Korean Circ J. 2025 Nov;55(11):1001-1013
https://doi.org/10.4070/kcj.2025.0048
pISSN 1738-5520·eISSN 1738-5555

kcj
Korean Circulation Journal

Original Research

Check for updates

Age-Dependent Role of Genetics and Renal Function for Atrial Fibrillation Development in Hypertrophic Cardiomyopathy

Hyemoon Chung, MD, PhD[1], Yoonjung Kim, MD, PhD[2], Jiwon Seo, MD[3], In-Soo Kim, MD[3], Sungsoo Cho, MD, PhD[3], Chul-Hwan Park, MD, PhD[4], Tae Hoon Kim, MD, PhD[4], Se-Joong Rim, MD, PhD[3], Kyung-A Lee, MD, PhD[2], and Eui-Young Choi, MD, PhD[3]

[1]Division of Cardiology, Department of Internal Medicine, Kyung Hee University School of Medicine, Seoul, Korea
[2]Department of Laboratory Medicine, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Korea
[3]Division of Cardiology, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Korea
[4]Department of Radiology, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Korea

OPEN ACCESS

Received: Feb 5, 2025
Revised: Apr 8, 2025
Accepted: Apr 29, 2025
Published online: Jun 16, 2025

Correspondence to
Eui-Young Choi, MD, PhD
Division of Cardiology, Heart Center, Gangnam Severance Hospital, Yonsei University College of Medicine, 211, Eonju-ro, Gangnam-gu, Seoul 06273, Korea.
Email: choi0928@yuhs.ac

ORCID iDs
Hyemoon Chung
https://orcid.org/0000-0002-5615-6245
Yoonjung Kim
https://orcid.org/0000-0002-4370-4265
Jiwon Seo
https://orcid.org/0000-0002-7641-3739
In-Soo Kim
https://orcid.org/0000-0003-2801-5514
Sungsoo Cho
https://orcid.org/0000-0003-2059-1584
Chul-Hwan Park
https://orcid.org/0000-0002-0004-9475
Tae Hoon Kim
https://orcid.org/0000-0003-3598-2529
Se-Joong Rim
https://orcid.org/0000-0002-7631-5581

AUTHOR'S SUMMARY

In patients with hypertrophic cardiomyopathy (HCM), lower estimated glomerular filtration rate and increased left atrial volume index were linked to future atrial fibrillation (AF), with impaired renal function independently contributing to AF, especially in patients aged 65 and older. Thus, intensive electrocardiographic (ECG) monitoring is recommended for this group. In patients under 65, the presence of sarcomere pathogenic, likely pathogenic variants, or variants of uncertain significance (VUS) also correlated with AF. Recognizing sarcomere VUS is important, and these younger patients similarly require close ECG monitoring. These findings highlight the role of genetic and structural factors in AF development in HCM.

ABSTRACT

Background and Objectives: The objective of this study was to investigate whether genetic, structural, and clinical factors were associated with atrial fibrillation (AF) in patients with hypertrophic cardiomyopathy (HCM).
Methods: Of the 212 prospectively enrolled patients in the HCM genetic registry, 33 had initial AF, and the remaining 179 (126 males, 58±13 years) were followed up for the development of new-onset AF.
Results: Patients with initial AF had older age, lower estimated glomerular filtration rate (eGFR), lower left ventricular (LV) global longitudinal strain, higher left atrial volume index (LAVI), and higher LV extracellular volume fraction. During a median follow-up period of 916 (400–1,327) days, AF occurred in 12 (6.7%) patients. In Cox regression analysis, lower eGFR (hazard ratio per 1 mL/min/1.73 m^2 increase, 0.93; p=0.007), LV ejection fraction (hazard ratio, 0.82; p=0.009), and higher LAVI (hazard ratio, 1.07; p=0.010) were associated with increased risk of future AF. The addition of eGFR to LAVI significantly increased the global χ^2 value (8.508 to 15.017; p=0.006). Among patients younger than 65 years (n=128), those with

Kyung-A Lee
https://orcid.org/0000-0003-3598-2529
Eui-Young Choi
https://orcid.org/0000-0003-3732-0190

Funding
This work was supported by the Basic Science Research Program through the National Research Foundation of Korea (NRF), funded by the Ministry of Education (2014R1A1A2055872).

Conflict of Interest
The authors have no financial conflicts of interest.

Data Sharing Statement
The data generated in this study is available from the corresponding authors upon reasonable request.

Author Contributions
Conceptualization: Chung H, Kim Y, Kim IS, Park CH, Lee KA, Choi EY; Data curation: Chung H, Kim Y, Lee KA, Choi EY; Formal analysis: Chung H, Kim Y, Park CH, Lee KA, Choi EY; Investigation: Chung H, Seo J, Kim TH, Rim SJ, Lee KA, Choi EY; Methodology: Chung H, Seo J, Kim IS, Cho S, Park CH, Kim TH, Rim SJ, Lee KA, Choi EY; Project administration: Cho S, Kim TH, Rim SJ, Choi EY; Resources: Choi EY; Software: Seo J, Choi EY; Supervision: Cho S, Choi EY; Validation: Choi EY; Writing - original draft: Chung H, Choi EY; Writing - review & editing: Choi EY.

any sarcomere variants (pathogenic and variants of uncertain significance [VUS], n=77) had a higher prevalence of overall AF (initial and new-onset, 82.4% vs. 56.8%; p=0.045).
Conclusions: In patients with HCM, decreased renal function provides an additive predictive value on LAVI for future AF. In patients younger than 65, the presence of sarcomere variants, including VUS, is related to a higher prevalence of AF.

Keywords: Atrial fibrillation; Hypertrophic cardiomyopathy; Genetics; Renal insufficiency; Left atrium

