Phase 2 Trial of Pharmacogenetic Guided Beta-Blocker Therapy with Bucindolol vs. Metoprolol for the Prevention of Atrial Fibrillation/Flutter in Heart Failure: GENETIC-AF AF Burden Substudy

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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.[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 population comprised of HFrEF (LVEF <0.40) and HFmrEF (LVEF ≥ 0.40 and <0.50) patients at high risk of AF/AFL recurrence.

Previous BEST Trial

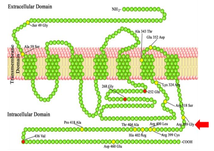
- BEST was a double-blind, placebo-controlled, Phase 3 trial of bucindolol in 2,708 CHF patients.[1]
  - Primary Endpoint: all-cause mortality (p = 0.053).
  - Improvements in 11 of 14 secondary endpoints (p < 0.05).
- The BEST genetic substudy of 1040 patients demonstrated genotype-dependent enhancements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

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

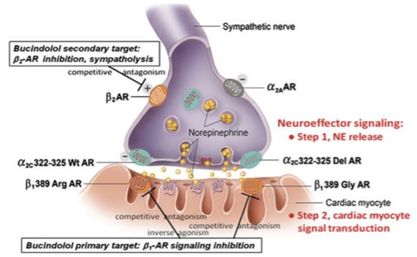
All endpoints presented as time to event analyses, with hazard ratios and 95% confidence intervals from a COX model and p-values generated using the log-rank statistic.

β_1-AR Polymorphisms

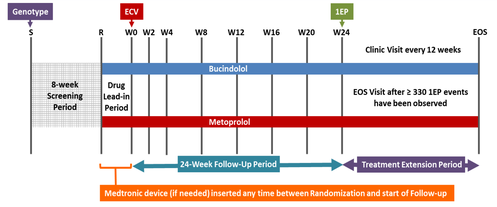
- The $\beta_1$389 Arg AR provides substantially greater adrenergic drive compared to the $\beta_1$389 Gly form of the receptor.[2]
  - 3-4X higher signal transduction capacity
  - Higher binding affinity for NE
  - More active state receptors



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



GENETIC-AF Design



- GENETIC-AF was a seamless Phase 2B/Phase 3 adaptive trial.
- Based on an interim efficacy analysis, the DSMB recommended completing the trial in Phase 2 with an enrollment of 267 subjects.
- 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 goal of the AFB/device substudy was to examine the utility of using ≥6 hours per day of AF burden for detection of AF/AFL events compared to intermittent, clinic-based ECG detection of symptomatic AF.
- An attenuation of treatment effect was observed in the BEST and GENETIC-AF trials with increasing HF and AF disease durations, respectively (unpublished data). Therefore, additional analyses were performed that excluded patients with long-standing HF or AF ≥ 12 years prior to randomization.

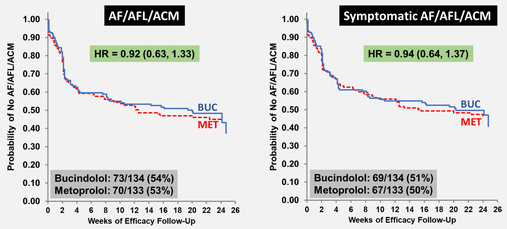
Patient Baseline Characteristics

Parameter	Entire Study		Device Substudy	
	Bucindolol N = 134	Metoprolol N = 133	Bucindolol N = 35	Metoprolol N = 34
Age, years	65.8 ± 10.3	65.5 ± 10.0	65.5 ± 11.5	66.8 ± 9.9
Male/Female, %	83 / 17	81 / 19	94 / 6	91 / 9
Race: W/B/A/O, %	96 / 1 / 1 / 2	96 / 2/ 1 / 1	94 / 0 / 3 / 3	97 / 3 / 0 / 0
LVEF	0.36 ± 0.10	0.36 ± 0.10	0.33 ± 0.08	0.36 ± 0.09
NYHA I/II/III, %	30 / 60 / 10	26 / 54 / 20	29 / 49 / 23	18 / 65 / 18
Ischemic/Non-Ischemic HF, %	31 / 69	33 / 67	29 / 71	26 / 74
Randomized in AF/Not in AF, %	49 / 51	52 / 48	63 / 37	68 / 32
Persistent/Paroxysmal AF, %	51 / 49	51 / 49	63 / 37	65 / 35
AF Dx Duration, days	1431 ± 2271	1180 ± 2209	1444 ± 1997	1263 ± 1995
HF Dx Duration, days	1252 ± 2070	1054 ± 1733	1208 ± 1880	1126 ± 1572
Systolic blood pressure, mm Hg	124.7 ± 14.9	121.8 ± 15.7	122.4 ± 15.7	124.2 ± 14.5
Diastolic blood pressure, mmHg	75.8 ± 11.0	74.8 ± 10.6	73.7 ± 9.9	76.3 ± 10.3
Heart Rate, bpm	76.5 ± 17.9	76.0 ± 17.7	76.8 ± 16.4	80.1 ± 18.1
Previous ECV/Ablation/Type III AADs, %	49 / 21 / 50	50 / 20 / 46	57 / 17 / 57	53 / 9 / 50
Device Type: ILR/CRT/ICD/PM, %	17 / 6 / 18 / 9	15 / 10 / 12 / 10	66 / 14 / 14 / 6	59 / 12 / 18 /12
Norepinephrine, pg/ml	682 ± 348	664 ± 359	710 ± 398	702 ± 339
NT-proBNP, pg/ml	1159 ± 1306	1343 ± 1846	1461 ± 1627	1678 ± 2438

