

ATRIAL FIBRILLATION AND PREVENTION OF THROMBOEMBOLIC EVENTS: A REVIEW OF CURRENT STRATEGIES

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ABSTRACT

Atrial fibrillation represents the most prevalent sustained supraventricular tachyarrhythmia in global clinical practice, configuring a serious public health problem due to its direct impact on cardiovascular morbidity and mortality and the risk of ischemic stroke. This review article analyzes and synthesizes contemporary pharmacological and non-pharmacological strategies aimed at preventing thromboembolic events in these patients. Methodologically, a systematic survey of high-impact national and international guidelines, controlled clinical trials, and meta-analyses was conducted. The results point to a paradigmatic shift in risk stratification, centered on objective structural comorbidities, in addition to the definitive consolidation of direct oral anticoagulants as first-line therapy due to their predictable pharmacokinetics and superior hemorrhagic safety profile. Additionally, percutaneous occlusion of the left atrial appendage is established as an effective mechanical alternative in scenarios of long-term pharmacological contraindication. It is concluded that an integrated and holistic approach, uniting the precision of modern anticoagulation with the rigorous management of underlying risk factors, is indispensable to mitigate catastrophic peripheral outcomes. However, gaps regarding the underrepresentation of populations with end-stage renal disease demand attention, suggesting that future investigations explore new factor XI inhibitors and the use of wearable devices to refine precision medicine in cardiology.

Keywords: Anticoagulants, Atrial fibrillation, Cerebrovascular accident, Secondary prevention, Thromboembolism.

INTRODUCTION

Atrial fibrillation (AF) is recognized as the most common sustained supraventricular tachyarrhythmia in global clinical practice, with a prevalence that progressively increases with age.¹ The clinical relevance of this arrhythmia lies in its direct association with increased cardiovascular morbidity and mortality, resulting in a fivefold higher risk of ischemic stroke, in addition to being associated with the development of heart failure.¹ Thromboembolic events associated with AF tend to be more severe, making the prevention of these outcomes the fundamental pillar of therapeutic management.¹

Historically, vitamin K antagonists (VKAs), such as warfarin, became the standard treatment for stroke prevention in AF.^{1,2} However, limitations such as a narrow therapeutic window, the need for frequent monitoring, and multiple drug interactions have driven the development of direct oral

anticoagulants (DOACs).^{1,2,3} Robust evidence indicates that drugs such as apixaban, dabigatran, edoxaban, and rivaroxaban provide efficacy equal to or greater than that of warfarin, with a favorable biological safety profile, particularly in reducing intracranial hemorrhage.³⁻⁶

Despite these advances, many gaps and uncertainties remain regarding the management of specific and highly vulnerable population subgroups. Very elderly patients, individuals with low body weight, or those with advanced chronic kidney disease have frequently been underrepresented in major clinical trials.⁷⁻¹⁰ In addition, the management of patients who survive spontaneous intracranial hemorrhage and require antithrombotic protection remains a complex therapeutic dilemma, in which the balance between ischemic benefit and the risk of new fatal bleeding events has not yet been fully established.¹¹

An updated synthesis of the evidence and improvement of stratification models are essential to guide personalized agent selection and the optimal timing of intervention.^{1,12,13} Addressing these nuances is essential to mitigate catastrophic outcomes and improve precision in cardiovascular health management. For patients with absolute contraindications to pharmacological anticoagulation, percutaneous left atrial appendage occlusion has emerged as an effective mechanical alternative, consisting of isolating the main thrombus-forming structure.^{14,15}

OBJECTIVES

To investigate current strategies for the prevention of thromboembolic events in patients with atrial fibrillation through an integrative literature review, evaluating risk stratification mechanisms, the efficacy and safety of direct oral anticoagulants, left atrial appendage occlusion therapies, and future perspectives related to factor XI inhibitors and continuous monitoring technologies.

METHODS

This is an integrative literature review with a qualitative approach and an analytical-descriptive design, conducted with the aim of analyzing the scientific evidence regarding the prevention of thromboembolic events in patients with atrial fibrillation. The search for studies was conducted in the PubMed, Virtual Health Library (VHL), and Scientific Electronic Library Online (SciELO) databases.

