Periprocedural myocardial injury according to optical characteristics of neointima and treatment modality of in-stent restenosis

Nejva Nano1 · Alp Aytekin1 · Gjin Ndrepepa1 · Masaru Seguchi1 · Jola Bresha2 · Hector Alfonso Alvarez Covarrubias1 · Philipp Nicol1 · Tobias Lenz1 · Shqipdona Lahu1 · Senta Gewalt · Felix Voll1 · Tobias Rheude1 · Jens Wiebe1 · Heribert Schunkert1,3 · Sebastian Kufner1 · Salvatore Cassese1 · Michael Joner1,3 · Adnan Kastrati1,3 · Erion Xhepa1

Received: 28 January 2022 / Accepted: 6 April 2022 / Published online: 27 April 2022 © The Author(s) 2022

Abstract
Aims Aim of the present study was to investigate the impact of increasing neointimal inhomogeneity and neoatherosclerosis as well as of treatment modality of in-stent restenosis (ISR) on the occurrence of periprocedural myocardial injury (PMI).

Methods and results Patients with normal or stable/falling increased baseline high-sensitivity troponin T (hs-cTnT) undergoing intravascular optical coherence tomography (OCT) and subsequent percutaneous coronary intervention (PCI) of ISR by means of drug-coated balloon (DCB) or drug-eluting stent (DES) were included. Overall, 128 patients were subdivided into low (n = 64) and high (n = 64) inhomogeneity groups, based on the median of distribution of non-homogeneous quadrants. No significant between-group differences were detected in terms of hs-cTnT changes (28.0 [12.0–65.8] vs. 25.5 [9.8–65.0] ng/L; p = 0.355), or the incidence of major PMI (31.2 vs. 31.2%; p = 1.000). Similarly, no differences were observed between DCB- and DES-treated groups in terms of hs-cTn changes (27.0 [10.0–64.0] vs. 28.0 [11.0–73.0] ng/L; p = 0.795), or the incidence of major PMI (28.9 vs. 35.6%; p = 0.566). Additionally, no significant interaction was present between optical neointimal characteristics and treatment modality in terms of changes in hs-cTnT (Pint = 0.432). No significant differences in PMI occurrence were observed between low and high neoatherosclerosis subgroups.

Conclusions In patients undergoing PCI for ISR, there was no association between increasing neointimal inhomogeneity, or increasing expression of neoatherosclerotic changes and occurrence of PMI. PMI occurrence was not influenced by the treatment modality (DCB vs. DES) of ISR lesions, a finding that supports the safety of DCB treatment for ISR.

* Erion Xhepa xhepa@dhm.mhn.de

1 Klinik Für Herz- Und Kreislauferkrankungen, Deutsches Herzcentrum München, Technische Universität München, Lazarettstrasse 36, 80636 Munich, Germany

2 Medizinische Klinik Und Poliklinik Innere Medizin I, Klinikum Rechts Der Isar, Technische Universität München, Munich, Germany

3 DZHK (German Centre for Cardiovascular Research), Partner Site Munich Heart Alliance, Munich, Germany

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Introduction

Although persistent iterations in drug-eluting stent (DES) technology have markedly reduced the occurrence of in-stent restenosis (ISR), such clinical entity still represents a significant burden for patients undergoing percutaneous coronary intervention (PCI) [1]. A recent nationwide registry in the United States found that ISR-PCI represented nearly 10% of the total PCI procedures, with approximately 25% of patients presenting with acute myocardial infarction (MI) [2].

Based on the currently available evidence, European guidelines recommend either drug-coated balloon (DCB) angioplasty or DES implantation as treatment options for ISR [3]. Periprocedural myocardial injury (PMI) represents an intrinsic risk of PCI, which has been reported in a significant proportion of patients undergoing PCI for stable coronary artery disease (CAD) [4–9]. While large periprocedural myonecrosis and MI almost invariably correlate with readily recognizable complications at angiography, PMI is frequently observed following otherwise uneventful PCI procedures. The prognostic implications of PMI remain controversial and data from available studies have reported discordant results [4, 5, 7–10]. Several imaging studies in the setting of native vessel PCI have shown a relationship between PMI and presence of lipid-rich plaques or large necrotic cores, which may predispose to peripheral embolization with resulting microvascular obstruction [11, 12]. A very limited number of studies have investigated the relationship between neointimal tissue characteristics and PMI following ISR-PCI [13, 14]. The use of intravascular optical coherence tomography (OCT) allows a

Keywords Drug-eluting balloon · Drug-eluting stent · In-stent restenosis · Neointimal characterization · Optical coherence tomography · Periprocedural myocardial injury

Abbreviations

CK-MB Creatine kinase myocardial band
DCB Drug-coated balloon
DES Drug-eluting stent
hs-cTnT High-sensitivity cardiac troponin T
ISR N-stent restenosis
OCT Optical coherence tomography
PMI Periprocedural myocardial injury
UDMI Universal definition of myocardial infarction
detailed analysis and classification of neointimal tissue in varying patterns that correlate with different histological substrates [15, 16].

