Journal of the American College of Cardiology
© 2006 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 48, No. 1, 2006
ISSN 0735-1097/06/$32.00
doi:10.1016/j.jacc.2006.02.055

CLINICAL RESEARCH **Clinical Trial**

Effects of Selective Matrix Metalloproteinase Inhibitor (PG-116800) to Prevent Ventricular Remodeling After Myocardial Infarction

Results of the PREMIER (Prevention of Myocardial Infarction Early Remodeling) Trial

Michael P. Hudson, MD, FACC,* Paul W. Armstrong, MD, FACC,† Witold Ruzyllo, MD,‡ Jose Brum, MD,§ Lisa Cusmano, MS,§ Piotr Krzeski, MD,§ Robert Lyon, PHD,§ Miguel Quinones, MD, FACC,‖ Pierre Theroux, MD, FACC,¶ Diana Sydlowski, MS,* Henry E. Kim, MD, FACC,* Mario J. Garcia, MD, FACC,# Wael A. Jaber, MD, FACC,# W. Douglas Weaver, MD, FACC*

Detroit, Michigan; Edmonton, Alberta, and Montreal, Quebec, Canada; Warsaw, Poland; Cincinnati and Cleveland, Ohio; and Houston, Texas

OBJECTIVES We sought to determine whether matrix metalloproteinase (MMP) inhibitor, PG-116800, reduced left ventricular (LV) remodeling after myocardial infarction (MI).

BACKGROUND PG-116800 is an oral MMP inhibitor with significant antiremodeling effects in animal models of MI and ischemic heart failure.

METHODS In an international, randomized, double-blind, placebo-controlled study, 253 patients with first ST-segment elevation MI and ejection fraction between 15% and 40% were enrolled 48 ± 24 h after MI and treated with placebo or PG-116800 for 90 days. Major efficacy end points were changes in LV volumes as determined by serial echocardiography, and clinical and safety outcomes were also collected.

RESULTS In total, 203 patients (80%) completed 90 days of treatment and had evaluable baseline and 90-day echocardiograms. The proportion of patients with anterior MI (78% vs. 81%) and primary percutaneous coronary intervention (90% vs. 91%) along with baseline LV ejection fraction (35.5% vs. 36.8%) did not differ between PG-116800-treated and placebo-treated patients. There was no difference in the change in LV end-diastolic volume index from days 0 to 90 with PG-116800 versus placebo (5.09 ± 1.45 ml/m^2 vs. 5.48 ± 1.41 ml/m^2, $p = 0.42$). Changes in LV diastolic volume, LV systolic volume, LV ejection fraction, sphericity index, plus rates of death or reinfarction were not significantly improved with PG-116800. PG-116800 was well tolerated; however, there was increased incidence of arthralgia and joint stiffness without significant increase in overall musculoskeletal adverse events (21% vs. 15%, $p = 0.33$).

CONCLUSIONS Matrix metalloproteinase inhibition with PG-116800 failed to reduce LV remodeling or improve clinical outcomes after MI. (J Am Coll Cardiol 2006;48:15–20) © 2006 by the American College of Cardiology Foundation

Left ventricular (LV) remodeling refers to alterations in LV chamber size, mass, geometry, and function that result after myocardial infarction (MI) or pressure/volume overload (1,2). After MI, LV remodeling is mediated by progressive structural changes in cardiac myocytes and the extracellular matrix (ECM), leading to LV dilation and worsening systolic function. Clinically, progressive LV remodeling may potentiate the development of ventricular arrhythmias, heart failure, and subsequent cardiovascular mortality (3–5).

Matrix metalloproteinases (MMPs) are a family of zinc-dependent proteolytic enzymes that promote ECM degradation (6,7). Enhanced activity of MMPs has been directly associated with cardiac ECM degradation and LV remodeling, leading to progressive heart failure in animal models and human patients (6–10). Both MMP levels and enzyme activity are increased after MI, suggesting their influence on LV remodeling (11–16). Matrix metalloproteinase inhibition prevents LV remodeling and improves systolic function in experimental models of MI (17–21) and heart failure (22–24).

