**Drug-Eluting Balloon versus New-Generation Drug-Eluting Stent for the Treatment of In-Stent Restenosis: An Updated Systematic Review and Meta-Analysis**

**Kong-Yong Cui, Shu-Zheng Lyu, Min Zhang, Xian-Tao Song, Fei Yuan, Feng Xu**

Department of Cardiology, Beijing Anzhen Hospital, Capital Medical University and Beijing Institute of Heart, Lung and Blood Vessel Diseases, Beijing 100029, China

**Abstract**

**Background:** Currently, drug-eluting balloon (DEB) appears to be an attractive alternative option for the treatment of in-stent restenosis (ISR). Nevertheless, the clinical outcomes of DEB have seldom been compared to those of new-generation drug-eluting stent (DES). Thus, this meta-analysis aimed to evaluate the safety and efficacy of DEB compared to those of new-generation DES in the treatment of ISR.

**Methods:** A comprehensive search of electronic databases including PubMed, EMBASE, and Cochrane Library up to November 2, 2017 was performed to identify pertinent articles comparing DEB to new-generation DES for the treatment of ISR. In addition, conference proceedings for the scientific sessions of the American College of Cardiology, American Heart Association, European Society of Cardiology, Transcatheter Cardiovascular Therapeutics, and EuroPCR were also searched. The primary endpoint was target lesion revascularization (TLR) at the longest follow-up. Dichotomous variables were presented as risk ratios (RRs) with 95% confidence intervals (CIs), while the overall RRs were estimated using the Mantel-Haenszel random-effects model.

**Results:** Five randomized controlled trials (RCTs) and eight observational studies involving 2743 patients were included in the present meta-analysis. Overall, DEB was comparable to new-generation DES in terms of TLR (RR = 1.24, 95% CI: 0.89–1.72, P = 0.21), cardiac death (RR = 1.55, 95% CI: 0.89–2.71, P = 0.12), major adverse cardiovascular event (RR = 1.21, 95% CI: 0.98–1.48, P = 0.07), myocardial infarction (RR = 1.12, 95% CI: 0.72–1.76, P = 0.62), and stent thrombosis (RR = 0.95, 95% CI: 0.38–2.42, P = 0.92). However, DEB was associated with higher risk of all-cause mortality than new-generation DES (RR = 1.65, 95% CI: 1.09–2.50, P = 0.02). This was especially true in the real-world observational studies (RR = 1.79, 95% CI: 1.12–2.88, P = 0.02). In RCTs, however, no significant difference was found between the two treatment strategies in the risk of all-cause mortality.

**Conclusions:** The current meta-analysis showed that DEB and new-generation DES had comparable safety and efficacy for the treatment of ISR in RCTs. However, treatment with DEB was associated with higher risk of all-cause mortality in the real-world nonrandomized studies.

**Key words:** Drug-Eluting Balloon; In-Stent Restenosis; Meta-Analysis; New-Generation Drug-Eluting Stent

**Introduction**

Currently, in-stent restenosis (ISR) remains a problem in percutaneous coronary intervention as it is associated with a high rate of repeat revascularization. Previous study has demonstrated the efficacy of drug-eluting stent (DES) for the treatment of ISR. Nevertheless, with increased risk of late stent thrombosis (ST) due to incomplete endothelialization and inflammatory response, first-generation DES is restricted to longer-term dual antiplatelet therapy compared with bare-metal stent (BMS). Recent network meta-analysis indicates that new-generation DES is associated with significantly lower rates of ST as compared to BMS and first-generation DES.
which makes it an appropriate choice for the treatment of ISR.\(^2\)

Drug-eluting balloon (DEB) is emerging as a potential alternative to the current treatment of ISR. It can deliver active drugs homogeneously to inhibit neointimal hyperplasia without remaining in the arteries permanently.\(^3\) Furthermore, in the updated European Society of Cardiology (ESC) guidelines, DEB receives a class I recommendation (level of evidence A) for both BMS-ISR and DES-ISR.\(^6\)

Most available studies have only compared DEB to the first-generation DES but not the new-generation DES, which appears to be most widely adopted to increase the safety and efficacy of DES implantation.\(^7\)

Previous meta-analysis involving 1065 patients has demonstrated that DEB was associated with higher incidence of target lesion revascularization (TLR) and major adverse cardiovascular event (MACE) as compared to new-generation DES for the treatment of ISR.\(^8\) However, this study was limited by a small sample size. In the past few years, there have been several studies comparing DEB with new-generation DES in treating ISR, though most of them were observational studies without adequate evidences. The recently presented Drug-Eluting Balloon for In-Stent Restenosis (DARE) Trial at the Transcatheter Cardiovascular Therapeutics (TCT) annual conference has shown that treatment with SeQuent Please was noninferior to XIENCE in terms of 6-month minimal lumen diameter (MLD).\(^9\)

Here, we performed a meta-analysis of all the currently available clinical trials to compare the safety and efficacy of DEB with those of new-generation DES in the treatment of ISR.

**Methods**

This study was performed in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement\(^10\) and Meta-analysis of Observational Studies in Epidemiology checklist.\(^11\)

**Search strategy**

A comprehensive search of electronic databases including PubMed, EMBASE, and Cochrane Library up to November 2, 2017 was performed to identify pertinent articles comparing DEB to new-generation DES for the treatment of ISR. In addition, conference proceedings for the scientific sessions of the American College of Cardiology, American Heart Association, ESC, TCT, and EuroPCR were also searched. The following medical subject headings and search terms were used: “drug-eluting balloon”, “drug-coated balloon”, “paclitaxel-coated balloon”, “paclitaxel-eluting balloon”, “stent”, “restenosis”, and “in-stent restenosis”. The references of the identified articles and relevant reviews were screened to include other potentially suitable trials. The authors of the original studies were not contacted for additional information.

