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**Article:**

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Comparison of new-generation drug-eluting stents versus drug-coated balloon for in-stent restenosis: a meta-analysis of randomised controlled trials

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ABSTRACT

Objective The study sought to compare angiographic and clinical outcomes of new-generation drug-eluting stents (DES) versus drug-coated balloon (DCB) in patients with coronary in-stent restenosis (ISR).

Design Meta-analysis using data from randomised trial performed therapeutic procedures for ISR mainly include cutting balloon angioplasty, plain old balloon angioplasty, drug-coated balloon (DCB) and DES. Several recent studies have reported that both new-generation DES and DCB are superior to other interventional strategies for ISR. Moreover, recent guidelines on myocardial revascularisation from the European Society of Cardiology recommend DCB and new-generation DES (class I, level A) for patients presenting with ISR. However, published literature comparing new-generation DES versus DCB in randomised settings conclude with diverging results. Additionally, these studies were constrained by the small sample size. To overcome these limitations, we performed a meta-analysis of randomised controlled trials (RCTs) to compare the clinical and angiographic outcome results of coronary artery disease. The rate of in-stent restenosis (ISR) in clinical practice is nearly 5% of patients treated with DES and 10% with BMS after 5 years. Given the number of patients undergoing a stent implantation, which amounts to approximately 1 000 000 per annum in the USA, ISR will continue to remain an undesirable adverse outcome.

The management of patients with ISR remains challenging. Currently, the treatment strategies for ISR mainly include cutting balloon angioplasty, plain old balloon angioplasty, drug-coated balloon (DCB) and DES. Several recent studies have reported that both new-generation DES and DCB are superior to other interventional strategies for ISR. Moreover, recent guidelines on myocardial revascularisation from the European Society of Cardiology recommend DCB and new-generation DES (class I, level A) for patients presenting with ISR. However, published literature comparing new-generation DES versus DCB in randomised settings conclude with diverging results. Additionally, these studies were constrained by the small sample size. To overcome these limitations, we performed a meta-analysis of randomised controlled trials (RCTs) to compare the clinical and angiographic outcome results of coronary artery disease. The rate of in-stent restenosis (ISR) in clinical practice is nearly 5% of patients treated with DES and 10% with BMS after 5 years. Given the number of patients undergoing a stent implantation, which amounts to approximately 1 000 000 per annum in the USA, ISR will continue to remain an undesirable adverse outcome.

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new-generation DES versus DCB in patients with coronary ISR.

METHODS
Search strategy and selection criteria
Randomised trials comparing new-generation DES versus DCB for coronary ISR were searched in PubMed, the Cochrane Library and ClinicalTrials.gov as well as the websites of major cardiovascular congresses. The subject keywords included coronary restenosis, drug-eluting balloon, paclitaxel-coated balloon, eluting stent(s) and randomised trial were applied to identify studies (online supplementary table 1). The last search was performed on 12 September 2016 by two independent investigators (J-ZC and Y-XZ). All studies comparing new-generation DES versus DCB irrespective of patients presenting with any types of ISR were included.

Data extraction and quality assessment
Two investigators (J-ZC and Y-XZ) independently screened the title and abstract of retrieved reports, reviewed the full articles of relevant citations in detail and extracted study characteristics, angiographic and longest available clinical outcomes. Any discrepancies or disagreements were settled by a third investigator (Y-JZ). The following variables were extracted from all eligible studies: enrolment periods, patient characteristics, types of ISR, definition of ISR, follow-up duration, dual antiplatelet therapy and clinical and angiographic outcomes. The risk of bias for individual trials was assessed in accordance with the Cochrane Collaboration’s tool.

Angiographic and clinical outcomes
The clinical outcomes of interest were cardiac death, all-cause death, myocardial infarction, target lesion revascularisation (TLR), target vessel revascularisation (TVR), major adverse cardiac events (MACE) and stent thrombosis. TLR was defined as any repeated revascularisation involving the target lesion. MACE was defined as individual trial. The angiographic endpoints were minimum lumen diameter (MLD), late lumen loss (LLL) and per cent diameter stenosis at 6 to 12 months. In-segment (the treated segment plus 5 mm proximal/distal margins) measurements were adopted for the analyses, but in-stent parameters was incorporated if in-segment data were not available.
The screening process is... The median sample size was 189... Apart... Analyses have been performed in the subsets of studies with a low proportion of missing data. Repeated analyses have been performed in the subsets of studies with a high level of risk of bias, and including only studies with a low proportion of missing data. Repeated analyses have been performed in the subsets of studies solely comparing paclitaxel-coated balloon versus everolimus-eluting stents; PL PCB, Pantera Lux paclitaxel-coated balloon; RCT, randomised controlled trial; SEDUCE, Safety and Efficacy of a Drug elUting balloon in Coronary artery rEstenosis; SES, sirolimus-eluting balloon; SP PCB, SeQuent Please paclitaxel-coated balloon; TLR, target lesion revascularisation; TVR, target vessel revascularisation; XP EES, Xience Prime everolimus-eluting stent.

