

# Symptomatic Congestive Heart Failure: Comparison of Mortality Observed in 3 Multicenter Clinical Trials

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## Mortality Abstract 377-M2

**Background.**—Two previous mortality abstracts on congestive heart failure (CHF) clinical trials have been published in the *Journal of Insurance Medicine*, in 1993 and 1997. The Veterans Administration (VA) multicenter study reported here includes symptomatic CHF patients with ventricular premature beats and an ejection fraction of under 0.40.

**Results.**—After a description of the VA study, comparative mortality results are derived from 2-year survival rates for both the placebo group and patients treated with amiodarone. Excess mortality was high, with no significant difference between placebo and treatment groups: mortality ratio in men with a mean age over 65 years about 500% and an excess death rate of about 130 per 1000 per year. In the placebo groups of the 3 series, the excess death rate ranged from 116 to 138 per 1000.

**Conclusion.**—Excess mortality is consistently high in patients with symptomatic CHF and reduced ejection fraction, with or without a ventricular arrhythmia. In the VA study, amiodarone did reduce the ventricular premature beats but did not reduce mortality, either overall or from sudden death. Different treatment drugs in the other 2 studies were associated with a reduction in overall mortality.

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## References

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## Objective of This Abstract

Our goals are to present the comparative mortality experience of a Veterans Administration (VA)-sponsored randomized clinical trial on patients with congestive heart failure (CHF) and more than 10 ventricular premature beats (VPBs) per hour, and to compare the excess mortality in this series with the excess mortality found in 2 other randomized clinical trials on CHF patients analyzed in mortality abstracts previously published in the *Journal of Insurance Medicine*.

**Table 1.** Comparative Mortality Within 2 Years in Multicenter Clinical Trials of Drug Treatment for Congestive Heart Failure

Series/Treatment	No. of Patients (ℓ)	Mean Age (x̄)	Ejection Fraction	NYHA* Class Score‡	Proportion of Cases		Duration of Follow-up (Δt)	Excess Death Rate per 1000 (q - q')
					Female (f)	CHF Cause† (f)		
Placebo groups								
Veterans Admin.	338	66.1	<0.40	2.36	1%	71%	2 years	126
SOLVD	1284	61.0	<0.36	2.24	20	72	2 years	138
Lovelace	398	58	<0.35	2.51	24	48	400 days	116
Treatment groups								
Amiodarone	336	65.0	<0.40	2.49	1%	70%	2 years	137
Enalapril	1285	60.7	<0.36	2.22	19	70	2 years	107
Carvedilol	696	58	<0.35	2.52	23	48	400 days	41

\* CHS indicates congestive heart failure; NYHA, designates New York Heart Association.

† Percentage due to ischemic heart disease (remainder classified as nonischemic).

‡ Weighted mean of NYHA Classes 1, 2, 3, and 4 for severity of CHF.

### SUBJECTS STUDIED

Patients were selected for this study<sup>1</sup> at 24 VA medical centers if they had a documented history of chronic CHF (shortness of breath on exertion or paroxysmal nocturnal dyspnea), and if they also had at least 10 ventricular beats per hour in a 24-hour electrocardiogram, without symptoms. All patients had ejection fraction (EF) determined by radionuclide ventriculography and were included in the study only if the EF was 0.40 or less. Patients were excluded if they had a major disease considered likely to be fatal within 3 years or if they had any one of the following: symptomatic VPBs, history of cardiac arrest or sustained ventricular tachycardia, need for antiarrhythmic therapy, history of myocardial infarction within 3 months, electrocardiogram prolongation of QS or QT intervals, uncontrolled thyroid disease, and symptomatic hypotension of systolic blood pressure under 90 mm Hg. Prior to randomization, patients were stratified according to hospital, cause of the CHF (ischemic or nonischemic), magnitude of EF (<0.30 and 0.30–0.40), and presumably according to age.

In the VA study, 674 patients out of 1303 screened were enrolled and randomized: 338

to the placebo group and 336 to a regimen of amiodarone (a drug that suppresses ventricular arrhythmia). Both groups were 99% male (women of childbearing age were excluded). In the placebo group, mean age was 66.1 ± 8.1 years, 65.7% had an EF of <0.30, 82.5% had heart enlargement sufficient to produce a computed tomographic (CT) ratio of >0.50, 54.7% were in New York Heart Association (NYHA) Class 2, 44.0% were in Class 3 or 4, only 1.2% were in Class 1, 70.7% had ischemic heart disease, and the mean number of VPBs was 279 per hour. In the amiodarone group, the mean age was 65.0 ± 8.5 years, 67.3% had an EF of <0.30, 86.0% had a CT ratio of >0.50, 56.3% were in NYHA Class 2, 42.4% were in Class 3 or 4, only 1.3% were in Class 1, 72.0% had ischemic heart disease, and the mean number of VPBs was 254 per hour. Randomization was therefore effective with respect to age, severity factors, and cause of the CHF. Some of these factors are also given in Table 1. Patients in the VA study were enrolled over a period of 3.5 years, but the calendar years are not given.