**Study selection**

Studies satisfying the following criteria were eligible: (1) randomized controlled trials (RCTs) or observational studies regarding ISR; (2) compared DEB to new-generation DES directly; (3) follow-up lasted for at least 6 months; and (4) reported endpoint data of interest. The selection was conducted by scanning of titles or abstracts, and full-text reviews were performed for further analysis. When several reports overlapped with each other, we selected the largest and the latest one. The studies were reviewed by two independent investigators to determine whether or not they met the inclusion criteria, and any disagreement was resolved by consensus.

**Data extraction**

The following data were extracted independently by two investigators using a standardized form from each study: study characteristics, patient characteristics, and outcomes (angiographic and clinical outcomes). Differences in assessments were resolved by discussing with a third investigator. The primary endpoint was TLR at the longest follow-up. The most similar endpoint, i.e., target vessel revascularization (TVR), was chosen in case TLR was not reported. All-cause death, cardiac death, MACE, myocardial infarction (MI), ST, late lumen loss (LLL), and MLD were the secondary outcomes. In addition, MACE was defined variable in each study.

**Quality assessment**

The quality of RCTs and observational studies was assessed. The RCTs were evaluated according to the following methodological criteria recommended by the Cochrane Collaboration: sequence generation, concealment of allocation, blinding, incomplete outcome data, selective outcome reporting, and other sources of bias.\(^12\) The observational studies were evaluated using the Newcastle-Ottawa Scale criteria.\(^13\)

**Statistical analysis**

Dichotomous data and continuous variables were presented as risk ratios (RRs) and mean differences (MDs) with 95% confidence intervals (CIs), respectively. For RRs, the Mantel-Haenszel random-effects model was used, and the overall MD was estimated using the inverse variance random-effects model. Potential heterogeneity among studies was quantified with \(I^2\) and \(I^2 \geq 50\%\) was defined as statistical heterogeneity. Furthermore, we used funnel plots to assess the potential publication bias. All statistical analyses were performed with Review Manager 5.1 (Cochrane Center, Denmark).

Subgroup analysis was carried out to explore the sources of heterogeneity (RCTs and observational studies). Another method to examine whether the RRs/MDs were significantly changed was to remove the studies according to the following variables: (1) lesions were restricted to BMS-ISR or DES-ISR; (2) DEB was restricted to SeQuent Please; (3) DES was restricted to everolimus-eluting stent (EES); and (4) excluding recurrent ISR. Sensitivity analysis was also performed to demonstrate the robustness of the results by omitting one study in each turn. All \(P\) values were two-sided, and results were considered statistically significant when the value of \(P < 0.05\).
**RESULTS**

**Eligible studies**

After a comprehensive search according to the inclusion criteria, 1643 potentially relevant articles were identified in the initial analysis. Among them, 26 articles were chosen for complete review. Finally, 13 studies (including 5 RCTs and 8 observational studies) involving 2743 patients were included in the present meta-analysis [Figure 1]. \[9,14-25\] Note that, the 3-year outcomes of RIBS IV trial were reported in TCT annual conference, with data not yet available, so the related study with 1-year clinical follow-up data was enrolled. \[15\]

The patient characteristics and methodology of the included studies are briefly depicted in Table 1. The baseline and procedural characteristics of patients are presented in Supplementary Table 1. Among the 13 trials, the adopted DEBs were varied, including SeQuent Please, In.PACT Falcon, and other paclitaxel-eluting balloons. Regarding the devices in control groups, EES was used exclusively in seven trials. \[9,14-17,21,25\] Overall, two trials enrolled patients with recurrent ISR, \[20,21\] three trials enrolled patients with BMS-ISR, \[14,16,25\] and five trials enrolled patients with DES-ISR \[15,17-20\] exclusively. The clinical follow-up period ranged from 12 to 36 months and the duration of angiographic follow-up varied from 6 to 12 months. Quality assessment results are described in Supplementary Tables 2 and 3. The assessment of the funnel plot was performed in terms of TLR and no publication bias was found [Supplementary Figure 1].

**Primary endpoint**

Overall, 11 trials and 2 trials reported the incidence of TLR and TVR, respectively. As shown in Figure 2, the risk of TLR was comparable between the DEB group and the new-generation DES group \( (RR = 1.24, 95\% CI: 0.89–1.72, P = 0.21, I^2 = 53\%) \). In addition, no difference was found between the two groups in RCTs \( (RR = 1.36, 95\% CI: 0.60–3.06, P = 0.46, I^2 = 61\%) \) and in observational studies \( (RR = 1.19, 95\% CI: 0.83–1.72, P = 0.35, I^2 = 53\%) \).

