Efficacy and Safety of a Novel Bioabsorbable Polymer-Coated, Everolimus-Eluting Coronary Stent
The EVOLVE II Randomized Trial

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Background—Drug eluting stents with durable polymers may be associated with hypersensitivity, delayed healing, and incomplete endothelialization, which may contribute to late/very late stent thrombosis and the need for prolonged dual antiplatelet therapy. Bioabsorbable polymers may facilitate stent healing, thus enhancing clinical safety. The SYNERGY stent is a thin-strut, platinum chromium metal alloy platform with an ultrathin bioabsorbable Poly(D,L-lactide-co-glycolide) abluminal everolimus-eluting polymer. We performed a multicenter, randomized controlled trial for regulatory approval to determine noninferiority of the SYNERGY stent to the durable polymer PROMUS Element Plus everolimus-eluting stent.

Methods and Results—Patients (n=1684) scheduled to undergo percutaneous coronary intervention for non–ST-segment–elevation acute coronary syndrome or stable coronary artery disease were randomized to receive either the SYNERGY stent or the PROMUS Element Plus stent. The primary end point of 12-month target lesion failure was observed in 6.7% of SYNERGY and 6.5% PROMUS Element Plus treated subjects by intention-to-treat (P=0.83 for difference; P=0.0005 for noninferiority), and 6.4% in both the groups by per-protocol analysis (P=0.0003 for noninferiority). Clinically indicated revascularization of the target lesion or definite/probable stent thrombosis were observed in 2.6% versus 1.7% (P=0.21) and 0.4% versus 0.6% (P=0.50) of SYNERGY versus PROMUS Element Plus–treated subjects, respectively.

Conclusions—In this randomized trial, the SYNERGY bioabsorbable polymer everolimus-eluting stent was noninferior to the PROMUS Element Plus everolimus-eluting stent with respect to 1-year target lesion failure. These data support the relative safety and efficacy of SYNERGY in a broad range of patients undergoing percutaneous coronary intervention.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT01665053.

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Key Words: drug-eluting stent ■ percutaneous coronary intervention

Drug-eluting stents (DES) that deliver antiproliferative drugs from a durable polymer have significantly reduced restenosis compared with bare metal stents.[1] However, durable polymers may be associated with inflammation, delayed healing, and incomplete endothelialization, which may contribute to the risk of late (30 days to 1 year) and very late (>1 year) stent thrombosis compared with bare metal stents.[2] Whether metal alloy coronary stent platforms with bioresorbable polymers are associated with improved clinical outcomes when compared with newer durable polymer DES has been the subject of debate[3,4] and may be influenced by additional factors, including stent strut thickness, polymer composition, distribution, and load.[5] Although current American College of Cardiology/American Heart of Association (ACC/AHA) clinical practice guidelines recommend at least 12 months of dual antiplatelet therapy (DAPT) after DES deployment in patients who are not at increased risk for bleeding,[1] recent studies suggest that even longer duration DAPT therapy (≥30 months) provides

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WHAT IS KNOWN

- Durable polymer on coronary drug-eluting stents may be associated with inflammation, neoatherosclerosis, and thrombosis.
- Bioabsorbable polymers may facilitate healing and enhanced clinical safety.

WHAT THE STUDY ADDS

- In a prospective, multicenter randomized single-blind trial, the Synergy stent, with a bioabsorbable polymer, proved noninferior to the PROMUS Element Plus stent for target lesion failure to 1 year.
- This study establishes comparable clinical safety and efficacy of everolimus elution from a bioabsorbable polymer thin strut platinum chromium metal platform in support of regulatory approval for this novel coronary stent device.

additional ischemic event reduction.[6] The SYNERGY stent (Boston Scientific Corporation, Marlborough, MA) is a novel thin-strut platinum chromium (PtCr) metal alloy stent that elutes everolimus from an ultrathin bioabsorbable Poly(D,L-lactide-co-glycolide) polymer applied to the abluminal surface.

The EVOLVE randomized controlled trial (EVOLVE: 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; NCT01135225) found SYNERGY to be noninferior to the durable polymer PROMUS Element everolimus-eluting stent (EES) for the angiographic end point of in-stent late lumen loss at 6 months,[7] but lacked sufficient power to provide meaningful comparison(s) of clinical events.[8] EVOLVE II represents the pivotal, randomized controlled clinical trial evaluating the clinical efficacy and safety of the SYNERGY stent for regulatory approval in a broad population of patients undergoing percutaneous coronary intervention (PCI).

Methods

EVOLVE II is a prospective, international, multicenter, randomized (1:1 SYNERGY versus PROMUS Element Plus), controlled, single-blind, noninferiority trial (EVOLVE RCT) conducted at 125 clinical sites. EVOLVE II also includes a concurrent, nonrandomized, single-arm, pharmacokinetic substudy (EVOLVE II PK), as well as a consecutively enrolled, nonrandomized, single-arm, diabetes mellitus substudy (EVOLVE II Diabetes; Figure 1), both of which will be reported separately. EVOLVE II was conducted in accordance with the US Food and Drug Administration's Guidance for Industry E6 Good Clinical Practice: Consolidated Guidance, the Declaration of Helsinki, the International Conference on Harmonisation, and all local regulations, as appropriate. Institutional Review Boards at each center approved the study protocol and all subjects provided written informed consent. The study is registered at www.clinicalTrials.gov under identifier NCT01665053.

Device Description

The SYNERGY stent is a thin-strut (74–81 μm), PtCr metal alloy platform with an ultrathin (4 μmol/L) bioabsorbable Poly(D,L-lactide-co-glycolide) abluminal polymer, which elutes everolimus (100 μg/cm^2). SYNERGY has been compared with the durable polymer PROMUS Element EES as described previously[9,10] (Table 1).

