Bucindolol is Associated with a Lower Incidence of Dose Limiting Bradycardia in Heart Failure Patients with Atrial Fibrillation: The GENETIC-AF Trial

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Disclosures

- Bristow, Dufton and Carroll are employees of ARCA biopharma, sponsor of bucindolol

- All other authors are members of the GENETIC-AF Steering Committee or are ARCA consultants

Background (1), Heart Rate in HFrEF and AF/HFrEF

- Heart rate is a major determinant of outcomes in heart failure with reduced LV ejection fraction (HFrEF)
  - In SR lowering HR to <70 bpm is associated with improved clinical outcomes (e.g. SHIFT Trial, Ivabradine vs. placebo)
  - In AF HR/VRR is more complicated; HRs <70 bpm may be associated with worse outcomes in patients treated with beta-blocking agents, while VRR >100 bpm may be associated with tachycardia cardiomyopathy
- Patients in/out of AF are more prone to bradycardia because of associated sinus node or conduction system disease
  - Tachy-brady syndrome
  - Nocturnal pauses
  - Higher prevalence of pacemaker implantation
  - Drugs used to treat AF (rate & rhythm control) often exacerbate sinus node dysfunction and/or affect AV nodal function

Background (2), Beta-blockers and AF/HF

- Beta-blockers are GDMT indicated for HFrEF, in AF/HF are used off label for:
  - Modest AF prevention effects
  - Rate control
  - Most commonly used beta-blocker in AF/HF is metoprolol

- Beta-blockers are pharmacologically diverse beyond class effect of beta$_1$-AR blockade

Metoprolol succinate	**Bucindolol HCl**
● Sustained release formulation of metoprolol; q.d. dosing	● Immediate release, b.i.d. dosing
● Selective β_1-AR antagonist (Classed as 2nd generation)	● High affinity β_1/β_2-AR antagonist, mild β_3-AR agonist
● No vasodilation, no ISA	● Mild vasodilation (weak α_{1A}-AR blockade), no ISA
● No pharmacogenetic differentiation for ADRB1 389Arg vs. Gly	● Marked pharmacogenetic differentiation for ADRB1 389Arg vs. Gly (Classed as 4th generation (pharmacogenetic) compound)

GENETIC-AF Trial: Seamless Ph 2b/Phase 3 Design

Bucindolol vs. Toprol-XL, Prevention of Recurrent Atrial Fibrillation in HFREF Patients with the $\beta_1$389 Arg/Arg Genotype post Electrical Cardioversion (ECV) or with recent (≤ 180d) AF History

Hx HF, LVEF <0.50 last 12 mos, Hx AF Sx (HF or Arrhy) last 180d;
At randomization NYHA I-III, No contra-indications to β-blockers;
$\beta_1$389 Arg/Arg (*ADRB1* Arg389Arg) genotype

94% were on β-blockers, 66% on metoprolol or bisoprolol

Sample Size Estimates			
n	**Effect size**	**Power (%)** α = 0.05	α = 0.01
200	25%	71 (1-T)	–
620	25%	98 (2-T)	90 (2-T)
Event rate M group 60%, ITT from time of randomization			

