

Associations of Atrial Cardiomyopathy Markers with Incident Heart Failure

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Abstract

Background: Atrial cardiomyopathy (AtCM) is increasingly recognized as an important substrate for heart failure (HF), but the comparative prognostic value of markers across different AtCM domains remains unclear.

Methods: We included 30,052 UK Biobank participants without prevalent HF. AtCM markers were derived from cardiovascular magnetic resonance imaging and electrocardiography. Associations with incident HF were examined using multivariable Cox proportional hazards models and restricted cubic splines. Incremental predictive value beyond the Atherosclerosis Risk in Communities HF risk score was assessed using time-dependent receiver operating characteristic analyses.

Results: Over follow-up, 288 participants developed incident HF. Left atrial markers, including left atrial maximum volume index (LAViMax), left atrial minimum volume index (LAViMin), and left atrial ejection fraction (LAEF), were independently associated with incident HF. In contrast, right atrial markers and P-wave duration were not consistently associated with HF risk. Restricted cubic spline analyses revealed a significant nonlinear association between LAEF and incident HF, with HF risk increasing at lower LAEF values. An LAEF threshold of approximately 50% identified participants at elevated HF risk. Incorporating LAEF into the ARIC HF risk model significantly improved discrimination for incident HF at both 3 and 5 years.

Conclusions: Among multiple domains of AtCM, left atrial markers were independently associated with incident HF. LAEF values below approximately 50% identified individuals at increased HF risk and improved risk prediction beyond the ARIC HF risk model, supporting its potential utility for HF risk stratification.

Introduction

Heart failure (HF), characterized by progressive cardiac structural remodeling and functional deterioration, remains associated with substantial morbidity, poor long-term prognosis, and a considerable healthcare burden worldwide.^[1] Emerging evidence suggests that abnormalities in the atria may precede overt ventricular remodeling and represent an early substrate for HF development.^[2] However, current prediction models for incident HF insufficiently capture preclinical atrial remodeling and rely predominantly on traditional cardiovascular risk factors.^[3–5] Similarly, the HFA-PEFF diagnostic algorithm for heart failure with preserved ejection fraction (HFpEF) incorporates only left atrial volume index (LAVi) in the assessment of atrial involvement.^[6]

The 2025 European Society of Cardiology (ESC) Heart Failure Association clinical consensus statement updated the concept of atrial cardiomyopathy (AtCM), providing a mechanistic framework that may facilitate earlier detection and improved risk stratification of HF.^[2] Markers of AtCM were categorized into four principal domains according to the consensus: electrical atrial dysfunction, mechanical atrial

dysfunction, atrial enlargement, and atrial fibrosis. Each domain encompasses multiple complementary indicators. Representative AtCM markers include P-wave duration (PWD) as a marker of electrical dysfunction; left atrial ejection fraction (LAEF) and left atrial strain as markers of mechanical dysfunction; and maximum and minimum left atrial volumes indexed to body surface area (LAViMax and LAViMin) as markers of atrial enlargement. Subclinical abnormalities across different domains of AtCM markers can be detected before the onset of overt cardiovascular disease, and accumulating evidence has linked individual markers to incident atrial fibrillation (AF), HF, and stroke.^[7–11]

However, the comparative prognostic significance of markers across different domains remains insufficiently understood. Specifically, there is still a lack of systematic evidence regarding which markers exhibit stronger associations with incident HF, while the abnormal thresholds of these indicators have yet to be clearly established. Accordingly, using data from the UK Biobank, the present study aimed to: (1) compare the prognostic relevance of AtCM markers across different domains in relation to incident HF, identify the markers most strongly associated with HF risk, and determine their potential abnormal thresholds; and (2) evaluate the incremental predictive value of these high-risk markers for incident HF, with potential implications for refining future HF risk prediction strategies.

Methods

Study Cohort

The UK Biobank is a large prospective population-based cohort study that enrolled more than 500,000 participants aged 40 to 69 years across the United Kingdom between 2006 and 2010.^[12] To date, participants have undergone several follow-up assessments, including a first repeat assessment visit (2012–2013), an imaging visit (initiated in 2014), and a first repeat imaging visit (initiated in 2019). The UK Biobank imaging visit included extensive cardiovascular phenotyping, including cardiovascular magnetic resonance (CMR) imaging and resting 12-lead electrocardiography (ECG), in addition to comprehensive clinical and lifestyle data.^[13]

In the present study, the imaging visit was defined as baseline. Among 91,974 participants who underwent the first imaging visit, 30,190 individuals with complete baseline, CMR, and ECG data were included in the analysis. Participants with prevalent HF at baseline ($n = 138$) were excluded. The study flowchart is shown in Figure S1.

