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Multidimensional Strategies to Prevent and Control Risk Factors in Patients with Nonvalvular Atrial Fibrillation: Mechanistic Explorations and Advances in Clinical Practice

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Abstract: Background: Non-valvular atrial fibrillation (NVAF), the most prevalent cardiac arrhythmia globally, poses a dual challenge of thromboembolic and bleeding risks, with stroke being the most devastating complication. Despite advancements in anticoagulation and rhythm control, patient outcomes remain suboptimal. Aim: This review synthesizes current evidence on the pathophysiological mechanisms, multidimensional management strategies, and emerging innovations in NVAF to inform clinical practice and future research directions. *Methods:* A systematic literature search was conducted across nine databases (CNKI, Wanfang, SinoMed, VIP, PubMed, Web of Science, Cochrane Library, Embase, and MEDLINE) using combined Medical Subject Headings (MeSH) and free-text terms, including "atrial fibrillation," "non-valvular atrial fibrillation," "risk factors," and "mechanism" (and their Chinese equivalents). Studies on NVAF pathogenesis, therapeutic interventions, and risk stratification tools were analyzed. *Results:* (1) Risk Factors and Pathophysiology: NVAF progression is driven by hemodynamic stress (e.g., hypertension), metabolic disorders (e.g., obesity, diabetes), chronic inflammation, and fibrosis. Biomarkers such as CRP and Galectin-3, along with TGF-β/Smad signaling, are central to atrial remodeling. (2) Anticoagulation Controversies: While NOACs reduce stroke risk compared to warfarin (HR = 0.79), challenges persist in extreme body weight populations and drug-drug interactions (e.g., with P-glycoprotein inhibitors). (3) Left Atrial Appendage Closure (LAAC): LAAC demonstrates non-inferiority to anticoagulation in stroke prevention (HR = 0.79) with reduced major bleeding (HR = 0.49), though device-related thrombosis (1.8–7%) remains a concern. (4) Precision Medicine: AI-driven models enhance stroke prediction (AUC = 0.71; sensitivity 92%), while genotype-guided warfarin dosing shortens INR stabilization by 40%. (5) Lifestyle Interventions: Combined Mediterranean diet and moderate exercise reduce AF burden (HR = 0.69) and reverse left atrial enlargement (LAVI reduced by 12%). (6) Multidisciplinary Care: Integrated "heart-brain team" approaches combining LAAC and PFO closure lower annual stroke recurrence from 8.2% to 2.1%, while comprehensive rehabilitation improves functional capacity (6MWD + 45 m) and quality of life (SF-36 + 12 points). *Conclusion:* NVAF management has evolved from isolated anticoagulation to a multidimensional paradigm integrating genomics, AI, and lifestyle modification. Future priorities include validating long-term outcomes of novel therapies, addressing evidence gaps in special populations, and implementing digitally enabled, cross-

disciplinary care models to mitigate the global burden of NVAF-related complications.

Keywords: Nonvalvular atrial fibrillation; Risk factors; Prevention and treatment; Mechanisms; Clinical practice; Advances

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1. Background

Bidirectional management of thromboembolic (especially stroke) and bleeding risks in non-valvular atrial fibrillation (NVAF), the most common arrhythmia globally, is a major challenge in the cardiovascular field [1]. Epidemiological data show that the global incidence of NVAF has shown a substantial increase over the last three decades[1]. A large number of studies have demonstrated a lifetime risk of approximately 33%, with high rates of disability and mortality [2], with a stroke risk in patients with NVAF that is five times higher than that of the general population, and a high annual incidence of bleeding events related to anticoagulant therapy of 2–4% [3]. Population aging and the prevalence of metabolic syndrome drive the continuous growth of NVAF prevalence, which is expected to exceed 30 million patients worldwide in 2030, becoming a major public health problem. The current aging population situation in China has intensified, and the China Blue Book of Self-Care shows that 85% of Chinese residents die of chronic diseases [4], in which the risk of stroke, heart failure, and other serious complications in patients with NVAF is also significantly increased, which imposes a heavy burden on the patients' individuals, families, and society [5]. Although several anticoagulants and rhythm control strategies have been used for NVAF treatment, the prognosis of patients is still unsatisfactory [1,5–8]. In recent years, the research paradigm has shifted from single anticoagulation therapy to multidimensional risk management, covering the exploration of pathomechanisms, the application of novel technologies, and individualized intervention strategies. In this article, the study systematically reviews the biological mechanisms of NVAF risk factors, the evidence-based progress of prevention and treatment strategies, and the direction of future research, with a view to providing a scientific basis for clinical practice.

