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John S Douglas Jr., *Emory University*
William Seth Weintraub, *Emory University*
David Holmes, *Emory University*

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Review

Rationale and Design of the Randomized, Multicenter, Cilostazol for RESTenosis (CREST) Trial

JOHN S. DOUGLAS, M.D., WILLIAM S. WEINTRAUB, M.D., DAVID HOLMES, M.D.*

Division of Cardiology, Emory Center for Outcomes Research, Emory University School of Medicine, Atlanta, Georgia; *Mayo Clinic, Rochester, Minnesota, USA

Summary: Restenosis of a segment of diseased coronary artery following metallic stenting is a common clinical problem and a major limitation of the procedure. Systemic pharmacologic interventions to deal with this problem have met with little success. Several small studies suggest that cilostazol, a phosphodiesterase III inhibitor whose pharmacologic properties include antiplatelet, antithrombotic, and vasodilatory effects; a beneficial effect on serum lipids; and in vitro inhibition of smooth muscle cell proliferation, may help prevent platelet aggregation and impede the accumulation of new intimal tissue in the stented artery. The Cilostazol for RESTenosis (CREST) trial will aim to evaluate more definitively the ability of cilostazol to prevent restenosis following uncomplicated stent implantation for de novo coronary artery stenosis. In this randomized, double-blind, multicenter study, 700 patients will receive clopidogrel, aspirin, and either cilostazol or placebo after successful intracoronary stent implantation. The primary endpoint is minimal luminal diameter (MLD) of the first lesion stented after 6 months; secondary endpoints include MLD in all lesions, mean percent diameter stenosis, target lesion revascularization, and major angiographic endpoints. Safety endpoints are abnormal complete blood count and liver function tests at 1, 3, and 6 months. The trial has been initiated, and enrollment is anticipated to be concluded in 2003. Cilostazol has properties that may reduce or avert in-stent coronary restenosis. The CREST trial is a large, rigorously conducted trial that may corroborate the favorable effects of cilostazol on coronary stent restenosis suggested by earlier studies.

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Address for reprints:

John S. Douglas, M.D.
1364 Clifton Road NE
Suite F606
Atlanta, GA 30322, USA
e-mail: john_douglas@emoryhealthcare.org

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Introduction

Restenosis of a target coronary artery lesion following percutaneous transluminal coronary angioplasty (PTCA) has been a persistent limitation of this intervention since it came into use in the 1970s.[1–4] Stent implantation has improved outcome, with a significantly lower incidence of restenosis than balloon angioplasty.[5, 6] However, loss of lumen within the deployed device (in-stent restenosis) can have substantial deleterious consequences, and preventing or minimizing such loss remains a significant clinical challenge.[2, 7–9]

Numerous approaches to reduce the incidence of in-stent coronary restenosis have met with limited success. Intracoronary radiation (brachytherapy) appears promising, but there are serious concerns about its long-term safety.[10, 11] Antiplatelet therapy by means of agents with rapid onset of action have had a sizeable impact on the incidence of early lumen loss, caused by increased platelet aggregation immediately following stent implantation.[12–14] However, later lumen loss, attributable in large part to neointimal hyperplasia and thrombus formation, has proved more problematic.[15, 16] It is thought to arise essentially from a peri-device inflammatory reaction resulting in migration of proliferative elements into the segment, with maximal tissue accumulation in the device by approximately the sixth month post implantation.[17]

Cilostazol, an antiplatelet agent that selectively inhibits phosphodiesterase type III, is approved for therapy of intermittent claudication. Although the precise mechanism by which cilostazol improves claudication has not yet been determined,[18–21] the drug has several important properties—antithrombotic, antiproliferative, and vasodilatory effects—that suggest its potential as a specific adjunct to PTCA and stent implantation.

Two animal studies[22, 23] and several small clinical trials in approximately 1,480 subjects[24–28] have demonstrated comparable or significantly increased antirestenosis effects for cilostazol versus aspirin and/or ticlopidine. Tsuchikane *et al.*, with quantitative coronary arteriography (QCA), found significantly less restenosis ($p < 0.001$), as well as lower rates of target lesion revascularization, larger minimal luminal diameter, and lower percent diameter stenosis for cilostazol versus aspirin in 211 patients after successful PTCA.[26] Another clinical trial in-

