Long-term outcomes following paclitaxel-coated balloons versus thin-strut drug-eluting stents for treatment of in-stent restenosis in chronic coronary syndrome (CCS Dragon-Registry)

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ABSTRACT

Background: The long-term outcomes for patients with in-stent restenosis (ISR) presenting with chronic coronary syndrome (CCS) are not well studied.

Aims: We aimed to investigate the outcomes for patients with drug-eluting stents (DES)-ISR and CCS undergoing percutaneous coronary intervention (PCI) with drug-coated balloons (DCB) or thin strut-DES.

Methods: A total of 846 consecutive patients from the Dragon-Registry with CCS and DES-ISR who underwent PCI with thin (strut thickness <100 µm) strut-DES (381 [45%]) or paclitaxel-DCB (465 [55%]) for DES-ISR were enrolled between February 2008 and October 2021. The median follow-up was 1006 (IQR 426–1770) days. The primary outcome was target lesion revascularization (TLR). Secondary outcomes were target vessel revascularization (TVR) and device-oriented composite endpoint (DOCE: cardiac death, TLR, or target vessel myocardial infarction [TV-MI]).

Results: Patients who received DES, compared with those who received DCB, had lower crude rates of TLR (hazard ratio [HR], 0.50 [95% CI, 0.34–0.74]; *P* <0.001), TVR (HR, 0.56 [95% CI, 0.39–0.86]; *P* <0.001), and DOCE (HR, 0.63 [95% CI, 0.45–0.88]; *P* = 0.007). The incidence of cardiac death and TV-MI were similar in both groups. After matching, the observed differences persisted in terms of TLR (HR, 0.54 [95% CI, 0.33–0.88]; *P* = 0.013), TVR (HR, 0.57 [95% CI, 0.41–0.80]; *P* = 0.009) and DOCE (HR, 0.65 [95% CI, 0.42–0.99]; *P* = 0.046) between the DES and DCB groups, respectively.

Conclusions: In long-term follow-up of CCS patients undergoing PCI of ISR, the use of DES was associated with reduced rates of TLR, TVR, and DOCE compared with patients treated with DCB.

Key words: drug-coated balloons, drug-eluting stents, in-stent restenosis, percutaneous coronary intervention

INTRODUCTION

Percutaneous coronary intervention (PCI) with stent implantation is the treatment of choice for significant *de novo* coronary stenosis. However, previously stented coronary arteries may develop in-stent restenosis (ISR), which is the most common cause of stent failure after PCI [1]. A reduction of ≥50% of the luminal diameter within the previously stented segment defines binary angiographic ISR [2]. Such lesions are associated with a higher incidence of adverse cardiac events, and their frequency is estimated at around 10% of all PCI cases [1, 3–5]. Drug-eluting stents (DESs) and drug-coated balloons (DCBs) are currently the only recommended methods of ISR treatment [6]. The use of DES improves coronary flow and reduces recurrent restenosis compared to balloon angioplasty; however, implantation of a second stent layer in the treated segment may lead to progressive luminal narrowing [7]. DCB has become an accepted alternative for selected ISR patients. DCBs deliver an antiproliferative drug directly to the lesion, without leaving another stent layer. Patients with DES-ISR are a selected high-risk population with primary failure of a stent, which is characterized by neointimal hyperplasia with late neoatherosclerotic lesions [8, 9]. Several randomized trials and retrospective studies have shown comparable long-term outcomes between DES and DCB in non-selected ISR patients [4, 10]. Baan et al. [10] demonstrated noninferiority of DCB versus DES use in terms of target vessel revascularization (TVR) in patients with any ISR and the mean 196 days angiographic follow-up (DES 7.1% vs. DCB 8.8%; *P* = 0.65). Results also vary depending on the type of stent implanted and clinical manifestation [11, 12]. There are no clear recommendations regarding which treatment method should be prorotized for DES-ISR in chronic coronary syndrome (CCS).

Therefore, we aimed to assess the long-term safety and efficacy of DCB versus DES in patients with ISR presenting with CCS.

Inclusion criteria

The CCS DRAGON Registry is a multicenter initiative involving consecutive patients with DES-ISR and CCS manifestation who were treated with a paclitaxel-DCB or a DES between February 2008 and October 2021. The characteristics of the centers depending on the number of included patients are presented in Supplementary material, *Table S1*, and the patient flowchart is presented in Figure 1. CCS diagnosis was based on the source documentation from particular centers and the final diagnosis on the discharge card. The diagnosis of acute coronary syndrome was based on the most recent European Society Guidelines [13], and those patients were excluded from the study. Patients with vessel thrombi diagnosed by intravascular imaging, if they did not meet the criteria for acute coronary syndrome, remained in the analysis. This study was non-randomized. Invasive angiography detecting ISR took place only in situations where exacerbation of clinical symptoms of CCS was demonstrated and cardiac origin was confirmed by prespecified exams, such as a new ischemic pattern on electrocardiography, new areas of contractility disorders on cardiac echocardiography, positive test results for myocardial ischemia, or abnormal results of imaging examination of coronary arteries, e.g., on coronary artery tomography. The entire qualification process for follow-up coronary angiography was carried out in accordance with the latest European Society of Cardiology guidelines currently in force. The exclusion criteria involved: the use of a DCB and DES during the same procedure, PCI of the bypass graft, and recurrent ISR. Thin strut stents were defined as those

WHAT'S NEW?

Current guidelines and expert consensus support using drug-eluting stents and drug-coated balloons to treat in-stent restenosis, but they do not mention specific clinical manifestations. Chronic coronary syndrome and acute coronary syndrome have different underlying mechanisms leading to myocardial ischemia. In patients with in-stent restenosis and chronic coronary syndrome, the use of percutaneous coronary interventions with drug-eluting stents is associated with reduced rates of target lesion revascularization, target vessel revascularization, and defined as composite of cardiac death, target lesion revascularisation and target vessel myocardial infarction in long-term follow-up compared with percutaneous coronary intervention with drug-coated balloons.

