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# Decreased Mortality With Beta-Blockers in Patients With Heart Failure and Coexisting Atrial Fibrillation

## An AF-CHF Substudy

Julia Cadrin-Tourigny, MD,[a] Azadeh Shohoudi, PhD,[b] Denis Roy, MD,[a] Mario Talajic, MD,[a] Rafik Tadros, MD, PhD,[a] Blandine Mondésert, MD,[a] Katia Dyrda, MD,[a] Léna Rivard, MD,[a] Jason G. Andrade, MD,[a] Laurent Macle, MD,[a] Peter G. Guerra, MD,[a] Bernard Thibault, MD,[a] Marc Dubuc, MD,[a] Paul Khairy, MD, PhD[a,b]

## ABSTRACT

**OBJECTIVES** The impact of beta-blockers on mortality and hospitalizations was assessed in the largest randomized trial of patients with both atrial fibrillation (AF) and heart failure with a reduced ejection fraction (HFrEF): the Atrial Fibrillation-Congestive Heart Failure trial.

**BACKGROUND** Although beta-blockers are the cornerstone of therapy for HFrEF, a recent patient-level meta-analysis cast doubt on their efficacy in patients with coexisting AF.

**METHODS** From a total of 1,376 subjects randomized in the AF-CHF trial, those without beta-blockers at baseline were propensity matched to a maximum of 2 exposed patients. All absolute standardized differences after matching were ≤10%. Primary analyses respected the intention-to-treat principle. In on-treatment sensitivity analyses, beta-blocker status was modeled as a time-dependent covariate.

**RESULTS** Baseline characteristics were comparable among the matched cohorts (mean age 70 ± 11 years, 81% male, and mean left ventricular ejection fraction 27 ± 6%). During a median follow-up of 37 months, beta-blockers were associated with significantly lower all-cause mortality (hazard ratio [HR]: 0.721, 95% confidence interval [CI]: 0.549 to 0.945; p = 0.0180) but not hospitalizations (HR: 0.886; 95% CI: 0.715 to 1.100; p = 0.2232). Similar results were obtained in sensitivity analyses that modeled beta-blockers as a time-dependent variable (HR: 0.668 for all-cause mortality; 95% CI: 0.511 to 0.874; p = 0.0032; HR: 0.814 for hospitalizations; 95% CI: 0.653 to 1.014; p = 0.0658). There were no significant interactions between beta-blockers and patterns (i.e., persistent vs. paroxysmal) or burden of AF with respect to mortality or hospitalizations.

**CONCLUSIONS** In propensity-matched analyses, beta-blockers were associated with significantly lower mortality but not hospitalizations in patients with HFrEF and AF, irrespective of the pattern or burden of AF. These results support current evidence-based recommendations for beta-blockers in patients with HFrEF, whether or not they have associated AF.
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Over the past few decades, several large randomized clinical trials have consistently demonstrated that beta-blockers decrease hospitalizations and improve survival in patients with heart failure and a reduced left ventricular ejection fraction (HFrEF). As such, beta-blockers have become a staple in the management of HFrEF and are strongly recommended (Class I, Level of Evidence: A) by North American (1,2) and European (3) management guidelines. More recently, the Heart

From the [a]Montreal Heart Institute, Université de Montréal, Montreal, Quebec, Canada; and the [b]Montreal Health Innovations Coordinating Center, Université de Montréal, Montreal, Quebec, Canada. The AF-CHF trial was funded by the Canadian Institutes of Health Research (MCT-41552). Dr. Macle has received lecture fees from Bayer, BMS-Pfizer, Boehringer-Ingelheim, Servier, Biosense-Webster, and St. Jude Medical, and research grants from Biosense-Webster, St. Jude Medical, and Boehringer-Ingelheim. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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**ABBREVIATIONS AND ACRONYMS**

**ACE** = angiotensin-converting enzyme

**AF** = atrial fibrillation

**ARB** = angiotensin receptor blocker

**CI** = confidence interval

**HFrEF** = heart failure with a reduced ejection fraction

**HR** = hazard ratio

**LVEF** = left ventricular ejection fraction

**NYHA** = New York Heart Association

Failure Collaborative Group called into question the role of beta-blockers in patients with HFrEF and concomitant atrial fibrillation (AF). In a patient-level meta-analysis of 10 randomized clinical trials that compared beta-blockers with placebo, beta-blockers were not associated with a mortality reduction in the subgroup of 3,063 patients with AF (4). Clinical implications of these provocative findings are substantial, considering that AF and HFrEF frequently coexist, with up to 50% of patients with heart failure developing AF over the course of their disease. However, subgroup analyses based on AF were not pre-specified in the studies included in the meta-analysis. Misclassification errors may arise from relying on a single baseline electrocardiogram to establish the diagnosis of AF because it is an insensitive screening tool for nonpermanent AF (5). Therefore, we sought to clarify the association between beta-blockers and cardiovascular outcomes in the largest randomized clinical trial of patients with both AF and HFrEF, the AF-CHF (Atrial Fibrillation and Congestive Heart Failure) trial. Moreover, because AF was well characterized in the AF-CHF trial, we assessed whether the impact of beta-blockers on outcomes was modulated by the pattern or burden of AF.

