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Improving Survival for Patients With Advanced Heart Failure: A Study of 737 Consecutive Patients

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Objectives. **This study sought to determine whether survival and risk of sudden death have improved for patients with advanced heart failure referred for consideration for heart transplantation as advances in medical therapy were systematically implemented over an 8-year period.**

Background. **Recent survival trials in patients with mild to moderate heart failure and patients after a myocardial infarction have shown that angiotensin-converting enzyme inhibitors are beneficial, type I antiarrhythmic drugs can be detrimental, and amiodarone may be beneficial in some groups. The impact of advances in therapy may be enhanced or blunted when applied to severe heart failure.**

Methods. **One-year mortality and sudden death were determined in relation to time, baseline variables and therapeutics for 737 consecutive patients referred for heart transplantation and discharged home on medical therapy from 1986 to 1988, 1989 to 1990 and 1991 to 1993. Medical care was directed by a single team of physicians with policies established by consensus. From 1986 to 1990, the hydralazine/isosorbide dinitrate combination or angiotensin-converting enzyme inhibitors were the initial vasodilators, and class I antiarrhythmic drugs were allowed. After 1990, captopril was the initial vasodilator, given to 86% of patients compared with 46% of patients before 1989. After mid-1989, class I agents were routinely withdrawn, and amiodarone was used for frequent ventricular ectopic beats or atrial fibrillation (53% of patients after 1990 vs. 10% before 1989).**

Results. **The total 1-year mortality rate decreased from 33% before 1989 to 16% after 1990 ($p = 0.0001$), and sudden death decreased from 20% to 8% ($p = 0.0006$). Adjusted for clinical and hemodynamic variables in multivariate proportional hazards models, total mortality and sudden death were lower after 1990.**

Conclusions. **The large reduction in mortality, particularly in sudden death, from advanced heart failure since 1990 may reflect an enhanced impact of therapeutic advances shown in large randomized trials when they are incorporated into a comprehensive approach in this population. This improved survival supports the growing practice of maintaining potential heart transplant candidates on optimal medical therapy until clinical decompensation mandates transplantation.**

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In the past 10 years, multicenter randomized trials have established benefits and risks of therapies in several patient populations with left ventricular dysfunction. Angiotensin-converting enzyme inhibitors improved survival for asymptomatic patients with left ventricular ejection fraction <40% after myocardial infarction in the Survival and Ventricular Enlargement (SAVE) trial (1). Similar therapy reduced progression of heart failure and improved survival for patients in New York Heart Association functional class I, II or III in the Study on Left Ventricular Dysfunction (SOLVD) trial (2) and provided greater benefit than the hydralazine/isosorbide dinitrate combination for patients with functional class I to II heart failure in the Vasodilators in Heart Failure Trial (V-HeFT) II (3). The multicenter Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS) trial for patients in functional class IV showed in 1987 that angiotensin-converting enzyme inhibition improved survival, but the actuarial mortality rate was still 46% at 1 year (4). The Cardiac Arrhythmia Suppression Trial (CAST) (5) demonstrated that several class I antiarrhythmic agents are deleterious when administered for ventricular ectopic activity after myocardial infarction.

Patients with severe heart failure characterized by functional class III or IV symptoms were once considered beyond

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medical therapy, with heart transplantation offering the only hope. These patients are now commonly referred to specialized centers where transplantation is an option, but the minority will actually receive a transplant because of donor shortage and common contraindications, such as advanced age and concomitant disease. The majority are discharged home after adjustment of medical therapy. Sudden death is a major risk in this population; even patients whose heart failure symptoms lessen on medical therapy after acceptance for transplantation may remain on the transplant waiting list because of this concern (6,7).

The purpose of the present analysis was to examine survival and mode of death over a 7-year period for all patients referred to a single center for evaluation of advanced heart failure and consideration for heart transplantation. During this time, therapy reflected a systematic approach to hemodynamic and arrhythmia management, which evolved by consensus of the team to include new trial results.