Two related clinical trials by the SOLVD Investigators (Studies of Left Ventricular Dys-

function) were reported in a mortality abstract,<sup>2</sup> but only the study on treatment of patients with definite CHF will be used for comparison with results of the VA study. In this treatment study, 1284 patients with CHF and an EF of  $<0.36$  were randomized to a placebo group, and 1285 to treatment with enalapril (a vasodilator drug of a type used in the therapy of CHF). Patients were not selected on the basis of presence of VPBs, although undoubtedly some such cases were present.

Demographic, severity, and cause characteristics are shown in Table 1, and these will be discussed in "Results" section. There were many reasons for exclusion from the study, including various high-risk conditions.

The other comparison study, also analyzed in a mortality abstract,<sup>3</sup> involved randomization of 398 CHF patients to a placebo group and 696 patients to a group treated with carvedilol (a  $\beta$ -blocker drug with other antagonist properties). All patients had documented CHF and an EF of  $<0.35$ . This was also a multicenter study planned and conducted through the Lovelace Scientific Resources, Albuquerque, NM. Demographic, severity and cause characteristics are again given in Table 1 and will be discussed later. Randomization in this study involved a complex relation to stratification to 3 categories of exercise tolerance.

### FOLLOW-UP

All patients in the VA study were followed to death or a maximum of 4.5 years after start of the enrollment period. End of maximum follow-up was 1.0 years after the end of the enrollment. Regular clinic visits were used to maintain follow-up of the surviving patients, with extensive data collected at each visit.

In the SOLVD study, all patients were followed to death or the end of follow-up observation, which ranged from 22 to 55 months. Results were presented in a way that permitted annual life-table data for 4 years. In the Lovelace study, tabular results were presented at intervals of 50 days to 400 days,

permitting calculation of exposures in patient-years for the full period of observation. The study was terminated at a maximum follow-up of 453 days, because the reduced mortality in the carvedilol group had achieved a high level of statistical significance.

### EXPECTED MORTALITY

No age distribution was given in the article describing the VA study. Because of the lack of detailed age data, I have approximated the expected mortality rates by adding 3 years to the mean age and using this adjusted age to enter the 1989–91 US Life Tables for the total male population. The rate extracted has been used as the mean of the 2-year duration of the observed annual mortality. As explained in chapter 4 of *Medical Risks—1991 Compend of Mortality and Morbidity*<sup>4</sup> this type of approximation is necessary because use of the mean age to enter the life table invariably yields a mortality rate substantially smaller than the mean mortality rate derived from an age distribution.

More elaborate methods of deriving expected mortality rates are described in the 2 mortality abstracts. US Life Tables were used in the Lovelace study, but in the SOLVD study, select insurance tables were used because of the high degree of selection. The lower expected rate would produce a somewhat higher excess death rate (EDR) in this study as compared with that of the other 2 studies, but the bias would be relatively small because expected rates are so much smaller in magnitude than the rates observed in CHF. At high levels of EDR, the impact of differences in expected mortality is much smaller on EDR than it is on the mortality ratio.

### RESULTS

Results of the VA survival trial are given in Table 2. In the published article, Kaplan-Meier survival curves for placebo and treatment groups are shown for total deaths and sudden deaths, for ischemic and nonischemic causes of the CHF, and for cases in which the

**Table 2.** Results of the Veterans Administration Survival Trial of Antiarrhythmic Therapy in Congestive Heart Failure at 24 Months of Follow-up

Mean Age		No. Alive at Start ( $\ell$ )	Observed Survival Rate		Mean Annual Mortality Rate per 1000			Mortality Ratio, % (100 $\check{q}/q'$ )
Observed ( $\bar{x}$ )	Adjusted ( $\bar{x} + 3$ )		Cumulative, 2-y ( $P$ )	Mean Annual ( $\check{p}$ )	Observed ( $\check{q}$ )	Expected* ( $q'$ )	Excess ( $\check{q} - q'$ )	
Placebo-randomized Patients								
66.1	69	338	0.708	0.841	159	33	126	480
Amiodarone-randomized Patients								
65.0	68	336	0.694	0.833	167	30	137	555

\* Basis of expected annual mortality within 2 years: rates from 1989–91 US Life Tables for the total male population at adjusted age,  $\bar{x} + 3$  years (see text).

