Advances in Cardiac Research

REVİEW

Update In Stroke Prevention In Atrial Fibrillation

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Abstract

Atrial fibrillation (AF) is the most common arrhythmia worldwide. Ischemic stroke and systemic embolism are the most significant risks associated with AF, leading to increased morbidity and mortality. Therefore, stroke prevention is the cornerstone of managing AF. The standard of care for stroke prevention in AF is oral anticoagulation, which includes both vitamin K antagonists and non-vitamin K antagonist oral anticoagulants. However, there are still unmet needs regarding stroke prevention including bleeding, drug adherence and residual thrombotic risks. Percutaneous left atrial appendage closure (LAAC) and oral anticoagulants including Factor XIa inhibitors have emerged as alternatives for stroke prevention in AF patients. Several studies have demonstrated their effectiveness and safety in different contexts, raising their importance in daily clinical practice. Herein we aimed to review recent data regarding with stroke prevention in AF with specific emphasis on oral anticoagulation and LAAC.

Keywords: Left atrial appendage closure, atrial fibrillation, NOAC

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Introduction

Atrial fibrillation (AF) is an important health concern that disproportionately affects the elderly population, significantly increasing both mortality and morbidity rates, particularly due to cerebrovascular events[1,2]. With several modifiable risk factors, the annual risk of stroke attributed to AF can reach as high as 12%[3]. Integrated management approaches recommended by guidelines have demonstrated the potential to reduce cardiovascular mortality by up to 60% and ischemic stroke by up to 45%[4]. The historical use of non-specific anticoagulants, beginning with warfarin, laid the foundation for stroke prevention in AF. However, warfarin's challenging administration and the necessity for regular monitoring have prompted the search for more user-friendly alternatives.

In response to these unmet needs, non-vitamin K antagonist oral anticoagulants (NOACs), offering ease of use, have gained prominence in everyday clinical practice, surpassing vitamin K antagonists (VKAs). Randomized trials have solidified NOACs as at least as effective as VKAs in preventing cerebrovascular events while demonstrating a reduced risk of bleeding. Yet, bleeding concerns still linger. Current anticoagulants are limited by the risk of bleeding that accompanies antithrombotic efficacy. Factor XI inhibitors, novel anticoagulant agents targeting more specific points in the coagulation cascade, show promise by mitigating thrombosis while reducing the risk of bleeding. Moreover, left atrial appendage occlusion (LAAO) presents an alternative nonpharmacological solution for preventing thromboembolic events in AF patients with high bleeding risk or recurrent ischemic cerebral events.

Herein we aimed to an update regarding with stroke prevention in AF from randomized studies, real-life data, and meta-analyses that have significantly influenced daily clinical practice with specific emphasis on oral anticoagulation and LAAO.

METHODS

In the preparation of this review on stroke prevention in AF, we adopted a systematic and structured methodology, including the following key steps:

1. Literature Search: We conducted extensive searches in electronic databases, including PubMed, Embase, and Google Scholar, to identify relevant articles and studies. Our search was

focused on randomized trials, real-life data, and meta-analyses that have significantly contributed to current clinical practice and guideline recommendations in the field of stroke prevention in AF.

2. Inclusion Criteria: We selected articles and studies that met our inclusion criteria, which involved a focus on stroke prevention in AF, the use of anticoagulant drugs (both VKAs and NOACs), factor XI inhibitors, and left atrial appendage occlusion as intervention strategies. We also considered studies that provided insights into the effectiveness and safety of these interventions.

3. Data Extraction: Relevant data and findings from selected articles and studies were systematically extracted and organized to provide a comprehensive overview of the current state of stroke prevention in AF.

ORAL ANTICOAGULATION

VKA (Vitamin K Antagonists)

VKAs, such as warfarin, have played a pivotal role in stroke prevention for patients with AF. Clinical trials have demonstrated their effectiveness, with VKAs reducing the risk of stroke by 64% and mortality by 24% when compared to placebo[5]. Particularly in patients with rheumatic heart disease (RHD) and mechanical heart valves, warfarin remains the gold standard, as highlighted by the INVICTUS trial and the PROACT Xa Trial[6,7] .

