

Pharmacological Treatment of Coronary Artery Disease With Recombinant Fibroblast Growth Factor-2 Double-Blind, Randomized, Controlled Clinical Trial

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Background—Single-bolus intracoronary administration of fibroblast growth factor-2 (FGF2) improved symptoms and myocardial function in a phase I, open-label trial in patients with coronary artery disease. We conducted the FGF Initiating Revascularization Trial (FIRST) to evaluate further the efficacy and safety of recombinant FGF2 (rFGF2).

Methods and Results—FIRST is a multicenter, randomized, double-blind, placebo-controlled trial of a single intracoronary infusion of rFGF2 at 0, 0.3, 3, or 30 $\mu\text{g}/\text{kg}$ ($n=337$ patients). Efficacy was evaluated at 90 and 180 days by exercise tolerance test, myocardial nuclear perfusion imaging, Seattle Angina Questionnaire, and Short-Form 36 questionnaire. Exercise tolerance was increased at 90 days in all groups and was not significantly different between placebo and FGF-treated groups. rFGF2 reduced angina symptoms as measured by the angina frequency score of the Seattle Angina Questionnaire (overall $P=0.035$) and the physical component summary scale of the Short-Form 36 (pairwise $P=0.033$, all FGF groups versus placebo). These differences were more pronounced in highly symptomatic patients (baseline angina frequency score ≤ 40 or Canadian Cardiovascular Society score of III or IV). None of the differences were significant at 180 days because of continued improvement in the placebo group. Adverse events were similar across all groups, except for hypotension, which occurred with higher frequency in the 30- $\mu\text{g}/\text{kg}$ rFGF2 group.

Conclusions—A single intracoronary infusion of rFGF2 does not improve exercise tolerance or myocardial perfusion but does show trends toward symptomatic improvement at 90 (but not 180) days. (*Circulation*. 2002;105:788-793.)

Key Words: coronary disease ■ angina ■ revascularization ■ angiogenesis ■ trials

Recent advances in vascular biology suggest the possibility of a novel therapeutic approach to treatment of advanced coronary artery disease (CAD) that relies on stimulating growth of collateral blood vessels. This approach seeks to augment normal collateral development by exposing the heart to growth factors capable of stimulating the growth of new blood vessels or the maturation of preexisting collaterals.¹

Preclinical studies have demonstrated that application of such factors, including the basic fibroblast growth factor (bFGF or FGF2), can lead to development of collateral circulation and restoration of myocardial perfusion and function in chronically ischemic myocardium.² A single-bolus intracoronary infusion of recombinant fibroblast growth factor-2 (rFGF2) seemed to be safe^{3,4} and potentially efficacious in an open-label, phase I clinical trial.^{4,5} The present

study was designed to evaluate safety and efficacy of intracoronary rFGF2 in patients with advanced CAD.

Methods

Patient Selection

The study population included patients with CAD who were considered suboptimal candidates for standard surgical or catheter-based revascularization. Exercise tolerance test (ETT) duration ≥ 3 minutes and < 13 minutes on a modified Bruce protocol on 2 consecutive tests (> 24 hours but < 2 weeks apart), with the difference between the 2 exercise times within 20% of their mean, was required for entry. Other inclusion criteria included the presence of inducible ischemia on a nuclear scan occupying at least 15% of the left ventricle and an ejection fraction $\geq 30\%$. Patients with unstable angina, myocardial infarction, coronary artery bypass surgery (CABG) or percutaneous transluminal angioplasty (PTCA) within the past 3 months, or malignancy within the past 10 years, were excluded, as were patients with renal dysfunction, retinopathy, or

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The Appendix lists the clinical sites and investigators that participated in FIRST.

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other conditions that, in the opinion of the investigators, made the patient unsuitable for rFGF2 treatment.

Study Design and Procedures

Patients were randomly assigned in a 1:1:1:1 ratio to receive 0.3, 3, or 30 μg/kg rFGF2 or placebo administered as a 20-minute intracoronary infusion divided between the 2 arterial conduits using a calibrated infusion pump. Patients received a single intravenous bolus of heparin (40 U/kg) 10 to 20 minutes before the study drug infusion. After dosing, patients were monitored for at least 6 hours and then followed at specified intervals over 180 days.

