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Does left atrial appendage occlusion eliminate the need for warfarin?

Left Atrial Appendage Occlusion Eliminates the Need for Warfarin

David R. Holmes, Jr, MD; Robert S. Schwartz, MD



Stroke is the third leading cause of mortality and is a leading cause of disability in the world today. Current estimates suggest a stroke incidence of 780 000 cases yearly, and it remains the most feared complication of cardiovascular disease.¹ Brain ischemia is multifactorial—it may result from carotid artery occlusion, plaque embolization, and aortic atheromatous debris. A major cause is cardiac emboli, most commonly occurring in patients with atrial fibrillation. This association is assuming increased importance as atrial fibrillation markedly increases with the aging population.

Response by Whitlock et al on p 1926

Atrial fibrillation is the most common sustained cardiac arrhythmia.^{2–11} Data from the Framingham study suggest a high incidence of atrial fibrillation.³ By age 40, 26% of men and 23% of women can expect to have at least 1 episode of atrial fibrillation in their remaining years.⁷ The overall rate of ischemic stroke among patients with nonrheumatic atrial fibrillation averages 5% per year, and this rate increases with age.⁷ The overall proportion of strokes thought to be due to atrial fibrillation was reported as 14.7%, a number that steadily increases with age from 6.7% (ages 50 to 59 years) to 36.2% for patients aged 80 to 89 years.¹² Moreover, cardioembolic strokes are associated with the worst long-term prognosis. Henriksson et al¹³ evaluated survival after stroke in 105 074 patients with and without atrial fibrillation from the Swedish Stroke Registry from 2001 to 2005.

In 31 821 patients with atrial fibrillation, a significantly higher death risk (relative risk 1.46, 95% confidence interval [CI] 1.43 to 1.49) was observed after adjustment for age and sex. Henriksson also evaluated the utility of the CHADS₂ score,¹⁴ a simple method to predict stroke risk in patients with atrial fibrillation. It is based on 5 risk factors: congestive heart failure, hypertension, age >75 years, diabetes mellitus, and prior stroke or transient ischemic attack. In the Swedish Stroke Registry,¹³ the stroke rate ranged from 1.9 to 18.2 per 100 patient-years in atrial fibrillation, and the CHADS₂ score accurately predicted clinical outcome after stroke. Patients with a CHADS₂ score of 0 (no risk factors other than atrial fibrillation) had 76.4 deaths per 1000 patient-years, whereas patients with the highest CHADS₂ score (6) suffered 593.7 deaths per 1000 patient-years, nearly an 8-fold increase. Additionally, less than half of the atrial fibrillation patients with a CHADS₂ score ≥ 1 survived more than 5 years.

Emboli in Atrial Fibrillation: The Left Atrial Appendage

Thrombogenesis in atrial fibrillation has generated considerable interest, beginning with Virchow, who proposed a set of criteria needed for thrombus formation. All 3 elements of Virchow Triad typically exist in the atrial fibrillation setting—structural and vessel wall abnormalities, abnormal blood flow patterns, and abnormal constituents in blood,