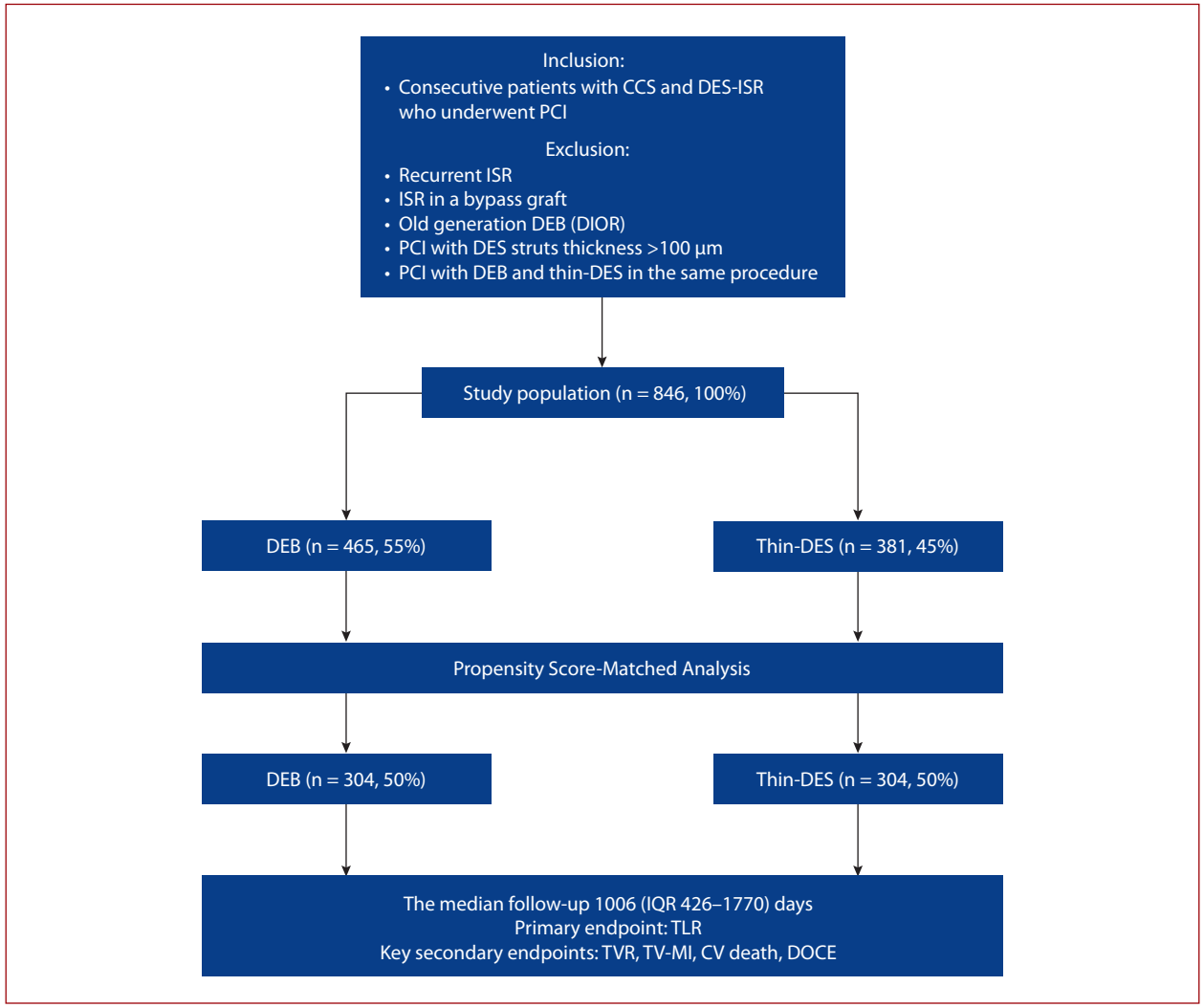

Figure 1. Patients flow chart

Abbreviations: CCS, chronic coronary syndrome; CV, cardiovascular; DEB, DES, drug-eluting stent; DOCE, device-oriented composite endpoint; ISR, in-stent restenosis; PCI, percutaneous coronary intervention; TLR, target lesion revascularization; TV-MI, target vessel myocardial infarction; TVR, target vessel revascularization

with strut thickness <100 µm. The following DES were used: Alex (Balton, Warsaw, Poland), Orsiro (Biotronik AG, Bülach, Switzerland), Promus (Boston Scientific, Natick, MA, US), Resolute (Medtronic CardioVascular, Santa Rosa, CA, US), Synergy (Boston Scientific, Natick, MA, US), Ultimaster (Terumo Corporation, Tokyo, Japan), and Xience (Abbott Vascular Devices, Santa Clara, CA, US). The paclitaxel-DCB used were: Agent (Boston Scientific, Natick, MA, US), Elutax (Aachen Resonance GmbH, Aachen, Germany), Essential (iVascular, Barcelona, Spain), In.Pact (Medtronic Vascular, Santa Clara, CA, US), Pantera Lux (Biotronik AG, Buulach, Switzerland), Restore DEB (Cardionovum GmbH, Bonn, Germany), and SeQuent Please Neo (B.Braun Interventional Group, Ltd, Melsulgen, Germany) (Supplementary material, *Table S2*). Patient data were anonymized at each center, combined into one database, and statistically analyzed as a single cohort. Cardiovascular risk factors, clinical presentation, and angiographic characteristics were recorded, along with the parameters of the implanted stents. The method of preparing the lesion, need to use cutting balloons, scoring balloons, non-compliant balloons, or high-pressure balloons as well as the ratio of the maximum diameter of the balloon to the diameter of the stent in which ISR was detected depended on the decision of the operator performing the procedure. The above data were derived from electronic patient records at each center. Mehran's angiographic classification was adopted for differentiation of ISR into four types: I – *focal;* II – *diffuse*; III – *proliferative*, and IV – *occlusive* [14]. The institutional review board approved the study protocol. Each patient signed consent to invasive examination of coronary arteries and angioplasty. All patients who met the study criteria and subsequently underwent procedures for ISR in participating centers, were followed up. Since the study was retrospective, consent was not necessary and was waived by the Bioethical Committee. The patient data were protected according to the requirements of Polish law, General Data Protection Regulation, and hospital Standard

Operating Procedures. The study was conducted in accordance with the Declaration of Helsinki and was registered at www.ClinicalTrials.gov (NCT04415216). The data that support the findings of this study are available from the corresponding author upon reasonable request.

