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INTERVENTIONAL CARDIOLOGY

Efficacy and Safety of Drug-Eluting Stents in Chronic Total Coronary Occlusion Recanalization

A Systematic Review and Meta-Analysis

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Objectives The aim of this study was to compare the efficacy and safety of drug-eluting stent (DES) and bare-metal stent (BMS) use in chronic total occlusion (CTO) recanalization.

Background The long-term effectiveness and safety of DES use in CTO recanalization are unclear, and performance of randomized clinical trials in the field is complex.

Methods Major electronic information sources were explored for articles comparing outcomes with DES and BMS use among patients with CTO. Assessed clinical outcomes were death, myocardial infarction, target vessel revascularization, major adverse cardiac events, and stent thrombosis; angiographic outcomes were stent restenosis and stent reocclusion.

Results Fourteen comparative studies were identified (a total of 4,394 patients). When compared with BMS, DES significantly reduced risk of major adverse cardiac events (relative risk [RR]: 0.45, 95% confidence interval [CI]: 0.34 to 0.60, $p < 0.001$) and TVR (RR: 0.40, 95% CI: 0.28 to 0.58, $p < 0.001$) without increasing death (RR: 0.87, 95% CI: 0.66 to 1.16, $p = 0.88$) or myocardial infarction (RR: 0.89, 95% CI: 0.54 to 1.46, $p = 0.80$). This benefit was sustained at ≥3 years of follow-up. Lower RRs for restenosis (RR: 0.25, 95% CI: 0.16 to 0.41, $p < 0.001$) and stent reocclusion (RR: 0.30, 95% CI: 0.18 to 0.49, $p < 0.001$) were also observed in the DES group. A strong trend toward a higher rate of stent thrombosis was documented in DES-treated patients (RR: 2.79, 95% CI: 0.98 to 7.97, $p = 0.06$).

Conclusions DES use in CTO recanalization is associated with significantly fewer major adverse cardiac events and fewer occurrences of target vessel revascularization, restenosis, and stent reocclusion than with BMS. Although a statistical trend toward a higher risk of stent thrombosis was observed, the use of DES in this context seems to be safe, with an overall benefit sustained in the long term. (J Am Coll Cardiol 2010;55:1854–66) © 2010 by the American College of Cardiology Foundation

Recanalization of chronic total occlusion (CTO) is one of the most challenging percutaneous coronary interventions (PCI). Procedural success is hampered by the difficulties associated with crossing the occluded segment with guidewires and recanalization devices, and long-term results are threatened by a high restenosis rate (1). The introduction of drug-eluting stents (DES), which have been demonstrated to cause less restenosis than bare-metal stents (BMS) in specific patient and stenosis subsets, has raised hopes of improving long-term vessel patency after CTO recanalization (2). However, limited evidence of the benefit and safety of DES use in CTO is available, partly due to inherent difficulties in conducting dedicated randomized clinical trials (RCTs) in this field. To shed further light on this issue, we performed a systematic review and meta-analysis at the study level of existing RCTs and non-RCTs reporting outcomes of DES versus BMS use in patients with CTO.

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Methods

Study objectives and clinical definitions. The aim of this systematic review and meta-analysis was to compare outcomes of DES and BMS for the treatment of CTO in RCTs and non-RCTs. Clinical outcomes of interest were death, myocardial infarction (MI), target vessel revascularization

tion (TVR), stent thrombosis (ST), and major adverse cardiac events (MACE). Angiographic outcomes were stent restenosis and reocclusion. Definitions of the end points used in the studies were contrasted with the standardized definitions proposed by Cutlip et al. (3) for coronary stent trials. If end points fell outside these standardized definitions, those used by the original authors are specified.

Study search strategy. A bibliographic search covering the period January 2002 to May 2009 was conducted independently by 2 investigators, first in MEDLINE and Cochrane Library databases, and then in conference proceedings of the Scientific Sessions of the American College of Cardiology, American Heart Association, European Society of Cardiology, Transcatheter Cardiovascular Therapeutics, and EuroPCR as well as their websites. Appropriate free text and various permutations of the MeSH terms "stent" or "drug-eluting stent" or "bare-metal stent" and coronary total occlusion or "comparative study" were used in the search. No language restrictions were applied.

