Mortality Abstract 370M1

SYMPTOMATIC AND INCIPIENT CONGESTIVE HEART FAILURE — THE SOLVD EXPERIENCE

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References

1. The SOLVD Investigators. Studies of left ventricular dysfunction (SOLVD) - rationale, design and methods: Two trials that evaluate the effect of enalapril on patients with reduced ejection fraction. *Am J Card* 1990;66:315-322.

2. The SOLVD Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. *New Engl J Med* 1991;325:293-302.

3. The SOLVD Investigators. Effect of enalapril on mortality and the development of congestive heart failure in asymptomatic patients with reduced left ventricular ejection fractions. *New Engl J Med* 1992;327:685-691.

Objective of This Abstract

To present results of the SOLVD 4-year clinical trials of enalapril on two groups of patients with left ventricular ejection fraction under 36%, one group with and the other group without symptomatic congestive heart failure. Observed mortality is compared with expected mortality derived from the 1975-1980 Basic Select Tables, because of the high degree of exclusion utilized for patients with associated risk factors, in the recruiting of patients for entry into the study.

Subjects Studied

Two separate but coordinated clinical trials were conducted by a Steering Committee, other committees and boards, and a Project Office at the Clinical Trials Branch of the National Heart, Lung and Blood Institute, Bethesda, Maryland.[1] Patients were selected on a basis of age 21-80, inclusive, and a left ventricular (LV) ejection fraction (EF) under 36% performed within 3 months of the randomization date, at one of 20 Clinical Centers in the U.S., or two in Canada, or a single center in Belgium. Each Clinical Center consisted of a group of 1 to 8 hospitals, a majority of which were teaching or tertiary care hospitals, with a total of 92 hospitals.[1] The EF was determined by one of three methods: radionuclide LV angiography, or LV contrast angiography, or 2-dimensional echocardiography. Randomization on a double-blind basis was carried out after each potential entrant had completed a treatment "run-in" trial of about 2-3 weeks to ensure satisfactory compliance and absence of reaction to the drug. Randomization was carried out first to a **Treatment Group**, if there was a history of or current congestive heart failure, or to a **Prevention Group**, in the absence of overt CHF, past or present. The second randomization within each group was to treatment with enalapril or placebo. Enalapril is one of a class of vasodilator drugs that inhibit the angiotensin-converting enzyme (ACE), drugs that have been considered to be promising in the treatment of CHF. The totals of patients randomized were 2117 to placebo and 2111 to enalapril in the Prevention Group, and 1284 to placebo and 1285 to enalapril in the Treatment Group. However, potential entrants to the studies on the basis of meeting the basic criteria and completing the run-in period to the satisfaction of the clinical investigators were excluded for any of the following reasons: other cardiovascular (CV) diseases such as valvular or congenital diseases, constrictive pericarditis, the presence of unstable angina pectoris or history of acute MI within 30 days, uncontrolled hypertension (pressure >140/95), cor pulmonale, cerebrovascular disease, collagen vascular disease, and active myocarditis, or other life-threatening nonCV diseases, such as cancer, chronic pulmonary disease, primary liver disease, renal failure, or other circumstance, such as lack of informed consent, probable nonadherence to the treatment protocol, participation in another clinical trial, or pregnancy.

Design and planning for SOLVD were carried out 1984-1985. The entry period was April, 1986 through March, 1989 for the Treatment Group, and July, 1986 through May, 1990 for the Prevention Group. Characteristics of the four randomized cohorts are given in *Table 370M1-1*. Mean age was slightly higher in the Treatment Group cohorts, 60.7-61.0 years vs. 59.1 years in the Prevention Group. The proportion of females and nonwhites was higher in the Treatment as compared with the Prevention Group. The outstanding difference between the Treatment and Prevention Groups was, of course, in the distribution of patients by New York Heart Association Functional Class: over two-thirds of the Prevention group patients were in NYHA Class I and the rest in Class II (5 Class III patients were accidentally assigned to the Prevention Group, and were not transferred or dropped); in the Treatment group 11% of the patients were in Class I (all had a history of past CHF), 57% were in Class II, 30% in Class III, and less than 2% in Class IV. The degree of CHF in the Treatment Group patients can

