

## Review Article

# Transcatheter Occlusion Devices for the Prevention of Stroke in Patients with Atrial Fibrillation

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**A**trial fibrillation (AF) is the most common sustained cardiac arrhythmia, affecting an estimated 2.2 million Americans.<sup>1</sup> Among patients with AF there is an approximate 5% annual stroke risk, a 5-fold increase over an age-matched population in sinus rhythm.<sup>2,3</sup> It is important to note that the incidence of atrial fibrillation increases significantly with age.<sup>4</sup> The efficacy of oral anticoagulation (OAC) in lowering the risk of stroke and death in patients with nonrheumatic AF has been clearly demonstrated by multiple randomized, controlled trials.<sup>5-8</sup> Warfarin confers a 68% relative risk reduction compared with non-warfarin-treated control subjects, reducing absolute risk from 4.8% to 1.8% per year.<sup>9</sup> Aspirin confers a lesser benefit, with a relative risk reduction as high as 44% compared with control subjects, but this may be substantially less in individuals at high risk for stroke.<sup>6,10</sup> Chronic OAC with warfarin appears to have problems of safety and acceptability for many patients. Patients treated with warfarin achieve a therapeutic range only on 50% to 68% of monitored days.<sup>11</sup> In clinical practice, oral anticoagulants are prescribed to only 15% to 66% of patients with AF who are at high risk for thromboembolic events and have no clear contraindication for their use.<sup>12</sup>

## Left atrial appendage and thromboembolism in AF

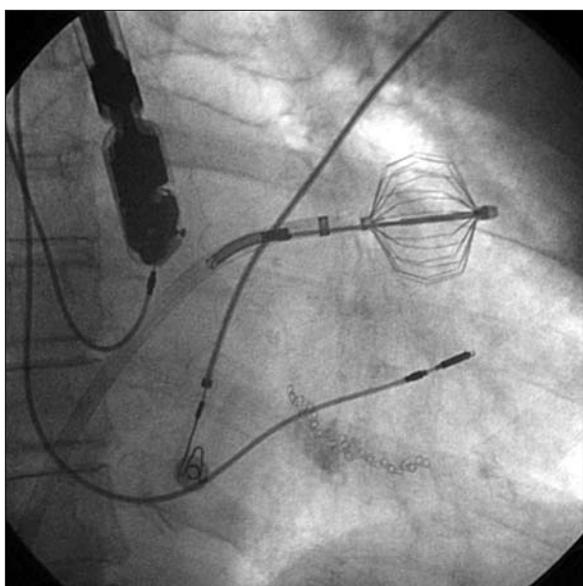
The most common location of thrombi (more than 90%), as has been proved by echocardiography in patients with nonrheumatic AF, is the left atrial appendage (LAA).<sup>5,9,13</sup> In most patients, the LAA is a discrete anatomic structure<sup>14-16</sup> and it may be relatively easily excluded from the systemic circulation. LAA amputation or oversewing of its orifice is routinely done to minimize the risk of future thromboembolism and it is often performed in surgery for rheumatic mitral valve disease, which is often accompanied by AF. Minimally invasive transthoracic techniques have also been used to achieve the same result, with mixed outcomes: suturing the LAA from either within or without may occlude the orifice of the LAA but persistent flow into and out of the LAA is frequently seen when such patients have echocardiograms at follow-up.

## Percutaneous transcatheter occlusion of the LAA

Currently, there are two devices specifically designed for percutaneous transcatheter LAA occlusion: the Percutaneous LAA Transcatheter Occlusion system (PLAATO, ev3 Inc., Plymouth, Minnesota, USA) and

the WATCHMAN LAA system (Atritech Inc., Plymouth, Minnesota, USA).

The PLAATO device (Figure 1) is a self-expanding nitinol cage ranging from 15 to 32 mm in diameter and is covered with a polytetrafluoroethylene membrane to close off flow into the LAA. The feasibility and safety of PLAATO was first described in a dog model,<sup>17</sup> and it has already been tested in a phase I clinical trial. The PLAATO System Trial included only patients with nonrheumatic AF who were at high risk for ischemic stroke and who were not candidates for long-term anticoagulation with warfarin. This group of patients had a history of stroke or transient ischemic attack, or at least one (in Europe) or two (in the United States) stroke risk factors (age >65 years, hypertension, heart failure, diabetes, coronary artery disease, and moderate or dense spontaneous echo contrast or velocity <20 cm/s in the LAA), with a predicted stroke risk based on the patients' adjusted CHADS score<sup>18</sup> distribution of 6.3% per year. According to the results of the trial, transcatheter implantation of the PLAATO device was feasible, reasonably safe, and raised the possibility that the incidence of stroke after PLAATO implantation was reduced. The observed annual stroke rate was 2.2%, representing a 65% relative stroke risk reduction with the PLAATO procedure. Of the 111 enrolled patients, over an average follow up of 9.8 months, two experienced a stroke, 173 and 215 days after the implant procedure. A later report in a larger group of PLAATO patients, with a mean follow up of 14.7 months,<sup>19</sup> indicated that the



**Figure 1.** Fluoroscopy of a successfully deployed PLAATO device.

actual stroke rate was reduced to 3.2% (a relative risk reduction of about 50%). Regarding the long-term risk of thrombus formation with the PLAATO procedure, thrombus was present in 2 patients after 48 months of follow up.<sup>20</sup> One thrombus had formed on the external surface of the device and the other on the interatrial septum. For the same follow-up period, peak flow velocities of the pulmonary veins were not significantly higher after positioning of the device, indicating that there was no development of pulmonary venous obstruction.