From the *Henry Ford Heart and Vascular Institute, Detroit, Michigan; †University of Alberta, Edmonton, Alberta, Canada; ‡National Institute of Cardiology, Warsaw, Poland; §Procter & Gamble Pharmaceuticals, Cincinnati, Ohio; ‖Montreal Heart Institute, Montreal, Quebec, Canada; ¶Baylor College of Medicine, Houston, Texas; and the #Cleveland Clinic Foundation, Cleveland, Ohio. This study was funded by Procter & Gamble Pharmaceuticals, Cincinnati, Ohio. Drs. Brum, Cusmano, Krzeski, and Lyon are employees of Procter & Gamble Pharmaceuticals. Dr. Theroux has equity holdings in Procter & Gamble. Dr. Armstrong has received research grant support and consultancy fees from Procter & Gamble Pharmaceuticals. Drs. Ruzyllo, Quinones, Theroux, and Weaver received consultancy fees for participating on PREMIER Trial Expert Panel. Preliminary findings of this study were presented as Oral Abstract/Late Breaking Sessions of the 54th Annual Scientific Sessions of the American College of Cardiology, Orlando, Florida, March 7, 2005.

Manuscript received September 16, 2005; revised manuscript received January 6, 2006, accepted January 9, 2006.

Abbreviations and Acronyms

ECM = extracellular matrix
LV = left ventricle/ventricular
LVEDVI = left ventricular end-diastolic volume index
MI = myocardial infarction
MMP = matrix metalloproteinase
PCI = percutaneous coronary intervention

Matrix metalloproteinase inhibitors have been evaluated clinically for a number of indications, including cancer, osteoarthritis, and rheumatoid arthritis. These studies have reported dose- and duration-dependent musculoskeletal side effects (arthritis, tendon nodules, decreased joint range of motion) termed the "musculoskeletal syndrome" that is generally reversible on cessation of the study drug (25,26). The precise etiology and mechanism(s) involved in these musculoskeletal adverse events are unknown; however, broad-spectrum MMP inhibition and particularly MMP-1 (collagenase) inhibition has been hypothesized to be causally related.

PG-116800 is an oral MMP inhibitor of the hydroxamic acid class with high affinity for MMP-2, -3, -8, -9, -13, and -14 and low affinity for MMP-1 and -7, which might produce cardiac antiremodeling benefits without musculoskeletal side effects. We hypothesized that selective MMP inhibition with PG-116800 may attenuate post-MI LV remodeling. Accordingly, we conducted a phase II, international, multicenter, randomized clinical trial—the PREMIER (Prevention of Myocardial Infarction Early Remodeling) trial—to determine the effects of PG-116800 on LV remodeling parameters and clinical outcomes.

METHODS

The PREMIER trial was a randomized, double-blind, placebo-controlled trial conducted at 54 centers in Poland, Canada, and the U.S. The study was conducted according to standards of International Committee on Harmonization Good Clinical Practice. The investigational review board at each site approved the protocol, and all patients provided written informed consent before enrollment. Patients were randomly assigned in a 1:1 ratio to receive PG-116800 (200-mg oral dose taken twice daily) or matching placebo for 90 days. Patients were followed up for an additional 90 days for vital status and adverse events. Randomization was accomplished through a telephone interactive voice response system and stratified according to region (North America or Poland) and gender. During the study, safety data from the CASPI (Cartilage-Sparing Proteinase Inhibitor) study indicated a dose-response increase in musculoskeletal symptoms among osteoarthritis patients receiving PG-116800 at dose of 200 mg twice daily (data on file, Procter & Gamble, Cincinnati, Ohio). PG-116800 dosing was then adjusted in the PREMIER trial to 200 mg twice daily for 30 days followed by 200 mg once daily for the subsequent 60 days.

Eligible patients were ages 18 to 80 years, with ST-segment elevation MI yielding elevated cardiac markers (creatine kinase-MB isoenzyme, troponin I or troponin T >3 times the upper limit of normal) and LV ejection fraction $\geq 15\%$ and $\leq 40\%$ as measured by echocardiography at the local center 48 ± 24 h after MI. Patients receiving primary percutaneous intervention (PCI), fibrinolysis, or no reperfusion therapy were all eligible. Exclusion criteria were prior MI, documented or suspected history of heart failure or depressed LV ejection fraction, severe renal insufficiency (creatinine >2.5 mg/dl), congenital heart disease, autoimmune or connective tissue disease, chronic substance abuse or psychiatric illness, hepatic impairment/elevated liver chemistries (alananine aminotransferase, aspartate aminotransferase, gamma-glutamyl-transpeptidase, or bilirubin $>1.6\times$ the upper limit of normal), uncontrolled hypertension (blood pressure $>160/100$ mm Hg), or severe blood dyscrasias (platelet count $<100{,}000$; hemoglobin <11 g/dl for men or <10 g/dl for women; or absolute neutrophil count $<1{,}000/\mu$l). In addition, patients were excluded if there was persistent cardiogenic shock, refractory pulmonary edema, or hemodynamic instability (blood pressure $<90/50$ mm Hg). Patients receiving cytochrome P450 inducers (carbamazepine, phenobarbital, or phenytoin) or P450 inhibitors (fluvoxamine, ketoconazole, itraconazole, or fluconazole) were also excluded.

