

## Optimal Medical Therapy With or Without Percutaneous Coronary Intervention to Reduce Ischemic Burden

### Results From the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) Trial Nuclear Substudy

Leslee J. Shaw, PhD; Daniel S. Berman, MD; David J. Maron, MD; G.B. John Mancini, MD; Sean W. Hayes, MD; Pamela M. Hartigan, PhD; William S. Weintraub, MD; Robert A. O'Rourke, MD; Marcin Dada, MD; John A. Spertus, MD, MPH; Bernard R. Chaitman, MD; John Friedman, MD; Piotr Slomka, PhD; Gary V. Heller, MD, PhD; Guido Germano, PhD; Gilbert Gosselin, MD; Peter Berger, MD; William J. Kostuk, MD; Ronald G. Schwartz, MD; Merrill Knudtson, MD; Emir Veledar, PhD; Eric R. Bates, MD; Benjamin McCallister, MD; Koon K. Teo, MD; William E. Boden, MD; for the COURAGE Investigators

**Background**—Extent and severity of myocardial ischemia are determinants of risk for patients with coronary artery disease, and ischemia reduction is an important therapeutic goal. The Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) nuclear substudy compared the effectiveness of percutaneous coronary intervention (PCI) for ischemia reduction added to optimal medical therapy (OMT) with the use of myocardial perfusion single photon emission computed tomography (MPS).

**Methods and Results**—Of the 2287 COURAGE patients, 314 were enrolled in this substudy of serial rest/stress MPS performed before treatment and 6 to 18 months (mean =  $374 \pm 50$  days) after randomization using paired exercise ( $n=84$ ) or vasodilator stress ( $n=230$ ). A blinded core laboratory analyzed quantitative MPS measures of percent ischemic myocardium. Moderate to severe ischemia encumbered  $\geq 10\%$  myocardium. The primary end point was  $\geq 5\%$  reduction in ischemic myocardium at follow-up. Treatment groups had similar baseline characteristics. At follow-up, the reduction in ischemic myocardium was greater with PCI+OMT ( $-2.7\%$ ; 95% confidence interval,  $-1.7\%$ ,  $-3.8\%$ ) than with OMT ( $-0.5\%$ ; 95% confidence interval,  $-1.6\%$ ,  $0.6\%$ ;  $P<0.0001$ ). More PCI+OMT patients exhibited significant ischemia reduction (33% versus 19%;  $P=0.0004$ ), especially patients with moderate to severe pretreatment ischemia (78% versus 52%;  $P=0.007$ ). Patients with ischemia reduction had lower unadjusted risk for death or myocardial infarction ( $P=0.037$  [risk-adjusted  $P=0.26$ ]), particularly if baseline ischemia was moderate to severe ( $P=0.001$  [risk-adjusted  $P=0.08$ ]). Death or myocardial infarction rates ranged from 0% to 39% for patients with no residual ischemia to  $\geq 10\%$  residual ischemia on follow-up MPS ( $P=0.002$  [risk-adjusted  $P=0.09$ ]).

**Conclusions**—In COURAGE patients who underwent serial MPS, adding PCI to OMT resulted in greater reduction in ischemia compared with OMT alone. Our findings suggest a treatment target of  $\geq 5\%$  ischemia reduction with OMT with or without coronary revascularization. (*Circulation*. 2008;117:1283-1291.)

**Key Words:** ischemia ■ perfusion ■ prevention ■ prognosis

Continuing medical education (CME) credit is available for this article. Go to <http://cme.ahajournals.org> to take the quiz.

Received October 3, 2007; accepted January 8, 2008.

From Emory University School of Medicine, Atlanta, Ga (L.J.S., E.V.); Cedars-Sinai Medical Center, Los Angeles, Calif (D.S.B., S.W.H., J.F., P.S., G. Germano); Vanderbilt University Medical Center, Nashville, Tenn (D.J.M.); Vancouver Hospital and Health Sciences Centre, Vancouver, British Columbia, Canada (G.B.J.M.); Veterans Affairs Cooperative Studies Program Coordinating Center, Veterans Affairs Connecticut Healthcare System, West Haven (P.M.H.); Christiana Care Health System, Newark, Del (W.S.W.); South Texas Veterans Health Care System, San Antonio, Tex (R.A.O., G.V.H.); Hartford Hospital, Hartford, Conn (M.D.); Mid America Heart Institute/University of Missouri-Kansas City, Kansas City, Mo (J.A.S., B.M.); St Louis University, St Louis, Mo (B.R.C.); Montreal Heart Institute, Montreal, Quebec, Canada (G. Gosselin); Geisinger Clinic, Danville, Pa (P.B.); London Health Sciences Centre, London, Ontario, Canada (W.J.K.); University of Rochester, Rochester, NY (R.G.S.); Foothills Hospital, Calgary, Alberta, Canada (M.K.); University of Michigan, Ann Arbor (E.R.B.); McMaster University, Hamilton, Ontario, Canada (K.K.T.); and Western New York Veterans Affairs Healthcare Network/Bufalo General Hospital/State University of New York, Buffalo (W.E.B.).

Clinical trial registration information—URL: <http://www.clinicaltrials.gov>. Unique identifier: NCT00007657.

The online-only Data Supplement is available with this article at <http://circ.ahajournals.org/cgi/content/full/CIRCULATIONAHA.107.743963/DC1>.

Correspondence to Leslee J. Shaw, PhD, Suite 1-N, 1256 Briarcliff Rd NE, EPICORE, Emory University, Atlanta, GA 30306. E-mail [leslee.shaw@emory.edu](mailto:leslee.shaw@emory.edu)

© 2008 American Heart Association, Inc.

*Circulation* is available at <http://circ.ahajournals.org>

DOI: 10.1161/CIRCULATIONAHA.107.743963

Stress myocardial perfusion single photon emission computed tomography (MPS), which measures extent and severity of inducible ischemia, is commonly used to risk stratify patients with stable coronary artery disease (CAD) and guide therapeutic decision making.<sup>1,2</sup> MPS provides an accurate estimation of risk for major cardiac events and is commonly used to select patients for coronary revascularization.<sup>1-5</sup> Observational data suggest that coronary revascularization provides a survival benefit over medical therapy when moderate to severe ischemia is present.<sup>2</sup>

### Clinical Perspective p 1291

The Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial was a strategy-driven trial randomizing 2287 patients to optimal medical therapy (OMT) with or without percutaneous coronary intervention (PCI).<sup>6</sup> The main trial results revealed no difference by treatment in the primary end point of death or acute myocardial infarction (MI) for a median 4.6 years of follow-up ( $P=0.62$ ).<sup>6</sup> The trial included a nuclear substudy to measure ischemic burden in a subset of patients.

