On average, every 20 seconds someone in the US1 or in Europe2 has a stroke. This adds up to a total of about 1.7 million strokes per year in these two continents, affecting about 0.22% of the population each year. In the US alone, every four minutes someone dies from stroke, yielding a total mortality of about 140,000 deaths per year. As a result, stroke is the world’s third leading cause of death, after heart disease and cancer.1 Moreover, stroke is the leading cause of severe, long-term disability and functional impairment. Not surprisingly, stroke is also a costly disease. For the US, the total direct and indirect costs associated with stroke in 2010 were estimated to be over US $70 billion.1 Similarly, high costs are associated with stroke in Europe.3

Ischaemic stroke accounts for about 87% of all stroke events. Among various risk factors, atrial fibrillation (AF) and patent foramen ovale (PFO) are two clinical conditions associated with an increased risk for ischaemic stroke. The former is the most common cardiac arrhythmia that increases the stroke risk four- to five-fold.4–6 As the prevalence of AF increases with age, the AF population consists of relatively older patients.7,8 A PFO is a haemodynamically insignificant intra-atrial communication with a prevalence of about 25% in the general population. However, case-control studies demonstrated persistent PFO in about 40% of patients who had a stroke of unknown cause.9 The relationship between a PFO and cryptogenic stroke seems to be stronger for patients aged less than 55 years.10 One potential explanation is that on the one hand, the relative low risk of stroke in young individuals with PFO and on the other hand, the higher risk of stroke with increasing age due to age-related risk factors (atherosclerosis and heart disease) that renders the relative risk of stroke due to PFO insignificant in comparison.

The mainstay of treatment for preventing ischaemic stroke is antiplatelet therapy and/or oral anticoagulation (OAC). In patients with AF, OAC with vitamin K antagonists (warfarin) reduces the stroke rate by two-thirds, whereas acetylsalicylic acid (aspirin) reduces the risk by one-fifth.11 The American College of Cardiology (ACC), American Heart Association (AHA) and European Society of Cardiology (ESC) guidelines recommend OAC for AF patients with a CHADS2 score >1, aspirin or OAC for AF patients with a CHADS2 score of 1 and only aspirin for AF patients without any risk factor for stroke.12 Regarding PFO, AHA and American Stroke Association (ASA) guidelines recommend antiplatelet agents as a reasonable therapy for patients who had a cryptogenic stroke and were diagnosed with a PFO and advise that warfarin may be offered to patients who have other indications for OAC.9

Concerning OAC, particularly when combined with antiplatelet agents, the associated risks of bleeding should be weighted against the potential benefits of ischaemic stroke prevention. For the older AF population, as well as for the somewhat younger PFO patients, this may lead to the consideration of alternative approaches, such as percutaneous closure of the PFO or occlusion of the left atrial appendage (LAA).

Stroke Prophylaxis by Percutaneous Closure of Patent Foramen Ovale and Left Atrial Appendage

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Abstract

Innovative percutaneous procedures for stroke prevention have emerged in the last two decades. Transcatheter closure of the patent foramen ovale (PFO) is performed in patients who suffered a cryptogenic stroke or a transient ischaemic attack (TIA) in order to prevent recurrence of thromboembolic events. Percutaneous occlusion of the left atrial appendage (LAA) has been introduced to reduce stroke risk in patients with atrial fibrillation (AF). The role of PFO and LAA in the occurrence of cerebrovascular events and the interventional device-based therapies to occlude the PFO and LAA are discussed.

Keywords

Stroke prevention, transcatheter, stroke prophylaxis, percutaneous closure, patent foramen ovale, left atrial appendage

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The relationship between a PFO and cryptogenic stroke seems to be stronger for patients aged less than 55 years.10 One potential explanation is that on the one hand, the relative low risk of stroke in young individuals with PFO and on the other hand, the higher risk of stroke with increasing age due to age-related risk factors (atherosclerosis and heart disease) that renders the relative risk of stroke due to PFO insignificant in comparison.

