Journal of the American College of Cardiology
© 2012 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 59, No. 15, 2012
ISSN 0735-1097/$36.00
doi:10.1016/j.jacc.2011.12.016

FOCUS ISSUE: TRANSCATHETER CARDIOVASCULAR THERAPEUTICS

Primary Endpoint Results of the EVOLVE Trial

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

Ian T. Meredith, MBBS, PHD,* Stefan Verheye, MD, PHD,† Christophe L. Dubois, MD,‡ Joseph Dens, MD,§ Jean Fajadet, MD,‖ Didier Carrié, MD,¶ Simon Walsh, MD,# Keith G. Oldroyd, MD,** Olivier Varenne, MD,†† Seif El-Jack, MD,‡‡ Raul Moreno, MD,§§ Anita A. Joshi, PHD,‖‖ Dominic J. Allocco, MD,‖‖ Keith D. Dawkins, MD‖‖

Clayton, Melbourne, Australia; Antwerpen, Leuven, and Genk, Belgium; Toulouse and Paris, France; Belfast and Glasgow, United Kingdom; North Shore City, Auckland, New Zealand; Madrid, Spain; and Natick, Massachusetts

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

From *MonashHeart, Clayton, Melbourne, Australia; †Ziekenhuisnetwerk Antwerpen Middelheim, Antwerpen, Belgium; ‡Universitaire Ziekenhuizen Leuven, Leuven, Belgium; §Ziekenhuis Oost-Limburg, Genk, Belgium; ‖Clinique Pasteur, Toulouse, France; ¶Hôpital Rangueil, Toulouse, France; #Belfast Health and Social Care Trust, Belfast, United Kingdom; **Golden Jubilee National Hospital, Glasgow, United Kingdom; ††Hôpital Cochin, Paris, France; ‡‡North Shore Hospital, North Shore City, Auckland, New Zealand; §§Hospital Universitario La Paz, Madrid, Spain; and the ‖‖Boston Scientific Corporation, Natick, Massachusetts. This work is supported by Boston Scientific Corporation, Natick, Massachusetts. Dr. Meredith has received honoraria from Abbott Vascular, Medtronic, and Boston Scientific. Dr. Dubois has received honoraria from Boston Scientific. Dr. Oldroyd has received consultancy fees/honoraria from Boston Scientific. Dr. Varenne has received consultancy fees/honoraria from Abbott Vascular, Boston Scientific, and Cordis. Dr. Joshi is a full-time employee of Boston Scientific. Drs. Allocco and Dawkins are full-time employees and stock holders of Boston Scientific. All other authors have reported they have no relationships relevant to the contents of this paper to disclose.

Manuscript received October 11, 2011; revised manuscript received December 6, 2011, accepted December 15, 2011.

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

using standard techniques. The aim was to obtain full lesion coverage with 1 stent. Treatment of 1 nontarget lesion in a nontarget vessel with a commercial treatment (excluding brachytherapy) was allowed if it occurred before target lesion intervention and was deemed a clinical and angiographic success (defined as visually assessed mean lesion diameter stenosis <50% [<30% for stents] with TIMI flow grade 3, without prolonged chest pain or MI). Planned revascularizations after the index procedure were prohibited.

Procedural anticoagulation was achieved with unfractionated heparin or an alternative antithrombotic such as enoxaparin or bivalirudin. Glycoprotein IIb/IIIa inhibitor use was permitted per investigator discretion. Loading doses of aspirin and clopidogrel (≥300 mg) were required for patients not taking these medications ≥72 h before the index procedure. Patients continued to take aspirin (at least 75 mg daily) indefinitely. Clopidogrel (75 mg daily) was required for at least 6 months after stent placement in all patients, and for at least 12 months in those not at high risk of bleeding. Prasugrel was permitted in accordance with approved country-specific labeling. Clinical follow-up was scheduled for 30 days, 6 months, 9 months, and annually from 1 to 5 years. Quantitative coronary angiography (QCA) follow-up was scheduled for 6 months post-procedure.

Study endpoints. The primary clinical endpoint was TLF, a composite of cardiac death or MI related to the target vessel, or ischemia-driven target lesion revascularization (TLR) at 30 days. Cardiac death was defined as any death other than those confirmed to have a noncardiac cause. Myocardial infarction was defined as either the development of new pathological Q waves in ≥2 leads (duration ≥0.04 s) with elevated levels of creatine kinase-myocardial band (CK-MB) or troponin; or, in the absence of new Q waves, elevation of CK >3 times normal (periprocedural MI, occurring within 48 h of the procedure) or >2 times normal (spontaneous MI) with elevated CK-MB, or troponin >3 times normal (periprocedural MI) or >2 times normal (spontaneous MI), plus any 1 of the following: 1) electrocardiographic changes indicative of new ischemia (new ST-T changes or left bundle branch block); 2) imaging evidence of new loss of viable myocardium; or 3) new regional wall motion abnormality. Target lesion revascularization and TVR were defined as revascularization of the target lesion and vessel with stenosis ≥50% by QCA, respectively, if associated with clinical or functional ischemia (positive functional study, electrocardiographic changes, or ischemic symptoms), or stenosis ≥70% in the absence of clinical or functional ischemia.

