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ORIGINAL RESEARCH

Physiological Left Atrial Staging and the Risk of New-Onset Atrial Fibrillation in Hypertrophic Cardiomyopathy

Jaehyun Lim, MD, PhD,[a,*] In-Chang Hwang, MD,[b,*] Jihoon Kim, MD,[c] Jae-Hyun Kim, MD,[a] Soongu Kwak, MD, PhD,[a] Ju Hi Park, MD,[a] Min-Ha Jeong, MD,[a] Jun-Bean Park, MD, PhD,[a] Seung-Pyo Lee, MD, PhD,[a] Yong-Jin Kim, MD, PhD,[a] Sang-Chol Lee, MD, PhD,[c,†] Hyung-Kwan Kim, MD, PhD, FESC[a,†]

ABSTRACT

BACKGROUND Atrial fibrillation (AF) is pervasive and an independent driver of stroke and death in hypertrophic cardiomyopathy (HCM). Despite guideline recommendations for AF surveillance, effective risk stratification remains elusive, and the hemodynamic and functional states of the left atrium (LA) preceding AF onset remain poorly characterized.

OBJECTIVES We aimed to delineate the hemodynamic and functional states of the LA in HCM, derive a novel LA staging system, and evaluate its prognostic performance for new-onset atrial fibrillation (NOAF).

METHODS This multicenter retrospective study included consecutive HCM patients with normal left ventricular systolic function from January 2007 to February 2024 at 2 academic referral centers. Patients with valvular heart disease or prior AF were excluded. Patients were categorized by combining the presence of elevated LA pressure (hemodynamic load) and LA contractile strain (intrinsic LA function): stage 1 (normal LA pressure and function), stage 2 (relative contractile augmentation for a given LA pressure), stage 3 (loss of relative contractile augmentation despite elevated LA pressure), stage 4 (elevated LA pressure with decreased LA contractile strain), and isolated LA contractile dysfunction. The primary outcome was NOAF. External validation was conducted in an independent HCM cohort.

RESULTS Of 1,856 patients screened, 705 were eligible (mean age 57.6 ± 13.0 years, 30.1% female). During a median follow-up of 7.5 years (Q1-Q3: 3.6-11.0 years), NOAF occurred in 101. The staging system was independently associated with a significant, stepwise increase in the risk of NOAF (adjusted HR: 1.83 per increment; 95% CI: 1.42-2.37; $P < 0.001$) and conferred incremental predictive value beyond established risk models (CHARGE-AF and HCM-AF). Consistent results were demonstrated in 1-year landmark and competing-risk analyses, as well as in an external validation cohort (n = 425; age 59.7 ± 13.5 years, 33.9% female). Importantly, serial echocardiography performed in 217 patients 4 to 6 years after baseline revealed a predominantly unidirectional evolution of the proposed LA stage, with most patients remaining stable (39.6%) or progressing to higher stages or AF (43.8%).

CONCLUSIONS The proposed LA staging framework offers mechanistic insights into how the LA adapts to progressive diastolic dysfunction in HCM. It is associated with a graded risk of NOAF and may help tailor AF surveillance strategies. (JACC. 2026;■:■–■) © 2026 by the American College of Cardiology Foundation.

From the [a]Division of Cardiology, Department of Internal Medicine, Seoul National University College of Medicine and Seoul National University Hospital, Seoul, Korea; [b]Division of Cardiology, Department of Internal Medicine, Seoul National University College of Medicine and Seoul National University Bundang Hospital, Gyeonggi-do, Korea; and the [c]Division of Cardiology, Department of Medicine, Samsung Medical Center and Sungkyunkwan University School of Medicine, Seoul, Korea. *These authors contributed to this work as co-first authors. †These authors contributed to this work as co-corresponding authors.

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ABBREVIATIONS AND ACRONYMS

ECG = electrocardiography

EF = ejection fraction

HCM = hypertrophic cardiomyopathy

LA = left atrium

LV = left ventricular

LVOT = left ventricular outflow tract

NOAF = new-onset atrial fibrillation

Hypertrophic cardiomyopathy (HCM) is the most common inherited myocardial disease, affecting 1 in 200 to 500 adults, and is characterized by left ventricular (LV) hypertrophy, hypercontractility, and diastolic dysfunction.[1,2] With progressive LV diastolic dysfunction, the left atrial (LA) pressure rises and leads to LA adverse remodeling, including chamber dilation and fibrosis.[3,4] This progressive atrial remodeling leads to the most common sustained arrhythmia in this population, atrial fibrillation (AF).[5] The LA was initially considered to be a passive barometer of LV diastolic dysfunction, but the subsequent impairment of LA function—particularly the development of AF—is now recognized as an independent determinant of prognosis.[4,6,7]

Although the LA size has been the primary imaging marker for the risk of new-onset atrial fibrillation (NOAF) in HCM, it is a relatively late and static marker representing the cumulative result of long-standing hemodynamic load.[8,9] A comprehensive understanding of the dynamic interplay between escalating LA pressure with disease progression, mechanical adaptation of the LA, and eventual development of AF, has remained elusive. Recent introduction of advanced echocardiographic techniques, particularly speckle tracking-derived LA strain, offers a more granular assessment of LA mechanics by directly quantifying LA function.

In this study, we sought to: 1) characterize the prevalence and prognostic significance of LV diastolic dysfunction and intrinsic LA function (ie, LA contractile strain) in HCM; 2) categorize patients into distinct stages combining the presence of elevated LA pressure (as a measure of hemodynamic load) and LA contractile strain (as a measure of intrinsic LA myocardial function); and 3) assess the prognostic implication of this novel staging system on the risk of NOAF.

METHODS

STUDY DESIGN AND POPULATION. This multicenter cohort study included patients with HCM evaluated from January 2007 to February 2024 at 2 academic referral centers. HCM was diagnosed according to contemporary guidelines: maximal LV wall thickness ≥15 mm, or ≥13 mm with a family history of HCM, in the absence of abnormal loading conditions.[10] Of 1,856 patients identified, we excluded those with documented AF before the index date, moderate or greater valvular heart disease, reduced left ventricular ejection fraction (LVEF <65%), or missing mitral early diastolic E velocity, early diastolic mitral annular velocity (e′), or LA strain parameters.

We externally validated the study findings with a geographically distinct, large cohort of HCM from an independent tertiary referral center. The study was approved by the Institutional Review Boards at each center, and informed consent was waived.

