

A Review of Antithrombotic Therapy After Left Atrial Appendage Closure

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Abstract:

Patients with atrial fibrillation (AF) have a higher incidence of thromboembolic events and poorer prognosis compared to the general population. However, the clinical application of anticoagulants as an antithrombotic strategy is limited by factors such as bleeding risk. Current research has confirmed that left atrial appendage closure (LAAC) can significantly reduce the risk of thromboembolism in AF patients. Therefore, LAAC is increasingly used as an alternative to long-term anticoagulation therapy. Post-operative antithrombotic therapy is crucial for preventing device-related thrombosis and ensuring the effectiveness of the procedure. However, current guidelines and expert consensus do not provide a clear antithrombotic regimen. This article reviewed the principle of LAAC and the status quo of anti-thrombotic therapy after operation.

Keywords:

Left Atrial Appendage Closure, Antithrombotic, Ischemic Stroke, Bleeding, Device-Related Thrombosis

1. Introduction

Atrial fibrillation (AF), as a very common arrhythmia in clinical practice, has attracted widespread attention. Its impact on patient health is significant, as it can substantially increase the risk of various serious health issues, including death, stroke, heart failure, cognitive dysfunction, and dementia among other complications [1,2,3]. According to relevant studies, it is estimated that by 2020, the global prevalence of AF had reached an astonishing figure of 50 million [4,5]. The primary danger of this phenomenon lies in the fact that AF significantly increases the likelihood of thromboembolic events, posing a serious threat to patient safety.

For AF patients who have not received anticoagulant treatment, the incidence of stroke, transient ischemic attack (TIA), and systemic embolism is approximately 3 to 5 times higher than that of individuals without AF [6]. Particularly, the incidence of strokes caused by AF is five times that of the general population, which not only indicates the higher risk faced by AF patients but also suggests that these patients

often experience more severe symptoms and have a relatively poor prognosis after a stroke [7,8]. Therefore, preventing thromboembolic events has always been a significant focus of the medical community and clinicians for AF patients. Through effective preventive measures, the risks faced by these patients can be significantly reduced, improving their quality of life and survival rates.

Oral anticoagulants (OACs) are the preferred option for non-valvular AF patients, effectively preventing thromboembolic events. However, the bleeding risks associated with anticoagulants and poor medication adherence can impact their practical application [9]. Data show that only 6% of high-risk individuals received anticoagulation treatment [10], and over half of thromboembolic high-risk patients do not receive oral anticoagulation due to concerns about bleeding [11]. Against this backdrop, percutaneous LAAC has become a key method for preventing thromboembolic events in AF patients.

The post-LAAC antithrombotic treatment strategy remains controversial. The PROTECT-AF study proposed a classic antithrombotic strategy of “anticoagulation + dual antiplatelet + single antiplatelet”, which involves taking warfarin for 45 days post-surgery, followed by 6 months of dual antiplatelet therapy (DAPT) with aspirin and clopidogrel, and then lifelong aspirin therapy [12]. In actual clinical practice, LAAC is primarily used in patients with strong contraindications to oral anticoagulation therapy, thereby limiting the treatment strategies for anticoagulants post-surgery. Recent consensus statements indicate that current data are insufficient to determine the optimal antithrombotic treatment regimen after LAAC [13]. Real-world registry studies show that the most commonly used antithrombotic treatment after LAAC is based on antiplatelet drugs, including single antiplatelet therapy (SAPT) and DAPT [14]. In this review, we summarize the clinical status of LAAC and post-operative antithrombotic treatment, and explore future research directions.

2. Principle of LAAC

The left atrial appendage (LAA), as an anatomically blind-ended structure of the left atrium, has abundant trabeculae and slow blood flow within its walls. In AF, the asynchronous mechanical contraction of the atria can lead to the formation of blood flow vortices, which in turn promote platelet aggregation and fibrin deposition, making it a primary site for thrombus formation. In non-valvular AF (NVAF) patients, 90% of left atrial thrombi are found in the LAA. In rheumatic valvular disease patients, 60% of embolic strokes originate from the LAA [15]. Even after treatment or spontaneous conversion to sinus rhythm in some patients with paroxysmal AF, the risk of thrombus formation remains due to suppressed LAA contraction.

