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## LONG-TERM TRENDS IN THE INCIDENCE OF AND SURVIVAL WITH HEART FAILURE

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### ABSTRACT

**Background** Heart failure is a major public health problem. Long-term trends in the incidence of heart failure and survival after its onset in the community have not been characterized.

**Methods** We used statistical models to assess temporal trends in the incidence of heart failure and Cox proportional-hazards regression to evaluate survival after the onset of heart failure among subjects in the Framingham Heart Study. Cases of heart failure were classified according to the date of onset: 1950 through 1969 (223 cases), 1970 through 1979 (222), 1980 through 1989 (307), and 1990 through 1999 (323). We also calculated 30-day, 1-year, and 5-year age-adjusted mortality rates for each period.

**Results** Heart failure occurred in 1075 subjects (51 percent of whom were women). As compared with the rate for the period from 1950 through 1969, the incidence of heart failure remained virtually unchanged among men in the three subsequent periods but declined by 31 to 40 percent among women (rate ratio for the period from 1990 through 1999, 0.69; 95 percent confidence interval, 0.51 to 0.93). The 30-day, 1-year, and 5-year age-adjusted mortality rates among men declined from 12 percent, 30 percent, and 70 percent, respectively, in the period from 1950 through 1969 to 11 percent, 28 percent, and 59 percent, respectively, in the period from 1990 through 1999. The corresponding rates among women were 18 percent, 28 percent, and 57 percent for the period from 1950 through 1969 and 10 percent, 24 percent, and 45 percent for the period from 1990 through 1999. Overall, there was an improvement in the survival rate after the onset of heart failure of 12 percent per decade ( $P=0.01$  for men and  $P=0.02$  for women).

**Conclusions** Over the past 50 years, the incidence of heart failure has declined among women but not among men, whereas survival after the onset of heart failure has improved in both sexes. Factors contributing to these trends need further clarification. (N Engl J Med 2002;347:1397-402.)

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HEART failure is a major public health problem. About 550,000 new cases occur each year in the United States, and in 1999, heart failure contributed to approximately 287,200 deaths.<sup>1</sup> Treatment of hypertension reduces the incidence of heart failure by about 50 percent,<sup>2,3</sup> and during the past three decades, important advances have occurred in the awareness, treatment, and control of high blood pressure.<sup>4</sup> Similarly, in the past 15 years several large-scale, randomized clinical trials have shown that various classes of medications<sup>5-11</sup> reduce the risk of death in patients with heart failure; these drugs are increasingly being used in such patients.<sup>12</sup> Widespread use of these proven strategies holds the promise of decreasing the incidence of heart failure and increasing survival after its onset. Although substantial improvements in survival were reported in two referral series<sup>13,14</sup> and in a hospital-based study,<sup>15</sup> community-based cohort studies have not shown any change over time in either the incidence of heart failure or the survival rate after its onset.<sup>16,17</sup>

We examined temporal trends in the incidence of and survival with heart failure among subjects in the Framingham Heart Study during a 50-year interval from the 1950s through the 1990s. The Framingham Heart Study has used uniform criteria and methods of ascertainment for the diagnosis of heart failure, and the study sample has been continuously monitored for heart failure and with respect to vital status.

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## METHODS

### Study Sample

In 1948, men and women from Framingham, Massachusetts, who were 28 to 62 years of age were enrolled in a prospective epidemiologic study. The selection criteria and study design have been described elsewhere.<sup>18</sup> Members of the original cohort have subsequently been evaluated at two-year intervals, updating their medical history and undergoing a physical examination and laboratory tests, including blood chemical measurements and electrocardiography. In 1971, the children of the original study participants and the spouses of these children were enrolled in the study.<sup>19</sup> Serial evaluations of the members of the offspring cohort began eight years after enrollment and approximately every four years thereafter. Written informed consent was obtained from study participants, and the research protocol was reviewed and approved by the institutional review board of Boston Medical Center.

