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Twelve-month clinical outcomes of everolimus-eluting stent as compared to paclitaxel- and sirolimus-eluting stent in patients undergoing percutaneous coronary interventions. A meta-analysis of randomized clinical trials

Salvatore Cassese, Raffaele Piccolo, Gennaro Galasso, Roberta De Rosa, Federico Piscione *

Department of Clinical Medicine, Cardiovascular Sciences and Immunology, "Federico II" University of Naples, Italy

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ABSTRACT

Background: It is well established that both PES and SES reduce the need for reintervention as compared with bare-metal stents. Whether everolimus-eluting stent (EES) a "second-generation" drug-eluting stent, further improves clinical outcomes compared to PES and SES still remains uncertain. The aim of this study was to perform a meta-analysis of randomized trials evaluating safety and efficacy of EES compared with paclitaxel- (PES) and sirolimus-eluting stent (SES), in patients undergoing percutaneous coronary intervention (PCI).
Methods: We undertook a literature search using Medline, EMBASE, the Cochrane Central Register of Controlled Trials, scientific session abstracts and relevant websites, until August 2010. Included studies comprised randomized trials evaluating EES vs PES/SES, in patients undergoing PCI, at 1-year follow-up.
Results: Five studies, enrolling 8058 patients, were included. At 12-month follow-up, patients treated with EES, as compared with PES/SES, experienced lower target-lesion revascularization (OR [95% CI] = 0.56 [0.45–0.70], $p<0.00001$) and myocardial infarction rates (OR [95% CI] = 0.57 [0.43–0.77], $p=0.0002$), without difference in mortality (OR [95% CI] = 0.88 [0.62–1.24], $p=0.46$). A trend towards lower stent thrombosis rates in favour of EES vs PES/SES was found (OR [95% CI] = 0.45 [0.20–1.01], $p=0.05$). However, after the exclusion of SES, EES significantly reduced stent thrombosis as compared with PES (OR [95% CI] = 0.35 [0.14–0.86], $p=0.02$).
Conclusions: At 12-month follow-up, treatment with EES is associated with decreased target-lesion revascularization and myocardial infarction rates, without differences in mortality, as compared with PES/SES. EES vs PES/SES use is associated with a trend towards lower stent thrombosis rates. Moreover, EES significantly reduce stent thrombosis with respect to PES.

1. Introduction

Drug-eluting stents (DES) are associated with a marked reduction in restenosis and target-vessel revascularization as compared to bare-metal stents (BMS), in patients undergoing percutaneous coronary interventions (PCI) [1,2]. Although at the beginning DES represented a perfect solution for interventional cardiologists, stent thrombosis (ST) and endothelial dysfunction after DES implantation still remain a matter of concern [3–5]. Paclitaxel-eluting stent (PES) and sirolimus-eluting stent (SES) are recognized as "first-generation" DES, since they were the first DES developed and therefore introduced in the market after approval. As a consequence, additional DES are usually referred to as "second-generation" DES, due to advances in stent platforms, delivery systems, as well as polymers and drugs biocompatibility, in association with the later time of approval. Furthermore, over to technical advantages, this second-generation DES may have superior safety with similar or greater clinical efficacy.

Everolimus is an anti-proliferative agent that inhibits cell proliferation by inducing cell cycle arrest in the late G1 stage [6]. Everolimus-eluting stent (EES – Xience V®, *Abbott Vascular, Santa Clara, CA, USA* or Promus®, *Boston Scientific Corp., Natick, Massachusetts*) is a second-generation DES composed of a stent delivery system coated with a formulation containing the anti-restenotic drug everolimus embedded in a durable biocompatible polymer of poly (n-butyl methacrylate) (PBMA), that adheres to the stent and drug coating (primer layer), and vinylidine fluoride and hexafluoropropylene monomers as the drug matrix layer containing everolimus (reservoir layer) [7].

According to first clinical data, EES use dramatically reduced restenosis as compared with BMS [8]. However, whether EES can further improve clinical outcomes compared to PES and SES still remains uncertain. Meta-analysis has the potential to increase power and summarize results from different, but comparable, individual studies. Therefore, we performed a meta-analysis at study-level of randomized clinical trials aiming to assess the EES vs PES/SES safety

* Corresponding author. Department of Clinical Medicine, Cardiovascular Sciences and Immunology, Federico II University of Naples, Italy, Via S. Pansini, 5, 80131, Naples, Italy. Tel.: +39 0817462234; fax: +39 0817462229.
E-mail address: piscione@unina.it (F. Piscione).