INTRODUCTION

Atrial fibrillation (AF) is a common arrhythmia associated with adverse cardiovascular events in patients with hypertrophic cardiomyopathy (HCM).[1-3] AF increases the risk of stroke and heart failure (HF) in patients with HCM.[2] The prognosis of HCM has significantly improved with the introduction of implantable cardioverter defibrillators and risk stratification models.[4] As a result, the age of HCM patients is increasing, making the development of AF a critical prognostic factor due to its association with HF and ischemic stroke.[3] In this context, renal function plays a crucial role in the development of HF with preserved ejection fraction (EF) and AF in the general population.[5][6] Thus, assessing the relevance of renal function for HCM patients is essential. Owing to the high thromboembolic risk of HCM, current guidelines recommend anticoagulation in patients with HCM and AF, regardless of the CHA2DS2-VASc score.[4] Therefore, early detection of AF is important in HCM. Current guidelines recommend 24-hour ambulatory (Holter) electrocardiographic (ECG) monitoring be repeated every 1–2 years, as well as at the first diagnosis of HCM. An annual 12-lead ECG is recommended for the evaluation of asymptomatic arrhythmias such as conduction delay and silent AF.[4] However, 12-lead ECGs are limited with regard to the evaluation of hidden AF. Selecting patients at high risk of developing AF and performing more intensive monitoring are necessary. The prevalence of AF increases with age, particularly in patients with chronic kidney disease (CKD).[6] AF is more prevalent even in the early stages of CKD compared with non-CKD populations.[5][7] Renal function can indirectly contribute to the development of AF through several mechanisms, such as volume overload and activation of the renin-angiotensin system (RAS) in HCM.[8] However, whether renal function contributes to future AF independent of age in patients with HCM has not been clearly investigated. Controversies exist with regard to the genetic contribution to the development of AF.[1][9] A previous genetic registry-based study showed that the development of AF was associated with pathogenic sarcomere mutations, particularly in young patients with HCM.[9] Sarcomere mutation was independently related to left atrial (LA) dysfunction, suggesting LA intrinsic myopathy.[10] However, other studies did not find any significant relationship between sarcomere mutations and new-onset AF.[1] Previous large-scale studies have focused primarily on major validated pathogenic variants.[9] However, recent research indicates that the phenotype of HCM is not solely due to single pathogenic mutations but rather involves a multigenic contribution, including rare variants and variants of uncertain significance (VUS), as well as interactions with combined clinical and structural risk factors such as hypertension, diabetes, renal function, and LA size.[11-13] Therefore, in this study, we aimed to investigate whether 1) clinical factors, including renal function; 2) extensive genetic test results, including VUS of sarcomere and other associated genes such as phenocopy and mitochondria related genes; and 3) left ventricular (LV) and LA structural and functional parameters were associated with overall and new-onset AF in patients with HCM.

kcj
Korean Circulation Journal

METHODS

Ethical statement

The study protocol conformed to the ethical guidelines of the Declaration of Helsinki (2013) and was approved by the Institutional Review Boards of Gangnam Severance Hospital (3-2015-0019). Written informed consent was obtained from each patient.

Study population

A total of 432 patients were enrolled in the HCM registry (HCMR) in a tertiary referral center that receives patients from private clinics, general hospitals, surgical departments following preoperative cardiac evaluations, and consultations from other medical departments between 2006 and 2019. Among them, 220 patients were excluded because of insufficient data, insufficient follow-up period, loss of follow-up, or refusal to consent for genetic study enrolment. Consecutive patients over 18 years old, diagnosed with HCM via echocardiography, and who agreed to participate in the genetic study were enrolled, whether they were in an outpatient clinic or hospitalized. The patients enrolled in the study had a maximal LV hypertrophy of >13 mm without an underlying cause of hypertrophy, such as uncontrolled hypertension, aortic stenosis, or metabolic diseases. Among the 212 patients, 105 were newly diagnosed with HCM at the time of the genetic test. The decision to perform cardiac magnetic resonance (CMR) was made by designated doctors for patients diagnosed with HCM. All patients underwent screening for Fabry disease and were confirmed to be negative for the galactosidase alpha variant.[11] We also performed phenocopy gene analysis for differential diagnosis of thickened myocardium.

Collection of clinical, biochemical, and electrocardiographic data

Using the HCMR database of our institution, we obtained demographic, clinical, and biochemical data of patients with HCM at the time of enrollment. Data on age, sex, blood pressure, and body mass index were retrieved, and baseline data were considered. Baseline ECG and Holter monitoring data were also reviewed. All the laboratory analyses were performed at our institution. The estimated glomerular filtration rate (eGFR, mL/min/1.73 m^2) was calculated using the CKD Epidemiology Collaboration 2021 formula equation.[14] For the development of new-onset AF, follow-up conventional ECG or 24-hour Holter monitoring was reviewed after the initial genetic study enrollment. The primary endpoint was a composite of new-onset AF occurrences (paroxysmal, persistent, or permanent) during follow-up. Follow-up information was collected every 6 months by a study coordinator through medical record reviews. If patients did not visit the hospital, the study coordinator conducted telephone contact, since this study relied on medical records.

Conventional echocardiography and speckle tracking echocardiography

Comprehensive echo-Doppler evaluation was performed according to the current guideline.[15] The E/e′ × LA volume was used to measure the diastolic mitral valve wall stress index from the LA side. Two-dimensional speckle tracking analysis was performed using the TomTec 2D Cardiac Performance Analysis program (TOMTEC Imaging Systems GmbH, Munich, Germany). The details are described in **Supplementary Data 1**.

Cardiac magnetic resonance imaging

CMR imaging was performed using a 1.5-T scanner (Magnetom Avanto; Siemens Medical Solutions, Erlangen, Germany) with a phased-array body coil. Details are described in **Supplementary Data 2**. The presence, patterns, and percentage of late gadolinium

https://doi.org/10.4070/kcj.2025.0048

enhancement (LGE) in the LV mass were measured using dedicated quantitative analysis software (QmassMR 7.5 or 8.1; Medis Medical Imaging, Leiden, The Netherlands) with phase-sensitive inversion recovery. To improve reproducibility, a radiologist and cardiologist with more than 10 years of experience analyzed the LGE sizes. In each short-axis slice image, the boundaries of the contrast-enhanced areas were automatically traced. On LGE-CMR images, the myocardium exhibiting abnormal enhancement was defined as an area of hyperenhancement exceeding 5 standard deviations from the remote myocardium. The remote myocardium was defined as a non-enhanced myocardium, in contrast to the hyperenhanced myocardium. The maximum signal was determined using computer-assisted window thresholding of the enhanced area. Obvious artifacts, such as those caused by motion, were excluded using software tools. The total LGE volume was calculated by summing the LGE volumes of all slices. Native T1 mapping with a modified look-locker technique was performed during the mid-diastolic phase, and post-T1 mapping was performed 15 minutes after contrast medium injection using the same slice axis and parameters as pre-T1 mapping. Native T1, post-T1, and extracellular volume fraction (ECV) analyses were performed using QMap and QECV-RE (Medis Medical Imaging). The myocardial ECV was automatically calculated with the following equation[16]:

$$\text{ECV} = (\Delta R1 \text{ of Myocardium} / \Delta R1 \text{ of LV Blood Pool}) \times (1 - \text{Hematocrit}),$$
$$\text{Where } R1 = 1/T1 \text{ and } \Delta R1 = \text{Post-contrast } R1 - \text{Pre-contrast } R1$$

Hypertrophic cardiomyopathy gene panel design and data analysis

A literature search of the PubMed database was performed to select targeted genes for a comprehensive HCM-specific panel. It included 82 nDNA genes (33 sarcomere protein genes, 6 phenocopy genes, and 44 nuclear genes linked to mitochondrial cardiomyopathy) (**Supplementary Figure 1**).[10] The sarcomere-related HCM gene panel consisted of 8 validated sarcomere genes and 25 putative HCM genes.[17] We divided the sarcomere genes into 2 subgroups: thick filament genes (*MYH7*, *MYBPC3*, *MYH6*, and *MYL3*) and thin filament genes (sarcomere genes other than thick filament genes). Pathogenicity was defined according to the 2015 American College of Medical Genetics and Genomics (ACMG) guidelines. Targeted mitochondria-related nDNA and mtDNA analyses were also performed. The detailed process of DNA preparation and data analysis of the HCM gene panel is described in **Supplementary Data 3**.

