Witness to Progress
Lynne Warner Stevenson, MD, FAHA; Reena Pande, MD

Clinicians caring for patients with heart failure appreciate that their patients are surviving longer in this century. This has been shown for patients discharged after heart failure hospitalization in Scotland and Sweden, for the Framingham community, and for outpatients with reduced ejection fraction in Olmsted County. The current UK-HEART study by Cubbon and colleagues, published in this issue of Circulation: Heart Failure, provides convincing evidence of improved outcomes, particularly for reduced sudden death, after outpatient referral for predominantly New York Heart Association class II heart failure (mean ejection fraction, 0.30), showing a 38% decrease in 1-year mortality rate from 12.5% to 7.8%. Although increasing awareness of the diagnosis may trigger earlier referral, patients from the 2 eras evaluated here appear similar in terms of objective disease severity. The average ejection fraction is similar, and a lower loop diuretic dose in the recent cohort is rendered more potent by the broader use of aldosterone antagonists. The major progress in therapy in this population of mild-moderate heart failure was an almost 10-fold increase in the use of β-blockers. When evaluating absolute survival, it should be noted that both cohorts excluded atrial fibrillation and diabetes, which affect approximately one-third of patients with heart failure and are generally associated with higher mortality rates.

Why the Decrease of Sudden Death Without Devices?

The decreased mortality rate in the recent UK-HEART cohort is most apparent in the deaths considered as sudden, which accounted for 34% of the mortality rate in the early era and only 13% in the recent experience. The risk for sudden death in the new era was reduced by 80% compared with the previous era. Once declared in the early 1990s as the next frontier for heart failure, sudden death and the proportion of deaths occurring suddenly have been steadily diminishing in this population, largely the result of the success of medical therapy for heart failure.

The trials of neurohormonal antagonists have shown consistent and additive decreases in sudden death, most strikingly the β-blocker trials (Figure). Unlike the remarkable universality of benefit with angiotensin-system inhibition and β-blockade, the population impact of aldosterone antagonists has not been evident, perhaps because of the counterweight of hyperkalemia risk in patients with impaired potassium handling. The population impact of aldosterone antagonists may become more positive with expanding use after recent evidence supporting extension to patients with moderate heart failure.

The marked reduction of sudden death in UK-HEART occurred despite the very limited use of ICDs and was clearly seen as well in the group that did not receive devices. With such a low rate of sudden cardiac death in this community population, it is not clear to what degree there could have been additional additive benefits from ICDs, which have been shown in trials of patients who are younger and have fewer comorbidities than the general heart failure population. With the increasing proportion of noncardiac deaths, it is not clear how many lives would have been prolonged in patients with preserved quality of life and function.

To Modify Disease as Well as Mortality

The decrease in sudden death seen with widespread implementation of recommended therapies probably reflects not only direct suppression of potentially lethal arrhythmias but also modification of the underlying myocardial substrate that gives rise to them. The absolute rate of death attributed to hemodynamic failure also declined. Disease modification is reflected in the decrease in ventricular remodeling in the current report and the previous experience in our class III–IV
patients described above, with smaller left ventricular dimensions at the time of referral than before 2000, despite longer duration of disease and very low ejection fraction.

The penetrance of neurohormonal antagonist therapy early in the course of disease has also diminished the contribution of chronic vasoconstriction to the hemodynamic profile of decompensation. Patients hospitalized with advanced heart failure in the ESCAPE trial had an average systemic vascular resistance of 1500 dyne·s·cm⁻², compared with 1800 dyne·s·cm⁻² in the Hy-C trial from 1992, tailoring oral vasodilators after nitroprusside, long before angiotensin-converting enzyme inhibitors (ACEIs) and β-blockers were routinely used before referral. (The major benefit for ACEIs compared with hydralazine in that trial resulted from a decrease in sudden death.)

Cardiac resynchronization has decreased ventricular dilatation and improved heart failure survival by virtually the same extent with and without an ICD, suggesting that interruption of primary tachyarrhythmias is not necessarily required for prolonged survival when function improves. Earlier use of disease-modifying therapies may be expected to further enhance the quality and length of the journey, as suggested by the recent trials of cardiac resynchronization and aldosterone antagonists in class II heart failure.

### Different Travelers, Different Journeys

The classic trials of ACE inhibition and β-blockers retain their relevance for patients with new or newly recognized heart failure in the present. Compared with these early trials, what has been described as “the patient journey” now proceeds in different directions when taken with neurohormonal antagonism from the time of diagnosis. For example, the absolute decrease of mortality with ACEI in the SOLVD trial over 12 years was 5.6% when started in asymptomatic patients, more than 5 times the 1% decrease in the treatment trial, although the latter was initially deemed the positive trial.

In the current era, we face an entirely new population of patients whose ejection fraction has improved to above 40%. This heart failure—better—ejection fraction group accounted for approximately one-third of the population followed in a contemporary heart failure referral clinic. What is the future of these patients, and is it different, depending on whether the improvement resulted from drug or device therapy? Is the disease actually reversed? If not, how should it be monitored, and are there unique therapies to reinforce stability? From a practical standpoint, what are the implications for employment and insurance?

The population with stable and recurrent symptomatic heart failure with persistently low ejection fraction is steadily growing as the result of decreased acute mortality from infarction, decreased sudden death, and delayed disease progression. After benefits realized from discharge planning and early follow-up after hospitalization have leveled off, the next focus may be empowerment of the patients at home to manage their volume status, much as gluoses are managed by patients with diabetes. What new therapies will add benefit to this management?