The primary angiographic endpoint was in-stent late loss as measured by an independent core laboratory QCA at 6 months. Technical success was defined as successful delivery and deployment of the study stent to the target vessel, without balloon rupture or stent embolization. Clinical procedural success was defined as visually assessed diameter stenosis <30% in 2 near-orthogonal projections with TIMI flow grade 3, without the occurrence of in-hospital MI, TVR, or cardiac death. Additional clinical endpoints included TLR, TVR, target vessel failure (TVF [defined as death related to the target vessel, MI related to the target vessel, or TVR]), cardiac death, noncardiac death, MI, and stent thrombosis according to the definitions provided by the Academic Research Consortium (15). Additional angiographic endpoints included in-segment late loss, percent diameter stenosis, acute gain, rate of binary restenosis, and minimal lumen diameter.

Quantitative coronary angiography. Coronary angiograms recorded at baseline, post-procedure, and 6-month follow-up were analyzed by an independent angiographic core laboratory (Beth Israel Deaconess Medical Center, Boston, Massachusetts) using an automated edge detection system (Medis Medical Imaging Systems, Leiden, the Netherlands). In each patient, QCA measures within the stent and the analysis segment (including the stented region and 5 mm edge regions) were analyzed and reported separately. Late loss was defined as the difference between the minimum lumen diameter post-procedure and at 6 months. Binary restenosis was defined as >50% diameter stenosis.

Statistical analysis. This trial was powered for testing of noninferiority for the 6-month primary angiographic endpoint. Based on the data available from the SPIRIT III (A Clinical Evaluation of the Xience V Everolimus Eluting Coronary Stent System) randomized trial, we anticipated the 6-month in-stent late loss to be 0.14 mm in all groups (16). The criterion for noninferiority was considered to have been met if the upper limit of the 1-sided 95.2% confidence interval for the difference between groups was not >0.20 mm. An interim analysis was performed after 50% of patients had been enrolled. The O'Brien-Fleming method was used to adjust the alpha level for the final analysis, where a p value <0.048 was required to reject the null hypothesis and conclude noninferiority. No adjustments for multiple comparisons were made as each SYNERGY dose was compared to the PROMUS Element control separately.

The study sample size was calculated for a 2-group (1:1 ratio) test of equivalence in means using nQuery Advisor, version 5 (Statistical Solutions, Saugus, Massachusetts). We estimated that 97 patients per group would provide the study with a statistical power of 85% to detect noninferiority, allowing for 20% patients lost to angiographic follow-up.

The testing of noninferiority was based on the per-protocol analysis cohort (only patients who received the assigned study stent). All other analyses were according to the intention-to-treat principle. Categorical variables are reported as numbers and percentages, and continuous variables as mean ± SD. Differences between treatment groups with 95% confidence intervals and p values, on the basis of the chi-square test or Fisher's exact test for categorical variables and Student *t* test for continuous variables, are reported. Analyses were performed with SAS, version 8.2 or higher (SAS Institute, Cary, North Carolina).

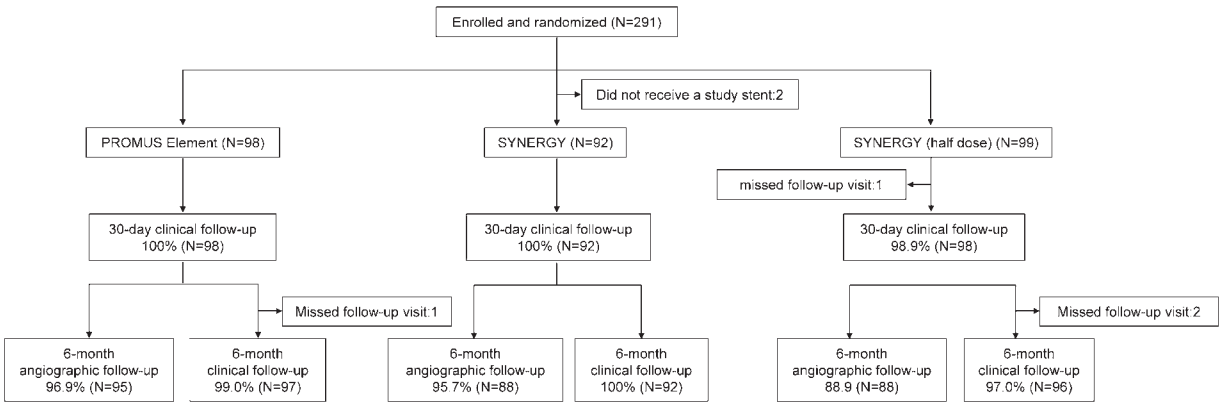

Figure 1 **Patient Flow in the EVOLVE Trial**

A total of 291 patients were enrolled and randomized in the EVOLVE trial, and 289 patients received the assigned study stent.

