

β-Blockers in Atrial Fibrillation Patients With or Without Heart Failure

Association With Mortality in a Nationwide Cohort Study

Peter Brønnum Nielsen, PhD; Torben Bjerregaard Larsen, PhD; Anders Gorst-Rasmussen, PhD; Flemming Skjøth, PhD; Gregory Y.H. Lip, MD

**Background**—Recent data suggest that β-blockers are associated with prognostic advantages in heart failure (HF) patients without concomitant atrial fibrillation (AF), but not in HF patients with concomitant AF. We aimed to investigate associations between β-blocker treatment and cardiovascular outcome and mortality in AF patients with and without HF.

**Methods and Results**—Three nationwide registries were used to identify patients with nonvalvular AF patients with or without concomitant HF. Patients were stratified into β-blocker users and β-blocker nonusers, and according to the presence of a HF diagnosis. We followed the patients ≤5 years after baseline. Six different cardiovascular outcomes were investigated, including all-cause mortality and fatal thromboembolic events. Crude event rates were ascertained and propensity-matched Cox regression was used to compare event rates according to β-blocker usage status. A total of 205,174 patients were included, where 39,741 patients had prevalent HF. In the latter subgroup of patients, the 1-year propensity-matched hazard ratio (HR) for all-cause mortality was 0.75 (95% confidence interval, 0.71–0.79; nontreated used as reference). For patients without concomitant HF, the propensity-matched HR for all-cause mortality was 0.78 (95% confidence interval, 0.71–0.76).

**Conclusions**—In this large nationwide cohort study, evidence of a lower mortality with β-blocker therapy in AF patients with concomitant HF was observed. In addition, this association was accompanied with indications that β-blocker treatment is also associated with a better prognosis in AF patients without concomitant HF. (Circ Heart Fail. 2016;9:e002597. DOI: 10.1161/CIRCHEARTFAILURE.115.002597.)

**Key Words:** atrial fibrillation ■ cohort studies ■ heart failure ■ mortality ■ prognosis

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Atrial fibrillation (AF) and heart failure (HF) are 2 burdensome chronic cardiac diseases with an increasing prevalence as the average life expectancy increases.1-3 HF can lead to atrial remodeling, which increases the risk of developing AF. Conversely, AF can lead to HF because of the consequences of the arrhythmia itself and impairment in diastolic filling.4 It has been estimated that ≤40% of patients with HF also have concomitant AF.5

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**See Clinical Perspective**

Current guidelines recommend treatment with β-blockers for patients with HF irrespective of rhythm disorders.6,7 In patients with AF, strict versus lenient rate control with β-blocker treatment were equally effective.8 Notwithstanding their use for rate control, it is an open question whether β-blocker usage is associated with prognostic benefits in AF patients with HF. Also, treatment with β-blockers has been shown effective in controlling the ventricular rate.9 Although symptomatic treatment of the AF burden is of importance for the individual patient, it remains of prognostic importance to investigate if β-blocker treatment is also associated with thromboembolism.

Recently, the β-Blockers in Heart Failure Collaborative Group meta-analyzed individual-level data from 10 randomized controlled trials, and suggested that β-blockers were associated with an improved prognostic advantage (with lower mortality, cardiovascular events, etc.) in HF patients without AF; however, no prognostic benefit was observed among HF patients with AF.10 The findings were consistent across demographic features and comorbidities, and also consistent with a previous meta-analysis.11 Large-scale randomized trials to investigate the potential prognostic benefits of β-blockers...
are desirable, but with the expiration of the patent protection of β-blockers, there is little incentive in the pharmaceutical industry for sponsoring such trials. Thus, carefully conducted large-scale register-based studies may add to the limited current evidence about β-blocker treatment in AF patients, with or without concomitant HF.

This study is a propensity-adjusted analysis of the prognosis with β-blocker therapy among AF and HF patients identified using Danish nationwide registries on prescription purchases and hospital discharge diagnoses. We hypothesized that β-blocker therapy would be associated with an improved cardiovascular outcome and mortality in AF patients both with and without HF.