The INVICTUS trial[7] was conducted to assess efficacy and safety of once-daily rivaroxaban compared with a dose-adjusted VKA for the prevention of cardiovascular events in patients with RHD-associated AF. A total of 4531 patients (age: 50.5 ± 14.6 years) were followed for 3.1 ± 1.2 years in which 560/2292 patients in the rivaroxaban group and 446/2273 in the VKA group had a primary-outcome adverse event. A higher incidence of death occurred in the rivaroxaban group than in the VKA group. No significant between-group difference in the rate of major bleeding was noted[7].

PROACT Xa (Prospective Randomized On-X Anticoagulation Clinical Trial) Trial[6] showed that among patients with an On-X mechanical aortic valve implanted ≥3 months earlier, apixaban 5 mg BID did not meet criteria for noninferiority compared with warfarin with a target INR of 2 to 3. The trial was terminated early by the Data and

Safety Monitoring Board due to higher risk of thromboembolic events in participants randomly assigned to apixaban than in those assigned to warfarin. The primary efficacy outcome (valve thrombosis or valve-related thromboembolism) for apixaban vs. warfarin: 4.2%/patient-year vs. 1.3%/ patient-year; rate difference: 2.9 (95% confidence interval 0.8-5.0)[6] .

Even in nonvalvular AF (NVAF), warfarin has shown its efficacy and safety, especially when time in therapeutic range (TTR) exceeds 70%[8]. High TTR levels have been associated with stroke prevention rates comparable to NOACs[9]. Thus, warfarin continues to be a viable alternative to NOACs in these specific patient populations.

There is ambiguity whether frail patients with AF managed with VKAs should be switched to a NOAC[10]. In FRAIL-AF trial[10] , 1,330 older AF patients living with frailty (age ≥75 years plus a Groningen Frailty Indicator (GFI) score ≥3) were randomized to switch from INR-guided VKA treatment to a NOAC or to continued VKA Mean age was 83 years, just over one-third of patients were female, the mean Groningen Frailty Indicator score was 4, and comorbidities were common. The study was open-label, and all four commercial NOACs were used, the most common being rivaroxaban (50.2%), followed by apixaban (17.4%), edoxaban (16.5%), and dabigatran (8.6%)[10].

At one year, the composite of major and clinically relevant bleeding had occurred in 9.4% of the VKA arm and 15.3% of the NOAC arm (HR 1.69; 95% CI: 1.23-2.32). Analyzed separately, rates of major bleeding and clinically relevant bleeds were all significantly lower in the VKA arm. FRAIL-AF revealed that switching VKA treatment to a NOAC in frail elderly patients with AF was associated with more bleeding complications compared to continuing a VKA. Furthermore, this higher bleeding risk with NOACs was not offset by a lower risk of thromboembolic events[10] .

NOACs (Non-vitamin K antagonist oral anticoagulants)

NOACs have revolutionized stroke prevention in AF patients. Randomized controlled clinical trials such as the RELY, ROCKET-AF, ARISTOTLE, and ENGAGE-TIMI AF have established the efficacy and safety of NOACs, including dabigatran, rivaroxaban, apixaban, and edoxaban[11-14]. All these studies have shown that appropriate doses of NOACs are at least as

effective in preventing stroke and systemic embolism as VKAs and intracranial and major bleeding rates are significantly lower than VKAs[11-14]. In the meta-analysis conducted with these studies, it was found that NOACs significantly reduced stroke or systemic embolic events by 19% compared with warfarin, mainly driven by a reduction in hemorrhagic stroke. NOACs also significantly reduced all-cause mortality and intracranial hemorrhage but increased gastrointestinal bleeding[15]. Again, real-life data of these drugs have also shown the same results on cardiovascular endpoints consistent with randomized trials[16-19]. In a meta-analysis based on real-life data in patients with NVAF, NOACs were found to protect significantly better from stroke and systemic embolism than warfarin and reduce the rate of major bleeding, gastrointestinal hemorrhage, all hemorrhage, and cardiovascular death and myocardial infarction[20].

Dabigatran, a direct thrombin inhibitor, emerged as the first NOAC and demonstrated noninferiority to warfarin in preventing stroke and thromboembolic events in both 110 mg and 150 mg doses[11]. Furthermore, the 150 mg dose showed superiority in preventing cardiovascular events without increasing major bleeding[11]. Real-world data have reinforced the advantage of dabigatran over warfarin in reducing ischemic stroke, major hemorrhages, and myocardial infarction[21] .