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therefore be characterized as mild to moderate, with few of the patents having severe symptoms. The Prevention Group patients were asymptomatic with respect to CHF and had a negative history thereof. Randomization of all demographic and medical characteristics between placebo and enalapril cohorts resulted in a nearly equal distribution by number or mean value for all of the characteristics. About 75 % of the patients in both groups had CHD or history of MI as a factor in their reduced EF or their overt CHF: 37% to 42% had hypertension, and current smokers were about 23% in both groups. The prevalence of cardiomyopathy, diabetes, and atrial fibrillation was higher in the Treatment than in the Prevention Group, but current angina was about 34% in both groups. A cardiothoracic ratio in excess of 0.50, heart enlargement, was found in nearly 57% of the Treatment Group, but in only 40% of the Prevention Group. Current use of digitalis or diuretics was very high in the Treatment Group, but only in about 15% of the Prevention Group, and in these patients for reasons other than treatment of CHF. Percentage distribution is given in the original articles[2,3] for each cohort, but only in the last column of *Table 370M1-1*, for the combined total of 6797 patients randomized to the four cohorts. Additional entry characteristics are also reported in the two follow-up articles.[2,3]

Follow-up

The cutoff date for follow-up was January 31, 1991 for the Treatment Group, with a range of follow-up from 22 to 55 months (mean 41.4 months); the vital status of all patients was known on the cutoff date. For the Prevention Group the cutoff date was August 31, 1991, and the range of follow-up was 14.6 to 62.0 months (mean 37.4 months); follow-up was 99.8% complete. Regular follow-up was maintained through clinic visits, and survival rates and numbers of survivors are reported at intervals of 6 months to 48 months, but many of the results are given as total deaths or hospitalizations to the end of maximum follow-up. Such "mortality" is given as a percentage of the entrants, but this is a quotient, not a rate, since there are withdrawals due to the end of follow-up starting in the second year. The exposure after 48 months can be calculated from the survivor data and maximum follow-up, so it is also possible to derive the total exposure to maximum follow-up, corresponding to the total deaths or total numbers of hospitalizations. In the Prevention Group development of CHF as a new event, regardless of hospitalization, was an additional outcome. All deaths were analyzed for cause of death, and hospitalizations were analyzed according to the medical reason. Mortality and other quotients were also reported according to three different subgroups of EF.

Expected Mortality

Because of the high degree of selection utilized in the formation of the Treatment and Prevention Groups, the most appropriate expected mortality rates were considered to be those of the 1975-1980 Basic Select Tables. No age distribution is given for the two groups, so I have set up assumed male and female distributions, similar to, but not identical with, the age/sex distribution for MI patients to be found in Abstract #607 in the 1990 *Medical Risks* monograph. Younger patients have been added because the mean ages reported (male and female combined) are smaller than the mean ages in #607. The reader should bear in mind that the age distribution for women is quite different from the male distribution, with more older patients and a higher mean age. These age distributions were adjusted until they produced a mean age corresponding to the mean age as actually reported (*Table 370M1-1*). Total first-year expected deaths for the placebo and enalapril cohorts in each group were used to calculate mean first-year q', separately for males and females in each cohort. Tabular ages were found corresponding to the mean first-year male q' and female q', and these were averaged in accordance with the reported proportion of females. Each mean q', male or female, was advanced to the second, third, and fourth years of duration in the Select Tables, and the q' derived for male and female patients combined. It is my belief that an assumed distribution of this sort yields a mean q' that is more accurate in each of the annual durations than any attempt to adjust the mean age upward - remember that the female mean age is higher than the male mean age.