**Secondary endpoints**

The all-cause death was reported in 10 trials. In general, DEB was associated with increased all-cause mortality \( (RR = 1.65, 95\% CI: 1.09–2.50, P = 0.02, I^2 = 0\%) \) compared with new-generation DES for the treatment of ISR. To be specific, the risk of all-cause mortality was different between the two treatment strategies only in the real-world observational studies \( (RR = 1.79, 95\% CI: 1.12–2.88, P = 0.02, I^2 = 0\%) \), whereas it was similar between the two treatment strategies in RCTs \( (RR = 1.24, 95\% CI: 0.52–2.96, P = 0.63, I^2 = 0\%); Figure 3a). The two treatment strategies were not significantly different in terms of other clinical outcomes including cardiac death \( (RR = 1.55, 95\% CI: 0.89–2.71, P = 0.12, I^2 = 0\%); Figure 3b), MACE \( (RR = 1.21, 95\% CI: 0.98–1.48, P = 0.07, I^2 = 22\%); Figure 3c), MI \( (RR = 1.12, 95\% CI: 0.72–1.76, P = 0.62, I^2 = 0\%); Figure 3d), and ST \( (RR = 0.95, 95\% CI: 0.38–2.42, P = 0.92, I^2 = 0\%); Figure 3e). Besides, the differences in these clinical outcomes were not significant between the two treatment strategies in RCTs or in observational studies.

The data about angiographic endpoints were reported in six studies. As shown in Figure 4, patients treated with DEB obtained similar LLL to those treated with new-generation DES \( (MD = −0.05\ mm, 95\% CI: −0.24–0.14\ mm, P = 0.64, I^2 = 86\%); Figure 4a)\). However, DEB is associated with smaller MLD compared with new-generation DES \( (MD = −0.20\ mm, 95\% CI: −0.36–0.04\ mm, P = 0.01, I^2 = 76\%); Figure 4b)\).

**Sensitivity analysis**

Sensitivity analysis was performed by evaluating the influence of variables on the pooled estimates. Subsequently, it was found that results were similar to the overall analysis results [Table 2]. Furthermore, sensitivity analysis conducted through the removal of any single trial showed that it did not essentially affect the overall pooled estimate of TLR. Note, however, that the statistical difference in all-cause mortality between the DEB group and the new-generation DES group no longer existed after excluding the study by Lee et al. \[22\] \( (RR = 1.48, 95\% CI: 0.91–2.40) \) or Marquis-Gravel et al. \[23\] \( (RR = 1.48, 95\% CI: 0.93–2.37); data not shown).
DES in the treatment of ISR in terms of TLR, cardiac death, MACE, MI, ST, and LLL. In addition, no significant difference in clinical outcomes was found between the DEB group and the new-generation DES group in RCTs. However, the use of DEB might increase the risk of all-cause mortality in observational studies.

Local drug delivery by DEB enables an immediate and homogenous drug uptake without stent struts or polymers.\(^5,28\) Furthermore, it complements the normal vessel anatomy by avoiding inflammatory reactions. Compared with DES, it avoids multiple stent strut layers in ISR lesions, thereby shortening the duration of dual antiplatelet therapy. In fact, previous studies have demonstrated the benefits of DEB in the treatment of BMS ISR and DES ISR.\(^6\) Compared with plain balloon angioplasty, DEB is more effective in treating coronary ISR with long-term clinical benefits of up to 5 years.\(^29\) Recently, similar results of using DEB and the first-generation DES have been reported in the treatment of ISR.\(^2\) Accordingly, updated ESC guidelines have suggested that DEB can be used in patients with ISR (class of recommendation I, level of evidence A).\(^6\)

New-generation DES, especially EES, is the most common type of DES used in the current interventional practice.\(^30,31\) EES made of cobalt-chromium or platinum-chromium alloys has a thinner strut than first-generation DES and it also uses a biocompatible fluoropolymer while the paclitaxel-eluting stent uses a durable polymer, which is associated with medial necrosis, positive remodeling, and excessive fibrin deposition.\(^32\) Previous meta-analysis has shown that the new-generation DES, such as EES or zotarolimus-eluting stent, has improved safety and efficacy.

### Table 1: Patient characteristics and methodology of the included studies

| Studies               | Years | Study period | Lesion characteristics | Comparison               | Number of patients | Angiographic follow-up (months) | Clinical follow-up (months) | Definition of MACE |
|-----------------------|-------|--------------|------------------------|--------------------------|-------------------|-------------------------------|--------------------------|-------------------|
| Adriaenssens et al.\(^14\) | 2014  | 2009–2011    | BMS ISR                | SeQuent Please versus EES | 50                | 9                             | 12                       | NA                |
| Alfonso et al.\(^31\) | 2015  | 2010–2013    | DES ISR                | SeQuent Please versus EES | 309               | 6–10                          | 12                       | Cardiac death, MI, or TLR |
| Alfonso et al.\(^38,39\) | 2016  | 2010–2012    | BMS ISR                | SeQuent Please versus EES | 189               | 6–9                           | 36                       | Death, MI, or TVR   |
| Almalla et al.\(^17,27\) | 2015  | 2006–2011    | DES ISR                | DEB versus EES            | 86                | NA                           | 36                       | Death, MI, or TLR   |
| Basavarajiah et al.\(^14\) | 2016  | 2009–2011    | DES ISR                | In.PACT Falcon versus 2\(^{nd}\) DES | 247               | NA                           | 24                       | Cardiac death, TVMI, or TVR |
| Henriques and Baan\(^9\) | 2017  | 2010–2015    | ISR                    | SeQuent Please versus EES | 278               | 6                            | 12                       | Death, TVMI, or TVR |
| Kang et al.\(^19\) | 2016  | 2007–2014    | DES ISR                | SeQuent Please versus 2\(^{nd}\) DES | 238               | NA                           | 24                       | Cardiac death, MI, ST, or TVR |
| Kawamoto et al.\(^23\) | 2015  | 2008–2013    | Recurrent DES ISR      | In.PACT Falcon/Pantera Lux versus 2\(^{nd}\) DES | 133               | NA                           | 24                       | Death, MI, or TLR   |
| Kubo et al.\(^21\) | 2015  | 2008–2012    | Recurrent DEB ISR      | SeQuent Please versus EES | 89                | 6–8                          | 24                       | NA                |
| Lee et al.\(^22\) | 2017  | 2008–2014    | ISR                    | DEB versus 2\(^{nd}\) DES | 628               | NA                           | 12                       | Death, MI, or revascularization |
| Marquis-Gravel et al.\(^23\) | 2013  | 2009–2012    | ISR                    | DEB versus 2\(^{nd}\) DES | 202               | NA                           | 16                       | Death, MI, or clinically-driven TLR |
| Naganuma et al.\(^24\) | 2016  | 2007–2012    | ISR with bifurcation    | In.PACT Falcon versus 2\(^{nd}\) DES | 158               | NA                           | 24                       | Cardiac death, MI, or TVR |
| Pleva et al.\(^27\) | 2016  | 2012–2014    | BMS ISR                | SeQuent Please versus EES | 136               | 12                           | 12                       | Cardiac death, MI, or TVR |