Limited information is available about the effectiveness of OMT with or without PCI in reducing the extent and severity of inducible ischemia in patients with stable CAD.<sup>7-12</sup> The primary aim of the nuclear substudy was to compare changes in ischemic burden after randomization to PCI+OMT compared with OMT alone and to explore associations with patient outcome.

### Methods

The methods of the COURAGE main trial and nuclear substudy (clinical trial No. NCT00007657) were described previously.<sup>6,13</sup> We screened 35 539 patients between 1999 and 2004 at 50 US and Canadian centers with local institutional review board approval.

### Patient Eligibility

This substudy was predefined and electively offered to interested sites. Patients were enrolled from 25 of the 50 COURAGE sites. Patients willing to participate were consecutively enrolled and underwent pretreatment and 6- to 18-month follow-up gated MPS. Enrollment in this substudy continued until completion of the main trial, resulting in a sample size of 314 patients (PCI+OMT,  $n=159$ ; OMT,  $n=155$ ). We estimated that a sample size of 170 patients would be adequate (power  $\geq 0.8$ ;  $\alpha$ ,  $P=0.01$ ) to detect treatment differences in ischemia reduction. The assumptions for this calculation were that nearly half of the patients would exhibit a significant reduction in ischemia compared with one quarter of patients receiving usual care. Given that our sample size calculation was based on small published series,<sup>9,10</sup> we oversampled both groups to attain an enrollment of  $\approx 300$  patients.

Substudy entry criteria included patients with medically stable CAD with  $\geq 70\%$  stenosis in at least 1 major epicardial coronary artery and MPS ischemia. Both criteria were assessed by the site investigator but subsequently evaluated at independent core angiographic and MPS laboratories. Patients undergoing other forms of stress testing were not eligible for study entry ( $n=556$ ). Patients with refractory heart failure symptoms, cardiogenic shock, ejection fraction  $<30\%$ , or coronary anatomy unsuitable for PCI were excluded from the main trial.

### Gated MPS Core Laboratory

The rest and stress gated MPS data were stored electronically at the site and sent to the nuclear core laboratory at Cedars-Sinai Medical Center (Los Angeles, Calif). Participating sites were required to pass

image quality and procedural standardization assessment before patient enrollment with the prescribed COURAGE gated MPS methods.<sup>13</sup> Image quality was assessed by nuclear cardiologists blinded to the site and randomization arm. Patients underwent a 1- or 2-day (22% were 2-day) protocol with either rest <sup>201</sup>Tl or <sup>99m</sup>Tc sestamibi combined with stress <sup>99m</sup>Tc sestamibi.

### Total Perfusion Defect Quantification

MPS scans were interpreted quantitatively with the use of the total perfusion defect (TPD).<sup>14</sup> The TPD is automatically derived by computer software (QPS, Cedars-Sinai Medical Center, Los Angeles, Calif) and designed to be equivalent to visual summed scores combining defect extent and severity on a pixel-by-pixel continuous basis. A floating-point score is assigned to each abnormal pixel on the polar map with a minimum abnormal score of 2.0 and a maximum abnormal score of 4.0 with the use of linear mapping, based on the degree to which the pixel value falls below the normal limit. A score of 0.0 is assigned to the pixels within normal limits and a maximum score of 4.0 is assigned to all pixels with values  $>70\%$  below the normal limit. The percent ischemic myocardium was calculated by subtracting the rest from the stress TPD. Less than 5% ischemic myocardium was considered minimal ischemia, 5% to 9% ischemic myocardium was considered mild ischemia, and  $\geq 10\%$  ischemic myocardium was considered moderate to severe ischemia.<sup>2,15</sup> TPD abnormalities were also ascribed to individual coronary arteries.<sup>16</sup> Left ventricular ejection fraction was computed with the use of quantitative gated single photon emission computed tomography software.<sup>17</sup>

### Treatment

Details about OMT and PCI in COURAGE were published with the main results.<sup>6</sup> Both groups received OMT, which included antiplatelet therapy (low-dose aspirin); anti-ischemic therapy (long-acting metoprolol, amlodipine, and isosorbide mononitrate, alone or in combination); lisinopril or losartan for hypertension, reduced ejection fraction, or secondary prevention; and low-density lipoprotein (LDL) cholesterol-lowering therapy with simvastatin alone or in combination with ezetimibe to achieve a target of 60 to 85 mg/dL. After achievement of the LDL target, secondary targets were (1) raising high-density lipoprotein cholesterol  $>40$  mg/dL and (2) lowering triglyceride levels  $<150$  mg/dL with exercise or in combination with extended-release niacin or fibrates. Lifestyle counseling for diet, smoking cessation, glycemic control, and weight loss was administered to both groups.

For patients randomized to PCI, target lesion revascularization was attempted in every case. Angiographic success was defined as normal coronary arterial flow as well as  $<50\%$  residual stenosis after balloon angioplasty or  $<20\%$  after stent implantation. The percent residual stenosis was assessed by quantitative coronary angiographic methods before and after PCI. Aspirin and clopidogrel were prescribed after PCI according to established treatment guidelines.

Details of treatment, angina status, risk factor profiles, and lifestyle modification data are presented in the Appendix in the online-only Data Supplement.

### Testing Sequence

All patients underwent gated MPS before treatment initiation. A follow-up scan was performed at 6 to 18 months (mean  $=374 \pm 50$  days) after PCI+OMT or OMT. The pretreatment MPS protocol required that patients discontinue  $\beta$ -blockers, other anti-ischemic therapies except short-acting nitroglycerin, and statins for 24 to 48 hours before testing. For the follow-up scan, patients were tested on all prescribed anti-ischemic and cholesterol-lowering therapies. The goal of the second scan was to assess the effectiveness of a patient's ongoing therapeutic regimen to reduce ischemia.

