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Longevity of the Placebo Effect in the Therapeutic Angiogenesis and Laser Myocardial Revascularization Trials in Patients With Coronary Heart Disease

Jamal S. Rana, MD, Arjuna Mannam, MD, Laurel Donnell-Fink, Ernesto V. Gervino, ScD, Frank W. Sellke, MD, and Roger J. Laham, MD

The long-term beneficial effects of placebo therapy were evaluated in angiogenesis and laser myocardial revascularization trials in patients who had end-stage coronary heart disease. Improvements in mean angina class, exercise treadmill time, and quality of life were mostly maintained at 30 ± 6 months of follow-up. Persistence of effect cannot be used as evidence of efficacy, and double-blinded trials are essential in this patient population. ©2005 by Excerpta Medica Inc. (Am J Cardiol 2005;95:1456–1459)

Clinical trials of angiogenesis and laser myocardial revascularization (LMR) have drawn attention to the tremendous power of the placebo effect in patients who have end-stage coronary disease.^{1–8} A remarkable consistency in these studies was the profound and confounding placebo effect, which was not limited to “soft” symptomatic end points but was also observed

in such “hard” end points as exercise time and magnetic resonance imaging.^{1–4} To study the longevity of the placebo effect, we systematically evaluated patients who had “no option” and were enrolled in clinical angiogenesis and LMR studies^{1–8} and investigated the persistence of the placebo effect on clinical outcomes, angina class, angina frequency score, and exercise time.

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The patients for our study were selected from angiogenesis and LMR trials.^{2–9} The study population for angiogenesis trials^{2–7} included patients who had coronary artery disease and were considered suboptimal candidates for standard surgical or catheter-based revascularization, with exercise tolerance test (ETT) durations of ≥3 and <13 minutes on a modified Bruce’s protocol. Other inclusion criteria included the presence of inducible ischemia on a nuclear scan that occupied ≥15% of the left ventricle and an ejection fraction ≥30%. Patients who had unstable angina, myocardial infarction, coronary artery bypass grafting, or percutaneous transluminal coronary angioplasty within the previous 3 months or malignancy within the previous 10 years were excluded, as were patients who had renal dysfunction and retinopathy.

In the Fibroblast Growth Factor-2 (FGF-2) study, patients were randomly assigned to therapy or placebo in a 1:1:1 ratio to receive 0.3, 3, or 30 μg/kg of

From the Angiogenesis Research Center and Division of Cardiology and Cardiac Surgery, Department of Medicine, Harvard Medical School and Beth Israel Deaconess Medical Center, Boston, Massachusetts. Dr. Laham’s address is: Angiogenesis Research Center and Interventional Cardiology Section, Division of Cardiology, BIDMC/Harvard Medical School, 330 Brookline Avenue, Boston, Massachusetts 02215. E-mail: rlaham@bidmc.harvard.edu. Manuscript received October 25, 2004; revised manuscript received and accepted February 8, 2005.

TABLE 1 Baseline Clinical Characteristics and Major Adverse Cardiac Events and Angina Pectoris Class at Follow-up	
	Patients (n = 129)
Baseline characteristics	
Age (yrs)	65 ± 10
Women	19 (14%)
Diabetes	46 (36%)
Systemic hypertension	40 (31%)
Cholesterol >200 mg/dl	106 (82%)
Previous myocardial infarction	57 (44%)
Previous coronary artery bypass graft	112 (87%)
Previous percutaneous intervention	125 (97%)
Baseline ejection fraction	44 (14%)
Mean angina class	3.0 ± 0.5
Class III or IV angina pectoris	106 (82%)
Major adverse cardiac events and angina class at follow-up of 30 ± 6 months	
Death	3 (2.3%)
Major myocardial infarction	3 (2.3%)
All myocardial infarctions	11 (12.4%)
Stroke	2 (1.4%)
Repeat revascularization	
Repeat percutaneous transluminal coronary angioplasty	9 (8.5%)
Repeat coronary artery bypass grafting	1 (0.7%)
Improvement by angina class	
By 1 class	99 (72%)
By 2 classes	53 (41%)
Values are means ± SEM or numbers of patients (percentages).	

