

A DOSE-DEPENDENT INCREASE IN MORTALITY WITH VESNARINONE AMONG PATIENTS WITH SEVERE HEART FAILURE

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ABSTRACT

Background Vesnarinone, an inotropic drug, was shown in a short-term placebo-controlled trial to improve survival markedly in patients with severe heart failure when given at a dose of 60 mg per day, but there was a trend toward an adverse effect on survival when the dose was 120 mg per day. In a longer-term study, we evaluated the effects of daily doses of 60 mg or 30 mg of vesnarinone, as compared with placebo, on mortality and morbidity.

Methods We enrolled 3833 patients who had symptoms of New York Heart Association class III or IV heart failure and a left ventricular ejection fraction of 30 percent or less despite optimal treatment. The mean follow-up was 286 days.

Results There were significantly fewer deaths in the placebo group (242 deaths, or 18.9 percent) than in the 60-mg vesnarinone group (292 deaths, or 22.9 percent) and longer survival ($P=0.02$). The increase in mortality with vesnarinone was attributed to an increase in sudden death, presumed to be due to arrhythmia. The quality of life had improved significantly more in the 60-mg vesnarinone group than in the placebo group at 8 weeks ($P<0.001$) and 16 weeks ($P=0.003$) after randomization. Trends in mortality and in measures of the quality of life in the 30-mg vesnarinone group were similar to those in the 60-mg group but not significantly different from those in the placebo group. Agranulocytosis occurred in 1.2 percent of the patients given 60 mg of vesnarinone per day and 0.2 percent of those given 30 mg of vesnarinone.

Conclusions Vesnarinone is associated with a dose-dependent increase in mortality among patients with severe heart failure, an increase that is probably related to an increase in deaths due to arrhythmia. A short-term benefit in terms of the quality of life raises issues about the appropriate therapeutic goal in treating heart failure. (N Engl J Med 1998;339:1810-6.)

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THE search for a positive inotropic drug that could relieve symptoms and improve the prognosis in patients with heart failure who were already being treated with angiotensin-converting-enzyme (ACE) inhibitors led to the development of vesnarinone, a drug with multiple mechanisms that appears to enhance contractility through ion-channel effects that augment sodium-calcium exchange.¹⁻³ Short-term administration of vesnarinone to patients with heart failure was associated

with limited and variable hemodynamic effects,⁴⁻⁶ but small placebo-controlled trials showed a favorable effect on the quality of life and morbidity.^{7,8} In a multicenter study initiated in 1990, 577 patients with New York Heart Association (NYHA) class III or IV heart failure were randomly assigned to receive placebo or 60 mg of vesnarinone daily for six months (some patients were assigned to 120 mg of vesnarinone, but this part of the trial was stopped early). The primary end point was combined mortality and major cardiovascular morbidity.⁹ A remarkable and significant 50 percent reduction in the combined end point and a 62 percent reduction in mortality from all causes were observed in the vesnarinone-treated group. Concern was aroused, however, by the occurrence of neutropenia, a dangerous side effect of the drug, in this and earlier clinical trials.⁶⁻⁹

These results were problematic for several reasons. First, the duration of the trial was short (six months), and the total number of events was small (46 deaths). Second, two vesnarinone regimens (60 mg and 120 mg daily) were studied, and the higher-dose regimen was discontinued early by the data and safety monitoring committee because of a trend toward an adverse effect on mortality. Finally, the side-effect profile suggested the need for a larger study to establish the risk-benefit ratio of the drug.

We therefore initiated the Vesnarinone Trial in January 1995 to study the long-term effects of 60 mg or 30 mg of vesnarinone daily in a trial sufficiently large to enable us to determine the effects of vesnarinone on both mortality and morbidity among patients who had reduced left ventricular ejection fractions and

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symptoms of severe heart failure while being treated with standard therapy, including ACE inhibitors.

METHODS

Patients

This randomized, double-blind study was carried out in 189 centers in the United States and Canada. Men and women over the age of 18 years were eligible if they had a history and physical findings of severe heart failure with an ejection fraction of 30 percent or less, as measured by radionuclide or radiographic contrast ventriculography within the previous 90 days. Patients had to have symptoms of NYHA class III or IV heart failure despite conventional therapy that could consist of any regimen of diuretics, digitalis, vasodilators, and ACE inhibitors that had not been changed during the 30 days before the study began.

