Minimally invasive left atrial appendage ligation in an animal model

Evaluation of: Lee RJ, Bartus K, Yakubov SJ: Catheter-based left atrial appendage (LAA) ligation for the prevention of embolic events arising from the LAA: initial experience in a canine model. *Circ. Cardiovasc. Interv.* 3(3), 224–229 (2010). Stroke is the most common reason for permanent disability in the developing world. Nearly 15% of all strokes can be attributed to atrial fibrillation. The overwhelming majority of thrombi related to atrial fibrillation occur in the left atrial appendage. Although conventional preventive treatment with anticoagulation substantially reduces stroke risk in patients with atrial fibrillation, owing to the associated bleeding risk and frequent failure to maintain a therapeutic range, many patients are either untreated or treated suboptimally. Therefore, alternative treatment strategies have been explored recently. Pharmacologic alternatives include direct thrombin inhibitors, novel vitamin K antagonists and Factor Xa antagonists. Although some agents, particularly thrombin antagonists, such as dabigatran, are promising, by virtue of the treatment mechanism (anticoagulation), a bleeding risk remains, as well as the potential for drug–drug interaction and other adverse effects. These limitations have fostered interest in mechanical isolation of the left atrial appendage, either surgically (e.g., with concomitant heart surgery) or percutaneously. The results of routine surgical left atrial appendage closure have been mixed. However, recently, percutaneous closure has been compared with conventional anticoagulation, demonstrating noninferiority with device therapy. Optimally, one would like to achieve reliable and complete closure without the use of a permanently implanted foreign object, which may be associated with thrombus formation. To this effect, Lee *et al.* have explored the feasibility of minimally invasive left atrial appendage ligation in an animal study. This technique avoids the implantation of a permanent foreign object. The study design and results will be summarized and discussed below.

KEYWORDS: atrial fibrillation ■ left atrial appendage occlusion ■ stroke

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A stroke is a devastating event, which frequently results in significant disability. It is not only catastrophic to the individual and their family, but is accompanied by a substantial economic burden. In developed countries, it is the most frequent cause of disability and ranks among the top causes of death. Nearly 15% of all strokes are attributed to atrial fibrillation [1], and the underlying thrombus nearly always originates from the left atrial appendage (LAA) [2]. Strokes related to atrial fibrillation are more frequently hemispheric and larger than those caused by atherosclerosis (e.g., carotid disease) [3]. To prevent this in the most perfect manner, one would like to exclude this structure from the systemic circulation entirely, in the safest way possible, so it does not have to be considered again in the future. Given limited surgical or percutaneous options, until recently, the best alternative was the use of anticoagulation, which, undoubtedly, has saved many lives, avoided disability and decreased associated healthcare costs. In pivotal trials, compared with no therapy, an impressive stroke risk reduction, close to two-thirds, along with a significant mortality reduction, has been demonstrated [4]. However, anyone involved in the care of patients on chronic anticoagulation will agree that anticoagulation is far from perfect. First, it requires patient compliance, responsibility and understanding, as well as significant resources to maintain a therapeutic range. Second, even under optimal (trial) circumstances, a therapeutic range can be maintained only two-thirds of the time, and only half of the time in clinical practice [5]. Third, therapeutic anticoagulation invariably comes at the expense of a major bleeding risk (7% annual risk), including a 0.5% annual risk of intracranial hemorrhage, which cannot be ignored [6]. A large number of patients who are considered to be at the highest stroke risk, particularly elderly individuals who are at increased fall risk, are also at the highest risk of bleeding. For example, the annual risk of major bleeding can be as high as 13% in

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octogenarians [6]. Up to 40% of patients with atrial fibrillation are considered to have contraindications to anticoagulation [7]. As a result, a large number of patients are not anticoagulated and, hence, more or less (with the exception of a small benefit from aspririn) are left unprotected, despite a high stroke risk [8]. Moreover, even in the absence of conditions that prohibit anticoagulation, patients are frequently not treated [9]. We clearly need to continue our quest for better alternatives.

