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ORIGINAL ARTICLE

Retrospective Study of First-Generation Drug-Eluting Stents, Second-Generation Drug-Eluting Stents and Non-Drug Eluting Stent Methods in the Treatment of Native Vessel In-Stent Restenosis in Real-World Clinical Practice

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Background The efficacy of second-generation drug-eluting stents (DES) in treating in-stent restenosis (ISR) compared to first-generation DES and non-DES treatment methods in real-world cohorts has not yet been adequately addressed. This research intends to examine optimum treatment of in-stent restenosis, considering first-generation DES, second-generation DES and non-DES treatment methods in a real-world cohort.

Methods Retrospective analysis was performed on 114 patients treated for native-vessel BMS or DES ISR. Thirty-two were treated with a first-generation DES (81% sirolimus, 19% paclitaxel), 32 with a second-generation DES (72% everolimus, 28% zotarolimus) and 28 with non-DES methods (32% bare-metal stent, 39% balloon angioplasty, 29% cutting balloon). The composite primary endpoint was total adverse cardiac events, recurrent stable angina, unstable angina, myocardial infarction (MI), target vessel revascularisation (TVR) and cardiac death at minimum clinical follow-up of six months.

Results Primary endpoint rates were significantly higher in the non-DES and second-generation DES treatment groups than in first-generation DES (42.9%, 25.9%, 6.2%; p = 0.004). Rates of MI and TVR were significantly higher in the non-DES treatment group, compared to first and second-generation DES (MI: 17.9%, 0%, 5.6%; p = 0.018; TLR: 21.4%, 3.1%, 7.4%; p = 0.041).

Conclusions First-generation DES may be superior to second-generation DES and non-DES in treating BMS or DES ISR with regard to overall adverse cardiac events.

Keywords In-stent restenosis • Paclitaxel • Sirolimus • Zotarolimus • Everolimus • Percutaneous coronary intervention

Abbreviations: BA, balloon angioplasty; BMS, bare-metal stent(s); CB, cutting balloon angioplasty; CCS, Canadian Cardiovascular Society; EES, everolimus-eluting stent(s); ISR, in-stent restenosis; PES, paclitaxel-eluting stent(s); SES, sirolimus-eluting stent(s); TIMI, Thrombolysis in Myocardial Infarction; ZES, zotarolimus-eluting stent(s)

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Introduction

Drug-eluting stent (DES) implantation in the treatment of coronary artery disease has been successful in reducing rates of target lesion revascularisation. First-generation sirolimus-eluting (SES) [1] and paclitaxel-eluting (PES) stents have been shown to be superior to bare-metal stents (BMS) with respect to target lesion revascularisation and major adverse cardiac events [2,3]. Second-generation everolimus (EES) and zotarolimus (ZES) eluting stents have also proved to be non-inferior to first-generation stents in the treatment of de-novo coronary lesions with respect to safety and efficacy [4–6].

Despite this success, DES in-stent restenosis (ISR) still occurs in 3-20% of patients [7] and given the continued use of BMS with their associated higher rates of ISR, a significant ISR burden continues in practice [8]. In terms of event-free survival, BMS implantation has been shown to be equivalent to both balloon angioplasty (BA) [9] and cutting balloon angioplasty (CB) [10] in the treatment of BMS ISR.

In contrast, SES and PES have been shown to be superior to balloon angioplasty in the treatment of BMS ISR [11–13]. Evidence also exists demonstrating the equivalence of first-generation SES and PES with respect to safety and efficacy in the treatment of SES ISR [14].

More limited data exist regarding the efficacy of second-generation DES in the treatment of either BMS or DES ISR, despite the widespread use of both stent types in ISR treatment. Current evidence has been limited to a prospective study directly comparing ZES and EES [15] with limited sample sizes and no comparison to first-generation DES. A larger non-randomised study compared EES to PES in BMS ISR only and found reduced adverse event rates at one year in the EES group, and no difference in rates at long-term follow-up [16]. A recent randomised study compared EES (n = 34) to SES (n = 32) in diffuse DES ISR lesions only and found that both were comparable in terms of angiographic and clinical outcomes [17].

Current research does not adequately consider the use of EES and ZES in the treatment of ISR lesions, nor does it compare either generation of DES to non-DES treatment methods in the same study population. Real world applicability of previous research is also limited by the treatment of DES or BMS ISR exclusively and in some studies, the restriction of treatment method to specific pre-defined lesion morphology.

Therefore, the aim of this research was to determine the optimal treatment method of BMS or DES ISR with respect to clinical outcomes, considering first-generation DES, second-generation DES and non-DES treatment modalities in a real-world setting.

Patients

Subjects 18 years and older with a native vessel, in-stent restenotic lesion, presenting clinically as chronic stable angina, acute coronary syndrome or with evidence of inducible ischaemia on functional testing, in addition to angiographic evidence of a ≥50% stenosis within the target lesion were enrolled. The de-novo lesion may have been treated with either a BMS or DES and the ISR lesion could be of any angiographic morphological type [18].

Methods

Study Design

This retrospective cohort study was performed at a single specialist tertiary referral centre in Australia. Subjects were treated between February 2007 and December 2011. Ethical approval was gained through the centre's human research ethics committee. Patients contacted for the purposes of the study were subject to a verbal informed consent process prior to data being collected.

Given the overall equivalence in previous research within non-DES treatment methods and first-generation DES, this study employed pooled treatment groups. These were defined as BA, CB or BMS for the non-DES treatment group, SES or PES for the first-generation DES group and either EES or ZES for the second-generation DES group. There were no restrictions placed upon stent brand or model within these groups. If a DES and either cutting balloon or rotational atherectomy were employed in ISR treatment, the patient was assigned to the relevant DES treatment group. Likewise, pre- or post-dilatation with balloon angioplasty did not affect assignment to DES treatment group. Patients who were treated with heterogeneous stent types within the same lesion segment were excluded from the study.

Treatment Procedure

Treatment for ISR lesions was performed using standard percutaneous coronary intervention procedures. Approach was either radial or femoral. Anti-platelet and anti-thrombin therapy was based on guideline-defined strategies during the period of treatment [19]. A majority of patients received life-long aspirin 100 mg/day following the procedure, and at least 12 months of clopidogrel 75 mg/day.

Study Endpoints and Definitions

The primary endpoint in this study was a composite of total adverse cardiac events. This was comprised of cardiac death, non-fatal myocardial infarction, unstable angina, recurrent stable angina and target vessel revascularisation. Secondary endpoints were composite safety and major adverse cardiac events. The safety endpoint comprised a composite of all-cause death and non-fatal myocardial infarction. Major adverse cardiac events, a composite of cardiac death, non-fatal myocardial infarction and target vessel revascularisation was considered for the purposes of increased comparability with previous studies [2,15,20]. To prevent double counting of individual end-points within the composite endpoints a hierarchical count of endpoints was utilised such that death took priority over MI over TVR over angina.

In accordance with ARC guidelines, a conservative approach was adopted with respect to cardiac death. All