A Novel AI-Derived Digital Biomarker for Monitoring Disease Progression in ATTR-CM

First-in-Trial Use of a Computer Vision AI-ECG Algorithm Within a Phase 3 Pivotal Randomized Controlled Trial

Rohan Khera,[1] Philip M. Croon,[1] Sumukh Vasisht Shankar,[1] Tracy Bergemann,[2] Gillian Murtagh,[2] John Whang,[2] and Lovedeep Dhingra[1]

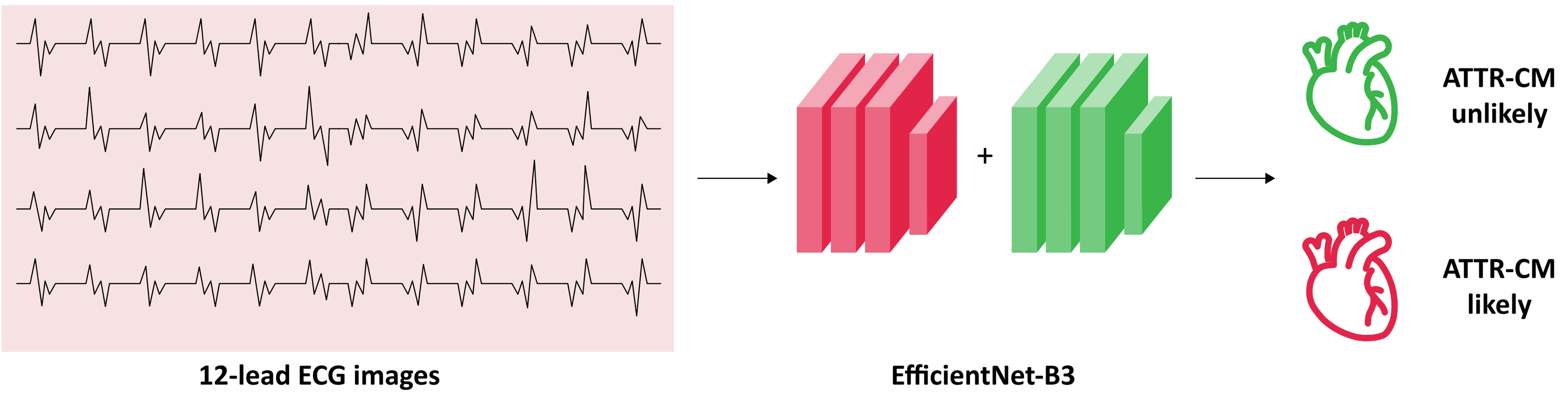
[1]Section of Cardiovascular Medicine, Department of Internal Medicine, Yale School of Medicine, New Haven, CT, USA; [2]BridgeBio Pharma, Inc., San Francisco, CA, USA