## METHODS

**STUDY DESIGN AND PARTICIPANTS.** The AF-CHF trial randomized 1,376 patients with AF and HFrEF from 123 centers to rhythm control treatment (n = 694) versus rate (n = 682) control treatment. The study protocol was previously described (6). In short, patients were required to have a left ventricular ejection fraction (LVEF) ≤35% with symptomatic congestive heart failure or a LVEF <25%, regardless of symptom status. The trial included patients with at least 1 electrocardiographically documented episode of AF that lasted >6 h or required cardioversion in the preceding 6 months, or an episode of AF that lasted >10 min in the preceding 6 months combined with cardioversion for AF at any time. Patients with AF that persisted for >12 months qualified for the study if sinus rhythm could be maintained for >24 h following cardioversion. The study protocol was approved by each center's institutional review board, and all patients provided written informed consent to participate.

Information regarding the baseline rhythm, pattern of AF (i.e., paroxysmal vs. persistent), and time since first diagnosis of AF were collected. The methodology to compute the proportion of time spent in AF was previously detailed (7). In brief, AF burden was quantified by dividing time intervals between visits into quartiles. "Sinus rhythm" or "AF" was assigned to each time point for every patient on the basis of electrocardiographic documentation and presence or absence of AF recurrences between visits. For each patient, the proportion of time spent in AF was calculated by dividing the total time in AF by follow-up duration. For the purposes of this analysis, patients were classified into 2 groups based on whether the proportion of time they spent in AF was equal or superior (i.e., "high AF burden") or inferior (i.e., "low AF burden") to the overall median value for proportion of time spent in AF.

**BETA-BLOCKERS.** Beta-blockers (i.e., metoprolol, carvedilol, or bisoprolol) were recommended for the treatment of heart failure along with angiotensin-converting enzyme (ACE) inhibitors/angiotensin receptor blockers (ARBs), aldosterone antagonists in patients with New York Heart Association (NYHA) functional class III or IV symptoms, and implantable cardioverter-defibrillators in selected patients. Recommended targeted doses for beta-blockers were 100 to 200 mg/day for metoprolol, 25 to 50 mg/day for carvedilol, and 10 mg/day for bisoprolol. Beta-blocker status was recorded at baseline and at each follow-up visit.

**FOLLOW-UP AND OUTCOMES.** Follow-up visits occurred every 4 months for the first 4 years and every 6 months thereafter. The primary outcome was all-cause mortality. Secondary outcomes consisted of cardiovascular mortality, all-cause hospitalizations, cardiovascular hospitalizations, and hospitalizations for worsening heart failure. All outcomes were reviewed and classified by an independent blinded adjudicating committee in the main AF-CHF trial.

**STATISTICAL ANALYSIS.** A matching propensity score approach was used to overcome indication bias in comparing patients who received and who did not receive beta-blockers. Propensity scores in the full cohort were estimated from a nonparsimonious multivariable logistic regression model in which beta-blocker use at baseline was modeled as the dependent variable, and the 28 baseline variables listed in Table 1 were included as covariates (8). These covariates were selected based on consideration of substantive knowledge and statistical associations. By using a greedy matching algorithm, each patient in the control group (n = 229) was matched to a maximum of 2 exposed patients (n = 426) (Figure 1). Improvements in balance across covariates were measured by absolute values of standardized differences in means or proportions of each covariate