For refractory heart failure, selection and timing for cardiac transplantation with prognostic scores has declined to an academic exercise because almost all ultimate recipients have deteriorated to wait in hospital or on mechanical circulatory devices. Similar selection criteria may eventually be transferred to mechanical circulatory devices for lifetime support, except that right ventricular dysfunction will replace pulmonary hypertension as a central focus for assessment of reversibility and eligibility. Improving outcomes will widen the option for support in patients who are “less sick,” with a greater emphasis on expected benefits in functional capacity and quality of life.

For most patients with heart failure, however, neither transplantation nor mechanical circulatory devices are in-

---

**Table. Changing Outlook After 2000 for Patients Referred With New York Heart Association Class III–IV Symptoms**

<table>
<thead>
<tr>
<th>Mean Values</th>
<th>1997 to 1998</th>
<th>2002 to 2003</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>56</td>
<td>57</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>54%</td>
<td>42%</td>
</tr>
<tr>
<td>Percent of total referral population</td>
<td>44%</td>
<td>40%</td>
</tr>
<tr>
<td>Median years known HF</td>
<td>1</td>
<td>3*</td>
</tr>
<tr>
<td>LV ejection fraction, %</td>
<td>21</td>
<td>19*</td>
</tr>
<tr>
<td>LV diastolic dimension</td>
<td>67</td>
<td>63*</td>
</tr>
<tr>
<td>QRS duration &gt;130 ms</td>
<td>51%</td>
<td>57%</td>
</tr>
</tbody>
</table>

Therapy before referral

| ACEI/ARB | 79% | 75% |
| β-blocker | 27% | 65%* |
| Diuretics | 91% | 82% |
| Spironolactone | 0% | 15% |
| Digoxin | 72% | 51%* |
| ICD | 11% | 30%* |
| Heart rate, bpm | 89 | 82* |
| Systolic blood pressure, mm Hg | 108 | 108 |
| Serum sodium, mEq/L | 137 | 137 |
| Creatinine, mg/dL | 1.5 | 1.5 |
| Peak VO₂, mL/kg per min | 13 | 11* |
| Patients receiving assist devices | 4.8% | 2.3% |
| 1-Year survival without death or urgent transplant | 66% | 82%* |

HF indicate heart failure; LV, left ventricular; ACEI, angiotensin-converting enzyme inhibitor; ARB, adrenergic receptor binder; and ICD, implantable cardioverter-defibrillator.

*From Reference 6.

---

**Figure.** Relative reduction in the risk of sudden death shown in trials of medical therapies for heart failure, each added to the previous for a cumulative effect. Reduction in sudden death observed with combined therapy in a general heart failure population in the UK-HEART study is shown for comparison. Figure design is modified with permission from a lecture by JoAnn Lindenfeld. Presented at Heart Rhythm Society Annual Scientific Meeting, San Francisco, CA, May 5, 2011.
cluded in their itinerary. Trials and the referral center experiences, including this one, have centered on populations with mean age in the low 60s, but even heart failure with low ejection fraction is now dominated by patients in their 70s and 80s. A rufel measure of success with heart failure may be that almost half of admissions and deaths for these patients are now due to other causes. Devices to prevent sudden cardiac death are a lesser priority in the community heart failure population, for whom only 14% of all mortality is attributed to cardiac causes occurring out of the hospital and only 6% to cardiac causes in patients living independently at home. Even without ICDs, however, the burden of distressing heart failure symptoms faced by patients and families during the last stage seems longer now than in previous eras when more deaths occurred suddenly. Although the trends for hospice therapy for end-stage cardiac disease are positive, there are twice as many emergency visits and intensive care unit stays at the end of life with heart failure than with cancer.

We have been privileged to witness the progress of therapy for heart failure, incorporating medications and devices from landmark trials, lessons on relief of congestion, and principles of nurse-guided disease management. The UK-HEART study strengthens evidence of this progress but also projects the different journeys now taken by patients with heart failure. Although we can see behind us to where this field began, every patient still takes only one forward journey, realizing not the fates that were averted but only those yet to be faced. For heart failure and low ejection fraction, the journey with good quality of life has been meaningfully extended past the exits from premature sudden death. Heart failure, like many forms of cancer, has been transformed from an imminently lethal disease to a slowly progressive condition. Unfortunately, the last stage of the journey will also be prolonged, imposing a heavier burden of limitation and suffering onto patients and families. This challenging stage will require ongoing integration of multiple aspects of care, patient priorities, and shared decisions that were rarely anticipated in the past.

The next impact on the patient journey is likely to reflect the unintended consequences of well-intended responses to national health care crises in each of our countries. The tidal wave to standardize and grade care may overrun the scientific mission to distinguish patterns of difference and the ethical mandate for personalized medicine. In our journeys, we will be recruited to serve as both witnesses and instruments for the next changes, not all of which will represent progress.

Disclosures
None.

References
Witness to Progress
Lynne Warner Stevenson and Reena Pande

Circ Heart Fail. 2011;4:390-392
doi: 10.1161/CIRCHEARTFAILURE.111.963066
Circulation: Heart Failure is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2011 American Heart Association, Inc. All rights reserved.
Print ISSN: 1941-3289. Online ISSN: 1941-3297

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circheartfailure.ahajournals.org/content/4/4/390

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation: Heart Failure can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation: Heart Failure is online at:
http://circheartfailure.ahajournals.org//subscriptions/