BMS: Bare-metal stent; DEB: Drug-eluting balloon; DES: Drug-eluting stent; EES: Everolimus-eluting stent; ISR: In-stent restenosis; MACE: Major adverse cardiac event; MI: Myocardial infarction; NA: Not applicable; ST: Stent thrombosis; TLR: Target lesion revascularization; TVMI: Target vessel myocardial infarction; TVR: Target vessel revascularization.

### Figure 2: Forest plot of target lesion revascularization associated with drug-eluting balloon (DEB) versus new-generation drug-eluting stent (DES) for patients with in-stent restenosis. CI: Confidence interval.

DES in the treatment of ISR in terms of TLR, cardiac death, MACE, MI, ST, and LL. In addition, no significant difference in clinical outcomes was found between the DEB group and the new-generation DES group in RCTs. However, the use of DEB might increase the risk of all-cause mortality in observational studies.
than the first-generation DES.[7] To date, however, there are few RCTs involving the comparison of DEB with the new-generation DES. The RIBS IV trial has reported that cobalt-chromium EES enables better clinical and angiographic results than SeQuent Please in 1 year.[15] Nevertheless, the DARE trial presented at TCT conference has shown that MLD in the SeQuent Please group is noninferior to that in the platinum-chromium EES group (1.71 ± 0.51 mm vs. 1.74 ± 0.61 mm, *P* noninferiority < 0.0001). Furthermore, SeQuent Please is associated with less LLL than platinum-chromium EES (0.17 ± 0.41 mm vs. 0.45 ± 0.47 mm, *P* < 0.001), while the combined clinical outcome measure (10.9% vs. 9.2%, *P* = 0.66) and the need for TVR (8.8% vs. 7.1%, *P* = 0.65) are similar between the two treatment strategies.[9] In this context, we performed this meta-analysis to evaluate the relative safety and efficacy of DEB to those of the new-generation DES.

Liou et al.[8] found that DEB tends to be associated with increased risk of TLR and MACE, but their study was limited by small sample size. Our meta-analysis of all the available

---

| Study or Subgroup | DEB | Total | Total | Total | Risk Ratio | Mc-Ran, 95% CI | Test for overall effect | Z value | P value |
|------------------|-----|-------|-------|-------|------------|----------------|------------------------|--------|--------|
| Forest plot       |     |       |       |       |            |                |                        |        |        |
| a. All-cause death |     |       |       |       |            |                |                        |        |        |
| b. Cardiac death  |     |       |       |       |            |                |                        |        |        |
| c. Major adverse cardiovascular event |     |       |       |       |            |                |                        |        |        |
| d. Myocardial infarction |     |       |       |       |            |                |                        |        |        |
| e. Stent thrombosis |     |       |       |       |            |                |                        |        |        |

---

**Figure 3:** Forest plot of all-cause death (a), cardiac death (b), major adverse cardiovascular event (c), myocardial infarction (d), and stent thrombosis (e) associated with drug-eluting balloon (DEB) versus new-generation drug-eluting stent (DES) for patients with in-stent restenosis. CI: Confidence interval.
trials indicated that the risk of TLR and MACE was similar between the DEB group and the new-generation DES group, especially in RCTs. This meant the superior angiographic outcome did not indicate significantly enhanced clinical outcomes, even though MLD was significantly smaller in the DEB group than in the new-generation DES group. Nevertheless, all-cause mortality was significantly higher in the DEB group in the real-world observational studies, where selection bias could not be avoided. In clinical scenarios, DEBs are more likely to be applied when patients are presented with complex lesions, recurrent restenosis, or co-morbidities hampering prolonged dual antiplatelet therapy. Notably, the incidence of all-cause death is not significantly different between the DEB group and the new-generation DES group in the RCTs.

Nowadays, EES is the most extensively applied new-generation DES, which has shown improved safety and efficacy than the first-generation DES. Nonetheless, analysis restricted to EES alone has demonstrated that EES is not superior to DEB in terms of primary and secondary endpoints. SeQuent Please, which is also widely employed, enables the complete release of paclitaxel on the first balloon expansion on the target site with higher bioavailability than DIOR. In this setting, the studies adopted SeQuent Please were reanalyzed exclusively. Fortunately, the analysis results show that SeQuent Please gives similar angiographic and clinical results to the new-generation DES.

