Canadian Journal of Cardiology 30 (2014) 87–95

Review

Cardiac Procedures to Prevent Stroke: Patent Foramen Ovale Closure/Left Atrial Appendage Occlusion

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ABSTRACT

Stroke is a major contributor to population morbidity and mortality. Cardiac thromboembolic sources are an important potential cause of stroke. Left atrial appendage (LAA) thromboembolism in association with atrial fibrillation is a major contributor to stroke occurrence, particularly in elderly individuals. Patent foramen ovale (PFO) acts as a potential conduit from the right-sided circulation to the brain, and has been suggested to be an important factor in cryptogenic stroke in the young patients. Advances in interventional cardiology have made it possible to deal with these potential stroke sources (LAA and PFO), but the available methods have intrinsic limitations that must be recognized. Furthermore, the potential value of LAA and PFO closure depends on our ability to identify when the target structure is importantly involved in stroke risk; this is particularly challenging for PFO. This article addresses the clinical use of PFO and LAA closure in stroke

RÉSUMÉ

L'accident vasculaire cerebral (AVC) est une cause importante de morbidité et de mortalité dans la population, les sources cardiaques étant des contributeurs fréquents. La thromboembolie provenant de l'auricule (AG) en association avec la fibrillation auriculaire est une cause importante de la survenue de l'AVC, particulièrement chez les personnes âgées. La persistance du foramen ovale (PFO) agit comme un conduit potentiel de la circulation issue du coeur droit vers le cerveau et semble être un important facteur de l'AVC cryptogénique chez les jeunes patients. Les avancées en cardiologie interventionnelle permettent de traiter ces sources potentielles d'AVC (AG et PFO). Par ailleurs, la valeur potentielle de la fermeture de l'AG et du PFO dépend de notre habileté à déterminer le moment où la structure cible est significativement impliqué dans le risque d'AVC; cela est particulièrement difficile dans le cas du PFO. Cet article porte sur l'utilisation

Stroke is a major contributor to population morbidity and mortality. The heart is an important source of ischemic strokes (cardioembolisms) in relation to different structures including the foramen ovale (paradoxical embolism) and the left atrial appendage (LAA) in patients with atrial fibrillation (AF). Advances in interventional cardiology, which have become a valid alternative to deal with these potential sources of stroke, are reviewed.

Patent Foramen Ovale Closure

Patent foramen ovale (PFO) is a vestige of the fetal circulation and results from the lack of fusion of the septum primum and secundum. Although the reasons for the patency are unknown, it seems to be associated with multifactorial inheritance.[1] Found in up to 25%[2] of unselected adults, most of them are discovered incidentally and have no clinical consequences. PFO has, however, been linked to multiple clinical conditions namely cryptogenic stroke,[3] platypnea-orthodeoxia syndrome,[4] decompression sickness in divers,[5] and migraine.[6] Cryptogenic stroke represents approximately 40% of all ischemic strokes.[7] In 1877, Julius Cohnheim hypothesized for the first time the relation between PFO and cryptogenic stroke. Nonetheless, the role of percutaneous PFO closure in patients with cryptogenic stroke has been very controversial for years because of a lack of clear evidence.[8]

PFO anatomy

The morphology of the PFO varies among subjects and there are some anatomical features that have been linked to higher risk of paradoxical embolism such as large anatomical defects (> 5 mm), persistent right-to-left shunting at rest, atrial septal aneurysms (ASAs) and the presence of a prominent

Received for publication October 15, 2013. Accepted November 12, 2013.

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See page 93 for disclosure information.

http://dx.doi.org/10.1016/j.cjca.2013.11.008

prevention. We discuss technical aspects of closure devices and methods, questions of patient selection, and clinical trials evidence. We conclude that for PFO closure, the clinical trials evidence is thus far negative in the broad cryptogenic stroke population, but closure might nevertheless be indicated for selected high-risk patients. LAA closure has an acceptable balance between safety and efficacy for atrial fibrillation patients with high stroke risk and important contraindications to oral anticoagulation. Much more work needs to be done to optimize the devices and techniques, and better define patient selection for these potentially valuable procedures.

clinique de la fermeture du FOP et de l'AG dans la prévention de l'AVC. Nous discutons des aspects techniques des dispositifs et des méthodes de fermeture, des questions portant sur la sélection des patients et des données des essais cliniques. Nous concluons que, pour la fermeture du PFO, les études sont négatives dans l'ensemble de la population ayant eu un AVC cryptogénique, mais que la fermeture pourrait néanmoins être indiquée chez certains patients ciblés. La fermeture de l'AG offre un équilibre acceptable entre l'innocuité et l'efficacité chez les patients ayant une fibrillation auriculaire qui sont exposés à un risque élevé d'AVC et qui ont des contre-indications à l'anticoagulation orale. Beaucoup d'autres travaux doivent être réalisés pour mettre au point les dispositifs et les techniques et pour mieux sélectionner les patients pour ces interventions potentiellement valables.

