Journal of the American College of Cardiology
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Published by Elsevier Inc.

Vol. 49, No. 13, 2007
ISSN 0735-1097/07/$32.00
doi:10.1016/j.jacc.2007.02.035

EXPEDITED REVIEWS

Initial Worldwide Experience With the WATCHMAN Left Atrial Appendage System for Stroke Prevention in Atrial Fibrillation

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Objectives This study assessed the feasibility of implanting a device in the left atrial appendage (LAA) in patients with atrial fibrillation (AF) to prevent thromboembolic stroke.

Background Meta-analyses confirmed that in cases of left atrial thrombus in nonrheumatic AF patients approximately 90% of them are in the LAA.

Methods The WATCHMAN Left Atrial Appendage System (Atritech Inc., Plymouth, Minnesota) is a nitinol device implanted percutaneously to seal the LAA. Patients were followed by clinical and transesophageal echocardiography at 45 days and 6 months with annual clinical follow-up thereafter.

Results Sixty-six patients underwent device implantation. Mean follow-up was 740 ± 341 days. At 45 days, 93% (54 of 58) devices showed successful sealing of LAA according to protocol. Two patients experienced device embolization, both successfully retrieved percutaneously. No embolizations occurred in 53 patients enrolled after modification of fixation barbs. There were 2 cardiac tamponades, 1 air embolism, and 1 delivery wire fracture (first generation) with surgical explantation but no long-term sequelae for the patient. Four patients developed a flat thrombus layer on the device at 6 months that resolved with additional anticoagulation. Two patients experienced transient ischemic attack, 1 without visible thrombus. There were 2 deaths, neither device related. Autopsy documented a stable, fully endothelialized device 9 months after implantation. No strokes occurred during follow-up despite >90% of patients with discontinuation of anticoagulation.

Conclusions Preliminary data suggest LAA occlusion with the WATCHMAN System to be safe and feasible. A randomized study is ongoing comparing oral anticoagulation with percutaneous closure. (J Am Coll Cardiol 2007;49: 1490–5) © 2007 by the American College of Cardiology Foundation

Atrial fibrillation (AF) is the most common cardiac abnormality associated with ischemic stroke. Among patients with AF, there is an approximate 5% annual stroke risk, a 5-fold increase over an age-matched population in sinus rhythm. Increased stroke risk correlates with age, previous transitory ischemic attack (TIA) or stroke, hypertension, diabetes, impaired left ventricular function, and a large left atrium. Most ischemic strokes associated with AF are thought to be secondary to embolization from the left atrial appendage (LAA). Transesophageal echocardiography (TEE) data show left atrial thrombi to be more frequent in AF patients with ischemic stroke as compared with AF patients without stroke (1).

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There is a wealth of published literature from controlled trials on stroke prevention in AF demonstrating the effectiveness of anticoagulation (2–5). The SPAF (Stroke Prevention in Atrial Fibrillation)-III studies confirmed that warfarin adjusted for a target international normalized ratio of 2 to 3 is optimal. Because the therapeutic dose of warfarin

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The registry was supported by Atritech Inc., Plymouth, Minnesota.

Manuscript received February 8, 2007; revised manuscript received February 26, 2007, accepted February 28, 2007.

is affected by a large number of drug, dietary, and metabolic interactions, it can be unpredictable in some patients and difficult to manage. The narrow therapeutic window, need for frequent blood drawing for monitoring, potentially lethal complications, and poor patient tolerance have resulted in a majority of patients with AF not receiving therapeutic anticoagulation, in particular older patients who are at increased risk of stroke. Aspirin, although generally better tolerated, is clearly less effective at stroke prevention (6).

Given the problems with the available pharmacologic approaches, a device-based solution has been sought to provide protection against thromboembolic events in patients with AF. The purpose of this study was to assess the safety and feasibility of deploying the WATCHMAN Left Atrial Appendage Occlusion Device (Atritech Inc., Plymouth, Minnesota) in a pilot trial.