The type of provocative stress was required to be the same on pretreatment and posttreatment MPS. The protocol recommended adenosine stress at pretreatment and posttreatment MPS to maintain consistency in the type and intensity of hyperemic stimulus, but exercise stress was acceptable. For exercising patients, injection of

**Table 1. Pretreatment Clinical Characteristics of Patients Enrolled in the COURAGE Nuclear Substudy**

	PCI+OMT (n=159)	OMT (n=155)	P
Age, y	62±10	64±10	0.03
% Female sex	10%	15%	0.20
Cardiac risk factors			
Hyperlipidemia	53%	46%	0.21
Hypertension	77%	75%	0.66
Diabetes	40%	46%	0.52
Family history of CAD	52%	50%	0.71
Current smoker	23%	22%	0.94
Body mass index	30.0±1.2	30.0±1.3	0.29
Other clinical history			
Heart failure symptoms	5%	4%	0.97
Prior MI	38%	37%	0.76
Prior PCI	18%	14%	0.31
Prior CABG	14%	14%	0.90
Angina class			0.99
I	41%	40%	
II	33%	33%	
III	13%	15%	
Duration of angina, mo	3 (1, 8)	3 (1, 9)	0.39
Episodes per week	3 (1, 5)	3 (1, 5)	0.78
Angiographic CAD			0.17
1 Vessel	27%	24%	
2 Vessels	34%	45%	
3 Vessels	39%	32%	
LAD disease	69%	76%	0.17
Proximal	47%	50%	0.62

Data for age and body mass index are presented as mean±SD. For duration of angina and episodes per week, data are presented as median (25th, 75th percentile). For the latter, a nonparametric Wilcoxon test was used to compare PCI+OMT vs OMT. CABG indicates coronary artery bypass grafting; LAD, left anterior descending artery.

the radiopharmaceutical was performed at a similar workload for the follow-up and baseline MPS. The results presented are combined and did not differ when the type of stress was analyzed separately.

### Statistical Methods

The primary end point of this substudy was a ≥5% reduction in percent ischemic myocardium when the follow-up MPS was compared with the pretreatment MPS.<sup>13</sup> Clinical data were aggregated for comparison of baseline tabular data, including continuous and categorical measures, with the use of *t* test or  $\chi^2$  statistics. When appropriate, paired *t* tests were used to compare differences in myocardial perfusion, ventricular function, and exercise time. Continuous measurements that were not distributed normally were compared with nonparametric statistics. Specifically, a Wilcoxon rank sum test was used to compare data across independent groups, and a Wilcoxon signed rank test was used to compare paired data between index and follow-up MPS. Additionally, we employed McNemar's  $\chi^2$  test to compare the percentage of patients with exertional chest pain.

A general linear model was used to compare pretreatment and posttreatment percent ischemic myocardium. It was predicted that patients with a greater extent and severity of pretreatment ischemia would exhibit greater degrees of resolution.<sup>9</sup> Thus, models evaluat-

**Table 2. Angiographic Outcomes as Measured by Quantitative Coronary Angiography for the 159 Patients Randomized to PCI+OMT**

	n (%)
No. of lesions	
No. of lesions attempted (n of patients)	265 (156)
No. of patients unable to cross	2
Noncritical stenosis	1
Stenosis diameter, mean±SD	
Stented lesions (n=212)	
Before PCI	64±16%
After PCI	8±18%
Nonstented lesions (n=53)	
Before PCI	59±17%
After PCI	35±16%
Angiographic success of attempted lesions*	93%
Clinical success†	87%

\*Angiographic success defined as <50% in nonstented lesion and <20% in stented lesion.

†Clinical success defined as angiographic success with no clinical events.

ing the change in percent ischemic myocardium by treatment were weighted by the baseline ischemic burden, although this did not affect the main comparison. A threshold reduction of ≥5% ischemic myocardium was deemed appropriate because it exceeded test repeatability.<sup>14</sup> Comparisons of rest and stress TPD measurements as well as ventricular function measurements were analyzed with a paired *t* test statistic.

Methods for collection of death or nonfatal MI were reported previously.<sup>6</sup> Follow-up time was initiated at the second MPS. Procedural MI was censored at the time of PCI. Kaplan–Meier survival analyses were calculated. Wald  $\chi^2$  statistics from a Cox proportional hazards model were used to compare survival groups. A multivariable Cox model, controlling for randomized treatment, was included for each prognostic analysis.

All authors had full access to and take full responsibility for the integrity of the data. All authors have contributed to the writing and agree to the manuscript as written.

## Results

### Pretreatment Clinical Characteristics

Compared with the main trial, patients enrolled in this substudy had less severe angina ( $P=0.013$ ) and less multivessel CAD ( $P=0.05$ ), with a similar frequency of ischemia ( $P=0.55$ ) (Table 1). Before treatment, substudy patient groups had similar proportions of Canadian Cardiovascular Society class I to II angina (74% for PCI+OMT versus 73% for OMT;  $P=0.99$ ) and angiographic multivessel CAD (73% for PCI+OMT versus 76% for OMT;  $P=0.38$ ). Substudy patients randomized to PCI+OMT were, on average, younger ( $P=0.03$ ).

### PCI Success

Of the 159 patients randomized to PCI+OMT, angiographic success of the initial PCI was 93% (Table 2).

### Pretreatment and 6- to 18-Month Posttreatment Stress Test Results

Patients randomized to PCI+OMT and OMT had similar pretreatment stress test results (Table 3). At the follow-up

**Table 3. Pretreatment and 6- to 18-Month Posttreatment Initiation Nonimaging Stress Test Results**

	PCI+OMT (n=159)			OMT (n=155)			Differences Between Treatment	
	Pretreatment	6 to 18 Months of Follow-Up	Paired Within-Treatment P	Pretreatment	6 to 18 Months of Follow-Up	Paired Within-Treatment P	Pretreatment P	Posttreatment P
ST-segment depression			<0.001			0.007	0.57	0.58
None	57%	74%		58%	69%			
<1 mm	8%	7%		7%	6%			
1–1.9 mm	24%	10%		19%	13%			
≥2 mm	11%	9%		15%	11%			
Exertional chest pain*	30%	11%	0.007	43%	28%	0.15	0.26	0.06
Exercise time, min*	7.8±2.7	9.0±2.7	0.003	6.7±2.0	7.9±2.3	<0.001	0.09	0.32
Duke treadmill score*			0.27			0.45	0.27	0.57
Low risk	18%	43%		24%	34%			
Intermediate risk	77%	46%		62%	58%			
High risk	5%	11%		14%	8%			

