ORIGINAL ARTICLE

Drug-eluting balloon angioplasty for in-stent restenosis: a systematic review and meta-analysis of randomised controlled trials

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ABSTRACT

Context The optimal treatment option for in-stent restenosis is currently unclear.

Objective Systematic review and meta-analysis of the effect of drug-eluting balloons (DEB) to treat in-stent restenosis.

Data sources Trials were identified through a literature search from 2005 through 7 November 2012.

Study selection Randomised clinical trials comparing DEB with a control treatment (plain balloon angioplasty or drug-eluting stents).

Data extraction and synthesis Main endpoints of interest were major adverse cardiac events (MACE), target lesion revascularisation (TLR), binary in-segment restenosis, stent thrombosis (ST), myocardial infarction (MI) and mortality. A random-effects model was used to calculate the pooled relative risks (RR) with 95% CIs.

Results Five studies and a total of 801 patients were included in this analysis. Follow-up duration ranged from 12 to 60months. Most endpoints were significantly reduced for DEB compared with the control groups. For MACE, the relative risk RR was 0.46 (0.31 to 0.70), p<0.001, for TLR it was 0.34 (0.16 to 0.73); p=0.006, for angiographic in-segment restenosis it was 0.28 (0.14 to 0.58); p<0.001. There was a lower mortality for DEB (RR 0.48 (0.24 to 0.95); p=0.034). The incidence of MI was numerically lower, but the differences were not statistically significant (RR 0.68 (0.32 to 1.48); p=0.337). There was no difference in the risk of ST (RR 1.12 (0.23 to 5.50), p=0.891).

Conclusions In-stent restenosis is the bane of coronary angioplasty, and drug-eluting balloon angioplasty is a promising treatment option in this situation. It reduces the risk for MACE compared with plain balloon angioplasty or implantation of a Taxus Liberte drug-eluting stent.

INTRODUCTION

Percutaneous coronary intervention (PCI) has evolved to the mainstream revascularisation method, far outnumbering coronary artery bypass grafting (CABG).[1] However, the major drawback of PCI is a higher rate of target lesion revascularisation (TLR) as compared with CABG due to in-stent restenosis (ISR). Even though the restenosis risk has markedly dropped for newer-generation drug-eluting stents (DES), DES have major drawbacks, such as need for prolonged dual antiplatelet therapy (DAPT) and a potentially increased risk for late stent thrombosis (ST) in certain subpopulations.[2 3]

There is currently no optimal treatment option for ISR, neither for bare-metal stent (BMS) restenosis nor for DES. Local application of antiproliferative substances with drug-eluting balloons (DEB) is an emerging approach for the treatment of ISR without the shortfalls of implanting an additional metal scaffold. These devices are increasingly being used by clinicians based on a number of small encouraging studies. However, these studies had limited statistical power regarding clinical endpoints. We aimed to perform a systematic review and meta-analysis of randomised controlled trials assessing the effectiveness of DEB.

METHODS

The study was performed according to the preferred reporting items for systematic reviews and meta-analyses guidelines for meta-analyses of randomised trials (see online supplementary file 1).[4 5]) Planning and study design were done by two authors (AI, PM) including creation of an electronic database with variables of interest (Microsoft EXCEL). Primary and secondary endpoints, variables of interest and search strategy (databases, sources for unpublished data) were defined in a strategy outline which can be obtained from the study authors on request.

Search strategy

We searched EMBASE, PubMed, MEDLINE, BIOS and ISI Web of Science from 2005 through 7 November 2012. In addition, abstract lists and conference proceedings from the 2006 to 2011 scientific meetings of the American College of Cardiology, the European Society of Cardiology, the symposium on Transcatheter Cardiovascular Therapeutics, the American Heart Association and the World Congress of Cardiology were searched. We also considered published review articles, editorials and internet-based sources of information ((http://www.tctmd.com, http://www.theheart.org) (http://www.europcronline.com) (http://www.cardiosource.com) and (http://www.crtonline.com)) to assess potential information on studies of interest. Reference lists of selected articles were reviewed for other potentially relevant citations. No language restriction was applied.

The detailed search syntax for the database, Medline, is shown in online supplementary file 2. The syntax for other databases was similar but was adapted where necessary.

