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ORIGINAL PAPER

Clinical outcomes of drug-coated balloon in coronary lesions: a real-world, all-comers study

Liang Pan[1] · Wenjie Lu[1] · Zhanying Han[1] · Sancong Pan[2] · Xi Wang[1] · Yingguang Shan[1] · Xule Wang[1] · Xiaolin Zheng[1] · Ran Li[1] · Yanjun Zhou[1] · Peng Qin[3] · Qiangwei Shi[1] · Shuai Zhou[1] · Wencai Zhang[1] · Sen Guo[1] · Peisheng Zhang[4] · Xiaofei Qin[1] · Guoju Sun[1] · Zhongsheng Qin[2] · Zhenwen Huang[1] · Chunguang Qiu[1]

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Abstract

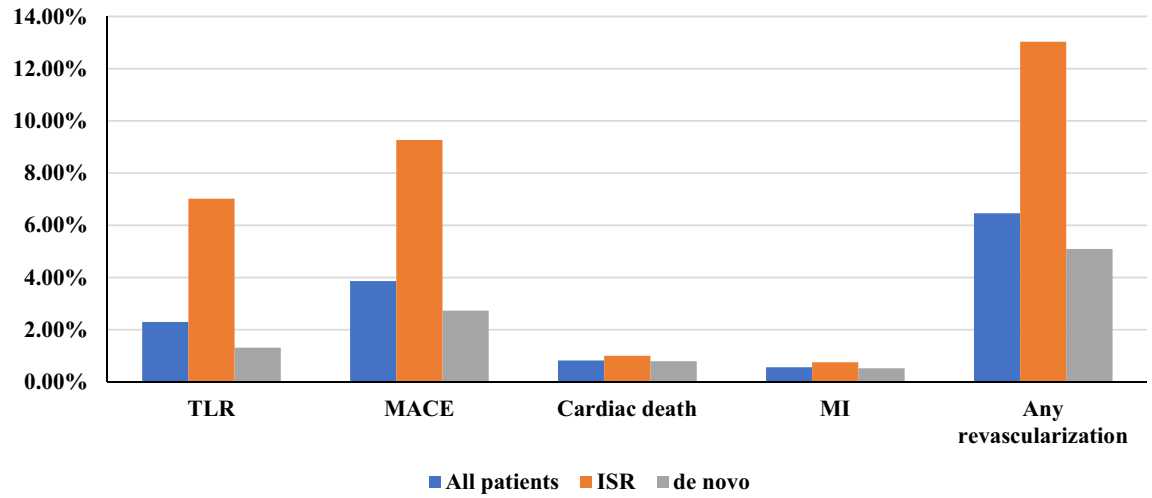
Backgrounds Although drug-eluting stents are the most common interventional devices for patients with coronary disease, drug-coated balloons (DCBs) represent a novel therapeutic alternative in certain scenarios. This prospective, observational all-comers study explored the clinical outcomes of DCB use in patients with coronary lesions.

Methods and results All patients treated with DCBs were enrolled in this study, including patients with in-stent restenosis (ISR) or de novo lesions. The primary outcome was the target lesion revascularization (TLR) rate at one year.

We enrolled 2306 patients with 2660 lesions and performed DCB angioplasty in 399 patients (17.3%) with ISR and 1907 patients (82.7%) with de novo lesions. During follow-up (366 ± 46 days), the TLR rate was lower in the de novo lesion group (1.31%) compared to the ISR group (7.02%) [odds ratio (OR) 0.176, 95% confidence interval (CI) 0.101–0.305, $p < 0.001$]. Patients with de novo lesions had a lower yearly incidence of MACE compared to ISR patients (2.73 vs. 9.27%, respectively, OR 0.274, 95% CI 0.177–0.424, $p < 0.001$) and a lower incidence of any revascularization (5.09 vs. 13.03%, OR 0.358, 95% CI 0.251–0.510, $p < 0.001$). No significant differences between groups were observed in the rates of cardiac death (OR 0.783, 95% CI 0.258–2.371, $p = 0.655$) or MI (OR 0.696, 95% CI 0.191–2.540, $p = 0.573$).

Conclusions DCB angioplasty in this all-comers, real-world, prospective study was safe and efficient with low TLR and MACE rates. Thus, DCB appears to be an attractive alternative for the stent-less treatment of de novo coronary lesions.

Graphic abstract



Liang Pan and Wenjie Lu contributed equally to this work.

Extended author information available on the last page of the article

ISR in-stent restenosis; OR odds ratio; CI confidence interval; TLR target lesion revascularization; MACE major adverse cardiovascular events; MI myocardial infraction. MACE defined as the composite outcome of cardiac death, myocardial infarction, and target vessel revascularization. Any revascularization includes any percutaneous coronary intervention, and coronary artery bypass grafting.

