



Left Atrial Reservoir Strain Predicts Atrial Fibrillation in Hypertrophic Cardiomyopathy:

Insights from the NHLBI HCM Registry

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Atrial fibrillation (AF) is the most common arrhythmia in hypertrophic cardiomyopathy (HCM) and a major contributor to its morbidity and mortality.¹ Because the risk of thromboembolic events is particularly high in this population, predictors of AF

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could improve risk stratification, personalized surveillance strategies, and guidance of anticoagulant therapy. Recent single-center studies have suggested that left atrial (LA) reservoir strain is associated with AF in HCM, but validation in larger, multicenter settings remains limited.^{2,3}

The utility of LA reservoir strain for predicting AF was investigated using data from the prospective NHLBI (National Heart, Lung, and Blood Institute) HCM Registry (NCT01915615).⁴ Inclusion required high-quality LA strain analysis and no history or evidence of AF at baseline. The primary endpoint was the occurrence of clinically relevant AF events (AF episodes requiring electrical cardioversion or catheter ablation, hospitalization because of AF for >24 hours, or clinical decisions to accept permanent AF).⁵ To evaluate the clinical utility of LA reservoir strain thresholds derived from the HCM Registry in a real-world setting, data from an independent observational single-center study conducted at Oxford University Hospitals NHS Foundation Trust were retrospectively analyzed. Clinical characteristics, demographics, and imaging data of this exploratory cohort have been published previously.³ The study protocol was approved by the institutional review boards at the participating institutions, and written informed consent was obtained from all patients.

Cardiovascular magnetic resonance was performed on 1.5-T or 3.0-T scanners from multiple vendors according to a standardized protocol.⁴ LA reservoir strain (peak LA longitudinal strain during ventricular systole) was assessed via feature tracking using cvi42 software (Circle Cardiovascular Imaging). The LA endocardial and epicardial boundaries were manually traced in the 2- and 4-chamber long-axis views using the integrated right ventricular contour tool as previously described.³ A total of 1,661 HCM patients without AF at baseline (median age: 51 years [Q1-Q3: 42-58 years]; 71.1% males; 15.8% belonging to an ethnic minority) were included in the present study. Most (63.6%) had sarcomere-negative HCM with a pattern of basal septal left ventricular hypertrophy (47.3%) or reverse septal curvature (39.5%). During a median follow-up time of 6 years (Q1-Q3: 5-7 years), 84 individuals (5.1%) presented with a first clinically relevant AF event determined by the clinical adjudication committee. These patients were slightly older (54 years [Q1-Q3: 49-60 years] vs 51 years [Q1-Q3: 41-58 years]; $P = 0.001$), had a higher body mass index (30 kg/m² [Q1-Q3: 26-34 kg/m²] vs 28 kg/m² [Q1-Q3: 25-32 kg/m²]; $P = 0.010$), and presented more often with NYHA functional class III or IV at baseline (15.7% vs 6.7%; $P < 0.004$). Resting left ventricular outflow tract gradient, mitral regurgitation grade, left ventricular mass, and extent of late gadolinium enhancement were all greater in these patients (P for all < 0.05). Patients with AF events had a larger LA diameter by echocardiography (49.1% vs 24.4% with LA diameter ≥ 4.5 cm; $P < 0.001$), and LA volume index (69.0 mL/m² [Q1-Q3: 54.7-82.7 mL/m²] vs 55.0 mL/m² [Q1-Q3: 43.9-67.3 mL/m²]; $P < 0.001$), together with lower LA reservoir strain ($11.4\% \pm 4.3\%$ vs $14.5\% \pm 4.2\%$; $P < 0.001$) and LA ejection fraction (59% [Q1-Q3: 46%-67%] vs 67% [Q1-Q3: 59%-73%]; $P < 0.001$), at baseline compared with those without.

After multivariable adjustment, LA reservoir strain and age, body mass index, NYHA functional class, LA volume index, and LA ejection fraction remained significantly associated with AF events (HR for LA reservoir strain: 0.91 [95% CI: 0.85-0.98]; P

< 0.01). Addition of LA reservoir strain to these independent predictors significantly improved the goodness-of-fit, indicating incremental prognostic value (likelihood ratio test P for all <0.001). Adjusted HRs of LA reservoir strain for AF-related events increased with lower cutoff values (Figure 1A). LA reservoir strain showed a good discriminatory performance for identifying patients who later developed AF events (C-index: 0.71 [95% CI: 0.65-0.78]; P < 0.001). The optimal threshold of 13.3%, derived by the Youden Index, yielded a sensitivity of 72.6%, a specificity of 62.3%, and a negative predictive value of 97.6%. Importantly, low LA reservoir strain was associated with less AF-free survival not only in the total study population but also in patients classified as low risk according to LA dimension cutoffs (<4.5 cm by echocardiography) recommended in current clinical guidelines (Figure 1B). Moreover, the incidence of AF-related clinical events was consistently higher in patients with LA reservoir strain <13.3% across a broad spectrum of disease subtypes and clinical phenotypes (apical and nonapical HCM, sarcomeric and nonsarcomeric HCM, left ventricular ejection >50% and <50%, in patients with and without left ventricular outflow tract obstruction; P log rank in all subgroups <0.01).

