Trends in Heart Failure Incidence and Survival in a Community-Based Population

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THE BURDEN OF HEART FAILURE and its societal cost are staggering. Approximately 4.9 million Americans have been diagnosed with the disease.1 Hospital discharges for heart failure increased by 155% during the last 20 years, and heart failure is the most frequent cause of hospitalization in persons aged 65 years or older. Within this context, heart failure constitutes a public health problem1 singled out as an emerging epidemic.2 Although the clinical and public health importance of heart failure is undisputed, this epidemic is not adequately understood. Data on the incidence of heart failure are relatively sparse and lack consistency. Most data are derived from hospital discharge records or self-report and thus do not reflect incidence, have uncertain validity caused by documented shifts in coding practices because of reimbursement incentives,3 and cannot fully capture the burden of the disease because of the shift of care toward outpatient settings. Thus, little is known about temporal trends in the incidence of heart failure and on survival after its onset.

In the Framingham Heart Study, the incidence of heart failure between 1950 and 1999 changed little among men but declined in women, whereas survival improved in both sexes.4 These findings require replication in other settings because the design of the Framingham Heart Study, as acknowledged by the authors, may impose a “healthy participant” effect.5 Furthermore, although using consistent research standards is necessary, such as the Framingham criteria to assess secular trends, it is important to examine their relationship to clinical diagnoses.

This study was designed to estimate the secular trends in the incidence of heart failure and in survival after its onset in a geographically defined community by using 2 sets of criteria: the Framingham criteria and clinical criteria. We hypothesized that, over time, the incidence of heart failure increased and that survival after its onset improved but that the trends in incidence and survival differed by age and sex.

Context The epidemic of heart failure has yet to be fully investigated, and data on incidence, survival, and sex-specific temporal trends in community-based populations are limited.

Objective To test the hypothesis that the incidence of heart failure has declined and survival after heart failure diagnosis has improved over time but that secular trends have diverged by sex.

Design, Setting, and Participants Population-based cohort study using the resources of the Rochester Epidemiology Project conducted in Olmsted County, Minnesota. Patients were 4537 Olmsted County residents (57% women; mean [SD] age, 74 [14] years) with a diagnosis of heart failure between 1979 and 2000. Framingham criteria and clinical criteria were used to validate the diagnosis.

Main Outcome Measures Incidence of heart failure and survival after heart failure diagnosis.

Results The incidence of heart failure was higher among men (378/100000 persons; 95% confidence interval [CI], 361-395 for men; 289/100000 persons; 95% CI, 277-300 for women) and did not change over time among men or women. After a mean follow-up of 4.2 years (range, 0-23.8 years), 3347 deaths occurred, including 1930 among women and 1417 among men. Survival after heart failure diagnosis was worse among men than women (relative risk, 1.33; 95% CI, 1.24-1.43) but overall improved over time (5-year age-adjusted survival, 43% in 1979-1984 vs 52% in 1996-2000, P<.001). However, men and younger persons experienced larger survival gains, contrasting with less or no improvement for women and elderly persons.

Conclusion In this community-based cohort, the incidence of heart failure has not declined during 2 decades, but survival after onset of heart failure has increased overall, with less improvement among women and elderly persons.

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sota, the characteristics of which are similar to those of US non-Hispanic whites. The Mayo Clinic and Olmsted Medical Center provide the majority of medical care for this population. Both organizations use a unit medical record system in which information is collected by health care clinicians in a single record, regardless of site of care. These records are easily retrievable because the Mayo Clinic has maintained extensive indices of diagnoses and procedures, which were extended through the Rochester Epidemiology Project to the records of other clinicians to county residents, resulting in the linkage of all medical records from all sources of care through a centralized system.

All persons with a first diagnosis of heart failure were identified with codes from the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM), similar to those used in other studies. These codes included 428 (heart failure), 402.01 (hypertensive heart disease malignant with congestive heart failure), 402.11 (hypertensive heart disease benign with congestive heart failure), 425 (cardiomyopathy), 429.3 (cardiomegaly), and 514 (pulmonary congestion). Codes 402.91 (hypertensive heart disease unspecified with congestive heart failure), 404.01 (malignant hypertensive heart and renal disease with heart failure), 404.11 (benign hypertensive heart and renal disease with congestive heart failure), and 404.91 (unspecified hypertensive heart and renal disease with congestive heart failure) were queried but not used as part of the coding practices during the study.