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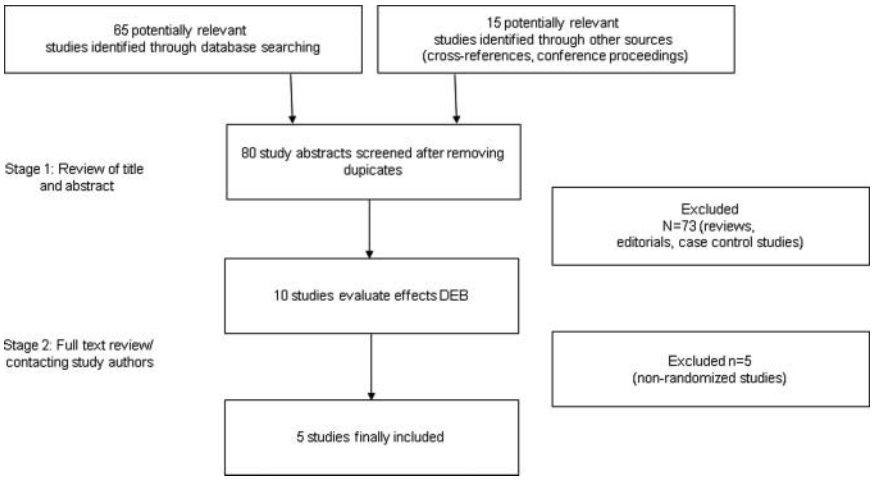

Figure 1 Study selection process. DEB, drug eluting balloons.

Study selection

In a two-step selection process, the titles and abstracts of all citations were reviewed by two researchers (PM, AI) to identify potentially relevant studies. In a second step, the corresponding publications were reviewed in full text to assess if studies met the following inclusion criteria: drug-eluting balloon versus comparator treatment, randomised controlled trial (figure 1).

Data extraction and quality assessment

Relevant information from the articles, including baseline clinical characteristics of the study population and outcome measures, were extracted using the prepared standardised extraction database (Microsoft EXCEL). We assessed trial quality by evaluating randomisation and allocation concealment, intention-to-treat analysis, blinded assessment of outcome measures, premature stopping of patient enrolment and reporting about dropouts, but without using a quality score given limitations inherent to such an approach (see online supplementary file 3).[6]

Endpoints and definitions

Baseline variables and clinical and angiographic data were extracted. Variables of interest were a composite of major adverse cardiac events (MACE), TLR, all-cause mortality, myocardial infarction (MI), ISR (≥50% diameter stenosis) and late lumen loss (LLL). For the definition in the individual trials see table 1.

Data synthesis and analysis

Data of included studies were combined to estimate the pooled impact (risk ratio, RR) of DEB versus a comparator treatment. Calculations were based on a DerSirmonian and Laird random-effects model.[7] This model assumes that the true effects vary between studies for unknown reasons. The primary summary measure usually reported is the estimated average effect across studies.[8] Continuity correction was used when no event occurred in one group to allow calculation of a RR.[9] Heterogeneity among trials was quantified with Higgins' and Thompson's I^2.[10] I^2 can be interpreted as the percentage of variability due to heterogeneity between studies rather than sampling error. An I^2 >50% was considered as at least moderate heterogeneity. We present our primary result estimates of the average effect across studies with 95% CIs in brackets. In addition, we also calculated 95% prediction intervals as described by Higgins *et al*.[8] These intervals predict the effect that we would potentially expect to see in a new study. These data are presented in the sensitivity analysis paragraph. We did not test for publication bias or small study effects due to the small number of studies included in this analysis.

We have performed subset analyses for the different comparator treatments (plain old balloon angioplasty (POBA) or DES) and for those with bare-metal stent in-stent restenosis (BMS ISR) or DES in-stent restenosis (DES ISR). All analyses were performed with R, V.2.10.1 (package 'meta').[11]

Table 1 Baseline characteristics of included trials

Study	Stent type	Drug-eluting balloon	Control	Setting	Clopidogrel (mts)	Follow-up (mts)	MACE	TLR
Habara *et al*[12]	DES	Sequent please	Uncoated balloon	Stable CAD	3	6	TLR, MI, death	Symptoms and stenosis >50%
PACCOCATH	96% BMS	Paccocath DEB	Uncoated balloon	Stable CAD/ACS	1	60	TLR, MI, stroke, death	Symptoms and/or angiographic findings
PEPCAD 2 ISR	BMS	Sequent please	Taxus Liberte	Stable CAD/ACS	3 (6 for control arm)	12	TLR, MI, ST, death	NA
PEPCAD DES	DES	Sequent please	Uncoated balloon	Stable CAD/ACS	6	6	TLR, MI, CV death	Symptoms and/or angiographic findings
ISAR-DESIRE	DES	Sequent please	Taxus Liberte, uncoated balloon	Stable CAD/ACS	6	12	TLR, death, MI	NA