Methods

Study design and inclusion/exclusion criteria. This was an open-label nonrandomized pilot study designed to demonstrate the safety and feasibility of the new WATCHMAN Left Atrial Appendage Occlusion Device. Adult patients over 18 years of age with a life expectancy of at least 2 years, documented chronic or paroxysmal nonvalvular AF who were eligible for warfarin therapy were screened as candidates for the WATCHMAN investigation. Patients had to have a minimum $CHADS_2$ score of at least 1. The $CHADS_2$ score is an overall risk assessment for stroke based on a scale of 0 to 6. To calculate a patient's score, 1 point is assigned for the presence of congestive heart failure, diabetes, history of hypertension, or age ≥75 years. Two points are assigned for prior stroke or TIA. The score can be used to approximate the annual risk of stroke (6). If patients had prior embolic stroke, full recovery without significant neurologic residual deficits had to be documented.

Patients with any congenital heart disease including atrial septal defect or septal aneurysms, symptomatic carotid disease, symptomatic valvular disease, aortic arch atheroma, or presence of a prosthetic valve were excluded. Other exclusion criteria included intracardiac thrombus, including LAA or spontaneous echo contrast visualized by TEE within 48 h before planned WATCHMAN implant. Left ventricular ejection fraction below 35% measured by transthoracic echocardiography, more than 1 pacemaker lead or an implanted cardioverter-defibrillator, hypercoagulable state, or pregnancy were also criteria for exclusion.

Device implantation. The WATCHMAN Left Atrial Appendage System is a 3-part system consisting of a trans-septal access sheath, a delivery catheter, and an implantable nitinol device. The system is designed to facilitate device placement via femoral venous access via the transseptal route into the LAA. The WATCHMAN implant comprises a self-expanding nitinol frame structure with fixation barbs and a permeable polyester fabric that covers the atrial facing surface of the device. The device is constrained within a delivery catheter until deployment into the LAA. The WATCHMAN implant (Fig. 1) is available in diameters of 21, 24, 27, 30, and 33 mm to accommodate the unique anatomy of each patient's LAA. Device size was chosen to be 10% to 20% larger than diameter of the LAA body to have sufficient compression for stable positioning of the device. A revised model of the device was introduced after the initial 16 patients with a reinforced delivery cable and a series of barbs to facilitate device attachment and prevent embolization.

Abbreviations and Acronyms

AF = atrial fibrillation
LAA = left atrial appendage
TEE = transesophageal echocardiography
TIA = transitory ischemic attack

The 14-F trans-septal access sheath is available in a double- and single-curve configuration (Fig. 2). The access sheath is utilized to gain access to the LAA and serves as a conduit for the delivery catheter. The WATCHMAN implant is deployed by retracting the sheath covering the device. The implant can be partially recaptured and redeployed if the implant location is deemed unsatisfactory or recaptured completely if a different sized device is determined to be more suitable.

The implantation procedure was performed under TEE guidance. After trans-septal puncture and catheter placement into the LAA and LAA angiography was performed, an optimal device size based on LAA measurements was selected. Proper device position was confirmed by angiography and echocardiography (Fig. 3). Patients were typically hospitalized overnight and discharged the next day. At 45 days after implantation, repeat TEE was performed and repeated at 6-month follow-up. Annual patient follow-up

Figure 1 **WATCHMAN Implant**

WATCHMAN device, nitinol cage with a polytetrafluoroethylene membrane on the surface, and fixation barbs around the perimeter

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Figure 2 Introduction Sheath With Double and Single Curve for Different Anatomical Situations

Introducer sheaths with different shapes

visits up to 5 years are planned with TEE only in case of clinical necessity.

Medical treatment. During implantation, heparin was given to achieve an activated clotting time of at least 250 s immediately after the trans-septal puncture to keep anticoagulation throughout the whole implantation procedure. After implantation intravenous heparin was stopped and replaced by low molecular weight heparin until an international normalized ratio of 2 was achieved with warfarin. Patients were discharged from hospital on aspirin 81 to 100 mg daily and warfarin for at least 45 days, with dosage of the latter adjusted to keep the international normalized ratio between 2 and 3. If echocardiographic criteria for successful sealing of the LAA (as mentioned in the following section) were fulfilled at 45 days, warfarin therapy was discontinued while aspirin was continued indefinitely.

End points. PRIMARY PERFORMANCE END POINT: DEVICE POSITION AT 45 DAYS AFTER PLACEMENT. The primary end point for this study was successful device implantation and successful sealing of the LAA as measured by TEE at 45 days after implant without major adverse events. The rate of successful placement was calculated as the percentage of patients with the device appropriately positioned, the LAA completely sealed with absence of flow or with minimal flow around the device (jet of <3 mm) as measured by TEE at 45 days after placement (Fig. 3).