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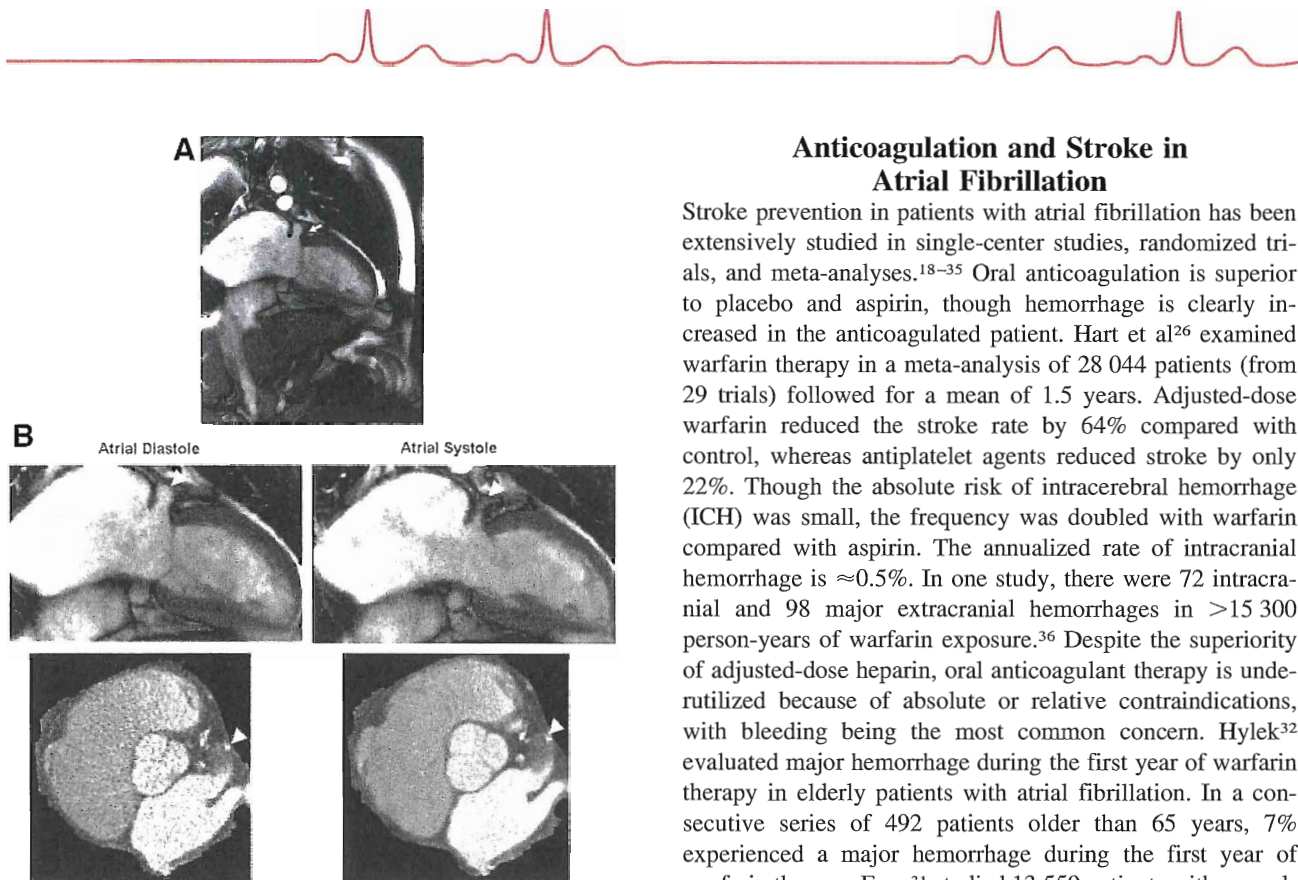


Figure 1. A, Cardiac magnetic resonance imaging showing the normal LAA attached to the superior left atrium. A wide body and narrow appendage neck are typical. LAA paralysis is frequent after an episode of atrial fibrillation, with or without direct current cardioversion. B, Upper row, Atrial systole and diastole in the heart from above, patient in normal sinus rhythm. Note the near obliteration of the LAA (white arrows) during atrial systole. Lower row, Cardiac computed tomography angiography from a different patient, also in normal sinus rhythm. This patient had been in atrial fibrillation and was electrically cardioverted 3 days before this scan was performed. Note that the LAA does not contract despite electrocardiographic sinus rhythm, and also note that the LAA fills very poorly, with contrast not passing beyond the orifice of the appendage.

summarized recently by Watson.¹⁵ Extra cardiac factors such as mobile aortic atherosclerosis or carotid arterial disease may also cause stroke in atrial fibrillation.

The left atrial appendage (LAA, Figure 1) has prompted considerable study as a cause of cardioembolic stroke. Goldsmith¹⁶ identified endocardial changes in the LAA muscular wall, and echocardiographic studies have long documented spontaneous echo contrast or ‘smoke’ that indicates intracavitary blood stasis. Pollick and Taylor¹⁷ studied 2-dimensional echo and Doppler LAA patterns in 82 patients and found it was associated with LAA dilation and poor contraction irrespective of whether the patient was in atrial fibrillation. Blackshear and Odel¹⁸ reviewed 23 studies that included patients with rheumatic and nonrheumatic atrial fibrillation. Distinct differences were noted in the frequency and distribution of LAA thrombus. In nonrheumatic atrial fibrillation, 91% of left atrial thrombi were isolated to or had originated in the LAA.