Results

Figure 1 shows the patient flow. A total of 291 patients were enrolled and randomly assigned to receive PROMUS Element (n = 98), SYNERGY (n = 94), or SYNERGY half dose (n = 99). Baseline clinical and angiographic characteristics (Table 1) were similar in the 3 groups, except for a larger reference vessel diameter in the SYNERGY half dose group compared with the PROMUS Element group (2.65 ± 0.40 mm vs. 2.53 ± 0.41 mm, p = 0.04).

Technical success was achieved in 100%, 98.9%, and 98.0% patients and clinical procedural success was achieved in 100%, 98.9%, and 97.0% patients in the PROMUS Element, SYNERGY, and SYNERGY half dose groups, respectively. One case of stent deformation was observed in the PROMUS Element arm. During the post-implant intravascular ultrasonography assessment, the catheter caught on the proximal edge of the stent. The operator was subsequently able to advance the intravascular ultrasound catheter through the stent, but noted malapposition and slight longitudinal compression afterward. Balloon angioplasty of the affected area was performed, with good result and no clinical sequelae.

Table 1 **Baseline Clinical and Lesion Characteristics**

Characteristics	PROMUS Element (n = 98)	SYNERGY (n = 94)	SYNERGY Half Dose (n = 99)	p Value: SYNERGY vs. PROMUS Element	p Value: SYNERGY Half Dose vs. PROMUS Element
Age, yrs	62.1 ± 10.0	64.9 ± 11.0	62.9 ± 10.2	0.07	0.61
Men	79.6	69.9	69.7	0.12	0.11
Current smoker	27.8	21.7	20.6	0.33	0.24
Diabetes mellitus	22.4	17.2	18.2	0.36	0.46
Hyperlipidemia	70.4	68.5	72.4	0.77	0.75
Hypertension	69.4	61.3	71.7	0.24	0.72
Previous MI	34.4	32.3	34.7	0.76	0.96
Previous PCI	32.7	33.3	38.4	0.92	0.40
Previous CABG	1.0	2.2	3.1	0.62	0.62
Unstable angina	21.1	22.6	30.6	0.80	0.13
Target vessel					
Left anterior descending	39.8	41.8	39.4	0.78	0.95
Left circumflex	31.6	26.4	33.3	0.43	0.80
Right coronary artery	28.6	31.9	27.3	0.62	0.84
RVD, mm	2.53 ± 0.41	2.60 ± 0.45	2.65 ± 0.40	0.22	0.04
MLD, mm	0.68 ± 0.30	0.68 ± 0.30	0.67 ± 0.31	0.96	0.94
Diameter stenosis	73.4 ± 9.9	74.0 ± 10.4	74.7 ± 10.5	0.69	0.35
Lesion length, mm	14.62 ± 5.81	13.41 ± 6.29	13.55 ± 5.76	0.16	0.21
AHA/ACC lesion classification B2/C	62.2	56.0	69.7	0.39	0.27

Values are mean ± SD or %.

ACC = American College of Cardiology; AHA = American Heart Association; CABG = coronary artery bypass graft; MI = myocardial infarction; MLD = minimal lumen diameter; PCI = percutaneous coronary intervention; RVD = reference vessel diameter.

JACC Vol. 59, No. 15, 2012
April 10, 2012:1362–70

Table 2 shows the clinical outcomes up to 6-month follow-up. The 30-day primary clinical endpoint of TLF occurred in 1.1% (n = 1) in the SYNERGY group and 3.1% (n = 3) in the SYNERGY half dose group compared with no events in the PROMUS Element group. All 4 TLF events in the SYNERGY groups were attributable to target vessel–related periprocedural non–Q-wave MIs. At 6 months, the TLF rate was 3.1%, 2.2%, and 4.1% in the PROMUS Element, SYNERGY, and SYNERGY half dose groups, respectively. The secondary endpoint of TLR occurred in 3.1%, 1.1%, and 1.0% patients in the PROMUS Element, SYNERGY, and SYNERGY half dose groups, respectively. There were no Q-wave MIs or cardiac deaths in any group. One noncardiac death due to a motorcycle accident occurred in the SYNERGY group at 191 days post-procedure. No stent thrombosis was reported in any group (Table 2). At 6 months, 99.0%, 98.9%, and 94.8% patients were taking DAPT in the PROMUS Element, SYNERGY, and SYNERGY half dose groups, respectively.

The primary angiographic endpoint of 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. The upper 1-sided 95.2% confidence limit of the difference between test and control was 0.02 for SYNERGY and 0.05 for SYNERGY half dose, both lower than the pre-specified noninferiority margin of 0.20 mm (p for noninferiority <0.001). Cumulative frequency distribution of in-stent late loss for the 3 groups is shown in Figure 2.

