Received: 23 July 2019 | Revised: 21 October 2019 | Accepted: 21 November 2019

DOI: 10.1002/ccd.28638

Check for updates

WILEY

ORIGINAL STUDIES

Efficacy of drug-coated balloon angioplasty in early versus late occurring drug-eluting stent restenosis: A pooled analysis from the randomized ISAR DESIRE 3 and DESIRE 4 trials

Tobias Koch MD[1] | Salvatore Cassese MD, PhD[1] | Erion Xhepa MD[1] | Katharina Mayer MD[1] | Ralph Tölg MD[3] | Petra Hoppmann MD[2] | Karl-Ludwig Laugwitz MD[2,4] | Robert A. Byrne MB, BCh, PhD[1,4] | Adnan Kastrati MD[1,4] | Sebastian Kufner MD[1]

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

[2]I. Medizinische Klinik, Klinikum rechts der Isar, Technische Universität München, Munich, Germany

[3]Herzzentrum der Segeberger Kliniken GmbH, Bad Segeberg, Germany

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

Correspondence
Sebastian Kufner, Deutsches Herzzentrum München, Technische Universität München, Lazarettstrasse 36, 80636 Munich, Germany.
Email: sebastian.kufner@gmx.de

Abstract

Background: Whether there exist differences concerning clinical outcomes between patients presenting with early versus late DES-ISR undergoing treatment with drug-coated balloons (DCB) remains a scientific knowledge gap.

Methods: This is a pooled analysis including patients with DES-ISR assigned to treatment with DCB in the setting of the ISAR DESIRE 3 and 4 trials. Clinical outcomes were evaluated according to time of occurrence of ISR after DES implantation, in patients presenting with early (≤12 months) versus late DES-ISR (>12 months) undergoing treatment with DCB. The primary endpoint of this analysis was major adverse cardiac event (MACE), defined as the combined incidence of death, myocardial infarction and target lesion revascularization (TLR) at 12 months after DCB treatment. Secondary endpoints included the incidence of death, myocardial infarction, TLR and target lesion thrombosis at 12 months after DCB treatment.

Results: This analysis included 352 patients, 199 patients presented with early-ISR, 153 patients with late-ISR. Concerning the primary endpoint, patients with early-DES-ISR as compared those with late-DES-ISR showed significant higher risk (25.9% vs. 17.0%; p = .04). In a multivariate analysis including diabetic status, clinical presentation, previous coronary bypass graft and diameter stenosis after DCB-treatment, the adjusted hazard ratio showed significant higher risk for MACE of early-DES-ISR as compared to late-DES-ISR (HR_{adj} = 1.8, [95% CI = 1.1–3.0], p = .02).

Conclusion: Clinical outcome at 12 months after treatment of DES-ISR with DCB, showed significant higher clinical event rates in patients presenting with early DES restenosis, as compared with patients presenting with late DES restenosis.

Abbreviations: ACS, acute coronary syndrome; BMS, bare-metal stent; DCB, drug-coated balloon; DES, drug-eluting stent; ISR, in-stent-restenosis; MACE, major adverse cardiac event; MI, myocardial infarction; NSTE-ACS, acute coronary syndromes without ST-segment elevation; OCT, optical-coherence tomography; TLR, target lesion revascularization.

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.
© 2019 The Authors. *Catheterization and Cardiovascular Interventions* published by Wiley Periodicals, Inc.

KEYWORDS
coronary artery disease, drug-coated/eluting balloon, drug-eluting stent, stent restenosis

1 | INTRODUCTION

The high antirestenotic efficacy of contemporary drug-eluting stent (DES) has considerably reduced restenosis rates.[1] However, when DES-in-stent-restenosis (ISR) occurs, treatment remains challenging.[2–4] Both, implantation of another DES or angioplasty with drug-coated balloon (DCB) represent guideline-recommended treatment strategies for patients presenting with DES-ISR.[5] Although, DCB showed inferior clinical efficacy as compared to repeat DES implantation, DCB provide an intuitively attractive treatment strategy with favorable results without the need of implantation of further stent layers.[2,4] Therefore, evaluation of DCB efficacy in specific patient subsets represents a scientific need, to identify patient and lesion subsets best suited for a DCB angioplasty based treatment approach.

Data from intravascular imaging studies suggest that mechanisms of restenosis follow a specific time course within months and years.[6,7] In particular, the high resolution of optical coherence tomography (OCT)-imaging revealed significant differences between lesion morphology of early ISR (time from DES implantation to ISR ≤12 months) and late ISR (time from DES implantation to ISR > 12 months).[8,9] The clinical implication of these findings however, remains unknown. Therefore, we analyzed clinical outcome out to 12 months in patients presenting with early versus late occurring DES-ISR undergoing treatment with DCB in the setting of the randomized ISAR DESIRE 3 and 4 trials.