VPBs were suppressed or not suppressed. These are on a rather small scale, from duration 0 to 54 months, with numbers at risk shown below the graph at 12, 24, 36, and 48 months. The survival curves for total deaths are virtually superimposed, and the authors state that 143 deaths were observed in the placebo group and 139 in the amiodarone group. With so many deaths, it is impossible to count the “steps” in the survival curves for the number of deaths in each year of follow-up, a necessary part of calculating exposure and complete life-table data on an annual basis. The small scale renders the measurement of  $P$  on the curves an inaccurate process. Fortunately, the authors give the overall 2-year survival rates,  $P_2$ , in the text to 3 decimal places: 70.8% for the placebo group and 69.4% for the amiodarone group. Table 2 is therefore restricted to data based on the only 2 accurate  $P$  values for total deaths, at the duration of 2 years, and geometric mean annual observed rates,  $\check{p}$  and  $\check{q}$ , are derived from these. Values of  $\check{q}$  are 159 per 1000 per year for the placebo group and 167 for the amiodarone group. Corresponding values of  $q'$  are 33 and 30 per 1000, respectively, mean age being a year older in the placebo group. In terms of EDR, excess mortality is thus found to be 126 per 1000 for the placebo group and 137 per 1000 for the amiodarone group. The corresponding values of the mortality ratio are 480% and 555%, respectively, extremely

high at this older age level. If I had chosen a lower  $q'$ , such as 23 per 1000, to allow for the effects of selection, in the placebo group the EDR would become 136 per 1000, a difference of only 8%, but the MR would increase from 480% to 690%. This illustrates how much less sensitive EDR is to changes in  $q'$  than is MR at these very high levels of observed and excess mortality.

Only these limited results on 2-year survival and mortality are presented herewith. For the full set of survival curves and results (duration to 4 years, sudden death, cause of CHF, etc), consult the published article.

Selected series characteristics and EDR values for these 3 clinical trials of patients with CHF are given in Table 1, the upper set for patients in the placebo groups and the lower set for the patients in the treatment groups. All studies involved patients with symptomatic CHF and low EF, but only the VA study required the presence of VPBs as a condition of entry. Patients in the VA series were older and included only 1% females, but severity by NYHA class was about the same as in the other 2 series: The severity score ranged only from 2.22 to 2.52 in the 6 groups (the severity score was obtained as the weighted mean of the class prevalence numbers in each group for the NYHA classes 1–4, with Class 1 being the least severe and Class 4 the most severe). As noted above, over 80% of the patients in each study had heart enlargement, manifest

by a CT ratio of more than 0.50 in the chest x-ray. With these multiple criteria, I feel that the patients in the 3 studies were in a similar range of the severity spectrum of CHF, and this is supported by an EDR range of 116 to 138 per 1000 in the 3 placebo groups. In the SOLVD study, the EDR fell to 107 per 1000 in the patients on enalapril, a moderate reduction, but in the Lovelace study, the patients in the carvedilol group had an EDR of only 41 per 1000. The authors reported that this reduction in mortality was highly significant, with a *P* value of  $<0.001$ . The ventricular-arrhythmia suppressor, amiodarone, on the other hand, had no effect on overall excess mortality. Again, for further details on the SOLVD and Lovelace studies, refer to the 2 previously published mortality abstracts and the original articles cited therein.

### COMMENTS

CHF is a major public health problem, with incidence cited as 250,000 new cases every year in the United States. Costs are very high

with respect to medical care, hospitalization, and disability. Mortality is also high but has a very wide range depending on the severity of the CHF. In the SOLVD study of patients with incipient CHF but EF of still  $<0.36$ , the EDR was 45 per 1000 in the placebo group and 40 in the enalapril group. Almost all of these patients were in NYHA Classes 1 and 2, with a severity score of about 1.7. When the severity score increases to about 2.4, as in the 3 placebo groups cited in Table 1, the EDR increases to about 125 per 1000, although this is reduced with the use of carvedilol, at least in the short term. If severity increases so that the patient is placed on a waiting list for a heart transplant (upper end of NYHA Class 4), and if this is not forthcoming in 1 year, there are no survivors, according to reports of the Stanford Medical Center, which has the longest experience with cardiac transplantation. Even the mildest forms of CHF are probably declinable for life insurance, if the EF is under 0.36. However, these results may be useful to medical directors if they are involved in underwriting high-risk cases for a structured settlement annuity.