AtCM Markers

AtCM markers were selected in accordance with the 2025 ESC Heart Failure Association clinical consensus statement on atrial cardiomyopathy, with inclusion restricted to parameters available within the UK Biobank dataset.^[2] PWD and prolonged PWD (defined as $PWD > 120$ ms) were selected as markers of electrical atrial dysfunction. LAViMax and LAViMin, together with maximum and minimum

right atrial volume indices (RAViMax and RAViMin), were used as markers of atrial enlargement. LAEF and right atrial ejection fraction (RAEF) were selected as markers of mechanical atrial dysfunction.

Quantitative cardiovascular magnetic resonance (CMR) phenotypes in the UK Biobank were previously derived using an automated machine learning–based image analysis pipeline.^[14] Available AtCM-related CMR parameters included left and right atrial maximum and minimum volumes, as well as LAEF and RAEF. Atrial emptying fraction was calculated as the difference between maximum and minimum atrial volumes divided by maximum atrial volume. Atrial volumes were further indexed to body surface area, yielding LAViMax, LAViMin, RAViMax, and RAViMin.^[15]

Standard resting 12-lead ECGs were acquired using a commercially available system (CASE/CardioSoft; GE Healthcare, Chicago, Illinois). ECG signals were digitally recorded and analyzed using the manufacturer's automated measurement algorithm. PWD was automatically determined as the interval between P-wave onset and offset. Consistent with prior literature and guideline recommendations, prolonged PWD was prespecified as > 120 ms.^[2]

Clinical Outcomes

Incident HF and all-cause mortality were ascertained through linkage to hospital inpatient records, national death registry data, and self-reported information. HF was defined using a composite algorithm incorporating International Classification of Diseases, Ninth Revision (ICD-9) and Tenth Revision (ICD-10) diagnostic codes, OPCS Classification of Interventions and Procedures version 4 (OPCS-4) procedure codes, and self-reported physician diagnoses. All-cause mortality was identified from national death registry records. Detailed outcome definitions are provided in Table S1.

To reduce potential reverse causality and minimize misclassification of prevalent but previously undiagnosed HF, incident HF and death events were required to occur more than 28 days after baseline assessment. Participants were censored at the date of death, loss to follow-up, or the end of follow-up according to the censoring dates specified by each UK Biobank data provider, whichever occurred first.

Statistical Analyses

Baseline characteristics are presented as mean $\pm$ SD or median (IQR) for continuous variables and counts (%) for categorical variables. Between-group comparisons used Student's t-test or Wilcoxon rank-sum test for continuous variables and chi-square test for categorical variables.

Time-to-event analyses were conducted using Cox proportional-hazards models, with follow-up from baseline to incident HF or censoring. The proportional-hazards assumption was assessed using Schoenfeld residuals. Multivariable models adjusted for age, sex, body mass index, race, hypertension, diabetes mellitus, coronary artery disease, AF, left ventricular mass index (LVMI), global longitudinal strain (GLS), left ventricular ejection fraction (LVEF), and CMR center. Atrial structural indices (LAViMax,

LAViMin, RAViMax, RAViMin, and PWD) were analyzed per 1-SD increase, whereas LAEF and RAEF were analyzed per 1-SD decrease. Fine–Gray subdistribution hazard models were additionally used to account for death as a competing event.

Potential nonlinear associations between AtCM markers and incident HF were evaluated using restricted cubic spline Cox models with 3 knots. Hazard ratios and 95% confidence intervals were estimated across marker distributions using the median as reference, and nonlinearity was tested with Wald tests.

The optimal LAEF cutoff for risk stratification was identified using maximally selected rank statistics based on the log-rank test with Lau94 approximation. Internal validation was performed with 5,000 bootstrap resamples, repeating the full selection process in each iteration. The distribution of selected cutoffs and optimism estimates were summarized, and the 10 most frequently selected cut points are shown in Table S2.

Predictive associations with incident HF were further examined using Cox models with the Breslow method for ties. Two models were evaluated: a base model including the ARIC HF risk score and an extended model additionally incorporating LAEF. The “Full Cohort sans NT-proBNP” ARIC model was used. Model discrimination was assessed using time-dependent ROC curves with marginal weighting for censoring, and AUCs were calculated at 3 and 5 years. Incremental predictive value was evaluated by differences in AUC (Δ AUC). Uncertainty was estimated using 1,000 bootstrap resamples, with percentile-based 95% confidence intervals and empirical two-sided P values.