2 | METHODS

2.1 | Study population

This is a pooled analysis of patients enrolled in the Intracoronary Stenting and Angiographic Results: Optimizing Treatment of Drug Eluting Stent In-Stent Restenosis (ISAR-DESIRE) 3 and 4 trials.[10] Full details of the studies population, methods, endpoints and primary analysis have been previously reported.[10,11] In brief, patients were included if they were older than 18 years; had ischemic symptoms or evidence of myocardial ischemia in the presence of a restenosis ≥50% located in a native vessel DES or proximal or distal margins; provided that written, informed consent by the patient or her/his legally-authorized representative for participation in the study was obtained. Patients with restenosis occurring in a DES eluting sirolimus or an analogue of sirolimus (e.g., biolimus A9, everolimus, or zotarolimus) were considered eligible for participation in the study. Patients with a target lesion located in the left main stem or in a coronary bypass graft; presented with acute ST-elevation myocardial infarction within the preceding 48 hours, cardiogenic shock, severe renal insufficiency malignancies, or life expectancy <12 months; with contraindications or known allergy to antiplatelet therapy, paclitaxel or pregnancy, were considered ineligible for the study.

All patients were evaluated at 1 and 12 months by phone contact or office visit.

The studies were conducted in accordance with the provisions of the Declaration of Helsinki and with the International Conference on Harmonization Good Clinical Practices. The trial protocols were approved by the institutional ethics committee responsible for the participating centers.

2.2 | Study devices endpoints and definitions

Patients who met all of the inclusion criteria and none of the exclusion criteria were randomly assigned to treatment with paclitaxel-eluting balloon (SeQuent Please, B Braun, Melsungen, Germany) in the setting of ISAR DESIRE 3 and paclitaxel-coated balloon (Pantera Lux, Biotronik, Bülach, Switzerland) with or without scoring balloon predilation (AngioSculpt; Spectranetics, Colorado Springs, CO) in the setting of ISAR DESIRE 4.[10,11]

In the current analysis, baseline lesion characteristics were classified according to time interval to occurrence of DES-ISR. Early ISR was defined as any DES-ISR occurring within the first 12 months after DES implantation. Late ISR was defined as any DES ISR occurring later than 12 months after DES implantation.

The primary endpoint of this analysis was the incidence of major adverse cardiac event (MACE), a composite of target lesion revascularization (TLR), death or myocardial infarction (MI) at 12 months. Secondary endpoints included TLR, all-cause death, cardiac death, myocardial infarction and target lesion thrombosis at 12 months in patients with early versus late ISR. Study definitions have been previously described in detail.[10] All events were adjudicated and classified by an event adjudication committee blinded to the treatment groups.

2.3 | Statistical analysis

Baseline descriptive statistics are presented as mean (±*SD*) 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. The

TABLE 1 Baseline patient-, lesion-, angiographic-, and procedural-characteristics in patients presenting with early versus late in-stent restenosis undergoing treatment with drug-coated balloon

	Early-ISR *n* = 199	Late-ISR *n* = 153	*p*-Value
Patients characteristics			
Age (years)	69.5 ± 10.4	68.4 ± 9.8	.32
Female sex	35 (17.6)	26(17.0)	.88
Diabetes mellitus	95 (47.7)	56 (36.6)	**.04**
Hypertension	133 (66.8)	100 (65.4)	.77
Hyperlipidemia	166 (83.4)	123 (80.4)	.46
Current smoker	35 (17.6)	21 (13.7)	.33
Prior MI	90 (45.2)	76 (49.7)	.41
Previous CABG	33 (16.6)	15 (9.8)	.07
Multivessel disease	182 (91.5)	134 (87.6)	.23
Clinical presentation			
NSTE-ACS	32 (16.1)	51 (33.3)	**<.01**
Ejection fraction[a]	53.5 ± 10.5	52.8 ± 10.8	.58
Lesion and procedural characteristics			
Time to ISR (days)	208 ± 51.3	1,086 ± 828.4	**<.01**
Target vessel			.22
LAD	66 (33.2)	62 (41.8)	
LCx	67 (33.7)	42 (27.5)	
RCA	66 (33.2)	47 (30.7)	
Index stent type			**.04**
Biolimus-eluting[b]	24 (12.1)	9 (5.9)	
Everolimus-eluting[c]	107 (53.8)	75 (49.0)	
Sirolimus-eluting[d]	46 (23.1)	54 (35.3)	
Zotarolimus-eluting[e]	22 (11.1)	15 (9.8)	
Restenosis morphology			.06
Focal	124 (62.3)	100 (65.4)	
Multifocal	26 (13.1)	8 (5.2)	
Diffuse	44 (22.1)	43 (28.1)	
Occlusive	5 (2.5)	2 (1.3)	
Bifurcation	57 (28.6)	39 (25.7)	.53
Ostial	55 (27.6)	40 (26.3)	.78
Vessel size (mm)	2.88 ± 0.50	2.87 ± 0.50	.67
Diameter stenosis, pre (%)	66.1 ± 13.3	65.5 ± 15.0	.70
MLD, pre (mm)	0.97 ± 0.41	0.99 ± 0.46	.71
Balloon size (mm)	3.12 ± 0.48	3.12 ± 0.47	.81
Max. balloon pressure (atm)	14.2 ± 3.9	13.8 ± 3.8	.38
MLD, post (mm)[c]	2.33 ± 0.42	2.27 ± 0.43	.19
Diameter stenosis, post (%)[d]	20.3 ± 8.9	22.3 ± 9.7	**.04**