Methods

In Denmark, all information on hospitalization and prescription claims are linked to a unique personal identifier, which is provided at date of birth or migration. We identified records from the National Patient Registry to obtain hospitalization diagnoses by using codes from the International Classification of Diseases (Eighth Revision until 1994, hereafter Tenth Revision).21 Prescription claims were identified from the National Prescription Registry, which uses codes from the Anatomic Therapeutic Classification system to identify the type of drug, and contains information on date of dispensation, dosage, and strength.13 Vital status, age, sex, and information on migrations were obtained from the Civil Registration System.14

Study Population and Follow-Up Information

We identified patients with a first-time hospital AF diagnosis between January 1, 1998 and December 31, 2013. Both hospitalized AF patients and patients referred to an ambulatory setting for AF were included. All patients with valvular AF were excluded; valvular AF was defined as presence of mitral stenosis or heart valve replacement at the time of AF diagnosis. We stratified patients according to the presence of a previous hospital diagnosis of HF. We excluded patients if they died or experienced a cardiovascular event within 7 days after the discharge date of the AF diagnosis (baseline).

We categorized patients as β-blocker users if they had claimed a β-blocker prescription within 4 months before and ≤7 days after hospital discharge with AF, with no claims in the period from 1 year before to 4 months before hospital discharge with AF. Patients were categorized as nonusers if they had not claimed a prescription in the year preceding the AF diagnosis. Finally, patients were excluded if they had claimed a prescription of β-blocker in the period 1 year before ≤4 months before hospital discharge with AF. The restriction to recent β-blocker initiators was used to reduce potential bias that might arise from inclusion long-time prevalent β-blocker users.15

We followed the patients in the Danish National Patient Register from 7 days after discharge with an AF diagnosis and ≤5 years after baseline. Follow-up was censored at the time of death, migration, end-of-study (December 31, 2013), or at the occurrence of an end point, whichever came first. Definitions of comorbidities and medications are presented in Table I in the Data Supplement.

Outcomes and Comorbidities

We examined 6 cardiovascular outcomes: the 2 primary end points were all-cause mortality and fatal thromboembolic events. The latter was defined as death within the following 30 days of ischemic stroke, systemic embolism (SE), pulmonary embolism (PE), or myocardial infarction (MI). We also studied secondary end points: a combined end point of ischemic stroke/SE and all-cause mortality; a combined end point of ischemic stroke/SE/PE/MI. In addition, we studied a combined end point of ischemic stroke/SE/PE; and finally (lone) ischemic stroke. Both primary and secondary diagnoses were included in all end point analyses (Table I in the Data Supplement); emergency room diagnoses were not included. The outcomes for individual patients were not adjudicated, but the National Patient Registry have previously been validated on selected outcomes with acceptable positive predictive values for this type of analyses.16,17 Cardiovascular comorbidities were assessed by the CHA2DS2-VASc score16; information on concomitant pharmacotherapy ≤1 year before baseline was also obtained. Ethical approval is not required for register-based studies in Denmark.

Statistical Methods

We performed 2 separate analyses, both according to β-blocker exposure: (1) among AF patients with concomitant HF and (2) among AF patients without concomitant HF.

Propensity Models

For describing the association between β-blocker treatment and the risk of a subsequent event, we used propensity matching to account for baseline differences between β-blocker users and β-blocker nonusers (controls). Propensity scores for β-blocker treatment were estimated using a logistic regression model, which included information on cardiovascular comorbidities and use of concomitant pharmacotherapy (binary indicators). Specifically, indicators from the CHA2DS2-VASc score were extracted (sex, hypertension, diabetes mellitus, previous stroke/transient ischemic attack, and vascular disease) and the following information on baseline medication: renin–angiotensin inhibitors, antiplatelet therapy with aspirin, oral anticoagulant treatment, calcium channel blockers, loop diuretics, nonloop diuretics, statins, digoxin, and amiodarone. Age at AF was included as a restricted cubic spline. When analyzing the cohort of patients with concomitant HF, the regression model also included time because the incident HF diagnosis (categories of months ≤1 year before inclusion; categories of years for time <1 year up to ≥5 years relative to inclusion). Propensity matching was done one-to-one (no replacement) based on the nearest neighbor method and a maximum difference (calliper) in the propensity score between 2 matched samples was set to 0.01 on a probability scale. Balance of baseline characteristics after matching was assessed by inspection of standardized mean differences; a standardized mean difference numerically <0.1 was considered acceptable.19

Comparison of Event Rates

Unmatched and propensity-matched study population characteristics were summarized according to β-blocker usage and to status of concomitant HF. Event rates for all the studied outcomes were calculated by dividing the number of events occurring during follow-up with the total person-years of follow-up. HRs contrasting β-blocker usage versus no β-blocker usage were estimated by means of Cox proportional hazards model in the propensity-matched cohorts. To describe the 1-year survival in the matched subgroups, we estimated the Kaplan–Meier survival curves stratified according to β-blocker usage and HF status. Stata version 13 was used for statistical analysis (StataCorp LP, College Station, TX), and a 2-sided P<0.05 was considered statistically significant.