2. Methods

The author searched a total of nine databases, including China Knowledge Network (CNKI), Wanfang Database, China Biomedical Literature Database (SinoMed), VIP, PubMed, Web of Science, Cochrane Library, Embase, and MEDLINE, on the computer. A combination of subject terms and free words was used for the search. The Chinese search terms were "atrial fibrillation," "non-valvular atrial fibrillation," "risk factors," and "mechanisms." The English search terms were "Atrial Fibrillation," "Non-valvular atrial fibrillation," "Risk Factor," "Mechanism," and "Machine."

3. Current research on patients with atrial fibrillation (AF)

A part of scholars have conducted a lot of research in terms of risk factors and the occurrence mechanisms of AF. Some scholars have shown that the prevalence of AF is 2% in the general population and 10–12% in people aged 80 years and above [10]. It has been concluded that: epidemiology confirms that AF is associated with a

variety of factors, which individually or in combination can contribute to the initial development of arrhythmias and the onset of disease features [11,12], aging is a major factor contributing to the pathogenesis of arrhythmias [11], arterial hypertension, obesity, diabetes mellitus, and genetics are notable predisposing factors to AF, and a variety of dietary components have a protective effect that may reduce the AF incidence [2,13]. A large prospective study involving 24,734 female participants investigated the relationship between inflammatory markers such as CRP, fibrinogen and intercellular adhesion molecule 1 and the incidence of AF, and the results suggested that inflammation is a strong indicator of the incidence of AF. In addition, some studies have confirmed that fibrosis is also an important factor in maintaining AF, and atrial remodeling caused by fibrosis is associated with AF promotion [6,14]. Meanwhile, most of the scholars also studied in terms of the complications of AF. Some scholars found that: the incidence and morbidity of AF are related to the redox potential of glutathione and cysteine, which are markers of oxidative stress, and that for every 10% increase in glutathione, the incidence of AF is 30% higher, and the same change leads to a 40% increase in the risk of AF [6,14]. Another study showed that the risk of stroke in patients with AF is five times higher than in normal subjects and 90% of cardiogenic embolic emboli originate from the atria or auricles [15]. With the increase in the incidence of AF has led to a continuous increase in the number of AF-related emergencies and hospitalizations, an increase in the number of sudden acute AF in various types of patients with acute and critical illnesses, which has seriously increased the economic pressure on the affected parties and the imbalance in the distribution of medical resources. Based on the existing research base of foreign scholars, it has been shown that the estimated lifetime risk of AF varies according to patient-level factors such as age, gender, ethnicity, and the burden of clinical risk factors, etc. In addition to genetic factors, risk factors for AF include hypertension, type 2 diabetes mellitus, and physical inactivity, which are the main factors that can increase the lifetime risk of AF [2,3]. However, interventions on risk factors can reduce the occurrence of AF [2,5,10–15], and play an important role in the secondary prevention of AF episodes.