**TABLE 1 Baseline Characteristics**

| | Before Propensity-Matching | | | After Propensity-Matching | | |
|---|---|---|---|---|---|---|
| | No Beta-Blocker (n = 291) | Beta-Blocker (n = 1,085) | p Value | No Beta-Blocker (n = 229) | Beta-Blocker (n = 426) | p Value |
| Covariates included in the propensity score | | | | | | |
| Age, yrs | 70.0 ± 11.4 | 66.4 ± 10.8 | <0.0001 | 70.3 ± 11.1 | 69.6 ± 10.1 | 0.4859 |
| Men | 80.4 | 82.0 | 0.5270 | 81.2 | 80.8 | 0.8817 |
| Non-Caucasian | 13.8 | 14.8 | 0.6671 | 14.4 | 14.1 | 0.9122 |
| Randomization to rhythm control | 47.4 | 50.9 | 0.4107 | 45.0 | 43.7 | 0.7552 |
| Left ventricular ejection fraction | 27.5 ± 5.7 | 26.7 ± 6.1 | 0.0544 | 27.5 ± 5.8 | 27.5 ± 5.7 | 0.9984 |
| NYHA class III or IV | 32.6 | 31.0 | 0.5836 | 31.4 | 31.2 | 0.9556 |
| Predominant cardiac diagnosis | | | | | | |
| Coronary artery disease | 50.2 | 47.0 | 0.3368 | 51.1 | 50.1 | 0.7856 |
| Nonischemic cardiomyopathy | 31.6 | 39.0 | 0.0210 | 33.2 | 38.3 | 0.4881 |
| Hypertensive heart disease | 8.6 | 8.8 | 0.8907 | 9.6 | 7.8 | 0.3855 |
| Valvular heart disease | 6.9 | 4.6 | 0.1185 | 6.1 | 5.9 | 0.8922 |
| Other | 2.8 | 0.3 | 0.0003 | 0.0 | 0.0 | – |
| QRS width, ms | 119 ± 33 | 114 ± 31 | 0.0236 | 118 ± 33 | 118 ± 35 | 0.9482 |
| Moderate/severe mitral regurgitation | 36.4 | 30.6 | 0.1445 | 39.7 | 37.1 | 0.5105 |
| Left atrial size, mm | 45 ± 16 | 45 ± 16 | 0.7676 | 46 ± 15 | 45 ± 16 | 0.7087 |
| Creatinine, mmol/L | 114 ± 34 | 112 ± 43 | 0.4503 | 114 ± 34 | 113 ± 36 | 0.7454 |
| Stroke, TIA, intracranial bleed | 10.3 | 8.7 | 0.3840 | 8.7 | 6.8 | 0.3561 |
| Heart rate, beats/min | 79 ± 18 | 78 ± 19 | 0.4448 | 79 ± 18 | 79 ± 20 | 0.9011 |
| Systolic blood pressure, mm Hg | 120 ± 21 | 119 ± 19 | 0.4395 | 119 ± 19 | 119 ± 19 | 0.7453 |
| ACE inhibitor or ARB | 95.2 | 95.7 | 0.7243 | 96.5 | 96.0 | 0.7466 |
| Aldosterone antagonist | 84.5 | 86.5 | 0.3791 | 85.6 | 85.4 | 0.9618 |
| Diuretic | 80.8 | 81.9 | 0.6441 | 79.9 | 70.6 | 0.9190 |
| Amiodarone | 44.0 | 45.2 | 0.5389 | 42.4 | 41.6 | 0.8425 |
| Digoxin | 63.9 | 64.5 | 0.8498 | 63.8 | 65.3 | 0.6815 |
| Oral anti-vitamin K antagonist | 80.1 | 90.5 | <0.0001 | 81.7 | 84.0 | 0.3789 |
| Lipid-lowering drug | 40.9 | 41.1 | 0.5287 | 39.3 | 37.8 | 0.7060 |
| Verapamil or diltiazem | 6.9 | 2.6 | 0.0004 | 6.1 | 4.0 | 0.1517 |
| Implantable cardioverter-defibrillator | 4.1 | 7.8 | 0.0281 | 3.5 | 4.5 | 0.5523 |
| Pacemaker | 15.5 | 11.3 | 0.0562 | 7.4 | 7.5 | 0.9676 |
| Clinical variables related to AF history (not included in propensity score) | | | | | | |
| AF on baseline electrocardiogram | 52.9 | 58.4 | 0.1014 | 55.0 | 60.1 | 0.2527 |
| High burden of AF | 45.0 | 48.3 | 0.5301 | 48.5 | 51.1 | 1.0000 |
| Time since diagnosis of AF | | | 0.0940 | | | 0.3378 |
| 0–6 mos | 54.3 | 57.4 | | 56.3 | 59.0 | |
| 6–12 mos | 19.9 | 22.6 | | 19.7 | 21.7 | |
| >12 mos | 25.8 | 20.0 | | 24.0 | 19.4 | |
| Paroxysmal (vs. persistent) AF | 39.9 | 29.0 | 0.0004 | 38.4 | 31.0 | 0.0390 |

Values are mean ± SD or %.