Note: Data shown as mean ± *SD* or number (%); lesion characteristics are based on in-stent analysis. Significant p-values are bold.
Abbreviations: CABG, coronary artery bypass graft; LAD, left anterior descending artery; LCx, left circumflex; LM, left main stem; MI, myocardial infarction; MLD, minimal lumen diameter; NSTE-ACS, acute coronary syndromes without ST-segment elevation; RCA, right coronary artery.
[a]Data available for 260 patients (73.9%).
[b]Biolimus-eluting stents = Biomatrix, Nobori.
[c]Everolimus-eluting stents = Promus, Xience.
[d]Sirolimus-eluting stents = Cypher, Orsiro, polymer-free sirolimus-eluting stent,[23] biodegradable polymer sirolimus-eluting stent,[24] probucol- and sirolimus-eluting stent (Dual-DES).[25]
[e]Zotarolimus-eluting stents = Endeavor, Resolute.

proportional hazards assumption was checked by the method of Grambsch and Therneau and was fulfilled in all cases in which we used Cox proportional hazards models.[12] Concerning the primary outcome analysis an additional multivariate analysis, adjusted for the factors: time of ISR (early ISR vs. late ISR), clinical presentation at index PCI (with or without acute coronary syndrome without ST-segment elevation[NSTE-ACS]), presence or absence of diabetes mellitus, previous CABG and percent diameter stenosis after DCB treatment. Overall *p*-value for interaction was obtained by entering an interaction term between the study groups and the variable defining the subgroup cutting balloon predilation, DCB type (Pantera Lux and Sequent Please). Statistical analysis was performed by using the R 3.5.1 Statistical Package (R Foundation for Statistical Computing, Vienna, Austria).

3 | RESULTS

The current analysis included 352 patients with DES-ISR, assigned to treatment with DCB (137 patients in the setting of ISAR-DESIRE 3 and 252 patients in the setting of ISAR DESIRE 4) with available data concerning time interval to DES-ISR occurrence. One hundred ninety-nine patients presented with early-ISR (≤12 months) and 153 patients presented with late-ISR (>12 months), mean time interval from DES implantation to ISR was 208 ± 51.3 days in early-ISR group as compared to 1,086 ± 828.4 days in the late-ISR-group ($p < .01$). A detailed description of the study cohort is displayed in Supporting Information Figure S1.

Baseline patient, lesion and procedural characteristics in patients presenting with early versus late ISR undergoing DCB treatment are summarized in Table 1. Diabetes mellitus was more frequent in patients with early-ISR as compared to patients with late ISR (47.7% vs. 36.6%, $p = .04$). Concerning clinical presentation at the time point of ISR treatment, acute coronary syndrome without ST-segment elevation (NSTE-ACS) was less frequent in patients presenting with early-ISR as compared to patients presenting with late-ISR (16.1% vs. 33.3%, $p < .01$).

Concerning angiographic acute results after DCB treatment diameter stenosis was lower in patients presenting with early-ISR as compared with patients presenting with late-ISR (20.3 ± 8.9% vs. 22.3 ± 9.7%, $p = .04$). All other baseline patient and lesion characteristic were well balanced throughout the study groups.

3.1 | Clinical results at 12 months

Clinical follow-up at 12 months was complete, except for two patients in each group (98.9%). Clinical results at 12 months are summarized in Table 2.

The primary endpoint, the combined incidence of death, myocardial infarction or TLR, (MACE) at 12 months, occurred significantly more frequent in early-ISR group as compared with late-ISR-group (51 patients in early-ISR-group [25.9%] vs. 26 patients in late-ISR-

TABLE 2 Clinical outcomes at 12 after DCB treatment in patients presenting with early versus late in-stent restenosis

	Early-ISR	Late-ISR	*p*-Value
Clinical outcomes at 12 months			
MACE	51 (25.9)	26 (17.0)	**.04**
Death	5 (2.5)	1 (0.7)	.21
Myocardial infarction	6 (3.0)	2 (1.3)	.29
Target lesion revascularization	47 (24.0)	24 (15.7)	.56
Death or myocardial infarction	11 (5.6)	3 (2.0)	.10
Cardiac death	3 (1.5)	0 (0.0)	.82
Cardiac death or myocardial infarction	9 (4.6)	2 (1.3)	.10

Note: Data shown as number (percentages are Kaplan–Meier estimates); *p*-value from log-rank test.
Abbreviations: ISR, in-stent-restenosis; MACE, major adverse cardiac event.

