Regional Differences in Heart Failure With Preserved Ejection Fraction Trials
When Nephrology Meets Cardiology but East Does Not Meet West

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In heart failure (HF) with reduced ejection fraction (HF-REF), renin-angiotensin-aldosterone system (RAAS) inhibitors are the Level 1A evidence-based cornerstones of pharmacological treatment. As a result of trial-based progress in medical therapy in the last 2 decades, mortality associated with HF-REF has declined almost 3-fold. In sharp contrast, HF with preserved ejection fraction (HF-P EF) is still lacking evidence-based therapies.1-2 Indeed, the 3 major outcome trials performed in HF-P EF with RAAS inhibitors did not meet their primary end points.2-4 A post hoc analysis of the latest trial, TOPCAT (Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist), identified an unusually large difference (≈4-fold) in the placebo group primary event rate of patients randomized from Russia and Georgia (Russia/Georgia) compared with those enrolled from the United States, Argentina, Brazil, and Canada (ie, the Americas).5

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

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may be considered in this context as possible pharmacological markers of the effects of RAAS inhibitors. The weakness or lack of such effects with spironolactone in TOPCAT patients from Russia/Georgia is challenging. The evidence provided by patients from the Americas in TOPCAT, although driven by post hoc data, suggests that the MRA could be acting similarly in HF-REF and in HF-PEF populations. In this setting, as rightly stated by the authors, in the absence of stronger data, TOPCAT results may be informative to physicians currently faced with clinical decisions for patients with HF-PEF with anticipated risks similar to those in patients enrolled from the Americas. Moreover, a second chance should be provided for MRAs (either generic or new-generation MRAs) to compete against placebo in future and, we hope, definitive HF-PEF trials.

However, a more objective and therefore rigorous selection process is eagerly warranted to select homogenous target HF-PEF populations more prone to benefit from any tested therapy. Indeed, patients from Eastern Europe displayed strikingly different baseline features, kidney behavior, and clinical outcomes, the last even in the placebo group. Patients from Russia/Georgia were selected mainly (89%) on the basis of the inclusion criteria of a previous HF hospitalization. They displayed an unexpectedly low event rate, close to that observed in the general population of these countries, thereby bringing into question whether they were truly suffering from HF-PEF.

The sizeable subgroup from Russia/Georgia (half of the TOPCAT population), with event rates much lower than anticipated, characteristics dissimilar from the expected HF-PEF typical clinical profile, and a weaker-than-expected pharmacological response (blood pressure, kidney, and potassium) to spironolactone, has most likely diluted the effect size in the trial. Interestingly, in this same issue of Circulation, Kristensen et al., motivated by the TOPCAT results, explored geographical differences and analyzed event rates of patients enrolled in both the Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity (CHARM)-Preserved3 and the Irbesartan in Heart Failure With Preserved Systolic Function (I-PRESERVE)4 trials, the 2 other large trials in HF-PEF that included patients from both Europe and North America. The authors equally performed a similar comparative analysis of 3 major trials in HF-REF: the CHARM-Alternative and CHARM-Added trials and the Controlled Rosuvastatin Multinational Trial in HF (CORONA) trial. The rates of the composite of cardiovascular death or HF hospitalization in the United States/Canada in CHARM-Preserved (10.9 per 100 patient-years) and I-PRESERVE4 the 2 other large trials in HF-PEF that included patients from both Europe and North America. The authors equally performed a similar comparative analysis of 3 major trials in HF-REF: the CHARM-Alternative and CHARM-Added trials and the Controlled Rosuvastatin Multinational Trial in HF (CORONA) trial. The rates of the composite of cardiovascular death or HF hospitalization in the United States/Canada in CHARM-Preserved (10.9 per 100 patient-years) and I-PRESERVE (10.3 per 100 patient-years) were similar to that of the primary composite outcome reported in the Americas in TOPCAT (12.6 per 100 patient-years). The rates of cardiovascular death or HF hospitalization in Eastern Europe/Russia (4.4 and 6.1 per 100 patient-years in CHARM-Preserved and I-PRESERVE, respectively), however, were not

Figure. Serum potassium (mmol/L) and creatinine (mg/dL) kinetics between treatment groups in EMPHASIS-HF (Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure) heart failure with reduced ejection fraction (HF-REF; A) vs TOPCAT (Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist) heart failure with preserved ejection fraction (HF-PEF; B) patients. A, Adapted from Rossignol et al.6a. B, Reprinted from Pfeffer et al7 with permission of the publisher. Copyright ©2014, the American Heart Association, Inc.
as low as that of the primary outcome in TOPCAT in Georgia/ 
Russia (2.3 per 100 patient-years), although they still were 
much lower than observed in the United States and Canada. 
Geographical differences were greater for HF-PEF than for 
HF-REF and higher for HF hospitalization than for mortality. 
The difference in HF hospitalization rates between the 
United States/Canada and Eastern Europe/Russia persisted 
after adjustment for key baseline prognostic variables, which 
importantly differed by geographical region in HF-PEF.13

