REVIEW

New approaches to the diagnosis and treatment of atrial fibrillation

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Abstract : Atrial fibrillation (AF) is a prevalent arrhythmia that exhibits an increased incidence with advancing age. AF has emerged as a critical public health concern due to its potential to precipitate cerebral infarction and heart failure. Therefore, it is imperative to implement preventive strategies for individuals at risk of AF, enable earlier diagnoses, and ensure reliable therapeutic interventions. Despite rapid advancements in diagnostic and therapeutic tools for AF, these remain insufficient. Recent studies have focused on developing diagnostic and therapeutic methodologies for AF, particularly regarding chronic inflammation. Clinical investigations have explored biomarkers of AF associated with various pathologies, including chronic inflammation, such as circulating pentraxin 3, microRNA, and fragmented cell-free DNA. Several studies have examined novel indicators that integrate conventional risk factors or the use of artificial intelligence to predict the onset of AF. We explore emerging therapeutic strategies for AF, focusing on the potential to inhibit its onset and progression by targeting factor Xa - protease-activated receptor-2 signaling. Additionally, we review the treatment of AF complicated by heart failure through catheter ablation, including the innovative technique of pulse field ablation. This review focuses on the advancement of innovative diagnostic and therapeutic strategies for AF through a multifaceted approach. J. Med. Invest. 73 : 1-11, February, 2026

Keywords **:** *atrial fibrillation, inflammation, biomarkers, anticoagulant therapy, catheter ablation*

INTRODUCTION

Atrial fibrillation (AF) is a prevalent arrhythmia that exhibits an increased incidence with advancing age. It is estimated that there are over one million patients with AF in Japan, including those who may potentially become AF patients (1). In AF, the atria produce irregular electrical vortices, or small reentries, at a frequency of 350 to 600 times per minute. A subset of these electrical signals reaches the ventricles, leading to irregular excitation and consequently resulting in arrhythmias. The incidence of AF increases with advancing age and is correlated with the onset of stroke, heart failure, and myocardial infarction. Established risk factors for AF encompass aging, hypertension, heart failure, coronary artery disease, valvular heart disease, obesity, diabetes, and chronic kidney disease (2, 3). Moreover, the management of AF encompasses : (1) anticoagulation therapy to prevent the risk of cerebral infarction ; (2) rhythm control to re-establish normal cardiac rhythm, thereby improving symptoms and preventing heart failure ; and (3) rate control to regulate the heart rate. In addition to pharmacological interventions, catheter ablation is rapidly advancing as a method for rhythm control. Nonetheless, the pathogenesis of AF, which is associated with chronic inflammation, remains largely unexplored. It is expected that new diagnostic and therapeutic approaches, including those for chronic inflammation, will be developed. This review article introduces and summarizes research concerning the development of AF as a manifestation of chronic inflammation. It further explores investigations into biomarkers associated with various pathologies, including chronic inflammation, and examines novel methodologies for predicting and diagnosing AF, incorporating the authors' studies. Additionally, this review addresses the advancement of innovative therapeutic strategies for AF linked with heart failure, which are anticipated to directly improve prognosis and clinical outcomes.

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ATRIAL FIBRILLATION AND A CHRONIC INFLAMMATION

AF, as previously noted, is a multifactorial condition influenced by risk factors such as aging, hypertension, heart failure, obesity, and diabetes. Chronic inflammation has been proposed as a fundamental mechanism underlying the pathogenesis of these various risk factors. This finding is robustly corroborated by prior studies, including the following : elevated serum levels of C-reactive protein (CRP) and interleukin (IL)-6 in patients with AF (4, 5) ; significantly higher incidence of new AF in patients with elevated CRP levels compared to those with lower CRP levels (6) ; a significantly greater infiltration of inflammatory cells, specifically macrophages, in the atria of patients with AF compared to those in sinus rhythm, with the degree of infiltration being more pronounced in patients with chronic AF than in those with paroxysmal AF (7, 8) ; a high incidence of AF following open-heart surgery which induces significant inflammation (9, 10) ; and a remarkable effectiveness of steroids, which effectively suppress inflammation, preventing the recurrence of AF in patients who have been restored to sinus rhythm through defibrillation (11). While numerous aspects of the mechanism remain to be elucidated, animal experimental models have

proposed the hypothesis that cytokine secretion from mast cells contributes to AF (12), and that myeloperoxidase present in neutrophils induces AF (13). Consequently, there is a growing focus on elucidating these mechanisms.

Toll-like receptor (TLR) 9 plays a crucial role in detecting bacterial DNA (14) and subsequently activating the innate immune response, while fragmented DNA released from mammalian cells induces inflammation (15). In a recent study, we demonstrated that TLR9 is integral to the progression of vascular inflammation and atherosclerosis by facilitating the proinflammatory activation of macrophages (16). Recent studies have shown that circulating mitochondrial free DNA (mt-cfDNA), a form of fragmented DNA that may contribute to inflammatory diseases, is associated with the presence of AF (17-20).

BIOMARKERS FOR ATRIAL FIBRILLATION

There is a growing body of evidence linking inflammation to AF, similar to its association with various other cardiovascular diseases (21). Numerous studies have examined the role of inflammatory molecules in the initiation and progression of AF from a pathophysiological perspective, highlighting their potential utility as biomarkers.