Methods

Patients. From January 1986 to April 1993, 737 consecutive patients with advanced, dilated heart failure (all with left ventricular ejection fraction <0.40) were referred to the University of California at Los Angeles cardiomyopathy service, admitted to the hospital for optimization of medical therapy in conjunction with evaluation for heart transplantation and then discharged from the hospital. Clinical and hemodynamic variables were prospectively collected during the hospital period (see later) and entered into a data base. Three patient groups were defined by date of initial hospital admission: group I from 1986 to 1988; group II in the transition period from 1989 to 1990; and group III from January 1991 to April 1993. Intervals were selected according to changes in therapy described herein.

Management of heart failure. Medical management was under the direction of the same physicians throughout the time period studied. After undergoing right heart catheterization for assessment of pulmonary pressures, all patients with initial pulmonary capillary wedge pressure >20 mm Hg or cardiac index <2.2 liters/min per m^2 received further adjustment of therapy under hemodynamic guidance. As previously described (8), the combination of elevated systemic vascular resistance and filling pressures was treated with nitroprusside and diuretic drugs to approach hemodynamic goals of systemic vascular resistance <1,200 dynes-s-cm^{-5}, pulmonary capillary wedge pressure ≤15 mm Hg and right atrial pressure ≤7 mm Hg while maintaining systolic blood pressure ≥80 mm Hg, which were then matched on combinations of oral vasodilators (captopril or hydralazine, or both, with isosorbide dinitrate).

Before 1988, the choice of oral vasodilator (captopril or hydralazine in combination with isosorbide dinitrate) was made arbitrarily by the attending cardiomyopathy team member. Unacceptable side effects or failure of the initial vasodilator to achieve the desired hemodynamic response of filling pressure and systemic vascular resistance led to use of the alternative. Between September 1988 and August 1989, the initial vasodilator was chosen randomly for 117 patients in the Hy-C trial (9) comparing captopril with hydralazine. During this time, isosorbide dinitrate was given to all patients with coronary artery disease or inadequate hemodynamic response to captopril or hydralazine as the primary vasodilator. After the V-HeFT and Hy-C trials (3,9) demonstrated greater reduction of mortality with angiotensin-converting enzyme inhibition, the cardiomyopathy team implemented a change in policy in late 1990 specifying that an angiotensin-converting enzyme inhibitor (usually captopril) be tried as the initial vasodilator. Because the survival benefit seen in the Hy-C trial with captopril occurred when 85% of patients were also taking isosorbide dinitrate, nitrate therapy was subsequently given to all patients if tolerated. Failure to achieve hemodynamic goals on this combination led to the addition of hydralazine, with continued captopril therapy if tolerated. Therapy with digoxin was at the discretion of the specific team physician. Anticoagulation was prescribed primarily for patients who, in addition to marked ventricular dilation, had atrial fibrillation, previous embolic events or mobile intracardiac thrombi observed on the echocardiogram. No patients underwent trials with investigational drugs during this period.

Arrhythmia management. During the hospital period, all patients were evaluated by the arrhythmia consultation service and questioned specifically about prior antiarrhythmic drug use and arrhythmia symptoms. Before 1989, patients who had premature ventricular contractions or atrial fibrillation controlled with class I antiarrhythmic drugs at the time of referral continued to receive these medications. In late 1989, after publication of the CAST results (5) showing increased mortality with similar agents, the team revised the approach to antiarrhythmic therapy. At the time of hospital admission, class I antiarrhythmic drugs were discontinued unless they had been administered for prophylaxis of sustained ventricular tachycardia or ventricular fibrillation, usually with efficacy documented by electrophysiologic testing. A 24-h electrocardiogram was obtained. Amiodarone was recommended for patients with nonischemic cardiomyopathy who had a mean of >40 ventricular ectopic beats/h or two or more episodes of nonsustained ventricular tachycardia (>3 consecutive beats); for patients with prior myocardial infarction who had a mean of >6 ventricular ectopic beats/h or any ventricular tachycardia (>3 consecutive beats); and for atrial fibrillation or flutter. The following were considered contraindications to amiodarone therapy: prior amiodarone intolerance, first-degree or higher atrioventricular (AV) block, bradycardia <60 beats/min, hepatic transaminases elevated more than twice normal and a pulmonary diffusing capacity or forced vital capacity <60% of predicted normal in patients accepted for future heart transplantation. Amiodarone was administered as 600 mg daily for 2 weeks, then 400 mg daily for 2 weeks, then 200 mg daily. There was careful attention to adjusting digoxin and warfarin doses as amiodarone therapy was initiated. Cardioversion was recommended to patients who remained in atrial fibrillation