**Table 1** Main characteristics of the included trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Type</th>
<th>Treatment arms</th>
<th>Sample size</th>
<th>Definition of ISR</th>
<th>Follow-up, months</th>
<th>DAPT, months</th>
<th>Definition of MACE</th>
</tr>
</thead>
<tbody>
<tr>
<td>TIS</td>
<td>BMS</td>
<td>SP PCB</td>
<td>68/68</td>
<td>&gt;50% DS</td>
<td>12</td>
<td>3</td>
<td>Death, any MI and TVR</td>
</tr>
<tr>
<td>RIBS IV</td>
<td>DES</td>
<td>SP PCB</td>
<td>154/155</td>
<td>&gt;50% DS</td>
<td>9</td>
<td>3</td>
<td>Death, MI and TLR</td>
</tr>
<tr>
<td>SEDUCE</td>
<td>BMS</td>
<td>XP EES</td>
<td>25/25</td>
<td>&gt;70% DS</td>
<td>9</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>RIBS V</td>
<td>BMS</td>
<td>XP EES</td>
<td>95/94</td>
<td>&gt;50% DS</td>
<td>9</td>
<td>3</td>
<td>Death, MI and TLR</td>
</tr>
<tr>
<td>BIOLUX</td>
<td>BMS</td>
<td>PL PCB, SES</td>
<td>157/72</td>
<td>n/a</td>
<td>6</td>
<td>n/a</td>
<td>Cardiac death, MI and TLR</td>
</tr>
</tbody>
</table>

BMS, bare-metal stents; DAPT, dual antiplatelet therapy; DCB, drug-coated balloon; DES, drug-eluting stents; DS, diameter stenosis; ISR, in-stent restenosis; MACE, major adverse cardiac events; MI, myocardial infarction; n/a, not available; PE EES, Promus Element everolimus-eluting stents; PL PCB, Pantera Lux paclitaxel-coated balloon; RCT, randomised controlled trial; SEDUCE, Safety and Efficacy of a Drug elUting balloon in Coronary artery rEstenosis; SES, sirolimus-eluting balloon; SP PCB, SeQuent Please paclitaxel-coated balloon; TLR, target lesion revascularisation; TVR, target vessel revascularisation; XP EES, Xience Prime everolimus-eluting stent.

**Statistical analysis**

Risk ratio (RR) and mean differences with 95% CI were used as summary statistics. The Mantel-Haenszel fixed-effects model and inverse variance fixed-effects model were used for categorical variables and continuous variables, respectively. We calculated the I² index and performed χ² test to measure statistical heterogeneity among studies. An I² >50% was considered as significant heterogeneity. A random-effects model was performed to calculate the risk estimation if a significant heterogeneity was detected. Sensitivity analyses were carried out by excluding the studies with a high level of risk of bias, and including only studies with a low proportion of missing data. Repeated analyses have been performed in the subsets of studies solely comparing paclitaxel-coated balloon versus everolimus-eluting stents (EES), and patients with only BMS-ISR. The Egger’s linear regression tests were employed to test funnel plot asymmetry at the P<0.10 level of significance. However, the analysis for publication bias can only be tentative, as there is not enough power to support the test results due to the limited number of studies included.

All the statistical analyses were performed using STATA V.13.0 and Review Manager V.5.3 (The Nordic Cochrane Centre, Copenhagen, Denmark).