The codes, which are not based on hospital billing codes, were assigned by coders primarily according to physician diagnoses for outpatient visits and on discharge diagnoses for hospitalizations. Samples of each code were reviewed only if not associated with code 428. Nonresidency in Olmsted County was an exclusion criterion. The yield of each code toward a validated diagnosis of heart failure was examined in aggregate, as well as according to time, age, and sex by using logistic regression. The resulting model was used to construct the validated heart failure incidence cohort, with 2 sets of criteria.

The Framingham criteria, which have been used consistently in various settings and can provide qualitative comparisons with results from other studies, were used as 1 standard (BOX). A second criterion, defined by a physician’s diagnosis of heart failure, was used to assess these trends in clinical practice. Three experienced abstractors reviewed the records, masked to the study hypothesis. Clinical characteristics, including comorbidity defined by the Charlson index, were collected in a stratified random sample of 11% of code 428 and 8% of each of codes 425, 429.3, and 514. Overt coronary disease was defined as history of myocardial infarction, angiographic coronary disease, or coronary artery bypass graft surgery. Myocardial infarction was defined by epidemiologic criteria. Angiographic coronary disease was defined as stenosis greater than 75% of the left anterior descending, left circumflex, or right coronary artery or 50% of the left main coronary artery.

Clinical diagnoses of valvular diseases as documented by attending physician were also recorded.

The feasibility of applying the Framingham criteria was assessed by determining the frequency with which the required components were characterized in the medical record. Missing values were rare, and the Framingham criteria could be applied in 98% of cases. The records of 30 patients were reabstracted to examine interabstractor variability and assess the reliability of ascertainment of heart failure. There was 100% interabstractor agreement for both classifications, indicating that these ascertainment methods are highly reproducible.

Ascertainment of Death
Follow-up was performed through 2003 by using the inpatient and outpatient medical records. The ascertainment of death includes several procedures. In addition to the deaths noted during clinical care, all death certificates for Olmsted County residents are obtained every year from the county office. The Mayo Clinic registration office records the obituaries and notices of deaths in the local newspapers. Finally, data on all Minnesota deaths are obtained from the State of Minnesota every year. The county population is overall stable, and health status has little influence on migration.

Statistical Analyses
Characteristics of patients with validated heart failure are presented as frequencies or mean values with SDs. Differences between men and women were

Box. Framingham Criteria for Heart Failure

Major Criteria
- Paroxysmal nocturnal dyspnea or orthopnea
- Neck vein distension
- Rales
- Cardiomegaly
- Acute pulmonary edema
- S3 gallop
- Increased venous pressure ≥16 cm H2O
- Circulation time ≥25 seconds
- Hepatomegaly
- Ankle edema
- Weight loss ≥4.5 kg in 5 days in response to treatment

Minor Criteria
- Neck vein distension
- Dyspnea on exertion
- Hepatomegaly
- Pleural effusion
- Vital capacity decreased one third from maximum
- Tachycardia rate ≥120/min
- Major or Minor Criterion
- Weight loss ≥4.5 kg in 5 days in response to treatment
- Heart failure present with 2 major or 1 major criterion plus 2 minor criteria

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tested with χ² tests for categorical variables and t tests for continuous variables.

Age-, sex-, and year-specific incidence rates of validated heart failure were calculated. The counts of validated heart failure were used as the numerators, and the denominators were the Olmsted County population, as determined by census data for 1970, 1980, 1990, and 2000, with linear interpolation for the intracensus years. The rates were adjusted directly to the age distribution of the 2000 US total population. Standard errors and 95% confidence intervals (CIs) around the point estimates were calculated assuming a Poisson error distribution.

A Poisson regression model (SAS GENMOD procedure, version 8; SAS Institute, Inc, Cary, NC) was used to examine the temporal trends in the incidence of validated heart failure, with categorical year variables and adjustment for age. Results are summarized by presenting the relative risk (RR) of validated heart failure for men and women in each year group, using 1979 to 1984 as the referent.