Patients were excluded if they had had an acute myocardial infarction or cardiac surgery within the previous 60 days, or if they had clinically significant obstructive valvular or subvalvular disease, reversible myocardial disease, an implanted defibrillator, a history of hematologic or immunologic disease, or cancer likely to limit life expectancy. Women of childbearing potential were excluded unless they were practicing effective contraception; women were not eligible within 60 days after childbirth. Treatment with beta-blockers or intermittent inotropic support excluded patients from participation. Patients on a waiting list for a heart transplant were eligible if they were unlikely to receive a transplant in the next six months.

Study Design

After a two-week stabilization period, during which all medications and clinical findings remained unchanged, eligible patients were randomly assigned to receive placebo, 30 mg of vesnarinone per day, or 60 mg of vesnarinone per day. Patients on a waiting list for a heart transplant underwent randomization separately. Baseline and periodic assessments included the Minnesota Living with Heart Failure questionnaire¹⁰ to assess the quality of life, electrocardiography, blood chemistry, hematologic measurements, ascertainment of adverse events, and physical examination.

Outcome Variables

The primary outcome variable was mortality from all causes, with the effects of 30 mg of vesnarinone and 60 mg of vesnarinone compared separately with those of placebo. One secondary outcome was the combination of mortality from all causes and major morbidity due to heart failure, defined as admission to the hospital for worsening heart failure that required treatment with intravenous inotropic or vasodilator drugs for at least four hours. Additional secondary outcomes included measures of the quality of life, the incidence of sudden death due to cardiac causes (as distinguished from death due to progressive heart failure), the number of hospitalizations and visits to an emergency room for heart failure, and the incidence of adverse events.

Statistical Analysis

On the assumption that mortality in the placebo group would be 20 percent in the first year and in order to give the study a 90 percent power of detecting a 30 percent reduction in mortality in the vesnarinone groups, a sample size of 3618 (1206 per treatment group) was required. An overall significance level of 0.05 for this trial was established; pairwise comparison of each active-drug group with placebo required a Bonferroni adjustment to set the alpha value for each two-sided comparison at 0.025. To reach the calculated power, the study was planned to end when 232 deaths had occurred in the placebo group. Sequential monitoring by the data and safety monitoring committee at six-month intervals was performed with use of the symmetric O'Brien-Fleming spending function to maintain an alpha level of 0.025 at the end of the trial for each drug-placebo comparison. Comparisons of survival were

made with use of the Cox proportional-hazards model. The final P value for each drug-placebo comparison was adjusted to account for the repeated testing performed by the data and safety monitoring committee. Survival and morbidity were evaluated by time-to-event analysis with adjustment for mortality-related covariates to improve the precision of the estimate of the effect of treatment. Survival curves and other time-to-event curves were calculated by the Kaplan-Meier method. All analyses were conducted on an intention-to-treat basis. Changes in the scores on the Minnesota Living with Heart Failure questionnaire were compared between treatment groups with the Wilcoxon rank-sum test, without adjustment for multiple comparisons.

RESULTS

A total of 3833 patients were enrolled between January 26, 1995, and July 10, 1996. The data and safety monitoring committee reviewed interim study data in June 1995, September 1995, December 1995, February 1996, and monthly thereafter until the study was stopped on July 31, 1996, at which point the prespecified total number of deaths in the placebo group had occurred.

Base-Line Demographic and Clinical Characteristics

Patients in the three groups were similar in terms of base-line characteristics (Table 1). They were an average of 63 years of age; approximately 76 percent were men; and 84 percent were white. Nearly 60 percent had been given a diagnosis of ischemic cardiomyopathy due to coronary artery disease. Ninety percent were taking an ACE inhibitor at the time of randomization. The ejection fraction averaged 21 per-

TABLE 1. BASE-LINE CHARACTERISTICS OF THE PATIENTS.*

CHARACTERISTIC	PLACEBO (N=1283)	130 mg OF VESNARINONE (N=1275)	60 mg OF VESNARINONE (N=1275)
Age (yr)	62.9±11.9	62.9±12.4	63.3±11.9
Male sex (%)	75.0	75.4	78.5
White race (%)	83.9	84.7	83.6
Ischemic cause of heart failure (%)	57.6	56.6	60.3
NYHA class (%)†			
III	84.9	85.3	84.4
IV	13.9	13.2	14.2
History of hypertension (%)	55.3	51.9	55.8
Smoker (%)	12.7	13.7	12.1
Excess alcohol consumption (%)	24.6	22.0	24.2
Time since diagnosis (mo)	51.0±51.7	52.8±56.3	52.5±52.9
On waiting list for transplantation (%)	4.7	4.9	5.3
ACE inhibitor treatment (%)	90.5	90.4	89.2
Ejection fraction (%)	20.9±6.0	20.9±6.0	20.9±6.0
Cardiothoracic ratio	0.56±0.07	0.56±0.08	0.56±0.07

*Plus-minus values are means ±SD. NYHA denotes New York Heart Association, and ACE angiotensin-converting enzyme.

