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CLINICAL RESEARCH

Bucindolol for the Maintenance of Sinus Rhythm in a Genotype-Defined HF Population

The GENETIC-AF Trial

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ABSTRACT

OBJECTIVES The purpose of this study was to compare the effectiveness of bucindolol with that of metoprolol succinate for the maintenance of sinus rhythm in a genetically defined heart failure (HF) population with atrial fibrillation (AF).

BACKGROUND Bucindolol is a beta-blocker whose unique pharmacologic properties provide greater benefit in HF patients with reduced ejection fraction (HFrEF) who have the $beta_1$-adrenergic receptor (*ADRB1*) Arg389Arg genotype.

METHODS A total of 267 HFrEF patients with a left ventricular ejection fraction (LVEF) <0.50, symptomatic AF, and the *ADRB1* Arg389Arg genotype were randomized 1:1 to receive bucindolol or metoprolol therapy and were up-titrated to target doses. The primary endpoint of AF or atrial flutter (AFL) or all-cause mortality (ACM) was evaluated by electrocardiogram (ECG) during a 24-week period.

RESULTS The hazard ratio (HR) for the primary endpoint was 1.01 (95% confidence interval [CI]: 0.71 to 1.42), but trends for bucindolol benefit were observed in several subgroups. Precision therapeutic phenotyping revealed that a differential response to bucindolol was associated with the interval of time from the initial diagnoses of AF and HF to randomization and with the onset of AF relative to that of the initial HF diagnosis. In a cohort whose first AF and HF diagnoses were <12 years prior to randomization, in which AF onset did not precede HF by more than 2 years (n = 196), the HR was 0.54 (95% CI: 0.33 to 0.87; p = 0.011).

CONCLUSIONS Pharmacogenetically guided bucindolol therapy did not reduce the recurrence of AF/AFL or ACM compared to that of metoprolol therapy in HFrEF patients, but populations were identified who merited further investigation in future phase 3 trials. (J Am Coll Cardiol HF 2019;7:586–98) © 2019 Published by Elsevier on behalf of the American College of Cardiology Foundation.

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Atrial fibrillation (AF) is a common and serious medical problem associated with significant morbidity and mortality, especially in patients with heart failure (HF) (1). Development of AF is associated with increased risk of adverse cardiovascular outcomes, and when AF occurs in patients with HF, these adverse effects are accentuated (2,3). AF and HF often coexist and have common risk factors as well as overlapping pathophysiologies (3). Therefore, there is a strong rationale for minimizing the occurrence of AF in patients with HF. Antiarrhythmic drugs can reduce AF burden but have many side effects, including proarrhythmia, and many agents are contraindicated in HF patients (1). Although catheter ablation shows promise for preventing recurrent AF in HF patients with reduced ejection fraction (HFrEF) (4,5), it may not be suitable or practical for many patients. Thus, there is an unmet need for safe and effective drugs to reduce AF in patients with HF. Beta-blockers are the first-line therapy for HFrEF due to their benefits in reducing morbidity and mortality and are widely used in HF patients with AF to control ventricular response rate. In addition, beta-blockers have modest AF prevention effects in HFrEF patients (6).

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Bucindolol is a nonselective beta-blocker with mild vasodilator properties and 2 unique antiadrenergic properties: a moderate sympatholytic effect (7) and an inverse agonism for the *ADRB1* Arg389 major allele gene product (8), a property which promotes inactivation of constitutively active beta$_1$-adrenergic receptors. The treatment effects of bucindolol appear to be enhanced in patients homozygous for *ADRB1* Arg389 (*ADRB1* Arg389Arg) (8,9). In patients with advanced HFrEF who carry this genotype, a 74% reduction in the development of AF was observed for patients in sinus rhythm at baseline who received bucindolol compared to those who received placebo (10). Metoprolol and carvedilol do not appear to confer similar clinical benefits in patients with an the *ADRB1* Arg389Arg genotype (11,12). Therefore, the GENETIC-AF (Genotype-Directed Comparative Effectiveness Trial of Bucindolol and Toprol-XL for the Prevention of Symptomatic Atrial Fibrillation/Atrial Flutter in Patients with Heart Failure) trial was designed to evaluate the efficacy of a pharmacogenetically guided rhythm control intervention with bucindolol compared to that with metoprolol for the prevention of AF or atrial flutter (AFL) in an *ADRB1* Arg389Arg population with HFrEF at risk of AF/AFL recurrence.

ABBREVIATIONS AND ACRONYMS

ADRB1 = beta$_1$-adrenergic receptor gene

AF = atrial fibrillation

AFL = atrial flutter

Arg = arginine

DTRI = diagnosis to randomization index

DxT = time from initial diagnosis to randomization

HF = heart failure

HFlrEF = HF with lower-range ejection fraction (LVEF <0.40)

HFmrEF = HF with mid-range ejection fraction (LVEF ≥0.40 to <0.50)

HFrEF = HF with reduced ejection fraction (LVEF <0.50)

ICM = insertable cardiac-monitor

METHODS

STUDY DESIGN. The GENETIC-AF study was a multicenter, randomized, double-blind, comparative efficacy trial in a genotype-defined population with HFrEF and AF. HFrEF was defined as a left ventricular ejection fraction (LVEF) <0.50 (Online Appendix). The trial had an adaptive design that allowed for a seamless transition from Phase 2B to Phase 3 based on review of interim data. The rationale and design of the trial have been previously reported (13).

Patients were randomly assigned to receive bucindolol or metoprolol and were up-titrated to target doses (Online Table 1). Following up-titration, electrical cardioversion (ECV) was performed if needed to establish sinus rhythm prior to the start of follow-up. During the 24-week follow-up period, heart rhythm was monitored by 12-lead electrocardiography (ECG) every 4 weeks (Online Figure 1). A prospectively defined device substudy permitted continuous heart rhythm monitoring to assess AF burden. Substudy participants had a pre-existing pacemaker or defibrillator with an atrial lead (Medtronic, Manalapan Township, New Jersey) or were implanted with a Reveal LINQ (Medtronic) insertable cardiac-monitor (ICM) prior to the start of follow-up. After week 24, patients continued to receive a blinded study drug and had clinic visits every 12 weeks for assessments of efficacy and safety.

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Patients who had LVEF <0.50 were assessed in the previous 12 months, and those with symptomatic paroxysmal or persistent AF were assessed in the previous 180 days and were receiving optimal anticoagulation therapy for stroke prevention. Patients were genotyped at screening, and those who were positive for the *ADRB1* Arg389Arg variant were eligible for randomization.

Exclusion criteria included New York Heart Association (NYHA) functional class IV symptoms, clinically significant fluid overload, permanent AF (defined as an ongoing AF event >1 year), antiarrhythmic therapies in the previous 7 days, prior atrioventricular node ablation, high-grade atrioventricular block, catheter ablation for AF/AFL in previous 30 days, and prior intolerance or contraindication to beta-blocker therapy. Details of the trial entry criteria have been previously reported (13).

