 (3–7)	4 (2–7)	0.006

DES drug-eluting stent, *BMI* body mass index, *ACS* acute coronary syndrome, *MI* myocardial infarction, *PCI* percutaneous coronary intervention, *LVEF* left ventricular ejection fraction, EuroSCORE European System for Cardiac Operative Risk Evaluation

Table 2 Angiographic and procedural characteristics

	New-generation DES, $n = 650$	Early-generation DES, $n = 607$	P value
RVD of uLMCA, mm	3.6 (3.4–3.9)	3.8 (3.4–4.1)	<0.001
Diseased vessels			
Two	162 (29)	172 (28)	0.86
Three	463 (71)	435 (72)	
Occluded RCA	66 (10)	87 (14)	0.02
Coronary artery dominance			
Right	550 (85)	480 (79)	0.04
Left	58 (9)	74 (12)	
Balanced	42 (6)	53 (9)	
Trifurcation morphology	103 (16)	56 (9)	<0.001
Lesion localization in uLMCA			
Ostium	75 (11)	70 (12)	<0.001
Midshaft	56 (9)	153 (25)	
Distal	519 (80)	384 (63)	
SYNTAX Score			
<23	156 (24)	204 (34)	<0.001
23–32	190 (29)	235 (38)	
>32	304 (47)	168 (28)	
Stenting technique			
Crush-stenting	7 (1)	–	<0.001
Single-stenting	417 (64)	302 (50)	
T-stenting	41 (6)	9 (1)	
Culotte-stenting	185 (29)	296 (49)	
Final kissing-balloon	235 (36)	303 (50)	<0.001
IABP use	15 (2)	8 (1)	0.19

DES drug-eluting stent, *RVD* reference vessel diameter, *uLMCA* unprotected left main coronary artery, *RCA* right coronary artery, *SYNTAX* SYNergy between PCI with TAXUS and cardiac surgery, *IABP* intra-aortic balloon pump

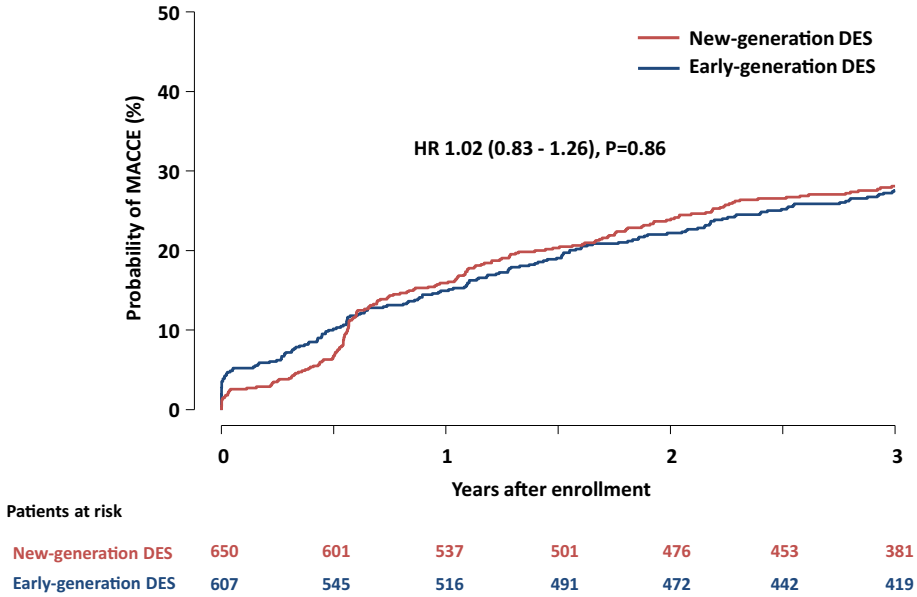

Fig. 2 Cumulative survival analysis curves at 3 years for MACCE by treatment group. *MACCE* major adverse cardiac and cerebrovascular event, *DES* drug-eluting stent

