Original Investigation

Association Between Use of β-Blockers and Outcomes in Patients With Heart Failure and Preserved Ejection Fraction

Lars H. Lund, MD, PhD; Lina Benson, MSc; Ulf Dahlström, MD, PhD; Magnus Edner, MD, PhD; Leif Friberg, MD, PhD

Editorial page 1977

Supplemental content at jama.com

CME Quiz at jamanetworkcme.com and CME Questions 2034

IMPORTANCE Heart failure with preserved ejection fraction (HFPEF) may be as common and may have similar mortality as heart failure with reduced ejection fraction (HFREF). β-Blockers reduce mortality in HFREF but are inadequately studied in HFPEF.

OBJECTIVE To test the hypothesis that β-blockers are associated with reduced all-cause mortality in HFPEF.

DESIGN Propensity score–matched cohort study using the Swedish Heart Failure Registry. Propensity scores for β-blocker use were derived from 52 baseline clinical and socioeconomic variables.

SETTING Nationwide registry of 67 hospitals with inpatient and outpatient units and 95 outpatient primary care clinics in Sweden with patients entered into the registry between July 1, 2005, and December 30, 2012, and followed up until December 31, 2012.

PARTICIPANTS From a consecutive sample of 41 976 patients, 19 083 patients with HFPEF (mean [SD] age, 76 [12] years; 46% women). Of these, 8244 were matched 2:1 based on age and propensity score for β-blocker use, yielding 5496 treated and 2748 untreated patients with HFPEF. Also we conducted a positive-control consistency analysis involving 22 893 patients with HFREF, of whom 6081 were matched yielding 4054 treated and 2027 untreated patients.

EXPOSURES β-Blockers prescribed at discharge from the hospital or during an outpatient visit, analyzed 2 ways: without consideration of crossover and per-protocol analysis with censoring at crossover, if applicable.

MAIN OUTCOMES AND MEASURES The prespecified primary outcome was all-cause mortality and the secondary outcome was combined all-cause mortality or heart failure hospitalization.

RESULTS Median follow-up in HFPEF was 755 days, overall; 709 days in the matched cohort; no patients were lost to follow-up. In the matched HFPEF cohort, 1-year survival was 80% vs 79% for treated vs untreated patients, and 5-year survival was 45% vs 42%, with 2279 (41%) vs 1244 (45%) total deaths and 177 vs 191 deaths per 1000 patient-years (hazard ratio [HR], 0.93; 95% CI, 0.86-0.996; $P = .04$). β-Blockers were not associated with reduced combined mortality or heart failure hospitalizations: 3368 (61%) vs 1752 (64%) total for first events, with 371 vs 378 first events per 1000 patient-years (HR, 0.98; 95% CI, 0.92-1.04; $P = .46$). In the matched HFREF cohort, β-blockers were associated with reduced mortality (HR, 0.89; 95% CI, 0.82-0.97, $P = .005$) and also with reduced combined mortality or heart failure hospitalization (HR, 0.89; 95% CI, 0.84-0.95; $P = .001$).

CONCLUSIONS AND RELEVANCE In patients with HFPEF, use of β-blockers was associated with lower all-cause mortality but not with combined all-cause mortality or heart failure hospitalization. β-Blockers in HFPEF should be examined in a large randomized clinical trial.

JAMA. 2014;312(19):2008-2018. doi:10.1001/jama.2014.15241

Author Affiliations: Unit of Cardiology, Department of Medicine, Karolinska Institutet, Stockholm, Sweden (Lund, Edner); Department of Cardiology, Karolinska University Hospital, Stockholm, Sweden (Lund); Department of Clinical Science and Education, Karolinska Institutet, South Hospital, Stockholm, Sweden (Benson); Department of Cardiology and Department of Medical and Health Sciences, Linköping University, Linköping, Sweden (Dahlström); Department of Clinical Sciences, Karolinska Institutet, Danderyd Hospital, Stockholm, Sweden (Friberg); Department of Cardiology, Danderyd Hospital, Stockholm, Sweden (Friberg).

Corresponding Author: Lars H. Lund, MD, PhD, Department of Cardiology, Section for Heart Failure, Karolinska University Hospital, N305, 171 76 Stockholm, Sweden (Lars.Lund@alumni.duke.edu).

Up to half of patients with heart failure have normal or near-normal ejection fraction,[1] termed *heart failure with preserved ejection fraction* (HFPEF) or *diastolic heart failure*. The mortality in HFPEF may be as high as in heart failure with reduced ejection fraction (HFREF), also termed *systolic heart failure*,[1] but there is no proven therapy.