The active comparator, metoprolol succinate (Toprol-XL), is a selective $beta_1$-adrenergic receptor blocker indicated for the treatment of HF. Metoprolol was selected as the active comparator to ensure continuity with previous HF trials and because it has demonstrated effectiveness in preventing AF in HFrEF patients (14,15) but does not appear to confer enhanced benefits in patients with an *ADRB1* Arg389Arg genotype (11,12).

Patients were randomized (1:1) to treatment with bucindolol or metoprolol, which was over-encapsulated to maintain blinding. Because bucindolol is administered twice daily whereas metoprolol is given once daily, a placebo dose was included for the metoprolol arm, and all study drugs were administered twice daily. Randomization was centralized and stratified by cause of HF (ischemic or nonischemic), LVEF (<0.35, ≥0.35), device type (ICM, pacemaker, defibrillator, or no device), and rhythm at randomization (sinus rhythm, AF/AFL), using 16,000 randomly generated numbers and a block size of 4. Study drug was titrated weekly to obtain a target dosage of 100 mg twice daily (50 mg twice daily if <75 kg) for bucindolol (16) and 200 mg once per day for metoprolol (17) (Online Table 1). Patients experiencing AF/AFL during follow-up remained receiving the blinded study drug therapy and could undergo ECV, ablation, or start therapy with amiodarone or dofetilide.

The *ADRB1* Arg389Gly genotype was determined by reverse transcription polymerase chain reaction using DNA extracted from whole blood. Systemic venous plasma norepinephrine was assayed by high-pressure liquid chromatography using electrochemical detection, and venous plasma N-terminal pro-B-type natriuretic peptide (NT-proBNP) was measured by electrochemiluminescence immunoassay.

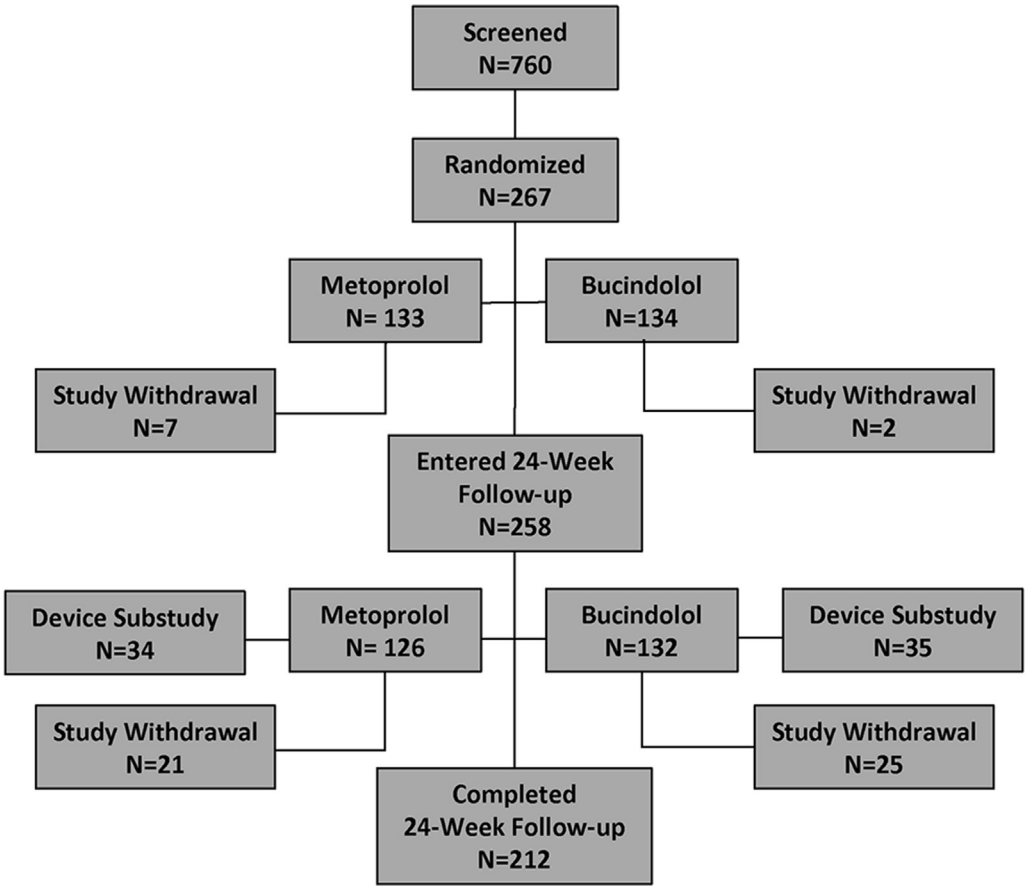
Study design, conduct, and performance were overseen by an 11-member steering committee and monitored by a 3-member data and safety monitoring committee (DSMB) who also performed the interim efficacy analysis (see committee composition in Online Appendix). The protocol was approved by the Institutional Review Board/Ethics Committee, and all patients provided written informed consent.

STATISTICAL ANALYSES. For the interim analysis, the endpoint of interest was time to first event of AF/AFL or all-cause mortality (ACM) during a 24-week follow-up period. The primary endpoint for the planned Phase 3 study was time to symptomatic AF/AFL or ACM, with symptoms captured by a study-specific questionnaire (Online Appendix). A clinical events committee, blinded to treatment assignment, adjudicated the first occurrence of the AF/AFL endpoint, including the association of new or worsening symptoms. Sample size for Phase 3 assumed a 60% event rate in the metoprolol arm, a 25% relative risk reduction with bucindolol, and an accrual of 330 primary events in approximately 620 patients for 90% power at an alpha value of 0.01.

The efficacy analysis was conducted according to intention-to-treat with censoring at 24 weeks for patients not experiencing an event. Hazard ratio (HR) and 95% confidence interval (CI) values were determined by Cox proportional hazards models with adjustment for the 4 randomization strata and treatment as a covariate. Testing for superiority was performed using a 2-sided significance level of 0.05. Patients who died prior to the start of follow-up and patients who were unable to establish sinus rhythm post-ECV were assigned an event on day 1. Patients were censored on day 1 if they were in AF/AFL and the ECV procedure was not performed or if they withdrew from the study prior to the start of follow-up.

Variables identified in the GENETIC-AF statistical analysis plan (SAP) (Online Appendix) that were potential predictors of the primary endpoint were investigated by precision therapeutic phenotyping. Hypothesis-based elements (e.g., AF duration, AF type, LVEF, NYHA functional class, and NT-proBNP and norepinephrine concentrations) and hypothesis-free elements (e.g., HF duration, initial study dose) were included in the multivariate methodology, which was applied to both obvious and nonobvious data to identify a therapeutic phenotype appropriate for investigating in Phase 3. To examine the relationship between HF duration and bucindolol effectiveness for reducing HF events, data from the BEST (Beta-Blocker Evaluation of Survival Trial;

FIGURE 1 Consort Diagram



The proportion of patients with the *ADRB1* Arg389Arg genotype was consistent with previous findings (8-11).