Table 1. Patient Characteristics

	1986–1988 (n = 243)	1989–1990 (n = 228)	1991–1993 (n = 266)	p Value
Male (%)	78	81	80	0.66
Age (yr)	49 ± 13	52 ± 12	53 ± 12	0.0001
CAD (%)	44	54	48	0.11
NYHA functional class IV (%)	63	59	54	0.14
Pacemaker (%)	6	9	10	0.23
Cardiac arrest (%)	13	11	8	0.2
Atrial fibrillation (%)	19	24	25	0.24
Syncope (%)	14	16	19	0.35
LVEF (%)	0.19 ± 0.06	0.22 ± 0.07	0.23 ± 0.07	< 0.0001
LVDI (mm/m^2)	40 ± 6	40 ± 7	39 ± 6	0.25
Hemodynamic variables				
On admission				
SBP (mm Hg)	107 ± 17	110 ± 19	113 ± 17	< 0.0001
HR (beats/min)	92 ± 18	90 ± 17	90 ± 18	0.23
RA (mm Hg)	12 ± 7	11 ± 7	11 ± 6	0.14
PAsys (mm Hg)	52 ± 18	49 ± 16	50 ± 17	0.05
PCW (mm Hg)	26 ± 10	24 ± 10	23 ± 10	0.001
CI ($liters/mm^2$)	2.1 ± 0.7	2.1 ± 0.7	2.1 ± 0.7	0.7
Before discharge				
SBP (mm Hg)	100 ± 15	102 ± 16	103 ± 16	0.08
HR (beats/min)	92 ± 16	88 ± 16	87 ± 16	0.001
RA (mm Hg)	7 ± 4	7 ± 4	7 ± 4	0.38
PAsys (mm Hg)	40 ± 12	40 ± 13	38 ± 12	0.16
PCW (mm Hg)	16 ± 6	15 ± 6	15 ± 6	0.15
CI ($liters/mm^2$)	2.6 ± 0.6	2.6 ± 0.6	2.5 ± 0.6	0.03
Serum Na (mEq/liter)	136 ± 5	135 ± 5	135 ± 4	0.24

Data presented are mean value ± SD or percent of patients. CAD = coronary artery disease; CI = cardiac index; HR = heart rate; LVEF = left ventricular ejection fraction; LVDI = left ventricular diastolic dimension index; Na = sodium; NYHA = New York Heart Association; PAsys = systolic pulmonary artery pressure; PCW = pulmonary capillary wedge pressure; SBP = systolic arterial pressure.

after 4 to 6 weeks of amiodarone therapy (10). Patients who were receiving therapy to prevent recurrence of sustained ventricular tachycardia or ventricular fibrillation were continued on that therapy, which had usually been selected by electrophysiologic testing before referral.

Follow-up. Patients were followed up at the Ahmanson-UCLA Cardiomyopathy Center in conjunction with their referring physician. Patient status was determined by telephone interview of patient, family or physician in April 1994 so that all surviving patients had a minimum of 1 year of follow-up. Only 19 patients (2.5%) were lost to follow-up. *Sudden death* was defined as death occurring instantaneously, within 15 min of a change in symptoms or unexpectedly during sleep.

