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# 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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**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)**

**Short title:** DCB vs. DES in CCS ISR

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**WHAT'S NEW?**

Current guidelines and expert consensus support drug-eluting stents and drug-coated balloons for treatment of in-stent restenosis, without mentioning 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 intervention with drug-eluting stents is associated with reduced rates of target lesion revascularization, target vessel revascularization and device-oriented composite endpoint in long-term observation compared with percutaneous coronary intervention with drug-coated balloons.

## ABSTRACT

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

**Aims**: To investigate the outcomes of 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. 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 group, respectively.

**Conclusions**: In long-term observation in patients with CCS undergoing PCI of ISR, the use of DES is 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 de novo significant coronary stenosis. However, previously stented coronary artery may develop in-stent restenosis (ISR) which is the most common cause of stent failure after PCI [1]. 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 its frequency is estimated on 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]. 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 patients with ISR. DCBs deliver an antiproliferative drug directly to the lesion, without leaving another stent layer. Patients with DES ISR comprise 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 patients with ISR [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 preferred 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 patients flow chart is presented on the Figure 1. The diagnosis of CCS was based on the source documentation in particular center and final diagnosis at discharge card. The diagnosis of acute coronary syndrome was based on to the most recent European Society Guidelines [13], and those patients has been excluded from the study. Also, patients with thrombi in a vessel diagnosed by intravascular imaging, if they did not meet the criteria for acute coronary syndrome, remained in the analysis. The presented study was non-randomized study. Invasive angiography detecting ISR took place only in situations where the exacerbation of clinical symptoms of CCS was demonstrated and cardiac origin was confirmed by prespecified exams, such as new ischemic pattern in electrocardiography, new areas of contractility disorders in cardiac

echocardiography, positive test result for myocardial ischemia, or abnormal result of imaging examination of coronary arteries, e.g., 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. Exclusion criteria involved: use of a DCB and DES during the same procedure, PCI of bypass graft and recurrent ISR. Thin struts stents were defined as ones 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), 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), SeQuent Please Neo (B.Braun Interventional Group, Ltd, Melsulgen, Germany) (Supplementary material, *Table S2*). The patients' 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, the 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. The 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 a consent to invasive examination of the coronary arteries and angioplasty, and all patients who met the study criteria, who subsequently underwent procedures for ISR in individual centers, were observed. Due to the fact that the study was retrospective, consent was not necessary and waived by the Bioethical Committee. The patient's 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 end point was target lesion revascularization (TLR). Secondary end points were device-oriented composite end point (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 end points 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 range (IQR) for not normally distributed continuous variables and as the number (n) of cases and percentage (%) for categorical variables. Statistical significance of differences between two groups were determined using the $\chi^2$ with Yates' continuity correction, 2-tailed Mann–Whitney U tests. Kaplan–Meier curves were used for 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 a logistic regression was used to identify significant predictors of receiving DCB vs. DEB ($\chi^2$ 4.6; DF = 9; $P$ = 0.87). To measure the distance we used Euclidean distance with the caliper 0.10* Sigma (Supplementary material, *Figure S1*, *Table S3*). Logistic regression was performed with DCB as a dependent variable and, as above described, 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). 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 on unmatched and matched groups [15]. Competing-risks regression analysis was also performed (TLV, TVR, MI). For all models 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), 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 group in the unmatched cohort. Patients treated with DCB compared with those receiving DES had more 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%; $P = 0.02$), respectively. Procedurally, left anterior descending coronary artery was the most often treated vessel due to ISR in both, the DCB and DES group. There were no differences in terms of length or diameter of previously implanted stent in the DCB compared with the DES group, respectively. Patients in the DCB group had 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 the median length 365 (180–365) days, whereas in patients treated with DES 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 length of the period 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 vs. DES strategy selection is shown in Supplementary material, *Table S4***.** Patients who received DES compared with those who received DCB (n = 465, 55%) had 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 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 Cox proportional hazards model for unmatched data. 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 prespecified 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 the other interactions were not found to be statistically significant. Results of the competing-risks regression analysis for TLV, TVR and MI are presented in Supplementary material, *Table S7* and *Figure S2*.