The descriptors indexed in the Health Sciences Descriptors (DeCS) and Medical Subject Headings (MeSH) were used: Atrial Fibrillation, Thromboembolism, Stroke Prevention, and Anticoagulants, combined using the Boolean operators AND and OR, with the following search strategy: ("Atrial Fibrillation") AND ("Thromboembolism" OR "Stroke Prevention") AND ("Anticoagulants").

Articles published between 2020 and 2026 in English, Portuguese, and Spanish were included. The inclusion criteria were: full-text articles available in full; studies related to the prevention of thromboembolic events in patients with atrial fibrillation; clinical trials, systematic reviews, meta-analyses, and clinical guidelines; as well as publications within the established time frame. Duplicate studies, case reports, letters to the editor, incomplete articles, and publications that did not directly address the proposed topic were excluded.

The study selection process occurred in three stages: identification, screening, and eligibility, following the principles of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). Initially, 290 articles were identified in the selected databases. Subsequently, titles and abstracts were reviewed to apply the inclusion and exclusion criteria. Potentially eligible articles underwent full-text review, resulting in the final selection of 20 studies that fully met the previously established criteria.

The following variables were analyzed: year of publication, type of study, population profile, thromboembolic prevention strategies, therapeutic efficacy and safety, as well as the main clinical outcomes related to the occurrence of thromboembolic events. The data were organized in tables and analyzed descriptively through a narrative synthesis of the evidence found.

As this study was based on secondary data available in the scientific literature, submission to a Research Ethics Committee was not required.

RESULTS AND DISCUSSIONS

Ten Thromboembolic Risk Stratification Mechanisms and Therapeutic Thresholds

The contemporary approach to the prevention of thromboembolic events in atrial fibrillation is based on the accurate identification of predictive factors for vascular injury and blood stasis. Historically, tools such as the CHADS₂ score served as an initial screening method; however, the international scientific literature has demonstrated significant limitations in its sensitivity, particularly in identifying patients classified as being at intermediate risk who, in fact, went on to experience catastrophic ischemic outcomes¹. The transition to the CHA₂DS₂-VASc score refined risk assessment by incorporating high-impact biological variables, such as peripheral vascular disease, sex, and more stratified age groups, allowing for more reliable calibration of the risk of ischemic stroke.¹

Data derived from the reviewed epidemiological studies confirm that the systematic application of CHA₂DS₂-VASc substantially modified the threshold for initiating oral anticoagulant therapy. Currently, the consensus recommendation establishes that a score equal to or greater than two points for men and equal to or greater than three points for women constitutes a class I indication for the introduction of antithrombotic agents.¹ However, the major debate in medical practice concerns management in the setting of borderline risk, represented by a score of one for men and two for women. In these scenarios, the individualized analysis of additional biomarkers and echocardiographic parameters, such as left atrial volume and left atrial appendage emptying velocity, serves as a highly precise clinical tiebreaker.¹ At the same time, bleeding risk assessment should not be used as an exclusion criterion for anticoagulation, but rather as a surveillance tool for the modification of risk factors amenable to intervention. The use of the HAS-BLED score has become established in clinical practice not to contraindicate protective therapy, but to alert the multidisciplinary team to the need for rigorous monitoring and strict control of variables such as uncontrolled arterial hypertension, concomitant use of nonsteroidal anti-inflammatory drugs, and labile international normalized ratio in warfarin users.¹ The compiled data demonstrate that patients with a high HAS-BLED score (greater than or equal to 3) paradoxically obtain the greatest net benefit in terms of mortality reduction when adequately anticoagulated with agents with a better safety profile.¹

Table 1¹: Thromboembolic Risk Stratification and Annual Stroke Rates According to the CHA2DS2-VASc.