Keywords Drug-coated balloon · All-comers · In-stent restenosis · De novo · Coronary artery disease

Introduction

Modern interventional cardiology was well established by the time balloon angioplasty for the treatment of coronary artery disease (CAD) was performed in 1977 [1]. Subsequently, in 1986, the first bare-metal stent (BMS) was introduced as a rescue strategy for frequently encountered complications after balloon angioplasty, such as coronary artery dissection, recoil or acute occlusion. Unfortunately, BMSs were hampered by a high in-stent restenosis (ISR) rate, which was observed in ~20–40% of cases [2]. Drug-eluting stents (DESs) have largely replaced BMSs, however, ISR remains a problem, affecting approximately 5% of all percutaneous coronary intervention (PCI) procedures [3]. Drug-coated balloons (DCBs) may be optimum in this scenario.

DCBs have been shown to be highly effective in treating ISR [4, 5] and have the additional benefit of preserving access for future coronary artery bypass grafting (CABG). Most clinical studies have also shown good performance of DCB in coronary de novo lesions [6–8], with a major benefit in small vessel disease. Differences in study results are mainly due to disparity in procedural approach, "DCB-only" or "hybrid" therapy. However, these studies were limited by the small number of patients, especially those with de novo coronary lesions. Therefore, we performed this all-comers study to examine the clinical effectiveness and safety of PCI using DCBs in contemporary real-world practice.

Methods

Patient population

Patients were prospectively enrolled in three Chinese medical centers from July 2014 to December 2019. Eligible patients had a reference diameter of the target vessel between 2.0 and 4.0 mm and either a de novo or in-stent restenosis lesion. Exclusion criteria were (1) ≥ type C dissection or residual stenosis > 30% after lesion preparation, (2) simultaneous treatment of ISR and de novo lesions, (3) revascularization within one month prior to the index procedure and (4) unstable hemodynamics or cardiogenic shock (Fig. 1).

Patients received aspirin (300 mg) before the intervention or were receiving long-term aspirin treatment. A clopidogrel loading dose of 600 mg, or ticagrelor loading dose of 180 mg was administered. Patients who underwent the DCB-only strategy were given dual antiplatelet therapy (DAPT) for at least 1 month after the procedure, while those with stent implantation simultaneously were given the duration of DAPT as guidelines recommended [9, 10]. Patients with contraindications or known hypersensitivity to DAPT, heparin, paclitaxel or limus, women with childbearing potential and those with a life expectancy less than 1 year were excluded. The protocol was approved by the First Affiliated Hospital of Zhengzhou University Institutional Review Board/Ethics Committee and all patients provided written informed consent. Data were captured using a common electronic case report form.

PCI procedure

During the intervention, special emphasis was given to adequate lesion preparation prior to DCB angioplasty. Pre-dilatation with a non-compliant balloon, scoring balloon, cutting balloon with a balloon-to-vessel ratio of 0.8–1.0 was mandatory (0.8–1.0 for de novo lesions and 1.0 for ISR lesions). Subsequently, DCB angioplasty was conducted only in the absence of a major, flow-limiting dissection (≥ type C according to the NHLBI classification) [11] and where residual stenosis was ≤30% based on at least two perpendicular angiographic views. The DCB used in this study had a paclitaxel/iopromide matrix coating (SeQuent™ Please, B. Braun, Melsungen, Germany). To avoid a geographic mismatch, the length of the DCB catheter was chosen to exceed the target lesion by at least 2 mm. The DCB diameters were adapted to the reference vessel diameters with a balloon-to-vessel ratio of 1.0. Recommended inflation time was at least 30 s at a pressure > 7 bars. New-generation DESs were implanted if the result after DCB-only therapy was not satisfactory due to severe residual stenosis or dissections.

Clinical endpoints and definitions

The primary outcome of this study was the 1 year target lesion revascularization (TLR) rate. Various secondary outcomes were also assessed, including the rates of major adverse cardiovascular events (MACE), defined as the composite outcome of cardiac death, myocardial infarction (MI) and target vessel revascularization (TVR), and repeat