Proportional hazards modeling was used to examine the association between year of heart failure diagnosis and survival while adjusting for age. Results are summarized by presenting the RR of validated heart failure in the various year groups compared with the 1979 to 1984 period for men and women at different ages. Sex-specific 30-day, 1-year, and 5-year mortality rates were estimated from the proportional hazards regression models and are presented for patients 75 years of age.

All analyses were stratified by sex. In the modeling, year was modeled categorically, and a nonlinear effect of age was assessed by testing the quadratic term. Comparison of time trends across age groups was accomplished by including interaction terms between year groups and age. P = .05 was selected for the threshold of statistical significance, except when an interaction was tested for, when P = .10 was used. All analyses were replicated in 1000 random samples to ensure that results were robust.

RESULTS

Between 1979 and 2000, 7298 cases of first diagnosis of heart failure identified by code 428 and 1877 cases of first diagnosis of heart failure identified by other codes in isolation without a code 428 occurred. Code 428 constituted the majority (80%) of heart failure codes. This proportion increased over time (77% in 1979-1984 vs 83% in 1996-2000; P for trend <.001).

Eighty-two percent of the cases coded as 428 met Framingham criteria for heart failure, whereas cases with other codes used in isolation without a code 428 met Framingham criteria in 14% to 30% of the cases. The proportion of code 428 cases meeting Framingham criteria did not change over time: 80% in 1979-1984 vs 79% in 1996-2000 (P for trend = .69). The validation rate for each of the target codes adjusted for age, sex, and time were combined with residency status in Olmsted County and incident nature of the event, allowing an incidence cohort of 4537 cases of validated heart failure to be assembled. Among these, 57% were women. The mean (SD) age at the diagnosis of heart failure was 74 (14) years, and 58% were aged 75 years or older.

Incidence of Heart Failure

According to the Framingham criteria, the age-adjusted incidence of heart failure was higher among men (378/100000 persons; 95% CI, 361 to 395) than women (289/100000 persons; 95% CI, 277 to 300) (P < .001). The incidence of heart failure did not change over time (TABLE 1). When analyzed with year as a continuous vari-

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**Table 1. Temporal Trends in the Age-Adjusted Incidence of Heart Failure**

<table>
<thead>
<tr>
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<tbody>
<tr>
<td><strong>Men</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incidence per 100,000 (95% CI)</td>
<td>360 (323-396)</td>
<td>390 (354-425)</td>
<td>375 (340-409)</td>
<td>383 (351-415)</td>
</tr>
<tr>
<td>RR (95% CI)</td>
<td>1.00</td>
<td>1.07 (0.94-1.22)</td>
<td>1.01 (0.88-1.15)</td>
<td>1.04 (0.92-1.18)</td>
</tr>
<tr>
<td><strong>Women</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incidence per 100,000 (95% CI)</td>
<td>284 (260-307)</td>
<td>292 (270-315)</td>
<td>260 (238-282)</td>
<td>315 (292-338)</td>
</tr>
<tr>
<td>RR (95% CI)</td>
<td>1.00</td>
<td>1.04 (0.93-1.16)</td>
<td>0.93 (0.83-1.05)</td>
<td>1.11 (1.00-1.24)</td>
</tr>
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**Table 2. Characteristics of Validated Cases of Heart Failure Stratified by Sex***

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>% (95% Confidence Interval)</th>
<th>P Value</th>
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<tbody>
<tr>
<td><strong>Women</strong> 79 (11)</td>
<td>73 (12)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td><strong>Men</strong> 25-30</td>
<td>30 (21-34)</td>
<td>.04†</td>
</tr>
<tr>
<td><strong>Body mass index &gt;30</strong></td>
<td>22 (16-28)</td>
<td>.02</td>
</tr>
<tr>
<td>Hypertension</td>
<td>72 (66-79)</td>
<td>.02</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>19 (14-25)</td>
<td>.03</td>
</tr>
<tr>
<td>Smoking</td>
<td>35 (28-41)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>16 (11-21)</td>
<td>.34</td>
</tr>
<tr>
<td>Comorbidity (Charlson index, ≥3 comorbid conditions)</td>
<td>22 (16-27)</td>
<td>31 (24-38)</td>
</tr>
<tr>
<td>Previous myocardial infarction</td>
<td>19 (14-25)</td>
<td>.14</td>
</tr>
<tr>
<td>Any documented coronary disease</td>
<td>24 (18-30)</td>
<td>.08</td>
</tr>
<tr>
<td>Valve disease</td>
<td>17 (12-23)</td>
<td>.11</td>
</tr>
<tr>
<td>Cases hospitalized at index</td>
<td>56 (49-63)</td>
<td>.59</td>
</tr>
</tbody>
</table>
able, the estimated annual percent increase was 0.15% (95% CI, –0.55 to 0.85) or 3% (95% CI, –11 to 20) for 1979 to 2000 for men and 0.37% (95% CI, –0.25 to 0.98) annually or 8% (95% CI, –5 to 23) for 1979 to 2000 for women.

