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

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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 (*RR*s) with 95% confidence intervals (*CI*s), while the overall *RR*s 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.[1] Previous study has demonstrated the efficacy of drug-eluting stent (DES) for the treatment of ISR.[2] 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).[3] 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,

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which makes it an appropriate choice for the treatment of ISR.[4]

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.[5] 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 (*RR*s) and mean differences (MDs) with 95% confidence intervals (*CI*s), respectively. For *RR*s, 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 >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 *RR*s/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].

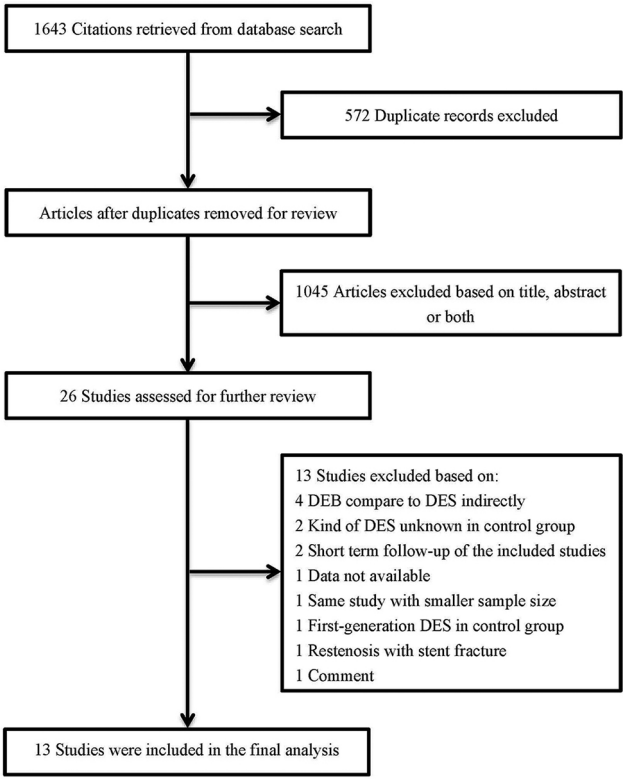

Figure 1: Flowchart of identification of eligible studies in this study. DEB: Drug-eluting balloon; DES: Drug-eluting stent.

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).

Discussion

This meta-analysis showed that although associated with smaller MLD, DEB was comparable to new-generation

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*.[15]	2015	2010–2013	DES ISR	SeQuent Please versus EES	309	6–10	12	Cardiac death, MI, or TLR
Alfonso *et al*.[16,26]	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
Basavarajaiah *et al*.[18]	2016	2009–2011	DES ISR	In.PACT Falcon versus 2nd 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 2nd DES	238	NA	24	Cardiac death, MI, ST, or TVR
Kawamoto *et al*.[20]	2015	2008–2013	Recurrent DES ISR	In.PACT Falcon/Pantera Lux versus 2nd 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 2nd DES	628	NA	12	Death, MI, or revascularization
Marquis-Gravel *et al*.[23]	2013	2009–2012	ISR	DEB versus 2nd DES	202	NA	16	Death, MI, or clinically-driven TLR
Naganuma *et al*.[24]	2016	2007–2012	ISR with bifurcation	In.PACT Falcon versus 2nd DES	158	NA	24	Cardiac death, MI, or TVR
Pleva *et al*.[25]	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.

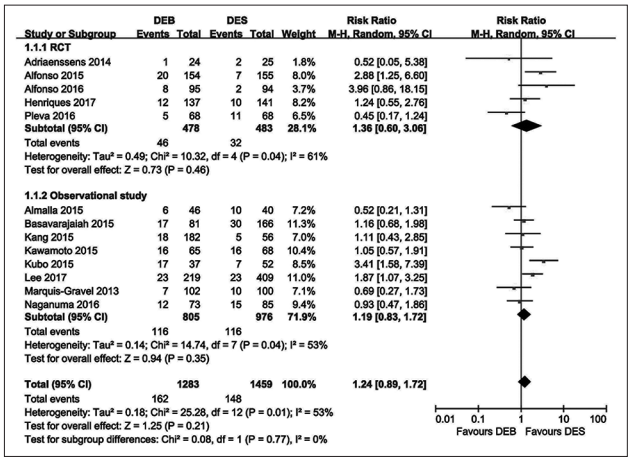

Figure 2: Forest plot of target lesion revascularization associated with drug-eluting balloon (DEB) versus new-generation drug-eluting stent (DES) for patients with in-stent restenosis. *CI*: Confidence interval.

