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Two-Year Outcomes After First- or Second-Generation Drug-Eluting or Bare-Metal Stent Implantation in All-Comer Patients Undergoing Percutaneous Coronary Intervention

A Pre-Specified Analysis From the PRODIGY Study (PROlonging Dual Antiplatelet Treatment After Grading stent-induced Intimal hyperplasia studY)

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Objectives This study sought to assess device-specific outcomes after implantation of bare-metal stents (BMS), zotarolimus-eluting Endeavor Sprint stents (ZES-S), paclitaxel-eluting stents (PES), or everolimus-eluting stents (EES) (Medtronic Cardiovascular, Santa Rosa, California) in all-comer patients undergoing percutaneous coronary intervention.

Background Few studies have directly compared second-generation drug-eluting stents with each other or with BMS.

Methods We randomized 2,013 patients to BMS, ZES-S, PES, or EES implantation. At 30 days, each stent group received up to 6 or 24 months of clopidogrel therapy. The key efficacy endpoint was the 2-year major adverse cardiac event (MACE) including any death, myocardial infarction, or target vessel revascularization, whereas the cumulative rate of definite or probable stent thrombosis (ST) was the key safety endpoint.

Results Clinical follow-up at 2 years was complete for 99.7% of patients. The MACE rate was lowest in EES (19.2%; 95% confidence interval [CI]: 16.0 to 22.8), highest in BMS (32.1%; 95% CI: 28.1 to 36.3), and intermediate in PES (26.2%; 95% CI: 22.5 to 30.2) and ZES-S (27.8%; 95% CI: 24.1 to 31.9) groups (chi-square test = 18.9, p = 0.00029). The 2-year incidence of ST in the EES group (1%; 95% CI: 0.4 to 2.2) was similar to that in the ZES-S group (1.4%; 95% CI: 0.7 to 2.8), whereas it was lower compared with the PES (4.6%, 95% CI: 3.1 to 6.8) and BMS (3.6%; 95% CI: 2.4 to 5.6) groups (chi-square = 16.9; p = 0.0001).

Conclusions Our study shows that cumulative MACE rate, encompassing both safety and efficacy endpoints, was lowest for EES, highest for BMS, and intermediate for PES and ZES-S groups. EES outperformed BMS also with respect to the safety endpoints with regard to definite or probable and definite, probable, or possible ST. (PROlonging Dual antiplatelet treatment after Grading stent-induced Intimal hyperplasia studY [PRODIGY]; NCT00611286) (J Am Coll Cardiol Intv 2014;7:20–8) © 2014 by the American College of Cardiology Foundation

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Randomized, controlled trials (1,2), meta-analyses (3), and observational studies (4) have consistently shown reduced rates of angiographic restenosis and ischemia-driven target vessel revascularization (TVR) with drug-eluting stents (DES) compared with bare-metal stents (BMS). As a result, most percutaneous coronary interventions worldwide are done with DES rather than BMS. However, the higher rates of very late stent thrombosis (ST) and the concern for a higher risk of late ST after early discontinuation of dual antiplatelet agents with first-generation DES have raised safety concerns (5,6). To address these issues, new DES have been developed with novel materials, designs, and delivery systems, with improved biocompatible polymers, and new antiproliferative agents compared with their predecessors. However, most of these second-generation stents were approved in non-inferiority trials compared with first-generation DES (7–10). Therefore, few studies have directly compared second-generation DES with each other or with BMS.

The purpose of this pre-specified analysis of the PRODIGY (PROlonging Dual Antiplatelet Treatment After Grading stent-induced intimal hyperplasia studY) (11) was to assess device-specific outcomes in an all-comer patient population receiving a balanced proportion of first- or second-generation DES or BMS at the time of intervention.

Methods

Study design and population. PRODIGY is a 4 × 2 randomized, multicenter, open-label clinical trial designed to evaluate the efficacy and safety of prolonging the duration of clopidogrel therapy for up to 24 months in all-comer patients receiving a balanced mixture of stents with varying anti-intimal hyperplasia potency and belonging to both first- and second-generation DES (11,12).

Patients undergoing elective, urgent, or emergent coronary angioplasty with intended stent implantation at 3 referral Italian sites were randomly assigned in a 1:1:1:1 fashion to 1 of 4 stent types, including everolimus-eluting stents (EES), paclitaxel-eluting stents (PES), zotarolimus-eluting Endeavor Sprint stents (ZES-S), or third-generation thin-strut BMS (Medtronic Cardiovascular, Santa Rosa, California). At 30 days, patients in each stent group were randomized in a balanced fashion to either 6 or 24 months of dual antiplatelet treatment. In the 6-month dual antiplatelet therapy group, clopidogrel discontinuation at any time after 30 days was allowed in patients who were randomized to BMS if coronary intervention was indicated by the presence of stable coronary artery disease (12).

Individuals eligible for enrollment were patients 18 years of age or older with chronic stable coronary artery disease or acute coronary syndromes, including non–ST-segment elevation myocardial infarction (MI) and ST-segment elevation MI. They were eligible if they had at least 1 lesion with a stenosis diameter of ≥50% that was suitable for coronary stent implantation in a vessel with a reference vessel diameter of at least 2.25 mm. Selection criteria were broad, reflecting routine clinical practice. We set no limit for the number of treated lesions, vessels, or lesion length and excluded no patients on the basis of comorbid disorders or age, apart from the following pre-specified criteria: known allergy to acetylsalicylic acid or clopidogrel; planned surgery within 24 months of percutaneous coronary intervention unless the dual antiplatelet therapy could be maintained throughout the perisurgical period; history of bleeding diathesis; major surgery within 15 days; active bleeding or previous stroke in the past 6 months; concomitant or foreseeable need for oral anticoagulation therapy; pregnancy; life expectancy <24 months; participation in another trial; and inability to provide informed consent.

The ethics committees of the 3 participating centers independently approved the protocol, and all participants gave written informed consent.

Treatment protocol and follow-up procedures. All patients received aspirin (160 to 325 mg orally or 500 mg intravenously as a loading dose and then 80 to 160 mg orally indefinitely) and clopidogrel (300 or 600 mg orally as a loading dose) and then 75 mg/day for the treatment duration according to the randomization scheme as follows: for either 6 months in the 6-month dual antiplatelet therapy group in patients randomized to BMS and presenting with stable coronary artery disease, a shorter (but not <30 day) duration of dual antiplatelet therapy was allowed to comply with available evidence or 24 months in the 24-month dual antiplatelet therapy arm irrespective of the previously implanted stent type or indication for the coronary procedure.

Abbreviations and Acronyms

BMS = bare-metal stent(s)
CI = confidence interval
CK-MB = creatine kinase myocardial band
DES = drug-eluting stent(s)
EES = everolimus-eluting stent(s)
MACE = major adverse cardiac event(s)
MI = myocardial infarction
PES = paclitaxel-eluting stent(s)
ST = stent thrombosis
TLR = target lesion revascularization
TVR = target vessel revascularization
ZES-S = zotarolimus-eluting Endeavor Sprint stent(s)

Anticoagulation during coronary intervention was accomplished through administration of either unfractionated heparin or bivalirudin. All interventions were performed according to current standard guidelines and the final interventional strategy, including administration of glycoprotein IIb/IIIa antagonists, pre- or post-dilation, or the use of intravascular imaging techniques, was left entirely to the discretion of the operator, except for the stent use. Angiographic success was defined as residual stenosis <30% by visual analysis in the presence of Thrombolysis In Myocardial Infarction flow grade 3.

Follow-up. All randomized patients who were not lost to follow-up, irrespective of their compliance with the assigned