DATA COLLECTION AND ECHOCARDIOGRAPHY. Baseline characteristics were collected and included symptoms, family history, and comorbidities. All patients were imaged using commercially available ultrasound machines (Vivid 7, 9, or E95, GE Healthcare; iE33 or EPIQ, Philips; or SC2000, Siemens Medical Solutions) in accordance with contemporary guidelines by expert sonographers and reviewed by cardiac imaging specialists.[10] Elevated LA pressure was defined based on the most recent guidelines, ie, septal E/e′ ≥15, peak tricuspid regurgitation (TR) velocity ≥2.8 m/s, or LA reservoir strain ≤18%.[11] For LA strain analyses, 2 highly experienced (>10 years) sonographers blinded to all clinical data and outcomes quantified LA strains based on contemporary guidelines with a vendor-independent postprocessing software (Imaging Arena 4.6, TomTec Imaging Systems).[12] All strain measurements were performed at a central core laboratory with the use of previously reported quality and measurement methodology.[4,13] Briefly, the LA endocardial borders were traced manually on the end-systolic frame from the non-foreshortened apical 4-chamber view and tracked throughout the cardiac cycle.[4,12,13] A decreased LA strain was defined as a value below the age- and sex-based lower limit of normal.[14] The intraclass correlation coefficients of intra- and interobserver variabilities were excellent for LA reservoir (0.95-0.96), contractile (0.93-0.95), and conduit (0.92-0.93) strain, with corresponding coefficients of variation of 4.9% to 6.0%, 13.9% to 14.9%, and 9.7% to 10.5%.

OUTCOMES. The primary outcome was NOAF, as documented on 12-lead electrocardiography (ECG) or lasting ≥30 seconds on continuous ECG monitoring

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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requiring medical attention.[15] Documentation of NOAF was obtained at routine outpatient follow-up visits (typically every 3 to 4 months) or during hospital admission, and further included clinically meaningful AF events documented at other hospitals when identifiable. Brief asymptomatic AF episodes identified fortuitously by ambulatory ECG or interrogation of implantable devices that did not lead to medical or interventional therapy were excluded from the analysis. Secondary and exploratory outcomes included incident ischemic stroke and all-cause mortality, respectively. All patients were followed from the index echocardiography to the outcome of interest, death, or the last clinical follow-up, whichever came first. Patients were censored at the time of any septal reduction therapy, cardiac myosin inhibitor initiation, or heart transplantation, because these interventions alter LA mechanics.[13,16-19]

STATISTICAL ANALYSIS. Continuous data are presented as mean ± SD or median (Q1-Q3), and categoric data as n (%). The chi-square test or Fisher test was used for categoric data. Student's *t*-test or Wilcoxon rank-sum test was used for comparing continuous data between 2 groups, and analysis of variance or Kruskal-Wallis test was used for normally and nonnormally distributed data, respectively, among multiple groups.

To assess potential nonlinear association between LA contractile strain and NOAF, LA contractile strain was modeled using restricted cubic splines with 4 knots, placed at the 5th, 35th, 65th, and 95th percentiles of their distributions. The minimum hazard was assigned an HR of 1.0 and nadir-referenced HRs were plotted with corresponding 95% CIs. Multivariable Cox proportional hazards regression models were used to assess the associations between the elevated LA pressure and outcomes, and septal E/e′ was used to further visualize this association using restricted cubic splines. Based on these associations, we categorized patients into distinct stages depending on LA contractile strain and the presence of elevated LA pressure. To stratify patients in the early stages of atrial myopathy, the optimal cutoff was derived using maximally selected rank statistics (Hothorn-Lausen method).

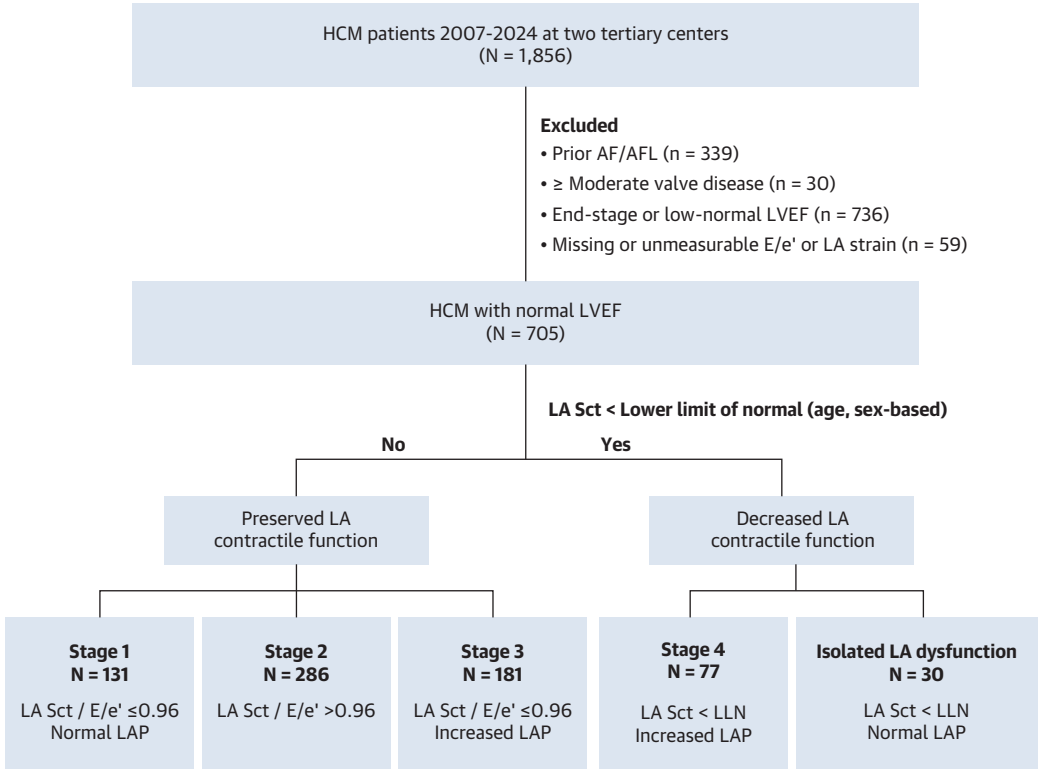
We estimated time-to-event data with the use of Kaplan-Meier techniques and the log-rank test for statistical comparison. Unadjusted and adjusted risks of NOAF by stage were calculated with the use of Cox proportional-hazards regression, with the lowest-risk stage as reference, and Firth correction was implemented to mitigate bias arising from the sparse number of events in this reference stage. For the multivariable model, we adjusted for sex and the variables from the CHARGE-AF score, involving age, height, weight, systolic and diastolic blood pressures, smoking, treatment for hypertension, diabetes, heart failure, and myocardial infarction.[20] Incremental predictive value of the proposed staging system was evaluated by comparing C-statistics for 10-year NOAF, as well as continuous and categoric net reclassification improvement (NRI) and integrated discrimination improvement, using 1,000 bootstrap resamples. Categoric NRI was assessed with the use of the following risk categories: <5%, 5% to 10%, and >10%. The same incremental analysis was conducted using an established HCM-specific model, the HCM-AF score.[15] Its constituent variables (age at evaluation, age at HCM diagnosis, LA size, and NYHA functional class) were used instead of the published point score, permitting direct comparison after refitting both models in the same cohort. Regarding incident ischemic stroke and death, variables from the CHA_2DS_2-VASc score were adjusted, including heart failure, hypertension, age, diabetes mellitus, previous stroke, vascular disease, and sex.[21]

Sensitivity analyses included 1-year landmark analyses to account for potentially undiagnosed AF at baseline and Fine-Gray competing-risk analyses to account for all-cause mortality.[22] We also evaluated models that further adjusted for HCM-specific measures (ie, maximal left ventricular outflow tract [LVOT] pressure gradient and maximal LV wall thickness) and for rhythm-monitoring frequencies (ie, 12-lead ECG and continuous monitoring). Firth's penalized likelihood was incorporated into all models to obtain stable estimates. The proportional-hazards assumption for all Cox models was tested with the use of Schoenfeld residuals. For the Fine-Gray competing-risk models, the proportional subdistribution hazards assumption was assessed by testing for time-dependent covariates. No violations were detected for any model. Analyses were conducted with the use of R statistical software version 4.4.3 (R Foundation), and a 2-tailed P value of < 0.05 was considered to be statistically significant.