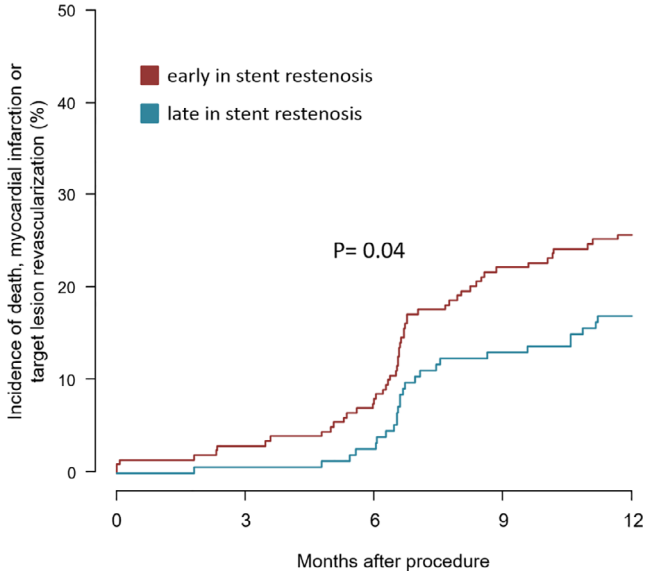

FIGURE 1 Kaplan–Meier analysis Incidence of MACE at 12 months in patients presenting with early-ISR versus late-ISR [Color figure can be viewed at wileyonlinelibrary.com]

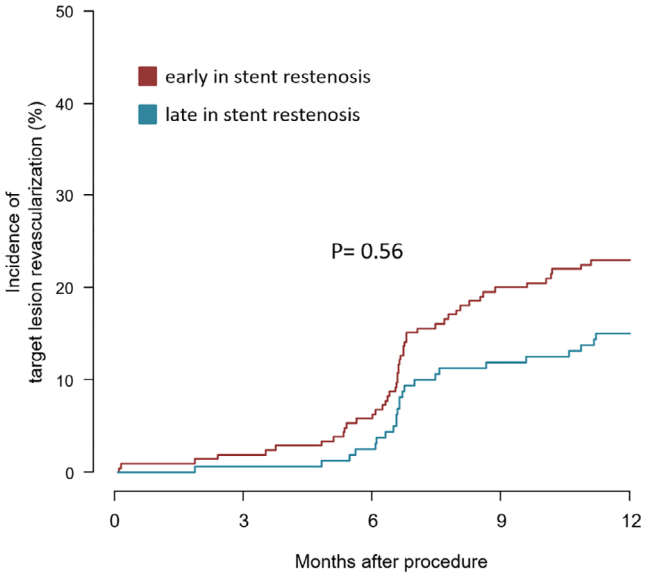

FIGURE 2 Multivariate analysis for the primary endpoint adjusted for the factors: clinical presentation at index PCI; diabetes mellitus; CABG, coronary artery bypass graft; diameter stenosis postdilatation; early-ISR [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 3 Primary endpoint at 12 months after DCB treatment in patients with early versus late in-stent restenosis according to clinical presentation

Clinical outcomes at 12 months	Early-ISR	Late-ISR	*p*-Value Early versus late ISR
With NSTE-ACS	37 (43.8)	16 (19.6)	**.02**
Without NSTE-ACS	14 (22.4)	10 (15.7)	.17
p-Value with versus without NSTE-ACS	**.01**	.56	

Note: Data shown as number (percentages are Kaplan–Meier estimates); *p*-value from log-rank test.
Abbreviations: ISR, in-stent-restenosis; NSTE-ACS, acute coronary syndromes without ST-segment elevation.

group [17.0%], p = .04). Kaplan–Meier curves of the incidence of the primary endpoint are displayed in Figure 1.

A multivariate analysis adjusted for the factors: time to occurrence of ISR after stent implantation (early ISR vs. late ISR), clinical presentation at index PCI (with or without acute coronary syndrome without ST-segment elevation [NSTE-ACS]), presence or absence of diabetes mellitus, previous CABG and percent diameter stenosis after DCB treatment, showed a significant higher risk of MACE in patients presenting with early-ISR (HR_{adj} = 1.8 [95% CI 1.09–2.97], p = .02) and in patients presenting with NSTE-ACS (HR_{adj} = 1.81 [95% CI 1.10–2.98], p = .02). The Results of the multivariate analysis are displayed in Figure 2.

In patients without NSTE-ACS at presentation the primary endpoint, at 12 months, occurred numerically more frequently in early-ISR group as compared with late-ISR-group (14 patients in early-ISR-group [22.4%] vs. 10 patients in late-ISR-group [15.7%], p = .17). In patients with NSTE-ACS at presentation the primary endpoint occurred significantly more frequent in early-ISR group as compared with late-ISR-group (37 patients in early-ISR-group [43.8%] vs. 16 patients in late-ISR-group [29.6%], p = .02). Detailed results are displayed in Table 3. Kaplan–Meier curves of the incidence of the primary endpoint according to treatment group and clinical presentation are displayed in Figure 3.

Results concerning the primary endpoint were consistent across different DCB types used in the ISAR DESIRE 3 and 4 trials ($p_{interaction}$ = 0.44) and different lesion preparation strategies (with or without cutting balloon predilation) ($p_{interaction}$ = 0.49).