C-reactive protein (CRP)

CRP serves as a biomarker predominantly utilized in clinical practice to assess the presence and severity of inflammation. Numerous clinical studies have documented the correlation between blood CRP levels and AF (22, 4). These findings suggest that inflammation plays a role in the development of AF. However, they may also be interpreted as evidence that AF induces inflammation.

Cytokine

Interleukin-6 (IL-6) is synthesized by macrophages, T-cells, and endothelial cells, and it exhibits both pro-inflammatory and anti-inflammatory properties. IL-6 has been identified as a potential biomarker for predicting the onset of AF in a specific cohort of patients, including those with coronary artery disease and chronic kidney dis ease (23, 24). In addition, IL-6 level was associated with mortality independent of established clinical risk factors and other strong cardiovascular biomarkers in patients with AF (25).

Pentraxin 3 (PTX3)

Elevated concentrations of CRP and IL-6 in patients with AF suggest the presence of systemic inflammation and do not necessarily indicate localized atrial inflammation. Conversely, pentraxin 3 (PTX3), categorized as a long pentraxin, is synthesized in response to inflammatory stimuli by local cells, including vascular endothelial cells, macrophages, smooth muscle cells, fibroblasts, and dendritic cells (26). In contrast to short pentraxins such as CRP, which are synthesized exclusively by the liver, PTX3 may serve as a valuable marker for local infection and inflammation. We hypothesized and subsequently examined whether elevated levels of circulating PTX3 serve as an indicator of local atrial inflammation in patients diagnosed with AF (27). Blood samples were obtained from both peripheral vessels and the left atrial appendage to evaluate PTX3 levels in patients undergoing AF ablation. Patients with WPW syndrome who underwent left atrial catheterization were utilized as the control group in the study. Analysis of the data revealed that patients with AF exhibited increased plasma PTX3 concentrations in both the peripheral circulation and the left atrial appendage when compared to control subjects. Additionally, in patients with AF, PTX3 levels were notably higher in the left atrial appendage than in the peripheral circulation. However, no significant differences were identified between left atrial appendage and peripheral PTX3 concentrations in the control group (Figure 1A) (27). On the other hand, no significant differences were identified in the levels of CRP, IL-6, and TNF-α between the left atrial appendage and peripheral blood in both patients with AF and the control groups. Moreover, immunohistochemical analysis in autopsy cases of AF demonstrated PTX3 expression in atrial endothelial cells and infiltrating macrophages (Figure 1B), supporting the clinical data. (27) The findings suggest that circulating PTX3 serves as a reflection of local atrial inflammation in AF and may hold potential as a biomarker for AF.

microRNAs

In recent years, there has been an increasing number of studies suggesting that microRNAs (miRs), a class of small non-coding RNA, serve as significant biomarkers for cancer and cardiovascular disease (28-30). The authors have indicated that circulating levels of miR-100 may serve as a valuable biomarker for identifying vulnerable plaque (29). While basic research has explored the association between microRNAs and AF (31), there is a lack of studies investigating the relationship between circulating microRNAs and AF or atrial remodeling in clinical contexts. The authors thus investigated the potential association between microRNAs that regulate genes, which involved in ion channels and fibrotic factors, and atrial remodeling related to AF (32). Plasma levels of miR-328, which target genes encoding L-type calcium channels, were observed to be significantly elevated in patients with AF compared to control subjects. In patients with AF, the levels of miR-328 in the left atrial appendage were significantly elevated compared to those in the peripheral and pulmonary veins, with miR-1 levels exhibiting a similar pattern. Moreover, the levels of miR-328 in the left atrial appendage of patients with AF demonstrated a significant positive correlation with both the left atrial voltage zone index (defined as the low-voltage area below 0.5 mV/total left atrial area, which serves as a quantitative assessment of intraatrial fibrosis) and the left atrial volume index (32). Considering the aforementioned factors, it is proposed that in patients with AF, circulating levels of miR-328 serve as indicators of left atrial remodeling and contribute to atrial structural remodeling. This observation highlights the potential of miR-328 as a novel biomarker.

Fragmented cell-free DNA

Recent studies have reported findings concerning the analysis of fragmented DNA or mitochondrial cell-free DNA (mt-cfDNA) in patients with AF. Wiersma *et al*. (17) observed that mt-cfDNA levels were significantly elevated during the early stage of AF (paroxysmal AF) in comparison to the control group, whereas these levels decreased in the late stage of AF (long-term persistent AF). Yamazoe *et al*. (18) demonstrated that the AF group exhibited elevated total cfDNA concentrations in comparison to the non-AF group and that patients with persistent AF showed higher mt-cfDNA levels than those with paroxysmal AF. In contrast, Miyamoto *et al*. (19) found no significant difference in mt-cfDNA levels between paroxysmal and persistent AF. Furthermore, they observed that patients with tachycardia-induced cardiomyopathy exhibited significantly lower mt-cfDNA levels compared to those without this condition. Recently, Pool *et al*. (20) reported that atrial tissue samples from patients with paroxysmal AF and persistent AF of less than 3 years' duration had a significantly progressively increased number of DNA lesions compared with patients in sinus rhythm. Moreover, the study revealed that mt-cfDNA levels in atrial tissue samples were diminished in patients with AF of more than 3 years' duration