RESULTS

STUDY POPULATION. The study population comprised 705 patients (Figure 1). The mean age was 57.6 ± 13.0 years and 30.1% were women. The mean LVEF was 69.2% ± 3.6%, and 18.1% had an obstructive phenotype. Approximately 41.3% of patients had increased LA pressure based on recent guidelines,[11] and

FIGURE 1 Study Flow Chart



AF = atrial fibrillation; AFL = atrial flutter; HCM = hypertrophic cardiomyopathy; LA = left atrium; LAP = left atrial pressure; LLN = lower limit of normal; LVEF = left ventricular ejection fraction; Sct = contractile strain.

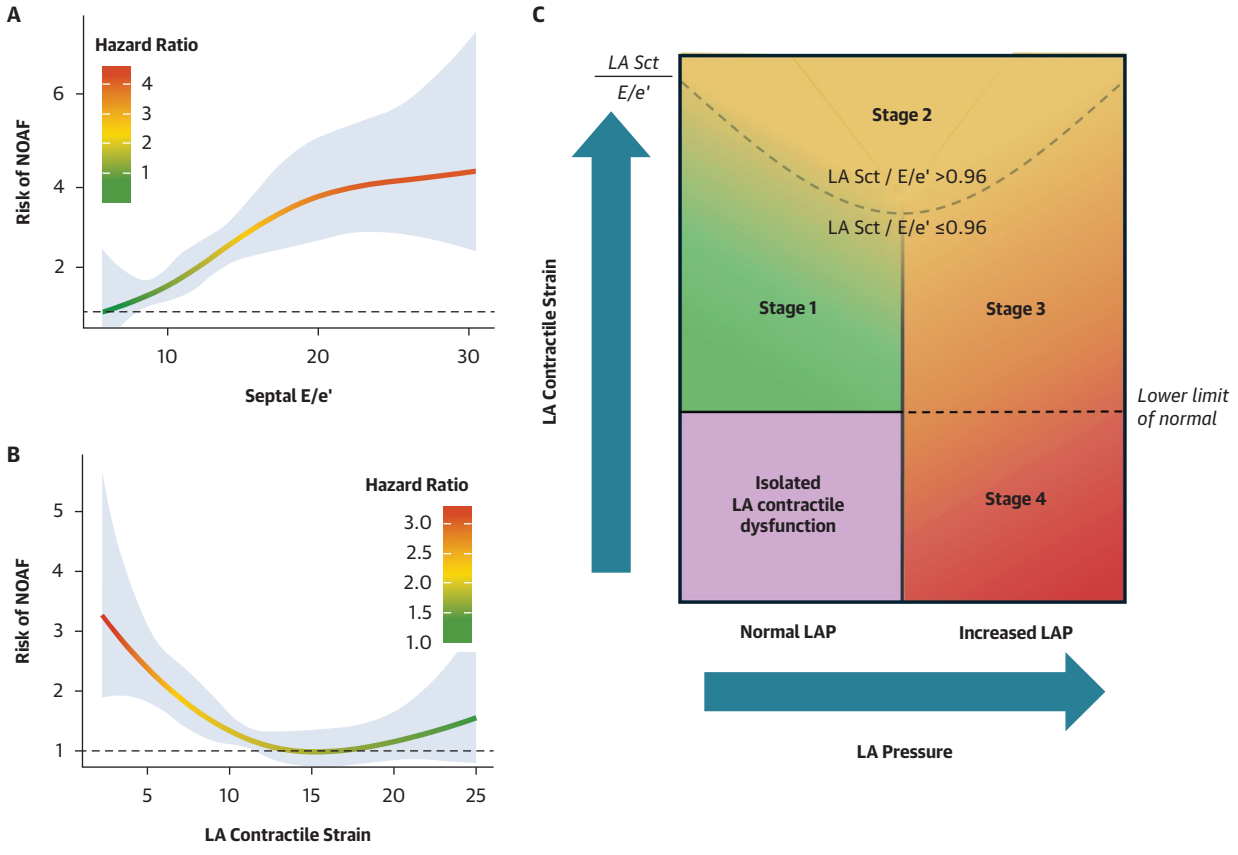
15.2% had decreased LA contractile function. NOAF occurred in 101 patients (14.3%) during a median follow-up of 7.5 years (Q1-Q3: 3.6-11.0 years), with an estimated cumulative incidence of 8.1% (95% CI: 5.8%-10.3%) at 5 years and 20.0% (95% CI: 16.1%-23.8%) at 10 years.

LA PRESSURE, LA CONTRACTILE FUNCTION, AND RISK OF NOAF. Increased LA pressure was associated with increased risk of NOAF in both the univariable (HR: 3.02; 95% CI: 1.94-4.71; $P < 0.001$) and multivariable models (adjusted HR [aHR] 2.99; 95% CI: 1.87-4.79; $P < 0.001$). Whereas septal E/e′ ratio demonstrated a linear relationship with the risk of NOAF, LA contractile strain showed a U-shaped relationship (Figures 2A and 2B).

NOVEL LA STAGING SYSTEM. Based on these observations, we categorized patients into 4 stages: stage 1: normal LA pressure and contractile function; stage 2: straining LA, defined as relatively augmented LA contractile function for a given LA pressure; stage 3: failing LA, characterized by the loss of relative contractile augmentation despite increased LA pressure; and stage 4: overt LA failure, defined by decreased LA contractile function below the lower limit of normal with increased LA pressure. In addition, there was an indeterminate category characterized by isolated LA contractile dysfunction (Figure 2C). Relative compensatory augmentation of LA contractile function against a given LA pressure was defined as an LA contractile strain to septal E/e′ ratio over a specified cutoff, which was calculated as 0.96 with the use of maximally selected rank statistics. Accordingly, patients with a ratio above this threshold were categorized into stage 2, whereas those at or below it were categorized as stages 1 or 3, depending on their LA pressure (Figure 2C).