Our meta-analysis presented several limitations that could not be ignored. First, this meta-analysis included both RCTs and observational studies, and the randomized data were limited. Notably, baseline differences originated from the nonrandomized real-world studies might affect the results. Second, consistent heterogeneity was observed for the TLR. Stratified analysis limited to more homogeneous subgroups of patients was performed and random effects model was used to account for the heterogeneity. Third, different types of new-generation DES in the various trials were an important source of heterogeneity. Fourth, there was a certain relevant heterogeneity with regard to the various DEBs although all the DEBs adopted were paclitaxel-coated balloons. To mitigate heterogeneity, analysis of SeQuent Please was conducted exclusively. Fifth, two studies with recurrent ISR were incorporated because studies comparing DEB and new-generation DES were limited. Fortunately, sensitivity analysis performed by excluding the two studies demonstrated that the results were mostly similar to the results of the overall analysis.

In conclusion, this meta-analysis showed that DEB and new-generation DES had comparable safety and efficacy for the treatment of ISR in RCTs. However, treatment with DEB was associated with higher risk of all-cause mortality in real-world nonrandomized studies. Further, large-scale and well-designed RCTs are expected to clarify the safety and efficacy of DEB and new-generation DES in ISR therapy.

**Table 2: Sensitivity analysis based on the influence of variables on the pooled estimates**

| Endpoints | Overall | BMS ISR | DES ISR | SeQuent Please exclusively | EES exclusively | Excluding recurrent ISR |
|-----------|---------|---------|---------|---------------------------|----------------|------------------------|
| TLR       | 1.24 (0.89, 1.72) | 0.98 (0.22, 4.41) | 1.16 (0.74, 1.84) | 1.56 (0.84, 2.87) | 1.36 (0.67, 2.76) | 1.14 (0.80, 1.61) |
| Death     | 1.65 (1.09, 2.50) | 2.15 (0.64, 7.19) | 1.02 (0.48, 2.16) | 1.28 (0.60, 2.72) | 1.23 (0.68, 2.24) | 1.71 (1.10, 2.66) |
| Cardiac death | 1.55 (0.89, 2.71) | 1.78 (0.37, 8.48) | 1.21 (0.47, 3.13) | 1.25 (0.46, 3.37) | 1.12 (0.45, 2.83) | 1.56 (0.88, 2.76) |
| MACE      | 1.21 (0.98, 1.48) | 0.81 (0.37, 1.79) | 1.15 (0.87, 1.52) | 1.18 (0.81, 1.73) | 1.04 (0.69, 1.56) | 1.21 (0.96, 1.51) |
| MI        | 1.12 (0.72, 1.76) | 0.74 (0.25, 2.22) | 1.95 (0.82, 4.62) | 1.07 (0.51, 2.21) | 1.09 (0.56, 2.12) | 1.04 (0.66, 1.66) |
| ST        | 0.95 (0.38, 2.42) | 1.44 (0.23, 9.01) | 0.60 (0.08, 4.83) | 1.88 (0.83, 4.19) | 1.30 (0.31, 5.36) | 0.78 (0.25, 2.39) |
| LLL       | −0.05 (−0.24, 0.14) | −0.06 (−0.36, 0.24) | 0.12 (−0.02, 0.26) | −0.05 (−0.24, 0.14) | −0.05 (−0.24, 0.14) | −0.07 (−0.28, 0.14) |

BMS: Bare-metal stent; DES: Drug-eluting stent; EES: Everolimus-eluting stent; ISR: In-stent restenosis; LLL: Late lumen loss; MACE: Major adverse cardiac events; MI: Myocardial infarction; ST: Stent thrombosis; TLR: Target lesion revascularization.

**Figure 4:** Forest plot of late lumen loss (a) and minimal lumen diameter (b) associated with drug-eluting balloon (DEB) versus new-generation drug-eluting stent (DES) for patients with in-stent restenosis. CI: Confidence interval.

**Supplementary information is linked to the online version of the paper on the Chinese Medical Journal website.**

**Financial support and sponsorship**

The study was supported by grants from the Key Project in the National Science and Technology Pillar.
Program during the Twelfth 5-Year Plan Period of China, Beijing, China (No. 2011BA111B05) and Beijing Lab for Cardiovascular Precision Medicine, Beijing, China (No. PXM2017_014226_000037).

Conflicts of interest
There are no conflicts of interest.

REFERENCES

1. Qin Z, Zheng FW, Zeng C, Zhou K, Geng Y, Wang JL, et al. Elevated levels of very low-density lipoprotein cholesterol independently associated with in-stent restenosis in diabetic patients after drug-eluting stent implantation. Chin Med J 2017;130:2326-32. doi: 10.4103/0366-6999.213575.

2. Lee JM, Park J, Kang J, Jeon KH, Jung JH, Lee SE, et al. Comparison among drug-eluting balloon, drug-eluting stent, and plain balloon angioplasty for the treatment of in-stent restenosis: A network meta-analysis of 11 randomized, controlled trials. JACC Cardiovasc Interv 2015;8:382-94. doi: 10.1016/j.jcicin.2014.09.023.

