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Experimental Efficacy of an Everolimus Eluting Cobalt Chromium Stent

Andrew J. Carter,[1]* DO, Anastasia Brodeur,[1] Robin Collingwood,[1] Sarah Ross,[1] Lori Gibson,[1] DVM, Chi-An Wang,[2] Scott Haller,[1] MS, Leslie Coleman,[2] DVM, and Renu Virmani,[3] MD

Introduction: Rapamycin and its analogs are now being coated on different stent platforms, using different polymer matrices to prevent restenosis by impairing vascular smooth muscle cell proliferation and neointimal formation. Methods: We evaluated the feasibility and compared the efficacy of biostable polymeric everolimus and sirolimus (CYPHER®, Cordis) eluting stents in a porcine coronary model. Cobalt chromium balloon expandable stents (ML VISION®, Guidant) were coated with a polymer containing everolimus (190 μg/cm^2). Twelve pigs underwent placement of 36 oversized sirolimus (n = 12), everolimus (n = 12), and bare metal (cobalt chromium, n = 12) stents in the coronary arteries. Results: At day 28, vessel injury scores were low (<0.25) and similar between each of the three test groups. The mean neointimal thickness was significantly lower in the everolimus- (0.13 ± 0.07 mm, P = 0.02) and sirolimus-eluting stents (0.13 ± 0.08 mm, P = 0.04) versus the bare metal stents (0.20 ± 0.07 mm). The mean percent area stenosis was similar for the everolimus-eluting stents [(20.8 ± 6.9)%] and the sirolimus-eluting stents [(20.8 ± 7.6)%], and each was significantly less than that of bare metal stents [(26.1 ± 7.8)%, P = 0.05]. Conclusion: Stent-based delivery of sirolimus and everolimus delivered via durable polymeric matrices are equally effective in the suppression of neointimal formation at day 28 in the porcine coronary model. Further study is necessary to document dose response and long-term comparative effects of these drug-eluting stents. © 2006 Wiley-Liss, Inc.

Key words: everolimus; stents; restenosis

INTRODUCTION

Drug-eluting stents have emerged as the most effective strategy for the prevention of restenosis. Stent based-delivery of potent cell cycle inhibitors, paclitaxel (TAXUS®, Boston Scientific) and sirolimus (CYPHER®, Cordis) significantly reduced the probability for restenosis in comparison with bare metal stents [1–4]. These combined drug and device therapies, presently used in more than 80% of PCI at our institution, have transformed the practice of interventional cardiology. The introduction of drug-eluting stents has also identified the need for device refinement to improve stent and drug delivery so as to treat more complex coronary lesions and further improve clinical outcomes.

Preliminary results from a multicenter randomized comparison of these first generation polymeric sirolimus-eluting and paclitaxel-eluting stents revealed a similar level of acute procedural success (~95%) in patients with focal native coronary arterial lesions [5]. The primary determinant of acute procedural success was the ability to deliver a CYPHER or TAXUS stent to the target lesion. The first generation drug-eluting stents have tubular stainless steel geometries with strut thickness greater than 0.005 in. Metallic stents manufactured from other alloys, such as cobalt chromium, have theoretical advantages of maintaining functional properties of the stent, compressive resistance and radiopacity, with similar geometries as stainless steel designs but with a lower strut profile (0.003 in) [6]. The physical characteristics of cobalt alloys enable the design of

[1]Medical Device Research Laboratory, Borgess Medical Center, Kalamazoo, Michigan
[2]Guidant Corporation, Santa Clara, California
[3]CV Path, Gaithersburg, Maryland

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*Correspondence to: Andrew J. Carter, Medical Device Research Laboratory, Borgess Medical Center, Kalamazoo, MI 49048.
E-mail: andrewcarter@borgess.com

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low-profile stent and delivery systems with longitudinal flexibility to potentially facilitate access to coronary lesions in complex and tortuous anatomy.