***Either classic arrhythmia or HF Sx**

≤180 d Sx* AF, now SR; or current persistent / paroxysmal Sx* AF

n = 134

n = 133

Bucindolol

Toprol-XL

ECV @ 3 wks if in AF

Phase 2b: 1° Endpoint = Recurrent AF/AFL or ACM, 24 weeks

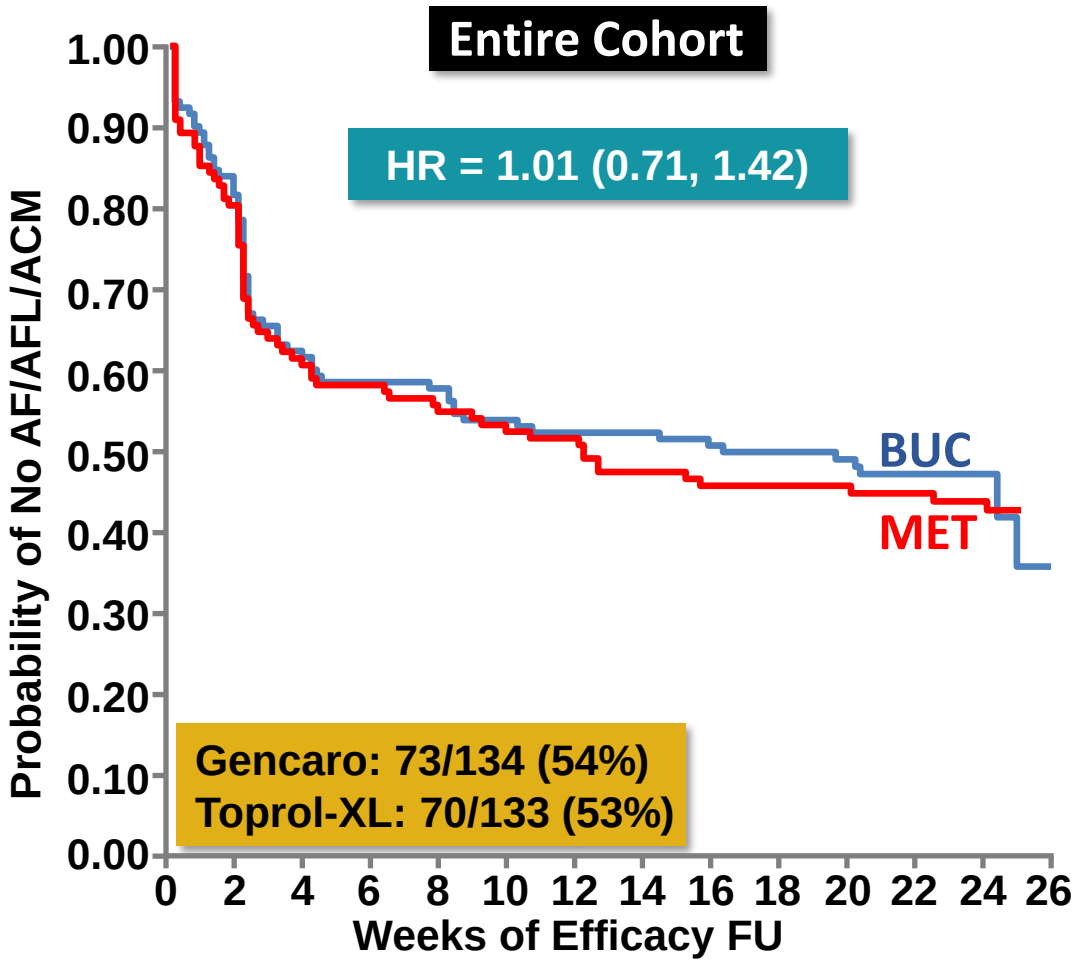
Interim analysis after ~200 pts randomized, ≥150 evaluable; Bayesian predictive probability (Ph 2 1EP) → Finish as Ph2