Study Design and Procedure

Eligible patients were aged ≥18 years and had either symptomatic coronary artery disease with objective evidence of ischemia or silent ischemia. Stents were implanted for treatment of ≤3 (maximum) discrete target lesions in ≤2 (maximum) 2 major epicardial vessels with lesion length ≤34 mm and reference vessel diameter ≥2.25 to ≤4.0 mm. Target stenoses were ≥50% and <100% with thrombolysis in myocardial infarction flow >1. Subjects were required to have either target stenosis ≥70% or a stenosis ≥50% to <70% with abnormal fractional flow reserve, elevated cardiac biomarkers, or objective evidence of myocardial ischemia (abnormal stress or imaging stress test). Patients with recent ST-segment–elevation myocardial infarction, left main disease, chronic total occlusions, vein graft disease, or

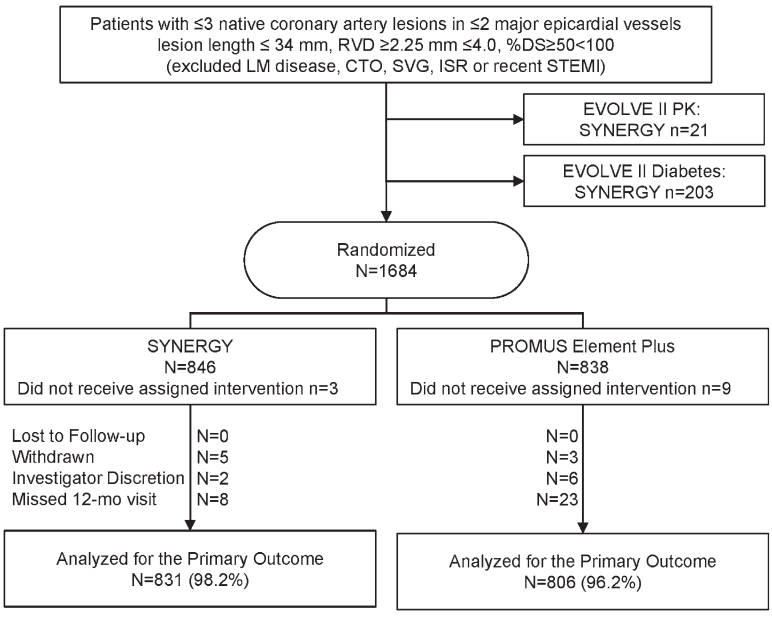

Figure 1. Patient flow and disposition in the EVOLVE II Trial. CTO indicates chronic total occlusion; DS, diameter stenosis; ISR, in-stent restenosis target lesion; LM, left main; PK, pharmacokinetic; RVD, reference vessel diameter; STEMI, ST-segment–elevation myocardial infarction; and SVG, saphenous vein graft target lesion.

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Table 1. Specific Design Characteristics of the SYNERGY and PROMUS Element Plus Stents

	SYNERGY	PROMUS Element Plus
Platform material	Platinum chromium	Platinum chromium
Stent strut thickness	74–81 μm	81–86 μm
Polymer	85:15 PLGA	PVDF-HFP PBMA
Polymer type	Biodegradable	Biostable
Polymer distribution	Abluminal	Conformal
Polymer thickness	4 μm	7.8 μm
Polymer duration	Approximately 4 mo	Permanent
Drug	Everolimus	Everolimus
Drug/polymer ratio in active layer (wt%/wt%)	45/55	17/83
Loaded drug dose	100 μg/cm^2	100 μg/cm^2

PLGA indicates Poly(D,L-lactide-co-glycolide); and PVDF, polyvinylidene fluoride.

in-stent restenosis were excluded per-protocol. Subjects who satisfied study selection criteria were randomly assigned 1:1 (stratified by diabetic status and enrollment site) to receive treatment with either SYNERGY or PROMUS Element Plus stents. Random permuted blocks were used to ensure approximate balance of treatment allocation within each stratum. EVOLVE II RCT is a single blind trial; subjects were blinded to treatment assigned and treatment received and will remain blinded until after trial completion. Packaging of the investigational control and test devices was different, therefore, the investigator performing the procedure was not blinded to the assigned treatment arm or resulting treatment. Site personnel conducting clinical follow-up, core laboratory personnel and the Clinical Events Committee were blinded to patient treatment assignment during the trial.

DAPT with aspirin and a $P2Y_{12}$ inhibitor was prescribed after PCI for at least 6 months (12 months in patients not at high risk of bleeding). An independent core laboratory evaluated all baseline and repeat angiograms (Beth Israel Deaconess Medical Center, Boston, MA). Clinical follow-up was required in-hospital at 30 days, 6, 12, and 18 months after PCI then annually between 2 and 5 years. There was no protocol-specified coronary angiography in follow-up.

Table 2. Baseline Characteristics of the Study Population

Variable*	SYNERGY n=846 Patients	PROMUS Element Plus n=838 Patients	*P* Value†
Male	70.6%	72.7%	0.34
Age, y, ±SD	63.5±10.4	63.9±10.5	0.40
White	77.4%	79.2%	0.37
Smoking, ever	61.7%	62.8%	0.63
Current smoker	21.8%	22.4%	0.76
Diabetes mellitus‡	31.1%	30.8%	0.89
Treated with insulin	12.3%	10.9%	0.36
Hyperlipidemia‡	74.0%	74.5%	0.82
Hypertension‡	77.3%	75.1%	0.29
Previous PCI	35.8%	37.3%	0.52
Previous CABG	4.6%	6.1%	0.18
History of CHF	8.3%	9.0%	0.63
Unstable angina	33.9%	34.8%	0.69
MI	25.9%	29.2%	0.12

CABG indicates coronary artery bypass graft; MI, myocardial infarction; and PCI, percutaneous coronary intervention.

*Number (percent) based on an intent-to-treat analysis.

†*P* values are 2-sided and from Student *t* test for continuous variables and the χ^2.

‡Medically treated.

End Points

The primary end point for EVOLVE II was the rate of 12-month target lesion failure (TLF), defined as the composite occurrence of any ischemia-driven revascularization of the target lesion, myocardial infarction (MI) related to the target vessel, or any cardiac death. Secondary clinical end points included individual components of TLF; target vessel failure defined as the composite occurrence of ischemia-driven target vessel revascularization, MI related to the target vessel or cardiac death related to the target vessel), all-cause death, and stent thrombosis (defined by the Academic Research Consortium; ST).[11] All major adverse events were adjudicated by a Clinical Events Committee and the decisions of the Clinical Events Committee superseded those of the investigational center in the event of a disparity. Spontaneous MI was defined as the rise and fall of cardiac biomarkers with ≥1 value >99th percentile of the upper reference limit with evidence of myocardial ischemia. The diagnosis of periprocedural MI required at least 1 of the following: (1) CK-MB >3× upper reference limit without clinical or imaging correlates, (2) new pathological Q waves, or (3) autopsy evidence of acute MI. MI was also independently assessed by Academic Research Consortium criteria as a secondary analysis.[11] Further details pertaining to the definition of MI are found in the Data Supplement document. Technical success was defined as successful delivery and deployment of the study stent to the target vessel, without balloon rupture or stent embolization with postprocedure diameter stenosis of <30% and thrombolysis in myocardial infarction 3 flow in the target lesion (as visually assessed by the treating