### Case Ascertainment

At each examination, interim cardiovascular disease events were identified on the basis of the medical history, findings on physical examination and 12-lead electrocardiography, and a review of medical records (hospital records, physicians' records, and pathology reports). The medical records of subjects who did not attend a given examination were obtained and evaluated for evidence of interim events. All suspected interim nonfatal and fatal cardiovascular disease events were reviewed by a panel of three experienced investigators using established protocols and the definitions of the Framingham Heart Study.<sup>20,21</sup> The Framingham Heart Study has always used uniform criteria for the diagnosis of heart failure, and these criteria have been described previously.<sup>22</sup>

Of the 10,333 subjects who attended the base-line examination, 14 were excluded because they had heart failure at or before their first examination, and 8 were excluded because there was no available follow-up. After these exclusions, 10,311 subjects (53.3 percent of whom were women) were eligible for this investigation.

### Definition of Covariates

The blood pressure of seated subjects was measured twice by the examining physician using a mercury-column sphygmomanometer and a cuff of appropriate size. The two readings were then averaged. Hypertension was defined by a systolic blood pressure of at least 140 mm Hg, a diastolic blood pressure of at least 90 mm Hg, or pharmacologic treatment for elevated blood pressure.<sup>23</sup> Diabetes was defined by a blood glucose level of at least 7.77 mmol per liter (140 mg per deciliter) after an overnight fast, a randomly obtained nonfasting blood glucose level of at least 11.11 mmol per liter (200 mg per deciliter), or the use of insulin or oral hypoglycemic agents. A subject was considered to have preexisting valve disease if the examining physician noted a systolic murmur of grade 3/6 or louder, any diastolic murmur, or a palpable thrill. Standard 12-lead electrocardiograms obtained at each examination cycle were analyzed for the presence of left ventricular hypertrophy.<sup>24</sup> The criteria for the diagnosis of myocardial infarction have been described previously.<sup>20</sup>

### Statistical Analysis

The 1075 cases of heart failure were classified according to the date of onset: 1950 through 1969 (223 cases), 1970 through 1979 (222), 1980 through 1989 (307), and 1990 through 1999 (323). We calculated the sex-specific, age-adjusted incidence of heart failure for each period, using a standardized, common age distribution that was the same for men and women. Owing to the extremely small number of subjects who were 80 years of age or older in the first period, we substituted data for subjects who were 80 to 84 years and 85 to 89 years of age from the second period. For analysis of incidence, 4 subjects with heart failure who were younger than 40 years of age and 74 subjects who were at least 90 years of age were

excluded. We calculated sex-specific, age-adjusted rate ratios of the incidence of heart failure using a Poisson model (Proc Genmod procedure). In each case, the second, third, and fourth periods were compared with the first period. For analyses of survival, we excluded 18 subjects for whom the diagnosis of heart failure coincided with the date of death.

Follow-up was restricted to the 10-year period after the onset of heart failure. Age-adjusted survival curves and age-adjusted 30-day, 1-year, and 5-year mortality rates were estimated for the overall study sample for each of the four periods, with separate estimates for men and women. Results are presented for the group of subjects who were 65 to 74 years of age, since this age range encompassed the mean age at the onset of heart failure in our study sample. Age was adjusted in the proportional-hazards models by the use of separate age strata (<55, 55 to 64, 65 to 74, 75 to 84, and ≥85 years) to accommodate nonlinearity in the relation of the hazard ratio (expressed as a logarithmic value) to age. In addition, within age groups, age at the diagnosis of heart failure was entered as a covariate. In secondary analyses, sex-specific, age-adjusted mortality rates at 1 year and 5 years were computed after the exclusion of subjects who died within 30 days after the onset of heart failure.