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Concerning OAC, particularly when combined with antiplatelet agents, the associated risks of bleeding should be weighted against the potential benefits of ischaemic stroke prevention. For the older AF population, as well as for the somewhat younger PFO patients, this may lead to the consideration of alternative approaches, such as percutaneous closure of the PFO or occlusion of the left atrial appendage (LAA).
studies on PFO prevalence in cryptogenic stroke patients. In older patients (>55 years), PFO was about 2.4 times more common in cryptogenic stroke patients younger than 55 years as compared to control patients with stroke of known cause. In patients older than 55 years, PFO was about 2.4 times more common in cryptogenic stroke patients. Similar findings were reported by a review of several studies on PFO prevalence in cryptogenic stroke patients. In younger patients (<55 years or <40 years), the prevalence of PFO in cryptogenic stroke patients was 45%, compared to 11% in patients with stroke of known cause. In older patients (>55 years in most of the analysed studies), the difference was less prominent, but still present (25% in cryptogenic stroke patients versus 14% in patients with stroke of known cause). As noted by the author, the risk attributable to PFO in the elderly may be equal or higher compared to younger patients, as stroke incidence increases with age.

Although the currently available data suggests that the presence of a PFO may increase the risk of stroke, there are other predisposing factors that may play a role in the stroke mechanism, such as anatomical characteristics, presence of an atrial septal aneurysm, haemodynamic factors and deep venous thrombosis. The influence of other factors on stroke recurrence in PFO was shown in a study including 581 patients aged 18 to 55 years who had ischaemic cryptogenic stroke and received aspirin for secondary prevention. The risk of recurrence within four years after the index stroke was 15.2% for patients with a PFO and an atrial septal aneurysm, whereas patients with no septal abnormality or with this abnormality only had a much lower risk of recurrence. Apart from this finding, the authors emphasised that the substantially high recurrence rate, in spite of antplatelet therapy, indicates the need to consider alternative preventive therapies.

In summary, available data suggests that a PFO may be associated with an increased risk of stroke, but most likely only in the presence of multiple predisposing factors.

Interventional Patent Foramen Ovale Closure

Percutaneous PFO closure has emerged as an alternative secondary prophylaxis for recurrent cryptogenic stroke (see Figure 1) since the catheter-based technique was introduced more than 30 years ago. More recently, several non-randomised studies reported a reduction in recurrent stroke or transient ischaemic attack (TIA) following interventional PFO closure. Ford et al. performed transcatheter PFO closure in 255 cryptogenic stroke patients and 118 patients who had a TIA (19). Overall, they observed a combined stroke/TIA recurrence rate of 0.9% at one year and 2.8% at four years. This compared well with the recurrence rates reported for standard medical therapy (3.8 to 12%).

In another study, 308 patients with cryptogenic stroke and PFO received either medical treatment (n=158) or underwent percutaneous PFO closure (n=150). At four years of follow-up, a non-significant reduction in death, recurrent stroke or TIA as compared to medical treatment was observed. It was concluded that percutaneous PFO closure is at least as equally effective as medical treatment for prevention of recurrent cerebrovascular events in cryptogenic stroke patients with PFO.

Schulenz et al. studied the recurrence of stroke in 280 patients, either receiving antplatelet therapy (n=66), OAC (n=47) or who were treated with percutaneous PFO closure (n=167). Interventional treatment was associated with a low annual stroke/TIA recurrence rate (0.6%) compared to antplatelet therapy (13%) and OAC (5.6%).

In a meta-analysis of ten studies (1,355 patients) of percutaneous PFO closure and six studies of medical therapy (895 patients) PFO closure showed a lower incidence of recurrent stroke or TIA at one-year follow-up (0 to 4.9% versus 3.8 to 12%). From the results of this meta-analysis, it was concluded that PFO closure may prevent a substantial proportion of cryptogenic strokes. However, this conclusion suffers from the limitations deriving from the lack of randomised controlled studies.