Sensitivity Analyses

With observational data, it is important to evaluate whether methodological limitations or decisions could bias findings. Accordingly, various sensitivity analyses were performed to investigate the robustness of our findings.

The subgroup of patients who received a concomitant HF diagnosis long before the AF diagnosis and survived until inclusion into this study may represent a selected group of HF survivors. Accordingly, to investigate whether associations were different among patients recently diagnosed with HF, we performed a sensitivity analysis by restricting the propensity-matched cohort to patients with recently diagnosed HF; that is, (first time) HF diagnosis within 4 months before baseline.

To investigate whether the definition of β-blocker usage by considering (recent) prevalent users might lead to healthy user bias, we performed a sensitivity analysis along the lines of the new-user design.11 Specifically, we excluded all prevalent β-blocker users and instead defined β-blocker users as patients who claimed a prescription within the first month after hospital discharge; accordingly, observation time was started 1 month after discharge from hospital.
We undertook a sensitivity analysis to assess the impact of the of analytic strategy on findings by using inverse probability–weighted Cox regression model.20,21 In detail, we constructed a logistic regression model using the same baseline variables used when constructing the propensity-matched cohort. We used this model to predict the (inverse) probability of receiving β-blocker treatment.22 The probability weights were entered in weighted Cox regression models, providing estimates of the HR contrasting the hypothetical scenario where all patients received β-blocker therapy, versus the scenario where no patients received β-blocker therapy.

Finally, given the increasing attention to patients with HF during the past 5 to 10 years, we performed a sensitivity analysis by restricting the time period for inclusion, that is, from January 1, 2008 to December 2013.

Results

We identified 227,431 patients with nonvalvular AF between January 1, 1998 and December 31, 2013; of those 205,174 met the inclusion criteria, with a mean follow-up time of 3.1 years. The propensity-matched cohort of AF patients without concomitant HF comprised 110,768 patients (67%), whereas the cohort of AF patients with concomitant HF comprised 23,896 patients (60%); see Figure 1 for flowchart and Table 1 for patient characteristics. In general, patients with concomitant HF were older than patients free from HF (mean age, 78 and 73 years, respectively), and more often had hypertension and vascular diseases, including previous MI. Propensity score models were able to balance the baseline covariates, as indicated by mean standardized difference <0.1. Further inspection revealed that those patients for whom no match could be found were slightly older and more often hypertensive; additionally, these patients more often received treatment with statins as well as oral anticoagulant treatment.

β-Blocker Treatment in AF Patients With Prevalent HF

In the original, unmatched population, event rates were higher among AF patients with concomitant HF compared with those without concomitant HF (Table 2). The 1-year mortality rate (per 100 person-years) for β-blocker users with concomitant HF was 23.2 versus 37.2 for β-blocker nonusers. Event rates for fatal thromboembolic events were also slightly lower for β-blocker users compared with nonusers, 2.6 versus 3.3, respectively. Event rates for any thromboembolic event were similar in the 2 groups, 9.9 for treated and 9.7 for those not treated.

In the propensity-matched analysis, AF patients with concomitant HF who were β-blocker users had lower all-cause mortality and fatal thromboembolic event rates compared with nonusers, HR 0.75 (95% confidence interval [CI], 0.71–0.79) and 0.87 (95% CI, 0.74–1.02; Figure 2; Table 3). Analyses of secondary outcomes yielded HRs close to 1, with the upper limits of CIs providing evidence against a harmful effect of β-blockers.