Patients meeting the above criteria provided informed consent, had baseline blood and urine specimens collected, were randomized to either PG-116800 or placebo, and received the study drug at the earliest possible time. Follow-up assessments were scheduled at hospital discharge/day 7 and on days 14, 30, 45, 60, 75, 90, 120, and 180. These visits included detailed inquiry of any musculoskeletal symptoms, assessment of upper extremity range of motion (goniometry), and examination of hand tendon abnormalities. Clinical events were collected and recorded from enrollment through 90 days, whereas vital status and adverse events were collected 180 days after enrollment.

Baseline echocardiograms were performed 48 ± 24 h after acute MI and sent to the Cleveland Clinic Echocardiography Core Laboratory for later LV dimension and ejection fraction quantification. Echocardiograms were obtained serially at days 14, 30, 90, 120, and 180 and forwarded to the Echocardiography Core Laboratory for blinded interpretation and analysis. Site investigators and sonographers received detailed training to obtain optimal standardized echocardiographic images, and perfluorocarbon-based contrast agents were used for LV cavity opacification. At the Echocardiography Core Laboratory, all echocardiograms were reviewed by two teams of a sonographer plus cardiologist to select the optimal image (noncontrast- vs. contrast-enhanced) for endocardial border definition. The echocardiogram with optimal endocardial border definition was selected as the primary data source for LV dimensions, volumes, and ejection fraction. Internal review of the first 100 paired echocardiograms (baseline, day 30, and day 90) was performed and verified no regional variability in echo-

cardiography image quality and <10% interobserver variability in LV dimension measurements.

Study end points. The primary study end point was the change from baseline at 90 ± 5 days in LV end-diastolic volume index (ΔLVEDVI) as measured by two-dimensional echocardiography. Secondary end points included LVEDVI change from baseline at 30 days along with LV volumes, ejection fraction, and sphericity change at 30 and 90 days, clinical outcomes, mortality, and safety outcomes. The LV end-diastolic and end-systolic diameters were measured at the cardiac base and at midcavity in the parasternal long axis view, and at the base, midcavity, and lower third of the LV cavity in the apical two- and four-chamber views. The LV long axis was measured in the apical two- and four-chamber views from the apex tip to the anterior/lateral corner of the mitral annulus. End-diastolic volume was derived by multiplying the largest long axis (L) by the largest end-diastolic diameter using the formula: $EDV = 3.42\ (Diameter_{max} \times L) - 6.44$ (27). The LV ejection fraction was calculated using the multiple diameter method, which uses the average of the LV diameters measured at end-diastole and end-systole from the parasternal long axis and apical views together along with an estimate of fractional long axis shortening (28).

Pertaining to clinical outcomes, severe heart failure was defined as dyspnea, edema, fatigue symptoms accompanied by pulmonary edema on chest radiography, need for intravenous diuretics, or hospitalization. During initial hospitalization, reinfarction was defined as ischemic symptoms plus either new ST-segment elevation or 25% re-elevation of creatine kinase-MB or cardiac troponins from the preceding value. After discharge, reinfarction was determined by ischemic symptoms plus elevated creatine kinase-MB/cardiac troponin greater than the upper limit of normal. Recurrent ischemia was defined as ischemic symptoms not meeting reinfarction criteria that were substantiated by new ECG abnormalities or leading to urgent/unplanned catheterization or revascularization. Recorded musculoskeletal adverse events included the following symptoms or findings: arthralgia, myalgia, joint stiffness, new tendon thickening or nodule, or ≥30% decrease in shoulder/elbow range of motion at two goniometry measurements.

Statistical analysis. Comparability of treatment groups for baseline characteristics and clinical outcomes were assessed with *t* tests and Fisher exact tests. Day 30 and day 90 echocardiographic changes (treatment efficacy) were compared using *t* tests for the least-square means and confirmed by an analysis of variance model with factors for treatment and stratification. The benefit of PG-116800 in decreasing LVEDVI versus placebo was expected to be ≥4 ml/m^2 with standard deviation 10 ml/m^2. Allowing for an attrition rate of 20%, enrollment was targeted at 250 patients to generate two treatment groups of 100 patients sufficient to detect the target LVEDVI (primary end point) benefit of 4 ml/m^2 with 80% power and two-sided alpha = 0.05. Statistical analyses were performed using SAS version 8.2 (SAS Institute Inc., Cary, North Carolina). One-sided p values were reported for the primary end point, whereas two-sided p values are reported otherwise.