NCT00000560) (16) and pharmacogenetic substudy (8) were analyzed for the endpoint of time to all-cause mortality or first HF hospitalization (ACM or HFH).

Time to first event of AF/AFL or ACM was assessed in the device substudy following methodology similar to that for the primary endpoint, with an AF/AFL event prospectively defined as an AF burden lasting ≥6 h per day as recorded by continuous monitoring. Six h of AF burden has previously been shown to be associated with an increased rate of hospitalization for HF (18). Due to the smaller sample size in the substudy, treatment effect estimates were determined based on Cox proportional hazards models with no adjustment for randomization strata.

Normally distributed continuous variables were analyzed by Student's *t*-tests or analysis of variance (ANOVA) where appropriate. Neurohormonal changes from baseline and diagnosis to randomization index (DTRI) data were analyzed by Wilcoxon signed rank test and between-group differences by the Wilcoxon rank sum test. Categorical variable differences were assessed by chi square or Fisher exact test.

An interim analysis examined data from the initial Phase 2B population. If the DSMB determined that the data were consistent with pre-trial assumptions, the trial was to seamlessly proceed to Phase 3 (see Online Appendix for SAP). To aid in signal detection, Bayesian predictive probability of success estimates (19,20) were generated and compared to pre-specified thresholds for each potential outcome (i.e., Phase 3 transition, Phase 2B completion, or futility). Based on the interim analysis, the DSMB recommended completion of Phase 2B, and the data from this population are presented below.

RESULTS

POPULATION AND BASELINE CHARACTERISTICS. The trial was conducted in 92 centers in 6 countries

TABLE 1 Baseline Characteristics

	Entire Study			Device Substudy		
	All Patients (N = 267)	Bucindolol (n = 134)	Metoprolol (n = 133)	All Patients (N = 69)	Bucindolol (n = 35)	Metoprolol (n = 34)
Age, yrs	65.6 ± 10.1	65.8 ± 10.3	65.5 ± 10.0	66.1 ± 10.7	65.5 ± 11.5	66.8 ± 9.9
Males/females	82/18	83/17	81/19	93/7	94/6	91/9
White/black/Asian/other	96/2/1/1	96/1/1/2	96/2/1/1	96/1/1/2	94/0/3/3	97/3/0/0
LVEF	0.36 ± 0.10	0.36 ± 0.10	0.36 ± 0.10	0.34 ± 0.08	0.33 ± 0.08	0.36 ± 0.09
NYHA functional classes I/II/III	28/57/15	30/60/10	26/54/20	23/57/20	29/49/23	18/65/18
Ischemic/nonischemic HF	32/68	31/69	33/67	28/72	29/71	26/74
Randomized in AF/not in AF	51/49	49/51	52/48	65/35	63/37	68/32
Persistent/paroxysmal AF	51/49	51/49	51/49	64/36	63/37	65/35
HF DxT duration, days	1,153 ± 1,909	1,252 ± 2,070	1,054 ± 1,733	1,168 ± 1,723	1,208 ± 1,880	1,126 ± 1,572
AF DxT duration, days	1,306 ± 2,240	1,431 ± 2,271	1,180 ± 2,209	1,355 ± 1,984	1,444 ± 1,997	1,263 ± 1,995
Systolic blood pressure, mm Hg	123.3 ± 15.3	124.7 ± 14.9	121.8 ± 15.7	123.3 ± 15.1	122.4 ± 15.7	124.2 ± 14.5
Diastolic blood pressure, mm Hg	75.3 ± 10.8	75.8 ± 11.0	74.8 ± 10.6	75.0 ± 10.1	73.7 ± 9.9	76.3 ± 10.3
Heart rate, beats/min	76.3 ± 17.8	76.5 ± 17.9	76.0 ± 17.7	78.4 ± 17.2	76.8 ± 16.4	80.1 ± 18.1
Previous ECV/AF ablation/type III AAD	49/21/48	49/21/50	50/20/46	55/13/54	57/17/57	53/9/50
Device type: ICM/PM/ICD	16/17/15	17/15/18	15/20/12	62/22/16	66/20/14	59/24/18
Norepinephrine, pg/ml	673 ± 353	682 ± 348	664 ± 359	706 ± 368	710 ± 398	702 ± 339
NT-proBNP, pg/ml	801 (384–1,420)	777 (355–1,326)	861 (420–1,607)	996 (457–1,645)	923 (365–1,506)	1,013 (537–1,806)

Values are mean ± SD, %, or median (interquartile range).

AAD = antiarrhythmic drug; AF DxT Duration = time from AF diagnosis to randomization; ECV = electrical cardioversion; HF DxT duration = time from HF diagnosis to randomization; ICD = insertable cardiac-defibrillator; ICM = insertable cardiac-monitor; NT-proBNP = N-terminal pro-B-type natriuretic peptide; PM = pacemaker.

(Canada, Hungary, the Netherlands, Poland, Serbia, and the United States) between April 2014 and December 2017. A total of 760 patients were screened (Figure 1); 362 (48%) were excluded by screening due to genotype, 73 (9.6%) did not meet other eligibility criteria, and 58 (7.6%) were excluded due to other reasons (e.g., withdrawal of consent, lost to follow-up). The remaining 267 patients were randomized to receive the study drug and were up-titrated to target doses. Compliance was >90% in both groups, with a higher proportion of patients attaining target doses for bucindolol than for metoprolol (84% and 72%, respectively; p = 0.035).

Baseline characteristics were well balanced between treatment groups (Table 1). Mean LVEF was 0.36 ± 0.10, 72% had NYHA functional class II or III symptoms at baseline, 51% had persistent AF, and plasma NT-proBNP concentrations were elevated at baseline (median: 801 pg/ml; interquartile range [IQR]: 384 to 1,420 pg/ml). ECV was required in 46% of patients to establish sinus rhythm prior to the start of follow-up. Approximately one-half of all patients (48%) had implanted monitoring devices, which included ICMs inserted for the trial (16%) and pre-existing pacemakers or defibrillators (32%). Nearly all patients (94%) were receiving beta blocker therapy during the screening period prior to randomization.

EFFICACY OUTCOMES. A total of 143 events were observed for the efficacy endpoint, including 121 AF/AFL events, 19 ECV failures, and 3 deaths. Nearly all AF/AFL events were adjudicated as symptomatic by a blinded clinical events committee (114 of 121 [94%]). Event rates for the bucindolol group were similar to those of the metoprolol group (54% and 53%, respectively), with a HR of 1.01 (95% CI: 0.71 to 1.42) for the covariate-adjusted Cox proportional hazards model (Figure 2). In a pre-specified analysis (Online Appendix, SAP and Phase 2B amendment) of regional subgroups (Table 2, Online Figure 3), a trend toward bucindolol benefit compared to metoprolol was observed in the U.S. subgroup (HR: 0.70; 95% CI: 0.41 to 1.19), which was not seen in Canada (HR: 1.52; 95% CI: 0.68 to 3.43) or in Europe (HR: 1.01; 95% CI: 0.48 to 2.14).