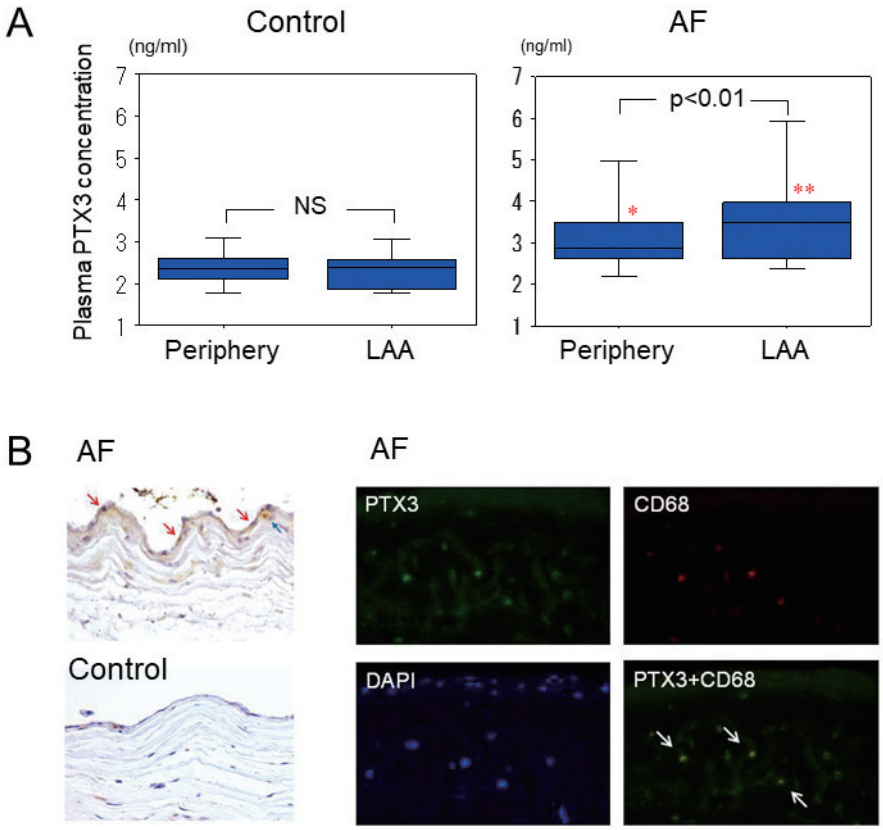

Figure 1. PTX3 in plasma and left atrium in patients with and without AF. (Adapted from Soeki *et al*. (27))
A. Plasma PTX3 concentrations in the periphery and LAA.
B. PTX3 expressions in left atrium in an autopsy case with AF (immunohistochemical staining).
Left : PTX3 expression was found in atrial endocardium (red arrows) and infiltrated macrophage (blue arrow) in LAA tissue from patients with AF (upper figure). It was less evident in left atrial tissue from patients without AF (lower figure). Right : Expression of PTX3- and CD68-positive macrophages in left atrium from patients with AF. The DNA binding dye (DAPI, blue) enables visualization of the cellular nucleus. The green signal shows the expression of PTX3 and the red signal shows the distribution of CD68-positive macrophages. Merged image shows overlapping expression (yellow staining indicated by white arrows)
*P<0.01, **P<0.05 vs control group.
AF, atrial fibrillation ; LAA, left atrial appendage ; PTX3, pentraxin 3.

compared to those with less than 3 years of AF. While these findings indicate that circulating cfDNA, particularly mt-cfDNA, is elevated in patients with AF, there remains ongoing debate regarding whether mt-cfDNA levels decrease or increase following the progression of AF. The reduction in mt-cfDNA levels observed in patients with long-persistent AF may be indicative of the severity of the disease, potentially reflecting mitochondrial functional exhaustion rather than an inflammatory response.

Challenges in Biomarker Development for AF

Although PTX3 is available as a commercially accessible ELISA kit with a well-established measurement system, its associated costs are significantly higher compared to existing inflammatory markers such as CRP. Its elevated levels have been reported in several inflammatory cardiovascular diseases including Kawasaki disease (33), and its specificity for AF is questionable. MicroRNAs are promising candidates for disease-specific biomarkers, including those for AF. However, the inherently low RNA concentrations involved introduce significant technical variability during processes such as extraction, reverse transcription, and quantitative PCR. Furthermore, measurement costs are high and results take time to obtain. Cell-free DNA results vary significantly depending on the extraction and quantification method (e.g., qPCR, fluorometry), and standardized protocols are lacking. Furthermore, variability has been reported in cancer and other conditions (34), making disease specificity problematic. As previously mentioned, these biomarkers currently face several challenges. Moreover, for their clinical application, it is essential to conduct large-scale prospective clinical trials that demonstrate their superiority over existing gold-standard markers and diagnostic methods in terms of diagnostic accuracy, prognostic predictive power, and treatment efficacy monitoring.