†Percentages do not total 100 because some patients had class II heart failure.

cent. The mean follow-up was 286 days; 90 percent of the patients who underwent randomization were followed from 59 to 489 days.

Mortality

During the course of the trial, there were 242 deaths in the placebo group (18.9 percent), 268 in the 30-mg vesnarinone group (21.0 percent), and 292 in the 60-mg vesnarinone group (22.9 percent). The time to death from any cause was significantly shorter in the 60-mg vesnarinone group than in the placebo group ($P=0.02$) (Fig. 1). After ad-

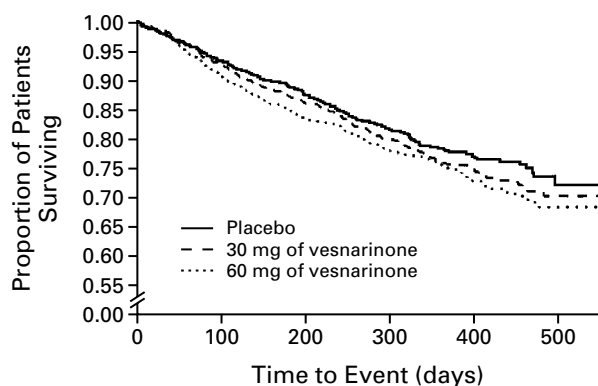


Figure 1. Survival in the Three Groups.

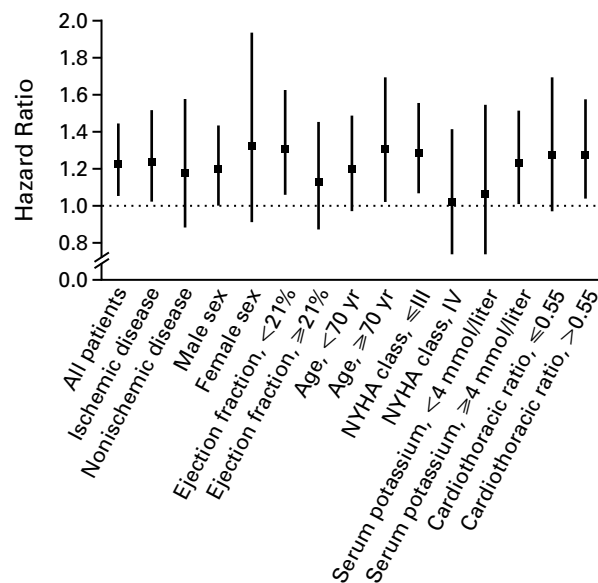


Figure 2. Subgroup Analysis of Hazard Ratios and 95 Percent Confidence Intervals for Death from Any Cause among Patients Assigned to Receive 60 mg of Vesnarinone per Day as Compared with Those Assigned to Receive Placebo. The dotted line (hazard ratio, 1.0) indicates the risk of death in the placebo group.

justment for multiple interim analyses, the P value remained 0.02. The trend toward an adverse effect of the 30-mg dose of vesnarinone, as compared with placebo, was not significant ($P=0.21$).

Since data on heart-transplant recipients were censored at the time of transplantation in the primary analysis, a secondary analysis was carried out to evaluate the time to death or heart transplantation. This analysis also showed an adverse effect of the 60-mg dose of vesnarinone as compared with placebo ($P=0.04$).

The effect of the 60-mg dose of vesnarinone on mortality from all causes was separately evaluated in a number of prespecified subgroups (Fig. 2). For the 60-mg vesnarinone group, the hazard ratio was greater than 1.0 for all subgroups. The 95 percent confidence interval for the hazard ratio did not overlap 1.0 for several subgroups: patients with ischemic heart disease, those with ejection fractions below the median (21 percent), those who were 70 years of age or older, those with a NYHA functional class of III or lower, and those with a cardiothoracic ratio greater than 0.55.

The number of deaths attributed to worsening heart failure by a morbidity and mortality committee whose members were unaware of the patients' treatment assignments was similar in the three groups, whereas the number of deaths presumed to be related to an arrhythmia (sudden death from cardiac causes) was higher in the vesnarinone groups (Table 2). The distribution of cause-specific deaths differed significantly between the 60-mg vesnarinone group and the placebo group ($P=0.02$). Analysis of time to death from cardiac causes ($P=0.04$) and time to sudden death from cardiac causes ($P=0.01$) showed a significant adverse effect of 60 mg of vesnarinone per day as compared with placebo.

