CLINICAL RESEARCH STUDY

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New-onset Atrial Fibrillation Predicts Heart Failure Progression

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ABSTRACT

BACKGROUND: Atrial fibrillation and heart failure with reduced left ventricular ejection fraction have interrelated pathophysiologies. New-onset atrial fibrillation in heart failure patients has been associated with increased mortality, but has not been definitively related to clinical heart failure progression.

METHODS: To test the hypothesis that new-onset atrial fibrillation is related to clinical heart failure progression, in 2392 patients without atrial fibrillation at randomization in the Beta-blocker Evaluation of Survival Trial we measured clinical endpoints in patients who did (Group 1, n = 190) or did not (Group 2, n = 2202) develop new-onset atrial fibrillation. Results were also compared with the 303 patients who entered the trial in atrial fibrillation (Baseline/chronic group), and in Group 1/2 patients we conducted a multivariate analysis of covariates potentially related to time to first heart failure hospitalization.

RESULTS: Compared with Group 2, Group 1 patients post atrial fibrillation onset had a ~2-fold increase in mortality ($P < .0001$) and a ~4.5-fold increase in all-cause or heart failure hospitalization days/patient (hospitalization burden, both $P < .0001$). In Group 1, both types of hospitalization burden were 2.9-fold greater than in the Baseline/chronic group ($P < .001$), and hospitalization burden increased ~6-fold ($P < .0001$) compared with the pre-event period. On multivariate analysis, new-onset atrial fibrillation was a highly significant ($P < .00001$) predictor of heart failure hospitalization.

CONCLUSIONS: In addition to being a discrete electrophysiologic event, in heart failure patients, new-onset atrial fibrillation is a predictor of and trigger for clinical heart failure progression.

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KEYWORDS: Atrial fibrillation; Beta-blockers; Heart failure markers; HFrEF

Chronic heart failure is increasing in prevalence,[1,2] and in its most common[3] form resulting from reduced left ventricular ejection fraction ("HFrEF," termed "heart failure" hereafter) is associated with significant morbidity and mortality from progressive pump dysfunction and arrhythmias. One of the most common associated arrhythmias is atrial fibrillation, which is substantially increased in incidence compared with non-heart-failure populations[4] and may increase stroke risk, worsen cardiac function,[4-6] and increase mortality.[6-9] The index pathophysiology of heart failure is ventricular eccentric hypertrophic structural remodeling,[10] while atrial fibrillation is the result of similar structural, as well as distinct electrical, atrial remodeling processes.[4] Additionally, atrial fibrillation may contribute to heart failure progression through tachycardia-mediated effects,[5] and heart failure progression contributes to the development of atrial fibrillation through elevated filling pressures and neurohormonal activation.[4]

We tested the hypothesis that new-onset atrial fibrillation is a predictor of clinical heart failure progression. This has been suggested in previous epidemiologic[7,8] and smaller observational[6,11] studies but has not been evaluated in a large longitudinal heart failure cohort with a substantial number of new-onset atrial fibrillation events and measures of hospitalizations. The Beta-blocker Evaluation of Survival

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Trial (BEST) is such a vehicle, as it enrolled 2708 patients with advanced heart failure, had a relatively long follow-up period,[12] extensive documentation of clinical events,[13] a large number of cases of new-onset atrial fibrillation (n = 190),[14] and, compared with other placebo-controlled β-blocker-heart failure Phase 3 trials, had 2-3 times the number of mortality and hospitalization events.

CLINICAL SIGNIFICANCE

- A marked increase in mortality and hospitalization burden occurs post atrial fibrillation (AF) event in heart failure (HF) patients with reduced left ventricular ejection fractions ("HFrEF"), resulting in new-onset AF being a predictor and marker of HF progression.
- This is likely due to multiple risk factors for heart failure progression plus the AF event itself.
- HFrEF patients who develop AF should be observed carefully, and many will need intensified HF therapy.