**RESULTS**

Five trials with a total of 913 patients treated either with new-generation DES (n=414) or DCB (n=499) were eligible and included.8,13,16 The screening process is described in figure 1. The median sample size was 189 (IQR 83–269). Only the prospective randomised Treatment of In-Stent Restenosis (TIS) trial was single centre, and the others were multicentre. Patients enrolled were from Czech in the TIS trial, Spain in the Restenosis Intra-stent of Bare Metal Stents: Paclitaxel-eluting Balloon vs. Everolimus-eluting Stent (RIBS) IV and RIBS V trials, Belgium in the Safety and Efficacy of a Drug elUting balloon in Coronary artery rEstenosis (SEDUCE) trial and Germany and Latvia in BIOLUX (Clinical performance of the Pantera Lux paclitaxel coated balloon vs. the drug-eluting Orsiro hybrid stent system in patients with in-stent restenosis) RCT. All trials had a high risk of bias with respect to performance bias and the details of methodology in BIOLUX RCT trial were not available. The summary of risk judgement in individual trials is shown in online supplementary figure 1. The trial, patient and angiographic characteristics are summarised (table 1, online supplementary tables 2 and 3). Apart from 229 patients (25.1%) with mixed types of ISR in one trial,8,15 309 patients (33.9%) with DES-ISR were recruited in one trial,8 while 375 patients (41.0%) with BMS-ISR were recruited in three trials.14–16 The follow-up of patients ranged from 6 to 12 months angiographically, and from 12 to 36 months clinically.

**TLR, TVR and MACE**

TLR was reported in four trials including 777 patients.8,13,16,17 The incidence of TLR in the DCB group (10.9%) was significantly higher than that in new-generation DES (5.2%) (RR: 1.96, 95% CI 1.17 to 3.28, P=0.01; I²=32%, P=0.22; figure 2A). TVR was not available in the BIOLUX RCT trial.17 There was no significant difference in the risk of TVR between DCB and DES (RR: 1.06, 95% CI 0.48 to 2.34, P=0.89; I²=60%, P=0.06; figure 2B).

All but the SEDUCE trial reported the rates of MACE.16 The rates of MACE between DCB (14.7%) and DES (9.0%) were comparable (RR: 1.21, 95% CI 0.67 to 2.17, P=0.53; I²=58%, P=0.07; figure 2C).

**Cardiac death, all-cause death, myocardial infarction and stent thrombosis**

Myocardial infarction, stent thrombosis and cardiac death were all available in five trials but all-cause death was not
reported in the BIOLUX RCT trial. The pooled RR showed no significant differences in cardiac death (RR: 1.80, 95% CI 0.60 to 5.39, P=0.29; I²=0%; P=0.92; figure 3A) and myocardial infarction (RR: 1.16, 95% CI 0.55 to 2.48, P=0.69; I²=0%; P=0.76; figure 3B) between the two arms, as well as all-cause death (RR: 1.50, 95% CI 0.62 to 3.62, P=0.37; I²=0%; P=0.55) and stent thrombosis (RR: 1.26, 95% CI 0.39 to 4.04, P=0.70; I²=0%; P=0.75; figure 3C).

### Angiographic endpoints

All five trials contributed to the angiographic follow-up results. Patients treated with new-generation DES had a significant increase of acute luminal gain (−0.31 mm, 95% CI −0.42 to −0.20, P<0.001; I²=52%, P=0.08; figure 3A) and reduction of per cent diameter stenosis (RR: 0.28, 95% CI 0.02 to 0.55, P=0.04; I²=72%, P=0.006; figure 3B) compared with DCB.

A strong trend towards an increase in MLD (−0.23 mm, 95% CI −0.47 to 0.01, P=0.06; I²=65%, P=0.02, figure 3A) was noted in the new-generation DES arm but this difference was not statistically significant compared with DCB.

All but the BIOLUX RCT trial reported the incidences of binary restenosis. Patients treated with new-generation DES were associated with a similar risk of binary restenosis (RR: 1.25, 95% CI 0.57 to 2.75, P=0.58; I²=56%, P=0.08; figure 5B) and LLL (−0.06 mm, 95% CI −0.37 to 0.25, P=0.71; I²=80%, P=0.0006; figure 5C) compared with DCB.