PREDICTORS OF ATRIAL FIBRILLATION

Combined score that integrate conventional risk factors

Prompt and accurate diagnosis, along with timely intervention, are essential in patients with AF to prevent stroke and heart failure associated with this condition. To accomplish this objective, it is crucial to implement optimal risk stratification prior to the onset of AF. Identified risk factors for AF encompass aging, hypertension, diabetes, obesity, and cardiovascular conditions such as heart failure, coronary artery disease, and valvular heart disease (2, 3). Moreover, echocardiographic

parameters, including left atrial size (35, 36) and the diastolic dysfunction index (36, 37), have been identified as predictors of the onset of AF. Furthermore, the frequency of premature atrial contractions (PACs) has been recognized as an important tool for the risk stratification of AF (38, 39). Nonetheless, it remains uncertain whether the integration of these traditional clinical measures, echocardiographic parameters such as left atrial size, and Holter electrocardiogram (ECG) indicators like PACs, can enhance the accuracy of risk stratification for AF. The authors addressed this inquiry by conducting a retrospective study involving 1,040 patients without AF who presented with suspected heart disease at Tokushima University Hospital (40). Over a median follow-up duration of 68.4 months, 103 out of 1,040 patients developed new-onset AF. Notably, patients who experienced AF were significantly older than those who did not. Patients who developed AF demonstrated a significantly reduced total heart rate and a markedly increased total daily count of PACs. Additionally, they exhibited a higher incidence of cardiac arrests and an increased maximum RR interval compared to patients without AF. Patients who developed AF also exhibited a significantly increased left atrial diameter. The multivariate Cox proportional hazards analysis identified that age, the total daily number of PACs, the maximum RR interval, and the left atrial diameter independently contributed to an increased risk of developing AF (Table) (40). Therefore, the combined score for AF prediction was calculated as the sum of the weighted scores (age≥58 years, 1 ; PACs≥80 beats/day, 2 ; maximum RR interval≥1.64 s, 1 ; left atrial diameter ≥4.5 cm, 1) derived from the Cox proportional hazards ratio. The incidence of AF exhibited an upward trend in association with increasing combined scores (Figure 2) (40). The findings indicate that a combined score, which includes age, maximum RR interval, PACs, and left atrial diameter, can enhance the predictive capability for AF. This score serves as a straightforward indicator that can be assessed within general clinical practice and is regarded as clinically applicable. The CHARGE-AF score, a clinical data-based AF prediction tool with robust evidence, was developed to forecast AF in three U.S. cohorts and subsequently validated in two European cohorts (41).

Table. Independent predictors of new-onset AF based on clinical, electrocardiographic, and echocardiographic perspectives (40)

	Univariate analysis			Multivariate analysis		
	Hazard ratio	95% CI	*P* value	Hazard ratio	95% CI	*P* value
Age (≥58 years)	3.522	1.968-6.302	<0.001	1.868	1.008-3.464	0.047
PAC count (≥80 beats)	4.164	2.751-6.303	<0.001	3.077	1.956-4.841	<0.001
Maximum RR interval (≥1.64 s)	2.628	1.777-3.887	<0.001	1.704	1.131-2.569	0.011
LAD (≥4.5 cm)	2.853	1.818-4.477	<0.001	1.839	1.155-2.927	0.010
Total heart beats (≥101600 beats)	2.155	1.418-3.271	<0.001			
Sinus pause (≥36/24 hr)	4.215	2.194-8.099	<0.001			

AF, atrial fibrillation ; CI, confidence interval ; LAD, left atrial diameter ; PAC, premature atria contraction.

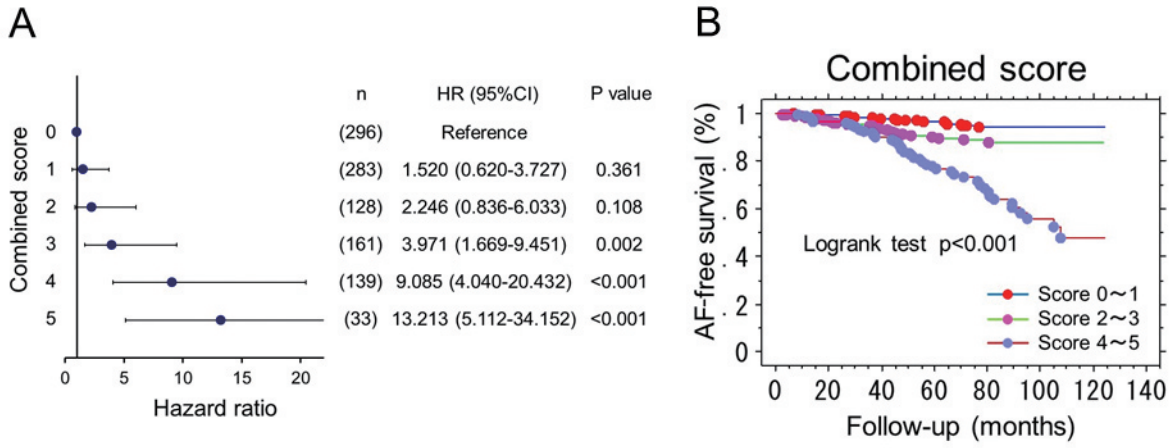

Figure 2. The prognostic value of a combined score in predicting the incidence of new-onset AF. (Adapted from Soeki *et al.* (40))
A. Hazard ratio for new-onset AF according to the combined score.
B. Kaplan-Meier estimate of survival free from new-onset AF according to the combined score for new-onset AF.
AF, atrial fibrillation.

