Pharmacogenetic Guided β-Blocker Therapy with Bucindolol for the Prevention of Atrial Fibrillation/Flutter in Heart Failure: Relationship of Left Ventricular Ejection Fraction to Treatment Effect

William T. Abraham, MD[1], Jonathan P. Piccini, MD, MHS, FHRS,[2] Jeff S. Healey, MD, FHRS,[3] Dirk J. Van Veldhuisen, MD,[4] Inder S. Anand, MD, PhD, FACC,[5] Michel White, MD,[6] Stephen B. Wilton, MD,[7] Ryan G. Aleong, MD, FHRS,[8] Christopher Dufton, PhD,[9] Michael R. Bristow, MD,[8,9] and Stuart J. Connolly, MD, FHRS,[3] on behalf of the GENETIC-AF Trial Investigators.

[1]Ohio State University Medical Center; [2]Duke University Medical Center, [3]McMaster University; [4]University of Groningen; [5]US Department of Veterans Affairs; [6]Montreal Heart Institute; [7]University of Calgary; [8]University of Colorado; [9]ARCA biopharma, Inc.

Background

- There are very few guideline recommended antiarrhythmic drugs for the treatment of atrial fibrillation (AF) in patients with heart failure (HF) and those that are recommended carry risks of end-organ toxicities and/or proarrhythmia.
- Bucindolol hydrochloride (bucindolol) is a nonselective β-adrenergic receptor (AR) blocking agent with mild vasodilator properties, which was previously studied in the BEST Phase 3 HF trial.[1] In a large pharmacogenomic substudy of the BEST trial, two unique pharmacologic properties of bucindolol, sympatholysis and inverse agonism, were shown to interact with AR polymorphisms in such a way that targeting specific genotypes of these variants could improve therapeutic index (Table 1).[3]
- Metoprolol (Toprol-XL), which is approved for the treatment of HF, has demonstrated mild efficacy for the prevention of new onset AF in a HF patient population and is often used off-label in this setting.[4] In contrast to bucindolol, metoprolol does not appear to confer added clinical benefits in HF patients that possess the $\beta_1$389Arg/Arg AR variant and limited data from the MERIT-HF DNA substudy did not indicate any evidence of a $\beta_1$389 Arg/Gly polymorphism differential effect for preventing AF.
- The goal of the GENETIC-AF trial was to compare the effects of pharmacogenetically-targeted bucindolol to metoprolol for the prevention of AF/AFL in a genotype-defined $\beta_1$389Arg/Arg HF population at high risk of AF/AFL recurrence.

BEST Trial

- BEST was a double-blind, placebo-controlled, Phase 3 trial of bucindolol in 2,708 CHF patients.[1]
  - Primary Endpoint: all-cause mortality (p = 0.053).
  - Improvements in 11 of 14 secondary endpoints (p < 0.05).
- The BEST genetic substudy of 1040 patients demonstrated genotype-dependent enhancements for several HF endpoints.[3]

Table 1: AF and HF endpoints in BEST genetic substudy by $\beta_1$389 genotype

Endpoint	$\beta_1$389 Arg/Arg (n = 493)	$\beta_1$389 Gly carrier (n = 547)
New Onset AF	0.26 (0.12, 0.57) p < 0.001	1.01 (0.56, 1.84) p = 0.970
ACM	0.62 (0.39, 0.99) p = 0.042	0.92 (0.63, 1.35) p = 0.661
CVM	0.52 (0.31, 0.88) p = 0.014	0.78 (0.51, 1.18) p = 0.233
ACM or HF Hospitalization	0.65 (0.48, 0.88) p = 0.005	0.86 (0.66,1.12) p = 0.26
HF Progression	0.66 (0.49, 0.88) p = 0.005	0.85 (0.66, 1.11) p = 0.233
HF Hospitalization	0.64 (0.46, 0.89) p = 0.007	0.85 (0.63, 1.15) p = 0.303
CV Hospitalization	0.64 (0.48, 0.86) p = 0.002	0.93 (0.72, 1.21) p = 0.588

All endpoints presented as time to event analyses, with hazard ratios and 95% confidence intervals from a COX model and p-values generated using the log-rank statistic.