Eustachian valve.[9] The ASA is defined as a membrane excursion of the interatrial septum of at least 10 mm from the plane of the septum.[10] The prevalence of ASA is 1% in autopsy-based studies,[11] and ranges between 2.2% and 4% in transesophageal echocardiographic (TEE) studies.[12] More than 60% of patients with ASA present PFO and, additionally, PFOs tend to be larger in patients with ASA.[13] Another common association is the presence of a Eustachian valve, a remnant of the right valve of the sinus venosus that points blood flow from the inferior vena cava to the fossa ovalis, easing the potential pass of thrombotic material through a PFO.

PFO diagnosis

Transthoracic echocardiography (TTE) is the most common diagnostic modality. Because Doppler colour-flow only detects the 5%-10% of the interatrial shunts, intravenous injection of agitated saline (2-4 mL) is generally needed, permitting visualization of microbubbles in the left atrium within 3 cardiac cycles.[14] The bubble injection is typically performed at rest and after increasing the right atrial pressure with different strategies such as coughing or the Valsalva manoeuvre.[15] The main limitation of TTE is, however, its relatively poor sensitivity compared with TEE (20% vs 42%) and the absence of accurate information regarding the morphology of the septum.

TEE should be considered if the TTE study is negative or inconclusive in the presence of a strong clinical suspicion of PFO. In fact, most centres use TEE instead of TTE to rule out cardioembolic sources because of its superior capacity to detect not only PFO but also the presence of thrombi in the LAA, spontaneous echo contrast in the left atrium, left ventricular thrombi, or atherosclerotic plaques in the aorta.

Transcranial Doppler (TCD) with agitated saline is another PFO diagnostic modality. The TCD transducer registers the middle cerebral artery flow through the temporal bone window. The sensitivity of TCD for PFO detection is very high (> 90%) although its specificity is lower (65%-90%).[16] In addition, TCD is not only useful to diagnose PFO but also to detect residual shunt after transcatheter closure.[17]

PFO and cryptogenic stroke

Cryptogenic stroke: searching for more evidence. As exclusion diagnosis, cryptogenic stroke must only be considered after ruling out other cardioembolic or arterial stroke sources with cardiac and carotid ultrasound. Because the thrombus is rarely observed through the PFO, the exclusion of deep vein thrombosis with Doppler ultrasound and, alternatively, pelvic vein visualization using magnetic resonance imaging or computed tomography should also be considered. In addition, coagulation tests are necessary to rule out thrombophilic disorders.

Medical therapy

Almost 5% of patients who suffered a cryptogenic stroke will present a new ischemic event within the first year despite medical treatment.[18] Moreover, there is no consensus on the optimal therapy because data comparing anticoagulant vs antiplatelet therapy are scarce. In the Warfarin-Aspirin Recurrence Stroke Study (WARSS),[19] 2206 patients with stroke were randomized to aspirin (325 mg/d) or warfarin (international normalized ratio, 1.4-2.8). At 2-year follow-up, no significant differences in stroke recurrence, death, or major bleeding were observed.[19] In a subanalysis of the study comparing aspirin and warfarin in patients with PFO and cryptogenic infarction (Patent Foramen Ovale in Cryptogenic Stroke [PICSS] trial), the stroke rate at 2 years was similar among groups but patients taking warfarin presented a higher rate of minor bleeding.[20] Currently, the American Heart Association and American Stroke Association recommend antiplatelet therapy as the first choice treatment and oral anticoagulation in case of deep venous thrombosis or hypercoagulability. However, the American Academy of Neurology considers that current evidence is insufficient to choose between aspirin and warfarin and some authors favour warfarin as first choice therapy.[21]