Assessments

The primary efficacy variable was the change in ETT duration from baseline to 90-day follow-up. Secondary efficacy variables included the change in ETT duration from baseline to 180-day follow-up; changes from baseline to 90- and 180-day follow-up in Canadian Cardiovascular Society (CCS) angina class and in quality of life as measured by the Seattle Angina Questionnaire (SAQ)⁶ and the Short Form-36 (SF-36); and changes in the magnitude of ischemia segments on single-photon emission computed tomography (SPECT) imaging from baseline to 90 and 180 days. Patients undergoing any form of coronary revascularization after study enrollment were excluded from analysis, as were patients who missed follow-up assessments or withdrew from the trial.

Myocardial perfusion imaging was performed with the dual isotope technique (rest Tl²⁰¹, stress Tc99 m-sestamibi) using dipyridamole stress. Patients with resting Tl²⁰¹ defects underwent additional redistribution imaging at 4 or 24 hours. Images were analyzed by the Cardiac Imaging Core Laboratory at New England Medical Center, Boston, Mass, using a semiquantitative grading system in a 20-segment left ventricular model. Grading was blind with regard to patient identity and treatment group assignment, as has been previously described.⁵

Materials

The rFGF2 used in this study (Chiron Corporation, Emeryville, Calif) was a 146–amino acid, nonglycosylated, monomeric, 16.5-kDa protein expressed in genetically engineered yeast. Placebo contained 10 mmol/L sodium citrate, 10 mmol/L monothioglycerol, 0.3 mmol/L EDTA, and 135 mmol/L sodium chloride, pH 5.0.

Ethics

This study was conducted in accordance with the Declaration of Helsinki and good clinical practice according to International Conference on Harmonisation guidelines.

Analysis and Statistics

Analyses of ETT, SAQ, and SF-36 data were performed using 2-way ANOVA with treatment and study center as factors. Pairwise comparisons of rFGF2 groups were performed at the nominal α-level. For all efficacy analyses, patients were excluded if they underwent standard revascularization procedures or were missing the assessment. Secondary analyses included patients with a revascularization or who were missing the assessment by assigning them the lowest rank and using the ANOVA of ranks method. For changes from baseline in nuclear imaging data, ANOVA and ANOVA of ranks were also used.

Results

Patient Characteristics and rFGF2 Safety

A total of 337 patients were randomized to receive a single intracoronary infusion of rFGF2 (0.3, 3.0, or 30 μg/kg) or placebo in a double-blind manner. The demographics and clinical characteristics of the patient population distributed equally across study groups (Table 1). Overall, the average age of the patients was 63 years (range, 33 to 86 years), and

TABLE 1. Study Patient Population

	Placebo	rFGF-2, μg/kg		
		0.3	3.0	30
Patients, n	86	82	84	85
Age, y	64±10	63±9	63±10	62±9
Sex, % male	86	84	80	86
Diabetes, %	32	33	37	25
Dyslipidemia, %	93	94	95	91
Hypertension, %	77	71	68	68
Current smokers, %	8	11	10	10
Prior MI, %	70	65	65	69
Prior CABG, %	91	89	88	89
Prior PTCA, %	67	54	55	55
Single-vessel CAD, %	19	14	11	12
Two-vessel CAD, %	27	34	32	40
Three-vessel CAD, %	51	45	52	45
Baseline ETT, s	513±160	527±139	525±159	514±148
Baseline CCS class II/III, %	87	87	90	89

MI indicates myocardial infarction.

84% were male. Virtually the entire population was dyslipidemic, with a high prevalence of hypertension and diabetes mellitus. Sixty-seven percent had a history of myocardial infarction, 89% had had a prior CABG, 58% had had a prior PTCA, and 53% had had both forms of revascularization. The majority had CCS class II or III angina (88%), and the baseline exercise time was 520 seconds.

Safety was monitored by evaluating adverse events, laboratory data, ophthalmological examinations, and antibody data. Complete safety data were available in 321 patients who completed the protocol. Overall, rFGF2 seemed safe (Table 2). Most adverse events were mild to moderate in severity; severe or life-threatening adverse effects occurred with similar frequency across groups. There were 6 deaths (1 in placebo group and 5 in FGF-treated groups); all were consistent with cardiovascular disease, and 5 of 6 were deemed possibly related to rFGF2 by investigators.

