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Benefits and Risks of Extended Dual Antiplatelet Therapy After Everolimus-Eluting Stents

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on behalf of the DAPT Study Investigators

ABSTRACT

OBJECTIVES The purpose of this study was to characterize outcomes for everolimus-eluting stent (EES)-treated subjects according to treatment with continued thienopyridine plus aspirin versus aspirin alone 12 to 30 months after stenting.

BACKGROUND In the DAPT (Dual Antiplatelet Therapy) study, continued thienopyridine plus aspirin beyond 1 year after coronary stenting reduced ischemic events. Given low rates of stent thrombosis and myocardial infarction (MI) for current drug-eluting stents, we examined outcomes among EES-treated subjects in the DAPT study.

METHODS The DAPT study enrolled 25,682 subjects (11,308 EES-treated) after coronary stenting. Following 12 months of treatment with thienopyridine and aspirin, eligible subjects continued treatment with aspirin and 9,961 (4,703 with EES) were randomized to 18 months of continued thienopyridine or placebo. Stent type was not randomized, and the EES subset analysis was post hoc.

RESULTS Among EES-treated patients, continued thienopyridine reduced stent thrombosis (0.3% vs. 0.7%, hazard ratio [HR]: 0.38, 95% confidence interval [CI]: 0.15 to 0.97; p = 0.04) and MI (2.1% vs. 3.2%, HR: 0.63, 95% CI: 0.44 to 0.91; p = 0.01) versus placebo but did not reduce a composite of death, MI, and stroke (4.3% vs. 4.5%, HR: 0.89, 95% CI: 0.67 to 1.18; p = 0.42), and increased moderate/severe bleeding (2.5% vs. 1.3%, HR: 1.79, 95% CI: 1.15 to 2.80; p = 0.01), and death (2.2% vs. 1.1%, HR: 1.80, 95% CI: 1.11 to 2.92; p = 0.02). Death due to cancer and not related to bleeding was increased (0.64% vs. 0.17%; p = 0.01).

CONCLUSIONS In EES-treated subjects, significant reductions in stent thrombosis and MI and an increase in bleeding were observed with continued thienopyridine beyond 1 year compared with aspirin alone. (The Dual Antiplatelet Therapy Study [DAPT Study]); NCT00977938) (J Am Coll Cardiol Intv 2016;9:138–47) © 2016 by the American College of Cardiology Foundation.

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In the DAPT (Dual Antiplatelet Therapy) study, patients who were free from major ischemic or bleeding events at 1 year after coronary stenting (either drug-eluting stents [DES] or bare-metal stents [BMS]), experienced significant reductions in stent thrombosis and myocardial infarction (MI) but increases in moderate or severe bleeding when treated with 30 months of thienopyridine plus aspirin compared with 12 months (1,2). Approved DES have been designed with different metallic scaffold designs, polymers, and eluted medications, resulting in different effectiveness and safety outcomes in clinical trials. Recent randomized trials and meta-analysis suggest that everolimus-eluting stents (EES), the most commonly used stent type in both the DAPT study as well as current clinical practice, are associated with lower rates of stent thrombosis compared with paclitaxel-eluting stents (3-5).

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Subjects treated with any DES approved and available in the United States at the time of study enrollment were eligible to be enrolled in the DAPT study. Although patients were not randomized to stent types, in adjusted analysis, there was heterogeneity in the relative reduction in major adverse cardiovascular and cerebrovascular events (MACCE) (a composite endpoint of death, MI, or stroke) according to stent type (1), and a large treatment benefit for continued therapy was observed among the subset of patients treated with paclitaxel-eluting stents (n = 2,666 randomized) (6). To determine whether the results of the DAPT study were generalizable to EES, we evaluated the benefits and risks of treatment with thienopyridine plus aspirin for 30 versus 12 months in the large subset of patients (11,308 enrolled, 4,703 randomized).

METHODS

DESIGN. The DAPT study was a double-blind, international, multicenter, randomized, placebo-controlled trial designed (7) to compare 30 versus 12 months of aspirin plus thienopyridine therapy (clopidogrel or prasugrel) after coronary stenting with either DES or BMS (NCT00977938). Randomization was stratified by DES/BMS, hospital site, subject complexity, and thienopyridine drug type. The results comparing randomized treatments among DES- (1) and BMS-treated (2) cohorts on ischemic and bleeding endpoints, as well as comparing BMS- versus DES-treated patients on these endpoints (8), have been reported. The institutional review board at each participating institution approved the study, and each participant provided written, informed consent.

The primary study analysis within all randomized DES-treated patients compared randomized treatments with respect to the primary effectiveness endpoints of stent thrombosis and MACCE from 12 to 30 months post-procedure and the primary safety endpoint of moderate or severe bleeding from 12 to 30 months post-procedure (1). DES types included EES (Xience, Abbott Vascular, Santa Clara, California; PROMUS, Boston Scientific, Marlborough, Massachusetts), sirolimus-eluting stents (Cypher, Cordis, Bridgewater, New Jersey), zotarolimus-eluting stents (Endeavor, Medtronic, Minneapolis, Minnesota), and paclitaxel-eluting stents (TAXUS, Boston Scientific, Marlborough, Massachusetts). Although stent type among various DES was not randomized, assessments of randomized treatment-by-DES type interactions on stent thrombosis and MACCE were pre-specified to determine whether the randomized treatment effect was consistent across DES types. Although randomized treatment effect on stent thrombosis did not vary

ABBREVIATIONS AND ACRONYMS

BMS = bare-metal stent(s)

CI = confidence interval

DAPT = dual antiplatelet therapy

DES = drug-eluting stent(s)

EES = everolimus-eluting stent(s)

HR = hazard ratio

MACCE = major adverse cardiovascular and cerebrovascular events

MI = myocardial infarction

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