ACS, acute coronary syndrome; BMS, bare-metal stent; CAD, coronary artery disease; CV, cardiovascular; DES, drug-eluting stent; ISR, in-stent restenosis; MACE, definition of major adverse cardiac events; MI, myocardial infarction; Mts, months; Paccocath DEB, paccocath drug-eluting balloon, paclitaxel eluting, Bayer AG, Leverkusen, Germany; Sequent please, paclitaxel eluting balloon, Bayer, Germany; SES, sirolimus eluting stents; ST, stent thrombosis; TLR, target lesion revascularisation.

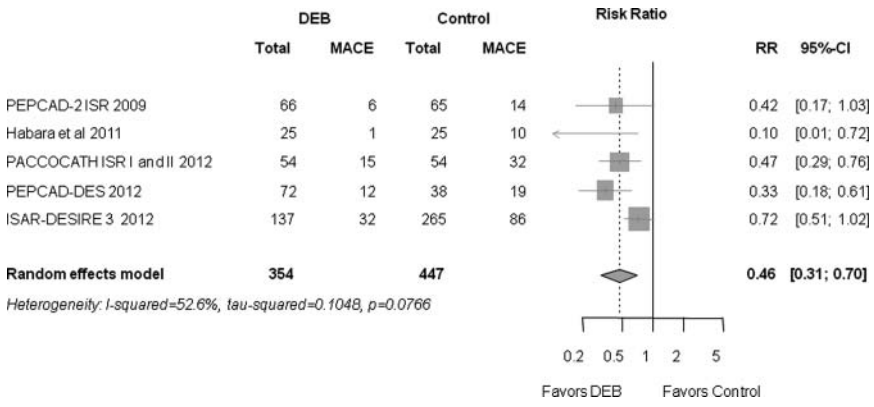

Figure 2 Forest plot of risk ratios (RR) for major adverse cardiac events. DEB, drug-eluting balloon; MACE, major adverse cardiac events; RR, risk ratio. Markers represent point estimates of risk ratios, marker size represents study weight in random-effects meta-analysis. Horizontal bars indicate 95% CIs.

RESULTS

Description of included studies

A total of 80 articles were reviewed, and five studies including 801 patients satisfied the predetermined inclusion criteria (figure 1).[12–16] Studies using DEB for de novo stenoses were not considered.[17] All five studies used paclitaxel-eluting balloons.

All study protocols included a routine angiographic follow-up. For the PACCOCATH (Treatment of ISR by Paclitaxel Coated PTCA Balloons) trial, the shorter term and the longer term outcomes (5 years) were reported. For this analysis, we used the 5 years' results.[13]

Three of the five studies compared DEB with conventional POBA, and two trials compared DEB with a first-generation DES (ie, paclitaxel-eluting stent) for the treatment of restenosis.[14]

One study only included patients with stable coronary artery disease (CAD),[12] while the other three included also enrolled patients with an acute coronary syndrome. The PEPCAD 2 ISR trial compared DEB with the paclitaxel-eluting Taxus Liberte stent, whereas the ISAR DESIRE 3 compared DEB with POBA and the paclitaxel-eluting Taxus Liberte stent, respectively.[14]

The ISAR-DESIRE trial is the most recent and largest study in this field.[16] This trial had three arms and compared DEB versus DES (Taxus Liberte) and versus POBA (table 1).

MACE

For all trials, the primary endpoint was a composite endpoint of MACE. The risk for this primary endpoint was significantly reduced for DEB compared with the control treatments (RR 0.46 (0.31 to 0.70), p<0.001) (figure 2). The definition of MACE differed slightly among the trials (table 1).

TLR

The need for TLR was significantly reduced for the DEB group (RR 0.34 (0.16 to 0.73); p=0.006) (figure 3). In most studies, TLR was clinically driven (table 1).

Binary in-segement restenosis

The rate of in-segment restenosis was smaller for DEB (0.28 (0.14 to 0.58); p<0.001) (figure 4).