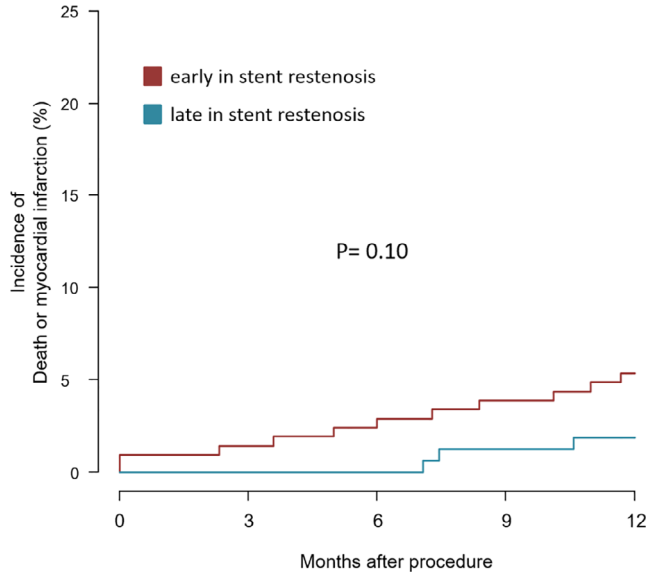

FIGURE 3 Kaplan–Meier analysis, Incidence of MACE at 12 months in patients presenting with early-ISR versus late-ISR according to clinical presentation (with NSTE-ACS [a], without NSTE-ACS [b]) and in patients presenting with NSTE-ACS versus without NSTE-ACS according to time to ISR (early ISR [c], late ISR [d]) [Color figure can be viewed at wileyonlinelibrary.com]

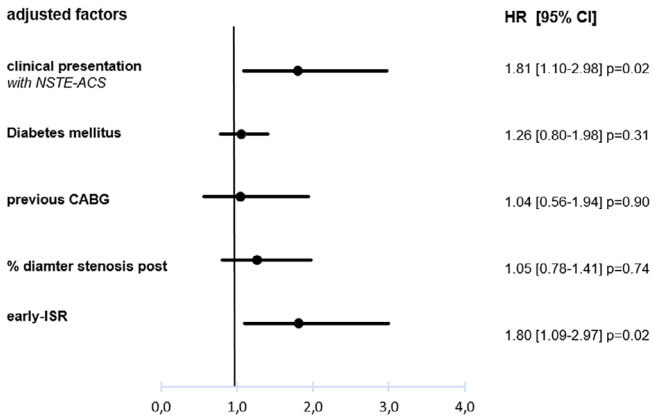

FIGURE 4 Kaplan–Meier analysis Incidence of target lesion revascularization at 12 months in patients presenting with early-ISR versus late-ISR [Color figure can be viewed at wileyonlinelibrary.com]

Concerning secondary endpoints, rates of TLR were numerically higher in early-ISR-group as compared to late-ISR-group with 47 patients in early-ISR-group (24.0%) versus 24 patients in late-ISR-group (15.0%, p = .56). Kaplan–Meier curves of the incidence of TLR are displayed in Figure 4.

Myocardial infarction occurred in 11 patients (3.0%) in early-ISR-group as compared to 3 patients (1.3%) in late-ISR-group (p = .29). Mortality rates were numerically higher in early-ISR-group as compared with late-ISR-group with five patients in early-ISR-group (2.5%) versus one patient (0.7%) in late-ISR-group (p = .10). Kaplan–Meier curves of the combined incidence of death or myocardial infarction are displayed in Figure 5. Concerning safety, the rate of target lesion thrombosis was low, with one event in the early-ISR-group (early-ISR-group 0.5% vs. late-ISR-group 0.0%, p = .90).

4 | DISCUSSION

This analysis evaluates clinical outcomes of patients presenting with early (time interval from DES implantation to ISR ≤12 months) versus late (time interval from DES implantation to ISR >12 months) DES restenosis undergoing treatment with DCB.

The main findings of the current study are: Patients presenting with early DES-ISR show significant higher clinical event rates as compared to patients presenting with late-ISR. The significant difference in the incidence of MACE derives from numerically higher event rates of all clinical endpoints.

Intravascular imaging by OCT has provided further insights in morphological characteristics of DES-ISR. Data suggest that mechanisms of restenosis follow a specific time course within months and years,[6,7] with changing morphological characteristics of DES-ISR over time.[13,14] Consequently, OCT-imaging studies report of significant differences between lesion morphology of early ISR (DES implantation to ISR ≤12 months) and late ISR (DES implantation to ISR > 12 months).[8,9] OCT-findings in late-ISR, were predominantly heterogeneous tissue patterns and showed significant higher incidence of neoatherosclerosis.[8,9] Neoatherosclerosis has been described as novel underlying substrate of DES-ISR reported in up to one of six patients presenting with ISR.[15] This is in line with previous reports suggesting that neoatherosclerosis occurs more often and earlier in DES as compared to BMS.[16] The occurrence of neoatherosclerosis is independently related to the elapsed time since stent implantation.[15] In previous OCT-imaging studies neoatherosclerosis was the predominant finding in all cases with very late ISR >1,080 days after stent implantation.[15] Mean time interval from DES implantation to ISR in the late-ISR group of the current analysis was 1,086 days. DES-ISR with neoatherosclerosis has been reported to result into worse acute results after treatment.