Results

Table 370M1-2 shows the comparative mortality by duration 0-4 years for the placebo and enalapril cohorts in the Treatment Group. This is a reconstructed life table that is theoretically exact for the first year, in which w = 0, and probably also for the second year, in which there appear to be no withdrawals in the enalapril cohort, and only three late ones in the placebo cohort. Actually, there are some small discrepancies between the d as the difference between successive ℓ values and as given in another duration table in the article.[2] I have assumed that the ℓ values are accurate and adjusted the d values to correspond (the maximum discrepancy is less than 1%). Mortality rates, ratios and EDR values tend to decrease somewhat by duration, with random variation. Mortality was higher in the placebo than in the enalapril cohort: 504 deaths, mortality ratio of 1780%, and EDR of 127 per 1000 in the placebo cohort, in contrast to respective values of 443 deaths, MR of 1520%, and EDR of 107 per 1000 in the enalapril cohort.

The total deaths were 510 in the placebo and 452 in the enalapril cohorts, a reduction in mortality reported by the authors as being highly significant ($p = 0.004$ by the log-rank test).

I have calculated total exposures to maximum follow-up of 55 months at 3814 patient-years for the placebo, and 3962 patient-years for the enalapril cohort. Mean annual mortality rates appear to be almost identical at 48 and 55 months: 135 vs. 134 per 1000 (placebo), and 115 vs. 114 per 1000 (enalapril). These are very high rates of observed and excess mortality. The high EDR values are not attributable to the use of select rates for expected mortality.

Observed and excess mortality rates were lower in the Prevention Group (*Table 370M1-3*). EDR was at the level of 45 extra deaths per 1000 per year in the placebo cohort, overall, and 40 per 1000 in the enalapril cohort, with correspondingly smaller mortality ratios. Mortality differences between the placebo and enalapril cohorts were not statistically significant. The much lower mortality levels in the Prevention Group are attributable, of course, to the absence of any symptoms of CHF in these patients, the better NYHA classification, and the higher EF values (see *Table 370M1-1*), despite the fact that patients in both groups all had an EF under 36%. It should be noted that the approximation of second-year and overall deaths is less certain in the Prevention than in the Treatment Group, because w at 1-3 years is a large number in the Prevention Group, and no independent data are given for the distribution of deaths by duration.[3] Although q and EDR are much lower in the Prevention Group, the reduced EF below 36% was clearly associated with a lot of excess deaths, as apparent from the d and d' data, and the overall mortality ratios exceeding 600% in both cohorts.

Distribution of deaths by cause is given in *Table 370M1-4*, and the derived comparative mortality rates by cause of death are shown in *Table 370M1-5*. Pump failure, with or without arrhythmia, was the predominant CV cause of death in both groups, as might be expected. The total exposure is used as the common denominator for placebo and enalapril cohorts in both groups, for the calculation of the rates in *Table 370M1-5*, with the individual numbers of deaths by cause as the numerator. In the latter table "EDR" is derived as the difference between the placebo and the enalapril mean annual mortality rates. Because the denominator is constant in each cohort, the EDR values are additive to the all-cause EDR, calculated by difference. This was 20 per 1000 per year in the Treatment Group, but only 3 per 1000 in the Prevention Group.

Table 370M1-6 gives morbid event data (numbers and mean annual rates per 1000), generally in terms of hospitalizations or numbers of patients hospitalized. Hospitalization rates were 743 and 605 per 1000 per year, total, in the two cohorts of the Treatment Group, and 504 and 306 per 1000 for CHF, but all of these rates were considerably lower in the Prevention Group. Many of the patients had multiple episodes of CHF, especially in the Treatment Group, and as a consequence had multiple hospitalizations. The rates for patients hospitalized are lower. Again, excess event rates are derived as the differences between the rates in the placebo and the enalapril cohorts. These differences are relatively higher than the EDR differences by cause of death, and many of them are statistically significant, including the ones involving hospitalization for CHF.[3] One additional outcome studied was the number of patients who developed CHF whether or not the patient was hospitalized. The last line of *Table 370M1-6* shows that this event rate was 102 per 1000 in the placebo, and 69 per 1000 in the enalapril cohort. The difference of 33 per 1000 per year was only slightly higher than the difference in rate associated with hospitalization for CHF.

