Meta-Analysis of Randomized Trials Comparing the Effectiveness of Different Strategies for the Treatment of Drug-Eluting Stent Restenosis

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The investigators performed a network meta-analysis of randomized trials comparing the effectiveness of currently available strategies for the treatment of drug-eluting stent (DES) restenosis. Despite the widespread use of DES in patients who undergo percutaneous coronary intervention, the optimal treatment for DES restenosis remains poorly defined. A systematic search of electronic resources was performed. The primary end point was diameter stenosis at follow-up angiography. Seven trials were included, enrolling a total of 1,586 patients with 1,728 restenotic lesions. The following treatment options were found: balloon angioplasty (BA) in 343 patients (19.3%), iopromide-based paclitaxel-eluting balloons (PEB) in 343 (21.6%), sirolimus-eluting stents in 441 (27.8%), paclitaxel-eluting stents in 462 (29.1%), and everolimus-eluting stents in 34 (2.2%). Compared with BA, PEB (−17.74%, 95% credible interval [CI] −25.17% to −11.31%), everolimus-eluting stents (−14.93%, 95% CI −33.47% to 1.16%), paclitaxel-eluting stents (−15.3%, 95% CI −22.96% to −8.35%), and sirolimus-eluting stents (−11.08%, 95% CI −17.89% to −3.4%) had similar reductions in diameter stenosis at follow-up angiography. PEB (85%) and everolimus-eluting stents (68%) had the greatest probabilities for being the best treatment option. Furthermore, PEB were the best treatment in terms of late luminal loss (85%) and binary restenosis (85%). BA had the lowest efficacy with respect to all study end points. In conclusion, in patients with DES restenosis, repeat DES implantation and iopromide-based PEB are valid alternatives. However, PEB had greater angiographic efficacy and therefore should be considered the new benchmark comparator in the treatment of DES restenosis. The use of BA should be discouraged in patients with DES restenosis. **(Am J Cardiol 2014;114:1339−1346)**

Drug-eluting stents (DES) represented a breakthrough technology in the treatment of patients who underwent percutaneous coronary intervention because of a dramatic reduction in the need for repeat revascularization compared with bare-metal stents (BMS).[1] However, in-stent restenosis after DES implantation still occurs, and its prevalence is not negligible as a result of the widespread use of DES in increasing complex subsets of lesions and patients.[2,3] Although several strategies have been proposed, the optimal treatment for DES restenosis remains poorly defined.[4] Recently, initial data from randomized studies have been reported, but direct evidence from head-to-head trials is still limited.[5] Network meta-analysis is an established research method in which direct evidence of different therapy comparisons is combined with indirect evidence that is derived from studies sharing a common comparator within the network frame.[6,7] Therefore, we sought to perform a network meta-analysis of randomized trials to evaluate the effectiveness of different treatment options in patients with DES restenosis.

Methods

We searched MEDLINE, the Cochrane Library, Scopus, scientific session abstracts (published in *Circulation*, the *Journal of the American College of Cardiology*, the *European Heart Journal*, and *The American Journal of Cardiology*), and Web sites (*www.acc.org*, *www.americanheart.org*, *www.escardio.org*, *www.europcronline.com*, *www.clinicaltrialresults.org*, and *www.tctmd.com*). The reference lists of relevant studies were additionally scanned. No language, publication date, or publication status restrictions were imposed. The last search was run on April 20, 2014. The following search terms were matched: "restenosis," "drug-eluting stent," "percutaneous coronary intervention," and "randomized." To be included, a citation had to meet the following criteria: random treatment allocation and inclusion of patients with DES restenosis. Exclusion criteria were ongoing studies and irretrievable data. Two investigators (R.P. and G.G.) independently assessed reports