Late luminal loss

Overall, there was lower late luminal loss (LLL) for DEB compared with the control group (mean difference −0.38 mm (−0.60 to−0.15), p=0.001) (figure 5).

Mortality

Mortality was numerically lower for DEB, but this difference was not statistically significant (RR 0.48 (0.24 to 0.95); p=0.034) (see online supplementary file 4). For the PEPCAD DES trial all-cause mortality was not reported, and cardiac mortality was used instead.[15]

Myocardial infarction

The risk for MI was numerically lower, but the difference was not statistically significant (RR 0.68 (0.32 to 1.48); p=0.337) (see online supplementary file 5).

Stent thrombosis

ST was a very rare event. Only two STs were observed, one in each treatment arm (RR 1.12 (0.23 to 5.50), p=0.891 (see online supplementary file 6).

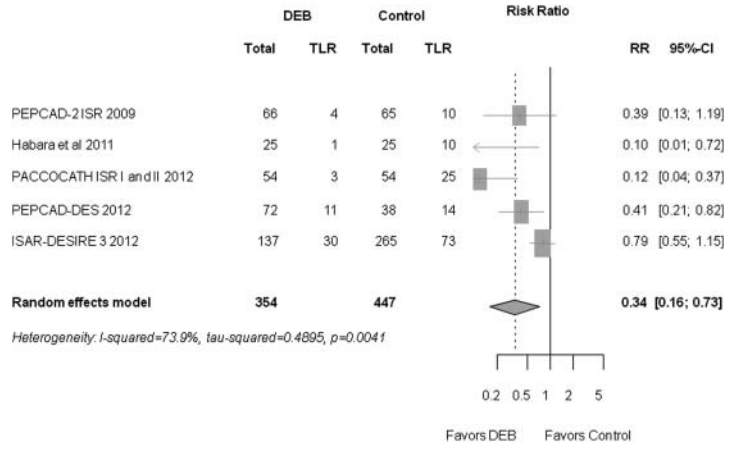

Figure 3 Forest plot of risk ratios (RR) for target lesion revascularisation. DEB, drug-eluting balloon; RR, risk ratio; TLR, target lesion revascularisation.

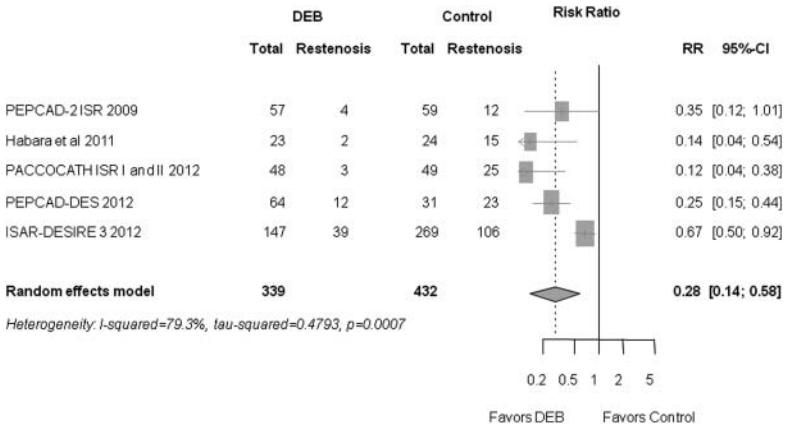

Figure 4 Forest plot of risk ratios (RR) for restenosis (≥ 50% diameter-stenosis). DEB: drug-eluting balloon. RR: risk ratio.

Subgroup analyses

The two trials which enrolled patients with BMS in-stent restenosis showed a more pronounced benefit of DEB over control therapy, while this effect was mitigated in the three trials in DES ISR (table 2).

The PEPCAD 2 and one arm of the ISAR- DESIRE 3 trial compared DEB with a paclitaxel-eluting stent, while four trials (including one arm of ISAR-DESIRE 3) used POBA as comparator. The DEB effect was more pronounced when compared with POBA than when compared with the Taxus Liberte stent (table 2). LLL, for example, was much lower for DEB compared with POBA (−0.51 mm (−0.69 to −0.33), p<0.001), while it was not significantly different when compared with Taxus (−0.11 mm (−0.39–0.18), p=0.483) (figure 5).