On the one hand this may be potentially related to thin cap fibroatheroma observed in more than 20% of cases with neoatherosclerosis in DES ISR,[16] resulting in slow or no reflow phenomenon after PCI with DCB and consecutive peri-procedural myocardial infarction. Interestingly, in the current analysis, no peri-procedural myocardial infarction was observed in the late-ISR group as compared to two cases in the early ISR group. On the other hand, inferior PCI results in DES-ISR with neoatherosclerosis may be related to insufficient lesion expansion due to severe calcification in lesions with calcified nodule.[15] This is consistent with inferior acute angiographic results, achieved in late-ISR as compared to early ISR group in the current analysis. Interestingly, these findings are not reflected in clinical revascularization rates and overall clinical outcomes.

The by protocol mandated careful lesion preparation with non-compliant-balloon or cutting-balloon devices before DCB treatment in the ISAR Desire 3 and 4 trials could serve as a potential explanation for these findings. Although, residual underexpansion might have

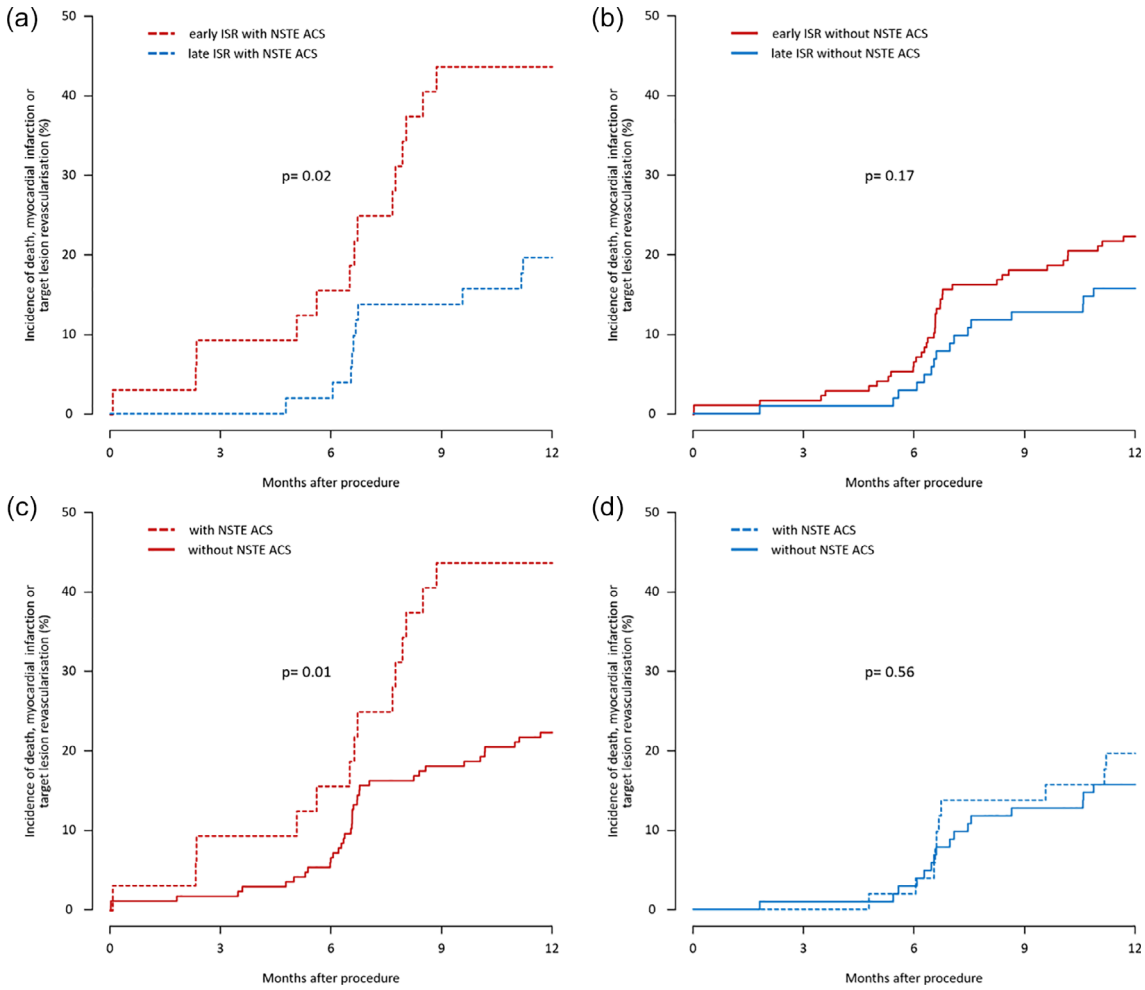

FIGURE 5 Kaplan–Meier analysis Incidence of death or myocardial infarction at 12 months in patients presenting with early-ISR versus late-ISR [Color figure can be viewed at wileyonlinelibrary.com]

contributed to worse acute angiographic results in some cases, aggressive predilation strategies including cutting balloons might have resulted in improved long-term efficacy especially in calcified lesions and underexpanded stents. Of note, clinical outcomes in early and late ISR were consistent across different treatment strategies of both trials, including different DCB-types and lesion preparation strategies with or without scoring balloon predilation.