Given that a small but statistically significant difference in baseline reference vessel diameter was observed between the SYNERGY half dose group and the PROMUS Element group, we performed a post-hoc analysis of covariance to adjust the primary angiographic endpoint of in-stent late loss for the difference in baseline reference vessel diameter. Adjusted 6-month in-stent late loss was 0.15 mm for PROMUS Element, 0.10 mm for SYNERGY, and 0.14 mm for SYNERGY half dose. The upper 1-sided 95.2% confidence limit of the difference between test and control was 0.04 for SYNERGY and 0.08 for SYNERGY half dose. Similar to the unadjusted in-stent late loss, both upper 1-sided 95.2% confidence limits for the difference in adjusted late loss were lower than the pre-specified noninferiority margin of 0.2 mm.

Table 3 shows QCA outcomes post-procedure and at 6 months. Angiographic measurements were comparable between the PROMUS Element group and the SYNERGY group, whereas small but statistically significant differences favoring SYNERGY half dose compared with PROMUS Element were observed for a number of post-procedure parameters, including in-stent minimum lumen diameter (2.58 ± 0.36 mm vs. 2.44 ± 0.36 mm, p = 0.008), in-stent acute gain (1.90 ± 0.38 mm vs. 1.76 ± 0.38 mm, p = 0.01), and in-segment percent diameter stenosis (17.08 ± 6.90 vs. 19.57 ± 9.26, p = 0.04). At 6 months post-procedure, in-stent minimum lumen diameter (2.45 ± 0.44 mm vs. 2.29 ± 0.50 mm, p = 0.02), and in-segment percent diameter stenosis (18.08 ± 8.54 vs. 22.02 ± 13.30, p = 0.02) continued to favor SYN-

Table 2 Clinical Outcomes

Clinical Outcomes	PROMUS Element (n = 98)	SYNERGY (n = 94)	SYNERGY Half Dose (n = 99)	p Value: SYNERGY vs. PROMUS Element	p Value: SYNERGY Half Dose vs. PROMUS Element
Events at 30 days					
Primary endpoint (TLF)	0.0	1.1	3.1	0.49	0.25
Cardiac death, related to TV	0.0	0.0	0.0	*	*
MI, related to TV	0.0	1.1	3.1	0.49	0.25
TLR	0.0	0.0	0.0	*	*
Events at 6 months					
TLF	3.1	2.2	4.1	1.00	0.72
TVF	6.1	4.3	5.2	0.75	0.77
All deaths	0.0	1.1	0.0	0.49	*
Cardiac deaths	0.0	0.0	0.0	*	*
MI, overall	0.0	1.1	3.1	0.49	0.12
Q-wave MI	0.0	0.0	0.0	*	*
Non–Q-wave MI	0.0	1.1	3.1	0.49	0.12
TVR, overall	6.1	3.2	2.1	0.50	0.28
TLR, overall	3.1	1.1	1.0	0.62	0.62
Non-TLR TVR, overall	3.1	2.2	1.0	1.00	0.62
Stent thrombosis, ARC definition					
Definite or probable	0.0	0.0	0.0	*	*

Values are %. *Not defined.

ARC = Academic Research Consortium; MI = myocardial infarction; TLF = target lesion failure; TLR = target lesion revascularization; TV = target vessel; TVF = target vessel failure; TVR = target vessel revascularization.

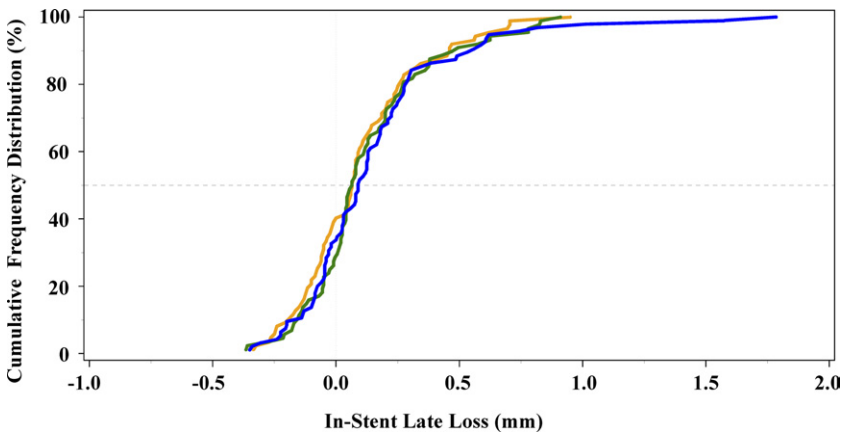

Figure 2 **Cumulative Frequency Distribution of In-Stent Late Loss**

Cumulative frequency distribution of in-stent late loss by study stent: PROMUS Element **(blue line)**, SYNERGY **(yellow line)**, and SYNERGY half dose **(green line)**.

ERGY half dose compared with PROMUS Element, respectively.