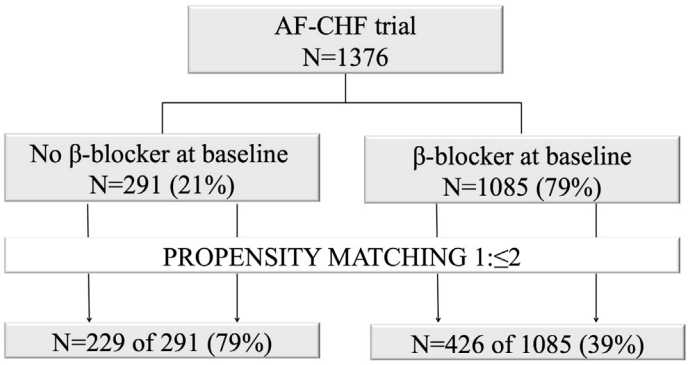
ACE = angiotensin converting enzyme; AF = atrial fibrillation; ARB = angiotensin receptor blocker; NYHA = New Heart Association; TIA = transient ischemic attack.

across exposure groups and expressed as a percentage of the pooled SD. Absolute standardized differences before and after matching were portrayed as Love plots (Figure 2). An absolute standardized difference ≤10%, as applied in our approach, was generally accepted as indicative of inconsequential residual bias.

Categorical variables are summarized as frequencies and percentages. Continuous variables are presented as mean ± SD. Comparisons of categorical covariates between exposed and unexposed groups were achieved using Pearson's chi-square tests, Wilcoxon rank-sum tests, or generalized estimating equation models where appropriate, before and after matching. Continuous variables were compared using Student *t* tests, mixed models, or generalized estimating equation models, where appropriate.

To assess the association between beta-blockers and outcomes, Kaplan-Meier event-free survival curves were estimated, and Cox proportional hazards analyses were conducted separately for each outcome. Time zero was defined as the time of

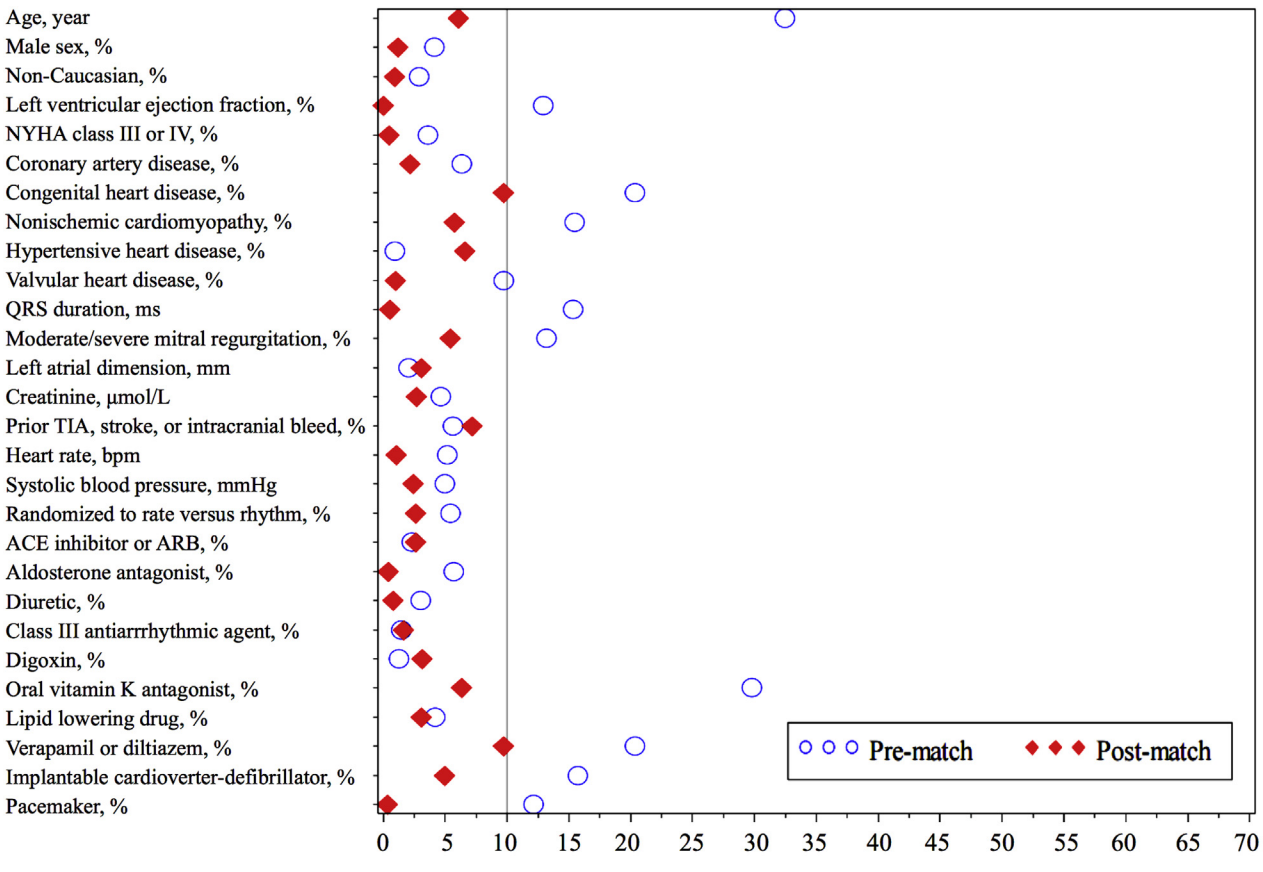
**FIGURE 1 Overview of the Study Cohort**




