Pharmacogenomic Guided Beta-Blocker Therapy with Bucindolol Reduces Atrial Fibrillation Burden Compared to Metoprolol Succinate: The GENETIC-AF Trial

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This trial was sponsored by ARCA biopharma

GENETIC-AF Device Substudy
Background

- Bucindolol is a genetically-targeted β-blocker/mild vasodilator with the unique pharmacologic properties of sympatholysis and ADRB1 Arg389 inverse agonism[1,2]
- In the GENETIC-AF trial, similar results were observed for bucindolol and metoprolol succinate for the primary endpoint of time to first ECG-detected AF event in 267 HF patients with the ADRB1 Arg389Arg genotype[2]
- Evidence of superior efficacy with bucindolol was observed for the primary endpoint in a subpopulation identified by precision phenotyping & marked AF and HF duration
  - AF/HF onset < 12 years and AF onset not >2 years prior to HF onset (PTP cohort) [2]
- **A subgroup of patients (N=69) underwent continuous heart rhythm monitoring via implanted cardiac monitors, CRTs, ICDs, and pacemakers to evaluate daily AF burden**

[1]*O'Connor et al. PLOS ONE 2012;* 7:e44324; [2]Piccini et al. JACC Heart Fail. 2019 Jul;7(7):586-598.

GENETIC-AF Device Substudy
Methods

- **Outcomes**
  - Assessed in all (n=69) substudy patients
  - Reported with HR and 95% CI values determined by Cox proportional hazards model
  - Tested for superiority with the log rank test.
- **Time to First Symptomatic AF/AFL or ACM (primary endpoint)[1]**
  - Event required AF/AFL on 2 ECGs separated by ≥10 min and new/worsening symptoms ± 1 week of ECGs.
  - All events adjudicated by a blinded clinical events committee.
- **Time to First Device-Detected AF/AFL or ACM[1]**
  - AF/AFL event defined as AFB ≥ 6 hours per day[2].

[1]Piccini et al. *JACC Heart Fail*. 2019;7:586-598.
[2]Sarkar S. *Am Heart J*. 2012;164:616-24

Note: Deaths prior to start of FU were counted as events on Day 1 (1 in MET group). AFB events censored at unblinding.

GENETIC-AF Device Substudy
Methods

- **Cumulative AF burden**
  - Included all substudy patients entering efficacy follow-up and on drug (N=68).
    - Intent-to-treat analysis not requiring patients to be on drug also reported.
  - Total days in AF = cumulative hours in AF as detected by continuous monitoring divided by 24 hours
  - AF Burden expressed as an incidence rate (IR) for each treatment group
    - Total days in AF divided by total number of patients in treatment group.
  - Comparisons between treatment groups were expressed by the IR Ratio ($IRR=IR_{BUC}/IR_{MET}$) and tested for significance using the Poisson regression test.
- **Example**

Group	Total # Pts (N)	Total # Days in AF	Incidence Rate (days/pt)	Incidence Rate Ratio (95% CI)
BUC	A	C	C/A	$\frac{C/A}{D/B}$
MET	B	D	D/B	