There were 131 patients (18.6%) in stage 1, 286 (40.6%) in stage 2, 181 (25.7%) in stage 3, and 77 (10.9%) in stage 4, and 30 (4.3%) had isolated LA contractile dysfunction. Baseline characteristics stratified by stage are presented in Table 1. There was

FIGURE 2 Risk of NOAF According to LA Pressure and Contractile Strain, and Staging Classification Proposal



(A) Restricted cubic spline curve showing the hazard ratio (solid line) with 95% CI (shaded area) for incident AF according to the continuous septal E/e′ ratio. (B) Restricted cubic spline curve showing the hazard ratio (solid line) with 95% CI (shaded area) for NOAF according to the continuous LA contractile strain. (C) Proposed staging system combining the presence of elevated LA pressure and LA contractile function. Elevated LA pressure was defined based on the most recent guidelines, ie, septal E/e′ ratio ≥15, peak tricuspid regurgitation velocity ≥2.8 m/s, or LA reservoir strain ≤18%. Stage 2 was defined as having relative compensatory augmentation of LA contractile function against a given LA pressure, which was defined as an LA contractile strain to septal E/e′ ratio over a specified cutoff of 0.96. Stages 1 and 3 were defined as not having this relatively augmented contractility, and stage 4 or isolated LA contractile dysfunction was defined as having LA contractile strain below the age- and sex-based lower limit of normal. LA = left atrium; NOAF = new-onset atrial fibrillation; Sct = contractile strain.

a stepwise increase in age across stages, and women were more prevalent in higher stages. Comorbidities, however, were similarly distributed, with the exception of a higher prevalence of hypertension in higher stages. Regarding echocardiographic parameters, there was no significant difference in LVEF. Maximal LV wall thickness, LV mass index, LVOT pressure gradient, LA cavity size and volume, E/e′ ratio, and TR velocity significantly increased with stage, but patients in stage 1 had modestly higher values for these indices and were more dyspneic than those in stage 2, with a higher proportion of obstructive phenotype. LA contractile strain, reservoir strain, and LA contractile strain to E/e′ ratio peaked at stage 2 and declined in subsequent stages, but LA conduit strain showed a stepwise decrease. Patients with isolated LA contractile dysfunction showed a mean age of 63.6 ± 10.9 years and were predominantly men. Although their overall echocardiographic profiles were similar to those of stages 1 and 2, they had a notably decreased LA contractile strain similarly to patients in stage 4.

PRIMARY OUTCOME. NOAF significantly and progressively increased with advancing stage (**Figure 3**, Supplemental Table 1). In both the univariable and multivariable analyses, patients in a higher stage had a significantly higher risk of NOAF (**Table 2**). The likelihood ratio test revealed no violation of the linear trend assumption ($P = 0.583$), and the aHR for NOAF was 1.83 (95% CI: 1.42-2.37; $P < 0.001$) per

