
Impact of Pharmacogenetic-guided Bucindolol versus Metoprolol Succinate on the Overall Burden of Clinical Events in Patients with AF and Heart Failure: The GENETIC-AF Trial

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Bucindolol for the Treatment of AF in HF Patients

Background

- Bucindolol is a genetically-targeted β -blocker/mild vasodilator
- Bucindolol has two unique pharmacologic properties
 - Sympatholysis and ADRB1 Arg389 inverse agonism^{1,2}
- BEST DNA substudy: 441 HF patients ADRB1 Arg389Arg genotype³
 - Time to first event of AF/AFL or ACM (vs. placebo)
 - HR = 0.26 (95% CI: 0.12, 0.57); p < 0.001
- GENETIC-AF trial: 267 HF patients with ADRB1 Arg389Arg genotype²
 - Time to first event of AF/AFL or ACM (vs. metoprolol succinate)
 - HR = 1.01 (95% CI: 0.71, 1.42); p = 0.961

GENETIC-AF

Precision Therapeutic Phenotyping (PTP)

- Two variables strongly associated with an attenuation of bucindolol response
 - Interval of time from the initial diagnosis of HF and AF to randomization
 - Onset of AF relative to initial HF diagnosis
- Large subgroup (N=196) identified with significant bucindolol 1EP response
 - PTP cohort: AF/HF onset < 12 years and AF onset not >2 years prior to HF²
 - Primary Endpoint: HR = 0.54 (95% CI: 0.33, 0.87); p = 0.011
- Current analysis examines cumulative clinical events for 24 weeks of follow-up
 - In GENETIC-AF population, PTP cohort, and PTP cohort with LVEF ≥ 40%

GENETIC-AF

Cumulative Events Methodology

- Analyses includes all patients entering efficacy follow-up (N=259)
 - 8 patients (6 MET/2 BUC) withdrew prior to start of efficacy follow-up
- ITT analysis for all events during 24 weeks of efficacy follow-up
 - On treatment analysis also reported
- Prevalence rates (PR; events/pt) generated for a composite endpoint of:
 - AF interventions: ECV, catheter ablation, start of Class III AADs
 - CV adverse events: All AEs in MedDRA SOC of “Cardiac Disorders”
 - Deaths included as events in all analyses to account for competing risk (3 MET/0 BUC).
- Comparisons between treatment groups expressed by PR Ratio ($PRR = PR_{BUC}/PR_{MET}$)
 - Poisson regression test for significance