The utility of the derived LA reservoir strain threshold to predict new-onset AF (defined as an irregular heart rhythm without P waves documented through either a 12-lead electrocardiogram or 24- to 48-hour Holter monitoring) was evaluated in an independent cohort of 236 AF-free HCM patients (age: 54 years [Q1-Q3: 44-64 years]; 77.1% male). When this exploratory HCM cohort was dichotomized according to the optimal discriminatory threshold of 13.3%, low LA reservoir strain was associated with a significantly higher incidence of new-onset AF. During a follow-up of 4 years [Q1-Q3: 2-6 years], new-onset AF was observed in 34.5% of patients with low LA reservoir strain compared with 10.2% in those with LA strain above the optimal diagnostic threshold (P < 0.001).

In conclusion, these findings from the large, multicenter HCM Registry support LA reservoir strain as a sensitive, independent predictor of AF, providing incremental prognostic value beyond established risk markers. A diagnostic cutoff of 13.3% demonstrated robust performance in stratifying AF risk even in patients traditionally considered low risk based on LA diameter. Future interventional studies evaluating LA reservoir strain to guide clinical decision-making and personalized risk assessment are warranted.

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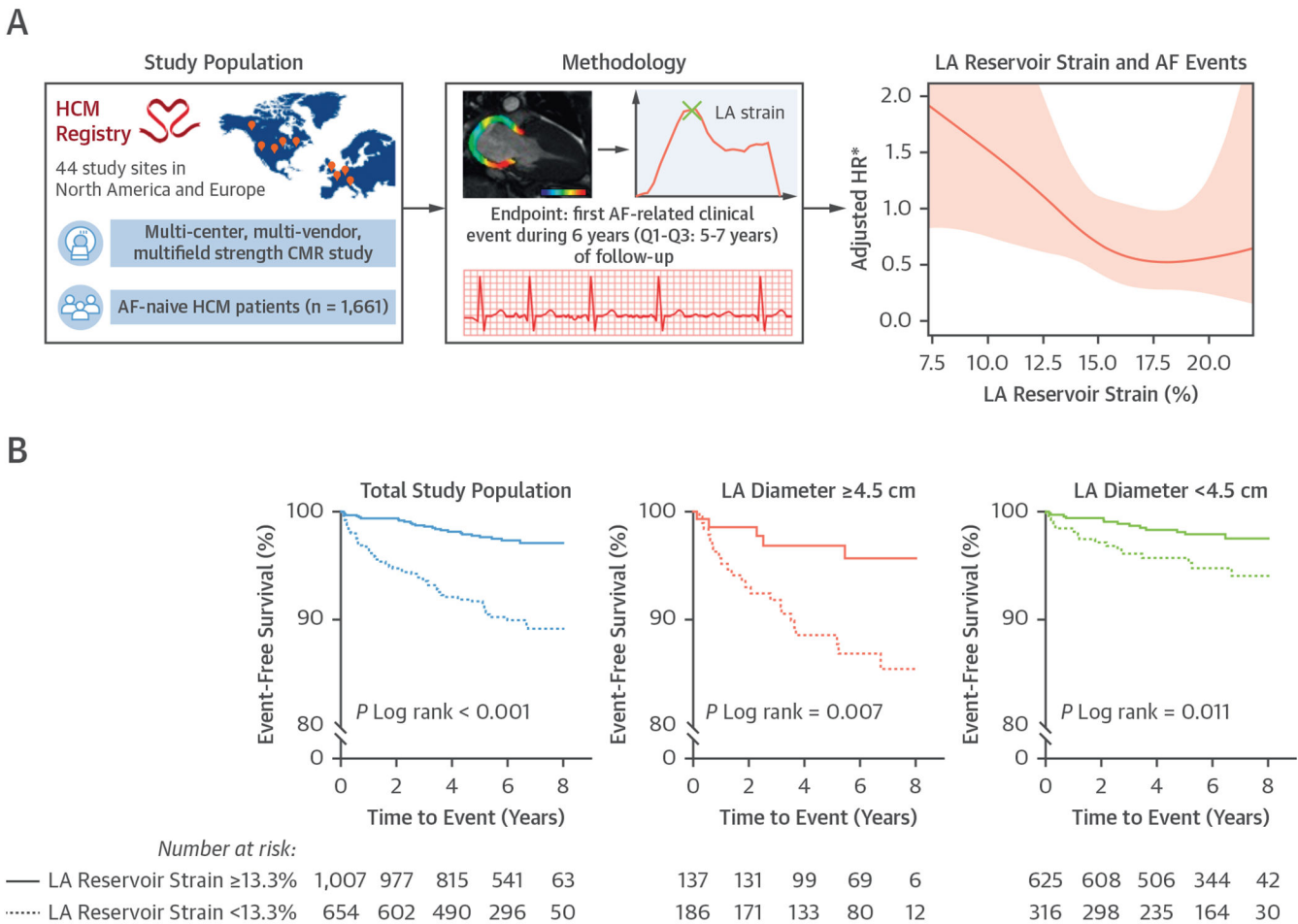


FIGURE 1. LA Reservoir Strain Is an Independent Predictor of Clinically Relevant AF Events in Patients With HCM

(A) Study design, methodology, and key finding. Restricted cubic spline analysis demonstrating the association between LA reservoir strain values and the risk of clinically relevant AF events. The red line indicates adjusted HRs. *Covariates for the adjusted model: age, sex, BMI, mitral regurgitation grade, NYHA functional class, LV mass index, LGE as a percentage of LV mass, LA volume index, and LA EF. (B) AF event-free survival analysis according to LA reservoir strain and LA diameter. Kaplan-Meier curves for all individuals in the HCM Registry population and patients stratified by echocardiography-derived LA diameter are shown. AF = atrial fibrillation; BMI = body mass index; EF = ejection fraction; HCM = hypertrophic cardiomyopathy; LA = left atrial; LGE = late gadolinium enhancement; LV = left ventricular.