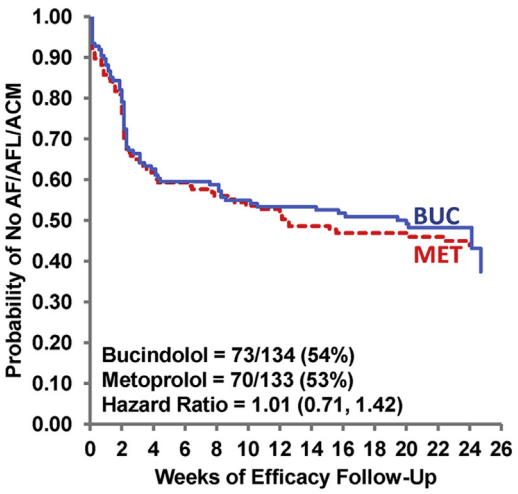
DEVICE SUBSTUDY. The device substudy included 69 patients from the United States (n = 42), Canada (n = 21), and Europe (n = 6) who underwent continuous atrial rhythm monitoring. Cardiac monitors were inserted in 43 patients for the trial, whereas 26 patients had pre-existing pacemakers or insertable cardioverter-defibrillators (ICDs). The baseline characteristics of the substudy were well balanced between the 2 groups and were generally similar to the overall population (Table 1); however, the substudy, compared to the overall population, had a higher proportion of males (93% vs. 82%, respectively), persistent AF (64% vs. 51%, respectively), and AF at the time of randomization (65% vs. 51%, respectively).

An analysis of time to first event of AF/AFL or ACM was conducted in the device substudy following similar methodology for the primary endpoint. As shown in **Figure 3**, a trend toward bucindolol benefit compared to metoprolol was observed by device-based detection (HR: 0.75; 95% CI: 0.43 to 1.32). Similar results were observed when the substudy population was assessed by intermittent, clinic-based 12-lead ECGs (HR: 0.69; 95% CI: 0.38 to 1.23); however, the device-detected endpoint generally occurred earlier than the ECG-based endpoint (median: 6.5 days; $p < 0.0001$). For detection of subsequent ECG-determined AF, AF burden lasting ≥6 h had a sensitivity of 100%, a specificity of 87%, and an accuracy of 96%.

PATIENT CHARACTERISTICS AND TREATMENT RESPONSE BY REGION. Differences among treatment response observed in the United States and those in non-U.S. cohorts prompted examination of baseline characteristics by region (Online Table 2). Generally, the non-U.S. cohort had less severe HF than the U.S. cohort, as demonstrated by significantly higher LVEF (0.39 vs. 0.33, respectively), systolic blood pressure (126 vs. 120 mm Hg, respectively), and NYHA functional class I symptoms (39% vs. 17%, respectively), as well as significantly lower plasma NT-proBNP concentrations (1,135 vs. 1,380 pg/ml, respectively) and NYHA functional class III symptoms (5% vs. 26%, respectively). Notably, patients in the non-U.S. cohort had a more recent diagnosis of HF (**Table 2**, Online Table 2), with a mean time from HF diagnosis to randomization that was less than one-half that in the U.S. group (2.0 vs. 4.5 years, respectively); whereas, the mean time from AF diagnosis to randomization was similar between the 2 groups (3.8 vs. 3.4 years, respectively).

To quantify the relationship between the initial development of AF and HF, an index termed the DTRI was derived from information provided in case report forms. This index represents the differences between the HF duration (i.e., the time of HF diagnosis to randomization) and the AF duration (i.e., the time of AF diagnosis to randomization), with positive values representing HF onset prior to AF and negative values representing AF onset prior to HF. As shown in **Table 2**, the U.S. and non-U.S. cohorts had significant differences in the relative timing of AF and HF onset as measured by mean DTRI ($p < 0.0005$). The U.S. cohort, on average, had HF for more than 1 year prior to developing AF, whereas, the non-U.S. cohort had a diagnosis of AF for nearly 2 years prior to developing HF. Interestingly, bucindolol response for the primary endpoint correlated with mean DTRI (rho [ρ] = −0.93; $p = 0.020$), with poor response seen in populations having long-standing AF prior to the development of HF (i.e., Hungary and Canada) and good response in populations with concurrent or previous onset of HF prior to the development of AF (i.e., United States, Poland, and Serbia).

FIGURE 2 Time to First AF/AFL/ACM Event



Number at Risk

Week	0	8	16	24
BUC	134	75	64	39
MET	133	68	55	41

The Cox proportional hazards model was adjusted for the 4 randomization strata. Nonstratified hazard ratio (HR) was 0.96 (95% confidence interval [CI]: 0.69 to 1.33). Stratified analysis including adjustment for the previous use of class III anti-arrhythmic drugs (yes/no) HR was 0.92 (95% CI: 0.63 to 1.33). AF = atrial fibrillation; AFL = atrial flutter; ACM = all-cause mortality; BUC = bucindolol; MET = metoprolol.

BASELINE CHARACTERISTICS PREDICTING ENDPOINT FREQUENCY AND INTERACTION WITH TREATMENT. Cox proportional hazards regression modeling was performed to explore pre-specified variables (SAP) (Online Appendix) that were potential predictors of the primary endpoint (Online Table 3). Three variables violated the Cox model proportionality of hazards assumption. Of these, atrial rhythm at randomization was previously addressed by randomization stratification, as was heart rate, which generally correlates with atrial rhythm. The third variable, prior treatment with functional class III anti-arrhythmic drugs, was not previously identified and was included as a covariate in all subsequent analyses to account for nonproportional influence on baseline hazard.

TABLE 2 Timing of AF and HF Onset Relative to Randomization

	HF DxT (yrs)		AF DxT (yrs)		DTRI (yrs)			Time to AF/AFL/ACM	
	Mean	Median	Mean	Median	Mean	Median	p Value*	Stratified HR (95% CI)	Nonstratified HR (95% CI)
U.S. (n = 127)	4.5	1.5	3.4	1.0	1.1	0.0	–	0.70 (0.41–1.19)	0.77 (0.48–1.22)
Non-U.S. (n = 140)	2.0	0.4	3.8	0.9	−1.8	0.0	0.0005	1.34 (0.79–2.28)	1.22 (0.76–1.96)
Canada (n = 59)	2.5	0.5	3.4	0.6	−0.9	0.0	0.024	1.52 (0.68–3.43)	1.42 (0.72–2.79)
Europe (n = 81)	1.6	0.4	4.0	1.7	−2.4	0.0	0.0009	1.01 (0.48–2.14)	1.06 (0.55–2.07)
Hungary (n = 33)	1.5	0.3	7.5	4.1	−5.9	−2.8	<0.0001	2.90 (0.71–11.8)	3.57 (0.99–12.9)
Poland (n = 23)	1.6	0.9	1.4	0.7	0.3	0.0	0.590	0.25 (0.03–2.22)	0.28 (0.07–1.14)
Serbia (n = 21)	0.4	0.3	0.9	0.4	−0.5	0.0	0.175	0.42 (0.08–2.18)	0.59 (0.15–2.36)
the Netherlands (n = 4)	8.0	7.1	6.4	3.8	1.6	−0.1	ND	ND	ND