Great effort in the search for better pharmacologic options has focused on improvement of efficacy and logistics. To this effect, it has become clear that, although it may be superior to aspirin alone [10], double antiplatelet therapy with aspirin and clopidogrel does not provide the same protection as conventional anticoagulation [11]. Results with thrombin inhibitors have been more promising. The first agent, ximelagatran, has not been approved, owing to safety concerns regarding liver toxicity, although it did offer equivalent stroke protection with a lower overall bleeding risk compared with warfarin [12]. However, dabigatran is not associated with hepatotoxicity, and was recently demonstrated to provide a stroke protection equivalent to warfarin with lower bleeding risk, and no need for therapeutic monitoring [13]. In the Randomized Evaluation of Long-term Anticoagulation Therapy (RE-LY) trial, 18,113 patients were randomized to dabigatran (at 110 or 150 mg twice daily) versus conventional warfarin therapy in a noninferiority design [13]. Dabigatran, at the lower dose, was noninferior to warfarin (equivalent primary end point of stroke or embolic event), but was associated with significantly lower bleeding risk. Furthermore, fewer strokes occurred with dabigatran at the higher dose than with warfarin, with no difference in hemorrhage. At the higher dose of dabigatran, there was a trend towards a lower overall mortality compared with warfarin. Importantly, the benefits in patients treated with dabigatran were even more pronounced compared with patients whose anticoagulation was poorly controlled on warfarin [14]. Nevertheless, some concerns have been raised in relation to a slightly higher risk of acute myocardial infarction with dabigatran in this trial. Conflicting results regarding the myocardial infarction risk were reported in studies using ximelagatran (as mentioned previously, also a thrombin inhibitor). In patients treated for deep venous thrombosis [15], or undergoing joint arthroplasty [16], the risk of myocardial infarction was higher with ximelagatran than warfarin. On the other hand, lower rates of reinfarction were reported in patients with acute myocardial infarction treated with ximelagatran [17]. Tecarfarin, a novel vitamin K antagonist, which is not metabolized by the cytochrome P450 enzyme and, therefore, is less susceptible to drug–drug and food–drug interactions, in a small open-label safety and tolerability study, has been shown to achieve a more reliable therapeutic range than warfarin [18]. However, in a larger randomized Phase II/III trial to assess the efficacy at maintaining therapeutic international normalized ratios, compared with warfarin, there was no significant difference [19]. Other pharmacological approaches (e.g., Factor Xa inhibitors [20,21], see later) are being studied. In short, despite significant progress in the exploration of novel pharmacological agents, none of them are perfect. Although perhaps lower than with warfarin, a bleeding risk, by virtue of the therapeutic mechanism (anticoagulation), will remain with any future agents and adverse effects and drug–drug interactions are to be expected with any medication.

Percutaneous device therapy to occlude the LAA has the advantage that, once the device is successfully deployed, endothelialized, and provided there is no residual orifice, stroke prevention is established in the absence of anticoagulation and its inherent risks. This concept has been tested recently in two devices specifically designed for LAA closure. The Percutaneous Left Atrial Appendage Occluder device, PLAATO (EV3, Inc., MN, USA), a self-expandable nitinol cage coated with polytetrafluoroethylene, was the first dedicated device tested in humans [22]. In the largest nonrandomized study evaluating this device, 111 patients with nonrheumatic atrial fibrillation and contraindications to anticoagulation underwent percutaneous implantation with a high success (97.3%) and low complication rate [23]. Four patients developed a pericardial effusion of which three required pericardiocentesis. In addition, a hemothorax and pleural effusion occurred in one patient respectively. At 6 days follow-up an asymptomatic device associated thrombus was discovered in one patient. The closure rate determined by follow-up transesophageal echocardiography was high at 98% and the annual stroke rate was 2.2%, which compared favorably to the stroke risk (6.3%) in a historical control matched for baseline stroke risk and treated with warfarin.

This benefit appears to persist at long-term follow-up [24]. Similar to the PLAATO device, the Watchman device (Aritech Inc., MN, USA) is a self-expanding nitinol frame, percutaneously implanted into the LAA. In the randomized trial comparing device therapy with conventional anticoagulation, the Watchman Left Atrial Appendage System for Embolic Protection in Patients with Atrial Fibrillation (PROTECT-AF) trial, noninferiority with device therapy was demonstrated [25]. A total of 707 patients were randomized in a 2:1 fashion to Watchman implantation, followed by brief (6 weeks) temporary anticoagulation only versus conventional permanent anticoagulation. The primary end point, composite of stroke, embolic events or cardiovascular death, was 3.0% annually with device therapy versus 4.9% with conventional warfarin therapy (probability of noninferiority of intervention greater than 99.9%). The potential problems noted were the occurrence of periprocedural complications, particularly, pericardial effusions requiring interventions (4.8%), which were more common with initial device implantation emphasizing operator experience with the device and the implantation technique. Device embolization occurred in three patients (0.6%), one of which underwent successful percutaneous retrieval and two underwent surgical removal. In addition, a peri-device leak (incomplete closure) remained in a small number of patients at follow-up transesophageal echocardiography requiring continuation of warfarin. In this trial, only patients eligible for temporary anticoagulation were included. Most importantly, however, the long-term efficacy is not yet entirely clear. Finally, although not common, device-associated thrombus has been reported [26].

To avoid the presence of a permanent foreign object in the heart and thus perhaps device related thrombi, Lee *et al.* tested the feasibility of minimally invasive LAA occlusion via an epicardial approach in an animal model [27].

Methods

The study by Lee *et al.* is a feasibility trial of minimally invasive LAA ligation by an epicardial approach in an animal model [27]. A total of 26 mongrel dogs underwent LAA ligation under direct fluoroscopy and echocardiographic guidance. A delivery catheter was positioned across the interatrial septum and a marker balloon was positioned in the LAA via the delivery catheter. Likewise, a catheter was positioned in the pericardial space and a snare around the orifice of the LAA with the marker balloon inflated. The appendage was subsequently suture-ligated. A total of 16 dogs were euthanized immediately after the procedure. The remaining ten dogs were euthanized at follow-up (7 days, 1 month and 3 months).