GENETIC-AF Device Substudy

Baseline Characteristics

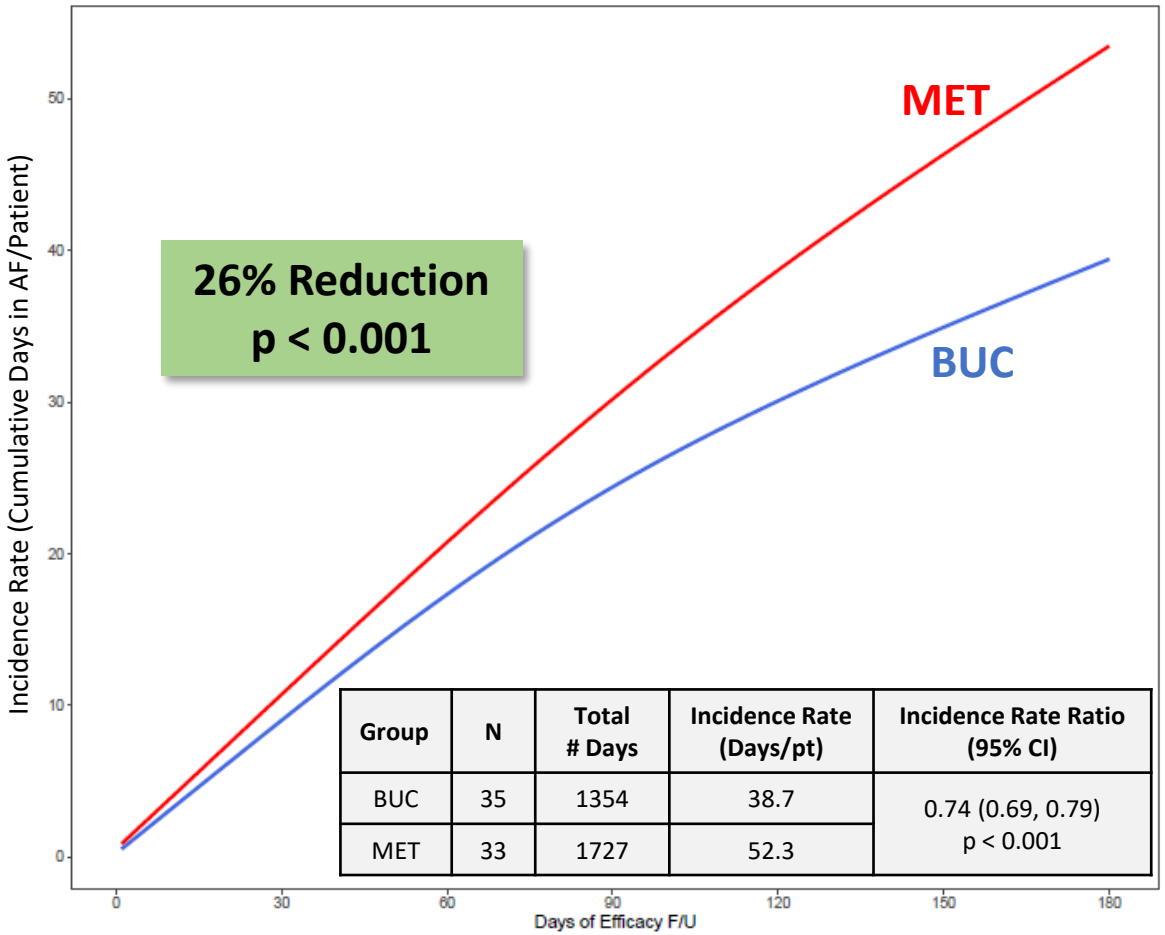
Parameter	Bucindolol N = 35	Metoprolol N = 34
Age, years	65.5 ± 11.5	66.8 ± 9.9
Male/Female, %	94 / 6	91 / 9
Race: W / B / A / O, %	94 / 0 / 3 / 3	97 / 3 / 0 / 0
LVEF	0.33 ± 0.08	0.36 ± 0.09
NYHA: I / II / III, %	29 / 49 / 23	18 / 65 / 18
Ischemic / Non-Ischemic HF, %	29 / 71	26 / 74
Randomized in AF / Not in AF, %	63 / 37	68 / 32
Persistent / Paroxysmal AF, %	63 / 37	65 / 35
HF DxT Duration, days	1208 ± 1880	1126 ± 1572
AF DxT Duration, days	1444 ± 1997	1263 ± 1995
Systolic blood pressure, mm Hg	122.4 ± 15.7	124.2 ± 14.5
Diastolic blood pressure, mmHg	73.7 ± 9.9	76.3 ± 10.3
Heart Rate, bpm	76.8 ± 16.4	80.1 ± 18.1
Previous ECV / AF Ablation / Type III AAD, %	57 / 17 / 57	53 / 9 / 50
Device Type: ICM / PM / ICD, %	66 / 20 / 14	59 / 24 / 18
Norepinephrine, pg/ml	710 ± 398	702 ± 339
NT-proBNP, pg/ml, median (IQR)	923 (365, 1506)	1013 (537, 1806)

W/B/A/O=White/Black/Asian/Other. HF DxT Duration=time from HF diagnosis to randomization. AF DxT Duration=time from AF diagnosis to randomization. ECV=electrical cardioversion. AAD=antiarrhythmic drug. ICM=insertable cardiac monitor. ICD=implanted cardiac defibrillator. PM=pacemaker. IQR=interquartile range. Note: mean ± standard deviations are presented unless otherwise specified.