Analyses were restricted to participants with complete data; no missing-data imputation was performed. All analyses were conducted in R version 4.5.2. Two-sided $P < 0.05$ was considered statistically significant.

Results

Study Population and Baseline Characteristics

A total of 30,052 participants from the UK Biobank were included in the analysis. During follow-up, 288 participants (0.96%) developed incident HF, and 838 participants (2.79%) experienced the composite outcome of HF or death. Baseline characteristics according to incident HF status are summarized in Table 1. Participants who developed incident HF were older than those who remained free of HF (mean age, 67.8 ± 6.9 vs. 63.3 ± 7.5 years) and had a higher body mass index (median, 27.1 vs. 25.8; $P < 0.001$). Current smoking was also more prevalent among participants with incident HF (6.6% vs. 3.5%; $P = 0.004$). Cardiometabolic comorbidities were substantially more common among participants who developed HF, including hypertension (51.4% vs. 28.7%), type 2 diabetes mellitus (13.2% vs. 4.8%), coronary artery disease (15.3% vs. 2.9%), and AF or flutter (2.8% vs. 1.3%) (all $P < 0.001$).

Associations of AtCM Markers With Incident HF

In multivariable-adjusted Cox proportional-hazards models (**Figure 1**), markers of left atrial remodeling and dysfunction were consistently associated with incident HF. Higher LAViMax and LAViMin were each associated with increased HF risk (hazard ratio [HR] per 1-SD increase, 1.21 [95% CI, 1.11–1.32] and 1.19 [95% CI, 1.10–1.28], respectively; both $P < 0.001$). Similarly, lower LAEF was independently associated with a higher risk of incident HF (HR per 1-SD decrease, 1.21; 95% CI, 1.08–1.36; $P = 0.001$). Associations for left atrial markers remained consistent in analyses of the composite outcome of HF or death and in competing-risk analyses treating death as a competing event (**Figures S2 and S3**).

In contrast, associations between right atrial markers and incident HF were attenuated and less consistent across sensitivity analyses. Although RAViMax was associated with incident HF in the primary analysis, this association was not retained for the composite endpoint (HR, 1.00; 95% CI, 0.94–1.08; $P = 0.926$) or in competing-risk analyses (HR, 1.08; 95% CI, 0.95–1.24; $P = 0.245$). Other right atrial indices were not significantly associated with incident HF across analyses. Likewise, neither PWD nor prolonged PWD was significantly associated with incident HF in any model (**Figure 1, Figures S2, Figure S3 and Table S2**).

Nonlinear Associations Between Left Atrial Markers and Incident HF

Restricted cubic spline analyses were performed to further characterize the associations between left atrial markers and incident HF (**Figure 2**). Associations of LAViMax and LAViMin with incident HF were approximately linear across the observed ranges (P for nonlinearity = 0.846 and 0.556, respectively), with progressively higher atrial volumes associated with incrementally increased HF risk.

In contrast, LAEF demonstrated a significant nonlinear association with incident HF (P for nonlinearity < 0.001). Lower LAEF values were associated with a steep increase in HF risk, whereas risk estimates plateaued at higher LAEF levels, suggesting a threshold-dependent relationship between impaired atrial mechanical function and incident HF. These findings motivated subsequent analyses to identify an optimal LAEF threshold for HF risk stratification.

LAEF Threshold and Incremental Prediction of Incident HF

Given the observed nonlinear association between LAEF and incident HF, the optimal LAEF threshold for risk stratification was determined using maximally selected rank statistics. The optimal cutoff value was 49.40% (maximally selected log-rank statistic, $M = 12.53$; $P < 0.001$) (**Figure 3**).

Bootstrap resampling (5,000 iterations) demonstrated a narrow distribution of selected cutoff values, supporting the robustness of the identified threshold. The mean selected cutoff was 49.78% (SD, 1.24%), with a median of 49.40% and a 95% confidence interval ranging from 49.13% to 54.31%. The most frequently selected cutoff was 49.40% (1,287 of 5,000 bootstrap samples), followed by 50.11% and 49.14% (Table S2).

In light of the close clustering of bootstrap-derived thresholds around 50%, and to facilitate clinical interpretability and implementation, an LAEF cutoff value of 50% was selected for subsequent analyses.

Kaplan–Meier analyses demonstrated a significantly higher cumulative incidence of HF among participants with LAEF <50% compared with those with LAEF ≥50% (log-rank $P < 0.0001$) (**Figure 4**).

