Beneficial Effects of Pimobendan on Exercise Tolerance and Quality of Life in Patients With Heart Failure

Results of a Multicenter Trial

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Background. This multicenter trial was conducted to determine the efficacy and safety of pimobendan, an inotropic agent with calcium-sensitizing properties and activity as a phosphodiesterase inhibitor, in patients with heart failure.

Methods and Results. One hundred ninety-eight ambulatory patients with symptoms of moderate to severe heart failure despite therapy with digitalis and diuretics with or without a single vasodilator were randomly assigned to receive either placebo (n=49) or pimobendan (n=149) in a double-blind fashion for 12 weeks. A dose range of pimobendan was used including 2.5 (n=49), 5 (n=51), or 10 mg/day (n=49). One hundred fifty-eight (80%) patients were taking a converting enzyme inhibitor (CEI) and 28 (14%) patients were taking a non-CEI vasodilator. At end point, the 5-mg dose of pimobendan significantly increased exercise duration compared with placebo (121.6±19.1 seconds, p<0.001), whereas the 10-mg dose produced an increase of borderline significance (81.1±19.5 seconds, p=0.05). Peak VO2 was significantly increased by 2.23±0.58 ml/kg/min in the 5-mg group (p<0.01 versus placebo). Furthermore, quality of life measured with the Minnesota Living With Heart Failure Questionnaire improved by 8.5±2.3 units in the 5-mg group compared with 1.3±2.2 units in the placebo group (p<0.01). There were a total of 23 all-cause hospitalizations in the placebo group, which was significantly greater compared with 33 in the three groups treated with pimobendan (p<0.01). There were no significant differences between the placebo and pimobendan groups with respect to changes in ejection fraction and plasma norepinephrine measured at baseline and at the completion of the 12-week study, proarrhythmic effect, or the number of patients with a significant adjustment in background therapy. Eleven patients died, including three (6%) on placebo and eight (5%) on pimobendan (p=NS). Among all adverse events, headache tended to be more common in the pimobendan groups compared with placebo, with the incidence increasing with dose (p<0.05).

Conclusions. These data demonstrate that pimobendan significantly increases exercise duration, peak VO2, and quality of life in patients with heart failure. Pimobendan appears to be useful adjunctive therapy when added to digitalis, diuretics, and vasodilators. (Circulation 1992;85:942–949)

Key Words • pimobendan • heart failure • inotropic agents • vasodilators

The intensive search for a safe, orally active inotropic agent is based on the fact that the clinical syndrome of heart failure results from a primary defect in myocardial contractility and that many patients have persistent symptoms despite intensive treatment with digitalis, diuretics, and vasodilators.1 Although several agents have demonstrated short-term hemodynamic effects, the enthusiasm for inotropic agents has lessened significantly since recent multicenter trials of the phosphodiesterase (PDE) inhibitors amrinone, milrinone, and enoximone have failed to demonstrate a significant improvement in exercise tolerance either alone or in combination with digitalis.2–4 Moreover, the recent premature termination of the Prospective Randomized Milrione Survival Evaluation (PROMISE) trial with milrinone because of excess mortality in the treatment group has increased previous concerns that long-term therapy with PDE inhibitors may decrease survival.5 However, data from these trials must be rigorously interpreted in terms of the specific agent being tested, as these adverse experiences may not be applicable to all inotropic agents, particularly those with mechanisms in addition to or independent of PDE inhibition.6–10 Furthermore, it is possible that

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Received July 22, 1991; revision accepted October 8, 1991.
differences in patient populations or the types of allowable background therapy may have affected the results of these trials.

Experimental data have demonstrated that pimobendan exerts a positive inotropic effect mediated in part by sensitization of the contractile proteins to intracellular calcium. In addition, pimobendan has activity as a PDE inhibitor and as a vasodilator.\(^{11-16}\) A preliminary 4-week controlled trial demonstrated beneficial effects of pimobendan on hemodynamics and exercise capacity in 52 patients with moderate to severe heart failure.\(^{17}\) Therefore, to further assess the potential efficacy and safety of pimobendan, we conducted a multicenter trial to compare the effects of three doses of pimobendan with placebo on exercise performance and quality of life in patients with heart failure who remained symptomatic despite background therapy with digitalis and diuretics with or without a single vasodilator.