Major adverse events. Major adverse events were defined as death, stroke, systemic embolism, and major bleeding requiring invasive treatment or blood transfusion. Adverse event data were analyzed as the number of adverse events in the patients' cumulative follow-up time (in patient-months), for each version of the device.

Statistical analysis. Estimates for frequency of occurrence of events are expressed as percentages or rates. Continuous variables are summarized by mean, standard deviation, and minimum and maximum values.

Ethics. Written informed consent was obtained from each individual, and the procedures were performed in accordance with the ethical standards of each participating institution and with the Helsinki Declaration of 1975, revised in 1983.

Results

Baseline characteristics. There were 75 patients in 3 cardiology centers in Europe and 4 centers in the U.S. who met all inclusion and exclusion criteria and were enrolled in the study. Mean patient age was 68.5 years (range 47.4 to 83.2 years), 64% were men. Of the 75 patients with attempted device placement, 66 had successful implantation (88%). In the remaining 9 patients, the trans-septal sheath could not be placed in the LAA due to a scar in the right groin in 1 and a core wire malfunction in 1 patient, while 7 had LAA anatomy that was unsuitable for device placement. The average $CHADS_2$ score of the 66 patients with implants was 1.8 ± 1.1 (range 0 to 5), indicating a moderate level of risk for stroke. The most frequently occurring $CHADS_2$ characteristic was hypertension (55 of 66 [83.3%]) followed by diabetes (22 of 66 [33.3%]).

The average LAA diameter was 19.6 mm, and median implant size was 24 mm. Nine patients received a 21-mm, 31 received a 24-mm, 17 received a 27-mm, and 8 received a 30-mm WATCHMAN device. A mean of 1 ± 1.6 devices per patient (range 1 to 4) were required until optimal

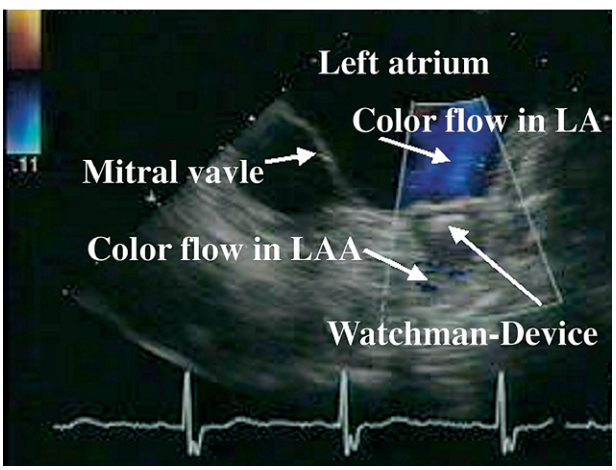

Figure 3 Six-Month TEE Control With a Well-Positioned WATCHMAN Device in the LAA

Little color flow is seen behind the device, and no flow around the margins. LAA = left atrial appendage; TEE = transesophageal echocardiography

Table 1 Summary of Adverse Events During and After Implantation

Adverse Events	First-Generation Patients (n = 16)	Second-Generation Patients (n = 59)
Implant failure due to anatomical reasons of LAA, scar in the groin	2	6
Air embolism without device implantation	1	0
Successful implantations	13	53
Stroke	0	0
Death, not device related	2	0
Core wire failure with surgical device explantation	1	0
Core wire failure without consequences	1	0
Device embolization	2	0
Internal bleeding due to retrieval after device embolization	1	0
Pericardial effusion/tamponade	1	1
Minor pericardial effusion without treatment	0	3
Thrombus on device (noted after 6 and 12 months)	0	4
TIA	1 (with thrombus on device)	1 (without thrombus visible)
Femoral pseudoaneurysm	1	1

LAA = left atrial appendage; TIA = transient ischemic attack.

LAA closure was obtained. Fifty-eight patients came for 45-day follow-up, 5 patients came for later follow-up, so currently 3 patients are definitely lost to follow-up. Ninety-three percent (54 of 58) of the devices satisfied the primary efficacy end point with complete closure of the LAA or without significant flow around the device. Mean follow-up was 24 ± 11 months. Thirteen patients have been followed for more than 4 years, 20 for more than 3 years, and 29 for more than 2 years after implantation.

