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CLINICAL RESEARCH

CORONARY

Three-Year Outcomes After Revascularization With Everolimus- and Sirolimus-Eluting Stents From the SORT OUT IV Trial

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ABSTRACT

OBJECTIVES The study sought to compare the risk of late outcome with a focus on very late definite stent thrombosis of the everolimus-eluting stent (EES) with that of the sirolimus-eluting stent (SES) at 3-year follow-up.

BACKGROUND In the SORT OUT IV (SORT OUT IV Trial), comparing the EES with the SES in patients with coronary artery disease, the EES was noninferior to the SES at 9 months. The SORT OUT IV trial provides long-term head-to-head randomized comparison of the EES with the SES.

METHODS We prospectively randomized 2,774 patients in the SORT OUT IV trial. Follow-up through 3 years was complete in 2,771 patients (99.9%). The 3-year pre-specified endpoints were composites of safety and efficacy (major adverse cardiac events [MACE]: cardiac death, myocardial infarction, target vessel revascularization, and definite stent thrombosis).

RESULTS At 3 years, the composite endpoint MACE occurred in 9.8% of the EES group and in 11.1% of the SES group (hazard ratio [HR]: 0.89, 95% confidence interval [CI]: 0.70 to 1.12). Overall rate of definite stent thrombosis was lower in the EES group (0.2% vs. 1.4%; HR: 0.15, 95% CI: 0.04 to 0.50), which was largely attributable to a lower risk of very late definite stent thrombosis: 0.1% versus 0.8% (HR: 0.09, 95% CI: 0.01 to 0.70).

CONCLUSIONS At 3-year follow-up, the MACE rate did not differ significantly between EES- and SES-treated patients. A significant reduction of overall and very late definite stent thrombosis was found in the EES group. (The SORT OUT IV TRIAL [SORT OUT IV]; NCT00552877). (J Am Coll Cardiol Intv 2014;7:840–8) © 2014 by the American College of Cardiology Foundation.

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In percutaneous coronary interventions, drug-eluting stent (DES) implantation has reduced the need for repeat revascularization compared with bare metal stents (1-3). Although DES are widely accepted as effective and safe, debate continues on the safety of first-generation DES, given the potential for late stent thrombosis, especially after discontinuation of dual antiplatelet therapy (4,5). Increased risk of late and very late stent thrombosis associated with first-generation drug-eluting stents led to recommendations for large-scale randomized clinical endpoint trials encompassing a variety of patient categories and types of coronary lesions to allow head-to-head comparison of DES with higher external validity than in the pivotal trials performed in more select lesions/patient populations. In the COMPARE (Second-Generation Everolimus-Eluting and Paclitaxel-Eluting Stents in Real-life Practice) trial (6) and the SPIRIT IV (Everolimus-Eluting Versus Paclitaxel-Eluting Stents in Coronary Artery Disease) trial (7), a lower rate of very late definite stent thrombosis in the second-generation everolimus-eluting stent (EES) compared with the first-generation comparator paclitaxel-eluting stent (PES) was found between 1 and 2 years after stent implantation. The favorable stent thrombosis rate for the second-generation DES has awaited confirmation in longer term follow-up randomized studies. In the RESOLUTE (Comparison of Zotarolimus-Eluting and Everolimus-Eluting Coronary Stents) trial (8), the everolimus-eluting stent (EES) was associated with significantly less definite stent thrombosis than the slow-release Resolute (Medtronic, Minneapolis, Minnesota) zotarolimus-eluting stent (ZES). However, in the SORT OUT III (SORT OUT IV Trial) trial, the fast-release Endeavor ZES (Medtronic) was associated with a reduced risk of very late definite stent thrombosis compared with the SES at 3-year follow-up (9) and in the ENDEAVOR IV Clinical Trial: A Trial of a Coronary Stent System in Coronary Artery Lesions, the rate of very late stent thrombosis was significantly lower with ZES compared with PES (10). The SORT OUT IV trial aimed to compare the safety and efficacy outcomes at 3 years with specific focus on very late definite stent thrombosis of the first-generation SES Cypher Select+ (Medtronic) and the second-generation EES Xience V/Promus stent (Medtronic) in a population-based setting, using registry-based event detection.

METHODS

PATIENTS AND STUDY DESIGN. SORT OUT IV (11) is a randomized, multicenter, single-blind, all-comer, 2-arm, noninferiority trial comparing the EES with the SES in treating atherosclerotic coronary artery lesions. The study period was August 2007 to June 2009. The detailed study protocol can be found in the main publication (12). Briefly, patients were eligible if they were at least 18 years of age, had chronic stable coronary artery disease or acute coronary syndromes, and at least 1 coronary lesion with >50% diameter stenosis, requiring treatment with a DES. If multiple lesions were treated, the allocated study stent had to be used in all lesions. No restrictions were placed on the number of treated lesions, the number of treated vessels, or lesion length. Exclusion criteria were life expectancy of <1 year; an allergy to aspirin, clopidogrel, sirolimus, or everolimus; participation in another randomized trial; or inability to provide written informed consent.

ABBREVIATIONS AND ACRONYMS

CI = confidence interval
DES = drug-eluting stent(s)
EES = everolimus-eluting stent(s)
HR = hazard ratio
MI = myocardial infarction
PES = paclitaxel-eluting stent(s)
SES = sirolimus-eluting stent(s)
TLR = target lesion revascularization
TVR = target vessel revascularization
ZES = zotarolimus-eluting stent(s)

RANDOMIZATION. Patients were enrolled by the investigators and randomly allocated to treatment groups after diagnostic coronary angiography and before percutaneous coronary intervention. Block randomization by center (permuted blocks of random sizes [2/4/6]) was used to assign patients in a 1:1 ratio to receive the EES (Xience V, Abbott Vascular, or PROMUS (Abbott Vascular's [Abbott Park, Illinois] privately labeled XIENCE V Everolimus Eluting Coronary Stent System distributed by Boston Scientific, Natick, Massachusetts) or the SES (Cypher Select+, Cordis [Miami, Florida], Johnson & Johnson [New Brunswick, New Jersey]). An independent organization computer-generated the allocation sequence, stratified by sex and the presence of diabetes. Patients were assigned to treatment through an automated telephone allocation service. Although operators were unblinded, all individuals analyzing data were masked to treatment assignment.

STUDY PROCEDURES. EES were available in diameters of 2.25 to 4.0 mm and lengths of 8 to 28 mm. The SES were available in diameters of 2.25 to 3.5 mm and lengths of 8 to 33 mm. Stents were implanted according to standard techniques. Direct stenting without previous balloon dilation was allowed. Before or at the time of the procedure, patients received at least 75 mg of aspirin, a 600-mg loading dose of clopidogrel, and a dose of unfractionated heparin (5,000 IU or 70 to 100 IU/kg). Glycoprotein IIb/IIIa inhibitors were used at the operator's discretion. Recommended post-procedure dual-antiplatelet regimens were aspirin 75 mg/day for life and clopidogrel 75 mg/day for 1 year.