β-Blocker Treatment in AF Patients Without HF

In the original, unmatched population, the all-cause mortality rate was lower for β-blocker users compared with nonusers (Table 2; Figure 2). In addition, the fatal thromboembolic event rate was slightly lower among β-blocker users compared with nonusers, 1.2 versus 1.7, respectively. Analyzing the combined end point of ischemic stroke/SE/PE/MI showed event rates for β-blocker users of 6.5 versus 7.0 for nonusers.

β-blocker treatment was associated with lower all-cause mortality, HR, 0.73 (95% CI, 0.71–0.76); and fatal thromboembolic events, 0.82 (95% CI, 0.74–0.92; Table 3). The HR for any thromboembolic events was 0.99 (95% CI, 0.94–1.05) for β-blocker users compared with nonusers, providing evidence against a harmful effect of β-blockers.

Long-Term Outcome Analyses

HRs for various outcomes using 5 years of follow-up were overall consistent with results from the analysis at 1 year for both the groups (concomitant HF or free from HF), with directions of associations unchanged (Table II in the Data Supplement). In contrast to the analysis at 1 year, there was a stronger evidence for reduced event rate on β-blocker treatment for the outcomes exploring thromboembolic events and ischemic stroke.

Sensitivity Analyses

The restriction to patients with a recent diagnosis of HF (within 4 months before baseline) yielded results which were consistent with the main findings: the HR for all-cause mortality was 0.75 (95% CI, 0.70–0.80) and for fatal thromboembolism HR, 0.77 (95% CI, 0.62–0.95). The sensitivity analyses in which prevalent users of β-blockers were excluded also yielded materially similar findings as in the main analysis (Table III in the Data Supplement).

The findings obtained from the inverse probability–weighted Cox proportional hazard model were consistent with the results obtained from the propensity-matched analysis (Table 3). Restricting the observation to most recent 5-year period did not alter the conclusions materially (data not shown).
In this large observational cohort reflecting clinical practice, we analyzed the prognosis with β-blocker usage separately in the subgroups of AF patients with and without concomitant HF, and found that in both subgroups, β-blocker therapy at baseline was associated with a better prognosis for various cardiovascular outcomes. Second, there was a reduction of all-cause mortality between 20% and 30% for patients on
Our data suggest a potential benefit of β-blocker treatment in patients with AF overall, corroborating current guideline recommendations on β-blocker usage. These results should preferably be confirmed in future studies.

The β-blockers in Heart Failure Collaborative Group reported an individual-level meta-analysis involving 18,254 clinical trial patients. β-Blocker therapy was in the meta-analysis associated with a significant reduction in all-cause mortality in patients with sinus rhythm (HR, 0.73; 95% CI, 0.67–0.80), but this was not seen in patients with AF and concomitant HF (HR, 0.97; 95% CI, 0.83–1.14). On the basis of these findings, they recommended that β-blockers should not be used preferentially for other rate-control medications and not regarded as standard therapy to improve prognosis in AF patients with concomitant HF, contrary to current treatment guidelines. Of note, the AF group comprised only 17% of the whole-patient cohort, and the obtained meta-analyzed results might reflect an underpowered analysis. The lack of statistical significance for the primary outcome was also noted in all subgroups of AF, including age, sex, left ventricular ejection fraction (LVEF), New York Heart Association (NYHA) class, heart rate, and baseline medical therapy. It is important to bear in mind that, although statistical significance was not reached, CIs from this meta-analysis were consistent with a reduction in mortality of ≤17%: and for cardiovascular death ≤23%.

Table 2. Event Rates Per 100 PY at 1 Year of Follow-Up According to Exposure of β-Blocker and Stratified by Prevalent Heart Failure (Unmatched Populations)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Prevalent Heart Failure</th>
<th></th>
<th>Free From Heart Failure</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No β-Blocker Treatment</td>
<td>Rate</td>
<td>β-Blocker Treatment</td>
<td>Rate</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>5639/15164</td>
<td>37.2</td>
<td>3867/16677</td>
<td>23.2</td>
</tr>
<tr>
<td>Fatal thromboembolic event*</td>
<td>507/15164</td>
<td>3.3</td>
<td>433/16677</td>
<td>2.6</td>
</tr>
<tr>
<td>Ischemic stroke/SE and all-cause mortality</td>
<td>6069/14862</td>
<td>40.8</td>
<td>4350/16347</td>
<td>26.6</td>
</tr>
<tr>
<td>Any thromboembolic event†</td>
<td>1409/14589</td>
<td>9.7</td>
<td>1583/15953</td>
<td>9.9</td>
</tr>
<tr>
<td>Thromboembolic events‡</td>
<td>934/14798</td>
<td>6.3</td>
<td>884/16280</td>
<td>5.4</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>736/14882</td>
<td>4.9</td>
<td>683/16377</td>
<td>4.2</td>
</tr>
</tbody>
</table>

PY indicates person-years; and SE, systemic embolism.