Discussion

In the EVOLVE trial, both dose formulations of the SYNERGY stent were noninferior compared with the PROMUS Element stent for the 6-month angiographic endpoint of in-stent late loss, confirming effective delivery of everolimus by a unique directional bioabsorbable polymer system. Six-month clinical event rates were low, and there were no significant differences among groups. A primary angiographic endpoint of in-stent late loss was selected for this study as late loss has been demonstrated to be highly predictive of clinical revascularization rates (17). The in-stent late loss recorded in the EVOLVE trial corresponds well with that reported at 6 months for the durable polymer Cypher sirolimus-eluting stent (Cordis, Warren, New Jersey) in the RAVEL (A Randomized Comparison of a Sirolimus-Eluting Stent with a Standard Stent for Coronary Revascularization) trial (−0.01 ± 0.33 mm) (18), and the durable polymer Xience V EES (Abbott Vascular, Santa Clara, California) in the SPIRIT FIRST (0.10 ± 0.21 mm) (19) and SPIRIT II (0.11 ± 0.27 mm) (20) trials, and is numerically less than that reported at 9 months for the durable polymer Resolute zotarolimus-eluting stent (Medtronic Cardiovascular, Santa Rosa, California) in the RESOLUTE (A Randomized Comparison of a Zotarolimus-Eluting Stent with an Everolimus-eluting Stent for Percutaneous Coronary Intervention) trial (0.22 ± 0.27 mm) (21). It is also consistent with that reported in first human experiences of bioabsorbable polymer stents, including the Nobori biolimus-eluting stent (Terumo Corporation, Tokyo, Japan) in the NOBORI I (Randomized Comparison of the Nobori-Biolimus A9-Eluting Coronary Stent with the TAXUS Liberte Paclitaxel-Eluting Coronary Stent in Patients with Stenosis in Native Coronary Arteries) phase 2 trial (0.11 ± 0.30 mm at 9 months) (22), the Nevo sirolimus-eluting stent (Cordis Corporation, Bridgewater, New Jersey) in the NEVO RES-I (NEVO Res-Elution I) trial (0.13 ± 0.31 mm at 6 months) (23), and the Orsiro sirolimus-eluting stent (Biotronik AG, Bulach, Switzerland) in the BIOFLOW-I (First in Man Experience with a Drug Eluting Stent in De Novo Coronary Artery Lesions) trial (0.12 ± 0.19 mm at 4 months) (24). A similar 6-month late loss has also been reported by Serruys et al. (25) for the bioabsorbable everolimus-eluting vascular scaffold (BVS, Abbott Vascular) in the ABSORB (A Clinical Evaluation of a Bioabsorbable Everolimus Eluting Coronary Stent System [BVS EECS] in the Treatment of Patients with de Novo Native Coronary Artery Lesions) cohort B study (0.19 ± 0.18 mm). Collectively, these results suggest that the efficacy of the SYNERGY stent is comparable to that of established durable polymer as well as newer-generation bioabsorbable polymer and bioabsorbable stent platforms delivering limus-based antiproliferative drugs.

Although late loss was comparable, it is noteworthy that several angiographic outcomes including acute gain, minimum lumen diameter, and percent diameter stenosis favored SYNERGY half dose compared with PROMUS Element. It is not clear whether these observations are a consequence of the difference in baseline reference vessel diameter between SYNERGY half dose and PROMUS Element or a play of chance. In either case, the angiographic outcomes of the EVOLVE study suggest that it may be possible to achieve at least comparable efficacy with a lower dose of everolimus than is used in commercially available EES. This finding needs to be confirmed in future randomized, controlled studies evaluating the low-dose formulation in a larger patient population.

By demonstrating a significant reduction in revascularization, stent thrombosis, and periprocedural MI compared

JACC Vol. 59, No. 15, 2012
April 10, 2012:1362–70

Table 3 Quantitative Coronary Angiography Outcomes

Angiography Outcomes	PROMUS Element (n = 98)	SYNERGY (n = 94)
Post-procedure		
MLD, in-stent, mm	2.44 ± 0.36 (2.15, 2.43, 2.67)	2.51 ± 0.37 (2.21, 2.46, 2.80)
MLD, in-segment, mm	2.05 ± 0.42 (1.79, 1.99, 2.33)	2.14 ± 0.41 (1.91, 2.11, 2.41)
Acute gain, in-stent, mm	1.76 ± 0.38 (1.45, 1.70, 2.04)	1.83 ± 0.39 (1.55, 1.82, 2.07)
Acute gain, in-segment, mm	1.38 ± 0.42 (1.12, 1.36, 1.61)	1.46 ± 0.44 (1.17, 1.43, 1.74)
Diameter stenosis, in-stent, %	3.77 ± 9.29 (−4.09, 5.17, 11.09)	3.23 ± 9.62 (−1.89, 2.18, 10.23)
Diameter stenosis, in-segment, %	19.57 ± 9.26 (13.37, 17.51, 23.12)	18.06 ± 8.46 (11.37, 16.34, 23.36)
6 months		
MLD, in-stent, mm	2.29 ± 0.50 (2.03, 2.30, 2.57)	2.41 ± 0.42 (2.13, 2.38, 2.70)
MLD, in-segment, mm	1.97 ± 0.48 (1.72, 1.96, 2.29)	2.06 ± 0.45 (1.75, 2.04, 2.42)
Diameter stenosis, in-stent, %	8.95 ± 14.97 (0.22, 8.05, 13.39)	6.59 ± 9.90 (−0.57, 5.83, 11.40)
Diameter stenosis, in-segment, %	22.02 ± 13.30 (14.07, 18.90, 25.62)	20.33 ± 10.96 (11.74, 19.00, 25.23)
Late loss, in-stent, mm	0.15 ± 0.34 (−0.05, 0.09, 0.26)	0.10 ± 0.25 (−0.08, 0.07, 0.24)
Late loss, in-segment, mm	0.08 ± 0.34 (−0.11, 0.04, 0.24)	0.07 ± 0.25 (−0.06, 0.02, 0.18)
Binary restenosis, in-stent, %	3.2 (3)	0.0 (0)
Binary restenosis, in-segment, %	5.3 (5)	2.3 (2)