DES in the treatment of ISR in terms of TLR, cardiac death, MACE, MI, ST, and 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

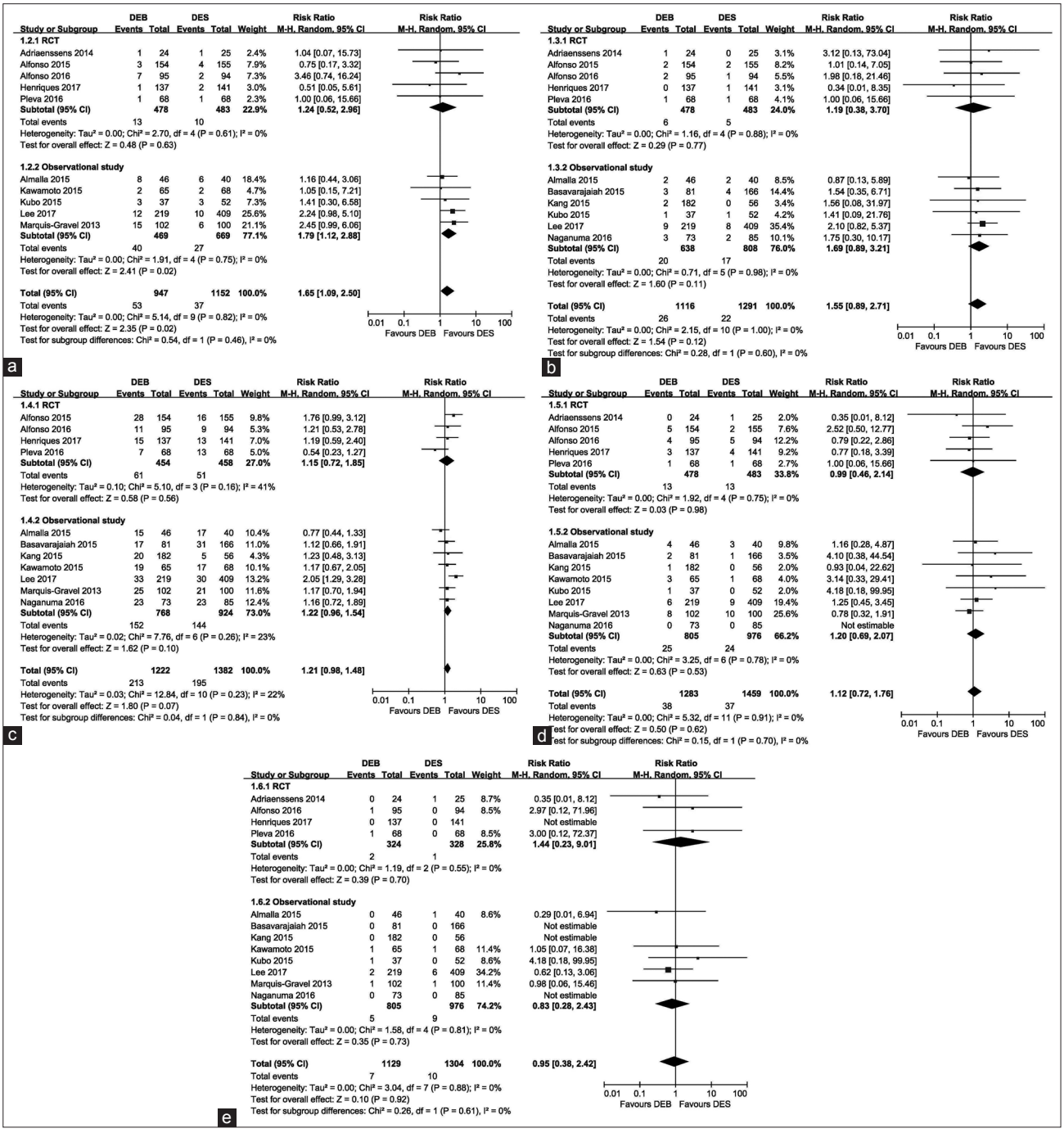

Figure 3: Forest plot of all-cause death (a), cardiac death (b), major adverse cardiovascular event (c), myocardial infarction (d), and stent thrombosis (e) associated with drug-eluting balloon (DEB) versus new-generation drug-eluting stent (DES) for patients with in-stent restenosis. *CI*: Confidence interval.