Results

The procedure was performed without complications in all dogs. Complete closure at the anatomic base was demonstrated immediately after the procedure. Furthermore, complete closure and endothelialization of the LAA orifice was demonstrated in the animals euthanized at later follow-up.

Significance

This study explores an elegant concept of LAA isolation with virtually no foreign material left behind in an *in vivo* model on a beating animal heart. Open surgical LAA occlusion has been performed during heart surgeries for other purposes (e.g., during coronary revascularization, valve repair or replacement) with mixed results. In the Left Atrial Appendage Occlusion Study (LAAOS), the only randomized trial available, follow-up transesophageal echocardiography demonstrated successful closure in only 45% of patients treated with suture ligation and in 72% of patients treated with combined suture and staple closure [28]. The study was underpowered (total of 77 patients) to assess clinical event rates. In a summary of five studies examining surgical LAA ligation, three suggested no advantage with surgical ligation, one a potential benefit and one, potential harm [29]. Complete left atrial occlusion on a nonbeating heart may appear attractive, however, direct visualization of this structure with the usual maneuvers is frequently not possible and the anatomical base or orifice can not be identified reliably. Moreover, the configuration and shape of the appendage in a decompressed heart may promote incomplete closure with a residual pouch.

The concept used by Lee *et al.* potentially allows more precise identification of the anatomical base of the appendage by direct visualization of this structure in a nondecompressed heart. In addition, the technique allows repositioning of the snare before final ligation. It leaves behind no foreign material with the exception of the suture. If this technique can be translated successfully into a human model with a complication rate equal to or below that achieved with percutaneous closure via

a femoral approach and, if equivalent efficacy to conventional anticoagulation therapy can be demonstrated, this may assume an important role, particularly for patients ineligible for anticoagulation and perhaps for patients who prefer a one-time procedural risk over that of permanent anticoagulation. However, the results of this research need to be confirmed in further studies. Then the feasibility will need to be investigated in humans and compared with whichever anticoagulant is considered to be the safest and most effective in a randomized fashion before definitive statements can be made.

Future perspective

In the quest for complete and safe prevention of strokes caused by atrial fibrillation, ongoing investigations of novel pharmacologic agents are underway. To this effect, two factor Xa antagonists are currently under investigation. In the ongoing ROCKET AF trial [21], rivaroxaban is compared with warfarin. Over 10,000 patients are enrolled and trial completion is expected this year. Likewise, in the ARISTOTLE trial, approximately 18,000 patients are planned to be randomized to apixaban versus warfarin [20] and trial completion is anticipated in April 2011. On the percutaneous transvenous device front, a new generation Watchman appendage occluder allowing better stability, as well as full recapture and redeployment is undergoing evaluation in the Evaluation of the Next Generation Watchman LAA Closure Technology in NonValvular AF Patients (EVOLVE) trial, comparing it to aspirin only, in a randomized fashion in patients with atrial fibrillation and contraindication to anticoagulation. A number of other percutaneous devices dedicated to LAA closure are being developed, some of which are undergoing preclinical or first-in-man testing.

Likewise, several epicardial techniques are under investigation. For example, the Anchorage Closure Device (Epitek™, MN, USA) device allows LAA ligation under endoscopic guidance. This device has been tested in animal models and first-in-man clinical trials are being planned. Similarly, the AtriClip™ Gillinov-Cosgrove Atrial Exclusion System (AtriCure, Inc., OH, USA) is designed to ligate the atrial appendage endoscopically using two titanium tubes connected by nitinol springs.

Lastly, given the more frequent use of catheter-based atrial fibrillation or flutter ablation, studies comparing the continuation of warfarin with aspirin only in patients thought to have been 'cured' of these arrhythmias are warranted.

Financial & competing interests disclosure

Horst Sievert is a principal investigator of the PLAATO studies and an investigator of the PROTECT-AF study. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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Executive summary

Background

- Percutaneus closure of the left atrial appendage (LAA) has been compared with anticoagulation in one randomized trial showing promising results. However, this technique leaves behind a foreign body that, until endothelialized, may be associated with thrombus formation. Optimally, one would prefer minimally invasive exclusion of the LAA without leaving any foreign material behind.

Method

- The evaluated study in this article is a feasibility study of LAA ligation in an animal model (26 mongrel dogs) via a minimally invasive technique, on a beating heart, leaving no foreign material behind. The animals were euthanized and the completeness of closure and endothelialization were assessed.

Results

- The procedure was performed in all animals successfully with no complications. Complete closure at the anatomic base was demonstrated in the animals euthanized immediately after the procedure and complete closure and endothelialization were demonstrated in the animals euthanized at follow-up.

Significance

- This study demonstrates that the concept of minimally invasive LAA closure on a beating heart, without leaving foreign material behind is feasible in an animal model.

Future perspective

- Although promising, further studies confirming the feasibility and safety of this technique in humans are warranted, as well as comparisons with anticoagulation or percutaneous closure in a randomized fashion, before this technique may be considered to be a treatment option.

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