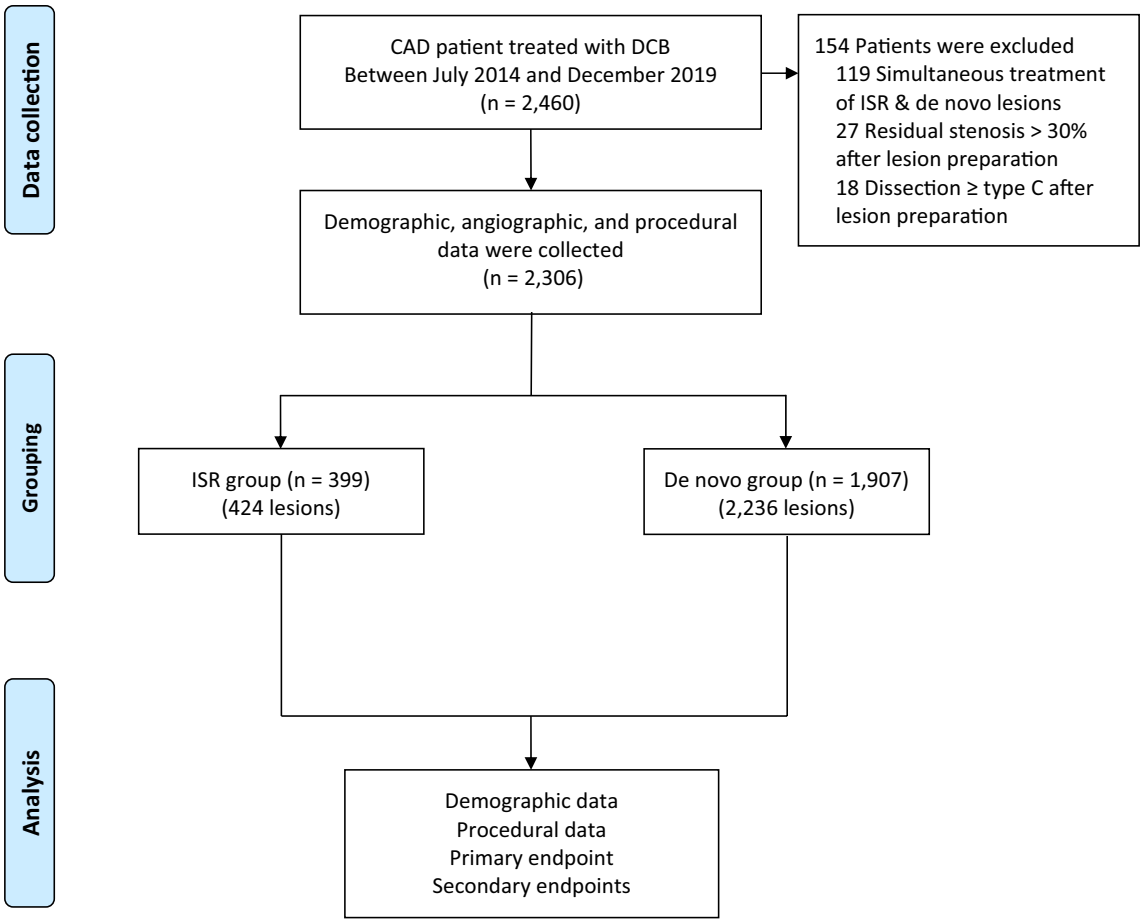


Fig. 1 Study population *CAD* coronary artery disease, *DCB* drug-coated balloon, *ISR* in-stent restenosis

revascularization (including PCI and CABG). MI was defined by typical clinical symptoms, relevant ECG changes and/or elevated cardiac troponin values with at least one value above the 99th percentile upper reference limit (type 4b or 4c MI, except for perioperative MI) [12]. Patients were followed by telephone or outpatient interview at 12 months post-surgery. Patients were classified as having suffered cardiogenic death if their cause of death was unknown or undeterminable.

Statistical analyses

All results were analyzed using the statistical packages R version 3.6.1 (The R Foundation, Vienna, Austria, http://www.r-project.org) and EmpowerStats (R) (X&Y Solutions Inc., http://www.empowerstats.com). Categorical variables were presented as frequencies (or %) and continuous variables as means ± standard deviations. Comparisons of the ISR and de novo groups were accomplished using a Fisher's exact test for categorical variables and Mann–Whitney–Wilcox nonparametric tests for continuous variables. Time-to-event data were visualized with Kaplan–Meier curves and compared using log-rank tests. Multivariate regression analysis was performed to evaluate risk factors for TLR after treatment of ISR or de novo lesions. The following variables were included in both models: age, gender, diabetes, hypertension, hyperlipidemia, renal insufficiency, acute coronary syndrome (ACS) and history of smoking. All analyses were two sided and statistical significance was determined by a p value < 0.05.

Results

Study population

We identified 2306 PCI patients treated with DCB who met our inclusion and exclusion criteria (Fig. 1), of which, 1907 patients (82.70%) exhibited de novo lesions. The baseline characteristics are presented in Table 1. In the overall study population, the mean patient age was 59.61 ± 11.02 years. Of note, 816 patients (35.39%) were diabetic. DCB angioplasty was conducted in 1573 patients (68.21%) who were diagnosed with an ACS. Clinical parameters such as age, gender

Table 1 Demographic characteristics

Variable	All patients	ISR	de novo	*p* value
Number of patients	2306	399	1907	
Age (years)	59.61 ± 11.02	60.17 ± 10.65	59.50 ± 11.09	0.388
Sex (male)	1644 (71.29%)	278 (69.67%)	1366 (71.63%)	0.432
Diabetes	816 (35.39%)	153 (38.35%)	663 (34.77%)	0.174
Hypertension	1184 (51.34%)	222 (55.64%)	962 (50.45%)	0.059
Hyperlipidemia	700 (30.36%)	128 (32.08%)	572 (29.99%)	0.410
History of smoking	757 (32.83%)	128 (32.08%)	629 (32.98%)	0.727
Renal insufficiency	115 (4.99%)	22 (5.51%)	93 (4.88%)	0.595
Acute coronary syndrome	1573 (68.21%)	286 (71.68%)	1287 (67.49%)	0.102
Unstable angina	1305 (56.59%)	240 (60.15%)	1065 (55.85%)	0.115
NSTEMI	173 (7.50%)	29 (7.27%)	144 (7.55%)	0.845
STEMI	95 (4.12%)	17 (4.26%)	78 (4.09%)	0.876
Previous MI history	235 (10.19%)	68 (17.04%)	167 (8.76%)	< 0.001
Previous PCI history	698 (30.27%)	399 (100.00%)	299 (15.68%)	< 0.001
Previous CABG history	47 (2.04%)	12 (3.01%)	35 (1.84%)	0.132
Family history of CAD	431 (18.69%)	74 (18.55%)	357 (18.72%)	0.935
LVEF	59.61 ± 7.61	59.35 ± 7.66	59.66 ± 7.60	0.422
Other vessel treated by DES alone	766 (33.22%)	67 (16.79%)	699 (36.65%)	< 0.001