Chinese-related studies have less data compared with foreign studies. The Chinese emergency management guidelines for acute atrial fibrillation (2024) [1] mentioned that the increase in the incidence of AF is likely to lead to a sustained increase in the number of related emergencies and hospitalizations, and seriously increase the economic pressure, and other views are consistent with the views of foreign scholars' studies [16]. Some epidemiological studies show that men are more likely to suffer from AF than women [17,18]. A multicenter prospective cohort study based on a Chinese community [9] reported the incidence of AF among people over 60 years of age in a Chinese community. Among 18738 subjects, 351 (1.87%) had new-onset AF during the four-year follow-up period; and the overall incidence rate of AF was 5.2/1000 person-years during the observation period of 67704 person-years. A study enrolling 80 patients with NVAF who were to undergo catheter ablation or electrical cardioversion for AF showed that left atrial volume index (LAVI), parietal emptying velocity (PEV), and the biomarker B-type brain natriuretic peptide (BNP) were independent risk factors for stroke risk in patients with NVAF, and PEV was more valuable in predicting stroke risk [19,20]. As for the risk factors and comorbid symptoms of AF, a small number of scholars constructed a prediction model for dementia in AF patients [21]. Meanwhile, a review study on AF showed that quality of life, physical activity, body weight, stress management, blood pressure, cardiovascular disease, heart failure, neurological disorders, cognitive dysfunction and dementia are the main influencing factors about the load of AF [22], which suggests that the occurrence of AF and its clinical consequences can be altered to a large extent by changing the life style, which is in line with the conclusions of the research of foreign scholars [2,3,5,10–15,20].

As a result, AF causes very high rates of disability and mortality, and has a poor prognosis. patients with

NVAF also have a significantly increased risk of serious complications, such as stroke and heart failure, which imposes a heavy burden on individuals, families and society, and has become an important challenge for global public health.

4. Current state of research on patients with non-valvular atrial fibrillation (NVAF)

In 2020, the European Society of Cardiology and the European Society for Cardiothoracic Anesthesia updated and published the 2020 European Society of Cardiology Guidelines for the Management of Atrial Fibrillation [5], which suggested that the AF diagnosis and treatment process should be jointly participated by the doctor and the patient. Subclinical AF can be identified with the help of devices, and the "4S-AF" process-oriented assessment, i.e., considering the structured characteristics of AF for all AF patients, comprehensively evaluating the risk factors of AF, and emphasizing lifestyle intervention and risk factor management [5,6]. The guideline also proposes the "CC To ABC" management pathway, i.e., based on individual assessment, stroke prevention, optimization of symptom control, etc., focusing on the identification and management of concomitant diseases and risk factors, and exploring lifestyle interventions, etc., for comprehensive management [5–8]. Similarly, China's "Healthy China 2030" Planning Outline and China's Medium- and Long-term Development Plan for the Prevention and Treatment of Chronic Diseases (2017–2025) both emphasize good chronic disease work. The 2018 China Atrial Fibrillation Guidelines recommend opportunistic screening for atrial fibrillation in high-risk populations, and for patients with a high risk of concomitant stroke, recommending a No less than 72 hours of long-duration ECG monitoring is recommended for the diagnosis of AF [9], and the 2019 Technical Program for Graded Diagnosis and Treatment of Atrial Fibrillation proposes that hospitals at all levels should emphasize the initial identification of AF in the population, and encourages hospitals at all levels to set up a remote ECG network based on the "Internet Plus" and strengthen the management of single diseases in the region. In summary, although a variety of anticoagulants and rhythm control strategies have been used for NVAF treatment, the prognosis of patients is still unsatisfactory.

4.1. Pathophysiologic classification of major risk factors

The pathogenesis of non-valvular atrial fibrillation (NVAF) is complex, involving multiple interactions such as electrical remodeling, structural remodeling and neuroendocrine activation. Recent studies have categorized risk factors into the following four groups: (1) Hemodynamic abnormalities: uncontrolled hypertension and heart failure lead to elevated atrial pressure, which activates the RAS system through mechanical stress, promoting myocardial fibrosis and electrical conduction heterogeneity; (2) Metabolic disorders: obesity and diabetes mellitus accelerate atrial matrix remodeling through insulin resistance and lipotoxicity, and upregulation of inflammatory factors; (3) Organ dysfunction: patients with chronic kidney disease (CKD) exacerbate vascular endothelial dysfunction due to uremic toxin accumulation and calcium and phosphorus metabolism disorders; hepatic dysfunction affects the synthesis of coagulation factors and the metabolism of anticoagulant drugs; (4) Inflammation and fibrosis cascade: biomarkers such as C-reactive protein (CRP) and Galectin-3 are positively correlated with the degree of myocardial fibrosis, and activation of the TGF-β/Smad signaling pathway is the core molecular mechanism of atrial fibrosis [11]. These factors drive atrial electrical activity through the "calcium imbalance-oxidative stress-mitochondrial dysfunction" axis, resulting in a prothrombotic state. Studies have demonstrated that NVAF patients have increased vWF release and decreased expression of thrombomodulin (TM) in left atrial endothelial cells, further promoting platelet activation and fibrin deposition [22].

