Changing Characteristics and Mode of Death Associated With Chronic Heart Failure Caused by Left Ventricular Systolic Dysfunction

A Study Across Therapeutic Eras

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Background—Therapies for patients with chronic heart failure caused by left ventricular systolic dysfunction have advanced substantially over recent decades. The cumulative effect of these therapies on mortality, mode of death, symptoms, and clinical characteristics has yet to be defined.

Methods and Results—This study was a comparison of 2 prospective cohort studies of outpatients with chronic heart failure caused by left ventricular systolic dysfunction performed between 1993 and 1995 (historic cohort: n = 281) and 2006 and 2009 (contemporary cohort: n = 357). In the historic cohort, 83% were prescribed angiotensin-converting enzyme inhibitors and 8.5% were prescribed β-adrenoceptor antagonists, compared with 89% and 80%, respectively, in the contemporary cohort. Mortality rates over the first year of follow-up declined from 12.5% to 7.8% between eras (P = 0.04), and sudden death contributed less to contemporary mortality (33.6% versus 12.7%; P < 0.001). New York Heart Association class declined between eras (P < 0.001). QTc dispersion across the chest leads declined from 85 ms (SD, 2) to 34 ms (SD, 1) and left ventricular end-diastolic dimensions declined from 65 mm (SD, 0.6) to 59 mm (SD, 0.5) (both P < 0.001).

Conclusions—Survival has significantly improved in patients with chronic heart failure caused by left ventricular systolic dysfunction over the past 15 years; furthermore, sudden death makes a much smaller contribution to mortality, and noncardiac mortality is a correspondingly greater contribution. This has been accompanied by an improvement in symptoms and some markers of adverse electric and structural left ventricular remodeling. (Circ Heart Fail. 2011;4:396-403.)

Key Words: chronic heart failure • mortality • morbidity

Chronic heart failure (CHF) secondary to left ventricular (LV) systolic dysfunction is a common syndrome defined by debilitating symptoms accompanied by physical signs and confirmed by objective evidence of reduced LV ejection fraction. CHF is a major cause of death and disability on a global scale. In the United States alone, 5 million people have been diagnosed with the disorder, and more than 500 000 new cases occur annually. Therapeutic approaches to treating patients with CHF have advanced substantially since the introduction of angiotensin-converting enzyme inhibitors in the late 1980s. Examining changes in

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patient characteristics and outcomes over this period of time is important if we are to affect the morbidity and mortality accompanying CHF.

Over the last 2 decades, a range of new therapies for patients with CHF and LV systolic dysfunction have been developed that target 1 or more of these abnormalities. Multiple pharmacological therapies have been shown to improve mortality in prospective, randomized, controlled trials. More recently, device-based therapies targeting electrical instability, abnormal LV activation, or both have been shown to reduce mortality rates in selected patients. Moreover, delivery of care through the use of an integrated multidisciplinary team approach has been shown to afford additional benefit to patients with CHF.

In community-based studies, the Framingham investigators showed a reduction in 1-year mortality rates between 1969 to 1999 of approximately 28%, whereas data from Olmsted County showed an increase in 5-year survival between 1979 to 2000 from 43% to 52%. In studies at a whole-country level, Jhund et al demonstrated an improvement in 1-year mortality rates in all patients hospitalized with heart failure in Scotland between 1986 and 2003. These findings were supported by hospital discharge data from Sweden examining outcomes between 1987 to 2003. These studies add significantly to our understanding of the change in natural history of heart failure at a population level. However, because they encompass all patients with CHF, around half will have preserved LV ejection fraction, and many will not be taking evidence-based medical therapies or receiving these at doses recommended by clinical trial data. Moreover, the studies from Scotland and Sweden were restricted to patients hospitalized with heart failure as opposed to outpatients. These studies are as a result unable to assess the change in phenotype of outpatients with CHF caused by LV systolic dysfunction treated with state-of-the-art therapies.

Between 1993 to 1995, and before the publication of landmark trials of β-adrenoceptor antagonists, aldosterone antagonists, angiotensin receptor blockers, and implantable devices, we performed a prospective cohort study of patients with CHF in 8 UK hospitals examining mortality rates and predictors of mortality/mode of death. Patients were characterized in detail and followed up for 5 years or until death. In 4 of these hospitals, we have now performed a similar study to validate predictors of mortality and mode of death in patients with CHF and LV systolic dysfunction treated with contemporary pharmacological and, where appropriate, device-based therapies. These 2 studies afford a unique opportunity to examine temporal trends in mortality and patient characteristics across therapeutic eras.