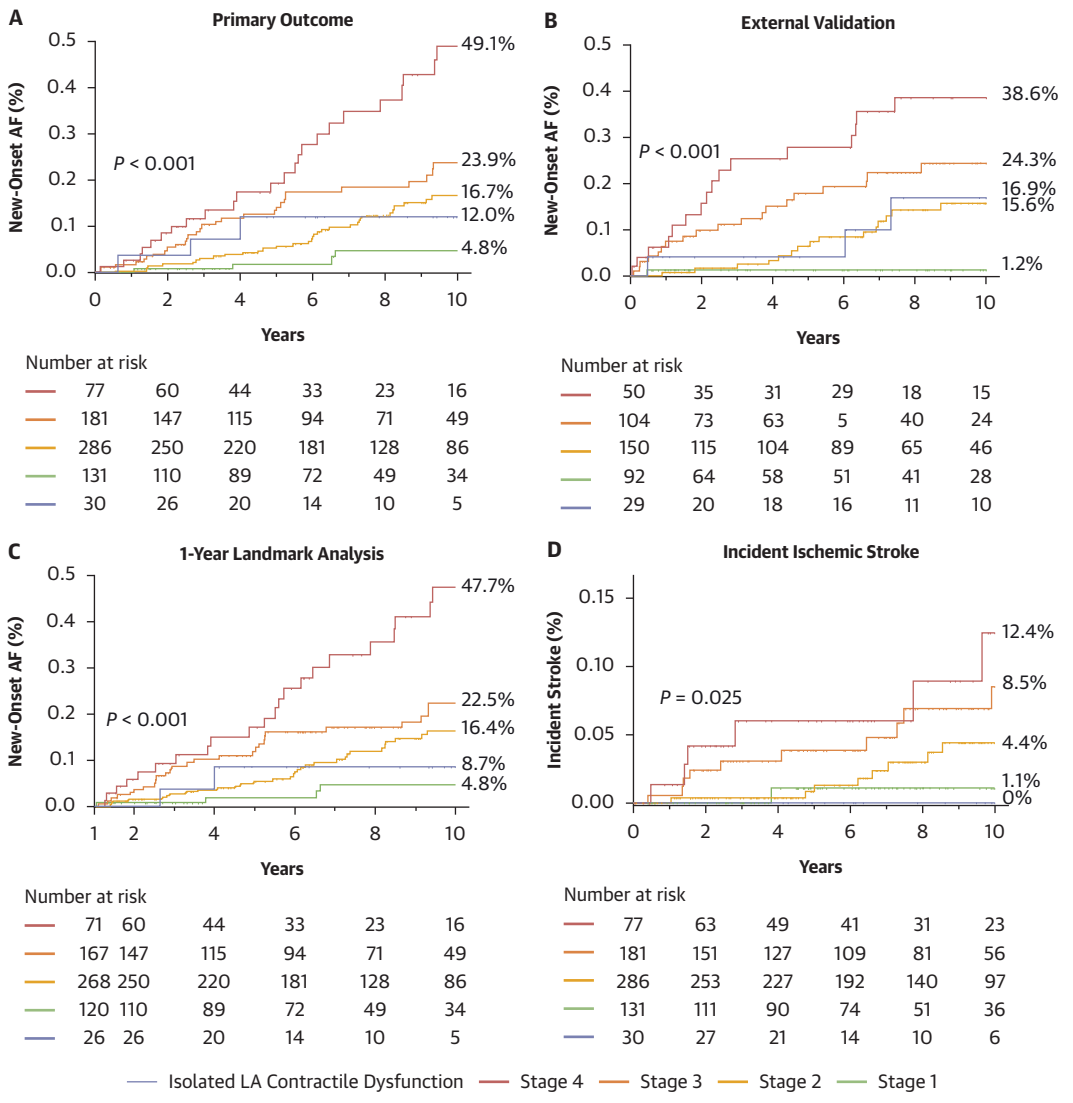
TABLE 1 Baseline Characteristics

	Stage 1 (n = 131)	Stage 2 (n = 286)	Stage 3 (n = 181)	Stage 4 (n = 77)	Isolated LA Contractile Dysfunction (n = 30)	*P* Value
Age, y	51.4 ± 13.2	56.0 ± 12.3	59.7 ± 12.0	66.5 ± 11.8	63.6 ± 10.9	<0.001
Men	95 (72.5)	240 (83.9)	102 (56.4)	34 (44.2)	22 (73.3)	<0.001
Obstructive HCM[a]	23 (17.6)	34 (12.0)	50 (27.6)	17 (22.4)	3 (10.0)	<0.001
Symptoms						
Dyspnea						<0.001
NYHA I	92 (70.8)	229 (80.4)	105 (59.3)	37 (48.1)	20 (69.0)	
NYHA II	34 (26.2)	55 (19.3)	62 (35.0)	33 (42.9)	9 (31.0)	
NYHA III	4 (3.1)	1 (0.4)	10 (5.6)	7 (9.1)	0 (0.0)	
Syncope	13 (9.9)	27 (9.4)	22 (12.2)	10 (13.0)	2 (6.7)	0.756
Chest pain	22 (27.8)	50 (26.3)	40 (34.2)	19 (43.2)	7 (36.8)	0.182
Nonsustained VT	18 (13.7)	29 (10.1)	24 (13.3)	19 (24.7)	9 (30.0)	0.002
Systolic BP, mm Hg	126.0 ± 15.6	127.5 ± 14.7	131.5 ± 18.4	125.3 ± 16.7	125.8 ± 14.2	0.010
Diastolic BP, mm Hg	73.8 ± 12.0	76.3 ± 10.1	76.4 ± 10.9	71.7 ± 9.9	75.8 ± 10.1	0.004
Heart rate, beats/min	68.2 ± 12.3	70.2 ± 11.6	68.3 ± 12.9	63.9 ± 11.0	65.8 ± 10.6	0.014
Body mass index, kg/m^2	24.8 ± 3.2	25.1 ± 2.9	25.4 ± 3.4	24.7 ± 3.6	24.2 ± 2.6	0.183
Comorbidities						
Hypertension	47 (35.9)	109 (38.1)	96 (53.0)	41 (53.2)	16 (53.3)	0.002
Diabetes mellitus	13 (9.9)	47 (16.4)	36 (19.9)	15 (19.5)	5 (16.7)	0.189
Dyslipidemia	30 (22.9)	78 (27.3)	44 (24.3)	19 (24.7)	11 (36.7)	0.556
Chronic kidney disease	2 (2.2)	7 (3.5)	6 (4.5)	1 (2.1)	2 (9.5)	0.519
Myocardial infarction	1 (0.8)	3 (1.0)	3 (1.7)	1 (1.3)	0 (0.0)	0.912
Previous stroke	4 (3.1)	13 (4.5)	9 (5.0)	5 (6.5)	3 (10.0)	0.530
Cancer	10 (7.6)	29 (10.1)	25 (13.8)	13 (16.9)	4 (13.3)	0.223
Smoking	36 (27.5)	86 (30.1)	34 (18.8)	12 (15.6)	8 (26.7)	0.019
Family history of HCM	9 (7.1)	24 (8.7)	9 (5.3)	6 (8.3)	1 (3.4)	0.631
Family history of SCD	16 (12.2)	31 (10.8)	11 (6.1)	7 (9.1)	2 (6.7)	0.345
Echocardiographic parameters						
LV ejection fraction, %	69.3 ± 3.8	69.3 ± 3.3	69.2 ± 3.7	68.9 ± 3.6	68.6 ± 4.0	0.781
LV end-diastolic diameter, mm	46.4 ± 5.4	46.6 ± 4.8	46.3 ± 4.8	45.9 ± 5.7	45.6 ± 4.7	0.736
LV end-systolic diameter, mm	25.9 ± 3.7	25.9 ± 3.1	25.8 ± 3.2	25.7 ± 3.6	25.8 ± 3.6	0.981
Maximal LV wall thickness, mm	18.3 ± 3.7	17.7 ± 3.7	19.0 ± 4.5	19.1 ± 3.5	18.9 ± 4.6	0.001
LV mass index, g/m^2	119.5 ± 35.6	113.3 ± 32.0	136.2 ± 44.7	133.6 ± 37.0	115.0 ± 41.8	<0.001
Maximal LVOT pressure gradient, mm Hg	15.3 ± 18.8	12.1 ± 19.3	31.2 ± 46.1	32.3 ± 49.5	10.4 ± 11.4	<0.001
LA size, mm	42.5 ± 5.6	41.4 ± 5.7	44.9 ± 6.0	46.8 ± 6.4	43.6 ± 5.3	<0.001
LA volume index, mL/m^2	39.7 ± 12.2	35.6 ± 10.2	47.7 ± 14.7	53.3 ± 16.6	40.8 ± 11.1	<0.001
E, m/s	0.59 ± 0.13	0.55 ± 0.15	0.68 ± 0.19	0.72 ± 0.21	0.60 ± 0.14	<0.001
A, m/s	0.61 ± 0.21	0.64 ± 0.17	0.76 ± 0.26	0.76 ± 0.29	0.63 ± 0.16	<0.001
Septal e′, cm/s	5.1 ± 1.5	5.4 ± 1.9	3.7 ± 1.3	4.1 ± 1.2	5.5 ± 1.2	<0.001
E/A	1.1 ± 0.5	0.9 ± 0.4	1.0 ± 0.5	1.1 ± 0.6	1.0 ± 0.4	0.001
Septal E/e′	11.5 ± 1.9	10.0 ± 2.9	19.2 ± 6.3	19.1 ± 7.6	10.9 ± 1.9	<0.001
Peak TR velocity, m/s	2.3 ± 0.3	2.2 ± 0.3	2.5 ± 0.3	2.6 ± 0.4	2.3 ± 0.2	<0.001
LA strain parameters						
LA reservoir strain, %	27.0 ± 5.2	33.0 ± 9.3	22.9 ± 7.0	17.2 ± 5.6	23.9 ± 4.6	<0.001
LA contractile strain, %	8.6 ± 2.3	15.3 ± 4.6	10.5 ± 3.9	4.7 ± 1.8	4.6 ± 1.9	<0.001
LA conduit strain, %	18.4 ± 5.4	17.7 ± 8.0	12.4 ± 5.8	12.5 ± 5.4	19.3 ± 5.0	<0.001
LA contractile strain to E/e′ ratio	0.8 ± 0.2	1.6 ± 0.6	0.6 ± 0.2	0.3 ± 0.2	0.4 ± 0.2	<0.001

Values are mean ± SD or n (%). [a]Obstructive physiology was defined as a maximal LVOT pressure gradient ≥30 mm Hg at rest or during the Valsalva maneuver.

BP = blood pressure; HCM = hypertrophic cardiomyopathy; LA = left atrium; LV = left ventricle; LVOT = left ventricular outflow tract; SCD = sudden cardiac death; TR = tricuspid regurgitation; VT = ventricular tachycardia.

FIGURE 3 Crude Kaplan-Meier Curves Regarding Primary and Secondary Outcomes According to the Stage



(A) New-onset AF. (B) New-onset AF in the external validation cohort. (C) 1-year landmark analysis for new-onset AF. (D) Incident ischemic stroke. AF = atrial fibrillation; LA = left atrium.

stage increase from stages 1 to 4. The risk of NOAF was numerically higher in patients with isolated LA contractile dysfunction, but it was not statistically significant. The results remained robust after additional adjustment for HCM-specific measures or rhythm-monitoring frequencies (Supplemental Table 2), and were consistent in both 1-year landmark analysis and competing risk analysis (**Figure 3C**, **Table 2**).

Adding the LA stage to the established risk models provided incremental predictive value for 10-year NOAF (for CHARGE-AF variables, C-statistic: 0.702-0.748 [ΔC 0.045; 95% CI: 0.013-0.087; $P = 0.008$]; for HCM-AF score variables, C-statistic: 0.765-0.791 [ΔC 0.026; 95% CI: 0.002-0.055; $P = 0.049$]). Detailed reclassification and discrimination metrics for both models are provided in Supplemental Table 3.

