Progress in Heart Failure Management?
Lessons from the Real World

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In recent years, we have learned a great deal about the pathophysiology of heart failure, and we have demonstrated a significant potential for improved clinical outcomes with medical treatments. However, it is important to continually gauge the impact that this incremental knowledge has had on health outcomes in the real world, within populations beyond those enrolled in clinical trials. The study by MacIntyre et al., which examines 66,547 consecutive patients with first-time admissions for heart failure in Scotland, provides an important new look at the population of patients with this condition. It offers an opportunity to grade our accomplishments and to identify new approaches required to improve outcomes further.

For their analysis, MacIntyre et al. used an imperfect, yet unique and valuable national database. Databases derived from clinical trials or registries have the advantage of tracking the onset of heart failure across the population. However, such databases have tended to yield far fewer cases of heart failure than those tracked by MacIntyre et al.

The Scottish National Health Service database has 2 major limitations. First, it lacks extensive clinical information, which would help characterize the population and help eliminate patients in whom the diagnosis was erroneous. Second, it includes only those patients hospitalized for heart failure and tracks outcomes from the time of initial hospitalization. These factors must be considered in comparing outcomes with those in other populations, including clinical trials. Nevertheless, this database, which covers every hospitalization across an entire country, is powerful in its size and completeness, and the findings provide several unique and important insights.

The populations enrolled in the heart failure trials with the greatest impact on present treatment (Table) have sharp contrasts with the characteristics of the population observed by MacIntyre et al. Clinical trials have largely been conducted in white, male populations with mean ages of ≈60 years. Although the racial characteristics of the MacIntyre study reflect those of Scotland, the findings of an older and more sex-balanced population are likely typical of the heart failure populations within most developed countries. Although partly driven by ejection fraction enrollment criteria, disparities between clinical trial populations and those of the “real world” also reflect the nature of patients presenting themselves to clinical trial sites.

These disparities leave us in a quandary. There exists some physiological rationale to anticipate differences in responses to such agents as angiotensin-converting enzyme (ACE) inhibitors and β-blockers across ages, sexes, and races. However, the data derived from the trials of these agents are insufficient to either prove or disprove such differences. The results of these trials provide less than convincing evidence for the benefit of ACE inhibitors in the elderly, in blacks, and in women; yet they also leave most observers with an appropriate concern that it would be unethical to perform additional placebo-controlled trials of ACE inhibitors in such populations.

The importance of studying older patients is highlighted by the marked influence of age on clinical outcomes. As age increased from <55 to >84 years, 1-year case fatality rates increased from 24.2% to 58.1%. Several factors may contribute to this finding in the elderly, including (1) variation in underlying pathophysiology, (2) high prevalence of comorbidities, (3) medication underutilization, and (4) reduced responsiveness or tolerance to treatments. Beyond uncertain-
ties in drug efficacy in the elderly, clinical trials have taught us little about optimal dosing for this group of patients, in whom metabolism and clearance rates are often diminished, tolerability may be reduced, and drug-drug interactions are common. We are in desperate need of more aggressive investigation focusing on this patient population.

Two exceptions illustrate the feasibility of molding trial populations to more closely match the overall heart failure population. The Evaluation of Losartan in the Elderly (ELITE) trials achieved average ages of 74 and 71 years, respectively. Although a more representative age range does not assure that the trial’s results can be generalized to every age segment, it makes subset analyses more credibly applicable to the elderly. If clinical trials are to represent a legitimate vehicle toward improving public health, then the representation of the populations at large.

Previous investigations have provided conflicting observations regarding the relative prognosis for women and men with heart failure. The study by MacIntyre et al provides novel insight into possible explanations for this discrepancy, because it contains a large enough cohort of younger women to demonstrate a complex interaction between sex, age, and prognosis. The 30-day mortality was lower for older women (≥65 years) and higher for younger women compared with their male counterparts. This finding may reflect a bimodal etiological distribution among women, with a high incidence of hypertensive, hypertrophic disease in older women and a preponderance of either premature coronary disease, with multiple coronary risks, or dilated cardiomyopathy in younger women.

This finding reinforces the diverse nature of heart failure and emphasizes the need for improved sophistication of patient characterization within observational studies and clinical trials. Furthermore, we need to move beyond our rudimentary, descriptive understanding of sex differences in cardiovascular outcomes by developing imaginative designs for physiological studies and prospective trials to develop a more precise understanding of the mechanisms behind these differences.

The mortality rates observed by MacIntyre et al are startlingly higher than those seen in most recent clinical trials, in which 1-year placebo-group mortality has ranged from 11% to 13% (Table). A number of factors are likely to contribute to these differences. The overall heart failure population is older and has a higher comorbidity rate than populations in clinical trials. Furthermore, an index hospitalization is not a typical entry criterion for long-term trials, and this requirement within the Scottish database selected a population with a worse short-term prognosis. Nevertheless, within the population at large, the effectiveness of medical management is probably lower than that within patients managed by clinical trial investigators. The poorer prognosis observed by MacIntyre et al may partly reflect the diminished efficacy of “proven” treatments in one or more population segments.

