Research Article

Interventional Cardiology

Possible risk factors contributing to atrial fibrillation occurrence in heart failure mildly reduced ejection fraction

Lusine Hazarapetyan[1], Parounak Zelveian[2], Svetlana Grigoryan[1*]

[1]Department of Cardiology, Yerevan State Medical University, Yerevan, Armenia

[2]Department of Preventive Cardiology, Hospital Polyclinic No.2, Yerevan, Armenia

*Author for correspondence:
Svetlana Grigoryan, Department of Cardiology, Yerevan State Medical University, Yerevan, Armenia, E-mail: s.grigoryan@interdiagnostika.com

Received date: 01-Oct-2024, Manuscript No. FMIC-24-149327;
Editor assigned: 04-Oct-2024, PreQC No. FMIC-24-149327 (PQ);
Reviewed date: 18-Oct-2024, QC No. FMIC-24-149327;
Revised date: 25-Oct-2024, Manuscript No. FMIC-24-149327 (R);
Published date: 01-Nov-2024, DOI: 10.37532/1755-5310.2024.16(S24).618

Abstract

Background: Heart Failure (HF) is often accompanied by Atrial Fibrillation (AF), which significantly worsens the outcome of both diseases. The purpose of study is to examine possible risk factors for the development of paroxysmal/persistent AF in patients with Heart Failure with moderately reduced Ejection Fraction (HFmrEF).

Methods: The study included 193 patients with HFpEF and non-valvular paroxysmal/persistent AF after successful cardioversion. As a control group the similar 76 patients without AF were examined. All patients underwent an examination, including electrocardiography, echocardiography, ambulatory blood pressure monitoring and Holter ECG monitoring. Levels of inflammatory markers, such as High-sensitivity C-Reactive Protein (Hs-CRP), Interleukin-6 (IL-6), Tumor Necrosis Factor-α (TNF-α) and the fibrotic marker Transforming Growth Factor-β1 (TGF-β1) measured using the Enzyme-Linked Immunosorbent Assay (ELISA) method. The results obtained were analyzed using Odds Ratios (OR).

Results: Frequent episodes of Hypertensive crisis (Hcr) and increased Body Mass Index (BMI) are possible risk factors for paroxysmal/persistent AF. An increase OR of diastolic and systolic parameters of the left ventricle was associated with significant atrial and ventricular remodeling. Higher levels of inflammatory markers OR are associated with an increased risk of AF in HFmrEF patients compared to some patients without AF. An increase in the OR of the fibrosis marker TGF-β1 was statistically significant in patients with persistent AF.

Conclusion: It could be considered that frequency Hcr, BMI, remodeling of the left atrium and ventricles and an increase of inflammation and fibrosis markers are possible risk factors for the occurrence of AF in HFmrEF patients.

Keywords: Atrial fibrillation • Cardiac fibrosis • Inflammation markers • Middle reduced ejection • Risk factors

Abbreviations: AF: Atrial Fibrillation; BMI: Body Mass Index; BP: Blood Pressure; CI: Confidence Interval; DBP: Diastolic Blood Pressure; DT: Deceleration Time; E peak: Early diastolic filling wave; EF: Ejection Fraction; HC: Hypertensive Crises; HF: Heart Failure; HFmrEF: Heart failure with Mildly Reduced Ejection Fraction; HFpEF: Heart Failure with preserved Ejection Fraction; HFrEF: Heart Failure with reduced Ejection Fraction; HR: Hazard Ratio; HsCRP: High sensitive C Reactive Protein; IHD: Ischemic Heart Disease; IL-6: Interlekine-6; IVRT: Isovolumetric Relaxation Time; IVST: Interventricular Septum Thickness; LAD: Left Atrial Diameter; LAV: Left Atrial Volume; LVEDD: Left Ventricle End-Diastolic Diameter; LVEDV: Left Ventricle End-Diastolic Volume; LVESD: Left Ventricle End-Systolic Diameter; LVESV: Left Ventricle End-Systolic Volume;