## DISCUSSION

In the current analysis we examined long-term outcomes of DES compared to several types of DCB in patients with CCS treated for their first event of DES-ISR. To our knowledge, this is the first analysis of ISR emphasizing the subset of CCS patients. The main finding of the 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 with the use of DCB. However, treatment with DCB and DES was associated with comparable long-term clinical outcomes in terms of MI, TV-MI and cardiovascular death. Notably, the CCS as a main inclusion criteria in the current study may have influenced the outcomes of the DCB group. ISR remains a significant clinical burden leading to repeated angiographies 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 in patients with ISR, providing strong evidence supporting the safety and efficacy of both types of treatment [16]. However, none of those studies was focused specifically on the CCS subgroup. For instance, 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-analysis of randomized clinical trials comparing paclitaxel DCB vs. DES for the treatment of ISR (DAEDALUS study) [16] showed similar incidence of TVR, all-cause death and MI at 3-year follow-up between DCB and DES. Moreover, during 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 assigned to 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 everolimus-eluting stent in terms of in-segment minimal lumen diameter during 6 to 9 months follow up. The outcomes of 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 different mechanism when compared with CCS. The main difference is the absence a ruptured or eroded coronary plaque in CCS. Coronary stents have proven to be effective in maintaining long-term patency of culprit vessels in patients with acute coronary syndrome [6]. To the contrary, lesion morphology in CCS usually does not present signs of instability and is not associated with disruption of endothelial layer. Thus, no need to cover an unstable plaque in CCS may have an advantage in DCB therapy. However, on the other hand additional thin struts stent layer with slow release of the drug may have an advantage over DCB. One of the reasons for this unexpected lower performance of DCB in the ISR setting can be attributable to the very low penetration of intravascular imaging, an intrinsic limitation of this type of real-world studies, like it has been shown in other studies also with different DCB [19]. Understanding the cause of ISR can tailor an adequate strategy of lesion preparation and subsequently the final treatment which may translate into much better long-term treatment results. In the work presented by our team, the average frequency of use of intravascular imaging techniques was below 10%, which certainly influenced the choice of treatment, and would certainly differ if they were used, and translated into clinical results. This is due to the fact that 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, the use of intravascular imaging techniques influences the type of tools used to prepare the lesion for angioplasty, e.g. cutting balloons, scoring balloons or those OPN type (super-high-pressure). But on the other hand, there are features that may increase the willingness to use DES when intravascular imaging techniques are used, e.g. vessel dissection, but certain features, such as small diameter of the vessel remain factors supporting the use of DCB. An adequately balanced study with ad hoc flow chart is of paramount importance to understand the best treatment of this complex lesion setting.

**Study limitations**

There are several limitations to this study. First, we had no intravascular imaging data and thus was the major factor, which 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 end points by the National Health Service database. Another limitation, is the absence of core laboratory to assess the angiographic characteristics of the lesions treated, including the type of ISR. Results may have varied depending on the type of stent implanted, requiring further follow-up. However, one of the most important limitation of current study was the lack of a randomized design. Although, we used adjustment for an array of potential confounders and propensity score matching, an impact of treatment selection bias cannot be entirely refuted. Morover we did not included into the matching process such important indices as type of ISR (proliferative, occlusive), length and type of dual antiplatelet therapy, residual stenosis and type of pre-dilatation due to limited access to data or their availability for a small percentage of patients, which, after selecting pairs, would significantly reduce the group of people observed. Based on the presented in the current analysis results, it could be concluded that treatment strategy for DES-ISR was associated with differences in TLR, TVR, and DOCE but not in mortality. Undoubtedly, a wide heterogeneity of building materials — in the DCB and DES realm should also be recognized as a potential confounder of final results and observations. It seems to us that the main causes may be multi-morbidities and deaths of unknown cause as well as junk coding by the Central Statistical Office (assigning ICD-10 codes to patients with an unclear cause of death according to doctor's decision declaring death). The results are certainly also influenced by the fact that the percentage of the post-procedural residual stenosis in the DCB group were significantly higher (mean at least 30% or above) even between the matched groups and that could explain the higher rates of TLR.