Statistical analysis

Continuous variables with normal distributions are reported as mean ± standard deviation or 95% confidence interval. Student's t-test was used to compare the means of continuous variables that were approximately normally distributed between the 2 groups. Normality was determined using the Shapiro-Wilk test. Comparisons of continuous variables without normal distribution were performed by the Mann-Whitney U test. Categorical variables are reported as counts (or percentages) and were compared using the χ^2 test.

To predict new-onset AF, Cox proportional hazards regression analysis was performed for multivariate adjustment. Since no patients died during the follow-up period, conventional survival analysis was performed rather than competing risk analysis. Variables with $p<0.05$ in univariate analysis were included with the enter method in multivariable analysis. To avoid the effects of collinearity between variables, the variance inflation factor (VIF) was measured. Among the variables with high VIF, only the most significant variable was included in the multivariate analysis. To identify the incremental value in the prediction of new AF,

https://doi.org/10.4070/kcj.2025.0048

the global χ^2 value at each step was compared. At each step, a p value<0.05 was taken as the required level of significance for entering a variable into the model. Therefore, 2 models were designed: 1) model I: LA volume index (LAVI) and 2) model II: LAVI + eGFR. All clinical statistical analyses were performed using SPSS (version 27.0; IBM Corp., Armonk, NY, USA). A 2-sided p value of <0.05 was considered to be statistically significant.

RESULTS

Baseline characteristics

Of the 212 patients enrolled in the HCM genetic registry, 33 were diagnosed with AF. Baseline characteristics of the 2 groups according to the presence of AF are shown in **Table 1**. Patients with initial AF were older (67.2±11.9 vs. 57.7±13.4 years; p<0.001) and had a lower eGFR (78.0±21.1 vs. 93.9±17.3 mL/min/1.73 m^2; p<0.001). They had a higher prevalence of non-sustained ventricular tachycardia (35.3% vs. 11.2%, p=0.018), a higher LAVI (53.5±25.4 vs. 33.8±13.9 mL/m^2; p<0.001), higher right ventricular (RV) systolic pressure (34.4±8.4 vs. 26.8±7.5 mmHg, p<0.001), and lower LV global longitudinal strain (GLS) (–11.7±4.0 vs. –15.0±4.0%; p<0.001) compared to patients without initial AF. In CMR imaging analysis (n=133), patients with initial AF had a higher LV ECV (35.1±4.7 vs. 31.7±4.5%; p=0.003), lower RV GLS (–22.3±7.3 vs. –28.1±8.0%; p=0.003), and lower total LA emptying fraction and reservoir function (all p<0.001) (**Supplementary Table 1**).

Factors associated with new-onset atrial fibrillation

Of the 179 patients who were not diagnosed with AF at the time of enrolment, AF occurred in 12 (6.7%) patients during a median 916 (400–1,327) days (**Supplementary Figure 2**). Of the 12 patients with new-onset AF, 5 were classified as having paroxysmal AF, and 7 as having persistent AF. Patients with new-onset AF (n=12) had increased creatinine levels (1.02±0.17 vs. 0.85±0.20 mg/dL; p=0.004); lower eGFR (79.0±13.8 vs. 95.1±17.0 mL/min/1.73 m^2; p=0.002) and late diastolic mitral annular velocity (a′, 6.2±1.8 vs. 7.7±1.9 cm/s; p=0.010); and a larger LAVI (52.1±23.2 vs. 32.4±12.1 mL/m^2; p=0.014), LV end-diastolic volume (EDV) (88.3±34.7 vs. 68.3±23.2 mL; p=0.006), and LV end-systolic volume (ESV) (32.9±12.3 vs. 23.5±9.7 mL; p=0.002), compared with those of patients who did not develop AF (n=167). The 5-year sudden cardiac death risk score was higher in patients with AF than in patients without AF (4.1±2.1 vs. 2.2±1.7%; p=0.021) (**Table 2**). In CMR with ECV imaging analysis (n=113), patients with new-onset AF (n=5) had a higher initial LV ECV (36.4% [35.5–41.5%] vs. 31.8% [28.6–35.0%]; p=0.020) than others. In univariate Cox regression analysis, lower eGFR, LV EF, a′, and systolic mitral annular velocity, and increased LV EDV, LV-ESV, and LAVI were associated with new-onset AF (all p<0.05). Multivariate Cox regression analysis showed that lower eGFR (hazard ratio [HR] per 1 mL/min/1.73 m^2 increase, 0.93; p=0.007), LVEF (HR, 0.82; p=0.009) and increased LAVI (HR, 1.07; p=0.010) were independently associated with an increased risk of future AF (**Table 3**). The addition of eGFR to LAVI significantly increased the global χ^2 value (8.508 to 15.017; p=0.006).

Association between genotypes and overall atrial fibrillation

Based on the ACMG guidelines,[18] 67 of 212 (31.6%) cases had 71 pathogenic or likely pathogenic variants in 33 sarcomere-associated genes (33 *MYBPC3*, 19 *MYH7*, 14 *TNNI3*, 2 *MYH6*, 1 *JPH2*, 1 *TNNC1*, and 1 *MYL3*). Of the 212 patients, 45 were diagnosed with AF before the final follow-up visit. Pathogenic and likely pathogenic sarcomere variants were detected in 29.3% (49/167) of patients without AF and 40.0% (18/45) of patients with AF, without