Rivaroxaban, a factor Xa inhibitor, has proven its safety and efficacy in comparison to warfarin through the ROCKET-AF study[17]. The convenience of a single daily dose has enhanced patient compliance. However, real-life data, as seen in the GLORIA-AF registry, revealed that stroke, myocardial infarction, and death rates were similar among rivaroxaban, apixaban, and dabigatran, but rivaroxaban had a higher incidence of major bleeding[22]. In a recent study reported by Talmor-Barkan et al[23]. clinical outcomes of three different NOACs in AF were compared. Data from 141 992 individuals with AF was used to emulate a target trial for head-to-head comparison of NOACs. Three-matched cohorts of patients assigned to NOACs were created. One-to-one propensity score matching was performed. The findings showed that patients treated with rivaroxaban had lower rates of mortality and ischemic stroke compared to those treated with apixaban (HR,0.88; 95% CI,0.78-0.99; P,0.037 and HR 0.92; 95% CI,0.86-0.99; P,0.024, respectively). There were no significant

differences in rates of myocardial infarction, systemic embolism, and overall bleeding among the NOAC groups. However, patients on rivaroxaban had a lower rate of intracranial hemorrhage but a higher rate of gastrointestinal bleeding compared to those on apixaban[23] . This study highlighted significant differences in outcomes between the three NOACs studied. The results suggest the need for randomized controlled trials to provide better guidance for selecting among rivaroxaban, apixaban, and dabigatran for AF patients.

Apixaban has demonstrated superiority to warfarin in protecting against ischemic and hemorrhagic strokes, primarily due to its significant reduction in hemorrhagic strokes[13] . In specific patient groups, like those with end-stage renal failure (ESRD) undergoing hemodialysis, apixaban has shown its effectiveness. The standard dose of apixaban proved comparable to warfarin in preventing stroke and systemic embolisms while significantly reducing major bleeding in these patients[24] . Additionally, a meta-analysis highlighted the superiority of apixaban over other NOACs in patients with reduced glomerular filtration rates[25]. In a cohort study performing the propensity score-matched analysis of Medicare data, outcomes of NOACs versus warfarin by frailty levels were analyzed. For older adults with AF, apixaban was associated with lower rates of adverse events across all frailty levels. Dabigatran and rivaroxaban were associated with lower event rates only among nonfrail patients[26] .

Edoxaban, the latest addition to the NOAC family, demonstrated noninferiority to warfarin in the prevention of cardiovascular events and systemic embolism in the ENGAGE-TIMI AF 48 study[14]. Edoxaban's benefits have been further emphasized in studies involving patients over 80 years of age[27] . In a randomized phase 3 double-blind trial (ELDERCARE-AF) from Japan, 984 patients over 80 years of age who were not candidates for using appropriate dose OAC, were divided into two arms. 15 mg edoxaban and placebo was compared in term of event rate of stroke, systemic embolism, and major bleedings. 15 mg low dose edoxaban arm was found that significantly better than placebo in prevention from stroke and systemic embolism without significantly increasing major bleeding[27].

Factor XIa inhibitors

Although NOACs have largely replaced VKAs in clinical practice, bleeding complications remain a concern. As such, there is growing interest in anticoagulants that offer effective thromboembolism prevention without compromising hemostasis. Factor XI/XIa (FXI/FXIa) offers an intriguing avenue for enhancing precision in anticoagulation. It predominantly participates in thrombus formation, with a lesser role in clotting and hemostasis. This suggests that inhibiting FXI/XIa could prevent the formation of pathological thrombi while preserving a patient's ability to clot in response to bleeding or trauma. Observational data supports this theory, showing that individuals with congenital FXI deficiency experience reduced rates of embolic events without an accompanying increase in spontaneous bleeding[28]. Factor XIa inhibitors have garnered attention in this regard, with promising results emerging in Phase II dose-finding studies in NVAF patients[28] . Mechanism of Factor XIa inhibitors is shown in Figure 1.

Milvexian is an oral small anticoagulant molecule that directly binds to active FXI with selective and high affinity. The AXIOMATIC-SSP Study investigated the effect of the factor XIa inhibitor milvexian in atherosclerotic patients with ischemic stroke or high-risk transient ischemic attack (TIA). The primary endpoints were ischemic stroke and new ischemic infarction on MRI. Five different doses were compared with a placebo, and a 90-day follow-up was performed. All patients received clopidogrel for the first 21 days and acetylsalicylic acid (ASA) for 90 days. No significant difference was observed in the patients compared to the placebo. When new infarcts are excluded on MRI, the probability of ischemic stroke tends to be numerically lower in milvexian. In the study, safety endpoints were BARC 3 or 5 hemorrhages, and the risk of bleeding was higher at high doses of milvexian than with the placebo[28] .