**Methods**

**Patient Population**

Twenty centers participated in this trial (see “Appendix”). Patients were recruited if they had persistent symptoms of moderate to severe heart failure despite background therapy with digitalis and diuretics with or without a single vasodilator. All patients were at least 18 years of age and had symptoms of heart failure for at least 3 months before the first visit. All patients had a left ventricular ejection fraction <45% as measured by radionuclide ventriculogram. The etiology of left ventricular dysfunction was ischemic heart disease, hypertensive heart disease, idiopathic dilated cardiomyopathy, or end-stage valvular heart disease. All patients were required to complete at least stage I of a modified Naughton treadmill test but not more than stage IX. All exercise tests were limited by dyspnea and/or fatigue. Each patient signed informed consent, and the study was approved by the institutional review board of each center.

Patients with marked day-to-day changes in status were excluded. Other reasons for exclusion were a resting blood pressure greater than 150/95 mm Hg, systolic blood pressure <80 mm Hg, myocardial infarction within the previous 3 months, primary renal or hepatic disease, or a history of sudden cardiac death or ventricular tachycardia with syncope. Patients were excluded if more than one vasodilator was required as part of background therapy, if vasodilator therapy was started within 3 months of the first visit, or if digitalis or diuretic therapy was started within 1 month of the first visit. The doses of background therapy had to remain stable for 2 weeks before the first visit. Patients were not allowed to take \( \beta \)-blockers, calcium channel blockers, or drugs that could induce hepatic enzymes.

**Study Design**

The baseline phase consisted of three to four visits over a 3–5-week period. Background therapy was maintained constant and patients performed symptom-limited exercise treadmill tests using the modified Naughton protocol\(^{18}\) at visits 1 and 2. If the total exercise time of these two tests differed by more than 10%, a third test was performed within 2 weeks. To be eligible for randomization, the durations of the last two tests had to be within 10% of each other. Within 1 week of the last exercise test, all patients were given an oral test dose of 5 mg pimobendan. Patients were excluded if this dose produced an excessive drop in blood pressure, defined as any change accompanied by symptoms or which, in the opinion of the investigator, compromised the safety of the patient. Four patients were excluded for this reason.

Patients were randomized in a double-blind manner to one of four groups to receive either placebo or pimobendan 2.5, 5, or 10 mg/day taken in two equal doses. Outpatient visits were scheduled at 1, 2, 4, 6, 8, and 12 weeks after randomization. The primary endpoints were 1) exercise duration measured during treadmill testing (weeks 2, 6, and 12), 2) patient self-assessment using the Minnesota Living With Heart Failure Questionnaire (weeks 4, 8, and 12), and 3) drug safety as monitored by 24-hour Holter recording (weeks 4, 8, and 12), electrocardiogram, blood tests, and clinical adverse events. The Minnesota Living With Heart Failure Questionnaire is a self-administered test of 21 questions specifically assessing the limitations commonly associated with heart failure.\(^{19}\) The questionnaire was completed before other assessments and after a brief set of standardized instructions. Proarrhythmia effects were assessed using Holter criteria,\(^{20}\) including the onset of arrhythmia that was not present at baseline, an increase in ventricular premature contractions per hour, or episodes of nonsustained ventricular tachycardia over 24 hours. Secondary end points included left ventricular ejection fraction measured at baseline and week 12, the number of hospitalizations, and the number of adjustments of background therapy for heart failure. Plasma norepinephrine was measured at baseline and at week 12 (\( n = 131 \)). These specimens were analyzed at the Cardiovascular Biochemistry Core Laboratory of the University of Minnesota with the use of a radioenzymatic assay.\(^{21}\) Finally, a subset of 128 patients from 13 centers had measurement of peak exercise oxygen consumption (\( V_{O2e} \), milliliter per kilogram per minute) with expiratory gas analysis.