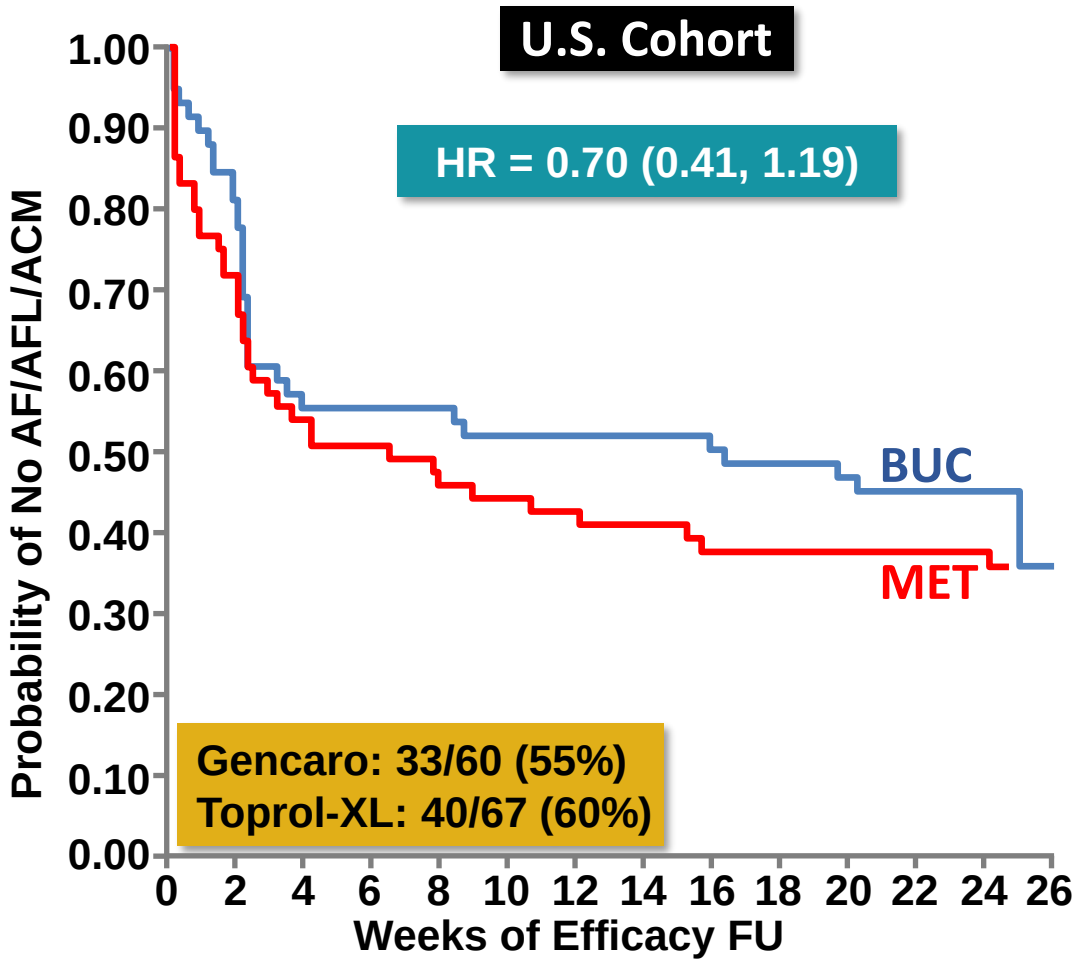
Time 0: ECV @ 3 wks (spontaneous conversion to SR counted as if ECV, i.e. f/u clock starts @ 3wks if SR