GENETIC-AF: Cumulative Days in AF during 24-week Efficacy Follow-up

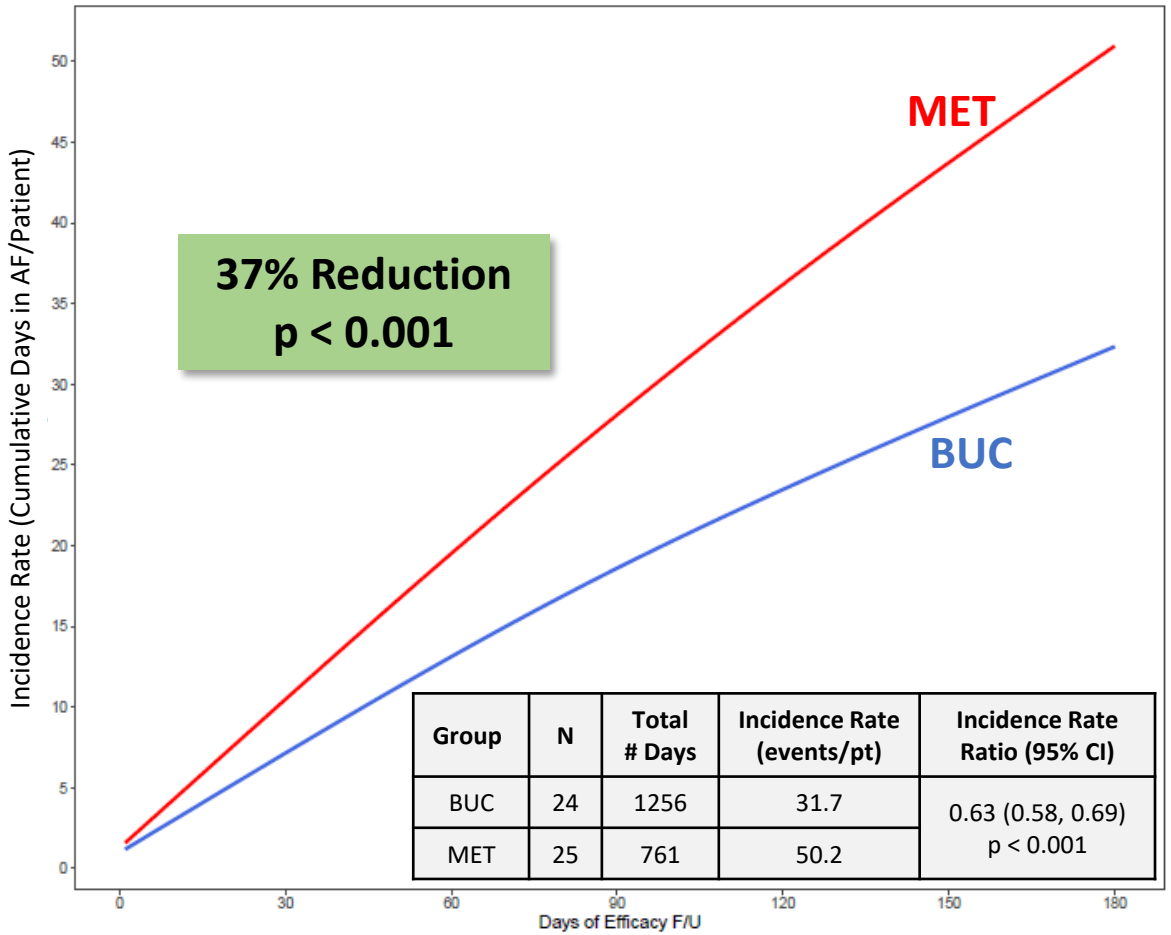
Days in AF by Continuous Monitoring in Device Substudy

