HOSPITAL CHRONICLES 2010, SUPPLEMENT: 137–140

ATHENS CARDIOLOGY UPDATE 2010

Atrial Fibrillation Obviating the Need for Anticoagulants: Percutaneous Closure of Left Atrial Appendage/ PLAATO & PROTECT-AF Trials

Andreas Synetos, MD

Ippokratio University Hospital, Athens, Greece

ABSTRACT

Left atrial appendage (LAA) occlusion is a potential alternative to warfarin in patients with atrial fibrillation who have contraindications to anticoagulation. Currently, there are two devices specifically designed for percutaneous LAA occlusion: the Percutaneous LAA Transcatheter Occlusion (PLAATO System, ev3 Inc., Plymouth, Minnesota) and the WATCHMAN LAA system (Atritech Inc., Plymouth, Minnesota). Despite early interesting and promising data from the PLAATO device, this device was withdrawn by the manufacturer in 2006. Early data on the WATCHMAN system were reported in 2007, and this device is the focus of the recently published PROTECT-AF (WATCHMAN Left Atrial Appendage System for Embolic Protection in Patients with Atrial Fibrillation) study. According to the results of the study, the efficacy of percutaneous closure of the LAA with this device was non-inferior to that of warfarin therapy, suggesting that closure of the LAA might provide an alternative strategy to chronic warfarin therapy for stroke prophylaxis in patients with nonvalvular atrial fibrillation.

KEY WORDS: *atrial fibrillation; anticoagulants; warfarin; left atrial appendage; percutaneous left atrial appendage occlusion; stroke*

INTRODUCTION

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, affecting an estimated 6 million Americans.[1] Among patients with AF, there is an approximate 5% annual stroke risk, a 5-fold increase over an age-matched population in sinus rhythm.[2] 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.[3-6] 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.[7] Aspirin (ASA) confers 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.[4,8] Chronic OAC with warfarin appears to have a lot of problems of safety and acceptability for many patients. Patients treated with warfarin achieve a therapeutic range only in 50% to 68% of monitored days.[9] In clinical practice, oral anticoagulants are prescribed to only 15% to 66% of patients

Correspondence to:
Andreas Synetos, MD
E-mail: synetos@yahoo.com

with AF who are at high risk for thromboembolic events and have no clear contraindication to their use.[10]

THE ROLE OF LEFT ATRIAL APPENDAGE IN THROMBOEMBOLISM IN ATRIAL FIBRILLATION

The risk of stroke is increased in patients with AF, presumably because stagnant blood flow within the left atrium leads to thrombus formation. The most common location of thrombi (>90%), proved by echocardiography in patients with nonrheumatic AF, is the left atrial appendage (LAA).[3,7,11] In most patients, the LAA is a discrete anatomic structure,[12-14] and it may be relatively easily excluded from 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 also have been used to achieve the same result with mixed outcomes—suturing the LAA either from 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 LEFT ATRIAL APPENDAGE

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

The PLAATO device 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,[15] 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[16] 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, with 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,[17] indicated that the actual stroke rate was reduced to 3.2% (a relative risk reduction of about 50%), while regarding the long-term risk of thrombus formation with the PLAATO procedure, thrombus formation was present in 2 patients after 48 months of follow up.[18] One thrombus was formed on the external surface of the device and the other thrombus was formed in 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 is no development of pulmonary venous obstruction. Despite early interesting and promising data from the PLAATO device, this device was withdrawn by the manufacturer in 2006.[19]

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-μm 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, developing a mechanical barrier to avoid embolization from the LAA.[20] Sick et al in 2007 published a study that demonstrated that implantation of the WATCHMAN device is a generally safe and feasible method for percutaneously sealing the LAA.[21] In a population of 66 patients with 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 end point 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 ±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.[22]

