JACC: CARDIOVASCULAR INTERVENTIONS VOL. 2, NO. 3, 2009

ISSN 1936-8798/09/$36.00
PUBLISHED BY ELSEVIER INC. DOI: 10.1016/j.jcin.2008.12.011

The GENESIS (Randomized, Multicenter Study of the Pimecrolimus-Eluting and Pimecrolimus/Paclitaxel-Eluting Coronary Stent System in Patients with De Novo Lesions of the Native Coronary Arteries) Trial

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Objectives The aim of this study was to compare, in a randomized multicenter trial, paclitaxel-eluting stents (CoStar, Conor Medsystems, Menlo Park, California) versus pimecrolimus-eluting stents (Corio, Conor Medsystems) versus stents with dual elution of both drugs (SymBio, Conor Medsystems) in native coronary arteries.

Background The CoStar cobalt-chromium reservoir-based stent platform, eluting paclitaxel in a controlled way via a bioresorbable polymer, reduces restenosis versus its respective bare-metal stent. The reservoir system allows the use of other drugs targeted to different mechanisms involved in the process of vascular restenosis and simultaneous loading of multiple, synergistic drugs.

Methods Patients with single de novo lesions were asymmetrically randomized to 1 of the 3 types of stent (1:2:2). Six-month coronary angiography was planned in all. The primary analysis was a noninferiority test for the primary end point of 6-month angiographic in-stent late lumen loss of Corio versus CoStar and SymBio versus CoStar. Secondary end points included binary angiographic restenosis and major adverse clinical events (cardiac death, myocardial infarction, target vessel revascularization).

Results The trial was prematurely suspended after 246 patients were enrolled (planned enrollment: 375 patients): 49 patients received CoStar, 97 received SymBio, and 100 received Corio. In-stent late loss was significantly reduced with CoStar versus either SymBio or Corio (0.58 $\pm$ 0.58 mm vs. 0.96 $\pm$ 0.73 mm and 0.58 $\pm$ 0.58 mm vs. 1.40 $\pm$ 0.67 mm, $p < 0.001$ for both comparisons). Binary in-stent restenosis rates were, 7.1%, 20%, and 40.9%, respectively ($p < 0.001$ for both comparisons); 6-month major adverse cardiac event rates were, 2.0%, 14.4%, and 39.0%, respectively ($p < 0.001$ for both comparisons).

Conclusions Stents eluting pimecrolimus or the dual combination of pimecrolimus and paclitaxel failed to show angiographic noninferiority when compared with paclitaxel-eluting stents. (A Randomized, Multi-Center Study of the Pimecrolimus-Eluting and Pimecrolimus/Paclitaxel-Eluting Coronary Stent Systems; NCT00322569) (J Am Coll Cardiol Intv 2009;2:205–14) © 2009 by the American College of Cardiology Foundation

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The CoStar stent (Conor Medsystems, Menlo Park, California) is a cobalt chromium alloy stent platform designed to elute paclitaxel without the use of a surface polymer and drug coating but with a technology consisting of multiple laser-cut reservoirs within the stent struts (Fig. 1). These reservoirs are filled with a polymer/drug matrix consisting of a bioresorbable poly-lactic-co-glycolic polymer and paclitaxel. The drug elution occurs with both directional and kinetic control. The CoStar paclitaxel-eluting stent (PES) has been proven superior to the respective bare cobalt chromium stent in reducing angiographic restenosis and repeated revascularizations at 8 months (1).

Whereas the CoStar PES failed to demonstrate noninferiority to the first-generation Taxus PES (Boston Scientific, Maple Grove, Minnesota) for the primary end point of 8-month major adverse cardiac events (MACE) in the COSTAR (Cobalt Chromium Stent with Antiproliferative for Restenosis) II trial (2), the concept of reservoir technology of the stent, associated with the bioresorbable polymer delivery matrix, still offers the potential for alternative dose kinetic and elution profile improvements aimed at developing more effective and safer drug-eluting stents. Indeed, this technology allows loading and independent elution control of drugs targeting various mechanisms involved in the restenotic process. It also permits simultaneous independent delivery from a single stent of more than 1 therapeutic agent by placing different polymer/drug combinations in alternate, adjacent reservoirs. This combined delivery can concurrently address multiple physiologic stimuli responsible for the pathological events after stent implantation (3). Once the discharge of the loaded drug(s) is complete, the polymeric delivery matrix is absorbed, leaving a bare metal stent implanted.