Percutaneous PFO closure

Since Bridges' first description in 1991,[22] percutaneous PFO closure has been used widely worldwide and several devices have been explored (Table 1). Percutaneous PFO closure is a relatively simple and safe procedure that is generally performed through the femoral vein using fluoroscopic and echocardiographic (TEE or intracardiac) guidance or fluoroscopy alone. Recent studies have shown a very low incidence of procedure-related complications, affecting < 1% of patients.[23-25]

Before the recent publication of the 3 available randomized trials, the evidence on the efficacy of PFO closure for cryptogenic stroke prevention consisted of a small number of

nonrandomized comparative studies, numerous case series, and meta-analyses of the published studies.[26-29]

CLOSURE I (Evaluation of the STARFlex Septal Closure System in Patients With a Stroke and/or Transient Ischemic Attack Due to Presumed Paradoxical Embolism Through a Patent Foramen Ovale)[23] was the first randomized study and compared medical treatment (warfarin, aspirin, or both) vs percutaneous closure with the STARFlex device (NMT Medical, Boston, MA) in 909 patients with PFO and cryptogenic stroke or transient ischemic attack (TIA). The primary end point, a composite of stroke/TIA at 2 years, 30-day mortality from any cause, and 2-year neurologic mortality, was observed in 5.5% of patients in the device group and 6.8% of those in the medical arm ($P = 0.37$). Moreover, no significant differences were observed in the stroke rate at 2-year follow-up (2.9% and 3.1%; $P = 0.79$). CLOSURE I was, however, heavily criticized for the low rate of effective closure (87%) and the high rate of device thrombosis (1.1%) and AF (6%) as a result of the device that was used, leading to a negative trial and to the removal of the device from the market.

The PC (**P**FO and **C**ryptogenic Embolism) trial[24] was similar in design, including 414 patients with PFO and ischemic stroke, TIA, or peripheral embolism. Patients were randomized to closure with the Amplatzer PFO Occluder (APO) device (St Jude Medical, Minneapolis, MN) or to receive medical therapy (antiplatelet or anticoagulation therapy). At 4 years, no significant differences in the combined primary end point of death, nonfatal stroke, TIA, or peripheral embolism were found between the device (3.4%) and the medical therapy (5.3%); $P = 0.63$. Interestingly, the rate of successful closure was high at 95.9% with a much lower rate of AF (2.9%).

In contrast with CLOSURE I and PC, RESPECT (**R**andomized **E**valuation of Recurrent **S**troke Comparing **P**FO Closure to **E**stablished **C**urrent Standard of Care **T**reatment)[25] only included patients with PFO and a previous ischemic stroke with symptoms that persisted > 24 hours or associated with an acute cerebral infarct on magnetic resonance imaging or computed tomography scans. In this trial, 980 patients were randomized to percutaneous closure with the APO or medical therapy (aspirin, aspirine/dypiridamole, warfarin, or clopidogrel). The primary results of the study were analyzed at 7 years, when the target of 25 primary end points were observed and adjudicated. In the intention-to-treat cohort, 9 patients in the closure group and 16 in the medical therapy group had a recurrence of stroke (hazard ratio with closure, 0.49; 95% confidence interval [CI], 0.22-1.11; $P = 0.08$). The between-group difference in the rate of recurrent stroke was significant in the prespecified per-protocol cohort (6 events in the closure group vs 14 events in the medical therapy group; hazard ratio, 0.37; 95% CI, 0.14-0.96; $P = 0.03$) and in the as-treated cohort (5 events vs 16 events; hazard ratio, 0.27; 95% CI, 0.10-0.75; $P = 0.007$). Interestingly, in the subgroup analysis, a greater benefit was observed in patients with a substantial right-to-left shunt and in those with ASA. Furthermore, the device was very safe with no thrombus and no excess of AF (same as the medical group).

Since the publication of the 3 available randomized trials, several meta-analyses have been published.[30-33] Most of them suggest a clear and consistent trend toward the fact that transcatheter PFO closure might be more effective than medical therapy alone for the prevention of recurrent thromboembolic events. Noteworthy, the differences between PFO closure and medical treatment became significant when analyzing the trials that only used APO for percutaneous closure (RESPECT and PC), suggesting the importance of the selected closure device.[32] In any case, all meta-analyses agreed on the need for further research to confirm these findings. In this sense, the GORE Helex Septal Occluder/Gore Septal Occluder and Antiplatelet Medical Management for Reduction of Recurrent Stroke or Imaging-Confirmed TIA in Patients With PFO (REDUCE) trial, a fourth randomized trial comparing PFO closure using the Gore Helex or Gore Septal Occluder device (Gore Medical, Flagstaff, AZ) vs medical therapy alone is ongoing. The REDUCE trial (NCT00738894) is expected to recruit 664 patients and will finish approximately in January 2015.