In time-dependent receiver-operating-characteristic analyses, incorporation of LAEF into the Atherosclerosis Risk in Communities (ARIC) HF risk model significantly improved discrimination for incident HF at both 3 and 5 years (**Figure 5**). At 3 years, the area under the curve (AUC) increased from 0.743 to 0.775 after inclusion of LAEF (ΔAUC , 0.032; $P = 0.006$). Similarly, at 5 years, the AUC improved from 0.748 to 0.778 (ΔAUC , 0.030; $P = 0.002$).

Discussion

In this large prospective cohort study derived from the UK Biobank, we systematically evaluated the associations between multiple domains of atrial cardiomyopathy (AtCM) and incident HF. Several key findings emerged. First, among multiple AtCM domains, AtCM markers of left atrial remodeling and dysfunction represented the earliest and strongest preclinical markers associated with incident HF. Second, whereas associations for LAViMax and LAViMin were approximately linear, LAEF demonstrated a significant nonlinear relationship with incident HF characterized by a threshold-dependent risk pattern. Third, an LAEF threshold of approximately 50% identified individuals at substantially increased risk of HF and provided incremental predictive value beyond the ARIC HF risk model.

Our findings demonstrating significant associations between left atrial AtCM markers and incident HF are consistent with prior studies across diverse imaging modalities and study populations. In the Atherosclerosis Risk in Communities (ARIC) study, Inciardi et al. used echocardiography to evaluate left atrial structure and function in 4,901 participants and demonstrated that, with the exception of LAViMax, both LAViMin and LA functional indices, including LAEF and LA strain, were associated with increased risk of incident HF or death.^[7] Similarly, a study using cardiac computed tomography angiography demonstrated that left atrial total emptying fraction was independently associated with HF hospitalization or cardiovascular death.^[8] Consistent findings have also been reported using CMR imaging. In the Dallas Heart Study, Gupta et al. evaluated left atrial structure and function in 1,802 community-based participants and found that lower LAEF was independently associated with increased mortality (hazard ratio per 1-SD decrease, 1.56; 95% CI, 1.32–1.87), whereas LAViMax was not independently predictive after multivariable adjustment.^[16] Despite differences in imaging techniques and study populations, these studies collectively support a robust and reproducible association between left atrial markers and adverse cardiovascular outcomes.

The mechanisms linking left atrial AtCM markers to incident HF remain incompletely understood, although several plausible explanations may account for these associations. First, impaired left atrial mechanical function may reduce left ventricular filling and effective stroke volume while simultaneously increasing left atrial pressure and reducing atrial compliance. These alterations may contribute to elevations in pulmonary venous and pulmonary arterial pressures, thereby promoting hemodynamic abnormalities associated with HF.^[17, 18] Second, analogous to ventricular remodeling, profibrotic

signaling pathways involving angiotensin II, transforming growth factor- β , and aldosterone have been implicated in the development of atrial fibrosis.^[19] Experimental studies have demonstrated that activation of these pathways may induce a more pronounced fibrotic response in the atria than in the ventricles, leading to atrial structural remodeling, arrhythmogenesis, and adverse cardiovascular outcomes.^[20–24] These observations raise the possibility that atrial remodeling may precede overt left ventricular remodeling in the evolution of HF. Accordingly, atrial enlargement and impaired atrial function may reflect early manifestations of myocardial disease rather than merely secondary adaptive changes. Collectively, these findings support the concept that AtCM may represent an early pathophysiologic substrate associated with the development of HF.

Although the 2025 ESC clinical consensus statement highlighted the need for standardized thresholds of left atrial structure and function to improve risk stratification and prognostic assessment in AtCM, no universally accepted cutoff value for LAEF has been established to date.^[2] Commonly used thresholds, including 45%, 46%, and 50%, have largely been derived from population-based distributions.^[25–27] Previous studies applying these thresholds have demonstrated associations between reduced LAEF and HF-related outcomes. For example, an LAEF < 50% was independently associated with New York Heart Association functional class (NYHA) $\geq$ II.^[28] An LAEF < 45% has also been proposed as a marker of AtCM and linked to increased risks of incident AF, stroke, and HF.^[10] However, these empirically derived thresholds primarily reflect statistical characteristics of the underlying study population rather than direct associations with clinically relevant outcomes. In contrast, the present study used an outcome-oriented approach to identify clinically meaningful risk thresholds for LAEF. Using data-driven methods, we identified an optimal LAEF cutoff associated with incident HF, thereby potentially improving the clinical interpretability and prognostic relevance of LAEF-based risk stratification. Nevertheless, this approach remains dependent on the characteristics of the underlying population and the distribution of clinical events. Accordingly, the identified threshold may exhibit population-specific variability and requires external validation in independent cohorts before broader clinical application.

