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Primary Endpoint Results of the EVOLVE Trial

A Randomized Evaluation of a Novel Bioabsorbable Polymer-Coated, Everolimus-Eluting Coronary Stent

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Objectives This study sought to compare the safety and efficacy of 2 dose formulations of SYNERGY, a novel bioabsorbable polymer everolimus-eluting stent (EES) (Boston Scientific Corp., Natick, Massachusetts) compared with the durable polymer PROMUS Element EES (Boston Scientific Corp.).

Background Durable polymer coatings on drug-eluting stents have been associated with chronic inflammation and impaired healing. Bioabsorbable polymer-coated drug-delivery systems may reduce the risk of late adverse events, including stent thrombosis, and thus the need for prolonged dual-antiplatelet therapy.

Methods A total of 291 patients with a de novo lesion ≤28 mm in length, in a coronary artery of ≥2.25 to ≤3.5 mm diameter, were enrolled in the EVOLVE study, a prospective, randomized, single-blind, noninferiority trial. Patients were randomly assigned in a 1:1:1 ratio to PROMUS Element, SYNERGY, or SYNERGY half dose. The primary clinical endpoint was the 30-day rate of target lesion failure, defined as cardiac death or myocardial infarction related to the target vessel, or target lesion revascularization. The primary angiographic endpoint was 6-month in-stent late loss measured by quantitative coronary angiography.

Results The 30-day primary clinical endpoint of target lesion failure occurred in 0%, 1.1%, and 3.1% of patients in the PROMUS Element, SYNERGY, and SYNERGY half dose groups, respectively. The 6-month in-stent late loss was 0.15 ± 0.34 mm for PROMUS Element, 0.10 ± 0.25 mm for SYNERGY, and 0.13 ± 0.26 mm for SYNERGY half dose (SYNERGY, difference −0.06, upper 95.2% confidence limit: 0.02, p for noninferiority <0.001; SYNERGY half dose, difference −0.03, upper 95.2% confidence limit: 0.05, p for noninferiority <0.001). Clinical event rates remained low and comparable between groups, with no stent thromboses in any group at 6 months.

Conclusions The EVOLVE trial confirms the effective delivery of everolimus by a unique directional bioabsorbable polymer system utilizing the SYNERGY stent. (A Prospective Randomized Multicenter Single-Blind Noninferiority Trial to Assess the Safety and Performance of the Evolution Everolimus-Eluting Monorail Coronary Stent System [Evolution Stent System] for the Treatment of a De Novo Atherosclerotic Lesion [EVOLVE]; NCT01135225) (J Am Coll Cardiol 2012;59:1362–70) © 2012 by the American College of Cardiology Foundation

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Drug-eluting stents delivering antiproliferative drugs from a durable polymer have significantly reduced angiographic and clinical measures of restenosis compared with bare-metal stents, with no apparent increase in the risk of adverse events including death and myocardial infarction (MI) (1–4). However, durable polymers have been associated with a hypersensitivity reaction, delayed healing, and incomplete endothelialization that may contribute to an increased risk of late (30 days to 1 year) and very late (beyond 1 year) stent thrombosis compared with bare-metal stents (5–7). Although the ability of prolonged dual-antiplatelet therapy (DAPT) with aspirin and a thienopyridine to prevent late thrombotic events is as yet unproven, current clinical practice guidelines in the United States and Europe recommend at least 12 months of DAPT after treatment with drug-eluting stents (8,9). Prolonged DAPT raises several potential concerns including the risk of bleeding, patient compliance, implications of DAPT interruption for invasive procedures, and the economic costs of prolonged drug treatment. A number of stent technologies are being developed in an attempt to modify the proposed mediators of late thrombotic events and the need for prolonged DAPT, including bioabsorbable polymers, nonpolymeric stent surfaces, and bioabsorbable stents. The SYNERGY stent (Boston Scientific Corp., Natick, Massachusetts) is a novel device consisting of a thin-strut platinum-chromium stent platform that delivers everolimus from an ultrathin bioabsorbable poly(DL-lactide-co-glycolide) (PLGA) polymer applied to the abluminal surface. Endothelialization is complete within 28 days of implantation in a porcine coronary artery model (10), and polymer reabsorption is complete within 4 months (11).