On the other hand, in the current analysis, patients with early-ISR undergoing treatment with DCB showed significant better acute angiographic results, however higher clinical event rates at 12 months. Concerning the underlying substrate of early ISR, the predominant OCT findings in early-ISR is reported to be homogeneous backscatter.[9] This tissue pattern is well correlated with neointima, rich in smooth muscle cells (SMC), in histopathological correlation studies.[17] This suggests neointimal proliferation as predominant cause of early-ISR. Clinical implications of these findings however, remain questionable. In the current analysis, DCB's predominant paclitaxel based antiproliferative and antimigratory mode of action,[18] is associated with inferior antirestenotic efficacy in early DES-ISR as compared to late-ISR. Only a few studies evaluated the association of tissue characteristics and clinical efficacy of ISR treatment strategies in ISR, reporting favorable results in lesions with homogeneous tissue backscatter of antiproliferative drug-based treatment strategies, repeat DES implantation and DCB as compared to POBA.[19,20] Therefore, the results of the current analysis, showing significant higher clinical event rates at 12 months in early ISR are somewhat surprising. This is particularly true as this difference derives from numerically higher event rates in both, efficacy (TLR) and safety (death or MI) endpoints. Interestingly, these data are consistent with previous reports: A recent intravascular imaging study reporting of numerically higher MACE rates in patients with early ISR as compared to patients with late ISR undergoing DCB treatment. Noteworthy, the presence of a heterogeneous neointima was an independent predictor of MACE in this analysis and was reported in almost 30% of patients presenting with early ISR.[21] In line, Zhao et al reports a significant higher clinical event-rates (MACE) in patients with early-ISR, mainly driven by higher TLR rates, in patients with DES-ISR treated with new-generation DES.[22]

In the current study, patients with early ISR had more often diabetes mellitus and numerically higher prevalence of previous CABG surgery. Patients with early ISR had superior angiographic acute results after DCB treatment. Interestingly, patients with early ISR as compared with late ISR presented more often with stable coronary artery disease. A multivariable

analysis of the current study revealed only early-ISR and clinical presentation with NSTE-ACS as independent predictor of MACE. In line patients with early-ISR presenting with NSTE-ACS were at highest risk for MACE in this analysis Figure 3A,C.

Although, the underlying mechanisms resulting in these findings remain open to question, both currently recommended treatment strategies,[4] repeat implantation of a new-generation DES and treatment with DCB seem to be associated with poorer outcomes in patients presenting with early ISR. Due to the absence of direct comparisons, it still remains unclear, whether or not repeat DES implantation might be related to higher antirestenotic efficacy as compared to DCB in patients presenting with early ISR. Irrespective of treatment strategy, patients with early ISR seem to deserve an increased degree of clinical and/or angiographic surveillance.

5 | LIMITATIONS

This analysis has some limitations that should be acknowledged. First, this is a post hoc, nonrandomized, pooled analysis, therefore current results should be considered as hypothesis generating. Although inclusion and exclusion criteria of the two randomized trials were identical, baseline characteristics featured significant differences. Despite a multivariate analysis adjusting for these factors was performed, other confounders cannot be ruled out.

Due to the lack of intravascular imaging data, current conclusions cannot be supported by intravascular imaging results obtained within the current study. Especially OCT data might have provided further insights in pathology and pathophysiology of the underlying substrates in early and late ISR.

6 | CONCLUSIONS

Clinical outcome at 12 months after treatment of DES restenosis with DCB, showed significant higher clinical event rates in patients presenting with early DES restenosis, as compared with patients presenting with late DES restenosis.

ORCID

Tobias Koch https://orcid.org/0000-0001-9918-9103
Salvatore Cassese https://orcid.org/0000-0002-8668-4313
Erion Xhepa https://orcid.org/0000-0002-0728-2819
Petra Hoppmann https://orcid.org/0000-0001-8103-8315
Sebastian Kufner https://orcid.org/0000-0002-8091-4552

