Review Article

Left atrial appendage closure for thromboembolism prevention in patients with atrial fibrillation: advances and perspectives

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Abstract: Atrial fibrillation (AF) is a frequent cause of stroke. More than 90% of thrombi were found in the left atrial appendage (LAA) in non-valvular AF. Transcatheter LAA closure has been developed as a novel approach to reduce the risk of stroke in patients with AF over the last decade. In this article, we review the recent advances and propose the possible challenges regarding the LAA closure for thromboembolism prevention in patients with AF.

Keywords: Atrial fibrillation (AF); stroke; left atrial appendage (LAA) closure

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Introduction

Thromboembolism is one of the most serious complications of atrial fibrillation (AF). For a long time, oral anticoagulation has been the main method for the prevention of thromboembolism in patients with AF. However, many problems of oral anticoagulation in patients with AF lead to a serious shortage of standard anticoagulant therapy in real world. Left atrial appendage (LAA) is thought to be the main source of thromboembolic events in patients with AF. Thus, LAA closure has become a new method of preventing thromboembolism in AF patients in recent years. This paper reviewed the relevant recent advances about the LAA closure for thromboembolism prevention.

AF and thromboembolism

AF is the most common sustained clinical arrhythmia, occurring in 0.5% to 1.3% general population. The prevalence of AF increases in parallel with age, increasing by about 1 time for each additional 10 years of age above the age of 50 years, and reaching up to 10% for those aged 80 years and older. According to conservative estimates, the AF population in China is currently over 8 million. Thromboembolism, the most serious risk of AF, leads to stroke, peripheral vascular thrombosis and other complications, and increases morbidity and mortality. The most serious complication of AF is stroke. About 15 million patients worldwide suffer from stroke each year, of which 20 % to 25% are due to AF. Many population-based epidemiological and clinical studies demonstrate that AF is a major independent risk factor for stroke, imparting a 3- to 5-fold increased risk at all ages. The risk of stroke increases substantially with age, from 1.5% in individuals aged 50-59 years to 23.5% for those aged 80-89 years (1). Most importantly, compared with the other causes of stroke, AF-related stroke had longer hospitalization, more recurrent stroke, higher morbidity and mortality. It imposed a huge social and economic burden.

The status of anticoagulant therapy for thromboembolism prevention

For a long time, long-term oral anticoagulation is the primary method of preventing blood clots in patients with AF. Warfarin, the predominant oral anticoagulant, was shown to reduce AF-related stroke by 60% in standardized treatment. However, the therapeutic dose of long-term

oral warfarin is often influenced by narrow therapeutic window, diet, metabolism and drug interactions. Additional challenges include the need for frequent blood draws, dose adjustments, and monitoring. The combination of the above factors leads to poor compliance, significantly affecting standardized anticoagulant therapy in AF patients. Recent studies in UK have reported that 32% of patients aged 80+ years received warfarin therapy compared to 55% in patients aged 70-79 years due to worrying the risk of bleeding (2). Based on China epidemiological study, the percentage of AF patients received oral anticoagulation therapy was extremely low—only 6.6% in hospitalized AF patients and only 1.7% in ordinary AF population. In addition, if there was bleeding tendencies or other contraindications of anticoagulation for patients with AF, they can't benefit from oral anticoagulation therapy. In recent years, some new anticoagulant drugs such as dabigatran, apixaban and rivaroxaban have been demonstrated to be at least non- inferior to warfarin, and are now considered a good alternative to warfarin. However, there are no sufficient evidence suggesting effective dose and demonstrating efficacy and safety for these new anticoagulant drugs in Chinese AF patients. Moreover, it's difficult to spread the application of these new anticoagulant drugs quickly because of expensive cost. In addition, these new anticoagulants are still unable to resolve the increased risk of bleeding and the need for long-term use.