Adverse events. A number of complications were associated especially with the first-generation device (Table 1). Three patients experienced device failure, 2 of which were embolizations, and 1 was a delivery system failure (fractured delivery wire). The 2 embolized devices were both retrieved percutaneously; 1 of these patients suffered from internal bleeding, but was discharged without negative consequences. One of the broken delivery wires of the first-generation devices did not result in clinically relevant sequelae for the patient: the device was implanted correctly and the broken delivery wire could be removed. Another patient, however, required surgical device explantation after incorrect positioning of the device without the possibility of correcting the position due to the broken wire. After modification of the delivery system in the second-generation devices, this was no longer an issue. In another patient, air embolism led to a malignant arrhythmia requiring cardiopulmonary resuscitation. The patient was discharged from hospital without any adverse consequences; a device, however, was not implanted. After the initial 16 patients, the device was redesigned. The remaining 53 patients underwent implantation with the second-generation device; no further embolizations occurred. Pericardial effusions occurred in 2 of the 75 cases (2.6%) related to the trans-septal puncture procedure. One pericardial effusion appeared related to an overly vigorous "tug test" usually performed for proof of stability of the device in the LAA. Because the LAA is quite thin, the technique was modified to observe the LAA during the tug, either by injecting contrast into the LAA to visualize the chamber, or with continuous TEE observation. No further tug-related effusions were observed.

During follow-up, there were no major strokes at all. Six patients were not followed at 6 months, 2 of them were the patients with device embolizations mentioned in the preceding text, and 4 of them missed follow-up but were seen later in the course of the study; all of them were off coumadin. So there were 60 patients at 6 months follow-up, and 91.7% (55 of 60) of patients had discontinued warfarin therapy. No ischemic stroke or systemic embolisms have occurred during a mean follow-up of 24 months. One patient with a history of TIA experienced a TIA at 4 months without thrombus visible on the device; another patient had a TIA at 6 months with a smooth layer of thrombus detected on the surface of the device (Fig. 4). There were 3 additional patients showing thrombus formation on the atrial surface of the device without neurological symptoms. One of these patients was noncompliant with anticoagulation treatment starting early after device implantation. After an additional 6 months of warfarin therapy, all thrombi had resolved, and patients were maintained on aspirin alone. There were 3

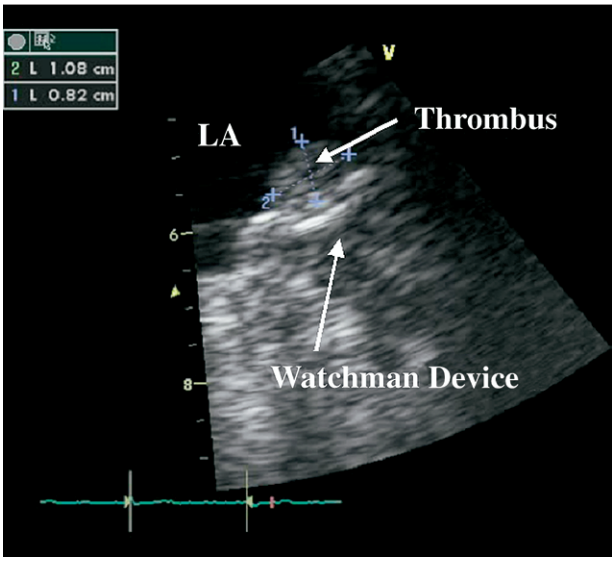

Figure 4 Layered Thrombus Formation on the Device 6 Months After Implantation

LA = left atrial.

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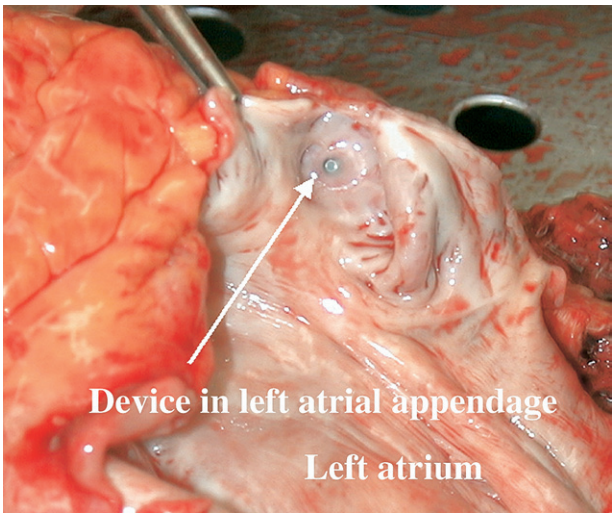