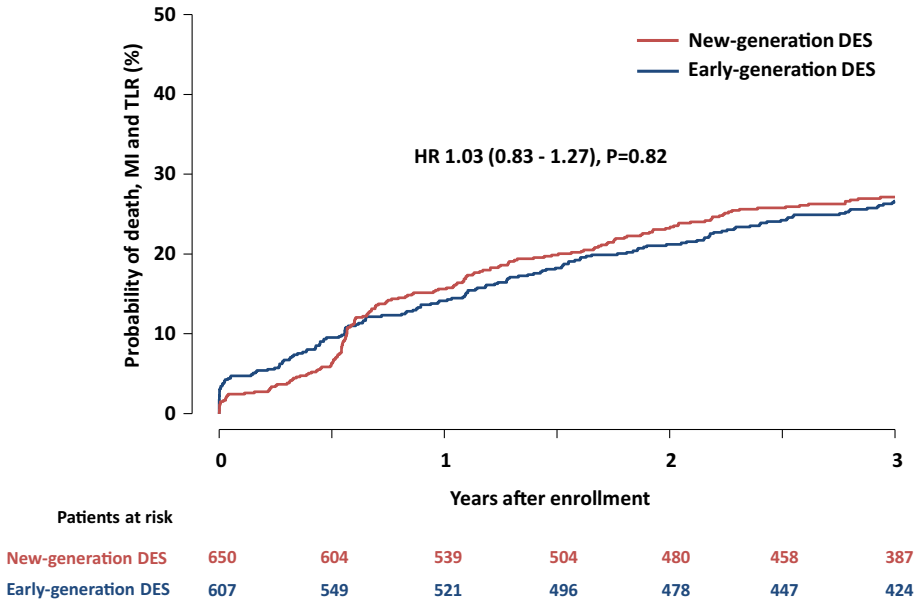

Fig. 3 Cumulative survival analysis curves at 3 years for death, MI and TLR by treatment group. *MI* myocardial infarction, *TLR* target lesion revascularization, *DES* drug-eluting stent

cases (1.3 %) treated with new-generation DES and 24 cases (4.0 %) treated with early-generation DES had experienced MI at 30 days (HR 0.31, 95 % CI 0.14–0.68; $P = 0.003$). Beyond 30 days and up to 3 years after index PCI, the risk of MACCE was comparable between groups (26.3 versus 23.7 %, HR 1.15, 95 % CI 0.91–1.44; $P = 0.24$ for new-generation DES versus early-generation DES, respectively). Similarly, beyond 30 days and up to 3 years after index PCI, the risk of MI was comparable between groups (1.6 versus 1.9 %, HR 0.84, 95 % CI 0.34–2.06; $P = 0.70$ for new-generation DES versus early-generation DES, respectively).

Death at 3 years had occurred in 83 cases (13.2 %) with new-generation DES and 77 cases (12.8 %) with early-generation DES without significant difference between groups (HR 1.04, 95 % CI 0.76–1.41; $P = 0.82$). Cardiac death at 3 years had occurred in 4.7 % of cases with new-generation DES and in 5.6 % of cases with early-generation DES without significant difference between groups (HR 0.84, 95 % CI 0.51–1.39; $P = 0.49$).

TLR at 3 years had occurred in 98 cases (16.2 %) with new-generation DES and in 76 cases (13.3 %) with early-generation DES without significant difference between groups (HR 1.26, 95 % CI 0.94–1.71; $P = 0.12$). Among