Major Morbidity

No significant difference in the numbers of patients hospitalized for major episodes of heart failure was observed among the three groups (placebo group, 237 patients; 30-mg vesnarinone group, 232 patients; 60-mg vesnarinone group, 217 patients). Death or major morbidity due to heart failure occurred in 29.8 percent of the placebo group, 31.0 percent of the 30-mg vesnarinone group, and 32.2 percent of the 60-mg vesnarinone group. The time to the combined end point of mortality and morbidity did not differ significantly among the three groups (60-mg vesnarinone group vs. placebo group, $P=0.25$; 30-mg vesnarinone group vs. placebo group, $P=0.63$). Only in the subgroup of patients with ischemia ($P=0.08$), the subgroup of patients 70 years of age or older ($P=0.08$), and the subgroup with NYHA class III or lower heart failure ($P=0.07$) was there a trend toward an adverse effect of 60 mg of vesnarinone per day as compared with

TABLE 2. CAUSES OF DEATH IN THE THREE GROUPS.*

VARIABLE	PLACEBO (N=1283)			30 mg OF VESNARINONE (N=1275)			60 mg OF VESNARINONE (N=1275)		
	NO.	% OF		NO.	% OF		NO.	% OF	
		RANDOMIZED PATIENTS	% OF DEATHS		RANDOMIZED PATIENTS	% OF DEATHS		RANDOMIZED PATIENTS	% OF DEATHS
Death from any cause	242	18.9	100	268	21.0	100	292	22.9	100
Death from cardiac causes	231	18.0	95.5	248	19.5	92.5	271	21.3†	92.8
Sudden death‡	117	9.1	48.3	136	10.7	50.7	157	12.3	53.8
Pump failure	109	8.5	45.0	106	8.3	39.6	106	8.3	36.3
Myocardial infarction	5	0.4	2.1	6	0.5	2.2	8	0.6	2.7
Death from noncardiac causes	11	0.9	4.5	20	1.6	7.5	21	1.6	7.2

*Because of rounding, not all percentages total 100.

†P=0.02 for the distribution of cardiac causes of death in the 60-mg vesnarinone group as compared with the placebo group.

‡Hazard ratio for sudden death in the 60-mg vesnarinone group as compared with the placebo group, 1.35 (95 percent confidence interval, 1.08 to 1.69).

TABLE 3. MAJOR MORBIDITY IN THE THREE GROUPS.

EVENT	PLACEBO (N=1283)	30 mg OF VESNARINONE (N=1275)	60 mg OF VESNARINONE (N=1275)
	number of patients (percent of total)		
Any hospitalization	635 (49.5)	602 (47.2)	617 (48.4)
For cardiac disease	509 (39.7)	488 (38.3)	487 (38.2)
For worsening heart failure	360 (28.1)	342 (26.8)	335 (26.3)
Emergency room visit	226 (17.6)	210 (16.5)	214 (16.8)
For cardiac disease	49 (3.8)	58 (4.5)	50 (3.9)

placebo. No significant difference in overall morbidity due to cardiovascular causes was observed among the three treatment groups (Table 3), and the time to a first hospitalization was similar in the three treatment groups.

Quality of Life

The median score on the Minnesota Living with Heart Failure questionnaire at base line was 55.7 (mean, 53.3), a value consistent with a severe degree of disability, as expected in patients with NYHA class III or IV heart failure. All three groups had improvement (indicated by a reduction in the score) during follow-up (Table 4). Improvements at 8 weeks and 16 weeks in the 60-mg vesnarinone group were significantly greater than those in the placebo group (P<0.001 and P=0.003, respectively). By 26 weeks the difference in the degree of improvement between the groups was not significant (P=0.41).

Scores on the Minnesota Living with Heart Failure questionnaire can be subdivided into emotional and physical scores. Both scores improved more with

60 mg of vesnarinone per day than with placebo (emotional dimension, P=0.001 at 8 weeks and P=0.005 at 16 weeks; physical dimension, P=0.009 at 8 weeks and P=0.01 at 16 weeks).

Since the quality of life can be assessed only for survivors, imputing the worst possible scores to patients who died or underwent heart transplantation is a standard technique in intention-to-treat analysis. Such imputation did not eliminate the overall benefit of the 60-mg dose of vesnarinone over placebo on the Minnesota Living with Heart Failure questionnaire at 8 weeks (P=0.003), but it did reduce the significance of the favorable effect at 16 weeks (P=0.08).