Although the right and left atria share similar substrates and remodeling patterns, evidence linking abnormalities in right atrial markers to the risk of HF remains limited. Compared with the left atrium, the right atrium primarily reflects the cumulative hemodynamic burden that develops during HF progression rather than early pathogenic changes.^[29] Therefore, RA indices may be better regarded as markers of HF severity and prognosis in established HF, rather than as early indicators of incident HF.^[30, 31] With respect to P-wave abnormalities, a previous study including 6,754 participants without overt cardiovascular disease demonstrated a significant association between prolonged PWD and incident HF.^[11] However, PWD has been more consistently associated with AF than with HF outcomes, and its prognostic significance for incident HF remains incompletely understood.^[10]

Limitations

This study has several limitations. First, the analysis was conducted within the UK Biobank, which predominantly includes participants of European ancestry, potentially limiting the generalizability of our findings to more diverse populations. Second, participation in the UK Biobank is voluntary and may introduce healthy volunteer bias, which could influence the prevalence and distribution of AtCM markers and limit external validity. Third, the UK Biobank does not include comprehensive assessments of atrial fibrosis, atrial strain, or continuous cardiac rhythm monitoring. Accordingly, we were unable to evaluate additional AtCM phenotypes derived from these modalities. Finally, because imaging assessments in the UK Biobank were initiated in 2014, follow-up duration after imaging remained relatively limited, restricting evaluation of longer-term clinical outcomes.

Conclusion

In this prospective UK Biobank study, left atrial AtCM markers, particularly LAViMax, LAViMin, and LAEF, were independently associated with incident HF among multiple AtCM domains. LAEF showed a nonlinear relationship with HF risk, with values below 50% identifying individuals at higher risk. Addition of LAEF significantly improved HF risk prediction beyond the ARIC model, supporting its potential role in future HF risk stratification.

Abbreviations

HF, Heart failure

AtCM, Atrial cardiomyopathy

LAViMax, Left atrial maximum volume index

LAViMin, Left atrial minimum volume index

LAEF, Left atrial ejection fraction

RAEF, Right atrial ejection fraction

RAViMax, Right atrial maximum volume index

RAViMin, Right atrial minimum volume index

CMR, Cardiovascular magnetic resonance

ECG, Electrocardiography

ARIC, Atherosclerosis Risk in Communities

Statements and Declarations

Funding

This study received no specific funding.

Competing Interests

The authors have no relevant financial or non-financial interests to disclose.

Ethical Approval

The UK Biobank study was approved by the North West Multi-centre Research Ethics Committee, and all participants provided written informed consent.

Data Availability

All data underlying this study are available through the UK Biobank. Bona-fide researchers can apply for access to the UK Biobank through <https://www.ukbiobank.ac.uk/enable-your-research/apply-for-access>. This research has been conducted using the UK Biobank Resource under application number 103736.

Clinical trial registration

Not applicable.

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Table

Table 1. The Baseline Characteristics of UK Biobank Participants

	Without Incident HF n=29764	With Incident HF n=288	P value
CMR center (%)			0.003
Cheadle	20327 (68.3)	224 (77.8)	
Reading	3723 (12.5)	25 (8.7)	
Newcastle	5714 (19.2)	39 (13.5)	
Age (mean (SD))	63.34 (7.54)	67.81 (6.89)	<0.001
Sex (%)			<0.001
Female	15646 (52.6)	98 (34.0)	
Male	14118 (47.4)	190 (66.0)	
Race (%)			0.058
White	27545 (92.5)	275 (95.5)	
non-White	2219 (7.5)	13 (4.5)	
BMI (median [IQR])	25.80 [23.41, 28.66]	27.09 [24.42, 30.64]	<0.001
Alcohol (%)			0.109
Never	949 (3.2)	6 (2.1)	
Previous	957 (3.2)	16 (5.6)	
Current	27689 (93.0)	264 (91.7)	
Smoking (%)			0.004
Never	18602 (62.5)	156 (54.2)	
Previous	9880 (33.2)	110 (38.2)	
Current	1036 (3.5)	19 (6.6)	
HR (median [IQR])	61 [55, 68]	61 [54, 69]	0.554
Hypertension (%)	8536 (28.7)	148 (51.4)	<0.001
Type 2 Diabetes (%)	1422 (4.8)	38 (13.2)	<0.001
Coronary Artery Disease (%)	865 (2.9)	44 (15.3)	<0.001
Atrial fibrillation/flutter (%)	379 (1.3)	8 (2.8)	<0.001