4.2. Pharmacologic basis and controversies of anticoagulation therapy

Based on Virchow's three-component theory of thrombosis, anticoagulation therapy reduces the risk of thromboembolism by intervening in the coagulation cascade. The advantages of novel oral anticoagulants (NOACs) over conventional warfarin are: (1) Specific target inhibition: rivaroxaban and dabigatran directly block key nodes of coagulation and reduce thrombin generation; and (2) Predictable pharmacokinetics: NOACs do not require routine monitoring of INR and have fewer food and drug interactions, but renal function-dependent metabolism leads to an increased risk of bleeding in CKD patients [23]. However, the use of NOACs in specific populations remains controversial: (1) Patients with extreme body weight: those weighing < 50 kg or > 120 kg may have abnormal drug concentrations due to changes in the volume of distribution, but there is a lack of evidence-based rationale for dose adjustments; and (2) Multi-drug combination scenarios: when combined with P-glycoprotein inhibitors, NOACs blood concentrations are elevated by 30–40%, and bleeding complications need to be guarded against [24].

4.3. Anatomical and clinical evidence for left auricular occlusion (LAAC)

90% of NVAF-associated thrombi originate in the left auricle (LAA), and its morphologic typing is strongly associated with embolic risk. Some studies have confirmed that LAAC is noninferior to warfarin in reducing stroke risk and significantly reduces major bleeding events (HR = 0.49). However, the incidence of postoperative device-related thrombosis (DRT) (approximately 3–7%) and residual shunting remains a clinical concern. In recent years, dual-disk occluders have reduced the risk of DRT to 1.8% by enhancing endothelial coverage and sealing [25].

4.4. Intelligent innovation of risk stratification tools

4.4.1. Optimization of the CHA2DS2-VASc score

The CHA2DS2-VASc-IL score proposed in 2022 integrates interleukin-6 (IL-6) and fibrinogen levels to significantly increase stroke prediction efficacy (AUC from 0.64 to 0.71) in low-risk populations (score ≤ 1).

4.4.2. Artificial intelligence dynamic prediction system

The AF-SCORE model based on deep learning algorithms realizes real-time assessment of stroke risk by analyzing ambulatory electrocardiogram, electronic health record (EHR) and wearable device data (sensitivity 92%, specificity 88%).

4.5. Precision medicine exploration of individualized anticoagulation strategies

4.5.1. Gene-directed dose adjustment

Testing for polymorphisms in the CYP2C9 and VKORC1 genes guided the initial dose of warfarin, resulting in a 40% reduction in time to INR attainment (from 28 to 17 days).

4.5.2. Renal function-adapted regimens

For CKD patients with eGFR < 30 mL/min, apixaban dose-adjustment (2.5 mg bid) reduced the risk of major bleeding by 31% compared with the standard dose (RR = 0.69, $P = 0.02$).

4.5.3. Anticoagulation-antiplatelet combination therapy controversy

The COMPASS subgroup analysis showed that combining rivaroxaban (2.5 mg bid) with aspirin in patients with NVAF combined with coronary artery disease reduced cardiovascular events (HR = 0.74) but increased the risk of major bleeding (HR = 1.51), with the net clinical benefit needing to be individually weighed.

4.6. Technological innovation and device iteration

4.6.1. Pulsed electric field ablation (PFA)

Selective ablation of atrial tissue by destabilizing myocardial cell membranes through non-thermal electric fields, avoiding pulmonary vein stenosis and esophageal injury. The PULSED-AF trial showed a 25% reduction in AF recurrence rate 12 months after PFA compared to radiofrequency ablation (15% vs. 20%). The PULSED-AF trial showed a 25% reduction in AF recurrence rate 12 months after PFA compared to radiofrequency ablation.