AF free/event: from 1 hr after ECV

GENETIC-AF: Phase 2B Genetically-Targeted Trial

Primary Endpoint: Time to AF/AFL/ACM





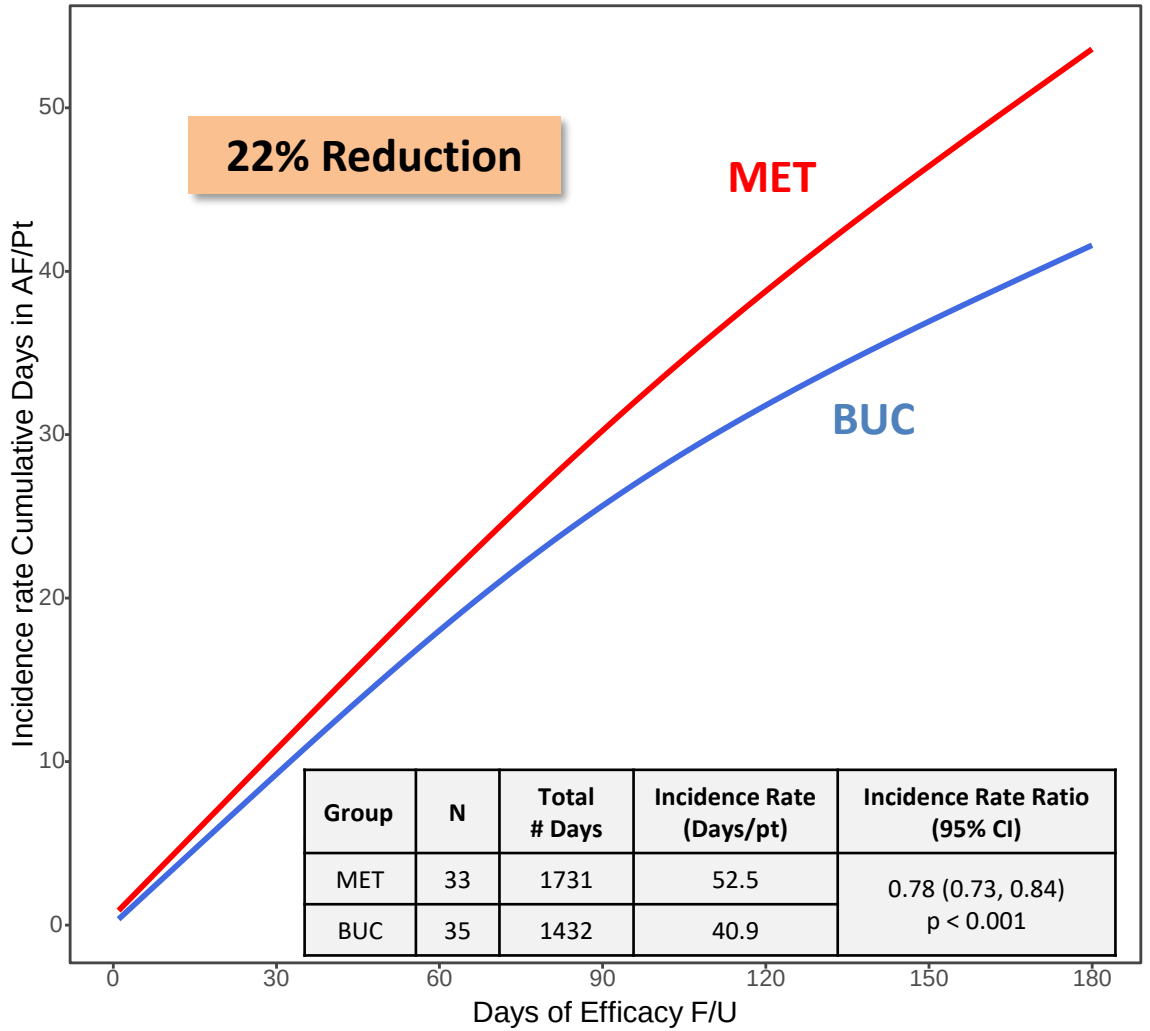
Cox proportional hazards model adjusted for the 4 randomization strata: 1) HF etiology, 2) LVEF, 3) rhythm at randomization 4) device type.