A prospective, randomized study, designed to prove the noninferiority of the WATCHMAN device to warfarin in patients with AF was published recently.[23,24] In the WATCHMAN Left Atrial Appendage System for Embolic PROTECTion in Patients With Atrial Fibrillation (PROTECT AF) study, a multicenter, non-inferiority trial, the efficacy and safety of implantation of the percutaneous LAA closure device was compared with that of long-term warfarin therapy. More than 700 patients fulfilled the inclusion criteria of having non-valvular atrial fibrillation, being suitable for anticoagulation, and having a CHADS2 risk score of 1 or more. Most of the patients who had the device implanted (349 of 408) stopped warfarin at 45 days (as predefined) once there was transoesophageal echocardiographic confirmation of LAA closure, and remained on aspirin and clopidogrel for 6 months after randomization, followed by long-term aspirin

monotherapy. The probability of non-inferiority of the device was greater than 99.9% with regard to the primary efficacy outcome (occurrence of all types of stroke, cardiovascular or unexplained death, or systemic emboli within up to 3 years), and patients who received the device had fewer hemorrhagic strokes than the controls. However, the primary safety endpoint (which combined major bleeding, serious pericardial effusion, and device embolization) was significantly greater in the device group than in the control group.[23]

The potential concerns with LAA exclusion devices include the elimination of the hemodynamics and endocrine properties of the LAA.[25] Data from animals and humans indicate that the LAA elimination may aggravate heart failure, and because of the anatomical proximity, LAA occlusion may impede flow in the left coronary artery circumflex branch.[13] Although rare, device migration, dislodgement or embolization, and cardiac perforation may be potential problems; and repeat procedures may be required. Furthermore iatrogenic small 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[18] that were evaluated with transesophageal echo (TEE), the role of which during the implantation process as well as in the follow up of the patients is of great importance.

CONCLUSION

The left atrial appendage occlusion is a potential alternative to warfarin in patients with atrial fibrillation who have contraindications to anticoagulation. As the PROTECT-AF study is the first randomized trial of its kind, the precise role of the WATCHMAN device in the current approach to stroke prevention in patients with atrial fibrillation is perhaps premature. However, we must admit that these results are very encouraging at least for the usage of the device as an alternative option for patients who are unable to take long-term warfarin.