The main issue is: Why? Why, despite uniform inclusion 
and exclusion criteria, are there striking differences in patient 
populations across 2 distinct regions such as those reported 
in these major trials? Indeed, these discrepancies are much 
greater by far than the inevitable expected variations within 
multinational, randomized, clinical trials related to variations 
in healthcare systems and practices.12 Despite a well-designed 
trial, the TOPCAT data are challenging to interpret because of 
this striking regional heterogeneity in the trial. It is alarming 
that these variations may have clouded a possible true clinical 
and wide-reaching benefit of spironolactone, a generic and 
inexpensive drug available worldwide, in a severe medical 
condition desperately lacking evidence-based effective ther-
apy. The TOPCAT, I-PRESERVE, and CHARM-preserved 
experience could challenge the whole concept of globaliza-
tion of clinical trials in HF-PEF unless undisputable objective 
diagnosis criteria ascertaining more homogeneity are used. 
Indeed, Eastern Europe versus Western Europe/US vari-
tions in HF trials have been reported sufficiently frequently 
over the last few years that some guidance in this area should 
be warranted. Undoubtedly, HF-PEF is a difficult diagnosis 
regardless of geography. Currently, the diagnosis of HF-PEF 
bas largely on signs or symptoms of HF, normal or mildly abnor-
mal left ventricular ejection fraction, and evidence of diastolic 
left ventricular dysfunction,13 the last unfortunately lacking in 
TOPCAT inclusion criteria (Table). Natriuretic peptides (brain 
natriuretic peptide [BNP] and N-terminal pro-BNP) corre-
late with symptomatic left ventricular diastolic dysfunction. 
Although the blood levels of these biomarkers can vary with 
age, sex, body weight, and several comorbidities, they are a 
very important addition to the enrollment criteria and should 
be considered more systematically in HF trials and more so 
in HF-PEF trials. Importantly, Kristensen et al11 noticed that 
when adjusted for baseline N-terminal pro-BNP concentra-
tion in I-PRESERVE, the geographical difference in HF hos-
pitalization rates was eliminated, whereas in the TOPCAT 
trial overall population, in the BNP stratum, spironolactone 
showed a major benefit (hazard ratio, 0.65; 95% confidence 
interval, 0.49–0.87; \( P=0.003 \)), but unfortunately a minority 
(11%, versus 45% in Americas) of the Russia/Georgia par-
ticipants were selected on this objective basis. Thus, with the 
acknowledgment that elevated BNP or NT pro-BNP values are 
not standalone evidence for symptomatic left ventricular dia-
stolic dysfunction and that additional echocardiography tests 
are required to confirm the diagnosis,13 future trials in HF-PEF, 
we hope including a second-chance MRA trial, should 
consider a combined assessment of these parameters, ideally by 
central laboratories to minimize the influence of regional dif-
ferences in HF-PEF patient diagnosis and management.

| Criteria for Diagnosing HF-PEF in the TOPCAT Trial (Adapted from Pitt et al10) |
|-------------------------------|------------------|----------------------|
| Heart failure as defined below. One symptom must be present at the time of screening and 1 sign must be present in the last 12 mo. Symptoms (at least 1 must be present at the time of screening): paroxysmal nocturnal dyspnea, orthopnea, or dyspnea on mild or moderate exertion. Signs (at least 1 in the last 12 mo): any rales after cough, jugular venous pressure \( \geq 10 \) \( \text{cm} \) \( \text{H}_2\text{O} \), lower-extremity edema, or chest x-ray demonstrating pleural effusion, pulmonary congestion, or cardiomegaly. |

BNP indicates brain natriuretic peptide; HF-PEF, heart failure with preserved ejection fraction; and TOPCAT, Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist. 

In contrast, history of HF hospitalization, although frequently used to enrich event rates in HF trials, is obviously a very weak and possibly confounding criterion when used as the main cri-
terion to ascertain the disease such as in TOPCAT in patients 
enrolled with no natriuretic peptide criteria. The threshold for 
admitting patients for HF varies so much in different geographical 
areas that history of HF admission, especially when not 
adjudicated (which is the most common practical option), is mis-
leading and should no longer be used in HF-PEF trials with no 
other strong criteria such as natriuretic peptides. The value of this 
criterion, even as a simple criterion to enrich event rate, is also 
challenged. The clinical meaningfulness and prognostic value of 
the history of HF admission criterion are obviously not met in 
Russia/Georgia in TOPCAT and in other HF trials. Possible geo-
ographical differences in medical practice may be one explanation. 
In the future, one should also carefully reassess trial practices 
across different regions, and procedures to monitor more care-
fully baseline characteristics and event rates during the conduct 
of trials should be in place with the aim of avoiding such unfortu-
nate outcomes and missed opportunities as in TOPCAT.

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References


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