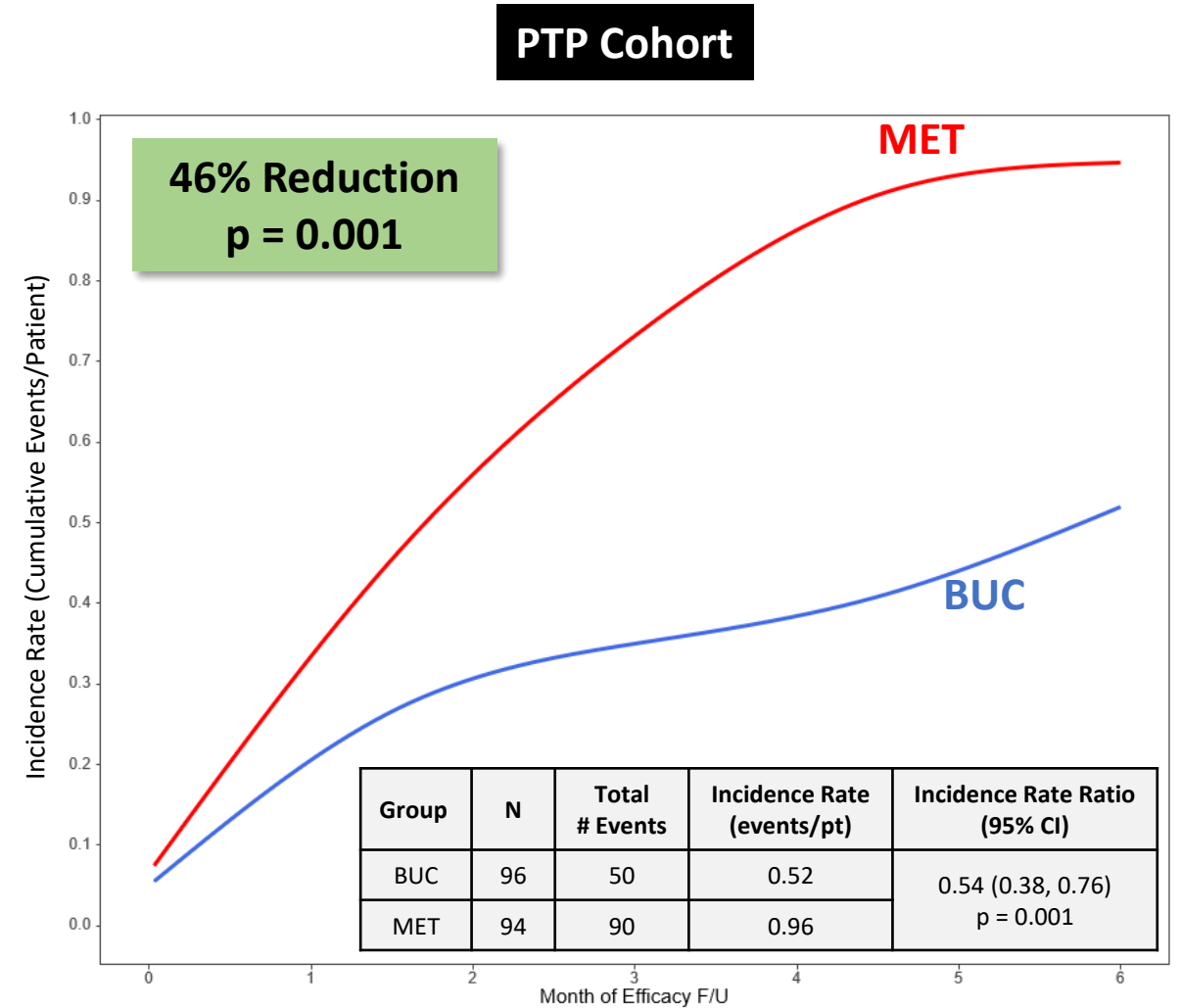
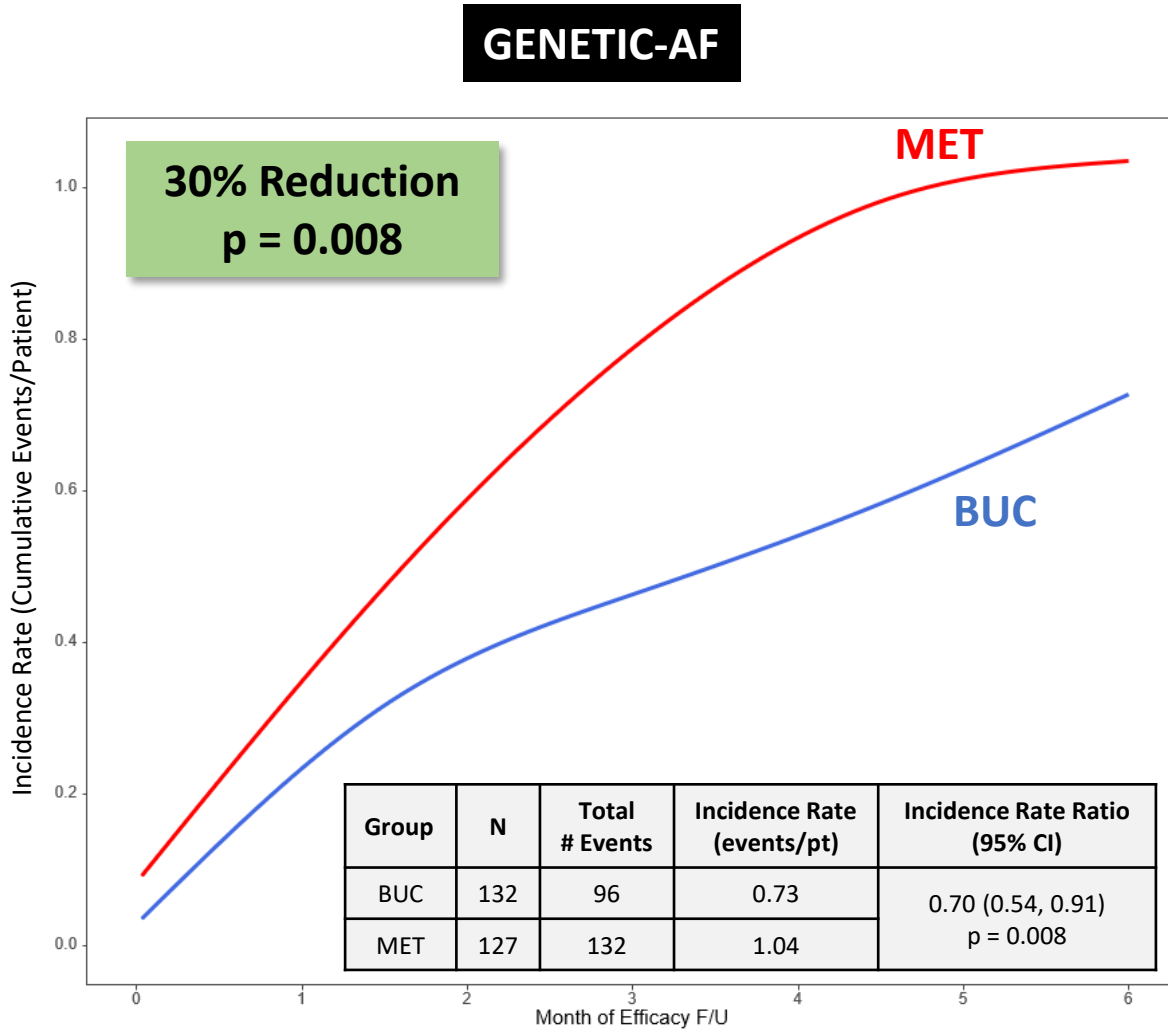
Baseline Characteristics