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and efficacy, among patients undergoing PCI, at twelve-month follow-up.

2. Methods

2.1. Search strategy and selection criteria

We searched Medline, EMBASE, the Cochrane Central Register of Controlled Trials (CENTRAL), scientific session abstracts in Circulation, Journal of the American College of Cardiology, European Heart Journal and The American Journal of Cardiology, and relevant websites (http://www.americanheart.org, http://www.europcronline.com, http://www.escardio.org, http://www.clinicaltrialresults.org, http://www.tctmd.com and http://www.theheart.org), starting from our previous meta-analyses [9,10]. The reference list of relevant studies was additionally scanned. No language, publication date, or publication status restrictions were imposed. The last search was run on August 2010. The following search terms were used: "percutaneous coronary intervention", "randomized trial", "everolimus-eluting stent", "Xience", "Promus", "drug-eluting stent", "paclitaxel-eluting stent" and "sirolimus-eluting stent". To be included, the citation had to meet the following criteria: 1) random treatment allocation and 2) everolimus-eluting stent implantation. Exclusion criteria were: 1) ongoing studies, 2) irretrievable data and 3) BMS implantation in the control arm.

2.2. Data collection and assessment of risk of bias

Two investigators (S.C. and R.P.) independently assessed reports for eligibility at title and/or at abstract level, with divergences resolved with a third reviewer (F.P.); studies that met inclusion criteria were selected for further analysis. Data of individual patients were not available and analyses were based on aggregate data as provided in the respective papers. The risk of bias was evaluated by the same two reviewer authors, in accordance with The Cochrane Collaboration methods [11] and considering the following methodological items: adequacy of sequence generation, adequacy of allocation concealment, blinding, incomplete data outcome, selective outcome reporting, other potential source of bias and sample size calculation. We did not use a quality score, since this practice has been previously discouraged [12].

2.3. Outcome variables

The primary endpoint of this meta-analysis was ischemia-driven target-lesion revascularization (TLR) at 12-month follow-up. Secondary endpoints were: death, myocardial infarction (MI) and ST. All clinical endpoints were evaluated according to per protocol definitions as reported in the Supplementary data file (Table 1).

2.4. Statistical analysis

The κ statistic was used to assess agreement between reviewers for study selection. Odds ratio (OR) and 95% confidence intervals (95% CI) were used as summary statistics. The pooled OR was calculated by using the fixed effects Mantel–Hænzel model, while, in case of significant heterogeneity across studies, the random effects DerSimonian and Laird model was used instead. In case of statistical significance, the number needed to treat (NNT) with relative CI was provided, in order to quantify the risk reduction associated with EES use. The Breslow–Day chi-squared test was calculated to test the statistical evidence of heterogeneity across the studies. In addition, we used the I^2 statistic, which describes the percentage variation across studies that is due to heterogeneity rather than chance. As a guide, I^2 values <25% indicated low, 25–50% indicated moderate, and >50% indicated high heterogeneity [13]. For the primary endpoint, small-study effects were analyzed by constructing a funnel plot, in which the standard error of the lnOR was plotted against OR for TLR. However, because graphical evaluation can be subjective, we performed both Harbord [14] and Peters tests, [15] as formal statistical tests for publication bias. The Harbord test is a modified version of Egger test and has a type I error close to the nominal level in the absence of between-study heterogeneity. Differently, the Peters test is a minor modification of Macaskill test and gives a more balanced type I error rates in the tail probability areas as compared to the Egger test. Moreover, a sensitivity analysis, in which the meta-analysis estimates are computed omitting one study at time, was performed. Statistical analyses were obtained by using Stata 10.0 statistical software (*STATA Corp, College Station, Texas, USA*). The study was realized in compliance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement [16].