Patients with validated heart failure diagnosis were elderly, particularly women who were also less likely to be overweight but more likely to be hypertensive than men (TABLE 2). Men were more likely to be current or past smokers. Forty-two percent of the cases were diagnosed in the outpatient setting. Among these cases, 74% were hospitalized within 1.7 (3.1) years of the diagnosis, whereas 26% were never hospitalized.

The use of angiotensin-converting enzyme inhibitors and β-blockers at diagnosis increased significantly between the first and last time period, from 0% to 51% for angiotensin-converting enzyme inhibitors and from 10% to 30% for β-blockers (both P for trend <.001).

**Survival After Heart Failure Diagnosis**

After a follow-up of 4.2 years (range, 0-23.8 years), 3347 deaths occurred, 1930 among women, 1417 among men, 1127 among patients younger than 75 years, and 2220 among patients aged 75 years or older. Mortality rates after the onset of heart failure, adjusted for age, was higher among men, irrespective of the period (RR for men vs women, 1.33; 95% CI, 1.24-1.43, P < .001) (TABLE 3).

Mortality declined over time, with an overall improvement from 57% in 1979 to 1984 to 48% in 1996 to 2000 for the age-adjusted 5-year mortality estimates (P <.01) (FIGURE). However, there were age and sex differences in the degree of improvement in survival (P <.001 for year-by-age interaction and year-by-sex interaction) (TABLE 4). Men in their 60s experienced a 52% improvement in survival between the first and the last period. Survival also improved, although to a lesser degree, among older men. Among women, survival improved in younger ages but to a lesser extent than it did among men and did not change in older age groups.

**Framingham Heart Failure vs Clinical Heart Failure**

All analyses were repeated with the clinical diagnosis. The yield of code 428 toward clinical heart failure was 90%, whereas that of other codes used in isolation without a code 428 ranged from 14% to 36%. According to the clinical diagnosis, 4962 cases of heart failure were identified, representing a 14% increment over those identified by the Framingham criteria. This increment was constant over time (P for trend = .80). The age and sex distributions of the clinical cases were similar. Compared with patients who met Framingham criteria, those who did not were more likely to be overweight or obese and to have had a previous myocardial infarction and were less likely...
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| Table 4. Relative Risk for Death After Onset of Heart Failure Defined by the Framingham Criteria |
|----------------------------------|-----------|-----------|-----------|
|                                  | Relative Risk (95% Confidence Interval) |
|----------------------------------|-----------|-----------|-----------|-----------|
| Men                              | 1.00      | 0.84 (0.69-1.02) | 0.63 (0.50-0.80) | 0.48 (0.36-0.64) |
| 60                               | 1.00      | 0.80 (0.63-1.03) | 0.95 (0.73-1.24) | 0.67 (0.48-0.92) |
| 70                               | 1.00      | 0.91 (0.77-1.06) | 0.99 (0.83-1.18) | 0.79 (0.64-0.96) |
| 80                               | 1.00      | 1.02 (0.90-1.15) | 1.03 (0.90-1.17) | 0.94 (0.82-1.09) |
| Women                            | 1.00      | 0.80 (0.63-1.03) | 0.95 (0.73-1.24) | 0.67 (0.48-0.92) |
| 60                               | 1.00      | 0.91 (0.77-1.06) | 0.99 (0.83-1.18) | 0.79 (0.64-0.96) |
| 70                               | 1.00      | 1.02 (0.90-1.15) | 1.03 (0.90-1.17) | 0.94 (0.82-1.09) |
| 80                               | 1.00      | 0.80 (0.63-1.03) | 0.95 (0.73-1.24) | 0.67 (0.48-0.92) |

to be hospitalized at diagnosis (P<.05 for all comparisons). Although the incidence of clinical heart failure was higher than that defined by the Framingham criteria, survival was similar. The secular trends in incidence and survival were similar, irrespective of the criteria used.