Study cohort overview. AF-CHF = Atrial Fibrillation-Congestive Heart Failure.

randomization in the survival analyses. Dependency among matched patients induced by the matching scheme was considered as appropriate, and all necessary assumptions were verified. To determine whether characteristics of AF modulated the effects of beta-blockers on mortality (all-cause and cardiovascular) and hospitalizations (all-cause, cardiovascular, and worsening heart failure), the following first-order interaction terms with beta-blockers were tested: high AF burden versus low AF burden; time since first diagnosis of AF; baseline rhythm (AF or sinus rhythm); and general pattern of AF (paroxysmal vs. persistent). All primary analyses respected the intention-to-treat principle. In on-treatment sensitivity analyses, beta-blocker status was modeled as a time-dependent covariate. Two-tailed p values $<0.05$ were considered statistically significant. All analyses

**FIGURE 2 Love Plot of the Absolute Standardized Differences for the 28 Baseline Characteristics**




Love plot of the absolute standardized differences for the 28 baseline characteristics between patients receiving and not receiving beta-blockers at baseline before and after propensity score matching. ACE = angiotensin converting enzyme; ARB = angiotensin receptor blockers; NYHA = New York Heart Association; TIA = transient ischemic attack.

were performed using SAS software version 9.4 (SAS Institute, Cary, North Carolina).