An independent Data and Monitoring Committee reviewed adverse event reports from study patients and monitored PG-116800 safety data from other clinical trials to safeguard study subjects and provide guidance to the sponsor (Procter & Gamble). The PREMIER trial expert panel functioned as an advisory committee for the trial and had complete access to all echocardiographic and clinical data after unblinding. All expert panel members and coauthors had a substantial role in trial design, data accrual, and data interpretation. Clinical data were collected in an electronic data collection form and entered into database managed by the trial sponsor. All final analyses were conducted by the sponsor in association with the expert panel.

RESULTS

In total, 128 ST-segment elevation MI patients were randomized to placebo and 125 patients were randomized to PG-116800. Comparing the PG-116800 and placebo groups, 99 (79%) versus 108 (84%) completed 90 days of study drug without significant differences in the rates of study drug discontinuation because of voluntary patient withdrawals, 11 (9%) versus 4 (3%), or because of adverse events, 8 (6%) versus 11 (9%). Among patients receiving the study drug for the full 90 days, 98% had evaluable baseline and 90-day echocardiograms for primary end point assessment.

Table 1. Baseline Characteristics

	PG-116800 (n = 125)	Placebo (n = 128)	p Value
Age (yrs)	59.7 ± 11.7	59.9 ± 10.2	0.93
Female	32 (26%)	34 (34%)	0.89
Region			0.89
Poland	86 (69%)	87 (68%)	—
U.S.	16 (13%)	19 (15%)	—
Canada	23 (18%)	22 (17%)	—
Diabetes	18 (14%)	21 (16%)	0.73
Hypertension	59 (47%)	58 (45%)	0.80
Anterior MI	97 (78%)	104 (81%)	0.53
Primary PCI	113 (90%)	116 (91%)	1.0
Fibrinolytic therapy	6 (5%)	7 (5%)	1.0
No reperfusion therapy	6 (5%)	5 (4%)	1.0
Peak troponin I (ng/ml)	76 ± 98	77 ± 67	0.93
Baseline LVEF (%)	35.4 ± 9.1	36.2 ± 8.2	0.50
Time, onset→ reperfusion (h)	2.9 ± 6.4	3.2 ± 6.5	0.71
Time, MI→ study drug (h)	54.4 ± 14.0	53.9 ± 14.6	0.81
Time, PCI→ study drug (h)	51.7 ± 15.3	50.5 ± 15.2	0.55
Post-MI medications			
Beta-blocker	116 (93%)	127 (99%)	0.01
ACEI/ARB	118 (94%)	120 (94%)	1.0
Loop diuretic	39 (31%)	55 (43%)	0.07
Spironolactone	32 (26%)	35 (27%)	0.78
Digoxin	6 (5%)	7 (6%)	1.0

Values are n (%) or mean ± SD.

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; LVEF = left ventricular ejection fraction; MI = myocardial infarction; PCI = percutaneous coronary intervention.

Table 2. Echocardiogaphic LV Remodeling End Points: Day 90 and Day 30 Change From Baseline

	PG-116800		Placebo		
	Baseline	Change (SE)	Baseline	Change (SE)	p Value*
Primary efficacy, day 90 change from baseline (n = 203)					
LVEDVI (ml/m^2)	63.6	5.09 (1.45)	61.3	5.48 (1.41)	0.42
U.S. (n = 24)	66.3	0.40 (4.23)	51.9	4.37 (4.19)	0.25
Canada (n = 31)	63.6	0.49 (3.63)	59.6	1.67 (3.76)	0.41
Poland (n = 148)	63.1	6.84 (1.73)	63.1	6.47 (1.65)	0.56
LV end-diastolic volume (ml)	122.4	8.43 (2.73)	117.9	10.35 (2.66)	0.31
LV end-systolic volume (ml)	79.8	0.58 (2.25)	75.2	2.23 (2.20)	0.30
LVEF (%)	35.5	4.85 (0.92)	36.8	4.25 (0.89)	0.32
Sphericity index (n = 181)	0.35	0.01 (0.01)	0.35	0.01 (0.01)	0.44
Secondary efficacy, day 30 change from baseline (n = 207)					
LVEDVI (ml/m^2)	63.1	5.00 (1.12)	61.1	4.94 (1.10)	0.52
U.S. (n = 27)	64.9	−1.10 (3.45)	54.0	2.56 (2.84)	0.21
Canada (n = 34)	62.6	3.84 (2.75)	59.3	3.29 (2.76)	0.56
Poland (n = 146)	62.9	6.28 (1.33)	63.0	5.75 (1.33)	0.61
LV end-diastolic volume (ml)	121.4	8.47 (2.15)	117.8	8.92 (2.10)	0.44
LV end-systolic volume (ml)	78.9	−0.98 (1.76)	74.8	1.23 (1.72)	0.19
LVEF (%)	35.7	5.71 (0.81)	36.8	4.12 (0.79)	0.08
Sphericity index (n = 194)	0.35	0.01 (0.01)	0.35	0.03 (0.01)	0.10