EXTERNAL VALIDATION. In the external validation cohort, 425 of 1,150 screened patients met the eligibility criteria. These patients had similar echocardiographic characteristics compared with the primary cohort, but were older (mean age 59.7 ± 13.5 y) and had more comorbidities, including hypertension (54.4% vs 43.8%), dyslipidemia (35.1% vs 25.8%), and

TABLE 2 Primary and Secondary Outcomes

	New-Onset Atrial Fibrillation				Ischemic Stroke			
	Unadjusted HR (95% CI)	*P* Value	Adjusted HR[a] (95% CI)	*P* Value	Unadjusted HR (95% CI)	*P* Value	Adjusted HR[b] (95% CI)	*P* Value
Primary analysis								
Stage 1	1 (reference)		1 (reference)		1 (reference)		1 (reference)	
Stage 2	2.98 (1.23-9.28)	0.013	2.52 (1.03-7.89)	0.042	2.21 (0.50-20.8)	0.328	1.91 (0.42-18.1)	0.438
Stage 3	5.02 (2.06-15.7)	<0.001	4.40 (1.77-13.9)	<0.001	4.72 (1.11-43.8)	0.034	3.90 (0.88-36.8)	0.076
Stage 4	10.3 (4.13-32.6)	<0.001	7.44 (2.83-24.3)	<0.001	7.33 (1.54-70.3)	0.011	5.55 (1.07-55.6)	0.041
Isolated LA contractile dysfunction	3.58 (0.80-14.7)	0.090	2.06 (0.45-8.70)	0.333	1.52 (0.01-28.6)	0.804	1.12 (0.01-21.8)	0.944
1-year landmark analysis								
Stage 1	1 (reference)		1 (reference)		1 (reference)		1 (reference)	
Stage 2	2.87 (1.18-8.94)	0.018	2.48 (1.01-7.79)	0.047	2.19 (0.49-20.6)	0.334	1.99 (0.44-18.9)	0.409
Stage 3	4.54 (1.85-14.2)	<0.001	4.05 (1.61-12.9)	0.002	4.26 (0.98-39.7)	0.053	3.44 (0.76-32.7)	0.118
Stage 4	9.58 (3.79-30.4)	<0.001	7.30 (2.74-24.1)	<0.001	6.23 (1.24-60.7)	0.025	4.73 (0.87-48.3)	0.074
Isolated LA contractile dysfunction	2.57 (0.45-11.6)	0.259	1.54 (0.26-7.16)	0.599	1.53 (0.01-28.7)	0.802	1.16 (0.01-22.5)	0.930
Competing risk analysis								
Stage 1	1 (reference)		1 (reference)		1 (reference)		1 (reference)	
Stage 2	3.12 (1.29-9.70)	0.010	2.71 (1.11-8.48)	0.027	2.27 (0.51-21.3)	0.312	2.04 (0.45-19.3)	0.389
Stage 3	4.99 (2.05-15.6)	<0.001	4.54 (1.83-14.3)	0.001	4.70 (1.11-43.6)	0.034	4.11 (0.94-38.6)	0.062
Stage 4	10.2 (4.08-32.2)	<0.001	7.80 (2.96-25.5)	<0.001	6.88 (1.45-66.0)	0.014	5.56 (1.08-55.7)	0.040
Isolated LA contractile dysfunction	3.41 (0.76-14.0)	0.102	2.04 (0.44-8.65)	0.340	1.44 (0.01-27.1)	0.827	1.02 (0.01-20.1)	0.990

[a]Risk of new-onset atrial fibrillation was adjusted for sex and variables in the CHARGE-AF: age, height, weight, systolic and diastolic blood pressure, current smoking, treatment for hypertension, diabetes, heart failure, and myocardial infarction. [b]Risk of incident ischemic stroke was adjusted for variables in the CHA_2DS_2-VASc score, including heart failure, hypertension, age, diabetes mellitus, previous stroke, vascular disease, and sex.

LA= left atrium.

myocardial infarction (5.6% vs 1.1%). The stepwise increase in age and the prevalence of comorbidities with advancing LA stages were similarly observed (Supplemental Table 4). During a median follow-up of 8.2 years (Q1-Q3: 3.9-11.4 years), NOAF occurred in 54 patients. The estimated cumulative incidence was 10.8% (95% CI: 7.3%-14.1%) at 5 years and 18.0% (95% CI: 13.4%-22.4%) at 10 years.

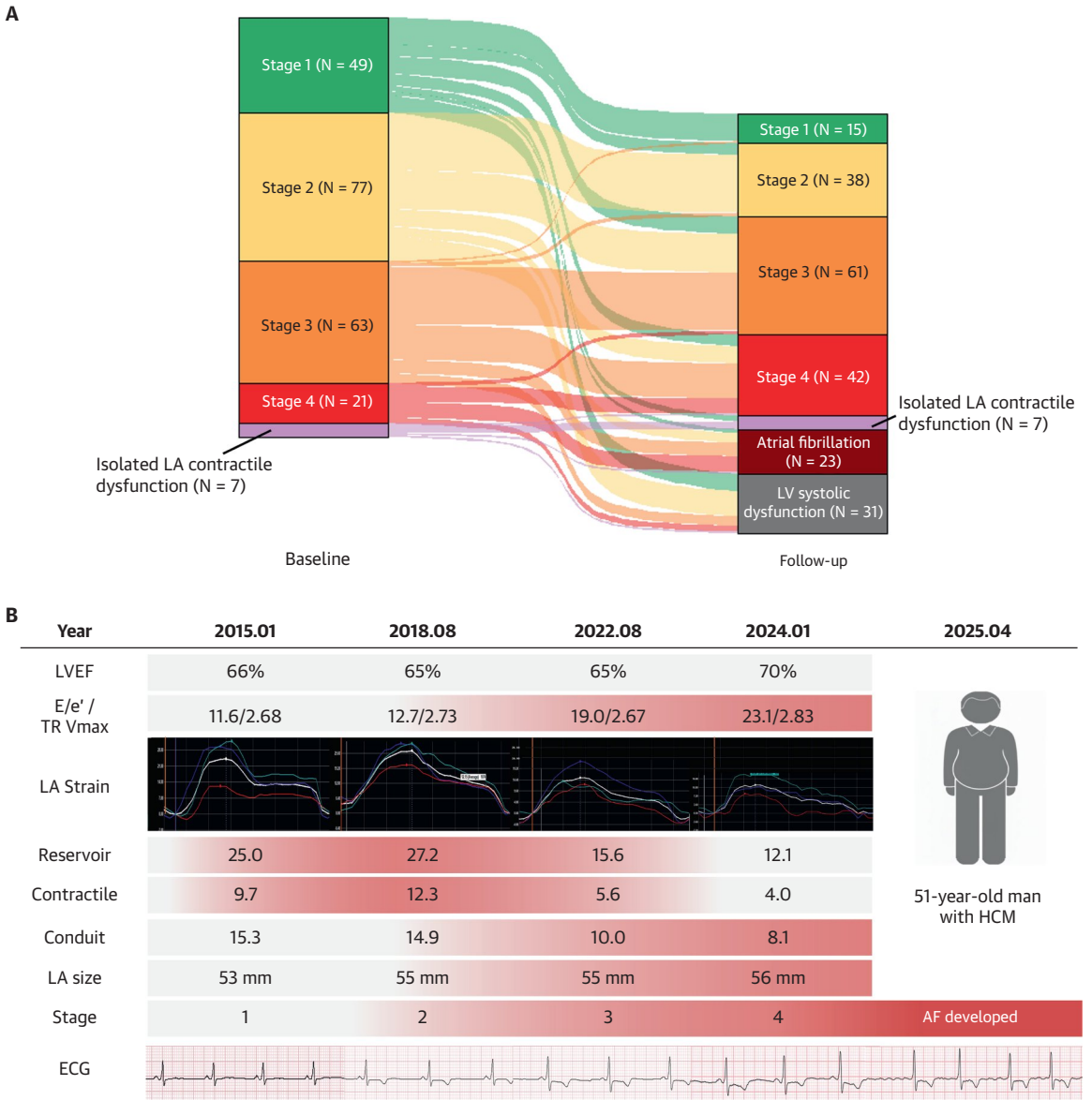
The results were consistent in the external validation cohort: Kaplan-Meier analysis revealed a clear hierarchic separation in the cumulative incidence of NOAF (**Figure 3B**), and the stage remained a significant predictor for NOAF after multivariable adjustment (aHR: 1.82 per stage increment; 95% CI: 1.33-2.50; $P < 0.001$) (Supplemental Table 5). Isolated LA contractile dysfunction group in this cohort was associated with a significant increase in the risk of NOAF (aHR: 6.20; 95% CI: 1.00-64.5; $P = 0.049$). Adding the LA stage to the established risk models also provided incremental predictive value in the external cohort (for CHARGE-AF variables, C-statistic 0.774-0.818 [ΔC 0.044; 95% CI: 0.016-0.078; $P = 0.007$]; for HCM-AF score variables, C-statistic: 0.806-0.833 [ΔC 0.027; 95% CI: 0.004-0.056; $P = 0.039$]) (Supplemental Table 3).