*Death within 30 days after an event of ischemic stroke, SE, pulmonary embolism, or myocardial infarction.
†Combined end point of ischemic stroke, SE, pulmonary embolism, or myocardial infarction.
‡Combined end point of ischemic stroke, SE, and pulmonary embolism.

Figure 2. Kaplan–Meier survival estimates (and corresponding 95% confidence interval bands) of atrial fibrillation patient with or without heart failure stratified according to β-blocker treatment (solid line) versus no β-blocker treatment (dashed line) for 1 year of follow-up (propensity-matched cohorts).
reduction. Careful inspection of the subgroup of patients with HF disclosed that 72% of the patients had an NYHA class of III or IV, with the majority of the patients being treated with an renin-angiotensin system inhibitors/angiotensin receptor blocker and diuretics, and also 83% in digoxin treatment. We cannot deduce whether these findings reflect a highly selected clinical trial population of (very) severely ill subgroup of HF and AF patients in the study by Kotecha et al,10 where benefit from β-blocker treatment would be diminishing. Nonetheless, our study corroborates a potential reduction in mortality with CIs from propensity-adjusted analyses suggesting a 20% to 30% reduction in mortality rates, consistently with other reports.23-26 This reduction was observed among AF patients both with and without concomitant HF.

We recognize that the discrepancy between obtained results in our study compared with the study by Kotecha et al10 may reflect differences in patient populations. Both studies involve selected patient groups (selected trial populations versus selected populations in clinical practice) and may not be directly comparable. In addition, we cannot rule out unmeasured or residual confounding in our analyses. However, sensitivity analyses, including analyses with more restrictive inclusion criteria, did not alter our main conclusions. Kotecha et al10 investigated symptomatic HF patients with reduced ejection fraction, whereas we did not have the option to distinct patients according to ejection fraction. In addition, the patients with AF included from the randomized trials were stable or patients with permanent AF, whereas this study started observation time at the onset of AF diagnosis. It has been previously shown that newly diagnosed patients with AF are associated with higher mortality rates, which could explain some of the discrepancies between the present findings and that of Kotecha et al.27 Altogether, definitive conclusions on the potential survival advantage with β-blocker treatments are likely to require large-scale randomized trials.

Our analyses of the secondary end point of thromboembolic events (end point including ischemic stroke, PE, SE, and MI) indicated no effect of β-blocker treatment, with CIs supporting neither a clear beneficial effect nor a clear adverse effect. This could reflect drug characteristics: it has been suggested that selective β-blockers may confer a higher risk of thromboembolism, compared with nonselective β-blockers.28 In our population, 88% with prevalent HF and 86% free from HF who received β-blocker treatment were prescribed a selective β-blocking type. In addition, the observed rates of the secondary end points (Table 2) may be underestimated because of a competing risk of death, which was not taking into account in the statistical analyses.

Although our findings are in line with the current recommendations on treatment with β-blocker, some caution in interpretation is warranted: we did only include <70% of the available populations into the propensity-matched cohorts. Hence, these artificially constructed cohorts might not generalize into the entire population. However encouraging, when applying a different methodological approach, that is, using inverse probability–weighted in the Cox model to produce contrasts, we observed materially equal results as those from the propensity matching (Table 3).