*The p values compare change in echocardiographic end points between PG-116800 versus placebo.
LVEDI = left ventricular end-diastolic volume index; other abbreviations as in Table 1.

Patient baseline and clinical characteristics are shown in Table 1. Study groups were well matched overall without significant differences in demographic variables, prognostic characteristics, or hospital treatments. The study population had mean age of 59.8 ± 10 years, and two-thirds of patients were enrolled in Poland. Most patients (79%) had anterior ST-segment elevation MIs and were treated with primary PCI (91%). Baseline LV ejection fraction (36% vs. 37%) and time interval from MI to study drug administration (54.4 ± 14.0 h vs. 53.9 ± 14.6 h) did not differ in the PG-116800 and placebo groups, respectively. Patients in both treatment groups had high rates of post-MI beta-blocker and angiotensin-converting enzyme inhibitor/angiotensin receptor blocker use exceeding 90%.

Table 2 and Figure 1 present echocardiographic LV remodeling results including the primary study end point—ΔLVEDVI—at 90 days. There was no difference in LVEDVI after 30 or 90 days of treatment with PG-116800 versus placebo. The LV systolic and diastolic volumes, ejection fraction, and sphericity index did not differ in the PG-16800 and placebo treatment groups. Although underpowered, subgroup analysis showed no significant differences in LVEDVI reduction associated with PG-116800 dose (p = 0.27). The 90-day change in LVEDVI did not differ significantly between patients receiving placebo (n = 104), original protocol/high-dose PG-116800 (n = 40), or amended protocol/reduced-dose PG-116800 (n = 59) (5.48 ± 1.41 ml/m^2 vs. 7.29 ± 2.28 ml/m^2 vs. 3.60 ± 1.88 ml/m^2), respectively.

Table 3 shows 90-day clinical outcomes according to treatment group. Given the small sample size, there were few clinical outcomes. Although not statistically significant, rates of death and reinfarction were higher in the PG-116800 treatment group. Table 4 shows adverse events experienced at 180 days (90 days during and 90 days after study drug treatment). The proportion of patients with serious adverse events and the proportion of patients withdrawn from the study drug because of suspected adverse

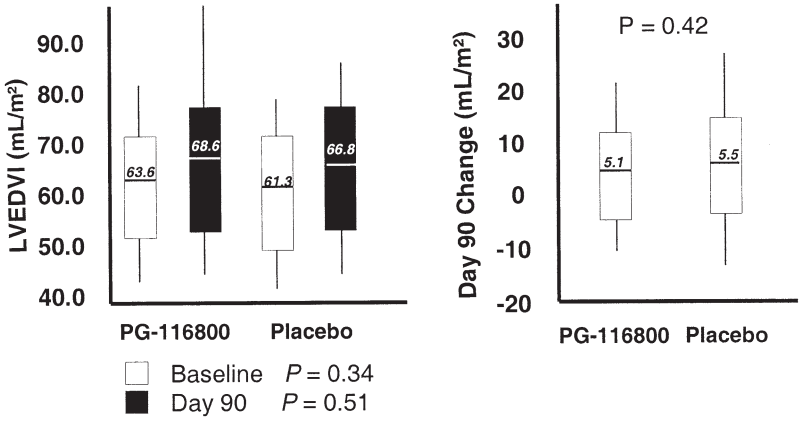

Figure 1. Primary end point/change in left ventricular diastolic volume index (LVEDVI), baseline to 90 days.