Figure 5 **Anatomical View of the WATCHMAN Device in the LAA in a Patient Who Died From Aortic Dissection**

This patient died 9 months after implantation. Stable position and endothelialization of the device were confirmed. LAA = left atrial appendage. Reproduced with permission from K. E. Hauptmann, Trier, Germany.

major bleeding complications, 2 of which were pericardial effusions treated percutaneously, and 1 internal bleed due to retrieval after device embolization; additionally there were 2 minor bleedings with hematomas in the groin requiring transfusion.

One patient died after 9 months due to an ascending aortic dissection. Autopsy documented a stable, well-endothelialized device with complete LAA occlusion (Fig. 5). One additional patient died of causes unrelated to the device; this patient had multiorgan failure after bowel surgery. Figure 6 illustrates implantation failures and drop outs during follow-up for the 2 generations of the device.

Discussion

More than 15% of cerebral ischemia is due to AF (7–9). Anticoagulation therapy is the method of choice for prevention of thromboembolic events in AF; however, only a low number of all patients with indication for anticoagulation are currently under treatment (10,11). It is well known in AF that if thrombi are found in the left atrium more than 90% are in the LAA (12–14). The WATCHMAN Left Atrial Appendage Device was developed as a mechanical barrier to avoid embolization from the LAA by sealing the orifice of the LAA.

This study demonstrated that implantation of the WATCHMAN device is a generally safe and feasible method for percutaneously sealing the LAA. Modification of the delivery system and the WATCHMAN implant resulted in marked reduction of complications associated with device delivery. Pericardial effusions appeared related to transseptal or tug techniques, both of which are expected to decline with operator experience and adoption of technique modifications as discussed in the previous text.

The expected annual risk of stroke based on the $CHADS_2$ score in this study cohort was calculated to be 1.9/year. In contrast, no strokes have occurred in any of

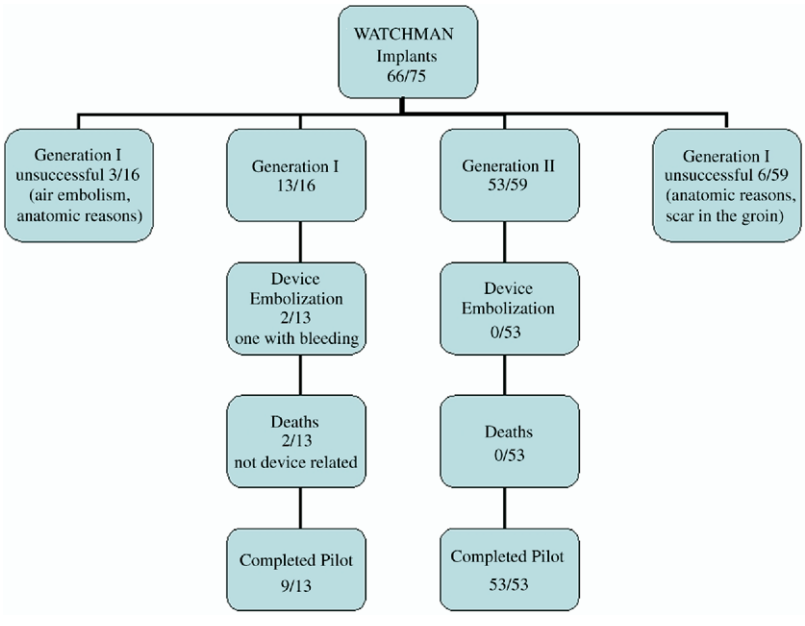

Figure 6 **Flow Chart of the Trial With Number of Implants and Attempts as Well as Drop Outs Dependent on Generation of Device**