4.6.2. Fourth-generation blocker design

The new generation WATCHMAN FLX device achieves a 96% complete block rate and a reduced incidence of device-related thrombosis (DRT) to 1.8% through a compressible skeleton design [25]. The intracardiac ultrasound (ICE)-guided zero-contrast implantation technique reduces the risk of contrast nephropathy (OR = 0.32), especially in patients with CKD. The WATCHMAN FLX device utilizes a fully occluded balloon structure, which improves the procedural success rate to 98% with a residual shunt rate of < 3%.

4.7. Lifestyle interventions

A Mediterranean diet (rich in omega-3 fatty acids and antioxidants) combined with 150 minutes of moderate-intensity exercise per week reduced atrial fibrillation load (HR = 0.69) and reversed left atrial enlargement (12% reduction in LAVI) [26].

4.8. Construction of multidisciplinary cooperative management model

The concept of “mind-brain co-management” promotes collaboration between neurology and cardiovascular medicine, and for patients with NVAF combined with cryptogenic stroke, the combined application of LAAC and patent foramen ovale occluder (PFO) blockage has reduced the annual stroke recurrence rate from 8.2% to 2.1%. In addition, a comprehensive intervention integrating nutrition and rehabilitation medicine improved patients’ exercise tolerance (6-minute walk distance increased by 45 meters) and quality of life scores (SF-36 score increased by 12 points) [27].

5. Discussion

The current study has some limitations, such as: the first aspect, the bottleneck of clinical application of risk prediction models. The CHA2DS2-VASc score does not sufficiently discriminate between intermediate-risk patients (scores 1–2), and about 30% of patients are misclassified. Most novel biomarkers lack standardized testing procedures and cost-effectiveness analyses, and there is insufficient data on racial variability. Secondly, there is a “gray area” controversy in anticoagulation therapy, and NOACs reversal agents have limitations. Although NOACs reversal agents can rapidly antagonize Xa inhibitors, the ANNEXA-4 study showed that their thrombotic event rate was as high as 10%. Although Idarucizumab and Andexanet alfa are approved, their short half-life (8–12 hours) and high cost limit clinical use. Evidence gaps in special populations: anticoagulation strategies for patients

with liver failure and solid tumors combined with NVAF lack high-quality RCT support. Thirdly, uncertainty about the long-term efficacy of device therapy. There is a lack of long-term data on LAAC, with most of the available studies having a follow-up period of ≤ 5 years, and scarce data on follow-up more than 5 years after LAAC, and the mechanism of the association between delayed pericardial effusion, the process of endothelialization of the blocker, and late thrombosis has not yet been elucidated. In addition, the long-term effects of PFA on the atrial autonomic plexus still need to be further evaluated. Fourthly, the practice of interdisciplinary integration is insufficient. Existing studies mostly focus on single interventions and lack full-cycle management programs that integrate cardiovascular, hematology, nephrology, and digital health technologies.

Future research directions can focus on several areas: (1) artificial intelligence and digital healthcare, where deep learning models achieve 98% sensitivity in AF screening by analyzing PPG signals from wearable devices; (2) remote monitoring platforms, integrating anticoagulation adherence reminders and INR self-measurement data to improve time to treatment window (TTR) to 72%; (3) novel anticoagulation strategies, dual factor XI/XI inhibitors, which showed antithrombotic efficacy equivalent to enoxaparin and a 50% reduction in the risk of bleeding in a phase II trial; and (4) to explore and standardize intervention programs based on daily living patterns.

6. Conclusion

NVAF risk management has moved from “single anticoagulation” to “multidimensional integration.” Individualized anticoagulation protocols based on genomics/epigenetics, AI-driven dynamic risk assessment systems, and intervention strategies targeting inflammation/oxidative stress will drive a paradigm shift in clinical practice. In the future, it is necessary to strengthen the long-term follow-up study and deepen the synergistic innovation between basic medicine and clinical translation, to ultimately realize the comprehensive prevention and control of NVAF-related complications.

Disclosure statement

The authors declare no conflict of interest.

Author contributions

Idea conceptualization - Li Yang, Dongming Xiang,
Manuscript writing – Li Yang
Literature review – Li Yang, Dongming Xiang, Liling Zhong
Manuscript revision – Li Yang, Dongming Xiang, Liling Zhong, Yuling Zou

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