Endpoints

Outcome data were obtained with clinical assessment, telephone consultations, or *via* primary care physicians and then recorded online or from the central database of the National Health Fund Service of the Ministry of Health. No patient was lost to follow-up. The primary efficacy endpoint was target lesion revascularization (TLR). Secondary endpoints were device-oriented composite endpoint (DOCE) (defined as a composite of cardiac death, TLR, and target vessel myocardial infarction [MI]), TVR, MI, and cardiac death. TVR and TLR were defined according to the definitions of endpoints for clinical trials. TVR was defined as any repeat PCI in the target vessel. TLR was defined as repeat PCI within the index procedure stent or 5 mm edge. All data were censored as of March 8, 2024.

Statistical analysis

We used the Kolmogorov–Smirnov test to assess the distribution of continuous variables. Data were presented as medians and interquartile ranges (IQRs) for not normally distributed continuous variables and as the numbers (n) of cases and percentages (%) for categorical variables. The statistical significance of differences between the two groups was determined using the χ^2 with Yates' continuity correction and 2-tailed Mann–Whitney U tests. Kaplan–Meier curves were used for the graphic presentation of time-dependent variables, and between-group comparisons were performed using a log-rank test. Propensity score matching with the nearest neighbor algorithm was performed to match the DES and DCB cohorts in terms of the set of core baseline variables including sex, age, atrial fibrillation, arterial hypertension, diabetes mellitus, kidney disease, extent of coronary artery disease, peripheral artery disease, history of myocardial infarction or cardiac surgery, left ventricular ejection fraction, and type of lesion (bifurcation, calcification). In the first stage, we used theoretical and empirical background and knowledge from previous studies. Preliminary statistical analyses, such as logistic regression, were used to identify significant predictors of receiving DCB vs. DEB (χ^2 4.6; DF = 9; $P = 0.87$). To measure the distance, we used the Euclidean distance with the 0.10* Sigma caliper (Supplementary material, *Figure S1*, *Table S3*). Logistic regression was performed with DCB as a dependent variable and, as described earlier, independent variables, including variables with univariable $P < 0.01$. The model was well-calibrated (the Hosmer–Lemeshow test ×2 7.79; 9 df; $P = 0.56$). The Cox proportional hazards model was calculated and used as a risk estimate for long-term follow-up event rates of TLR, TLV, DOCE, MI, target vessel MI, and death in the unmatched and matched groups [15]. Competing-risks regression analysis was also performed (TLV, TVR, MI). For all models, the variables included in the multivariable models were initially selected based on a significance level of $P \leq 0.1$ in univariate analyses. Schoenfeld residuals and Pearson correlation statistics were used to test for the proportional-hazards assumption. Data were collected and analyzed using MS Excel (Microsoft, 2022, version 16.8). All analyses were performed using XL Stat (Addinsoft, 2020, version 2022.04.01, New York, NY, US), and Stata (StataCorp LLC, 2020, version 17, Lakeway Drive, TX, US). For all analyses, we set the level of statistical significance at $P < 0.05$.

RESULTS

A total of 846 patients were included in the pooled analysis, of whom 381 (45%) were treated with a DES and 465 (55%) with a DCB. The median follow-up was 1006 (426–1770) days. Table 1 shows the baseline and procedural characteristics. There were several differences between the DCB and DES groups in the unmatched cohort. Patients treated with DCB, compared with those receiving DES, more often had diabetes requiring insulin (16.1% vs. 11%; $P = 0.013$), hypertension (91.4% vs. 86.9%; $P = 0.03$), atrial fibrillation (18.3% vs. 11.8%; $P = 0.009$), family history of CAD (26.4% vs. 40.2%; $P < 0.001$), and prior coronary artery bypass surgery (20.6% vs. 14.4%; $P = 0.02$). Procedurally, the left anterior descending coronary artery was the most often treated vessel due to ISR in both, the DCB and DES groups. There were no differences in terms of length or diameter of the previously implanted stent in the DCB group compared with the DES group. Patients in the DCB group had a higher prevalence of focal ISR (58.1% vs. 38.6%; $P < 0.001$) and diffuse ISR (29.9% vs. 31.5%; $P < 0.001$), while those in the DES group more often had proliferative ISR (8.2% vs. 29.1%; $P < 0.001$). DES patients had less residual stenosis (3.4% vs. 10.3%; $P < 0.001$) but without differences in Thrombolysis In Myocardial Infarction (TIMI) flow grade post-PCI. Dual antiplatelet therapy in patients treated with DCB was administered for a median duration of 365 (180–365) days, whereas in patients treated with DES, the median administration period was 365 (365–365) days ($P < 0.001$) (Table 2). After propensity score matching, 304 pairs of patients were generated.

Long-term outcomes

The median duration from prior PCI to ISR-PCI was 480 (270–1680) days. There was no difference when using DCB (465 [267–1770]) vs. DES (510 [270–1560]) $P = 0.72$. Detailed multivariable logistic regression analysis comparing DCB and DES strategy selection is shown in Supplementary material, *Table S4*. Patients who received DES, compared with those who received DCB (n = 465, 55%), had a lower hazard ratio (HR, 0.50 [95% CI, 0.34–0.74]; $P < 0.001$) of TLR, TVR (HR, 0.56 [95% CI, 0.39–0.86]; $P < 0.001$) and DOCE (HR, 0.63 [95% CI, 0.45–0.88]; $P = 0.007$). The incidence of cardiac death (HR, 2.24 [95% CI, 0.94–5.37]; $P = 0.07$) and

Table 1. Patients' characteristics, risk factors, and clinical presentation according to the type of device