Given the low event rates of stroke recurrence in PFO patients with cryptogenic stroke, complications of device implantation must be carefully accounted for. In general, periprocedural and device-related complications of percutaneous PFO closure are reported to be up to 6%, are not usually severe and do not require emergency intervention. Completeness of PFO closure differs among the different devices available and ranges between 51 and 100% with a mean closure rate of 86%.

A number of randomised controlled studies on device-based stroke prevention in patients with PFO are currently ongoing and for one of them the key results have been reported.

The CLOSURE I study, the first randomised controlled study in this clinical setting, enrolled 909 patients of 60 years or younger with cryptogenic stroke or TIA and PFO. Patients were randomised to either medical treatment or percutaneous PFO closure and were followed for two years. The study had a combined primary end-point including two-year rate of stroke or TIA, 30-day all cause mortality after PFO closure and neurological death during remaining follow-up period. The results of this study were reported at the AHA 2010 Scientific Sessions and showed no statistically significant difference in the composite end-point between the randomisation arms. The medical treatment patients had 13 strokes, while in the device arm 12 strokes were observed, three of which were classified as periprocedural (within 30 days of the interventional procedure).
The REDUCE study is currently enrolling patients, who will be followed for up to five years. The final results are not to be expected before 2015. This study includes cryptogenic stroke or TIA patients, but unlike the CLOSURE I study, the TIA has to be confirmed by magnetic resonance imaging (MRI) to qualify the patient for inclusion. Of note, a device different from that used in the CLOSURE I is evaluated in the study. Thus, REDUCE may show the impact of this device on the overall comparison between medical treatment and percutaneous PFO closure. The primary end-point is freedom from recurrent ischaemic stroke, TIA confirmed by MRI, or death due to stroke.

In 2011, results are expected from the RESPECT study. The study will eventually enrol a total of 900 patients randomising them to either medical treatment or interventional therapy. The primary end-point is recurrence of non-fatal stroke, post-randomisation mortality, or fatal ischaemic stroke. This study started enrollment in 2003 and has a follow-up period of eight years.

Device-based PFO closure has the aim of long-term prevention for recurrent stroke. Therefore, the initial lack of clinical benefit due to periprocedural complications may be compensated by better long-term stroke prevention. As this will only be confirmed by long-term follow-up, the currently ongoing REDUCE and RESPECT studies will certainly add to our knowledge regarding percutaneous PFO closure. Moreover, the use of slightly different inclusion criteria and other devices will broaden our understanding regarding patient selection, procedural aspects and device selection.

Left Atrial Appendage Occlusion in Atrial Fibrillation Patients

Atrial Fibrillation, Left Atrial Appendage and Stroke

Patients with AF are at increased risk for stroke.4,5 The first-choice therapy in these patients is OAC that is recommended by the current guidelines. However, many aspects of OAC including a narrow therapeutic window, long half-life, intra- and inter-patient response variability and the dependence on several factors, such as food and drugs, create management difficulties. This therapy is also associated with the risk of bleeding, which may be relatively low, but potentially fatal particularly in case of cerebral haemorrhage.

Moreover, it requires periodic monitoring. New anticoagulation drugs are being developed and tested, but the associated bleeding risk is still existing. In addition, OAC is underused in AF patients, as shown by observational studies. Most frequently, this is due to a physician’s underestimation of the therapeutic benefits and overestimation of the associated risk and patient noncompliance. These considerations have prompted the development of non-pharmacological approaches for stroke prevention in AF patients, not as a full alternative to OAC but as a new option for patients, as shown by observational studies. Most frequently, this is due to a physician’s underestimation of the therapeutic benefits and overestimation of the associated risk and patient noncompliance. These considerations have prompted the development of non-pharmacological approaches for stroke prevention in AF patients, not as a full alternative to OAC but as a new option for patients undergoing mitral valve surgery is recommended by current guidelines.