Table 3. Baseline Lesion Characteristics

	SYNERGY n=1059 Lesions n=846 Patients	PROMUS Element Plus n=1043 Lesions n=838 Patients	*P* Value*
Target lesions†	1.25±0.50	1.24±0.49	0.77
2 lesions treated	18.6%	19.3%	0.69
3 lesions treated	3.3%	2.4%	0.26
>3 lesions treated	0.0%	0.1%	0.50
Target lesion location‡			
LAD	41.3%	41.5%	0.91
LCx	25.0%	26.4%	0.48
RCA	33.7%	32.0%	0.41
LM	0.0%	0.1%	0.50§
RVD, mm‡	2.62±0.49	2.63±0.50	0.63
RVD <2.25 mm	23.9%	23.3%	0.76
MLD, mm‡	0.89±0.35	0.89±0.36	0.99
Diameter stenosis, %‡	66.02±12.03	66.26±11.75	0.65
Lesion length, mm‡	14.09±7.50	13.67±7.00	0.18
Length >20 mm	19.2%	16.7%	0.14
Modified AHA/ACC B2/C‡	76.8%	74.3%	0.19

ACC indicates American College of Cardiology; AHA, American Heart of Association; LM, left main; MLD, minimum lumen diameter; and RVD, reference vessel diameter.

*P values are 2-sided and from Student *t* test for continuous variables and the χ^2 unless indicated otherwise.

†Per patient number (percent) based on an intent-to-treat analysis.

‡Per lesion.

§Fisher exact test.

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Table 4. Procedural Characteristics

	SYNERGY n=1059 Lesions n=846 Patients n=1011 Stents	PROMUS Element Plus n=1043 Lesions n=838 Patients n=1079 Stents	*P* Value*
Technical success†	98.3%	96.9%	0.04
Clinical procedural success‡	94.9%	94.3%	0.56
Stents per patient‡	1.31±0.60	1.29±0.56	0.46
Stents per target lesion†	1.05±0.25	1.04±0.25	0.32
Total stent length implanted, mm†	21.45±9.04	20.81±9.16	0.11
Predilatation, %†	97.1%	98.0%	0.18
Postdilatation, %†	60.7%	61.0%	0.90
Max pressure overall, atm†	15.98±3.06	16.09±3.13	0.41
Longitudinal stent deformation§	0.1%‖	0.1%	>0.99

*P values are 2-sided and from Student *t* test for continuous variables and the χ^2.
†Per lesion.
‡Per patient number (percent) based on an intent-to-treat analysis.
§Per stent.
‖Occurred in a PROMUS Element Plus stent used in a SYNERGY assigned patient.

physician). Clinical procedural success was defined as postprocedure diameter stenosis <30%, thrombolysis in myocardial infarction 3 flow in all target lesions and the absence of in-hospital MI, TVR, or cardiac death. All procedural and follow-up (through 12 months) angiograms were systematically evaluated for longitudinal stent deformation by the independent angiographic core laboratory.

Statistical Methods

The study primary end point, powered for noninferiority, was the rate of 12-month TLF. A 2-group Farrington–Manning test was used to test the 1-sided hypothesis of noninferiority in proportions. Specifically, if the *P* value from a 1-sided Farrington–Manning test was <0.025 in both the intention-to-treat and per-protocol patient populations, SYNERGY would be concluded to be noninferior to PROMUS Element Plus. This corresponds to the 1-sided upper 97.5% confidence bound for the difference in 12-month TLF rates (SYNERGY–PROMUS Element Plus) being less than the noninferiority margin. On the basis of an assumed event rate in the test (SYNERGY) and control (PROMUS Element Plus) groups of 8.0% and a noninferiority margin of 4.4%; 1684 randomized subjects (842 per group) were required (assuming a 5% attrition) to provide power (1-β) of 0.89. Continuous variables were estimated as mean±SD and compared with the Student *t* test. Discrete variables were reported as counts and percentages, and differences were assessed by means of the χ^2 or Fisher exact tests. Cumulative event rates were estimated by the Kaplan–Meier method.

Table 5. Postprocedural Angiographic Characteristics

Per Lesion	SYNERGY n=1059 Lesions	PROMUS Element Plus n=1043 Lesions	*P* Value*
MLD, in-stent, mm	2.44±0.44	2.46±0.44	0.23
MLD, in-segment, mm	2.10±0.47	2.10±0.47	0.78
%DS, in-stent, %	7.19±9.16	6.55±9.71	0.12
%DS, in-segment, %	20.60±8.41	20.93±9.13	0.39
Acute gain, in-stent, mm	1.55±0.45	1.57±0.45	0.33
Acute gain, in-segment, mm	1.22±0.48	1.21±0.47	0.72

DS indicates diameter stenosis; and MLD, minimum lumen diameter.
*P values are 2-sided and from Student's *t* test for continuous variables and the χ^2.

Results

Patients and Enrollment

Between November 2012 and August 2013, 1684 patients were enrolled and randomized at 125 sites in North America, Europe, Australia, New Zealand, Japan, and Singapore. Of these, 846 were randomized to SYNERGY and 838 to PROMUS Element Plus (Figure 1). One-year follow-up was available in 831 (98.2%) SYNERGY and 806 (96.2%) PROMUS Element Plus stent–treated patients.