Abbreviations and Acronyms

IVUS = intravascular ultrasound

MACE = major adverse cardiac event

MI = myocardial infarction

MLD = minimal luminal diameter

QCA = quantitative coronary angiography

PES = paclitaxel-eluting stent(s)

RVD = reference vessel diameter

TLR = target lesion revascularization

TVR = target vessel revascularization

Pimecrolimus is a compound, currently approved by the U.S. Food and Drug Administration and the European Medicines Agency for the topical treatment of atopic dermatitis. It is an anti-inflammatory agent with immunosuppressant properties, belonging to the class of calcineurin-inhibitors. Pimecrolimus inhibits the activation and proliferation of T-lymphocytes and the release of several growth factors. In addition, it targets mast cell release of pro-inflammatory mediators including histamine, cytokines, tryptase, and eicosanoids (4). Even though this agent does not exert any specific antiproliferative action, it might reduce the response of smooth muscle cell proliferation and neointimal hyperplasia by decreasing the localized inflammatory response and the resultant cascade of physiologic reactions secondary to the arterial injury caused by stent implantation (5,6).

This study was designed to determine the effectiveness of the anti-inflammatory molecule pimecrolimus alone and the synergistic combination of pimecrolimus with an antiproliferative agent such as paclitaxel (with the potential of simultaneous inhibition of 2 different mechanisms of restenosis), loaded in a drug-eluting stent with the Conor reservoir technology, on the neointimal reaction process assessed in humans by angiography.

Methods

The GENESIS (randomized, multicenter study of the pimecrolimus-eluting and paclitaxel-elutinG coronary stent system in patiENts with de novo lEsionS of the native coronary arterIeS) trial is a prospective, asymmetrically randomized, multicenter, open-label, 3-arm trial. The local ethics committee of every hospital enrolling patients approved the trial design.

Patient population. Patients were included if they were >18 years of age, with documented stable or unstable angina pectoris and had 1 de novo target lesion ≤25 mm in length, with a reference vessel diameter (RVD) of 2.5 to 3.5 mm and with visually estimated stenosis of ≥50% and <100%, localized in a native coronary artery.

Clinical exclusion criteria were: woman of childbearing potential; myocardial infarction (MI) within the previous 72 h; cardiogenic shock; documented left ventricular ejection fraction <25%; acute or chronic renal dysfunction (creatinine >2.0 mg/dl); cerebrovascular accident within the past 6 months; gastrointestinal bleeding within the past 3 months; thrombocytopenia (platelet count <100,000/mm^3); contraindications to aspirin, clopidogrel, or contrast

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Manuscript received December 15, 2008; accepted December 21, 2008.

Figure 1. The CoStar Stent

Photograph of the CoStar stent **(A)**. Magnification demonstrates the laser-cut reservoirs and a bridge element **(B)**.

agents; known sensitivity to pimecrolimus, paclitaxel, cobalt chromium, or the poly-lactic-co-glycolic polymer; current assumption of colchicine; chronic systemic steroid or immunosuppressant therapy or systemic paclitaxel assumption within 12 months of the index procedure; life expectancy <24 months; or current participation in another investigational drug or device study. Angiographic exclusion criteria were: prior revascularization of the target vessel within the preceding 6 months, left main stenosis, ostial stenosis, bifurcation lesion, severe calcification or the presence of thrombus by visual estimation, pretreatment of the target lesion with any unapproved device or atherectomy or laser or cutting balloon, or prior brachytherapy in the target vessel. All enrolled patients provided written informed consent before the index procedure.

Procedural protocol, randomization, and follow-up. After percutaneous access was obtained, heparin was administered to maintain an activated clotting time >250 s (or >200 s if glycoprotein IIb/IIIa inhibitors were given). Glycoprotein IIb/IIIa inhibitors were given at the operator's discretion. Randomization was performed after baseline angiography was obtained, with a computerized central randomization service. Randomization was stratified by site and was accomplished at each site with an interactive voice randomization system. Eligible patients were randomized in a ratio of 1:2:2, respectively, to 1 of 3 treatment arms: CoStar PES (11-μg nominal dose in a 3.0 × 16 mm stent) or SymBio (Conor Medsystems) pimecrolimus/paclitaxel-eluting stent (162.5-μg pimecrolimus/11-μg paclitaxel nominal dose in a 3.0 × 16 mm stent) or Corio (Conor Medsystems) pimecrolimus-eluting stent (325-μg nominal dose in a 3.0 × 16 mm stent). Direct stenting was allowed and left at operator's discretion. In case of dissection or incomplete lesion coverage, the use of additional stents of the same type as the assigned stent was mandated. The first 30 patients enrolled into each arm were automatically allocated into an intravascular ultrasound (IVUS) substudy; IVUS was performed at the end of the procedure according to standard protocols after injection of 0.2 mg of nitroglycerin with a 20- to 40-MHz ultrasound probe and with a motorized pullback (speed: 0.5 mm/s). Aspirin (100 to 300 mg/day) was given daily, and clopidogrel (loading dose of at least 300 mg before procedure and 75 mg/day thereafter) was administered for at least 6 months in all patients. Serial blood samples for creatine kinase and creatine kinase-myocardial band were routinely obtained 8 to 12 and 16 to 24 h after the intervention.