Sex-specific Cox proportional-hazards regression analysis<sup>25</sup> was used to compare survival across the four time periods. Multivariable models also adjusted for the presence or absence of hypertension, electrocardiographic evidence of left ventricular hypertrophy, diabetes, valve disease, and a history of myocardial infarction. The resulting values were expressed as hazard ratios and 95 percent confidence intervals, with the first period (1950 through 1969) serving as the reference category. A P value for trend of less than 0.05 was considered to indicate statistical significance. All survival analyses were performed with the use of SAS software, version 6.12 (SAS Institute).<sup>26</sup>

## RESULTS

Heart failure occurred in 1075 study participants (51 percent of whom were women) between 1950 and 1999. The mean ( $\pm$ SD) age at the diagnosis of heart failure was  $62.7 \pm 8.8$  years in the period from 1950 through 1969 and  $80.0 \pm 10.1$  years in the period from 1990 through 1999.

### Trends in the Incidence of Heart Failure

The age-adjusted rates of heart failure were higher among men than among women in all four periods (Table 1). As compared with the rate in the period from 1950 through 1969, there was no significant change in the age-adjusted incidence of heart failure among men in the three subsequent periods. Among women, however, the incidence of heart failure declined by 31 to 40 percent in the decades following the first time period.

### Survival after the Onset of Heart Failure

Age-adjusted survival rates after the onset of heart failure improved over time (Fig. 1). The 30-day, 1-year, and 5-year adjusted mortality rates, computed separately for men and women, are shown in Table 2. The 30-day mortality rate among women declined from 18 percent in the period from 1950 through 1969 to 10 percent in the period from 1990 through 1999. During the four consecutive periods of observation (1950 through 1969, 1970 through 1979, 1980

**TABLE 1.** TEMPORAL TRENDS IN THE AGE-ADJUSTED INCIDENCE OF HEART FAILURE.\*

PERIOD	MEN		WOMEN	
	INCIDENCE OF HEART FAILURE	RATE RATIO	INCIDENCE OF HEART FAILURE	RATE RATIO
	rate/100,000 person-yr		rate/100,000 person-yr	
1950–1969†	627 (475–779)	1.00	420 (336–504)	1.00
1970–1979	563 (437–689)	0.87 (0.67–1.14)	311 (249–373)	0.63 (0.47–0.84)
1980–1989	536 (448–623)	0.87 (0.67–1.13)	298 (247–350)	0.60 (0.45–0.79)
1990–1999	564 (463–665)	0.93 (0.71–1.23)	327 (266–388)	0.69 (0.51–0.93)

\*All values were adjusted for age (<55, 55 to 64, 65 to 74, 75 to 84, and ≥85 years). Values in parentheses are 95 percent confidence intervals.

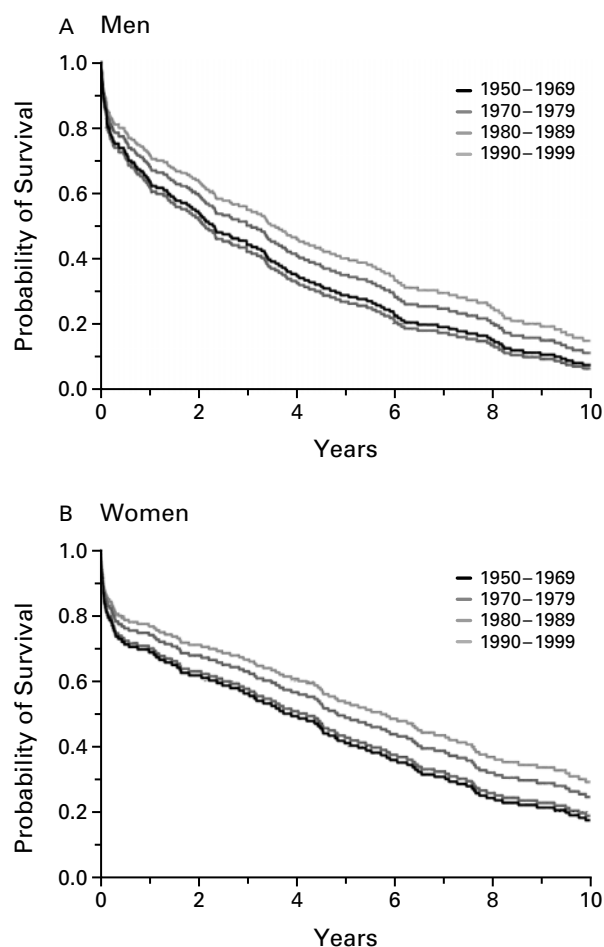
†This period served as the reference period.