Comment

There is a very wide range for the annual mortality rate in CHF and in patients with a reduced ejection fraction or other measure of left ventricular function, or dysfunction, as the SOLVD investigators term it. The "Mortality" (d/ℓ) in the asymptomatic patients of the Prevention Group[3] was reported to be about 12% with an EF 0.33-0.35, 14% with an EF 0.28-0.32, and much higher with an EF <0.28: 20.6% in the placebo cohort and 17.9% in the enalapril cohort (there was virtually no difference between cohorts in the other two EF categories). In the placebo cohort of the Treatment Group[2] such quotients were 28% (EF 0.30-0.35), 39% (EF 0.23-0.29), and 50% (EF <0.25); in the enalapril cohort the quotients were 31%, 35%, and 41%, respectively. The New York Heart Association Classification was also used in the Treatment Group. The quotients in the placebo cohort were 30% (Class I), 35% (Class II), 51% (Class III), and 64% (Class IV); in the enalapril cohort there was no difference in Class IV, but the quotients were about 5% lower than their Placebo counterparts, in Classes I through III. The EDR in the placebo cohorts was 53 per 1000 with patients predominantly NYHA Class I (*Table 370M1-2*), and 135 per 1000 with the NYHA mixture in the Treatment Group, mostly Classes II-III (*Table 370M1-3*). The mixture may have been similar to the mixture for all CHF patients combined, 0-5 years, in the 1950-1968 experience of the Framingham Study, with an EDR of about 120 per 1000 per year (Abstract #381 in the 1976 *Medical Risks* monograph). For the Class

IV patients in the VA study described in Abstract #627 in the 1990 *Medical Risks* monograph, the EDR during 0-3 years was 387 per 1000. In reporting results of cardiac transplantation at Stanford, Shumway and his colleagues have described 100% mortality within 12 months for the candidates on the waiting list who did not come to operation because a suitable donor heart was not available. Such candidates have the most severe symptoms of CHF and the most severe left ventricular dysfunction, at the "bottom" of Class IV. We can estimate an EDR at about 50 per 1000 per year in presymptomatic CHF with EF under 36%, and in CHF Class II-IV a range of EDR from about 100 to nearly 1000 per 1000 per year, depending on severity of symptoms and left ventricular dysfunction. Hospitalizations are frequent.

The high mortality and morbidity of CHF present a challenging public health and economic problem, in view of an estimated prevalence in the U.S. of 2 million patients, and an incidence of approximately 250,000 new cases per year.[1] Clinical implications of the use of enalapril are discussed in the articles[2,3] and in editorials in each of these *NEJM* issues.

Table 370M1-1
Characteristics of 4 Cohorts of Patients with Left Ventricular Ejection Fraction <36%, the SOLVD Experience

	Prevention Group		Treatment Group		Total - All Patients	
Characteristic*	Placebo	Enalapril	Placebo	Enalapril	Number	Distribution
Age in Years - Mean	59.1	59.1	61.0	60.7	—	
- Range	21-80	21-80	21-80	21-80	—	
Mean Ejection Fraction	0.28	0.28	0.25	0.25	—	
Mean Systolic Pressure	126	125	124	125	—	
Mean Diastolic Pressure	78	78	76	77	—	
Mean Heart Rate	75	75	80	80	—	
Number of Patients						
Total	2117	2111	1284	1285	6797	100.0%
Female	241	243	259	245	988	14.5
Nonwhite	286	283	243	267	1079	15.8
New York Heart Assoc.						
Class I	1422	1402	136	147	3107	45.7
Class II	693	706	727	730	2856	42.0
Class III	2	3	395	388	788	11.6
Class IV	0	0	25	20	45	0.7
History of CHD	1755	1763	926	902	5346	78.1
History of MI	1681	1699	855	852	5067	74.5
Current Angina	716	714	499	464	2393	35.2
Hypertension	790	777	533	550	1950	28.7
Cardiomyopathy	214	182	230	239	805	12.7
Diabetes Mellitus	316	325	345	320	1301	19.1
Current Smoker	510	481	275	293	1291	19.0
Cardiothoracic Ratio >50%	851	836	714	740	3141	46.2
Treatment with Digitalis	279	247	876	844	2246	33.0
Treatment with Diuretics	360	342	1095	1100	2897	42.6

* CHD = Coronary Heart Disease; MI = Myocardial Infarction.

