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-PFEF) is still lacking evidence-based treatments. Indeed, the 3 major outcome trials performed in HF-PFEF with RAAS inhibitors did not meet their primary end points. 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).

In an effort to better understand this regional heterogeneity, in this issue of Circulation, Pfeffer et al performed a comprehensive assessment of clinically relevant variables that may have led to such striking regional discrepancies in terms of patient response to spironolactone. Beyond the inherent limitations of any post hoc analysis, the present data provide major insights into the TOPCAT results that may help change practice in HF-PFEF, given the lack of other available therapy in this syndrome. Within each region, the randomized treatment groups were well balanced, whereas between these regions, for almost every variable, baseline characteristics were distinctly different. Over and above the differences in baseline features, the magnitude of changes in blood pressure, kidney function, and potassium kinetics in patients receiving spironolactone was strikingly different across the different geographical areas, being strikingly less pronounced in patients from Russia/Georgia. In the Americas, these changes were more in line with that previously observed in patients with HF-REF and mild symptoms treated with the mineralocorticoid receptor antagonist (MRA) eplerenone compared with placebo with regard to potassium and creatinine kinetics (Figure). Such obvious differences between East and West despite proper multiple adjustments for baseline features known to influence kidney response (eg, age, diabetes mellitus, kidney function, other RAAS inhibitor use) may suggest that the populations from the 2 geographies were strikingly different from a pathophysiological point of view. Patients from the Americas displayed a heart-kidney interaction pattern very similar to that observed in HF-REF patients, whereas patients from Russia/Georgia exhibited a minor blood pressure, kidney, and potassium response to the pharmacological inhibition of the mineralocorticoid receptor. Interestingly, in a large recent meta-analysis of 57 HF trials and registries (1076104 HF patients, 34% of patients with HF-PFEF in 27 studies), chronic kidney disease was frequent (32% of patients with HF) and was associated with a higher mortality rate, even more so in HF-PFEF compared with HF-REF patients. Together, the findings in patients from the Americas enrolled in TOPCAT substantiate the concept that there could be a true pathophysiological continuum from HF-PFEF to HF-REF involving cardio renal interactions and response profiles similar to RAAS inhibition therapy, with increased rates of worsening renal function and hyperkalemia in patients from the Americas treated with MRA, albeit with better clinical outcomes. Similarly, although a serum potassium level >5 mmol/L has been shown to be associated with an increase in cardiovascular deaths in patients with HF-REF without or with chronic kidney disease, trials have shown that patients with HF-REF receiving an angiotensin-converting enzyme inhibitor, an angiotensin receptor antagonist, or an MRA (spironolactone or eplerenone) have better clinical outcomes despite experiencing more frequent episodes of hyperkalemia and or worsening renal function shortly after RAAS inhibitor initiation or thereafter. In HEAAL (Heart Failure End Point Evaluation of Angiotensin II Antagonist Losartan) and EMPHASIS-HF (Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure), high-dose losartan or eplerenone was associated with more frequent worsening renal function and hyperkalemia than low-dose losartan or placebo, respectively. However, this did not influence the mortality benefit of high-dose losartan or eplerenone. In some way, creatinine and potassium changes...
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.11 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-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
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.11

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 therapy. The TOPCAT, I-PRESERVE, and CHARM-preserved experiences could challenge the whole concept of globalization of clinical trials in HF-PEF unless undisputable objective diagnosis criteria ascertaining more homogeneity are used. Indeed, Eastern Europe versus Western Europe/US variations 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 is based on signs or symptoms of HF, normal or mildly abnormal 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) correlate 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 al13 noticed that when adjusted for baseline N-terminal pro-BNP concentration in I-PRESERVE, the geographical difference in HF hospitalization 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),3 but unfortunately, a minority (11%, versus 45% in Americas) of the Russia/Georgia participants 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 diastolic 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 differences in HF-PEF patient diagnosis and management.

Table. Criteria for Diagnosing HF-PEF in the TOPCAT Trial
(Adapted from Pitt et al3)

| 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 ≥10 cm H 2O, lower-extremity edema, or chest x-ray demonstrating pleural effusion, pulmonary congestion, or cardiomegaly. |
| Left ventricular ejection fraction (ideally obtained by echocardiography, although radionuclide ventriculography and angiography are acceptable) ≥45% (per local reading). The ejection fraction must have been obtained within 6 mo before randomization and after any myocardial infarction or other event that would affect the ejection fraction. |
| At least 1 hospital admission in the last 12 mo for which heart failure was a major component of the hospitalization (transient heart failure in the context of myocardial infarction does not qualify) or BNP in the last 30 d ≥100 pg/mL or N-terminal pro-BNP ≥360 pg/mL and not explained by another disease entity. |

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 criterion 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 misleading 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 geographical 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 carefully baseline characteristics and event rates during the conduct of trials should be in place with the aim of avoiding such unfortunate outcomes and missed opportunities as in TOPCAT.

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References


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