Patients were evaluated clinically 1 and 6 months after the procedure. Coronary angiography was planned at 6 months (±30 days) in all patients, and IVUS analysis was planned in the cohort of patients receiving IVUS at baseline. Angiography was performed earlier if there were recurrent symptoms, but if restenosis was not found during this

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repeat angiography, a new angiography was done at 6 months.

Quantitative coronary angiography and IVUS analysis. Digital coronary angiograms were analyzed offline by an independent core laboratory, with a validated automated edge detection system (Medis, Leiden, the Netherlands) (7). Matched views were selected for angiograms recorded before and immediately after the intervention and at 6-month follow-up. Angiographic measurements were made both in the stent and in the stented segment (defined as the stent plus the 5-mm edges proximal and distal to the stent) during diastole with the contrast-filled guiding catheter for magnification calibration. In case overlapping stents were placed, a single in-stent value was measured, and the segment was considered as the entirely stented segment plus the 5 mm proximal to the more proximal stent and the 5 mm distal to the more distal stent implanted. Lesion RVD, minimal luminal diameter (MLD), percent diameter stenosis, and length were obtained at baseline. The RVD, MLD, and diameter stenosis were evaluated at the end of the procedure and at follow-up, for the in-stent, proximal edge, distal edge, and in-segment sections. Acute gain was defined as the difference between the in-stent MLD at the end of the intervention and the MLD at baseline. Late lumen loss was calculated as the difference in MLD between measurements immediately after the procedure and at follow-up. Binary angiographic restenosis was defined as diameter stenosis ≥50% by quantitative coronary angiography (QCA), at the follow-up angiogram (8). Restenosis patterns were assessed with the Mehran classification system (9).

Quantitative IVUS analysis was performed offline by an independent core laboratory, with validated software (echoPlaque, Indec Systems, Mountain View, California), allowing semi-automated detection of luminal and stent boundaries in reconstructed longitudinal planes. Volumetric quantitative coronary ultrasound analysis was obtained for vessel, stent, and lumen. Neointimal volume was computed as the difference between stent volume and lumen volume. Percent volume obstruction was calculated as the ratio between the neointimal volume and stent volume × 100. Incomplete stent apposition was defined as 1 or more stent struts clearly separated from the vessel wall with evidence of blood speckles behind the strut in a vessel segment not associated with any side branches (10).

End points and definitions. The primary end point of the study was 6-month in-stent late lumen loss (11,12). Secondary angiographic end points included in-segment late loss, in-stent and -segment binary restenosis (≥50% diameter stenosis), and in-stent and -segment MLD at 6 months after the procedure. Secondary IVUS end points were percent volume obstruction of the stent and incidence of late acquired incomplete stent-to-vessel apposition at 6 months. Secondary clinical end points were 30-day and 6-month MACE rates, defined as an adjudicated composite of cardiac death, new MI not clearly attributable to a nonintervention vessel, or clinically driven target vessel revascularization (TVR). In addition, clinically driven target lesion revascularization (TLR) at 6 months after the procedure was evaluated. Death was divided into 2 categories: cardiac and noncardiac. Cardiac death was defined as death due to acute MI or to a complication of the index procedure (including bleeding, vascular repair, transfusion reaction, or bypass surgery) or any death in which a cardiac cause cannot be excluded. Noncardiac death was defined as a death not due to cardiac causes. Myocardial infarction was defined in 2 ways: 1) Q-wave MI was diagnosed when chest pain or symptoms consistent with myocardial ischemia and new pathological Q waves in 2 or more contiguous electrocardiogram leads were present; and 2) non–Q-wave MI was defined as creatine kinase elevated >2 times the upper laboratory normal with the presence of elevated creatine kinase-myocardial band in the absence of new pathological Q waves. Clinically driven TVR and TLR were defined as revascularizations at the target vessel or lesion, respectively, associated with positive functional ischemia study or ischemic symptoms and an angiographic diameter stenosis ≥50% by QCA or revascularization of a target vessel or lesion with diameter stenosis ≥70% by QCA without either angina or a positive functional study. Stent thrombosis was defined according to the Academic Research Consortium criteria (13).

Additional secondary end points were device, lesion, and procedural success. Primary device success was defined as attainment of <50% in-stent residual stenosis of the target lesion with only the assigned device in the absence of device malfunction and device-related complication. Lesion success was defined as attainment of <50% residual stenosis of the target lesion with the assigned device or any percutaneous method. Procedure success was defined as attainment of a final lesion success and no in-hospital MACE.

An independent clinical events committee unaware of the patients' treatment assignment adjudicated all the clinical events, and an independent data safety monitoring board also reviewed clinical data periodically throughout the trial.