Table 3. Clinical Outcomes, 90 Days

	PG-116800 (n = 125)	Placebo (n = 128)	p Value
Death	4 (3%)	1 (1%)	0.21
Reinfarction	5 (4%)	4 (3%)	0.50
Death or reinfarction	9 (7%)	5 (4%)	0.17
Recurrent ischemia	3 (1%)	3 (1%)	1.0
Severe heart failure	13 (10%)	12 (9%)	0.84
Cardiogenic shock	2 (2%)	1 (1%)	0.62
Cardiac arrest	4 (2%)	0 (0%)	0.06
Cardiac tamponade	0 (0%)	1 (1%)	1.0
Major arrhythmia	9 (7%)	2 (2%)	0.03
Death, reinfarction, cardiac arrest, or major arrhythmia	13 (10%)	7 (5%)	0.10

events did not differ. Dyspepsia symptoms occurred more frequently in PG-116800–treated patients but were unexpectedly absent in the placebo group. Rates of arthralgia and joint stiffness were higher in the PG-116800 treatment group, whereas there was no statistically significant difference in overall musculoskeletal adverse events (21% vs. 15%, p = 0.33) between treatment groups.

DISCUSSION

Given the marked improvement in short-term outcomes after contemporary ST-segment elevation MI reperfusion therapy, recent attempts at further reducing death and disability have been aimed at limiting infarct size and LV remodeling. We and others have observed that ventricular remodeling occurs commonly after MI and leads to progressive heart failure, exercise intolerance, and other adverse outcomes.

Both MMP gene expression and activity are increased after MI, leading to collagen and elastic fiber degradation, structural remodeling of the extracellular matrix, impaired collagen formation, and myocardial fibrosis (11–16). Inhibition of MMP prevents progressive ventricular remodeling in MI and heart failure experimental models (17–24). PG-116800 is a selective MMP inhibitor with a high affinity for MMP-2, -3, -8, -9, -11, -13, and -14 and minimal affinity for MMP-1 and -7. PG-116800 and its dehydrated salt form PG-530742 had impressive outcomes in preclinical animal studies, significantly reducing LV volumes along with infarct zone collagen content in a post-MI porcine model (21) and reducing LV volumes plus improving ejection fraction in a microembolization, chronic heart failure canine model (24). Prior studies also suggested that MMP-1 inhibition is associated with musculoskeletal complaints and that MMP-7 positively contributed to wound healing. Thus PG-116800 looked particularly promising because of its MMP selectivity and its expected favorable efficacy-toxicity profile.

Major findings. In this first therapeutic human study of MMP inhibition after acute MI, we report that 90 days of treatment with PG-116800 initiated 48 h after MI had no beneficial effect on LV remodeling (ΔLV end-diastolic volume index) or clinical outcomes. PG-116800 was generally well tolerated and produced no significant increase in overall musculoskeletal adverse outcomes. Based on prior studies, 90 days should have provided ample time to observe a change in LVEDVI (29). We did encounter considerable individual variability among the serial LVEDVI measurements; however, the absolute change per group (~5 ml/m^2) and variability (14%) were similar to the prestudy estimates, giving us adequate statistical power to observe a change. It is unlikely that a different cardiac imaging modality (i.e., cardiac magnetic resonance imaging) or diagnostic assessment of LV remodeling would have affected our results. Echocardiography was chosen to assess LV remodeling because it was readily available in most centers, permitted efficient screening of potential patients, and had substantiated the benefits of angiotensin-converting enzyme inhibitors and beta-blockers on LV volumes and ejection fractions in prior post-MI studies (30–32).

Study limitations. The combined use of contemporary MI therapies may have diminished any potential therapeutic efficacy of MMP inhibition in our study patients. Primary PCI, beta-blockers, angiotensin-converting enzyme inhibitors, and statins were used by >90% of patients in both treatment groups. Because these contemporary therapies along with aldosterone inhibition (33) prevent LV remodeling, it is possible that an additional salutary PG-116800 effect may have been diminished or gone undetected.

Inadequate PG-116800 dosing also may have affected our results. At study onset, we planned to administer 200 mg of PG-116800 twice daily for 90 days. Based on reports of musculoskeletal adverse events in a parallel trial using PG-116800 for osteoarthritis and subsequent concerns raised by Health Canada, we amended our protocol, reduced PG-116800 cumulative dose by 33%, and completed the study with PG-116800–treated patients receiving a dosing regimen lacking prior experimental efficacy. It is uncertain whether more potent MMP inhibition might prevent LV remodeling; conversely our results showed no dose response relationship between PG-116800 and