through 1989, and 1990 through 1999), the respective one-year mortality rates were 30 percent, 41 percent, 33 percent, and 28 percent among men, and 28 percent, 28 percent, 27 percent, and 24 percent among women. The five-year mortality rate among men declined from 70 percent in the period from 1950 through 1969 to 59 percent in the period from 1990 through 1999, whereas the respective rates among women declined from 57 percent to 45 percent. The 1-year and 5-year age-adjusted mortality rates among men and women who survived at least 30 days after the onset of heart failure are shown in Table 3.

In comparison with the survival rate for the period from 1950 through 1969, the death rate for the most recent period declined by approximately one third in both men and women in multivariable analyses with adjustment for multiple risk factors (Table 4). The overall trend across time periods was a decline in the risk of death of 12 percent per decade (P for trend, 0.01 in men and 0.02 in women). Analyses restricted to cases of heart failure among subjects who were 65 to 74 years of age yielded results that were not materially different from those shown in Table 4.

## DISCUSSION

In our carefully monitored cohort, the incidence of heart failure changed little among men from the 1950s through the 1990s but declined by about one third among women during this period. After adjustment for several covariates, the rates of death after the onset of heart failure declined by about one third from the 1950s to the 1990s in both sexes. Despite the favorable trends in survival, heart failure remains highly fatal; among subjects who were given a diagnosis of heart failure in the 1990s, more than 50 percent were dead at five years.



**Figure 1.** Temporal Trends in Age-Adjusted Survival after the Onset of Heart Failure among Men (Panel A) and Women (Panel B). Values were adjusted for age (<55, 55 to 64, 65 to 74, 75 to 84, and ≥85 years). Estimates are shown for subjects who were 65 to 74 years of age.

**TABLE 2.** TEMPORAL TRENDS IN AGE-ADJUSTED MORTALITY AFTER THE ONSET OF HEART FAILURE AMONG MEN AND WOMEN 65 TO 74 YEARS OF AGE.\*

PERIOD	30-DAY MORTALITY		1-YEAR MORTALITY		5-YEAR MORTALITY	
	MEN	WOMEN	MEN	WOMEN	MEN	WOMEN
percent (95 percent confidence interval)						
1950–1969	12 (4–19)	18 (7–27)	30 (18–40)	28 (16–39)	70 (57–79)	57 (43–67)
1970–1979	15 (7–23)	16 (6–24)	41 (29–51)	28 (17–38)	75 (65–83)	59 (45–69)
1980–1989	12 (5–18)	10 (4–16)	33 (23–42)	27 (17–35)	65 (54–73)	51 (39–60)
1990–1999	11 (4–17)	10 (3–15)	28 (18–36)	24 (14–33)	59 (47–68)	45 (33–55)

\*All values were adjusted for age (<55, 55 to 64, 65 to 74, 75 to 84, and ≥85 years).