Beside neointimal tissue characteristics, treatment modality may represent an additional mechanism influencing PMI occurrence in the setting of ISR-PCI. Indeed, in order to improve its solubility and prevent clumping of particles on the DCB surface, paclitaxel is mixed with a hydrophilic excipient and, as occasionally observed in preclinical studies, DCB angioplasty may be associated with a risk of distal embolization of particulate balloon coating, consisting of antirestenotic drug and excipient [17].

Against this background, the aim of the present study was to investigate the impact of increasing neointimal inhomogeneity and neoatherosclerosis, as well as of treatment modality (DCB vs. DES) on the occurrence of PMI.

Methods

Patients, procedures and definitions

Patients undergoing intravascular OCT and subsequent DCB angioplasty or DES implantation for ISR at the Department of Cardiology of the German Heart Centre Munich were included. In order to attribute with certainty increases in cardiac biomarkers to the PCI procedure, according to the fourth universal definition of myocardial infarction (UDMI) [6], only patients with normal baseline high-sensitivity troponin T (hs-cTnT) (≤ 99th percentile upper reference limit [URL]) or with stable/falling increased baseline values (≥ 99th percentile URL) were included. PMI was defined according to the criteria of the 4th UDMI and of a recent ESC/EAPCI consensus document [9]. In patients with normal baseline values, an increase of hs-cTnT > 99th percentile URL was considered as minor PMI and an increase of hs-cTnT > 5 × 99th percentile URL was considered as major PMI. In patients with stable/falling increased baseline hs-cTnT, the diagnosis of PMI required in addition a rise of hs-cTnT > 20% of the baseline value. Informed consent was obtained prior to each procedure. Clinical follow-up was performed by office visit, phone contact or structured follow-up letter.

Angiographic and OCT image acquisition and analysis

Baseline and post-procedural angiograms and raw data of OCT image acquisitions were recorded and assessed offline in a core laboratory (ISAResearch Center, Munich, Germany). Quadrant-based neointimal characterization was performed at the frame displaying the maximal % area stenosis and the five preceding and following analyzed frames [15, 18]. Neointimal tissue was categorized as homogeneous or inhomogeneous, the latter category including heterogeneous, layered or neoatherosclerosis quadrants. Atherosclerotic changes of the neointima were defined by the presence of one or more of the following: macrophage infiltration, lipid-laden tissue within the stent or neointimal calcification (Fig. 1). Further details and definitions regarding angiographic and OCT analysis are provided in the Supplementary Appendix.

To investigate the impact of an increasing presence of inhomogeneous quadrants on PMI, the study population was divided in low and high inhomogeneity groups, based on the median of distribution of non-homogeneous quadrants; the high inhomogeneity patient subgroup was further classified in low and high neoatherosclerosis subgroups.

Biochemical measurements

Blood samples for hs-cTnT measurements were collected in tubes containing lithium-heparin anticoagulant at the time of admission, 3–6 h after PCI, at 6 h intervals in case of rising values, and on a daily basis thereafter. The plasma concentration of hs-cTnT was measured using a high-sensitivity assay on a Cobas e411 immunoanalyser based on electrochemiluminescence technology (Roche Diagnostics, Rotkreuz, Switzerland). The limit of blank for this assay—the concentration below which analyte-free samples are found with a probability of 95%—is ≤ 3 ng/L. The functional sensitivity—the lowest analyte concentration that can be reproducibly measured with a coefficient of variation ≤ 10%—is ≤ 13 ng/L. The 99th URL is 14 ng/L. Baseline and peak post-procedural hs-cTnT were used for the current analysis. Other biochemical parameters were measured using standard laboratory methods.