Asundexian is another oral FXIa inhibitor. In the PACIFIC STROKE study, a phase II dose-finding study, doses of asundexian at 10mg, 20mg, 50mg, and a placebo were compared for secondary stroke prevention in patients who had already received single or dual antiplatelet therapy. The mean follow-up period was 26-52 weeks. Control MRI was performed at the start of randomization and at the end of 26 weeks or at the time of stroke after randomization. The primary efficacy endpoint

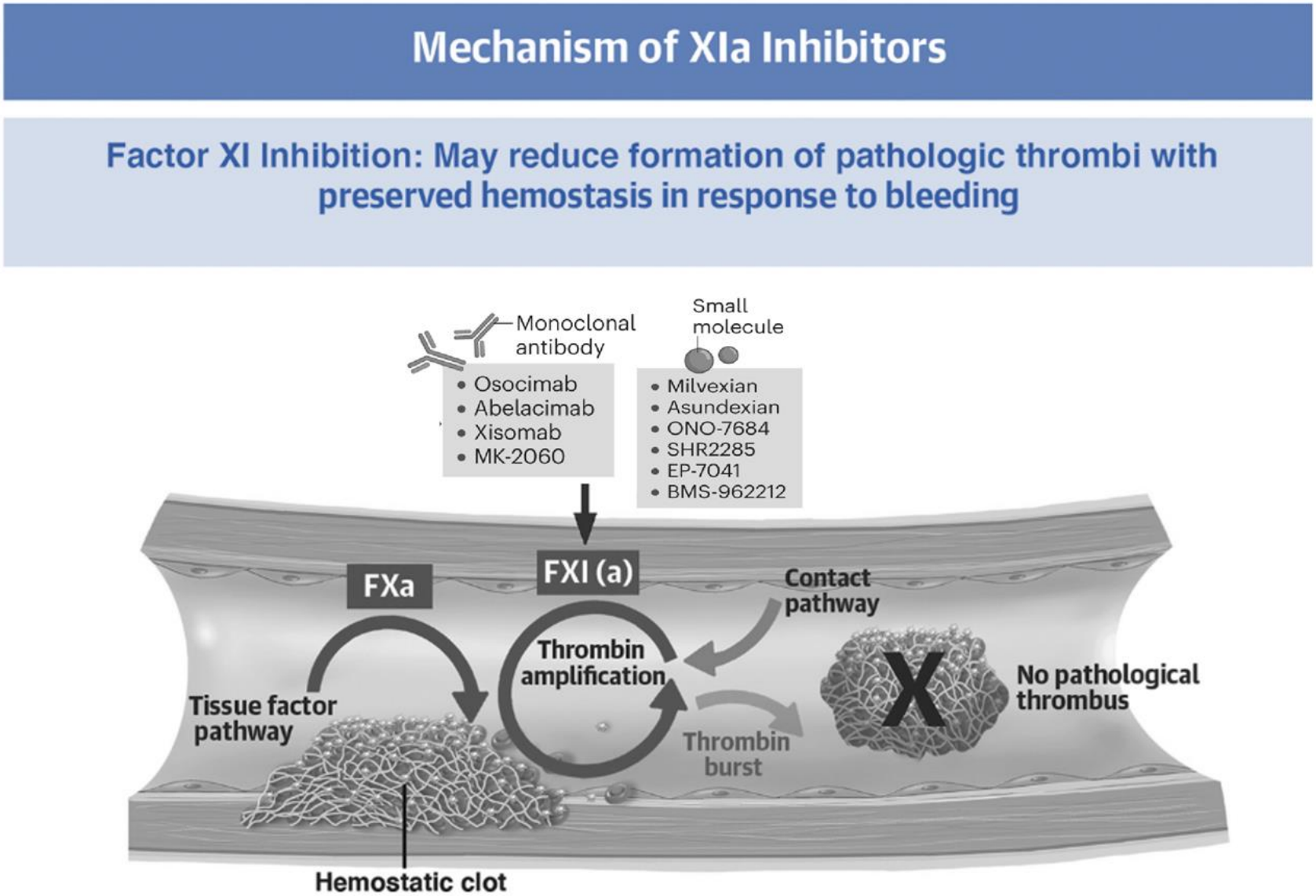

Figure 1. Mechanism of Factor XIa inhibitors.