volving 300 patients randomized to aspirin and ticlopidine, or aspirin and cilostazol, found that cilostazol was as efficacious as the standard regimen in preventing stent thrombosis.[24] A trend toward specific increased drug-related events (e.g., neutropenia) was seen for ticlopidine but not for cilostazol.[24] In another investigation involving 409 patients treated with ticlopidine or cilostazol, the overall rate of restenosis was similar for both agents, but a significantly lower rate of restenosis was seen among subjects with diabetes who received cilostazol (21.7% of cilostazol-treated patients with diabetes vs. 50.0% of ticlopidine-treated patients with diabetes, $p < 0.05$).[28] There was also a significantly lower rate of diffuse in-stent restenosis in all patients treated with cilostazol (26.8 vs. 54.2%, $p < 0.05$). Park *et al.*, in a study of 490 patients in whom the primary endpoint was a composite of cardiac death, myocardial infarction (MI), stent thrombosis, or need for repeat revascularization, reported equivalent results with cilostazol and ticlopidine.[25] No major adverse events or deaths occurred with the agents used in these trials, although cilostazol showed some evidence of greater safety than ticlopidine.

The favorable results demonstrated by cilostazol in these studies suggest the need for validation by a larger, more rigorously controlled trial. The Cilostazol for RESTenosis (CREST) trial will be a Phase III study designed to test the hypothesis that cilostazol will decrease or prevent restenosis, as measured by QCA, following uncomplicated coronary stent implantation.

Methods

Study Design

The CREST trial is an Institutional Review Board-approved multicenter, randomized, double-blind, placebo-controlled clinical investigation of 700 patients enrolled at 20 clinical sites. Prior to stent implantation, patients will receive aspirin and a loading dose of clopidogrel of at least 300 mg. Treatment with a glycoprotein IIa/IIIb receptor inhibitor is at the operator's discretion. Treatment will consist of either clopidogrel, aspirin, and cilostazol, or clopidogrel, aspirin, and placebo, to be initiated approximately 6 h following successful intracoronary stent implantation. Patients will be followed in-hospital until any complications are resolved, and then will be discharged. Study drug and aspirin will be continued for 6 months, clopidogrel for only 1 month. Planned follow-up will consist of phone contact and lab work at 1 month; clinic visits and lab work at 3 and 6 months; and QCA and electrocardiography (ECG) at 6 months (window of opportunity, 4 to 8 months) at a local and a designated core facility (Table I). Patients with early angiograms (4 months prior), showing restenosis (> 50% diameter stenosis) and/or target lesion revascularization, will have reached the primary study endpoint. Those with early (< 4 months) angiograms indicating no restenosis or no revascularization will require additional an-

TABLE I Study schedule

	Entry	Hospital course	1 Month	3 Months	6 Months	As needed
Randomization	x					
Demographics	x					
Baseline data	x					
PTCA	x					
Hospital discharge		x				
1- Month telephone F/U + lab data [a]			x			
3-Month clinic F/U + lab data				x		
6-Month clinic F/U + lab data					x	
Angiographic F/U (local lab)					x	
Angiographic analysis (core lab)	x				x	x
ECG (core lab)	x	x			x	x
Serious adverse events						x
Death report						x
Rehospitalization						x
Myocardial infarction						x
Stroke						x
Bleeding event						x
Additional catheterization						x
Additional PTCA						x
Seattle Angina Questionnaire	x		x	x	x	
EuroQol	x		x	x	x	
UB92 formulation of the hospital bill		x				x

[a] Complete blood count and liver function tests (SGOT, SGPT, or ALT) at baseline, 1, 3, and 6 months. Study drug will be discontinued for platelets < 125,000, and platelet count repeated.

Abbreviations: ECG = electrocardiogram, F/U = follow-up, PTCA = percutaneous transluminal coronary angioplasty.

giography within the 4- to 8-month window. This study will be conducted in accordance with the Declaration of Helsinki.

Endpoints

The primary endpoint is minimal luminal diameter (MLD) at 6 months of the first lesion stented per patient, assessed by QCA at the angiographic core laboratory. Secondary endpoints include MLD in all lesions, mean percent diameter stenosis per patient and per stented segment, binary restenosis (defined as > 50% diameter stenosis per patient and per stented segment), target lesion revascularization, and major angiographic and clinical endpoints. Safety endpoints are abnormal complete blood count and liver function tests at 1, 3, and 6 months. A platelet count < 125,000 will require study drug discontinuation.

Study Population

Men and women who are candidates for coronary catheterization with percutaneous revascularization are eligible for inclusion. Patients may be recruited prior to the procedure or when fully recovered from sedation, when informed consent will be obtained. The trial will include patients ≥ 18 years old who have documentation of a target lesion with de novo stenosis > 50% and < 100% diameter by visual estimate, uncomplicated placement of an intracoronary stent in a native coronary artery segment (< 10% residual stenosis by visual estimate), Thrombolysis in Myocardial Infarction (TIMI) III flow with no residual dissection, and a stented segment < 40 mm by visual estimate (any stent approved by the US Food and Drug Administration is acceptable). Also included will be women of childbearing potential with a negative pregnancy test, and a commitment to abstain from sexual intercourse or to use contraception for the duration of the study.