Statistical analysis. The study compared 2 experimental stents, SymBio and Corio, with the CoStar control stent. The comparisons of interest for the primary outcome of in-stent late loss were SymBio versus CoStar and Corio versus CoStar. The sample size of 375 patients (150:150:75) was based on the noninferiority hypothesis that the difference between late loss of SymBio or Corio and late loss of CoStar was <0.32 mm with a power of approximately 95%, assuming a pooled SD of 0.40 and a significance level of 0.025 for each comparison. All analyses were conducted according to the intention-to-treat principle. For the 2

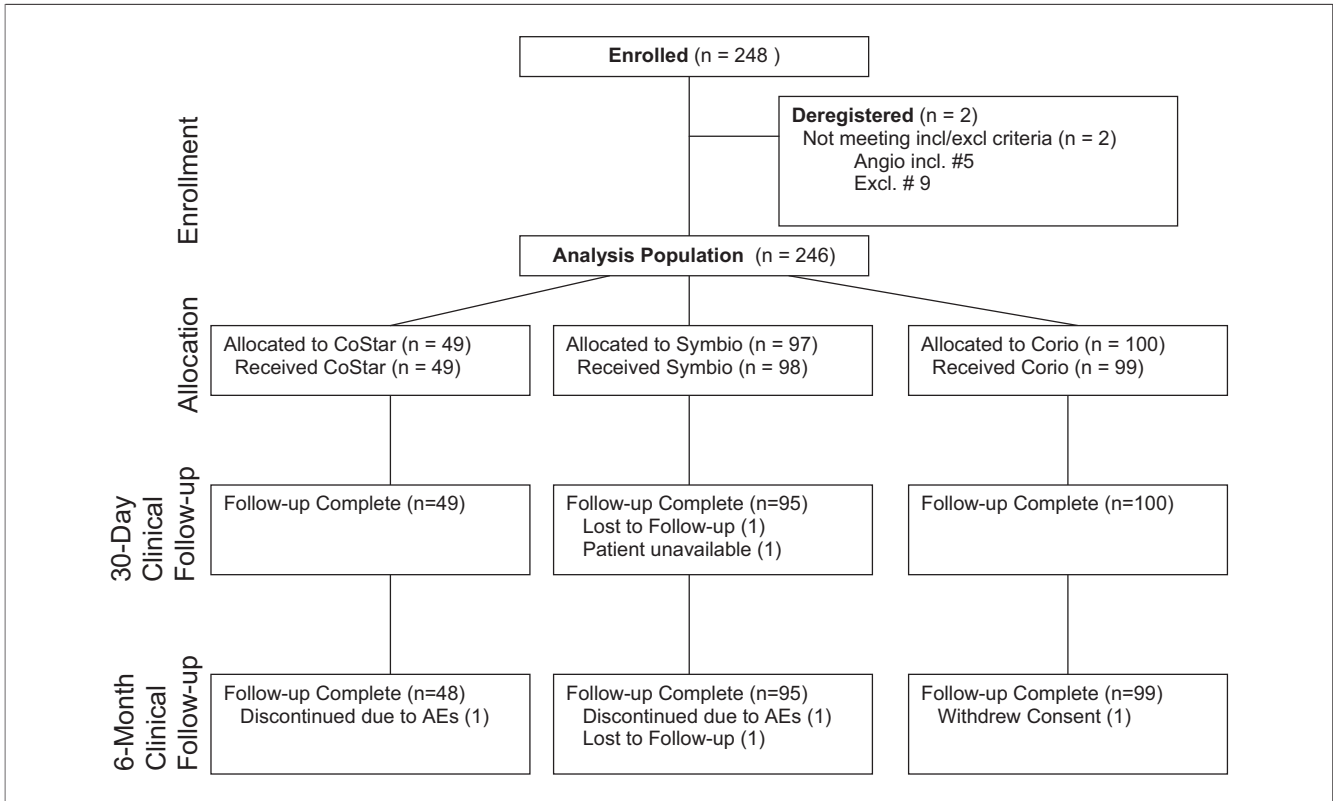

Figure 2. Flow Diagram of the GENESIS Trial

Flow diagram of subject progress through phases of the GENESIS trial. AE = adverse events.

primary comparisons, a 1-sided p value of <0.025 was considered significant. Analysis of variance tests and chi-square tests were employed, respectively, for continuous and categorical variables, to compare differences between the 3 study arms. A 2-sided p value <0.05 was considered significant for all tests. Continuous data are expressed as mean ± SD, whereas dichotomous data are summarized as frequencies for all other secondary comparisons. Due to incomplete patient enrollment, statistical analyses were restricted to the primary end point of in-stent late loss and to the predefined QCA, IVUS, and clinical secondary end points.

Results

The study was prematurely interrupted in April 2007, after 246 patients had been enrolled. This decision—made by the study principal investigators in consultation with the study sponsor, Conor Medsystems, and with concurrence of the data safety monitoring board—followed notification by the manufacturer of pimecrolimus, Novartis Corporation (Basel, Switzerland), of the preliminary results from an Avantec-sponsored (Sunnyvale, California) First-in-Man study evaluating the safety and efficacy of the Avantec pimecrolimus-eluting stent. Subsequently, the COSTAR II trial, also using the CoStar PES, failed to demonstrate noninferiority for the MACE primary end point when compared with the Taxus PES (Boston Scientific) (2). Commercial sale of the CoStar PES was then discontinued in the markets where it was already available. The investigators and the sponsor decided to analyze the data available on all enrolled patients at the time of trial suspension.