SECONDARY AND EXPLORATORY OUTCOMES. There was a stepwise increase in the cumulative incidence of ischemic stroke, and the risk significantly increased with advancing stage (aHR: 1.81; 95% CI: 1.13-2.95; $P = 0.014$ per stage increase from stages 1 to 4) (**Figure 3D**). However, with only 1 event (0.8%) occurring in stage 1, statistical significance in the categoric model was reached only at stage 4 (**Table 2**).

Kaplan-Meier curves were nearly identical for the initial 6 years across stages, although a trend toward higher late-term mortality appeared in advanced stages (Supplemental Figure 1). There was no significant association between stage and all-cause death (Supplemental Table 6).

LONGITUDINAL ANALYSIS. Given the stepwise increase in mean age of approximately 4 to 6 years per stage, longitudinal changes in LA stage were further assessed in 217 patients with available follow-up echocardiography performed during the corresponding time frame. This longitudinal assessment revealed that most patients either maintained (39.6%) or progressed to a higher stage or NOAF (43.8%), with 14.3% developing LV systolic dysfunction (**Figure 4A**). The longitudinal transition patterns did not differ according to stages, except for NOAF (Supplemental Table 7). Of note, a small number of patients moved between the main staging system and the isolated LA contractile dysfunction category during follow-up.

FIGURE 4 **Longitudinal Changes in LA Stage During Follow-Up and a Representative Real-World Example**

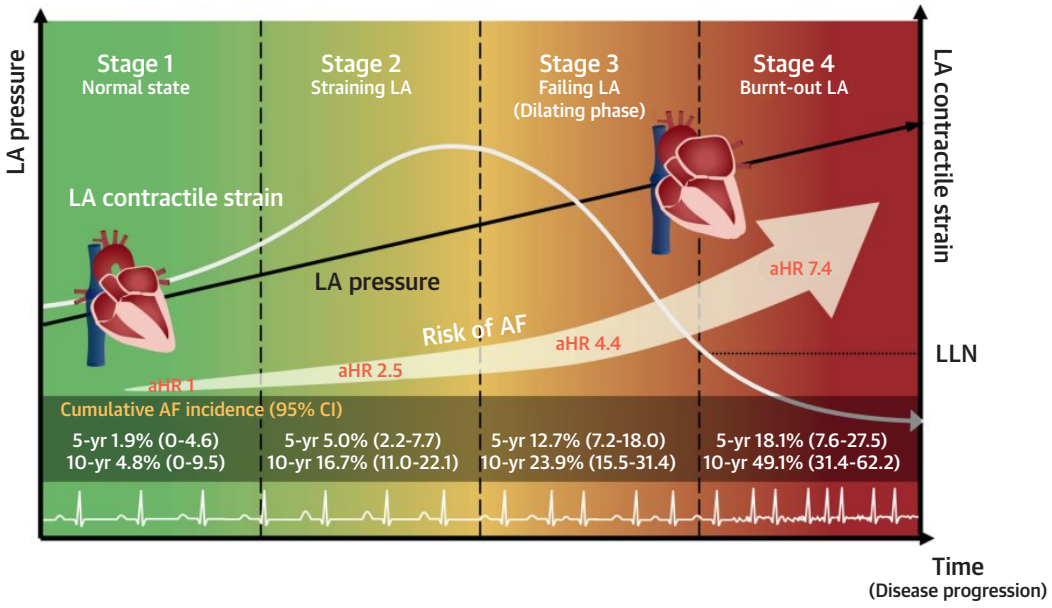


(A) Sankey diagram showing longitudinal changes in LA stage over 4-6 years. (B) Representative longitudinal case of a 51-year-old man with HCM who progressed through each stage and eventually developed AF. AF =atrial fibrillation; ECG = electrocardiography; HCM = hypertrophic cardiomyopathy; LA = left atrium; LV = left ventricle; LVEF = left ventricular ejection fraction; TR Vmax = peak tricuspid regurgitation velocity (m/s).

DISCUSSION

Drawing on a large multicenter cohort, the present study describes a physiologically intuitive classification system that reflects the progressive maladaptive evolution of the LA in HCM and carries prognostic implications. Results were consistent in both 1-year landmark and competing risk analyses, as well as in an external validation cohort. Furthermore, the staging system provided significant incremental predictive values when added to established risk models, including CHARGE-AF and HCM-AF.[15,20] A stepwise increase in mean age of approximately 4-6 years per stage was consistently observed in both primary and external validation cohorts, and the longitudinal analysis over this time frame revealed

CENTRAL ILLUSTRATION **The Proposed Staging System and Risk of New-Onset Atrial Fibrillation (AF) in Hypertrophic Cardiomyopathy**



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Patients are categorized into 4 stages based on the interplay between hemodynamic load (LA pressure) and intrinsic myocardial function (LA contractile strain). With the progressive rise in LA pressure, we propose an initial compensatory phase in which LA contractile function is augmented relative to the rising pressure (stage 2), followed by loss of this augmentation with LA enlargement (stage 3), and an eventual "burnt-out" phase of overt LA contractile failure (stage 4). Importantly, there was a stepwise increase in the cumulative incidence of new-onset atrial fibrillation across the stages. In addition, there was an indeterminate group of "isolated LA contractile dysfunction," characterized by impaired LA contractility despite normal loading conditions. aHR = adjusted hazard ratio; LA = left atrium; LLN = lower limit of normal (age- and sex-based).

that most patients remained stable or progressed to higher stages or AF, further supporting the sequential nature of the proposed LA staging system.