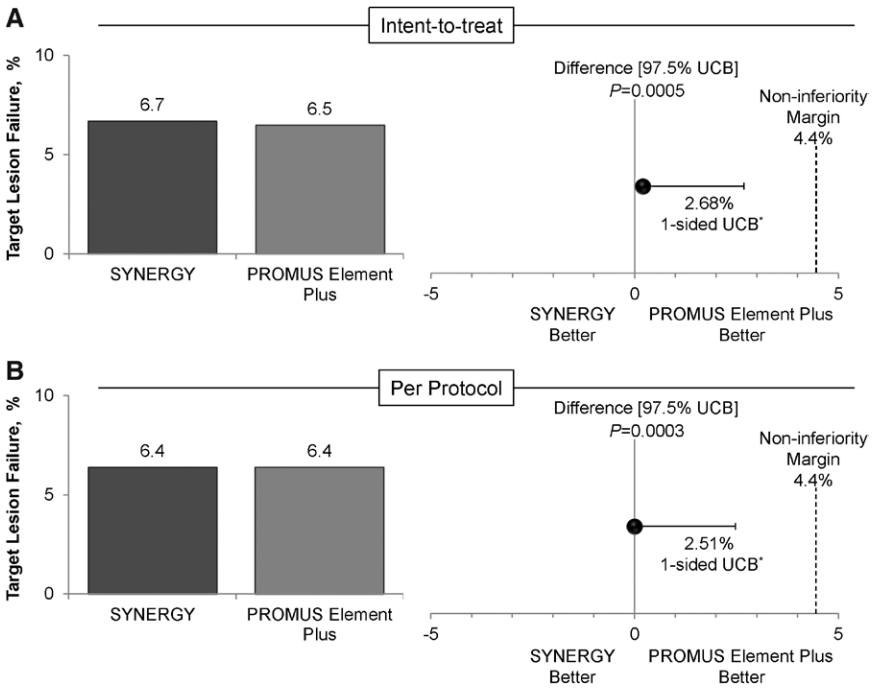

Figure 2. Primary end point of target lesion failure (TLF) at 1 year. One-year TLF in the SYNERGY (blue) and PROMUS Element Plus (red) cohorts in the intent-to-treat (**A**) and per-protocol (**B**) patient populations are shown on the left. On the right, the plot shows the difference in TLF between SYNERGY and PROMUS Element Plus (black circle) with the 1-sided 97.5% Farrington–Manning upper confidence bound (UCB*) indicated by the error bar. The *P* values for noninferiority testing are 1-sided.

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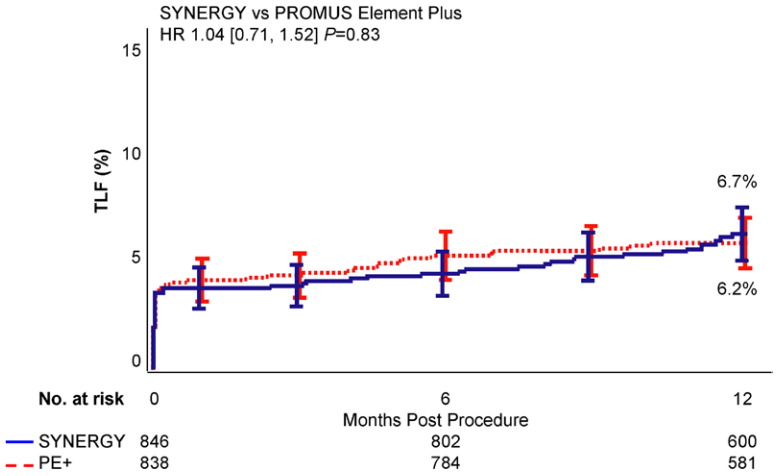

Figure 3. Time-to-event curve for the composite primary end point of target lesion failure (TLF) through 1 year. The event rates presented here were calculated by Kaplan–Meier methodology and compared with the log-rank test. Event rate±1.5 SE. HR indicates hazard ratio (95% confidence intervals).

Baseline patient clinical demographics and quantitative coronary angiographic characteristics were similar between treatment groups (Tables 2 and 3). The average age was 64 years, 31% of subjects had medically treated diabetes mellitus, more than a third had unstable angina, and more than quarter had MI diagnosed before the index PCI (Table 2). More than 20% of patients in each treatment group had multilesion (≥2 lesion) PCI and ≈75% of target lesions were classified as AHA/ACC B2/C lesion complexity (Table 3) by core laboratory adjudicated quantitative coronary angiography. Procedural characteristics (Table 4) and postprocedural angiographic results (Table 5) were similar between treatment groups with the exception that site-reported technical success was more frequent among SYNERGY-treated patients (98.3% SYNERGY versus 96.9% PROMUS Element Plus; P=0.04). Two instances of longitudinal stent deformation were observed through 12 months, both of which involved PROMUS Element Plus Stents; 1 in the PROMUS Element Plus arm and 1 in the SYNERGY arm (occurring in a PROMUS Element Plus stent mistakenly used during the index procedure). Compliance with DAPT to 6 and 12 months was 97.7% and 89.7% for SYNERGY and 96.9% and 87.3% for PROMUS Element Plus with no significant differences between stent types.

Primary End Point Analyses

The trial primary end point of TLF analyzed by intention-to-treat was observed in 6.7% of SYNERGY and 6.5% of PROMUS Element Plus–treated patients (1-sided 97.5% Farrington–Manning upper confidence bound of 2.68%) P=0.0005 noninferiority (Figure 2). Per-protocol analysis demonstrated TLF to be 6.4% in each treatment group (upper confidence bound, 2.51%; P=0.0003 for noninferiority). Because both intention-to-treat and per-protocol analyses demonstrate P<0.025, the SYNERGY stent is determined to