LVPWT: Left Ventricle Posterior Wall Thickness; OR: Odds Ratio; P_{dis}: P-wave dispersion; P_{max}: P-wave maximum; SBP: Systolic Blood Pressure; TNF-α: Tumor Necrosis Factor-α; TGF-β1: Transforming Growth Factor-β1

Introduction

HF as a clinical syndrome is widespread worldwide: The number of HF cases doubled from 33.5 million in 1990 to 64.3 million in 2018 and global prevalence remains high [1]. HF is associated with structural and functional abnormalities of the myocardium [2]. The main pathogenic mechanisms contributing to HF include increased hemodynamic overload, ischemia-related dysfunction, contractile protein mutations, ventricular remodeling and altered neurohumoral stimulation [3,4]. Based on the huge variety of etiology and pathogenesis HF has multiple causes that make precise classification and treatment difficult [5,6]. Comparison of clinical characteristics, comorbidities, outcomes and prognosis among patients with HF who have either preserved ejection fraction (EF) (>50%, HFpEF) or moderately reduced ejection fraction. (40%-49%, HFmrEF) or reduced ejection fraction (<40%, HFrEF) leads to consideration of HFmrEF as an intermediate HF phenotype [6,7]. HFmrEF was first recognized as a new HF phenotype by the European Society of Cardiology in 2016 [8]. Of the more than 6.5 million patients with HF in the United States, 13%-24% had HFmrEF [9]. Recent research suggests that patients with HFmrEF benefit from therapies designed to improve outcomes for people with reduced EF [10,11]. However, the characteristics of HFmrEF and its therapeutic potential remain poorly understood. AF is the most common sustained and heterogeneous type of arrhythmia. There is plausible published evidence linking its onset and progression to inflammation and fibrosis [12,13]. Although AF and HF are distinct diseases, they are increasingly found to overlap and are associated with high morbidity and mortality; in addition, patients with comorbid HF and AF suffer from even more severe symptoms and a worse prognosis [14]. Data from the Framingham Heart Study suggest that AF occurs in more than half of individuals with HF and that HF occurs in more than one-third of individuals with AF. Thus, HF and AF are commonly encountered together and are closely interrelated with similar risk factors and each predisposes to the others [15]. However, while HFmrEF is well described, the determinants and outcomes of HFmrEF with concomitant AF remain unclear [16]. In this study, we aimed to identify possible risk factors associated with the onset and progression of AF in patients with HFmrEF.

Materials and Methods

Blood samples were collected from patients with heart failure in the Department of Arrhythmia at the Research Institute of Cardiology under a protocol approved by the Ethical Committee of the Institute of Cardiology and with informed consent from the patients.

Study patients

We were enrolled in the study, 193 patients with non-valvular AF and HFmrEF admitted to the Research Institute of Cardiology and underwent successful cardioversion. Similar 76 patients with HFmrEF but without AF were examined as the control group. Moreover, the inclusion criteria were the following: HFmrEF (49%-40%, BNP>35 pg/ml, or NT-proBNP>125 pg/ml) and the presence of ischemic or hypertensive heart disease. Ischemic etiology was defined based on a documented history of myocardial infarction or coronary angiography. Furthermore, the exclusion criteria included the following-HF due to valvular heart disease, chronic obstructive pulmonary disease, systemic inflammatory diseases and diabetes. Patients were followed up according to the usual practice of the center. All participants underwent a detailed physical examination that included resting 12-lead electrocardiography recording, 24 h blood pressure monitoring, echocardiography and 24 h ambulatory Holter monitoring. BP in rest was calculated from the mean of the second and third readings and peak of BP by 24 h blood pressure monitoring. BMI was calculated as weight divided by height and expressed as kg/m². All examined patients were asked to complete a questionnaire about their lifestyle (e.g., smoking, drinking and nutrition) and the presence of potential comorbidities. Table 1 presents the clinical characteristics of the patients.

Table 1: Baseline demographics and clinical characteristics in all observed HFmrEF patient with and without AF. Data represented as mean (range<0).