ISR in-stent restenosis, *DM* diabetes mellitus, *NSTEMI* non-ST-segment elevation myocardial infarction, *STEMI* ST-segment elevation myocardial infarction, *MI* myocardial infarction, *PCI* percutaneous coronary intervention, *CABG* coronary artery bypass grafting, *CAD* coronary artery disease, *LVEF* left ventricular ejection fraction, *DES* drug-eluting stent

distribution, diabetes, hypertension, hyperlipemia, history of smoking, renal insufficiency, ACS, previous CABG history, family history of CAD and left ventricular ejection fraction (LVEF) were not significantly different between groups. The proportion of patients in the ISR group with a history of MI and/or PCI was significantly higher than that of patients in the de novo group ($p < 0.05$), however, the incidence of DES-only implantation in non-target vessels was significantly higher in de novo lesion patients compared to the ISR group ($p < 0.05$).

PCI-related characteristics

Table 2 shows the procedural baseline characteristics. In this study, there were 2660 lesions, of which, 424 (15.94%) were classified as ISR lesions and 2236 (84.06%) were de novo lesions. Over the course of the study, the target lesions were located in the left anterior descending coronary artery (44.55%), circumflex coronary artery (32.14%), right coronary artery (22.14%), left main artery (15.68%) or grafts (0.72%). Overall, studied lesions were considered fairly complex. We included lesions with heavy calcification, intracoronary thrombus, diffuse disease, total occlusions, bifurcation lesions, and even left main diseases.

Lesion preparation was performed in all lesions by predilatation with non-compliant balloons, scoring balloons, cutting balloons, or rotational atherectomy. Equipment and procedures used in the preparation of lesions differed by the type of lesion. A total of 2940 DCBs were used in the treatment of all 2660 lesions. The total length of DCBs was 24.68 ± 12.38 mm in each lesion, with a mean diameter of 2.77 ± 0.47 mm. Mean inflation pressure was 8.34 ± 2.63 bars. DCBs for de novo disease were generally smaller in diameter and shorter in length ($p < 0.001$) than those used for treating ISR lesions, however, mean DCB inflation pressure was higher in the ISR group ($p < 0.001$) than in the de novo lesion group. Although a significantly higher frequency of bailout stenting ($p = 0.001$) was required for de novo lesions (4.20%) after DCB angioplasty compared to ISR lesions (0.94%), absolute numbers were low (3.68% overall). In addition, 12.01% (277) of patients underwent intravascular imaging during PCI, including intravascular ultrasound (IVUS) and optical coherence tomography (OCT).

In-hospital events

In this study, the incidence of in-hospital acute events was extremely low. Among the 2306 patients, 9 (0.39%) patients with de novo lesions had acute ischemic events. And these events all occurred within 4 h after operation. Emergency angiography revealed that 6 (0.26%) cases had TIMI flow of 0–2. 3 of 6 (0.13%) patients had target vessel acute occlusion, and 1 (0.04%) patient who failed to accept recanalization had Q-wave myocardial infarction severe dissection and hematoma was observed by intravascular imaging evaluation, and bailout DES implantation was performed.

Table 2 Procedural and device characteristics

Variable	All patients	ISR	de novo	*p* value
Number of lesions	2660	424	2236	
Treated vessel				< 0.001
Left anterior descending coronary artery	1185 (44.55%)	218 (51.41%)	967 (43.25%)	
Left circumflex coronary artery	855 (32.14%)	79 (18.63%)	776 (34.70%)	
Left main coronary artery	417 (15.68%)	26 (6.13%)	391 (17.49%)	
Right coronary artery	589 (22.14%)	124 (29.25%)	465 (20.80%)	
Bypass graft	19 (0.72%)	0 (0.00%)	19 (0.85%)	
Number of lesions treated by DCB (per patient)				< 0.001
1	1983 (85.99%)	375 (93.98%)	1608 (84.32%)	
2	295 (12.79%)	23 (5.76%)	272 (14.26%)	
3	25 (1.08%)	1 (0.25%)	24 (1.26%)	
4	3 (0.13%)	0 (0.00%)	3 (0.16%)	
Total occlusion	317 (11.92%)	30 (7.08%)	287 (12.84%)	< 0.001
Intracoronary thrombus	12 (0.45%)	1 (0.24%)	11 (0.49%)	0.471
Diffuse vessel disease	591 (22.22%)	91 (21.46%)	500 (22.36%)	0.683
Ostial lesion	479 (18.01%)	22 (5.19%)	457 (20.44%)	< 0.001
Bifurcation lesion	844 (31.73%)	38 (8.96%)	806 (36.05%)	< 0.001
Lesion preparation	2660 (100%)	424 (100%)	2236 (100%)	
Semi-compliant balloon	1786 (67.14%)	231 (54.48%)	1555 (69.54%)	< 0.001
NSE	723 (27.18%)	85 (20.05%)	638 (28.53%)	< 0.001
Cutting balloon	803 (30.19%)	235 (55.42%)	568 (25.40%)	< 0.001
DWB	106 (3.98%)	10 (2.36%)	96 (4.29%)	0.062
Non-compliant balloon	734 (27.59%)	272 (64.15%)	462 (20.66%)	< 0.001
ROTA	54 (2.03%)	2 (0.47%)	52 (2.33%)	0.013
Number of DCBs used (per lesion)	1.11 ± 0.36	1.30 ± 0.60	1.07 ± 0.27	< 0.001
DCB diameter (mm)	2.77 ± 0.47	3.04 ± 0.41	2.72 ± 0.47	< 0.001
Total length of DCB balloon (mm)	24.68 ± 12.38	33.24 ± 18.99	23.05 ± 9.87	< 0.001
Inflation pressure (bar)	8.34 ± 2.63	8.62 ± 2.92	8.29 ± 2.56	< 0.001
Bailout stenting	98 (3.68%)	4 (0.94%)	94 (4.20%)	0.001