the patients in this trial despite discontinuation of anticoagulation in >90% and an average follow-up of 2 years. Although the number of patients does not provide sufficient power to demonstrate equivalence or superiority to anticoagulation, the results appear generally comparable to those reported for the PLAATO System (ev3 Inc., Plymouth, Minnesota), which has also been demonstrated in 205 of 210 implanted patients to have a lower event rate of stroke (5 strokes at a mean follow-up of 14.7 months) compared with the expected stroke rate predicted by the $CHADS_2$ score (15,16). Four patients did have thrombus seen on the device at follow-up, including 1 of the 2 patients who had a TIA. Given the known occurrence of spontaneous thrombus formation in AF patients despite therapeutic anticoagulation (17), this finding may not be surprising. The endothelialization process may not be finished at 45 days after implantation when warfarin is discontinued, so we have modified our therapeutic regimen to include concomitant therapy with aspirin and clopidogrel between 45 days and the 6-month follow-up. Complete endothelialization was documented at 9 months in the patient who died due to an aortic aneurysm (Fig. 5).

Study limitations. This study was a feasibility trial primarily designed to test the safety of the implantation procedure. The use of a first-generation device and incorporation of operator learning curves potentially biased the early results. The study size was not intended to be of sufficient power to address efficacy.

Conclusions

In conclusion, LAA occlusion with the WATCHMAN device appears to be safe with preliminary results consistent with low stroke risk despite discontinuation of anticoagulation. Because of the growing prevalence of AF in the elderly and others, in whom anticoagulation carries a high risk or is contraindicated, these devices may offer an attractive solution to the AF-related emboli problem. A randomized trial commenced in February 2005 comparing anticoagulation therapy with WATCHMAN implantation to assess if percutaneous LAA occlusion is an alternative treatment strategy to long-term anticoagulation.

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REFERENCES

1. 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;93:1262–77.
2. Blackshear JL, Baker VS, Rubino F, et al. 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;348:633–8.
3. 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;1:175–9.
4. Anderson DC, Asinger AW, Newburg SM, et al. Stroke Prevention in Atrial Fibrillation Study. Final results. Circulation 1991;84:527–39.
5. Chesebro JH, Wiebers DO, Holland AE, et al. Warfarin versus aspirin for prevention of thromboembolism in atrial fibrillation: Stroke Prevention in Atrial Fibrillation II Study. Lancet 1994;343:687–91.
6. Gage BF, Waterman AD, Shannon W, Boechler M, Rich MW, Radford MJ. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. JAMA 2001;285:2864–70.
7. Sandercock P, Bamford J, Dennis M, et al. Atrial fibrillation and stroke: prevalence in different types of stroke and influence on early and long term prognosis (Oxfordshire Community Stroke Project). BMJ 1992;305:1460–5.
8. Wolf PA, Benjamin EJ, Belanger AJ, Kannel WB, Levy D, D'Agostino RB. Secular trends in the prevalence of atrial fibrillation: the Framingham Study. Am Heart J 1996;131:790–5.
9. Kannel WB, Wolf PA, Benjamin EJ, Levy D. Prevalence, incidence, prognosis, and predisposing conditions for atrial fibrillation: population-based estimates. Am J Cardiol 1998;82:2N–9N.
10. Brass LM, Krumholz HM, Scinto JM, Radford M. Warfarin use among patients with atrial fibrillation. Stroke 1997;28:2382–9.
11. Bungard TJ, Ghali WA, Teo KK, McAlister FA, Tsuyuki RT. Why do patients with atrial fibrillation not receive warfarin? Arch Intern Med 2000;160:41–6.
12. Aberg H. Atrial fibrillation. I. A study of atrial thrombosis and systemic embolism in a necropsy material. Acta Med Scand 1969;185:373–9.
13. 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;25:452–9.
14. Blackshear JL, Odell JA. Appendage obliteration to reduce stroke in cardiac surgical patients with atrial fibrillation. Ann Thorac Surg 1996;61:755–9.
15. Onalan O, Lashevsky I, Hamad A, Crystal E. Nonpharmacologic stroke prevention in atrial fibrillation. Expert Rev Cardiovasc Ther 2005;3:619–33.
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. Zabalgoitia M, Halperin JL, Pearce LA, Blackshear JL, Asinger RW, Hart RG. Transesophageal echocardiographic correlates of clinical risk of thromboembolism in nonvalvular atrial fibrillation. Stroke Prevention in Atrial Fibrillation III Investigators. J Am Coll Cardiol 1998;31:1622–6.