Statistics. Statistical analysis was performed with BMDP programs (11). Continuous variables were compared with analysis of variance with the Tukey method applied to assess individual differences between groups (BMDP program 7D). Chi-square tests were used to evaluate proportions. One-year cumulative probabilities of sudden death and total mortality were constructed using the Kaplan-Meier method and compared with the Mantel-Cox test. Patients who underwent heart transplantation were removed from survival analysis at the date of operation.

To adjust for baseline differences other than changes in therapy, Cox proportional hazards models were constructed for total mortality and for sudden death end points. The variables assessed were age; left ventricular ejection fraction; serum sodium levels; admission and predischarge systolic blood, pulmonary capillary wedge and pulmonary artery systolic pressures; predischarge cardiac index and heart rate; history of syncope, atrial fibrillation or cardiac arrest; coronary artery disease; permanent pacemaker; implantable defibrillator; and entry after year 1990. Variables were entered into a stepwise model if their level of significance was <0.2. Treatment after 1990 was then entered into the model. A second model was then constructed that included amiodarone, class I antiarrhythmic drugs and angiotensin-converting enzyme inhibitors to determine whether the improvement in survival after 1990 was independent of these changes in therapy. The 606 patients with complete data for all of the variables were included in the multivariate analyses.

Results

At the time of hospital admission, all groups defined by period of referral had severely depressed left ventricular function, poor functional class and a similar incidence of syncope, prior cardiac arrest and atrial fibrillation (Table 1). Patients referred from 1986 to 1988 were younger, and the prevalence of coronary artery disease was slightly, although not

Table 2. Therapy at Discharge

	1986–1988	1989–1990	1991–1993	p Value
ACEI	46	57	86	< 0.0001
Hydralazine	42	38	19	< 0.0001
Amiodarone	10	49	53	< 0.0001
Class I AAD	31	16	7	< 0.0001
Digoxin	39	70	72	< 0.0001
Warfarin	24	36	42	< 0.0001
Nitrates	68	64	77	< 0.0001
ICD	0.8	5	5	0.02

Data presented are percent of patients. AAD = antiarrhythmic drugs; ACEI = angiotensin-converting enzyme inhibitors; ICD = implantable cardioverter-defibrillator.

statistically, lower. Before 1989, mean left ventricular ejection fraction and hemodynamic variables on admission were slightly worse than after 1989, but mean serum sodium was 135 mEq/liter after 1989 compared with 136 mEq/liter before, and all three groups achieved similar hemodynamic variables on tailored therapy, with a reduction in cardiac filling pressures and increase in cardiac index (Table 1). After 1990, final heart rate and cardiac index were slightly lower, probably because of less frequent use of hydralazine and greater use of amiodarone (see later).

By design, medications at hospital discharge changed markedly over the study period (Table 2). The administration of angiotensin-converting enzyme inhibitors increased from 46% to 86% of patients, whereas hydralazine use decreased from 42% to 19%. Administration of class I antiarrhythmic drugs decreased from 31% to 7% of patients, and amiodarone administration increased from 10% to 53%. Presence of implantable cardioverter-defibrillators increased from 0.8% to 5% of patients, all of whom had a prior history of sustained ventricular tachycardia or ventricular fibrillation. Digoxin administration increased from 39% to 72% of patients. Long-term anticoagulation with warfarin was also used more frequently after 1988.

Survival and sudden death. Cumulative mortality and sudden death during the year after evaluation decreased during the study period (Fig. 1 and 2). The total mortality rate decreased from 33% during 1986 to 1988 to 16% during 1991 to 1993 (p = 0.0001). Sudden death decreased from 20% to 8% (p = 0.0006). The improvement in outcome occurred despite a similar proportion of patients accepted for transplantation in each group, a trend toward fewer patients undergoing transplantation and a longer median time to transplantation after 1990 (Table 3). Once accepted, candidates underwent transplantation solely on the basis of size, blood type and time listed, without preference to clinical severity, except for the few patients warranting urgent transplantation (7% before 1989, 8% after 1990).