Figures

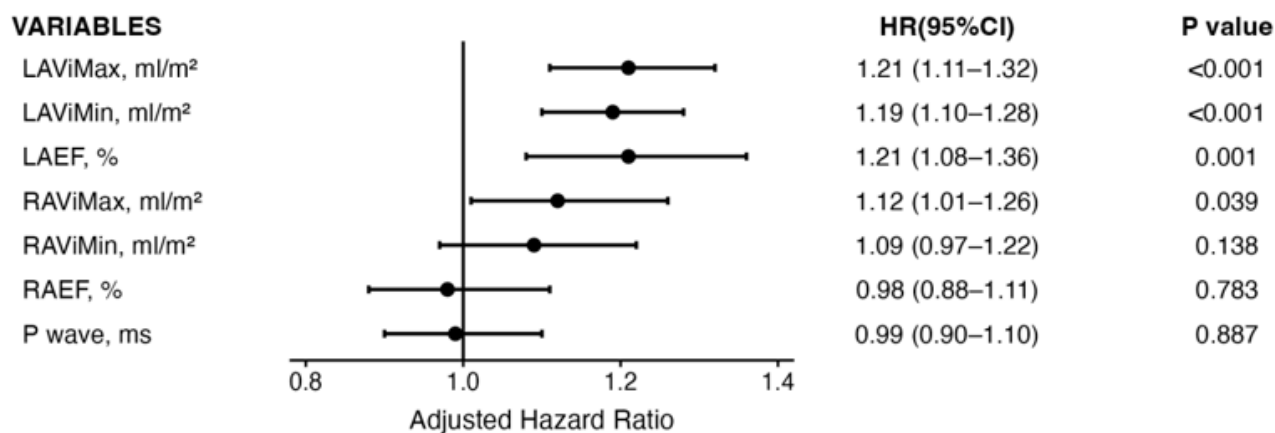


Figure 1

The Associations Between AtCM Markers and Incident Heart Failure

The Cox regression model was adjusted for age, sex, body mass index, race, hypertension, type 2 diabetes, coronary artery disease, atrial fibrillation, CMR imaging center, left ventricular mass index, global longitudinal strain, and left ventricular ejection fraction. The continuous variables of LAViMax, LAViMin, RAViMax and RAViMin were standardized, and Hazard ratios represent the association per 1–standard deviation increase. The continuous variables of LAEF and RAEF were standardized, and Hazard ratios represent the association per 1–standard deviation decrease.

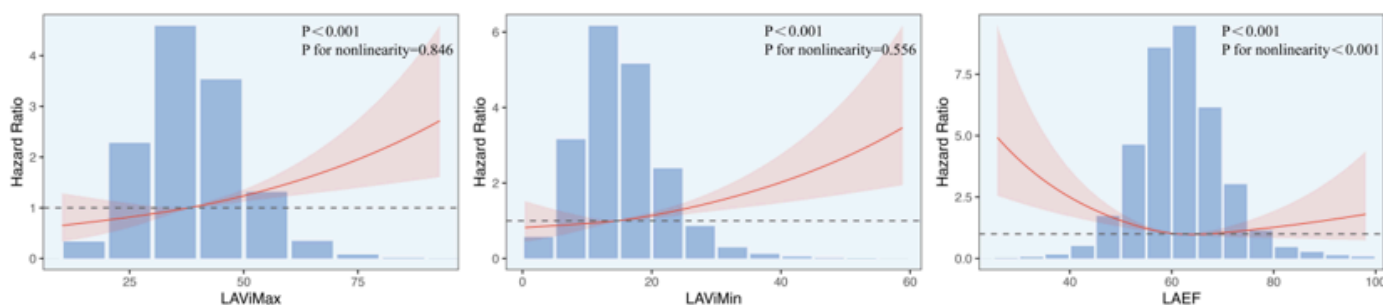


Figure 2

Restricted Cubic Spline Analyses of the Associations Between AtCM Markers and Incident Heart Failure

Bars represent frequencies; the dotted lines indicate the 95% CIs. Hazard ratios (HRs) and 95% confidence intervals were estimated using Cox proportional-hazards models. The reference value was set at the median level of each marker. Models were adjusted for age, sex, body mass index, race,

hypertension, type 2 diabetes, coronary artery disease, atrial fibrillation, CMR imaging center, left ventricular mass index, global longitudinal strain, and left ventricular ejection fraction.