In the randomized, first-human-use EVOLVE (A Prospective Randomized Multicenter Single-Blind Non-inferiority Trial to Assess the Safety and Performance of the Evolution Everolimus-Eluting Monorail Coronary Stent System [Evolution Stent System] for the Treatment of a De Novo Atherosclerotic Lesion) trial (Evolusion has been renamed to SYNERGY), we compared the safety and efficacy of 2 dose formulations of the SYNERGY stent with those of the durable polymer PROMUS Element everolimus-eluting stent (EES) (Boston Scientific Corp.), which has demonstrated an excellent safety and efficacy profile and has been shown to be noninferior to predicate cobalt-chromium EES for target lesion failure (TLF) at 12 months (12,13). The safety and efficacy of lower doses of everolimus have not been adequately studied. In the EVOLVE trial, we evaluated 1 formulation of the SYNERGY stent with a total everolimus dose similar to that of the currently available EES and a second formulation with half the dose of everolimus to determine if comparable efficacy could be achieved with a lower, and therefore potentially safer, drug dose. In this report, we present the primary endpoint results of the EVOLVE trial.

Methods

Study design and patients. The EVOLVE study is a prospective, randomized, multicenter, single-blind, noninferiority trial conducted at 29 sites in Europe, Australia, and New Zealand. From July 29, 2010, to January 20, 2011, 291 patients 18 years of age and older with symptomatic coronary artery disease or silent ischemia were recruited. Patients were eligible for inclusion if they had a de novo lesion that was ≤28 mm in length in a native coronary vessel with a reference diameter of 2.25 mm to 3.5 mm. Additional key eligibility criteria were stenosis ≥50% and absence of coronary occlusion (Thrombolysis In Myocardial Infarction [TIMI] flow grade ≥1). Major exclusion criteria were acute or recent MI, lesions located in the left main coronary artery, restenotic lesions, lesions involving a side branch ≥2 mm in diameter, or the presence of thrombus in the target vessel. All eligible patients provided written informed consent. The study complied with the Declaration of Helsinki, and the protocol was approved by the ethics committee at all participating sites. An independent clinical events committee adjudicated all deaths, stent thromboses, target vessel revascularizations (TVRs), and MIs, and an independent data monitoring committee monitored patient safety.

Abbreviations and Acronyms

CK-MB = creatine kinase-myocardial band
DAPT = dual-antiplatelet therapy
EES = everolimus-eluting stent(s)
MI = myocardial infarction
PLGA = poly(DL-lactide-co-glycolide)
QCA = quantitative coronary angiography
TLF = target lesion failure
TLR = target lesion revascularization
TVF = target vessel failure
TVR = target vessel revascularization

Study devices. The SYNERGY stent consists of a thin-strut, balloon-expandable platinum-chromium stent platform delivering everolimus from an ultrathin (4 μm) bioabsorbable PLGA polymer applied to the abluminal surface. One formulation (SYNERGY) has a similar dose (38 μg to 179 μg, depending on stent length) and release profile as PROMUS Element, whereas the second formulation (SYNERGY half dose) has a similar release profile but half the dose of everolimus (19 μg to 90 μg, depending on stent length) as PROMUS Element (14). The durable polymer platinum-chromium PROMUS Element stent, which served as a control in this study, has been described previously (12,13).

Randomization and blinding. The randomization schedule was computer generated and stratified by study site and the presence or absence of medically treated diabetes mellitus. Patients were assigned in a 1:1:1 ratio to PROMUS Element, SYNERGY, or SYNERGY half dose. Study investigators were not blinded to treatment assignment; however, the patients and members of the independent clinical events committee, data monitoring committee, core laboratory, and the sponsor were blinded.

Procedures. Study stents were available in diameters ranging from 2.25 mm to 3.5 mm and lengths of 8 mm, 20 mm, and 32 mm. Percutaneous coronary intervention was performed