**TABLE 3.** TEMPORAL TRENDS IN AGE-ADJUSTED MORTALITY AMONG MEN AND WOMEN 65 TO 74 YEARS OF AGE WHO SURVIVED AT LEAST 30 DAYS AFTER THE ONSET OF HEART FAILURE.\*

PERIOD	1-YEAR MORTALITY		5-YEAR MORTALITY	
	MEN	WOMEN	MEN	WOMEN
percent (95 percent confidence interval)				
1950–1969	20 (10–29)	13 (4–21)	66 (52–76)	47 (32–59)
1970–1979	30 (18–41)	14 (5–22)	71 (58–80)	51 (36–62)
1980–1989	25 (14–34)	19 (9–28)	60 (48–69)	46 (33–56)
1990–1999	18 (9–26)	16 (7–25)	54 (41–64)	40 (27–50)

\*All values were adjusted for age (<55, 55 to 64, 65 to 74, 75 to 84, and ≥85 years).

A previous community-based study has reported on trends in the incidence of heart failure.<sup>17</sup> In that investigation, the incidence of heart failure in a 1981 cohort was not different from that in a 1991 cohort. Our study, however, had longer follow-up and began in an era when the treatment of risk factors for heart failure was minimal.

The differences in long-term trends in the incidence of heart failure among men and women may be due in part to sex-based differences in the causes of heart failure. Whereas hypertension predominates as an etiologic risk factor for heart failure in women, more so than in men, myocardial infarction is responsible for a higher proportion of cases of heart failure in men.<sup>27</sup> Increasing use of antihypertensive medications, which has led to a decline in the prevalence of high blood pressure<sup>4</sup> and nearly eradicated stage IV hypertension<sup>28</sup> (defined as a systolic blood pressure greater than 210 mm Hg or a diastolic blood pressure of more than 120 mm Hg), may have affected the incidence of heart failure, especially among women. Improvements in the treatment of myocardial infarction,<sup>29,30</sup>

leading to a greater proportion of patients surviving with residual myocardial damage who are highly susceptible to heart failure, may explain the lack of a decline in the incidence of heart failure among men.

In an earlier investigation from the Framingham Heart Study, there was no significant difference in overall survival after the diagnosis of heart failure between 341 subjects who received a diagnosis between 1948 and 1974 and 311 subjects who received a diagnosis between 1975 and 1988.<sup>16</sup> In a similar vein, a prior investigation in Rochester, Minnesota, did not identify a significant improvement in survival after the diagnosis of heart failure between 107 patients with new-onset heart failure (defined according to the criteria of the Framingham Heart Study) in 1981 and 141 patients in whom heart failure was diagnosed in 1991.<sup>17</sup> We investigated trends in survival in a larger number of subjects for whom a half-century of follow-up data was available.

A recent hospital-based retrospective study in Scotland<sup>15</sup> and two hospital-based referral series<sup>13,14</sup> found substantial temporal declines in mortality after hospitalization for heart failure. In many patients, however, heart failure is diagnosed outside the hospital, and these studies evaluated survival after hospitalization for heart failure, not after the first occurrence of heart failure. In contrast, we examined survival after the initial diagnosis of heart failure (whether or not it occurred in the hospital) over a period of 50 years in a cohort in which uniform criteria for heart failure were used throughout and for which ascertainment of vital status was complete. Hospital-based studies are hampered by several types of bias. First, increased understanding on the part of physicians of the clinical manifestations of heart failure and increasing use of new forms of technology such as echocardiography as a diagnostic tool may lead to the earlier identification of mild cases of heart failure, resulting in an apparent improvement in survival owing to lead-time bias.<sup>31</sup> Second, payments based on diagnosis-