Parameter	All Patients		PTP Cohort	
	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
HF DxT Duration, days	1252 ± 2070	1054 ± 1733	810 ± 1071	749 ± 1060
AF DxT Duration, days	1431 ± 2271	1180 ± 2209	583 ± 831	495 ± 742
Systolic blood pressure, mm Hg	124.7 ± 14.9	121.8 ± 15.7	125.2 ± 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 / AF Ablation / Type III AAD, %	49 / 21 / 50	50 / 20 / 46	47 / 15 / 42	50 / 14 / 42
Device Type: ICM / PM / ICD, %	17 / 15 / 18	15 / 20 / 12	3 / 8 / 19	8 / 7 / 10
Norepinephrine, pg/ml	682 ± 348	664 ± 359	681 ± 355	630 ± 268
NT-proBNP, pg/ml, median (IQR)	777 (355, 1326)	861 (420, 1607)	777 (329, 1309)	812 (436, 1463)

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 Events during 24-week Efficacy Follow-up

Composite of AF Interventions and CV Adverse Events



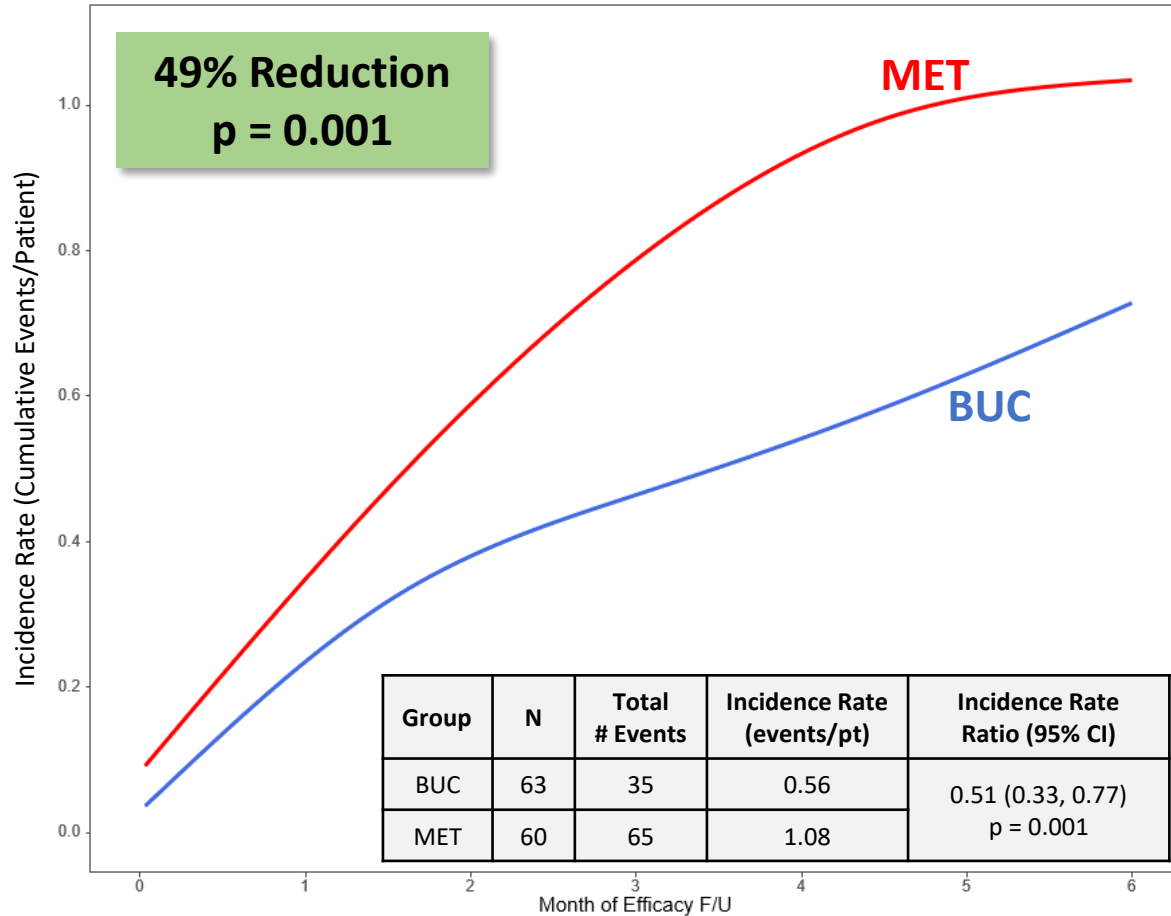
PTP cohort: AF/HF onset < 12 years and AF onset not > 2 years prior to HF onset.