Statistical analysis

Continuous data are presented as mean ± SD or median (25th–75th percentiles) depending on the distribution pattern of the variable. Categorical data are presented as absolute and relative frequencies (%). Differences between groups were compared using the Student’s t test or the Wilcoxon rank sum test for continuous variables and the Pearson $\chi^2$ test (or Fischer’s exact test where any expected cell count of the contingency table was < 5) for categorical variables. To account for the clustered nature of the data, a linear mixed model was used for the analysis of OCT data. The model contained a fixed-effects term (neointimal pattern) and a random intercept as random-effects term for patient in case of frame-level analysis and as nested random-effects term for patient and frame for strut-level analysis. A multivariable model including baseline clinical, angiographic and procedural...
characteristics in addition to the optical pattern of neointima was performed to evaluate the potential independent impact of neointimal pattern of ISR on changes in hs-cTnT. An interaction test was conducted in order to assess whether the relation between optical characteristics of neointima and PMI occurrence is influenced by the treatment modality of ISR. Event-free survival was estimated by the Kaplan–Meier method for each clinical outcome. Hazard ratios (HR) with two-sided 95% confidence intervals (95%CI) were calculated using Cox proportional hazards models. All tests were two-sided and assessed at a significance level of 5%. Statistical analysis was performed using the R 3.6 Statistical Package (R Foundation for Statistical Computing, Vienna, Austria).

Results

Baseline clinical, angiographic and procedural characteristics

Overall, 128 patients were included, with one lesion being imaged/treated per patient. Based on the median of distribution of non-homogeneous quadrants, patients were divided into low ($n=64$) and high ($n=64$) inhomogeneity groups. Baseline clinical, angiographic and procedural characteristics according to neointimal tissue characterization are shown in Table 1 and Table 2. Besides target coronary vessel, no differences in terms of clinical, angiographic or procedural characteristics were observed between the groups. The underlying stent requiring repeat PCI due to presence of ISR was mostly represented by a DES. Treatment modality consisted of DES implantation in 45 (35.2%) and DCB angioplasty in 83 (64.8%) patients. Finally, no significant differences in terms of quantitative coronary analysis (QCA) parameters were observed between the groups. Supplementary Tables 1 and 2 report the clinical, angiographic and procedural characteristics according to treatment modality and Supplementary Tables 3 and 4 report the same characteristics according to extent of neatherosclerosis in the subgroup of patients with high neointimal inhomogeneity.

Optical coherence tomography analysis

OCT morphometric data according to neointimal tissue characteristics are shown in Table 3. Morphometric analysis included a total of 2315 frames (22,338 struts) in the low inhomogeneity group and 2175 frames (21,191 struts) in the high inhomogeneity group. There were no differences in terms of stent diameter/area, lumen diameter/area or neointimal thickness/area between the groups.
OCT morphometric data according to neointimal tissue characteristics are shown in Supplementary Tables 5 and 6 for the subgroups undergoing DCB and DES treatment, respectively, while Supplementary Table 7 shows OCT morphometric data according to the extent of neatherosclerosis in the subgroup of patients with high neointimal inhomogeneity.

**Changes in cardiac biomarkers according to neointimal tissue characteristics and treatment modality**

Table 4 shows changes in hs-cTnT and CK-MB as well as the incidence of minor and major PMI according to the prevalence of inhomogeneous quadrants and/or treatment modality (DCB vs. DES). There were no significant differences in terms of changes in hs-cTnT or CK-MB levels, or minor/major PMI incidence, neither according to prevalence of inhomogeneous quadrants, nor to treatment modality. Even after adjusting for potential confounders, type of neointimal tissue did not independently correlate with changes in hs-cTnT (\( P_{\text{int}} = 0.432 \)). Cumulative frequency distribution curves for baseline, peak post-procedural and changes in hs-cTnT and CK-MB in the low and high inhomogeneity groups are shown in Figs. 2, 3. Finally, no significant differences in terms of peak values or changes in hs-cTnT or CK-MB were detected according to the extent of neatherosclerosis in the subgroup of patients with high neointimal inhomogeneity.

**Clinical outcomes according to optical characteristics of the neointima**

There were no significant differences in terms of MACE (42.7 vs. 28.7%; HR 1.66 [95% CI, 0.85–3.24], \( p = 0.14 \)) (Fig. 4), composite of death or MI (7.5 vs. 4.6%; HR 1.40 [95% CI, 0.24–8.41], \( p = 0.71 \)) (Fig. 5), or clinically driven TLR (40.1 vs. 24.4%; HR 1.84 [95% CI, 0.91–3.74], \( p = 0.092 \)) (Fig. 6) between the groups displaying low and high neointimal inhomogeneity.