kcj
Korean Circulation Journal

Table 1. Baseline characteristics according to the presence of initial AF

Characteristics	Total (n=212)	No AF (n=179)	AF (n=33)	p value
Age (years)	59.2±13.6	57.7±13.4	67.2±11.9	<0.001
Male	149 (70.3)	126 (70.4)	23 (69.7)	0.936
Hypertension	119 (56.1)	96 (53.6)	23 (69.7)	0.087
Diabetes	39 (18.4)	31 (17.3)	8 (24.2)	0.346
eGFR (mL/min/1.73 m^2)	91.2±18.9	93.9±17.3	78.0±21.1	<0.001
BUN (mg/dL)	16.4±4.9	16.0±4.8	18.2±5.4	0.036
Creatinine (mg/dL)	0.91±0.37	0.87±0.20	1.10±0.75	0.001
FHx of SCD-1st	15 (7.1)	11 (6.1)	4 (12.1)	0.219
FHx of SCD-2nd	13 (6.1)	12 (6.7)	1 (3.0)	0.419
NSVT*	18 (14.5)	12 (11.2)	6 (35.3)	0.018
5-year SCD risk (%)*	2.25±1.63	2.18±1.64	2.66±1.54	0.253
ACEi use	9 (4)	6 (3)	3 (9)	0.133
ARB use	98 (46)	73 (41)	25 (76)	<0.001
BB use	139 (66)	122 (68)	17 (52)	0.064
CCB use	73 (34)	59 (33)	14 (42)	0.293
P/LP sarcomere variants	67 (31.6)	55 (30.7)	12 (36.4)	0.545
P/LP thick filament variants	52 (24.5)	45 (25.1)	7 (21.2)	0.142
P/LP thin filament or regulatory variants	15 (7.1)	10 (5.6)	5 (15.2)	
Echocardiographic analysis				
Apical HCM	101 (47.6)	86 (48.0)	15 (45.5)	0.784
Maximal wall thickness (mm)	18.9±3.5	19.0±3.6	18.5±3.2	0.418
LVOT or mid-LV obstruction	49 (23.1)	46 (25.7)	3 (9.1)	0.038
Peak trans-LVOT or mid-LV PG (mmHg)	20.5±30.6	22.1±31.9	12.1±21.0	0.084
LV EDV (mL)	67.8±24.1	69.6±24.5	59.4±21.3	0.026
LV ESV (mL)	23.8±10.0	24.2±10.1	22.2±9.2	0.299
LAV (mL)	64.6±29.8	59.2±22.1	93.8±45.8	<0.001
LAVI (mL/m^2)	36.8±17.7	33.8±13.9	53.5±25.4	<0.001
MR ≥ moderate grade	3 (1.4)	2 (1.1)	1 (3.0)	0.401
LVEF (%)	64.6±6.4	65.1±5.5	61.9±9.5	0.065
E (cm/s)	69.4±19.8	67.8±19.6	77.9±18.6	0.007
DT (ms)	210.2±57.4	215.5±57.3	179.9±48.1	0.001
e′ (cm/s)	5.1±1.7	5.0±1.7	5.5±1.6	0.095
s′ (cm/s)	6.8±1.7	7.0±1.6	5.4±1.7	<0.001
E/e′	14.9±5.9	14.8±5.8	15.5±6.4	0.550
LV-GLS (%)	−14.5±4.2	−15.0±4.0	−11.7±4.0	<0.001
RVSP (mmHg)	28.1±8.2	26.8±7.5	34.4±8.4	<0.001
LAWS (1/mL)	999.5±638.7	924.4±606.4	1,407.4±664.1	<0.001

Values are presented as number (%) or mean ± standard deviation.
ACEi = angiotensin converting enzyme inhibitor; AF = atrial fibrillation; ARB = angiotensin II receptor blocker; BB = beta blocker; CCB = calcium channel blocker; DT = deceleration time; E = early transmitral inflow peak velocity; e′ = early diastolic mitral annular velocity; EDV = end-diastolic volume; eGFR = estimated glomerular filtration rate; ESV = end-systolic volume; FHx = family history; GLS = global longitudinal strain; HCM = hypertrophic cardiomyopathy; LAV = left atrial volume; LAVI = left atrial volume index; LAWS = left atrial wall stress; LV = left ventricular; LVEF = left ventricular ejection fraction; LVOT = left ventricular outflow tract; MR = mitral regurgitation; P/LP = pathogenic/likely pathogenic; PG = pressure gradient; RVSP = right ventricular systolic pressure; SCD-1st = sudden cardiac death of 1st-degree family; SCD-2nd = sudden cardiac death of 2nd-degree family.
*Analysis of 123 patients who underwent the 24-hour Holter test; 17 and 106 patients with or without atrial fibrillation, respectively.

significant differences. *MYH6* was more prevalent in the AF group (2/45, 4.4%) than in the non-AF group (0/167, p=0.044), and *TNNI3* tended to be more prevalent in the AF group (6/45, 13.3%) than in the non-AF group (8/167, 4.8%) (p=0.051) (**Supplementary Table 2**). With the addition of sarcomere VUS (19 *OBSCN*, 10 *MYH7*, 9 *MYBPC3*, 9 *TTN*, 8 *RYR2*, 6 *MYOM1*, 5 *MYH6*, 4 *ACTN2,* 3 *MYO6,* 3 *VCL*, 2 *BAG*, 2 *CSRP3*, 2 *FHL1*, 2 *LDB3*, 2 *MYPN*, 2 *TPM1*, 1 *ACTC1*, 1 *ANKRD1*, 1 *MYOZ2*, 1 *NEXN*, 1 *TCAP*, and 1 *TNNC1*), 119 patients had sarcomere variants. The prevalence of overall AF (initial and new-onset) was not different between patients with any sarcomere variants (including pathogenic, likely pathogenic, and VUS, n=29/119, 24.4%) and those without sarcomere variants (n=16/93, 17.2%, p=0.205). However, in patients younger than 65 years (n=128), those with any sarcomere variants, including VUS (n=77, 60.2%), had a higher prevalence of overall AF (14/77 [18.2%] vs. 3/51 [5.9%];

https://doi.org/10.4070/kcj.2025.0048

Table 2. Baseline characteristics according to the new-onset AF among patients without initial AF

Characteristics	No AF (n=167)	New AF (n=12)	p value
Age (years)	57±14	61±9	0.323
Male	116 (69.5)	10 (83.3)	0.309
Hypertension	88 (52.7)	8 (66.7)	0.349
Diabetes	30 (18.0)	1 (8.3)	0.394
eGFR (mL/min/1.73 m^2)	95.13±17.04	79.00±13.83	0.002
BUN (mg/dL)	15.9±4.8	17.7±3.1	0.209
Creatinine (mg/dL)	0.85±0.20	1.02±0.17	0.004
FHx of SCD-1st	9 (5.4)	2 (16.7)	0.116
FHx of SCD-2nd	12 (7.2)	0 (0)	0.336
NSVT*	8 (7.9)	4 (66.7)	<0.001
5-year SCD risk (%)*	2.20±1.69	4.06±2.09	0.021
P/LP sarcomere variants	49 (29.3)	6 (50.0)	0.192
P/LP thick filament variants	40 (24.0)	5 (41.7)	0.323
P/LP thin filament or regulatory variants	9 (5.4)	1 (8.3)	
Echocardiographic analysis			
Apical HCM	81 (48.5)	5 (41.7)	0.647
Maximal wall thickness (mm)	18.9±3.6	19.8±2.9	0.395
LVOT or mid-LV obstruction	43 (25.7)	3 (25.0)	0.954
Peak trans-LVOT or mid-LV PG (mmHg)	22.3±32.7	19.2±18.3	0.748
LV EDV (mL)	68.3±23.2	88.3±34.7	0.006
LV ESV (mL)	23.5±9.7	32.9±12.3	0.002
LAV (mL)	56.9±19.0	92.4±34.3	0.004
LAVI (mL/m^2)	32.4±12.1	52.1±23.2	0.014
MR ≥ moderate grade	1 (0.6)	1 (8.3)	0.131
LVEF (%)	65.3±5.4	62.3±5.9	0.062
E (cm/s)	68.2±19.5	63.0±20.9	0.379
A (cm/s)	70.0±21.2	60.5±17.5	0.132
DT (ms)	216.8±58.2	197.9±42.3	0.272
e' (cm/s)	5.1±1.8	4.2±1.1	0.089
a' (cm/s)	7.7±1.9	6.2±1.8	0.010
s' (cm/s)	7.1±1.6	5.9±1.6	0.013
E/e'	15±6	15±3	0.660
GLS (%)	−15.1±4.0	−13.4±3.6	0.163
RVSP (mmHg)	27±8	27±5	0.970
LAWS (1/mL)	884±571	1,480±820	0.030