Per protocol analysis: GAF = 0.72 (95% CI: 0.54, 0.95), p = 0.021; PTP = 0.56 (95% CI: 0.38, 0.81), p = 0.002.

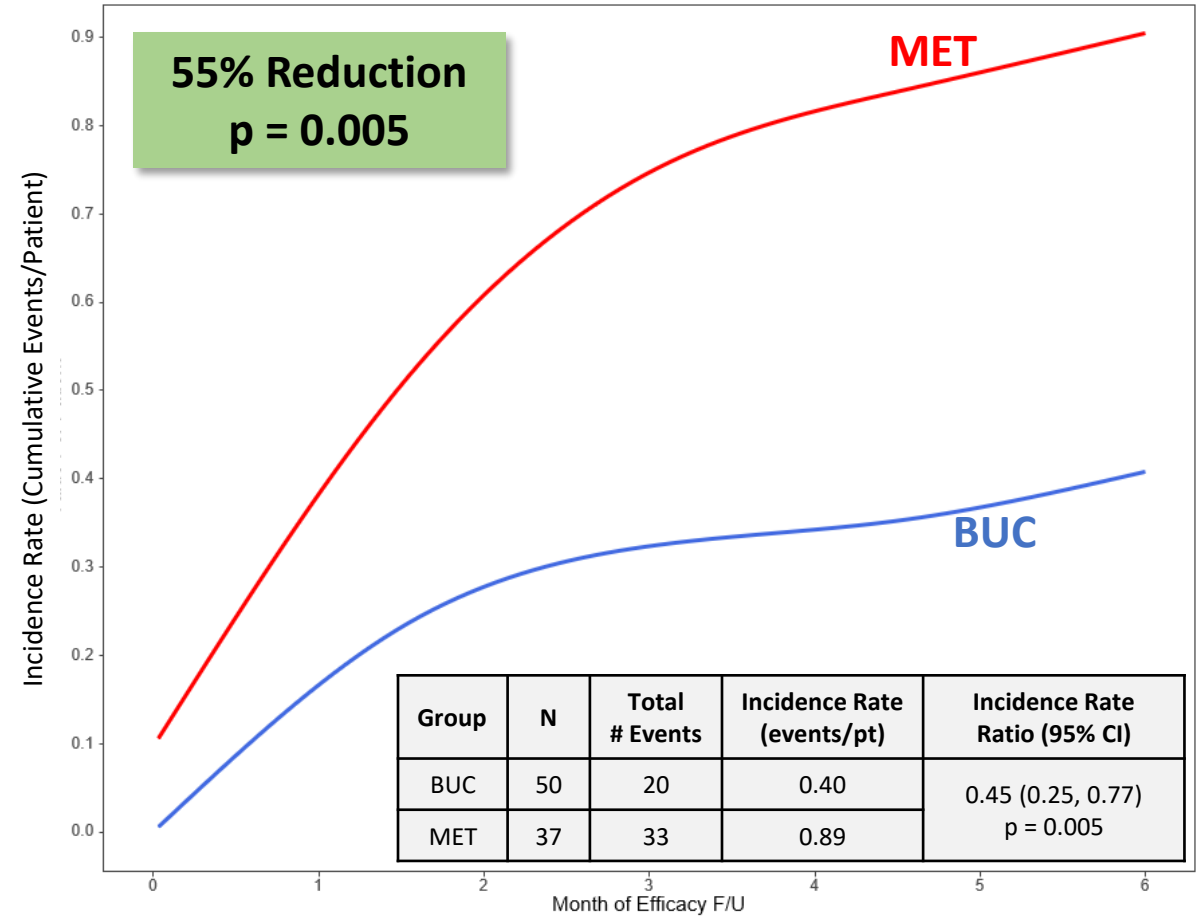
GENETIC-AF: Cumulative Events during 24-week Efficacy Follow-up