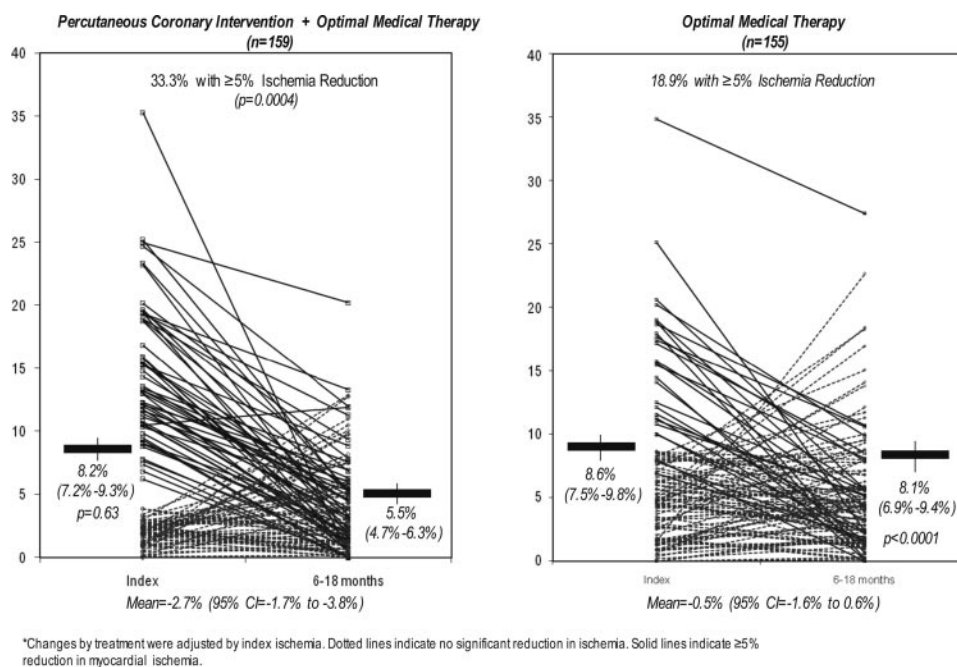
Statistical analyses include comparisons within treatment groups: (1) paired *t* test for exercise time, (2) McNemar's  $\chi^2$  statistic for exertional chest pain, and (3) Wilcoxon signed rank test for ST-depression data and Duke treadmill scores. For within-patient differences between treatments, (1) we applied a Wilcoxon rank sum test for ST depression, chest pain, and the Duke treadmill score; and (2) differences in exercise time were compared with a 2-sample *t* test.

\*Exercise chest pain, time, and the Duke treadmill score were only calculated in the exercising patients (n=83).

MPS, the frequency of exercise ST segment depression was lower in both treatment groups but did not differ significantly between groups. Exercise duration increased significantly in both treatment groups ( $\approx 1.1$  minute; both  $P < 0.01$ ) with no significant between-group differences. There was a trend toward a greater frequency of exertional chest pain in patients randomized to OMT (11% for PCI+OMT versus 28% for OMT;  $P = 0.06$ ) (Table 3).

**Pretreatment and 6- to 18-Month Posttreatment Gated MPS Results**

The pretreatment percent ischemic myocardium was similar for those randomized to PCI+OMT compared with OMT alone (8.2%; 95% confidence interval, 7.2% to 9.3% versus 8.6%; 95% confidence interval, 7.5% to 9.8%;  $P = 0.63$ ) (Figure 1). At baseline, moderate to severe ischemia was noted in 34% of PCI+OMT versus 33% of OMT patients ( $P = 0.81$ ).



**Figure 1.** Comparison of inducible ischemia with MPS pretreatment and after 6 to 18 months of OMT with or without PCI.

**Table 4. Rest and Poststress Gated MPS and Ventricular Function Measurements**

	PCI+OMT (n=159)			OMT (n=155)			Difference by Treatment	
	Pretreatment	6 to 18 Months	P	Pretreatment	6 to 18 Months	P	P	P
Rest TPD	6.4±7	3.4±6	<0.0001	6.1±7	3.3±6	<0.0001	0.70	0.83
Stress TPD	14.6±10	8.9±8	<0.0001	14.7±11	11.4±10	<0.0001	0.87	0.018
Territory								
Right coronary artery	2.5±3	1.4±2	<0.0001	2.7±4	2.1±3	<0.0001	0.60	0.012
Left anterior descending artery	5.8±5	3.6±4	<0.0001	5.9±5	4.8±5	<0.0001	0.97	0.021
Left circumflex artery	5.3±4	3.6±4	<0.0001	5.3±5	4.2±4	<0.0001	0.96	0.26
% Ischemia			<0.0001			<0.0001	0.40	0.019
0 to 4.9%	43.0%	53.4%		37.9%	46.0%			
5% to 9.9%	26.0%	30.9%		29.1%	27.0%			
≥10%	31.0%	15.8%		33.0%	27.0%			
Left ventricular ejection fraction								
Rest	57.0±11	57.0±9	0.97	57.0±9	57.7±6	0.30	0.97	0.14
Poststress	51.0±11	54.8±10	0.001	53.4±10	54.2±12	0.38	0.09	0.49
End-diastolic volume								
Rest	103.2±40	105.2±38	0.41	100.0±30	102.6±32	0.43	0.26	0.30
Poststress	112.7±40	111.0±38	0.44	102.3±33	105.9±35	0.21	0.13	0.33
End-systolic volume								
Rest	47.6±29	47.9±28	0.84	45.2±23	45.0±25	0.88	0.13	0.30
Poststress	57.2±29	52.5±29	0.02	49.5±23	49.8±24	0.88	0.33	0.49

All values are mean±SD. At baseline, missing ventricular function measurements, n=141; at follow-up, missing ventricular function measurements, n=26. Statistical analyses similar to those that were applied to Table 3 apply to Table 4, including comparisons within treatment groups: paired *t* test for MPS measurements and Wilcoxon signed rank test for percent ischemic myocardium. For within-patient treatment differences, we applied a Wilcoxon rank sum test for percent ischemia and differences in MPS measurements using a 2-sample *t* test. A total of 86 and 86 paired comparisons were available for the PCI+OMT and OMT subsets.

On the 6- to 18-month MPS (mean=374±50 days), significant ischemia reduction was noted in both groups; however, the reduction in percent ischemic myocardium was greater in the PCI+OMT group than the OMT group (-2.7%; 95% confidence interval, -1.7% to -3.8% versus -0.5%; 95% confidence interval, -1.6% to 0.6%; *P*<0.0001) (Figure 1). On follow-up MPS, more PCI+OMT patients had no inducible ischemia (15.2% versus 8.8%; *P*=0.06), and fewer had ≥10% residual ischemic myocardium (15.8% versus 27.0%; *P*=0.02) (Tables 4 and 5). The primary end point, significant ischemia reduction, occurred in 33% of PCI+OMT patients compared with 19% of OMT patients (*P*=0.0004). Among patients with moderate to severe pretreatment ischemia, more PCI+OMT patients demonstrated a significant reduction in ischemia compared with OMT patients (78% versus 52%; *P*=0.007). In the subset of patients with significant ischemia reduction, the average reduction was similar between groups (10.6% for PCI+OMT versus 10.5% for OMT; *P*=0.96). In this subset, the frequency of perfusion normalization was higher for PCI+OMT patients than for OMT patients (31.4% versus 17.8%; *P*=0.006) (Table 5).

Rest and poststress ventricular function measurements were generally similar between groups at baseline and follow-up (Table 4). There was a small decrease in poststress end-systolic volume (*P*=0.02) and rise in ejection fraction (*P*=0.001) on the 6- to 18-month follow-up MPS for PCI+OMT patients.