## CONCLUSIONS

In patients with CCS 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 of MI, TV-MI and cardiovascular death.

**Supplementary material**

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

**Article information**

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**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; MI, myocardial infraction; MVD, multi vessel disease

**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

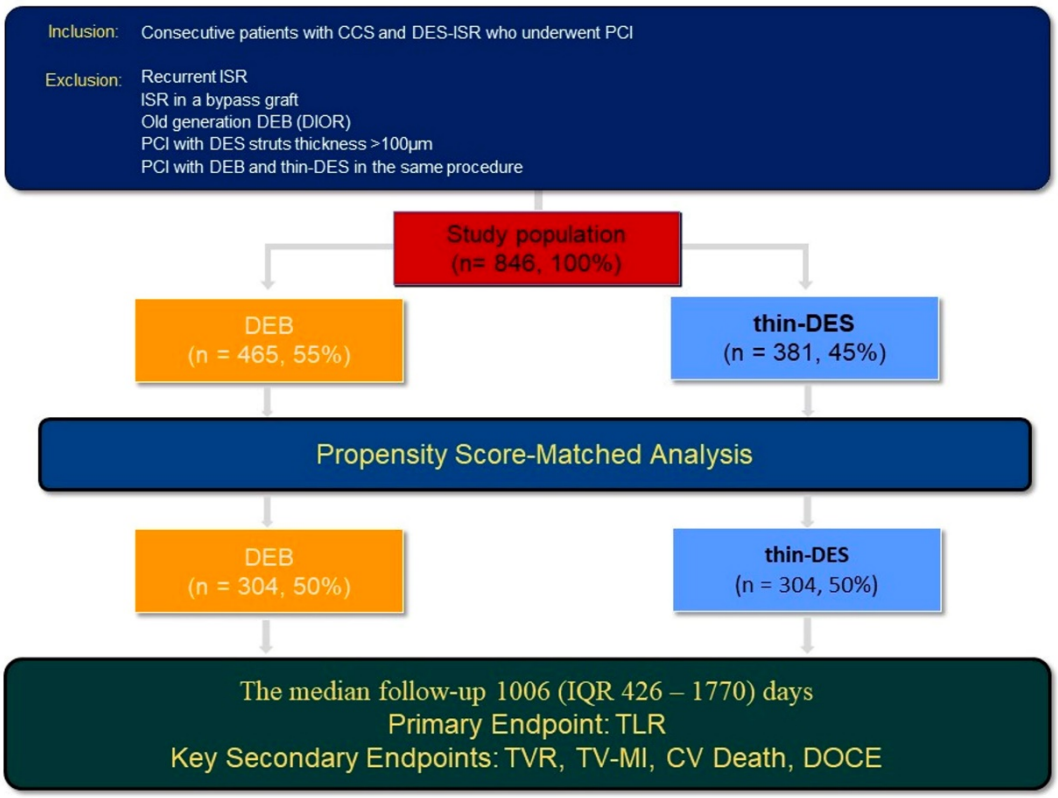


**Figure 1.** Patients flow chart

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

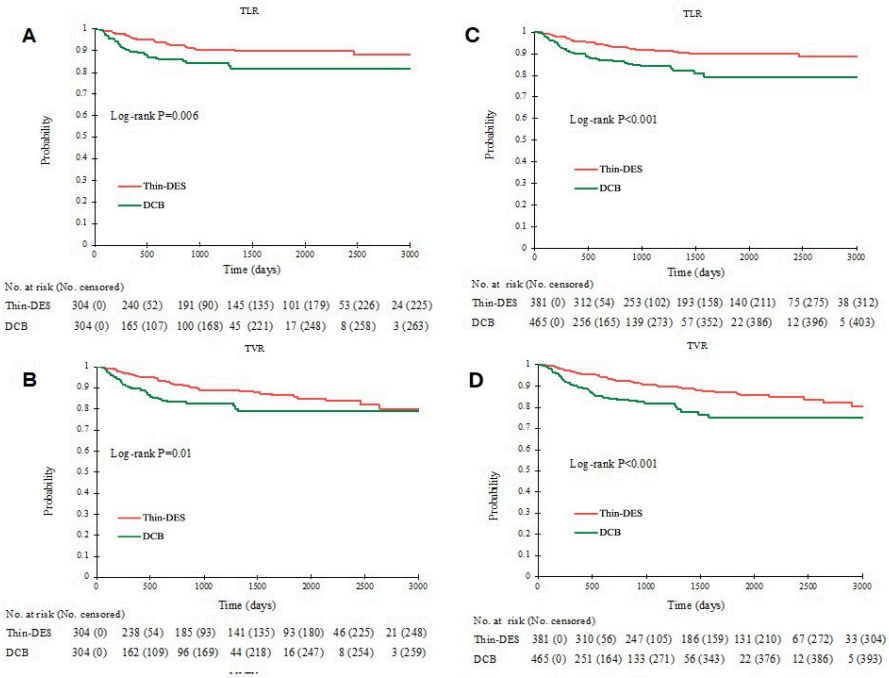