Then, it has demonstrated superiority over other clinical scoring systems (42). Nevertheless, the computation of the CHARGE-AF score necessitates either manual or automated data extraction, which may prove to be burdensome in clinical practice.

Prediction using artificial intelligence (AI)

Recently, the application of artificial intelligence (AI) in predicting the onset of AF has attracted considerable scholarly interest. Attia *et al*. (43) demonstrated that a single 12-lead ECG in sinus rhythm is capable of identifying the presence of AF, albeit within the context of a retrospective study. The study reported an area under the curve of 0.87, a sensitivity of 79.0%, a specificity of 79.5%, an F1 score of 39.2%, and an overall accuracy of 79.4%. Noseworthy *et al*. (44) conducted a study to evaluate an AI algorithm for predicting AF from sinus rhythm ECGs. The study monitored AF onset in 1,003 patients over 22.3 days through continuous monitoring. The results demonstrated an odds ratio of 4.98 for the high-risk group identified by the AI algorithm in comparison to the low-risk group. Moreover, another study revealed that a convolutional neural network, employing deep learning on 907,858 outpatient sinus rhythm ECGs, successfully predicted AF within 31 days across a diverse demographic and comorbidity population (45). The findings indicate that routinely recorded ECGs may serve as a valuable tool for the early detection of future risk through the application of AI algorithms. This represents a paradigm shift from the traditional medical practice of treating patients after the onset of symptoms to an innovative approach that emphasizes the identification and mitigation of risks before symptoms manifest.

A NEW APPROACH TO TREATING ATRIAL FIBRILLATION

Anti-inflammatory treatment for AF

Anti-inflammatory drugs and drugs targeting inflammatory molecules have been investigated as potential drugs for the treatment of AF. Corticosteroids are frequently employed in the management of severe infections, and evidence suggests that they decrease the incidence of AF in patients following pharmacological or electrical defibrillation (11), catheter ablation (46), and coronary artery bypass grafting (47). Colchicine is an anti-inflammatory medication that is clinically employed in the management of pericarditis within the context of cardiovascular disease. In the treatment of AF, colchicine has been shown to significantly reduce serum CRP and IL-6 levels, thereby preventing the recurrence of AF following catheter ablation (48). Additionally, it has been reported to be effective in the prevention of postoperative AF (49). Several studies have demonstrated the efficacy of statins, which are HMG-CoA reductase inhibitors used in the treatment of hypercholesterolemia, in both the primary and secondary prevention of AF, probably through their anti-inflammatory effects (50). While these agents are currently employed in clinical practice for indications other than AF suppression, and the barriers to their clinical application for AF are minimal, it remains crucial to establish their efficacy in suppressing AF through large-scale prospective studies.

Factor Xa-PAR-2 signaling and cardiovascular disease

Previous research has demonstrated that multiple coagulation factors, specifically proteases, play an important role not only in thrombus formation but also in mediating inflammatory responses through protease-activated receptors (PARs) expressed on various cell types (51). Four types of PARs have been identified to date : PAR-1, PAR-3, and PAR-4 primarily function as thrombin receptors, whereas PAR-2 is predominantly activated by factor Xa. Among the PAR subtypes, PAR-2 is considered to play a pivotal role in the context of chronic inflammation (52). PAR-2 is extensively distributed throughout the body and is involved in the regulation of numerous physiological functions. Within the circulatory system, expression has been documented in the vascular endothelium, vascular smooth muscle, and cardiac muscle. In recent investigations, we observed an upregulation of PAR-2, the Xa receptor, in ApoE-deficient mice, which serve as a model for atherosclerosis. Subsequently, we reported that the administration of the Xa inhibitor rivaroxaban effectively suppressed the formation of atherosclerosis and mitigated plaque instability in this model, while also reducing the expression of inflammatory mediators in the aorta (53). In our study utilizing PAR-2/ApoE-deficient mice, we were the first to demonstrate that factor Xa-PAR-2 signaling activates macrophages, thereby inducing vascular inflammation and facilitating the progression of atherosclerosis. Additionally, we identified that bone marrow-derived PAR-2 is crucial in the development of atherosclerotic lesions (54). Furthermore, studies have indicated that PAR-2-deficient mice, in comparison to wild-type mice, exhibit a reduction in inflammatory responses and infarct size following myocardial ischemia/reperfusion, thereby maintaining cardiac function over an extended duration (55). This finding implies that PAR-2 may also play a role in ventricular remodeling through its involvement in cardiac inflammation. Furthermore, the clinical AFIRE trial revealed that in patients with AF and stable coronary artery disease, rivaroxaban monotherapy was not inferior to combination therapy with an antiplatelet agent in preventing ischemic events and was superior in reducing the risk of major bleeding (56). Although the involvement of factor Xa-PAR-2 signaling in this context remains unknown, this finding suggests that Xa inhibitors may exert effects beyond anticoagulation, such as anti-atherosclerosis and anti-vascular inflammation, potentially leading to expanded indications in the future.

