Circulation: Heart Failure

ORIGINAL ARTICLE

Detection of Left Atrial Myopathy Using Artificial Intelligence–Enabled Electrocardiography

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BACKGROUND: Left atrial (LA) myopathy is common in patients with heart failure and preserved ejection fraction and leads to the development of atrial fibrillation (AF). We investigated whether the likelihood of LA remodeling, LA dysfunction, altered hemodynamics, and risk for incident AF could be identified from a single 12-lead ECG using a novel artificial intelligence (AI)-enabled ECG analysis.

METHODS: Patients with heart failure and preserved ejection fraction (n=613) underwent AI-enabled ECG analysis, echocardiography, and cardiac catheterization. Individuals were grouped by AI-enabled ECG probability of contemporaneous AF, taken as an indicator of underlying LA myopathy.

RESULTS: Structural heart disease was more severe in patients with higher AI-probability of AF, with more left ventricular hypertrophy, larger LA volumes, and lower LA reservoir and booster strain. Cardiac filling pressures and pulmonary artery pressures were higher in patients with higher AI-probability, while cardiac output reserve was more impaired during exercise. Among patients with sinus rhythm and no prior AF, each 10% increase in AI-probability was associated with a 31% greater risk of developing new-onset AF (hazard ratio, 1.31 [95% CI, 1.20–1.42]; $P<0.001$). In the population as a whole, each 10% increase in AI-probability was associated with a 12% greater risk of death (hazard ratio, 1.12 [95% CI, 1.08–1.17]; $P<0.001$) during long-term follow-up, which was no longer significant after adjustments for baseline characteristics.

CONCLUSIONS: A novel AI-enabled score derived from a single 12-lead ECG identifies the presence of underlying LA myopathy in patients with heart failure and preserved ejection fraction as evidenced by structural, functional, and hemodynamic abnormalities, as well as long-term risk for incident AF. Further research is required to determine the role of the AI-enabled ECG in the evaluation and care of patients with heart failure and preserved ejection fraction.

Key Words: atrial fibrillation ■ echocardiography ■ exercise ■ heart failure ■ probability

Patients with heart failure and preserved ejection fraction (HFpEF) frequently display findings indicative of underlying left atrial (LA) myopathy, evidenced by LA remodeling and dysfunction, abnormal LA and pulmonary vascular hemodynamics, and a heightened risk for development of atrial fibrillation (AF).[1–7] Thus, patients with HFpEF and LA myopathy may be considered as a distinct phenotype, potentially requiring specific treatment. To operationalize phenotyping in clinical practice and trials, it is necessary to have robust, easily applicable methods for detection. Echocardiography provides robust characterization of LA structure and function but is not obtained in all patients.[1–7] AF can be viewed as the ultimate electrophysiological consequence of LA myopathy and is readily diagnosed by the 12-lead ECG.[5] However, an isolated ECG provides only a 10-second snapshot of cardiac rhythm, and LA myopathy exists long before development of AF.[1,5,8]

Attia and colleagues recently developed and then validated a novel artificial intelligence (AI) algorithm, enabling identification of patients with contemporaneous AF (within 1 month), even when they were not actively in AF, based on analysis of a single 12-lead ECG acquired in normal sinus rhythm.[9] The AI-enabled ECG approach was predicated

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WHAT IS NEW?

- An artificial intelligence (AI)-enabled 12-lead ECG was applied in patients with heart failure and preserved ejection fraction.
- The AI algorithm, by evaluating complex spatial and temporal ECG features, identifies and quantifies the presence and severity of underlying atrial myopathy in heart failure and preserved ejection fraction.
- Atrial myopathy, as detected by the AI-enabled ECG, was associated with higher cardiac filling pressures at rest and lower cardiac output reserve.
- Higher AI-probability predicts new atrial fibrillation development in patients without atrial fibrillation history, which remained significant after multivariable adjustment.

WHAT ARE THE CLINICAL IMPLICATIONS?

- The AI-enabled ECG could facilitate phenotyping of patients with heart failure and preserved ejection fraction and provides a quantitative measurement of atrial myopathy.
- The AI-enabled ECG could enable earlier detection of patients with atrial myopathy, who are at greater risk of developing atrial fibrillation and right heart failure, and warrants further study in prospective trials to determine whether it can be useful to better inform clinical decision making.

Nonstandard Abbreviations and Acronyms

AF	atrial fibrillation
AI	artificial intelligence
HFpEF	heart failure with preserved ejection fraction
HR	hazard ratio
LA	left atrial
NT-proBNP	N-terminal of the pro-hormone of B-type natriuretic peptide

on the idea that subtle abnormalities in atrial structure and function lead to specific ECG abnormalities that are detectable using nonlinear machine-learning neural networks. While the AI-enabled ECG was initially applied to detect occult, contemporaneous, paroxysmal AF among patients in sinus rhythm, the hypothesis in this study is that the same spatial and temporal ECG features would directly relate to the presence and severity of underlying LA myopathy. As a corollary, we also hypothesized that a higher LA myopathy probability score would be associated with greater risk for development of new-onset AF during long-term follow-up. This could be important in phenotyping and might allow identification of patients at greater risk of right heart failure and poorer outcomes.[10,11] To test this hypothesis, we performed AI-enabled ECG interpretation in a large cohort of well-characterized patients with HFpEF and long-term follow-up.

METHODS

Transparency and Openness Promotion Statement

All data from the current study are available upon request from a third party.

Study Design

This retrospective cohort study includes a contemporary population of patients with definite HFpEF. To ensure broad representation across the spectrum of disease, 2 separate cohorts were included: (1) outpatients with unexplained exertional dyspnea diagnosed with HFpEF based on elevated pulmonary arterial wedge pressure during invasive cardiopulmonary exercise testing and (2) inpatients hospitalized because of unambiguously decompensated HFpEF treated with intravenous loop diuretics. A previously validated AI algorithm that was developed to estimate the probability that paroxysmal AF is present based on analysis of a 12-lead ECG in sinus rhythm[9] was applied in this study as a measure of the probability of underlying LA myopathy. Patients were stratified into quartiles of AI-enabled ECG probability for analysis. In the case of multiple ECGs being available, the ECG closest to cardiac catheterization (outpatients) or hospital admission (inpatients) was used. Patients without ECG within 7 days of catheterization or hospitalization were excluded. The Mayo Clinic Institutional Review Board has approved the study protocol and all subjects provided written informed consent. All authors had full access to the data, take responsibility for its integrity, contributed to the writing of the article, and agree to this report as written.