**Methods**

The United Kingdom Heart Failure Evaluation and Assessment of Risk Trial (UK-HEART) 1 and 2 are prospective studies carried out in the same cardiology outpatient clinics of UK general hospitals; all patients were referred by their primary care physician or a non-heart failure–specializing secondary care physician. UK HEART-1 recruited 553 consecutively attending ambulant patients with CHF between December 1993 and April 1995. UK-HEART-2 recruited 628 consecutively attending unselected ambulant patients with CHF, associated with LV ejection fraction ≤45%, between July 2006 and January 2009. The ethics committee at each institution approved the protocol, and all patients gave informed consent. In both studies, patients were eligible for inclusion if they were ambulant outpatients with stable clinical signs and symptoms of CHF present for at least 3 months. UK-HEART 1 required that symptoms be associated with objective evidence of cardiac dysfunction at rest (pulmonary venous congestion, pulmonary edema, a cardiac output ratio >0.55 on at least 1 chest radiograph, or a radionuclide or echocardiographic ejection fraction ≤45%), therefore patients with preserved LV systolic function on echocardiography were included; to facilitate heart rate variability analyses, patients with diabetes, atrial fibrillation, and renal dialysis dependence were excluded. Patients recruited to UK-HEART 2 were ambulant outpatients with stable clinical signs and symptoms of heart failure present for at least 3 months, with LV ejection fraction ≤45% on transthoracic echocardiography. After harmonizing exclusion criteria for both cohorts (LV ejection fraction ≤45%, no atrial fibrillation, no diabetes mellitus, and no renal dialysis dependence), 281 patients from UK-HEART 1 (historic cohort; 272 patients excluded from total cohort because of LV ejection fraction >45%) and 357 patients from UK-HEART 2 (contemporary cohort; 271 patients excluded from total cohort: 154 [57%] because of diabetes, 114 [42%] because of atrial fibrillation, and 3 [1%] because of dialysis dependence) were included in this analysis.

All patients underwent resting ECG and 24-hour ambulatory ECG; posterior-anterior chest radiographs were performed, and blood was drawn for measurement of urea and electrolytes, plasma creatinine, and nonfasting glucose. Clinical status was assessed using the New York Heart Association (NYHA) classification.

All patients were registered with the United Kingdom Office of Population Censuses and Surveys that provided details of death including location and date (census date: May 31, 2000, historic cohort; December 31, 2010, contemporary cohort). Classification criteria for the mode of death were defined before the study commenced. All deaths were evaluated by at least 2 senior physicians who reviewed death certificates, autopsy findings, and hospital and primary care physicians' records; when these physicians believed that insufficient information was available, the mode of death was deemed unclassifiable. Mode of death was classified as (1) sudden cardiac, if it occurred within 1 hour of a change in symptoms or during sleep or while the patient was unobserved; (2) progressive heart failure, if death occurred after a documented period of symptomatic or hemodynamic deterioration; (3) other cardiovascular death, if not occurring suddenly or in association with progression of heart failure; and (4) noncardiovascular death.

**Twelve-Lead ECG**

Standard 12-lead ECGs recorded at 25 mm/s were analyzed by 2 cardiologists (R.M.C. and A.R.) blinded to patient characteristics. QRS duration was measured manually. QT interval and QRS durations were measured manually and expressed as the maximum of measurements from all 12 leads of the ECG; QT interval was corrected for heart rate by means of the Bazett formula. Corrected QT interval dispersion, a potential marker of electric instability, was defined as the difference between maximum and minimum values across the chest leads. LV hypertrophy was assessed by means of the Sokolow-Lyon Voltage criteria (sum of the amplitude of the S wave on lead V1 and the R wave on V5 or V6 ≥3.5 mV).

**Echocardiography**

Two-dimensional echocardiography was performed according to American Society of Echocardiography recommendations. LV dimensions and ejection fractions were calculated according to recommended guidelines.