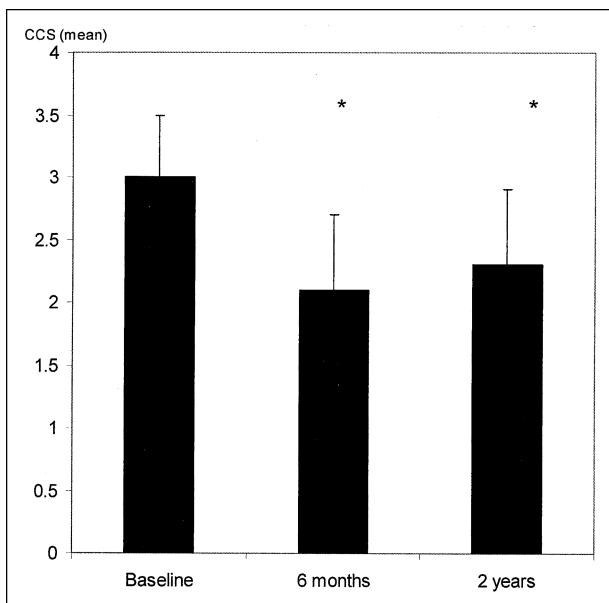


FIGURE 1. Angina class (Canadian Cardiovascular Society [CCS]) at baseline, 6 months, and 2 years in the placebo arms of the angiogenesis trials. Data are presented as mean ± SEM. **p* <0.001 for 6 months and 2 years.

recombinant FGF-2 or placebo administered as a 20-minute intracoronary infusion that was 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 mon-

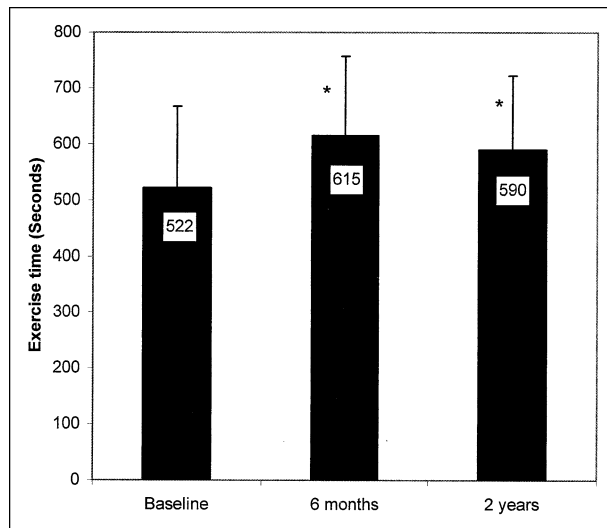


FIGURE 2. ETT times in patients in the placebo arms of angiogenesis studies with matched baseline and follow-up protocols showed significant improvement at 6 months and 2 years. Data are presented as mean ± SEM. **p* <0.001 for 6 months and 2 years.

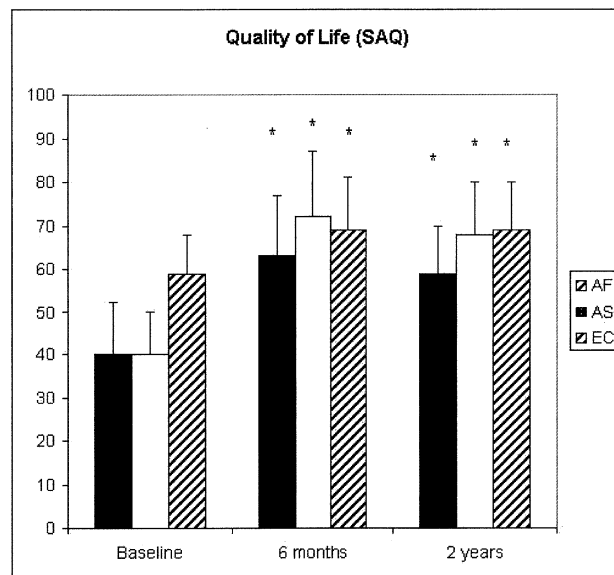


FIGURE 3. Quality-of-life assessment using the Seattle Angina Questionnaire showed significant improvements in 3 scales; angina frequency (AF; black bar), angina stability (AS, white bar), and exertional capacity (EC, striped bar) at 6 months and 2 years compared with baseline. Data presented as mean ± SEM. *Statistical significance, *p* <0.001.

itored for ≥6 hours and then followed at specified intervals over 2 years.