TABLE 2. Safety of Intracoronary Administration of rFGF-2

	Placebo	rFGF-2, μg/kg		
		0.3	3.0	30
Patients, n	86	82	84	85
Death, n (%)	1 (1)	1 (1)	3 (3)	1 (1)
Carcinoma, n (%)	1 (1)	0	1 (1)	1 (1)
Angina pectoris, n (%)	15 (17)	11 (13)	7 (8)	17 (20)
Unstable angina admissions, n (%)	13 (15)	8 (10)	4 (5)	14 (16)
Myocardial infarction, n (%)	5 (6)	2 (2)	5 (6)	5 (6)
Revascularization, n (%)	5 (6)	5 (6)	3 (4)	6 (7)
Proteinuria >300 mg/24 h, n (%)	3 (4)	5 (6)	3 (4)	3 (4)
Retinal changes, n (%)	0	0	0	2 (2)
All SAE, n (%)	29 (34)	29 (35)	22 (26)	35 (41)

SAE indicates serious adverse events.

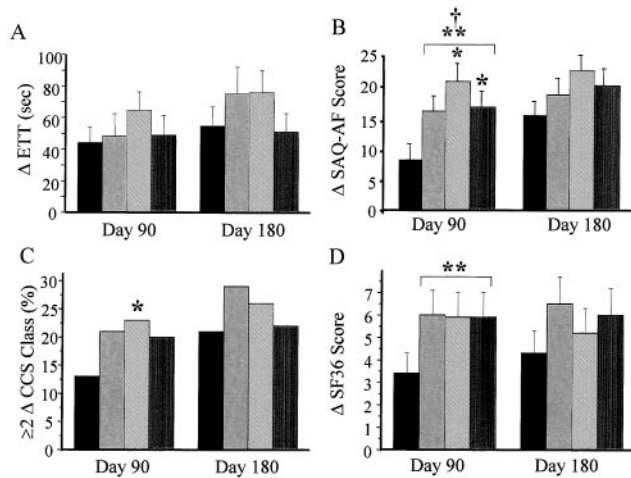


Figure 1. Three- and 6-month outcomes after intracoronary rFGF2 administration. Changes in ETT (seconds) (A), SAQ-AF scale (B), 2 or more CCS angina classes (C), or SF-36 physical component summary scale (PSSC) (D) from baseline to day 90 and day 180 are presented for the placebo group (black bars) and (from left to right) for the 0.3- μ g/kg (gray bars), 3.0- μ g/kg (striped bars), and 30- μ g/kg (stippled bars) rFGF2 groups. * P <0.05 by pairwise t test; ** P <0.05 by pairwise t test vs any FGF2 group; and †overall P <0.05. Change in CCS scores is expressed as % of patients in each group demonstrating ≥ 2 class improvement.

Angina pectoris of any severity was reported in 15% of the patients, whereas unstable angina requiring hospitalization occurred in 11.5% of the patients. Both were distributed equally across all groups. There were no differences in occurrence of new myocardial infarctions, frequency of revascularizations, or significant changes in the use of anti-anginal medications among the study groups.

Hypotension in association with dosing occurred more frequently in the high-dose FGF2 group. Proteinuria was reported as an adverse event in 1% to 2% of patients in each group; significant proteinuria (>300 mg per 24 hours) was equally prevalent among the 4 groups. Malignancies occurred in 3 patients: a recurrent renal cell carcinoma in the placebo group (day 250), a prostate carcinoma in mid-dose group (day 94), and a basal cell carcinoma in high-dose group (day 169).

Significant retinal changes were reported in 2 patients (2%) in the high-dose group: a subretinal lesion (day 79) and severe diabetic retinopathy and iris neovascularization (day 308). Infusion of rFGF2 was not associated with the development of immune response to rFGF2 as measured by FGF2 antibody titers.

Efficacy: Prespecified Analyses

Change in ETT time from baseline to 90 days was available in 313 patients and at 180 days in 296 patients. The excluded patients were equally distributed among all 4 groups. All groups demonstrated increases in the treadmill exercise time at 90 days of follow-up, and this was maintained at 6 months (Figure 1A). rFGF2 therapy was not significantly better than placebo at either 90 days ($P=0.64$) or 180 days ($P=0.44$).