	Unselected cohort			Propensity score-matched groups		
	DES n = 381 (45%)	DCB n = 465 (55%)	*P*-value	DES n = 304	DCB n = 304	*P*-value
Demographic data						
Age, years, median (IQR)	67 (61–67)	67 (62–73)	0.66	67 (61–74)	67 (62–73)	0.93
Male, n (%)	253 (66.4)	327 (70.3)	0.22	202 (66.4)	205 (67.4)	0.79
BMI, median (IQR)	28 (25.8–30.7)	28.4 (25.7–31.4)	0.36	28.3 (25.9–30.7)	28.4 (25.8–31.3)	0.92
CAD history						
Previous MI, n (%)	224 (58.8)	276 (59.4)	0.87	180 (59.2)	185 (60.9)	0.68
Previous CABG, n (%)	55 (14.4)	96 (20.6)	0.02	47 (15.5)	49 (16.1)	0.82
CAD risk factors						
Diabetes mellitus, n (%)	149 (39.1)	204 (43.9)	0.16	124 (40.8)	121 (39.9)	0.8
Insulin requiring, n (%)	42 (11)	75 (16.1)	0.03	37 (12.2)	36 (11.8)	0.9
Hypertension, n (%)	331 (86.9)	425 (91.4)	0.03	279 (91.8)	278 (91.4)	0.88
Hyperlipidemia, n (%)	338 (88.7)	401 (86.2)	0.28	265 (87.2)	263 (86.5)	0.81
Chronic kidney disease, n (%)	65 (17.1)	95 (20.4)	0.21	59 (19.4)	59 (19.4)	>0.99
Dialysis, n (%)	6 (1.6)	9 (1.9)	0.69	5 (1.6)	5 (1.6)	>0.99
Atrial fibrillation, n (%)	45 (11.8)	85 (18.3)	0.009	42 (13.8)	40 (13.2)	0.81
Current smoker, n (%)	61 (16)	89 (19.1)	0.24	48 (15.8)	50 (16.4)	0.83
Family history of CAD, n (%)	153 (40.2)	117 (26.4)	<0.001	100 (32.9)	94 (30.9)	0.6
Concomitant disease and left ventricular ejection fraction						
Pulmonary disease, n (%)	33 (8.7)	38 (8.2)	0.80	26 (8.6)	26 (8.6)	>0.99
Peripheral artery disease, n (%)	48 (12.6)	92 (19.8)	0.005	46 (15.1)	46 (15.1)	>0.99
LVEF%, median (IQR)	50 (45–55)	50 (40–60)	0.79	50 (45–55)	50 (40–60)	0.24

Abbreviations: BMI, body mass index; CABG, coronary artery bypass graft; CAD, coronary artery disease; DAPT, dual antiplatelet therapy; DCB, drug coating balloon; DES, drug-eluting stent; ISR, in-stent restenosis; IQR, interquartile range; LVEF, left ventricular ejection fraction; MI, myocardial infraction; MVD, multi vessel disease

TV-MI (HR, 0.63 [95% CI, 0.3–1.35]; *P* = 0.24) were similar in both groups. After matching, the observed differences persisted in terms of TLR (HR, 0.54 [95% CI, 0.33–0.88]; *P* = 0.013), TVR (HR, 0.57 [95% CI, 0.41–0.80]; *P* = 0.009), and DOCE (HR, 0.65 [95% CI, 0.42–0.99]; *P* = 0.046) between the DES and DCB group, respectively (Table 3; Supplementary material, *Table S5*). In *Table S6* we presented the results of the Cox proportional hazards model for unmatched data. The Kaplan–Meier curves for the cumulative incidence of selected outcomes are shown in Figures 2–4. The results of the combined clinical outcome measures and target lesion revascularization were consistent across 10 pre-specified subgroups (Figure 5). Among others, the results of Figure 4 showed that DES was significantly more effective (p-int <0.040) than DCB in short lesions (<22 mm; *P* <0.001), whereas other interactions were not found to be statistically significant. The results of the competing-risks regression analysis for TLV, TVR, and MI are presented in Supplementary material, *Table S7* and *Figure S2*.

DISCUSSION

In this analysis, we examined the long-term outcomes of DES compared to several types of DCB in CCS patients treated for their first event of DES-ISR. To our knowledge, this is the first analysis of ISR involving this subset of CCS patients. The main finding of our study is that in patients with CCS and DES-ISR, the use of DES was associated with lower rates of TLR, TVR, and DOCE in long-term follow-up compared to DCB use. However, treatment with DCB and DES was associated with comparable long-term clinical outcomes in terms of MI, TV-MI, and cardiovascular death. Notably, CCS as the main inclusion criterion in this study may have influenced the outcomes for the DCB group. ISR remains a significant clinical burden leading to repeated angiography and revascularization not only significantly impairing quality of life but influencing long-term prognosis in affected patients with prior PCI. So far, numerous studies have assessed the outcomes of DCB and DES for ISR patients, providing strong evidence on the safety and efficacy of both types of treatment [16]. However, none of those studies was focused specifically on the CCS subgroup. For instance, the ISAR-DESIRE 3 randomized trial showed comparable results between paclitaxel DCB and paclitaxel DES in DES-ISR [17]. Similarly, one of the most recent meta-analyses of randomized clinical trials comparing paclitaxel DCB vs. DES for ISR treatment (DAEDALUS study) [16] showed a similar incidence of TVR, all-cause death, and MI at 3-year follow-up between DCB and DES. Moreover, during the early post-procedural period, a trend towards an increased incidence of MI after DES implantation, compared with DCB, was observed. Nevertheless, in this meta-analysis patients who received DCB showed a 32% relative risk increase of TLR compared with those receiving DES. The benefit of TLR reduction in patients treated with DES was mainly seen in the RIBS IV randomized trial [18], where authors compared an everolimus-eluting stent with a paclitaxel DCB in 309 patients. They also showed that DCB was inferior to the everolimus-eluting stent in terms of

Table 2. Angiographic, procedural, medications data according to the type of device before and after propensity score matching