Patients were candidates for the LMR trials^{7,8} if they (1) had symptomatic coronary artery disease with chronic refractory angina, defined as Canadian Cardiovascular Society class III to IV angina, despite best tolerated pharmacologic therapy and (2) were poor candidates for percutaneous transluminal coronary angioplasty or surgical revascularization. Major exclusion criteria included severe left ventricular dysfunction (ejection fraction <0.30), myocardial infarction

within 1 month, recent angioplasty within 4 months, chronic atrial fibrillation, and major co-morbidity. Patients were randomly assigned to therapy or placebo in a 1:1:1 ratio to receive large- or small-dose LMR, and placebo administered with the Biosense LMR system (Cordis, New Jersey). Informed consent was obtained from all patients.

The primary efficacy variable was the change in ETT duration from baseline to 90-day follow-up. Secondary efficacy variables included change in ETT duration from baseline to 2-year follow-up, change from baseline to 2-year follow-up in Canadian Cardiovascular Society angina class, and change in quality of life as measured by the Seattle Angina Questionnaire.⁹ Patients who underwent 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.

Analyses of ETT, Seattle Angina Questionnaire, and Short Form-36 data were performed using 2-way analysis of variance with treatment as factors. Pairwise comparisons of recombinant FGF-2 and LMR groups were performed at the nominal α level. Secondary analyses included patients who underwent revascularization or who were missing an assessment by assigning them the lowest rank and using analysis of variance of ranks.

A total of 129 patients enrolled in these trials was followed for a mean follow-up of 30 ± 6 months (range 24 to 42). For ETT and quality-of-life variables, 92 patients were followed for >6 months. Demographics and clinical characteristics of the patient population are listed in Table 1.

Mean angina class at baseline was 3.0 ± 0.5 (Canadian Cardiovascular Society) and decreased to 2.1 ± 0.6 at 6 months ($p < 0.001$), with 24.6% of patients showing a decrease by ≥ 2 angina classes. At final follow-up, the angina class was 2.3 ± 0.6 ($p < 0.001$ vs baseline), with persistent improvement in ≥ 2 angina classes in 26.2% of patients (Figure 1). Baseline time on ETT was 522 ± 145 seconds. This increased to 615 ± 142 seconds at 6-month follow-up ($p < 0.001$) and improvement persisted at 2-year follow-up with a mean ETT time of 590 ± 132 seconds ($p < 0.001$; Figure 2). Baseline Seattle Angina Questionnaire scores were indicative of the end-stage nature of this patient population. The angina frequency score was 40 ± 12 , the angina stability score was 44 ± 10 , and the exertional capacity score was 45 ± 9 . These scores increased to 63 ± 14 , 72 ± 15 , and 68 ± 12 at 6 months, respectively ($p < 0.001$ for all scores). This improvement was maintained at 2-year follow-up in the 92 patients who were assessed, with an angina frequency score of 59 ± 11 , an angina stability score of 69 ± 12 , and an exertional capacity score of 69 ± 11 ($p < 0.001$ for all scores; Figure 3).

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In this systematic evaluation and follow-up of patients who had end-stage coronary heart disease and were enrolled in angiogenesis and LMR trials, we found that the beneficial effects of placebo therapy persisted over long-term follow-up. The initial im-

proved outcomes in these patients persisted as indicated by angina class, angina frequency score, and exercise time.

In the phase I, randomized, double-blind, placebo-controlled trial of FGF-2,^{1,2} in which FGF-2 was delivered to a viable and ischemic but ungraftable myocardial area in patients who underwent coronary bypass grafting, there was initial improvement at 6-month follow-up in the intervention group compared with the placebo group. However, after 2-year follow-up,¹ the placebo group caught up, and differences in symptoms became negligible. A similar, incremental "creep" effect of placebo was observed at 90 and 180 days in the FGF Initiating Revascularization Trial⁴ and the Therapeutic Angiogenesis with Recombinant Fibroblast Growth Factor-2 for Intermittent Claudication trial.¹⁰ These study findings mirrored another study of therapeutic angiogenesis using vascular endothelial growth factor in which the phase I, open-label study was markedly positive in terms of symptoms, angiographic findings, and improvements in nuclear perfusion scans.¹¹ However, the phase II, open-label, randomized, placebo-controlled study showed no benefit of therapy over placebo, with all 3 groups demonstrating significant improvements in all outcome measurements that were lower than those in the phase I study.¹²

Longer term follow-up was advocated to allow disappearance of the placebo effect. However, we have shown that the benefits of placebo therapy are maintained at 2-year follow-up. Thus, persistence of therapeutic effect in open-label studies cannot be used as evidence of efficacy, because the placebo effect may last as long. In addition, double-blinded trials remain essential in this patient population, and blinding should be maintained long term, if possible. These results warrant a better understanding of the placebo effect.