Study population, procedural and in-hospital outcomes. Among the 246 patients enrolled, 49 were randomized to CoStar, 97 to SymBio, and 100 to Corio (1 patient in the Corio Group received a Symbio stent) (Fig. 2). Baseline clinical characteristics of the patients as well as the angiographic and procedural characteristics of the lesions treated are shown in Table 1. No deaths occurred during the hospital stay. The rate of periprocedural MI was 5% in the Corio group versus 0% in the other 2 groups. Of the 5 periprocedural MIs, 4 were creatine kinase elevations alone without clinical sequelae, thought to be due to the procedure and not attributed to the stent. The fifth was an unsuccessful direct stenting, followed by predilation and successful stent placement complicated by a distal dissection that was unsuccessfully treated with 2 additional stents resulting in no flow.

Table 1. Baseline Clinical and Procedural Characteristics of the Patients and the Lesions in the 2 Groups

	CoStar (n = 49)	SymBio (n = 97)	Corio (n = 100)	p Value
Age (yrs)	64.4 ± 9.6	59.9 ± 10.1	64.1 ± 10.0	
Male sex	35 (71.4%)	76 (78.4%)	80 (80%)	
Diabetes mellitus	18 (36.7%)	17 (17.5%)	32 (32%)	
Insulin dependent	3/18 (16.7%)	2/17 (11.8%)	15/32 (46.9%)	
Hypertension	36 (73.5%)	65 (67%)	66 (66%)	
Hypercholesterolemia	36 (73.5%)	69 (71.1%)	82 (82%)	
Current smoker	8 (16.3%)	35 (36%)	20 (20%)	
Prior myocardial infarction	11 (22.5%)	29 (29.9%)	26 (26%)	
Prior percutaneous intervention	13 (26.5%)	28 (28.9%)	33 (33%)	
Prior bypass surgery	3 (6.1%)	0	2 (2%)	
Unstable angina	10 (20.4%)	34 (35%)	25 (25%)	
Ejection fraction (%)	61.8 ± 8.9	63.7 ± 12.5	63.7 ± 12.1	
Glycoprotein IIb/IIIa inhibitors	1 (2%)	5 (5.2%)	6 (6%)	
Target vessel				
Left anterior descending	20 (40.8%)	50 (51.5%)	49 (49%)	
Circumflex	12 (24.5%)	17 (17.8%)	24 (24%)	
Right coronary artery	17 (34.7%)	30 (30.7%)	27 (27%)	
ACC/AHA lesion type				
A	9 (18.4%)	22 (22.7%)	30 (30%)	
B1	14 (28.6%)	31 (31.9%)	31 (31%)	
B2	23 (46.9%)	29 (29.9%)	35 (35%)	
C	3 (6.1%)	15 (15.5%)	4 (4%)	
Direct stenting	29 (59.2%)	55 (56.7%)	53 (53%)	
After dilation	13 (26.5%)	34 (35%)	30 (30%)	
Max inflation pressure (atm)	14.2 ± 2.5	13.6 ± 2.6	13.9 ± 2.5	
Number of stents/lesion	1.04 ± 0.20	1.12 ± 0.41	1.12 ± 0.41	
1	47 (95.9%)	88 (90.7%)	91 (91%)	
2	2 (4.1%)	6 (6.2%)	6 (6%)	
3	0	3 (3.1%)	3 (3)	
Stent diameter used (mm)	(n = 51)	(n = 109)	(n = 112)	
2.5	10 (19.6%)	19 (17.4%)	25 (22.3%)	
3.0	24 (47.1%)	47 (43.1%)	62 (55.4%)	
3.5	17 (33.3%)	43 (39.5%)	25 (22.3%)	
Stent length used (mm)	(n = 51)	(n = 109)	(n = 112)	
10	9 (17.6%)	17 (15.6%)	15 (13.4%)	
16	24 (47.1%)	57 (52.3%)	64 (57.2%)	
22	12 (23.5%)	25 (22.9%)	24 (21.4%)	
28	6 (11.8%)	10 (9.2%)	9 (8.0%)	
Device success*	48 (98%)	95 (97.9%)	92 (92%)	0.11
Lesion success*	49 (100%)	97 (100%)	98 (98%)	0.68
Procedural success*	49 (100%)	97 (100%)	94 (94%)	0.02

Data are presented as n (%) or mean ± SD, unless otherwise specified. *Device success was not achieved when the post-procedural residual stenosis was >50% (n = 1), there was a device-related AE (n = 4), the device failed or malfunctioned (n = 2), or the treatment of the lesion was not completed with the assigned device only (n = 2) or any combination of the preceding (n = 2). Lesion Success was not achieved if the post-procedure residual stenosis was >50% (n = 2). Procedure Success was not achieved if lesion success was not achieved (n = 1) or the patient experienced a periprocedural major adverse cardiac event (n = 4) or both (n = 1).