REFERENCES

1. Rockson SG, Albers GW. Comparing the guidelines: anticoagulation therapy to optimize stroke prevention in patients with atrial fibrillation. *J Am Coll Cardiol* 2004; 43:929-935.
2. Prystowsky EN, Benson DW, Jr., Fuster V, et al. Management of patients with atrial fibrillation. A Statement for Healthcare Professionals. From the Subcommittee on Electrocardiography and Electrophysiology, American Heart Association. *Circulation* 1996; 93:1262-1277.
3. Blackshear JL, Odell JA. Appendage obliteration to reduce stroke in cardiac surgical patients with atrial fibrillation. *Ann Thorac Surg* 1996; 61:755-759.
4. Petersen P, Boysen G, Godtfredsen J, Andersen ED, Andersen B. Placebo-controlled, randomised trial of warfarin and aspirin for prevention of thromboembolic complications in chronic atrial fibrillation. The Copenhagen AFASAK study. *Lancet* 1989; 1:175-179.
5. Stroke Prevention in Atrial Fibrillation Study. Final results. *Circulation* 1991; 84:527-539.
6. Warfarin versus aspirin for prevention of thromboembolism in atrial fibrillation: Stroke Prevention in Atrial Fibrillation II Study. *Lancet* 1994; 343:687-691.
7. Risk factors for stroke and efficacy of antithrombotic therapy in atrial fibrillation. Analysis of pooled data from five randomized controlled trials. *Arch Intern Med* 1994; 154:1449-1457.
8. Adjusted-dose warfarin versus low-intensity, fixed-dose warfarin plus aspirin for high-risk patients with atrial fibrillation: Stroke Prevention in Atrial Fibrillation III randomised clinical trial. *Lancet* 1996; 348:633-638.
9. Gottlieb LK, Salem-Schatz S. Anticoagulation in atrial fibrillation. Does efficacy in clinical trials translate into effectiveness in practice? *Arch Intern Med* 1994; 154:1945-1953.
10. Onalan O, Lashevsky I, Hamad A, Crystal E. Nonpharmacologic stroke prevention in atrial fibrillation. *Expert Rev Cardiovasc Ther* 2005; 3:619-633.
11. Stoddard MF, Dawkins PR, Prince CR, Ammash NM. Left atrial appendage thrombus is not uncommon in patients with acute atrial fibrillation and a recent embolic event: a transesophageal echocardiographic study. *J Am Coll Cardiol* 1995; 25:452-459.
12. Donal E, Yamada H, Leclercq C, Herpin D. The left atrial appendage, a small, blind-ended structure: a review of its echocardiographic evaluation and its clinical role. *Chest* 2005; 128:1853-1862.
13. Stollberger C, Schneider B, Finsterer J. Elimination of the left atrial appendage to prevent stroke or embolism? Anatomic, physiologic, and pathophysiologic considerations. *Chest* 2003; 124:2356-2362.
14. Al-Saady NM, Obel OA, Camm AJ. Left atrial appendage: structure, function, and role in thromboembolism. *Heart* 1999; 82:547-554.
15. Nakai T, Lesh MD, Gerstenfeld EP, Virmani R, Jones R, Lee RJ. Percutaneous left atrial appendage occlusion (PLAATO) for preventing cardioembolism: first experience in canine model. *Circulation* 2002; 105:2217-2222.
16. Ostermayer SH, Reisman M, Kramer PH, et al. Percutaneous left atrial appendage transcatheter occlusion (PLAATO system) to prevent stroke in high-risk patients with non-rheumatic atrial fibrillation: results from the international multi-center feasibility trials. *J Am Coll Cardiol* 2005; 46:9-14.
17. Bayard YL, Ostermayer SH, Sievert H. Transcatheter occlusion of the left atrial appendage for stroke prevention. *Expert Rev Cardiovasc Ther* 2005; 3:1003-1008.
18. Schmidt H, Hammerstingl C, von der Recke G, Hardung D, Omran H. Long-term follow-up in patients with percutaneous left atrial appendage transcatheter occlusion system (PLAATO): risk of thrombus formation and development of pulmonary venous obstruction after percutaneous left atrial append-

age occlusion (Abstr). *J Am Coll Cardiol* 2006; 47:36A.
19. Block PC, Burstein S, Casale PN, et al. Percutaneous left atrial appendage occlusion for patients in atrial fibrillation suboptimal for warfarin therapy: 5-year results of the PLAATO (Percutaneous Left Atrial Appendage Transcatheter Occlusion) Study. *JACC Cardiovasc Interv* 2009; 2:594-600.
20. Block PC. Watching the watchman. *J Am Coll Cardiol* 2007; 49:1496-1497.
21. Sick PB, Schuler G, Hauptmann KE, et al. Initial worldwide experience with the WATCHMAN left atrial appendage system for stroke prevention in atrial fibrillation. *J Am Coll Cardiol* 2007; 49:1490-1495.
22. Onalan O, Crystal E. Left atrial appendage exclusion for stroke prevention in patients with nonrheumatic atrial fibrillation. *Stroke* 2007; 38:624-630.
23. Holmes DR, Reddy VY, Turi ZG, et al. Percutaneous closure of the left atrial appendage versus warfarin therapy for prevention of stroke in patients with atrial fibrillation: a randomised non-inferiority trial. *Lancet* 2009; 374:534-542.
24. Fountain RB, Holmes DR, Chandrasekaran K, et al. The PROTECT AF (WATCHMAN Left Atrial Appendage System for Embolic PROTECTion in Patients with Atrial Fibrillation) trial. *Am Heart J* 2006; 151:956-961.
25. Stollberger C, Schneider B, Finsterer J. WATCHMAN: an effective protection against stroke? *Am Heart J* 2006; 152:e35; author reply e37-38.