Both HFPEF and HFREF share numerous features including catecholamine and other neurohormonal activation,[2,3] elevated filling pressures, and classical heart failure signs and symptoms.[4] β-Blockers improve outcomes in HFREF[5] and may be beneficial in HFPEF by lowering blood pressure and reducing left ventricular hypertrophy[6] and diastolic dysfunction[7] and by slowing heart rate and reducing myocardial oxygen demand. However, data on β-blockers to treat HFPEF are sparse and inconclusive,[8-13] and β-blockers are currently not indicated for treating HFPEF.[14,15] Therefore, we tested the hypothesis that β-blockers are associated with reduced mortality in HFPEF.

Methods

Study Design and Setting

The Swedish Heart Failure Registry provided the study population and baseline clinical characteristics and medications. This nationwide registry has been previously described.[16] Inclusion criteria are clinician-judged heart failure. The protocol, registration form and annual reports are available at http://www.rikssvikt.se. Ejection fraction is categorized as less than 30%, 30% to 39%, 40% to 49%, and 50% or higher. The 2 highest ejection fraction categories define HFPEF, which we used for setting our inclusion criteria (eFigure 1 in the Supplement). An ejection fraction ranging from 40% through 49% is generally not considered normal. It was included herein because randomized clinical trials (RCTs) included only patients with ejection fractions ranging from less than 35% to 40%. However, we also performed prespecified subgroup analyses by ejection fractions from 40% through 49% and 50% or higher.

Patients were included in this study if the index date was between July 1, 2005, and December 30, 2012. The index date was defined as the date of an outpatient visit or hospital discharge; patients who died during the index hospitalization were excluded. Follow-up was until December 31, 2012.

The Swedish Board of Health and Welfare (http://www.socialstyrelsen.se) maintains the Death Registry, the Patient Registry, and the Dispensed Drug Registry. The Death Registry provided date of death. The Patient Registry provided additional baseline comorbidities and the outcome heart failure hospitalization. It contains *International Statistical Classification of Diseases, Tenth Revision (ICD-10)* codes (eTable 3 in the Supplement) for encounters as inpatients and as outpatients at specialty clinics and is updated and validated annually (last update and thus end of follow-up for this study, December 31, 2012). The positive predictive value for most diagnoses is between 85% and 95%[17]; a heart failure diagnosis was verified in between 86% and 91% of cases.[18] Comorbidities present at baseline (or prior) were defined by corresponding *ICD-10* codes in any position between January 1, 1997, when use of *ICD-10* codes began, and up to and including the index date (except for malignancy and musculoskeletal and psychiatric disorders, counted only if the corresponding *ICD-10* code was present, ie, a health care encounter for this diagnosis had occurred, in the 3 years preceding the index date). The outcomes heart failure hospitalization and death were defined as between the day after the index date and end of follow-up, December 31, 2012, for which a heart failure diagnosis was required as the primary or first secondary diagnosis for hospitalization. In the main analysis, the exposure, β-blocker use, was analyzed at baseline, without consideration of potential crossover during follow-up, but in a per-protocol consistency analysis, the dispensed-drug registry was used to assess β-blocker use throughout follow-up, with censoring at crossover. This registry contains details about every prescription filled in Sweden since July 1, 2005, which was therefore the date for the start of this study. All pharmacies are required to participate by law, ensuring that it is essentially 100% complete because data are transferred electronically when drugs are dispensed. Statistics Sweden maintains socioeconomic data on all Swedish citizens and provided additional baseline data.

All Swedish citizens have unique personal identification numbers that enable linking of disease-specific health registries and governmental health and statistical registries. Establishment of the heart failure registry and this analysis with linking to the above registries were approved by a multisite ethics committee. Individual patient consent was not required, but patients were informed of entry into national registries and allowed to opt out.

Propensity Scores

A propensity score for treatment with β-blockers was estimated for each patient with logistic regression[19] using 52 relevant baseline variables (**Table 1**, **Table 2**, and **Table 3**). The propensity score is the propensity from 0 to 1 of receiving a treatment given a set of known variables and is used to attempt to adjust for potential selection bias, confounding, and differences between treatment groups in observational studies.[19,20]

Continuous variables were modeled using restricted cubic splines with 3 *df*s. Missing data were handled by estimating separate logistic regressions for each missing variable pattern on available observations (yielding a total of 1248 unique missing data patterns and thus logistic regression models). Each individual received the propensity score from the model that incorporated all nonmissing variables for that individual. Using matching without replacement,[21] a cohort was constructed matching each untreated patient to the 2 closest treated patients in which age differed by 5 or fewer years and the propensity score differed by 0.01 or less. The ability of matching to balance the groups was assessed visually (eFigure 2 in the Supplement) and the ability of the propensity score to balance baseline characteristics was assessed by absolute standardized differences (the difference in percentage between the means for the 2 groups divided by the mutual standard deviation; Table 1). Standard differences of less than 10% are considered inconsequential.[22]