Table 370M1-2
SOLVD Mortality Experience - 4-Year Clinical Trial of Enalapril in Treatment of Patients with Symptomatic Congestive Heart Failure (Treatment Group, Ejection Fraction <36%)*

Interval No.	Start-End	No. Alive at Start	Exposure Pt.-Yrs.	No. of Deaths Obs.	Exp.+	Mortality Ratio	Mean Ann. Mort. Rate per 1000 Observed	Expected	Excess	Cum. Surv. Rate
i	t to t+Δt	ℓ	E	d	d′	100d/d′	q	q′	(q-q′)	P
				Patients Randomized to Placebo						
1	0-1 yr.	1284	1284	199	6.03	3300%	155	4.7	150	0.845
2	1-2	1085	1085	145	7.60	1900	134	7.0	127	0.732
3	2-3	939	857	106	8.48	1250	124	9.9	114	0.647
4	3-4	669	501	54	6.26	865	108	12.5	96	0.572
5	4 up	299	(87)	(6)	—	—	—	—	—	—
1-4	0-4	1264	3727	504	28.37	1780	135	7.6	127	0.572
				Patients Randomized to Enalapril						
1	0-1	1285	1285	158	6.04	2600%	123	4.7	118	0.877
2	1-2	1127	1127	127	7.89	1480	104	7.0	97	0.786
3	2-3	1010	914	121	9.05	1340	132	9.9	122	0.682
4	3-4	697	539	47	6.73	595	87	12.5	75	0.623
5	4 up	333	(97)	(9)	—	—	—	—	—	—
1-4	0-4	1285	3865	443	29.11	1520	115	7.5	107	0.623

* Life table reconstructed from ℓ data, Figure 1, and d data, Table 3 (*Ref. 2*).
+Basis of expected deaths: rates from 1975-80 Basic Select Table, matched by age and sex to assumed first-year M and F age distributions consistent with the actual mean age (M+F).

Table 370M1-3
SOLVD Mortality Experience 4-Year Clinical Trial of Enalapril in the Prevention of Congestive Heart Failure in Patients with CV Disease and Ejection Fraction <36%*

Interval No.	Start-End	No. Alive at Start	Exposure Pt.-Yrs.	No. of Deaths Obs.	Exp.+	Mortality Ratio	Mean Ann. Mort. Rate per 1000 Observed	Expected	Excess	Cum. Surv. Rate
i	t to t+Δt	ℓ	E	d	d′	100d/d′	q	q′	(q-q′)	P
				Patients Randomized to Placebo						
1	0-1 yr.	2117	2117	108	9.53	1160%	51	4.5	47	0.949
2	1-2	2039	1900	99	13.49	735	52	7.1	45	0.900
3	2-3	1566	1337	58	12.84	455	43	9.6	33	0.861
4	3-4	934	694	53	8.47	625	76	12.2	64	0.796
5	4 up	399	(233)	(16)	—	—	—	—	—	—
1-4	0-4	2117	6048	318	49.33	775	53	7.8	45	0.796
				Patients Randomized to Enalapril						
1	0-1	2111	2111	111	9.50	1170%	52	4.5	48	0.948
2	1-2	2000	1848	60	13.09	460	60	7.1	25	0.918
3	2-3	1580	1216	67	12.42	570	52	9.6	42	0.870
4	3-4	935	721	51	8.76	525	70	12.2	58	0.810
5	4 up	432	(233)	(16)	—	—	—	—	—	—
1-4	0-4	2111	5976	289	43.77	660	48	7.6	40	0.810

* Life table reconstructed from ℓ and measured P, Figure 1 of *Ref. 3*. Results precise for first year. ℓ and d data approximate after duration 1 year.
+Basis of expected deaths: rates from 1975-80 Basic Select Tables, matched by age and sex to assumed first-year M and F age distributions consistent with the actual mean age (M+F).

