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Drug eluting balloon versus drug eluting stent in percutaneous coronary interventions: Insights from a meta-analysis of 1462 patients

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ABSTRACT

Background: Drug eluting balloons (DEB) have been developed to overcome the limitations of drug eluting stents (DES), but clinic results of various DEB studies are still not consistent. Thus, we performed a meta-analysis to compare outcomes of DEB and DES for the treatment of coronary artery disease (CAD).
Methods: Medline/Web databases were searched for studies comparing DEB and DES for obstructive CAD, reporting late lumen loss (LLL) and rates for overall mortality, myocardial infarction (MI), stent thrombosis (ST) and target lesion revascularization (TLR).
Results: 8 studies (1462 patients) were included in the meta-analysis. Compared with DES, DEB treated patients showed non-significantly higher LLL (weighted mean difference [WMD] 0.32, 95% confidence interval [CI] −0.15 to 0.78, P = 0.18) and non-significantly higher rate of binary restenosis (odds ratio [OR] 1.40 [0.68–2.48], P = 0.36). Mortality (OR 1.13[0.54–2.37], P = 0.74), MI (OR 0.95, [0.50–1.80], P = 0.87), ST (OR 1.12, [0.34–4.19], P = 0.77) and TLR rates (OR 1.19[0.60–2.38], P = 0.61) were similar between the 2 treatments. A pre-specified meta-regression analysis showed that LLL WMD and TLR OR were inversely correlated to the prevalence of diabetes (P < 0.0001) and directly correlated to reference coronary diameters (P < 0.001).
Conclusions: The present meta-analysis showed that compared to DES, DEB use resulted in similar clinical efficacy and safety. Thus DEB could be considered a reasonable alternative to DES for the treatment of CAD in selected clinical settings (Clinicaltrials.gov identifier: NCT01760200).

1. Background

In the last few years drug-eluting balloons (DEBs) have emerged as a therapeutic alternative to drug eluting stents (DES), to reduce restenosis and target lesion revascularization (TLR) rates after percutaneous coronary interventions (PCI) [1]. Although DES technology has reduced rates of restenosis and late lumen loss (LLL) compared with bare metal stents (BMS) it has been associated with increased rates of late and very late stent thrombosis (LST, VLST) [1–6]. Delayed healing and poor endothelialisation are common in vessels treated with first generation DES [7], in which the mechanism for incomplete neointimal coverage seems to go beyond the antiproliferative potency of the drug and also involve a type IVb hypersensivity [8].

To overcome these limitations research efforts have pursued the development of DEBs, which achieve short-term transfer of antiproliferative substances to the arterial wall without a permanent drug delivery apparel, thus potentially reducing unwanted effects correlated with polymer-based stent technologies [9]. DEBs may offer benefit to treat in-stent restenosis [10] where vessel scaffolding is guaranteed by the previously deployed stent, but data about the efficacy of DEBs, used alone [11] or with provisional [12] or systematic [13] bare metal stent (BMS) deployment in de novo coronary stenoses are still controversial.

The aim of the present meta-analysis is to summarize the evidence from randomized controlled trials (RCT) and cohort studies in which DEBs were compared with DES in treating CAD patients.

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2. Methods

2.1. Search strategy

The meta-analysis was performed according to the recommended methods [14,15]. A systematic search for eligible studies involved MEDLINE, CENTRAL, Embase, Highwire Press, Scopus and Google Scholar databases and was conducted without language restriction by two independent investigators (A.L. and A.R.), using the following keywords: "drug", "eluting" "balloon(s)", "DEB", "coronary", "angioplasty". Divergences were resolved by consensus. The references of retrieved studies were searched manually for additional trials, and efforts to contact authors were performed to obtain further study details or additional references. The search is updated to April 2013.

2.2. Selection criteria

Citations were screened at title/abstract level and retrieved as full reports. Inclusion criteria were: 1) randomized studies or cohort studies reporting a comparison between a DEB treated group and a DES treated group; 2) availability of reports of LLL and/or overall death and/or myocardial infarction (MI) and/or stent thrombosis (ST) and/or target lesion revascularization (TLR). Exclusion criteria were: 1) duplicate reporting (in which case the manuscript reporting the largest sample or the longest follow-up was selected), 2) follow up of less than 6 months; 3) studies presenting composite major adverse cardiac events (MACE) without mentioning individual end points. Data were abstracted on pre-specified forms by 2 unblinded reviewers (A.L. and A.R.); divergences were resolved by consensus.

2.3. Internal validity

The present meta-analysis was performed according to the Guidelines for randomized controlled trials of the Cochrane Collaboration [14] and for non randomized studies in compliance with the Guidelines of the MOOSE group [15]. Quality of included studies was appraised by 2 unblinded investigators (A.L. and G.G.S.). The risk of selection, performance, detection, and attrition bias (expressed as low risk of bias [A], moderate risk of bias [B], high risk of bias [C], or incomplete reporting leading to inability to ensure the underlying risk of bias [D]) were evaluated separately, as recommended [14]. Non-randomized studies were evaluated using the Newcastle-Ottawa Scale [16] a validated technique in assessing the quality of non-randomized studies.