Angina frequency as measured by the SAQ was reduced by rFGF2 infusion at 90 days (overall $P=0.035$; pairwise $P=0.08, 0.004, 0.05$ for the low-, mid-, and high-dose

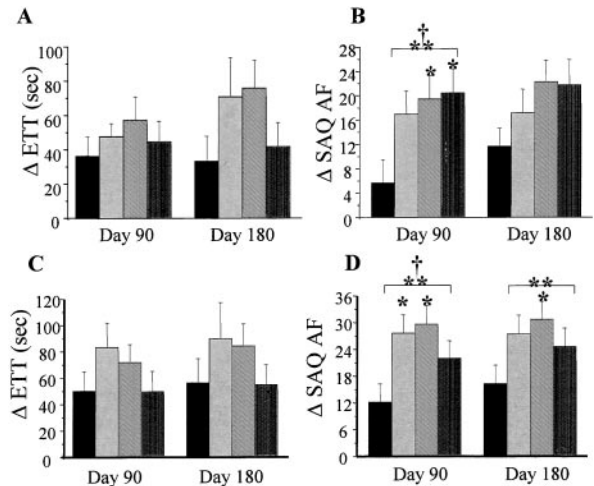


Figure 2. Effect of rFGF2 therapy on exercise tolerance and angina frequency in patients with severe (CCS class III and IV) angina (A and B) and lower median SAQ-AF scores (C and D). Changes in ETT (A) and SAQ-AF scores (B) from baseline to day 90 and day 180 are shown for patients with CCS class angina III and IV at the initiation of the study. Changes in ETT (C) and SAQ-AF scores (D) from baseline to day 90 and day 180 are shown for patients with baseline SAQ-AF scores ≤ 40 (median SAQ-AF score=40 for the entire trial). * P <0.05 by pairwise t test; ** P <0.05 by pairwise t test vs any FGF2 group; and †overall P <0.05.

groups, respectively) (Figure 1B). However, the difference between the FGF-treated and placebo groups was lost at 180 days because of continued improvement in the placebo group. Other domains of the SAQ scale, including the exertional capacity, treatment satisfaction, and disease perception domains, did not demonstrate a significant difference between FGF-treated groups and placebo at 90 days or 180 days.

Investigator assessment of CCS angina class confirmed the results of the patient assessment of angina frequency. The improvement reached statistical significance at 90 days for the mid-dose group ($P=0.012$). As with the SAQ angina frequency (AF) scale, the difference was lost at 180 days because of continued improvement in the control group (Figure 1C). The physical component summary score of the SF-36 form was increased by rFGF2 infusion at 90 days (pairwise comparison of any FGF group versus placebo group, $P=0.033$). No significant difference in physical component summary score was seen at 180 days (Figure 1D).

Nuclear perfusion imaging demonstrated no significant changes in the rest or stress perfusion, including average stress or rest scores and average reversibility score (magnitude of ischemia) between the placebo and the rFGF2 groups at 90 or 180 days.

Efficacy Assessment: Post Hoc Analysis

To gain further insight into biological effects of rFGF2 therapy and to potentially define a patient population that might significantly benefit from this form of angiogenic therapy, we conducted retrospective analyses. Because more symptomatic patients might benefit most from rFGF2, we stratified the study population by baseline CCS class (class III or IV versus class I or II) and SAQ angina frequency scale (≤ 40 versus >40).

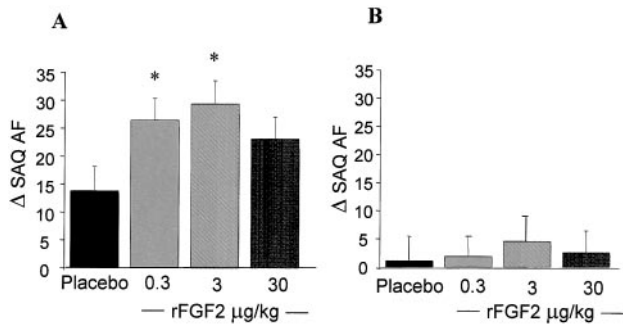


Figure 3. Effect of baseline angina frequency on symptomatic response to rFGF2 therapy. Change in SAQ-AF scores in rFGF2 or placebo-treated patients at 90 days of follow-up stratified by the baseline median SAQ-AF score. Note significant improvement in patients with lower than median SAQ-AF scores (A) and virtually no change in patients with higher than medium baseline SAQ-AF scores (B). * $P < 0.05$ by pairwise t test.

Patients with baseline CCS class III or IV angina showed no significant improvement in ETT at 90 days after rFGF2 therapy compared with placebo, although direction of change favored FGF-treated groups at 90 and 180 days (Figure 2A). However, these patients had a reduction in angina frequency at 90 days (overall $P = 0.035$ rFGF2 versus placebo) (Figure 2B). This difference disappeared by 180 days.