Study Population

The outpatient cohort comprises consecutive patients diagnosed with HFpEF after undergoing invasive hemodynamic assessment at rest and during exercise in the Mayo Clinic Rochester catheterization laboratory between January 2006 and July 2015. All subjects had clinical symptoms of HF (exertional dyspnea or fatigue), an ejection fraction ≥50%, and demonstrated an elevated pulmonary arterial wedge pressure (≥15 mm Hg at rest and/or ≥25 mm Hg during exercise). The inpatient cohort includes consecutive patients who were admitted between January 2010 and December 2015 at Mayo Clinic Rochester for decompensated HF with a left ventricular ejection fraction ≥50% and received treatment with intravenous loop diuretics within 24 hours of admission for a duration ≥48 hours. Patients with HF and any history of reduced ejection fraction (<50%), isolated right-sided HF, unstable coronary disease, cardiac amyloidosis, hypertrophic cardiomyopathy, or constrictive pericarditis, were excluded.

Characterization of Left Atrial Myopathy

Cardiac Structure and Function

Comprehensive transthoracic echocardiography was performed according to contemporary guidelines.[12,13] A detailed

description of the measurements performed is provided in the Supplemental Methods. LA volume was measured with the area-length method and averaged from the apical 4- and 2-chamber views. In the outpatient cohort, strain measurements were available with the average strain in 6 segments from the apical 4- and 2-chamber views used to calculate LA reservoir and booster strain over a sample of 3 beats. LA strain was measured using the QRS as fiducial point because of the absence of P-waves in AF. LA compliance was estimated as the ratio of LA reservoir strain over the height of the invasively measured V-wave.

Invasive Hemodynamic Assessment at Rest and During Exercise

Patients in the outpatient cohort underwent symptom-limited cardiopulmonary exercise testing on a supine bicycle with invasive hemodynamic assessment at rest and during exercise. A detailed description is provided in the Supplemental Methods. Briefly, right radial artery catheterization and right heart catheterization through jugular venous access were performed. Following hemodynamic assessment at rest, subjects performed a supine bicycle exercise test until self-reported exhaustion with the first stage at 20 W for 5 minutes, followed by 20 W increments in workload until subject-reported exhaustion (2 minute stages) with continuous registration of hemodynamics.

AF Status

History of AF was determined through detailed chart review by experienced cardiologists. In the ambulatory cohort, patients in AF at the time of catheterization were considered to have persistent/permanent AF, while those with a history of AF but not currently in AF were considered to have paroxysmal AF. In hospitalized patients, paroxysmal AF was defined as a previously documented episode, with absence of AF or spontaneous conversion to sinus rhythm during the index admission. Patients who continuously demonstrated AF during the index admission or underwent electrical/medical cardioversion, were classified as persistent/permanent AF. For all analyses, atrial flutter was considered an equivalent of AF. A diagnosis of AF required objective evidence by a 12-lead ECG, Holter monitoring tracing, or an intracardiac electrogram from an implantable cardiac device. For Holter monitor tracings and intracardiac electrograms, only episodes with a duration ≥6 minutes were considered as clinically relevant AF episodes.[14]

AI Algorithm

The AI algorithm applied in this study is a convolutional neural network using the Keras Framework with a Tensorflow (Google, Mountain View, CA) backend and Python.[15] Its development has been described elsewhere in detail.[9] Briefly, the network architecture was adjusted to have spatial and temporal feature extraction layers. By adjusting the weights of the convolutional filters during training, the network operates to extract meaningful and relevant features in an unsupervised way. The only data input for training were raw 12-lead ECG signals with an underlying rhythm confirmed as sinus rhythm, yet the patients with those ECGs could develop AF at a later point in time. The AI algorithm was trained to recognize AF probability using 454 789 10-second, 12-lead ECG signals from 126 526 unique patients. In 2 subsequent validation sets with in total 195 142 different ECG tracings, the area under the receiver operated characteristic curve to detect contemporaneous AF (clinically detected within 31 days) was 0.87 (0.86–0.88).[9]

The output from the AI-enabled ECG was developed as a probability of having underlying occult AF, ranging from 0% to 100% for each individual. Because the probability of occult AF is fundamentally related to subtle changes in cardiac structure and function detected by the AI-enabled ECG, we defined the probability score in this analysis as a surrogate measure of underlying LA myopathy. Patients were grouped according to quartiles of AI-enabled ECG algorithm score trained for contemporaneous AF probability (henceforth abbreviated as AI enabled ECG) for analysis. In the original derivation study, the AI-enabled ECG analysis was only applied to ECGs obtained in sinus rhythm.[9] However, in the current study, the same algorithm was applied in all patients, including patients in sinus rhythm, AF, or with cardiac pacing at the time of evaluation. Importantly, the AI-enabled algorithm was not trained to identify current heart rhythm on the 12-lead ECG, but rather to evaluate other complex spatial and temporal characteristics associated with AF. As such, AI-enabled AF probability is frequently and paradoxically <100% even among patients currently in AF at the time of assessment.

Study End Points

New-onset AF was ascertained blinded from the results of the AI-enabled ECG, through detailed chart review in patients without any prior AF history, including all records from Mayo Clinic Rochester as well as those from outside hospitals using the "Care Everywhere" platform in the electronic health record (Epic, Verona, WI). Vital status was determined from the Mayo Clinic registration database and the Rochester Epidemiology Project death database, which ascertains mortality data from medical records, death certificates, obituaries, and notices of death in the local newspapers. Data on all Minnesota deaths are obtained from the State of Minnesota annually. Patient follow-up was initiated on the day of cardiac catheterization or hospital admission. Patients were censored at last follow-up contact or August 28, 2019, whichever came first.

Statistical Analysis

Continuous variables are expressed as mean±SD if normally distributed, or otherwise as median (interquartile range). ANOVA and the Kruskal-Wallis *H* test were used as indicated for comparisons among groups. Categorical data are expressed as percentages and compared with Pearson χ^2-test. Correlations were assessed with Spearman ρ. A Cox-proportional hazards model was used to calculate the hazard ratio (HR) with corresponding 95% CI for the risk of development of new-onset AF and death, as well as to adjust for age, sex, presence of coronary artery disease and diabetes, left atrial volume index, as well as log-transformed NT-proBNP (N-terminal of the pro-hormone of B-type natriuretic peptide) levels. The Kaplan-Meier method was used to construct time to failure and survival curves, with the log-rank test used for comparison between groups. A sensitivity analysis was performed in patients who were not in AF at the time of assessment, while at the same time excluding all ECGs with ventricular pacing, as this reflects how the AI algorithm was developed and trained. Statistical significance was

set at a 2-tailed probability level of <0.05. All statistics were performed using JMP 14.1.0. (SAS Institute, Cary, NC).

RESULTS

Study Population

Between January 2006 and July 2015, 424 consecutive subjects with unexplained exertional dyspnea underwent invasive hemodynamic assessment with exercise in the Mayo Clinic Rochester catheterization laboratory. From this group, 184 were diagnosed with HFpEF and fulfilled all inclusion criteria for the outpatient study cohort (Figure 1). In this group, 28 subjects had paroxysmal AF (15%) and 22 persistent/permanent AF (12%). Outpatients were on average 67±11 years old, with 58% women, and had median (interquartile range) NT-proBNP levels of 299 ng/L (96–899 ng/L).