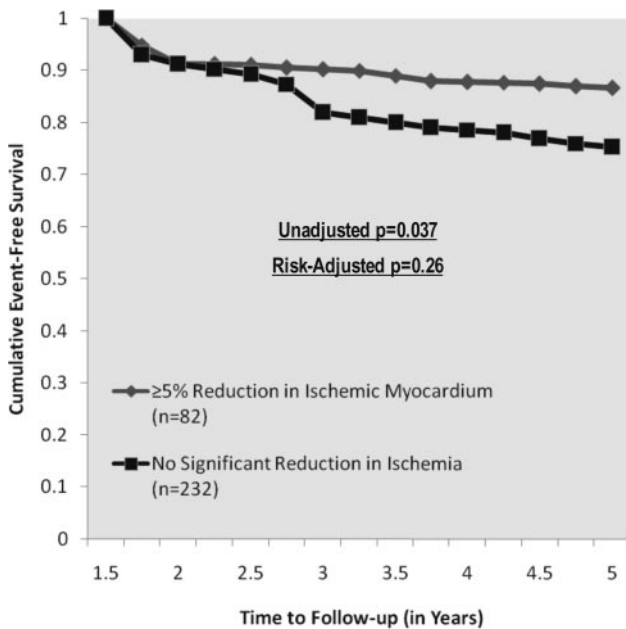
**Pretreatment and 6- to 18-Month Posttreatment Risk Factor Profiles and Lifestyle Modifications**

After 6 to 18 months of aggressive risk factor and lifestyle modification, significant reductions in LDL cholesterol and blood pressure and significant increases in physical activity were reported for both treatment groups. Patients randomized to OMT experienced a greater decline in LDL cholesterol (*P*=0.03). See Appendix A in the online-only Data Supplement.

**Table 5. Residual Ischemia on 6- to 18-Month Follow-Up MPS**

	PCI+OMT	OMT	P
Overall (n=314)	n=159	n=155	0.047
No ischemia	15.2%	8.8%	
Minimal ischemia	40.0%	39.8%	
Mild ischemia	29.0%	24.4%	
Moderate to severe ischemia	15.8%	27.0%	
Ischemia reduction ≥5% (n=82)	n=53	n=29	0.04
No ischemia	31.4%	17.8%	
Minimal ischemia	26.6%	28.5%	
Mild ischemia	36.5%	43.0%	
Moderate to severe ischemia	5.5%	10.7%	

Treatment comparisons with Wilcoxon rank sum test: (1) n=314: (a) no vs ischemia, *P*=0.06; (b) moderate to severe vs no to mild ischemia, *P*=0.02; (2) n=82: (a) no vs ischemia, *P*=0.006; (b) moderate to severe vs no to mild ischemia, *P*=0.32.



**Figure 2.** Kaplan–Meier survival for patients with  $\geq 5\%$  reduction in ischemic myocardium and for those without significant reduction in ischemia after 6 to 18 months of PCI+OMT or OMT. Overall event-free survival was 86.6% vs 75.3% for patients with vs without significant ischemia reduction ( $P=0.037$ ). In a risk-adjusted Cox model (controlling for randomized treatment), this difference was not significant ( $P=0.26$ ).

### Follow-Up Anginal Status at 6 to 18 Months After Treatment

At follow-up, improvement by  $\geq 1$  Canadian Cardiovascular Society class was more frequent in the PCI+OMT group than the OMT group (82% versus 70%;  $P=0.007$ ). At 6 to 18 months of follow-up, 70% of PCI+OMT and 63% of OMT patients were angina free ( $P=0.15$ ). Among patients with significant ischemia reduction, nearly 80% of both treatment groups were angina free.

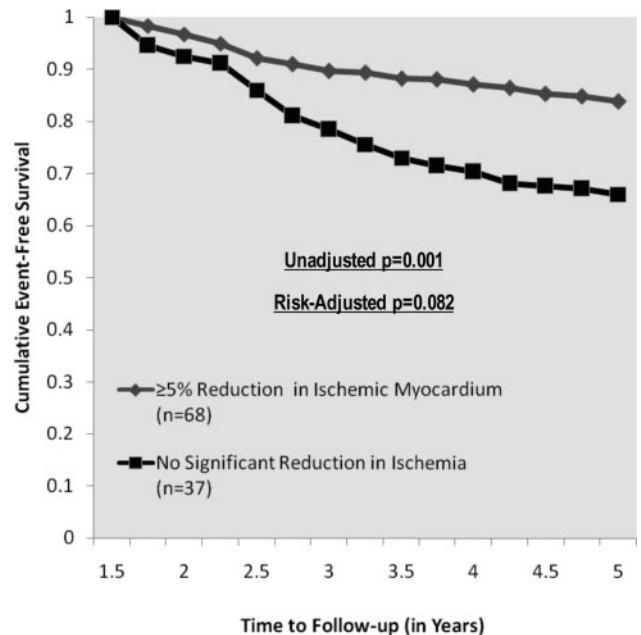
### 18-Month Follow-Up Anti-Ischemic Therapy

Anti-ischemic therapies were similar for both groups, except that fewer PCI+OMT patients were taking long-acting nitrates at follow-up (64% versus 75%;  $P=0.03$ ). See Appendix B in the online-only Data Supplement.

### Reduction of Ischemic Burden and Clinical Outcomes

Patients who exhibited no significant ischemia reduction on follow-up MPS were more likely to subsequently cross over to revascularization (from the OMT group) or undergo repeat revascularization (from the PCI+OMT group) (Figures 2 to 4). Thirty-two of 155 patients (21%) randomized to OMT crossed over to revascularization after the second MPS; 80% of those had exhibited no significant reduction in ischemia. Approximately 15% of those randomized to PCI+OMT underwent repeat revascularization after the second MPS, in whom 75% had exhibited no significant ischemia reduction.