Everolimus is an immunosuppressive macrolide bearing a stable 2-hydroxyethyl chain substitution at position 40 on the sirolimus (rapamycin) structure. Everolimus, which has greater polarity than sirolimus, was developed in an attempt to improve the oral bioavailability of sirolimus [7]. Everolimus has a mechanism of action similar to that of sirolimus [7,8]. Everolimus, like sirolimus, is a cytostatic inhibitor of cellular proliferation in the late G1 phase of the cell cycle via effects on cyclin-dependent kinases and inactivation of mTOR (molecular Target of Rapamaycin). Everolimus binds the intracellular receptor FKBP-12 (FK506-binding protein 12) and forms a complex with mTOR to inhibit its activation. In vitro, everolimus and sirolimus demonstrate equipotent inhibition of smooth muscle cell proliferation at subnanomolar concentrations following stimulation with fetal calf serum [9]. Farb et al. demonstrated dose-dependent inhibition of neointimal formation with oral administration of everolimus in a rabbit iliac stent model [10]. The purpose of the present study was to determine the feasibility and efficacy of a polymeric everolimus-eluting cobalt chromium stent. The histological endpoints for the everolimus-eluting stents were compared with bare metal cobalt chromium and a polymeric sirolimus-eluting stent.

METHODS

The experimental protocol was approved by the Institutional Animal Care and Use Committee and conformed to the guidelines of the American Heart Association for experimental research. Cobalt chromium balloon expandable tubular 3.0-mm diameter and 12-mm long stents (ML VISION®, Guidant, Santa Clara, CA) were coated with a thin layer of a nonerodable copolymer (polyvinylidine fluoride and hexafluoropropylene) containing everolimus (190 μg/cm^2, 40-*O*-(2-hydroxyethyl)-rapamycin, Novartis, Basel, Switzerland; Fig. 1). The drug load for everolimus was selected to achieve a similar quantity of compound per unit surface area of stent as a sirolimus-eluting stent [11]. Pharmacokinetic studies demonstrated ~80% drug release at day 28. Commercially available stainless steel balloon expandable 3.0-mm diameter and 13-mm long stents coated with a co-polymer containing sirolimus (~140 μg/cm^2; CYPHER®, Cordis, Johnson and Johnson, Warren, NJ) were used as positive controls for comparison with everolimus-eluting stents [11].

The stents were randomly implanted into the right, left anterior descending, or left circumflex coronary artery of 12 juvenile farm swine (35–50 kg), following premedication with aspirin 650 mg, clopidogrel 150 mg, and nifedepine extended release 30 mg by mouth at least 12 hr prior to the procedure. The guide catheter was used as a visual reference to obtain 10–20% oversizing as compared with baseline vessel diameter. Stents were implanted using one balloon inflation (9–16 atm) for ~30 sec. Coronary angiography was then completed to document the placement of the stents. Animals were allowed to recover and returned to care facilities where they received a normal diet, aspirin 81 mg and clopidogrel 75 mg daily for the duration of the study. After 28 days, following coronary angiography, the animals were killed, hearts were harvested, and coronary arteries were perfused at 100 mm Hg via the aortic stump, with lactated Ringer's solution followed by 10% neutral buffered formalin for histological sections to determine treatment effect.

Quantitative Coronary Angiography Analysis

Coronary angiograms at baseline, after stent deployment and at day 28, were saved to a CD-ROM disk in a standard DICOM format. The angiograms were analyzed on a PC-based quantitative coronary angiography (QCA) analysis software program (QCA-CMS®, MEDIS medical imaging systems, The Netherlands). The guiding catheter served as a reference for calibration for all measurements. Measurements included mean baseline vessel diameter, balloon inflated diameter, poststent minimal lumen diameter, and the reference vessel diameter at day 28, minimal lumen diameter, and percent diameter stenosis. The balloon to artery ratio was calculated as the mean balloon inflated diameter/mean baseline vessel diameter. The percent diameter stenosis was calculated as: $100 \times [1 - (\text{minimal lumen diameter/reference vessel diameter})]$.