Entire Cohort



Group	N	Total # Days	Incidence Rate (Days/pt)	Incidence Rate Ratio (95% CI)
BUC	35	1354	38.7	0.74 (0.69, 0.79) p < 0.001
MET	33	1727	52.3	

PTP Cohort



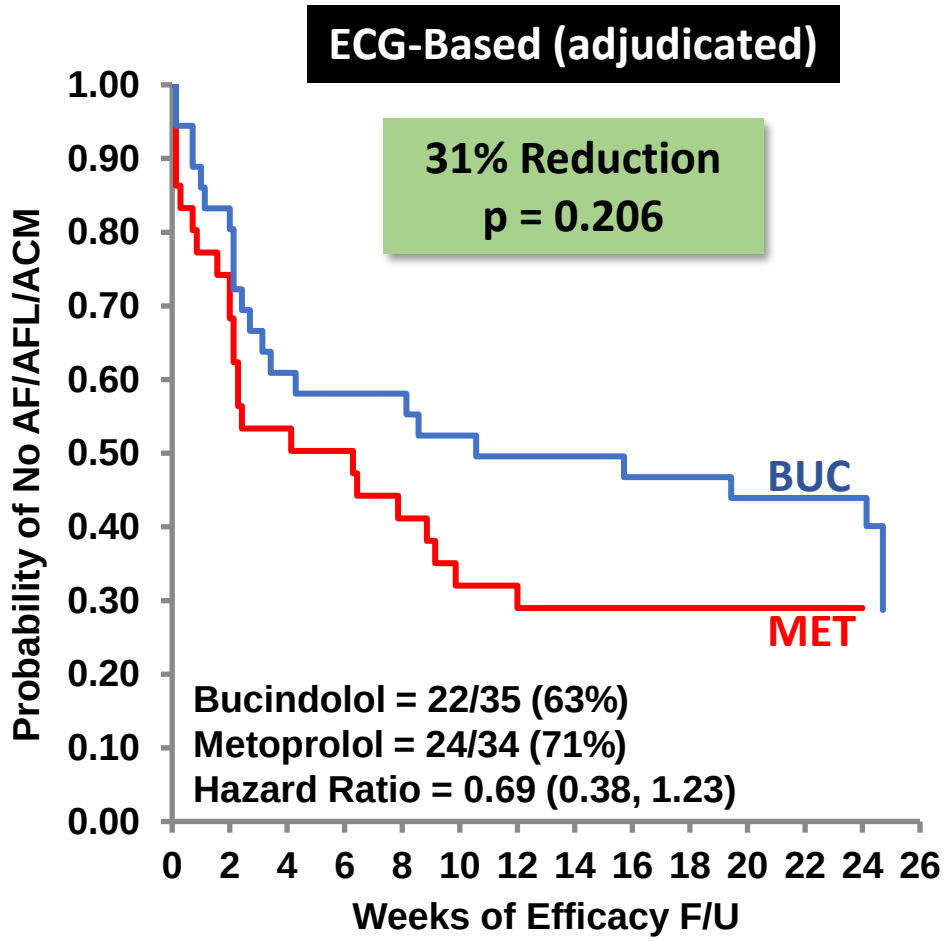
Group	N	Total # Days	Incidence Rate (events/pt)	Incidence Rate Ratio (95% CI)
BUC	24	1256	31.7	0.63 (0.58, 0.69) p < 0.001
MET	25	761	50.2	