β_1-AR Polymorphisms

- The $B_1$389 Arg AR provides substantially greater adrenergic drive compared to the $B_1$389 Gly form of the receptor.[2]
  - 3-4X higher signal transduction capacity
  - Higher binding affinity for NE
  - More active state receptors

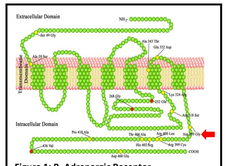

Figure 1: B_1 Adrenergic Receptor

- Bucindolol hydrochloride (Gencaro™) has two unique pharmacologic properties:
  - Sympatholysis: decreases adrenergic drive/norepinephrine release.
  - Inverse agonism: inhibition of constitutively active β_1ARs.

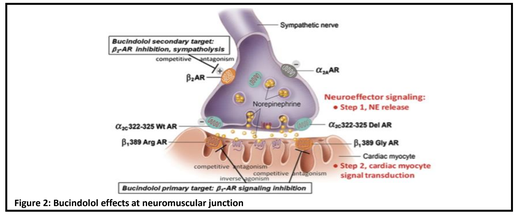

Figure 2: Bucindolol effects at neuromuscular junction

GENETIC-AF Trial

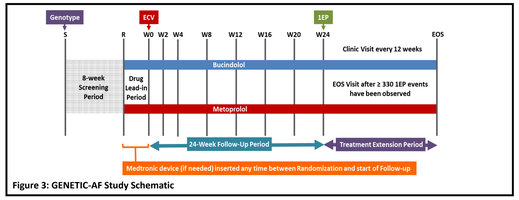

Figure 3: GENETIC-AF Study Schematic

- GENETIC-AF was a double-blind, genotype-directed, active-controlled, adaptive-designed, superiority trial that compares the effects of bucindolol and metoprolol for the prevention of AF recurrence in HF patients.
- 267 HF patients with reduced LVEF (range: 0.12 to 0.55) who had symptomatic persistent or paroxysmal AF in the past 180 days were enrolled.
- The primary endpoint was time to first event of AF/AFL or ACM assessed by ECG after establishment of stable SR on study drug.
- A subgroup of patients (N=69) had continuous rhythm monitoring via implanted loop recorders or other devices to evaluate AF burden.
- The trial had a seamless Phase 2B/Phase 3 adaptive design. Based on an interim efficacy analysis, the DSMB recommended completing the trial in Phase 2.
- Similar results were observed in the bucindolol and metoprolol groups for the primary endpoint. However, precision therapeutic phenotyping identified a large population of HF patients with an ADRB1 Arg389Arg genotype who display a differential response to bucindolol compared to metoprolol for the prevention of AF/AFL recurrence.[8]

Patient Baseline Characteristics

Table 2: Baseline Demographics

Parameter	Entire Study		PTP Cohort (DxT12/DTRI-2)	
	Bucindolol N = 134	Metoprolol N = 133	Bucindolol N = 98	Metoprolol N = 98
Age, years	65.8 ± 10.3	65.5 ± 10.0	65.6 ± 10.1	64.9 ± 9.7
Male/Female, %	83 / 17	81 / 19	80/20	81/19
Race: W/B/A/O, %	96 / 1 / 1 / 2	96 / 2/ 1 / 1	98 / 1 / 1 / 0	95 / 3 / 1 / 1
LVEF	0.36 ± 0.10	0.36 ± 0.10	0.37 ± 0.10	0.36 ± 0.09
NYHA I/II/III, %	30 / 60 / 10	26 / 54 / 20	31 / 57 / 12	26 / 56 / 18
Ischemic/Non-Ischemic HF, %	31 / 69	33 / 67	34 / 66	31 / 69
Randomized in AF/Not in AF, %	49 / 51	52 / 48	48 / 52	48 / 52
Persistent/Paroxysmal AF, %	51 / 49	51 / 49	54 / 46	50 / 50
AF Dx Duration, years	3.9 ± 6.2	3.2 ± 6.0	1.6 ± 2.3	1.4 ± 2.0
HF Dx Duration, years	3.4 ± 5.7	2.9 ± 4.7	2.2 ± 2.9	2.0 ± 2.9
Systolic blood pressure, mm Hg	124.7 ± 14.9	121.8 ± 15.7	125.1 ± 15.2	122.6 ± 15.5
Diastolic blood pressure, mmHg	75.8 ± 11.0	74.8 ± 10.6	76.1 ± 10.7	74.6 ± 10.0
Heart Rate, bpm	76.5 ± 17.9	76.0 ± 17.7	75.8 ± 19.2	75.5 ± 17.8
Previous ECV/Ablation/Type III AADs, %	49 / 21 / 50	50 / 20 / 46	47 / 15 / 42	50 / 14 / 42
Device Type: ILR/CRT/ICD/PM, %	17 / 6 / 18 / 9	15 / 10 / 12 / 10	16 / 3 / 19 / 8	17 / 8 / 10 / 7
Norepinephrine, pg/ml	682 ± 348	664 ± 359	681 ± 355	630 ± 268
NT-proBNP, pg/ml	1159 ± 1306	1343 ± 1846	1132 ± 1302	1234 ± 1657