### Table 1 Clinical characteristics according to neointimal tissue characterization

|                       | Low inhomogeneity | High inhomogeneity | \( p \) value |
|-----------------------|------------------|------------------|--------------|
| \( N = 64 \)          | \( N = 64 \)     |                  |              |
| Age, years \( 66.8 \pm 10.8 \) | \( 68.3 \pm 8.9 \) | 0.380           |
| Sex, male \( 10 (15.6) \) | \( 13 (20.3) \) | 0.645           |
| Body mass index, kg/ m² \( 28.6 \pm 3.8 \) | \( 28.4 \pm 4.6 \) | 0.787           |
| Current smoker \( 13 (20.3) \) | \( 10 (15.6) \) | 0.645           |
| Ex-Smoker \( 20 (31.2) \) | \( 23 (35.9) \) | 0.708           |
| Hypercholesterolemia \( 43 (67.2) \) | \( 44 (68.8) \) | 1.000           |
| Arterial hypertension \( 61 (95.3) \) | \( 63 (98.4) \) | 0.619           |
| Diabetes mellitus \( 29 (45.3) \) | \( 28 (43.8) \) | 1.000           |
| Oral therapy \( 16 (25.0) \) | \( 16 (25.0) \) | 1.000           |
| Insulin therapy \( 11 (17.2) \) | \( 6 (9.4) \) | 0.298           |
| Previous coronary artery bypass surgery \( 10 (15.6) \) | \( 12 (18.8) \) | 0.815           |
| Previous myocardial infarction \( 34 (53.1) \) | \( 30 (46.9) \) | 0.596           |
| Clinical presentation |                  |                  | 0.206         |
| Silent Ischemia \( 16 (25.0) \) | \( 14 (21.9) \) |                  |
| Stable Angina Pectoris \( 37 (57.8) \) | \( 45 (70.3) \) |                  |
| Unstable Angina Pectoris \( 11 (17.2) \) | \( 5 (7.8) \) |                  |
| Number of diseased coronary arteries |                  |                  | 0.621         |
| One vessel \( 6 (9.4) \) | \( 8 (12.5) \) |                  |
| Two vessels \( 10 (15.6) \) | \( 13 (20.3) \) |                  |
| Three vessels \( 48 (75.0) \) | \( 43 (67.2) \) |                  |
| Multi-vessel disease \( 58 (90.6) \) | \( 56 (87.5) \) |                  |
| Left ventricular ejection fraction, % \( 52.7 \pm 10.0 \) | \( 51.9 \pm 10.3 \) | 0.786           |

Data are shown as counts (%) or mean ± SD (standard deviation).
Discussion

The key findings of this report can be summarized as follows: (1) the incidence of PMI following PCI for ISR is high and broadly comparable to the incidence of PMI following native vessel PCI; (2) there was no association between increasing neointimal inhomogeneity and PMI occurrence; (3) within the high neointimal inhomogeneity subgroup, increasing expression of neoatherosclerotic changes did not impact the occurrence of PMI; (4) PMI occurrence was not influenced by treatment modality (DCB or DES) of ISR lesions.
PMI has been reported in a high proportion of patients following otherwise uneventful PCI procedures for stable CAD [4–8]. However, the reported incidence of PMI varies significantly depending on cardiac biomarker and definition used; moreover, due to discordant study results [4, 5, 7, 8, 10], the prognostic relevance of PMI represents an object of ongoing controversy and the cut-off thresholds for defining PMI have been mostly based on expert consensus opinions [6, 19]. Based on the results of a recent patient-level pooled analysis (PMI incidence according to 4th UDMI of 52.8 and 79.8% if restricted to hs-cTn) [8], a recent consensus document subdivided PMI in prognostically relevant, “major” PMI and “minor” PMI [9]. Applying such definition, the incidence of hs-cTnT-based major PMI in the present study was ≈30%, thereby confirming the relevant occurrence of PMI not only in native vessel but also in ISR-PCI. The number of studies investigating neointimal characteristics and PMI occurrence in the setting of PCI for ISR is extremely limited [13, 14]. Kimura et al. [14] evaluated the relationship between PMI occurrence (defined as CK-MB > 99th percentile URL) and optical characteristics of neointima in 125 patients undergoing PCI for ISR. The authors found a significant association between increased expression of neoatherosclerotic changes and thin-cap fibroatheroma and the occurrence of PMI. In the present study, which combined a detailed, quadrant-based multi-frame neointimal characterization coupled to systematic pre- and post-procedural hs-cTnT measurements, we did not observe any significant differences in terms of major or minor PMI occurrence between patients with high versus those with low neointimal inhomogeneity. Moreover, an increasing expression of neoatherosclerotic changes had no impact on PMI occurrence.