	Unselected cohort			Propensity score-matched cohort		
	DES n = 381 (45%)	DCB n = 465 (55%)	*P*-value	DES n = 304	DCB n = 304	*P*-value
Angiography						
1-vessel disease, n (%)	214 (56.2)	249 (53.5)	0.48	175 (57.6)	169 (55.6)	0.88
2-vessel disease, n (%)	116 (30.4)	140 (30.1)		29.3 (89)	92 (30.3)	
MVD, n (%)	51 (13.4)	76 (16.3)		40 (13.2)	43 (14.1)	
Bifurcation, n (%)	73 (19.2)	88 (18.9)	0.93	47 (15.5)	46 (15.1)	0.91
Calcification, n (%)	15 (3.9)	30 (6.5)	0.11	13 (4.3)	15 (4.9)	0.69
Stenosis, %, median (IQR)	85 (75–90)	80 (70–90)	0.02	80 (75–90)	80 (75–90)	0.76
Target lesion						
Left main, n (%)	40 (10.5)	44 (9.5)	0.62	20 (6.6)	22 (7.2)	0.75
Left anterior descending, n (%)	160 (42)	202 (43.4)	0.67	128 (42.1)	129 (42.4)	0.94
Left circumflex, n (%)	65 (17.1)	114 (24.5)	<0.001	59 (19.4)	56 (18.4)	0.76
Right coronary artery, n (%)	119 (31.2)	141 (30.3)	0.78	100 (32.9)	102 (33.6)	0.86
Original stent-length, mm, median (IQR)	20 (15–25)	22 (18–26)	0.53	20 (16–24)	22 (18–24)	0.53
Original stent-diameter, mm, median (IQR)	3 (3.0–3.5)	3 (2.8–3.5)	0.13	3.0 (3.0–3.5)	3.0 (3.0–3.5)	0.13
Type of ISR						
Focal, n (%)	147 (38.6)	270 (58.1)	<0.001	144 (47.4)	154 (50.7)	0.42
Diffuse, n (%)	120 (31.5)	139 (29.9)	0.61	99 (32.6)	108 (35.5)	0.44
Proliferative, n (%)	111 (29.1)	38 (8.2)	<0.001	61 (20.1)	29 (9.5)	<0.001
Occlusive, n (%)	3 (0.8)	18 (3.8)	0.004	0 (0)	13 (4.3)	<0.001
Balloon pre-dilatation						
Predilatation, n (%)	227 (61.7)	401 (90.5)	<0.001	185 (63.6)	255 (88.9)	<0.001
Length, mm, median (IQR)	15 (12–20)	15 (15–20)	0.14	15 (12–20)	15 (15–20)	0.95
Diameter, mm, median (IQR)	3 (2.5–3.5)	3 (2.5–3.5)	0.83	3.0 (2.5–3.5)	3.0 (2.5–3.5)	0.79
Device data						
Length, mm, median (IQR)	18 (15–28)	20 (17–20)	0.8	18 (15–24)	20 (18–24.5)	0.27
Diameter, mm, median (IQR)	3 (3.0–3.5)	3 (3.0–3.5)	0.77	3.0 (3.0–3.5)	3.0 (3.0–3.5)	0.24
Post-procedure						
Residual stenosis, n (%)	13 (3.4)	48 (10.3)	<0.001	7 (2.3)	29 (9.5)	<0.001
TIMI-3, n (%)	378 (99.2)	462 (99.4)	0.71	303 (99.7)	302 (99.3)	0.56
Perforation, n (%)	0 (0)	0 (0)	–	0 (0)	0 (0)	–
Dissection, n (%)	11 (2.9)	9 (1.9)	0.4	9 (3)	7 (2.3)	0.61
No reflow, n (%)	3 (0.8)	2 (0.4)	0.73	1 (0.3)	1 (0.3)	0.99
Intracoronary imaging and drug therapy						
Use of intracoronary imaging, n (%)	18 (4.7)	26 (5.6)	0.65	13 (4.3)	13 (4.3)	0.99
Glycoprotein IIb/IIIa inhibitors, n (%)	6 (1.6)	0 (0.0)	0.01	4 (1.3)	0 (0)	0.04
Length of DAPT, days, median (IQR)	365 (365–365)	365 (180–365)	<0.001	365 (365–365)	365 (180–365)	<0.001

Abbreviations: TIMI, Thrombolysis in Myocardial Infarction risk score; other — see Table 1

Table 3. Follow up according to the device before and after propensity score matching. The hazard ratios presented in this table are based on univariable analyses

	Crude analysis			Propensity score analysis		
	DES n = 381	DCB n = 465	HR (95% CI) *P*-value	DES n = 304	DCB n = 304	HR (95% CI) *P*-value
TLR, n (%)	33 (8.7)	58 (12.5)	0.5 (0.34–0.74) <0.001	27 (8.9)	39 (12.8)	0.5 (0.3–0.83) 0.006
TVR, n (%)	47 (12.3)	68 (14.6)	0.56 (0.39–0.86) <0.001	38 (12.5)	43 (14.1)	0.56 (0.36–0.88) 0.01
MI, n (%)	31 (8.1)	29 (6.2)	0.78 (0.51–1.2) 0.26	26 (8.6)	18 (5.9)	0.89 (0.47–1.66) 0.71
TV-MI, n (%)	11 (2.9)	16 (2.6)	0.63 (0.3–1.35) 0.58	11 (3.6)	6 (2)	1.07 (0.39–3.08) 0.89
CV death, n (%)	19 (5)	5 (0.1)	2.24 (0.94–5.37) 0.07	13 (4.3)	4 (1.3)	2 (0.64–6.29) 0.24
DOCE, n (%)	50 (13.1)	64 (13.8)	0.63 (0.45–0.88) 0.007	40 (13.2)	44 (14.5)	0.61 (0.39–0.94) 0.03

Abbreviations: CI, confidence interval; CV, cardiovascular; DOCE, device oriented composite endpoint; HR, hazard ratio; TLR, target lesion revascularization; TV, target vessel; TVR, target vessel revascularization; other — see Table 1