ACC/AHA = American College of Cardiology/American Heart Association.

QCA and IVUS outcomes. In the Symbio group, 1 patient was lost to follow-up. At 6 months, 7 CoStar patients (14.3%), 2 SymBio patients (2.1%), and 7 Corio patients (7%) did not receive angiographic follow-up. Angiographic data are presented in Table 2. In-stent late loss was progressively and significantly higher with SymBio (0.96 ± 0.73 mm) and Corio (1.40 ± 0.67 mm) versus CoStar (0.58 ± 0.58 mm). On average, in-stent late loss of SymBio and of Corio was, respectively, 0.38 ± 0.13 mm and 0.82 ± 0.12 mm higher than CoStar ($p < 0.001$ for both). Thus, the

Table 2. Quantitative Coronary Angiography Analysis of the Lesions Treated in the 3 Groups

	CoStar	SymBio	Corio	p Value
Before procedure	(n = 49)	(n = 97)	(n = 100)	
Reference vessel diameter (mm)	2.81 ± 0.47	2.87 ± 0.50	2.79 ± 0.45	
Minimal luminal diameter (mm)	0.72 ± 0.31	0.78 ± 0.37	0.76 ± 0.38	
Diameter stenosis (%)	74 ± 11	72 ± 13	73 ± 12	
Lesion length (mm)	14.4 ± 6	13.8 ± 5.4	14.9 ± 5.5	
After procedure	(n = 49)	(n = 97)	(n = 100)	
In-segment				
Minimal luminal diameter (mm)	2.41 ± 0.49	2.41 ± 0.45	2.33 ± 0.47	
Diameter stenosis (%)	16 ± 7	17 ± 8	18 ± 12	
Acute gain (mm)	1.69 ± 0.52	1.63 ± 0.46	1.57 ± 0.50	
Proximal edge				
Minimal luminal diameter (mm)	2.76 ± 0.53	2.83 ± 0.50	2.82 ± 0.52	
Diameter stenosis (%)	12 ± 8	12 ± 9	11 ± 8	
In-stent				
Minimal luminal diameter (mm)	2.82 ± 0.42	2.83 ± 0.39	2.81 ± 0.38	
Diameter stenosis (%)	5 ± 6	7 ± 6	6 ± 5	
Acute gain (mm)	2.10 ± 0.49	2.05 ± 0.46	2.04 ± 0.43	
Distal edge				
Minimal luminal diameter (mm)	2.53 ± 0.57	2.54 ± 0.53	2.47 ± 0.50	
Diameter stenosis (%)	10 ± 7	11 ± 9	12 ± 7	
Follow-up	(n = 42)	(n = 95)	(n = 93)	
In-segment				
Minimal luminal diameter (mm)	2.01 ± 0.61	1.71 ± 0.68	1.30 ± 0.68	<0.001
Diameter stenosis (%)	29 ± 16	40 ± 21	54 ± 22	
Proximal edge				
Minimal luminal diameter (mm)	2.59 ± 0.56	2.51 ± 0.71	2.39 ± 0.74	
Diameter stenosis (%)	11 ± 12	14 ± 18	15 ± 21	
In-stent				
Minimal luminal diameter (mm)	2.27 ± 0.64	1.89 ± 0.81	1.41 ± 0.75	<0.001
Diameter stenosis (%)	19 ± 19	33 ± 25	47 ± 25	
Distal edge				
Minimal luminal diameter (mm)	2.34 ± 0.60	2.29 ± 0.61	2.03 ± 0.75	
Diameter stenosis (%)	13 ± 10	13 ± 16	19 ± 23	
Late loss (mm)				
In-segment	0.42 ± 0.48	0.69 ± 0.58	1.07 ± 0.59	<0.001
In-stent	0.58 ± 0.58	0.96 ± 0.73	1.40 ± 0.67	<0.001
Binary angiographic restenosis				
In-stent	3 (7.1%)	19 (20%)	38 (40.9%)	<0.001
In-segment	4 (9.5%)	21 (22.1%)	42 (45.2%)	<0.001

Data are presented as mean ± SD or n (%).

primary end point of the study, noninferiority of SymBio or Corio in-stent late loss versus CoStar, was not met.

In-segment late loss and binary in-stent and -segment restenosis rates were also progressively higher with SymBio and Corio as compared with CoStar. Among the 4 CoStar in-segment restenoses, 3 were focal (75%) and 1 was diffuse (25%). Among the 21 SymBio restenoses, 10 were focal (48%), 7 were diffuse (33%), 3 were proliferative (14%), and 1 was occlusive (5%). Among the 42 Corio restenoses, 11 were focal (26%), 19 were diffuse (46%), 9 were proliferative (21%), and 3 were occlusive (7%).