3. Liu R, Xiong F, Wen Y, Ma YL, Yao Y, Gao Z, et al. Comparison of efficacy and safety between first and second generation drug-eluting stents in patients with stable coronary artery disease: A Single-center retrospective study. Chin Med J 2017;130:1654-61. doi: 10.4103/0366-6999.209904.

4. Palmerini T, Benedetto U, Biondi-Zoccai G, Della Riva D, Bacchi-Reggiani L, Smits PC, et al. Long-term safety of drug-eluting and Bare-metal stents: Evidence from a comprehensive network meta-analysis. J Am Coll Cardiol 2015;65:2496-507. doi: 10.1016/j.jacc.2015.04.017.

5. Scheller B, Speck U, Abramjuk C, Bernhardt U, Böhm M, Nickenig G, et al. Paclitaxel balloon coating, a novel method for prevention and therapy of restenosis. Circulation 2004;110:810-4. doi: 10.1161/01. ECR.0000138929.71660.E0.

6. Authors/Task Force members, Windecker S, Kolh P, Alfonso F, Collet JP, Cremer J, et al. Safety and efficacy outcomes of first and second generation durable polymer drug eluting stents and biodegradable polymer bioresorbable eluting stents in clinical practice: Comprehensive network meta-analysis. BMJ 2013;347:f6530. doi: 10.1136/bmj.f6530.

7. Liu K, Jepson N, Cao C, Luo R, Pala S, Ooi SY, et al. Drug-eluting balloon versus second generation drug eluting stents in the treatment of in-stent restenosis: A Systematic review and meta-analysis. Heart Lung Circ 2016;25:1184-94. doi: 10.1016/j.hlc.2016.04.001.

8. Henriques JP, Baan J. A Randomized Comparison of Paclitaxel-Eluting Balloon Versus Everolimus-Eluting Stent for the Treatment of any In-Stent Restenosis: The DARE Trial. Presented at Transcatheter Cardiovascular Therapeutics Annual Conference. Denver, Colorado; 30 October, 2017.

9. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. PLoS Med 2009;6:e1000097. doi: 10.1371/journal.pmed.1000097.

10. Group DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, et al. Meta-analysis of observational studies in epidemiology: A proposal for reporting. Meta-analysis in epidemiology (MOOSE) group. JAMA 2000;283:208-12. doi: 10.1001/jama.283.15.2088.

11. Lundh A, Gistzsche PC. Recommendations by cochrane review groups for assessment of the risk of bias in studies. BMC Med Res Methodol 2008;8:22. doi: 10.1186/1471-2288-8-22.

12. Stang A. Critical evaluation of the newcastle-ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses.

Eur J Epidemiol 2010;25:603-5. doi: 10.1007/s10654-010-9491-z.

13. Adriaenssens T, Dens J, Ughi G, Bennett J, Dubois C, Sinnaeve P, et al. Optical coherence tomography study of healing characteristics of paclitaxel-eluting balloons vs. Everolimus-eluting stents for in-stent restenosis: The SEDUCE (Safety and efficacy of a drug elUting balloon in coronary artery reStenosis) randomised clinical trial. EuroIntervention 2014;10:439-48. doi: 10.4244/EIJ10i4A77.

14. Alfonso F, Pérez-Vizcaíno MJ, Cárdenas A, García Del Blanco B, García-Touchard A, López-Mingüez JR, et al. A prospective randomized trial of drug-eluting balloons versus everolimus-eluting stents in patients with in-stent restenosis of drug-eluting stents: The RIBS IV randomized clinical trial. J Am Coll Cardiol 2015;66:23-33. doi: 10.1016/j.jacc.2015.04.063.

15. Alfonso F, Pérez-Vizcaíno MJ, García Del Blanco B, Otáegui I, Masotti M, Zueco J, et al. Long-term results of everolimus-eluting stents versus drug-eluting balloons in patients with bare-metal in-stent restenosis: 3-year follow-up of the RIBS V clinical trial. JACC Cardiovasc Interv 2016;9:1246-55. doi: 10.1016/j.jcin.2016.03.037.

16. Almalla M, Reith S, Vogt F, Marx N, Schroeder J. Three-year clinical outcomes after treatment of drug-eluting Stent restenosis with paclitaxel-eluting balloon vs. Everolimus-eluting stent. Eur Heart J 2015;36:1166.

17. Basavarajiah S, Naganuma T, Latib A, Stichti A, Cigonce G, Panoulas V, et al. Treatment of drug-eluting stent restenosis: Comparison between drug-eluting balloon versus second-generation drug-eluting stents from a retrospective observational study. Catheter Cardiovasc Interv 2016;88:522-8. doi: 10.1002/ccd.26368.

18. Kakani JS, Shehata I, Shin DR, Kim JS, Kim BK, Ko YG, et al. Comparison between drug-coated balloon angioplasty and second-generation drug-eluting stent placement for the treatment of in-stent restenosis after drug-eluting stent implantation. Heart Vessels 2016;31:1405-11. doi: 10.1007/s00380-015-0747-6.

19. Kawamoto H, Ruparelia N, Latib A, Miyazaki T, Sato K, Mangieri A, et al. Drug-coated balloons versus second-generation drug-eluting stents for the management of recurrent multilayered-in-stent restenosis. JACC Cardiovasc Interv 2015;8:1586-94. doi: 10.1016/j.jcicin.2015.04.032.

20. Kubo S, Kadota K, Otsuru S, Hasegawa D, Habara S, Tada T, et al. Everolimus-eluting stent implantation versus repeat paclitaxel-coated balloon angioplasty for recurrent in-stent restenosis lesion caused by paclitaxel-coated balloon failure. EuroIntervention 2015;10:e1-8. doi: 10.4244/EIJ10i9A180.