The substudy sample size was not powered to examine differences in clinical outcomes according to change in ischemic burden. Therefore, the following data are for hypothesis-generating purposes. After an average follow-up

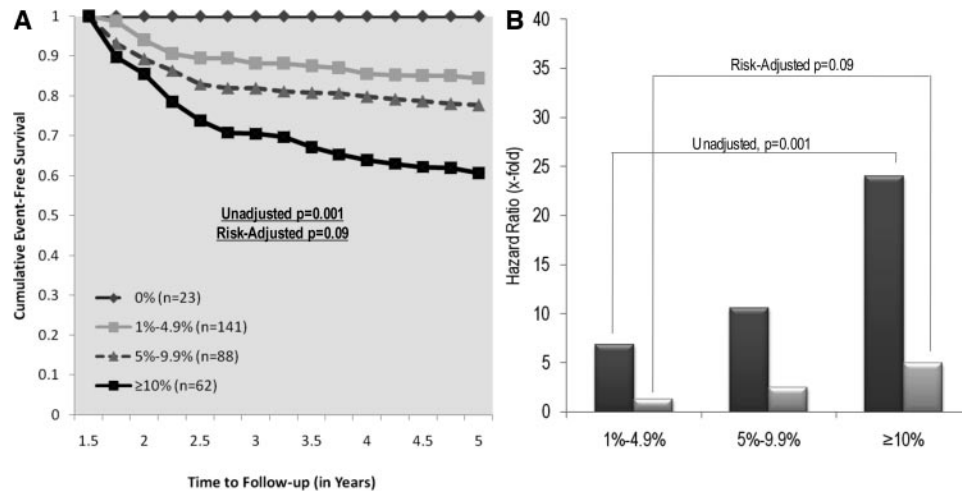


**Figure 3.** Kaplan–Meier survival for the subset of 105 patients with moderate to severe pretreatment ischemia including a comparison of patients with  $\geq 5\%$  reduction in ischemic myocardium compared with those without a significant reduction in ischemia after 6 to 18 months of PCI+OMT or OMT. Overall event-free survival was 83.8% vs 66.0% for patients with vs without significant ischemia reduction ( $P=0.001$ ). In a risk-adjusted Cox model (controlling for randomized treatment), this difference was not significant ( $P=0.082$ ).

of 3.6 years following the second MPS, the overall rate of death or nonfatal MI was 21.7%; of this, nearly three fourths were nonfatal MI. Multivariable Cox models were devised for this nonrandom comparison, controlling for index treatment. In each case, risk adjustment attenuated comparative differences for Figures 2 through 4. The unadjusted rate of death or nonfatal MI was 13.4% for patients exhibiting significant ischemia reduction compared with 24.7% for those without significant ischemia reduction (Figure 2; unadjusted  $P=0.037$ ; risk-adjusted  $P=0.26$ ). Similarly, for the 105 patients whose pretreatment MPS had moderate to severe ischemia, the death or MI rate was 16.2% for those exhibiting significant ischemia reduction compared with 32.4% for those with no significant ischemia reduction or worsening ischemia on follow-up MPS (Figure 3; unadjusted  $P=0.001$ ; risk-adjusted  $P=0.082$ ). A final analysis explored the role of residual ischemia and outcome (Figure 4; unadjusted  $P=0.001$ ; risk-adjusted  $P=0.09$ ). There was a graded relationship between risk of events and the extent and severity of residual ischemia. The rate of death or MI ranged from 0% for patients with no ischemia to 39.3% for patients with  $\geq 10\%$  ischemic myocardium on their follow-up MPS. Risk-adjusted hazard ratios ranged from 1.3 to 7.5 for mild (1% to 4.9% ischemic myocardium) to moderate to severe ischemia ( $\geq 10\%$  ischemic myocardium) on the follow-up MPS ( $P=0.09$ ).

### Discussion

In this subset of COURAGE patients, the addition of PCI to OMT resulted in more effective reduction of ischemia than



**Figure 4.** A, Kaplan–Meier survival for patients by residual ischemia including 0%, 1% to 4.9%, 5% to 9.9%, and  $\geq 10\%$  ischemic myocardium, respectively, after 6 to 18 months of PCI+OMT or OMT. Overall event-free survival was 100%, 84.4%, 77.7%, and 60.7%, respectively, for 0%, 1% to 4.9%, 5% to 9.9%, and  $\geq 10\%$  ischemic myocardium ( $P=0.001$ ). In a risk-adjusted Cox model (controlling for randomized treatment), this difference was not significant ( $P=0.09$ ). B, Unadjusted (dark gray bars) and risk-adjusted (light gray bars) hazard ratios for the extent and severity of residual ischemia at 6 to 18 months of follow-up.

OMT alone, and complete normalization of MPS was more common in the PCI+OMT group. For PCI+OMT patients, the greater reduction in ischemic burden was associated with improvements in angina class and less reliance on nitrate therapy for symptom relief, results that mirror near-term improvements reported within the main trial.<sup>6</sup> Moreover, the majority of patients from both treatment groups with ischemia reduction were angina free at 6 to 18 months of follow-up. Regardless of treatment assignment, we found that the magnitude of residual ischemia on follow-up MPS was proportional to the risk for death or MI, although our outcome comparisons were limited to a small subset of enrolled patients and should be viewed for purposes of hypothesis generation. Similarly, although underpowered for estimation of prognosis, our preliminary observations were that patients randomized to either treatment with a  $\geq 5\%$  reduction in ischemia had a reduced rate of death or MI, although this was not statistically significant in risk-adjusted analyses. Although univariable associations with serial MPS results were not retained in risk-adjusted models, these trends should form the basis for additional exploration regarding the value of MPS ischemia to guide therapeutic decision making.

In our substudy, the anti-ischemic benefit of PCI was greatest for patients with more severe ischemia at baseline. Moderate to severe ischemia, defined as  $\geq 10\%$  ischemic myocardium on the pretreatment MPS, was previously reported from observational series as a cut point beyond which improvement in event-free survival with coronary revascularization was greater than that of medical therapy.<sup>2</sup> In the COURAGE substudy, patients randomized to PCI+OMT with moderate to severe pretreatment ischemia more commonly experienced a significant reduction in ischemia at 6 to 18 months of follow-up compared with those receiving OMT (78% versus 52%). This study reports the largest series to date on ischemia reduction with medical therapy in a clinical trial. The COURAGE trial, utilizing meticulous risk factor control and lifestyle management strategies as well as tar-

geted anti-ischemic therapies, was able to reduce ischemia in nearly 1 in 5 OMT patients. Of the OMT patients exhibiting significant ischemia reduction, the majority were also angina free, with generally mild residual ischemia on their follow-up MPS. Prior series examining ischemia reduction with medical therapy have been limited to very small patient samples.<sup>7–11</sup> In series of 20 to 25 patients, smaller perfusion defects were noted in patients receiving statin therapy compared with placebo.<sup>9,10</sup> In the Adenosine Sestamibi Post-Infarction Evaluation of 205 low-risk, uncomplicated postinfarction patients, nearly 80% of patients treated with coronary revascularization or medical therapy experienced significant ischemia suppression.<sup>18</sup> In COURAGE, the focus of treatment for all patients was an array of anti-ischemic and effective secondary prevention therapies including not only nitrates,  $\beta$ -blockers, and calcium channel blockers but also statin therapy with an established anti-ischemic benefit. Our findings, coupled with prior evidence, underscore the feasibility of achieving important reductions in ischemia with antianginal therapy combined with a strategy of optimal risk factor control and lifestyle modification.