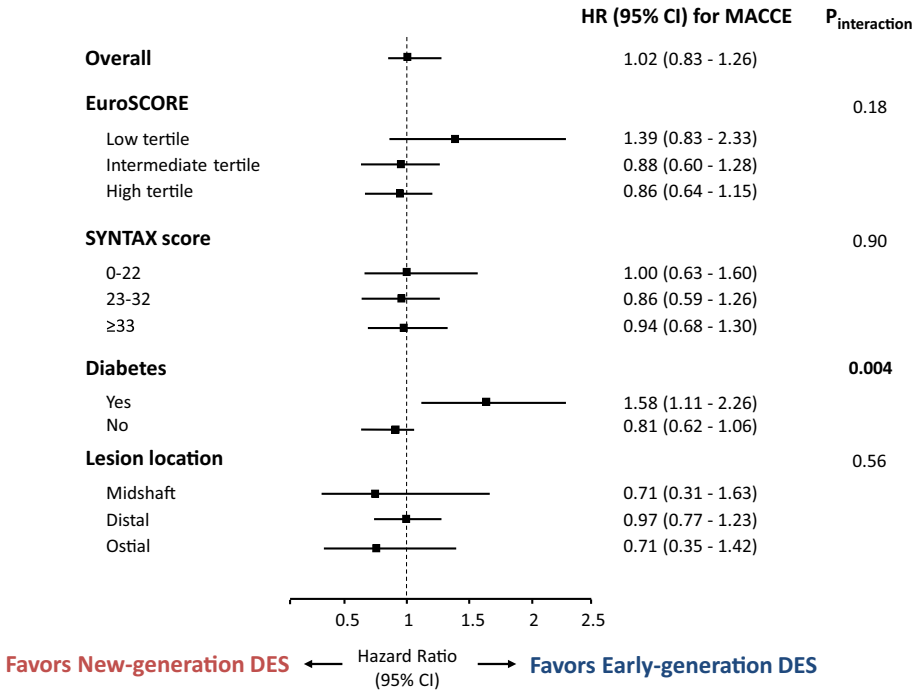

Fig. 4 Risk estimates of MACCE at 3 years according to surgical risk, CAD complexity, diabetic status and lesion location by treatment group. For EuroSCORE and SYNTAX score, the *P* for interaction is calculated by comparing the higher tertile versus the intermediate/lower tertiles; a *P* value <0.05 indicates significance. *MACCE* major adverse cardiac and cerebrovascular event, *CAD* coronary artery disease, *HR* hazard ratio, *CI* confidence interval. Other abbreviations as reported in the Tables

patients undergoing TLR, the proportion of patients treated with repeat PCI (15.2 versus 12.1 %, HR 1.30, 95 % CI 0.95–1.78; $P = 0.09$) or bypass surgery (1.0 versus 2.0 %, HR 0.52, 95 % CI 0.19–1.42; $P = 0.20$) was comparable between patients assigned to receive new-generation DES versus early-generation DES. In patients treated with repeat PCI, balloon angioplasty was performed in 56 % of cases with new-generation DES and 44 % of cases with early-generation DES.

Stroke at 3-year follow-up had occurred in ten cases (1.8 %) treated with new-generation DES and in 14 cases (2.5 %) treated with early-generation DES (HR 0.69, 95 % CI 0.30–1.54; $P = 0.36$) without significant difference between groups.

The composite of death, MI and TLR at 3 years had occurred in 173 cases (27.2 %) with new-generation DES and 161 cases (26.6 %) with early-generation DES without significant difference between groups (HR 1.03, 95 % CI 0.83–1.27; $P = 0.82$; Fig. 3).

Definite/probable ST at 3-year follow-up had occurred in five cases (0.8 %) treated with new-generation DES and in nine cases (1.6 %) treated with early-generation DES (HR 0.52, 95 % CI 0.18–1.57; $P = 0.25$) without significant difference between groups. The risk of definite/probable ST within 30 days (0.8 versus 1.0 %, HR 0.78, 95 % CI 0.24–2.57; $P = 0.69$) was comparable between patients assigned to receive new-generation DES versus early-generation DES. Beyond 30 days and up to 3 years after index PCI, three cases of definite/probable ST (0.6 %) occurred in patients treated with early-generation DES and no case among patients treated with new-generation DES. Definite ST at 3 years had occurred in four cases (0.7 %) treated with new-generation DES and in seven cases (1.2 %) treated with early-generation DES (HR 0.54, 95 % CI 0.16–1.85; $P = 0.33$).

Subgroup analysis

There was no significant interaction in terms of MACCE between the use of new-generation DES versus early-generation DES and surgical risk ($P_{\text{interaction}} = 0.16$), CAD complexity ($P_{\text{interaction}} = 0.90$), or lesion location ($P_{\text{interaction}} = 0.56$). The presence of diabetes significantly modified the risk estimates for MACCE with a higher risk associated with new-generation DES versus early-generation DES in patients with diabetes ($P_{\text{interaction}} = 0.004$, Fig. 4). Among patients with diabetes and concomitant uLMCA disease the risk of MACCE was comparable between PES and SES (25.7 versus 31.6 %, $P = 0.40$) and lower with EES versus ZES (31.0 versus 51.7 %, $P = 0.01$).