Composite of AF Interventions and CV Adverse Events for $LVEF \geq 40\%$ and $\leq 55\%$

GENETIC-AF



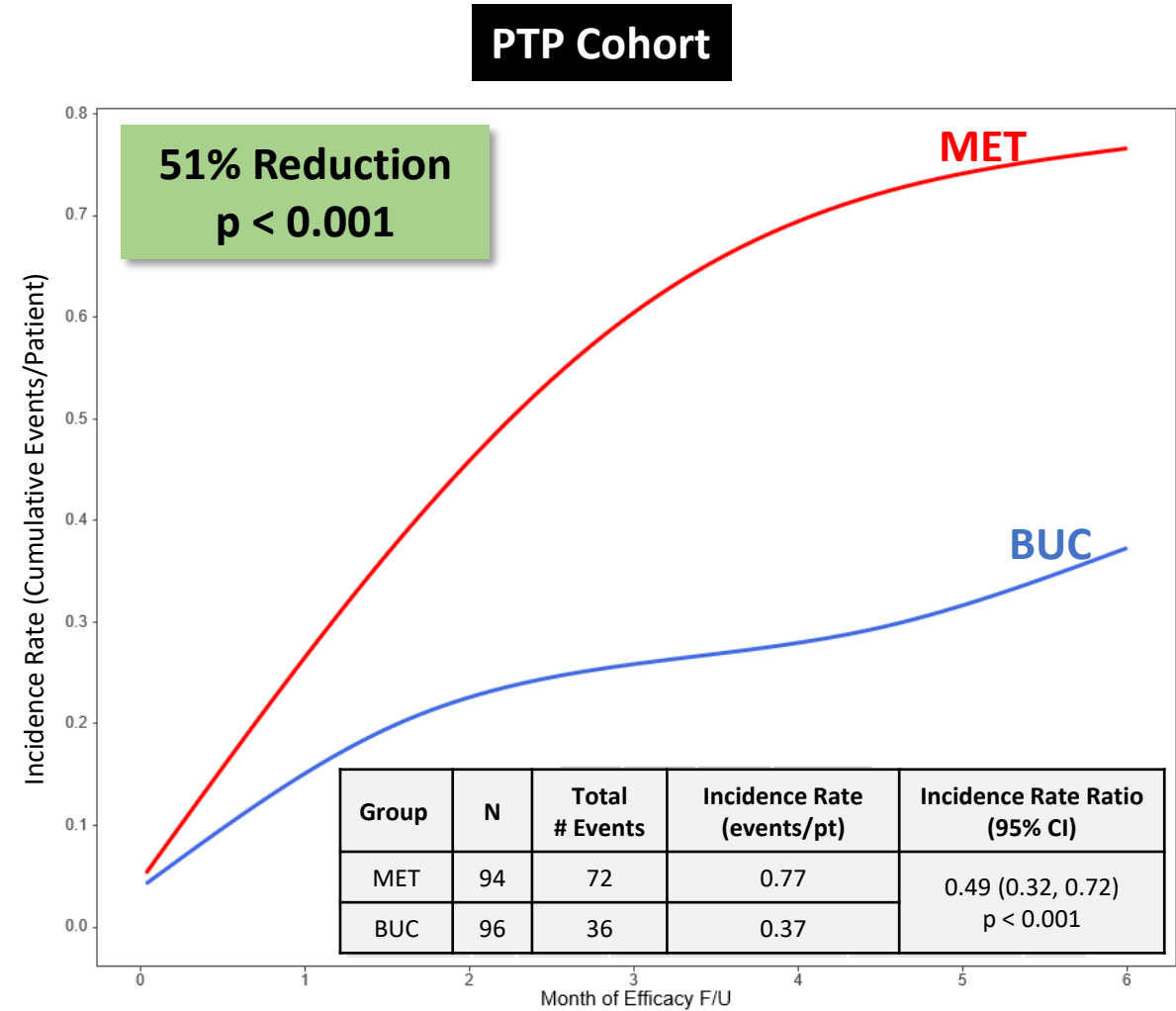
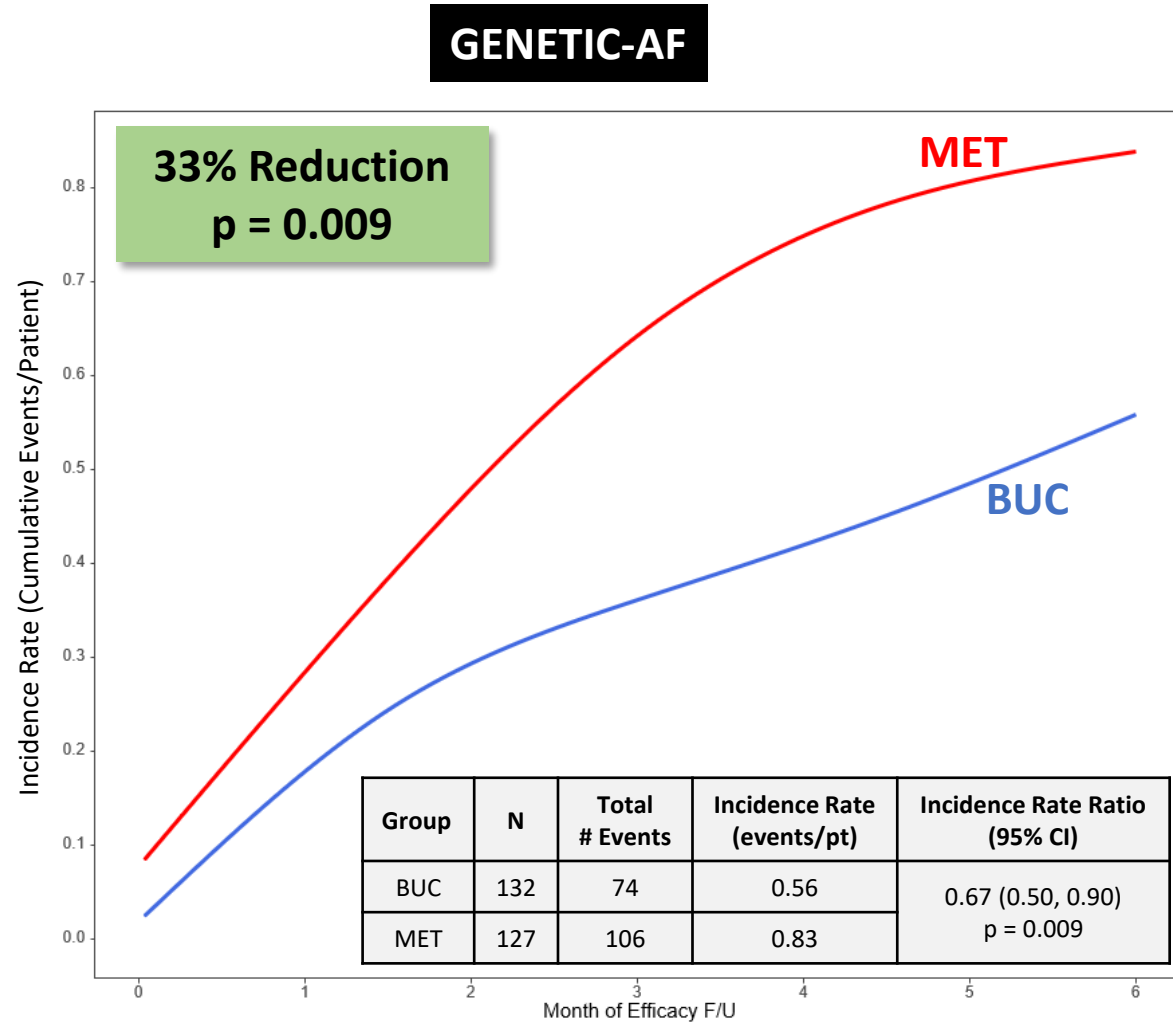
PTP Cohort



PTP cohort: AF/HF onset < 12 years and AF onset not >2 years prior to HF onset.

Per protocol analysis: GAF = 0.51 (95% CI: 0.33, 0.77), p = 0.002; PTP = 0.46 (95% CI: 0.25, 0.82), p = 0.010.