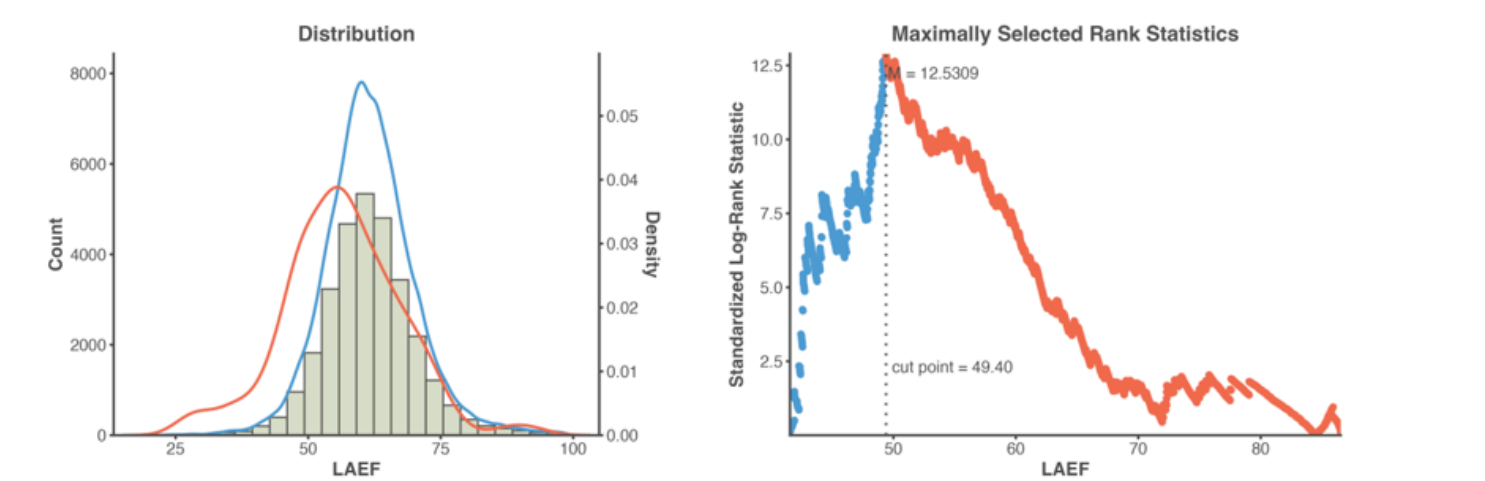


Figure 3

Distribution of LAEF and Identification of the Optimal Cut Point for Incident HF

The histogram represents the frequency distribution of LAEF values, with the blue curve indicating the kernel density estimate for the overall cohort and the red curve indicating the density for participants who developed heart failure.