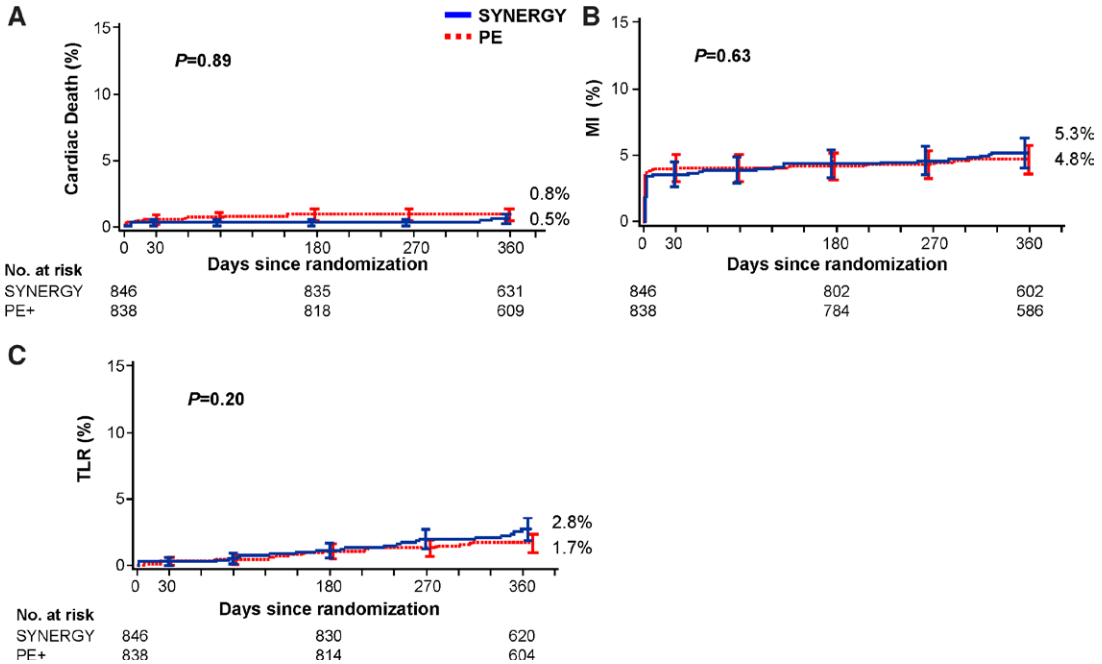

Figure 4. Time-to-event curves for the components of target lesion failure through 1 year. Target lesion failure (primary end point) is a composite of any cardiac death (**A**), target vessel-related myocardial infarction (MI; **B**), and clinically indicated revascularization of the target lesion (TLR; **C**). Event rate±1.5 SE; P value from a log-rank test.

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Table 6. Clinical End Points Through 12 Months

Variable*	SYNERGY n=846 Patients	PROMUS Element Plus n=838 Patients	*P* Value†
Death, %	1.1% (9/832)	1.1% (9/808)	0.95
Cardiac death, %	0.5% (4/832)	0.9% (7/808)	0.34
MI, %	5.4% (45/832)	5.0% (40/808)	0.68
Q-wave MI	0.2% (2/832)	0.2% (2/808)	>0.99‡
Non–Q-wave MI	5.2% (43/832)	4.7% (38/808)	0.66
TVR, %	3.8% (32/832)	3.6% (29/808)	0.78
PCI, %	3.0% (25/832)	3.2% (26/808)	0.80
CABG, %	0.8% (7/832)	0.4% (3/808)	0.34‡
TLR, %	2.6% (22/832)	1.7% (14/808)	0.21
PCI, %	2.0% (17/832)	1.7% (14/808)	0.64
CABG, %	0.6% (5/832)	0.0% (0/808)	0.06‡
Non-TLR TVR, %	1.8% (15/832)	2.2% (18/808)	0.54
PCI, %	1.4% (12/832)	1.9% (15/808)	0.51
CABG, %	0.4% (3/832)	0.4% (3/808)	>0.99‡
Stent thrombosis, %§			
Definite/probable	0.4% (3/832)	0.6% (5/808)	0.50‡
Definite	0.2% (2/832)	0.2% (2/808)	>0.99‡
Probable	0.1% (1/832)	0.4% (3/808)	0.37‡

CABG indicates coronary artery bypass graft; MI, myocardial infarction; PCI, percutaneous coronary intervention; and TLR, revascularization of the target lesion.

*Binary event rates. Number (percent) based on an intent-to-treat analysis.

†*P* value from χ^2 test unless otherwise noted.

‡*P* value from Fisher exact test.

§Stent thrombosis adjudicated according to Academic Research Consortium definition.

be noninferior to the PROMUS Element Plus stent for TLF at 1 year. Kaplan–Meier curves for TLF event rate occurrence over time were similar for both the stents (Figure 3), as were the individual components of TLF (Figure 4). Revascularization event rates to 1 year were similar between stent platforms as well (Table 6). There were 3 definite/probable STs in the SYNERGY arm (0.4%) and 5 in the PROMUS Element Plus arm (0.6%; *P*=0.50). The 2 definite STs in the SYNERGY arm were acute (≤24 hours) and the 1 probable ST was subacute (6 days) postprocedure. One of the SYNERGY acute ST events involved a patient who was not treated with preprocedural aspirin. All the 5 definite/probable STs in the PROMUS Element Plus arm occurred subacutely (between 2 and 30 days; Figure 5).

Discussion

In this pivotal trial designed to support regulatory approval of the first bioabsorbable polymer DES available in the United States, the SYNERGY stent proved to be noninferior to the PROMUS Element Plus stent for TLF at 1 year. Furthermore, rates of target vessel MI, clinically indicated/ischemia-driven revascularization of the target lesion and stent thrombosis to 1 year were low and similar for both stents.

These clinical observations complement the finding of noninferiority of SYNERGY (versus PROMUS Element) for quantitative coronary angiographic late lumen loss (0.10 versus 0.15 mm, respectively) at 6 months reported from the EVOLVE randomized first human use trial, and provide adequate sample size from which to make more definitive conclusions about important clinical outcomes.[7,8] In this regard, EVOLVE II supports the premise that the safety and efficacy of SYNERGY are at least comparable to the predicate PtCr durable polymer EES.

Although polymer provides a reservoir for programmed drug release, it has no function after drug release is complete and may affect the late/very late safety and efficacy of DES. First generation DES polymers (EVA-BMA [SurModics, Minneapolis, MN] and SIBS-translute [Boston Scientific]) were, at times, associated with inflammation, foreign body giant cell reaction, negative vessel remodeling, and late (acquired) stent malapposition with thrombus formation.[2,12,13] Durable polymers may also contribute to delayed/incomplete endothelial coverage and impaired stent healing.[2,14] Although newer durable polymers may have enhanced biocompatibility and seem to be associated with improved clinical outcomes, they have still been incriminated in the occurrence of inflammation, neoatherosclerosis, and thrombosis.[15,16] Indeed, neoatherosclerosis occurs earlier and with increased prevalence after DES compared with bare metal stents and has been observed with similar frequency among both first as well as newer generation DES.[17] Early randomized controlled clinical trials as well as meta-analyses suggested that biodegradable polymer DES were associated with lower rates of late/very late stent thrombosis when compared with either first generation DES or bare metal stents.[4,18] Conversely, more recent network meta-analyses and observational studies have suggested that the newer generation cobalt chromium (CoCr) and PtCr durable polymer (polyvinylidene fluoride) EES are associated with even lower rates of stent thrombosis when compared with other durable polymer DES, early biodegradable polymer DES, and even bare metal stents.[3,19–21] Furthermore, a randomized controlled clinical trial comparing the CoCr EES with its corresponding bare metal stent platform demonstrated lower rates of stent thrombosis at 1 and 2 years after primary PCI for ST-elevation MI in the CoCr EES group.[21] These observations are consistent with bench and preclinical data, which suggest that the durable polyvinylidene fluoride polymer may be thromboprotective against stent thrombosis.[22] Finally, a large-scale randomized controlled trial comparison of the CoCr EES versus the Nobori biodegradable polymer