**TABLE 4.** LONG-TERM TRENDS IN THE ADJUSTED RISK OF DEATH AFTER THE ONSET OF HEART FAILURE, 1950 THROUGH 1999.

PERIOD	MEN		WOMEN	
	AGE-ADJUSTED*	ADJUSTED FOR MULTIPLE VARIABLES†	AGE-ADJUSTED*	ADJUSTED FOR MULTIPLE VARIABLES†
	hazard ratio (95 percent confidence interval)			
1950–1969‡	1.00	1.00	1.00	1.00
1970–1979	1.06 (0.79–1.41)	1.02 (0.76–1.37)	0.96 (0.68–1.33)	0.93 (0.67–1.30)
1980–1989	0.85 (0.63–1.13)	0.82 (0.61–1.10)	0.80 (0.58–1.11)	0.77 (0.55–1.07)
1990–1999	0.74 (0.54–1.01)	0.69 (0.50–0.95)	0.71 (0.50–1.00)	0.68 (0.48–0.98)
Overall trend	0.90 (0.82–0.99)	0.88 (0.80–0.97)	0.89 (0.80–0.99)	0.88 (0.78–0.98)
P value for trend	0.03	0.01	0.03	0.02

\*All values were adjusted for age (<55, 55 to 64, 65 to 74, 75 to 84, and ≥85 years).

†All values were adjusted for age (<55, 55 to 64, 65 to 74, 75 to 84, and ≥85 years) and the presence or absence of hypertension, electrocardiographic evidence of left ventricular hypertrophy, diabetes mellitus, valve disease, and a history of myocardial infarction.

‡This period served as the reference category.

related groups may have contributed to a higher rate of diagnosis of heart failure as hospitals sought to maximize reimbursements,<sup>32</sup> a practice that could introduce considerable bias. Third, reliance on hospital records and death certificates for the identification of heart failure may bias a study toward the inclusion of sicker hospitalized patients.<sup>33</sup>

National data on the rate of death from heart failure<sup>34–37</sup> are derived from death certificates and permit only the examination of deaths attributed to heart failure; they provide no insight into survival after the onset of heart failure. Furthermore, the death certificate is a poor method of identifying cases of heart failure, since in only a small fraction of cases of heart failure is death classified as due to heart failure. In addition, the reliability and comparability of mortality statistics are seriously limited by variations in data collection and coding and by differences in the approach to the diagnosis of heart failure within and between communities and over time.<sup>38</sup>

Our population-based sample comprises a large, unselected series of subjects who had a fixed case definition of heart failure, with nearly equal numbers of men and women. The 50-year follow-up was essentially complete and included the pre- and post-vasodilator era. Lead-time bias is an unlikely explanation for the temporal improvement in survival after the onset of heart failure, since we used the same diagnostic criteria throughout the study, there was no significant change in the incidence of heart failure among men, and there was a decline in the incidence of heart failure among women. Thus, rising incidence due to an increase in the diagnosis of milder cases of heart failure in the more recent periods of observation is unlikely.

Nonetheless, our study had several limitations. First,

our study sample was almost exclusively white, and the results may not be applicable to different racial and ethnic groups, in which the causes and prognosis of heart failure may differ. Second, participants in the Framingham Heart Study may have better access to preventive care and better outcomes after the onset of heart failure than other patients with heart failure. Some mild cases of heart failure may not have been detected by our clinical criteria. Lastly, we were unable to examine the effect of therapy on survival after the onset of heart failure because many subjects with new-onset heart failure died before they could attend the next clinic visit at which medication use was routinely ascertained.

Our study provides strong evidence that the incidence of heart failure has declined in women and that survival after the onset of heart failure has improved in men and women in recent decades. Further evaluation is warranted to determine the extent to which these improvements are a consequence of changes in the relative contributions of such conditions as hypertension, coronary heart disease, and valve disease<sup>39</sup>; changes in the pathophysiological process (for instance, changes in the proportion of patients with heart failure who have impaired left ventricular systolic function as opposed to unimpaired function); or the increasing use of pharmacologic therapies<sup>5–11</sup> that prolong survival in patients with heart failure due to left ventricular systolic dysfunction. A large proportion of patients with heart failure in the general population have preserved left ventricular systolic function,<sup>40</sup> and the effect of treatment on survival in these patients is unknown. Despite the favorable temporal trends that we observed, in the light of the unacceptably high mortality rate associated with heart failure, greater emphasis

must be placed on the primary prevention of this condition.

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