REFERENCES

1. Cassese S, Byrne RA, Tada T, et al. Incidence and predictors of restenosis after coronary stenting in 10 004 patients with surveillance angiography. Heart. 2014;100(2):153-159.
2. Buccheri D, Piraino D, Andolina G, Cortese B. Understanding and managing in-stent restenosis: a review of clinical data, from pathogenesis to treatment. J Thorac Dis. 2016;8(10):e1150-e1162.
3. Kastrati A, Joner M, Kufner S. What treatment should we dare in patients with in-stent restenosis? JACC Cardiovasc Interv. 2018;11(3):284-286.
4. Siontis GC, Stefanini GG, Mavridis D, et al. Percutaneous coronary interventional strategies for treatment of in-stent restenosis: a network meta-analysis. Lancet. 2015;386(9994):655-664.
5. Neumann FJ, Hochholzer W, Siepe M. ESC/EACTS guidelines on myocardial revascularization 2018: the most important innovations. Herz. 2018;43(8):689-694. ESC/EACTS-Leitlinien zur Myokardrevaskularisation 2018.
6. Yonetsu T, Kim JS, Kato K, et al. Comparison of incidence and time course of neoatherosclerosis between bare metal stents and drug-eluting stents using optical coherence tomography. Am J Cardiol. 2012;110(7):933-939.
7. Lee SY, Hong MK, Mintz GS, et al. Temporal course of neointimal hyperplasia following drug-eluting stent implantation: a serial follow-up optical coherence tomography analysis. Int J Cardiovasc Imaging. 2014;30(6):1003-1011.
8. Song L, Mintz GS, Yin D, et al. Characteristics of early versus late in-stent restenosis in second-generation drug-eluting stents: an optical coherence tomography study. EuroIntervention. 2017;13(3):294-302.
9. Jinnouchi H, Kuramitsu S, Shinozaki T, et al. Difference of tissue characteristics between early and late restenosis after second-generation drug-eluting stents implantation—an optical coherence tomography study. Circ J. 2017;81(4):450-457.
10. Kufner S, Joner M, Schneider S, et al. Neointimal modification with scoring balloon and efficacy of drug-coated balloon therapy in patients with restenosis in drug-eluting coronary stents: a randomized controlled trial. JACC Cardiovasc Interv. 2017;10(13):1332-1340.
11. Byrne RA, Neumann FJ, Mehilli J, et al. Paclitaxel-eluting balloons, paclitaxel-eluting stents, and balloon angioplasty in patients with restenosis after implantation of a drug-eluting stent (ISAR-DESIRE 3): a randomised, open-label trial. Lancet. 2013;381(9865):461-467.
12. Grambsch P, Therneau T. Proportional hazards tests and diagnostics based on weighted residuals. Biometrika. 1994;81:515-526.
13. Byrne RA, Joner M, Kastrati A. Stent thrombosis and restenosis: what have we learned and where are we going? The Andreas Gruntzig Lecture ESC 2014. Eur Heart J. 2015;36(47):3320-3331.
14. Habara M, Terashima M, Nasu K, et al. Morphological differences of tissue characteristics between early, late, and very late restenosis lesions after first generation drug-eluting stent implantation: an optical coherence tomography study. Eur Heart J Cardiovasc Imaging. 2013;14(3):276-284.
15. Garcia-Guimaraes M, Antuna P, Maruri-Sanchez R, et al. Calcified neoatherosclerosis causing in-stent restenosis: prevalence, predictors, and implications. Coron Artery Dis. 2019;30(1):1-8.
16. Nakazawa G, Otsuka F, Nakano M, et al. The pathology of neoatherosclerosis in human coronary implants bare-metal and drug-eluting stents. J Am Coll Cardiol. 2011;57(11):1314-1322.
17. Kufner S, Xhepa E, Lutter C, Cassese S, Joner M. Optical coherence tomography in drugeluting stent restenosis: a technique in need of a strategy. Minerva Cardioangiol. 2017;65(1):61-67.
18. Axel DI, Kunert W, Goggelmann C, et al. Paclitaxel inhibits arterial smooth muscle cell proliferation and migration in vitro and in vivo using local drug delivery. Circulation. 1997;96(2):636-645.
19. Tada T, Kadota K, Hosogi S, et al. Association between tissue characteristics evaluated with optical coherence tomography and mid-term results after paclitaxel-coated balloon dilatation for in-stent restenosis lesions: a comparison with plain old balloon angioplasty. Eur Heart J Cardiovasc Imaging. 2014;15(3):307-315.
20. Tada T, Kadota K, Hosogi S, et al. Association between tissue characteristics assessed with optical coherence tomography and mid-term results after percutaneous coronary intervention for in-stent restenosis lesions: a comparison between balloon angioplasty, paclitaxel-

coated balloon dilatation, and drug-eluting stent implantation. Eur Heart J Cardiovasc Imaging. 2015;16(10):1101-1111.
21. Lee JH, Jung HW, Kim JS, et al. Different neointimal pattern in early vs. late in-stent restenosis and clinical outcomes after drug-coated balloon angioplasty—an optical coherence tomography study. Circ J. 2018;82(11):2745-2752.
22. Zhao LZW, Guo C, Fang D, Hao P, Chi Y. Comparison of repeated drug eluting stent for treatment of early and late in-stent restenosis after drug eluting stent implantation. Paper presented at: 25th Great Wall International Congress of Cardiology Asia; October 16-19, 2014; Beijing, China.
23. Mehilli J, Kastrati A, Wessely R, et al. Angiographic restenosis—test equivalence between 2 drug-eluting stents trial I. Randomized trial of a nonpolymer-based rapamycin-eluting stent versus a polymer-based paclitaxel-eluting stent for the reduction of late lumen loss. Circulation. 2006;113(2):273-279.
24. Byrne RA, Kastrati A, Kufner S, et al. 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(20):2441-2449.
25. Massberg S, Byrne RA, Kastrati A, et al. Polymer-free sirolimus- and probucol-eluting versus new generation zotarolimus-eluting stents in coronary artery disease: the intracoronary stenting and angiographic results: test efficacy of sirolimus- and probucol-eluting versus zotarolimus-eluting stents (ISAR-TEST 5) trial. Circulation. 2011;124(5):624-632.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

How to cite this article: Koch T, Cassese S, Xhepa E, et al. Efficacy of drug-coated balloon angioplasty in early versus late occurring drug-eluting stent restenosis: A pooled analysis from the randomized ISAR DESIRE 3 and DESIRE 4 trials. *Catheter Cardiovasc Interv*. 2019;1–8. https://doi.org/10.1002/ccd.28638