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Absence of Seasonal Variation in Myocardial Perfusion, Enzymatic Infarct Size, and Mortality in Patients With ST-Segment Elevation Myocardial Infarction Treated With Primary Angioplasty

Giuseppe De Luca, MD, PhD, Harry Suryapranata, MD, PhD,
Jan Paul Ottervanger, MD, PhD, Arnoud W.J. van't Hof, MD, PhD,
Jan C.A. Hoorntje, MD, PhD, A.T. Marcel Gosselink, MD, PhD,
Jan-Henk E. Dambrink, MD, PhD, and Menko-Jan de Boer, MD, PhD

The present study investigated any seasonal variation in myocardial perfusion, enzymatic infarct size, and 1-year mortality in 1,548 patients who underwent primary angioplasty for ST-segment elevation myocardial infarction. No seasonal variation was observed in patients' demographic and clinical characteristics. No difference was observed in the prevalence of heart failure at presentation and in myocardial perfusion, enzymatic infarct size, and 1-year mortality. ©2005 by Excerpta Medica Inc.

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Recent studies have shown a seasonal variation in the incidence of acute myocardial infarction and cardiac death, which has been observed more frequently in the winter.^{1–3} A previous report has described a seasonal variation in infarct size among patients who were treated with thrombolysis and those who were not,⁴ with larger infarcts during the winter. These findings have been accounted for by a potential effect of cold temperature on platelet activation, fibrinogen, and vascular resistance.^{5–7} The present study investigated any seasonal variation in myocardial perfusion, enzymatic infarct size, and 1-year mortality in patients who underwent primary angioplasty for ST-segment elevation myocardial infarction (STEMI).

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Between April 1997 and October 2001, all patients who had STEMI and presented within 6 hours from

symptom onset or 6 to 24 hours if they had persistent or recurrent chest pain and/or ST-segment elevation underwent acute angiography at our institution and were included in the study in case primary angioplasty was performed. A total of 1,548 of 1,683 consecutive patients who had STEMI and underwent acute angiography underwent primary angioplasty. Informed consent was obtained from each patient before the angiogram. Our study was approved by the institutional review board.

All patients received aspirin (500 mg) and heparin (10,000 IU) intravenously before the procedure. All patients were on aspirin after the procedure. Patients who underwent stenting also received additional 4-week antiplatelet therapy (ticlopidine or clopidogrel after July 1999).

Angiograms and electrocardiograms were analyzed by an independent core laboratory (Diagram BV, Zwolle, The Netherlands). Thrombolysis In Myocardial Infarction flow grade and myocardial blush grade were assessed after primary angioplasty, as previously described.⁸ Angiographic success was defined as a postprocedural Thrombolysis In Myocardial Infarction flow grade 3 and residual stenosis <50%.

Enzymatic infarct size was estimated, as previously described, by cumulative enzyme release (lactate dehydrogenase) from serial measurements up to 48 hours after symptom onset.⁹

Before discharge, left ventricular ejection fraction was measured by radionuclide ventriculography, as previously described.⁹

Records of included patients who visited our outpatient clinic were reviewed. For all other patients, information was obtained from the patient's general physician or by direct telephone interview with the patient. No patient was lost to follow-up.

Statistical analysis was performed with SPSS 12.0 (SPSS, Inc., Chicago, Illinois). Continuous data were

From the Department of Cardiology, ISALA Klinieken, Hospital De Weezenlanden, Zwolle, The Netherlands. Dr. Suryapranata's address is: ISALA Klinieken, Hospital De Weezenlanden, Department of Cardiology, Groot Wezeland 20, 8011 JW Zwolle, The Netherlands. E-mail: h.suryapranata@diagram-zwolle.nl. Manuscript received December 9, 2004; revised manuscript received and accepted February 2, 2005.