Indices, units	HFmrEF no AF (n=76)	HFmrEF/Paroxysmal AF (n=103)	HFmrEF persistent AF (n=90)
Age (years)	56 (49-74)	54 (47-71)	56 (51-73)
Male (%)	53.2	50.8	52.4
BMI (kg/m²)	29.8 (27-32)	30.1 (27-34)	31.1 (28-36)
History of smoking (%)	42.2	44.6	41.7
History of drinking (%)	11.9	14.7	12.6
IHD (%)	74.7	72.7	73.3
Hypertension (%)	87.4	88.7	89.1

Hypercholesterolemia (%)	47.9	48.9	46.8
Resting Heart Rate (bpm)	75.2 (68-89)	76.7 (72-91)	74.3 (65-90)
Peak Heart Rate (bpm)	116.8 (92-131)	121.7* (92-133)	115.8 (96-123)
Resting SBP (mmHg)	141.9 (125-155)	144.9 (131-160)	145.9 (131-150)
Peak SBP (mmHg)	164.1 (145-180)	168.8 (140-185)	167.1 (40-180)
Resting DBP (mmHg)	83.7 (75-95)	78.1 (70-90)	84.7 (75-95)
Peak DBP (mmHg)	91.2 (80-110)	95.2* (80-105)	92.1 (80-110)
Note: (*): p.05			

Materials

Levels of IL-6, TNF-α, TGF-β1 and Hs-CRP were measured by ELISA kits according to manufacturer's instructions. ELISA kits for analysis of IL-6, TNFα and TGF-β1 were purchased from BioSource (Belgium) and Hs-CRP from DRG International Inc (USA).

Electrocardiography

Since one of the main electrophysiological factors in the occurrence and maintenance of AF is the inhomogeneity of atrial conduction velocity, the ECG display of this process is the dispersion of the P wave (P_{dis}), which is defined as the difference between the maximum (P_{max}) and minimum (P_{min}) duration of the P wave recorded during lead II of the ECG.

Echocardiography

To measure LVEF according to standard criteria, traditional transthoracic echocardiography "Medison SonoAceX6" (Hungary) was used. Echocardiography measurements of chamber sizes, as well as systolic and especially early diastolic cardiac dysfunction were carried out in accordance with established recommendations

Biochemical blood measurements

Quantifications were determined using standard laboratory procedures established at the Institute of Cardiology. Plasma levels of inflammation markers Hs-CRP, IL-6, TNFα and TGF-β1 were determined by ELISA using the Stat Fax 303 Plus analyzer (Awareness Technology, Palm City, FL, USA).

Statistical analysis

Statistically significant differences between parameters were identified using two-step cluster analysis. The findings were modeled using binary logistic regression using the OR. OR is one of the most common approaches to describe how the absence or presence of a particular outcome is associated with the presence or absence of a particular factor in a particular statistical group. Thus, the results of using the OR include determining the statistical significance of the relationship between the factor and the result (outcome), as well as its quantitative assessment. It is very important to assess the statistical significance of the identified association between the outcome and the risk factor. If the OR is greater than 1, then the chances of detecting a risk factor in this group are greater; that is, the factor has a direct relationship with the probability of the outcome. Moreover, in each case, the statistical significance of the OR is necessarily assessed based on the values of the 95% CI (p-value<0.05 was considered significant). The studies were conducted using simple randomized protocols using the universal statistical package SPSS 13.0.

Results

Clinical characteristics of the study participants

Table 1 presents the demographic and clinical characteristics of all studied patients. When analyzing the demographic characteristics of patients, all groups were comparable in terms of gender, age and BMI. The groups were also similar in the proportion of patients who smoked and drinking habits There were no significant changes in heart rate at rest in the three examined groups. However, peak heart rate in patients with paroxysmal AF was significantly higher than in patients with persistent AF and patients without AF. There were no significant differences in SBP and DBP at rest between the 3 groups of patients. However, peak DBP was significantly higher in patients with paroxysmal AF than in patients with persistent AF and the control group (p<0.05).

