POINT OF VIEW

Is the Prognosis of Heart Failure Improving?

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Few conditions in medicine have a prognosis as bleak as chronic heart failure (1,2), but recent developments have engendered hope that matters may be improving. There is now a greater understanding of the wide range of physiologic abnormalities associated with heart failure (3,4) facilitating the development of effective pharmacologic therapies as well as innovative surgical and device-related treatments (5–8). Over 20,000 patients with heart failure have been randomized in clinical trials of angiotensin-converting enzyme (ACE) inhibitors and beta-adrenergic blockers alone, the combination of which has halved the annual mortality of the patients in these trials (9). However, patients are carefully selected for inclusion into trials and represent only a small subset of all patients with heart failure. Therefore, it is unwise to simply assume or to hope that treatments shown to improve prognosis in the context of a clinical trial also do so in the heart failure population at large. Evidence should be sought that the benefits observed in clinical trials also translate into a benefit for the wider patient population.

A number of epidemiologic studies and analyses provide clues as to whether the prognosis of heart failure has improved. There was no evidence of an age-adjusted difference in prognosis in the Framingham study for patients with heart failure diagnosed in the periods 1948 to 1974 and 1975 to 1988, with five-year mortality rates of 75% and 62% for men and women, respectively (1). The Olmsted county study, which used Framingham clinical criteria for a case definition of heart failure, retrospectively investigated the natural history of two cohorts of incident heart failure (10). One hundred and seven patients were followed up for 1,061 days and 147 patients for 1,233 days (median periods) in the 1981 and 1991 incident heart failure cohorts, respectively. No significant difference in survival was seen between the two cohorts either before or after adjustment of age, gender and New York Heart Association class; one-year mortality was 28% and 23% in the 1981 and 1991 cohorts, respectively. Similarly, Spencer et al. (11) identified no improvement in one-year survival between 1975 and 1995 in Worcester, Massachusetts, in a retrospective analysis of first-time heart failure complicating acute myocardial infarction, a large subset of the incident heart failure population (12). Recently, Cowie et al. (13) in the United Kingdom used clinical criteria and objective evidence of cardiac dysfunction by echocardiography to identify new cases of heart failure from a local population of 151,000. They identified 220 new cases of heart failure over a 20-month period in 1995 to 1996. The 6- and 12-month mortality was 30% and 38%, respectively (2), remarkably similar to the Framingham data set extending back to 1948 (Fig. 1). Some of the lack of evidence for an improvement in the diagnosis of heart failure may reflect differing case definitions of heart failure and changes in the demographics of the population studied, factors that may confound the assessments' temporal changes (13–16). However, in summary, the cumulative evidence from epidemiologic studies suggests, in contrast with the results of clinical trials, that there has been no improvement in the prognosis of heart failure over the last 40 years.

There are many explanations for the apparent discrepancy between clinical trials, demonstrating the effectiveness of new treatments for heart failure, and the epidemiologic evidence. Many patients with heart failure and left ventricular systolic dysfunction are not taking ACE inhibitors (17–19). Only 40% of the population were taking them in the Olmsted 1991 cohort, and the most recent incident cases of heart failure reported in the Framingham study occurred before the era of widespread ACE inhibitor use. Patients in clinical trials are a highly selected group (20). Only patients with chronic, stable heart failure are recruited. These patients are “natural survivors” of the first 90 days following the diagnosis of heart failure, a period associated with a very high attrition rate (2,20), partly explaining the relatively low mortality rates in both active and placebo groups in clinical trials (6,7). Also, the mean age of patients with heart failure in the community is roughly a decade greater (21,22), and there is a much higher proportion of women than is observed in clinical trials (23). Whereas most trials have recruited patients with left ventricular systolic dysfunction, up to 50% of patients with heart failure in the community have preserved systolic function (24–26), and it is not clear that ACE inhibitors or beta-blockers are effective for these patients. Studies are only now getting underway that will address some of these treatments in patients with heart failure with preserved systolic function (25,27). Angiotensin-converting enzyme inhibitors may have only a modest effect in prolonging mean survival (23), perhaps only four to six months (28), making it difficult to detect changes in the population, although clinical trials generally under-
estimate the true benefit of effective treatments, by employing intention-to-treat analyses in which crossovers dilute treatment benefits. Also, over the 40 years of observation in the Framingham study, improvement in the treatment of hypertension could have shifted the incident heart failure population to a higher risk one, as coronary artery disease replaced hypertension as the leading etiology for heart failure (29). Finally, the above studies are probably too small to detect a difference in prognosis when one assumes any change, if present, to have been small.

Recently an attempt was made to address some of these issues (30). Using a national database, all patients with a first-time hospitalization for heart failure admitted to Scottish hospitals in the years 1984, 1988 and 1992 were identified. International Classification of Disease (ICD)-9 coding was used as the case definition for heart failure. The dates were selected as they corresponded to the time window in which the CONSENSUS study (late 1987) (5) and the SOLVD-treatment study (late 1991) (6) were published revealing mortality and morbidity benefits with ACE inhibitors in heart failure. There was evidence of increasing use of ACE inhibitors during this period (31). The cohorts identified in this way, including over 30,000 patients, approximate to an incident population since the available evidence suggests that 70% to 80% (13,26) of first diagnosis of heart failure in the United Kingdom occurs in hospital. The cohorts also appear representative of the broad spectrum of heart failure in the community when compared with more formal epidemiologic studies (22). The cohorts were then tracked, each for a period of three years, using a nationally linked database, during which time almost 20,000 of the patients died.

Comparing the 1984 to 1987 to the 1992 to 1995 follow-up periods, the absolute reduction in three-year mortality was 12% (relative risk reduction, 23%) in patients <65 years (53% to 41%, from 1984 to 1992, p < 0.001), while the absolute reduction in three year mortality in patients >65 years was 5% (relative risk reduction, 7%), a small but still statistically significant effect (71% to 66%, p < 0.0001). There was also an improvement for the combined end points of death or heart failure hospitalization in both of the above cohorts but not for death or hospitalization for any cause. These results persisted after controlling for differences such as age, gender, etiology and comorbidities among the three cohorts.

Further prospective series, in a community setting, will be required to confirm the findings of this first, tantalizing piece of evidence of an improvement in the prognosis of heart failure. Failure to implement known effective treatments may be the major factor limiting the translation of benefits in clinical trials to the community setting (32). Hopefully, larger effects will be seen with the introduction of beta-blockers and possibly spironolactone to the therapeutic armamentarium. In the future, widespread acceptance of new treatments may require clinical trials to replicate clinical reality and not exclude high risk groups, although this strategy also has its hazards, as it may be difficult to alter prognosis in very elderly patients.

Perhaps the biggest lesson to be learned from these analyses is that the onset of heart failure should be delayed.

Figure 1. Survival following the diagnosis of heart failure.
as long as possible by application of effective measures for primary and secondary prevention. This may include screening for asymptomatic left ventricular systolic dysfunction with new cost-effective techniques, although such a strategy awaits conclusive supporting evidence (33,34). However, because of the aging of the population, it is unlikely that any single strategy will counter the projected rise in the incidence and prevalence of heart failure. Furthermore, as new treatments improve prognosis, the prevalence of heart failure will increase. Heart failure is a "medical hydra" with no easy solution, and it remains one of the major challenges to physicians in the new millennium (35). More research is required, and new strategies for the delivery of care need to be explored if we hope to arrest the inexorable progression of this malignant condition.

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