was the dose-response effect on the composite of incident MRI-detected covert brain infarcts and recurrent symptomatic ischemic stroke at or before 26 weeks after randomization. Primary safety endpoints were major or clinically significant non-major bleeding as defined by the International Society on Thrombosis and Haemostasis criteria. Consequently, at a mean follow-up of 36 weeks, it was observed that asundexian did not reduce covert brain infarcts on MRI, nor did it reduce the occurrence of strokes. Additionally, it did not increase the occurrence of major or clinically significant bleeding when compared to the placebo[29].

In the PACIFIC-AF Study, another dose-finding study of asundexian, patients with non-valvular AF who were over 45 years of age and had a high bleeding risk (CHA2DS2-VASc ≥2 in men, ≥3 in women) were enrolled. Doses of asundexian at 20mg and 50mg daily were compared with a twice-daily dose of 5mg of apixaban. Major or clinically significant non-major bleedings were examined as primary endpoints. The average CHA2DS2-VASc score was 3.9. At the end of the study, it was observed that the 20mg and 50mg doses of asundexian significantly reduced the bleeding rate compared to the standard dose of apixaban. The frequency of occurrence of any side effects was similar in all three groups[30] .

Abelacimab is a monoclonal antibody of FXI and active FXI and is used subcutaneously. LILAC-TIMI 76 was randomized, double-blind, prospective study which was designed to compare abelacimab with placebo at 1:1 randomization. In high-risk AF patients who are not eligible for OAC, a single subcutaneous dose of 150 mg of abelacimab per month will be compared with placebo for prevention from stroke and systemic embolism at primary endpoints and for BARC 3c-5 hemorrhages at safety endpoints. Patient recruitment started at the beginning of 2023. On the other hand, the AZALEA TIMI 71 study was a dose-finding study of abelacimab and completed patient recruitment. The appropriate dose of rivaroxaban (20 mg and 15 mg) and 2 different doses of abelacimab were planned to be compared in terms of major and clinically significant nonmajor bleedings.

Phase II randomized controlled trials (RCTs) investigating FXI inhibitors have yielded promising results, although they have often been constrained by limited statistical power when assessing clinical outcomes. In a noteworthy effort, Galli et al.[31]

conducted a systematic review and meta-analysis of RCTs comparing FXI inhibitors to other anticoagulants (such as enoxaparin or NOACs) or placebo, in combination with antiplatelet therapy.

In comparison to enoxaparin, the introduction of FXI inhibitors did not alter the incidence of major bleeding but did lead to a reduction in bleeding events of any cause. Furthermore, the study-defined efficacy endpoints were less favorable for FXI inhibitors, particularly in high-dose treatment regimens. When compared to NOACs (novel oral anticoagulants), the clinical efficacy endpoints and major bleeding rates were comparable, but the occurrence of bleeding events of any cause was numerically lower in the FXI inhibitor arm.

In comparison to a placebo, the FXI inhibitors exhibited an increased risk of bleeding events of any cause in the high-dose groups, and although major bleeding occurred more frequently in the FXI inhibitor arm, this difference did not reach statistical significance. No significant disparities were noted in clinical efficacy endpoints. As per this study's findings, FXI inhibitors demonstrated a superior safety and efficacy profile when compared to enoxaparin, although they fell short of achieving comparable efficacy to NOACs. Additionally, the addition of particularly high doses of these drugs to antiplatelet therapy was linked to an elevated risk of bleeding, without a corresponding improvement in efficacy when compared to a placebo[31] .

The findings from this comprehensive meta-analysis of FXI inhibitors reveal enhanced safety and efficacy in comparison to enoxaparin, along with a modest improvement in safety when compared to NOACs. The utilization of FXI inhibitors in conjunction with antiplatelet therapy, when juxtaposed with placebo, seems to be associated with a dose-dependent increase in bleeding events, without any discernible improvement in efficacy.