ISR = in-stent restenosis, *DCB* drug-coated balloon, *NSE* non-compliant scoring balloon, *DWB* dual wire balloon, *ROTA* rotational atherectomy

Clinical outcomes

Most patients (2072 of 2306, 89.85%) underwent a clinical follow-up examination at an average of 366 ± 46 days post-surgery. Patients with ISR lesions had a higher yearly incidence of TLR (7.02%) than patients with de novo lesions (1.31%) [odds ratio (OR) 0.176, 95% confidence interval (CI) 0.101–0.305, $p < 0.001$] (Table 3 and Fig. 2A). Diabetes ($p = 0.007$) and lesion type (ISR) ($p < 0.001$) were significant risk factors for TLR (Fig. 3). Kaplan–Meier curves (Fig. 2) indicated that the cumulative overall rate of MACE was higher in the ISR group (9.27%) than in the de novo group (2.73%) at 1 year (OR 0.274, 95% CI 0.177–0.424, $p < 0.001$). Similarly, the frequency of any revascularization procedure was higher in the ISR group (13.03%) than in the de novo group (5.09%) (OR 0.358, 95% CI 0.251–0.510, $p < 0.001$). The Kaplan–Meier curves indicated that the 1-year incidence of cardiac death was similar between groups (ISR 1.00% vs. de novo 0.79%, OR 0.783, 95% CI 0.258–2.371, log rank $p = 0.655$). There was no significant difference in the incidence of MI (OR 0.696, 95% CI 0.191–2.540, log rank $p = 0.573$) between the two groups.

Subgroup analysis

A subgroup analysis was performed and lesion preparation with semi-compliant balloon only was compared with scoring balloon dilation (including non-compliant balloon, non-compliant scoring balloon, dual wire balloon, and cutting balloon). In ISR patients, lesion preparation with semi-complaint balloon only had a higher incidence of TLR (20.00%) than that with scoring balloon (6.15%) (OR 3.815, 95% CI 1.313–11.089, $p = 0.009$). For patients with de novo lesions or the overall population, the above difference did not reach statistical significance ($p > 0.05$) (Supplementary Table 1).

Table 3 Risk of primary and secondary clinical outcomes at 1-year follow-up

Variable	All patients	ISR	de novo	OR (95% CI)	*p* value	Log-rank *p*
Number of patients	2306	399	1907			
TLR	53 (2.30%)	28 (7.02%)	25 (1.31%)	0.176 (0.101, 0.305)	< 0.001	< 0.001
MACE[a]	89 (3.86%)	37 (9.27%)	52 (2.73%)	0.274 (0.177, 0.424)	< 0.001	< 0.001
Cardiac death	19 (0.82%)	4 (1.00%)	15 (0.79%)	0.783 (0.258, 2.371)	0.664	0.655
MI	13 (0.56%)	3 (0.75%)	10 (0.52%)	0.696 (0.191, 2.540)	0.581	0.573
Any revascularization[b]	149 (6.46%)	52 (13.03%)	97 (5.09%)	0.358 (0.251, 0.510)	< 0.001	< 0.001

ISR in-stent restenosis, *OR* odds ratio, *CI* confidence interval, *TLR* target lesion revascularization, *MACE* major adverse cardiovascular events, *MI* myocardial infraction

[a]MACE defined as the composite outcome of cardiac death, myocardial infarction, and target vessel revascularization

[b]Any revascularization includes any percutaneous coronary intervention, and coronary artery bypass grafting

Discussion

The main finding of this prospective, all-comers study, which included more than two thousand patients, was that treatment of CAD with DCB angioplasty was safe and resulted in a low rate of TLR. In addition, when comparing two groups of patients defined by ISR or de novo lesions, the incidence of TLR and MACE resulting from DCBs in de novo lesions was significantly lower than that in the ISR group. An appreciable number of patients in the de novo lesion group had small vessel disease, and these were the patients with poor prognosis after DES implantation.