### Publication bias and sensitivity analyses

No publication biases were found in all clinical and angiographic outcomes (online supplementary figure 2). Sensitivity analyses suggested that DCB was associated with a high risk of MACE (RR: 1.57, 95% CI 1.04 to 2.38, P=0.03; I²=19%, P=0.29) as well as an increase in in MLD (−0.29 mm, 95% CI −0.55 to −0.03, P=0.03; I²=64%, P=0.04) and binary restenosis (RR: 1.85, 95% CI 1.11 to 3.10, P=0.02; I²=0%, P=0.99) while excluding the TIS trial which comes from a single centre. Detailed methodology in BIOLUX RCT trial was not available; however, MLD remained greater in the DES group when the BIOLUX RCT trial was omitted (−0.29 mm, 95% CI −0.55 to −0.04,
P=0.03; I^2=60%, P=0.06). In the setting of patients with BMS-ISR,13 15 16 no significant differences were found in DCB versus new-generation DES in all angiographic and clinical outcomes except for acute luminal gain (−0.39 mm, 95% CI −0.50 to −0.28, P<0.001; I^2=0%, P=0.40). Patients treated exclusively with EES had significant low incidence of TLR (RR: 2.64, 95% CI 1.35 to 5.18, P=0.005; I^2=12%, P=0.32), increased acute luminal gain (−0.32 mm, 95% CI −0.47 to −0.17, P<0.001; I^2=64%, P=0.04) and superior MLD (−0.29 mm, 95% CI −0.55 to −0.04, P=0.03; I^2=60%, P=0.06). But no statistical differences in other clinical and angiographic outcomes were observed between the two groups.

**DISCUSSION**
This meta-analysis included five randomised trials examining the angiographic and clinical outcomes of new-generation DES versus DCB in the treatment of any type of coronary ISR. The study, for the first time, showed that new-generation DES appears to be associated with an improved angiographic and clinical outcomes when compared with DCB irrespective of the types of ISR at short-term follow-up. The main findings are as follows: (1) new-generation DES were associated with a significant reduction in TLR compared with DCB at the longest available follow-up; (2) there were no statistical differences in cardiac death, myocardial infarction and MACE between the two treatment strategies; (3) new-generation DES were associated with favourable angiographic results with significant increase in acute luminal gain and reduction in per cent diameter stenosis at 6-month to 12-month follow-up.

**Previous meta-analyses**
The choice of therapeutic methods for coronary ISR remains debatable. Several meta-analyses demonstrated that DCB and DES had comparable clinical and angiographic results for patients with coronary ISR.5 10 20 However, obvious pitfalls existed in these studies. First,
Mamuti et al. combined new-generation DES and first-generation DES in the same group, whereas cumulative evidence has illustrated the difference in clinical performance of different-generation DES. Liou et al. demonstrated no superiority of the new-generation DES over DCB but their analysis included four observational studies in which an inequality of baseline characteristics was observed. A further limitation of this meta-analysis was the small number of randomised patients ($n=548$ from three RCTs). Additionally, in a Bayesian network meta-analysis comparing the performance of all therapeutic treatments for ISR, EES was considered as optimal strategy with pronounced improvements in clinical outcomes. However, the effect was mainly derived from indirect comparison.

In the present meta-analysis, we, for the first time, included only randomised trials of new-generation DES in comparison with DCB, so the possibility of confounders influencing estimates for various endpoints is less likely. Furthermore, this meta-analysis included the largest number of patients with ISR to date and demonstrated that contemporary DES with improved design were associated with favourable outcomes and a lower risk of reintervention at midterm follow-up, compared with DCB.

**Angiographic and clinical outcomes**

Compared with DCB, new-generation DES were related to favourable prognosis for coronary ISR with superior angiographic outcomes and reduced TLR. The advantages of new-generation DES comprised of persistent radial strength which prevents acute or subacute prolapse of the disrupted plaque and elastic recoil of the vessel wall, sufficient antiproliferative drugs and subsequent excellent neointimal hyperplasia inhibition compared with DCB. Interestingly, the rate of recurrent binary restenosis was similar in two groups. The difference of TLR was possibly related to the fact that presence of an existing additional stent layer in the DES group discouraged the operator from repeat intervention. Although one may argue that DES add one more stent layer in the finite lesion segment, 80–100 µm of lumen loss due to the implants seems negligible when considering that new-generation DES assume less reintervention. Although one may express concern regarding the long-term safety of stent implantation, studies have shown that the vascular inflammatory response with the thin-strut platform profile and also its biocompatibility or biodegradable polymer is extremely low.

The present study, however, remains limited by its small sample size and short periods of follow-up. By virtue of previously published literature, it is reasonable to assume that the short-term (less than 1 year) benefit of new-generation DES will remain consistent.

In the RIBS V trial, the authors have observed one TLR event in the EES group and two in the DCB group from 1 to 3 years. In the RESTENT-ISR (Prospective Randomised Comparison of Clinical and Angiographic Outcomes Between Everolimus-eluting vs Zotarolimus-eluting Stents for Treatment of Coronary Restenosis in Drug-Eluting Stents: Intravascular Ultrasound Volumetric Analysis) trial, Hong et al. reported an approximate rate of 6.0% in late (>1 year) TLR in patients with ISR treated with EES and zotarolimus-eluting stents, similar to several subgroups from all-comers study. The present study, however, remains limited by its small sample size and short periods of follow-up. By virtue of previously published literature, it is reasonable to assume that the short-term (less than 1 year) benefit of new-generation DES will remain consistent.