Piccini et al. JACC Heart Fail. 2019 Jul;7(7):586-598.

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

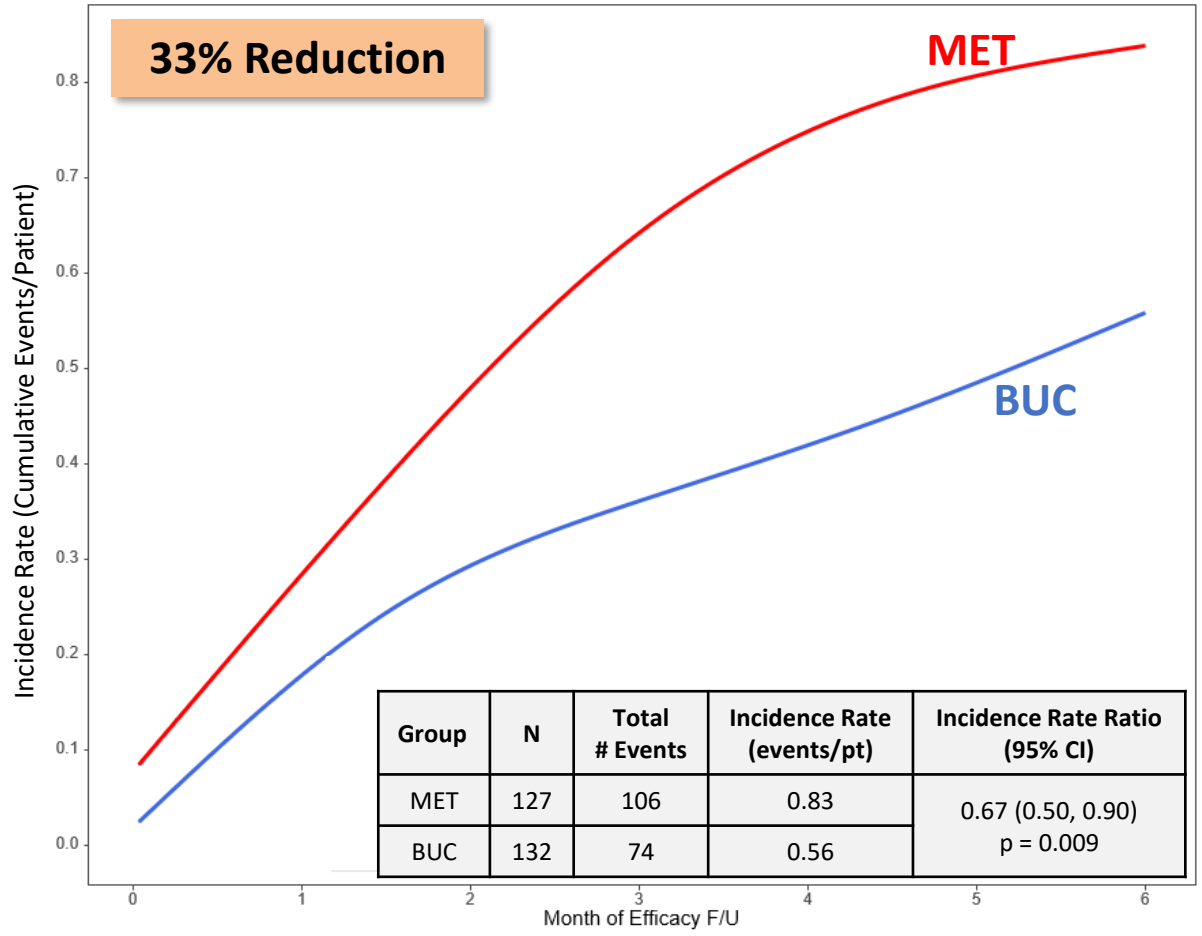
Days in AF by Continuous Monitoring in Device Substudy; AF interventions in Entire Cohort