The present study aimed to develop a purely LA-specific staging framework, integrating LA pressure as a measure of hemodynamic load and LA contractile strain as a measure of intrinsic atrial function. Other LA strain parameters were not adopted, given that conduit strain primarily reflects LV diastolic properties, and reservoir strain, as a composite of conduit and contractile components, is confounded by this ventricular contribution.[23] Accordingly, this framework provides novel insights into the mechanical cascade of the LA in response to progressive LV diastolic dysfunction. **Figure 4B** provides a representative real-world longitudinal example of a patient who progressed sequentially through each stage to eventual AF. Beginning from a state of normal physiology (stage 1), we postulate that the LA first adapts to the rising pressure by mounting a compensatory hypercontractile response, delivering a forceful atrial kick against a hypertrophied, noncompliant LV (stage 2), potentially exceeding the anticipated rise in LA contractility according to the Frank-Starling mechanism.[24] This adaptive stage seems to be accompanied by a modest increase in LA reservoir strain as an adjunctive mechanism to further ensure adequate LV filling. The presence of this relatively augmented contractility is supported by previous observations.[13,16,25,26] Specifically, previous echocardiographic and cardiac magnetic resonance studies have demonstrated higher LA EF and contractile strain in patients with HCM than in those with heart failure with preserved ejection fraction (HFpEF).[25,26] Reduced LA contractility after septal reduction therapy for obstructive HCM further aligns with this observation.[16] Indeed, we have also reported a reduction in LA contractile strain following the unloading of LA pressure with mavacamten therapy in obstructive HCM, but this was exclusively observed in

patients with less-advanced LA damage.[13] This body of evidence led us to hypothesize a transitional stage of relatively augmented LA contraction against a given LA pressure, "straining LA" stage (stage 2), representing a finite compensatory response that precedes functional decline. When the LA can no longer sustain its compensatory response, it enters the "failing LA (dilating)" stage (stage 3), characterized by the loss of relatively augmented contractility with elevated LA pressure. In this stage, the compensatory strategy seems to shift toward LA enlargement to maintain LV filling. This maladaptive process eventually leads to a "burnt-out" LA where contractile function falls below the lower limit of normal (stage 4) with a more dilated LA (**Central Illustration**). Importantly, a similar transient increase in LA contractile (booster) strain during early diastolic dysfunction with later decrease with worsening diastolic dysfunction was independently observed in an American cohort of patients with preserved ejection fraction.[27]

Given that HCM serves as a prototypical model of severe, progressive LV diastolic impairment, the pathophysiologic adaptation of the LA elucidated in the present study may also be relevant to the growing population of patients with HFpEF. The higher proportion of women in advanced stages should also be noted, which may support previous observations regarding increased NOAF and ischemic stroke in women with HCM.[28,29] The nonsignificant association of the staging with all-cause mortality is consistent with its targeted utility as a specific predictor for NOAF. Notably, a small subset exhibited isolated LA contractile dysfunction without significant increase in LA pressure. This phenotype may reflect intrinsic atrial myopathy independent of hemodynamic-driven remodeling, potentially linked to underlying genetic or microvascular factors.[30,31] If this represents an independent LA-selective process, some patients within the pressure-driven stages of evolving atrial myopathy may also be affected. However, given the small sample size and inconsistent associations of that group with NOAF across cohorts, that category should be considered as exploratory and warrants further investigation with genetic and histologic correlation.

The proactive stance of the 2024 American guidelines on AF surveillance in HCM is a welcome development.[10] Here, annual or biennial follow-up for 12-lead ECG and extended ambulatory monitoring for patients deemed to be at high risk for developing AF is recommended. However, there is a paucity of evidence on how to stratify that risk. We think that the present study addresses this gap. One of the notable findings is a very low incidence of NOAF in stage 1. This may justify de-escalation of surveillance for these patients, while simultaneously allowing resources to be allocated to higher risk patients. Conversely, a strikingly high AF incidence (~5%/year) in stage 4 is notable and may warrant closer and more sustained monitoring in those patients. Equally noteworthy is the approximately 1% annual stroke incidence in stages 3-4, a rate that approaches the threshold for considering anticoagulation in patients with overt AF.[21,32]

STUDY LIMITATIONS. This study has several limitations. First, the data were analyzed retrospectively in a predominantly Asian cohort. Although similar LA physiology, particularly a state of augmented contractility, appears in previous Western studies,[16,27] the present study should be viewed as a physiologically grounded framework rather than confirmation of a set of precise numeric thresholds which therefore requires prospective multiethnic validation. Second, the study was limited to patients with normal LVEF.[33] However, this was an intentional approach to establish a pure pathophysiologic model of LA adaptation to progressive diastolic dysfunction and the resultant LA pressure overload, without the confounding effects of advanced disease stages. Indeed, even patients with low-normal LVEF typically present with established moderate to severe LV diastolic dysfunction, marked LA dilation, and spontaneous reduction or loss of dynamic LVOT obstruction with substantial LV fibrosis.[33,34] Whether this staging system remains applicable or requires specific recalibration for patients with low-normal LVEF or end-stage HCM remains to be elucidated in future studies. Third, a small number of patients exhibited minor backward transitions on follow-up; however, these were considered to lie within the expected measurement variability of LA strain analysis. Finally, we censored patients at the time of septal reduction therapy or initiation of cardiac myosin inhibitor, because the study was designed to focus on the natural changes in LA function and hemodynamics as not interfered by any interventions.[13,16-19] How this novel LA staging system interacts with those interventions will be a critical area for future research.

CONCLUSIONS

We propose a novel LA staging system in HCM that characterizes the adaptation of the LA against LA pressure and carries prognostic significance regarding NOAF. Further studies are warranted to prospectively validate this classification and to

explore how it could tailor AF screening strategies in this highly vulnerable population.

DATA AVAILABILITY De-identified participant data supporting the findings of this study will be available from the corresponding authors on reasonable request, following approval from the Institutional Review Boards of the participating centers.

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ADDRESS FOR CORRESPONDENCE: Dr Hyung-Kwan Kim, Section of Cardiovascular Imaging, Division of Cardiology, Cardiovascular Center, Department of Internal Medicine, Seoul National University Hospital, Seoul National University College of Medicine, 101 Daehak-ro, Jongno-gu, Seoul 03080, Republic of Korea. E-mail: hkkim73@snu.ac.kr OR cardiman73@gmail.com. OR Dr Sang-Chol Lee, Division of Cardiology, Department of Medicine, Samsung Medical Centre, Heart Vascular Stroke Institute, Sungkyunkwan University School of Medicine, 81, Irwon-ro, Gangnam-gu, Seoul 06351, Republic of Korea. E-mail: chrislee.echo@gmail.com.

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APPENDIX For supplemental tables and a figure, please see the online version of this paper.