An important finding of the present study was the absence of significant differences in PMI occurrence following treatment of ISR with DCB as compared with treatment with DES. Indeed, DCB angioplasty might be associated with a risk of distal embolization of particulate balloon coating, consisting of antirestenotic drug and excipient [17]. Examination of downstream microvascular beds in preclinical studies has occasionally revealed distal embolization of microparticles of matrix coating. The findings of the present study, which confirm those of a previous report from our group [20], speak against a relevant difference in subclinical myocardial injury and support the safety of DCB use for the treatment of ISR.

Some limitations of the present study should be mentioned. First, this was a single-center, moderate-sized,
Table 4 Biomarker values according to neointimal tissue characterization and/or treatment modality

| | Low inhomogeneity N=64 | High inhomogeneity N=64 | p value |
|---|---|---|---|
| Baseline hs-cTnT, ng/L | 10.0 (7.0–18.2) | 11.5 (8.0–18.0) | 0.697 |
| Peak post-procedural hs-cTnT, ng/L | 40.5 (23.5–99.8) | 40.5 (23.2–80.2) | 0.728 |
| Delta hs-cTnT, ng/L | 28.0 (12.0–65.8) | 25.5 (9.8–65.0) | 0.355 |
| Major PMI | 20 (31.2%) | 20 (31.2%) | 1.000 |
| Minor PMI | 62 (96.9%) | 62 (96.9%) | 1.000 |
| Baseline CK-MB, U/l | 14.9 (11.2–17.4) | 15.3 (12.4–18.0) | 0.416 |
| Peak post-procedural CK-MB, U/l | 14.5 (11.2–20.1) | 14.4 (12.3–18.7) | 0.684 |
| Delta CK-MB, U/l | − 0.2 (− 2.9–3.4) | − 0.1 (− 1.80–2.6) | 0.562 |

Cardiac biomarker values according to treatment modality

| | Drug-coated balloon N=83 | Drug-eluting stent N=45 | p value |
|---|---|---|---|
| Baseline hs-cTnT, ng/L | 10.0 (7.0–18.5) | 12.0 (8.0–18.0) | 0.288 |
| Peak post-procedural hs-cTnT, ng/L | 39.0 (22.5–79.0) | 46.0 (24.0–99.0) | 0.445 |
| Delta hs-cTnT, ng/L | 27.0 (10.0–64.0) | 28.0 (11.0–73.0) | 0.795 |
| Major PMI | 24 (28.9%) | 16 (35.6%) | 0.566 |
| Minor PMI | 80 (96.4%) | 44 (97.8%) | 1.000 |
| Baseline CK-MB, U/l | 15.2 (11.6–17.7) | 14.5 (11.7–17.9) | 0.853 |
| Peak post-procedural CK-MB, U/l | 14.4 (12.3–18.3) | 14.5 (11.4–21.4) | 0.882 |
| Delta CK-MB, U/l | 0.0 (− 1.8–2.8) | − 0.6 (− 2.7–3.0) | 0.653 |

Cardiac biomarker values according to neointimal tissue characterization in the subgroup treated with drug-coated balloon

| | Low inhomogeneity N=38 | High inhomogeneity N=45 | p value |
|---|---|---|---|
| Baseline hs-cTnT, ng/L | 9.5 (7.0–23.5) | 10.0 (7.0–14.0) | 0.985 |
| Peak post-procedural hs-cTnT, ng/L | 44.0 (26.5–113.0) | 30.0 (20.0–66.0) | 0.075 |
| Delta hs-cTnT, ng/L | 31.0 (18.2–82.2) | 18.0 (9.0–55.0) | 0.031 |
| Major PMI | 13 (34.2%) | 11 (24.4%) | 0.462 |
| Minor PMI | 37 (97.4%) | 43 (95.6%) | 1.000 |
| Baseline CK-MB, U/l | 15.2 (11.7–17.5) | 15.3 (11.9–17.8) | 0.936 |
| Peak post-procedural CK-MB, U/l | 14.6 (12.1–20.6) | 14.4 (12.4–17.5) | 0.731 |
| Delta CK-MB, U/l | 0.0 (− 1.8–2.8) | − 0.6 (− 2.7–3.0) | 0.653 |