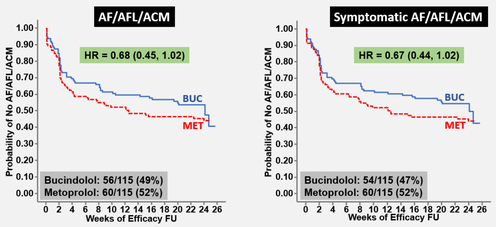
W/B/A/O = White/Black/Asian/Other; AADs = antiarrhythmic drugs.
AF Dx Duration = time from AF diagnosis to randomization. HF Dx Duration = time from AF diagnosis to randomization.
Note: mean ± standard deviations are presented unless otherwise specified.

Primary Endpoint

All AF/AFL/ACM and Symptomatic AF/AFL/ACM from ECG-Based Detection (N=267)

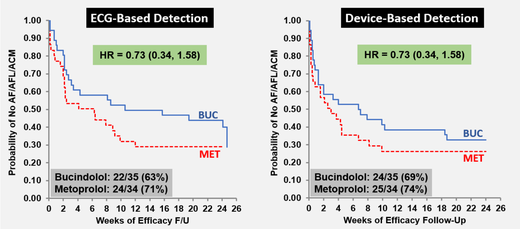


AF/AFL/ACM from Patients with AF and HF Diagnoses < 12 Years (N=230)



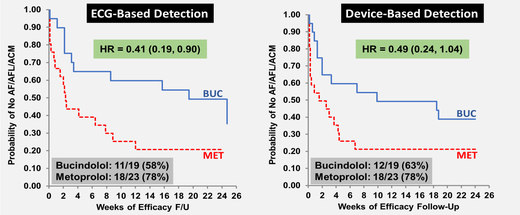
ECG vs. Device Based Detection

AF/AFL/ACM from ECG-Based and Device-Based Detection in Entire Cohort (N=69)



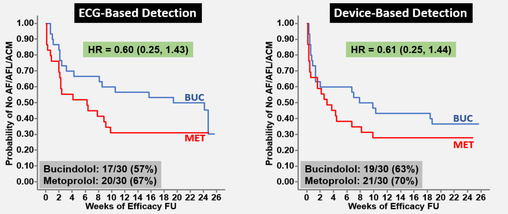
For non-stratified analysis: HR=0.69 (0.38, 1.23) and 0.75 (0.43, 1.32) for ECG and device-based detection, respectively.

AF/AFL/ACM from ECG-Based and Device-Based Detection in U.S. Cohort (N=42)



Non-stratified analysis. Stratified analysis could not be performed due to small sample size.

AF/AFL/ACM from Patients with AF and HF Diagnoses < 12 Years (N=60)



For non-stratified analysis: HR=0.61 (0.32, 1.17) and 0.71 (0.38, 1.32) for ECG and device-based detection, respectively.

Statistical Methodology

- Unless otherwise stated, hazard ratios and 95% confidence intervals 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).

Summary

- In patients with heart failure (HF), a total AF burden (AFB) ≥ 6 hours per day, as measured by cardiac electronic implanted devices, has been previously shown to be associated with an increased rate of HF hospitalizations.
- In GENETIC-AF, similar treatment effect estimates were observed by continuous device-based monitoring compared to intermittent ECG-based clinical monitoring when AFB ≥ 6 hours per day was used to define an AF event.
- Event rates were slightly higher for device-based monitoring and the device-based endpoint occurred a median of 6.5 days prior to clinical AF/AFL detection (p <0.0001).
- Trends for bucindolol benefit compared to metoprolol for AF prevention were observed by both heart rhythm methods in the U.S. cohort and in a cohort of patients who had AF and HF for less than 12 years prior to randomization.
- 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.
- In a population of HFrEF and HFmrEF patients at risk of AF recurrence, a total AF burden ≥ 6 hours per day:
  - has high predictive accuracy for clinical AF/AFL
  - can reinforce the validity of clinical AF endpoint detection
  - has potential as a surrogate marker of impending clinical AF episodes.

References

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