Score	Risk Category	Annual Ischemic Stroke Rate (%)	Therapeutic Recommendation
0 (Men) / 1 (Women)	Low	0.0 - 0.2	No antithrombotic therapy
1 (Men) / 2 (Women)	Intermediate	0.6 - 1.3	Anticoagulation should be considered
Maior ou igual a 2 (Homens) / Maior ou igual a 3 (Mulheres)	High	2.2 - 9.6	Oral anticoagulation is mandatory

Source: Adapted from the Brazilian Guideline on Atrial Fibrillation – 2025.¹

Comparative Efficacy and Safety Profile of Direct Oral Anticoagulants

The introduction of direct oral anticoagulants (DOACs) has changed the paradigm of antithrombotic management in non-valvular atrial fibrillation. Combined data from major phase III randomized clinical trials — comparing rivaroxaban, apixaban, dabigatran, and edoxaban with traditional warfarin — have shown that the newer agents are at least non-inferior to vitamin K antagonists in the prevention of ischemic stroke and systemic embolism³⁻⁶. However, the major competitive advantage of DOACs lies in their biological safety profile, demonstrated by a consistent reduction of more than 50% in the occurrence of intracranial hemorrhage, which represents the most feared complication of traditional anticoagulant therapy.³⁻⁶

From a pharmacokinetic perspective, the direct inhibition of specific factors in the coagulation cascade — factor Xa by rivaroxaban, apixaban, and edoxaban, and factor IIa (thrombin) by dabigatran — eliminates the biological instability characteristic of warfarin, dispensing with routine laboratory monitoring and mitigating the risk of therapeutic fluctuations caused by dietary variations or antibiotic use.¹⁻² Additionally, subgroup analyses based on real-world data show that apixaban has the best gastrointestinal safety profile among factor Xa inhibitors, while dabigatran 150 mg demonstrated statistical superiority in reducing ischemic stroke when directly compared with the standard dose of warfarin.^{3,4,6,7}

A critical challenge discussed in the literature concerns the management of elderly patients and

those with varying degrees of chronic renal dysfunction, since all DOACs depend, to a greater or lesser extent, on renal clearance for elimination. Dabigatran has the highest rate of renal excretion (approximately 80%), which requires extreme caution or contraindication in patients with an estimated glomerular filtration rate below 30 mL/min^{1,8}. For the management of this complex patient population, factor Xa inhibitors, notably apixaban and rivaroxaban, adjusted according to strict dose-reduction criteria based on serum creatinine, age, and body weight, have been shown to be safer and more effective in preserving long-term renal function and preventing major bleeding.⁸

Advances in Interventional Therapy: Left Atrial Appendage Occlusion

For the subgroup of patients affected by atrial fibrillation who present formal and absolute contraindications to long-term anticoagulation — such as survivors of recurrent spontaneous intracranial hemorrhages, patients with inaccessible cerebral arteriovenous malformations, or individuals with severe gastrointestinal bleeding from a non-treatable source — cardiovascular medicine has developed strategies based on mechanical barriers. Since more than 90% of thrombi originating in the left atrium in patients with non-valvular atrial fibrillation develop within the left atrial appendage, the mechanical isolation of this anatomical structure has become a highly attractive and effective therapeutic target.^{14,15}

The clinical results of long-term randomized trials confirm that percutaneous left atrial appendage occlusion, using endovascular devices, provides protection against ischemic stroke that is non-inferior to that provided by warfarin.^{14,15} With regard to long-term safety outcomes, mechanical exclusion of the appendage resulted in a marked reduction in overall bleeding rates after the initial device endothelialization period, which typically requires short-term transient antithrombotic therapy with antiplatelet agents or low-dose anticoagulation.^{14,15}



Figure 1¹⁶: Schematic representation of the mechanism of percutaneous left atrial appendage occlusion.

Source: Montenegro et al.¹⁶ Image courtesy of St. Jude Medical Inc.

The selection of patients who are candidates for mechanical occlusion should be conducted by a multidisciplinary cardiology team, based on high-resolution imaging examinations. Two-dimensional and three-dimensional transesophageal echocardiography, together with cardiac computed tomography angiography, constitutes the gold standard for mapping the complex anatomy of the atrial appendage, which varies among the phenotypes known in the medical literature as chicken wing, windsock, broccoli,

or cactus.^{14,15} Studies indicate that successful implantation and the absence of significant residual peridevice leaks (less than or equal to 5 mm) are directly correlated with a sustained reduction in embolic events and with successful permanent discontinuation of systemic anticoagulant therapy.^{14,15}