Analyses replicated in 1000 samples yielded similar results.

COMMENT

In this large geographically defined community, the incidence of heart failure has remained stable during the past 2 decades in men and women. The incidence of heart failure is higher among men, and survival after its onset is worse among men. Although survival after the onset of heart failure improved over time, there were disparities in the magnitude of the improvement, which was greater among men and younger individuals.

The clinical diagnostic criteria identified slightly more cases of heart failure than the Framingham criteria, but the secular trends were similar, irrespective of the criteria, attesting to their robustness.

Information on the incidence of heart failure and how it may have changed over time is limited. Studies of hospital discharges are event based, not person based, with multiple hospitalizations for the same individuals counted so that incidence cannot be measured. Furthermore, standardized diagnostic criteria are seldom used, and case ascertainment is affected by shifts in hospital discharge diagnoses preferences.\(^3\),\(^16\),\(^17\) Patients diagnosed and treated for heart failure in the outpatient setting constitute an increasingly important component of the cases but are seldom included. Given these limitations, it should not be unexpected that published data on the incidence of heart failure lack consistency. For instance, using Medicare hospital claims in 1986 and 1993, Croft et al\(^18\) reported an increase in the initial hospitalization for heart failure. Conversely, Stewart et al\(^19\),\(^20\) suggested that trends in hospitalization in Scotland in the 1990s had “leveled off.”

Although these data are limited by the lack of validation and restriction to inpatient data, they prompt the question of whether the stabilization of heart failure hospitalization rates could be offset by increasing outpatient care patterns. Few studies included outpatient data.\(^21\)-\(^24\) The present study underscores the importance of doing so because 42% of the cases were diagnosed as outpatients, and among these, 26% were never hospitalized and thus would not have been identified by using hospital-based surveillance. Data from the Henry Ford Health system, a managed care organization,\(^25\) indicated that the prevalence of heart failure was increasing over time but did not report a secular change in the incidence of heart failure or mortality after its onset. In addition, the Framingham Heart Study recently reported a decline in the incidence of heart failure in women but not among men and an improvement in survival in both sexes.\(^26\) As acknowledged by the authors, these data could be affected by the healthy participant effect.\(^5\)

The absolute magnitude of the incidence of heart failure cannot be compared qualitatively between the 2 studies because of different age-adjustment strategies. However, the use of identical criteria and the inclusion of outpatient cases in both studies facilitate the qualitative comparison of trends. The Framingham Heart Study reported no change in the incidence of heart failure among men but found a decline in women, primarily in the earlier periods. Conversely, our study did not detect a change in either sex. Our sample size, larger than that of the Framingham Heart Study, provided power to detect a change (either increase or decrease) in the incidence of heart failure of 0.8% per year, or 18% during the 22 years of the study. Thus, although we cannot exclude smaller changes, the size of our cohort was adequate to detect changes of clinical and public health significance.

Our study supports and extends the concept brought forth by Framingham investigators that the heart failure epidemic is not related to an increase in incidence but also challenges the notion that further progress is being made in preventing heart failure in the community. Because heart failure is a disease of the elderly, the stagnation of incidence rates among an aging and growing population will increase the number of cases of heart failure and its public health burden.

Estimates of the prevalence of coronary disease in studies of heart failure vary from 68% among clinical trial enrollees\(^25\) to 36% in a population-based study, relying on physician adjudication.\(^26\) Our study reports a prevalence of coronary disease of 28% by using rigorous criteria for overt disease that are conceivably conservative. However, determining the etiology of heart failure is complex, particularly in the community, given the nonuniform use of coronary angiography and that several of the putative etiologies of heart failure, such as hypertension, diabetes, and coronary disease, may coexist. Thus, their
respective responsibility in the genesis of heart failure may be difficult to establish.