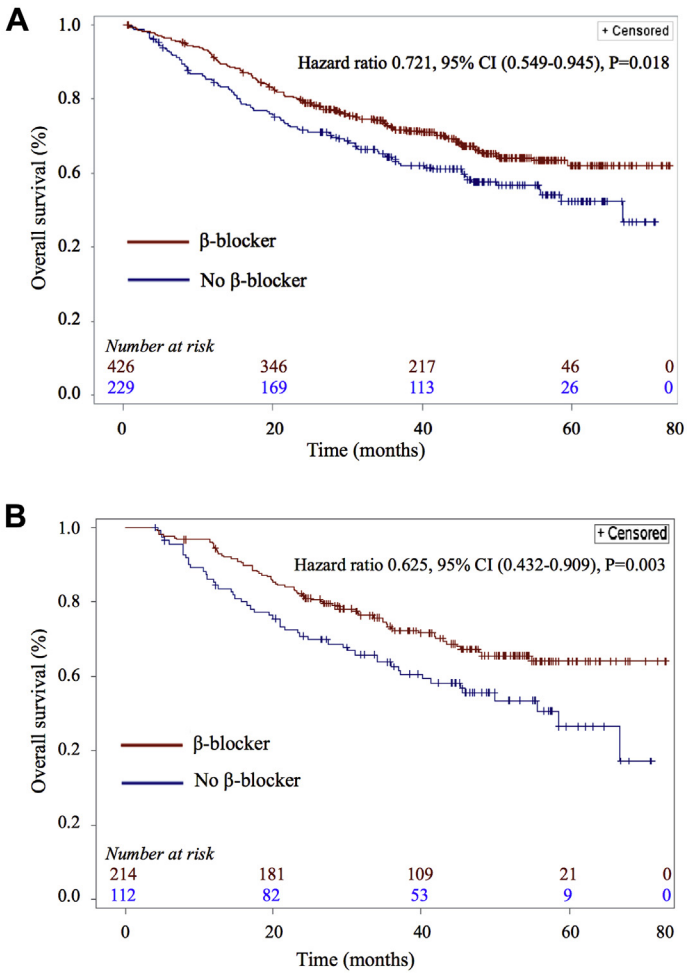
## RESULTS

**BASELINE CHARACTERISTICS.** At baseline, 1,085 (79%) patients in the AF-CHF trial received beta-blockers. In the 291 (21%) patients who did not receive beta-blockers, the reported justification was physician preference in 42%, pulmonary disease in 24%, intolerance in 18%, and other in 16%. Baseline characteristics before and after propensity matching are summarized in Table 1. Before matching, patients not on beta-blockers were significantly older, had a wider QRS interval, and were less likely to have nonischemic cardiomyopathy. They were less likely to receive an oral vitamin K antagonist and more likely to be on a calcium channel blocker. After propensity matching, there were no significant differences in baseline characteristics between those who received and those who did not receive beta-blockers. As shown in Figure 2, post-matching standardized differences for all 28 baseline covariates were <10%. Matched patients were a mean age of 70 ± 11 years, 81% were men, 14% were non-Caucasian, and 31% had NYHA functional class III or IV symptoms. The mean LVEF was 27 ± 6%, and 50% had ischemic cardiomyopathy. Overall, 96% received an ACE inhibitor or ARB, and 85% received an aldosterone antagonist. The median AF burden was 34%, 58% were in AF on the baseline electrocardiogram, 58% were diagnosed with AF within 6 months of randomization, and 66% had persistent AF.

**MORTALITY.** A total of 231 (35%) matched patients died during follow-up: 95 (42%) without beta-blockers and 136 (31%) with beta-blockers. Corresponding survival curves are depicted in Figure 3. As summarized in Table 2, beta-blockers were associated with significantly lower mortality (hazard ratio [HR]: 0.721; 95% confidence interval [CI]: 0.549 to 0.945; p = 0.0180). Overall, 78% of deaths were classified as cardiovascular. The impact of beta-blockers on cardiovascular mortality did not achieve statistical significance (HR: 0.763; 95% CI: 0.562 to 1.037; p = 0.0838). Similar results were obtained in on-treatment sensitivity analyses that modeled beta-blockers as a time-dependent variable (HR: 0.668 for all-cause mortality; 95% CI: 0.511 to 0.874; p = 0.0032; HR: 0.748 for cardiovascular mortality; 95% CI: 0.539 to 1.039; p = 0.0832).

**HOSPITALIZATIONS.** Over the course of the study, 420 (64%) patients were hospitalized: 338 (80%) for cardiovascular reasons and 167 (40%) with worsening heart failure. As shown in Table 2, beta-blockers at baseline were not associated with a significant reduction in all-cause hospitalizations, cardiovascular hospitalizations, or worsening heart failure. Similar results were obtained in on-treatment sensitivity analyses that modeled beta-blockers as a time-dependent variable. In these analyses, beta-blockers were associated with a nonsignificant trend toward fewer overall hospitalizations (HR: 0.814; 95% CI: 0.653 to 1.014; p = 0.0658). Specific causes for hospitalizations are listed in the Online Table 1, none of which were significantly different between groups. A trend toward a higher rate of hospitalizations for AF in patients on beta-blockers (20.7% vs. 13.3%; p = 0.008) was counterbalanced, in part, by numerically

**FIGURE 3 Kaplan-Meier Survival Curves for All-Cause Mortality in Patients With and Without Beta-Blockers at Baseline**




Kaplan-Meier survival curves for all-cause mortality in patients with and without beta-blockers at baseline in the **(A)** matched cohort and in the **(B)** subgroup of matched patients with a high atrial fibrillation burden. CI = confidence interval.

**TABLE 2 Outcomes in Propensity-Matched Cohorts**

| | Events | | | |
|---|---|---|---|---|
| | No Beta-Blockers (n = 229) | Beta-Blockers (n = 426) | HR (95% CI) | p Value |
| Primary intention-to-treat analyses | | | | |
| All-cause mortality | 95 (41.5) | 136 (31.2) | 0.721 (0.549–0.945) | 0.0180 |
| Cardiovascular mortality | 72 (31.4) | 109 (25.6) | 0.763 (0.562–1.037) | 0.0838 |
| All-cause hospitalization | 149 (65.4) | 271 (63.6) | 0.886 (0.715–1.100) | 0.2732 |
| Cardiovascular hospitalization | 119 (52.2) | 219 (51.5) | 0.914 (0.721–1.158) | 0.4557 |
| Hospitalization for worsening HF | 62 (27.1) | 105 (24.7) | 0.894 (0.659–1.214) | 0.4744 |
| Sensitivity analyses (modeling beta-blockers as a time-dependent covariate) | | | | |
| All-cause mortality | – | – | 0.668 (0.511–0.874) | 0.0032 |
| Cardiovascular mortality | – | – | 0.748 (0.539–1.039) | 0.0832 |
| All-cause hospitalization | – | – | 0.814 (0.653–1.014) | 0.0658 |
| Cardiovascular hospitalization | – | – | 0.929 (0.731–1.182) | 0.5505 |
| Hospitalization for worsening HF | – | – | 0.876 (0.644–1.191) | 0.3969 |

Values are n (%).

CI = confidence interval; HF = heart failure; HR = hazard ratio (estimated).

lower rates of hospitalizations for worsening heart failure, acute coronary syndromes, and bradycardia.