Progress prevention of thromboembolic closure of the LAA

The LAA is a long, tubular, hooked structure which is usually crenellated and has a narrow junction with the venous component of the atrium, and it's different from the fully developed left atrium. There are a lot of pectinate muscles and trabecular muscles in LAA. LAA thrombosis is rare while in sinus rhythm because of its normal contractility. The LAA flow velocity decreases when atrium filling and emptying in AF patients, resulting in deposition of blood in the LAA, and it's the pathological basis of thrombus formation in LAA. Approximately 90% of atrial thrombi in non-rheumatic AF and 60% of such thrombi in patients with rheumatic mitral valve disease are found within the LAA (3). Thus, LAA closure to preventing thromboembolism has important theoretical basis in patients with AF. Over the last decade, several percutaneous LAA closure devices have been developed and tested in humans, such as PLAATO device, WATCHMAN device, Amplatzer Cardiac Plug (ACP) device and the Lariat device.

PLAATO occlude is a self-expanding nitinol cage covered with an occlusive expanded polytetrafluoroethylene (ePTFE) membrane, which is laminated directly to the frame structure so that the perimeter has intimate contact with the inner wall of the appendage. Small anchors along the struts and passing through the occlusive membrane assist with device anchoring and encourage healing response. In August 2001, the percutaneous LAA transcatheter occlusion (PLAATO) system became the first percutaneous LAA closure device employed in humans, and it was used to high risk of stroke in AF patients and to have contraindications to warfarin anticoagulation. In 2009, Block *et al*. (4) reported the 5-year outcomes of patients enrolled in this North American study. Of 64 patients, only 1 event (cardiac tamponade) was adjudicated as related to the implant procedure. After up to 5 years of follow-up, the annualized stroke/transient ischemic attack (TIA) rate was 3.8%. The anticipated stroke/TIA rate (with the CHADS2 scoring method) was 6.6%/year. These favorable outcomes illustrated that the PLAATO system is safe and effective. The European PLAATO study registry of 180 patients with contraindications to anticoagulation demonstrated 162 implant success, including 2 death within 24 hours of the procedure, and 6 cardiac tamponades (2 cases, surgical drainage of the tamponade). The follow-up time stroke rate of 2.3% compared favorably to the CHADS2 predicted rate of 6.3%. It was confirmed that PLAATO apparatus is relatively safe and effective (5). Currently, PLAATO occluder has been discontinued because of commercial reasons.

The WATCHMAN implant is comprised of a self-expanding nitinol frame structure with fixation barbs and a permeable polyester fabric that covers the left atrial facing surface of the device. In PROTECT-AF, 707 patients from fifty-nine centers in the USA and Europe were randomized 2:1 to device versus standard warfarin therapy. The trial was designed to examine the efficacy and safety of percutaneous closure of the LAA in patients with nonvalvular AF and to assess noninferiority of WATCHMAN to standard warfarin therapy. The efficacy of percutaneous closure of the LAA with WATCHMAN device was non-inferior to that of warfarin therapy. But there was a higher rate of adverse safety events in the intervention group than in the control group (6). With additional long-term follow-up in the PROTECT AF study and additional implant experience in the Continued Access Protocol (CAP), there is a significant improvement in the safety of Watchman LAA closure with

increased operator experience (7). PROTECT-AF trial was extended to 2.3 years of follow-up is further confirmed that the LAA "local" strategy of LAA closure is noninferior to "systemic" anticoagulation with warfarin (8).

PROTECT-AF trial also found that, regardless of whether the enrolled patients had received prior warfarin therapy, the LAA closure significantly improved the quality of life of patients (9). For oral anticoagulation is contraindicated in patients with AF, ASAP registration study also showed WATCHMEN implant thromboembolism prophylaxis is safe and effective (10).

The ACP device consists of two elements, a cylindrical nitinol plug anchoring the device in the LAA lobe and a nitinol disc covering the appendage ostium. The disc is attached to the plug in a jointlike fashion. The initial human trials, conducted in Europe, demonstrated a 96% procedural success rate in 137 patients. Serious complications occurred in ten patients (11). The initial Asian-Pacific experience in 20 patients from two Asian centers was also recently published, procedural success in 19 patients and complications in 3 patients (catheter-related thrombus, coronary artery air embolism, and TEE-induced esophageal injury). Of all the 19 patients who received the ACP implants, no peri-device leakage was observed during 4 weeks of follow-up. One year follow-up showed no incidence of stroke or death (12). Urena *et al*. (13) found that LAA closure using the ACP device significantly reduced thromboembolic and bleeding events in patients with nonvalvular AF at high risk of cardioembolic events and absolute contraindications to anticoagulation at the follow-up of 20 months. No cases of severe residual leak or device thrombosis were observed at the 6-month follow-up.