Values are presented as number (%) or mean ± standard deviation.
ACEi = angiotensin converting enzyme inhibitor; AF = atrial fibrillation; ARB = angiotensin II receptor blocker; BB = beta blocker; CCB = calcium channel blocker; DT = deceleration time; E = early transmitral inflow peak velocity; e′ = early diastolic mitral annular velocity; EDV = end-diastolic volume; eGFR = estimated glomerular filtration rate; ESV = end-systolic volume; FHx = family history; GLS = global longitudinal strain; HCM = hypertrophic cardiomyopathy; LAV = left atrial volume; LAVI = left atrial volume index; LAWS = left atrial wall stress ; LV = left ventricular; LVEF = left ventricular ejection fraction; LVOT = left ventricular outflow tract; MR = mitral regurgitation; P/LP = pathogenic/likely pathogenic; PG = pressure gradient; RVSP = right ventricular systolic pressure; SCD-1st = sudden cardiac death of 1st-degree family; SCD-2nd = sudden cardiac death of 2nd-degree family.
*Analysis of 107 patients for whom 24-hour Holter test was performed; 6 and 101 patients with or without new atrial fibrillation, respectively.

p=0.045). The p for interaction between age groups regarding the relationship between sarcomere variants (including VUS) and the prevalence of AF was not significant (p=0.504). However, the prevalence of mitochondrial-related variants did not differ (**Table 4**). The mutation-positive group had a lower prevalence of male sex and hypertension, and a higher 5-year sudden cardiac death risk score. In addition, these patients had a higher LAVI, lower a′, and higher prevalence of non-apical HCM. However, in patients ≥65 years, no significant difference was found between mutation-positive and -negative groups (**Table 5**). Genotypes of patients are listed in **Supplementary Table 3**.

https://doi.org/10.4070/kcj.2025.0048

Table 3. Univariate and multivariate Cox regression analyses of new-onset atrial fibrillation

Characteristics	Univariate analysis			Multivariate analysis (enter method)		
	HR	95% CI	p value	HR	95% CI	p value
Age (per years)	1.02	0.97–1.07	0.456	0.98	0.89–1.07	0.652
Male	1.35	0.29–6.30	0.700	1.60	0.18–14.43	0.676
eGFR (per mL/min/1.73 m^2)	0.94	0.90–0.98	0.002	0.93	0.88–0.98	0.007
LAVI (per mL/m^2)	1.05	1.02–1.07	<0.001	1.07	1.02–1.13	0.010
LV EDV (per mL)	1.02	1.003–1.04	0.023	0.99	0.97–1.02	0.994
LV ESV (per mL)	1.06	1.02–1.10	0.008			
LVEF (per %)	0.91	0.83–0.998	0.046	0.82	0.70–0.95	0.009
e′ (per cm/s)	0.79	0.53–1.17	0.232			
a′ (per cm/s)	0.62	0.43–0.898	0.011	0.93	0.55–1.56	0.789
s′ (per cm/s)	0.68	0.47–0.99	0.044	0.71	0.38–1.33	0.286
LV-GLS (per %)	0.93	0.81–1.07	0.322			
ACEi use	2.77	0.59–13.02	0.197			
ARB use	0.76	0.24–2.41	0.639			
BB use	1.06	0.32–3.51	0.929			
CCB use	1.96	0.62–6.20	0.251			

a′ = late diastolic mitral annular velocity; ACEi = angiotensin converting enzyme inhibitor; ARB = angiotensin II receptor blocker; BB = beta blocker; CCB = calcium channel blocker; CI = confidence interval; e′ = early diastolic mitral annular velocity; EDV = end-diastolic volume; eGFR = estimated glomerular filtration rate; ESV = end-systolic volume; GLS = global longitudinal strain; HR = hazard ratio; LAVI = left atrial volume index; LV = left ventricular; LVEF = left ventricular ejection fraction.

Table 4. Overall genetic relevance to AF

	All (n=212)			<65 years (n=128)			≥65 years (n=84)			p for interaction between age groups
	No AF (n=167)	Overall AF (n=45)	p value	No AF (n=111)	Overall AF (n=17)	p value	No AF (n=56)	Overall AF (n=28)	p value	
Pathogenic sarcomere variants (P/LP)	49 (29.3)	18 (40.0)	0.172	38 (34.2)	9 (52.9)	0.136	11 (19.6)	9 (32.1)	0.205	0.630
Pathogenic sarcomere thick filament variant	40 (24.0)	12 (26.7)	0.145	29 (26.1)	7 (41.2)	0.328	11 (19.6)	5 (17.9)	0.844	
Pathogenic sarcomere thin filament or regulatory gene variant	9 (5.4)	6 (13.3)		9 (8.1)	2 (11.8)		0	4 (14.3)		
Any sarcomere variants (P/LP + VUS)	90 (53.9)	29 (64.4)	0.205	63 (56.8)	14 (82.4)	0.045	27 (48.2)	15 (53.6)	0.643	0.504
Any sarcomere thick filament variants	54 (32.3)	15 (33.3)	0.319	36 (32.4)	9 (52.9)	0.114	18 (32.1)	6 (21.4)	0.211	
Any sarcomere thin filament or regulatory gene variants	36 (21.6)	14 (31.1)		27 (24.3)	5 (29.4)		9 (16.1)	9 (32.1)		
Mitochondria-related nDNA or mtDNA variants	35 (21.0)	7 (15.6)	0.420	21 (18.9)	4 (23.5)	0.655	14 (25.0)	3 (10.7)	0.124	0.100

Values are presented as number (%).
AF = atrial fibrillation; mtDNA = mitochondrial deoxyribonucleic acid; nDNA = nuclear deoxyribonucleic acid; P/LP = pathogenic/likely pathogenic; VUS = variants of uncertain significance.