**Electrolytes and Renal Function**

A venous blood sample was taken at rest for measurements of electrolyte concentrations and assessment of renal and liver function.
Table 1. Patient Characteristics Within Historic and Contemporary Cohorts

<table>
<thead>
<tr>
<th></th>
<th>Historic Cohort (n=281)</th>
<th>Contemporary Cohort (n=357)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>62 (0.6)</td>
<td>66 (0.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male sex, % (n)</td>
<td>81 (227)</td>
<td>71 (254)</td>
<td>0.005</td>
</tr>
<tr>
<td>Ischemic etiology, % (n)</td>
<td>79 (221)</td>
<td>62 (222)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NYHA class, % (n)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>1 (3)</td>
<td>25 (91)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>II</td>
<td>51 (144)</td>
<td>43 (153)</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>46 (129)</td>
<td>29 (103)</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>2 (5)</td>
<td>3 (9)</td>
<td></td>
</tr>
<tr>
<td>Nonfasting glucose, mmol/L</td>
<td>5.0 (4.6–5.8)</td>
<td>5.2 (4.8–5.8)</td>
<td>0.29</td>
</tr>
<tr>
<td>Sodium, mmol/L</td>
<td>140 (0.2)</td>
<td>140 (0.2)</td>
<td>0.39</td>
</tr>
<tr>
<td>Potassium, mmol/L</td>
<td>4.3 (0.03)</td>
<td>4.4 (0.02)</td>
<td>0.004</td>
</tr>
<tr>
<td>eGFR, mL/kg per minute</td>
<td>58 (1.1)</td>
<td>56 (0.9)</td>
<td>0.08</td>
</tr>
<tr>
<td>Cardiothoracic ratio</td>
<td>0.54 (0.004)</td>
<td>0.55 (0.003)</td>
<td>0.13</td>
</tr>
<tr>
<td>LV end-diastolic dimension, mm</td>
<td>65 (0.6)</td>
<td>60 (0.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LV end-systolic dimension, mm</td>
<td>56 (0.6)</td>
<td>49 (0.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LV ejection fraction, %</td>
<td>30 (0.5)</td>
<td>31 (0.5)</td>
<td>0.44</td>
</tr>
<tr>
<td>QRS maximum, ms</td>
<td>138 (1.9)</td>
<td>134 (1.8)</td>
<td>0.09</td>
</tr>
<tr>
<td>QRS maximum &gt;120 ms, % (n)</td>
<td>70 (168)</td>
<td>58 (176)</td>
<td>0.003</td>
</tr>
<tr>
<td>QTc maximum, ms</td>
<td>502 (3.1)</td>
<td>471 (2.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>QTc dispersion, ms</td>
<td>82 (61–104)</td>
<td>30 (19–43)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LV hypertrophy on ECG, % (n)</td>
<td>9 (22)</td>
<td>20 (60)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

eGFR indicates estimated glomerular filtration rate. Continuous data are expressed as mean (SD); categorical data are expressed as % (n).

Statistics

Descriptive group data are given as mean with standard error of the mean, or median with interquartile ranges unless stated otherwise. Categorical data are shown as number (percentage). All statistical analyses were performed using SPSS version 13.0 (SPSS Inc, Chicago, IL) and Stata version 11.1 (Stata Corp, College Station, TX). Groups were compared with the use of the Student t test or Mann–Whitney test for continuous data and Pearson χ² for categorical data, using 2-sided tests. Survival of groups was compared with log-rank tests. Cox proportional hazards regression analysis was used to define adjusted mortality in further analyses; when included as a variable, furosemide dose was modeled by using a linear spline with a knot at 40 mg because of a nonlinear relationship with mortality over the full range of observed doses. Statistical significance was accepted at P<0.05.

Results

Patient characteristics at presentation within the historic and contemporary cohorts are provided in Table 1. Data for 2091 patient-years of follow-up are presented. Patients in the historic group were younger, more often male, and had LV ejection fraction similar to the contemporary group. There was no difference in renal function as measured by estimated glomerular filtration rate or serum sodium, though serum potassium was lower in the historic group. Drug and device treatment are shown in Table 2. Mean bisoprolol equivalent dose was 3.2 mg (0.15) in the contemporary group; equivalent data are not available for the historic cohort, although the low proportion of patients receiving β-adrenoceptor antagonists would make the resultant mean dose very low in this group. Furosemide equivalent dose, an alternative surrogate for loop diuretic dosage.

Mortality and Symptom Status

NYHA class improved between eras (Table 1: P<0.001). Mortality rates during the first year of follow-up declined from 12.5% to 7.8% between eras (P=0.026 by log-rank test; see Figure); this equates to a relative reduction of 38%. Over the entire study follow-up, age-sex–adjusted mortality risk was 40% lower in the contemporary cohort (P=0.002), and further addition of ischemic etiology to this analysis indicated a 39% reduction in mortality rate (P=0.004). To account for the possibility of lead time bias underlying these observations, a separate Cox regression multivariable analysis including furosemide dose and age as covariates was performed. This indicated a 32% reduction (P=0.029) in all-cause mortality between therapeutic eras; this observation persisted when furosemide dose was replaced with NYHA class.