Risk factors associated with paroxysmal AF

An OR method was used to assess the risk of developing paroxysmal AF compared with the control group without AF. Moreover, the indicators associated with an increased risk of developing paroxysmal AF in patients with HFmrEF included the following: Age (OR=1.8; CI=1.08-1.28, p=0.05); high DBP (OR=1.09, CI=1.01-1.17, p=0.017); high frequency of hypertensive crises (OR=1.17, CI=1.07-1.43, p=0.01) high BMI (OR=1.13, CI=0.93-1.27, p=0.031) According to electrocardiographic findings, P-wave maximum (P_{max}) and P-wave dispersion (P_{dis}) were significantly prolonged and associated with increased risk for both paroxysmal AF (P_{max}: OR=3.92, CI=3.88-3.96, p=0.002; P_{dis}: OR=3.91, CI=3.87-3.95, p=0.002) and persistent AF (P_{max}: OR=4.81, CI=4.07-5.94, p<0.001; P_{dis}: OR=4.90, CI=4.86-5.93, p<0.001). In addition, based on echocardiographic measurements, it was found that with an increased LAV, the risk of paroxysmal AF was significantly increased (LAV: OR=1.76, CI=1.66-1.88, p=0.002). It is worth noting that an increase in the level of

markers of systemic inflammation (Hs-CRP: OR=5.57, CI=3.38-7.87, p=0.010; IL-6: OR=4.80, CI=2.72-6.88, p=0.001; TNF-α: OR=2.56, CI=1.43-4.73, p=0.002) contributes to a high risk of developing paroxysmal and persistent AF in patients with HFmrEF as shown in the Table 2.

Table 2: The analysis of odds ratio values at a 95% confidence interval of various clinical hemodynamic and structural-functional parameters and markers of inflammation and fibrosis in HFmrEF patients with paroxysmal AF compared to the control group.

HFmrEF with paroxysmal AF (n=103)			
Indices	**Odds Ratio (OR)**	**95% CI**	**p-value**
Sex	0.24	0.10-0.58	0.07
Age	1.18	1.08-1.28	0.05*
SBP	1	0.94-1.05	0.987
DBP	1.09	1.01-1.17	0.017*
Heart rate	1.03	0.98-1.08	0.182
HrC	1.17	1.07-1.43	0.01*
Transitory ischemic attacks	0.65	0.14-2.93	0.583
IHD	1.16	0.39-3.42	0.788
Myocardial infarction	1.6	0.65-4.33	0.285
P_{max}	3.92	3.88-3.96	0.002*
P_{dis}	3.91	3.87-3.95	0.002*
QRS	0.1	0.96-1.04	0.989
BMI	1.13	0.93-1.27	0.031*
LAD	0.86	0.70-1.06	0.167
LAV	1.76	1.66-1.88	0.002*
LVEDD	0.92	0.71-1.20	0.558
LVEDV	0.99	0.94-1.04	0.811
LVESD	0.98	0.89-1.08	0.77
IVST	0.94	0.68-1.31	0.751
LVPWT	0.96	0.64-1.45	0.877
EF	1.11	0.94-1.30	0.188
E peak	1	0.96-1.03	0.959
A peak	1	0.93-1.08	0.927
E/A	1.05	0.04-2.32	0.975
DT	0.99	0.97-1.02	0.777
IVRT	0.99	0.95-1.03	0.661
HsCRP	5.57	3.38-7.87	0.010*
IL-6	4.8	2.72-6.88	0.001*
TNF-α	2.56	1.43-4.73	0.002*
TGF-β1	0.57	0.00-4.2	0.995

Note: (*): p.05.