GENETIC-AF: Cumulative Events during 24-week Efficacy Follow-up AF Interventions Only (ECV, Ablation, Class 3 AAD)

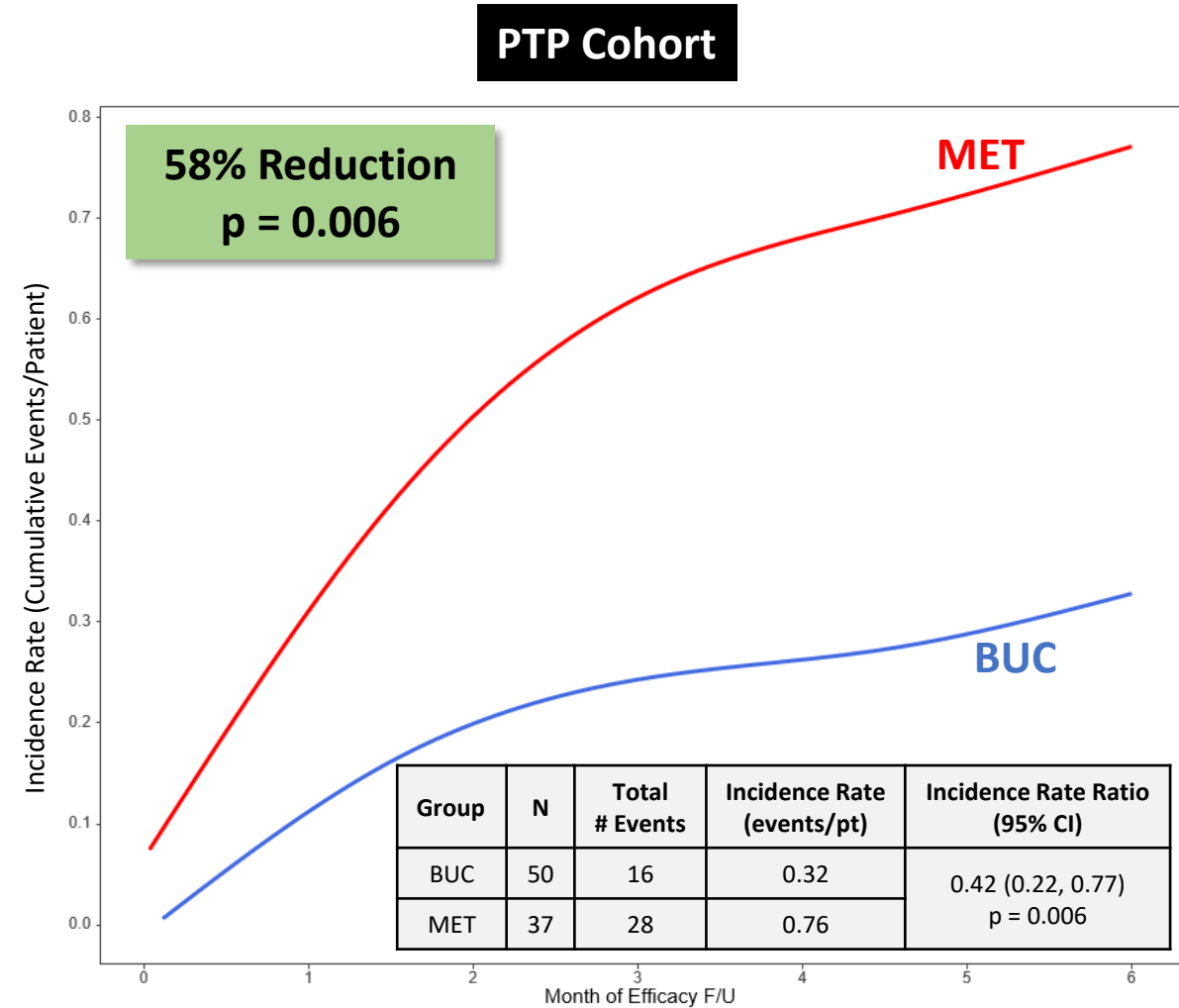
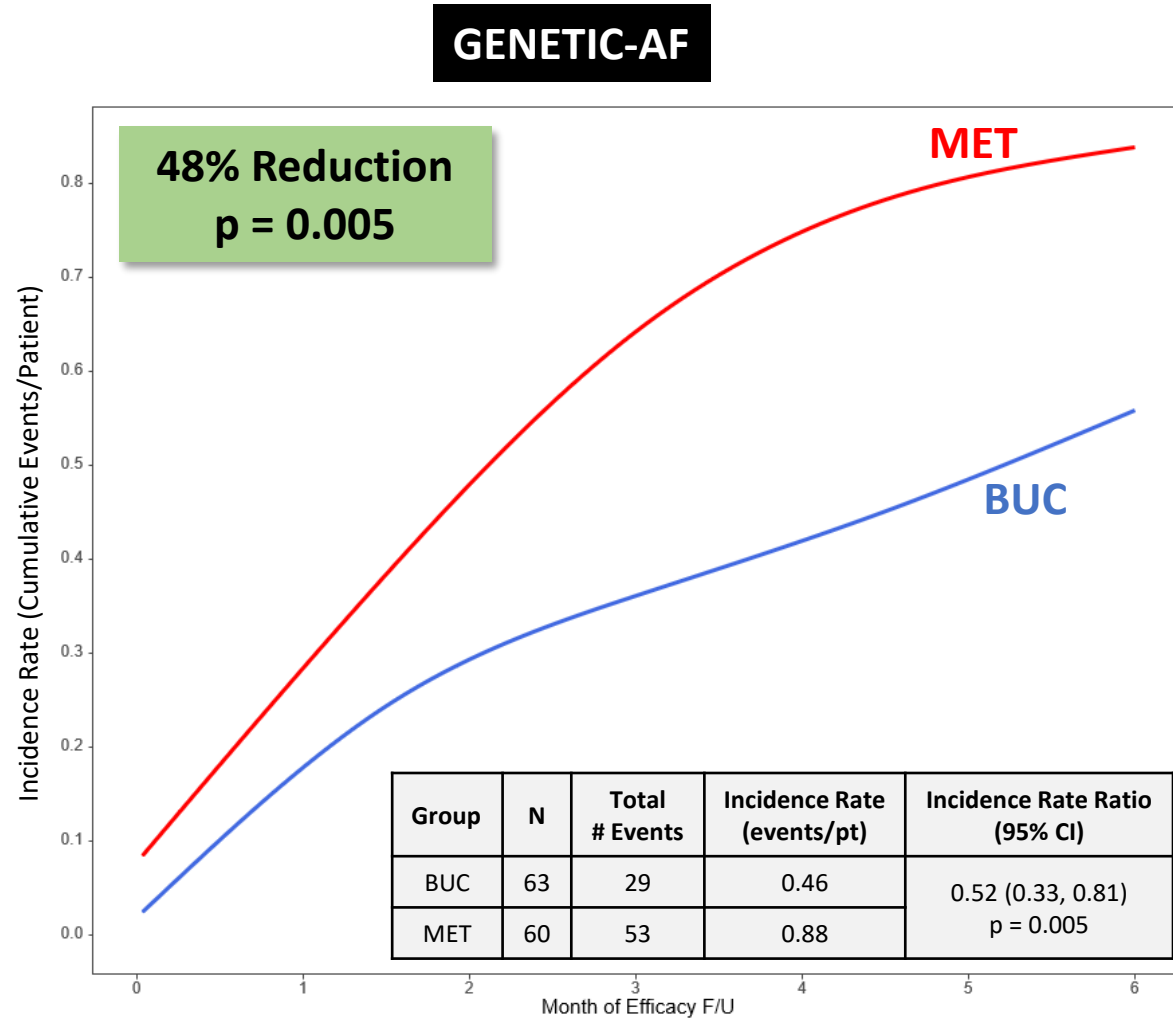