**BETA-BLOCKERS AND AF CHARACTERISTICS.** As noted in Online Table 2, there was no significant interaction among beta-blockers and pattern of AF (i.e., persistence vs. paroxysmal), time since diagnosis of AF, presence of AF on the baseline electrocardiogram, and a high burden of AF versus low burden of AF with respect to all-cause mortality, cardiovascular mortality, and hospitalizations. As summarized in **Table 3**, in the subgroup of patients with a high AF burden (n = 326), beta-blockers were associated with a reduction in all-cause mortality (HR: 0.625; 95% CI: 0.432 to 0.904; p = 0.0126) and cardiovascular mortality (HR: 0.662; 95% CI: 0.442 to 0.991; p = 0.0453), along with a nonsignificant reduction in hospitalizations (HR: 0.749; 95% CI: 0.558 to 1.006; p = 0.0552).

**TABLE 3 Outcomes in Patients With a High Burden of Atrial Fibrillation**

| | Events | | | |
|---|---|---|---|---|
| | No Beta-Blockers (n = 112) | Beta-Blockers (n = 214) | HR (95% CI) | p Value |
| All-cause mortality | 50 (44.6) | 66 (30.8) | 0.625 (0.432–0.904) | 0.0126 |
| Cardiovascular mortality | 38 (33.9) | 53 (24.8) | 0.662 (0.442–0.991) | 0.0453 |
| All-cause hospitalization | 77 (68.8) | 132 (61.7) | 0.749 (0.558–1.006) | 0.0552 |
| Cardiovascular hospitalization | 63 (56.2) | 108 (50.4) | 0.792 (0.566–1.108) | 0.1727 |
| Hospitalization for worsening HF | 31 (27.7) | 59 (27.6) | 0.951 (0.594–1.523) | 0.1425 |

Values are n (%).

Abbreviations as in Table 2.

## DISCUSSION

In propensity-matched cohorts with HFrEF and AF, the primary intention-to-treat analysis revealed that beta-blockers were associated with a 28% reduction in all-cause mortality. The magnitude of effect was even more pronounced in an on-treatment analysis, with beta-blockers associated with 33% lower mortality. Detailed information regarding AF history collected in the AF-CHF trial permitted exploratory analyses to assess whether characteristics of AF modulated the association between beta-blockers and mortality. Results were consistent regardless of whether patients had paroxysmal or persistent AF, a high or low burden of AF, or a brief history of AF versus a long-standing history of AF. Although trends favored beta-blockers for secondary outcomes, including cardiovascular mortality and hospitalizations, these analyses did not reach statistical significance. Overall, our results supported current evidence-based recommendations to pursue beta-blockers in all patients with HFrEF, barring contraindications (1,3), regardless of whether they had coexisting AF, which is a highly prevalent condition.

Importantly, our results diverged from an individual patient-level meta-analysis conducted by Kotecha et al. (4), which included data from 10 randomized trials of beta-blockers versus placebo in HFrEF, as well as a smaller preceding meta-analysis (9). In the pooled analysis of 18,254 patients, 26.8% of whom had AF, beta-blockers were associated with significantly lower mortality in patients with sinus rhythm (HR: 0.73; p < 0.001) but not AF (HR: 0.97; p = 0.73) (4). As such, the investigators concluded that beta-blockers "should not be used preferentially over other rate-control medications and not regarded as standard therapy to improve prognosis in patients with concomitant heart failure and AF." Although this meta-analysis challenged the status quo, it was criticized on the basis of methodological issues and biological plausibility (5).

For example, AF was not a pre-specified subgroup in the studies included in the meta-analysis, such that the investigators relied on a single baseline electrocardiogram to diagnose AF. This likely led to a differential misclassification error, a source of potential information bias, by classifying a sizeable proportion of patients with nonpermanent AF as having no AF. The low reported prevalence of AF (17%) in a population with HFrEF was consistent with such a misclassification error (10). To reconcile the discrepant findings, it could be hypothesized that the mortality benefit associated with beta-blockers in HFrEF was modulated by the proportion of time spent in AF, with

beta-blockers being less effective with a higher burden of AF. We specifically addressed this hypothesis by assessing whether AF burden modulated the effect of beta-blockers on mortality. The interaction was nonsignificant (HR: 0.999; 95% CI: 0.995 to 1.004). More specifically, in patients with a high AF burden, beta-blockers were associated with a significant reduction in all-cause (HR: 0.625; $p = 0.0126$) and cardiovascular (HR: 0.662; $p = 0.0453$) mortality.