Risk factors associated with persistent AF

In the analysis of possible risk factors in HFmrEF patients with persistent AF significant risk factors relative to the control group were: The frequency of hypertonic crisis (OR=1.56, CI=1.041-1.971, p=0.001) and increased BMI (OR=1.97, CI=0.98-2.21, p=0.044). The OR values for LAD and LAV were also significantly increased (OR=3.69, CI=2.58-4.82, p=0.002; OR=3.80, CI=2.65-4.09, p=0.040, respectively). An analysis of echocardiological data has revealed that left ventricular diastolic dysfunction is a possible risk factor in HFmrEF patients with persistent AF compared to those with paroxysmal AF. Statistically significant increases were observed in IVST (OR=1.69, CI=1.48-1.98, p=0.042), E peak (OR=3.05, CI=3.01-3.05, p=0.012) and IVRT (OR=3.94, CI=3.90-4.99, p=0.016). Moreover, in patients with persistent AF, impaired LV systolic function is important. The risk of persistent AF was associated with increased LVEDD (OR=1.76, CI=1.58-1.99, p=0.046), LVEDV (OR=1.93, CI=1.89-2.09, p=0.019) and some reduction in EF (OR=1.30, CI=1.08-1.57, p=0.05). A significant increase in the levels of OR markers of inflammation was also revealed (Hs-CRP: OR=6.37, CI=5.24-8.59, p=0.002; IL-6: OR=5.58, CI=4.71-7.87, p=0.001; TNF-α: OR=2.51, CI=2.51-4.68, p=0.002) which may also contribute to the high risk of developing persistent AF in patients with HFmrEF. Moreover, an increase in the OR of profibrotic TGF-β1 (OR=3.84, CI=2.10-6.23, p=0.005), in contrast to paroxysmal AF, may also be a possible risk factor for the development of persistent AF in patients with HFmrEF as shown in the Table 3.

Table 3: The analysis odds ratio value of various clinical hemodynamic and structural-functional parameters, as well as markers of inflammation and fibrosis in HFmrEF patients with persistent AF compared with the control group.

HFmrEF with Persistent AF (n=90)			
Indices	**Odds Ratio (OR)**	**95% CI**	**p-value**
Sex	0.3	0.12-0.74	0.09
Age	1.06	0.98-1.14	0.101
SBP	0.98	0.94-1.04	0.661
DBP	1	0.94-1.07	0.801
Heart rate	0.96	0.92-1.01	0.142
HrC	1.56	1.04-1.97	0.001*
Transitory ischemic attacks	0.69	0.14-2.93	0.583
ICD	1.32	0.45-3.83	0.608
Myocardial infarction	2.2	0.81-5.95	0.12
P_{max}	4.81	4.07-5.94	0.001*
P_{dis}	4.9	4.86-5.93	0.001*
QRS	0.97	0.93-1.01	0.168
BMI	1.97	0.98-2.21	0.044*
LAD	3.8	2.65-4.09	0.040*
LAV	3.69	2.58-4.82	0.002*
LVEDD	1.76	1.58-1.99	0.046*
LVEDV	1.93	1.89-2.09	0.019*
LVESV	0.96	0.88-1.06	0.48
IVST	1.69	1.48-1.98	0.042*
LVPWT	0.83	0.55-1.24	0.368
EF	1.3	1.08-1.57	0.05*
E peak	3.05	3.01-3.09	0.012*
A peak	0.93	0.86-1.00	0.059
E/A	1.05	1.02-2.55	0.72
DT	0.97	0.95-1.00	0.071
IVRT	3.94	3.90-4.99	0.016*
HsCR	6.37	5.24-8.59	0.002*
IL-6	5.78	4.71-7.87	0.001*
TNF-α	2.51	2.37-4.68	0.002*
TGF-β1	3.84	2.10-6.23	0.005*

Note: (*): p.05.

Discussion

AF is the most common and heterogeneous arrhythmia in the spectrum of symptoms. Currently, much attention is paid to assessing the quality of life, possible risk factors and concomitant diseases that contribute to atrial remodeling, thereby leading to a worsening of the course and prognosis of AF.

It has been demonstrated that LA dysfunction, as well as their structural abnormalities, play an important role in the initiation of AF, i.e., electrical and structural remodeling of the atria contributes to the development and progression of AF [16,17]. Currently, existing data undeniably indicate the participation of inflammation in the pathogenesis of AF. Moreover, AF is known to have a strong association with HF, as many studies have shown that AF and HF often coexist, share common predisposing factors and may worsen the overall prognosis [18-20]. We examined clinical, structural and biochemical predictors of paroxysmal/persistent AF in HFmrEF patients and compared them with similar patients without AF. The results of our studies show that the tendency to obesity is one of the possible risk factors for the occurrence of AF in patients with HF. Overweight people have a higher incidence, prevalence, severity and progression of AF than people of normal weight. Obese patients often have multiple risk factors for developing AF that improve in response to weight loss; this makes a consolidated approach to weight loss and management of AF risk factors preferable [21]. A meta-analysis of 10 studies involving 108,996 patients found that for every 5% increase in weight, the incidence of AF increased by 13% (Hazard Ratio (HR)=1.13; 95% CI=1.04-1.23; p<0.1). The authors of this study concluded that weight gain is associated with an increased risk of AF [22,23]. Our data suggest that patient BMI is a significant predictor of the occurrence of paroxysmal and persistent AF in patients with HFmrEF.