Values are mean ± SD (25th percentile, median, 75th percentile) or % (n). The p values are from the Student *t* test; the p values in parentheses are from the Wilcoxon rank sum test. The Wilcoxon rank sum test was performed as a post-hoc analysis as the data were not normally distributed. Similar results were observed with both tests.

MLD = minimal lumen diameter.

with earlier-generation paclitaxel-eluting stents, durable polymer EES have become the most widely used drug-eluting stents worldwide (26,27). The SYNERGY stent is the only bioabsorbable polymer EES that is currently undergoing clinical investigation. Besides delivering a potent antirestenotic drug, the SYNERGY stent provides additional features that may improve clinical outcomes. First, the thin-strut platinum-chromium stent platform is designed to improve radiopacity, deliverability, radial strength, and fracture resistance while reducing recoil, compared with predicate stainless steel and cobalt-chromium stent platforms. Second, the ultrathin bioabsorbable PLGA polymer delivering everolimus is applied only to the abluminal surface of the stent, avoiding both drug and polymer on the luminal surface. The polymer degrades into carbon dioxide and water within 4 months, leaving only the biologically inert bare-metal platform behind (11). Elimination of chronic exposure to the drug and polymer holds potential to reduce late adverse events and the need for prolonged DAPT. Although some patient populations have been shown to benefit from longer DAPT (28), shorter DAPT may enhance the clinical benefit of drug-eluting stents in a wide range of patient populations including those who are at an increased risk for bleeding complications, patients resistant to DAPT, patients with coexisting requirements for anticoagulation therapy with warfarin, and patients requiring unplanned invasive procedures. Moreover, in the current era, as cost effectiveness has become an integral component for evaluation of treatment options, the possible reduction in DAPT can potentially offer an economic benefit. Indeed, ongoing investigations of bioabsorbable polymeric stents with long-term follow-up have shown promising outcomes. In the LEADERS (Limus Eluted from A Durable versus ERodable Stent coating) trial, the noninferiority of bioabsorbable polymer biolimus-eluting stent (BioMatrix Flex, Biosensors, Newport Beach, California) for major adverse cardiac events compared with the durable polymer sirolimus-eluting stent (Cypher SELECT, Cordis, Miami Lakes, Florida) observed at 1 year (29), was maintained to 4 years with a lower risk of definite stent thrombosis between 1 and 4 years in the biolimus group (rate ratio: 0.20, 95% confidence interval: 0.06 to 0.67, p = 0.004) (30). Additionally, in the post-marketing surveillance CREATE (Multi-Center Registry of EXCEL Biodegradable Polymer Drug-Eluting Stents) registry, which enrolled 2,077 "real-world" patients, the 3-year cumulative incidence of stent thrombosis was 1.53% despite 80% of patients discontinuing thienopyridine therapy within 6 months after implantation of a bioabsorbable polymer sirolimus-eluting stent (EXCEL, JW Medical System, Weihai, China) (31).

In the EVOLVE trial, the efficacy of the SYNERGY stent was comparable to that of the PROMUS Element stent at 6 months, with comparable safety outcomes. Furthermore, no stent thrombosis was reported in any group through 6 months. These preliminary data are encouraging, and warrant further investigation in a larger randomized trial.