We chose to define a significant reduction in ischemia as  $\geq 5\%$  on the basis of observational reports that this threshold denotes patients with significantly improved near-term CAD event rates.<sup>2,11,19</sup> The present results represent an important advancement over those reported from the Angioplasty Compared with Medicine Study, in which patients randomized to percutaneous transluminal coronary angioplasty had medical therapies tapered and were taken off all antianginal medications at the time of their planar <sup>201</sup>Tl scan.<sup>20</sup> Another important departure of the COURAGE nuclear substudy methods from traditional practice was to retest patients on all antianginal and statin medications with the aim of examining the adequacy of therapy in reducing a patient's pretreatment ischemic burden.

Our exploratory analysis of clinical outcomes revealed that rates of death or MI were directly proportional to the extent

and severity of ischemia on the 6- to 18-month MPS study. These results trend in the same direction as the Angioplasty Compared with Medicine Study, an older study reporting that ischemia normalization was associated with improved event-free survival in long-term follow-up.<sup>20</sup> Our results suggest that treatment targets of  $\geq 5\%$  ischemia reduction or elimination of residual ischemia are therapeutic goals that should be tested in a randomized clinical trial, especially in patients with moderate to severe ischemia at baseline.

### Study Limitations

Although patients in the main trial were randomized, results from the present series are nonrandom comparisons by treatment. A comparison of clinical characteristics reveals that substudy patients were generally lower risk than patients in the main trial. MPS ischemia testing was not mandated in the main study protocol, and, as such, treatment comparisons may be the result of selection bias. Sites were encouraged to enroll consecutive patients when clinically feasible. Studies such as the Bypass Angioplasty Revascularization Investigation-2 Diabetes trial may provide new insights into the value of routine pretreatment stress MPS,<sup>21</sup> a required test within this trial. This substudy was not statistically powered to examine differences in long-term prognosis. Although when taken out of context, the substudy results suggest that subjects randomized to PCI+OMT would have lower risk for death or MI than those randomized to OMT alone, we know that this was not found in the main COURAGE trial results.<sup>6</sup> This suggests that the sample in this nonrandomized substudy is selected and deviates from the overall COURAGE population.

### Conclusions

From this substudy of selected COURAGE patients who underwent serial MPS imaging, adding PCI to OMT resulted in greater reduction in inducible ischemia compared with OMT alone, and the benefit was greatest among patients with more severe baseline ischemia. Our exploratory analysis of clinical outcomes revealed that, regardless of treatment assignment, the magnitude of residual ischemia on follow-up MPS was proportional to the risk for death or MI, and a  $\geq 5\%$  reduction in ischemia was associated with a significant reduction in risk. These observations should inform the design of future randomized controlled trials to test the utility of reducing myocardial ischemia to  $\leq 5\%$  in patients with moderate to severe pretreatment ischemia to optimize prognosis.

### Sources of Funding

This study was supported by the Cooperative Studies Program of the Department of Veterans Affairs Office of Research and Development. Support for this nuclear substudy was provided by Astellas Healthcare and Bristol-Myers Squibb in the form of unrestricted research grants to the Department of Veterans Affairs.

### Disclosures

Drs Shaw and Berman have declared a conflict for this substudy with grant support from Astellas Healthcare and Bristol-Myers Squibb Medical Imaging. Drs Berman, Germano, and Slomka participate in royalties from licensure of computer software. The other authors report no conflicts.

### References

1. American College of Cardiology/American Heart Association. Chronic stable angina: ACC/AHA 2002 guideline update for management of patients with chronic stable angina. Available at: [http://www.acc.org/qualityandscience/clinical/guidelines/stable/stable\\_clean.pdf](http://www.acc.org/qualityandscience/clinical/guidelines/stable/stable_clean.pdf). Accessed February 1, 2008.
2. Hachamovitch R, Hayes SW, Friedman JD, Cohen I, Berman DS. Comparison of the short-term survival benefit associated with revascularization compared with medical therapy in patients with no prior coronary artery disease undergoing stress myocardial perfusion single photon emission computed tomography. *Circulation*. 2003;107:2900–2907.
3. Shaw LJ, Hachamovitch R, Berman DS, Marwick TH, Lauer MS, Heller GV, Iskandrian AE, Kesler KL, Travin MI, Lewin HC, Hendel RC, Borges-Neto S, Miller DD. The economic consequences of available diagnostic and prognostic strategies for the evaluation of stable angina patients: an observational assessment of the value of precatheterization ischemia. *J Am Coll Cardiol*. 1999;33:661–669.
4. Hachamovitch R, Berman DS, Kiat H, Cohen I, Cabico JA, Friedman J, Diamond GA. Exercise myocardial perfusion SPECT in patients without known coronary artery disease: incremental prognostic value and use in risk stratification. *Circulation*. 1996;93:905–914.
5. Hachamovitch R, Berman DS, Shaw LJ, Kiat H, Cohen I, Cabico JA, Friedman J, Diamond GA. Incremental prognostic value of myocardial perfusion single photon emission computed tomography for the prediction of cardiac death: differential stratification for risk of cardiac death and myocardial infarction. *Circulation*. 1998;97:535–543.
6. Boden WE, O'Rourke RA, Teo KK, Hartigan PM, Maron DJ, Kostuk WJ, Knudtson M, Dada M, Casperson P, Harris CL, Chaitman BR, Shaw L, Gosselin G, Nawaz S, Title LM, Gau G, Blaustein AS, Booth DC, Bates ER, Spertus JA, Berman DS, Mancini GB, Weintraub WS. Optimal medical therapy with or without PCI for stable coronary disease. *N Engl J Med*. 2007;356:1503–1516.
7. Gould AL, Davies GM, Alemao E, Yin DD, Cook JR. Cholesterol reduction yields clinical benefits: meta-analysis including recent trials. *Clin Ther*. 2007;29:778–794.
8. Hung G-U, Lee K-W, Chen C-P, Yang K-T, Lin WY. Worsening of left ventricular ejection fraction induced by dipyridamole on TI-201 gated myocardial perfusion imaging predicts significant coronary artery disease. *J Nucl Cardiol*. 2006;13:225–232.
9. Schwartz RG, Pearson TA, Kalaria VG, Mackin ML, Williford DJ, Awasthi A, Shah A, Rains A, Guido JG. Prospective serial evaluation of myocardial perfusion and lipids during the first six months of pravastatin therapy. *J Am Coll Cardiol*. 2003;42:600–610.
10. Mostaza JM, Gomez MV, Gallardo F, Salazar ML, Martin-Jadraque R, Plaza-Celemin L, Gonzalez-Maqueda I, Martin-Jadraque L. Cholesterol reduction improves myocardial perfusion abnormalities in patients with coronary artery disease and average cholesterol levels. *J Am Coll Cardiol*. 2000;35:76–82.
11. Berman DS, Kang X, Schisterman EF, Gerlach J, Kavanagh PB, Areeda JS, Sharir T, Hayes SW, Shaw LJ, Lewin HC, Friedman JD, Miranda R, Germano G. Serial changes on quantitative myocardial perfusion SPECT in patients undergoing revascularization or conservative therapy. *J Nucl Cardiol*. 2001;8:428–437.
12. Rinaldi CA, Linka AZ, Masani ND, Avery PG, Jones E, Saunders H, Hall RJC. Amlodipine and isosorbide mononitrate on the time course and severity of exercise-induced myocardial stunning. *Circulation*. 1998;98:749–756.
13. Shaw LJ, Heller GV, Casperson P, Miranda-Peats R, Friedman J, Hayes SW, Schartz R, Weintraub WS, Maron DJ, Dada M, King S, Teo K, Hartigan P, Boden WE, O'Rourke RA, Berman DS, for the COURAGE Investigators. Gated myocardial perfusion single photon emission computed tomography imaging in the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation Trial. *J Nucl Cardiol*. 2006;13:685–698.
14. Slomka PJ, Nishina H, Berman DS, Akincioglu C, Abidov A, Friedman JD, Hayes SW, Germano G. Automated quantification of myocardial perfusion SPECT using simplified normal limits. *J Nucl Cardiol*. 2005;12:66–77.
15. Berman DS, Abidov A, Kang X, Hayes SW, Friedman JD, Sciammarella MG, Cohen I, Gerlach J, Waechter PB, Germano G, Hachamovitch R. Prognostic validation of a 17-segment score derived from a 20-segment score for myocardial perfusion SPECT interpretation. *J Nucl Cardiol*. 2004;11:414–423.
16. Matzer L, Kiat H, Van Train K, Germano G, Papanicolaou M, Siligan G, Eigler N, Maddahi J, Berman D. Quantitative severity of stress