To adjust for baseline differences between groups excluding therapies, Cox proportional hazards models were constructed. The variables that met criteria for inclusion (p < 0.2) in the models are shown in Table 4. Treatment after 1990 was

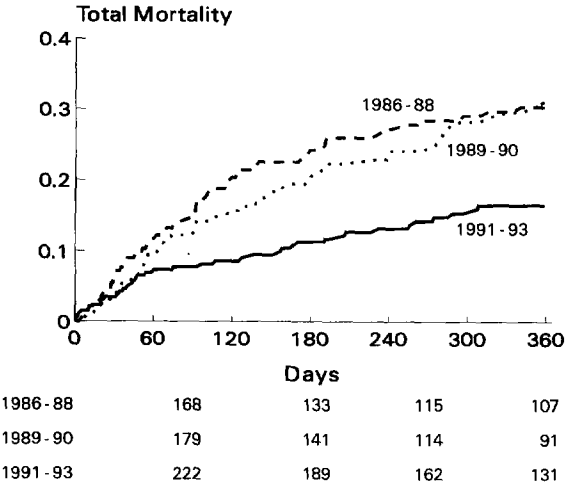

Figure 1. Cumulative deaths from all causes for patients evaluated during 1986 to 1988, 1989 to 1990 and 1991 to 1993. Total mortality was significantly less for patients evaluated after 1990 than during 1986 to 1988 (p = 0.0001) or 1989 to 1990 (p = 0.001). **Numbers below graph** = number of patients remaining in each time period.

associated with a lower total mortality rate (risk ratio [RR] 0.55, 95% confidence interval [CI] 0.37 to 0.84). When therapy with angiotensin-converting enzyme inhibitors (p = 0.02), amiodarone (p = 0.19) and class I antiarrhythmic drugs (p = 0.19) was entered into the model, treatment after 1990 was no longer independently associated with better survival (RR 0.68, 95% CI 0.43 to 1.1). Thus, in this model the improvement in survival over time could largely be explained by these changes in therapy.

In the multivariate model for sudden death, patients treated after 1990 had a lower risk (RR 0.56, 95% CI 0.32 to 0.99). When therapy with angiotensin-converting enzyme inhibitors (p = 0.002) was entered into the model, treatment after 1990 was not independently associated with a greater sudden death

Figure 2. Cumulative sudden deaths for patients evaluated during 1986 to 1988, 1989 to 1990 and 1991 to 1993. Sudden death was significantly less for patients evaluated during 1991 to 1993 than during 1986 to 1988 (p = 0.0006), but the difference did not reach statistical significance versus 1989 to 1990 (p = 0.13).

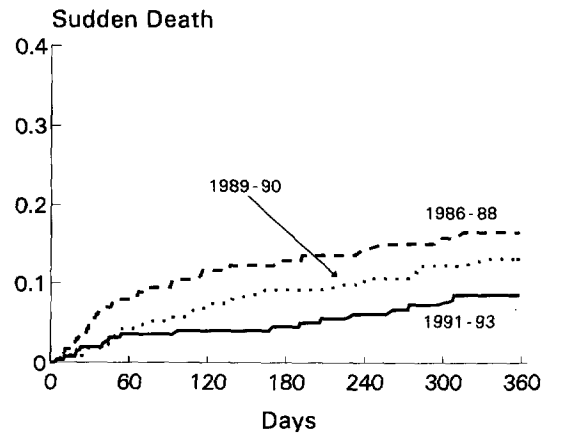

Table 3. Heart Transplantation

	1986–1988	1989–1990	1991–1993	p Value
Accepted for waiting list (%)	52	52	56	0.52
Transplantation (%)	33	35	29	0.27
Urgent transplantation (%)	7	11	8	0.29
Median time to transplantation (days)	195	178	216	

Unless otherwise indicated, data presented are percent of patients.

risk (RR 0.76, 95% CI 0.41 to 1.4). Therapy with amiodarone ($p = 0.68$) and class I drugs ($p = 0.21$) did not meet criteria for entry into the multivariate model for sudden death.

