Lessons from the TOPCAT Trial

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Some patients with the clinical syndrome of heart failure have a normal or near-normal left ventricular ejection fraction. To date, no treatment has been shown to improve outcomes in this condition, usually designated heart failure with a preserved ejection fraction. The care of such patients can be difficult and is typically limited to efforts to relieve symptoms.

Mineralocorticoid-receptor antagonists such as spironolactone are highly efficacious in patients with heart failure and a reduced ejection fraction. Pitt et al. now report in the Journal the findings of a trial comparing spironolactone with placebo in patients with heart failure and a preserved ejection fraction. In the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) trial, patients with at least one symptom and one sign of heart failure were included if they had an ejection fraction of at least 45%. In addition, either an elevated natriuretic peptide level in the previous 60 days or a hospital admission in the previous year “with management of heart failure a major component of the care provided” was required, and these eligibility criteria were used to stratify patients at randomization. In all, 3445 patients underwent randomization in 6 countries (Argentina, Brazil, Canada, Georgia, Russia, and the United States).

After a mean follow-up of 3.3 years, the incidence rate of the primary composite outcome of death from cardiovascular causes, aborted cardiac arrest, or hospitalization for heart failure was 5.9 events per 100 person-years in the spironolactone group and 6.6 events per 100 person-years in the placebo group (hazard ratio, 0.89; 95% confidence interval, 0.77 to 1.04; P=0.14). There was a nominally significant reduction in the secondary outcome of hospitalization for heart failure with spironolactone. Overall, however, the results of the TOPCAT trial were neutral.

More controversially, the TOPCAT trial investigators report a subgroup interaction that raises questions about the trial inclusion criteria and the globalization of clinical research. Of the 22 prespecified subgroups analyzed, only the eligibility stratum showed a significant treatment interaction. Spironolactone seemed to benefit patients who were enrolled in the natriuretic peptide stratum but not those in the hospitalization stratum.

The authors recognized that this treatment interaction may have been a chance finding (especially because there was no correction for multiplicity). They nonetheless explored the interaction further. They found that patients enrolled on the basis of the hospitalization criterion had a lower event rate than those enrolled on the basis of the natriuretic peptide criterion. Patients in the hospitalization stratum were much younger, with fewer coexisting conditions and a lower risk profile. The majority of patients from Russia and Georgia were enrolled in the hospitalization stratum and thus were at lower risk, whereas those from the Americas were more evenly balanced between the two strata and were at higher overall risk. In a post hoc analysis, spironolactone seemed to benefit patients in the Americas but not those in Russia or Georgia.

How do we interpret these observations? It is noteworthy that geographic differences in outcomes have been a focus of concern in some previous trials involving patients with heart failure. Possible factors in such geographic variation include differences in the clinical characteristics of the patient population in each region as well
as differences in standards of care and methodologic expertise in the conduct of clinical trials.

The most anomalous finding in the TOPCAT trial is the low event rate in the hospitalization stratum, which reduced the potential for a benefit of spironolactone therapy in this subgroup. In previous trials, a history of hospitalization for heart failure has been predictive of high event rates, even in heart failure with a preserved ejection fraction. In the Irbesartan in Heart Failure with Preserved Ejection Fraction Study (I-PRESERVE), the overall rate of death from cardiovascular causes or hospitalization for heart failure (a composite outcome similar to that in the TOPCAT trial) was 6.84 per 100 patient-years; it was 10.47 per 100 patient-years among patients with a hospitalization for heart failure in the previous 6 months, as compared with 4.38 per 100 patient-years among those without such a hospitalization (with data derived from Fig. 2 of the article). The wording of the hospitalization inclusion criterion in the TOPCAT trial, which differed from that in previous trials, may therefore have been important. Indeed, we wonder whether some of the patients in the hospitalization stratum actually had heart failure with a preserved ejection fraction, not least because this is a diagnosis that is not straightforward and that relies on the ruling out of other potential causes of dyspnea and edema.

These observations suggest that investigators in future trials should specify more precisely what they mean by hospitalization for heart failure and may wish to verify the details of such admissions, at least in a proportion of cases, as well as monitor event rates according to inclusion stratum and region during follow-up. The TOPCAT trial also underscores the importance of natriuretic peptide levels as a predictor of adverse outcomes in heart failure and their value as an inclusion and quality criterion in clinical trials, nowhere more so than in heart failure with a preserved ejection fraction, which remains difficult to define.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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Renal Denervation for Resistant Hypertension?
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Ever since Schlaich et al. first reported on a patient with a blood pressure of 161/107 mm Hg (despite treatment with seven different antihypertensive drugs) that decreased to 127/81 mm Hg after renal denervation, the medical community has been enamored with this procedure. Resistant hypertension evolved into a fashionable diagnosis, and the number of publications pertaining to it grew rapidly. Medical-device companies fancied renal denervation as the next big innovation and as a blockbuster therapy for millions of patients. A press release from the American Heart Association even touted renal denervation as a potential “cure” for mild hypertension.