The WATCHMAN LAA system is another percutaneous device for LAA occlusion that is placed in the LAA through a transseptal approach. The implant has a 160  $\mu$ m polyethylene membrane on the proximal face of a nitinol frame structure covered with a permeable polyester fabric that allows blood inflow but excludes passage of thrombi out of the LAA, thus forming a mechanical barrier to avoid embolization from the LAA.<sup>21</sup> A recently published study demonstrated that implantation of the WATCHMAN device is a generally safe and feasible percutaneous method for sealing the LAA.<sup>22</sup> In a population of sixty-six patients with an average CHADS score of 1.8, indicating a moderate level of risk for stroke, and a follow-up period of 45 days, 99% of the devices satisfied the primary efficacy endpoint with complete closure of the LAA. The expected annual risk of stroke for the studied group based on the CHADS score was calculated to be 1.9 per year. At a mean follow-up of  $24 \pm 11$  months, no strokes were reported, despite discontinuation of anticoagulation in >90% of the patients. Two patients experienced device embolization; both were successfully retrieved percutaneously and no further embolizations occurred, while five pericardial effusions and one major air embolism occurred without long-term sequelae.<sup>23</sup>

A prospective, randomized study, designed to prove the noninferiority of the WATCHMAN device to warfarin in patients with AF is currently recruiting patients.<sup>24</sup> In the WATCHMAN Left Atrial Appendage System for Embolic PROTECTION in Patients With Atrial Fibrillation (PROTECT AF) study, the patients will be randomized either to LAA occlusion or oral anticoagulation and will be followed up for 60 months. The results of this study are awaited with great anticipation as well as skepticism.<sup>25</sup> There is concern that a patient randomized to WATCHMAN is not only exposed to possible complications associated with the presence of a widely unknown device in his LAA — one that has not been tested in animals — but also runs the risk of heart failure and bleeding.

A comparison of the two different devices or the combination of the results of the trials in order to understand the outcomes is not appropriate. Regarding post-implantation treatment with anticoagulants the two trials followed different strategies. For the patients treated with the PLAATO system, the combination of clopidogrel and aspirin initially and long-term aspirin alone was used. On the other hand, patients treated with the WATCHMAN device required anticoagulation with warfarin for 45 days, followed by clopidogrel 75 mg/d for 6 months until endothelialization of the device was complete, and then aspirin 325 mg/d. Patients who could not take warfarin because of bleeding or other problems were excluded from the WATCHMAN trial.

The inhomogeneity of the studied populations in the two major studies is more pronounced when one focuses on the overall risk assessment for stroke, as expressed by the CHADS score. For the patients treated with the WATCHMAN device the average CHADS score was  $1.8 \pm 1.1$  compared with  $2.5 \pm 1.3$  for the PLAATO group, indicating that the better results so far from the WATCHMAN study regarding the incidence of stroke during follow up may be due to the lower predicted risk for stroke. The complication rate for the PLAATO device was 6-7% while for the WATCHMAN device it was 10%. It should be noted that, because of the high complication rates during implantation with the first generation of the WATCHMAN device that was used for the first 16 patients of the study, the device was redesigned. The remaining patients underwent implantation with the second generation device, with markedly improved results.<sup>23</sup>

The potential concerns with LAA exclusion devices include the elimination of the hemodynamics and endocrine properties of the LAA.<sup>25</sup> Data from animals and humans indicate that LAA elimination may aggravate heart failure, and because of the anatomical proximity LAA occlusion may impede flow in the left coronary artery circumflex branch.<sup>15</sup> Although rare, device migration, dislodgment or embolization, and cardiac perforation may be potential problems, and repeat procedures may be required. Furthermore, small iatrogenic atrial septal defects can be created. They usually disappear within 6 months of the procedure. Persistence of atrial septal defects up to 6 months was observed in three of 48 (6%) patients treated with the PLAATO device<sup>20</sup> who were evaluated with transesophageal echocardiography, whose role is of great importance during the

implantation process as well as in the follow up of the patients.

## Conclusion

LAA occlusion is a potential alternative to warfarin in patients with atrial fibrillation who have contraindications for anticoagulation. Present results suggest that LAA occlusion may reduce the long-term risk for stroke. However, available data are still very limited. Although occluding the LAA seems technically feasible and limited testing has provided good intermediate results, its long-term safety and ability to reduce stroke incidence remain unproven. We must wait for the results of randomized studies that will clarify the usefulness of LAA occlusion devices as an alternative treatment strategy to long-term anticoagulation.

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