Histology

A single independent observer completed all histopathologic analyses. According to published methods, stented coronary artery segments were processed for plastic embedding, staining, and histomorphometric analysis of three sections (proximal, mid, distal) to evaluate the neointimal response and the presence of inflammation, granulomas, percent fibrin deposition, degree of luminal endothelialization, and vessel wall injury [12–14]. Vessel wall injury scores were calculated according to a modified method of Schwartz, in which the median injury score was identified in each section and for the stent [12]. Percent fibrin was determined as the percentage of stent struts in the cross section with residual fibrin deposition in the neointima. Percent endo-

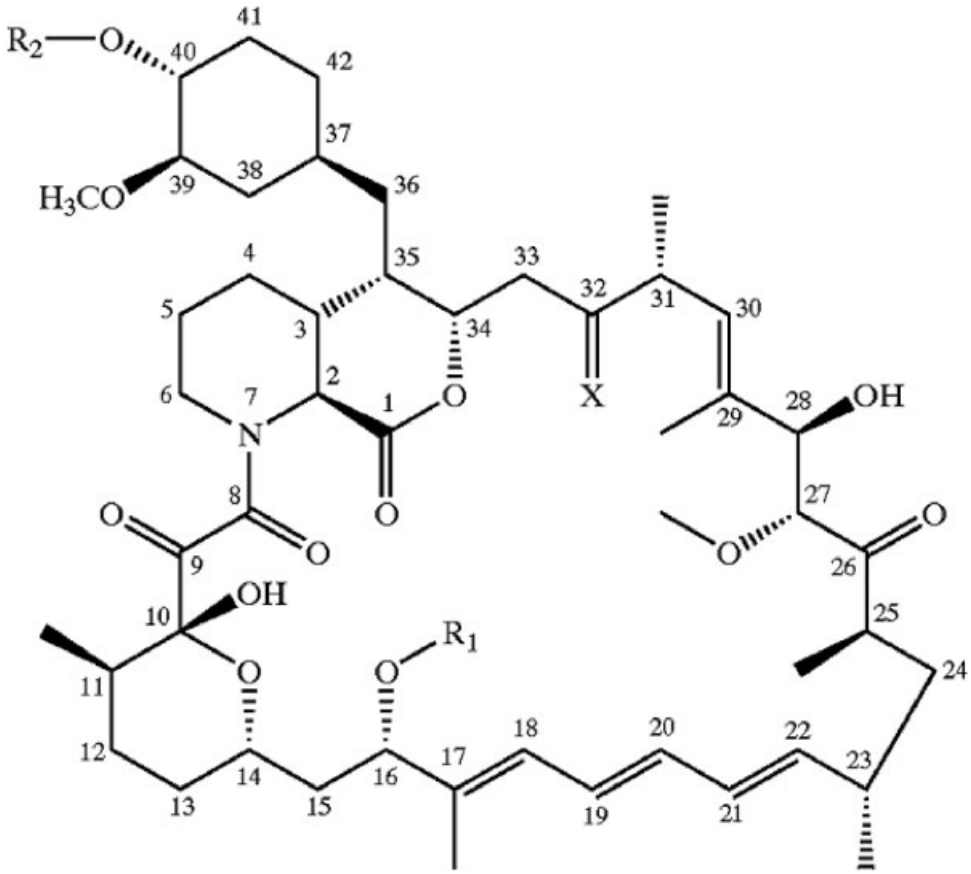

Fig. 1. This diagram depicts the chemical structure of the macrocylic lactone everolimus (MW 958.25). R_2 denotes the location of a hydroxyethyl chain at position number 40.

thelium was defined as the percentage of the lumen circumference covered by endothelial cells. Vessel morphometry was completed with a digital software program (IP Lab v3.2.4, Scanalytics, Fairfax, VA).

Statistical Analysis

The morphometric measurements from each of the 3-stent sections were summed and divided by 3 to generate the mean value for each parameter within the stent. For continuous variables, such as morphometric parameters, the mean differences between treatment groups were tested with ANOVA. For morphologic parameters, scores were assigned to each of the three sections within the stented segment, and the median value was used as the score for the stent. The data were ranked within each cohort and stratified. An ANOVA was performed on these ranks. Categorical data were compared with chi-square analysis. Data are expressed as mean ± SD unless otherwise stated. All statistical analyses were performed with SAS® system software.

