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**EDITORIAL**

# Geographic variation in heart failure trials: time for scepticism?

**Bertram Pitt[1,*] and Mihai Gheorghiade[2]**

[1]University of Michigan School of Medicine, Ann Arbor, MI, USA; and [2]Center of Cardiac Innovation, Northwestern Feinberg School of Medicine, Chicago, IL, USA

**This editorial refers to 'International differences in clinical characteristics, management, and outcomes in acute heart failure patients: better short-term outcomes in patients enrolled in Eastern Europe and Russia in the PROTECT trial,' by R.J. Mentz *et al.*, published in this issue on pages 614–624.**

Randomized trials that affect regulatory approval, guideline, and third party payer considerations in patients with cardiovascular disease have increasingly required a relatively large number of patients and reliance upon geographic locations around the world. The reasons for inclusion of geographic locations around the world in these large-scale studies varies but, in general, these are related to speed of recruitment and costs. Centres in several parts of the world such as Eastern Europe have a relatively lower cost per site and a record of relatively rapid recruitment. The wide geographic and ethnic spectrum of patients in these large-scale trials has important advantages beyond ease of recruitment and costs, including worldwide applicability of results and impact upon global health. There are, however, disadvantages, including increased patient heterogeneity and the number of sites, often with a low number of patients per site.[1–3] These disadvantages are of particular concern in designing and interpreting trials in patients with heart failure (HF). Trials of new strategies in patients with myocardial infarction, atrial fibrillation, and hypertension, for example, have commonly accepted definitions for inclusion and for endpoint adjudication while the definition of HF hospitalization, an inclusion criteria and a component of the primary endpoint in many large HF trials, is more problematic. It is often difficult on clinical grounds to be sure that patients with chronic HF have worsening heart failure that requires hospitalization. Various definitions, such as the need for intravenous therapy and an overnight stay have been used to define 'hospitalization for HF'. Changing health-care practices in many areas provide a challenge to this definition in that, increasingly, patients with worsening signs or symptoms of HF may receive intravenous diuretics in an infusion unit or outpatient setting without an overnight stay in a hospital. There have been several studies of geographic variation in large-scale HF trials that have pointed out some of the difficulties in assuming that the overall results of a trial apply equally to all of the geographic areas included.[1,4–6]

Mentz *et al.*[7] have analysed data from the PROTECT trial in which 2033 patients with acute HF and renal dysfunction hospitalized at 173 sites in 17 countries were randomized to rolofylline or placebo in an attempt to explore the implications of geographic distribution. They noted significant geographic differences in baseline characteristics, HF phenotype, in-hospital diuretic and vasodilator strategies, and length of stay. Following multivariable adjustment, region was an independent predictor of the risk of mortality/hospitalization at 60 days, with a then lowest risk in Russia vs. Western Europe (HR 0.39) because of lower re-hospitalization, but little difference in long-term mortality. They comment on the clinical implications of these findings and emphasize that after risk adjustment re-hospitalization rather than mortality was the driving factor for geographic differences in composite outcomes and note that these findings are consistent with previous studies showing a poor correlation between re-hospitalization and mortality.[1,4–6]

While the geographic variations noted by Mentz *et al.*[7] and others[1,4–6] in patients with HF clearly influence the rate of re-hospitalizations, they may also influence mortality. For example, in the Everest trial that enrolled 4,133 patients hospitalized with worsening chronic HF and a reduced ejection fraction the mortality was 30% in North America compared with 20% in Eastern Europe.[1] In the recent TOPCAT trial[8] evaluating the role of spironolactone in 3,445 patients with HF with preserved ejection fraction (HFpEF) the placebo cardiovascular mortality rates in patients from Russia and the Republic of Georgia were several-fold less than in those patients recruited from the Americas (Canada, USA, Brazil, and Argentina). Patients could be included into TOPCAT either on the basis of a previous hospitalization, a major component of which was HF or signs and or symptoms of HF with an elevated BNP or *N*-terminal pro-BNP. The vast majority of patients randomized from Russia and the Republic of Georgia were included on the basis of a previous history of hospitalization for HF. The non-specific definition of HF, as alluded to above, may have resulted in many patients with shortness of breath or dyspnoea owing to obesity, chronic obstructive pulmonary disease (COPD), or other factors being classified as having a hospitalization for HF. While the explanation for the significant difference in mortality between patients randomized from Russia and the Republic of Georgia compared with the Americas remains uncertain, this difference