**Statistical Analysis**

One randomized patient was excluded from all statistical analyses because he developed a late adverse effect after the test dose and never took the blinded drug. Another patient who had a baseline ejection fraction of 70% and was entered into the study by error was excluded from all efficacy analyses. Intent-to-treat analyses for all primary and points were first completed for patients who were randomized in the study, and the end point response was taken as the last available measurement after randomization to study drug. Patients who had data at every time point were analyzed to assess the time course of changes. A fixed-effects analysis of variance (ANOVA) model was used to evaluate the mean change from baseline response. There was no significant center by treatment interaction in any of these analyses, so the ANOVA models included an adjustment for a center effect only. The number of hospitalizations, adverse events, and changes in background therapy were compared by Fisher’s exact test, Jonckheere’s test for ordered alternatives,\(^{22}\) or extended
Mantel-Haenszel tests. In all cases, the patient was used as the unit of analysis. All probability values were based on two-tailed tests. All data are expressed as mean±1 SEM except where indicated. Differences between placebo and pimobendan are considered significant at p<0.05.

**Results**

Table 1 summarizes the baseline characteristics of the 198 patients who were randomized and took the study drug. There were no significant differences between the patients randomized to pimobendan and placebo in terms of age, sex, duration of heart failure, New York Heart Association classification, ejection fraction, questionnaire score, exercise time, or peak oxygen consumption. For etiology of heart failure, more patients in the 10-mg/day group had ischemic heart disease than idiopathic cardiomyopathy, whereas in the other three treatment groups, an equal or slightly higher proportion of patients had idiopathic cardiomyopathy. At entry into the trial, 80% of patients were taking angiotensin converting enzyme inhibitors, 89% were taking digitalis, and 98% were taking diuretics.

Overall, 169 (86%) patients completed the 12-week trial (Table 2), including 44 (90%) placebo patients and 125 (84%) patients randomized to pimobendan. Eleven patients (6%) died during the 12-week study, including three (6%) receiving placebo and eight (5%) receiving pimobendan (p=NS). Sixteen (8%) patients were discontinued from the trial for adverse events, including two (4%) on placebo and 14 (9%) on pimobendan (p=NS). From the 5-mg group, three of the five patients who were discontinued were experiencing a ventricular arrhythmia in comparison with no patients in the placebo or 2.5-mg groups and one patient in the 10-mg group. Otherwise, although more patients were discontinued due to adverse events in the combined pimobendan groups compared with placebo, no trends in the type of event leading to discontinuation were noted.

The changes in exercise duration at end point for the four groups of patients are shown in Figure 1 (right-
In the placebo group, exercise duration at end point increased by 29.6 ± 18.4 seconds. Exercise duration tended to increase with the 2.5-mg dose of pimobendan, but this increment was not significantly greater than with placebo. In contrast, the 5-mg dose produced a significant increase of 121.6 ± 19.1 seconds (p < 0.001 versus placebo). The increase in exercise duration of 81.1 ± 19.5 seconds with the 10-mg dose was of borderline significance compared with placebo (p = 0.05). The changes in exercise duration over time for the 147 patients who had data at every time point are also shown in Figure 1 (left-hand panel). The placebo group showed only a small increment in exercise time over the 12-week study. The 2.5-mg group showed a slightly larger but nonsignificant increase in exercise duration compared with placebo. For the 5-mg dose, there was a significant increase in exercise duration by 6 weeks that was maintained at 12 weeks. The increase in exercise duration for the 10-mg group was also significant at weeks 6 and 12.

Peak VO₂ measurements are shown (Figure 2) for patients with end point data (n = 128, right-hand panel) and patients who had data at every time point (n = 92, left-hand panel). Peak VO₂ fell slightly at end point in the placebo group. Peak VO₂ tended to increase in the 2.5- and 10-mg groups, but these responses were not significantly different from placebo. For the 5-mg dose, peak VO₂ increased significantly by 2.23 ± 0.58 ml/kg/min (p < 0.01 versus placebo). Peak VO₂ was stable over time for placebo and the 2.5- and 10-mg groups and showed marginally significant increases at weeks 6 and 12 for the 5-mg dose (p = 0.06 and p < 0.05, respectively).

Questionnaire scores are summarized in Figure 3. At end point (right-hand panel), there was a trend for improvement with the 2.5- and 10-mg doses compared with placebo. The change with the 5-mg dose (8.5 ± 2.3 units) was significant compared with placebo (1.3 ± 2.2 units, p < 0.05). The time course of the changes in this patient self-assessment tended to be more stable over the 12-week study compared with the progressive increases in exercise duration. For the 5-mg dose, the significant improvement in scores was of similar magnitude at weeks 4, 8, and 12.