Recent studies have demonstrated a correlation between changes in the anatomical structure of the atria and the level of inflammatory cytokines [24,25]. This phenomenon has been accepted as a new insight into the study of the pathogenesis of AF, especially in patients with HF [26].

Comparison of risk factors associated with paroxysmal and persistent AF suggests that predictive factors have different effects on the occurrence and progression of AF in patients with HFpEF. In paroxysmal AF, special attention should be paid to the frequency of Hcr, markers of inflammation OR. And in the persistent form of AF, possible risk factors are to inflammatory markers also a fibrosis marker

Our comparison of possible risk factors associated with paroxysmal and persistent AF suggests that predictor factors contribute differently to the occurrence and progression of AF. Thus, the OR of indicators of atrial electrical remodeling (P_{max} and P_{dis}) turned out to be quite informative in the analysis, which can emphasize the particular importance of atrial damage in the occurrence of AF.

Based on the study of the relationship between left ventricular diastolic function (peak E, peak A, E/A ratio and IVRT deceleration time) and the risk of AF, it turned out that these parameters do not play an important role in the occurrence of paroxysmal AF, but are decisive in persistent AF.

Conclusion

In summary, our principal findings are as follows:

- In patients with HFmrEF, electrical remodelling of the atria, as well as BMI, play an important role in the occurrence of paroxysmal/persistent AF.
- Deterioration of LV diastolic function and changes in LA geometry are possible risk factors when paroxysmal/persistent forms of AF occur in patients with HFmrEF.
- An increase in the concentration of inflammatory markers contributes to the appearance of paroxysmal/persistent AF in patients with HFmrEF. An increase in the level of a profibrotic marker increases the likelihood of persistent AF in these patients.

Acknowledgments

The authors thank the patients who participated in this study and donated their samples, the staff of the Department of Arrhythmia and Immunological laboratory of the Research Institute of Cardiology.

Ethical Approval of Study Participants

Database is collected from atrial fibrillation patients in the Department of Arrhythmia at the Research Institute of Cardiology named after Levon Hovhannisyan (Yerevan, Armenia), approved by the Local Ethical Committee (Protocol no.3 of the 05.11.2021) and with informed consent from the patients.

Funding

Our group of authors did not use any foundation and had no financial support.

Conflict of Interest

The authors declare no conflict of interest.

References

1. Bragazzi NL, Zhong W, Shu J, et al. Burden of heart failure and underlying causes in 195 countries and territories from 1990 to 2017. Eur J Prev Cardiol. 28(15):1682-1690 (2021).
2. Shen L, Jhund PS, Petrie MC, et al. Declining risk of sudden death in heart failure. N Engl J Med. 377(1):41-51 (2017).
3. Al-Khatib SM, Benjamin EJ, Albert CM, et al. Advancing research on the complex interrelations between atrial fibrillation and heart failure: A report from a us national heart, lung, and blood institute virtual workshop.

Circulation. 141(23):1915-1926 (2020).

4. Carlisle MA, Fudim M, de Vore AD, et al. Heart failure and atrial fibrillation, like fire and fury. JACC Heart Fail. 7(6):447-456 (2019).

5. Nso N, Bookani KR, Metzl M, et al. Role of inflammation in atrial fibrillation: A comprehensive review of current knowledge. J Arrhythmia. 37:1-10 (2021).

6. Peters AE, Mentz RJ, Sun JL, et al. Patient-reported and clinical outcomes among patients hospitalized for heart failure with reduced versus preserved ejection fraction. J Card Fail. 28(12):1652-1660 (2022).

7. McDonagh TA, Metra M, Adamo M, et al. 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: Developed by the task force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). With the special contribution of the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail. 24(1):4-131 (2022).