21. Lee JM, Rhee TM, Hahn JY, Hwang D, Park J, Park KW, et al. Comparison of outcomes after treatment of in-stent restenosis using newer generation drug-eluting stents versus drug-eluting balloon: Patient-level pooled analysis of Korean multicenter in-stent restenosis registry. Int J Cardiol 2017;230:181-90. doi: 10.1016/j.ijcard.2016.12.176.

22. Marquis-Gravel G, Noisieux N, Gobeil F, Stevens LM, Mansour S. Comparison of paclitaxel-eluting balloons with drug-eluting stents for treatment of in-stent restenosis: A retrospective analysis of an all-comers cohort. J Am Coll Cardiol 2013;62:B138.

23. Naganuma T, Latib A, Costopoulos C, Oreglia J, Testa L, De Marco F, et al. Drug-eluting balloon versus second-generation drug-eluting stents for the treatment of in-stent restenosis with bare metal stent-in-stent restenosis: The RIBS-V clinical trial. JACC Cardiovasc Interv 2016;9:1246-55. doi: 10.1016/j.jcin.2016.03.037.

24. Almalla M, Schröder J, Pross V, Marx N, Hoffmann R. Paclitaxel-eluting balloon versus everolimus-eluting stent for...
treatment of drug-eluting stent restenosis. Catheter Cardiovasc Interv 2014;83:881-7. doi: 10.1002/ccd.25072.

28. De Labriolle A, Pakala R, Bonello L, Lemesle G, Scheinowitz M, Waksman R, et al. Paclitaxel-eluting balloon: From bench to bed. Catheter Cardiovasc Interv 2009;73:643-52. doi: 10.1002/ccd.21895.

29. Scheller B, Clever YP, Kehsch B, Hehrlein C, Bocksch W, Rutsch W, et al. Long-term follow-up after treatment of coronary in-stent restenosis with a paclitaxel-coated balloon catheter. JACC Cardiovasc Interv 2012;5:323-30. doi: 10.1016/j.jcin.2012.01.008.

30. Yano H, Horinaka S, Ishikawa M, Ishimitsu T. The efficacy of everolimus-eluting stent implantation in patients with ST-segment elevation myocardial infarction: outcomes of 2-year clinical follow-up. Heart Vessels 2016;31:1609-15. doi: 10.1007/s00380-015-0783-9.

31. Kappetein AP, Serruys PW, Sabik JF, Leon MB, Taggart DP, Morice MC, et al. Design and rationale for a randomised comparison of everolimus-eluting stents and coronary artery bypass graft surgery in selected patients with left main coronary artery disease: the EXCEL trial. EuroIntervention 2016;12:861-72. doi: 10.4244/EIJV12I7A141.

32. Goel SS, Dilip Gajulapalli R, Athappan G, Philip F, Gupta S, Murat Tuzcu E, et al. Management of drug eluting stent in-stent restenosis: A systematic review and meta-analysis. Catheter Cardiovasc Interv 2016;87:1080-91. doi: 10.1002/ccd.26151.

33. Cremers B, Biedermann M, Mahnkopf D, Böhm M, Scheller B. Comparison of two different paclitaxel-coated balloon catheters in the porcine coronary restenosis model. Clin Res Cardiol 2009;98:325-30. doi: 10.1007/s00392-009-0008-2.

34. Hee L, Terluk A, Thomas L, Hopkins A, Juergens CP, Lo S, et al. Late clinical outcomes for SeQuent please paclitaxel-coated balloons in PCI of instent restenosis and de novo lesions: A single-center, real world registry. Catheter Cardiovasc Interv 2017;89:375-382. doi: 10.1002/ccd.26546.
药物洗脱球囊与新型药物洗脱支架治疗支架内再狭窄的对比：一项更新的系统性回顾和荟萃分析

摘要

背景：当前，使用药物洗脱球囊可能是治疗支架内再狭窄的新方法，但是药物洗脱球囊与新型药物洗脱支架治疗支架内再狭窄的临床研究较少。因此，本研究旨在对药物洗脱球囊与新型药物洗脱支架治疗支架内再狭窄的安全性与有效性进行对比。

方法：从PubMed、EMBASE和Cochrane Library三大数据库中充分检索药物洗脱球囊与新型药物洗脱支架治疗支架内再狭窄对比的研究，检索截止时间为2017年11月2日。此外，也对美国心脏病学会(ACC)、美国心脏协会(AHA)、欧洲心脏病学会(ESC)、经导管心血管治疗(TCT)和欧洲血运重建大会(EuroPCR)等会议的会议论文进行检索。主要终点为最长随访时间的靶血管血运重建发生率。二分变量用风险比(RR)和95%置信区间(CI)表示，采用Mantel-Haenszel随机效应模型对总体RR进行估计。