The IVUS results, presented in Table 3 and representing a subset of enrolled patients, substantially confirm the QCA data of the complete cohort.

30-day and 6-month clinical outcomes. Clinical events are presented in Table 4. Between the end of the hospital stay and the first month after treatment, 1 additional MI, caused by early stent thrombosis and treated with percutaneous revascularization, was recorded in the Corio group. At 6 months, no cardiac deaths occurred, whereas 1 MI in the SymBio group (caused by late stent thrombosis, and treated with percutaneous revascularization) and 2 addi-

Table 3. Intravascular Ultrasound Analysis of the Lesions Treated in the 3 IVUS Subgroups

	CoStar	SymBio	Corio	p Value
After procedure	(n = 29 analyzed = 14)	(n = 36 analyzed = 24)	(n = 32 analyzed = 17)	
Target segment length (mm)	20.1 ± 4.8	21.3 ± 8.7	20.4 ± 9.3	
Vessel volume (mm^3)	252.1 ± 109.4	281.6 ± 93.9	320.4 ± 139.1	
Stent volume (mm^3)	126.8 ± 42.9	145.5 ± 57.6	150.7 ± 77.8	
Lumen volume (mm^3)	125.6 ± 41.9	144.7 ± 57.6	149.9 ± 77.5	
Incomplete stent apposition	4/24 (16.7%)	8/27 (29.6%)	6/26 (23.1%)	
Follow-up	(n = 29 analyzed = 16)	(n = 36 analyzed = 26)	(n = 32 analyzed = 16)	
Target segment length (mm)	20.8 ± 5.4	21.0 ± 8.3	22.1 ± 9.3	
Vessel volume (mm^3)	319.3 ± 144.7	293.6 ± 100.8	330.3 ± 150.3	
Stent volume (mm^3)	149.6 ± 66.5	139.5 ± 55.6	161.4 ± 85.4	
Lumen volume (mm^3)	122.0 ± 50.5	100 ± 39.9	98.8 ± 62.3	
Neointimal volume (mm^3)	27.6 ± 26.6	39.5 ± 24.7	62.6 ± 29.4	
Percent volume obstruction (%)	16.6 ± 12	27.1 ± 12.4	41.2 ± 11.5	<0.001
Incomplete stent apposition	3/20 (15%)	5/28 (17.8%)	2/20 (10%)	0.91
Late acquired	0	0	0	
Persistent	3/20 (15.0%)	5/28 (17.8%)	2/20 (10.0%)	

Data are presented as mean ± SD or n (%).

tional MIs in the Corio group (both periprocedural during TVR) were recorded. According to the angiographic results, also the rates of TLR and TVR were progressively reduced by CoStar versus SymBio versus Corio, as was the cumulative MACE rate.

Discussion

Given the negative outcome of the CoStar II trial in which the CoStar paclitaxel-eluting stent was shown to be inferior to the Taxus-Liberte stent, one might question whether failure of the Conor reservoir technology is an explanation for the results in this trial. The data in this trial do not support this explanation, because the angiographic and clinical outcomes in the CoStar arm in this study are similar to those reported in the trials that led to CE Mark approval and are markedly better than historical data on bare metal stent outcomes in a similar cohort of patients. In fact, outcomes on the CoStar II trial were attributed to elution of paclitaxel, a drug with a narrow therapeutic index, at the lower end of the release kinetic specification in the CoStar stents used in this trial versus previous trials that, although within allowable specifications, were inadequate for the more complex 2-vessel disease patients studied in that trial. This conclusion was supported by a post hoc analysis demonstrating that noninferiority was met in patients with only single lesions in this trial (14). Additional evidence that the reservoir technology successfully delivered drug is the observation of clinical outcomes in the pimecrolimus arm that were worse than expected compared with historical bare metal stent data. Thus, there seem to be 3 main findings of this study comparing different drugs as eluted from the Conor reservoir-based stent: 1) pimecrolimus is not effective as an antirestenotic agent; 2) paclitaxel demonstrates activity as an antirestenotic agent; and 3) dual drug delivery with independent release kinetic and profile, using the Conor reservoir-based stent, is feasible.

Table 4. 30-Day and 6-Month Clinical Events in the 3 Groups

	CoStar (n = 49)	SymBio (n = 97)	Corio (n = 100)	p Value
30-day				
Death	0	0	0	
Myocardial infarction	0	0	6 (6%)	
Target vessel revascularization	0	0	1 (1%)	
Major adverse cardiac events	0	0	6 (6%)	0.02
Stent thrombosis	0	0	1 (1%)	
6-month				
Death	1 (2%)	0	0	
Cardiac death	0	0	0	
Myocardial infarction	0	1 (1%)	8 (8%)	
Target lesion revascularization	1 (2%)	14 (14.4%)	32 (32%)	<0.001
Target vessel revascularization	1 (2%)	14 (14.4%)	35 (35%)	
Major adverse cardiac events	1 (2%)	14 (14.4%)	39 (39%)	<0.001
Stent thrombosis	0	1 (1%)	1 (1%)	

Data are presented as n (%).