We also analyzed the distribution of changes in scores on the Minnesota Living with Heart Failure questionnaire. At 8 weeks, scores had improved by more than 15 points among 28.9 percent of the patients in the 60-mg vesnarinone group, as compared with 23.8 percent of the patients in the placebo group. Similarly, scores had worsened by more than 15 points among 6.2 percent of the patients in the 60-mg vesnarinone group, as compared with 8.4 percent of those in the placebo group. The favorable individual response to vesnarinone at eight weeks was particularly apparent in patients with class IV heart failure; among such patients, 38.9 percent of the 60-mg vesnarinone group had scores showing improvement and 5.9 percent had scores showing a decline in the quality of life, as compared with 20.6 percent and 9.2 percent, respectively, in the placebo group. The changes in scores at 16 weeks were similar.

Adverse Events

Vesnarinone was well tolerated, with a similar incidence of adverse events in the three groups except for significant dose-related increases in the incidence of diarrhea and leukopenia in the vesnarinone groups. Diarrhea was reported by 17.0 percent of the pa-

TABLE 4. QUALITY-OF-LIFE SCORES IN THE THREE GROUPS.*

VARIABLE	PLACEBO		30 mg OF VESNARINONE			60 mg OF VESNARINONE		
	MEDIAN	MEAN \pm SD	MEDIAN	MEAN \pm SD	P VALUE	MEDIAN	MEAN \pm SD	P VALUE
Base-line score	55	53.3 \pm 23.6	-56	53.4 \pm 24.5		56	53.3 \pm 24.4	
Change at 8 wk	-5	-5.9 \pm 18.0	-5	-6.9 \pm 18.5	0.34	-7	-8.8 \pm 18.2	<0.001
Change at 16 wk	-6	-7.3 \pm 20.1	-5	-7.4 \pm 20.3	0.74	-8	-10.1 \pm 19.7	0.003
Change at 26 wk	-7	-8.6 \pm 21.4	-7	-8.4 \pm 21.7	0.83	-7	-10.0 \pm 20.9	0.41

*Lower scores indicate better quality of life. P values are for the comparison of the medians with those in the placebo group.

tients in the 60-mg vesnarinone group, as compared with 12.0 percent of the patients in the placebo group ($P < 0.001$) and 14.5 percent of the patients in the 30-mg vesnarinone group (P not significant). Leukopenia, which occurred in 2.5 percent of the vesnarinone group in previous trials, was less common in this study. Agranulocytosis occurred in 15 patients assigned to 60 mg of vesnarinone per day (1.2 percent), as compared with 3 (0.2 percent) of those in the 30-mg vesnarinone group and none in the placebo group ($P < 0.001$).

DISCUSSION

Heart failure is a syndrome characterized by an impaired quality of life, morbidity requiring frequent hospitalizations, and shortened life expectancy. Although the therapeutic goal has been improvement in all of these adverse outcomes, data from recent clinical trials have suggested that symptoms and life expectancy are determined independently and may not respond in concert to therapeutic interventions.¹¹ Furthermore, the end point of improvement in exercise tolerance or quality of life is usually evaluated in short-term trials, lasting three to six months, whereas mortality and morbidity are usually evaluated in very large, longer-term trials.

The first multicenter trial of vesnarinone was relatively small and lasted six months, features that raised questions about the likelihood that the observed benefit would be confirmed in a larger and longer trial. In addition, the unusual dose–mortality response in that trial — in which the 60-mg dose of vesnarinone had a favorable effect on mortality and the 120-mg dose had an adverse effect — aroused concern about the safety of the drug and its optimal dosage. The current trial was designed to address all these issues and to compare a 30-mg and a 60-mg dose of vesnarinone with placebo in a trial with high statistical power.

The dose-related increase in mortality in response to vesnarinone in our trial was unexpected on the basis of earlier reports, but it is consistent with the drug-related increase in mortality previously observed in

trials of drugs with purported positive inotropic effects.¹²⁻¹⁴ Although oral vesnarinone has not been demonstrated to have the hemodynamic effect of potent cardiac stimulation in patients with heart failure,⁴⁻⁶ its cellular effects on ion channels would be expected to increase the availability of cytosolic calcium for myocyte contraction.¹⁵

The increased mortality in the vesnarinone groups was attributed to an increased incidence of sudden death. This has also been true of the observed increase in mortality in response to milrinone and flosequinan in previous trials.^{13,16} Whether these drugs exert direct arrhythmic effects or accelerate structural remodeling of the ventricle, thus providing the substrate for ventricular tachycardia and fibrillation, is unknown. The favorable effects of ACE inhibitors, the combination of isosorbide dinitrate and hydralazine, and beta-blockers on the incidence of sudden death appear to be associated with the regression of structural ventricular remodeling, thus suggesting a link between ventricular dilatation and lethal arrhythmias.^{17,18} The effect of vesnarinone on ventricular volume was not assessed in this trial.