Discussion

Heart transplantation has improved survival and quality of life but can be provided to <2,500 patients with heart failure/year (7). Its promise attracts patients with heart failure to 250 centers in the world, where attempts are also made to optimize medical therapy for candidates on the outpatient waiting list for transplantation and for ineligible patients. The severity of illness and need for individualization of therapy in such patients limit their inclusion in multicenter trials, such as the V-HeFT (3) and SOLVD (2) trials, in which class IV heart failure was present in 0.35% and 1.7% of patients, respectively (2,3). The present study of patients with severe heart failure demonstrates relative decreases in the total mortality and sudden death rates of 51% and 70% in temporal relation to changes in medical therapy for heart failure and arrhythmias, which were instituted on the basis of published trial results. Patients were managed according to uniform guidelines at a single center. All patients discharged after hospital admission for heart failure and transplant evaluation were included. No patients were treated with investigational inotropic medications, some of which have subsequently been associated with increased mortality (12,13).

Table 4. Multivariate Analysis for Total Mortality and Sudden Death

	Total Mortality		Sudden Death	
	Risk Ratio	95% CI	Risk Ratio	95% CI
After 1990	0.55	0.37–0.84	0.56	0.32–0.99
Serum Na (mEq/liter)	0.93	0.89–0.96	0.97	0.92–1.03
SBP adm (mm Hg)	0.99	0.98–1.0		
PCW adm (mm Hg)	1.01	0.99–1.03		
PCW final (mm Hg)	1.05	1.02–1.09	1.05	0.99–1.1
Atrial fib	1.3	0.9–2.0		
Cardiac arrest	2.1	1.3–3.3	2.1	1.1–3.9
Syncope	1.8	1.2–2.7	2.4	1.4–4.3
LVEF			0.98	0.95–1.2
PAsys final (mm Hg)			1.02	0.99–1.04
Age (yr)			0.97	0.95–0.99

Variables with $p \leq 0.2$ were included in the models. For continuous variables, the risk ratio reflects the change in risk for a 1-unit change in the variable. adm = on admission; CI = confidence interval; fib = fibrillation; other abbreviations as in Table 1.

Vasodilator therapy. Before 1989, it was known that mortality in heart failure was reduced by either hydralazine combined with isosorbide dinitrate or angiotensin-converting enzyme inhibitors (4,14). From 1983 to 1988, the initial oral vasodilator administered was chosen by the attending cardiomyopathy team physician based on clinical judgment or, in 104 patients, according to a randomization scheme (9). Subsequently, captopril and enalapril were shown to improve survival more than the hydralazine and isosorbide dinitrate combination (3,9). The treatment protocol was then altered to include angiotensin-converting enzyme inhibitors as the preferred vasodilator, adding or changing to hydralazine only in the event of a poor hemodynamic response or intolerance. These results continue to support the use of angiotensin-converting enzyme inhibitors as first-line therapy in patients with advanced heart failure (2,15). Although the separate effects of oral nitrates have not been assessed by a randomized trial, isosorbide dinitrate was routinely prescribed at this center after 1990, because the captopril/nitrate combination was associated with a relatively low mortality in the Hy-C trial (9).