Factor Xa-PAR-2 signaling and AF

Based on the results of previous research on PAR-2, we have recently formulated and empirically tested the hypothesis that PAR-2 signaling facilitates atrial remodeling through its inflammatory and fibrotic effects, thereby predisposing individuals to AF (57). Upon administration of angiotensin II (Ang II) to both PAR-2-deficient and wild-type mice, the wild-type mice exhibited accelerated atrial fibrosis and a marked increase in the inducibility of AF. In contrast, the PAR-2-deficient mice demonstrated reduced fibrosis and no significant difference in the inducibility of AF compared to the control group (Figure 3) (57). In a subsequent phase of the study, spontaneously hypertensive rats were administered the factor Xa inhibitor rivaroxaban orally. The group treated with rivaroxaban exhibited a significant reduction in the expression of inflammatory biomarkers and those associated with fibrosis, in comparison to both the control and warfarin groups. Furthermore, the inducibility of AF was markedly lower in the rivaroxaban-treated group compared to the warfarin-treated and control groups. Histological analysis revealed a significant reduction in atrial fibrosis in the group treated with rivaroxaban compared to both the warfarin-treated and control groups (Figure 3) (57). The findings indicate that signaling through factor Xa-PAR2 facilitates atrial remodeling and increases susceptibility to AF via inflammation-induced profibrotic mechanisms and that rivaroxaban acts as an inhibitor of the factor Xa pathway, which leads to the suppression of atrial inflammatory responses and the prevention of AF onset (Figure 4). However, these findings are based on animal studies and thus require rigorous validation in a clinical setting. It is generally considered challenging to prospectively examine the impact of Xa inhibitors on the suppression of AF. Nevertheless,

Xa inhibitors are extensively utilized to prevent thromboembolism in patients with AF. Given the substantial volume of clinical data available, it is anticipated that it will be feasible to extract and analyze the effects of Xa inhibitors on AF suppression. It is further hoped that the efficacy of Xa inhibitors in suppressing AF will be substantiated through meta-analyses and similar methodologies.

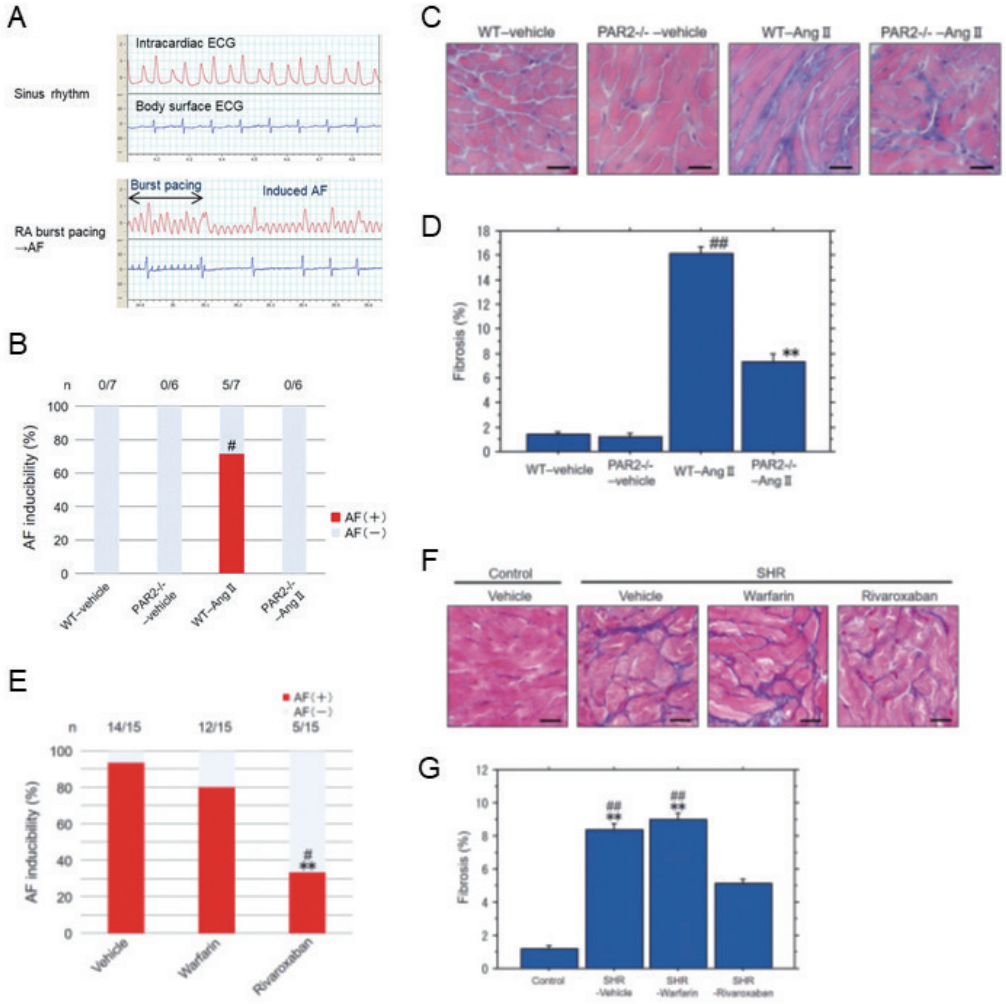

Figure 3. The role of the factor Xa–PAR2 pathway in AF inducibility associated with atrial fibrosis and the impact of the factor Xa inhibitor, rivaroxaban, on atrial remodeling and AF inducibility. (Adapted from Matsuura *et al*. (57))

A. Representative body-surface and intracardiac ECG recordings before and after right atrial burst pacing.

B. AF inducibility in PAR2-deficient and wild type mice.

Angiotensin II markedly increased the AF induction rate in wild type mice (71%), but it did not induce AF in PAR2-deficient mice.