Other differences in study populations include a higher prevalence of NYHA functional class III or IV symptoms in Kotecha et al.'s (4) study (70% vs. 30%), a higher proportion of patients on digoxin therapy (83% vs. 65%), and a lower proportion receiving oral anticoagulation (58% vs. 82%). It remains unknown whether more advanced disease, a higher prevalence of relative bradycardia, and/or excess mortality due to digoxin (11) or lack of anticoagulation (12) might have offset the benefits of beta-blockers on mortality.

Our results were consistent with data from 2 registries (13,14). In the Swedish Heart Failure Registry that included 7,392 patients with HFrEF and AF (identified by a single electrocardiogram), beta-blockers were associated with a 29% reduction in mortality (13). A second registry of patients with AF included 39,741 subjects with prevalent heart failure (14). At 1-year follow-up, beta-blockers were associated with 25% lower mortality. However, the study could not distinguish between patients with heart failure and a preserved versus reduced LVEF, nor could it adjust for other important covariates such as NYHA functional class.

Reasons as to why beta-blockers were not associated with a significant reduction in hospitalizations in our study, despite events in >60% of patients, remain speculative. Our analyses suggested that the salutary effects of beta-blockers were counterbalanced, in part, by a trend toward a higher rate of hospitalizations for AF. The high rate of hospitalizations for AF overall (i.e., 20%) might reflect the AF-CHF trial design, in which the rhythm control strategy was associated with aggressive attempts to maintain sinus rhythm. Nevertheless, all HRs that assessed the impact of beta-blockers were numerically <1 in intention-to-treat and on-treatment analyses, despite the lack of statistical significance. Providing further reassurance, a nearly statistically significant reduction in hospitalizations was observed in patients with a high AF burden (HR: 0.749; $p = 0.0552$).

**STUDY LIMITATIONS.** The study was retrospective in nature and subject to associated limitations. Beta-blocker therapy was not randomly assigned, which raised the potential for indication bias. To address this limitation, a propensity-matching approach was used based on a comprehensive analysis of variables that included randomization to rate versus rhythm control, demographic data, etiology of the cardiomyopathy, LVEF, NYHA functional class symptoms, and pharmacotherapy. All baseline covariates were well balanced between groups following propensity matching. Although the choice of beta-blocker (i.e., metoprolol, carvedilol, or bisoprolol) and targeted doses were recommended by the study protocol, selected agents and doses received were not recorded. Therefore, a class effect was assumed, and dose-response relationships could not be assessed. The study population in the AF-CHF trial was limited to patients with HFrEF and nonpermanent (i.e., paroxysmal or persistent) AF at baseline, such that results could not be directly extrapolated to heart failure patients with a preserved ejection fraction or permanent AF. The subgroup of patients with a high AF burden was likely most comparable to the study population with AF in the work by Kotecha et al. (4). Considering that AF characteristics did not modulate the impact of beta-blockers on mortality, patients with permanent AF might be expected to derive similar benefits from beta-blockers, although this remains to be demonstrated. Finally, p values were not corrected for multiple comparisons. Although there are arguments for and against such adjustments, reducing the type I error comes at the expense of increasing the risk of a type II error, which could result in discounting potentially important associations identified by exploratory research (15).

## CONCLUSIONS

In the largest randomized trial of patients with HFrEF and coexisting AF, beta-blockers were associated with significantly lower all-cause mortality but not hospitalizations. The mortality reduction was not modulated by AF characteristics, including type of AF (i.e., paroxysmal or persistent), proportion of time spent in AF, and time since first diagnosis. Notwithstanding the acknowledged limitations and the smaller sample size, our results challenged a contemporary patient-level meta-analysis and lent credence to current guidelines, which recommend beta-blockers for patients with HFrEF, without distinguishing between those with or without AF.

**REPRINT REQUESTS AND CORRESPONDENCE:** Dr. Paul Khairy, Montreal Heart Institute, 5000 Bélanger Street East, Montreal, Quebec H1T 1C8, Canada. E-mail: paul.khairy@umontreal.ca.

## PERSPECTIVES

**COMPETENCY IN MEDICAL KNOWLEDGE 1:** Beta-blockers are associated with a reduction in all-cause mortality in patients with HFrEF and concomitant paroxysmal or persistent AF.

**COMPETENCY IN MEDICAL KNOWLEDGE 2:** The mortality reduction associated with beta-blockers in patients with HFrEF is not modulated by the pattern of AF or proportion of time spent in AF.

**TRANSLATIONAL OUTLOOK:** Further studies are required to determine whether the mortality reduction associated with beta-blockers in patients with HFrEF and AF represents a class effect and whether a dose-response relationship can be established.

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**KEY WORDS** atrial fibrillation, beta-blockers, heart failure, mortality

**APPENDIX** For supplemental tables, please see the online version of this article.