结果：5项前瞻性随机对照研究和8项观察性研究共2743例患者入选。与新型药物洗脱支架相比，药物洗脱球囊组的靶病变血运重建(RR = 1.24, 95% CI: 0.89–1.72, P = 0.21)、心源性死亡(RR = 1.55, 95% CI: 0.89–2.71, P = 0.12)、主要不良心血管事件(RR = 1.21, 95% CI: 0.98–1.48, P = 0.07)、心肌梗死(RR = 1.12, 95% CI: 0.72–1.76, P = 0.62)和支架内血栓(RR = 0.95, 95% CI: 0.38–2.42, P = 0.92)发生率无明显差异。但是药物洗脱球囊组患者的全因死亡率高于新型药物洗脱支架组(RR = 1.65, 95% CI: 1.09–2.50, P = 0.02)。这主要是由于真实世界观察性研究的结果导致的(RR = 1.79, 95% CI: 1.12–2.88, P = 0.02)。在前瞻性随机对照研究中，两种治疗方式间的全因死亡率没有明显差别。

结论：这项荟萃分析发现在前瞻性随机对照研究中，药物洗脱球囊和新型药物洗脱支架治疗支架内再狭窄的安全性和有效性相当。但在真实世界研究中，接受药物洗脱球囊治疗患者的全因死亡率更高。
## Supplementary Table 1: Baseline and procedural characteristics of patients of the included studies

| Studies                        | Age (years) | Male (%) | Smoking (%) | Diabetes (%) | Hypertension (%) | Dyslipidemia (%) |
|-------------------------------|-------------|----------|-------------|--------------|------------------|------------------|
| Adriaenssens et al. in 2014   | 67.6/64.2   | 72/100   | 20.8/12     | 24/4         | 64/60            | 96/96            |
| Alfonso et al. in 2015        | 66/66       | 82/84    | 58/56       | 49/43        | 71/78            | 71/78            |
| Alfonso et al. in 2016        | 67/64       | 86/87    | 59/75       | 32/20        | 72/72            | 73/66            |
| Almalla et al. in 2015        | 69.6/67.7   | 82/70    | 30.4/52.5   | 39.1/35      | 80.4/85          | NA               |
| Basavarajaiah et al. in 2016  | 66.8/65.7   | 90.1/86.1| 8.6/7.2     | 46.9/33.1    | 70.4/71.1        | 72.8/76.5        |
| Henriques et al. in 2017      | 66/65       | 72/84    | 17/13       | 31/33        | 64/67            | 59/60            |
| Kang et al. in 2016           | 63.1/59.5   | 68.7/64.3| 46.7/46.4   | 44.0/28.6    | 72.5/69.6        | 90.7/82.1        |
| Kawamoto et al. in 2015       | 67.2/64.9   | 87.7/92.6| 9.2/13.2    | 43.1/41.2    | 78.5/79.4        | 78.6/79.6        |
| Kubo et al. in 2015           | 69.7/71.3   | 86.5/78.8| 75.7/69.2   | 48.6/50.0    | 81.1/78.8        | 64.9/71.2        |
| Lee et al. in 2017            | 66.2/65.3   | 63.9/70.4| 16.9/23.7   | 53.0/45.7    | 75.3/70.2        | 53.0/49.6        |
| Marquis-Gravel et al. in 2013 | NA          | NA       | NA          | NA           | NA               | NA               |
| Naganuma et al. in 2016       | 67.2/65.2   | 91.8/87.1| 6.8/7.1     | 39.7/37.6    | 71.2/71.8        | 74/81.2          |
| Pleva et al. in 2016          | 65.6/65.5   | 63.2/67.7| 45.6/42.7   | 25.0/26.5    | NA               | NA               |

The data of the DEB group are on the left side of the oblique line, while the data of the new-generation group are on the right side of the oblique line.

**DEB**: Drug-eluting balloon; **DES**: Drug-eluting stent; **DS**: Diameter stenosis; **MLD**: Minimal lumen diameter; **NA**: Not applicable.

## Supplementary Table 2: Assessment of randomized controlled trials

| Study                        | Sequence generation | Concealment of allocation | Blinding of participants, personnel and outcome assessors | Incomplete outcome data addressed | Free of selective reporting | Free of other bias |
|-----------------------------|---------------------|---------------------------|--------------------------------------------------------|----------------------------------|---------------------------|-------------------|
| Adriaenssens et al. in 2014 | Low                 | Low                       | High                                                   | High                             | Low                       | Low               |
| Alfonso et al. in 2015      | Low                 | Low                       | Moderate                                               | Low                              | Low                       | Low               |
| Alfonso et al. in 2016      | Low                 | Low                       | Moderate                                               | Low                              | Low                       | Low               |
| Henriques et al. in 2017    | NA                  | NA                        | NA                                                     | NA                               | NA                        | NA                |
| Pleva et al. in 2016        | NA                  | NA                        | Moderate                                               | Low                              | Low                       | Low               |

**NA**: Not applicable.

## Supplementary Table 3: Assessment of observational studies

| Studies                        | Selection | Comparability | Outcome | Total score |
|-------------------------------|-----------|---------------|---------|-------------|
| Almalla et al. in 2015        | 4         | 0             | 3       | 7           |
| Basavarajaiah et al. in 2015  | 4         | 0             | 2       | 6           |
| Kang et al. in 2015           | 4         | 0             | 3       | 7           |
| Kawamoto et al. in 2015       | 4         | 0             | 3       | 7           |
| Kubo et al. in 2015           | 4         | 0             | 3       | 7           |
| Lee et al. in 2017            | 4         | 0             | 3       | 7           |
| Marquis Gravel et al. in 2013 | NA        | NA            | NA      | NA          |
| Naganuma et al. in 2016       | 4         | 0             | 2       | 6           |

**NA**: Not applicable.
Supplementary Figure 1: Funnel plot of target lesion revascularization.

RR: Risk ratio; RCT: Randomized controlled trial.