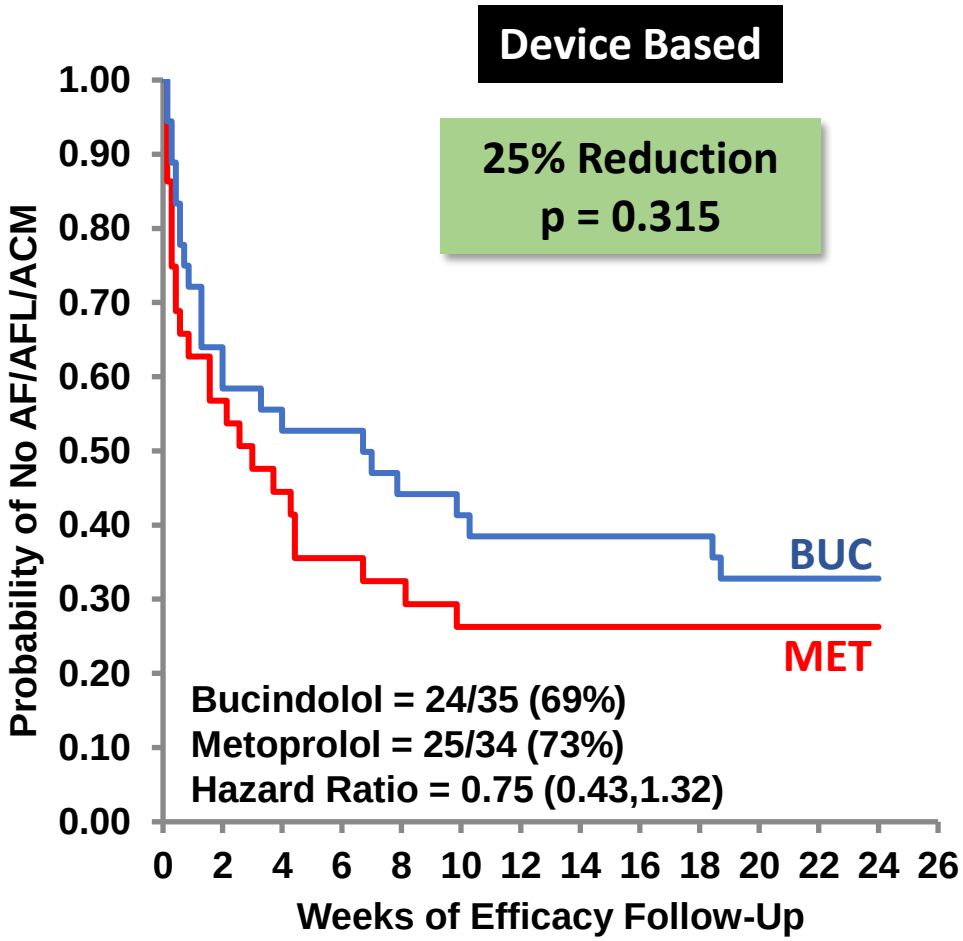
PTP Cohort = AF & HF onset <12 years and AF onset not >2 years prior to HF onset.
Mean follow-up per patient (days): GAF (BUC=157; MET=158), PTP (BUC=158; MET=158).

IRR for ITT analysis: GAF = 0.77 (p < 0.001); PTP = 0.63 (p < 0.001)

GENETIC-AF: Time to First AF/AFL/ACM Event during 24-week Efficacy Follow-up[7]