Additional data also suggest that in patients with endocardial leads (pacemaker or defibrillator), the presence of a PFO on a routine echocardiography is associated with a substantially increased risk of embolic stroke/TIA.[34] In 6075 patients followed for a mean of 4.7 ± 3.1 years, stroke/TIA was observed in 8.2% of patients with PFO and only 2% of those without (hazard ratio 3.49; 95% CI, 2.33-5.25; $P < 0.0001$). This association remained significant after multivariable adjustment for age, sex, previous stroke/TIA, AF, and baseline aspirin/warfarin use (hazard ratio, 3.30; 95% CI, 2.19-4.96; $P < 0.0001$). This finding suggests a role of screening for PFOs in patients who require cardiac implantable electronic devices. If a PFO is detected, PFO closure, anticoagulation, or extravascular devices might be considered.

Conclusions

Cryptogenic stroke represents 40% of ischemic strokes and PFO might be involved in a large percentage of them. Some anatomic features such as large shunts or the presence of ASA seem to be associated with an increased risk of stroke. Likewise, the presence of a thrombus in the veins and hypercoagulability disorders are also findings that favour the hypothesis of a paradoxical embolism. Despite the fact that none of the randomized studies demonstrated a significant difference on the primary end point, the relevant signal toward the benefit of PFO closure in the subsequent meta-analysis might justify an invasive strategy in high-risk patients such as those with evidence of venous thrombosis and/or recurrent stroke despite medical therapy. PFO management remains, however, controversial but acceptable in selected young (younger than 60 years old) patients without atherosclerotic risk factors and/or high-risk anatomies (including the presence of shunt at rest, ASA, or Eustachian valves) particularly in clinical circumstances suggesting a paradoxical event (Valsalva, immobilization, etc).

LAA Occlusion

AF is the most common type of arrhythmia with a prevalence that increases with age.[35] The lifetime risks for development of AF are 25% for men and women older than 40 years of age.[36]

Oral anticoagulation: efficacy and limitations

AF is associated with a 4- to 5-fold increase in the risk of ischemic stroke and accounts for up to 30% of all strokes.[37] The risk of stroke ranges from 1.9% to 18.2% per year

Table 1. General description of devices most often used for PFO closure

Device (manufacturer)	Device description	Size (mm)	Advantages	Disadvantages	Images and Web site
Amplatzer PFO Occluder (St Jude Medical, Minneapolis, MN)	Two self-expanding flat discs made of nitinol wire connected by a short and flexible waist and filled with a polyester patch	18, 25, 30, and 35	• Most used • Easy to retrieve and to replace • Long past experience	• Few cases of late erosion • Exposure to nickel	https://professional-intl.sjm.com/products/sh/heart-occluders/pfo-closure-devices/amplatzer-pfo-occluder
Helex (HSO) and Gore (GSO) Septal Occluders (Gore Medical, Flagstaff, AZ)	Single (HSO) vs 5-wire (GSO) frame made with platinum-filled nickel-titanium (nitinol) alloy cover with a thin ePTFE membrane	15, 20, 25, 30, and 35 for HSO 15, 20, 25, and 30 for GSO	• Soft and flexible device • Easy to retrieve • Low profile	• Wire fracture • Limited experience (GSO) • Complex implantation and higher residual shunt (HSO)	http://www.goremedical.com/helex http://www.goremedical.com/eu/septaloccludereu
Occlutech Figulla Flex II PFO (Occlutech, Jena, Germany)	Double-disk device made of a self- expanding nitinol wire mesh filled with PET patch	18, 25, 30, and 35	• Less mesh wire provides more flexibility and lower profile • No distal pin (left side) • Cover with titanium oxide to increase biocompatibility • Shapeable and flexible (50°) delivery system	• Design similar to Amplatzer	http://www.occlutech.com/index.php/en/products/occlutech-figulla-flex-ii
Cera (Lifetech, Shenzhen, China)	Double-disk device made of a self- expanding nitinol wire mesh filled with PET patch	18, 25, 30, 35, and 40	• Preloaded • Cover with titanium nitride provides less nickel release	• Design similar to Amplatzer	http://www.lifetechmed.com/en/pro_cera.html
UltraSept PFO (Cardia, Eagan, MN)	Self-expanding double umbrella design consisting of nitinol covered by polyvinyl alcohol	20, 25, 30, and 35	• Conforms to the anatomy (dual articulating sails) • Low profile • No distal pin (left side)	• Higher thrombus formation with first generation (currently seventh generation)	http://www.cardiainc.com/pfo.html

ePTFE, polytetrafluoroethylene; GSO, Gore Septal Occluder; HSO, Helex Septal Occluder; PET, polyethylene; PFO, patent foramen ovale.