Table 4. Mortality and Adverse Events, 180 Days

	PG-116800 (n = 125)	Placebo (n = 128)	p Value
Death	4 (3%)	1 (1%)	0.21
SAE	38 (30%)	36 (28%)	0.78
Withdrew because of SAE	6 (5%)	7 (5%)	1.0
Renal failure	3 (2%)	4 (3%)	1.0
Dyspepsia/gastrointestinal upset	16 (13%)	0 (0%)	<0.01
Anxiety	10 (8%)	3 (2%)	0.05
Musculoskeletal adverse events*	26 (21%)	19 (15%)	0.33
Arthralgia	17 (14%)	10 (8%)	0.16
Myalgia	3 (2%)	2 (2%)	0.68
Joint stiffness	7 (6%)	0 (0%)	0.01
Decreased range of motion	2 (2%)	4 (3%)	0.68
Tendon disorders†	7 (6%)	3 (2%)	0.21
Extremity nodule	4 (3%)	4 (3%)	1.0

*Arthralgia, myalgia, joint stiffness, ≥30% decrease in shoulder or elbow range of motion, tendon disorder, or extremity nodule. †Tendon contracture or tendonitis.
SAE = serious adverse events.

LVEDVI change and no diminution of drug efficacy after protocol change and study drug dose reduction.

Conclusions. Contrary to animal and preclinical data, our disappointing results cast doubt on whether MMP inhibition might ameliorate post-MI remodeling. Selective MMP inhibition with PG-116800 is ineffective for treating this condition, yet our current understanding of which MMP(s) contribute most to ventricular remodeling is rudimentary. Future research in post-MI patients is needed to better identify the clinical and biologic determinants of LV remodeling, to understand the timing and sequence of MMP activation and inhibition, and to identify alternative, more-specific MMP targets (34). Additionally, the association between MMP inhibition and musculoskeletal adverse events needs increased study because our results suggest that selective sparing of MMP-1 inhibition is not sufficient to avoid all MMP musculoskeletal side effects.

Reprint requests and correspondence: Dr. W. Douglas Weaver, Henry Ford Heart and Vascular Institute, Henry Ford Hospital (K-14), 2799 West Grand Boulevard, Detroit, Michigan 48202. E-mail: wweaver1@hfhs.org.