### Limitations

This was an observational study, which can be subject to unmeasured and residual confounding. In addition, the analysis might be subject to confounding by indication despite the efforts made to resolve this by using propensity matching approach. Moreover, our definitions based on prevalent medical conditions and medication usage may have led to selection bias, including healthy user/survivor bias. Although we investigated these issues by means of various sensitivity analyses, and found virtually identical results as in the main analysis, it is unlikely that we have fully accounted for all sources of selection and confounding biases. In addition, we acquired data from administrative registries and misclassification bias including coding errors, cannot be ruled out. The AF diagnosis has been shown to be accurate in Danish registries.29 However, we were not able to distinguish between new-onset AF from carry-over diagnosis in relation to another condition (or

### Table 3. HR for Different Outcomes in Propensity-Matched Cohorts Contrasting Treatment With β-Blocker in a Stratum of Prevalent HF (Reference: No β-Blocker Treatment)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Prevalent HF HR (95% CI)</th>
<th>Free From HF HR (95% CI)</th>
<th>Prevalent HF HR (95% CI)</th>
<th>Free From HF HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td>0.75 (0.71–0.79)</td>
<td>0.73 (0.71–0.76)</td>
<td>0.78 (0.75–0.82)</td>
<td>0.72 (0.70–0.75)</td>
</tr>
<tr>
<td>Fatal thromboembolic event*</td>
<td>0.87 (0.74–1.02)</td>
<td>0.82 (0.74–0.92)</td>
<td>0.95 (0.81–1.11)</td>
<td>0.79 (0.72–0.88)</td>
</tr>
<tr>
<td>Ischemic stroke/SE and all-cause mortality</td>
<td>0.77 (0.74–0.82)</td>
<td>0.77 (0.75–0.80)</td>
<td>0.80 (0.77–0.84)</td>
<td>0.76 (0.74–0.79)</td>
</tr>
<tr>
<td>Any thromboembolic event†</td>
<td>1.02 (0.93–1.12)</td>
<td>0.99 (0.94–1.05)</td>
<td>1.04 (0.95–1.13)</td>
<td>0.98 (0.94–1.03)</td>
</tr>
<tr>
<td>Thromboembolic events‡</td>
<td>0.93 (0.83–1.05)</td>
<td>0.93 (0.87–0.98)</td>
<td>0.95 (0.85–1.06)</td>
<td>0.90 (0.86–0.95)</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>0.94 (0.82–1.07)</td>
<td>0.96 (0.90–1.03)</td>
<td>0.95 (0.84–1.08)</td>
<td>0.93 (0.88–0.99)</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; HF, heart failure; HR, hazard ratio; and SE, systemic embolism.

*Death within 30 days after an event of ischemic stroke, SE, pulmonary embolism, or myocardial infarction.

†Combined end point of ischemic stroke, SE, pulmonary embolism, and myocardial infarction.

‡Combined end point of ischemic stroke, SE, pulmonary embolism, and myocardial infarction.
planned follow-up visit to an ambulatory), or if it indeed is new onset of HF.

In addition, we studied patients with nonvalvular AF by excluding those patients with mitral stenosis and valve replacement. Recently, the precise definition on valvular/nonvalvular AF has been debated.36 For the HF diagnosis, a validation study involving a single Danish hospital showed this diagnosis to be specific (99% specificity) but under-reported (29% sensitivity)10; the extent to which these findings generalize to all hospitals in Denmark is unclear. In all, we cannot completely rule out misdiagnosis of HF nor underdiagnosis of AF (silent or asymptomatic).

An important clinical procedure in patients with HF is to ascertain the left ventricular ejection fraction. In our data, we have not been able to separate patients with preserved left ventricular ejection fraction from those with reduced left ventricular ejection fraction. Yet, these 2 groups may exhibit 2 different HF populations with different prognosis.11 Furthermore, it was not possible to obtain an NYHA classification from patients because this information was not available from the registries. However, as we only included patients with a hospital diagnosis of HF, we speculate that this subgroup comprises patients with an NYHA class II and above.

In clinical practice, β-blocker dose administration is optimized for the individual patient, an approach which has been shown to be associated with improved outcomes.32 Because our registers do not contain this data, we could not investigate if patients followed such recommendations or were attended by, for example, an HF specialist nurse (or other healthcare personnel). This may affect outcomes in terms of benefit versus no benefit from β-blocker treatment. Finally, it is important to note that our analysis uses as an exposure the β-blocker treatment status at baseline only. Analyzing the prognosis with continuous treatment by taking into account treatment discontinuation/initiation during follow-up may lead to difference but is beyond scope of this article.

Conclusions
We observed significantly reduced all-cause mortality among β-blocker users with and without HF compared with nonusers. The rate of thromboembolic events was similar between users and nonusers. Although randomized studies are currently needed to confirm these observational findings, this study is consistent with current guideline recommendations of β-blocker treatment to patients with AF and concomitant HF, as well as a clinical benefit for AF patients without concomitant HF.