Between January 2010 and December 2015, 3823 patients with preserved ejection fraction (≥50%) were admitted to Mayo Clinic Rochester with the diagnosis of acute HF according to ICD (implantable cardioverter defibrillator) coding. From this group, 424 met the inclusion criteria for the inpatient study cohort (Figure 1). In this group, 85 patients had paroxysmal AF (20%) and 172 persistent/permanent AF (40%). Inpatients were on average 78±12 years old, with 60% women, and had median (interquartile range) NT-proBNP levels of 2841 ng/L (1209–5559 ng/L).

Characteristics of AI-Probability Groups

In the population as a whole, the AI-enabled probability was 42% (14%–69%). A histogram of distribution is provided as Figure S1. Baseline characteristics of the study population according to quartiles of AI-probability are presented in Table 1. Higher AI-probability was associated with older age, lower blood pressure, greater prevalence of diabetes, coronary artery disease, and cardiac pacing, higher NT-proBNP levels, lower hemoglobin, a longer intraventricular conduction delay, and more frequent use of diuretics.

In 502 patients (82%), transthoracic echocardiography data were available within 30 days of the index ECG, and both investigations were performed within <24 hours in 358 (58%). With higher AI-probability, underlying structural heart disease was more severe, as indicated by more pronounced left ventricular hypertrophy and more severe left ventricular diastolic dysfunction (Table 2).

Higher AI-Probability Reflects Greater Left Atrial Myopathy Burden Across Multiple Domains

LA function decreased progressively with higher AI-probability, as reflected by greater LA volumes, reductions in LA reservoir (40.8±18.1 to 15.7±7.1; $P<0.001$; Figure 2) and booster strain (18.6±10.1 to 10.5±7.4; $P=0.040$), and a reduction in LA compliance from the lowest to highest AI-probability quartile, respectively

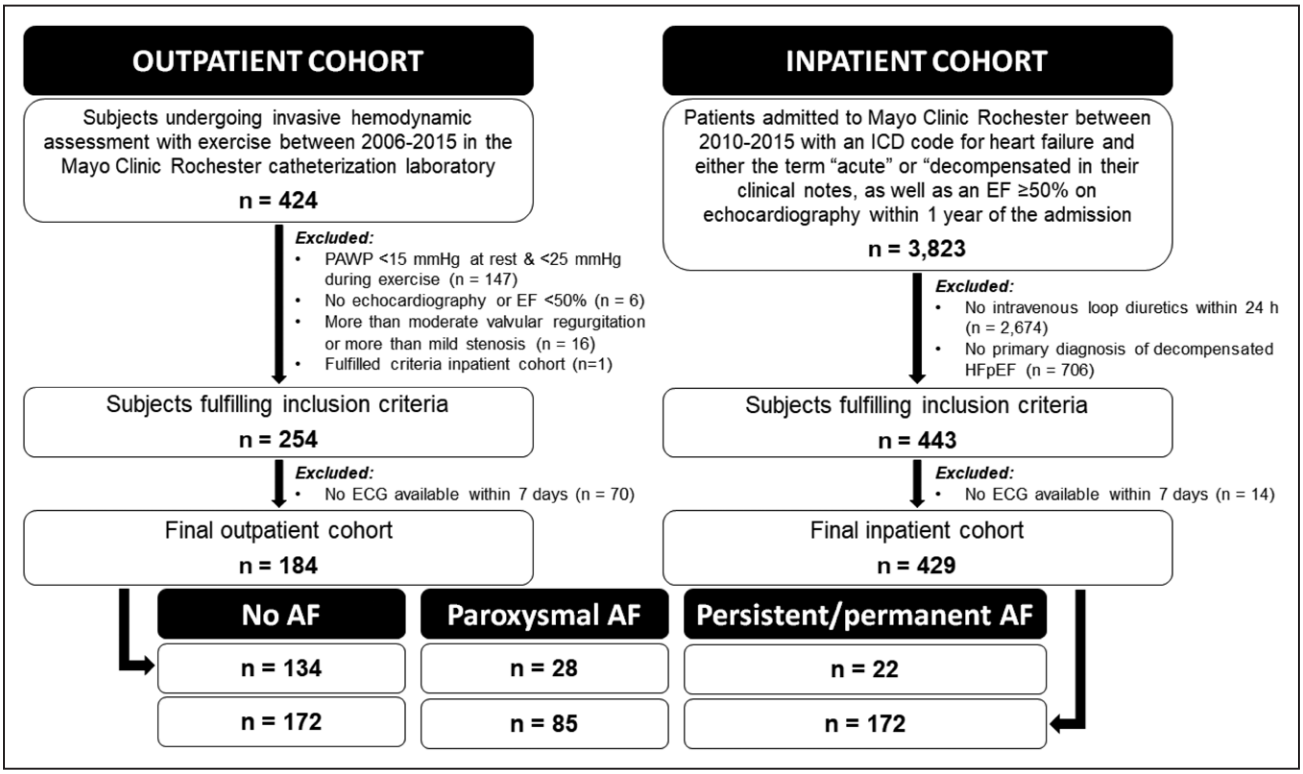

Figure 1. Study flowchart.
AF indicates atrial fibrillation; EF, ejection fraction; HFpEF, heart failure with preserved ejection fraction; ICD, implantable cardioverter defibrillator; and PAWP, pulmonary arterial wedge pressure.

Table 1. Baseline Characteristics of the Study Population According to the AI-Probability

AI-probability	0%–13%	14%–42%	43%–68%	69%–100%	*P* value
N	151	157	150	155	
Age, y	66±13*	75±13*	79±11	80±10	<0.001
Women	67%	55%	66%	50%	0.005
Heart rate, bpm	74±16	79±22	79±22	74±18	0.01
Blood pressure, mm Hg					
Systolic	141±28	135±26	133±24	132±22	0.006
Diastolic	71±13	67±14	65±15	66±13	0.003
Body mass index, kg/m^2	35.0±9.7	35.5±10.2	34.9±9.4	32.2±7.4†‡	0.007
AF diagnosis					
No AF history	88%	61%	33%	17%	
Paroxysmal AF	12%	23%	22%	17%	<0.001
Persistent/permanent AF	0	16%	45%	66%	
Comorbid conditions					
Hypertension	81%	89%	86%	85%	0.36
Diabetes	36%	52%	57%	59%	<0.001
Coronary artery disease	37%	50%	55%	55%	0.004
ECG					
Atrial pacing	1%	1%	5%	5%	0.034
Ventricular pacing	0	1%	8%	26%	<0.001
QRS width, ms	90 (82–98)	92 (84–109)	94 (84–123)†	100 (88–138)†‡	<0.001
Nonspaced QRS width, ms	90 (82–98)	92 (84–110)	92 (82–112)	94 (86–108)†	0.009
Left bundle branch block	1%	3%	11%	19%	<0.001
Right bundle branch block	5%	13%	12%	8%	0.036
Medication use					
Renin-angiotensin system blocker	42%	50%	53%	46%	0.28
Beta blocker	56%	64%	73%	67%	0.018
Diuretic	53%	73%	71%	82%	<0.001
Laboratory measurements					
NT-proBNP, ng/L	410 (104–1408)*	1446 (595–3806)*	2789 (1136–6106)	2678 (1247–5178)	<0.001
Hemoglobin, g/dL	12.0±1.9	11.7±1.9	11.7±1.9	11.4±1.7	0.021
eGFR, mL/min per 1.73 m2	59±30	53±27	50±23	51±21	0.11

AF indicates atrial fibrillation; AI, artificial intelligence; eGFR, estimated glomerular filtration rate by the Chronic Kidney Disease Epidemiology Collaboration formula; and NT-proBNP, N-terminal of the pro-hormone of B-type natriuretic peptide.