RESULTS

Quantitative Coronary Angiography

The QCA measurements at implant and at day 28 for each group are summarized in Table I. There were no significant differences in implant parameters between either drug-coated or bare metal groups. At day 28, all vessels remained patent and free from intraluminal filling defect, aneurysm formation, or side-branch occlusion. There was a trend toward reduction in the percent diameter stenosis for both the everolimus-[(4.32 ± 5.66)%] and the sirolimus-eluting stents [(5.52 ± 12.64)%] versus the bare metal control [(11.34 ± 7.25)%] (Table I).

Histology and Morphometric Analysis

The histomorphometry for the bare metal, everolimus, and sirolimus stents is summarized in Table II. Vessel injury scores were low (<0.25) and were not significantly different between each of the three groups. The mean neointimal thickness was significantly lower in the everolimus- (0.13 ± 0.07 mm, $P = 0.02$) and

TABLE I. Summary of Quantitative Coronary Angiography for Bare Metal Cobalt Chromium, Everolimus-Eluting, and Sirolimus-Eluting Stents at Implant and 28 Days After Placement in Normal Porcine Coronary Arteries

	At implant			After 28 days				
Group	Baseline diameter (mm)	Balloon diameter (mm)	Balloon: artery ratio	Reference diameter (mm)	Minimal lumen diameter (mm)	% Diameter stenosis	*P* value[a] vs. control	*P* value[a] vs. sirolimus
Cobalt Chromium ($n = 12$)	2.76 ± 0.24	3.29 ± 0.22	1.20 ± 0.09	2.87 ± 0.45	2.56 ± 0.54	11.3 ± 7.3		
Everolimus ($n = 12$)	2.70 ± 0.21	3.18 ± 0.19	1.18 ± 0.08	2.74 ± 0.35	2.62 ± 0.37	4.3 ± 5.7	0.067	0.747
Sirolimus ($n = 12$)	2.73 ± 0.20	3.20 ± 0.15	1.17 ± 0.07	2.76 ± 0.34	2.60 ± 0.43	5.5 ± 12.6	0.124	

Data are expressed as mean ± standard deviation.
[a]*P* value for comparison of angiographic percent diameter stenosis.

TABLE II. Summary of Histomorphometry Data for Bare Metal Cobalt Chromium, Everolimus, and Sirolimus Stents at 28 Days After Placement in Normal Porcine Coronary Arteries

Group	EEL area (mm^2)	IEL area (mm^2)	Lumen area (mm^2)	Medial area (mm^2)	Neointimal area (mm^2)	% Area stenosis	Neointimal thickness (mm)	Injury score
Cobalt Chromium ($n = 12$)	7.75 ± 0.93	6.28 ± 0.72	4.61 ± 0.85	1.48 ± 0.26	1.67 ± 0.45	26.9 ± 7.8	0.20 ± 0.07	0.18 ± 0.25
Everolimus ($n = 12$)	7.34 ± 0.64	6.09 ± 0.53	4.83 ± 0.66	1.24 ± 0.15	1.26 ± 0.43*	20.8 ± 6.9†	0.13 ± 0.07†	0.08 ± 0.11
Sirolimus ($n = 12$)	8.22 ± 0.83	6.80 ± 0.69	5.41 ± 0.90	1.42 ± 0.22	1.40 ± 0.48	20.8 ± 7.6†	0.13 ± 0.08†	0.15 ± 0.25

Data are expressed as mean ± standard deviation.
*$P = 0.03$ for everolimus versus cobalt chromium.
†$P \leq 0.04$ for everolimus or sirolimus versus cobalt chromium.

sirolimus-eluting stents (0.13 ± 0.08 mm, $P = 0.04$) versus the bare metal stents (0.20 ± 0.07 mm; Fig. 2). The mean percent area stenosis was similar for the everolimus-eluting stents [(20.8 ± 6.9)%] and the sirolimus-eluting stents [(20.8 ± 7.6)%], and each was significantly less than bare metal stents [(26.1 ± 7.8)%, $P = 0.05$].