Study limitations. The EVOLVE trial has several important limitations. First, the trial was not powered to detect differences in clinical event rates. Second, similar to other first human use trials, patients with relatively simple de novo lesions were enrolled, and hence these results may not apply to more complex patients or lesions. Finally, the EVOLVE

Table 3 Continued

SYNERGY Half Dose (n = 99)	p Value: SYNERGY vs. PROMUS Element	p Value: SYNERGY Half Dose vs. PROMUS Element
2.58 ± 0.36 (2.31, 2.51, 2.74)	0.17 (0.16)	0.008 (0.01)
2.21 ± 0.40 (1.93, 2.19, 2.47)	0.14 (0.11)	0.01 (0.005)
1.90 ± 0.38 (1.59, 1.94, 2.15)	0.20 (0.20)	0.01 (0.01)
1.54 ± 0.41 (1.21, 1.54, 1.87)	0.17 (0.15)	0.007 (0.008)
2.90 ± 7.94 (−1.79, 2.66, 7.88)	0.68 (0.59)	0.50 (0.28)
17.08 ± 6.90 (11.92, 16.95, 21.89)	0.21 (0.26)	0.04 (0.11)
2.45 ± 0.44 (2.18, 2.46, 2.72)	0.08 (0.15)	0.02 (0.03)
2.17 ± 0.41 (1.94, 2.11, 2.45)	0.15 (0.27)	0.003 (0.006)
7.27 ± 9.47 (1.16, 5.96, 11.48)	0.18 (0.59)	0.34 (0.28)
18.08 ± 8.54 (13.21, 15.61, 21.43)	0.31 (0.45)	0.02 (0.01)
0.13 ± 0.26 (−0.02, 0.07, 0.24)	0.19 (0.28)	0.56 (0.81)
0.04 ± 0.25 (−0.10, 0.03, 0.12)	0.70 (0.86)	0.27 (0.36)
0.0 (0)	0.25	0.25
1.1 (1)	0.45	0.21

trial does not address whether the bioabsorbable polymer reduces thrombotic events and the necessity of prolonged DAPT. A larger study in a broader patient population that is adequately powered to detect clinical differences and a separate study comparing long and short DAPT regimens are planned to elucidate important clinical and cost-effectiveness outcomes.

Conclusions

In this prospective, randomized, multicenter, first human use trial, the 2 dose formulations of the SYNERGY stent were noninferior to the PROMUS Element stent for the primary angiographic endpoint of in-stent late loss at 6 months. Clinical event rates were low and comparable, with no stent thrombosis in any group. These results support the safety and efficacy of the abluminal bioabsorbable polymer SYNERGY EES for the treatment of patients with de novo coronary artery disease.

Acknowledgment

The authors thank Jian Huang, MD, MS, (Boston Scientific), for data analysis.

Reprint requests and correspondence: Dr. Ian T. Meredith, MonashHeart, Southern Health, 246 Clayton Road, Clayton, Melbourne, Australia. E-mail: ian.meredith@myheart.id.au.

REFERENCES

1. Moses JW, Leon MB, Popma JJ, et al. Sirolimus-eluting stents versus standard stents in patients with stenosis in a native coronary artery. N Engl J Med 2003;349:1315–23.
2. Stone GW, Ellis SG, Cox DA, et al. A polymer-based paclitaxel-eluting stent in patients with coronary artery disease. N Engl J Med 2004;350:221–31.
3. Stettler C, Wandel S, Allemann S, et al. Outcomes associated with drug-eluting and bare-metal stents: a collaborative network meta-analysis. Lancet 2007;370:937–48.
4. Spaulding C, Daemen J, Boersma E, Cutlip DE, Serruys PW. A pooled analysis of data comparing sirolimus-eluting stents with bare-metal stents. N Engl J Med 2007;356:989–97.
5. Kotani J, Awata M, Nanto S, et al. Incomplete neointimal coverage of sirolimus-eluting stents: angioscopic findings. J Am Coll Cardiol 2006;47:2108–11.
6. Finn AV, Joner M, Nakazawa G, et al. Pathological correlates of late drug-eluting stent thrombosis: strut coverage as a marker of endothelialization. Circulation 2007;115:2435–41.
7. Daemen J, Wenaweser P, Tsuchida K, et al. Early and late stent thrombosis of sirolimus-eluting and paclitaxel-eluting stents in routine clinical practice: data from a large two-institutional cohort study. Lancet 2007;369:667–78.
8. King SB 3rd, Smith SC Jr., Hirshfeld JW Jr., et al. 2007 focused update of the ACC/AHA/SCAI 2005 guideline update for percutaneous coronary intervention: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2008;51:172–209.
9. Wijns W, Kolh P, Danchin N, et al. Guidelines on myocardial revascularization: the Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J 2010;31:2501–55.
10. Wilson GJ. Comparison of the SYNERGY stent with PROMUS (XIENCE V) and bare metal and polymer-only Element controls in porcine coronary arteries. Paper presented at: Annual Meeting of the American College of Cardiology; April 4, 2011; New Orleans, LA.
11. Meredith IT. Clinical and angiographic outcomes of the EVOLVE trial: a randomized evaluation of a novel bioabsorbable polymer-coated, everolimus-eluting coronary stent. Paper presented at: Annual Meeting of Transcatheter Cardiovascular Therapeutics; November 7, 2011; San Francisco, CA.
12. Stone GW, Teirstein PS, Meredith IT, et al. A prospective, randomized evaluation of a novel everolimus-eluting stent: the PLATINUM trial. J Am Coll Cardiol 2011;57:1700–8.
13. Meredith IT, Whitbourn R, Scott D, et al. PLATINUM QCA: a prospective, multicentre study assessing clinical, angiographic, and