AFB substudy



Group	N	Total # Days	Incidence Rate (Days/pt)	Incidence Rate Ratio (95% CI)
MET	33	1731	52.5	0.78 (0.73, 0.84) p < 0.001
BUC	35	1432	40.9	

Cumulative {ECV, catheter ablation, Class III AADs}

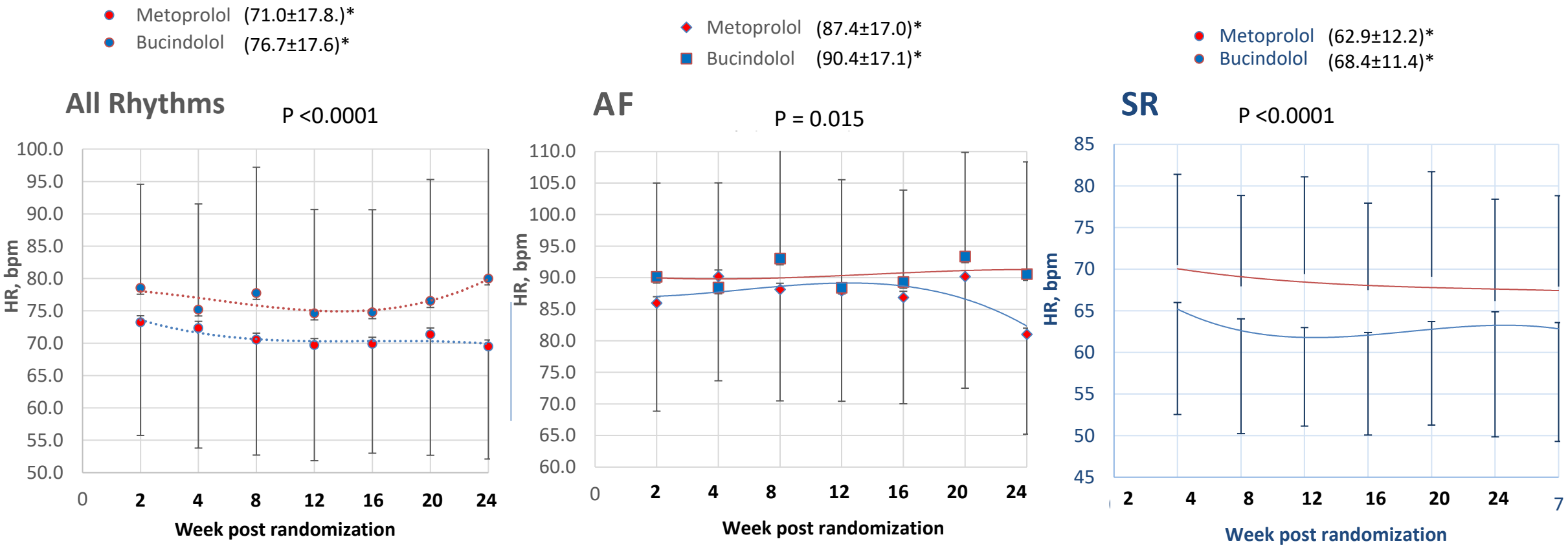


Group	N	Total # Events	Incidence Rate (events/pt)	Incidence Rate Ratio (95% CI)
MET	127	106	0.83	0.67 (0.50, 0.90) p = 0.009
BUC	132	74	0.56	

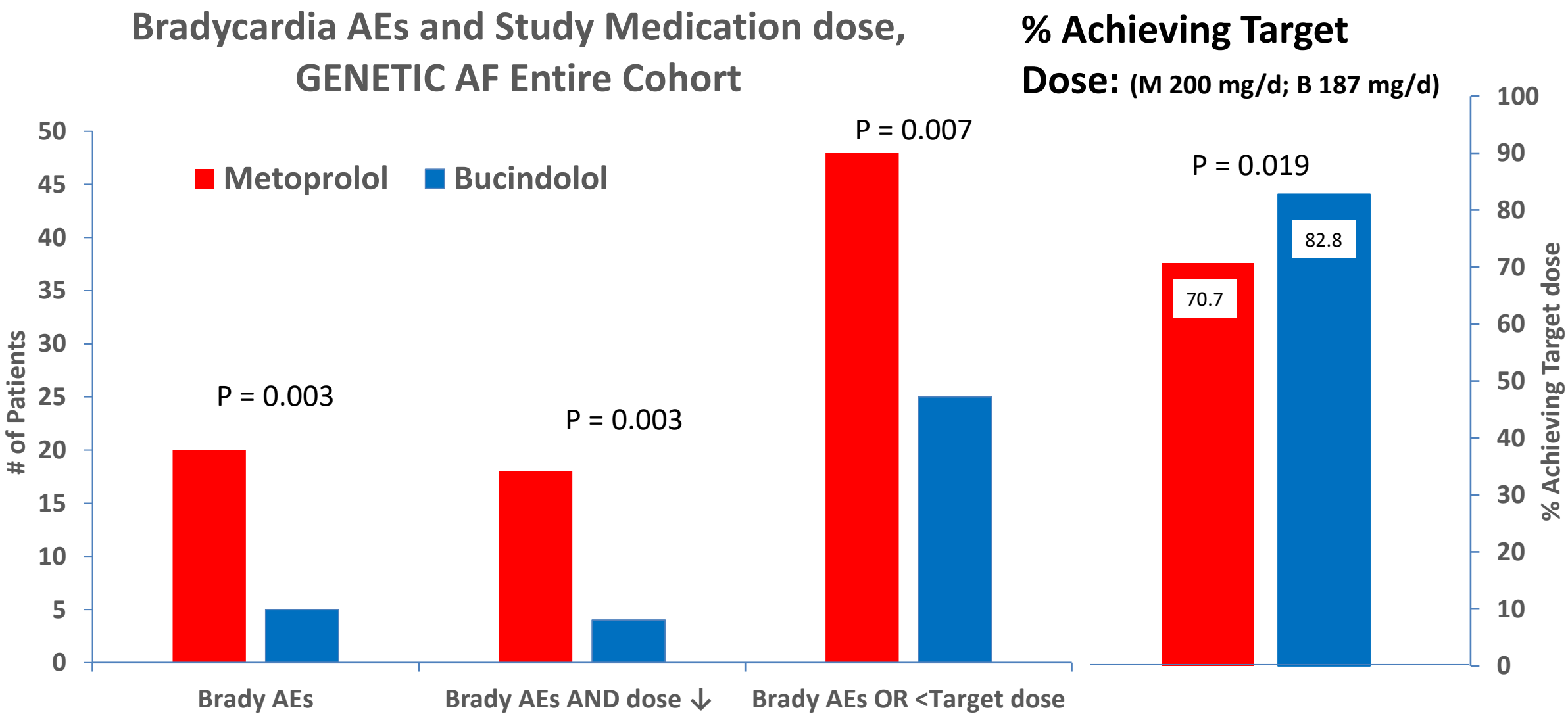
Time in AF determined by continuous monitoring with implanted cardiac monitors in patients participating in the device substudy.