8. Mesquita ET, Barbetta L, Correia ETO. Heart failure with mid-range ejection fraction-state of the art. Arq Bras Cardiol. 112(6):784-790 (2019).

9. Tsuji K, Sakata Y, Nochioka K, et al. Characterization of heart failure patients with mid-range left ventricular ejection fraction-a report from the CHART-2 study. Eur J Heart Fail. 19(10):1258-1269 (2017).

10. Koh AS, Tay WT, Teng THK, et al. A comprehensive population-based characterization of heart failure with mid-range ejection fraction. Eur J Heart Fail. 19(12):1624-1634 (2017).

11. Sartipy U, Dahlström U, Fu M, et al. Atrial fibrillation in heart failure with preserved, mid-range, and reduced ejection fraction. JACC Heart Fail. 5(8):565-574 (2017).

12. Bassand JP, Accetta G, Camm AJ, et al. Two-year outcomes of patients with newly diagnosed atrial fibrillation: Results from GARFIELD-AF. Eur Heart J. 37(38):2882-2889 (2016).

13. Marrouche NF, Wazni O, McGann C, et al. Effect of MRI-guided fibrosis ablation *vs.* conventional catheter ablation on atrial arrhythmia recurrence in patients with persistent atrial fibrillation: The DECAAF-II randomized clinical trial. JAMA. 327(23):2296-2305 (2022).

14. Pandey A, Kim S, Moore C, et al. Predictors and prognostic implications of incident heart failure in patients with prevalent atrial fibrillation. JACC Heart Fail. 5(1):44-52 (2017).

15. Santhanakrishnan R, Wang N, Larson MG, et al. Atrial fibrillation begets heart failure and vice versa: Temporal associations and differences in preserved versus reduced ejection fraction. Circulation. 133(5):484-492 (2016).

16. Kornej H, Börschel CS, Benjamin EJ, et al. Epidemiology of atrial fibrillation in the 21st century novel methods and new insights. Circ Res. 127:4-20 (2020).

17. Gopinathannair R, Chen LJ, Mina K, et al. Managing atrial fibrillation in patients with heart failure and reduced ejection fraction: A scientific statement from the American heart association. Circ Arrhythm Electrophysiol. 14(7):e000078 (2021).

18. Kyoung M, Park JJ, Lim NK, et al. Impact of atrial fibrillation in patients with heart failure and reduced, mid-range or preserved ejection fraction. Heart. 106:1160-1168 (2020).

19. Lippi G, Sanchis-Gomar F, Cervellin G. Global epidemiology of atrial fibrillation: An increasing epidemic and public health challenge. Int J Stroke. 16(2):217-221 (2021).

20. Hindricks G, Potpara T, Dagres N, et al. 2020 ESC guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): The task force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. Eur Heart J. 42(5):373-498 (2021).

21. Magnussen C, Niiranen TJ, Ojeda FM, et al. Sex differences and similarities in atrial fibrillation epidemiology, risk factors, and mortality in community cohorts: Results from the BiomarCaRE consortium (Biomarker for cardiovascular risk assessment in Europe). Circulation. 136(17):1588-1597 (2017).

22. Vyas V, Lambiase P. Obesity and atrial fibrillation: Epidemiology, pathophysiology and novel therapeutic opportunities. Arrhythm Electrophysiol Rev. 8(1):28-36 (2019).

23. Jones NR, Taylor KS, Taylor CJ, et al. Weight change and the risk of incident atrial fibrillation: A systematic review and meta-analysis. Heart. 105(23):1799-1805 (2019).

24. Ihara K, Sasano T. Role of inflammation in the pathogenesis of atrial fibrillation. Front Physiol. 13:862164 (2022).

25. Saljic A, Grandi E, Dobrev D. TGF-β1-induced endothelial-mesenchymal transition: A potential contributor to fibrotic remodelling in atrial fibrillation?. J Clinincal Investigation. 132(13):e161070 (2022).

26. Yao Y, Yang M, Liu D, et al. Immune remodelling and atrial fibrillation. Front Physiol. 13:927221 (2022).