Subjects will be excluded from the study if they have known intolerance to study medication; acute MI with creatine kinase elevated to three times the upper limit of normal within 24 h; prior PTCA within 6 months; heart failure or ejection fraction < 30%; target lesion encompassing side branches > 2 mm in diameter; moderate to severe target lesion calcification; intraluminal thrombus at the target lesion; thrombocytopenia, defined as platelet level < 150,000/ml; known bleeding diathesis; active peptic ulcer disease or other gastrointestinal bleeding; renal insufficiency with creatinine > 2.5 mg/dl; concurrent coumadin use; known hepatic dysfunction; current participation in another randomized trial; inability to return for follow-up angiography; major life-threatening illness; or an inability to give informed consent.

Randomization and Study Drug

Patient randomization and allocation of drug or placebo will be undertaken by the coordinating center, based on the development of a blocked design randomization scheme. Matching bottles of cilostazol or placebo, marked with a patient allocation number, will be distributed to study sites. The sites will receive a list of their sequential allocation numbers, and drugs will be made available to patients based on those numbers.

Treatment Regimen

Patients will receive cilostazol 100 mg b.i.d., taken as two 50 mg tablets twice daily. Cilostazol is metabolized by the cytochrome P450 isozymes 3A4 and 2C19. At the treating physician's discretion, the cilostazol dose will be adjusted to one 50 mg tablet b.i.d. in patients who must receive medications that interfere with isozymes 3A4 or 2C19. Patients will be asked not to drink grapefruit juice on a regular basis for the duration of the study. Medication sufficient for 4 months will be given at hospital discharge and renewed at 3 months. Pill count will be performed at 3 and 6 months.

Follow-Up

Patients will be contacted by phone for follow-up at 1 month, when blood testing, including monitoring of liver enzymes, can be performed by a local physician. At 3 months, patients will revisit the clinic, and at 6 months will return for angiography and blood tests at the clinical site.

Coronary Angiograms

All coronary angiograms will be obtained after intracoronary administration of 100 to 200 μg of nitroglycerin, unless omitted at operator discretion for safety reasons. Initial and follow-up angiography will be performed in the same two orthogonal views.

All angiographic films or digital media obtained at the study site will be forwarded to the angiographic core laboratory for interpretation. The core facility will be blinded to study interventions and will determine the following quantitative measurements: MLD of target lesion and other native stented segments, MLD of reference sites; percent diameter stenosis, target lesion and other native stented site lengths; and target lesion and other native stent total stent lengths (or total length of stent deployed). Descriptive results will include American College of Cardiology/American Heart Association (ACC/AHA) lesion type (A, B1, B2, or C), caliber of TIMI flow, and presence of intraluminal filling defects.

Electrocardiograms will be collected at baseline, prior to discharge, at 3- and 6-month follow-up, and during intercurrent hospitalizations for chest pain, heart failure, or suspected acute myocardial infarction.

Data Analysis and Power Calculation

Continuous variables will be displayed as mean ± standard deviation and compared by unpaired *t*-test or analysis of variance as appropriate. Categorical variables will be displayed as proportions and compared by chi-square tests. All data will be analyzed by intention-to-treat analysis. A p value < 0.05 will be considered significant. Correlates of binary categorical variables will be determined by logistic regression and correlates of continuous variables by multiple regression.

The power calculation was based on an expected baseline restenosis rate of 30% and a cilostazol-treated restenosis rate of 20%. To achieve 80% power, 294 patients per study arm will be required. To account for possible dropouts, approximately 350 patients will be recruited per treatment arm. A second power calculation, according to the results of Kunishima *et al.*[28] for the continuous variable MLD, will be based on expected mean MLDs of 1.65 (treated) and 1.40 (untreated). To achieve 90% power, 123 patients per treatment arm will be required.

Organizational Structure

The trial will be run by the Executive Committee, which will also serve as a publication committee. All clinical endpoints will be adjudicated by an independent endpoint committee, and all data will be reviewed by an independent Data and Safety Monitoring Board. There will be two core laboratories, one for angiography and one for electrocardiography. All sites will be monitored during the trial.

Current Status of Study

This randomized placebo-controlled trial has been initiated, and enrollment is anticipated to be concluded in 2003.

Conclusions

Cilostazol possesses antiplatelet, antiproliferative, and other properties that may minimize or prevent in-stent coronary restenosis. Early work has shown a favorable effect on coronary stent restenosis. The CREST trial is a larger, more rigorously conducted trial that may confirm an important role for cilostazol in the long-term management of patients with coronary artery disease after uncomplicated coronary stent implantation.

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