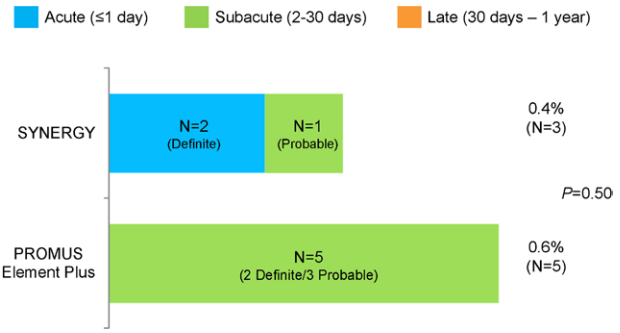

Figure 5. Stent thrombosis through 12 months. Definite/probable stent thrombosis rates through 12 months. Timing is separated into acute (≤1 day; blue), early (2–30 days; green), and late (>30 days–1 year; orange). Binary event rate; *P* value from a χ^2 test.

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DES demonstrated similar long-term outcomes for both the stents.[23] These apparent inconsistencies may, at least in part, be explained by differences in biodegradable polymer DES platform design.

Both the time course and extent of endothelial stent coverage, as well as the function and maturation of endothelial cells may be influenced by multiple factors, including metal alloy, stent strut thickness, polymer composition, and distribution as well as the time course for polymer bioresorption.[5,24,25] In this regard, the SYNERGY stent was designed to enhance/expedite stent healing in hopes of improving clinical outcomes by incorporating thin (74 μm) PtCr struts with an ultrathin (4 μm) Poly(D,L-lactide-co-glycolide) everolimus-eluting polymer applied only to the abluminal stent surface and which is resorbed within 4 months.[7,26] The bare metal PtCr platform which remains after polymer resorption may be less proinflammatory in cell assay when compared with gold, CoCr, or cobalt nickel alloy platforms, and seems to both expedite endothelial cell stent coverage and reduce platelet adhesion when compared with PtCr covered by polyvinylidene fluoride durable polymer.[25] Whether these putative preclinical attributes of the SYNERGY stent may translate into clinical benefit (reduction in stent related ischemic events or the relative treatment benefit recently observed for longer-term DAPT therapy[6]) will require further study.

Limitations

Several potential limitations to this study deserve mention. First, because the study design was single-blind (patient), physician operators were not blinded with respect to stent type deployed. Second, EVOLVE II is not adequately powered to evaluate the individual components of TLF. Third, specific complex patient and target lesion subsets were excluded from the study (ST-segment–elevation myocardial infarction, left main or saphenous vein graft target stenosis, chronic total occlusion, in-stent restenosis). Despite the lack of all-comers inclusion criteria the study population seems to reflect current clinical PCI practice with regard to the number of lesions/vessels undergoing PCI, target lesion length and angiographic complexity.[27] Finally, current follow-up duration is limited to only 1 year. Indeed, longer follow-up in more complex patient/lesion subsets may better differentiate between stent platforms with different structural design or polymer-healing attributes. Previous studies comparing DES with bioresorbable and durable polymers have, at times, demonstrated progressive differences in clinical outcomes >1 year.[18]

Conclusions

The EVOLVE II randomized controlled trial demonstrates the SYNERGY coronary stent to be noninferior to the predicate PROMUS Element Plus stent for the occurrence of TLF at 1 year. Secondary end points, including ischemia-driven–revascularization of the target lesion and ST, were also similar between stents. EVOLVE II establishes comparable clinical safety and efficacy of everolimus elution from a bioresorbable polymer—PtCr metal platform when compared with the established PtCr durable polymer EES. The longer-term relative efficacy and safety of SYNERGY will be evaluated in 5-year follow-up.

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Disclosures

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SUPPLEMENTAL MATERIAL

Supplemental Methods

EVOLVE II Clinical Trial Support

Clinical Events Committee

- Joseph Kannam, MD (Chairperson, Needham Cardiology Beth Israel Deaconess Needham, Needham, MA, USA)
- Germano DiSciascio, MD (Università Campus Biomedico, Roma, Italy)
- Claude Hanet, MD (UCL Saint-Luc, Brussel, Belgium)
- Goran Stankovic, MD (Diagnostic and Catheterization Lab, Belgrade, Serbia)

Data Monitoring Committee

- W Douglas Weaver, MD (Chairperson, Henry Ford Heart and Vascular Institute, Detroit, MI, USA)
- David P. Faxon, MD (Brigham and Women's Hospital, Boston, MA, USA)
- Steven R. Bailey, MD (University of Texas, San Antonio, TX, USA)
- Jan G P Tijssen, PhD (DMC Statistician, University of Amsterdam, Amsterdam, The
- Netherlands)
- David Rizik, MD (Heart & Vascular Division at Scottsdale Healthcare Scottsdale, AZ, USA)

Core Laboratories (Angiogram Evaluation)

Harvard Medical Physicians Faculty at Beth Israel Deaconess Medical Center
Dr. Jeffrey Popma, MD Director
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Boston, MA 02215

EVOLVE II Enrollment by Site

Investigator	Clinical Site	State and Country	# Subjects Enrolled
R. Lee Jobe	Wake Medical Center	Raleigh, NC USA	71
Shamir Mehta	Hamilton General Hospital	Hamilton, ON Canada	64
Ian Sarembock	Lindner Center for Research and Education at Christ Hospital	Cincinnati, OH USA	63
Robert Feldman	Mediquest Research at Munroe Regional Medical Center	Ocala, FL USA	47
Bernardo Stein	Morton Plant Mease Healthcare System	Clearwater, FL USA	44
Christophe Dubois	University Hospital Leuven	Leuven, Belgium	39
Timothy Grady	Aspirus Heart and Vascular Institute – Research and Education	Wausau, WI USA	37
Shigeru Saito	Shonan Kamakura General Hospital	Kamakura, Japan	30
Ameer Kabour	Mercy St. Vincent Medical Center	Toledo, OH USA	29
Alain Bouchard	Baptist Medical Center Princeton	Birmingham, AL, USA	27
Annapoorna Kini	Mount Sinai Medical Center	New York, NY USA	27