W/B/A/O = White/Black/Asian/Other; AADs = antiarrhythmic drugs. AF Dx Duration = time from AF diagnosis to randomization. HF Dx Duration = time from AF diagnosis to randomization. DTRI = HF DxT – AF DxT.
Note: mean ± standard deviations are presented unless otherwise specified.

Precision Therapeutic Phenotyping

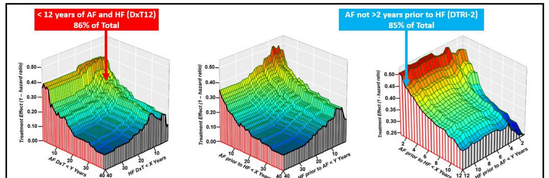

Figure 4: Precision Therapeutic Phenotyping (PTP) of the GENETIC-AF Time to first AF/AFL or ACM endpoint
HF DxT = time from HF diagnosis to randomization. AF DxT = time from AF diagnosis to randomization.
DTRI (Diagnosis to Randomization Index) = HF DxT – AF DxT.

- As shown in Figure 4, bucindolol response for the primary endpoint correlated with AF DxT (r = -0.92; 95% CI: -0.96, -0.85), HF DxT (r = -0.64; 95% CI: -0.79, -0.41), years of AF prior to HF (DTRI lower boundary; r = -0.93; 95% CI: -0.96, -0.88), and years of HF prior to AF (DTRI upper boundary; r = -0.86; 95% CI: -0.92, -0.74).[8]
- As shown in Figure 5, bucindolol benefit for the primary endpoint was observed in patients with AF and HF < 12 years who did not have AF for more than 2 years prior to developing HF (PTP cohort; N=196). Similar results were observed with device-based detection with an AF/AFL event defined as ≥6 hours per day.[8]

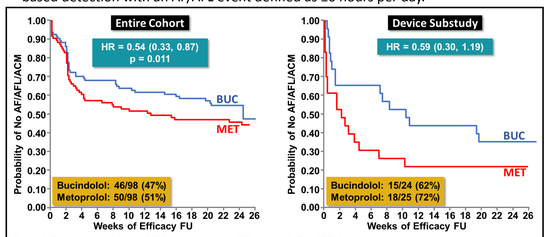

Figure 5: Time to first AF/AFL or ACM endpoint for the PTP cohort (DxT12/DTRI-2)
ECG detection: Cox proportional hazards model adjusted for: 1) HF etiology, 2) LVEF, 3) rhythm at randomization 4) device type, 5) Previous Class 3 AA use.
Device detection: AF burden ≥ 6 hours per day. Non-stratified analysis.

AF/AFL/ACM by Baseline LVEF

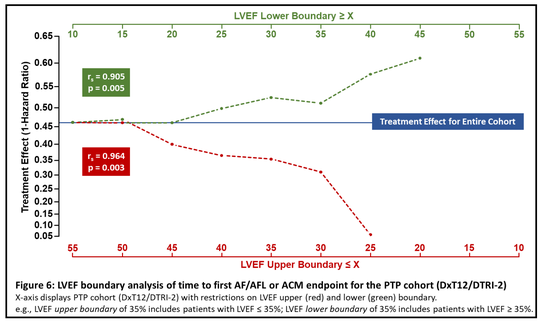

Figure 6: LVEF boundary analysis of time to first AF/AFL or ACM endpoint for the PTP cohort (DxT12/DTRI-2)
X-axis displays PTP cohort (DxT12/DTRI-2) with restrictions on LVEF upper (red) and lower (green) boundary.
e.g., LVEF *upper boundary* of 35% includes patients with LVEF ≤ 35%; LVEF *lower boundary* of 35% includes patients with LVEF ≥ 35%.