The endocardial/epicardial Lariat approach to LAA occlusion leaving no foreign material in the heart is more complicated. A lassolike suture is positioned by a percutaneous technique epicardially at the base of the LAA and tightened followed by suture ligation. There are but preliminary data on the use of Lariat technique. A recently published series described the patients undergoing 1-year, there was 98% complete LAA closure, including the patients with previous leaks. Long-term follow-up revealed severe pericarditis, late stroke, and sudden death in two patients each and late pericardial effusion in one patient (14,15).

Based on the increasing evidence of LAA closure for thromboembolism prevention in AF patients, 2012 ESC AF guideline have already recommended percutaneous LAA closure may be considered in patients with a high stroke risk and contraindications for long-term oral anticoagulation (IIb,B) (16). Although there is no clear recommendation on LAA closure for thromboembolism prophylaxis in 2014 AHA/ACC/HRS AF guidelines, experts comprehensively reviewed its latest clinical evidence (17), indicating that LAA closure prevention of thromboembolic has attracted much attention.

Future challenges

Although the safety and efficacy of LAA closure for the prevention of thromboembolism in AF patients have been initially confirmed, as a new technology, it still faces many challenges: (I) the source for stroke in AF patients. Epidemiological data showed that cardio-embolic stroke is a common type of ischemic stroke, but only accounted for 20% of ischemic stroke. Thus, in theory, LAA closure only is not sufficient to effectively prevent the occurrence of thromboembolic events. In addition, in non-valvular AF patients, a smaller proportion of thrombi were located outside the appendage. However, in certain subgroups (i.e., non anti-coagulated, left ventricular dysfunction or prior stroke), the chances of left atrial cavity thrombus are higher (18), in which the efficacy of LAA closure may be poor; (II) residual peri-device leakage after LAA closure. Ideal device and technology should completely occlude the LAA, but there were different degrees of LAA leakage in about 1/3 patients after LAA closure (19). The residual peri-device flow into the LAA after percutaneous closure was common, and is not associated with an increased risk of thromboembolism. However, this finding should be interpreted with caution as the low event rate decreases the confidence of this conclusion. It still needs more clinical studies to assess the relationship between device leakage after LAA closure and thromboembolism in the future; (III) thrombus and antithrombotic therapy after LAA closure. In recent years, device-associated thrombus was reported, even after complete endothelialization of the device (20). In addition, patients need antithrombotic therapy after LAA closure, but the choice of antithrombotic drugs and the time of antithrombotic therapy are still lack of consensus; (IV) novel oral anticoagulants (NOACs). Existing clinical trials for comparison with the LAA closure studies are anticoagulant warfarin. The current clinical evidence suggests that the NOACs were non-inferior to warfarin. However, non-direct contrast suggested that LAA closure may not reach the end point of inferiority to NOACs (21); (V) long-term efficacy and safety. Current clinical evidence of LAA closure for the prevention of thromboembolism

mainly obtained from single-center, non-randomized study, and the follow-up time was shorter. Therefore, large-scale, prospective, multi-center, randomized controlled trials are needed for further confirming the efficacy and safety of LAA closure; (VI) economic evaluation. Percutaneous LAA closure represents a novel therapy for stroke reduction that is cost-effective compared with warfarin for patients at risk who have nonvalvular AF. Currently, it is an expensive option for Chinese AF patients to prevent thromboembolism. However, it should be noted that he majority of LAA closure costs are borne in the first year, while costs for pharmaceutical strategies continue to accrue year on year. Thus, LAA closure represents an opportunity for savings to healthcare systems in the long term (22).

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