Mode of death changed significantly between eras (P<0.001), with broadly similar proportions of progressive heart failure deaths but a reduction in sudden death and concomitant increase in the contribution of noncardiovascular death in the contemporary group (Table 3). Cox proportional hazards analysis revealed that age-sex–adjusted mortality...
caused by progressive heart failure and sudden death fell by 52% \((P=0.006)\) and 78% \((P<0.001)\), respectively. To account for changes in heart failure etiology and ventricular remodeling, ischemic etiology and LV end-diastolic dimension were added to the age-sex–adjusted analysis; death caused by progressive heart failure did not fall significantly, whereas sudden death fell by 77% \((P<0.001)\). All adjusted analyses are outlined in Table 4.

Separate analyses were performed after the exclusion of patients with implantable cardioverter-defibrillators \((n=57)\) to assess whether this therapeutic modality underlies our observations (Table 3 and Figure). All-cause mortality at 2 years fell from 21.4% to 14.7%, representing a 31% relative risk reduction \((P=0.04)\); this persisted after age-sex adjustment (37%; \(P=0.007)\), though further addition of \(\beta\)-blocker therapy to this analysis resulted in a nonsignificant mortality reduction between eras (29%; \(P=0.14)\). Age-sex–adjusted sudden cardiac death fell by a relative 85% \((P<0.001)\), and the addition of \(\beta\)-blocker therapy to this analysis resulted in a 69% reduction in sudden death between eras \((P=0.047)\). Separate analyses excluding cardiac resynchronization therapy (CRT) recipients but not implantable cardioverter-defibrillator recipients revealed similar relative magnitudes of crude and age-sex–adjusted all-cause mortality reduction (data not presented).

### ECG Data

ECG data are shown in Table 1. The historic cohort exhibited longer maximum QTc interval, with greater dispersion of QTc across the chest leads. Maximum QRS width was similar between groups, though QRS width >120 ms was more common in the historic group. ECG LV hypertrophy was more common in the contemporary group.

### Echocardiographic Data

Echocardiographic data are shown in Table 1. Although ejection fraction remained similar, LV dimensions were reduced significantly between study eras.

### Discussion

The present study describes a number of important findings: (1) In outpatients, patients with stable CHF caused by LV systolic dysfunction, mortality, and symptom status have improved significantly between 1995 and 2009; (2) sudden cardiac death has become much less common, with a concomitant rise in noncardiovascular death, as a proportion of overall mortality; and (3) in keeping with an improvement in
mortality, measurements of cardiac remodeling and electric instability have also improved substantially.

**Mortality and Symptoms**

We have demonstrated in well-matched patients with CHF caused by LV systolic dysfunction, referred by the same routes to be treated in the same hospitals, that annual unadjusted mortality rate has improved by 38%, and NYHA class, a measurement of symptom status, has also improved significantly. Moreover, sudden death made a much smaller contribution to contemporary mortality, whereas noncardiovascular death has increased. Thus, it appears that “optimal” therapy may have had a major impact on outcomes and symptom status in patients with CHF caused by LV systolic dysfunction. In particular, it is likely that the advances in pharmacotherapy (especially β-blockers and aldosterone antagonists), device provision, and advancing models of care involving more frequent patient contact and improved patient education have contributed to reducing adverse outcomes.

Our data set adds to recently published population-based studies, which have also demonstrated an improvement in mortality in patients with CHF per se.