WHY THIS MATTERS

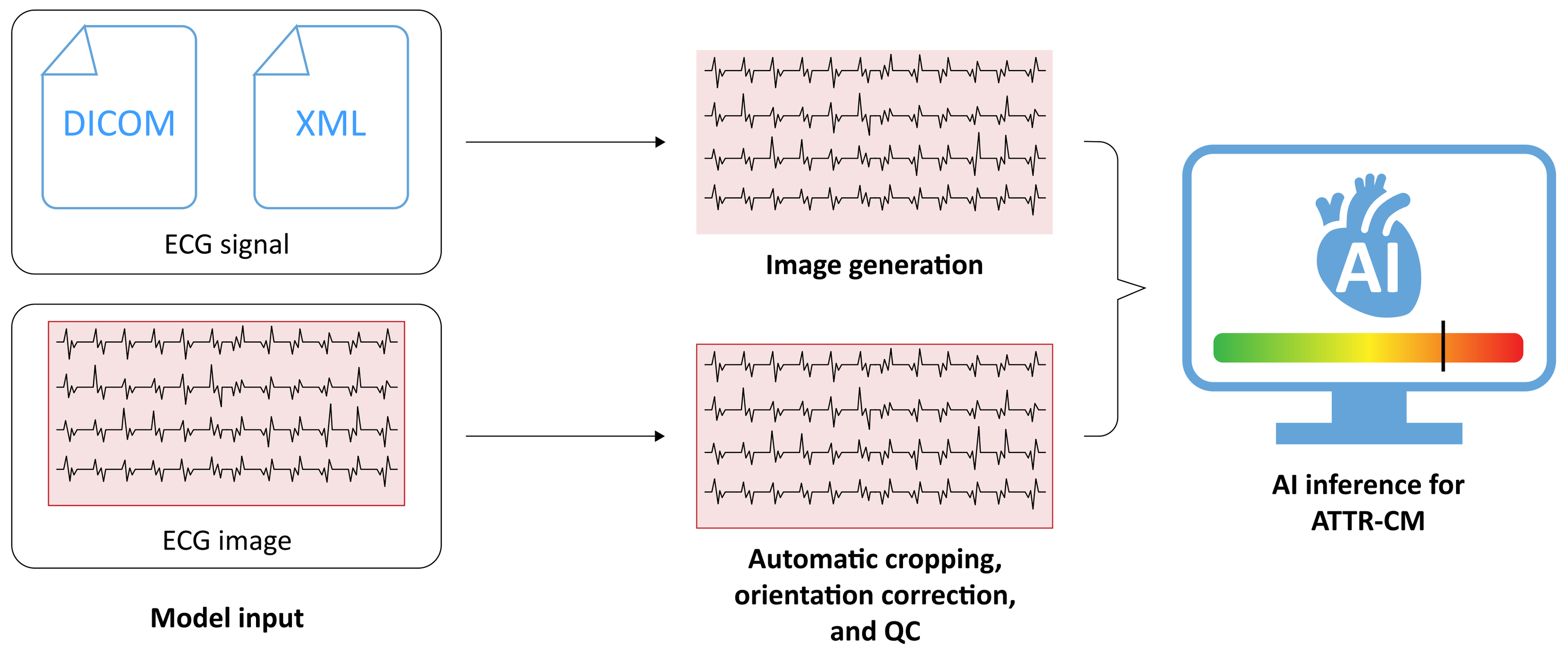
- **AI-ECG algorithms have emerged as powerful tools to screen for cardiomyopathies such as ATTR-CM; however, the potential of AI-ECG prediction scores to function as a quantitative digital biomarker to track disease burden and progression has not been established[1–3]**
- **Acoramidis, a TTR stabilizer that achieves near-complete (≥ 90%) TTR stabilization and is approved for the treatment of ATTR-CM in the USA, the European Union, and other countries,[4–10] was evaluated in the phase 3 ATTRibute-CM RCT (NCT03860935)[11]**
- **In ATTRibute-CM, acoramidis treatment reduced the cumulative risk of cardiovascular mortality or recurrent cardiovascular-related hospitalization over 30 months by 49% compared with placebo[11]**
- **We report the first deployment of a computer vision AI-ECG algorithm operating directly on ECG images in an RCT involving participants with ATTR-CM in ATTRibute-CM**

METHODS

Development of an AI-ECG Model for the Detection of ATTR-CM



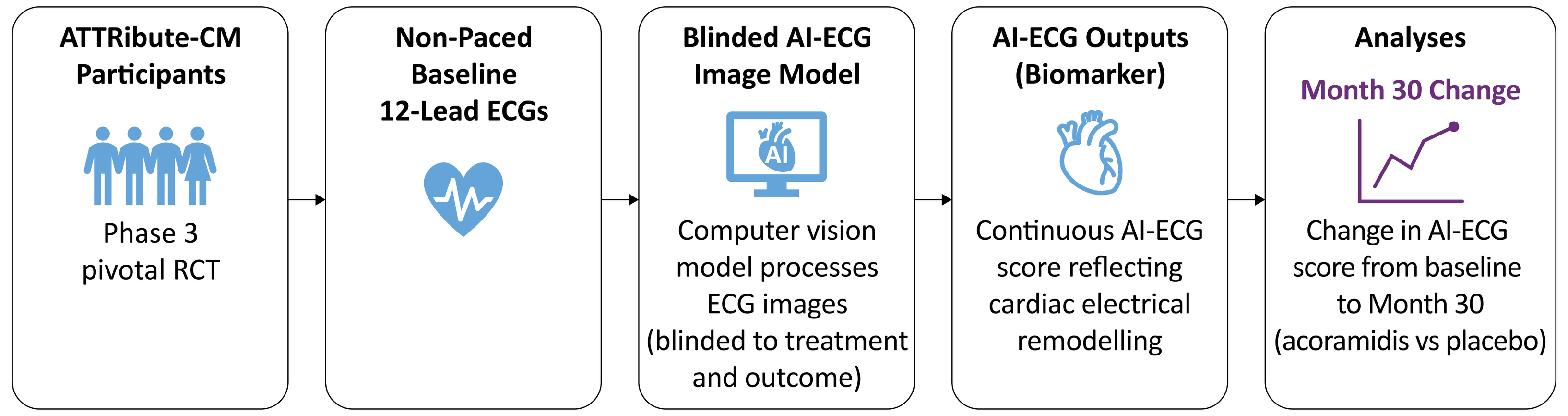
Development of an Easily Deployable and Format-Agnostic QC and Inference Pipeline