Study selection. Identified studies were reviewed and selected if they reported a direct comparison of DES (sirolimus or paclitaxel) and BMS in CTO recanalization and included clinical or angiographic outcome data at ≥6-month follow-up after stent implantation.

Inclusion or exclusion of studies was performed hierarchically based on the title of the report first, followed by the abstract, and then by the full text. If the initial study was followed by a more complete study or studies that included the original dataset, the most recent and complete report was chosen. Such linked studies were identified on the grounds of authorship, institutions, design, length of follow-up, and study populations. Disagreement on study selection was resolved by consulting a third investigator.

Study classification. Studies were classified according to the Cochrane Intervention Meta-analysis Handbook into 4 categories (4): 1) nonrandomized, controlled trials (CTO patients were nonrandomly allocated to DES or BMS treatment); 2) retrospective cohort studies (patients with CTO treated with DES or BMS were retrospectively identified and long-term outcomes were assessed); 3) historically controlled trials (outcome of patients with CTO treated with DES were compared with a nonconcurrent group treated with BMS); and 4) RCTs (CTO patients were randomly allocated to DES or BMS treatment). We refer generically to categories 1, 2, and 3 as nonrandomized comparative studies (NRCS).

Data extraction and assessment of quality. Two investigators independently assessed appropriate treatment allocation and adequacy of analysis in each study. Extracted data included first author, publication year, study design, clinical and angiographic characteristics, type of intervention (number of patients allocated to BMS or DES implantation), stent type, length of follow-up, and outcomes of interest. The quality of studies was scored using the Cochrane Collaborations tool for assessing risk of bias for RCTs (4) and the Newcastle-Ottawa scale for NRCS (5). Discrepancies were resolved by discussion with a third investigator.

Statistical analysis. Interobserver agreement was performed using Cohen's weighted kappa. The relative risk (RR) for each study outcome was calculated from abstracted data using the inverse variance method. Statistical heterogeneity was assessed using Cochrane's Q via the chi-square test and further quantified with the I^2 test. The number needed to treat (NNT) was calculated to depict the clinical effect of treatment. Overall treatment effect was first calculated separately for RCTs and NRCS and then for pooled data. To be conservative, a random-effects model was used. Whenever I^2 was >50% and $p < 0.1$, bivariate meta-regressions were performed to investigate the potential sources of heterogeneity. This included regressions of the log RR on clinical and methodological variables. Sensitivity analysis for each outcome was performed; a ≥20% modification of the overall effect by exclusion of a given study was considered significant. Stratified analysis was performed to assess the effect of study quality and clinical factors. Weighted regression analysis was performed to investigate the relationship between baseline patient risk and treatment benefit. Publication bias was assessed using funnel plots, Begg's correlation, and Egger's regression. In assessing heterogeneity, $p < 0.1$ was considered statistically significant; otherwise, $p < 0.05$ was used to indicate significance. Analyses were performed using Review Manager Version 5.1 (Cochrane Collaboration, Software Update, Oxford, United Kingdom) and Epidat version 3.1 (Xunta de Galicia/Panamerican Health Organization WHO).

Abbreviations and Acronyms

- **BMS** = bare-metal stent(s)
- **CI** = confidence interval
- **CTO** = chronic total occlusion
- **DES** = drug-eluting stent(s)
- **MACE** = major adverse cardiac event
- **MI** = myocardial infarction
- **NNT** = number needed to treat
- **NRCS** = nonrandomized comparative study/studies
- **PCI** = percutaneous coronary intervention
- **RCT** = randomized clinical trial
- **RR** = relative risk
- **RRR** = relative risk reduction
- **ST** = stent thrombosis
- **TVR** = target vessel revascularization

Results

Literature search. Figure 1 shows the QUORUM flow chart, providing a description of publication screening and reasons for exclusion. Agreement between investigators regarding data search was good (kappa = 0.89). Fourteen studies (2 RCTs and 12 NRCS) were finally selected for data extraction (6–19). The authors of 2 conference proceedings were contacted, and they provided additional information on their studies (14,15).

Quality assessment. Agreement between reviewers on quality assessment was good in NRCS (kappa = 0.85), and complete in RCTs (kappa = 1.00). Table 1 summarizes