Discussion

In the present paper we report the long-term clinical efficacy and safety of new-generation DES versus early-generation DES for percutaneous revascularization of uLMCA disease. The principal findings are that at 3-year follow-up: (1) clinical outcomes are generally favorable in both groups; (2) new-generation DES displays similar efficacy

as compared to early-generation DES; (3) there were no cases of thrombotic stent occlusion with new-generation DES beyond 30 days; and (4) presence of diabetes significantly influences the risk of MACCE associated with new-generation DES, in particular with ZES.

Patients with uLMCA disease represent a high-risk cohort due to the large area of myocardium subtended by such lesions [2]. Guidelines-writing authorities recommend either PCI (class I or IIa recommendation unless high-grade anatomical complexity exists) or bypass surgery (class I recommendation for all anatomies unless surgical ineligibility exists) for uLMCA disease, with details of recommendations varying slightly between the US and Europe [2, 14]. However, the evidence supporting these recommendations relies predominantly on underpowered comparisons of PCI with early-generation DES versus bypass surgery for uLMCA and/or multivessel CAD [15–17]. Early drug-eluting stent platforms represented a breakthrough for percutaneous revascularization of CAD [5]. However, evidence of delayed vascular healing and chronic inflammation at the stented site with inherent risk of late events [6, 18, 19] somewhat dampened the initial enthusiasm for early-generation DES, especially in high-risk subsets such as uLMCA disease. On the one hand, available data suggests comparable survival with early-generation DES (both PES [15] and SES [16, 17]) or bypass surgery in selected cohorts of patients with uLMCA disease. On the other hand, recent meta-analyses have shown that new-generation DES outperforms early-generation DES by reducing the rates of death, MI, ST and repeat revascularization at long-term follow-up [20, 21]. Notwithstanding this, the superiority of new-generation DES in patients with uLMCA disease is open to question [22, 23], since these patients are generally poorly represented in earlier randomized trials.

Considering available evidence, two main issues remain to be addressed. First, the long-term clinical impact of PCI with new-generation DES versus bypass surgery in patients with uLMCA disease is not well investigated. Second, the long-term comparative efficacy and safety of PCI with new-generation versus early-generation DES in patients with uLMCA is largely unknown. In the first case, the results of two randomized trials comparing PCI with new-generation DES versus bypass surgery for uLMCA disease [Evaluation of XIENCE Everolimus Eluting Stent Versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization (EXCEL)—NCT01205776; Coronary Artery Bypass Grafting versus Drug Eluting Stent Percutaneous Coronary Angioplasty in the Treatment of Unprotected Left Main Stenosis (NOBLE)—NCT01496651] are expected to shed more light on this issue in the near future [24]. In the second case, there are no randomized trials specifically designed to investigate the clinical impact of PCI therapy with new-generation DES versus early-generation DES for uLMCA disease. Moreover as early-generation DES is no longer available, such a study is will not be performed. Against this background, the current report aims at investigate this latter topic by means of a pooled analysis of patient-level data from the ISAR-LEFT MAIN and ISAR-LEFT MAIN 2 randomized trials.

The present study demonstrates sustained efficacy of new-generation DES for uLMCA disease at 3-year follow-up, and strengthens the evidence in support of PCI-therapy with contemporary high-performance devices as an attractive and effective alternative to bypass surgery for patients with uLMCA disease [2]. Although the MACCE rate of 28 % observed in this study appears fairly high for a population with a mean age of 70 years, it is consistent with previous reports dealing with this specific patient subset [15]. The overall similar efficacy of new-generation versus early-generation DES for uLMCA observed in the current report supports findings of an earlier registry [25]. Despite the adjustment for baseline confounders, the findings must be interpreted with caution in view of differences in baseline risk between the two groups: patients assigned to treatment with new-generation DES had higher baseline clinical (e.g. higher surgical risk, lower ejection fraction) and anatomical complexity (e.g. higher proportion of distal uLMCA involvement and trifurcation morphology) as compared to those belonging to the early-generation DES group, and in general to previous observations on the same topic [25, 26]. Under these circumstances, the 3-year probability of TLR with new-generation DES observed in the present analysis is noteworthy.