Several studies have reported on improved inhospital mortality of heart failure. However, these studies are fraught with biases related to lack of consistent criteria over time and the ensuing differences in case mix; decreasing length of hospital stay, which in turn confound trends in outcomes; and lack of inclusion of outpatient cases. These factors limit generalizability of these data to a large number of persons with heart failure.

Among studies including outpatient cases, previous data from Olmsted County reported no temporal trends in heart failure survival but were powered to detect only large trends. The Framingham Heart Study reported improvement in the survival of heart failure in both sexes. Because this improvement applies to a closed cohort, it is unclear how much of this change reflects survivor bias vs true improvement in outcome.

The present results from a larger community-based population indicated a substantial improvement in survival after heart failure in younger men, contrasting with less improvement in women and the elderly.

The hypothetical explanations for these trends are likely multifactorial. Treatment effectiveness may play a role. Trials that demonstrated the efficacy of angiotensin-converting enzyme inhibitors were published in the late 1980s. The ensuing clinical practice changes could have participated in the improved survival after the onset of heart failure noted in most recent years. Our observed increase in use of angiotensin-converting enzyme inhibitors at heart failure diagnosis would support this construct.

The improvement in heart failure survival could also be related to earlier diagnosis as the use of cardiac diagnostic procedures increases over time, resulting in lead-time bias. While this factor may play a role, it could not by itself explain contrasting sex-specific trends in survival. The mechanism of heart failure may differ by sex and could affect outcomes. A greater proportion of women with heart failure also have hypertension, suggesting that diastolic heart failure may play a greater role in women, which in turn may explain why less improvement in outcome was noted among women because there is no effective therapy for diastolic heart failure. Irrespective of these hypothetical explanations, these differences in improvement in survival according to age and sex call for additional studies to identify the reasons for these disparities.

Potential limitations of the study include the racial and ethnic composition of Olmsted County, which limits the generalizability of these data to groups underrepresented in the population. Although no single community can completely represent the nation as a whole, studies of chronic diseases in Olmsted County indicate that results from the county can be extrapolated to a large part of the population, and the characteristics of the Olmsted County population are similar to those of US whites, with the exception of slightly higher income and education. This study should, however, be replicated in other racial and ethnic groups.

Medication use in heart failure in Olmsted County has been reported to be similar to that in other settings. Providing detailed information on medications used in this cohort is beyond the scope of this article; however, we observed an increase over time in the use of β-blockers and angiotensin-converting enzyme inhibitors at diagnosis. β-Blockers were not recognized as improving survival in heart failure until the late 1990s, so the period covered by the cohort largely precedes this evidence. Furthermore, to gain relevant insight into the use of medications, data on the introduction or withdrawal of drugs during follow-up would be needed but are unavailable for this cohort. Finally, because this is an observational study, adjustment for medication use would not indicate causality.

Our study, conducted in a community-based population, has several important strengths. We used 2 sets of criteria to classify heart failure, adding clinical ascertainment to the Framingham criteria and thereby providing a robust connection with clinical practice. Second, we include outpatient data. Third, the size of our cohort confers additional power to detect effect modification and thus identify disparities such as the ones presented here. Finally, our study reports on the experience of an open cohort and thus reflects the experience of a community without the survivor bias that might affect results in a closed cohort.

CONCLUSION

This community-based cohort study demonstrates no substantial reduction in the incidence of heart failure during more than 2 decades. Moreover, women and the elderly experienced less improvement in survival after the onset of heart failure, suggesting that the apparent gains in secondary prevention have not been achieved equally. These findings highlight the increasing population burden of heart failure mediated by stagnating incidence and unequal improvement in survival within the context of an aging and growing population.

Author Contributions: Dr Roger had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Roger, Weston, Jacobsen.

Acquisition of data: Roger, Weston, Hellermann, Killian, Jacobsen.

Analysis and interpretation of data: Roger, Weston, Hellermann, Killian, Jacobsen.

Drafting of the manuscript: Roger, Killian, Jacobsen.

Critical revision of the manuscript for important intellectual content: Roger, Weston, Redfield, Hellermann, Killian, Jacobsen.

Statistical analysis: Roger, Weston, Killian, Jacobsen.

Obtained funding: Roger, Jacobsen.

Administrative, technical, or material support: Roger, Jacobsen.

Study supervision: Roger, Hellermann.

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