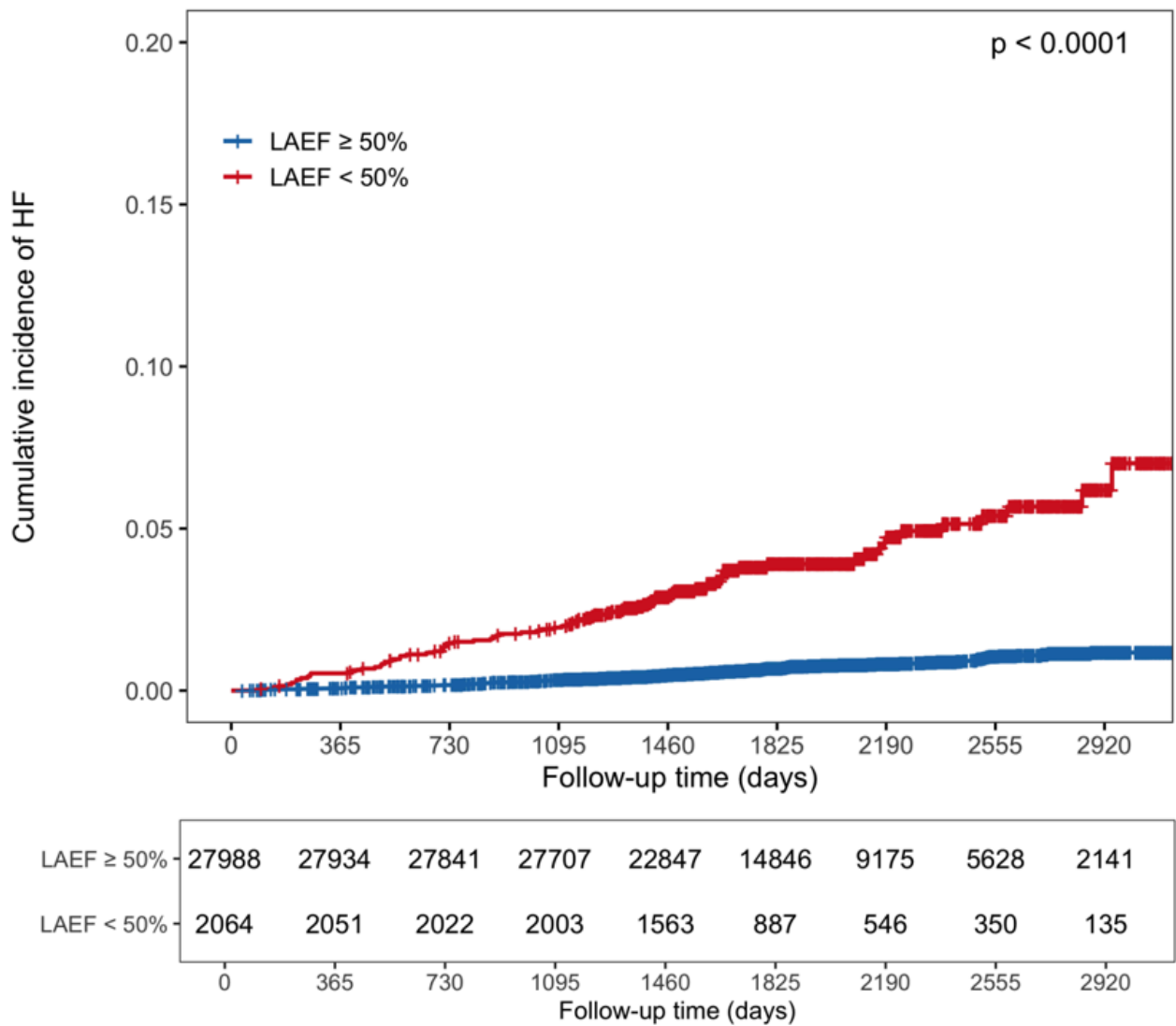


Figure 4

Kaplan–Meier Curves for LAEF and Incident Heart Failure

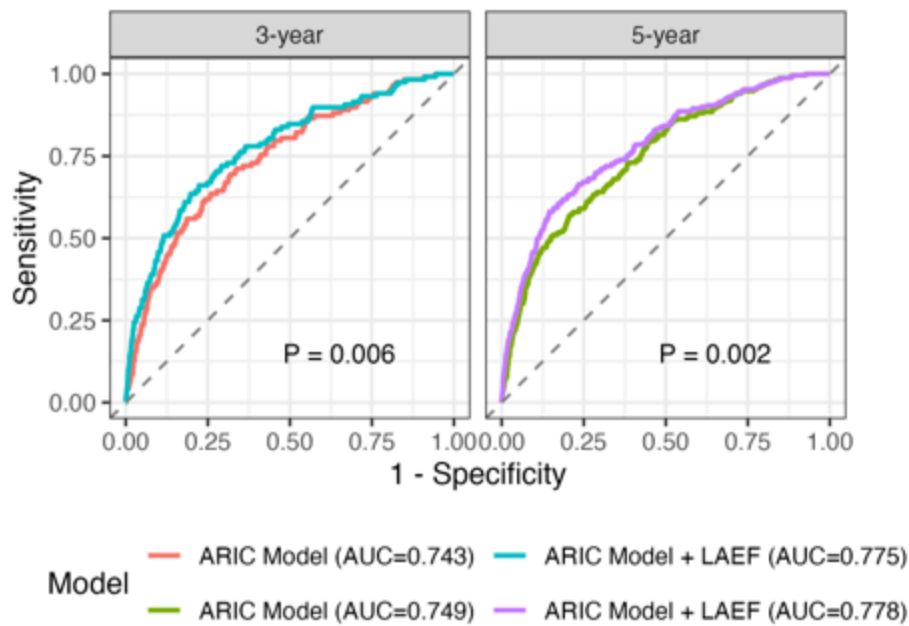


Figure 5

Time-dependent ROC curves comparing ARIC score with and without LAEF for prediction of heart failure at 3 and 5 years

The ARIC model includes age, race, sex, heart rate, systolic blood pressure, antihypertensive medication use, diabetes, prevalent coronary heart disease, smoking status, and body mass index. P values were calculated using 1000 bootstrap resamples to assess differences in AUC between models.

Supplementary Files

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- [SupplementalMaterial.docx](#)