DISCUSSION

This study reports major findings regarding AF. First, LA enlargement and dysfunction were associated with both prevalent and new-onset AF. Second, lower eGFR had an additive predictive value on the LAVI for future AF. Third, expanded LV ECV and bi-ventricular dysfunction were related to AF. Finally, the presence of sarcomere variants, including VUS, was associated with AF in patients younger than 65 years old. Multimodal imaging and genetic characteristics play a crucial role in predicting clinical outcomes in patients with HCM. In this context, a key strength of our study is that we comprehensively collected and analyzed not only clinical data but also CMR and genetic data to investigate the factors associated with the development of AF in patients with HCM.

Previous studies have reported that reduced kidney function is associated with AF and diabetes mellitus in the general population.[7)19)] A meta-analysis of 3 cohorts reported that lower eGFR is associated with a greater risk of AF in participants without prevalent AF in population-based studies.[5)] Moreover, decreased renal function is a well-known predictor of

Table 5. Comparison of clinical profiles and cardiac structural and functional parameters according to age and sarcomere variants

Characteristics	Age <65 years (n=128)			Age ≥65 years (n=84)		
	Any sarcomere variants (n=77, 60.2%)	No sarcomere variants (n=51, 39.8%)	p value	Any sarcomere variants (n=42, 50%)	No sarcomere variants (n=42, 50%)	p value
Age (years)	49.4±10.6	52.4±8.4	0.086	71.5±5.5	73.1±5.5	0.180
Male	54 (70.1)	46 (90.2)	0.007	25 (59.5)	24 (57.1)	0.825
Hypertension	26 (33.8)	28 (54.9)	0.018	27 (64.3)	38 (90.5)	0.004
Diabetes	12 (15.6)	8 (15.7)	0.988	9 (21.4)	10 (23.8)	0.794
5-year SCD risk (%)	2.74±2.10	2.06±0.89	0.042	1.79±1.11	1.63±1.27	0.676
FHx of SCD-1st	9 (11.7)	3 (5.9)	0.270	2 (4.8)	1 (2.4)	0.557
eGFR (mL/min/1.73 m^2)	100.7±17.2	96.7±16.2	0.214	80.5±17.4	80.6±15.4	0.989
Echocardiographic analysis						
Apical HCM	26 (33.8)	32 (62.7)	0.001	20 (47.6)	23 (54.8)	0.513
Maximal wall thickness (mm)	19.6±3.8	19.3±3.7	0.714	18.6±2.8	17.5±2.9	0.080
LVMI by echo (g/m^2)	130.9±40.2	123.3±30.1	0.252	134.2±39.4	121.6±28.5	0.097
LVOT or mid-LV obstruction	15 (19.5)	16 (31.4)	0.124	8 (19)	10 (23.8)	0.595
Resting peak trans-LVOT or mid-LV PG (mmHg)	11.2±22.0	14.8±16.2	0.323	10.0±9.9	18.7±23.0	0.064
Valsalva peak trans-LVOT or mid-LV PG (mmHg)	20.3±30.5	26.2±26.6	0.306	16.3±16.9	36.7±51.5	0.040
LAVI (mL/m^2)	36.6±19.4	29.7±9.9	0.019	45.1±22.0	37.6±13.3	0.065
LVEF (%)	64.2±7.1	65.2±4.8	0.352	63.5±6.9	65.7±6.1	0.125
E (cm/s)	72.3±21.4	69.5±15.6	0.396	65.3±21.8	68.0±18.7	0.547
A* (cm/s)	60.2±17.1	66.1±18.0	0.068	75.5±21.8	85.0±21.4	0.077
DT (ms)	197.7±51.9	213.3±59.1	0.123	213.6±53.7	226.0±64.8	0.348
e′ (cm/s)	5.5±1.7	5.6±1.8	0.676	4.2±1.4	4.4±1.4	0.522
a′* (cm/s)	7.1±2.0	7.9±1.9	0.037	7.2±1.5	8.1±2.2	0.082
s′ (cm/s)	6.9±1.8	7.4±1.6	0.108	6.2±1.4	6.3±1.8	0.900
E/e′	14.2±6.1	13.1±3	0.274	16.8±5.5	16.6±6.7	0.884
GLS (%)	−14.7±4.2	−14.9±4.2	0.826	−13.3±3.7	−14.6±4.5	0.130
Tricuspid regurgitation velocity (m/s)	2.3±0.4	2.2±0.3	0.086	2.5±0.4	2.5±0.4	0.638
Overall AF	14 (18.2)	3 (5.9)	0.045	15 (35.7)	13 (31.0)	0.643

Values are presented as number (%) or mean ± standard deviation.
a′ = late diastolic mitral annular velocity; AF = atrial fibrillation; DT = deceleration time; E = early transmitral inflow peak velocity; e′ = early diastolic mitral annular velocity; eGFR = estimated glomerular filtration rate; FHx = family history; GLS = global longitudinal strain; HCM = hypertrophic cardiomyopathy; LAVI = left atrial volume index; LV = left ventricular; LVEF = left ventricular ejection fraction; LVMI = left ventricular mass index; LVOT = left ventricular outflow tract; PG = pressure gradient; SCD = sudden cardiac death; SCD-1st = sudden cardiac death of 1st-degree family.
*Absence in patients with AF.

thromboembolic events.[20] Our study revealed that risk factors for future AF in patients with HCM were consistent with those in the general population and patients with other clinical entities. Although it is not strong but lower eGFR was associated with future AF events in this study. We compared the age of this study (59.2±13.6) with the Sarcomeric Human Cardiomyopathy Registry (SHaRe) population (45.8 [30.9–58.1])[9] or the Hypertrophic Cardiomyopathy Registry (HCMR) study population (49±11 years).[1] As our study age was older than other studies, the new-onset AF prevalence during the 3-year follow-up was also higher than in other studies (6.9% in our study vs. 3.6% in the HCMR study). As HCM patients age, the role of renal function becomes increasingly important in their clinical presentation. The major clinical presentation of HCM is diastolic HF, which increases the risk of renal impairment. Longstanding diastolic dysfunction causes LA remodeling and increases the risk of AF. In addition, renal dysfunction is related to the activation of the RAS, which may also be linked to the development of AF.[21] The RAS promotes atrial fibrosis, consequently leading to arrhythmogenic electrophysiological abnormalities. This could be due to increased LV mass-related longstanding LV diastolic dysfunction, which contributes to the hemodynamic load on the left atrium.

