The Globalization of Heart Failure Research

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“The world is flat.”
—Thomas L. Friedman (1)

As the demand to have clinically meaningful endpoints in heart failure trials has become greater and the quality and standards of care have improved, the necessary sample size requirements have also increased. Heart failure trials have therefore evolved into “mega trials” requiring an increasingly large number of patients, which necessitates global enrollment. The globalization of clinical trials has resulted in numerous advantages but several challenges, with the ultimate goal of improving cardiovascular human health. The globalization of trials has allowed a harmonization of best practices and definitions, standardization of analytical techniques, and monitoring, and conformity in interpretation of results. However, the diversity in geography has the potential to influence outcomes through differences in practice patterns, standards of care, etiologies of disease, comorbidities, health care systems, and genetics. These challenges all may contribute to variations in outcomes across the globe by geography (2).

Over the past several decades, there have been important clinical trials that have demonstrated differences in clinical outcomes by continent or geographic region. Whether these differences can be attributed to the geography itself, the delivery of care, background therapy, phenotypes, genetics, environmental interactions, statistical chance, or unknown factors is unclear. However, as we plan clinical trials going forward, we have to take into account the demographics of the potential enrollees so that the underlying foundation of the clinical trial is not jeopardized. New therapies, such as LCZ696 and ivabradine, will be utilized at different rates across the globe, which may influence outcomes in future trials (3,4). Methods need to be put in place to monitor disease severity, practice patterns, and the uptake of new therapies. Clinical trials that enroll large numbers of patients in countries such as Eastern Europe or Russia may find that the length of stay for their hospitalized heart failure patients is longer and that readmission rates at 30 days are lower while having a similar mortality rate. These factors may directly influence the event rates, the choice of primary or secondary endpoint, and the weighted distribution of enrollment from these particular regions of the world. Other factors, such as the use of inotropes, vasodilators, and other therapies, vary broadly across the globe and can potentially interact with the intervention and influence outcomes. Thus, there is a need to attempt to standardize background therapy and to develop manuals of operations that suggest what ideal clinical care should be and which therapies to avoid.

In addition, patients enrolled in the United States are represented by a high percentage of African-Americans who have unique etiologies of heart failure, different background standard therapy (i.e., hydralazine, isosorbide dinitrate), different rates of adherence to evidence-based medicines, and even differences in genetics. Variations in the alpha-2C adrenergic receptor (alpha-2C del 322–325) have been associated with differential responses to therapy, and the frequency of the loss of function variant is approximately 10-fold higher in African-Americans (5).

Although global clinical trials are necessary to achieve enrollment goals within a reasonable timeframe, a vision and foresight to plan appropriately for the diversity of outcomes is also required. Some of these considerations are:

1. The planning process should include the approximate percentage of recruitment by various continents, regions, and countries.
2. The expected variation event rates by region of the world should be considered.
3. The expected variation in baseline demographics should be incorporated into the planning process.
4. A detailed manual of operations should be standardized as much as possible for delivery of health care.

5. Surveillance of patient demographics, practice patterns, and aggregate event rates over time should occur.

In summary, as we highlight the importance of global research in this issue of JACC: Heart Failure, we also want to pay attention to how research is conducted across the globe and where and what the advantages and challenges are to this process.

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**REFERENCES**