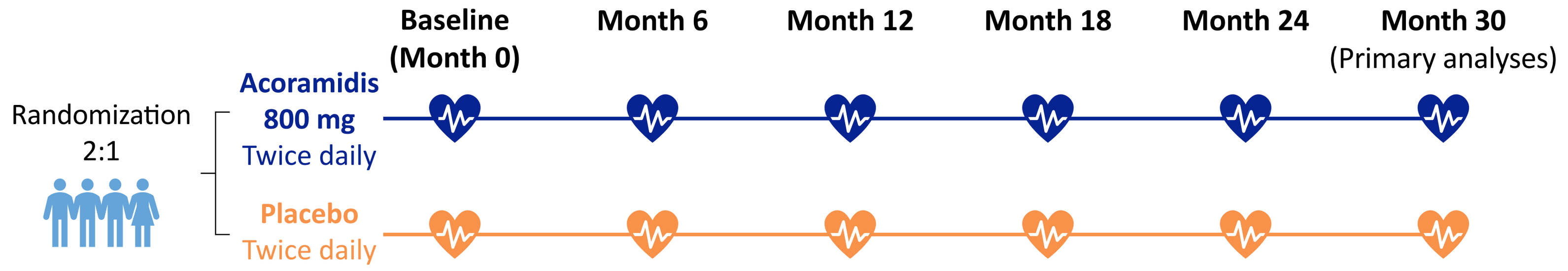
- The AI-ECG model was developed and trained to identify amyloidosis using images of 12-lead ECGs among cases and controls (1:20)
- The AI-ECG model was validated externally in 7 cohorts and applied to baseline and longitudinal ECG data collected in the ATTRibute-CM phase 3 RCT of ATTR-CM patients
- Placeholder bullet for statement about blinding

METHODS

Study Design and AI-ECG Analysis Framework



ATTRibute-CM Randomized Controlled Period (0–30 Months)



ECG Schedule (Non-Paced 12-Lead)

- All ECGs collected per protocol at each visit window
- ECGs analysed with blinded AI-ECG model

- The AI-ECG algorithm derived an ATTR-CM/amyloid ECG signature score from 0 to 1
- Post hoc exploratory analyses of changes to Month 30

RESULTS

PATIENTS

N = 516 with baseline ECGs

Acoramidis **343** | Placebo **173**

N = 290 with paired baseline and Month 30 ECGs

Acoramidis **199** | Placebo **91**

RESULTS

- Across study arms, baseline AI-ECG prediction scores were higher in:
  - — Participants aged < 75 years vs those aged ≥ 75 years
  - — Male vs female participants
  - — Participants with ATTRv-CM vs ATTRwt-CM
  - — Participants with elevated vs non-elevated NT-proBNP levels (> 3000 vs ≤ 3000 pg/mL) (**Table**)

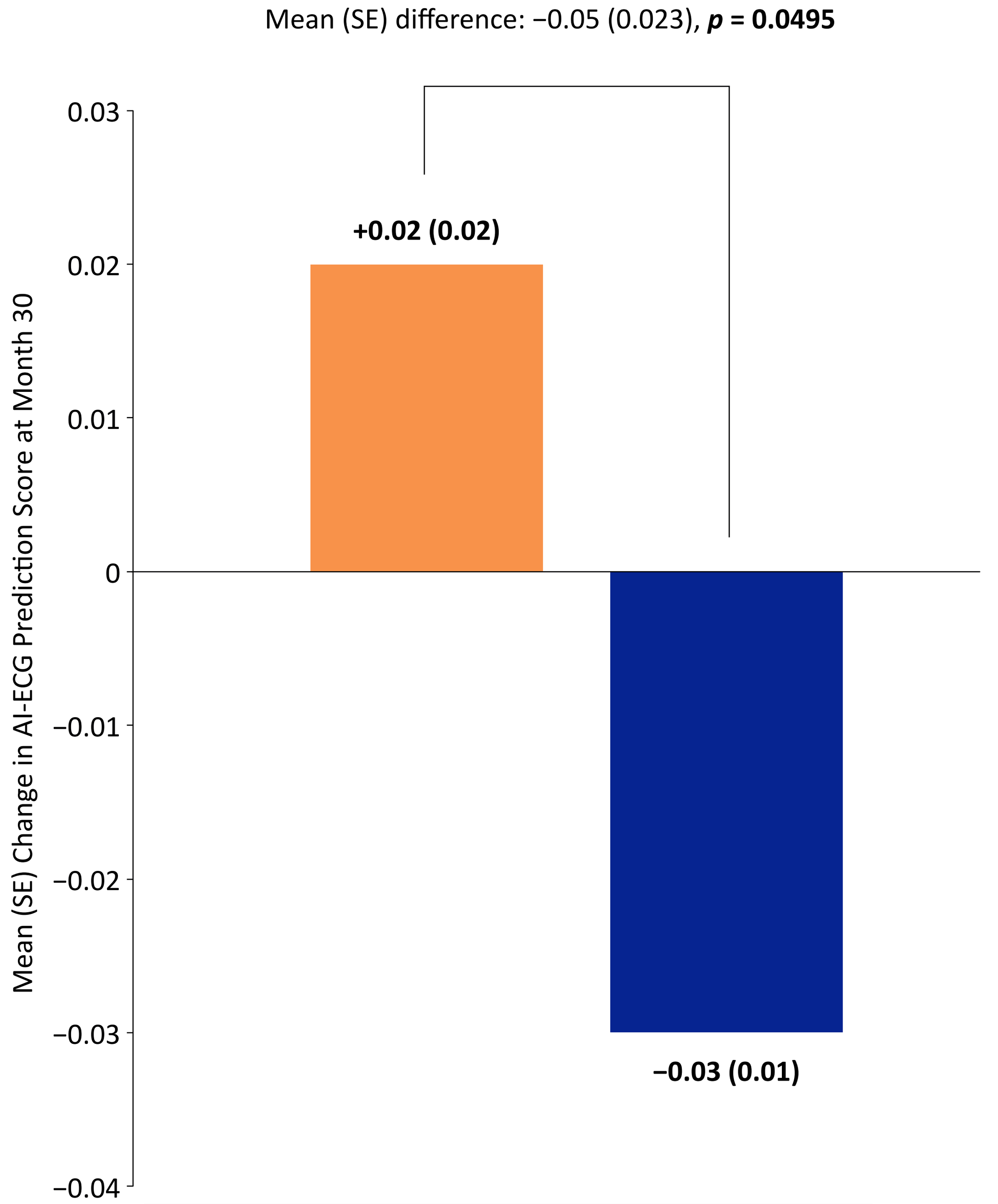
TABLE: Baseline AI-ECG Prediction Scores by Baseline Participant Demographics and Characteristics