Our unique data set compares 2 well-matched samples of patients from the same geographic region, across therapeutic eras. These data demonstrate a significant improvement in crude and adjusted mortality rates and symptomatic status. Equally important is the secular decline in the contribution of sudden death to overall mortality—a phenomenon that, to the authors’ knowledge, has not been studied in prior observational studies. The reasons for this are unclear, although it is tempting to speculate that incremental advances in CHF therapy have made a major contribution. Data from the pivotal MERIT-HF and CIBIS-II studies of β-blocker therapy in heart failure demonstrate an approximate 40% reduction in sudden death. The dramatic rise in β-blocker use between our historic and contemporary cohorts may therefore offer some explanation for the observed reduction in sudden death, and this is supported by our multivariate analyses after exclusion of patients receiving device therapy. A similar magnitude of sudden death reduction has been noted with the addition of aldosterone receptor antagonists; the significant increase in prescription of these agents between our study eras may again make some contribution to the declining rates of sudden death. With regard to device therapy, the COMPANION study, albeit in a population with more severe CHF than our own (in which progressive heart failure death would be expected to predominate), indicated that contemporary medical therapy in isolation was associated with a 23% contribution of sudden death, versus 16% in the cohort additionally treated with CRT-D. However, this study demonstrated no reduction in sudden death in patients treated with CRT-P over a mean 15.7 months of follow-up. Perhaps more in keeping with the longer-term follow-up of our study, the CARE-HF study demonstrated that CRT-P was associated with a 53% reduction in sudden death over 36 months of follow-up.

It is also interesting that the observed reduction in sudden death remains pronounced even after accounting for changes in heart failure etiology and ventricular dilatation, whereas progressive heart failure death reduction became much less marked. This suggests that other phenomena may also contribute to the reduction in sudden death. As outlined next, the detailed characterization of the phenotype of our cohorts also affords us the opportunity to place our observed improvements in outcome in the context of concomitant changes in cardiac structure and function.

**Electric Instability**

It is well established that the principal mechanisms/modes of death in patients with CHF and LV systolic dysfunction are a sudden arrhythmic event or a progressive decline in LV function. In the present analysis, we have demonstrated that across therapeutic eras, patients with CHF caused by LV systolic dysfunction have evidence of a significant improvement in a number of markers of electric instability. More importantly, the relative contribution of sudden death to overall mortality has fallen dramatically.

It is likely that the major electric feature necessary for the development of sustained ventricular tachyarrhythmia, and thus sudden death, is electric inhomogeneity. Because the QRS complex represents ventricular depolarization, increased QRS duration on the 12-lead ECG may be a marker

**Table 4. Adjusted Mortality Analyses**

<table>
<thead>
<tr>
<th>Adjustment Variables</th>
<th>Outcome Measure</th>
<th>Hazard Ratio, Contemporary Versus Historic (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, sex</td>
<td>All-cause mortality</td>
<td>0.60 (0.43–0.83)</td>
<td>0.002</td>
</tr>
<tr>
<td>Age, NYHA class</td>
<td>All-cause mortality</td>
<td>0.63 (0.45–0.89)</td>
<td>0.009</td>
</tr>
<tr>
<td>Age, furosemide dose</td>
<td>All-cause mortality</td>
<td>0.68 (0.49–0.96)</td>
<td>0.029</td>
</tr>
<tr>
<td>Age, sex, ischemic etiology, LV end-diastolic dimension, furosemide dose, QRS width &gt;120 ms, corrected QT interval, eGFR</td>
<td>All-cause mortality</td>
<td>0.73 (0.48–1.11)</td>
<td>0.135</td>
</tr>
<tr>
<td>Age, sex, ischemic etiology, LV end-diastolic dimension</td>
<td>Sudden death</td>
<td>0.23 (0.10–0.53)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age, sex, ischemic etiology, LV end-diastolic dimension</td>
<td>Progressive heart failure death</td>
<td>0.67 (0.39–1.16)</td>
<td>0.15</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; eGFR, estimated glomerular filtration rate.
of inhomogeneity of depolarization, creating an environment that substantially increases the likelihood of initiating tachyarrhythmia. A link between inhomogeneous electric depolarization and arrhythmic death in heart failure caused by LV systolic dysfunction has been suggested.\textsuperscript{30,31} The present data set demonstrates a significant reduction in prolonged QRS duration (>120 ms) and QTc dispersion, consistent with a favorable effect on electric remodeling and increased electric stability of the failing left ventricle.

Increasing QRS width is associated with advancing age and worsening LV function,\textsuperscript{32} whereas CRT would be expected to reduce QRS width; wider QRS intervals are also associated with slower repolarization, in the form of increasing corrected QT interval, and increased dispersion of the QT interval.\textsuperscript{33,34} Furthermore, dispersion of the QT interval in reduced by angiotensin-converting enzyme inhibitors, β-blockers, and potassium-sparing diuretics.\textsuperscript{35–37} Clearly, the factors that influence ECG measures of electric instability are complex and interrelated, and so it is not possible to suggest a causal, as opposed to associated, link with falling sudden death.