Investigator	Clinical Site	State and Country	# Subjects Enrolled
Luc Janssens	Imelda Ziekenhuis	Bonheiden, Belgium	27
Michael Foster	Sisters of Charity Providence Hospital	Columbia, SC USA	25
Robert Stoler	Baylor Heart & Vascular Hospital	Dallas, TX USA	24
Thomas Stuckey	Moses H. Cone Memorial Hospital - LeBauer Cardiovascular Research Foundation	Greensboro, NC USA	24
Wayne Batchelor	Tallahassee Memorial Hospital	Tallahassee, FL USA	24
Josep Rodes-Cabau	Institut universitaire de Cardiologie et de Pneumologie de Quebec	Ste-Foy, Canada	24
Tommy Lee	Bakersfield Memorial Hospital	Bakersfield, CA USA	24
Arthur Reitman	Wellstar Kennestone Hospital	Marietta, GA USA	24
Andrejs Erglis	P. Stradins University Hospital	Riga, Latvia	23
Mark Dorogy	Medical Center of Central Georgia	Macon, GA USA	23
Barry Bertolet	North Mississippi Medical Center	Tupelo, MS USA	22
Louis Cannon	Northern Michigan Hospital	Petoskey, MI USA	21
Juhani Airaksinen	Turku University Hospital	Turku, Finland	21
Craig Siegel	St. David's Round Rock Medical Center	Round Rock, TX USA	21
Akil Loli	Banner Good Samaritan Regional Medical Center	Phoenix, AZ USA	20
David Mego	Arkansas Heart Hospital	Little Rock, AR USA	20
Kenji Ando	Kokura Memorial Hospital	Kitakyushu, Japan	20
Toshiya Muramatsu	Saiseikai Yokohama-City Eastern Hospital	Yokohama, Japan	20
Francis Stammen	H-Hartziekenhuis Roeselare-Menen vzw	Roeselare, Belgium	20
Michael Curtis	Foothills Medical Center	Calgary, Canada	19
Steffen Helqvist	Rigshospitalet Copenhagen	Copenhagen, Denmark	19
Michael Ball	St. Vincent's Hospital	Indianapolis, IN USA	18
Aaron Wong	National Heart Centre	Singapore	18
Patrizia Presbitero	Instituto Clinico Humanitas	Rozzano, MI Italy	18
Lee MacDonald	South Denver Cardiology Associates, PC	Littleton, CO USA	18
Andrew Taussig	Florida Hospital	Orlando, FL USA	17
Daniel Simon	University Hospitals of Cleveland	Cleveland, OH USA	17
Mark Meier	Northern Indiana Research Alliance - Lutheran Hospital	Ft. Wayne, IN USA	16
James Blankenship	Geisinger Medical Center	Danville, PA USA	15
Monica Masotti	Hospital Clínic de Barcelona	Barcelona, Spain	15
John Wang	Union Memorial Hospital	Baltimore, MD USA	15
Kartik Giri	Our Lady of Lourdes Medical Center	Haddon Heights, NJ USA	15
John Lasala	Washington University School of Medicine	St. Louis, MO USA	15
Henry Lui	Jackson-Madison County General Hospital	Jackson, TN USA	15
Junji Yajima	The Cardiovascular Institute Hospital	Minato, Japan	15
Laura Mauri	Brigham and Women's Hospital	Boston, MA USA	14
Joseph Dens	Ziekenhuis Oost Limburg	Genk, Belgium	14
Brian Price	King's Daughters Medical Center - Kentucky Heart Institute	Ashland, KY USA	14
Javier Escaned	Hospital Clinico San Carlos	Madrid, Spain	13
Olivier Varenne	Hôpital Cochin	Paris, France	13
Darren Walters	The Prince Charles Hospital	Brisbane, Australia	13
Wilson Ginete	St. Mary's Duluth Clinic Regional Heart Center	Duluth, MN USA	12

Investigator	Clinical Site	State and Country	# Subjects Enrolled
Bruno Farah	Clinique Pasteur	Toulouse, France	12
Paul Myers	Centennial Medical Center	Nashville, TN USA	12
Atsushi Hirayama	Nihon University Itabashi Hospital	Itabashi, Japan	12
Geoffrey Kunz	New Mexico Heart Institute, PA	Albuquerque, NM USA	11
Clemens Von Birgelen	Medisch Spectrum Twente	Enschede, Netherlands	11
Magdi Ghali	Mercy Hospital Medical Center	West Des Moines, IA USA	11
Maurice Buchbinder	Alvarado Hospital	San Diego, CA USA	11
Ronald Waksman	Washington Hospital Center	Washington, DC USA	10
Johannes de Swart	Medisch Centrum Alkmaar	Alkmaar, Netherlands	10
Raul Moreno	Hospital La Paz	Madrid, Spain	10
Ronald Jenkins	Kootenai Medical Center	Coeur d'Alene, ID USA	10
Nobuhisa Hagiwara	Tokyo Women's Medical University Hospital	Shinjuku, Japan	10
James Zidar	Rex Hospital	Raleigh, NC USA	10
Takafumi Ueno	Kurume University Hospital	Kurume, Japan	10
Thomas McGarry	Oklahoma Heart Hospital	Oklahoma City, OK USA	9
Robert Whitbourn	St. Vincent's Hospital (Melbourne)	Fitzroy, Australia	9
Huay Cheem Tan	National University Hospital	Singapore	9
Jacques Berland	Clinique Saint-Hilaire Rouen	Rouen, France	9
Kari Niemelae	University Hospital, Heart Centre	Tampere, Finland	9
Masato Nakamura	Toho University Ohashi Medical Center	Meguro, Japan	9
Nilesh Goswami	St. John's Hospital	Springfield, IL USA	8
Shing-Chiu Wong	New York Presbyterian Hospital	New York, NY USA	8
Steven Laster	St. Luke's Hospital of Kansas City	Kansas City, MO USA	8
Pamela Gordon	Kaiser Foundation Hospitals	Honolulu, HI USA	8
Takeshi Kimura	Kyoto University Hospital	Kyoto, Japan	8
Satoshi Yasuda	National Cerebral and Cardiovascular Center Hospital	Suita, Japan	8
Michele Voeltz	Henry Ford Hospital	Detroit, MI USA	7
Ian Meredith	Monash Medical Centre	Clayton, Australia	7
Vincent Pompili	Ohio State University Medical Center	Columbus, OH USA	7
Richard Kovach	Deborah Heart and Lung Center	Brown Mills, NJ USA	7
Douglas Scott	Middlemore Hospital	Otahuhu, New Zealand	7
Maciej Lesiak	Samodzielny Publiczny Szpital	Poznan, Poland	7
Yuji Hamazaki	Showa University Hospital	Shinagawa, Japan	7
R. Lee Jobe	Rex Hospital	Raleigh, NC USA	7
Warwick Jaffe	Ascot Angiography	Auckland, New Zealand	6
John Petersen	Swedish Medical Center	Seattle, WA USA	6
Alan Heldman	University of Miami Hospital	Miami, FL USA	6
Seif El-Jack	North Shore Hospital	Takapuna, New Zealand	6
Takaaki Isshiki	Teikyo University Hospital	Itabashi, Japan	6
Michael Kutcher	Wake Forest University School of Medicine	Winston-Salem, NC USA	5
Dougal McClean	Christchurch Hospital	Christchurch, New Zealand	5
Minh Bui	Henrico Doctors' Hospital	Richmond, VA USA	5
Eric Cohen	Sunnybrook Health Sciences Centre	Toronto, Canada	4