Cardiac biomarker values according to neointimal tissue characterization in the subgroup treated with drug-eluting stent

| | Low inhomogeneity N=26 | High inhomogeneity N=19 | p value |
|---|---|---|---|
| Baseline hs-cTnT, ng/L | 11.5 (8.0–15.5) | 13.0 (8.0–21.5) | 0.295 |
| Peak post-procedural hs-cTnT, ng/L | 33.5 (22.0–73.0) | 73.0 (33.0–130.0) | 0.061 |
| Delta hs-cTnT, ng/L | 19.0 (11.0–56.2) | 48.0 (17.5–96.0) | 0.215 |
| Major PMI | 7 (26.9%) | 9 (47.4%) | 0.271 |
| Minor PMI | 25 (96.2%) | 19 (100%) | 1.000 |
| Baseline CK-MB, U/l | 14.5 (11.0–15.4) | 15.4 (12.7–20.2) | 0.278 |
| Peak post-procedural CK-MB, U/l | 13.6 (10.9–18.9) | 16.2 (11.7–22.9) | 0.242 |
| Delta CK-MB, U/l | − 1.0 (− 4.1–2.2) | 0.2 (− 1.9–3.2) | 0.304 |

Cardiac biomarker values in the subgroup with high neointimal inhomogeneity, according to the extent of neoatherosclerosis

| | Low neoatherosclerosis N=33 | High neoatherosclerosis N=31 | p value |
|---|---|---|---|
| Baseline hs-cTnT, ng/L | 12.0 (8.0–19.0) | 9.0 (6.0–14.0) | 0.049 |
| Peak post-procedural hs-cTnT, ng/L | 33.0 (26.0–97.0) | 47.0 (22.5–75.5) | 0.989 |
| Delta hs-cTnT, ng/L | 15.0 (6.0–73.0) | 31.0 (14.5–57.5) | 0.295 |
| Major PMI | 10 (30.3%) | 10 (32.3%) | 1.000 |
A retrospective study and selection bias might have occurred in the decision to perform intravascular imaging. Second, treatment modality of ISR was at the discretion of the operator and consequently additional selection bias might have been introduced at this stage. Third, this study was not powered to detect differences in mortality according to the presence or absence of PMI.

### Conclusions

In patients undergoing DCB or DES treatment of ISR lesions, the incidence of PMI is high and broadly comparable to PMI incidence following native vessel PCI. There was no association between increasing neointimal inhomogeneity, or increasing expression of neoatherosclerotic changes, and occurrence of PMI. Despite evidence of distal particulate embolization of DCB matrix coating in preclinical studies, the treatment modality of ISR (DCB- or DES-based)

### Table 4 (continued)

|                          | Low neoatherosclerosis N = 33 | High neoatherosclerosis N = 31 | p value |
|--------------------------|-------------------------------|--------------------------------|---------|
| Minor PMI                | 31 (93.9%)                    | 31 (100%)                      | 0.493   |
| Baseline CK-MB, U/l      | 15.3 (12.4–17.4)              | 15.2 (12.5–18.6)               | 0.697   |
| Peak post-procedural CK-MB, U/l | 14.5 (12.4–19.3)              | 14.4 (11.6–18.3)               | 0.693   |
| Delta CK-MB, U/l         | − 0.1 (− 1.8–3.4)             | − 0.0 (− 1.7–1.2)              | 0.673   |

Data are shown as counts (%) or median [25th–75th percentiles]

### Conclusions

In patients undergoing DCB or DES treatment of ISR lesions, the incidence of PMI is high and broadly comparable to PMI incidence following native vessel PCI. There was no association between increasing neointimal inhomogeneity, or increasing expression of neoatherosclerotic changes, and occurrence of PMI. Despite evidence of distal particulate embolization of DCB matrix coating in preclinical studies, the treatment modality of ISR (DCB- or DES-based)
did not appear to impact the occurrence of PMI, thereby supporting the safety of DCB angioplasty for the treatment of ISR.

**Fig. 4** Two-year cumulative incidence of major adverse cardiac events according to neointimal tissue characterization CI confidence interval, HR hazard ratio, MACE major adverse cardiac events

**Fig. 5** Two-year cumulative incidence of death or myocardial infarction according to neointimal tissue characterization CI confidence interval, HR hazard ratio, MI myocardial infarction

**Fig. 6** Two-year cumulative incidence of target-lesion revascularization according to neointimal tissue characterization CI confidence interval, HR hazard ratio, TLR target-lesion revascularization

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00392-022-02024-z.

**Funding** Open Access funding enabled and organized by Projekt DEAL. None.

**Declarations**

**Conflict of interest** No conflicts of interest related to the present work.

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