Demographic/ Characteristic	n	Summary Statistic, Mean (SD)	*p* Value
Age			
< 75 years	178	0.40 (0.213)	**0.0044**
≥ 75 years	338	0.34 (0.205)	
Sex			
Female	51	0.29 (0.227)	**0.0056**
Male	465	0.37 (0.206)	
Genotype			
ATTRv-CM	51	0.43 (0.206)	**0.0117**
ATTRwt-CM	465	0.35 (0.208)	
NAC stage			
I	303	0.35 (0.212)	0.3294
II	166	0.38 (0.214)	
III	47	0.37 (0.172)	
NYHA class			
I	56	0.34 (0.203)	0.1657
II	373	0.37 (0.209)	
III	87	0.33 (0.214)	
NT-proBNP			
≤ 3000 pg/mL	343	0.34 (0.212)	**0.0074**
> 3000 pg/mL	173	0.39 (0.201)	

Kruskal-Wallis rank sum tests were used to compare prediction scores between baseline categories.

- In the placebo and acoramidis treatment arms, baseline mean (SD) AI-ECG prediction scores were 0.31 (0.23) and 0.38 (0.21), respectively (*p* = NS) (**Figure**)
- From baseline to Month 30, mean AI-ECG prediction scores increased by 0.02 with placebo and decreased by 0.03 with acoramidis

FIGURE: Change in AI-ECG Prediction Score From Baseline to Month 30: Placebo vs Acoramidis



Baseline Digital Biomarker Scores	Placebo	Acoramidis
n	91	199
Mean (SD)	0.31 (0.23)	0.38 (0.21)

KEY TAKEAWAYS

- **An image-based AI-ECG algorithm was applied to baseline ECGs from the ATTRibute-CM study and demonstrated discrimination across clinical subgroups at baseline**
- **In a post hoc exploratory analysis of Month 30 ECG data, AI-ECG prediction scores were lower among the acoramidis-treated group and higher among the placebo-treated group compared with baseline; however, longitudinal complete-case ECG results may be affected by survival and follow-up ECG availability**
- **These findings support further investigation of AI-ECG-derived prediction scores as digital biomarkers in clinical trials but require survivor-aware methods before use as a treatment-response measure**

CORRESPONDING AND PRESENTING AUTHOR: Rohan Khera, rohan.khera@yale.edu

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ABBREVIATIONS: AI-ECG, artificial intelligence electrocardiogram; ATTR-CM, transthyretin amyloid cardiomyopathy; ATTRv-CM, variant transthyretin amyloid cardiomyopathy; ATTRwt-CM, wild-type transthyretin amyloid cardiomyopathy; ECG, electrocardiogram; NAC, National Amyloidosis Centre; NS, not statistically significant; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; QC, quality control; RCT, randomized controlled trial; SD, standard deviation; SE, standard error; TTR, transthyretin.

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