Over the 12-week study, there were a total of 23 all-cause hospitalizations in the placebo group (n = 49) compared with only 33 in the three pimobendan groups (n = 149) (p < 0.01). This included 12, 10, and 11 hospitalizations for the 2.5-, 5-, and 10-mg groups respectively. Because some patients had multiple hospitalizations, the data were analyzed with respect to the number of patients who had at least one hospitalization. There were 17 patients in the placebo group (35%) compared with 28 patients (19%) in the three pimobendan groups (p < 0.05). This included 11, eight, and nine patients for the 2.5-, 5-, and 10-mg groups, respectively.

Significant adjustments in background therapy were defined as the addition of a new class of drug, an increase in dosage lasting more than 2 weeks, more than one increase in dosage, or an increase in dosage of more than one background drug. Overall, 14 (29%) placebo patients required a significant adjustment compared with 27 (18%) pimobendan patients (p = NS).

There were no treatment-related changes in ejection fraction or plasma norepinephrine in any group. Ejection fractions at baseline and at 12 weeks were 22.5 and 23.7% in the placebo group (n = 44), 22.0 and 22.3% in the 2.5-mg group (n = 41), 23.5 and 25.0% in the 5-mg group (n = 41), and 20.8 and 23.6% in the 10-mg group (n = 38). None of these changes in ejection fraction were significantly different among the groups. At baseline, plasma norepinephrine levels were 685 ± 59, 644 ± 39, 681 ± 92, and 820 ± 77 pg/ml in the placebo (n = 37), 2.5-mg (n = 33), 5-mg (n = 32), and 10-mg (n = 29) groups, respectively. There were no significant differences in baseline levels among groups. Increases in plasma norepinephrine at week 12 were variable and not significantly different for any group (39 ± 81, 37 ± 48, 80 ± 66, and 2 ± 63 pg/ml, respectively).
There was a total of 11 deaths during the 12-week study (Table 2). Each death was classified by a treatment blinded reviewer. In the placebo group, all three deaths were due to progressive heart failure that required aggressive treatment and/or hospitalization. There were no deaths in the patients randomized to 2.5 mg pimobendan. In the 5-mg group, there was one death caused by myocardial infarction and two sudden deaths in the setting of relative clinical stability. There were five deaths in the patients randomized to 10 mg pimobendan, including two patients with progressive heart failure and three patients with sudden death.

Adverse events in the four treatment groups are summarized in Table 3. Serious nonfatal events were defined as any event that was immediately life threatening or resulted in or increased the length of hospitalization. These events were observed in 17 (35%) placebo patients and were significantly less frequent in the pimobendan groups (28 patients, 19%; p<0.05). There were no significant differences in rates or types of serious adverse events among the different doses of pimobendan. There were reports of 131 different types of adverse events defined as any event that was new or worse on treatment compared with baseline. Forty-three (88%) placebo patients and 127 (85%) pimobendan patients experienced an event. The incidence of headache rose with dose of pimobendan (p<0.05). Otherwise, there were no significant differences between placebo and pimobendan in the incidence of adverse events.

Proarrhythmic effects were assessed according to criteria defined by Morganroth.20 At weeks 4, 8, and 12, between 15% and 44% of patients met criteria for proarrhythmia changes. However, these changes were highly variable among patients and were not consistently observed at weeks 4, 8, and 12. Therefore, patients who had a consistent proarrhythmia effect during all three follow-up Holter recordings were considered separately. This included 5.0, 7.9, 11.8, and 6.1% of patients in the placebo, 2.5-, 5-, and 10-mg groups, respectively, without significant differences among the groups.

Discussion

These data demonstrate that pimobendan significantly increased exercise duration, peak VO₂, and quality of life in ambulatory patients with heart failure who had persistent symptoms despite background therapy with digitalis, diuretics, converting enzyme inhibitors, or a single vasodilator. Furthermore, pimobendan was associated with a significant reduction in hospitalization rates compared with placebo. Pimobendan was well tolerated and compared with placebo did not demonstrate significant differences in the need to change background therapy, rates of serious adverse effects, proarrhythmia effects, ejection fraction, plasma norepinephrine levels, or death rates. The 5-mg/day dose of pimobendan produced the largest increase in exercise duration, peak oxygen consumption, and quality of life. This trial therefore confirms the beneficial effects of pimobendan on exercise duration and peak VO₂ that was demonstrated in a previous short-term study of 52 patients with heart failure.17 These suggest that pimobendan may be useful adjunctive therapy in ambulatory patients with symptoms of heart failure that persist despite conventional therapy.