*P<0.05 vs all.

†P<0.05 compared with first quartile

‡P<0.05 compared with second quartile.

(Table 2). In regression analysis, AI-probability correlated directly with LA volume index (ρ=0.48; P<0.001) and inversely with LA reservoir strain (ρ=–0.60; P<0.001). Results were unaffected when patients with a bundle branch block were excluded.

Patients with higher AI-probability also displayed more abnormal LA and pulmonary vascular hemodynamics, with higher estimated cardiac filling pressures (E/e′ ratio), higher estimated right ventricular systolic pressure on echocardiography, and more low-grade mitral and tricuspid valve regurgitation (Figures 2 and 3). Upon invasive assessment, pulmonary vascular pressures and pulmonary arterial wedge pressure were greater at rest among patients with higher AI-probability, and those displayed higher pulmonary vascular resistance and more limited cardiac output reserve to stress as well (Table 3, Figure 4).

Higher AI-probability was associated with greater burden of AF at baseline evaluations, increasing from 16% (4%–44%) in patients with no history of AF, to 46% (24%–65%) in patients with paroxysmal AF, to 70% (55%–82%) in patients with persistent/permanent AF (P<0.001; Figure S2).

AI-Probability and Outcomes

The median (interquartile range) follow-up duration was 41 months (11–71 months). In the 306 patients without

Table 2. Cardiac Morphology and Function According to the AI-Probability

AI-probability	0%–13%	14%–42%	43%–68%	69%–100%	*P* value
N	113	124	129	136	
Cardiac morphology					
Interventricular septum thickness, mm	11.0±1.9*†	11.5±1.8	11.8±1.9	11.6±2.0	0.015
Posterior wall thickness, mm	10.3±1.9*†	10.7±1.7	11.0±1.9	11.2±1.9	0.004
LV end-diastolic diameter, mm	48.1±5.1	48.9±5.5	48.7±6.3	48.5±6.1	0.75
LV end-diastolic volume, mL	110±27	114±30	114±33	113±32	0.68
LV end-diastolic volume index, mL/m^2	53±12	54±12	55±14	56±15	0.5
Left atrial volume, mL	72±25*†	84±27*†	96±29	103±34	<0.001
Left atrial volume index, mL/m^2	34±11‡	40±12‡	47±13	51±15	<0.001
Left ventricular mass, g	192±64*†	206±58	213±62	213±70	0.036
LV mass index, g/m^2	92±27*†	97±21†	104±28	104±29	0.001
LV ejection fraction, %	64±5†§	62±6	63±6	62±6	0.006
Diastolic function and filling pressures					
E-wave velocity, m/s	0.89±0.32‡	1.03±0.39†‖	1.14±0.35	1.19±0.34	<0.001
A-wave velocity, m/s	0.9 (0.7–1.0)	0.8 (0.5–1.0)	0.4 (0–0.8)‡	0 (0–0.4)‡	<0.001
E/A ratio	1.0 (0.7–1.3)‡	1.1 (0.8–1.5)‡	1.4 (1.0–2.1)	1.8 (1.3–2.8)	<0.001
Medial e´ velocity, m/s	0.069±0.021‡	0.063±0.021	0.063±0.019	0.064±0.021	0.07
E/e´ medial	12.0 (10.0–16.9)‡	15.7 (11.7–22.0)	17.1 (14.0–24.3)	18.3 (13.8–24.0)	<0.001
TR velocity, m/s	2.80±0.47	2.84±0.45	2.95±0.42‖	3.04±0.47§‖	<0.001
RVSP, mm Hg	39±13	41±13	45±12§‖	49±14§‖	<0.001
Left atrial strain and compliance					
Left atrial reservoir strain	40.8±18.1 (n=52)‡	31.9±15.4 (n=20)†‖	24.6±11.2 (n=15)	15.7±7.1 (n=24)	<0.001
Left atrial booster strain	18.6±10.1 (n=51)	17.5±9.8 (n=19)	11.3±5.7 (n=11)	10.5±7.4 (n=7)	0.04
Left atrial compliance	6.9 (3.0–10.6) (n=50)	5.4 (1.8–15.8) (n=20)	2.0 (1.2–3.7) (n=14)‖	1.2 (0.7–1.7) (n=23)§‖	<0.001
Valvular lesions					
More than mild MR	12%	12%	20%	28%	0.002
More than moderate MR	0	2%	3%	1%	0.29
More than mild TR	17%	23%	34%	53%	<0.001
More than moderate TR	0	3%	12%	16%	<0.001

AI indicates artificial intelligence; LV, left ventricular; MR, mitral valve regurgitation; RVSP, right ventricular systolic pressure; and TR, tricuspid valve regurgitation.
*P<0.05 compared with third quartile 3.
†P<0.05 compared with fourth quartile 3.
‡P<0.05 vs all.
§P<0.05 compared with second quartile.
‖P<0.05 compared with first quartile.

prior history of AF, 72 developed new-onset AF (24%). For each 10% increase in AI-probability, there was a 31% greater risk for the development of new-onset AF (HR, 1.31 [95% CI, 1.20–1.42; P<0.001; Figure 5A). The time for 25% of patients to develop new-onset AF was 112 months for an AI-probability <5% (n=88), 66 months for an AI-probability 5% to 25% (n=95), 34 months for an AI-probability 25% to 50% (n=60), and 16 months for an AI-probability >50%. After adjusting for age, sex, presence of coronary artery disease and diabetes, left atrial volume index, and NT-proBNP levels, AI-probability remained a statistically significant predictor of the development of incident AF (HR, 1.13 [95% CI, 1.02–1.26]; P=0.02).

In the population as a whole, 322 patients died (53%), including 189 individuals with established AF at baseline (20.3 deaths per 100 patient-years). In patients without AF history, 43 died after developing new-onset AF (13.3 deaths per 100 patient-years), while 90 died without experiencing any AF episode (11.0 deaths per 100 patient-years). Every 10% increase in AI-probability was associated with a 12% increased risk of all-cause mortality (HR, 1.12 [95% CI, 1.08–1.17]; P<0.001; Figure 5B; baseline characteristics of groups in Table S2). After adjusting for age, sex, presence of coronary artery disease and diabetes, as well as NT-proBNP levels, AI-probability was no longer independently associated with mortality (HR, 0.99 [95% CI, 0.95–1.04]; P=0.80).