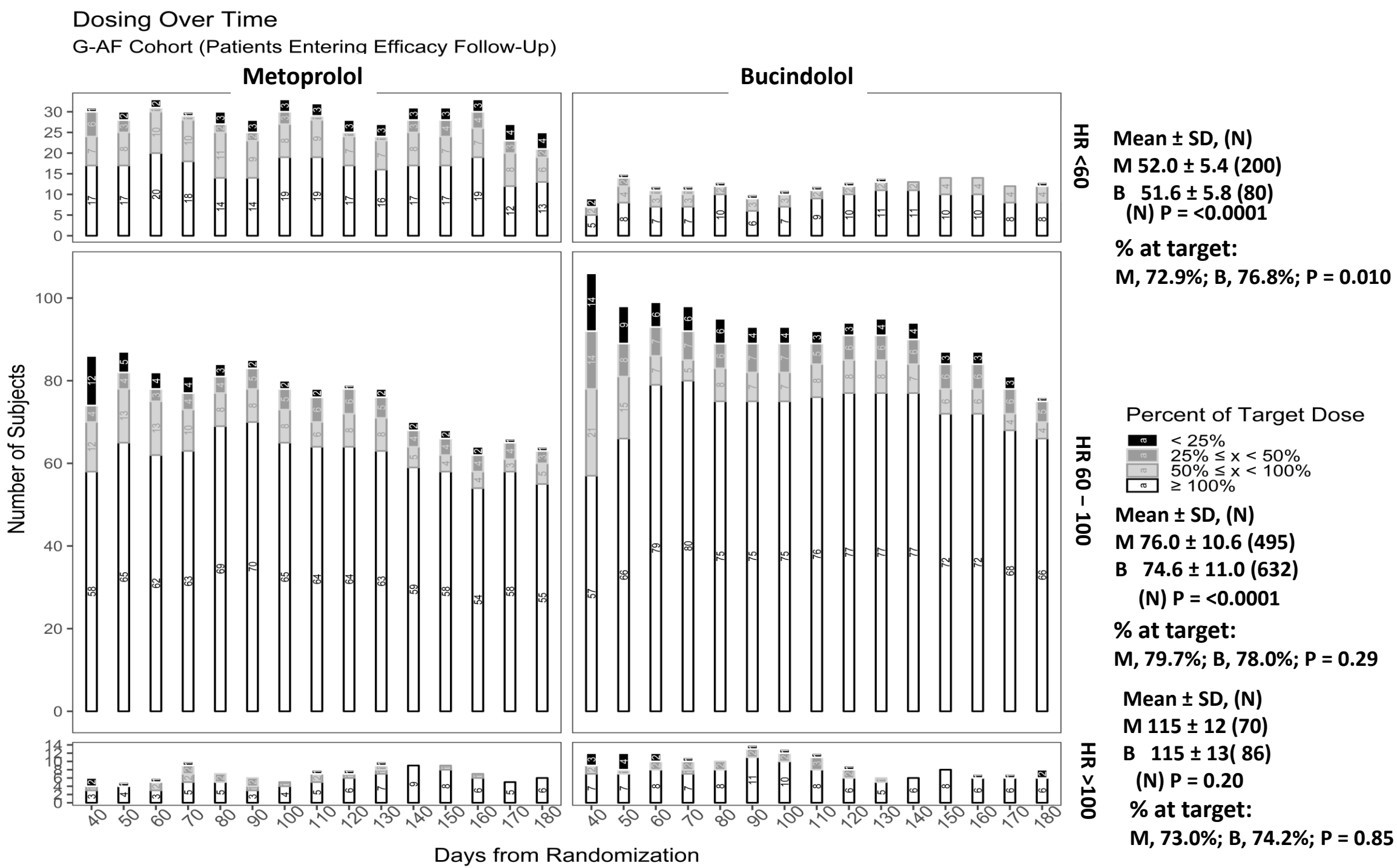
Incidence Rate Ratio = Incidence Rate$_{BUC}$ / Incidence Rate$_{MET}$.
Includes all patients entering the efficacy follow-up period.