Sensitivity analyses

We also calculated the prediction intervals for those clinical endpoints which were statistically significant. These intervals predict the effect that we would potentially expect to see in a future study. The prediction intervals all crossed 1.0 and are, therefore, not significant. (see online supplementary file 7).

The influence analyses, omitting one trial at a time, showed rather robust results which were not relevantly influenced by a single trial (see online supplementary file 8).

DISCUSSION

This is the first systematic review and meta-analysis assessing the clinical effectiveness of DEB to treat ISR in previously implanted BMS or DES. Our data suggests that DEB are useful to treat ISR; they seem to reduce the risk of MACE and of TLR, and they also seem to reduce the mortality risk compared with POBA and Taxus Libete DES.

DEBs are slightly more effective in treating BMS in-stent restenoses than for DES ISR. Also, DEB appears clearly superior to POBA while there is no relevant significant difference when compared with implanting a Taxus DES. However, DEB avoids the problem of multiple layers of stents.

What do the guidelines say?

The American College of Cardiology (ACC)/ American Heart Association (AHA)/ Society for Cardiovascular Angiography and Interventions (SCAI) guidelines and the European (European Society of Cardiology, ESC) guidelines currently recommend

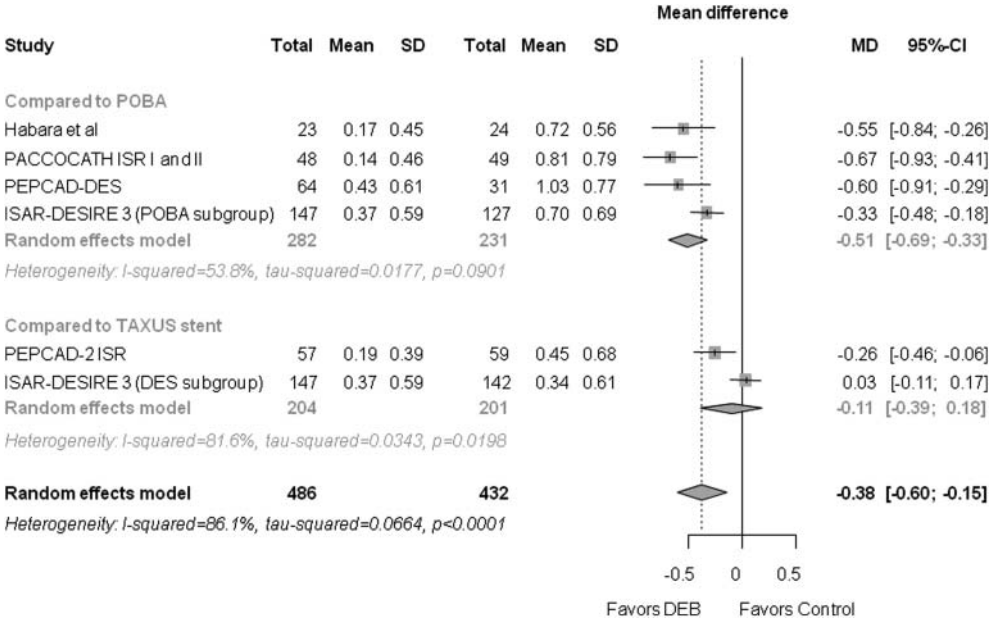

Figure 5 Forest plot of risk ratios (RR) for late lumen loss. DEB, drug-eluting balloon.

Table 2 Subset analyses

Endpoint	BMS ISR	DES ISR
MACE	0.46 (0.30 to 0.70); p<0.001	0.41 (0.18 to 0.93); p=0.032
TLR	0.22 (0.07 to 0.71); p=0.018	0.48 (0.21 to 1.06); p=0.068
Binary restenosis	0.21 (0.07 to 0.58); p=0.003	0.33 (0.14 to 0.81); p=0.016
	Comparator Taxus stent	Comparator POBA
MACE	0.77 (0.27 to 2.18), p=0.624	0.44 (0.32 to 0.60); p<0.001
TLR	0.89 (0.21 to 3.67); p=0.867	0.31 (0.15 to 0.62); p=0.001
Binary restenosis	0.69 (0.22 to 2.14); p=0.520	0.26 (0.13 to 0.49); p<0.001

BMS ISR, in-stent restenosis in a bare-metal stent; DES, ISR in a drug-eluting stent; MACE, major adverse cardiac events; POBA, plain old balloon angioplasty; RR, relative risk (and 95% CIs); TLR, target lesion revascularisation.