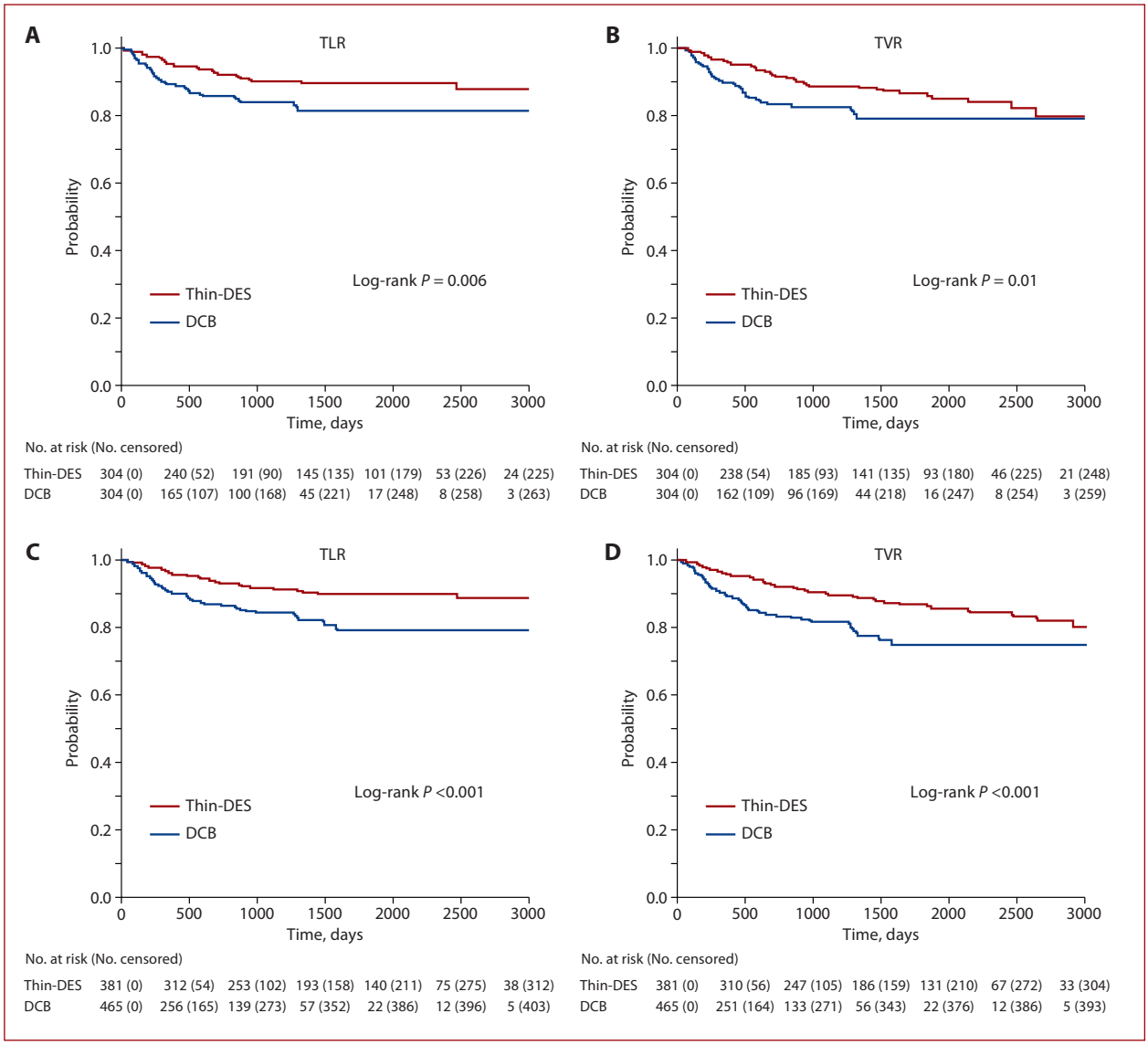

Figure 2. Kaplan–Meier curves according to the device driven outcomes. **A.** Propensity score–matched cohort for cumulative incidence of TLR. **B.** Propensity score matched cohort for cumulative incidence of TVR. **C.** Unselected cohort for cumulative incidence of TLR. **D.** Unselected cohort for cumulative incidence of TVR

Abbreviations: DCB, drug-coating balloon; MI, myocardial infarction; TVL, target lesion revascularization; other — see Figure 1

in-segment minimal lumen diameter during 6 to 9 months of follow-up. The outcomes from our real-life registry are in line with those findings showing long-term reduction of TLR with implantation of DES compared with DCB.

Ongoing ischemia in acute coronary syndrome has a different mechanism when compared with CCS. The main difference is that in CCS there is no ruptured or eroded coronary plaque. Coronary stents have been shown to be effective in maintaining long-term patency of culprit vessels in patients with acute coronary syndrome [6]. On the contrary, lesion morphology in CCS usually does not present signs of instability and is not associated with disruption of the endothelial layer. Thus, no need to cover an unstable plaque in CCS may have an advantage in DCB therapy. On the other hand, an additional thin struts stent layer with slow release of the drug may have an advantage over DCB. One of the reasons for this unexpectedly lower performance of DCB in the ISR setting can be attributed to the very low penetration of intravascular imaging, an intrinsic limitation of this type of real-world studies as it has been also shown in other studies with different DCB [19]. Understanding the cause of ISR can tailor an adequate strategy for lesion preparation and, subsequently, the final treatment which may ensure much better long-term treatment results. In the work presented by our team, the average use of intravascular imaging techniques was below 10%, which certainly influenced the choice of treatment and would certainly differ if they had been used and translated into clinical results. This is because the presented data come from the era in which intravascular imaging was not reimbursed, while currently it is fully reimbursed in the case of the assessment of lesions such as stent failure. Certainly,