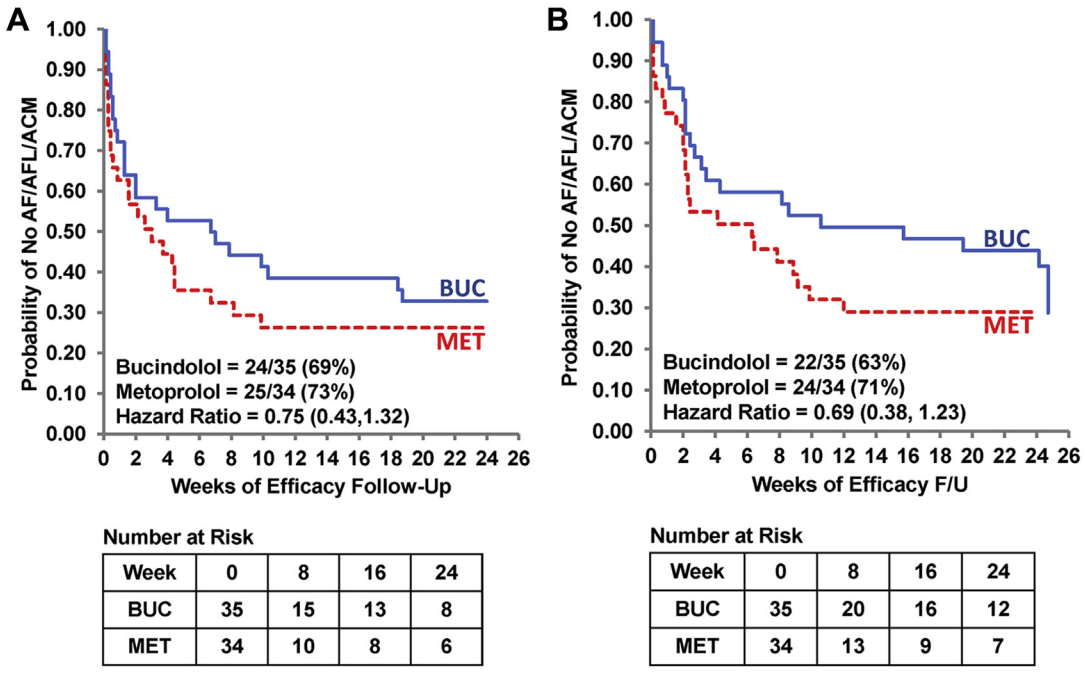
*Wilcoxon rank sum test was used for comparison to the U.S. cohort.

AF DxT = time from diagnosis of atrial fibrillation to randomization; CI: confidence interval; DTRI = diagnosis to randomization index [HF DxT – AF DxT]; HF DxT = time from diagnosis of HF diagnosis to randomization; HR = hazard ratio; ND = not done.

On multivariate analysis, 10 variables predicted the occurrence of the primary endpoint. In addition to the initial dose of study drug, which was based on beta-blocker therapy prior to enrollment, the 2-predictor model identified 5 variables related to the degree or duration of HF (i.e., systolic blood pressure, HF duration, HF cause, NT-proBNP concentration, and NYHA functional class), and 4 variables related to heart rhythm (i.e., rhythm at randomization, baseline heart rate, AF type, and the number of prior ECVs). The only predictor by treatment interaction variable having a p value of <0.05 was duration of time from initial AF diagnosis to randomization (i.e., AF DxT).

The time from initial HF diagnosis to randomization (i.e., HF DxT) was a significant predictor for the occurrence of the primary endpoint but did not

FIGURE 3 Time to First Event of AF/AFL/ACM in the Device Substudy



Number at Risk

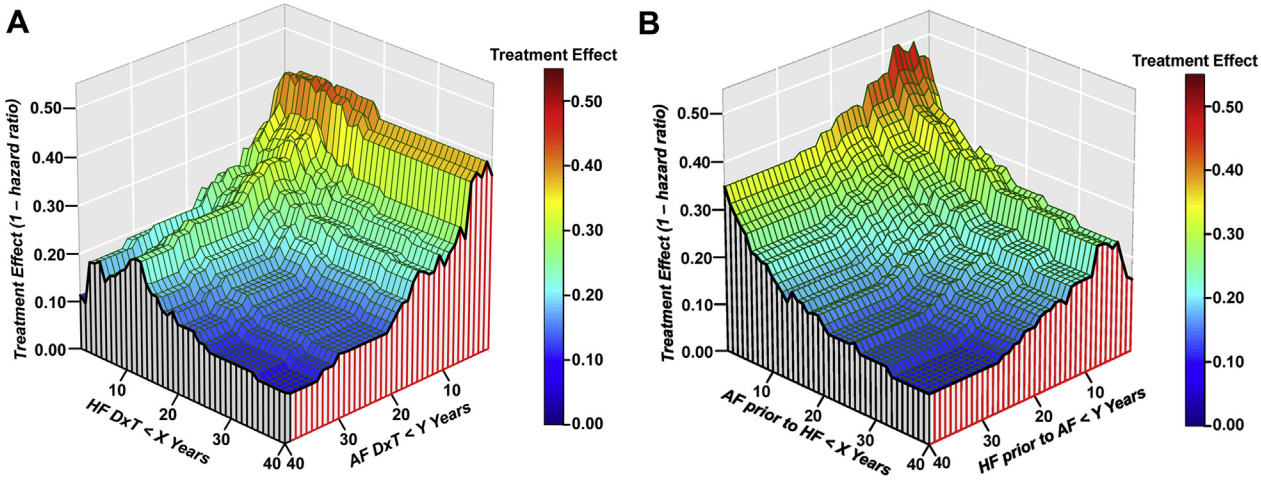
Week	0	8	16	24
BUC	35	15	13	8
MET	34	10	8	6

Number at Risk

Week	0	8	16	24
BUC	35	20	16	12
MET	34	13	9	7

(A) Device-based detection. **(B)** ECG-based detection. For device-based detection, an AF or AFL event was defined as AF burden lasting ≥6 h per day. Nonstratified Cox proportional hazards model was used. ECG = electrocardiography; other abbreviations as in Figure 2.

CENTRAL ILLUSTRATION **Treatment Effect by Duration and Relative Onset of AF and HF Prior to Randomization**



Piccini, J.P. et al. J Am Coll Cardiol HF. 2019;7(7):586–98.