https://doi.org/10.4070/kcj.2025.0048

LA remodeling is a well-known risk factor for AF and can increase the risk of thromboembolic events.[22)23)] Both LA remodeling and decreased LA function contribute to the occurrence of AF, as demonstrated in previous studies.[24-27)] Our study showed a consistent result, stating that a higher LAVI was modestly but significantly related to future AF events in multivariable analysis. In the cross-sectional analysis, ECV of LV was higher in patients with AF than in those without AF, suggesting that ventricular myocardial fibrosis is also associated with AF in patients with HCM through long-standing diastolic dysfunction or by reflecting LV myopathy. Guo et al.[28)] reported that preoperative transforming growth factor-beta (TGF-β) independently predicts postoperative AF in HCM after surgical ventricular septal myectomy. TGF-β is a profibrotic cytokine that promotes cardiac fibrosis, including ventricular fibrosis, and previous studies demonstrated that TGF-β promotes atrial fibrosis.[29)] Disease severity-associated ventricular remodeling is a crucial factor associated with AF, in addition to atrial remodeling. Interestingly, RV GLS and RV fractional area changes determined by feature tracking analysis of CMR were lower in patients with initial AF than in those without initial AF in this study. Doesch et al.[30)] demonstrated that the RV tricuspid annular plane systolic excursion is lower in patients with HCM and AF compared with patients with HCM and sinus rhythm. We found that biventricular components contributed to AF in patients with HCM. We suggest that the association between ventricular and atrial remodeling may apply not only to the left heart but also to the right heart.

We observed that the presence of sarcomere variants was associated with the onset of AF at a young age <65 years. Although the p-for-interaction between the two groups did not reach statistical significance, precluding a definitive conclusion regarding age-specific differences in outcomes, an age-related trend was nonetheless observed. Despite the limited number of events and the insufficient sample size to confirm these findings statistically, the results may still provide mechanistic insights into potential age-related differences. Chronologically younger HCM patients are more likely to have experienced a shorter duration of LA hemodynamic load due to LV diastolic dysfunction compared to older patients. Therefore, in young HCM patients with mutations, intrinsic LA myopathy might play a more significant role in the development of AF than in older patients. This is consistent with our previous observation that pathogenic sarcomere mutations are related to LA dysfunction, independent of LV diastolic dysfunction, suggesting the presence of primary atrial myopathy.[10)] Therefore, in young patients with HCM, genetic testing should report not only pathogenic mutations but also VUS. Patients with young HCM and any sarcomere variants, including VUS, may benefit from regular rhythm monitoring using Holter monitoring systems, 12-lead ECG, or new wearable devices for early detection of AF. However, in our study, mitochondria-related nDNA or mtDNA did not show any differences in the development of AF.

This study has several limitations. First, it was performed at a single tertiary center with a small number of patients. Therefore, many patients have already been diagnosed with AF, resulting in a small number of patients with newly developed AF. However, when compared to other studies, the rate was not low because HCMR new onset-AF rate was 3.4% during 3-year follow-up. It would be from older age in our study compared to the HCMR study (59±14 vs. 49±11 years).[1)] In addition in our overall AF rate was 21%, which was similar to lifetime AF ratio of 20% in SHaRe.[9)] A longer-term study with a large sample size is required. Second, the ECG follow-up period was heterogeneous for each patient, which could have affected the detection rate of newly developed AF. Third, we diagnosed HCM based on echocardiography with criteria of maximal thickness >13 mm. Not all the patients underwent CMR, therefore concerns of misdiagnosing as HCM in cases of HCM-mimicking diseases may exist.

https://doi.org/10.4070/kcj.2025.0048

However, we excluded patients with underlying cause of hypertrophy, such as uncontrolled hypertension, aortic stenosis or metabolic diseases. All patients underwent screening for Fabry disease and other phenocopy diseases by genetic testing, therefore the possibility of misdiagnosis would be very low. Fourth, the interpretation of the subgroup analysis should be cautious because the p value for interaction between age groups was not significant. Therefore, the effect of the sarcomere variant on the prevalence of AF was not specific to the younger group under the age of 65. Finally, because CMR imaging was performed in a small number of patients, we could not analyze the predictive value of cardiac fibrosis or inflammation in the development of AF.

In patients with HCM, lower eGFR and increased LAVI were associated with future AF. In addition to known risk factors, such as cardiac remodeling and decreased function, decreased renal function independently provided an additive predictive value for future AF. As AF is related to crucial clinical outcomes, such as thromboembolic events, this study suggests more intensive ECG monitoring in patients with HCM with lower eGFR and a higher LAVI. Patients with any sarcomere mutations, including VUS, are also related to patients aged <65 years with AF. Therefore, reporting and recognizing sarcomere mutation, including VUS, is important, as this group of patients may benefit from regular rhythm monitoring for early detection of AF, even in young patients with HCM.

ACKNOWLEDGMENTS

We appreciate Ms. Minjee Kim for study coordination and data collection.

SUPPLEMENTARY MATERIALS

Supplementary Data 1
Conventional echocardiography and speckle tracking echocardiography

Supplementary Data 2
Cardiac magnetic resonance imaging

Supplementary Data 3
Genetic analysis

Supplementary Table 1
Comparisons of cardiac magnetic resonance findings between presence and absence of initial AF

Supplementary Table 2
Pathogenic or likely pathogenic sarcomere variants of patients according to presence of overall AF

Supplementary Table 3
Nonsynonymous variants in the 33 sarcomere associated genes classified according to the refined ACMG standards and guidelines for inherited cardiac conditions

Supplementary Figure 1

Comprehensive HCM-specific gene panel. (A) Thirty-three sarcomere associated genes, (B) 5 phenocopy genes, (C) 44 mitochondrial related nuclear DNA genes.

Supplementary Figure 2

Study flow diagram of the study population.