- thallium-201 myocardial perfusion SPECT defects in one-vessel coronary artery disease. *Am J Cardiol.* 1993;72:273–279.
17. Germano G, Kiat H, Kavanagh P, Moriel M, Mazzanti M, Su HT, Van Train K, Berman DS. Automatic quantification of ejection fraction from gated myocardial perfusion SPECT. *J Nucl Med.* 1995;36:2138–2147.
  18. Mahmarijan JJ, Dakik HA, Filipchuk NG, Shaw LJ, Iskander SS, Ruddy TD, Keng F, Henzlova MJ, Allam A, Moye LA, Pratt CM. An initial strategy of intensive medical therapy is comparable to that of coronary revascularization for suppression of scintigraphic ischemia in high-risk but stable survivors of acute myocardial infarction. *J Am Coll Cardiol.* 2006;48:2458–2467.
  19. Califf RM, Armstrong PW, Carver JR, D'Agostino RB, Strauss WE. Stratification of patients into high, medium, and low risk subgroups for purposes of risk factor management. *J Am Coll Cardiol.* 1996;27:964–1047.
  20. Parisi AF, Hartigan PM, Folland ED. Evaluation of exercise thallium scintigraphy versus exercise electrocardiography in predicting survival outcomes and morbid cardiac events in patients with single- and double-vessel disease: findings from the Angioplasty Compared to Medicine Study. *J Am Coll Cardiol.* 1997;30:1256–1263.
  21. Iskandrian AE, Heo J, Mehta D, Tauxe EL, Yester M, Hall MB, MacGregor JM. Gated SPECT perfusion imaging for the simultaneous assessment of myocardial perfusion and ventricular function in the BARI 2D trial. *J Nucl Cardiol.* 2006;13:83–90.

### CLINICAL PERSPECTIVE

Considerable controversy was generated by the main results from the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial, in which no difference in long-term outcome was reported for stable patients with coronary disease randomized to an initial strategy of percutaneous coronary intervention (PCI) plus optimal medical therapy versus optimal medical therapy alone. The COURAGE nuclear substudy published in this issue of *Circulation* was designed a priori to evaluate the near-term effectiveness of treatment on ischemia as measured quantitatively by myocardial perfusion imaging. The greater relative effectiveness of PCI to reduce ischemia in patients with moderate to severe baseline ischemia is consistent with the observation that patients randomized to early PCI had better initial relief from angina. The findings support the efficacy of PCI to reduce ischemia and improve symptoms and set the stage for a future randomized clinical trial using quantitative measures of ischemia. The message from the COURAGE trial remains that PCI may be safely deferred in stable patients but may be refined such that patients with substantial residual ischemia on optimal medical therapy should be considered for crossover PCI. These conclusions from the COURAGE nuclear substudy should be greeted with cautious enthusiasm because of its nonrandomized nature and small sample size.

**Go to <http://cme.ahajournals.org> to take the CME quiz for this article.**

**Optimal Medical Therapy With or Without Percutaneous Coronary Intervention to Reduce Ischemic Burden: Results From the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) Trial Nuclear Substudy**

Leslee J. Shaw, Daniel S. Berman, David J. Maron, G. B. John Mancini, Sean W. Hayes, Pamela M. Hartigan, William S. Weintraub, Robert A. O'Rourke, Marcin Dada, John A. Spertus, Bernard R. Chaitman, John Friedman, Piotr Slomka, Gary V. Heller, Guido Germano, Gilbert Gosselin, Peter Berger, William J. Kostuk, Ronald G. Schwartz, Merrill Knudtson, Emir Veledar, Eric R. Bates, Benjamin McCallister, Koon K. Teo and William E. Boden  
for the COURAGE Investigators

*Circulation*. 2008;117:1283-1291; originally published online February 11, 2008;  
doi: 10.1161/CIRCULATIONAHA.107.743963

*Circulation* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Copyright © 2008 American Heart Association, Inc. All rights reserved.

Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the  
World Wide Web at:

<http://circ.ahajournals.org/content/117/10/1283>

Data Supplement (unedited) at:

<http://circ.ahajournals.org/content/suppl/2009/01/13/CIRCULATIONAHA.107.743963.DC1>

**Permissions:** Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Circulation* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the [Permissions and Rights Question and Answer](#) document.

**Reprints:** Information about reprints can be found online at:  
<http://www.lww.com/reprints>

**Subscriptions:** Information about subscribing to *Circulation* is online at:  
<http://circ.ahajournals.org/subscriptions/>