Table 370M1-4
Cause of Death Distribution,
SOLVD Treatment and Prevention Groups

Cause of Death	Treatment Group		Prevention Group	
	No. Deaths	Distribution	No. Deaths	Distribution
	d	% Total	d	% Total
Patients Randomized to Placebo				
Exposure (Patient-Years)	3814		3281	
Deaths - All Causes	510	100.0%	334	100.0%
All Cardiovascular Causes	461	90.4	298	89.2
Pump Failure ± Arrhythmia	251	49.2	106	31.7
Primarily Arrhythmia	113	22.2	105	31.4
Myocardial Infarction	53	10.4	52	15.6
Other Cardiovascular	44	8.6	35	10.5
All Noncardiovascular Causes	49	9.6	36	10.8
Patients Randomized to Enalapril				
Exposure (Patient-Years)	3962		6231	
Deaths - All Causes	452	100.0%	313	100.0%
All Cardiovascular Causes	394	88.2	265	84.7
Pump Failure ± Arrhythmia	209	46.2	85	27.8
Primarily Arrhythmia	105	23.2	98	31.3
Myocardial Infarction	40	8.8	46	14.7
Other Cardiovascular	45	10.0	36	11.5
All Noncardiovascular Causes	53	11.7	48	15.3

Table 370M1-5
Mean Annual Mortality Rates per 1000 by Cause of Death —
SOLVD Treatment and Prevention Groups

Cause of Death	Treatment Group Rates			Prevention Group Rates		
	Placebo	Enalapril	Difference	Placebo	Enalapril	Difference
	q_p	q_e	$(q_p - q_e)$	q_p	q_e	$(q_p - q_e)$
Total Death Rates, All Causes	134	114	20	53	50	3
All Cardiovascular	121	101	20	47	43	4
Pump Failure ± Arrhythmia	66	53	13	16.9	13.6	3.3
Primarily Arrhythmia	30	27	3	16.7	15.7	1.0
Myocardial Infarction	13.9	10.1	3.8	8.3	7.4	0.9
Other Cardiovascular	11.5	11.4	0.1	5.6	5.8	-0.2
All Noncardiovascular	12.8	13.4	-0.6	5.7	7.7	-2.0

Table 370M1-6

Congestive Heart Failure, Hospitalization, New Events and Corresponding Annual Rates per 1000 in Patients of Treatment and Prevention Groups - SOLVD Morbidity Experience.

Hospitalization/Reason/Event*	No. of Events		Mean Annual Event Rates per 1000		
	Placebo	Enalapril	Placebo	Enalapril	Difference
	n_p	n_e	r_p	r_e	$(r_p - r_e)$
	2569 Patients Randomized in the Treatment Group				
Exposure (Patient-Years)	3814	3962			
Number of Hospitalizations					
All Reasons	2833	2396	743	605	138
Congestive Heart Failure	971	683	255	172	83
Number of Patients Hospitalized					
At least once, CV or NCV reason	950	893	249	225	24
At least once, for CV reason	810	729	212	183	29
At least once for CHF	470	332	123	84	39
Twice or more, for CHF	234	157	61	40	21
At least once for NonCV reason	460	399	121	75	46
	4228 Patients Randomized in the Prevention Group				
Exposure (Patient-Years)	6281	6231			
Number of Hospitalizations					
All Reasons	2839	2645	455	375	80
Congestive Heart Failure	504	306	80	49	31
Number of Patients Hospitalized					
At least once, CV or NonCV reason	1202	1167	191	186	5
At least once for CV reason	967	876	154	139	15
At least once for CHF	273	184	43	29	14
Twice or more, for CHF	102	58	16	9	7
At least once for NonCV reason	545	595	87	94	-7
Number of Patients, 1+ CHF Episode	640	438	102	69	33