Arrhythmia management. Angiotensin-converting enzyme inhibitors decrease sudden death compared with the hydralazine–isosorbide dinitrate combination, but sudden death still accounts for 28% to 68% of deaths in recent trials (3,4,9,15–18). There are several possible causes of sudden death and even a variety of definitions among investigators, making this end point less reliable. However, ventricular arrhythmias are likely to be important (18). Nonsustained ventricular tachycardia and complex ventricular ectopic activity are observed in 20% to 80% of patients with heart failure, and the optimal approach to management is unclear. Early in the present study, class I antiarrhythmic drugs were continued in patients receiving these medications before referral. In 1989 it became clear that treatment with encainide or flecainide increased mortality after myocardial infarction (5). In an analysis of the nonrandomized patients in our center up to that time, patients treated with class I drugs had a higher risk of sudden death than those treated with amiodarone or receiving no antiarrhythmic drugs. A policy was then instituted to discontinue class I antiarrhythmic drugs unless they had been effective in controlling sustained ventricular arrhythmias. This approach has been further supported by the recent report of

Flaker et al. (19) that antiarrhythmic drug therapy was associated with increased mortality in patients with atrial fibrillation and heart failure. In the current study, amiodarone was recommended for patients with frequent ventricular ectopic activity or if an antiarrhythmic agent was required for prevention of atrial fibrillation. Amiodarone was selected because it is well tolerated during long-term therapy in patients with heart failure, and initial studies (20–23) suggested that it was unlikely to increase mortality, at least in postinfarction patients. This approach to arrhythmia management appears to be reasonably safe because it was followed by a dramatic reduction in sudden death. A recent randomized trial (24) found that amiodarone improved survival in severe heart failure. Amiodarone did not affect survival in another trial (25) in patients with less severe heart failure. Our data cannot ascertain the relative importance of amiodarone, withdrawal of class I drugs and increased use of angiotensin-converting enzyme inhibitors. Precautions that were taken with regard to antiarrhythmic therapy deserve emphasis. In patients with heart failure, bradyarrhythmias are a cause of sudden death that can be provoked by amiodarone (6,22). Amiodarone was not administered to patients with evidence of sinus or AV node dysfunction, even if these were asymptomatic. Antiarrhythmic drugs were withdrawn only in patients without a history of sustained ventricular tachycardia or cardiac arrest and were withdrawn during ECG monitoring in hospital.

Digoxin and anticoagulation. The use of digoxin also increased over the study period, during which several trials (26–28) demonstrated benefit of digoxin on ventricular function, exercise capacity, clinical stability and autonomic balance. The effect of digoxin on mortality is not yet known. The use of anticoagulation also increased, but the expected impact of this change on mortality is slight because of the low incidence of embolic events in this population (29).

Transplantation. Although ~50% of our patients were candidates for transplantation, only 33% of those seen before 1989 and 29% after 1990 underwent transplantation (Table 3). Once a patient is accepted for addition to the outpatient waiting list, selection for transplantation depends on matching with an available donor for body size and blood type, with further priority based on the duration of time the patient has been on the waiting list. Time of transplantation is a relatively unbiased censored event in the survival analysis except when deterioration requires urgent transplantation, which occurred in only 7% of patients before 1989 and 8% after 1990.

Study limitations. The present study was not a randomized trial of therapy. We cannot exclude the possibility that subtle changes in factors that were not assessed, such as better patient compliance with risk factor modifications, smoking cessation and diet, may have contributed to better outcomes. Community awareness of therapy for heart failure may have improved. These factors may explain the referral of patients with slightly less baseline hemodynamic compromise during the later years. However, differences were relatively small, and the hemodynamic profiles before hospital discharge were similar. The average serum sodium levels also suggest comparable severity of heart failure in the later group. In the proportional hazards model, those patients treated after 1990 had lower mortality and sudden death after adjustment for baseline differences. Furthermore, angiotensin-converting enzyme inhibitors or change in antiarrhythmic therapies, or both, appeared largely to account for the reduction in mortality. The follow-up periods were restricted to 1 year to allow comparison of the treatment groups.

Clinical implications. The present study demonstrates over an 8-year period in a single center a marked improvement in 1-year survival and reduction in sudden death in of patients with advanced heart failure. This result is most likely related to improvements in medical management of heart failure and arrhythmias. The reduction in sudden death risk to 8% at 1 year for patients discharged after referral to a transplant center indicates that most ambulatory patients may safely be maintained on optimal medical therapy until clinical deterioration mandates transplantation.

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