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Disclosures
Dr Lip has served as a consultant for Bayer/Jensen &J, Astellas, Merck, Sanofi, BMS/Pfizer, Biotronik, Medtronic, Portola, Boehringer Ingelheim, Microlife, and Daiichi-Sankyo, and has been on the speaker bureaus for Bayer, BMS/Pfizer, Medtronic, Boehringer Ingelheim, Microlife, Roche and Daiichi-Sankyo. Dr Larsen has served as an investigator for Janssen Scientific Affairs, LLC, and Boehringer Ingelheim, and has been on the speaker bureaus for Bayer, BMS/Pfizer, Roche Diagnostics, Boehringer Ingelheim, and Takeda Pharma. The other authors report no conflicts. All authors read, revised, and approved the final manuscript; all authors confirm that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted.

References
β-Blockers in AF Patients With or Without HF

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CLINICAL PERSPECTIVE

Atrial fibrillation (AF) and heart failure (HF) are 2 burdensome chronic cardiac diseases with an increasing prevalence as the average life expectancy increases. Current guidelines recommend treatment with β-blockers for patients with HF irrespective of rhythm disorders. Recently, the β-Blockers in Heart Failure Collaborative Group meta-analyzed individual-level data from 10 randomized controlled trials, and suggested that β-blockers were associated with an improved prognostic advantage (with lower mortality, cardiovascular events, etc.) in HF patients without AF; however, no prognostic benefit was observed among HF patients with AF. We aimed to investigate associations between β-blocker treatment and cardiovascular outcome and mortality in AF patients with and without HF. The data were obtained from Danish nationwide registries and comprised a total of 205,174 patients with AF where 39,741 had concomitant HF. We constructed 2 propensity-matched cohorts to balance (baseline) covariates observed in β-blockers users versus nonusers. After 1 year of follow-up, we found a propensity-matched hazard ratio for all-cause mortality of 0.75 (95% confidence interval, 0.71–0.79; nontreated used as reference). For patients without concomitant HF, the propensity-matched hazard ratio for all-cause mortality was 0.78 (95% confidence interval, 0.71–0.76). Hence, based on clinical practice data, a lower mortality with β-blocker therapy in AF patients with concomitant HF was observed. In addition, this association was accompanied with indications that β-blocker treatment is also associated with a better prognosis in AF patients without concomitant HF.
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Supplemental Material

**Supplemental Table 1. Definitions of outcomes and medication**

<table>
<thead>
<tr>
<th>Condition</th>
<th>International Classification of Diseases 10th revision (ICD-10) code</th>
<th>Anatomical Therapeutic Chemical (ATC) code</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congestive heart failure</td>
<td>I11.0; I13.0; I13.2; I42.0; I50</td>
<td>CO3C</td>
</tr>
<tr>
<td>Left ventricular dysfunction</td>
<td>I50.1; I50.9</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td>See specified definition*</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>E10.0; E10.1; E10.9; E11.0; E11.1; E11.9</td>
<td>A10</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>I63; I64</td>
<td></td>
</tr>
<tr>
<td>Systemic embolism</td>
<td>I74</td>
<td></td>
</tr>
<tr>
<td>Transient ischemic disease</td>
<td>G45</td>
<td></td>
</tr>
<tr>
<td>Aortic plaque</td>
<td>I70.0</td>
<td></td>
</tr>
<tr>
<td>Peripheral arterial disease</td>
<td>I70.2-I70.9; I71; I73.9; I74</td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>I21-I23</td>
<td></td>
</tr>
<tr>
<td>Abnormal renal function</td>
<td>I12; I13; N00-N05; N07; N11; N14; N17-N19; Q61</td>
<td>581 582 583 584 59009 59320 59321 59322</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>I48</td>
<td></td>
</tr>
<tr>
<td>Abnormal renal function</td>
<td>I12 I13 N00 N01 N02 N03 N04 N05 N07 N11 N14 N17 N18 N19 Q61</td>
<td>581 582 583 584 59009 59320 59321 59322</td>
</tr>
<tr>
<td>Pacemaker/ICD</td>
<td>Z950</td>
<td></td>
</tr>
</tbody>
</table>