Investigator	Clinical Site	State and Country	# Subjects Enrolled
David Dobies	Genesys Regional Medical Center	Grand Blanc, MI USA	4
Bernard Rensing	St. Antonius Ziekenhuis	Nieuwegein, Netherlands	4
Martine Gilard	CHU de Brest-Hopital de la Cavale Blanche	Brest, France	4
Simon Elhadad	CH Lagny-Marne-la-Vallee	Jossigny, France	4
Alan Whelan	Fremantle Hospital	Fremantle, Australia	4
David Leeman	Beth Israel Deaconess Medical Center	Boston, MA USA	3
Mirle Kellett	Maine Medical Center	Portland, ME USA	3
Philippe L'Allier	Institut de Cardiologie de Montreal	Montreal, Canada	3
Ivan Chavez	Abbott Northwestern Hospital	Minneapolis, MN USA	3
Reginald Low	University of California, Davis Medical Center	Sacramento, CA USA	3
Abram Rabinowitz	Methodist Texsan Hospital	San Antonio, TX USA	3
Brian O'Murchu	Temple University Hospital	Philadelphia, PA USA	3
Robert Hodson	Providence Portland Medical Center	Portland, OR USA	3
Jon Robken	Genesis Medical Center	Davenport, IA USA	2
Uta Hoppe	Univ. Klinik für Herzchirurgie Landeskliniken	Salzburg, Austria	2
Michael Isaac	Medical City Dallas Hospital	Dallas, TX USA	2
Gennaro Sardella	Ospedale Umberto I - Roma	Roma, Italy	2
Manish Parikh	Columbia University Medical Center	New York, NY USA	1
Barry Cohen	Morristown Memorial Hospital	Morristown, NJ USA	1
Sergio Waxman	Lahey Clinic Hospital	Burlington, MA USA	1
Irene Lang	Allgemeines Krankenhaus AKH	Vienna, Austria	1
Didier Carrie	Centre Hôpital Universitaire Rangueil	Toulouse, France	1
Adam Witkowski	National Institute of Cardiology	Warsaw, Poland	1
Carey Kimmelstiel	Tufts Medical Center	Boston, MA USA	1
Daniel McCormick	Pennsylvania Hospital	Philadelphia, PA USA	1
Dariusz Dudek	SP ZOZ Szpital Uniwersytecki w Krakowie	Krakow, Poland	1
David Roberts	Sutter Memorial Hospital	Sacramento, CA USA	1
Maurizio D'Amico	Azienda Ospedaliera San Giovanni Battista	Turin, Italy	1
James Beckmann	North Colorado Medical Center	Greeley, CO USA	1

Supplemental Methods

Definition of MI

In the EVOLVE II trial, MI will be defined according to the EVOLVE II definition and the Universal definition provided below. The EVOLVE II definition for MI will be used for the primary endpoint.

EVOLVE II Definition

Spontaneous MI: Detection of rise and/or fall of cardiac biomarkers (CK-MB or troponin) with at least one value above the 99th percentile of the upper reference limit (URL) together with evidence of myocardial ischemia with at least one of the following:

- Symptoms of ischemia;
- ECG changes indicative of new ischemia (new ST-T changes or new left bundle branch block [LBBB]);
- Development of pathological Q waves in the ECG;
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

Percutaneous Coronary Intervention-Related Myocardial Infarction

Peri-PCI MI is defined by any of the following criteria. Symptoms of cardiac ischemia are not required.

i. Biomarker elevations within 48 hours of PCI:

- CK-MB > 3X URL or
- CK-MB not measured and CK > 2X URL or
- Neither CK-MB nor CK measured and troponin > 3X URL

and no evidence that cardiac biomarkers were elevated prior to the procedure OR both of the following must be true:

- ≥ 50% increase in cardiac biomarker result
- Evidence that cardiac biomarker values were decreasing (e.g., two samples 3-6 hours apart) prior to the suspected MI

ii. New pathological Q waves

iii. Autopsy evidence of acute MI

Coronary Artery Bypass Grafting-Related Myocardial Infarction

Peri-CABG MI is defined by the following criteria. Symptoms of cardiac ischemia are not required.

i. Biomarker elevations within 72 hours of CABG:

- Troponin or CK-MB (preferred) > 5X URL **and**

- No evidence that cardiac biomarkers were elevated prior to the procedure OR both of the following must be true:
    - ≥50% increase in the cardiac biomarker result
    - Evidence that cardiac biomarker values were decreasing (e.g., two samples 3-6 hours apart) prior to the suspected MI.

AND

- One of the following:
    - New pathological Q-waves persistent through 30 days
    - New persistent non-rate-related LBBB
    - Angiographically documented new graft or native coronary artery occlusion
    - Other complication in the operating room resulting in loss of myocardium
    - Imaging evidence of new loss of viable myocardium

OR

ii. Autopsy evidence of acute MI

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Efficacy and Safety of a Novel Bioabsorbable Polymer-Coated, Everolimus-Eluting Coronary Stent: The EVOLVE II Randomized Trial

Dean J. Kereiakes, Ian T. Meredith, Stephan Windecker, R. Lee Jobe, Shamir R. Mehta, Ian J. Sarembock, Robert L. Feldman, Bernardo Stein, Christophe Dubois, Timothy Grady, Shigeru Saito, Takeshi Kimura, Thomas Christen, Dominic J. Allocco and Keith D. Dawkins

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