Interestingly in the first 30 days after PCI, patients treated with new-generation DES had fewer adverse events as compared to those treated with early-generation DES. However the higher proportion of patients undergoing intervention with a two-stenting strategy in the early-generation DES group should be taken in consideration [27]. In this regard, the lower risk of MI at 30 days observed with new-generation DES as compared with early-generation DES might be related at least in part to the predominant single-stenting strategy in the new-generation DES group, which has been associated with better outcomes, including lower rates of periprocedural MI, in patients receiving PCI of bifurcation lesions [28].

The very low incidence of ST with new-generation DES for uLMCA disease and the lack of thrombotic events beyond 30 days support the high safety profile of contemporary stent platforms. Although thrombotic events were numerically more frequent in the early-generation DES group, no significant difference was observed. The low incidence of thrombotic stent occlusions is important,

as in patients treated with PCI for uLMCA disease ST is associated with a very high mortality [29].

In the subgroup analysis, diabetic status but not CAD complexity influenced the risk of MACCE at 3 years in patients treated with new-generation DES as compared to early-generation DES for uLMCA disease. In particular, the risk of MACCE at 3 years was increased in those patients assigned to receive ZES. Although exploratory, this analysis deserves further discussion. On the one side, there is conflicting data regarding the efficacy of new-generation DES in patients with diabetes mellitus and CAD [30, 31], though the evidence in patients with uLMCA disease is not exhaustive [32]. On the other side, the sub-optimal performance of "limus"-based DES in diabetics has historically been ascribed to a potential resistance of "limus" drugs at their target receptor mTOR—the mammalian target of rapamycin—in the presence of hyperglycemia [33, 34]. The present data cannot definitively point-out whether bypass surgery should be the therapy of choice in diabetics with uLMCA disease regardless of the CAD complexity. However, the discrimination of patients with uLMCA disease suitable for PCI based on CAD complexity alone appears insufficient. In addition, dedicated randomized trials should explore a differential, device-specific impact of DES in diabetics with uLMCA disease.

Study limitations

The current report has some important limitations. First, the design of the ISAR-LEFT MAIN and ISAR-LEFT MAIN 2 randomized trials was a comparative efficacy trial with 6–9 month angiographic surveillance and a primary clinical outcome at 1 year. Accordingly, the present comparison at 3 years should be regarded as post hoc and hypothesis generating. Second, the original trials were not specifically powered for the detection of differences in rare clinical outcomes. Therefore, the results of this analysis must be interpreted with caution and findings should be verified in larger trials powered for such infrequent endpoints. Third, the study compares stent platforms implanted in different historical periods with possible differences in the ancillary therapies. Fourth, though adjustment in the risk estimate calculation for primary outcome baseline differences exist between groups with more complex patients treated with new-generation DES. Fifth, as efficacy and safety among different drug-eluting stent platforms may vary, the results observed in this analysis might not be generalizable to other devices. In addition, although early-generation DES is no longer available in contemporary practice, long-term follow-up of such stent platforms and comparisons with new-generation DES remain of broad clinical interest. Finally, although all treatment groups received a recommendation for dual antiplatelet therapy after index PCI, data relating to compliance or actual duration of dual antiplatelet therapy received was not available.

Conclusions

At 3-year follow-up a strategy of PCI with new-generation DES as compared with early-generation DES for uLMCA disease displays comparable efficacy. Late safety outcomes for new-generation DES are particularly encouraging. The presence of diabetes but not the anatomical complexity of coronary artery disease significantly impacts the risk adverse events in patients assigned to receive new-generation DES. Whether the long-term efficacy and safety of contemporary drug-eluting-stent platforms is comparable to bypass surgery in patients with uLMCA disease remains to be determined in specifically designed randomized trials.

Compliance with ethical standards

Conflict of interest RAB reports receiving lecture fees from B. Braun, Biotronik and Boston Scientific. The other authors declare no conflicts of interest.

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