LAAC involves delivering a closure device (such as Watchman, Amulet, etc.) to the LAA ostium via a vascular access established through femoral vein puncture. The device utilizes its self-expanding properties or anchoring mechanisms to achieve anatomical isolation, thereby eliminating the anatomical basis for thrombus formation. The selection of the closure device should be based on the patient's specific LAA anatomy and precise size. Currently, commonly used closure devices in clinical practice include the Watchman device and the Amulet device.

Since the clinical application of LAAC, subsequent large-scale randomized controlled trials and further clinical studies have been published, demonstrating that LAAC can significantly reduce the risk of ischemic stroke and systemic embolism in patients with non-valvular atrial fibrillation (NVAF). The efficacy of this technique is

almost comparable to that of long-term warfarin oral anticoagulation in preventing thromboembolic events. In terms of bleeding safety, LAAC performs significantly better than warfarin [12,16].

Furthermore, in patients with high stroke and high bleeding risk, LAAC via catheter is no less effective than novel oral anticoagulants (NOACs) in preventing composite adverse events such as stroke, TIA, systemic embolism, cardiovascular death, major bleeding, clinically relevant non-major bleeding, and procedure-related complications [17]. In the long term, the treatment cost of LAAC is lower than that of vitamin K antagonists (VKAs) and NOACs [18]. Therefore, LAAC has gradually become an important clinical treatment for stroke prevention in AF patients, attracting increasing attention and emphasis from doctors and patients.

3. Device-Related Thrombus (DRT)

Studies report a DRT incidence of only 2%-4%, with slightly higher rates (7%-8%) observed in some real-world studies. Research indicates that DRT is an independent predictor of thromboembolic ischemic events, increasing the risk of TIA, stroke, and systemic embolism by 4-5 times (HR 4.39, 95% CI: 1.05-18.43)[19]. Intensified antithrombotic therapy is recommended for patients who develop DRT [20], with warfarin, NOACs, or short-term (1-3 months) low molecular weight heparin anticoagulation being the preferred options. Nevertheless, most patients with DRT do not experience subsequent thromboembolic events.

Due to the unpredictable timing of device endothelialization, the occurrence of DRT is also unpredictable. Current recommendations suggest transesophageal echocardiogram (TEE) and cardiac computed tomography angiography (CTA) for evaluation at least 6 weeks to 3 months after LAAC, but more than half of patients may still develop DRT after 3 months. Studies also suggest that DRT detection rates are related to the frequency of monitoring [19]. Therefore, establishing standardized follow-up protocols for DRT is crucial for assessing its detection rate and its correlation with subsequent thromboembolic events, but no uniform protocol currently exists. A history of prior stroke, peripheral vascular disease, coronary artery disease, persistent AF, reduced left ventricular ejection fraction, and excessive left atrial appendage diameter are predictive factors for post-operative DRT [19,21]. Excessive device implantation depth and lack of coverage of the left superior pulmonary vein ridge may also increase the incidence of post-operative DRT [22]. Some studies also suggest that lower-intensity antithrombotic therapy after LAAC may be associated with DRT [23], while others argue that DRT is unrelated to the post-operative antithrombotic regimen [24].

4. Indications for LAAC

In the United States, LAAC has been approved by the Food and Drug Administration (FDA) and is primarily indicated for patients with non-valvular AF who have a CHADS₂ score of ≥ 2 or a CHA₂DS₂-VASc score of ≥ 3 . These patients are typically those who can tolerate short-term oral anticoagulant therapy. However, outside the United States, the indications for LAAC are broader, mainly recommended for patients at high risk of thromboembolism, particularly those with relative or absolute contraindications to OAC therapy due to recent bleeding events, or those with difficult-to-control high bleeding risks.

According to the latest Chinese medical guidelines [9], for patients with AF who are diagnosed with absolute contraindications to long-term OAC, such as a platelet count below $50 \times 10^9/L$, severe anemia of unknown cause, uncorrectable life-threatening or disabling bleeding (e.g., recurrent intracranial or intramedullary hemorrhage due to amyloidosis or irreparable vascular malformations, and severe gastrointestinal, genitourinary, or respiratory bleeding due to vascular dysplasia), and hemorrhagic diseases such as hereditary hemorrhagic telangiectasia, LAAC should be considered to effectively reduce their risk of stroke. LAAC can also be considered for patients with relative contraindications to OAC, such as those with certain malignancies associated with an increased bleeding tendency, end-stage chronic kidney disease (CKD), chronic bacterial endocarditis, and those in certain high-risk occupations (e.g., pilots, firefighters), to further enhance their cardiovascular protection.