C. Representative results of Masson's trichrome staining of the left atrium in PAR2-deficient and wild type mice.

D. Quantitative ratio of the area of fibrosis to the area of reference tissue in PAR2-deficient and wild type mice.

In wild type mice, the administration of angiotensin II significantly increased atrial fibrosis. In contrast, in PAR2-deficient mice, the atrial fibrosis induced by angiotensin II was notably attenuated.

E. AF inducibility in spontaneously hypertensive rats.

In spontaneously hypertensive rats, the administration of rivaroxaban significantly decreased the inducibility of AF compared to the vehicle administration group. In contrast, warfarin administration did not demonstrate a reduction in the inducibility of AF.

F. Representative results of Masson's trichrome staining of the left atrium of spontaneously hypertensive rats that received vehicle, warfarin, and rivaroxaban.

G. Quantitative ratio of the area of fibrosis to the area of reference tissue in spontaneously hypertensive rats.

In spontaneously hypertensive rats treated with vehicle, there was a significant increase in atrial fibrosis compared to control normotensive rats. Administration of rivaroxaban effectively suppressed atrial fibrosis, whereas warfarin administration did not exhibit a comparable effect.

B, D. : $^{\#\#}P<0.01$, $^{\#}P<0.05$ vs. WT–vehicle group, PAR2−/−–vehicle group and PAR2−/−–Ang II group. $^{**}P<0.01$ vs WT–vehicle group and PAR2−/−–vehicle group. E : $^{**}P<0.01$ vs. vehicle group. $^{\#}P<0.05$ vs. warfarin group. G : $^{**}P<0.01$ vs control group. $^{\#\#}P<0.01$ vs SHR-rivaroxaban group.

AF, atrial fibrillation ; Ang II, angiotensin II ; ECG, electrocardiogram ; PAR, protease-activated receptor ; RA, right atrial ; SHR, spontaneously hypertensive rats ; WT, wild type.

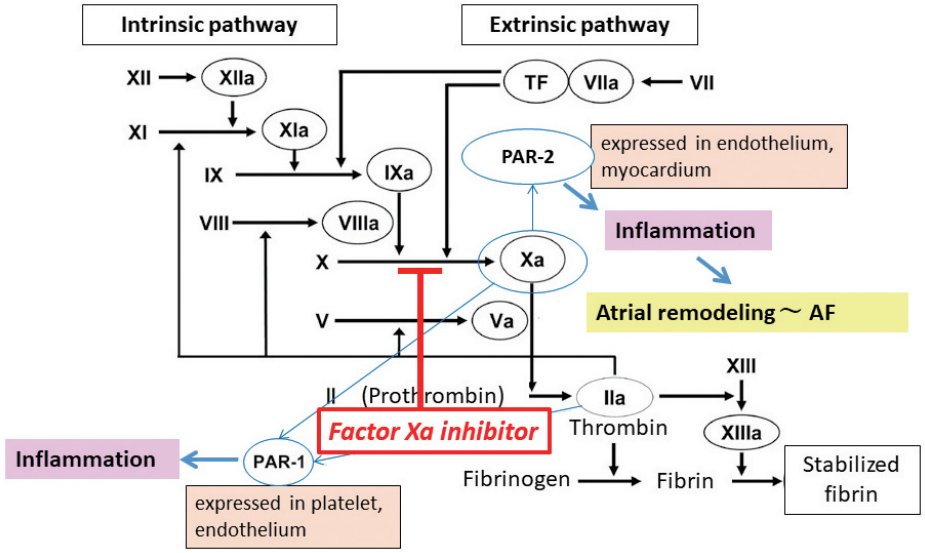

Figure 4. Coagulation cascade and PARs signaling
Factor Xa acts as a ligand for PAR-2, which is expressed in endothelial cells and cardiomyocytes and has been implicated in chronic cardiac inflammation. Moreover, our research indicates that PAR-2 also plays a role in inflammation-mediated atrial remodeling. Additionally, the factor Xa inhibitor, rivaroxaban, may attenuate PAR-2-mediated atrial remodeling and prevent the onset of AF.
AF, atrial fibrillation ; PAR, protease-activated receptor ; TF, tissue factor.

CATHETER ABLATION FOR ATRIAL FIBRILLATION COMLICATED WITH HEART FAILURE

AF and heart failure

Patients diagnosed with AF exhibit a 1.5-fold increase in mortality rate, a 2.3-fold increase in the risk of stroke, and a 5-fold increase in the risk of heart failure compared to those without AF (58). Although anticoagulant therapy can prevent many strokes, a significant number of cardiovascular deaths associated with AF are due to the progression of heart failure and sudden cardiac death (59). AF and heart failure are associated with shared risk factors, including advanced age, hypertension, diabetes, and structural heart disease (60). A study from a Japanese registry revealed that over 30% of patients aged 75 years or older, and approximately 20% of those under 75 years of age with atrial fibrillation, subsequently developed heart failure (61). Our recent study has demonstrated that the prevalence of heart failure among the elderly progressively increases in the presence of sarcopenia, an age-related skeletal muscle disorder, AF, and the concurrent presence of both conditions. Furthermore, it has also revealed that the combination of sarcopenia and AF is independently associated with heart failure, regardless of other cardiovascular risk factors (62). In addition to inflicting direct damage on mitochondrial structures within the ventricles (63), sarcopenia may exacerbate AF through mechanisms involving mitochondrial dysfunction and heightened inflammatory responses (64), thereby increasing the likelihood of heart failure. This indicates that the management of sarcopenia is crucial for the prevention of heart failure in elderly individuals with AF.