**Figure 4** Forest plots of risk ratios for acute lumen gain and per cent diameter stenosis. Size of data markers indicates weight of each trial included in the meta-analysis: (A) acute lumen gain and (B) per cent diameter stenosis (DS). DCB, drug-coated balloon; DES, drug-eluting stents.
The Intracoronary Stenting and Angiographic Results: Drug Eluting Stent In-Stent Restenosis: 3 Treatment Approaches (ISAR-DESIRE 3) and PEPCAD China ISR (A Prospective, Multicenter, Randomised Trial of Paclitaxel-Coated versus Paclitaxel-Eluting Stent for the Treatment of Drug-Eluting Stent In-Stent Restenosis) trials have shown a late mortality benefit of DCB treatment versus first-generation DES treatment on longer follow-up. On the other hand, there were similar deaths in the EES group and DCB group from 1 to 3 years in the RIBS V trial. Thus, any potential long-term benefit of DCB compared with additional new-generation DES implantation remains unproven.

The studies included in this meta-analysis have several differences. First, The RIBS IV trial contributed significantly in the endpoint of TLR in favour of DES on the basis of our sensitivity analysis. The RIBS IV and RIBS V trials, which account for nearly 64% of studied patient populations in this meta-analysis, allowed acute predilatation residual stenosis of up to 50% before DCB application. This is in strong opposition to what is accepted by most high-volume DCB centres and published as the German Consensus Recommendations. Moreover, our study presented high heterogeneities in the majority of angiographic and clinical outcomes, which were mainly driven by the TIS trial. Furthermore, the use of scoring balloons and implantation of another bail-out stent were more common in TIS trial, which may have a potential role in improving the antiproliferation potency of DCB. Further researches with a careful follow-up protocol and large sample size should be performed to provide more confirmative information.

**Future perspectives**

Both new-generation DES and DCB for the treatment of ISR are on the same class I (A) recommendation in the latest European Society of Cardiology guideline on myocardial revascularisation. However, our meta-analysis suggests that new-generation DES represent a superior treatment strategy with similar safety and improved angiographic and clinical efficacy at short-term follow-up. Nevertheless, concerns remain about multilayers of...
metal stents in the vessel wall which may entail difficulty in further treatments and an inherent poorer clinical prognosis. Similarly, for patients with intolerable long-term dual antiplatelet therapy or high risk of bleeding, DCB may be more suitable. Biodegradable scaffold (BRS) may be an alternative treatment choice in the future. The ongoing AbsorbISR (Absorb Biodegradable Scaffold vs Drug Coated Balloon for Treatment of In-Stent-Restenosis, NCT02474485) trial comparing biodegradable vascular scaffold with DCB to treat ISR will shed light in terms of clinical utility of BRS for coronary ISR. Finally, further refinements in DCB technology and auxiliary strategies such as use of scoring balloon before DCB are warranted.

Limitations
The following potential limitations of the present study are acknowledged. First, the results were based on the trial level and share the limitations of the original trials. Specially, the clinical outcomes of TLR, TVR and MACE were only reported in four trials, respectively, which may, in some degree, affect the outcomes of this meta-analysis. Second, the studied DCB group included Sequent Please and Pantera Lux paclitaxel-eluting balloons, which have different coatings design, as well as the implemental methods of DCB in individual trials. Thirdly, the definitions of clinical and angiographic parameters were not identical in some studies. Finally, in light of the fairly highly selected criteria in our study, only a total of 913 patients were enrolled. However, our study demonstrates the largest patient population presenting with ISR and is likely to remain the most powerful evidence base for evaluation of DCB versus new-generation DES.

CONCLUSIONS
New-generation DES seems an acceptable treatment strategy with comparable safety and favourable angiographic and clinical efficacy compared with DCB for coronary ISR at short-term follow-up. Further larger-scale randomised trials with longer term follow-up are warranted.

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Y-J.Z is the guarantor. Y-J.Z, J-Z.C, Y-X.Z, X-Y.W, H.Z, C.V.B, J.I, P.C and A.M drafted the manuscript. P.C, A.M, S-J.D and J.I revised the manuscript for important intellectual content. All authors have read and approved this article.

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Competing interests
None declared.

Patient consent
Not required.

Data sharing statement
No additional data are available.

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