The positive results of the two trials with pimobendan should be contrasted to previous experience with enoximone, amrinone, and milrinone, which did not demonstrate improvement in exercise capacity when added to digitalis.2,3,24 One possible explanation may be related to differences in mechanisms of action for pimobendan. Amrinone, milrinone, and enoximone are thought to act primarily via inhibition of PDE, leading to increased intracellular cAMP concentrations.6–9 Although pimobendan demonstrates activity as a PDE inhibitor, experiments using papillary muscle preparations have demonstrated that pimobendan also causes an upward and leftward shift of the calcium-force relation.15,16,25 This calcium-sensitizing property appears to be related to an increased binding of calcium to troponin C and was not observed with milrinone.15,16 Experiments using myocardium from patients with heart failure have confirmed this calcium-sensitizing property.26 Although extrapolations from in vitro data are difficult and one cannot determine that calcium sensitization is responsible for the effects observed clinically, it is possible that the greater beneficial effects of pimobendan are related to the fact that it has an additional mechanism of action.

An alternative explanation to account for at least some of the benefit of pimobendan is related to the fact that pimobendan also has vasodilator activity. It is well established that vasodilators improve hemodynamics and often increase exercise capacity in patients with heart failure. However, in this clinical trial, it is not possible to determine the relative contributions of the vasodilator and inotropic actions.

Two specific features of this trial may have increased the ability to detect a statistically significant effect of pimobendan. In contrast to the high dropout rates noted with milrinone and enoximone,2,3 pimobendan was well tolerated with very few dropouts. Moreover, unlike the placebo groups in other studies, the placebo group in this trial did not demonstrate increases in exercise duration or peak VO₂. The clinical stability of the placebo patients may be related to background therapy with digitalis, diuretics, and vasodilators. Secondly, this trial evaluated a dose range of pimobendan rather than depending on a single fixed dose. By using a range of doses, it was possible to determine that 5 mg pimobendan was associated with maximal efficacy. The factors contributing to the trend for smaller improvements with the 10-mg dose are not known, because the previous invasive study demonstrated that a 10-mg dose of pimobendan produced the largest hemodynamic improvements.17 These data therefore emphasize the importance of conceptual differences between the dose of a drug that provides the maximal hemodynamic response initially and the dose that results in clinical improvements long-term. It is possible that the previous trials with milrinone and enoximone were limited by titration to a high dose that was chosen for maximal hemodynamic improvement.

The concordance of positive effects with pimobendan provide additional support for its potential clinical usefulness. In addition to the beneficial effects on exercise duration, peak oxygen consumption, and quality of life, the number of hospitalizations was lower in the pimobendan group. Moreover, pimobendan was not
associated with a significant effect on serious adverse events, proarrhythmic changes, or plasma norepinephrine. This lack of an effect on plasma norepinephrine may be important because excessive sympathetic stimulation has been associated with increased mortality in patients with heart failure.\(^{27}\) The lack of change in ejection fraction in response to an inotropic agent was unexpected. However, improvements in ejection fraction with inotropic agents have not been consistent in all studies,\(^1\) and the ability to augment ejection fraction in patients already treated with digoxin and vasodilators is unknown. Moreover, the small sample size may have limited the ability to detect a statistically significant change in ejection fraction.

**Study Limitations**

There are a number of limitations to this study. First, the 12-week duration and sample size of this study do not permit a true assessment of the effects of pimobendan on long-term efficacy and mortality. Trials using an appropriate sample size and longer follow-up will be necessary to accurately assess the impact of pimobendan on mortality. Second, this study included only patients who were ambulatory, able to complete an exercise test, and who remained symptomatic despite being treated with digitalis and diuretics with or without a single vasodilator. Additional studies are needed to assess the effects of pimobendan in patients with milder degrees of heart failure or those patients with end-stage heart failure who have symptoms at rest. Because pimobendan was added to background therapy, this study does not provide data on the efficacy of pimobendan compared with digoxin, diuretics, converting enzyme inhibitors, or vasodilators.