Light microscopy documented less neointimal formation for everolimus and sirolimus stents versus bare metal stents (Fig. 3). The neointima of the everolimus- and sirolimus-eluting stents consisted of smooth muscle cells and matrix proteoglycans, with regions of residual fibrin deposition adjacent to the stent struts. The percentage of stent struts with residual fibrin deposition was significantly greater in the everolimus and sirolimus treatment groups (~45%) versus bare metal group (12.8%, $P < 0.0001$; Table III). Strut-associated inflammation scores and the percentage of struts with granulomas were similar for the cobalt chromium, everolimus-eluting, and sirolimus-eluting stents. All sections demonstrated nearly complete endothelialization of the luminal surface by light microscopy at day 28.

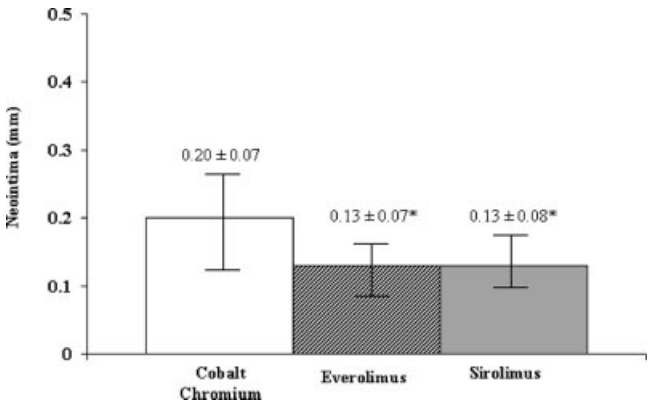

Fig. 2. Bar graph depicts the mean neointimal thickness of cobalt chromium, everolimus- and sirolimus-eluting stents at day 28. *$P \leq 0.04$ for everolimus and sirolimus versus cobalt chromium.

DISCUSSION

The present study documents the feasibility and efficacy of a novel low strut profile balloon expandable polymeric everolimus-eluting stent in a porcine coronary model. Histological observations demonstrated a similar morphological appearance and equivalent suppression of neointimal formation for the polymeric everolimus-eluting stent as compared with a polymeric sirolimus-eluting stent. In this naive porcine coronary artery model of oversized stent placement, histomorphometry demonstrated a similar reduction (~35%) of neointima for the everolimus-eluting stents as compared with that for the sirolimus-eluting stents at day 28. Therefore, this low strut profile polymeric slow release everolimus-eluting stent appears to be a potentially viable clinical alternative to the higher strut profile polymeric sirolimus-eluting stent for the prevention of restenosis.