AF and heart failure with preserved ejection fraction (HFpEF) exhibit a strong interrelation. Beyond the previously mentioned risk factors, patients frequently present with additional clinical comorbidities, including obesity, chronic kidney disease, obstructive sleep apnea, alcohol consumption, and smoking. These comorbidities contribute to systemic inflammation and are linked to elevated levels of pro-inflammatory mediators (65). Longitudinal observational studies have indicated that individuals with elevated baseline levels of pro-inflammatory markers are at an increased risk of developing HFpEF and AF during subsequent follow-up periods (65). At present, as we anticipate the development of a treatment targeting inflammation, which links AF and HFpEF, it is crucial to ensure the proper execution of each treatment to disrupt this vicious cycle. Notably, catheter ablation for AF has demonstrated high efficacy and is therefore highly recommended for preventing the onset of heart failure, including HFpEF.

Catheter ablation for AF complicated with heart failure

Research indicates that pharmacological maintenance of sinus rhythm does not improve the prognosis of patients with both heart failure and AF when compared to rate control strategies (66). This phenomenon may be primarily attributed to the adverse effects of medications and the difficulties encountered in maintaining sinus rhythm. In contrast, the maintenance of sinus rhythm through catheter ablation is anticipated to surpass pharmacological interventions in terms of both adverse effects and efficacy in sustaining sinus rhythm. In fact, a meta-analysis of randomized controlled trials (RCTs) comparing the efficacy of medication (rate control therapy) and catheter ablation in patients with heart failure with reduced cardiac function (HFrEF) demonstrated that the catheter ablation group exhibited a higher left ventricular ejection fraction (LVEF), enhanced quality of life, and increased maximum oxygen consumption compared to the medication group (67). The CASTLE-AF trial (68) investigated the comparative effects of catheter ablation versus medical therapy (either rate or rhythm control) for AF on the long-term prognosis of patients with both heart failure and AF. The study focused on individuals with New York Heart Association (NYHA) stage II or higher, or a LVEF of less than 35%, and those with paroxysmal or persistent AF who had an implantable cardioverter-defibrillator or cardiac resynchronization therapy defibrillator implanted. As aresult, the catheter ablation group exhibited a significant reduction in all-cause mortality and hospitalizations attributable to worsening heart

failure. A subanalysis of the CASTLE-AF study (68) has indicated that catheter ablation may be particularly beneficial for patients with AF and HFrEF who are relatively young (under 65 years of age), exhibit mild heart failure symptoms (NYHA Class II), and possess minimally preserved left ventricular systolic function (LVEF≥25%). Moreover, the CAMERA-MRI study (69) analyzed MRI findings and demonstrated that the extent of left ventricular fibrosis, as determined by delayed myocardial enhancement (LGE), was inversely associated with the degree of LVEF improvement following AF ablation. Considering these findings, patients with AF and HFrEF who are most likely to benefit from catheter ablation are those who are younger, exhibit mild heart failure (NYHA class II or lower), show no LGE on cardiac MRI, have paroxysmal or early persistent AF, display mild left atrial enlargement on echocardiography, and are suspected of having tachycardia-induced cardiomyopathy.

Pulse field ablation for AF with heart failure

Recently, there has been a paradigm shift regarding the energy source utilized for catheter ablation. Conventional thermal energy modalities, such as radio frequency ablation and cryoablation, can adversely affect tissues adjacent to the myocardium, potentially resulting in complications such as atrioesophageal fistula, phrenic nerve paralysis, and pulmonary vein stenosis (70). In contrast, pulsed field ablation (PFA), a non-thermal energy technique employing a high-voltage electric field to induce irreversible electroporation and destabilization of cell membranes, leading to cell necrosis, specifically targets the myocardium, thereby mitigating such complications (71, 72). Recent RCTs have demonstrated that PFA and thermal ablation exhibit comparable efficacy in the treatment of AF (73). Given this context, PFA is increasingly becoming mainstream ; however, its efficacy in enhancing the prognosis of heart failure remains uncertain, necessitating further data collection.

CONCLUSION

Despite the decline in Japan's population, the incidence of AF continues to increase, attributed to the emergence of a super-aging society. This trend is anticipated to persist for a considerable period even after reaching its peak. Under these circumstances, it is crucial to develop efficient preventive strategies for individuals susceptible to AF, to facilitate earlier and more accurate diagnostic processes, and to deliver treatments that are both highly reliable and safe. Currently, various tools for the diagnosis and treatment of AF are being rapidly developed ; however, they remain insufficient. In the future, it will be essential to develop innovative tools for the diagnosis and treatment of AF through a multifaceted approach, in conjunction with advancements in diagnostic and therapeutic technologies.

CONFLICT OF INTERESTS

None

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Graphical summary