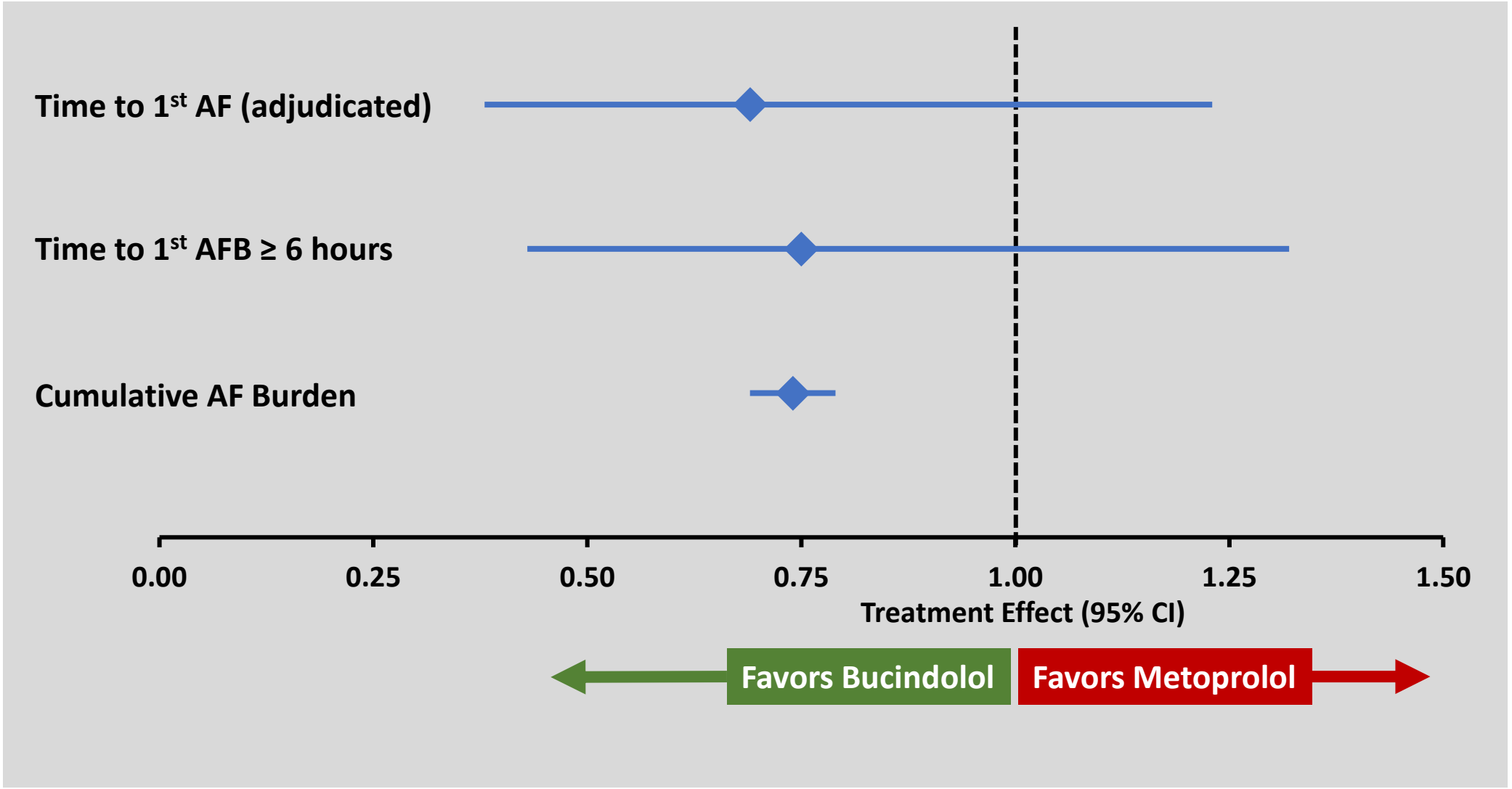
Device Substudy Cohort





Device detected AF event defined as AF burden ≥ 6 hours per day.
Non-stratified analysis.

GENETIC-AF: Estimate of Treatment Effect
Time to First AF Event vs. Cumulative AF Burden



Treatment effect = Hazard ratio (HR) for time to first AF event analyses and incidence rate ratio (IRR) for cumulative AF burden

GENETIC-AF: Device Substudy
Summary and Conclusions

Method	Time to First AF Event	Time to First AF Event	Cumulative AF Burden
	ECG Detection + Symptom Adjudication	Device Detection AFB ≥ 6 hours/day	Total Time in AF by Device
Entire Cohort (N=69)	**31% Reduction p = 0.206**	**25% Reduction p = 0.315**	**26% Reduction p < 0.001**

- In a pharmacogenetically-defined HF population at risk for AF recurrence, bucindolol significantly decreased cumulative AF burden compared to the active control metoprolol succinate.
- Treatment effect estimates for cumulative AF burden were consistent with time to first AF event analyses.
- Cumulative AF burden evaluates more information than time to first event methods, providing greater power to detect clinically meaningful differences between groups with limited sample size.

Thank you