according to the **C**ongestive Heart Failure, **H**ypertension, **A**ge, **D**iabetes, **S**troke/Transient Ischemic Attack ($CHADS_2$) score.[38] These cardioembolic strokes are generally more disabling and more lethal than other sources.[39]

For the past decades, many treatment strategies have been tested in patients with nonvalvular AF (NVAF). Aspirin alone showed a reduction of 20% in the risk of ischemic stroke.[40] The combination of aspirin and clopidogrel[41] resulted in a 28% risk reduction but this association was not as effective as the use of vitamin K antagonists, such as warfarin, which reduced the risk by at least 40%.[42] For that reason, vitamin K antagonists became initially the standard of care in patients with NVAF despite many limitations including bleeding hazard, food or drug interactions, need for dosage monitoring and potential international normalized ratio instability.[43] In fact, large administrative database surveys indicate that between 30% and 50% of patients who might be considered candidates for oral anticoagulation are not receiving it.[43,44]

The recent introduction of new-generation drugs such as dabigatran,[45] apixaban,[46] or rivaroxaban[47] has modified the approach of patients with NVAF. However, despite more convenient administration and less intracranial bleeding associated with these new agents, oral anticoagulation still constitutes a problem for many patients because gastrointestinal bleeding remains unaltered and the rate of major bleeding ranges between 2.1% and 3.6% per year.[45,47,48] In addition, patients at higher risk of bleeding were not included in those clinical trials.[45,47,48] Other factors such as the elevated and recurrent cost of the agents, the twice-daily dosage (dabigatran, apixaban), and several adverse effects such as dyspepsia[45] or hepatotoxicity[45] might also limit the treatment compliance. In fact, recent data show that, even since the introduction of dabigatran, the rate of patients who should but do not take oral anticoagulation is still 40%.[49]

LAA: function, anatomy, and stroke relationship

The LAA is an embryologic remnant of the left atrium with a potential relevant role in pressure-volume homeostasis as a thirst mediator.[50,51] The LAA is located on the lateral wall of the left atrium and it is in close relation with the circumflex artery and is 1 cm away from the mitral valve and the left superior pulmonary vein.[52] LAA anatomy is heterogeneous in size, thickness, and morphology. In general, the entrance of the LAA is oval and 80% of patients present more than 1 lobe.[53]

In sinus rhythm, the LAA is a contracting structure that generally empties its content in every single heart beat.[54] In AF, the LAA loses its contraction and becomes a dilated cavity with decreased blood velocities and higher risk of thrombus formation.[54] According to Blackshear and Odell,[55] the LAA contains 90% of the thrombus in patients with NVAF. Such high prevalence of thrombus inside the LAA in patients with NVAF has led many physicians to think that LAA exclusion might constitute an alternative to anticoagulation without increasing the bleeding hazard. Surgical and percutaneous techniques have been proposed as strategies to exclude the LAA from the general circulation.[56]

Surgical LAA closure

LAA ligation was first proposed in the 1940s as a prophylactic measure to prevent emboli during mitral valvotomy.[57] Even with similar techniques, the rates of successful LAA closure are highly variable ranging from 17% to 100% according to the series.[58] Overall, conventional surgical removal with scissors or electrocautery and suture sewn appears to be the most successful technique.[58] Other surgical dedicated devices for LAA occlusion are also available including the Lariat (see *LARIAT Suture Delivery Device* section) and the Atriclip PRO. The Atriclip PRO (Atricure, West Chester, OH), an LAA exclusion system using direct visualization that is also available for thoracoscopic application, has shown promising results with a 95% successful closure rate and durable LAA sealing at 3-month follow-up.[59]