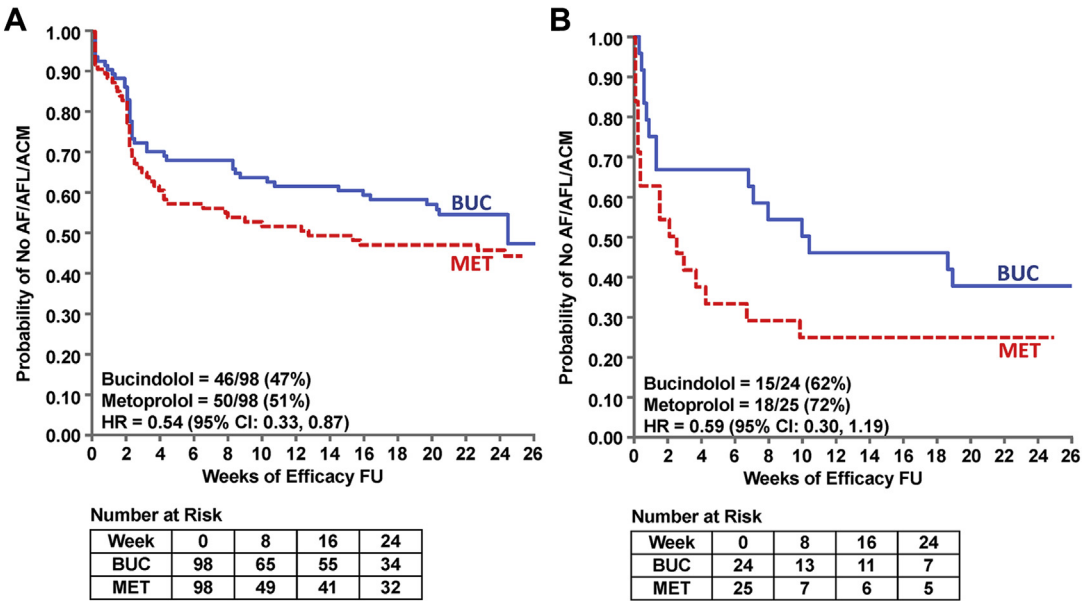
(A) Three-dimensional plot of HF DxT (x-axis) versus AF DxT (y-axis) versus treatment effect (z-axis). **(B)** Three-dimensional plot of AF onset prior to HF (x-axis) versus HF onset prior to AF (y-axis) versus treatment effect (z-axis). The hazard ratio is for time to the endpoint AF, AFL, or ACM. AF DxT = time from initial AF diagnosis to randomization. ACM = all-cause mortality; AF = atrial fibrillation; AFL = atrial flutter; DTRI = diagnosis to randomization index; DxT = time from initial diagnosis to randomization; HF = heart failure.

predict treatment or treatment by predictor interactions in Cox modeling of the primary endpoint (Online Table 3). However, because AF DxT predicted bucindolol response for the prevention of AF recurrence, data were examined from the placebo-controlled BEST HF trial (16) to determine whether HF DxT had a similar relationship to bucindolol response for the HF endpoint, ACM, or first HFH. As shown in Online Figure 3, an attenuation of treatment response for the BEST ACM HFH endpoint was observed in cohorts with greater values of HF DxT upper bound (i.e., inclusion of long-standing HF prior to randomization). This strong, negative correlation was observed in both the entire cohort (n = 2,708; r = −0.82; 95% CI: −0.92 to −0.59) and for the *ADRB1* Arg389Arg subgroup (n = 493; r = −0.79; 95% CI: −0.91 to −0.54).

EFFECT OF DURATION AND RELATIVE ONSET OF AF AND HF ON TREATMENT EFFECT. To further examine the effects of AF and HF duration identified in the above-described analyses, a 3-dimensional (3D) plot was constructed using treatment effect (i.e., 1-hazard ratio) for the GENETIC-AF primary endpoint as the dependent variable (**Central Illustration** z-axis) and HF DxT (**Central Illustration** x-axis) and AF DxT (**Central Illustration** y-axis) as independent variables. As shown in **Central Illustration** panel A, an attenuation of treatment effect was associated with increasing values of both AF and HF DxT. When equivalent DxT values (both AF and HF DxT values had to be less than the timepoint duration on the x-axis [**Central Illustration**]) were used to examine the combined effects of AF and HF duration (Online Figure 4), a strong negative correlation was observed (r = −0.94; 95% CI: −0.97 to −0.89), with substantial attenuation of treatment effect seen with the inclusion of a small proportion of patients with both AF and HF durations >12 to 15 years.

To examine the effects of the relative onset of AF and HF on treatment effect, a 3D plot was constructed with treatment effect as the dependent variable (**Central Illustration** z-axis), and the absolute value of DTRI lower bound (i.e., years of AF prior to HF) and DTRI upper bound (i.e., years of HF prior to AF) and as independent variables. As shown in **Central Illustration** panel B, there is an attenuation of treatment effect associated with increasing absolute values of DTRI lower and upper bounds (i.e., increasing time between the initial presentations of AF and HF). When equivalent absolute values for DTRI lower and upper bounds were used to examine the concept of contemporaneous AF and HF development (Online Figure 5A), there was a nearly linear,

FIGURE 4 Time to First Event of AF, AFL, or ACM in the DxT12 or DTRI-2 Cohort



Number at Risk

Week	0	8	16	24
BUC	98	65	55	34
MET	98	49	41	32

Number at Risk

Week	0	8	16	24
BUC	24	13	11	7
MET	25	7	6	5

(A) ECG-based detection in the entire cohort. **(B)** Device-based detection in the substudy cohort. For device-based detection, an AF or AFL (AF/AFL) event was the AF burden lasting ≥6 h per day. DTRI-2 = diagnosis to randomization index <2 years; DxT12 = time from initial diagnosis to randomization <12 years; FU = follow-up; HR = hazard ratio.

negative correlation with treatment effect (r = −0.96; 95% CI: −0.98 to −0.92).

PREVENTION OF AF RECURRENCE IN THE PRECISION THERAPEUTIC SELECTED PHENOTYPE. Duration and relative onset of AF and HF are indirectly related characteristics that may have additive or overlapping effects. Therefore, we examined their use in combination to identify a precision therapeutic phenotype appropriate for further study. Details of the precision therapeutic phenotype analyses are presented in the Online Appendix.

In the example presented below, a population was selected with an AF and an HF DxT <12 years (i.e., a DxT12 cohort), as this cutoff retained a high proportion (86%) of the overall population while minimizing attenuation of the observed treatment effect. A DTRI lower bound of −2 years (DxT12/DTRI-2 cohort) (i.e., AF not preceding HF by more than 2 years) was then applied, as this cutoff retained 85% of the DxT12 cohort. As shown in Online Figure 6, restriction of DTRI upper bound (i.e., years of HF prior to AF) was not required when examined against a DxT12 background.