Patients with baseline SAQ angina frequency score ≤ 40 showed no significant improvement after rFGF2 therapy compared with placebo in ETT performance at 90 or 180 days (Figure 2C). However, these patients had a significant reduction in angina frequency at 90 days (overall $P = 0.02$) that was reduced by 180 days (overall $P = 0.12$). (Figure 2D). To determine the effect of baseline symptom burden on rFGF2 response, we compared improvement in SAQ angina frequency in patients with above- or below-median baseline SAQ-AF score. Although there was a substantial improvement in the below-median baseline SAQ-AF group (Figure 3A), patients with the low baseline symptom burden (above-median SAQ-AF group) had no detectable symptomatic improvements (Figure 3B). Stratification by baseline median CCS class produced similar results (data not shown).

Discussion

A single intracoronary infusion of rFGF2 in patients with advanced CAD seemed to be safe and well tolerated but showed no significant improvement in ETT time at 90 or 180 days. There was a reduction in angina frequency at 90 days; at 180 days this effect was lost because of continued improvement in the placebo group. Patients who were more symptomatic at baseline, as measured by CCS angina class or SAQ angina frequency score, showed the greatest improvement.

FGF2 is a pluripotent growth factor capable of stimulating growth and migration of a number of cell types⁷ of and promoting vascular tree branching.⁸ The factor signals through tyrosine kinase receptors⁹ and syndecan-4 heparan sulfate core protein.¹⁰ Increased expression of these receptors in the ischemic myocardium enhances responsiveness to FGF2 stimulation. Preclinical studies of FGF2 showed therapeutic efficacy in chronic ischemia models, as demonstrated

by augmentation of coronary flow^{11,12} and ventricular function.¹³ In addition, a small, double-blind, randomized trial of sustained-release FGF2 implanted in the myocardium during surgery suggested clinical efficacy.¹⁴ Thus, a significant body of research supports efficacy of FGF2 as an angiogenic agent.

The mode of growth factor delivery may alter its efficacy significantly. In a preclinical study, a single intracoronary injection of FGF2 improved perfusion and function¹⁵ despite the initial (1 hour) retention of $< 1\%$ of the total dose in the myocardium and a rapid washout of the retained protein.¹⁶ Although these small amounts of retained FGF2 are effective in healthy, young animals, they may be insufficient in older patients with diffuse atherosclerotic disease. Other delivery modalities, including intrapericardial instillation¹⁷ and intramyocardial injections, result in higher initial and late retention of FGF2 in the myocardium.¹⁸

The patient population chosen for this study constituted a “no option/poor option” group. These individuals have demonstrated inadequate native angiogenic response, making them particularly challenging for biological agents designed to stimulate the very same process. Moreover, several over-the-counter and cardiac medications may significantly interfere with the angiogenic activity of growth factors,¹⁹ a feature not controlled for in this study. Nevertheless, the present trial identifies a population of highly symptomatic individuals who appear to demonstrate a beneficial response to angiogenic therapy.

The remaining critical consideration is the choice of study end points.²⁰ In particular, the relatively long baseline ETT time in this trial (540 seconds) may make it harder to demonstrate a significant improvement. In this regard, only half the patients stopped the exercise test because of cardiac symptoms (angina or shortness of breath).

Symptom-related end points, including changes in angina frequency and physical well-being, indicate a significant improvement. In addition, the severity of symptoms at baseline, stratified by either the median angina frequency score or advanced (class III or IV) angina class, identifies a subgroup of patients with a better response, whereas patients with lower angina burden demonstrated little or no improvement.

The lack of overall improvement on nuclear scans is an important and puzzling observation. Open-label phase I studies of nonsurgical therapeutic angiogenesis reported improved SPECT perfusion in patients receiving intracoronary vascular endothelial growth factor²¹ and FGF2,⁵ as well as intramyocardial injections of vascular endothelial growth factor plasmid.^{22,23} One potential explanation is the difference in patient populations in these trials versus the patient population of the VEGF (vascular endothelial growth factor) in Ischemia for Vascular Angiogenesis (VIVA) and FIRST trials. Alternatively, a genuine improvement in the placebo group may be caused by enhanced medical care in trial setting, thereby “washing out” significant effect of growth factors on nuclear scanning–assessed perfusion. The magnitude of the placebo effect seen here (45 seconds) is similar to the improvement in ETT noted in the Angioplasty Compared to Medicine (ACME) trial (30 seconds) after institution of aggressive medical therapy.²⁴ Alternatively, perfusion nuclear imaging may lack the spatial resolution and the sensi-

tivity to demonstrate changes in myocardial perfusion in the setting of growth factor therapy in a trial of this size. Other imaging modalities, including MR perfusion,^{25–27} collateral-sensitive imaging,²⁸ or PET imaging, may be more suitable.