LAA OCCLUSION

Standard of care for stroke prevention in AF has been OAC. Warfarin, the traditional oral anticoagulant, is limited by dietary restrictions, and the need for routine blood testing to maintain a narrow therapeutic window can lead to patient nonadherence. Despite ease of administration, 30% of patients taking NOAC are nonadherent at 2 years. Other patients cannot tolerate long-term OAC because of bleeding complications, cognitive

impairment, fall risk, and other factors (eg, drug allergy, drug interactions, renal dysfunction). Older patients often have unfavorable bleeding risk profiles for OAC, leading physicians not to offer or to discontinue OAC. This treatment gap has created an unmet clinical need for an effective and safe nonpharmacologic therapy for stroke prevention in patients with AF[32] . Left atrial appendage (LAA) occlusion (LAAO) has emerged as an alternative strategy to anticoagulation for stroke prevention in NVAF patients. The PROTECT-AF[33,34] and PREVAIL[35] studies demonstrated that LAA closure with devices like WATCHMAN is noninferior to warfarin in preventing strokes. However, device-related complications, including major bleeding, were more frequent. The ASAP Study revealed that LAA closure with the WATCHMAN device, particularly in patients with recurrent bleeding or high bleeding risk, can effectively reduce stroke and systemic embolism rates[36].

The AMPLATZER AMULET device has shown noninferiority to the WATCHMAN device in stroke and systemic embolism prevention. The AMULET device continued its safety and efficacy in the 3-year follow-up study[37,38]. The RCT Amulet IDE Trial[37], a randomized controlled trial, included 1878 high-risk patients for LAAO and compared the Amplatzer Amulet device to the WATCHMAN 2.5 device. The primary endpoint of the trial was a residual leak at 45 days. The Amplatzer Amulet device demonstrated a significant improvement in the primary endpoint, with no residual leak observed in 63% of patients compared to 46% with the WATCHMAN 2.5 device. However, no significant difference was observed in severe peri-device leaks (>5 mm), which occurred in 1% of the Amplatzer Amulet group and 3% of the WATCHMAN group. Notably, a higher risk of pericardial effusion was observed in the Amplatzer Amulet group: 2.43% versus 1.23%. Similar findings were reported in the SWISS-APERO trial, which compared the Amplatzer Amulet device (111 patients, 50.2%) to the WATCHMAN device (25 patients with WATCHMAN 2.5 and 85 patients with WATCHMAN FLX). No significant difference was observed in the peri-device leaks at follow-up, but a higher risk of periprocedural complications was observed in the Amplatzer Amulet group (9.0% versus 2.7%; $p = 0.047$)[39]. Real-world data from observational studies have also demonstrated the efficacy and safety of the Amplatzer Amulet device in various complex clinical scenarios[40] .

Another question about LAA closure is whether the devices met noninferiority with warfarin in preventing from thromboembolic events, they can still maintain the same consistency against NOACs with lower bleeding effects than VKA. In the PRAGUE-17 study designed to answer this question, WATCHMAN or AMULET device was randomized 1:1 with NOACs (95% apixaban; because the NOAC which has lowest risk of bleeding) and assessed for thromboembolic events, cardiovascular death, clinically significant hemorrhages, and device/procedure-related complications at the primary composite endpoints. At the end of a mean follow-up of 3.5 years, LAA closure was found to be noninferior to NOACs[41]. In the light of these studies, European and Asian guidelines recommend LAA closure may be used with evidence level 2b indication in patients with NVAF who are at high risk of bleeding or who cannot use warfarin for any reason in the prevention of stroke as an alternative to OAC therapy[2,42] .

CONCLUSION

The fact that the bleeding complications of NOACs cannot be ignored, on the other hand, in patients with recurrent bleeding or strokes due to anticoagulant treatments or who cannot use anticoagulants for any reasons, the prevention from stroke in patient with AF still has a gap to need look for more effective approach in this area. FXI inhibitors and LAA closure devices that do not disrupt hemostasis and protect from thromboembolic events are promising approaches in this field. While NOACs have become the standard of care for stroke prevention in NVAF patients, concerns about bleeding complications persist. Emerging FXI inhibitors and LAA closure devices offer promising alternatives, as they effectively prevent thromboembolism without compromising hemostasis. These novel approaches hold value for patients with recurrent bleeding, contraindications to anticoagulation, or high bleeding risk. It is crucial to continue investigating these options to refine stroke prevention strategies in AF patients.

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