Percutaneous Left Atrial Appendage Closure

Transcatheter closure of the LAA (see Figure 2) was first reported by Sievert et al. in 2002. Following this initial report, a number of non-randomised studies reported lower stroke rates in AF patients undergoing percutaneous LAA occlusion compared to that expected according to their stroke risk factors.

Stratification of stroke risk in AF patients is often based on the CHADS2 score. This estimates the stroke risk based on a number of well-established risk factors, including congestive heart failure, hypertension, age over 75 years, diabetes and previous stroke or TIA. In 64 patients with paroxysmal AF who were followed for five years after percutaneous LAA closure, an annual stroke/TIA rate of 3.8% was observed, whereas the CHADS2 predicted rate was 6.6% per year. Similarly, in 71 patients in whom the LAA was occluded with this technique, Park et al. observed no stroke during a two-year follow-up. The calculated annual stroke rate based on the CHADS2 score in this population was 5%. Similar results were found in other observational studies on transcatheter occlusion of the LAA in AF patients.

The Embolic protection in patients with atrial fibrillation (PROTECT AF) trial compared the percutaneous LAA occlusion with OAC for stroke prophylaxis in non-valvular AF patients. The study randomised 707 patients who were candidates for long-term OAC to either percutaneous LAA occlusion with subsequent discontinuation of warfarin (463 patients) or to OAC (244 patients). The primary composite end-point was stroke, cardiovascular death and systemic embolisation. A lower efficacy event rate was demonstrated in the intervention group compared to the warfarin therapy group (3 and 4.9% per year, respectively), leading to the conclusion that the interventional treatment was not inferior to OAC. The higher event rate in the intervention treatment group was of some concern (7.4% per patient/year versus 4.4%). In most cases, these events were procedure-related complications.
Coronary Patent Foramen Ovale

Indeed, percutaneous LAA closure was associated with a substantial risk of periprocedural complications (7%), including stroke, systemic embolism, device embolization and cardiac tamponade. Similarly, in another study that enrolled 180 patients from 2003 until 2005, eight major adverse events related to the implantation procedure occurred, including two deaths. Similar to other studies, the authors noted that most of the procedure-related complications occurred in centres with limited experience and during the early learning curve of the participating centres. It is therefore anticipated that procedure-related complication rates will likely decrease with increasing experience.

In addition, extensive training and proctoring by experienced physicians is also expected to reduce the complication rate associated with transcatheter implantation of LAA occlusive devices.

Recently, the National Institute for Health and Clinical Excellence (NICE) issued a guidance document that recommends the selection of potential candidates for percutaneous LAA closure by a multidisciplinary team including a cardiologist and other clinicians experienced in the management of patients with AF at risk of stroke.10

Conclusions

The contribution of the LAA in cardioembolic stroke in AF patients is generally recognised. Although the role of the PFO in cryptogenic stroke is less clearly established, available data strongly suggest that a PFO may increase stroke risk, particularly when associated with other predisposing factors.

Both LAA and PFO are potential targets for percutaneous device-based therapy. Regarding PFO occlusion, data from early non-randomised studies show a reduction in recurrent stroke rates compared to historical medical controls. The first randomised study with two-year follow-up after percutaneous PFO occlusion failed to show superiority of this therapy over medical treatment. However, randomised studies with five to eight years of follow-up are ongoing and will shed light on the long-term benefits of this therapy.

OAC remains the therapy of choice for AF patients at risk for stroke. However, in selected patients at high risk for stroke and with warfarin contraindications, percutaneous LAA occlusion is an acceptable alternative. This therapy has shown to effectively reduce the stroke rate when compared to that estimated on the basis of identified risk factors. First randomised evidence is available demonstrating the non-inferiority of percutaneous LAA occlusion compared to OAC therapy.

As with every clinical procedure, percutaneous closure of PFO and LAA are associated with periprocedural complications. Complications of PFO closure are usually minor and do not require emergency intervention, while LAA occlusion may be associated with more severe adverse events. For both device-based therapies, periprocedural complication rates may be reduced with increasing experience and more intensive operator training.

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