The clinical benefit in stroke prevention among surgical studies is not clear. Katz et al.[60] showed that 50% of the unsuccessful closures had spontaneous echo contrast or thrombus in the LAA and 22% had subsequent thromboembolic events. In agreement with these results, Garcia-Fernandez et al.[61] showed that no LAA closure and incomplete LAA closure were the main risk factors for future thromboembolic events. In addition, the study suggested that incomplete LAA closure might be worse than no closure at all because it was associated with the highest risk of thromboembolic events.[61] The potential risk of ending in a worse situation, the absence of conclusive data, and the physiologic advantages of preserving the cardiac appendages are probably the reasons that some physicians believe that prophylactic exclusion of the LAA during cardiac surgery should not be recommended as a standard practice.[62] After an initial pilot study that showed the procedure is safe with acceptable rates of occlusion,[63] an ongoing multicentre Canadian trial (**L**eft **A**trial **A**ppendage **O**cclusion **S**tudy III [LAAOS III], NCT01561651) should help to define if surgical LAA occlusion at the time of cardiac surgery with the use of cardiopulmonary bypass prevents stroke.

Percutaneous LAA occlusion

Percutaneous LAA closure systems have become available during the past decade. The first device was the PLAATO, a self-expandable device made of nitinol and covered by a polytetrafluoroethylene membrane (Figure 1B of reference 56). In 2005, Ostermayer et al.[64] published the first multicentre study evaluating the safety and efficacy of the PLAATO system in 111 patients. Noteworthy, the annual stroke rate observed in the study (2.2% per year) was reduced by 65%, depicted by the estimated rate of 6.3% per year in patients taking aspirin but without anticoagulation. Surprisingly, and despite the positive data supporting the safety and efficacy of the PLAATO system, the developing program was cancelled and the device is no longer available.

Currently, most of the reported data on percutaneous LAA closure is concentrated on the 2 most used devices, the Watchman (Boston Scientific, Natick, MA) and the Amplatzer Cardiac Plug (ACP) (St Jude Medical). Like the PLAATO, both systems require a femoral vein access, a transseptal puncture, and a dedicated delivery sheath. Although most operators perform the procedure using general anaesthesia with TEE and fluoroscopic guidance, the procedure can also be performed using conscious sedation and fluoroscopic guidance with or without intracardiac echocardiography.

The Watchman device

The Watchman is a self-expanding nitinol device with stabilizing anchors covered by a polytetrafluoroethylene

membrane (Figure 1B of reference 56). In contrast with the ACP, the ostium of the LAA is not covered as the most proximal part of the device is implanted at a depth of 10 mm from the appendage orifice.

The first feasibility study with the Watchman system was published in 2007.[65] The WATCHMAN LAA System for Embolic **Protect**ion in Patients With **A**trial **F**ibrillation (PROTECT AF) trial[66] was the first published randomized trial comparing percutaneous LAA closure vs oral anticoagulation in patients with NVAF. In a 2:1 ratio, 707 patients were randomized to LAA closure using the Watchman device (n = 463) vs oral anticoagulation with warfarin (n = 244). Percutaneous LAA closure was shown to be noninferior to warfarin for the primary end point (ischemic or hemorrhagic stroke, systemic emboli, and cardiovascular or unexplained death) with an annual rate of 1.9% vs 4.6% in the warfarin group. Despite the promising results in terms of efficacy, PROTECT AF was criticized because the primary safety events were more frequent in the intervention group. In fact, 4.1% of the patients presented serious pericardial effusions requiring drainage, 3.5% major bleedings, 0.5% procedural-related strokes, and 0.6% device embolization. Part of these complications seemed to be associated with the learning curve of operators demonstrated by the reduction in events and especially cardiac tamponade in the second half of the study.[67] In addition, a nonrandomized continued access program (CAP Registry) in 460 patients revealed a significant improvement in the results with the increasing experience of operators depicted by the greater rate of successful implantation (from 89% to 95%), the shorter procedural times, the lower rates of pericardial effusions requiring drainage (from 4.4% to 2.2%), and no more procedural-related strokes (from 0.5%).[67] Moreover, results from PROTECT AF at 2.3-year follow-up confirmed the noninferiority of LAA occlusion compared with warfarin[68] and results at 5 years (not yet published) suggested that LAA occlusion might be superior to anticoagulation for stroke prevention with no more excess of complications. The **P**rospective **R**andomized **Eva**luation of the WATCHMAN LAA Closure Device **i**n Patients With Atrial Fibrillation vs **L**ong-Term Warfarin Therapy (PREVAIL) study, a second randomized trial comparing warfarin vs LAA occlusion with the Watchman in patients with NVAF, will shortly be published and might confirm the initial trial.