**Figure 2.** Kaplan–Meier curves according to the device driven outcomes. **A.** Propensity score–matched cohort for cumulative incidence of TLR. **B.** Propensity score matched cohort for cumulative incidence of TVR. **C.** Unselected cohort for cumulative incidence of TLR. **D.** Unselected cohort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

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

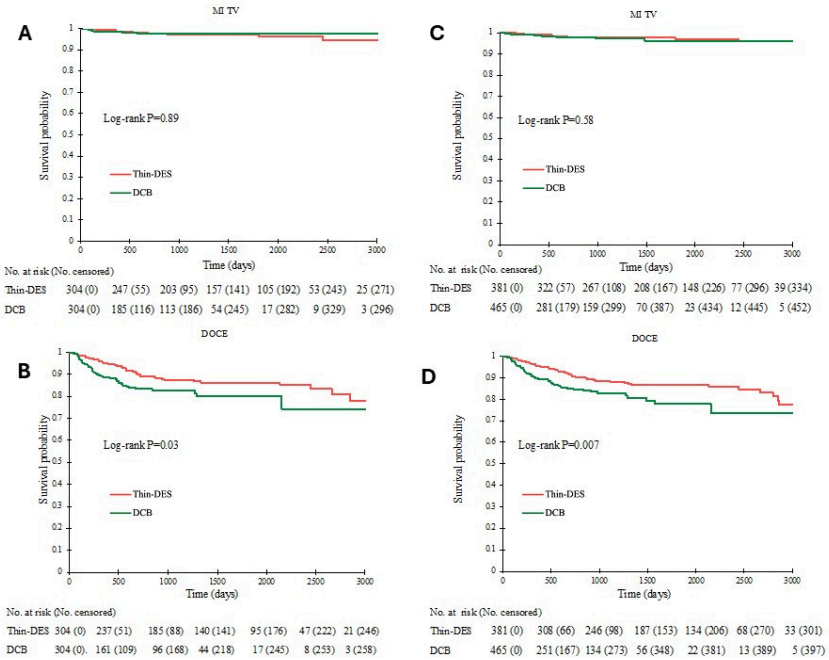

**Figure 3.** Kaplan–Meier curves according to the device driven outcomes. **A.** Propensity score–matched cohort for cumulative incidence of MI-TV. **B.** Propensity score–matched cohort for cumulative incidence of DOCE. **C.** Unselected cohort for cumulative incidence of MI-TV. **D.** Unselected cohort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