Sensitivity Analysis Restricted to Sinus Rhythm

AF was present in 178 patients at the time of ECG assessment (29%), while 63 patients were paced (10%).

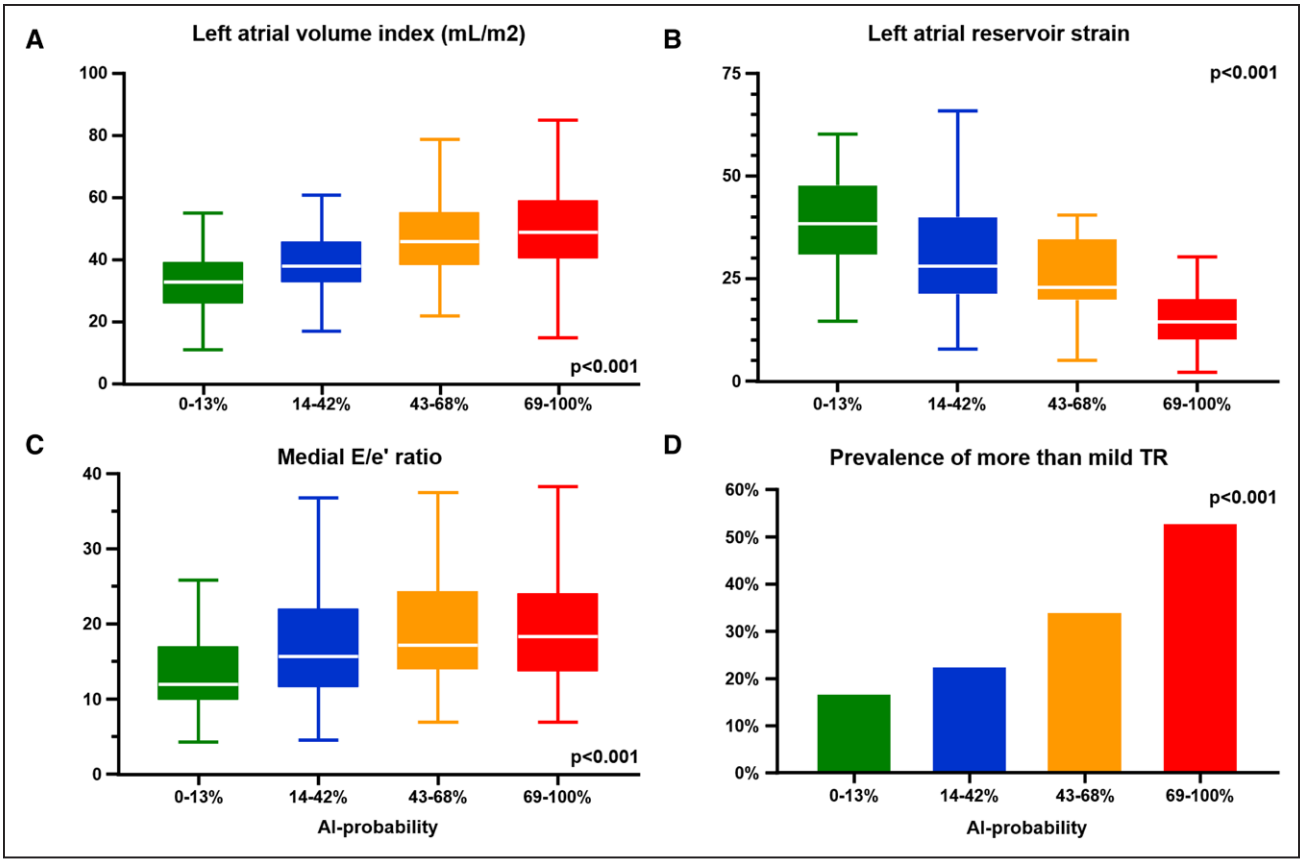

Figure 2. Echocardiographic findings according to artificial intelligence (AI)-probability.
A, Left atrial volume index, (**B**) left atrial reservoir strain, (**C**) medial E/e′ ratio, and (**D**) prevalence of more than mild tricuspid valve regurgitation (TR).

In a sensitivity analysis restricted to patients in sinus rhythm without pacing (n=372), increasing AI-probability remained highly predictive of development of new AF (HR, 1.36 [95% CI, 1.25–1.49]; *P*<0.001). Similarly, the impact of the AI-probability on all-cause mortality was similar when restricted to patients in sinus rhythm [HR, 1.16 [95% CI, 1.10–1.23]; *P*<0.001]. Differences in cardiac structure, function, and hemodynamics were similar to findings in the population as a whole in this sensitivity analysis (Tables S2 and S3) as well as in the subpopulation without AF history at baseline (Tables S4 and S5).

DISCUSSION

This study evaluated the utility of an AI-based ECG algorithm in a contemporary population of patients with HFpEF, with the specific aim to identify the presence of more severe LA myopathy assessed across mechanical, hemodynamic, and electrical domains. The key findings are that higher AI-probability is associated with (1) more severe underlying structural heart disease, particularly greater LA remodeling and dysfunction; (2) higher cardiac filling pressures at rest, a lower cardiac output reserve with exercise, and higher pulmonary vascular resistance at peak effort; and (3) greater risk for developing new-onset AF, even years after assessment and independent of other covariates. Although the AI algorithm was originally devised agnostically to detect occult paroxysmal AF in patients residing in sinus rhythm, the current study clearly supports its use in detecting LA myopathy and secondary hemodynamic abnormalities that lead to morbidity and mortality in this syndrome. Moreover, for the first time, it is shown that the AI-enabled ECG can predict long-term development of AF.