REFERENCES

1. Kramer CM, DiMarco JP, Kolm P, et al. Predictors of major atrial fibrillation endpoints in the national heart, lung, and blood institute HCMR. *JACC Clin Electrophysiol* 2021;7:1376-86. PUBMED | CROSSREF
2. Siontis KC, Geske JB, Ong K, Nishimura RA, Ommen SR, Gersh BJ. Atrial fibrillation in hypertrophic cardiomyopathy: prevalence, clinical correlations, and mortality in a large high-risk population. *J Am Heart Assoc* 2014;3:e001002. PUBMED | CROSSREF
3. Rowin EJ, Link MS, Maron MS, Maron BJ. Evolving contemporary management of atrial fibrillation in hypertrophic cardiomyopathy. *Circulation* 2023;148:1797-811. PUBMED | CROSSREF
4. Ommen SR, Mital S, Burke MA, et al. 2020 AHA/ACC guideline for the diagnosis and treatment of patients with hypertrophic cardiomyopathy: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation* 2020;142:e558-631. PUBMED | CROSSREF
5. Bansal N, Zelnick LR, Alonso A, et al. eGFR and albuminuria in relation to risk of incident atrial fibrillation: a meta-analysis of the Jackson Heart Study, the Multi-Ethnic Study of Atherosclerosis, and the Cardiovascular Health Study. *Clin J Am Soc Nephrol* 2017;12:1386-98. PUBMED | CROSSREF
6. Guo Y, Gao J, Ye P, et al. Comparison of atrial fibrillation in CKD and non-CKD populations: a cross-sectional analysis from the Kailuan study. *Int J Cardiol* 2019;277:125-9. PUBMED | CROSSREF
7. Alonso A, Lopez FL, Matsushita K, et al. Chronic kidney disease is associated with the incidence of atrial fibrillation: the Atherosclerosis Risk in Communities (ARIC) study. *Circulation* 2011;123:2946-53. PUBMED | CROSSREF
8. Bae NY, Rhee TM, Park CS, et al. Mildly reduced renal function is associated with increased heart failure admissions in patients with hypertrophic cardiomyopathy. *J Korean Med Sci* 2024;39:e80. PUBMED | CROSSREF
9. Ho CY, Day SM, Ashley EA, et al. Genotype and lifetime burden of disease in hypertrophic cardiomyopathy: insights from the Sarcomeric Human Cardiomyopathy Registry (SHaRe). *Circulation* 2018;138:1387-98. PUBMED | CROSSREF
10. Chung H, Kim Y, Park CH, et al. Contribution of sarcomere gene mutations to left atrial function in patients with hypertrophic cardiomyopathy. *Cardiovasc Ultrasound* 2021;19:4. PUBMED | CROSSREF
11. Chung H, Kim Y, Cho SM, et al. Differential contributions of sarcomere and mitochondria-related multigene variants to the endophenotype of hypertrophic cardiomyopathy. *Mitochondrion* 2020;53:48-56. PUBMED | CROSSREF
12. Chiswell K, Zaininger L, Semsarian C. Evolution of genetic testing and gene therapy in hypertrophic cardiomyopathy. *Prog Cardiovasc Dis* 2023;80:38-45. PUBMED | CROSSREF
13. Lopes LR, Syrris P, Guttmann OP, et al. Novel genotype-phenotype associations demonstrated by high-throughput sequencing in patients with hypertrophic cardiomyopathy. *Heart* 2015;101:294-301. PUBMED | CROSSREF
14. Inker LA, Eneanya ND, Coresh J, et al. New creatinine- and cystatin C-based equations to estimate GFR without race. *N Engl J Med* 2021;385:1737-49. PUBMED | CROSSREF
15. Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr* 2015;28:1-39.e14. PUBMED | CROSSREF
16. Chung H, Kim Y, Park CH, et al. Effect of sarcomere and mitochondria-related mutations on myocardial fibrosis in patients with hypertrophic cardiomyopathy. *J Cardiovasc Magn Reson* 2021;23:18. PUBMED | CROSSREF
17. Walsh R, Buchan R, Wilk A, et al. Defining the genetic architecture of hypertrophic cardiomyopathy: re-evaluating the role of non-sarcomeric genes. *Eur Heart J* 2017;38:3461-8. PUBMED | CROSSREF

18. Whiffin N, Walsh R, Govind R, et al. CardioClassifier: disease- and gene-specific computational decision support for clinical genome interpretation. *Genet Med* 2018;20:1246-54. PUBMED | CROSSREF
19. Hallström S, Pivodic A, Rosengren A, Ólafsdóttir AF, Svensson AM, Lind M. Risk factors for atrial fibrillation in people with type 1 diabetes: an observational cohort study of 36,258 patients from the Swedish National Diabetes Registry. *Diabetes Care* 2019;42:1530-8. PUBMED | CROSSREF
20. Parsons C, Cha S, Shen WK, et al. Usefulness of the addition of renal function to the CHA2DS2-VASc score as a predictor of thromboembolism and mortality in patients without atrial fibrillation. *Am J Cardiol* 2018;122:597-603. PUBMED | CROSSREF
21. Kuzniatsova N, Shantsila E, Lip GY. Blockade of the renin-angiotensin system in atrial fibrillation. *Nat Rev Cardiol* 2010;7:428-30. PUBMED | CROSSREF
22. Rowin EJ, Hausvater A, Link MS, et al. Clinical profile and consequences of atrial fibrillation in hypertrophic cardiomyopathy. *Circulation* 2017;136:2420-36. PUBMED | CROSSREF
23. Kim HD, Cho DH, Kim MN, et al. Left atrial dysfunction, fibrosis and the risk of thromboembolism in patients with paroxysmal and persistent atrial fibrillation. *Int J Heart Fail* 2022;4:42-53. PUBMED | CROSSREF
24. Tsang TS, Barnes ME, Bailey KR, et al. Left atrial volume: important risk marker of incident atrial fibrillation in 1655 older men and women. *Mayo Clin Proc* 2001;76:467-75. PUBMED | CROSSREF
25. Fatema K, Barnes ME, Bailey KR, et al. Minimum vs. maximum left atrial volume for prediction of first atrial fibrillation or flutter in an elderly cohort: a prospective study. *Eur J Echocardiogr* 2009;10:282-6. PUBMED | CROSSREF
26. Abhayaratna WP, Fatema K, Barnes ME, et al. Left atrial reservoir function as a potent marker for first atrial fibrillation or flutter in persons > or = 65 years of age. *Am J Cardiol* 2008;101:1626-9. PUBMED | CROSSREF
27. Hirose T, Kawasaki M, Tanaka R, et al. Left atrial function assessed by speckle tracking echocardiography as a predictor of new-onset non-valvular atrial fibrillation: results from a prospective study in 580 adults. *Eur Heart J Cardiovasc Imaging* 2012;13:243-50. PUBMED | CROSSREF
28. Guo Y, Wu X, Zheng X, Lu J, Wang S, Huang X. Usefulness of preoperative transforming growth factor-beta to predict new onset atrial fibrillation after surgical ventricular septal myectomy in patients with obstructive hypertrophic cardiomyopathy. *Am J Cardiol* 2017;120:118-23. PUBMED | CROSSREF
29. Gramley F, Lorenzen J, Koellensperger E, Kettering K, Weiss C, Munzel T. Atrial fibrosis and atrial fibrillation: the role of the TGF-β1 signaling pathway. *Int J Cardiol* 2010;143:405-13. PUBMED | CROSSREF
30. Doesch C, Lossnitzer D, Rudic B, et al. Right ventricular and right atrial involvement can predict atrial fibrillation in patients with hypertrophic Cardiomyopathy? *Int J Med Sci* 2016;13:1-7. PUBMED | CROSSREF