Despite the dose-related increase in mortality in response to vesnarinone, the 60-mg dose of the drug had a significant favorable effect on the quality of life as compared with placebo. This benefit, which was apparent in both the physical and emotional scores on the questionnaire, suggests that the drug may exert a positive action either on the function of the heart or on some aspect of circulatory or neurohormonal abnormalities in patients with heart failure, possibly including an anticytokine effect.¹⁹ The improvement in the quality of life appeared to be short-lived, however, since it was present at 8 and 16 weeks but was no longer significant at the final 26-week assessment.

The contrasting effects of vesnarinone on the quality of life and on mortality raise profound issues about therapy for heart failure. Although the increase in mortality associated with vesnarinone would appear to eliminate it as a useful drug for heart failure, patients with severe heart failure are often willing to

accept a greater risk of death in return for an improvement in the quality of life.²⁰ Furthermore, despite the drug-related increase in the incidence of death, the difference in mortality among all randomized patients during the trial was only 4 percentage points (mortality, 18.9 percent in the placebo group vs. 22.9 percent in the 60-mg vesnarinone group), whereas the difference in the proportion with marked improvement in the quality of life between the 60-mg vesnarinone group and the placebo group at eight weeks was 5 percentage points (rate of improvement, 23.8 percent in the placebo group vs. 28.9 percent in the vesnarinone group). In patients with class IV heart failure, the 60-mg dose of vesnarinone improved the quality of life more than did placebo (38.9 percent vs. 20.6 percent, a difference of 18.3 percentage points).

At least three important questions are raised by these data. First, is the improvement in the quality of life in individual patients great enough to justify the increased risk of death in this population? Second, can patients who are likely to die suddenly while receiving vesnarinone be identified so that the use of this drug can be avoided in these patients? Third, can the sudden death associated with vesnarinone be prevented so that the benefit in terms of the quality of life can be obtained without increased mortality? In addition, the apparent limitation of the improved quality of life to the first 16 weeks of treatment raises the further issue of why the benefit appears to wane. Our results emphasize the complexity of applying data from clinical trials to the case of individual patients. Physicians' practice is generally to prescribe drugs that benefit patients and to discontinue drugs that appear to be ineffective. Such clinical judgment cannot be introduced into the design of a clinical trial that relies on intention-to-treat analysis and focuses on mean responses in large, heterogeneous groups of patients.²¹

Although a relatively high incidence of neutropenia in the earlier clinical trials of vesnarinone⁶⁻⁹ aroused concern about safety and led to frequent monitoring of white-cell counts during the first 16 weeks of the protocol, only 1.2 percent of the patients assigned to the 60-mg dose in our trial had agranulocytosis, as compared with a 2.5 percent incidence in previous trials. The reason for the lower incidence in the current trial is unknown.

Another important issue is the contradiction between the results of the earlier, smaller multicenter trial and those of the present large study. Examination of the patient populations in the two trials reveals no differences that could reasonably account for the opposite response to the daily administration of 60 mg of vesnarinone. The progressive increase in mortality in our trial from placebo to 30 mg of vesnarinone per day to 60 mg per day, when combined with the striking increase in mortality with a daily

dose of 120 mg of vesnarinone in the earlier trial,⁹ indicates a nearly linear adverse dose-response effect of vesnarinone. The implication is that trials assessing mortality or mortality and morbidity in patients with heart failure should have sufficient power, with enough events and long enough follow-up, to ensure that the results reliably reflect the long-term effects of the drug as compared with placebo.