PCI with DES is the most common type of interventional revascularization procedure for CAD, however, ISR rates remain high [13, 14]. The high frequency of ISR may be attributable to the presence of durable metallic implants that interfere with vascular healing processes after PCI. Such interactions may lead to chronic inflammation and neoatherosclerosis, which may serve as a morphological explanation for target lesion failure after stent-based PCI [15]. Non-stent-based local drug delivery using a DCB has been developed because this procedure leaves no metallic mesh in the vessel wall. Current clinical studies utilizing DCBs have shown promising outcomes for the treatment of ISR [16–19], and DCBs are considered a class I indication to treat ISR (BMS-ISR or DES-ISR) according to current European Society of Cardiology guidelines [10].

Due to the successful treatment of ISR using DCBs, the use of DCBs was proposed as an alternative to DES for de novo coronary lesions. The effectiveness and safety of DCBs for treating de novo coronary diseases have been extensively studied and the results of these studies have been promising [20]. The clinical feasibility of DCBs for treating small vessel disease has been reported in several nonrandomized studies and registries [21–23]. Several randomized clinical trials subsequently compared DCBs with plain balloon angioplasty, BMS and DES [24–27]. In some of these trials, the lack of superior efficacy of DCBs versus angioplasty alone [24] was attributed to a very low event rate when using DCBs versus DES [26]. Accordingly, an earlier meta-analysis showed inferior results for DCBs compared with DES [28]. In addition to the poor performance of the DCBs used in some studies, BMSs were used as the bailout stents in some studies. A previous study confirmed that use of a BMS as the bailout is a risk factor for TLR in DCB patients [23]. BASKET-SMALL 2 (Basel Stent Kosten Effektivitäts Trial Drug Eluting Balloons vs. Drug Eluting Stents in Small Vessel Interventions) study made a comparison between paclitaxel-coated DCB and the second-generation DES, and it was proved reported that paclitaxel-coated DCBs were not inferior in terms of clinical endpoints to second-generation DESs in patients with small vessel disease [27]. Growing evidence supports the effectiveness and safety of the DCB-only strategy for treating de novo lesions in large (≥ 3.0 mm) coronary arteries [29, 30]. Previous research by our team supported the safety and effectiveness of DCBs in this setting [6], however, randomized data for comparisons between DCBs and DESs for this indication are lacking.

Contrary to previous studies [21, 23], all of the ISR patients we have treated had DES-ISR, and the overall clinical safety and effectiveness are worth noting. In this study, more than 80% of the patients had de novo lesions. The DCB-only strategy was applied successfully in most patients due to proper and sufficient lesion preparation. Moreover, the proportion of patients who received bailout stenting after DCB angioplasty was extremely low (4.20%). All bailout stents in our study were new-generation drug-eluting stents that performed well and appeared to be safe for at least 1 year after procedure, which was consistent with previous studies [31, 32].

As noted above, our lesion preparation resulted in a low incidence of acute events after PCI, the rate of acute ischemic events was 0.39% (9 of 2306) and the Q-wave myocardial infarction rate was 0.04% (1 of 2306). The low incidence of adverse events suggests that our procedures were safe and acceptable. Eight of the nine patients had successfully guidewire crossing. And intravascular imaging confirmed that acute