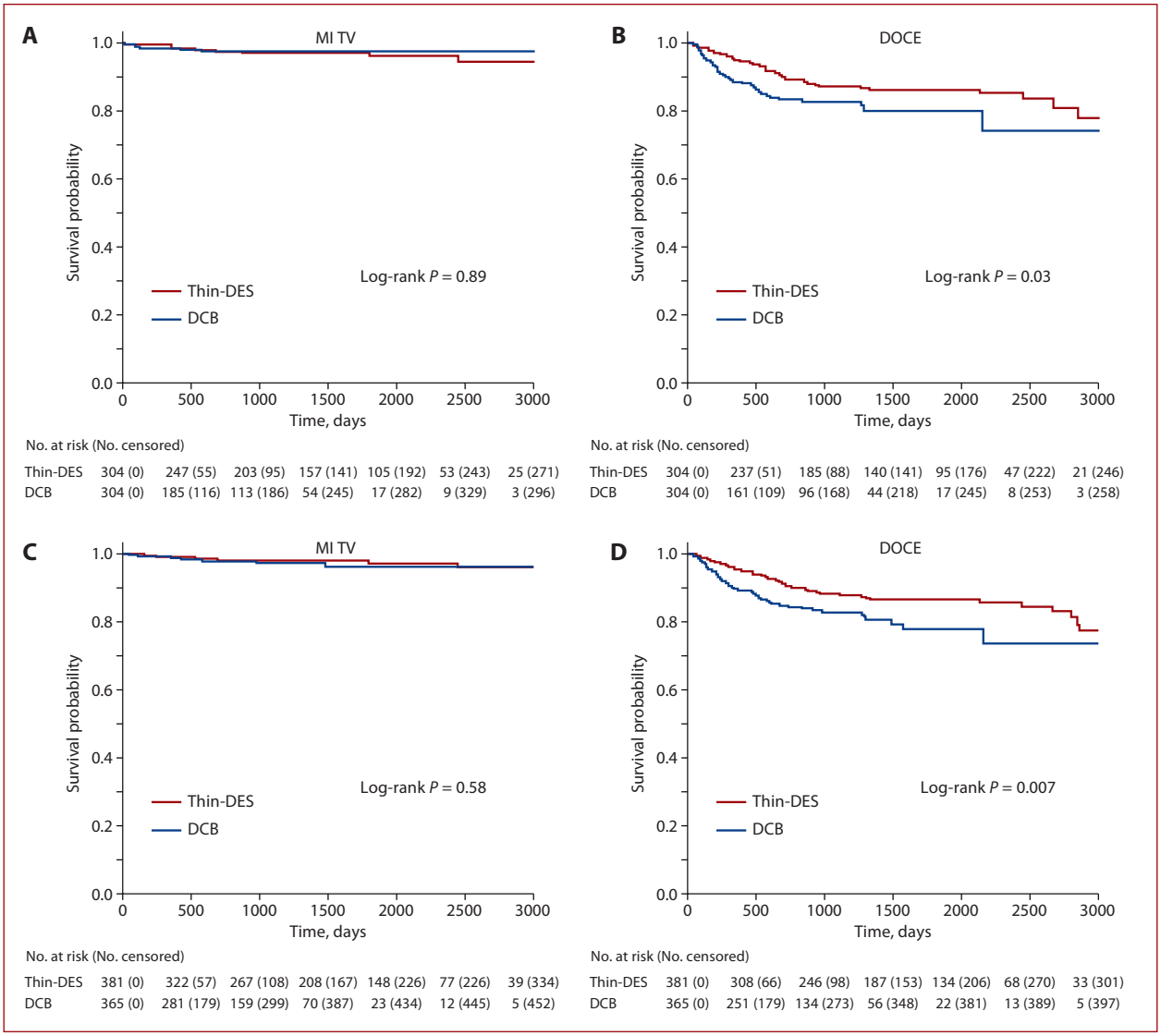

Figure 3. Kaplan–Meier curves according to the device driven outcomes. **A.** Propensity score–matched cohort for cumulative incidence of MI-TV. **B.** Propensity score–matched cohort for cumulative incidence of DOCE. **C.** Unselected cohort for cumulative incidence of MI-TV. **D.** Unselected cohort for cumulative incidence of DOCE

Abbreviations: see Figures 1 and 2

the use of intravascular imaging techniques influences the type of tools used to prepare the lesion for angioplasty, e.g. non-compliant (NC) balloons, cutting balloons, scoring balloons, or very high-pressure NC OPN ballons. On the other hand, some features may increase the willingness to use DES when intravascular imaging techniques are used, e.g. vessel dissection, but certain features, such as the small diameter of the vessel remain factors supporting DCB use. An adequately balanced study with an ad hoc flowchart is of paramount importance to identify the best treatment in this complex lesion setting.

Study limitations

There are several limitations to this study. First, we had no intravascular imaging data, and this was the major factor that limited insight into the mechanism of restenosis. The decisions on the choice of treatment were not random but based on the operator's preference. While the sample size of this study was large, the study was a retrospective analysis with inherent limitations. However, this was balanced by an all-comer design with broad inclusion criteria, a 100% follow-up rate, and confirmation of the endpoints in the National Health Service database. Another limitation is the absence of a central laboratory to assess the angiographic characteristics of the lesions treated, including ISR types. Results may have varied depending on the type of stent implanted, requiring further follow-up. However, one of the most important limitations of this study was the lack of a randomized design. Although we used adjustment for an array of potential confounders and propensity score matching, the impact of treatment selection bias cannot be entirely