Finally, it is important to put this trial in perspective with other trials of angiogenic growth factor therapy. A number of small open-label trials,^{23,29,30} including a phase I rFGF2 trial,⁴ generated much enthusiasm by demonstrating very significant functional and symptomatic improvement in enrolled patients. The discrepancy in results between open-label and double-blind studies clearly indicates the need for blinding and controls in evaluation of angiogenic therapies.

In summary, single intracoronary rFGF2 infusion seems to result in short-term symptomatic improvement that is most pronounced in the more symptomatic patient subgroups; however, this did not translate into improved exercise tolerance. Given the favorable safety profile, additional trials of intracoronary rFGF2, enrolling highly symptomatic patients and using high-resolution perfusion imaging modalities, are warranted to further assess this mode of angiogenic growth factor therapy.

Appendix

The following sites and investigators participated in FIRST (The first name listed for each site is the site's principal investigator; the second name is the site's study coordinator): Duke/VA Medical Center, Durham, NC (Brian Annex, MD; Dawn Landis); Duke University Medical Center, Durham, NC (Brian Annex, MD; Cathy Martz); University of Texas, San Antonio, Tex (Steven Bailey, MD; Geraldine Cooper-Read); Cardiology of Georgia, Atlanta, Ga (Charles Brown III, MD; Kristina Picardi); Albert Einstein Hospital, Bronx, NY (David Brown, MD; Miriam Zavala, RN); UCSF Moffitt Hospital, San Francisco, Calif (Tony M. Chou, MD; Alisa Gaskin, RN, MS); University of Massachusetts Medical Center, Worcester, Mass (Harold Dauerman, MD; Steven Ball, RN); USC Medical Center—Cardiology Division, Los Angeles, Calif (David Faxon, MD; Wendy Hill); New York Medical College, Valhalla, NY (William Frishman, MD; Jane Rainaldi, RN); Hennepin County Medical Center, Minneapolis, Minn (Timothy Henry, MD; Kathy Peterson-Nordby, RN); The Lidner Center, Cincinnati, Ohio (Dean Kereiakes, MD; Karen Ibanez); Florida Cardiovascular Research, Atlantis, Fla (Joshua Kieval, MD; Elizabeth Dagher); Methodist Hospital, Houston, Tex (Neal Kleiman, MD; DeeDee Copeland, RN); Atlanta Cardiology Group, Atlanta, Ga (Nicolas Chronos, MD; Shebrenia Williams); University of Michigan, Ann Arbor, Mich (Robert Lederman, MD; Ann Luciano); Emory University Hospital, Atlanta, Ga (Mark Leimbach, MD; Pamela Hyde, RN, BSN); Oklahoma Heart Institute, Tulsa, Okla (Wayne Leimbach, MD; Jolene Durham, RN); Mercy Heart Institute, Sacramento, Calif (Reginald Low, MD; Kori Harder); Lenox Hill Hospital, New York, NY (Jeff Moses, MD; Diana Bernal); Falk Cardiovascular Research Center, Sanford, Calif (Stanley Rockson, MD; Frankie Burckhardt, RN); Wake Medical Center—Wake Heart Association, Raleigh, NC (Joel Schneider, MD; Mary S. Hill); Beth Israel Deaconess Medical Center, Boston, Mass (Michael Simons, MD; Deanna Neimann, RN); New England Medical Center, Boston, Mass (John J. Smith, MD; Veronika Testa, RN, BSN); Iowa Heart Center, Des Moines, Iowa (Mark Tannenbaum, MD; Teresa Coulson, RN); Scripps Clinic, La Jolla, Calif (Paul Teirstein, MD; Hilary Kimes); Minneapolis Heart Institute, Minneapolis, Minn (Jay Traverse, MD; Lisa Mayberry, RN); Seattle Cardiovascular Research, Seattle, Wash (Jeffrey Werner, MD; Staci Eggert); St Thomas Cardiology Group, Nashville, Tenn (Robert Wheatley, MD; Judy McCarthy); and

Presbyterian Medical Center, Philadelphia, Pa (Robert Wilensky, MD; Sharon Hanlon, RN, MSN).

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