Mean ECG HR±SD, on Study Medication at each clinic visit, GENETIC-AF Entire Cohort



(*Mean ± SD HR for entire 24 wk study period)


Bradycardia AEs and Study Medication dose, GENETIC AF Entire Cohort
Metoprolol
Bucindolol
# of Patients
50
45
40
35
30
25
20
15
10
5
0
P = 0.003
P = 0.003
P = 0.007
Brady AEs
Brady AEs AND dose ↓
Brady AEs OR <Target dose
% Achieving Target Dose: (M 200 mg/d; B 187 mg/d)
P = 0.019
70.7
82.8
100
90
80
70
60
50
40
30
20
10
0
% Achieving Target dose


Dosing Over Time
G-AF Cohort (Patients Entering Efficacy Follow-Up)
Metoprolol
Bucindolol
HR <60
HR 60 – 100
HR >100
Number of Subjects
Days from Randomization
Percent of Target Dose
< 25%
25% ≤ x < 50%
50% ≤ x < 100%
≥ 100%
Mean ± SD, (N)
M 52.0 ± 5.4 (200)
B 51.6 ± 5.8 (80)
(N) P = <0.0001
% at target:
M, 72.9%; B, 76.8%; P = 0.010
Mean ± SD, (N)
M 76.0 ± 10.6 (495)
B 74.6 ± 11.0 (632)
(N) P = <0.0001
% at target:
M, 79.7%; B, 78.0%; P = 0.29
Mean ± SD, (N)
M 115 ± 12 (70)
B 115 ± 13(86)
(N) P = 0.20
% at target:
M, 73.0%; B, 74.2%; P = 0.85

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

Bradycardia (Investigator ECG interpretation) & Study Drug Dose Reductions

Population	GENETIC-AF			
Event Type	Bradycardia		Dose Reductions	
Group	BUC	MET	Brady	No Brady
Total # Patients	132	127	71	188
Total # Events	71	151	22	14
Incidence Rate (events/pt)	0.54	1.19	0.31	0.07
Incidence Rate Ratio (95% CI)	0.45 (0.34, 0.60) p < 0.001		4.16 (2.15, 8.32) p < 0.001	

- **49-55% reduction in treatment-limiting bradycardia**
- **61-65% reduction in cohorts with LVEF ≥ 40%**

GENETIC-AF (G-AF) Cohort = randomized cohort of GENETIC-AF that entered efficacy follow-up.
Bradycardia = bradycardia on ECG as assessed by the investigator.
Incidence Rate Ratio by Treatment = Incidence Rate$_{BUC}$ / Incidence Rate$_{MET}$

Incidence Rate Ratio by Bradycardia = Incidence Rate$_{Brady}$ / Incidence Rate$_{NoBrady}$.
Includes all patients entering the efficacy follow-up period.
Deaths included as events due to competing risk.

Bucindolol is Associated with a Lower Incidence of Dose Limiting Bradycardia than Metoprolol in HFrEF Patients with Atrial Fibrillation, *Summary*:

- In GENETIC-AF both AF and SR patients had lower HRs on metoprolol vs. bucindolol
  - The AF difference was smaller
  - Mechanism for difference in HRs uncertain, ? $beta_3$ agonism in bucindolol
- The lower HRs in metoprolol treated patients were associated with
  - Lower doses relative to target
  - A greater number of bradycardia AEs and ECG reads, both associated with dose reduction
  - Failure to achieve target on M vs. B was largely confined to patients in the <60 HR range; patients in higher HR ranges achieved target doses for the two beta-blockers equally
- Bradycardia may limit the dosing of conventional beta-blockers in AF/HFrEF
  - Beta-blocker efficacy for HF event reduction in HFrEF is very dose-related
  - Failure to achieve target doses may be at least part of the explanation for why conventional beta-blockers lack efficacy in AF/HFrEF (Reinstra et al JHF 2013, Kotecha et al, Lancet 2014), and why bucindolol has substantial efficacy for lowering HF events in ADRB1 389 Arg homozygous HFrEF patients in AF (Kao et al, EJHF 2013)