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APPENDIX

The following persons and institutions participated in the Vesnarinone Trial: Executive Committee — J.N. Cohn (study chairman), S. Goldstein, B.H. Lorell, B.H. Greenberg; Mortality and Morbidity Committee — A. Feldman (cochairman), J. Young (cochairman), R. Bourge, P. Carson, and B. Jaski; Data and Safety Monitoring Committee — R. Capone (chairman), J. Wilson, B.W. Brown, Jr., M. Hess; Independent Statistician — D. DeMets; Clinical centers and investigators — E. Kasper, Johns Hopkins Hospital, Baltimore; J. Strobeck, Valley Hospital, Ridgewood, N.J.; T. LeJemtel, Albert Einstein Hospital, Bronx, N.Y.; E. Powers, University of Virginia, Charlottesville; G. Hendrix, Medical University of South Carolina, Charleston; S. Gottlieb, Johns Hopkins Bayview Medical Center, Baltimore; M. Higginbotham, Duke University Medical Center, Durham, N.C.; T. DeMarco, University of California, San Francisco; P. Carson, Veterans Affairs Medical Center and Georgetown University Hospital, Washington, D.C.; M. Gilbert, University of Utah, Salt Lake City; R. Schlant, Emory University School of Medicine, Atlanta; R. Wright, Pacific Heart Institute, Santa Monica, Calif.; J. O'Brien, Fairfax Hospital, Falls Church, Va.; R. Hershberger, Oregon Health Sciences University, Portland; B. Jaski, San Diego Cardiac Center, San Diego, Calif.; G.W. Dec, Massachusetts General Hospital, Boston; M. Goodman, Cardiovascular Medical Associates, Garden City, N.Y.; R. Lee, Mayo Clinic, Scottsdale, Ariz.; M. Jessup, Medical College of Pennsylvania, Philadelphia; A. Feldman, Presbyterian University Hospital, Pittsburgh; C. Pepine, Veterans Affairs Medical Center, Gainesville, Fla.; A.B. Miller, University of Florida, Jacksonville; J. Abrams, University of New Mexico, Albuquerque; U. Thadani, University of Oklahoma, Oklahoma City; R. Bourge, University of Alabama, Birmingham; G. Levy, Methodist Hospital, Houston; W. Abraham, University of Colorado, Denver; M.A. Silver, Loyola University Medical Center, Maywood, Ill.; G. Bhat, University of Cincinnati, Cincinnati; F. McGrew, III, Cardiology Group of Memphis, Memphis, Tenn.; M. Fowler, Stanford University School of Medicine, Stanford, Calif.; R. Hobbs, Cleveland Clinic Foundation, Cleveland; C.A. Vander Ark, University of Wisconsin, Madison; T.B. Levine, Henry Ford Hospital, Detroit; B. Abramowitz, Christ Hospital and Medical Center, Oak Lawn, Ill.; S. Kubo, University of Minnesota, Minneapolis; S. Brozena, Allegheny University Hospitals, Philadelphia; R. Roddeheffer, Mayo Clinic, Rochester, Minn.; C.W. Yancy, Jr., University of Texas Southwestern Medical Center, Dallas; D. Schulman, Allegheny General Hospital, Pittsburgh; C. Moore, University of Mississippi Medical Center, Jackson; M.R. Costanzo, Rush-Presbyterian-St. Luke's Medical Center, Chicago; C.-S. Liang, University of Rochester Medical Center, Rochester, N.Y.; G.S. Uhl, Nevada Research Consultants, Las Vegas; S. Krueger, Lincoln Cardiology Associates, Lincoln, Nebr.; R. Chahine, Jackson Memorial Hospital, Miami; J. Boehmer, Milton S. Hershey Medical Center, Hershey, Pa.; S. Khan, Cedars-Sinai Medical Center, Los Angeles; D. Fishbein, University of Washington, Seattle; E. Hausslein, California Pacific Medical Center, San Francisco; M. Greenspan, Buxmont Cardiology Associates, Sellersville, Pa.; M. Koren, Jacksonville Cardiovascular Clinic, Jacksonville, Fla.; L. Miller, St. Louis University Hospital, St. Louis; R. Oren, University of Iowa, Iowa City; M. Kukin, Mount Sinai Medical Center, New York; J. Ghali, Louisiana State University, Shreveport; P. McLaughlin, University of Missouri, Columbia; G. Cintron, University of South Florida, Tampa; I. Anand, Veterans Affairs Medical Center, Minneapolis; D. Zipes, Krannert Institute, Indianapolis; J. Thatcher, Park Nicollet Heart Center, St. Louis Park, Minn.; R.D. Ensley, Cardiology of Tulsa, Tulsa, Okla.; R. Stafford, Mayo Clinic, Jacksonville, Fla.; J. Revkin, Yale University, New Haven, Conn.; B. Clemson, Heart Care Midwest, Peoria, Ill.; R. Di Bianco, Washington Adventist Hospital, Tacoma Park, Md.; D. Gottlieb, South Seattle Consulting, Seattle; G.C. Fonarow, University of California at Los Angeles; P. Fenster, University of Arizona Health Sciences Center, Tucson; E. Smart, Ochsner Transplant Center, New Orleans; K. Browne, Watson Clinic, Lakeland, Fla.; M. Frey, Heart Center of Sarasota, Sarasota, Fla.; A. Cross, University of Kentucky, Lexington; S. Gottlieb, University of Mary-