REFERENCES

1. Cohn JN, Ferrari R, Sharpe N. Cardiac remodeling: concepts and clinical implications: a consensus paper from an International Forum on Cardiac Remodeling. J Am Coll Cardiol 2000;35:569–82.
2. Udelson JE, Patten RD, Konstan MA. New concepts in post-infarction ventricular remodeling. Rev Cardiovasc Med 2003;4 Suppl 3:S3–12.
3. St. John Sutton M, Pfeffer MA, Plappert T, et al., for the SAVE Investigators. Quantitative two-dimensional echocardiographic measurements are major predictors of adverse cardiovascular events after acute myocardial infarction. Circulation 1994;89:68–75.
4. St. John Sutton M, Lee D, Rouleau JL, et al. Left ventricular remodeling and ventricular arrhythmias after myocardial infarction. Circulation 2003;107:2577–82.
5. Bolognese L, Neskovic AN, Parodi G, et al. Left ventricular remodeling after primary coronary angioplasty. Circulation 2002;106: 2351–7.
6. Creemers EEJM, Cleuthens JPM, Smits JFM, Daemen MJAP. Matrix metalloproteinases after myocardial infarction: a new approach to prevent heart failure. Circ Res 2001;89:201–10.
7. Spinale FG. Matrix metalloproteinases—regulation and dysregulation in the failing heart. Circ Res 2002;90:520–30.
8. Spinale FG, Coker ML, Thomas CV, et al. Time-dependent changes in matrix metalloproteinase activity and expression during progression of congestive heart failure: relation to ventricular myocyte function. Circ Res 1998;82:482–95.
9. Spinale FG, Coker ML, Krombach SR, et al. Matrix metalloproteinase inhibition during the development of congestive heart failure: effects on left ventricular dimensions and function. Circ Res 1999;85: 364–76.
10. Coker ML, Thomas CV, Clair MJ, et al. Myocardial matrix metalloproteinase activity and abundance with congestive heart failure. Am J Physiol 1998;274:H1516–23.
11. Cleutjens JPM, Kandala JC, Guarda E, et al. Regulation of collagen degradation in the rat myocardium after infarction. J Mol Cell Cardiol 1994;27:1281–92.
12. Peterson JT, Li H, Dillon L, et al. Evolution of matrix metalloproteinase and tissue inhibitor expression during heart failure progression in the infarcted rat. Cardiovasc Res 2000;46:307–15.
13. Hirohata S, Kusachi S, Murakami M, et al. Time dependent alterations of serum matrix metalloproteinase-1 and metalloproteinase-1 tissue inhibitor after successful reperfusion of acute myocardial infarction. Heart 1997;78:278–84.
14. Etoh T, Joffs C, Deschamps AM, et al. Myocardial and interstitial matrix metalloproteinase activity after myocardial infarction in pigs. Am J Physiol 2001;281:H987–94.
15. Wilson EM, Moainie SL, Baskin JM, et al. Region- and type-specific induction of matrix metalloproteinases in post-myocardial infarction remodeling. Circulation 2003;107:2857–63.
16. Chen J, Tung C, Allport JR, et al. Near-infrared fluorescent imaging of matrix metalloproteinase activity after myocardial infarction. Circulation 2005;111:1800–5.
17. Ducharme A, Frantz S, Aikawa M, et al. Targeted deletion of matrix metalloproteinase-9 attenuates left ventricular enlargement and collagen accumulation after experimental myocardial infarction. J Clin Invest 2000;106:55–62.
18. Rohde LE, Ducharme A, Arroyo LH, et al. Matrix metalloproteinase inhibition attenuates early left ventricular enlargement after experimental myocardial infarction in mice. Circulation 1999;99:3063–70.
19. Mukherjee R, Brinsa TA, Dowdy KB, et al. Myocardial infarct expansion and matrix metalloproteinase inhibition. Circulation 2003; 107:618–25.
20. Lindsey ML, Gannon J, Aikawa M, et al. Selective matrix metalloproteinase inhibition reduces left ventricular remodeling but does not inhibit angiogenesis after myocardial infarction. Circulation 2003;105:753–8.
21. Yarbrough WM, Mukherjee R, Escobar GP, et al. Selective targeting and timing of matrix metalloproteinase inhibition in post-myocardial infarction remodeling. Circulation 2003;108:1753–9.
22. King MK, Coker ML, Goldberg A, et al. Selective matrix metalloproteinase inhibition with developing heart failure; effects on left ventricular function and geometry. Circ Res 2003;92:177–85.
23. Peterson JT, Hallak H, Etoh T, Spinale FG. Matrix metalloproteinase inhibition attenuates left ventricular remodeling and dysfunction in a rat model of progressive heart failure. Circulation 2001;103:2303–9.
24. Sabbah HN, Morita H, Suzuki G, et al. PG-530742, a novel matrix metalloproteinase inhibitor, improves left ventricular function and attenuates remodeling in dogs with chronic heart failure (abstr). J Am Coll Cardiol 2004;43 Suppl A:22A.
25. Hutchinson JW, Tierney GM, Parsons SL, Davis TRC. Dupuytren's disease and frozen shoulder induced by treatment with a matrix metalloproteinase inhibitor. J Bone Joint Surg 1998;80-B:907–8.
26. Tierney GM, Griffin NR, Stuart RC, et al. A pilot study of the safety and effects of the matrix metalloproteinase inhibitor Marimastat in gastric cancer. Eur J Cancer 1999;35:563–8.
27. Tortoledo FA, Quinones MA, Fernandez GC, et al. Quantification of left ventricular volumes by two-dimensional echocardiography: a simplified and accurate approach. Circulation 1983;67:579–84.
28. Quinones MA, Waggoner AD, Reduto LA, et al. A new, simplified and accurate method of determining ejection fraction with two-dimensional echocardiography. Circulation 1981;64:744–53.
29. Alam M, Graham L, Divine G, et al. Left ventricular remodeling after acute myocardial infarction. Am J Hypertens 2000;13:159A.
30. Greenberg B, Quinones M, Kolpillai C, et al. Effect of long-term enalapril on cardiac structure and function in patients with left ventricular dysfunction. Circulation 1995;91:2573–81.
31. Galcera-Tomas J, Castillo-Soria JC, Villegas-Garcia M, et al. Effects of early use of atenolol or captopril on infarct size and ventricular volume. Circulation 2001;103:813–9.
32. Dougthy RN, Whalley GA, Walsh HA, et al. Effect of carvedilol on left ventricular remodeling after acute myocardial infarction: the CAPRICORN Echo Substudy. Circulation 2004;109:201–6.
33. Hayashi M, Tsutamoto T, Wasa A, et al. Immediate administration of mineralocorticoid receptor antagonist spironolactone prevents post-infarct left ventricular remodeling associated with suppression of a marker of myocardial collagen synthesis in patients with first anterior acute myocardial infarction. Circulation 2003;107:2559–65.
34. Feldman AM, Li YY, McTiernan CF. Matrix metalloproteinases in pathophysiology and treatment of heart failure. Lancet 2001;357: 654–5.

APPENDIX

For a list of the participants in the PREMIER trial, please see the online version of this article.