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ORIGINAL ARTICLE

Drug-eluting Balloon versus Second Generation Drug Eluting Stents in the Treatment of In-stent Restenosis: A Systematic Review and Meta-analysis

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Background In-stent restenosis (ISR) remains a significant mode of stent failure following PCI. The optimal treatment strategy, however, remains undefined and the role of drug-eluting balloons (DEB) in the management of ISR is also unclear.

Methods A meta-analysis was performed to compare the efficacy of DEB in the treatment of ISR against second generation drug eluting stents (DES).

Results Seven studies comprised of 1,065 patients were included for analysis. The follow-up period ranged from 12-25 months. The use of DEB was associated with an inferior acute gain in minimal luminal diameter (MLD) (0.36, 95% CI: 0.16-0.57 mm), higher late loss in MLD (0.11, 0.02-0.19 mm) and a higher binary restenosis rate at follow-up (risk ratio: 2.24, 1.49-3.37). No significant differences were noted in the overall incidence of the analysed clinical parameters between the two groups. When only the randomised controlled trials (RCT) were considered however, there was a strong trend towards higher target lesion revascularisation (TLR; 9.9% vs. 3.6%; RR: 2.5, p=0.07) and a significantly higher major adverse cardiovascular event (MACE) rate (15.7% vs. 8.8%; RR 1.78; p=0.02) with DEB.

Conclusion While equipoise has been demonstrated in selected clinical outcomes between DEB and second generation DES in the treatment of ISR, the suboptimal angiographic outcome at follow-up and the higher TLR and MACE rates associated with DEB observed in the RCT are concerning. The results of the present analysis should be regarded as preliminary, although the generalised adoption of DEB in the treatment of ISR currently cannot be recommended.

Keywords Drug eluting balloon • Drug eluting stent • In-stent restenosis • Coronary artery disease • Percutaneous coronary intervention • Outcome assessment

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Introduction

Q2 Ten years after the first percutaneous transluminal coronary angioplasty was described [1], Sigwart et al. reported their experience with coronary stent implantation in 19 patients, demonstrating its efficacy in the prevention of early vessel occlusion and restenosis [2]. Over the ensuing decades, the use of coronary stents experienced an exponential growth, and the dramatic improvement in patients' clinical and procedural outcomes has resulted in its widespread adoption as a standard part of percutaneous coronary interventions (PCI).

Notwithstanding its overwhelming benefit, the long-term outcome of stent implantation remains significantly constrained by the occurrence of in-stent restenosis (ISR) over time. While many factors such as stent malapposition and stent fracture have been shown to be contributory, the fundamental mechanisms of ISR relate to the progressive increase in cellularity from either neointimal formation, neoatherosclerosis, or a combination of both. The use of bare metal stents (BMS) has been associated with a 16-44% incidence of ISR [3]. This risk was somewhat mitigated by the development of drug eluting stents (DES), although the incidence of ISR remains significant at 5-15% with first generation DES [3], which is only marginally improved with the second generation DES [4]. Furthermore, the increasing off-label use of DES in patients with small arteries, long lesions, complex coronary lesions, diabetes, and history of bypass surgery render ISR an unavoidable legacy of PCI in the long term.

The optimal treatment strategy for ISR however remains undefined. Previous reports have demonstrated clear superiority in the treatment of BMS ISR with DES when compared with Plain Old Balloon Angioplasty (POBA) [5], BMS [6] or brachytherapy [7]. While DES is also used routinely in the treatment DES ISR, the outcome is less compelling when compared to DES treatment of BMS ISR [8]. Whether the use of second generation DES influences this observation is not clear.

Drug eluting balloon (DEB) therapy has emerged as a potential treatment for ISR due in part to its ability to deliver anti-proliferative agents to a restenotic arterial segment without adding extra layers of metal stents. Its efficacy against other treatment strategies has been demonstrated in both randomised controlled trials [9] and in the real world setting [10]. Comparisons to date however have predominantly been between DEB, POBA and first generation DES [9], and individual studies comparing DEB to second generation DES have been relatively small in scale [11–17]. Herein we present the findings of our meta-analysis examining the efficacy of DEB in the treatment of ISR specifically in comparison to second generation DES.

Materials and Methods

Search Strategy

A systematic literature search was performed by two authors (K.L. and S.P.) in August 2015 using Ovid Medline, Embase, Cochrane Register of Controlled Trials (CCTR), Cochrane Database of Systematic Reviews (CDSR), American College of Physician (ACP) Journal Clubs, and Database of Abstracts of Reviews of Effects (DARE) with no date restriction. Search hedges were created with the assistance of C.C. using the following search terms: (''drug eluting balloon'' OR ''DEB''), AND (''drug eluting stent'', OR ''DES'', OR ''everolimus eluting stent'', OR ''EES'', OR ''Xience'', OR ''Promus'', OR ''Zotarolimus eluting stent'', OR ''ZES'', OR ''Resolute''), AND (''in stent restenosis'', OR ''ISR''). Further, the reference lists of relevant studies were reviewed for additional citations. Studies were limited to human studies.

Eligibility Criteria

We followed the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines where possible in performing our systematic review. Two co-authors (K.L. and R.L.) reviewed and chose the studies based on the following inclusion criteria: 1) prospective or retrospective studies (randomised controlled trials or observational studies) where DEB is directly compared with a second generation DES in the treatment of ISR; 2) studies including at least 20 adult patients; 3) studies containing raw data for retrieving directly or permitting indirect derivation of outcomes of interest as well as the associated 95% confidence intervals (CI). Abstracts, case reports, editorials and expert opinions were excluded. Review articles were similarly omitted because of potential publication bias and duplication of results. When institutions published duplicated studies with accumulating numbers of patients or increased lengths of follow-up, only the most complete reports were included for assessment.

Outcomes of Interest

The primary outcome of interest is Target Lesion Revascularisation (TLR) as a marker of lesion failure. Secondary clinical outcomes include the incidence of Major Adverse Cardiovascular Events or MACE, myocardial infarction (MI), target vessel revascularisation (TVR), all-cause mortality, and cardiovascular mortality. The acute gain in minimal luminal diameter (MLD), late luminal loss and incidence of binary restenosis at follow-up were also analysed.

Methodological Quality Evaluation and Data Extraction

The quality of the retrieved citations was assessed against pre-specified checklist criteria by K.L. and S.P (Supplementary Figure S1). The data was extracted independently by three of the co-authors (K.L., R.L. and S.P.) and summarised into a standardised extraction sheets. Any disagreements in data collected were resolved by consensus. The study was prospectively registered with the PROSPERO database of systematic reviews (registration number: CRD42015019538).

Statistical Analysis

Heterogeneity among studies was examined with the Cochran's Q and I^2 statistic, with $p<0.10$ indicating the presence of study heterogeneity, and I^2 values of 25, 50 and 75% corresponding to low, moderate and high degrees of heterogeneity, respectively. Publication bias is assessed based on

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