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, $P_{\text{noninferiority}} < 0.0001$). 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

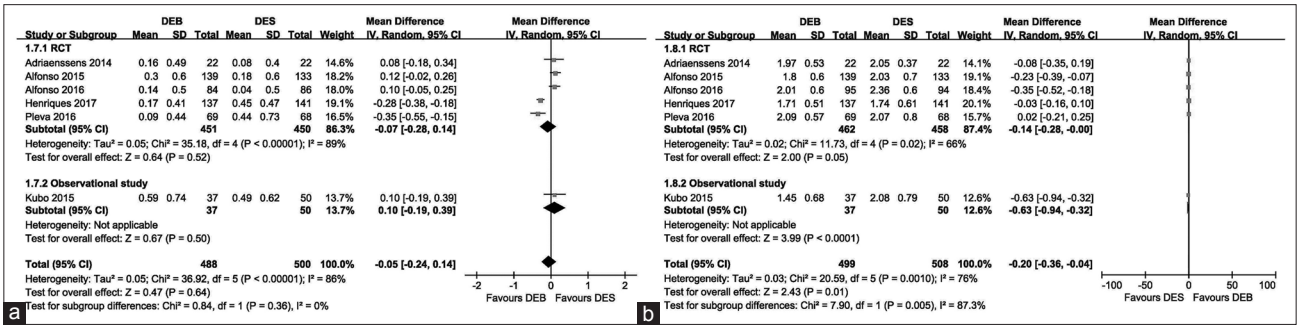

Figure 4: Forest plot of late lumen loss (a) and minimal lumen diameter (b) associated with drug-eluting balloon (DEB) versus new-generation drug-eluting stent (DES) for patients with in-stent restenosis. *CI*: Confidence interval.

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 (0.38, 9.20)	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.

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.[7] 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 after the first balloon expansion on the target site with higher bioavailability than DIOR.[33,34] 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.

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

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Conflicts of interest

There are no conflicts of interest.

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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	78.5/79.4
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

Studies	Lesion length (mm)	Pre-DS (%)	Pre-MLD (mm)	DEB/DES diameter (mm)	DEB/DES length (mm)	Post-DS (%)	Post-MLD (mm)
Adriaenssens *et al*. in 2014	NA	67.7/79.4	0.98/0.57	3.2/3	23.3/26	26.6/25.9	2.13/2.12
Alfonso *et al*. in 2015	10.4/10.7	69/72	0.79/0.75	NA	19/19	18/13	2.10/2.22
Alfonso *et al*. in 2016	13.7/13.8	61/65	1.02/0.93	NA	20/23	19/11	2.16/2.38
Almalla *et al*. in 2015	9.0/12.3	NA	0.57/0.51	2.96/2.84	21.2/20.5	NA	2.42/2.50
Basavarajaiah *et al*. in 2016	NA	NA	NA	3/3.2	35.4/19.8	NA	NA
Henriques *et al*. in 2017	NA	69.7/69.3	0.77/0.79	3.3/2.9	22.4/22.1	29.9/26.2	1.72/1.84
Kang *et al*. in 2016	19.5/21.3	71.7/74.6	0.8/0.8	3/3.2	21.7/21.9	20.6/13.6	2.2/2.7
Kawamoto *et al*. in 2015	18.7/16.1	74.8/81.2	0.74/0.66	3.14/3.20	33.7/25.0	18.2/13.8	2.34/2.65
Kubo *et al*. in 2015	16.7/15.7	67.0/72.2	0.96/0.80	2.98/2.90	24.1/19.4	31.8/16.2	2.02/2.56
Lee *et al*. in 2017	NA	NA	NA	NA	NA	NA	NA
Marquis-Gravel *et al*. in 2013	NA	NA	NA	NA	NA	NA	NA
Naganuma *et al*. in 2016	NA	NA	NA	3.1/3.1	37.3/23.5	NA	NA
Pleva *et al*. in 2016	NA	71.8/78.0	2.64/2.66	3.32/3.31	22.5/28.5	19.5/16.3	2.18/2.51

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

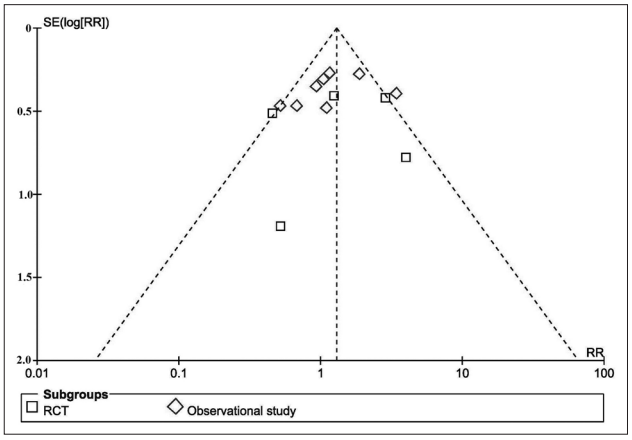
Study	Sequence generation	Concealment of allocation	Blinding of participants, personnel and outcome assessors	Incomplete outcome data addressed	Free of selective reporting	Free of other bias
Adriaenssens *et al*. in 2014	Low	Low	High	High	Low	Low
Alfonso *et al*. in 2015	Low	Low	Moderate	Low	Low	Low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