METHODS

Study Population

BEST was a randomized trial of the experimental β-blocker/sympatholytic agent bucindolol vs placebo in patients with New York Heart Association Class III-IV symptoms and left ventricular ejection fraction ≤0.35.[12] The trial had a median follow-up of 24 months, and the protocol and main outcomes have been described previously.[12,13] In a post hoc analysis, new-onset atrial fibrillation events were identified from prospectively collected adverse event case report forms and event-associated electrocardiograms (ECGs) that were certified by cardiologist investigators at each site,[14] as well as from planned study ECGs performed at baseline, 3 months, and 12 months.[14] Cause-specific mortality was adjudicated by an endpoints committee, while all-cause and cause-specific hospitalizations were assessed by investigator case report forms.[12,13] A history of atrial fibrillation prior to study entry was obtained from prerandomization screening questionnaires.

Statistical Analysis

Patients without atrial fibrillation at randomization were divided into 2 groups for the primary analysis: Group 1, patients who developed atrial fibrillation during the trial; and Group 2, patients who remained free of atrial fibrillation. The primary analysis was a Group 1 vs 2 comparison of mortality and hospitalization burden (hospitalization days/patient, a measure that encompasses all hospitalizations plus lengths of stay), as well as a multivariate analysis of time to first hospitalization due to heart failure in Groups 1/2. A comparison of mortality and hospitalization burden between Group 1 and patients who had atrial fibrillation on their baseline ECG (Baseline/chronic group) was a secondary analysis.

For baseline characteristics, continuous and categorical variables were compared using Student's *t* test and chi-squared, respectively. Mortality rates were compared by hazard ratios generated by Cox modeling, with significance levels determined by the log-rank statistic. As per the trial's prespecified statistical analysis plan, Cox modeling was adjusted for study treatment as well as the randomization stratification variables of ± coronary artery disease, left ventricular ejection fraction ≤0.20/>0.20, race, and sex. Within the subset of patients free of atrial fibrillation at baseline, those who developed atrial fibrillation during the trial represent a "survivors" analysis, with a zero risk of mortality prior to the event. Therefore, in Group 1, mortality was assessed from the time of the event, a form of left truncation. Follow-up was censored at the time of cardiac transplantation. Because the data were not normally distributed, hospitalization burden was evaluated by nonparametric methods.

Step-wise multivariate analysis modeling of the time to first heart failure hospitalization utilized the 4 randomization stratification variables, as well as the 9 other prespecified subgroup analysis variables in the BEST protocol.[12] On a post hoc basis, new-onset atrial fibrillation, decline in left ventricular ejection fraction by ≥5 units (fraction × 100) at 12 months, and anti-arrhythmic drug use were added to the model. The multivariate analysis cohort contained a complete set of all 16 variables in the model; Baseline/chronic group patients were excluded because they could not have developed new-onset atrial fibrillation.

RESULTS

Atrial Fibrillation Events

Thirteen of the 2708 entire cohort patients had missing baseline ECGs and were not included in the analysis. At study entry there were 2392 patients not in atrial fibrillation (2176 sinus rhythm and 216 other rhythms) (**Table 1**). Of these, 190 developed new-onset atrial fibrillation (Group 1) at a mean of 381 ± 318 (median 307) days from randomization, for overall and annualized rates of 7.9% and 4.0%, respectively. Of the 190 events, 161 (85%) had an adverse event case report form, while 29 (15%) were detected from routine follow-up ECGs with no adverse event report.[14] Sixty-eight percent of the new-onset episodes lasted >7 days, and 91% >24 hours.[14] Of the 303 Baseline/chronic group patients, 29 (9.6%) converted to sinus rhythm during the trial.[15]

Baseline Characteristics

Compared with Group 2, Group 1 patients differed in multiple baseline characteristics that are associated with worse outcomes in heart failure, including older age, more males, lower left ventricular ejection fractions, a longer