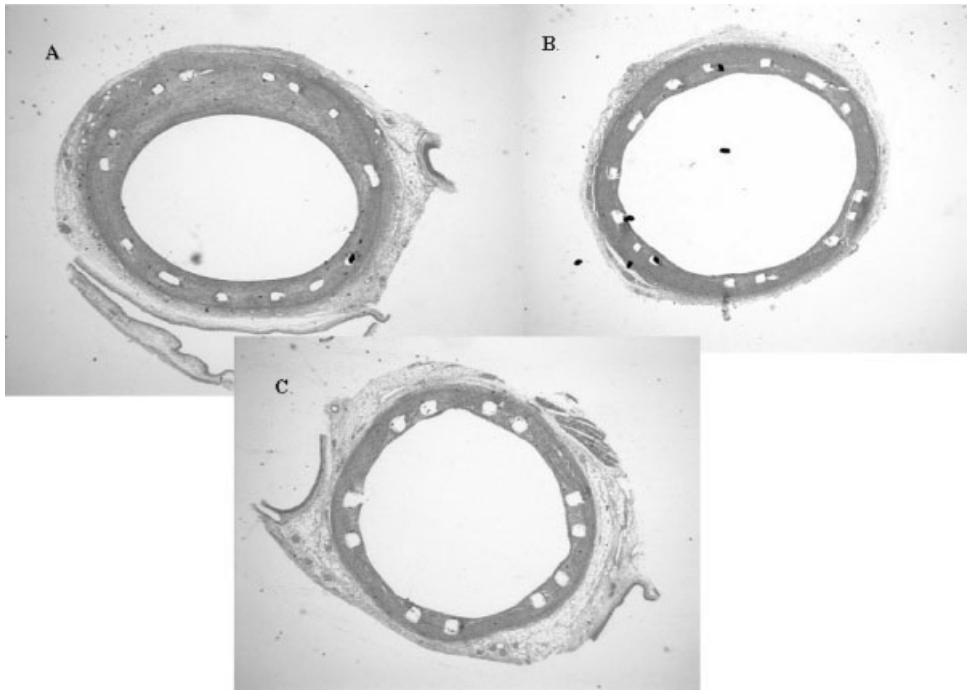

Fig. 3. Photomicrographs after oversized bare metal (A), everolimus-eluting (B), and sirolimus-eluting (C) stents in normal porcine coronary arteries at day 28. Note reduction in neointimal area for the everolimus- and sirolimus-eluting stents in comparison with bare metal cobalt chromium control (×2 magnification; H&E).

TABLE III. Summary of the Semiquantitative Histological Parameters at 28 Days After Placement of Bare Metal Cobalt Chromium, Everolimus, and Sirolimus Stents in a Porcine Coronary Model

Group	% Struts with fibrin	Fibrin score	Inflammation score	% Struts with granulomas	% Endothelialization
Cobalt chromium ($n = 12$)	5.4 ± 5.9	0.08 ± 0.15	0.89 ± 0.57	1.9 ± 6.4	100.0 ± 0.0
Everolimus ($n = 12$)	76.9 ± 31.5*	1.36 ± 0.66*	0.75 ± 0.29	0.4 ± 1.3	100.0 ± 0.0
Sirolimus ($n = 12$)	88.4 ± 7.7*	1.61 ± 0.31*	0.75 ± 0.29	0.0 ± 0.0	99.3 ± 2.1

Data are expressed as mean ± SD.
*$P < 0.0001$ for everolimus and sirolimus versus cobalt chromium.

Drug-Eluting Stent Geometry

Single institution randomized clinical trials and experimental studies suggest that stent geometry and strut thickness affect neointimal formation and restenosis [15–17]. For tubular stents, strut profile appears to correlate with greater late lumen loss and restenosis. The Intracoronary Stenting and Angiographic Results: Strut Thickness Effect on Restenosis Outcome (ISAR-STEREO-2) clinical trial randomly assigned 611 patients with symptomatic coronary artery disease to receive either a thin-strut (50 μm; Multilink®, Guidant, Santa Clara, California) or a thick-strut (140 μm; BX Velocity™, Cordis, Miami, Florida) stent. The frequency of angiographic restenosis was significantly lower in the lesions treated with thin-strut stents (17.9%) as compared with the lesions treated with thick-strut stent (31.4%) [15]. Target vessel revascularization occurred in 12.3% of the patients randomized to the thin-strut stents and 21.9% of the patients treated with the thick-strut stent. Thus, for bare metal stents some clinical evidence supports that a lower profile strut stent elicits less angiographic and clinical restenosis than a thicker-strut stent.

The effects of stent geometry and strut thickness on neointimal formation and restenosis are presently unknown for drug-eluting stents. Computational modeling suggests that stent geometry influences polymeric and nonpolymeric stent-based delivery of pharmaceutical compounds to the vessel wall [18]. Stents with open or closed cell geometries can have different patterns of vessel wall contact that may alter drug delivery and uptake in the vessel wall. Furthermore, stent design dependent perturbations of laminar patterns of blood flow generate abnormal focal or oscillatory shear stress that may alter drug uptake in the vessel wall and local pharmacody-

namics [19,20]. Thus, basic features of stent design, such as tubular geometry and strut thickness, could be important determinants of efficacy for drug-eluting stents.