New Frontiers and Future Perspectives: Factor XI Inhibitors and Wearable Devices

The ongoing pursuit of a definitive dissociation between antithrombotic efficacy and bleeding risk has driven translational science toward new targets within the coagulation cascade. Coagulation factor XI has emerged as an ideal biological component for this new generation of modulation. Genetic and epidemiological studies have observed that individuals with congenital factor XI deficiency have a significantly reduced risk of thromboembolic events and ischemic strokes, without showing a tendency toward spontaneous bleeding or major hemorrhage resulting from severe trauma.^{18,19}

Preliminary data from phase II clinical trials evaluating factor XI inhibitors — including parenterally administered monoclonal antibodies, small synthetic oral compounds, and antisense oligonucleotides — in patients with atrial fibrillation have shown extremely promising results. These new drugs demonstrated a dose-dependent reduction in factor XI activity, associated with bleeding event rates virtually identical to those observed in placebo-treated groups, while maintaining protective efficacy equivalent to that of conventional DOACs. This innovation opens a new treatment perspective for the population currently neglected because of high bleeding risk, introducing the concept of anticoagulation with near-zero hemorrhagic potential.^{18,19}

Alongside pharmacological innovations, the digital transformation in cardiology, driven by the use of wearable devices for continuous monitoring, has changed the detection and temporal management of atrial fibrillation. Smartwatches and portable sensors equipped with photoplethysmography and single-lead electrocardiography algorithms enable the early diagnosis of subclinical arrhythmia in asymptomatic individuals. Current discussion in the medical literature focuses on the concept of targeted or intermittent anticoagulation, popularly known as the “pill-in-the-pocket” approach, in which patients at intermediate risk initiate temporary antithrombotic therapy only when the wearable device detects an atrial fibrillation burden above a critical threshold of continuous hours, thereby avoiding unnecessary exposure to bleeding risks during prolonged periods of stable sinus rhythm.^{1,17}

CONCLUSION

The optimization of thromboembolic prevention strategies in atrial fibrillation has become established as one of the most effective pillars for reducing morbidity and prolonging overall survival in the population with cardiovascular disease. The evolution of scientific evidence clearly demonstrates that the management of this arrhythmia has moved beyond the restricted view of purely electrophysiological control of cardiac rhythm or heart rate. The contemporary approach requires an integrated and holistic perspective in which antithrombotic protection is prioritized and guided by more objective and simplified clinical risk stratification tools, which remove demographic variables of low specificity and focus decision-making on actual and modifiable cardiovascular comorbidities.

The establishment of direct oral anticoagulants as first-line therapy has transformed the safety profile and therapeutic adherence in clinical practice, overcoming the historical limitations and pharmacokinetic instabilities associated with older vitamin K modulators. It has been shown that the predictability of the biological response of these newer pharmacological classes has dramatically reduced the incidence of catastrophic hemorrhagic outcomes, particularly intracranial bleeding, without compromising efficacy in the prevention of ischemic stroke. At the same time, for the subgroup

of patients with formal contraindications or refractoriness to long-term anticoagulant management, advances in interventional techniques for percutaneous left atrial appendage occlusion have become established as a safe, mechanical, and biologically viable therapeutic alternative.

Despite conceptual and clinical advances, this review study has limitations inherent to the temporal transition of medical guidelines and to the heterogeneity of the patient profiles evaluated in the literature, since populations with end-stage renal dysfunction or severe rheumatic valvular disease remain frequently underrepresented in major clinical trials of direct anticoagulants. Additionally, variability in infrastructure and access to advanced imaging examinations and high-cost interventional therapies across different public healthcare settings limits the universal and immediate applicability of certain cutting-edge recommendations.

For future investigations and research, the development of randomized clinical trials focused on validating the safety and efficacy of new coagulation factor XI inhibitors is suggested, as these agents promise to further dissociate thrombotic risk from bleeding risk, ushering in an era of anticoagulation with near-zero bleeding potential. Longitudinal studies aimed at integrating artificial intelligence and wearable devices for continuous monitoring are also recommended, evaluating the clinical impact of intermittent anticoagulation or anticoagulation strictly guided by arrhythmia burden episodes detected in real time, thereby refining the principles of precision medicine in cardiology.

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