*Corresponding author: University of Michigan Medical Center, Alfred Taubman Health Care Center, 1500 East Medical Center Drive, Ann Arbor, MI, 48109–0366. Tel: +1 734 9365260; Fax: +1 734 9365256; Email: bpitt@umich.edu

makes interpretation of the overall results, which failed to show a significant benefit of spironolactone on the primary endpoint (which included the combination of cardiovascular mortality, resuscitated cardiac arrest, and re-hospitalization for HF) difficult to interpret. This was because in approximately half of the patients recruited from the Americas, who had a placebo event rate comparable to previous studies of patients with HFpEF, there was a significant reduction in the primary endpoint, whereas in Russia and the Republic of Georgia, where the placebo event rate was comparable to patients with a risk factor such as hypertension without evidence of HF, it would be difficult to detect a beneficial effect on the primary endpoint given the overall sample size and the number of patients recruited from these countries.

The issues raised by Mentz *et al.*[7] and TOPCAT[8] pose a problem for regulators, guideline committees, third party payers, and individual clinicians in deciding whether or not the results of a large-scale multinational trial applies to the patients they are responsible for. Ideally, one would design and carry out these large-scale pivotal trials in geographic areas with similar practice patterns and baseline cardiovascular risk and/or have a sufficient number of patients from a geographic region to reach a meaningful conclusion as to the effectiveness and safety of a given strategy in that region. However, in view of the need for large numbers of patients it is, likely that we will continue to face the dilemma posed by geographic variation. The differences noted by Mentz *et al.*[7] are however just the tip of the iceberg in that there are many other factors that have not been adequately addressed in these analyses, including genetic background, dietary preferences, lifestyle, social support, mental status, and wellbeing, that may influence the effect of a strategy on clinical outcomes. For example, an ethnic group or individuals from a particular geographic area may consume a diet higher in sodium than in another area, such that an agent that reduces salt intake or increases sodium excretion could be effective in the first group of patients while potentially harmful in the other group with a lower sodium intake. There may be no easy solution to the applicability of the results of large-scale multinational trials to patients in the USA, Central Europe, or any other geographic area when geographic differences are detected. We should, however, make a greater effort to understand the potential baseline differences and practice patterns in individual geographic regions before undertaking a large-scale international trial. A pre-trial registry simulating the execution of the trial but without intervention may identify characteristics of the patient population that can be site- or region-specific.[9] Only after examining pre-trial registry data should sites be selected. This will allow us to understand not only the potential of a site to enrol patients but will also ensure some homogeneity of the patient population. There should also be clear and objective definitions of the inclusion criteria and if a history of HF is one of the criteria for inclusion, as it often is, there should be objective means of verifying that the patients symptoms are caused by HF, for example by requiring evidence of an elevated BNP or NT pro-BNP level. While not a perfect guide to the presence of worsening HF in a patient with chronic HF, biomarkers such as BNP provide at least an easily verifiable and objective means that should be applicable across all geographic regions. For example, in Everest the medium BNP was 1031 pg/mL in North America compared with 536 pg/mL in Eastern Europe.[1] When unexpected geographic differences appear, as they frequently do, these should prompt a thorough analysis of potential factors that could account for the differences. The sample size of the trial may not allow statistical validity comparing the results of one region with another. However, when differences are detected and the majority of patients and or events are obtained from regions where there has been particularly rapid recruitment, and/or have a different pattern of health-care delivery, one should be reassured that the placebo event rates between regions are similar. Adjustment of baseline factors and propensity matching may help in reassuring us as to the applicability of the results across geographic regions but owing to the many potential differences in ethnicity, life style, and health-care delivery between regions it would be prudent to maintain a high degree of scepticism before adopting or rejecting any new strategy if large geographic differences are detected but not explained.

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