ACP and Amplatzer Amulet

The ACP is a self-expanding device made of a nitinol mesh with 2 polyester patches sewn to a distal lobe and a proximal disc that are connected by an articulated waist (Figure 1C of reference 56). The distal lobe conforms to the inner LAA wall in a depth of approximately 10 mm, the articulated waist allows a proper orientation of the device into the LAA, and the proximal disc seals the ostium of the appendage (pacifier effect).[69] The distal lobe contains stabilizing wires designed to anchor the system and decrease the risk of embolization.

In contrast with the Watchman device, no randomized studies are currently available for the ACP. A randomized trial called the Amplatzer Cardiac Plug Trial (ACP-TRIAL) will evaluate the efficacy and safety of LAA closure using the ACP in subjects with NVAF compared to warfarin and dabigatran. To date, most of the ACP implantations have been conducted in patients with a formal contraindication to anticoagulation or at high risk of bleeding. Several registries from all over the world have been published.[70-76] As shown in Table 2, the ACP is associated with a high successful implantation rate that ranges between 95% and 99%. In agreement with other devices registries, a substantial learning curve and therefore a progressive reduction in the number of complications was also observed.[74]

A second generation of the ACP called Amplatzer Amulet (St Jude Medical) presents a novel design intended not only to facilitate the implantation process but also to reduce the number of complications. The first-in-man implantation was performed at the Montreal Heart Institute in July 2012.[77]

LARIAT suture delivery device

The LARIAT (SentreHEART Inc, Palo Alto, CA), a percutaneous ligation suture system, involves a more complex implantation technique that requires a double endocardial and epicardial approach. A magnet-tipped wire is positioned inside the LAA via transseptal puncture and a 40-mm closure snare device ligates the appendage from the epicardium via pericardial puncture. Bartus et al.[78] showed in an observational study with 89 patients that LAA closure with the LARIAT device can be performed effectively with acceptably low access complications and periprocedural adverse events. Further studies with larger series of patients will be needed to confirm these initial results.

Conclusions

NVAF is a growing condition that currently affects several million people around the world but will be much more prevalent within the next years. For multiple reasons, between 30% and 50%[79] of patients with a formal indication for oral anticoagulation are not receiving it and treatment compliance does not seem to improve despite the recent introduction of

Table 2. In-hospital and follow-up outcomes of different series of patients treated with the Amplatzer Cardiac Plug

		In-hospital outcomes				Follow-up outcomes		
Reference (publication year) - location	n	Procedural success, %	Stroke, %	Device embolism, %	Pericardial tamponade, %	Mean follow-up, months	Stroke/TIA, %	Device thrombosis, %
Park et al.[74] (2011) - Europe	143	96	2.1	1.4	3.5	0	—	—
Walsh[75] (2012) - Europe	204	96	0	1.5	1.5	6	0.9	2.4
Lam et al.[71] (2012) - Asia-Pacific	20	95	0	0	0	13	0	0
Italian Registry[70] (2011) - Italy	100	99	0	0	2	0	—	—
Guérios et al.[72] (2012) - Brazil	85	99	2.3	2.3	1.1	12	0	0
López-Minguez et al.[73] (2012) - Spain	35	97	0	0	0	21	2.8	14
Ureña et al.[76] (2013) - Canada	52	98	0	1.9	1.9	20	1.9	1.9

TIA, transient ischemic attack.

novel oral anticoagulant agents.[49] Although PROTECT AF did not include patients with contraindications to oral anticoagulation or at high risk of bleeding, data from additional nonrandomized publications suggest that LAA closure might be an alternative for those patients (Class IIb indication).[80] Percutaneous LAA closure using the Watchman or the ACP offer a promising balance between efficacy and safety when performed by expert operators. PREVAIL and ACP-TRIAL, 2 randomized studies comparing LAA closure vs oral anticoagulation in NVAF patients, will help to confirm if LAA occlusion can be a valid alternative to warfarin and novel anticoagulants even in patients without contraindication.

Disclosures

Drs Ibrahim, Freixa, and Tzikas are consultants and proctors for St Jude Medical. Dr Noble is a proctor for Medtronic. The rest of authors have no conflicts of interest to disclose.

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