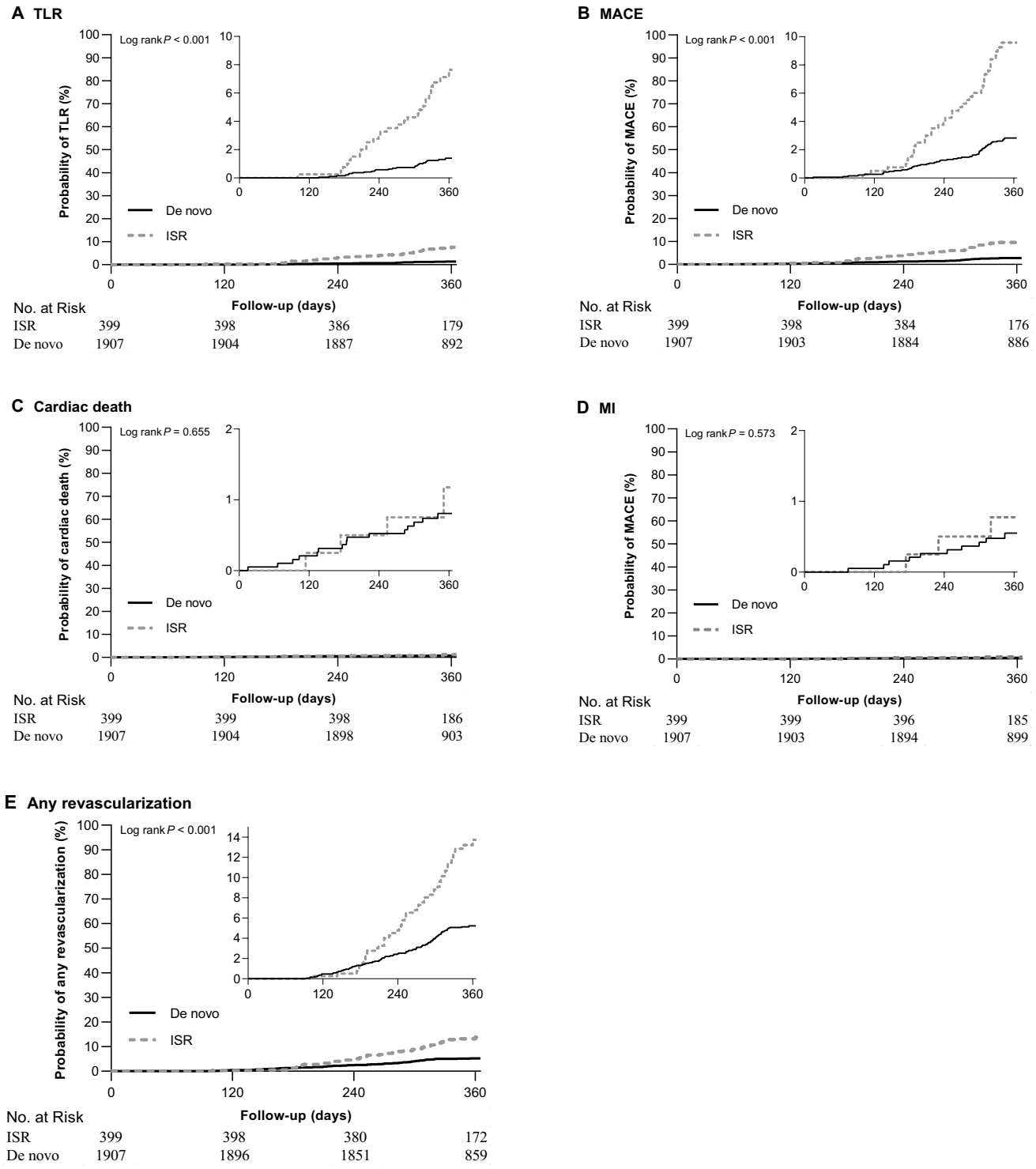


Fig. 2 Cumulative risks of the study outcomes [TLR (**A**), MACE (**B**), cardiac death (**C**), MI (**D**), any revascularization (**E**)] at 1 year follow-up *ISR* in-stent restenosis, *TLR* target lesion revascularization, *MACE* major adverse cardiovascular events, *MI* myocardial infraction In each panel, the inset shows the same data on an enlarged y axis

ischemic events were resulted by severe dissection and hematoma, which would gradually aggravate and eventually lead to severely restricted flow or vascular occlusion. However, the slow progression to vascular occlusion allows sufficient time to perform bailout stenting. And all of these ischemic events occurred within 4 h after the procedure. One point that