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REFERENCES

1. Taira N, Endoh M, Iijima T, et al. Mode and mechanism of action of 3,4-dihydro-6-[4-(3,4-dimethoxybenzyl)-1-piperazinyl]-2(1H)-quinolone (OPC-8212), a novel positive inotropic drug, on the dog heart. *Arzneimittelforschung* 1984;34:347-55.
2. Yatani A, Imoto Y, Schwartz A, Brown AM. New positive inotropic agent OPC-8212 modulates single Ca²⁺ channels in ventricular myocytes of guinea pig. *J Cardiovasc Pharmacol* 1989;13:812-9.
3. Cavusoglu E, Frishman WH, Klapholz M. Vesnarinone: a new inotropic agent for treating congestive heart failure. *J Card Fail* 1995;1:249-57.
4. Sasayama S, Inoue M, Asanoi H, et al. Acute hemodynamic effects of a new inotropic agent, OPC-8212, on severe congestive heart failure. *Heart Vessels* 1986;2:23-8.
5. Asanoi H, Sasayama S, Iuchi K, Kameyama T. Acute hemodynamic effects of a new inotropic agent (OPC-8212) in patients with congestive heart failure. *J Am Coll Cardiol* 1987;9:865-71.
6. Kubo SH, Rector TS, Strobeck JE, Cohn JN. OPC-8212 in the treatment of congestive heart failure: results of a pilot study. *Cardiovasc Drugs Ther* 1988;2:653-60.
7. Asanoi H, Sasayama S, Kameyama T, Ishizaka S, Iuchi K. Sustained inotropic effects of a new cardiotonic agent: OPC-8212 in patients with chronic heart failure. *Clin Cardiol* 1989;12:133-8.
8. Feldman AM, Becker LC, Llewellyn MP, Baughman KL. Evaluation of a new inotropic agent, OPC-8212, in patients with dilated cardiomyopathy and heart failure. *Am Heart J* 1988;116:771-7.
9. Feldman AM, Bristow MR, Parmley WW, et al. Effects of vesnarinone on morbidity and mortality in patients with heart failure. *N Engl J Med* 1993;329:149-55.
10. Rector TS, Kubo SH, Cohn JN. Validity of the Minnesota Living with Heart Failure questionnaire as a measure of therapeutic response to enalapril or placebo. *Am J Cardiol* 1993;71:1106-7.
11. Cohn JN. The management of chronic heart failure. *N Engl J Med* 1996;335:490-8.
12. The Xamoterol in Severe Heart Failure Study Group. Xamoterol in severe heart failure. *Lancet* 1990;336:1-6. [Erratum, *Lancet* 1990;336:693.]
13. Packer M, Carver JR, Rodeheffer RJ, et al. Effect of oral milrinone on mortality in severe chronic heart failure. *N Engl J Med* 1991;325:1468-75.
14. Just H, Hjalmarsson A, Remme WJ, et al. Pimobendan in congestive heart failure: results of the PICO Trial. *Circulation* 1995;92:Suppl I:I-722. abstract.
15. Lathrop DA, Schwartz A. Evidence for possible increase of sodium channel open time and involvement of Na/Ca exchange by a new positive inotropic drug: OPC-8212. *Eur J Pharmacol* 1985;117:391-2.
16. Packer M, Rouleau J, Swedberg K, et al. Effect of flosequinon on survival in chronic heart failure: preliminary results of the PROFILE study. *Circulation* 1993;88:Suppl I:I-301. abstract.
17. Cintron G, Johnson G, Francis G, Cobb F, Cohn JN. Prognostic significance of serial changes in left ventricular ejection fraction in patients with congestive heart failure. *Circulation* 1993;87:Suppl VI:VI-17-VI-23.
18. Bristow MR, Gilbert EM, Abraham WT, et al. Carvedilol produces dose-related improvements in left ventricular function and survival in subjects with chronic heart failure. *Circulation* 1996;94:2807-16.
19. Matsumori A, Shioi T, Yamada T, Matsui S, Sasayama S. Vesnarinone, a new inotropic agent, inhibits cytokine production by stimulated human blood from patients with heart failure. *Circulation* 1994;89:955-8.
20. Rector TS, Tschumperlin LK, Kubo SH, et al. Use of the Living With Heart Failure questionnaire to ascertain patients' perspectives on improvement in quality of life versus risk of drug-induced death. *J Card Fail* 1995;1:201-6.
21. Cohn JN. Intent-to-treat: a curse of clinical trials. *J Card Fail* 1998;4:1-2.