PTP cohort: AF/HF onset < 12 years and AF onset not >2 years prior to HF onset.

Per protocol analysis: GAF = 0.75 (95% CI: 0.55, 1.02), p = 0.070; PTP = 0.59 (95% CI: 0.38, 0.89), p = 0.014

GENETIC-AF: Cumulative Events during 24-week Efficacy Follow-up

AF Interventions Only (ECV, Ablation, Class 3 AAD) for LVEF $\geq 40\%$ and $\leq 55\%$



PTP cohort: AF/HF onset < 12 years and AF onset not > 2 years prior to HF onset.

Per protocol analysis: GAF 0.54 (95% CI: 0.33, 0.85), p = 0.009; PTP = 0.46 (95% CI: 0.24, 0.87), p = 0.019.

GENETIC-AF: Cumulative Clinical Events during 24-week Efficacy Follow-up

Summary and Conclusions

- Bucindolol decreased AF interventions and CV adverse events compared to metoprolol succinate in a pharmacogenetically-defined HF population
- Bucindolol decreased AF interventions (i.e., ECVs, ablations, and Class 3 AADs) compared to metoprolol succinate
- Significant and numerically greater results were observed in the PTP cohort
- Similar significant results observed for PTP cohort with LVEF $\geq 40\%$ and $\leq 55\%$