The AI-Enabled ECG Detects Left Atrial Myopathy

Patients with HFpEF frequently display LA myopathy, which can be defined as the LA remodeling and dysfunction that develops secondary to aging, elevation in left heart filling pressures, inflammation, and metabolic stress, which causes characteristic hemodynamic abnormalities and increases the risk for development of AF.[16] The strong tie between LA myopathy and risk of AF was utilized as a means to apply machine-learning in the detection of occult paroxysmal AF.[9] Initially, the algorithm was trained to assess the 12-lead ECG of an individual in sinus rhythm to predict the risk of underlying, occult AF that was demonstrated to be present on a separate ECG obtained within 31 days.[9] In the current study, we show that the AI-probability score for AF is in fact associated

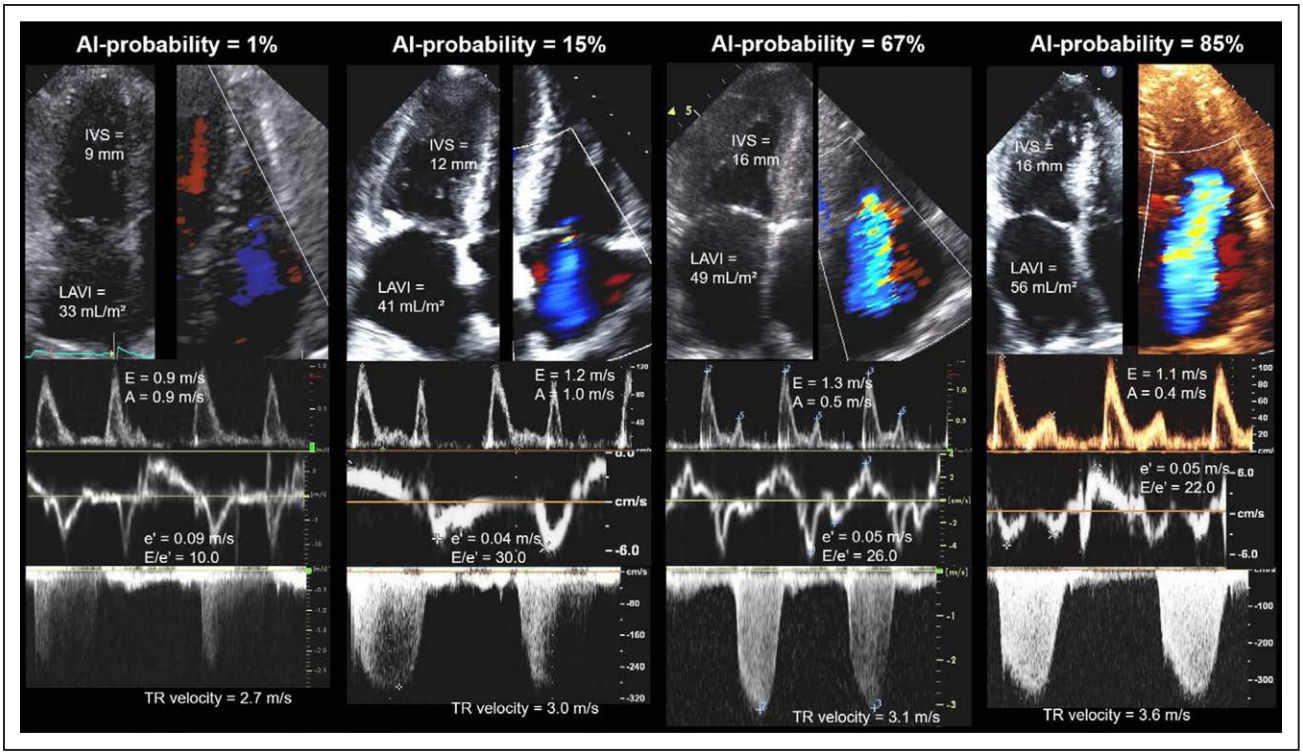

Figure 3. This figure represents transthoracic echocardiography findings in 4 study patients who are representative for quartiles of artificial intelligence (AI)-probability.
IVS indicates interventricular septum thickness in diastole; LAVI, left atrial volume index; and TR, tricuspid valve regurgitation.

with the severity of underlying LA myopathy, which likely explains why it predicts development of new-onset AF during long-term follow-up, months to years following index evaluation. Importantly, this was independent of other potential predictors of LA myopathy or AF such as natriuretic peptide levels. This is consistent with but greatly extending upon the previous observation that AI-probability is able to detect patients with contemporaneous AF (within 1 month only). With higher AI-probability, more pronounced left ventricular hypertrophy and more severe left ventricular diastolic dysfunction, but not dilation was observed. In addition, mitral and tricuspid valve regurgitation was more frequent and more severe in patients with higher AI-probability. Although most measurements indicating diastolic function and/or cardiac filling pressures showed statistically significant differences over strata of AI-probability, e' was similar among groups. Because the neural network is agnostic of ventricular and atrial structural changes, we can only speculate on the pathophysiologic explanations. However, it would seem likely that the greater LV hypertrophy observed is due to the association of the latter with LA remodeling and dysfunction.

In addition to predicting chronic risk of AF development, the other important and novel finding from the present study is thus that AI-enabled ECG assessment allows identification of patients with greater LA myopathy, as well as other findings that are related to LA myopathy in HFpEF, including abnormal hemodynamics at rest and during exercise.[5] Previous studies have demonstrated that by evaluating complex spatial and temporal characteristics within the 12-lead ECG, AI algorithms are able to predict age, sex, and the presence of low ejection fraction.[9,17,18] We demonstrate that the AI-enabled ECG approach identifies a population that is characterized by many distinct features associated with more advanced ventricular disease and LA myopathy, including left ventricular hypertrophy, LA dilation and dysfunction, elevated cardiac filling pressures, functional mitral and tricuspid valve regurgitation, and diminished cardiac output reserve. This builds on earlier observations that an AI-enabled ECG provides good discrimination for left ventricular hypertrophy and diastolic dysfunction as binary traits with reasonably good accuracy to diagnose pulmonary arterial hypertension, hypertrophic cardiomyopathy, amyloid, and mitral valve prolapse.[19] Importantly, we observed that the AI-enabled ECG could detect evidence of underlying LA myopathy even when patients with any history of AF were excluded (Tables S3 and S4). This emphasizes the potential added value of this technique as compared with conventional ECG aimed at evaluation of heart rhythm and conduction.

While the presence of these abnormalities would not be inferred from the AI-enabled ECG algorithm alone, the risk estimate provided by AI-enabled ECG allows for identification of patients at higher risk for displaying these abnormalities, which can then be used by clinicians

Table 3. Invasive Hemodynamics at Rest and During Exercise in Outpatients According to the AI-Probability