Abbreviations: see Figures 1 and 2

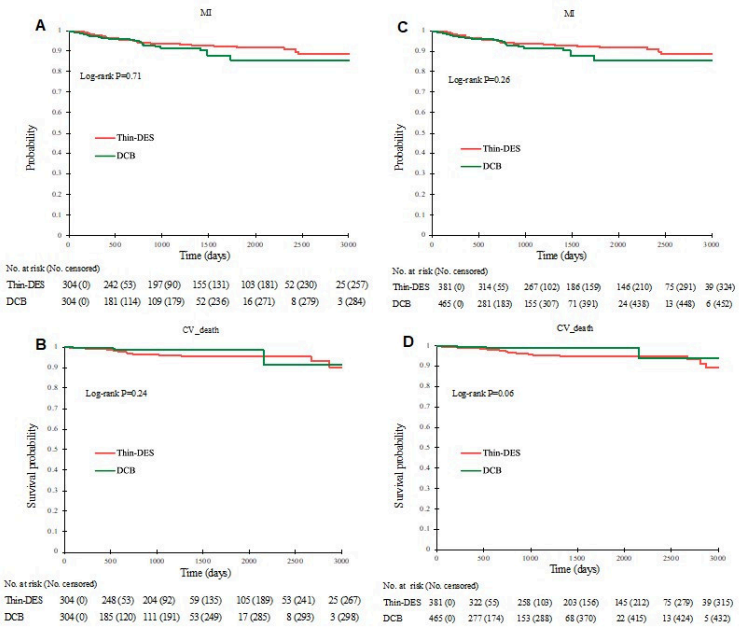


**Figure 4.** Kaplan–Meier curves according to the clinical driven outcomes. **A.** Propensity score–matched cohort for cumulative incidence of MI. **B.** Propensity score-matched cohort for cumulative incidence of CV death. **C.** Unselected cohort for cumulative incidence of MI. **D.** Unselected cohort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

Abbreviations: see Figures 1 and 2

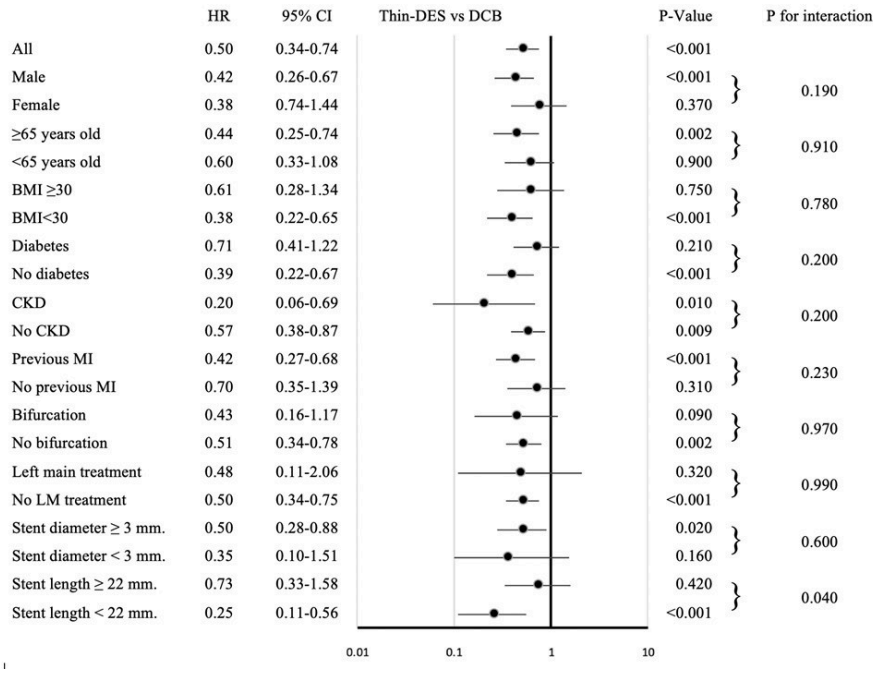


**Figure 5.** Risk of target lesion revascularization during follow-up

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