Histological data from the present study demonstrated similar mean neointimal area and percent area stenosis for the thin-strut everolimus-eluting stent as compared with that for the thick-strut sirolimus-eluting stent at day 28 in the porcine coronary model. These data suggest that the biological effects of the drug, rather than the geometric features of a stent, predominates the inhibition of neointimal formation for strut-based delivery of a potent lipophilic cell-cycle inhibitor via a biocompatible polymer matrix. Further studies are necessary to confirm these observations, to determine interactions of strut thickness with stent overlap, and applicably to stent-based delivery of other compounds with different physical or biological properties.

Comparison of Clinical Studies with Everolimus- and Sirolimus-Eluting Stents

Safety, feasibility, and dose-response studies have been conducted with biodegradable and nonbiodegradable polymeric everolimus-eluting stents. The First Use To Underscore restenosis Reduction with Everolimus (FUTURE) I trial was a phase I prospective, single-blind, randomized clinical trial designed to evaluate the safety and efficacy of poly-L-lactide everolimus-eluting stents (197 $\mu g/mm^2$, 70% drug elution at 30 days) compared with stainless steel stents [21]. Forty-two patients with focal *de novo* native coronary lesions were randomized to everolimus ($n = 27$) or bare metal stents ($n = 15$). The frequency of binary angiographic in-stent restenosis was 0% versus 9.1%, with an associated late lumen loss of 0.11 mm versus 0.85 mm for everolimus and bare metal stent groups, respectively. The SPIRIT First Trial was a multicenter randomized controlled trial conducted to assess the feasibility and safety of a tubular balloon expandable cobalt chromium biostable polymeric everolimus-eluting stent (100 $\mu g/cm^2$, 80% drug elution at 30 days, XIENCE™® V Everolimus-Eluting Coronary Stent System, Guidant Vascular Intervention, Santa Clara, CA) compared with a metallic stent [22]. At 6 months after treatment, the primary endpoint, angiographic in-stent late lumen loss, was significantly less for the everolimus-eluting stent (0.10 mm) as compared with the metallic stent. Together, these phase I clinical trials demonstrate similar biological efficacy of stent-based delivery of everolimus to inhibit neointimal formation after PCI, despite the different metallic alloys, stent geometry, polymer matrix, and pharmacokinetic properties of each device. Importantly, the angiographic late lumen loss observed in the phase I clinical trials with everolimus-eluting stents is similar to published reports with polymeric slow release sirolimus-eluting stents (Cypher, Cordis) [1,2]. Randomized clinical trials are necessary to establish the comparative safety and efficacy of this biostable polymeric everolimus-eluting cobalt chromium stent with other drug-eluting stents.

Limitations

The present study was conducted in an experimental model of restenosis with a limited number of observations. The biological efficacy observed with polymeric sirolimus-eluting stents in the porcine coronary model differs from the human clinical dose response. Therefore, the observations with everolimus-eluting stents in this experimental model may not correlate with the clinical response. The primary objectives of this study were to document the feasibility, safety, and potential efficacy of polymeric everolimus-eluting cobalt chromium stent. Thus, only a single drug dose ($\sim$190 $\mu g/cm^2$ everolimus) was evaluated in the present study. Further experimental studies are needed to confirm these preliminary observations, determine the dose-response, and characterize *in vivo* systemic and arterial tissue pharmacokinetics. Nonetheless, the present experimental study documents the safety, feasibility, and preliminary efficacy of a polymeric everolimus-eluting cobalt chromium stent in the porcine coronary model.

CONCLUSIONS

Stent-based delivery of sirolimus and everolimus delivered via polymeric matrices are equally effective in the suppression of neointimal formation at day 28 in the porcine coronary model. Further study is necessary to document dose response and long-term comparative effects of these drug-eluting stents.