**Conclusions**

The documentation of significant improvement in exercise capacity and quality of life with pimobendan has an important implication for treatment strategies for patients with moderate to severe heart failure.

**Table 3. Adverse Events**

<table>
<thead>
<tr>
<th>Serious nonfatal events§</th>
<th>Placebo</th>
<th>Pimobendan (daily dose)</th>
<th>All doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total treated</td>
<td>49</td>
<td>49</td>
<td>51</td>
</tr>
<tr>
<td>Total with at least one event</td>
<td>17 (35%)</td>
<td>12 (24%)</td>
<td>7 (14%)</td>
</tr>
<tr>
<td>Chest pain</td>
<td>1 (2%)</td>
<td>2 (4%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Coronary heart failure</td>
<td>6 (12%)</td>
<td>6 (12%)</td>
<td>2 (4%)</td>
</tr>
<tr>
<td>Ventricular tachycardia</td>
<td>3 (6%)</td>
<td>0</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Ventricular fibrillation</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Fever</td>
<td>1 (2%)</td>
<td>0</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Syncope</td>
<td>1 (2%)</td>
<td>0</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>0</td>
<td>1 (2%)</td>
<td>0</td>
</tr>
<tr>
<td>Hypotension</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
<td>0</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>1 (2%)</td>
<td>0</td>
<td>1 (2%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Most frequent adverse events§</th>
<th>Placebo</th>
<th>Pimobendan (daily dose)</th>
<th>All doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total with at least one event</td>
<td>43 (88%)</td>
<td>41 (84%)</td>
<td>42 (82%)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>7 (14%)</td>
<td>4 (8%)</td>
<td>8 (16%)</td>
</tr>
<tr>
<td>Headache†</td>
<td>6 (12%)</td>
<td>4 (8%)</td>
<td>14 (27%)</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>8 (16%)</td>
<td>10 (20%)</td>
<td>9 (18%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>9 (18%)</td>
<td>4 (8%)</td>
<td>4 (8%)</td>
</tr>
</tbody>
</table>

*p<0.05 vs. placebo.

†p<0.05 by Jonckheere's test of increasing incidence with increasing dose.

§Defined as any event that was immediately life threatening or resulted in or increased the length of hospitalization; table includes only those events that occurred in two or more of the 198 total patients.

$ Defined as any event that was new or worse on treatment compared with baseline; table includes events that occurred in ≥10% of the 198 total patients but does not repeat events listed in "Serious nonfatal events."
Despite the disappointing results with PDE inhibitors in other clinical trials, these data suggest that the concept that inotropic agents would have clinical utility in this patient population cannot be entirely dismissed, and that studies of drugs with different mechanisms of action should be considered. Furthermore, although additional safety and efficacy trials are necessary, these data suggest that pimobendan may be useful adjunctive therapy for patients who remain symptomatic despite the use of digitalis, diuretics, converting enzyme inhibitors, or a single vasodilator.

Appendix
Participating Centers, Principal Investigators, and Study Coordinators

University of Alabama, Birmingham: Robert Bourge, MD, principal investigator; Danielle Thomas, RN, study coordinator; Tonya Hollis, RN, study coordinator.

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Veterans Administration Medical Center, Washington, DC: Steven Singh, MD, principal investigator; Margaret Shand, RN, study coordinator; Melanie Herr, RN, study coordinator; Mary Smith, RN, study coordinator.

Duke University Medical Center, Durham, N.C.: Martin Sullivan, MD, principal investigator.

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Study chairman: Jay N. Cohn, MD, University of Minnesota, Minneapolis.

Boehringer Ingelheim Pharmaceuticals: Jan Troha, Associate Director, Clinical Research; John Wecker, PhD, Manager, Clinical Research; Joan Kemplethorne-Rawson, PhD, Senior Statistician; Susan Huyck, MS, Supervisor, Medical Data Management; Ridgefield, Conn.

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_Circulation_. 1992;85:942-949
doi: 10.1161/01.CIR.85.3.942
_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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