AI-probability	0%–13%	14%–42%	43%–68%	69%–100%	*P* value
N	90	41	22	31	
Resting hemodynamics					
Heart rate, bpm	68±10	68±13	64±6	66±9	0.44
Systolic blood pressure, mm Hg	143±30	145±32	137±29	134±25	0.32
Diastolic blood pressure, mm Hg	73±12*	72±10	67±12	66±12	0.009
Central venous pressure, mm Hg	9±4	9±3	9±4	11±4†‡	0.035
sPAP, mm Hg	37±9§*	39±11	45±15	45±14	<0.001
dPAP, mm Hg	15±6*	15±5	18±6	18±7	0.008
mPAP, mm Hg	24±6	25±7	29±9	30±10	<0.001
PAWP, mm Hg	14±5*	15±5	18±5	18±7	0.002
Stroke volume, mL	79±27	80±24	71±21	73±20	0.41
Stroke volume index, mL/m^2	38.6±11.6	38.7±10.0	37.1±10.8	35.6±10.0	0.59
Cardiac output, L/min	5.42±1.72	5.40±1.27	4.74±1.16	4.87±1.02	0.13
Cardiac index, L/min per m^2	2.66±0.74	2.64±0.10	2.46±0.15	2.40±0.51	0.22
SVR, dynes/s per cm^{-5}	2216±984	2140±683	2282±499	2107±688	0.87
PVR, dynes/s per cm^{-5}	161±89	157±60	207±136	191±102	0.1
Hemodynamics at maximal exercise					
Heart rate, bpm	106±19*	98±18	100±33	91±18	0.008
Systolic blood pressure, mm Hg	193±35	191±35	183±32	160±42‡†	0.011
Diastolic blood pressure, mm Hg	84±13	82±14	81±12	68±10‖	<0.001
Central venous pressure, mm Hg	18±8	19±6	18±8	19±6	0.72
sPAP, mm Hg	62±18	64±17	70±13	67±13	0.16
dPAP, mm Hg	25±9	24±8	27±7	25±7	0.37
mPAP, mm Hg	45±11	43±11	48±9	47±10	0.23
PAWP, mm Hg	31±7	31±5	31±5	31±5	0.91
Stroke volume, mL	96±30	87±26	76±22	81±29	0.018
Stroke volume index, mL/m^2	46.6±12.3*	41.5±9.0	39.6±9.1	39.4±12.7	0.007
Cardiac output, L/min	10.01±2.85‖	8.36±2.47	7.24±1.93	6.94±2.49	<0.001
Cardiac index, L/min per m^2	4.91±1.28‖	4.01±1.00	3.76±0.89	3.38±1.10	<0.001
SVR, dynes/s per cm^{-5}	993±472	1112±444	1283±343	1004±302	0.26
PVR, dynes/s per cm^{-5}	121±102	140±99	212±94†	220±133†‡	<0.001

AI indicates artificial intelligence; dPAP, diastolic pulmonary arterial pressure; mPAP, mean pulmonary arterial pressure; PAWP, pulmonary arterial wedge pressure; PVR, pulmonary vascular resistance; sPAP, systolic pulmonary arterial pressure; and SVR, systemic vascular resistance.

*P<0.05 compared with fourth quartile 3.

†P<0.05 compared with first quartile.

‡P<0.05 compared with second quartile.

§P<0.05 compared with third quartile 3.

‖P<0.05 vs all.

to guide further evaluation using advanced imaging and hemodynamic assessments. AI-enabled ECG assessment may also be useful as an entry criterion for clinical trials, to enrich the population with patients that display more LA dysfunction and are at greater risk for developing AF. Low-grade mitral and tricuspid valve regurgitation also increased with higher AI-enabled AF probability. Importantly, in these patients, the regurgitation was due to functional etiologies rather than structural disease. A recent study has shown that functional mitral valve regurgitation in HFpEF is due to atrial rather than ventricular disease, which is yet another reflection of LA myopathy, even in the absence of AF.[7] Tricuspid valve regurgitation is also caused by both right atrial and ventricular remodeling, as well as right ventricular dysfunction that develops secondary to pulmonary hypertension with progressive LA myopathy.[5]

Clinical Implications

Applying AI-enabled ECG analysis in a systematic way to patients with HFpEF could result in earlier identification of patients with LA myopathy at high risk for AF and for development of pulmonary hypertension and

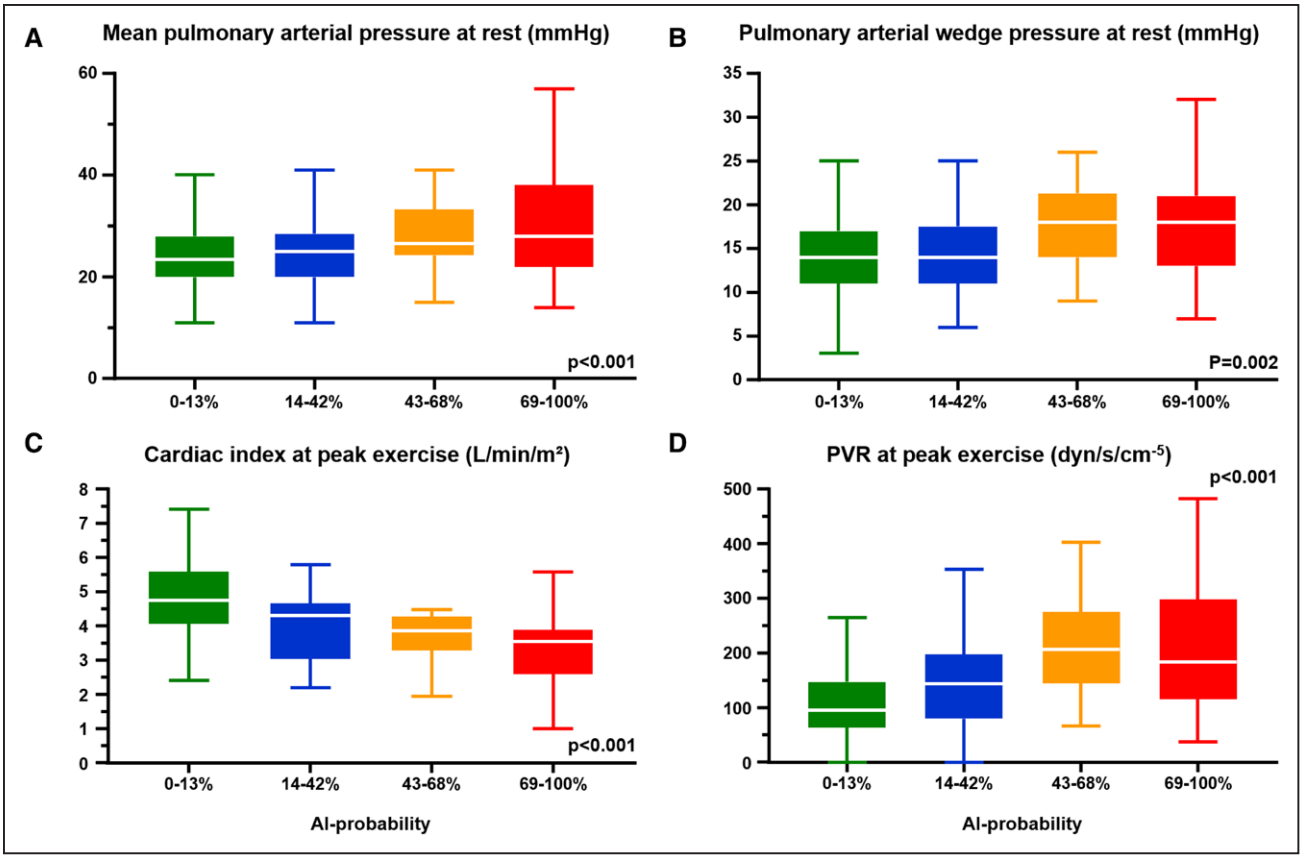

Figure 4. Invasive hemodynamics according to artificial intelligence (AI)-probability.
A, Mean pulmonary arterial pressure and (**B**) pulmonary arterial wedge pressure at rest, as well as (**C**) cardiac index and (**D**) pulmonary vascular resistance (PVR) at peak exercise.

right heart failure, which develop frequently secondary to LA dysfunction.[5,11,20,21] As most patients with HFpEF fulfil guideline criteria of elevated thromboembolic risk (for whom initiation of oral anticoagulation is indicated), this could have major therapeutic consequences. Data from the current study suggest that in patients with HFpEF but no prior history of AF, 1 in 4 with an AI-predicted AF probability score >50% will develop AF within 16 months. Patients with such a high event rate would be an ideal population to enroll in clinical trials, such as those testing direct oral anticoagulants to reduce risk of stroke, or other interventions to reduce incident AF.