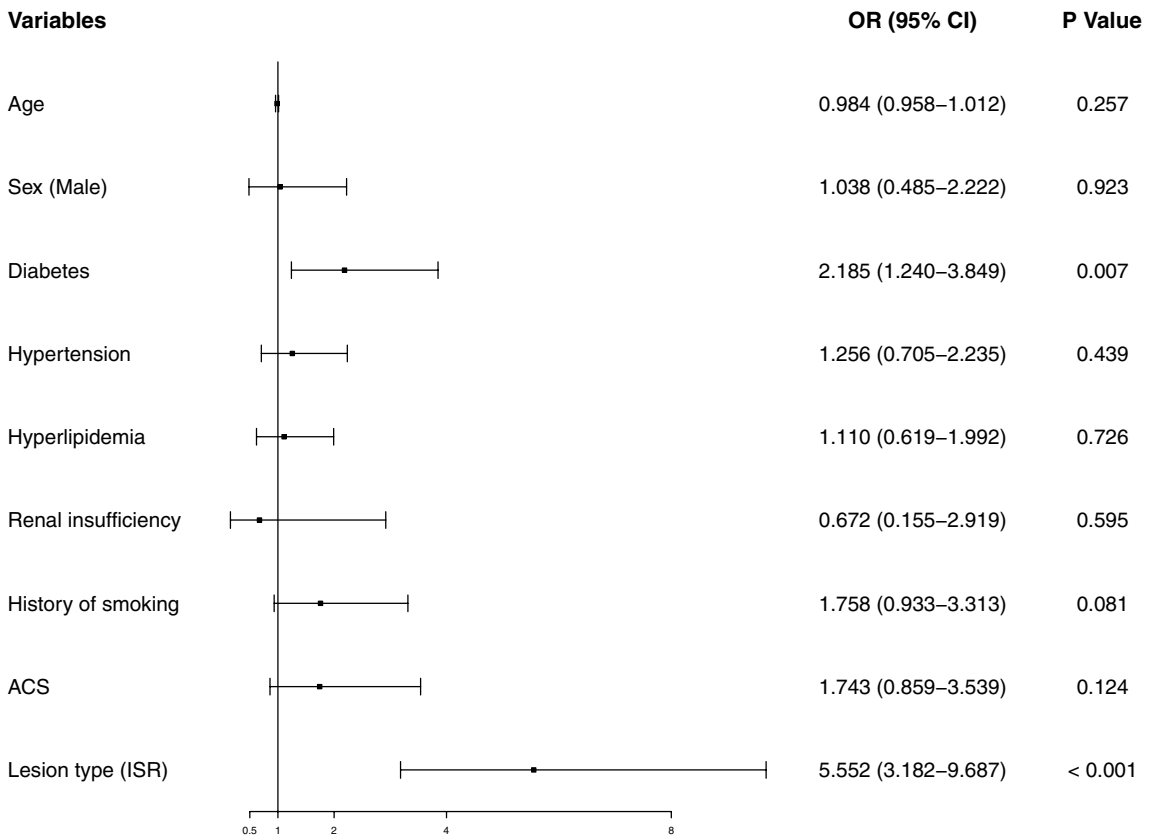


Fig. 3 Odds ratios for various explanatory variables for 1-year TLR based on a logistic regression model *ISR* in-stent restenosis, *OR* odds ratio, *CI* confidence interval, *ACS* acute coronary syndrome

needs to be raised is that these events all occurred in the early stages of this study. Later, with the accumulation of experience, the proportion of scoring balloons (cutting balloons, etc.) increased, more intravascular imaging guidance, and more rigorous intraoperative and postoperative dynamic observation, no such event occurred in the past 2 years.

Although not mentioned in the results section above and not used as a research endpoint, we did not find any thrombotic events during the entire research process. To avoid thrombosis in the early stages of the procedure, the use of GP IIb/IIIa receptor inhibitors following surgery has reached 70%, and experience with DCBs has led to a reduction in tirofiban use. Furthermore, the logistic regression analysis revealed that diabetes and the type of ISR lesion were independent predictors for 1-year TLR, which differs from previous results [23].

Limitations

Limitations to our methods and analysis should be considered. This was a prospective, observational study that adds important new insight into DCB therapy for large-scale randomized trials. The advantages and disadvantages of using DCBs versus DESs require further evaluation. In addition, as part of our overall PCI strategy, 33.22% of the patients received DES implantation in a different coronary artery during the same procedure, which may affect the occurrence of clinical events. Finally, our hospitals did not have an angiographic core laboratory, therefore, the frequency and impact of some angiographic details (such as geographic miss, reference diameter and exact balloon-to-vessel ratio) were unknown.

Conclusions

In this contemporary cohort of patients, DCB angioplasty was safe and efficient with low TLR and MACE rates. The efficacy of DCB in ISR has been confirmed once again. For de novo lesions, DCB is undoubtedly very attractive as a treatment without any implantation. Moreover, based on adequate and appropriate lesion preparation, the proportion of bailout stenting can be very low.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00392-021-01895-y.

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Author contributions Conceptualization: CGQ, WJL, ZYH, and LP. Data curation: SCP, XW, PQ, YGS, YJZ, SZ, QWS, WCZ, SG, XLW, XLZ, RL, PSZ, and ZSQ. Formal analysis: CGQ and LP. Funding and acquisition: CGQ and ZYH. Investigation: all authors. Methodology: CGQ, WJL, and ZYH. Project administration, recources and supervision: CGQ and ZYH. Resources: CGQ, ZYH, GJS, XFQ, SCP, PSZ, and ZWH. Visualization: LP. Writing original draft: LP and WJL. Writing, review and editing: all authors. All authors gave final approval of the manuscript, and agreed to be accountable for all aspects of work ensuring integrity and accuracy.

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Declarations

Conflict of interest The authors declare that this research was conducted in the absence of any commercial or financial relationships that may be construed as a potential conflict of interest.

Ethical approval The protocol was approved by the First Affiliated Hospital of Zhengzhou University Institutional Review Board/Ethics Committee.

Consent to participate Informed consent was obtained from all individual participants included in the study.

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Authors and Affiliations

Liang Pan[1] · Wenjie Lu[1] · Zhanying Han[1] · Sancong Pan[2] · Xi Wang[1] · Yingguang Shan[1] · Xule Wang[1] · Xiaolin Zheng[1] · Ran Li[1] · Yanjun Zhou[1] · Peng Qin[3] · Qiangwei Shi[1] · Shuai Zhou[1] · Wencai Zhang[1] · Sen Guo[1] · Peisheng Zhang[4] · Xiaofei Qin[1] · Guoju Sun[1] · Zhongsheng Qin[2] · Zhenwen Huang[1] · Chunguang Qiu[1]

✉ Chunguang Qiu
qcg123@163.com

[1] Department of Cardiovascular Medicine, The First Affiliated Hospital of Zhengzhou University, No. 1, Jianshe East Road, Zhengzhou, Henan, China

[2] Department of Cardiovascular Medicine, Jincheng People's Hospital, No. 456, Wenchang East Road, Jincheng, Shanxi, China

[3] Department of Geriatric Cardiology, The First Affiliated Hospital of Zhengzhou University, No. 1, Jianshe East Road, Zhengzhou, Henan, China

[4] Department of Cardiology, The Fifth Affiliated Hospital of Zhengzhou University, No. 3, Kangfu Qianjie, Zhengzhou, Henan, China