LV Remodeling
Natural history studies have shown that CHF caused by LV systolic dysfunction is characterized by a deleterious change in LV size, shape, and function,\textsuperscript{38} a process also known as LV remodeling. LV remodeling is directly related to future deterioration in LV performance and a less favorable clinical course.\textsuperscript{38–40} We have shown that similar patients, when compared across therapeutic eras, have significantly different LV internal dimensions.

Study Limitations and Strengths
Our study has a number of potential limitations that should be highlighted. First, data were collected for each patient at a single visit, so we are only able to comment on the change in variables (eg, LV remodeling) between cohorts rather than within cohorts over time. Second, we only studied patients with evidence of LV systolic dysfunction, so our data set does not apply to the large number of patients with the heart failure syndrome associated with preserved LV ejection fraction. Third, because all patients were seen in hospital, outpatients we are unable to apply these findings to patients treated solely in the primary care setting. Fourth, we cannot exclude some contribution to our findings of earlier detection of cardiac failure in the contemporary cohort (perhaps because of increased awareness of the importance of CHF), or lead-time bias,\textsuperscript{41} given improving access to specialist heart failure services. However, the population studied with established symptomatic CHF referred to hospital outpatients, as opposed to covert LV dysfunction, reduces the likelihood of this influencing our findings. Furthermore, by adjusting for changes in age and furosemide dose (as a marker of disease progression), we have attempted to minimize the impact of lead time bias to our conclusions. Fifth, the exclusion criteria applied to standardize the heart failure populations (no diabetes or atrial fibrillation) recruited within the historic and contemporary cohorts reduce the relevance of our observations to some subgroups of patients with heart failure. Indeed, our cohorts are younger and more represented by men than those presented in some community epidemiological studies.\textsuperscript{42} This may also reflect referral of some older patients with heart failure to geriatricians, as opposed to cardiologists. Equally, changes in clinical practice resulting in lower thresholds for hospital admission between eras could underlie our finding of decreased sudden death, though we do not have data to assess this. Finally, our study observations are based on relatively small cohorts of patients, though detailed analysis of subjects becomes much more challenging in large observational studies. The duration of follow-up is also greater in our historic cohort, and therefore we cannot account for the possibility of long-term “catch-up” in the mortality of the contemporary group.

Despite these limitations, our study has a number of important strengths. First, we used 2 cohorts of patients recruited from the same geographic region and hospitals. Second, patients were characterized in detail, and the second cohort was studied after the publication and establishment into usual care of all currently used drug and device–based therapies. Third, studies of large populations do not reflect the effect of delivery of optimal treatment strategies because it is well established that many patients with CHF do not receive evidence-based therapies, and, if they do, these therapies are often delivered at suboptimal doses.

Conclusions
This cohort-based study of ambulant patients with CHF and LV systolic dysfunction spanning therapeutic eras demonstrates a significant and important improvement in mortality of patients with CHF. It is important to note that the reduction in total mortality rate is accompanied by a substantial reduction in the proportion of sudden cardiac deaths and corresponding increase in noncardiovascular deaths, a fact that has major implications for prognosis and therapies to improve this. This improvement in mortality rate has been accompanied by an improvement in symptoms and measurements of some of the key pathophysiological features of the heart failure syndrome phenotype. Despite this improvement in patient outcomes, the prognosis of patients with CHF and LV systolic dysfunction remains poor, and so the development of new therapeutic avenues, along with strategies to deliver these effectively, remains a priority for this growing group of patients.

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References


Evidence-based therapy for chronic heart failure has advanced significantly over the past 15 years, with the widespread adoption of β-adrenoreceptor antagonists, aldosterone antagonists, and device therapy in selected patient groups, along with models of care involving heart failure specialist teams. The real-world impact of these strategies on symptoms, mortality rates, and mode of death is, however, unclear. Our investigation, comparing 2 observational cohort studies spanning this period, reveals that mortality rate has indeed fallen significantly, with a concomitant alteration in the mode of death—a dramatic reduction in the proportion of sudden deaths and corresponding increase in noncardiovascular mortality. These observations are accompanied by beneficial alterations in the symptomatic status, indices of cardiac dilatation/function, and electrophysiological parameters of patients. It is likely that the observed improvements in outcome relate to a combination of altering phenotype of heart failure at first presentation and improvement in chronic heart failure therapeutic strategies. These trends suggest the continuing need to revise the prognosis and targets for heart failure care as our therapies improve.
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