- As shown in Figure 6, restriction of the population to higher LVEFs was associated with increasing bucindolol response (r_s = 0.905, p = 0.005); whereas, restriction of the population to lower LVEFs was associated with decreasing bucindolol response (r_s = 0.964; p = 0.003).
- As shown in Table 3, a trend for greater bucindolol response in patients with LVEF values ≥ 0.40 and < 0.55 compared to LVEF values < 0.40 was observed in each of the cohorts examined; however, tests for interaction between these two groups were not statistically significant.

Table 3: Time to first AF/AFL or ACM endpoint in the PTP cohort by LVEF subgroup

Group	LVEF < 0.55		0.40 ≤ LVEF < 0.55		LVEF < 0.40	
	N (%)	HR (95% CI)	N (%)	HR (95% CI)	N (%)	HR (95% CI)
Entire Cohort	267 (100)	0.92 (0.63, 1.33)	128 (100)	0.78 (0.45, 1.33)	139 (100)	1.03 (0.58, 1.83)
DxT12 Cohort	230 (86)	0.68 (0.45, 1.02)	113 (88)	0.61 (0.34, 1.10)	117 (84)	0.74 (0.38, 1.44)
PTP Cohort (DxT12/DTRI-2)	196 (73)	0.54 (0.33, 0.87)	91 (71)	0.42 (0.21, 0.86)	107 (77)	0.69 (0.33, 1.43)

DxT12 = AF diagnosis (AF DxT) and HF diagnosis (HF DxT) < 12 years prior to randomization.
DTRI (Diagnosis to Randomization Index) = HF DxT – AF DxT.
DTRI-2 = AF DxT not greater than 2 years prior to HF DxT.

Statistical Methodology

- Hazard ratios and 95% confidence intervals for the primary endpoint were generated per Cox proportional hazards model stratified by: 1) HF etiology (ischemic/non-ischemic); 2) LVEF (< 0.35/≥ 0.35); 3) type of Medtronic device (Reveal/Non-Reveal/No Device); 4) rhythm at randomization: (SR/AF) and 5) previous Class 3 antiarrhythmic use (Yes/No).
- For the Device substudy an AF/AFL event was predefined as a total AF burden ≥ 6 hours per day. Due to sample size considerations in the substudy, hazard ratios and 95% confidence intervals for the time to first AF/AFL/ACM event endpoint were generated per a non-stratified Cox proportional hazards model.
- 3-dimensional plots were constructed with treatment effect (1-hazard ratio) for the primary endpoint as the dependent variable (z-axis), with independent variables (i.e., DxT and DTRI) on the x- and y-axes.
- LVEF boundary analysis displays treatment effect (1-hazard ratio) for the primary endpoint in the PTP cohort (i.e., DxT12/DTRI-2) with restrictions on LVEF upper and lower boundary. A Spearman's Rho test [r_s] was used to measure the strength of association between LVEF upper or lower boundary and treatment effect.

Conclusions

- In this exploratory Phase 2 trial with limited sample size and statistical power, we identified HF populations who respond differentially to two beta-blockers based on genetic targeting.
- For the prevention of AF recurrence, a differential response in favor of bucindolol was associated with:
  1) time from the initial diagnosis of AF and HF to randomization (AF and HF DxT).
  2) time of AF onset relative to initial HF diagnosis (DTRI).
- Bucindolol benefit was observed in a subpopulation of HF patients in which AF is likely being driven by an underlying HF pathophysiology.
- For the prevention of AF recurrence, bucindolol response appears to be greater in patients with higher LVEF values.
- Beta blocker therapy may be less effective in patients with long-standing HF and/or AF, perhaps due to an inability to modify substrate in advanced stages of their disease.

Limitations

- AF DxT and HF DxT were prespecified prior to unblinding as potential predictors of treatment response, but the onset relationship derived from these variables (i.e., DTRI) was retrospectively defined.
- 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.

References

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