DES to treat ISR, regardless of whether the initial stent was a bare-metal or a DES.[18 19] However, the evidence for this recommendation is weak, especially with regard to DES in-stent restenosis. Many operators tend to use a different DES type to treat in-stent restenosis of drug-eluting stents. This common practice is not based on evidence; the ISAR-DESIRE 2 (Intracoronary Stenting and Angiographic Results: Drug Eluting Stents for ISR 2) trial did not reveal any difference in stenting an ISR of a sirolimus-eluting stent (SES) with either another SES or with a paclitaxel-eluting stent.[20] For the treatment of a BMS in-stent restenosis, we know that there are similar outcomes with either using another BMS or POBA,[21] while the ISAR-DESIRE trial showed a benefit of using a DES in this situation.[22]

Does timing matter?

The reduction in lumen diameter following coronary stenting is the result of arterial damage with subsequent neointimal proliferation. In the early stage of restenosis, there is significant cell proliferation of smooth muscle cells and infiltration of macrophages. At a later stage, there can be increased neointimal thickness due to cell proliferation. At very late stages, there seems to be a process of cell depletion, and the restenosis predominantly contains myxoid tissue with extracellular matrix (ECM), enriched with proteoglycans.[23] Very recent data even suggest that a 'neoatheroslerosis' process may play a role in late in-stent restenosis.[24] It can be hypothesised that this may affect the effectiveness of different restenosis treatments. A large amount of ECM is likely to have an impact of recoil, stent expansion, tissue extrusion through the stent struts, and other factors contributing to restenosis. However, our data do not allow to test this hypothesis, but future trial will hopefully address this question.

Are there predictors for ISR?

Several clinical and technical factors have been found to potentially influence the risk for restenosis. The presence of some of these factors often influences clinical decision making regarding coronary bypass surgery. Some operators prefer surgery in such higher restenosis risk situations because of the high recurrence rates and limited treatment options for ISR. Drug-coated balloons may change this practice paradigm.

The clinical risk factor that has been described to increase the rate of restenosis for BMS is diabetes. Technical factors that have been described are multiple stents and stent size.[25] However, the predictive value of these factors remains controversial, and their impact appears modest at best.[26] A simple and very powerful marker that has been recently described is the degree of coronary collateralisation. Patients with well-developed collaterals seem to have a 40% increased risk for restenosis.[27]

For DES, the predictive value of clinical factors is probably even lower.[28] Interestingly, the treatment of ISR was among the most prominent predictors of restenosis risk (OR of 4.2 (1.6 to 11.00)), and a good treatment for ISR is therefore warranted.[29]

The introduction of DES has markedly reduced the need for specialised revascularisation devices, like rotational or directional atherectomy, cutting balloon, laser angioplasty and high-pressure balloons. This changing practice is reflected by the 2009 ACC/AHA/SCAI guideline update for PCI concluded that there were no long-term studies demonstrating clinical advantage with any of the specialised devices for the treatment of ISR.[19] Conversely, the 2005 ESC task force for PCI recommends to consider cutting balloon angioplasty for avoiding slipping-induced vessel trauma during PCI of ISR.[18]

Even though our meta-analysis did not allow interaction analyses regarding vessel size due to sample size limitations, and because we only had study-level data, we hypothesise that DEB are especially useful in ISR of small vessels where an additional stent layer will further reduce the luminal area.

Value of DEB

While it may seem rather counterintuitive that a short balloon inflation with a DEB should be superior to DES which have a much longer duration of drug delivery, there are several theoretical advantages of DEB:

- Avoiding the problem of a permanent implant which might trigger inflammation and tissue ingrowth.
- Delivery of antiproliferative medication when needed, for instance, immediately after the barotrauma induced by balloon angioplasty.
- Avoiding multiple layers of stents.
- Avoiding the potential risk of corrosion of the stent: the mechanical friction between overlapping stents and chemical reaction between dissimilar alloys if mixing different stent types could lead to corrosion. Stent alloys form a protective oxide film, insulating the stent struts from the corrosive body fluids. There is a risk of mechanical damage of the oxide film caused by micromotion at points of stent overlap. If this protective film is getting scratched off, for instance, by overlapping stent struts (stent in stent), the underlying stent struts get exposed and may undergo corrosion.
- Overlapping stents of different alloys could theoretically lead to galvanic corrosion. This can be avoided by DEB. However, these concerns are rather theoretical, there is no clinical evidence which indicates a problem of using different types overlapping stents.[30]