**Medication**

- Dabigatran                            | B01AE07                                                           |
- Rivaroxaban                            | B01AE07                                                           |
- Apixaban                               | B01AF02                                                           |
- Coumarin derivatives                   | B01AA                                                            |
- Aspirin                                | B01AC06                                                           |
- Beta-blockers                          | C07                                                              |
- Calcium channel blockers               | C07F; C08; C09BB; C09DB                                           |
We identified subjects with hypertension from combination treatment with at least two of the following classes of antihypertensive Drugs:

1. Alpha adrenergic blockers (C02A, C02B, C02C)
2. Non-loop diuretics (C02DA, C02L, C03A, C03B, C03D, C03E, C03X, C07C, C07D, C08G, C09BA, C09DA, C09XA52)
3. Vasodilators (C02DB, C02DD, C02DG, C04, C05)
4. Beta blockers (C07)
5. Calcium channel blockers (C07F, C08, C09BB, C09DB)
6. Renin-angiotensin system inhibitors (C09)
**Supplemental Table 2.** Hazard ratio for different outcomes in propensity matched cohorts contrasting treatment with beta-blocker in a stratum of prevalent HF (reference: no beta-blocker treatment) using five years of follow-up.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Propensity matched cohort</th>
<th>Inverse probability weighted cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Prevalent heart failure</td>
<td>Free from heart failure</td>
</tr>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>0.78 (0.75 – 0.80)</td>
<td>0.77 (0.76 – 0.79)</td>
</tr>
<tr>
<td>Fatal thromboembolic event†</td>
<td>0.87 (0.78 – 0.97)</td>
<td>0.86 (0.80 – 0.92)</td>
</tr>
<tr>
<td>Ischemic stroke/SE and all-cause mortality</td>
<td>0.78 (0.75 – 0.81)</td>
<td>0.81 (0.79 – 0.82)</td>
</tr>
<tr>
<td>Any thromboembolic event‡</td>
<td>0.91 (0.86 – 0.97)</td>
<td>0.99 (0.96 – 1.03)</td>
</tr>
<tr>
<td>Thromboembolic events*</td>
<td>0.86 (0.79 – 0.93)</td>
<td>0.96 (0.92 – 1.00)</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>0.87 (0.80 – 0.95)</td>
<td>0.99 (0.95 – 1.04)</td>
</tr>
</tbody>
</table>

† Death within 30 days after an event of ischemic stroke, systemic embolism, pulmonary embolism or myocardial infarction.
‡ Combined endpoint of ischemic stroke, systemic embolism, pulmonary embolism and myocardial infarction.
* Combined endpoint of ischemic stroke, systemic embolism and pulmonary embolism.
**Supplemental Table 3.** Hazard ratio for different outcomes in propensity matched cohorts applying principals from a ‘new user’ design. Reference: no beta-blocker treatment; one year of follow-up.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Prevalent heart failure HR (95% CI)</th>
<th>Free from heart failure HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td>0.66 (0.62 – 0.72)</td>
<td>0.71 (0.68 – 0.74)</td>
</tr>
<tr>
<td>Fatal thromboembolic event†</td>
<td>0.73 (0.58 – 0.92)</td>
<td>0.67 (0.59 – 0.76)</td>
</tr>
<tr>
<td>Ischemic stroke/SE and all-cause mortality</td>
<td>0.68 (0.64 – 0.74)</td>
<td>0.75 (0.72 – 0.78)</td>
</tr>
<tr>
<td>Any thromboembolic event‡</td>
<td>0.97 (0.85 – 1.10)</td>
<td>1.04 (0.98 – 1.10)</td>
</tr>
<tr>
<td>Thromboembolic events*</td>
<td>0.85 (0.72 – 1.00)</td>
<td>0.92 (0.86 – 0.99)</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>0.83 (0.68 – 1.00)</td>
<td>0.94 (0.87 – 1.01)</td>
</tr>
</tbody>
</table>

† Death within 30 days after an event of ischemic stroke, systemic embolism, pulmonary embolism or myocardial infarction.
‡ Combined endpoint of ischemic stroke, systemic embolism, pulmonary embolism and myocardial infarction.
* Combined endpoint of ischemic stroke, systemic embolism and pulmonary embolism.