5. Current Status of Antithrombotic Therapy After LAAC

The effectiveness of percutaneous left LAAC in preventing AF-related thromboembolic events has been clinically recognized. However, in the early period after LAAC, the implanted occluder surface is not completely endothelialized, making it prone to DRT. The adverse outcomes caused by DRT have attracted widespread attention. Subsequent studies have shown that DRT events are significantly associated with an increased risk of composite endpoint events, including death, ischemic stroke, or systemic embolism (HR = 2.37) [25]. The occurrence of DRT is directly related to postoperative antithrombotic therapy [26-29]. Therefore, to reduce the occurrence of adverse outcomes after LAAC, postoperative antithrombotic regimens have been a key focus.

The antithrombotic strategy following LAAC remains a subject of debate. Current major post-procedural antithrombotic strategies include: (1) Oral anticoagulation (VKA/DOAC); (2) Oral anticoagulation (full-dose or half-dose) + SAPT; (3) DAPT; (4) No antithrombotic therapy.

The PROTECT-AF study proposed the classic antithrombotic strategy of “anticoagulation + DAPT + SAPT,” which involves taking warfarin for 45 days postoperatively, followed by 6 months of DAPT with aspirin and clopidogrel, and then lifelong aspirin [12].

In actual clinical practice, LAAC is mainly used for patients with strong contraindications to oral anticoagulation therapy (OAT), which limits the postoperative anticoagulation treatment strategies. A recently published consensus states that current data are insufficient to determine the optimal antithrombotic regimen after LAAC [13]. Real-world registry studies show that the most commonly used antithrombotic regimens after LAAC are based on antiplatelet drugs, including SAPT and DAPT [14].

According to the European device label recommendation, DAPT should be taken for 3 months after implantation of WATCHMAN or Amplatzer heart occluder /Amulet (Abbott) if standard PROTECT-AF investigatory therapy is not available [30]. Therefore, in Europe, 3-month DAPT has been established as the primary treatment option after LAAC. This decision was based in part on previous clinical experience with coronary stents, patent foramen ovale, and atrial septal defect occluders.

Major bleeding events within the first year after LAAC are not uncommon (5%-10%) [31,32,33]. For patients with a high risk of serious or life-threatening bleeding, LAAC can be used to prevent stroke, but they may not be able to tolerate DAPT or short-term OAC. In these extreme cases, postoperative SAPT or even no antithrombotic therapy are options adopted in clinical practice.

DAPT generally refers to aspirin combined with clopidogrel. The rationale is that it can more effectively prevent thrombosis by inhibiting different activation pathways of platelets. However, it cannot be ignored that DAPT also significantly increases the risk of bleeding, especially serious bleeding events such as gastrointestinal bleeding and intracranial hemorrhage, which may offset its benefits in preventing thrombosis to some extent. Although SAPT relatively reduces the risk of bleeding, there is currently a lack of sufficient evidence to support whether its antithrombotic effect is comparable to that of DAPT.

6. Conclusions

The clinical effectiveness of LAAC has been confirmed. Currently, clinical studies focusing on the effectiveness and safety of this procedure are gradually being conducted, but most are observational trials, lacking randomized controlled trials. The current lack of clinical data leads to diverse and uncertain antithrombotic strategies after surgery in clinical practice. Because most patients have contraindications to anticoagulation, the effectiveness and safety of post-operative antiplatelet therapy are currently receiving widespread clinical attention. We hope that more relevant clinical research data will be published to fill the current gap in clinical research, provide a scientific basis for updating relevant clinical guidelines and expert consensus, and develop more individualized antithrombotic regimens. This will reduce the risk of thromboembolic events while minimizing bleeding complications, thereby improving patients' quality of life and prognosis. The promotion of percutaneous left atrial appendicular closure and postoperative antithrombotic treatment is moving towards standardization and precision, providing more evidence-based medical support for the treatment of patients with AF. We should develop a safer and more effective individualized antithrombotic therapy program to reduce the risk of thromboembolism and the occurrence of bleeding complications, so as to improve the quality of life and prognosis of patients with AF.

Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this article.

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