2.4. Data analysis and synthesis

Odds ratios (ORs) were computed from individual studies and pooled according to a fixed effect (e.g. inverse variance weighting) or random effect model in case of statistical heterogeneity. Four separate subgroup analyses were pre-specified: a) randomized studies; b) studies in which DEBs were used always together with BMS deployment; c) studies with the Dior™ DEB (in which paclitaxel is not mixed with a non-polymeric carrier like other DEBs but is encapsulated in a shellac™ cover).

Results were presented as overall meta-analysis and subgroups meta-analyses for DEB vs DES comparisons. Outcomes appraised were in-stent LLL, overall death, MI, ST and TLR. We used the Mantel-Haenszel method for combining ORs, a validated method to pool the data in a meta-analysis of binary outcomes. For the in-stent LLL outcome, the mean difference of 6-month LLL compared with baseline was used and the overall weighted mean difference (WMD) was built with the inverse variance method, as recommended [14].

Heterogeneity was assessed by Cochran's Q test, with 2-tailed $p = 0.1$ as recommended [14,17]. Statistical inconsistency test (I^2) was also employed to overcome the low statistical power of Cochran's Q test [18,19].

The potential publication bias was examined by constructing a "funnel plot", in which sample size was plotted against odds ratios. In addition, a mathematical estimate of the asymmetry of this plot was provided by a linear regression approach [20,21]. Asymmetry was considered to be present if the intercept of the regression line did deviate significantly from zero.

To explore and mitigate heterogeneity [22], pre-specified covariates (prevalence of diabetes in the study population and reference coronary vessel diameter) as potential confounders were considered in the meta-regression analysis.

Pooling of data, subgroup analyses and publication bias tests were performed with Review Manager 5.1 (The Nordic Cochrane Center, Købehvn, Denmark). Meta-regression analyses were built with Comprehensive Meta-analysis Version 2 (Biostat, Englewood, New Jersey, United States).

3. Results

The reviewing process is presented in Fig. 1. From a total pool of 69 initial citations, 50 hits were excluded at the title or abstract level. Twelve studies were excluded after closer inspection. Specific reasons for their exclusion were lack of a control group and failure to report any of the pre-specified end-points.

Finally, 7 randomized studies [11,13,23–27] and 1 cohort study [12], enrolling a total of 1462 patients with a median clinical follow up of 12 months and median angiographic follow up of 6 months were included in our meta-analysis. The main characteristics of the included studies are summarized in Table 1. Quality analysis of the included studies is shown in Table 2. No publication bias was appraised by graphical inspection of the Funnel plots and Egger test for each end-point investigated.

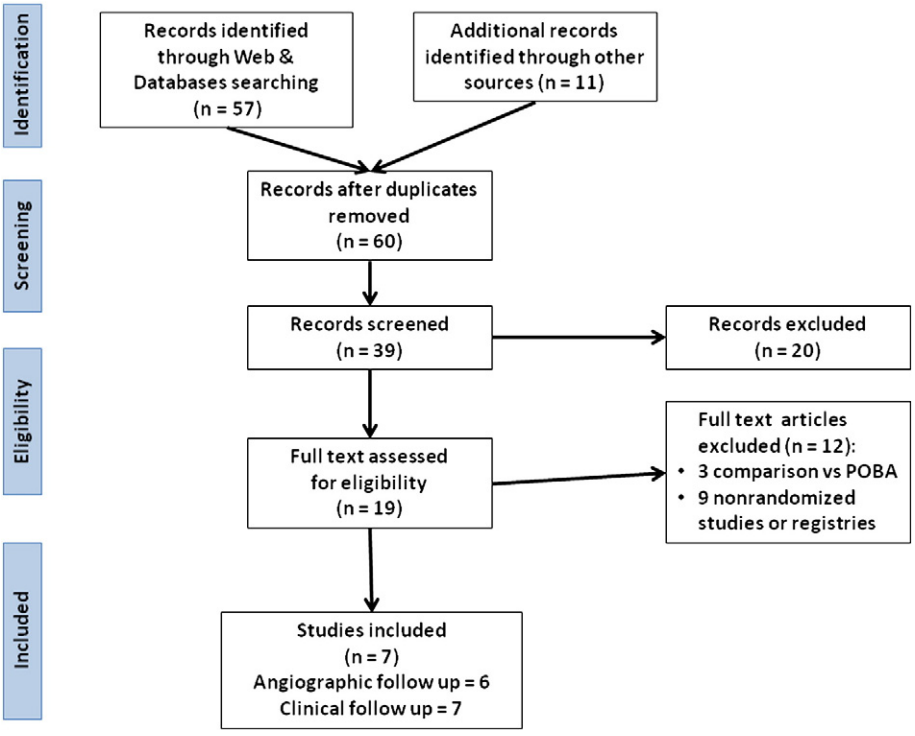

Fig. 1. Flow diagram of the reviewing process according to QUOROM statement.