The unexpected outcome of this study was that the GENESIS trial failed to show a significant angiographic or clinical benefit of pimecrolimus. Although underpowered and not designed to assess clinical end points, the GENESIS trial outcomes suggest that in humans the drug might exacerbate the restenotic response, thus leading to results worse than those observed with bare metal stents. Indeed in the GENESIS trial, stents eluting only pimecrolimus

showed the worst late loss, which compares unfavorably with the late loss reported in published reports for bare-metal stents in similar lesions and patients.

Pimecrolimus has been approved as topical treatment for inflammatory dermatologic diseases. Despite its "limus" name, it is not a rapamycin analogue. It is best classified as a tacrolimus analogue that exerts multiple anti-inflammatory effects, including inhibition of interleukin-2 synthesis via calcineurin inhibition and inhibition of interleukin-4, interferon-γ, and the release of inflammatory cytokines from mast cells. In contrast to other "limus" drugs, such as sirolimus, it does not bind to the mammalian target of rapamycin. Thus, it does not specifically exert antiproliferative actions, having no direct effect on cell cycle regulation. However, it has been assumed that it might do so indirectly by interleukin-2 inhibition. Several animal studies strongly suggested that it would be clinically effective in humans as an antirestenotic molecule when applied locally to atherosclerotic plaques treated with stent implantation (15,16).

However, the suggestions of clinical efficacy from the animal data were not confirmed by this current human study. The reasons for this failure are currently unknown. However, several explanations can be hypothesized. First, discrepancies in results between animal experiments and human trials are well known. The porcine model for the pathologic reaction to stent implantation is best-suited for determination of safety. Relative human efficacy is less predictable in this model and can only be definitely ascertained in clinical trials (17). Moreover, it is possible that, whereas inflammation can play an important role in neointimal proliferation in porcine stent models, the inflammatory response to stent implantation as affected by this drug might play a minor if not insignificant role as a determinant of the restenotic process in humans. Because pimecrolimus has no antiproliferative properties but mainly antiinflammatory and immunosuppressant actions, its lack of efficacy would tend to undermine the role of inflammation as central in the restenotic process in humans. Indeed, other drug-eluting stents aimed at inhibiting the inflammatory and immune reaction to stent implantation, such as stents eluting dexamethasone, failed to show benefits when compared with traditional bare-metal stents (18–20).

Despite market withdrawal, the CoStar PES provided encouraging results in this study, confirming the positive outcomes of previous trials, where this stent showed the lowest late loss among currently available PES (21,22) and superiority to the respective bare-metal stent (1). The outcomes of patients treated with CoStar in the GENESIS trial are similar to those reported in the COSTAR II trial, where examination of the outcomes suggested that the release of paclitaxel—a drug with a narrow therapeutic index—was insufficient for the more complex lesions and patients enrolled in the COSTAR II study (14).

The CoStar PES differs from other available drug-eluting stents, because it has the drug—mixed with a bioresorbable polymer—loaded in reservoirs cut into the stent rather than having the drug and the polymer on the surface of the stent. This property reduces the exposure of the vessel wall to the polymer and results in an inert bare-metal stent, after the elution of the drug and the dissolution of the polymer. Moreover, these technological advancements of the Conor stent platform—with its laser cut reservoirs and its bioresorbable polymer, which also allow controlled release of drugs—open the road to further investigations with different drugs loaded in the reservoirs and with specific release patterns, tailored to the different mechanisms involved in the pathophysiologic reaction to stent implantation. The GENESIS trial is the first trial to use the Conor reservoir technology to enable dual drug delivery for the treatment of coronary lesions. This trial has indeed demonstrated the ability to deliver 2 drugs independently, with each drug having a different effect on the tissue response to coronary intervention. The theoretical advantages of the delivery of more than 1 drug include the ability to release multiple agents that synergistically work on different mechanistic pathways to inhibit neointimal growth or produce other biologic effects. Other drugs of interest also include antithrombotic agents or pharmacological therapies that can inhibit reperfusion injury during acute MI.

Study limitations. The major limitation of this study was the early termination of enrollment. Thus, the study is underpowered for its primary angiographic end point. All analyses are post-hoc in nature: descriptive statistics only are presented for the primary and secondary end points, and no statistical analysis on differences in clinical end points (which the trial was not originally powered for) can be made. Moreover, the external validity of the trial is limited by the specific inclusion and exclusion criteria, thus limiting the applicability of the findings to the enrolled cohort of patients with selected lesions.

Conclusions

In native coronary artery lesions, stents eluting pimecrolimus or the dual combination of pimecrolimus and paclitaxel failed to show angiographic noninferiority when compared with paclitaxel-eluting stents.

Acknowledgments

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Key Words: coronary artery disease ■ paclitaxel-eluting stent ■ pimecrolimus-eluting stent ■ restenosis.