Beyond potential differences in drug efficacy, proven treatments are underused. The most optimistic data suggest that ACE inhibitors are prescribed to only 55% of Medicare patients discharged with heart failure (73% among patients considered ideal candidates). An analysis of Medicare data from 10 large US states shows disturbing evidence for a downward trend in ACE inhibitor prescription for patients with increasing age, decreasing from 58.9% among patients 65 to 74 years to 49.6% among patients 85 years (77.9% to 67.0% among ideal candidates). Lower utilization rates for such drugs contribute to a worse prognosis across the broad population compared with the idealized clinical trial setting.

### Patient Characteristics and Control Group Mortality in Selected Heart Failure Trials With the Greatest Impact on Current Treatment: Comparison With Findings of MacIntyre et al

<table>
<thead>
<tr>
<th>Study</th>
<th>Drug</th>
<th>Class*</th>
<th>n</th>
<th>Mean Age, y</th>
<th>% Men</th>
<th>1-Year Mortality†</th>
</tr>
</thead>
<tbody>
<tr>
<td>CONSENSUS§</td>
<td>Enalapril</td>
<td>IV</td>
<td>253</td>
<td>71</td>
<td>71</td>
<td>52%</td>
</tr>
<tr>
<td>SOLVD T</td>
<td>Enalapril</td>
<td>I–III</td>
<td>2569</td>
<td>61</td>
<td>80</td>
<td>15.5%</td>
</tr>
<tr>
<td>V-HeFT II§</td>
<td>Enalapril</td>
<td>II, III</td>
<td>804</td>
<td>61</td>
<td>100</td>
<td>13%‡</td>
</tr>
<tr>
<td>SOLVD P</td>
<td>Enalapril</td>
<td>I, II</td>
<td>4228</td>
<td>59</td>
<td>89</td>
<td>5.1%</td>
</tr>
<tr>
<td>Carvedilol US</td>
<td>Carvedilol</td>
<td>II, III</td>
<td>1094</td>
<td>58</td>
<td>77</td>
<td>11%</td>
</tr>
<tr>
<td>DIG</td>
<td>Digoxin</td>
<td>I–III</td>
<td>6800</td>
<td>63</td>
<td>78</td>
<td>12.5%</td>
</tr>
<tr>
<td>CIBIS 2</td>
<td>Bisoprolol</td>
<td>III, IV</td>
<td>2647</td>
<td>61</td>
<td>81</td>
<td>13.2%</td>
</tr>
<tr>
<td>MERIT-HF §</td>
<td>Metoprolol</td>
<td>II–IV</td>
<td>3991</td>
<td>64</td>
<td>77</td>
<td>11.0%</td>
</tr>
<tr>
<td>RALES</td>
<td>Spironolactone</td>
<td>III,§ IV</td>
<td>1663</td>
<td>65</td>
<td>73</td>
<td>25.3%</td>
</tr>
</tbody>
</table>

| Totals and weighted averages | | | 24 049 | 62 | 81 | |

| MacIntyre et al | 66 547 | 75 | 47 | 44.5% |

*New York Heart Association class for most patients.
†In control group.
‡Control group.
§Required class IV symptoms within 6 months of randomization.

CONSENSUS indicates Cooperative North Scandinavian Enalapril Survival Study; SOLVD, Studies of Left Ventricular Dysfunction; T, treatment trial; P, prevention trial; V-HeFT II, Vasodilator Heart Failure Trial II; DIG, Digitalis Investigation Group study; CIBIS, Cardiac Insufficiency Bisoprolol Study; MERIT-HF, Metoprolol controlled-release Randomized Intervention Trial in Heart Failure; and RALES, Randomized Aldactone Evaluation Study.
Despite the independent nature of physicians, we must develop and accept processes to guarantee patients uniform utilization of drugs and procedures that are known to improve outcomes in a cost-effective manner.

The good news is that prognosis seems to be improving. Between 1986 and 1995, median survival increased from 1.23 to 1.64 years. Factors other than treatment advances may have contributed to this improvement, including an evolving etiological spectrum of heart failure and changing thresholds for hospital admission. However, similar trends were not seen in 2 previously reported databases, in which the reporting periods ended before the publication of the Studies of Left Ventricular Dysfunction (SOLVD) trial. The observed improvement in survival probably reflects, at least in part, the impact of ACE inhibitors.

There is a concerning trend toward less improvement in women (17% reduction in 30-day case fatality rate) compared with men (26% reduction). This finding further emphasizes the need to extend investigations of the basis for sex differences and to include a greater proportion of women in clinical trials.

The study by MacIntyre et al suggests progress. We see the best evidence to date that improved heart failure treatment has resulted in improved outcomes. However, there is much more to do. Heart failure represents a growing epidemic in the elderly. Over 10 years of observation, MacIntyre et al found increases in the median age of patients admitted with heart failure from 76.0 to 79.0 years in women and from 70.7 to 73.0 years in men. As the median age in society rises, we will face a growing population of elderly heart failure patients for whom we will have no recourse but to offer management based on outcome trials performed predominantly in middle-aged, white men. We can do better. We can more aggressively pursue the physiological bases for potential sex, race, and age differences. We can design clinical trials out of need rather than expediency. And we can implement healthcare processes that deliver cost-effective treatments in a more uniform manner. The findings of MacIntyre et al represent important additions to our fund of knowledge regarding the epidemiology of heart failure. They also help identify deficiencies in our investigational and clinical practices, which we will need to correct if we are to maximally improve outcomes within this growing patient population.

References


KEY WORDS: Editorials, heart failure, trials, survival, mortality
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