This meta-analysis only considers one potential treatment approach for ISR, there are alternative options. Using a DES with a different drug is a rather commonly used strategy for DES ISR. Even though this seems to make sense, there has been very little supporting evidence. However, a recent observational study lends support to this idea. The Spanish RIBS III (Restenosis Intra-Stent: Balloon Angioplasty Versus Drug-Eluting Stent) study) enrolled 363 patients with DES ISR.[31] This study found a reduced restenosis rate for the 'switch' group compared with all other strategies for treating ISR, but we have to be aware that this was not a randomised trial.

Some cardiologists consider coronary bypass surgery for patients with in-stent restenosis. There are no randomised studies evaluating this approach, but since we know that the risk of another restenosis is rather high in patients with ISR, this can be a useful option. However, since we have several probably effective options at hand, such as DEB or switching to another

DES, this decision should consider other factors, such as type of restenosed stent, its location, the temporal course of restenosis, concomitant CAD and comorbidities.

Limitations

This meta-analysis is only based on five rather small trials. Even though the pooling did increase the statistical power, it is still insufficient for rare outcomes, such as ST and mortality. Although the formal testing did not reveal a major interstudy heterogeneity, there is certainly relevant heterogeneity with regard to the comparator (POBA or Taxus Liberte DES), the setting (BMS ISR or DES ISR), follow-up duration and so on. Due to the small study number, we were not able to meaningfully test for the influence of covariates. This was a study-level meta-analysis. An individual patient data analysis may provide further insights.

The results of MI, ST and death need to be interpreted with care since the meta-analysis might be too small to detect statistical differences in such rare events. Nevertheless, we find it reassuring that there is no difference between DEB and DES from a safety standpoint. The studies had a significant number of dropouts which limits the robustness of the results. The PACCOCATH trial, for instance, had lost 13 patients in the control group and five in the DEB group at 5 years follow-up (18 of the total 108 patients).

In the PEPCAD 2 ISR trial, patients in the stent arm only received DAPT for 6 months instead of the currently recommended 12 months. The curves for major cardiovascular events started to separate only after 6 months, in disfavour of DES, which may be partially explained by the short-duration DAPT.

All studies comparing stenting versus DEB used the Taxus Liberte stent as a comparator. Newer-generation and '-limus' eluting stents may alter the relative effectiveness of DEB. On the other hand, it seems reasonable to compare paclitaxel-eluting stents with paclitaxel-eluting balloons.

Outlook

Even the pooled analysis of the five trials has a limited statistical power. There are several ongoing trials and prospective trials, such as the DARE trial, which is assessing the effect of the SeQuent Please DEB versus the Xience Prime DES for the treatment of ISR (ClinicalTrials.gov Identifier: NCT01127958). The investigators intend to recruit 270 patients. Another trial, RIBS IV (restenosis intrastent of DES: paclitaxel-eluting balloon vs everolimus-eluting stent), which aims to randomise 310 patients to either a paclitaxel DEB or an everolimus-eluting stent for DES in-stent restenosis (NTC01239940). It is rather likely that next-generation balloons will have improved drug delivery properties, and they may therefore be even more effective. The PEPPER (International First in Man Trail With A Novel Drug Eluting Balloon in Patients Presenting with ISR) trial was a first-in-man study testing a novel DEB, incorporating paclitaxel into a microcrystalline structure in 81 patients. The first results have been rather impressive, with minimal LLL over 6months and very few adverse events.[32]

CONCLUSIONS

DEBs represent a useful treatment option for in-stent restenosis of BMS and DES. They reduce the risk of MACE, mainly driven by a reduced need for TLR, but also a reduced mortality risk compared with plain balloon angioplasty and compared with the Taxus Liberte DES. DEBs were superior to treat both, BMS and DES in-stent restenoses. Compared with Taxus stent implantation, DEB results were similar, and they avoid ending up with multiple layers of stents.

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Contributors All authors have read and approved the final version of the manuscript. All authors have significantly contributed to the conception and design of the study, the analysis and interpretation of data, drafting of the manuscript or revising it to justify authorship.

Competing interests None.

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