Spironolactone for Heart Failure with Preserved Ejection Fraction

Bertram Pitt, M.D., Marc A. Pfeffer, M.D., Ph.D., Susan F. Assmann, Ph.D., Robin Boineau, M.D., Inder S. Anand, M.D., Brian Gaggett, Ph.D., Nadine Clausell, M.D., Ph.D., Alexis S. Desai, M.D., M.P.H., Rafael Diaz, M.D., Jerome L. Flug, M.D., Ivan Gorelov, M.D., Ph.D., Brian Harty, M.A., John F. Heitner, M.D., Christopher T. Kenwood, M.S., Eldrin F. Lewis, M.D., M.P.H., Eileen O'Meara, M.D., Jeffrey L. Pottsfield, M.D., Tamaz Shaburishvili, M.D., Ph.D., Sanjiv J. Shah, M.D., Scott D. Solomon, M.D., Nancy K. Switzer, M.D., Ph.D., Song Yang, Ph.D., and Sonja M. McKinlay, Ph.D. for the TOPCAT Investigators

BACKGROUND
Mineralocorticoid-receptor antagonists improve the prognosis for patients with heart failure and a reduced left ventricular ejection fraction. We evaluated the effects of spironolactone in patients with heart failure and a preserved left ventricular ejection fraction.

METHODS
In this randomized, double-blind trial, we assigned 3445 patients with symptomatic heart failure and a left ventricular ejection fraction of 45% or more to receive either spironolactone (15 to 45 mg daily) or placebo. The primary outcome was a composite of death from cardiovascular causes, aborted cardiac arrest, or hospitalization for heart failure.

RESULTS
With a mean follow-up of 3.3 years, the primary outcome occurred in 320 of 1722 patients in the spironolactone group (18.6%) and 351 of 1723 patients in the placebo group (20.4%) (hazard ratio, 0.89; 95% confidence interval [CI], 0.77 to 1.04; P=0.14). Of the components of the primary outcome, only hospitalization for heart failure had a significantly lower incidence in the spironolactone group than in the placebo group (206 patients [12.0%] vs. 245 patients [14.2%]; hazard ratio, 0.83; 95% CI, 0.69 to 0.99, P=0.04). Neither total deaths nor hospitalizations for any reason were significantly reduced by spironolactone. Treatment with spironolactone was associated with increased serum creatinine levels and a doubling of the rate of hyperkalemia (18.7%, vs. 9.1% in the placebo group) but reduced hypokalemia. With frequent monitoring, there were no significant differences in the incidence of serious adverse events, a serum creatinine level of 3.0 mg per deciliter (265 μmol per liter) or higher, or dialysis.
CONCLUSIONS

In patients with heart failure and a preserved ejection fraction, treatment with spironolactone did not significantly reduce the incidence of the primary composite outcome of death from cardiovascular causes, aborted cardiac arrest, or hospitalization for the management of heart failure. (Funded by the National Heart, Lung, and Blood Institute; TOPCAT ClinicalTrials.gov number, NCT00094302.)

The content of this article does not necessarily represent the views of the National Heart, Lung, and Blood Institute or of the Department of Health and Human Services.

Supported by a contract from the National Heart, Lung, and Blood Institute, National Institutes of Health (HHSN268200425207C).

Dr. Pitt reports receiving consulting fees from and holding stock and stock options in AuralSense Therapeutics, receiving consulting fees from and holding stock options in Relypsa and BG Medicine, receiving consulting fees from Pfizer, Bayer, AstraZeneca, Amrycose, Mesoblast, Takeda Pharmaceutical, and Gambro, receiving fees for serving on data and safety monitoring boards from Novartis and Johnson & Johnson, receiving fees for serving on a clinical-events committee from Juventas Therapeutics, receiving grant support from Forest Laboratories, and holding a pending patent related to site-specific delivery of eplerenone to the myocardium (14/175,733). Dr. Pfeffer reports receiving consulting fees and grant support from Amgen, consulting fees from Aastrom Biosciences, Abbott Vascular, Cerenis Therapeutics, Concert Pharmaceuticals, FibroGen, GlaxoSmithKline, Medtronic, Merck, Roche, Servier, and Teva Pharmaceuticals, and grant support from Celllation, Novartis, and Sanofi-Aventis and being a coinventor on patents related to the use of inhibitors of the renin-angiotensin system in selected survivors of myocardial infarction, which are licensed to Novartis and Boehringer Ingelheim (5,972,960 and 5,977,160). Dr. Desai reports receiving consulting fees from Novartis. Boston Scientific, Reata Pharmaceuticals, CardioMEMS, SAM Ventures, Intel, and Relypsa, travel support from Amgen, and tonometry devices from AlCor Medical for use in an ancillary trial and providing expert testimony for Coverys on behalf of the defendant in a malpractice action regarding failure to diagnose heart failure. Dr. Lee is reports receiving grant support from Novartis, Amgen, and Sanofi-Aventis. Dr. O’Meara reports receiving consulting fees, lecture fees, and grant support from Servier, consulting fees and lecture fees from Pfizer, and consulting fees from Novartis. Dr. Shah reports receiving consulting fees from Novartis and Bayer and grant support from Gilead. Dr. Solomon reports receiving consulting fees and grant support from Novartis and consulting fees from Bayer. No other potential conflict of interest relevant to this article was reported.

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

Drs. Pitt, Pfeffer, and McKinlay contributed equally to this article.

This article was updated on April 10, 2014, at NEJM.org.

SOURCE INFORMATION

From the University of Michigan School of Medicine, Ann Arbor (B.P.); the Cardiovascular Division, Brigham and Women’s Hospital, Boston (M.A.P., B.C., A.S.D., E.F.L., S.D.S.); New England Research Institutes, Watertown, MA (S.F.A., B.H., C.T.K., S.M.M.); National Heart, Lung, and Blood Institute, Bethesda, MD (R.B., J.L.F., S.Y.); Veterans Affairs Medical Center and University of Minnesota, Minneapolis (U.S.A.); Hospital de Clinicas de Porto Alegre, Porto Alegre, Brazil (N.C.); Estudios Clinicos Latinoamericana, Rosario, Argentina (R.D.); Pirogov Russian National Research Medical University, Moscow (I.G.); New York Methodist Hospital, Brooklyn (J.F.H.); Montreal Heart Institute, Montreal (E.O.); University of Washington Medical Center, Seattle (J.L.P.); Diagnostic Services Clinic, Tbilisi, Georgia (T.S.); Northwestern University, Chicago (S.J.S.); and the University of Wisconsin, Madison (N.K.S.).

Address reprint requests to Dr. Pfeffer at the Cardiovascular Division, Brigham and Women’s Hospital, 75 Francis St., Boston, MA 02115, or at mpfeffer@rics.bwh.harvard.edu.

A complete list of investigators and committees in the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) trial is provided in the Supplementary Appendix, available at NEJM.org.

Access this article: Subscribe to NEJM | Purchase this article