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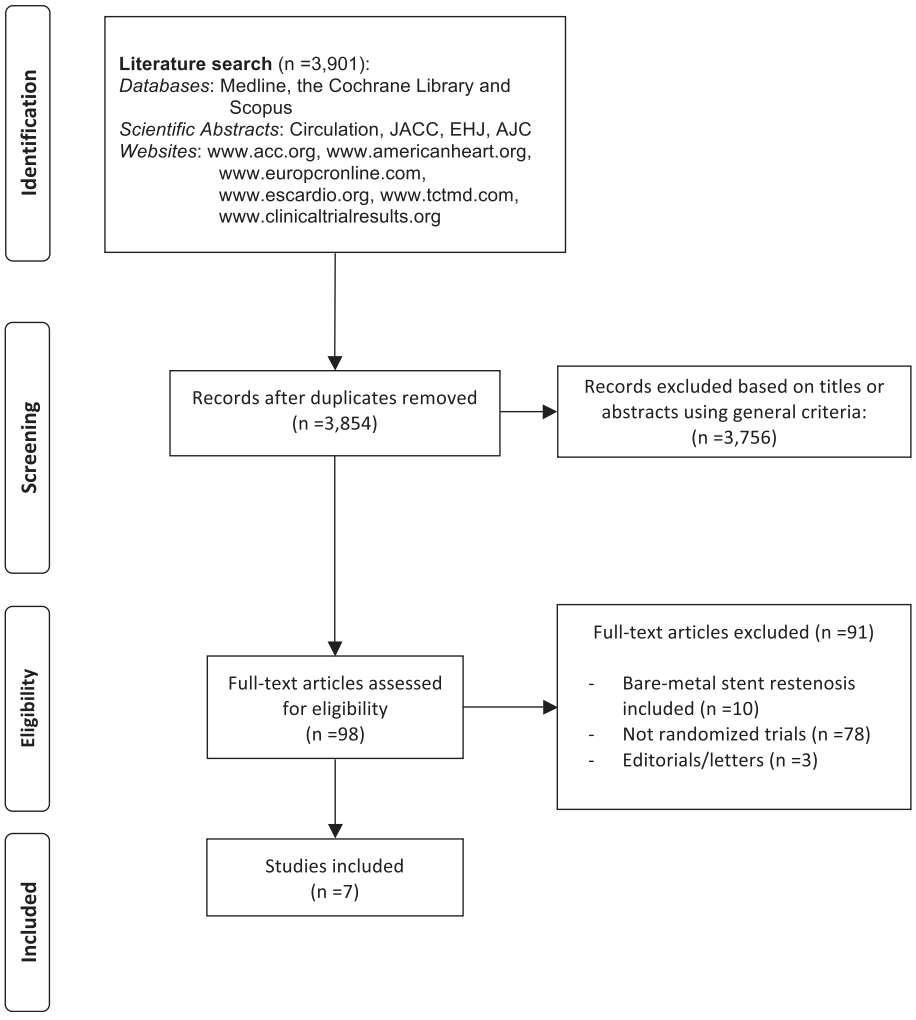

Figure 1. Flow diagram of trial selection. AJC = *The American Journal of Cardiology*; EHJ = *European Heart Journal*; JACC = *Journal of the American College of Cardiology*.

for eligibility at the title and/or abstract level, with divergences resolved by consensus; studies that met the inclusion criteria were selected for further analysis. The study validity was evaluated by the same 2 reviewers, according to the risk-for-bias tool recommended by the Cochrane Collaboration.[8] The primary end point of this study was diameter stenosis at follow-up angiography. Secondary end points were late luminal loss (LLL), defined as the change in minimal luminal diameter from final to follow-up angiography on quantitative coronary angiography; binary restenosis, defined as percentage diameter stenosis $\geq$50% on follow-up angiography; and target-lesion revascularization (TLR), defined as any clinically driven revascularization procedure involving the target lesion. Statistical analysis was performed by using the Aggregate Data Drug Information System, version 1.16.3, software package.[9] First, we performed standard pairwise meta-analysis for trials that directly compared different treatment arms. Than we performed Bayesian network meta-analysis to compare different therapies for DES restenosis. The following 5 treatment arms were identified: (1) balloon angioplasty (BA), defined as plain-old balloon or cutting BA; (2) paclitaxel-eluting balloon (PEB); (3) sirolimus-eluting stent (SES); (4) paclitaxel-eluting stent (PES); and (5) everolimus-eluting stent (EES). The κ statistic was used to assess agreement between reviewers for study selection. Mean differences or odds ratios (OR) with 95% confidence intervals (CIs) were used as summary statistics for traditional pairwise analyses, by applying the random-effects DerSimonian and Laird model.[10] Heterogeneity of treatment effects across studies was assessed by I^2 statistics and the Cochran Q test.[11] Network meta-analysis was performed by using the Bayesian hierarchical random-effects model proposed by Lu and Ades.[7,12] The pooled estimates were obtained using the Markov-chain Monte Carlo method. For each model, we generated 100,000 simulations for each of 2 sets of different initial values, and we discarded the first 20,000 simulations as the burn-in period. The achievement of convergence was assessed with the Brooks-Gelman-Rubin method, which compares within-chain and between-chain variance.[13] When a loop connected 3 treatments, it was possible to evaluate the inconsistency between direct and indirect evidence. We used the node-splitting method to calculate the inconsistency of the model, which separated