3. Results

3.1. Eligible studies

As reported in Fig. 1, we screened the title and/or the abstract of 1749 potentially eligible publications. Of these, 1702 citations were excluded since not relevant to this study or were duplicated publications. Thus, 47 studies were assessed for eligibility and 42 records were discarded since inclusion criteria were not met. Finally, 5 trials [17–21] were included in the meta-analysis, enrolling a total of 8058 patients (4879 or 60.55% randomized to EES and 3179 or 39.45% randomized to PES/SES). The inter-observer agreement for study selection was good, with $\kappa = 0.94$. Main characteristics of included studies were reported in Table 1. Four trials [17,18,20,21] compared EES with PES. The remaining trial randomized patients in a 2:1:1 ratio to receive a biodegradable-polymer SES or durable-polymer SES or EES [19]. One trial [20] adopted a "second-generation PES" consisting of a different stent platform carrying on the same polymer. MI rates were retrievable from all trials, except for one [19]. All trials adjudicated stent thrombosis according to Academic Research Consortium criteria [22]. The mean patients age ranged from 62 to 67 years. In three [17–19] out of five trials a routine angiographic follow-up was pre-specified for all patients or specific subgroups, according to study protocol. In all studies but one [17] a 300 to 600 mg loading dose of clopidogrel was used before or after PCI. Dual antiplatelet therapy (aspirin plus clopidogrel) was received for at least 6 months in all studies, with the exception of one trial [20] prescribing 12 months of clopidogrel administration, while aspirin was prescribed indefinitely in all trials. The risk of bias among studies was reported in Table 2.

3.2. Clinical endpoints

TLR occurred in a total of 345 patients (4.31%). As reported in Fig. 2 (Panel A), treatment with EES was associated with a significant TLR reduction (3.20% vs 6.03%, EES vs PES/SES, respectively; OR [95% CI] = 0.56 [0.45–0.70], $p<0.00001$), NNT = 40 (32–58, 95% CI). There was a low heterogeneity across trials ($I^2 = 25\%$, $p_{het} = 0.26$).

Death occurred in 139 patients (1.74%). As reported in Fig. 3 (Panel A), no significant differences were found between EES and PES/SES (1.54% vs 2.03%, respectively; OR [95% CI] = 0.88 [0.62–1.24], $p = 0.46$). No evidence of heterogeneity was observed across trials ($I^2 = 0\%$, $p_{het} = 0.97$).

MI rates were available for 6680 participants (83.63%) [17,18,20,23]. A total of 189 patients experienced MI (2.39%). As shown in Fig. 3 (Panel B), EES use significantly reduced MI incidence (2.15% vs 3.96%, EES vs PES; OR [95% CI] = 0.57 [0.43–0.77], $p = 0.0002$), NNT = 61 (46–114, 95% CI). No evidence of heterogeneity was noted across trials ($I^2 = 0\%$, $p_{het} = 0.93$).

Definite or probable ST occurred in a total of 79 patients (0.99%). As reported in Fig. 3 (Panel C), a trend towards lower ST rates in favour of EES was observed (0.60% vs 1.59%, EES vs PES/SES respectively; OR [95% CI] = 0.45 [0.20–1.01], $p = 0.05$). Since a trend toward significant heterogeneity was noted across trials ($I^2 = 57\%$, $p_{het} = 0.06$), the pooled OR was calculated with random-effect models.

3.3. Small studies effect and sensitivity analysis

As depicted in Fig. 1 (Panel B), no small-study effects were observed for the primary endpoint: moreover, both Harbord ($p = 0.42$) and Peters tests ($p = 0.23$) were not significant. Sensitivity analysis showed that omitting ISAR-TEST-4 trial [19], in which SES was implanted, a significant difference in terms of stent thrombosis rate was found between EES and PES (OR [95% CI] = 0.30 [0.16–0.55], $p<0.0001$). Since a trend toward significant heterogeneity was noted across trials ($I^2 = 56\%$, $p_{het} = 0.08$), the pooled OR was calculated with random-effect models. EES confirmed superiority over PES with respect to TLR occurrence (OR [95% CI] = 0.48 [0.36–0.63], $p<0.00001$, $I^2 = 0\%$, $p_{het} = 0.52$), NNT = 42 (34–59, 95% CI), without difference in mortality (OR [95% CI] = 0.88 [0.56–1.40], $p = 0.60$, $I^2 = 0\%$, $p_{het} = 0.92$).