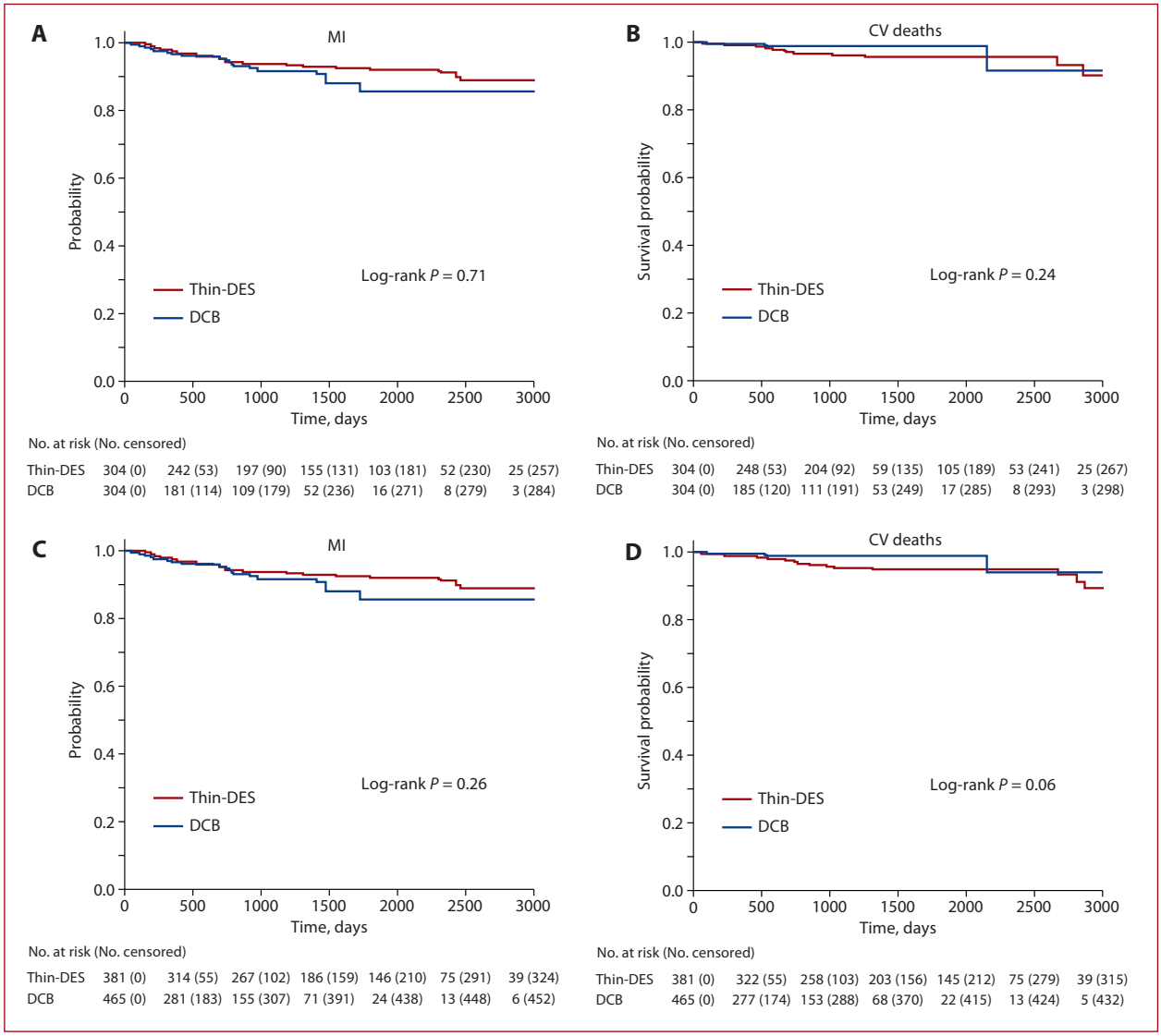

Figure 4. Kaplan–Meier curves according to the clinical driven outcomes. **A.** Propensity score–matched cohort for cumulative incidence of MI. **B.** Propensity score-matched cohort for cumulative incidence of CV death. **C.** Unselected cohort for cumulative incidence of MI. **D.** Unselected cohort for cumulative incidence of CV death

Abbreviations: see Figures 1 and 2

ruled out. Moreover, we did not include in the matching process such important indices as ISR type (proliferative, occlusive), duration and type of dual antiplatelet therapy, residual stenosis, and type of pre-dilatation due to limited access to data or their availability only for a small percentage of patients, which, after selecting pairs, would significantly reduce the group of patients followed up. Undoubtedly, a wide heterogeneity of materials used in DCB and DES should also be recognized as a potential confounder. It seems to us that generating bias in the results could be caused by multi-morbidities and deaths of unknown causes as well as unconsidered coding by the Central Statistical Office (assigning ICD-10 codes to patients with an unclear cause of death according to the decision of the doctor declaring death). The results have certainly been also influenced by the fact that the percentage of the post-procedural residual stenosis in the DCB group was significantly higher (mean at least 30% or above) even between the matched groups, which could explain the higher rates of TLR.

CONCLUSIONS

In CCS patients undergoing PCI for ISR, the use of DES is associated with reduced 3-year rates of TLR, TVR, and DOCE compared with patients treated with DCB, with no differences in MI, TV-MI, and cardiovascular death rates.

Supplementary material

Supplementary material is available at https://journals.viamedica.pl/polish_heart_journal.

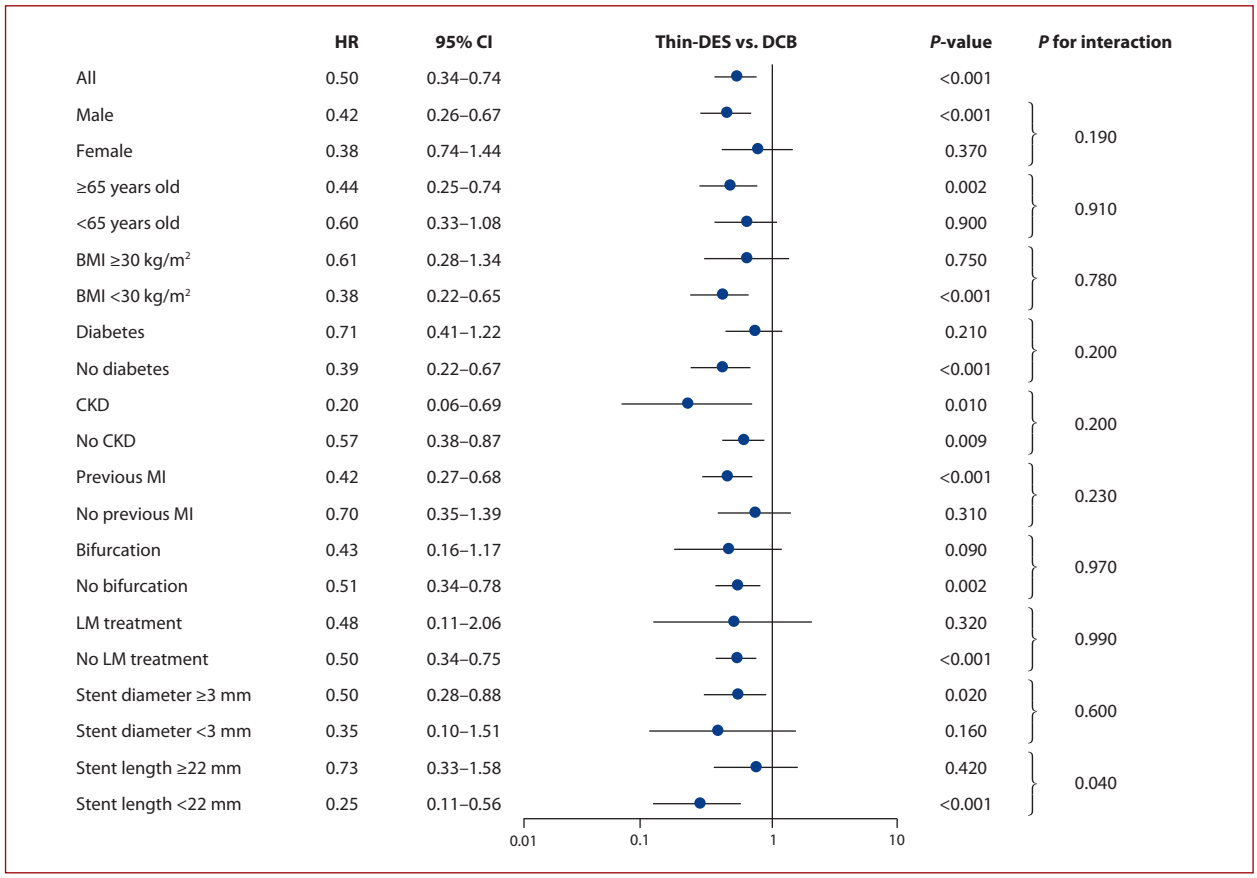

Figure 5. Risk of target lesion revascularization during follow-up

Abbreviations: BMI, body mass index; CI, confidence interval; CKD, chronic kidney disease; HR, hazard ratio; LM, left main; other — see Figures 1 and 2

Article information

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