intravascular ultrasound outcomes with the novel platinum chromium thin-strut PROMUS Element everolimus-eluting stent in de novo coronary stenoses. EuroIntervention 2011;7:84–90.
14. Meredith IT. The bioabsorbable SYNERGY stent and the EVOLVE trial. Paper presented at: Annual Meeting of Transcatheter Cardiovascular Therapeutics; September 22, 2010; Washington, DC.
15. Cutlip DE, Windecker S, Mehran R, et al. Clinical endpoints in coronary stent trials: a case for standardized definitions. Circulation 2007;115:2344–51.
16. Stone GW, Midei M, Newman W, et al. Comparison of an everolimus-eluting stent and a paclitaxel-eluting stent in patients with coronary artery disease: a randomized trial. JAMA 2008;299:1903–13.
17. Mauri L, Orav EJ, Kuntz RE. Late loss in lumen diameter and binary restenosis for drug-eluting stent comparison. Circulation 2005;111: 3435–42.
18. Morice MC, Serruys PW, Sousa JE, et al. A randomized comparison of a sirolimus-eluting stent with a standard stent for coronary revascularization. N Engl J Med 2002;346:1773–80.
19. Serruys PW, Ong AT, Piek JJ, et al. A randomized comparison of a durable polymer everolimus-eluting stent with a bare metal coronary stent: the SPIRIT first trial. EuroIntervention 2005;1:58–65.
20. Serruys PW, Ruygrok P, Neuzner J, et al. A randomized comparison of an everolimus-eluting coronary stent with a paclitaxel-eluting coronary stent: the SPIRIT II trial. EuroIntervention 2006;2:286–94.
21. Meredith IT, Worthley S, Whitbourn R, et al. Clinical and angiographic results with the next-generation resolute stent system: a prospective, multicenter, first-in-human trial. J Am Coll Cardiol Intv 2009;10:977–85.
22. Chevalier B, Silber S, Park SJ, et al. Randomized comparison of the Nobori-Biolimus A9-eluting coronary stent with the Taxus Liberté paclitaxel-eluting coronary stents in patients with stenosis in native coronary arteries: the NOBORI 1 trial—phase 2. Circ Cardiovasc Interv 2009;2:188–95.
23. Ormiston JA, Abizaid A, Spertus J, et al. Six-month results of the NEVO Res-Elution I (NEVO RES-I) trial: a randomized, multicenter comparison of the NEVO sirolimus-eluting coronary stent with the TAXUS Liberté paclitaxel-eluting stent in de novo native coronary artery lesions. Circ Cardiovasc Interv 2010;3:556–64.
24. Hamon M. First-in-man experience with DES Orsiro in the treatment of patients with single de novo coronary artery lesions (BIOFLOW-I). Paper presented at: Annual meeting of EuroPCR; May 17, 2011; Paris, France.
25. Serruys PW, Onuma Y, Ormiston JA, et al. Evaluation of the second generation of a bioresorbable everolimus drug-eluting vascular scaffold for treatment of de novo coronary artery stenosis: six-month clinical and imaging outcomes. Circulation 2010;122:2301–12.
26. Stone GW, Rizvi A, Newman W, et al. Everolimus-eluting versus paclitaxel-eluting stents in coronary artery disease. N Engl J Med 2010;362:1663–74.
27. Kedhi E, Joesoef KS, McFadden E, et al. Second-generation everolimus-eluting and paclitaxel-eluting stents in real-life practice (COMPARE): a randomised trial. Lancet 2010;375:201–9.
28. Collet JP, Montalescot G. Optimizing long-term dual aspirin/clopidogrel therapy in acute coronary syndromes: when does the risk outweigh the benefit? Int J Cardiol 2009;133:8–17.
29. Windecker S, Serruys PW, Wandel S et al. Biolimus-eluting stent with biodegradable polymer versus sirolimus-eluting stent with durable polymer for coronary revascularisation (LEADERS): a randomised non-inferiority trial. Lancet 2008;372:1163–73.
30. Stefanini GG, Kalesan B, Serruys, et al. Long-term clinical outcomes of biodegradable polymer biolimus-eluting stents versus durable polymer sirolimus-eluting stents in patients with coronary artery disease (LEADERS): 4 year follow-up of a randomised non-inferiority trial. Lancet 2011;378:1940–8.
31. Han Y, Jing Q, Li Y, et al. Sustained clinical safety and efficacy of a biodegradable-polymer coated sirolimus-eluting stent in "real-world" practice: 3-year outcomes of the CREATE (multi-center registry of EXCEL biodegradable polymer drug eluting stents) study. Catheter Cardiovasc Interv 2011 Nov 30 [E-pub ahead of print].

Key Words: bioabsorbable polymer ■ everolimus-eluting stents ■ PROMUS Element ■ SYNERGY.