Based upon the current data and evidence from prior studies, it seems likely that many patients with HFpEF and sinus rhythm, but high AI-probability scores may have occult AF.[5,9] Further study is warranted to determine whether novel approaches using implantable or wearable recorders can enhance AF detection and improve outcomes in this high-risk cohort.

In addition, earlier detection of occult paroxysmal AF, before the onset of substantial LA remodeling, might improve the selection of candidates for catheter ablation or medical therapies to reduce AF burden.[5] Ablation in patients with AF improves quality of life and, if AF burden is successfully reduced, might be associated with a lower risk of HF and cardiovascular mortality.[22,23] This could be particularly important in HFpEF, where the development of new-onset AF is strongly associated with the development of right ventricular dysfunction and increased risk of death.[11,21]

Study Limitations

The AI algorithm used in this study was trained and validated in a single highly specialized referral center and the study population was drawn from the same center. This may limit generalizability and thus our results should be confirmed in independent study cohorts. Only 63 patients in this study had an implantable cardiac device and data on the exact number and length of individual AF episodes were not captured. As a result, AF burden in this study was assessed clinically, using the AF stages of paroxysmal versus persistent/permanent AF. Short or asymptomatic episodes likely went undetected, but this limitation mirrors what occurs in current clinical practice, where the presence of AF is ascertained through periodic ECG assessments and clinical chart review. Quantitative measures such as QRS angle and P wave amplitude/duration were not available, so we could not compare the incremental value of the AI-enabled ECG to these simple ECG markers.

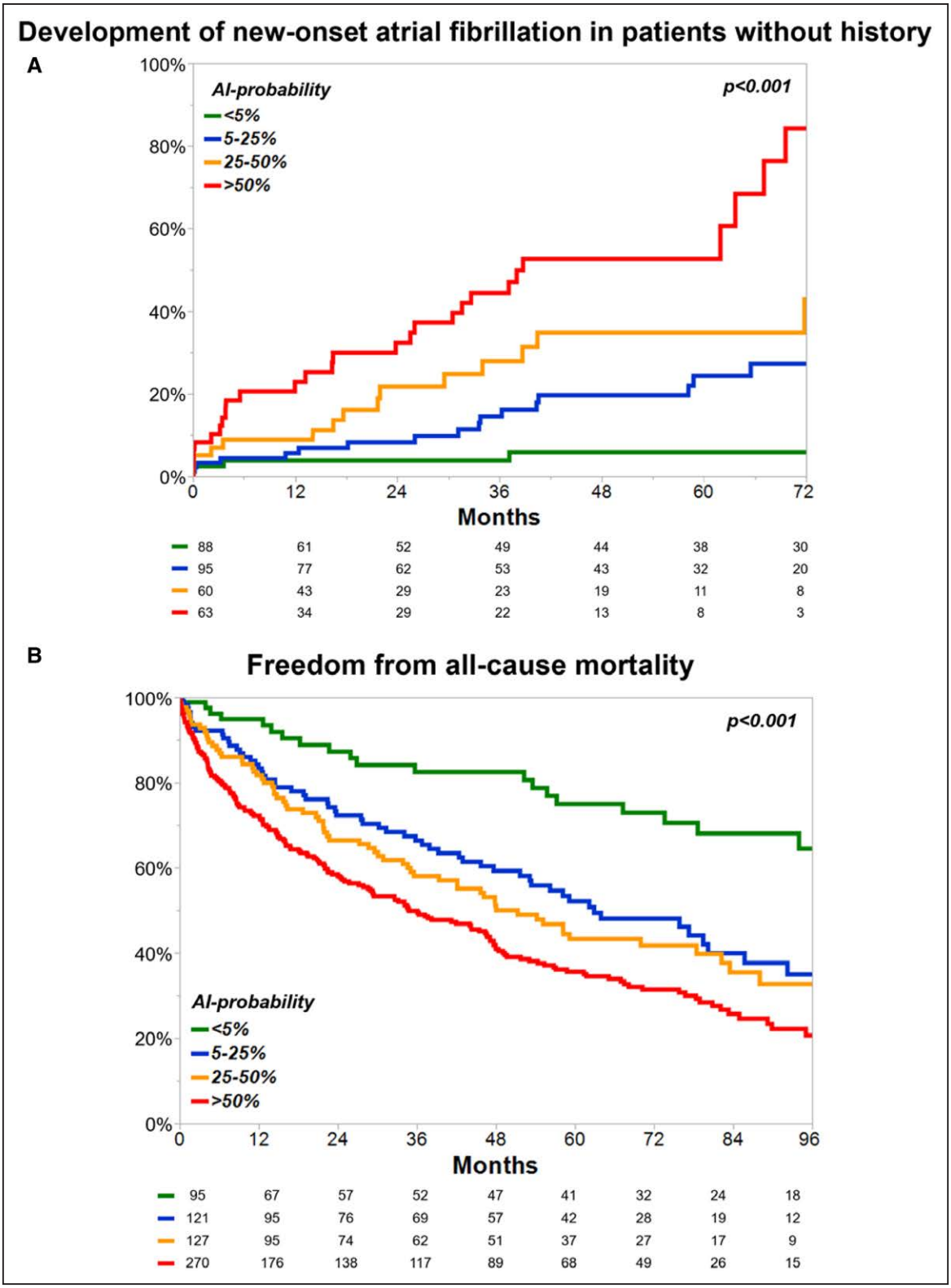

Figure 5. Clinical outcome according to artificial intelligence (AI)-probability.
A, Development of new-onset atrial fibrillation in patients without history according to AI-probability. **B**, Freedom from all-cause mortality.

Conclusions

Analysis of a single 12-lead ECG using AI can facilitate identification of patients with HFpEF displaying greater underlying left atrial myopathy, more severe hemodynamic abnormalities, and those who demonstrate a higher risk for developing AF in the future. These data

suggest that application of an AI-enabled ECG may be useful to aid in phenotypic characterization, better inform the need for further testing, and identify patients who may benefit from novel interventions to treat or prevent AF and LA myopathy in HFpEF.

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Disclosures

None.

Supplemental Material

Supplemental Methods
Tables S1–S5
Figure S1

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