Global Differences in the Outcome of Heart Failure
Implications for Clinical Practice*

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The diagnosis, management, and treatment of heart failure in clinical practice is guided by evidence accrued from high-quality clinical trials, cohort studies, epidemiological studies, observational data, and a consensus of clinical experience. Recommendations are proffered in many guidelines from the continents of the world (1–5). Patients benefit from adherence to guidelines (6,7) and appropriate treatment. The expectation would be that medical practice would be similar, or almost so, in all parts of the world. Any differences, which exist not only in heart failure, but also in many other cardiovascular disorders (8–10), would be accounted for by simple clinical variables. If that were so, and it is not (11,12), then outcomes measured as mortality, morbidity, use of procedures, or hospitalization would be universally similar, and measurement of those outcomes would provide an indicator of performance, which would have validity within regions of a particular country, between countries, and between continents. What nirvana that would be for providers of health care. But the reality is otherwise.

For many years, researchers in the field of heart failure have sought to identify which patient characteristics predict prognosis, using data from registries, patient cohorts, and large clinical trials. An obvious example of the clinical use of such an approach is the selection of patients for heart transplantation. A further ambition has been to identify subgroups of patients who might respond more favorably to a particular treatment or management strategy. The findings from such analyses depend critically on what baseline variables have been included and on the known limitations of subgroup analysis (13,14). A common procedure is to include in a multivariate analysis only those variables that had a positive association in a univariate analysis. That may miss the possibility that some combination of more easily obtainable characteristics would have at least as good a predictive value as a single but expensive or complex characteristic. Any variable that correlates with New York Heart Association functional class or the severity of heart failure is likely to predict outcome. It is almost a tautology. Heart failure is a progressive disease so that the presence of heart failure predicts worsening heart failure, which, in turn, predicts advanced heart failure and death. The major criteria predicting outcome can usefully be grouped into measures of heart structure (heart size or ejection fraction in those with enlarged hearts, systolic heart failure), measures of cardiovascular performance (such as maximal exercise capacity or the 6-min walk test), and measures of the body response (the simplest are renal function and the plasma sodium) (15). Adjustments are often made for a large number of variables in an attempt to remove any variance in the response to an intervention that might be attributable to small differences in the baseline characteristics. A major characteristic, ejection fraction, is often misassessed in this type of analysis because the database may have only included patients with large hearts (low ejection fraction, systolic heart failure), excluding patients with normal-sized hearts (heart failure with a small heart, often referred to as diastolic heart failure). A second key characteristic where differences may arise is gender (16), and that is not just problematic in heart failure, since in several recent trials of intervention in cardiovascular medicine, the response in women has been unexpected (17). A third and vital characteristic is geography. Geography becomes important because it reflects race, ethnicity, social circumstances, health resources, and cultural attitudes; such variables impact on health delivery and thus outcomes. In many analyses, patients are included who come from different continents across the globe (18).

Geographical variability is examined in the paper by Blair et al. (19) in this issue of the Journal. The paper reports the results of the EVEREST (Efficacy of Vasopressin Antagonism in Heart Failure: Outcome Study with Tolvaptan) trial, which tested the idea that short-term treatment with a vasopressin antagonist, tolvaptan, would be useful in the treatment of patients admitted to the hospital with worsening heart failure. At 7 days, or discharge from the hospital if earlier, there was no difference in patient-assessed global clinical status but there was a greater reduction in body weight. At a mean follow-up of 9.9 months, no beneficial effects were observed, the 2 primary end points being all-cause mortality and the composite of cardiovascular death or hospitalization for heart failure. Large clinical trials of this sort require the enrollment of many centers (359

*Editorials published in the Journal of the American College of Cardiology reflect the views of the authors and do not necessarily represent the views of JACC or the American College of Cardiology.

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sites, 1,251, 699, 5,641, and 619 patients, respectively, in North America, South America, Western Europe, and Eastern Europe in the EVEREST trial. The baseline characteristics and treatment showed more uniformity and adherence to guidelines than in earlier similar studies (20). A surprising finding in view of the lack of evidence is the small but much greater use of positive inotropic drugs in North America. The authors adjusted for baseline characteristics. Before adjustment, mortality was similar in the Americas and Western Europe but markedly less in Eastern Europe (numerically younger, higher ejection fraction, lower serum creatinine, lower median B-type natriuretic peptide, less intervention, and more atrial fibrillation). After adjustment, only South America stood out as having a high mortality. The impact on change in global status at day 7 or discharge was not different in the regions of the world. Although statistically the p value for interaction was 0.02, the slightly lower loss of weight in patients from South America may have limited clinical meaning.

Adjustments were made for race, which has been implicated in some studies in patients with heart failure (21–24) but not others (25–28). Race should not be confused with ethnicity; race is largely related to genetics, whereas ethnicity includes social and cultural differences. As people move between continents, race will not change, but ethnicity may be altered even in unanticipated directions.

The type of analysis used in this paper has limitations that are critical to the interpretation of the data. The dangers of subgrouping and the issue of generalizability need emphasis (13,14,29). Adjustment is made only for characteristics that are well understood and can easily be measured. Other characteristics influence observed differences in outcomes between continents and are far more subtle and difficult to measure. These include medical attitudes of physicians, which could determine previous care; differences in the approach to diagnosis and etiology; availability of resources; health policies (30); and social and cultural circumstances. Considerable variation exists across continents in access to medical care, the reasons for hospital admission, prevention strategies, equity in the delivery care, financing of medical care, drug availability, and procedural outcomes. What is evident from this report is that some of these factors, and the specific factors are not identified, may have a substantial impact. A consequence is that comparing outcomes across continents almost certainly does not answer the question as to whether care is of an equal standard between continents. Worse, the same problem arises among countries in the same continent. This has been demonstrated in the U.S. (31), Canada (32), and Europe (33). Within a country and between hospitals, only where economic, social, and cultural differences are minimal can conventional outcomes be compared and used for the purposes of assessing performance.

There are 3 important implications of this work. The first is that researchers designing large clinical trials need to take account of differences in outcomes between continents; these may influence the power calculation and the definitions used for particular outcomes. Second, if the result of a trial is to be applied globally, experience from centers in several continents is advisable. Health authorities and drug regulators may be uncertain about approving drug usage in one continent when the trial has been largely conducted in another (34). Third, and of the greatest importance, there is a need to study the social origins of heart failure and the impact of systems for health delivery. This will require more careful description of end points other than mortality, such as hospitalization and measures relating to quality of life and the determinants of health delivery. Establishing and validating uniform standards across the world, so that clinical outcomes in many cardiovascular entities including heart failure can meaningfully be compared, may take many years. The challenge is daunting but necessary; the idea is old but the need is timely.

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Key Words: heart failure • regional differences • outcomes.