Patient characteristics of the DxT12 and DxT12 and DTRI-2 cohorts are shown in Online Table 4. Patients excluded by the DxT12 criteria had characteristics consistent with longstanding AF and HF; whereas the population excluded by the DTRI of more than −2-year criteria had characteristics consistent with longstanding AF as primary diagnosis and treatment history, with primarily mild left ventricular dysfunction. Of note, patients who had contemporaneous development of both AF and HF (i.e., DTRI values within 2 years of zero) were the majority of those included in the 230-patient DxT12 cohort ("DTRI included"); whereas DTRI patients with values ±2 years were conspicuously absent from the 37-patient cohort excluded by the DxT12 criteria (i.e., those with the first diagnosis of both AF and HF at ≥12 years prior to randomization) (Online Figure 5B). The accumulation of a substantial number (>10) of patients with DTRI values ±2 years did not occur until the DxT cutoff was restricted to <6 years (data not shown).

The primary endpoint of time to first event of AF, AFL, or ACM for the DxT12/DTRI-2 cohort (n = 196) is shown in **Figure 4**. In HFrEF patients (LVEF <0.50), the HR was 0.54 (95% CI: 0.33 to 0.87) by ECG-based detection, with similar results observed by device-based detection (HR: 0.59; 95% CI: 0.30 to 1.19;

n = 49). In HF patients with mid-range ejection fraction (LVEF ≥0.40 to <0.50) (HFmrEF), the HR was 0.42 (95% CI: 0.21 to 0.86; p = 0.017) and in HF patients with lower-range ejection fraction (HFlrEF) LVEF <0.40, the HR was 0.69 (95% CI: 0.33 to 1.43; p = 0.32). Device-based estimates for HFmrEF and HFlrEF are not presented due to the small sample size (see Online Table 5 for more details).

EFFECTS ON NOREPINEPHRINE AND NT-proBNP. Plasma norepinephrine concentrations at baseline in the bucindolol (682 ± 348 pg/ml [n = 128]) group were similar to those in the metoprolol (664 ± 359 pg/ml [n = 134]) group. At 4 weeks, there was a significant decrease from baseline in the bucindolol group (−124 ± 26 pg/ml; p < 0.001) that was not observed in the metoprolol group (−36 ± 32 pg/ml; p = 0.30). The changes from baseline at 4 weeks were significantly different between the 2 groups (p = 0.012).

Plasma NT-proBNP was non-normally distributed in both groups, and median values at baseline were similar (777 and 861 pg/ml, respectively; p = 0.38) (Online Table 6). There were significant decreases from baseline in the bucindolol group at week 4 (−96 pg/ml; p = 0.003) and week 12 (−96 pg/ml; p = 0.002) that were not observed in the metoprolol group. At week 24, significant decreases relative to baseline values were observed in both the bucindolol (−197 pg/ml; p = 0.005) and the metoprolol (−100 pg/ml; p = 0.014) groups, but the changes from baseline were not significantly different between the 2 groups (p = 0.220).

SAFETY. The proportions of patients experiencing adverse events were similar in the 2 groups (**Table 3**). More patients in the metoprolol group had symptomatic bradycardia or bradycardia leading to dose reduction or discontinuation of study drug than in the bucindolol group (9.0% vs. 3.0%, respectively; p = 0.042). Three patients (2.3%) in each group died while receiving the study drug or within 30 days of their last dose. All deaths in the metoprolol group occurred during the primary endpoint period (worsening HF at day 25; sudden cardiac death at day 43; motor vehicle accident at day 77). All deaths in the bucindolol group occurred during the long-term extension period (respiratory failure at day 385; sudden death at day 535; cardiac tamponade at day 779). Rates of HF hospitalization (7.5% vs. 8.3%, respectively) and ACM HFH (8.2% vs. 9.0%, respectively) were similar for the bucindolol and metoprolol groups. There were no strokes in either treatment group; 93% of patients received oral anticoagulants prior to randomization.

TABLE 3 Treatment Emergent Adverse Events

Endpoint	Bucindolol (n = 134)	Metoprolol (n = 133)
Any adverse event	100 (74.6)	95 (71.4)
AE possible or probably related to the study drug	32 (23.9)	40 (30.1)
AE leading to permanent study drug discontinuation	11 (8.2)	11 (8.3)
AE leading to study withdrawal (excluding death)	2 (1.5)	2 (1.5)
AE of symptomatic bradycardia or bradycardia leading to dose reduction or discontinuation of study drug	4 (3.0)	12 (9.0)
Any serious adverse event	34 (25.4)	27 (20.3)
AE leading to death	3 (2.3)	3 (2.3)

Values are n (%) and presented from randomization through 30 days after the last dose of the study drug.
AE = adverse event.

DISCUSSION

The GENETIC-AF trial had an adaptive design allowing for seamless transition from Phase 2B to Phase 3 if evidence from the Phase 2B population suggested that efficacy was likely to be observed upon expansion to the larger Phase 3 sample size (9). In the Phase 2B analysis, pharmacogenetically guided bucindolol did not reduce the recurrence of AF/AFL or ACM compared to metoprolol in the overall population. However, trends for bucindolol benefit were observed in key subgroups, particularly in those without longstanding and heavily treated AF prior to the development of HF. A lower proportion of patients with longstanding AF diagnosed prior to the development of HF likely contributed to the favorable bucindolol treatment effect in Unite States and device substudy patients, who were mostly from the United States. In addition to the findings relevant to the investigational drug, this study also has several important findings relative to detection of AF in clinical trials.

GENETIC-AF also represents several firsts in the conduct of pharmacogenetic studies in cardiovascular disease and AF in particular. It is the first pharmacogenetically targeted, randomized, controlled trial of rhythm control therapy in AF. Moreover, it is the first pharmacogenetic trial for prevention of recurrent AF in HFrEF, defined as HF with any decrease in LVEF (21). It is also the first study to compare AF burden to symptomatic AF/AFL as determined by adjudication of symptoms and ECG data. Finally, it represents the first comparative beta-blocker trial to include HF patients with HFmrEF, defined as an LVEF ≥0.40 and <0.50 (22).

There are several important findings from the GENETIC-AF study regarding AF in this HFrEF population. For example, nearly all patients who experienced AF recurrence had symptomatic AF, defined as

new or worsening symptoms as adjudicated by a blinded clinical events committee. Recently, there has also been considerable interest in methods of AF diagnosis in clinical practice, including telemetry and device-based technologies (23,24). The device substudy defined an AF/AFL event as an AF burden lasting ≥6 h per day because this amount of burden had previously been shown to be associated with an increased rate of HFH (18). It was found that the AF burden lasting ≥6 h per day as recorded by continuous monitoring exhibited high predictive accuracy for clinically symptomatic AF/AFL and tended to identify these events earlier than intermittent ECG monitoring.