REFERENCES

1. Sousa JE, Costa MA, Sousa AG, et al. Two-year angiographic and intravascular ultrasound follow-up after implantation of sirolimus-eluting stents in human coronary arteries. Circulation 2003; 107:381–383.
2. 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;346:1773–1780.
3. Moses J, 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;349:1315–1323.
4. Stone GW, Ellis SG, Cox DA, Hermiller J, O'Shaughnessy C, Mann JT, Turco M, Caputo R, Bergin P, Greenberg J, Popma JJ, Russell ME. A polymer-based, paclitaxel-eluting stent in patients with coronary artery disease. N Engl J Med 2004;350:221–231.
5. Morice MC. Prospective randomized multi-center head-to-head comparison of the sirolimus-eluting stent (Cypher) and the pacli-

taxel-eluting stent (Taxus) (REALITY). Late breaking clinical trials. In Annual Scientific Session, American College of Cardiology, Orlando, FL, 2005.
6. Kereiakes DJ, Cox DA, Hermiller JB, Midei MG, Bachinsky WB, Nukta ED, Leon MB, Fink S, Marin L, Lansky AJ. Usefulness of a cobalt chromium coronary stent alloy. Am J Cardiol 2003; 92:463–466.
7. Dancey JE. Inhibitors of the mammalian target of rapamycin. Expert Opin Investig Drugs 2005;14:313–328.
8. Kirchner GI, Meier-Wiedenbach I, Manns MP. Clinical pharmacokinetics of everolimus. Clin Pharmacokinet 2004;43:83–95.
9. Schuler W, Sedrani R, Cottens S, et al. SDZ RAD, a new rapamycin derivative: Pharmacological properties *in vitro* and *in vivo*. Transplantation 1997;64:36–42.
10. Farb A, John M, Acampado E, Kolodgie FD, Prescott MF, Virmani R. Oral everolimus inhibits in-stent neointimal growth. Circulation 2002;106:2379–2384.
11. Suzuki T, Kopia G, Hayashi S, et al. Stent-based delivery of sirolimus reduces neointimal formation in a porcine coronary model. Circulation 2001;104:1188–1193.
12. Schwartz RS, Huber KC, Murphy JG, Edwards WD, Camrud AR, Vlietstra RE, Holmes DR. Restenosis and the proportional neointimal response to coronary artery injury: Results in a porcine model. J Am Coll Cardiol 1992;19:267–274.
13. Kornowski R, Hong MK, Tio FO, et al. In-stent restenosis: Contributions of inflammatory responses and arterial injury to neointimal hyperplasia. J Am Coll Cardiol 1998;31:224–230.
14. Carter AJ, Aggarwal M, Kopia G, et al. Long-term effects of sirolimus eluting stents in the porcine coronary model. Cardiovasc Res 2004;63:617–624.
15. Pache J, Kastrati A, Mehilli J, Schuhlen H, Dotzer F, Hausleiter J, Fleckenstein M, Neumann FJ, Sattelberger U, Schmitt C, Muller M, Dirschinger J, Schomig A. Intracoronary stenting and angiographic results: Strut thickness effect on restenosis outcome (ISAR-STEREO-2) trial. J Am Coll Cardiol 2003;41:1283–1288.
16. Rogers CR, Edelman ER. Endovascular stent design dictates experimental restenosis and thrombosis. Circulation 1995;91:2995–3001.
17. Rogers CR, Edelman ER. Stent-versus-stent equivalency trials: Are some stents more equal than others? Circulation 1999;100: 896–898.
18. Hwang CW, Wu D, Edelman ER. Physiological transport forces govern drug distribution for stent-based delivery. Circulation 2001; 104:600.
19. LaDisa JF Jr, Hettrick DA, Olson LE, et al. Stent implantation alters coronary artery hemodynamics and wall shear stress during maximal vasodilation. J Appl Physiol 2002;93:1939–1946.
20. Hwang CW, Levin AD, Jonas M, Li PH, Edelman ER. Thrombosis modulates arterial drug distribution for drug-eluting stents. Circulation 2005;111:1619–1626.
21. Grube E, Sonoda S, Ikeno F, et al. Six- and twelve-month results from first human experience using everolimus-eluting stents with bioabsorbable polymer. Circulation 2004;109:2168–2171.
22. Serruys PW. 6-Month clinical and angiographic results from the SPIRIT FIRST clinical trial. In Transcatheter Cardiovascular Therapeutics, Washington, DC, September 28, 2004. Available at www.TCTMD.com (accessed August 23, 2005).