Approximately one-half of the patients screened for this trial had the *ADRB1* Arg389Arg genotype, consistent with previous findings (8-11). In this genotype, only norepinephrine high-affinity $beta_1$ Arg389 receptors are present, providing a substrate for the favorable effect of sympatholysis (9) that was again observed for bucindolol. Bucindolol lowered plasma norepinephrine levels after 4 weeks of treatment, which was not observed for metoprolol. Plasma NT-proBNP levels also decreased significantly with bucindolol treatment but not with metoprolol. These data indicate that the pharmacodynamic profile that contributes to the pharmacogenetic differentiation of bucindolol was operative in the trial.

It is also notable there were no safety concerns identified with bucindolol. Similar rates of death and hospitalization were observed in both treatment arms, although power was limited for detection of uncommon events. Interestingly, bradycardia was significantly lower in the bucindolol arm, suggesting that bucindolol may lead to less bradycardia than metoprolol in patients with the *ADRB1* Arg389Arg genotype.

A major goal of a Phase 2 clinical trial is to further refine the study population that will be investigated in Phase 3. To this end, an exercise in precision therapeutic phenotyping, or "individual treatment effect modeling" (21), was conducted, designed to identify both pre-specified obvious and nonobvious variables associated with a beneficial treatment effect of bucindolol. Exploration of factors contributing to the heterogeneity in the response observed for regional subgroups led to the examination of the timing of AF and HF onset prior to randomization and relative to one another. This led to identification of 2 variables that were strongly associated with an attenuation of bucindolol response: 1) the interval of time from the initial diagnosis of AF and HF to randomization (i.e., DxT); and 2) the onset of AF relative to initial HF diagnosis (i.e., DTRI). AF duration has previously been reported to modulate response to other drug therapies post-ECV (25) and for catheter ablation (26). Less well appreciated are how HF duration may impact medical therapy and how these 2 variables interact in HF patients with concomitant AF. It should also be noted that GENETIC-AF compared 2 members of a drug class that had been administered chronically to this population in some cases for years prior to randomization. As such, a survivor effect due to loss of patients who developed AF and HF within a few years of each other, potentially due to adverse effects on mortality with the combination (27), may be responsible for altering the composition of certain subpopulations (i.e., those with longstanding AF and HF DxT) (Online Figure 5B) in a manner that influences treatment response (Online Figure 6). If a contemporaneous relationship between the onset of AF and HF is optimal for bucindolol to maintain sinus rhythm, potentially related to higher levels of adrenergic activity when both conditions manifest in some proximity (10,27), then this would explain the phenotype identified in our analysis. Additionally, it is also possible that the DTRI effect has a biological origin based on differences in atrial and ventricular pathophysiology when AF precedes or dominates HF, the major difference residing in chamber interstitial fibrosis being a more prominent feature in AF (28,29).

For comparative efficacy studies that seek to observe a differential response between 2 drugs in the same drug class, it is critical to identify a study population with high potential for overall response to the drug class. This is necessary because a differential response is, by definition, a fraction of the overall response to a specific drug and, therefore, is more difficult to observe in a given study population. In this exploratory Phase 2 trial with limited sample size and statistical power, HF populations were identified who responded differentially to 2 beta-blockers based on genetic targeting. This approach circumvented potential issues associated with conventional subset analyses by evaluating monotonicity and consistency of trends across the full continuum of candidate variables such that the classifiers were readily conducive to numerical calibration (see examples in Online Appendix). The authors propose that increasing the permissible limits of variation (i.e., tolerance) for the phenotype selection criteria increases the likelihood of reproducibility of these results in future studies.

STUDY LIMITATIONS. The results of this Phase 2B trial are best considered in light of its limitations. Given the conclusion of the study at Phase 2B, the power was not adequate to definitively test superiority. Although AF DxT and HF DxT were prespecified in the SAP prior to unblinding as potential predictors of treatment response, the onset relationship derived from these variables (i.e., DTRI) was retrospectively defined. Multiplicity through subgroup analysis can lead to false discovery, although this was tempered by examination for consistent trends across the entire dataset and other comparable datasets (i.e., BEST study). Finally, the selection of the precision therapeutic phenotype was based on response but also considered the sample size needed to maintain feasibility for enrollment in future trials. As such, the treatment effect estimates derived from these analyses are hypothesis generating only and will need to be evaluated in a subsequent, prospectively designed trial.

CONCLUSIONS

In the first trial of a pharmacogenetically guided rhythm control intervention, bucindolol did not reduce the recurrence of AF/AFL or ACM compared to that with metoprolol in the overall population. However, precision therapeutic phenotyping identified a large population of HF patients with an *ADRB1* Arg389Arg genotype who displayed a differential response to bucindolol compared to that to metoprolol for the prevention of AF/AFL. This experience underscores the utility of performing relatively large Phase 2 studies consisting of heterogeneous populations in order to generate the data necessary to identify appropriate therapeutic phenotypes suitable for Phase 3 investigation.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: The intersection of atrial fibrillation and heart failure is common; at this point the prognosis of each disorder is worse, and treatment lacks effective, easily administered and safe drug therapy. In the BEST trial pharmacogenetic substudy, relative to placebo in patients with an *ADRB1* Arg389Arg genotype, the fourth-generation beta-blocker bucindolol reduced the risk of developing AF by 74%, leading to design and performance of the Phase 2 trial GENETIC-AF trial in which 267 high-risk AF patients with HFrEF were randomized to bucindolol or to the conventional, second-generation compound metoprolol succinate. Overall there were no differences in effectiveness (HR: 1.01; 95% CI: 0.71 to 1.42), but a trend for benefit with bucindolol was observed in the U.S. subgroup (n = 127; HR: 0.70; 95% CI: 0.41 to 1.19) and in patients with implanted devices (n = 69; HR: 0.75; 95% CI: 0.43 to 1.32). The trial exhibited marked regional heterogeneity, which was attributed to 2 countries predominantly enrolling patients whose AF diagnosis preceded HF by many years and in countries that enrolled patients with a more contemporaneous presentation of AF; and HF bucindolol was associated with a positive efficacy signal.

TRANSLATIONAL OUTLOOK: The theoretical basis for bucindolol's advantage over conventional beta-blockers for preventing AF and reducing HF events in HFrEF patients who carry the *ADRB1* Arg389Arg genotype is its more powerful inhibition of the higher functioning Arg389 polymorphic variant of the $beta_1$-adrenergic receptor. The *ADRB1* Arg389Gly polymorphism is not present in other species but can be and has been investigated by transgenic overexpression in mice. In terms of the potential for reverse translation, precision therapeutic phenotyping in GENETIC-AF identified a group of patients who had AF developed many years prior to HF, who did not respond favorably to bucindolol, suggesting different pathophysiology than in patients who develop AF and HF contemporaneously. This putative pathophysiologic difference and its impact on therapy, potentially related to a greater burden of atrial and ventricular fibrosis associated with longstanding AF, could be translationally investigated in animal models of AF and HF.

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KEY WORDS atrial fibrillation, beta-blocker, bucindolol, heart failure, pharmacogenetics, precision medicine

APPENDIX For supplemental information, tables, and figures, please see the online version of this paper.