Anticoagulation and Stroke in Atrial Fibrillation

Stroke prevention in patients with atrial fibrillation has been extensively studied in single-center studies, randomized trials, and meta-analyses.^{18–35} Oral anticoagulation is superior to placebo and aspirin, though hemorrhage is clearly increased in the anticoagulated patient. Hart et al²⁶ examined warfarin therapy in a meta-analysis of 28 044 patients (from 29 trials) followed for a mean of 1.5 years. Adjusted-dose warfarin reduced the stroke rate by 64% compared with control, whereas antiplatelet agents reduced stroke by only 22%. Though the absolute risk of intracerebral hemorrhage (ICH) was small, the frequency was doubled with warfarin compared with aspirin. The annualized rate of intracranial hemorrhage is $\approx 0.5\%$. In one study, there were 72 intracranial and 98 major extracranial hemorrhages in $>15\,300$ person-years of warfarin exposure.³⁶ Despite the superiority of adjusted-dose heparin, oral anticoagulant therapy is underutilized because of absolute or relative contraindications, with bleeding being the most common concern. Hylek³² evaluated major hemorrhage during the first year of warfarin therapy in elderly patients with atrial fibrillation. In a consecutive series of 492 patients older than 65 years, 7% experienced a major hemorrhage during the first year of warfarin therapy. Fang³¹ studied 13 559 patients with nonvalvular atrial fibrillation and found that major hemorrhage and particularly ICH were significantly higher in older patients taking warfarin, worrisome in that atrial fibrillation increases with age. In a community-based study, Flaherty³⁷ found increased ICH associated with anticoagulation in a study covering 1998 to 2003. Clinically important bleeding is an important problem in patients taking warfarin. Older patients >70 years of age have the highest rate, 10.5/100 patient-years compared with 6.0/100 patient-years in those younger than 70 years of age. The rate was also higher during the first 90 days of treatment compared with later. One fifth of bleeds occur at low anticoagulation intensity (international normalized ratio [INR] <2), but rapidly increase with rates 4.8, 9.5, 40.5, and 200 at INRs 2.0 to 2.9, 3 to 3.4, 4.5 to 6.9, and >7 , respectively.^{38–39} Because of these data, patients with a history of significant bleeding are usually not given warfarin.

Warfarin is underused for many other reasons, including gait disturbance or disability with the potential for falls, a narrow therapeutic index, and the wide variability in dosing schedules. Because of these and other considerations, only $\approx 50\%$ of high-risk atrial fibrillation patients are treated with warfarin.³³ Fewer than 60% of those treated have therapeutic INR levels. Warfarin use is not well implemented across large populations. Obtaining and maintaining therapeutic INR values are dependent on the practitioner and patient characteristics. Although some clinical problems related to warfarin use are avoidable, many are quite difficult. In the ideal setting of clinical trials for example, maintaining therapeutic INR is not well achieved, and reports indicate it may vary from 50% to 80% depending on center. For example, Connolly⁴⁰

showed a wide variation in INR therapeutic values across center. Nonadherence to warfarin is also a problem. The mean percentage of days of nonadherence to taking proper warfarin dose was reported as 22%. Patients typically take too few pills rather than too many extra pills. Adherence worsens over time and is typically in the 20% to 30% range over time.^{41,42} These features highlight the substantial difficulties associated with warfarin use, ranging from poor therapeutic control to catastrophic complications such as ICH in the elderly.

Due in large part to these difficulties with warfarin therapy, dual antiplatelet therapy has been studied as an alternative to warfarin. The multicenter Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE W) trial²⁹ randomized 6706 patients with atrial fibrillation and 1 or more stroke risk factor to oral warfarin therapy or aspirin and clopidogrel. The primary outcomes were first stroke occurrence, non-central nervous system systemic embolism, myocardial infarction, or vascular death. This trial was stopped early because warfarin was definitely superior to antiplatelet therapy. Connolly⁴⁰ recently evaluated oral anti-coagulant therapy compared with dual antiplatelet therapy in the ACTIVE W trial as a function of the time the patient was in therapeutic range. They found wide variation across centers and countries and found this variation had major implications for clinical benefit. Accordingly, currently dual antiplatelet therapy is not a substitute for warfarin in patients with atrial fibrillation at risk for stroke.

New anticoagulant strategies are being developed and tested, including factor Xa-inhibiting agents.^{43,44} Earlier drugs were associated with substantial toxicity, which limited their approval. Whether these newer drugs will avoid such toxicity is unclear, and it is also unclear whether these drugs will be as effective as warfarin has proven to be. In addition to these issues, bleeding hazard will almost certainly be increased, and the inconvenience and cost of taking these new daily medications indefinitely will also add complexity to therapy.

Alternative Approaches

LAA Obliteration

The multiple problems with anticoagulant therapy have led to a search for alternative approaches for stroke prevention in atrial fibrillation. These approaches are predicated on the fact that in nonvalvular atrial fibrillation, the embolus originates from the LAA in roughly 90% of cases.⁴⁵ This has led to a strategy of mechanically obliterating the LAA and excluding it from the systemic circulation. Anatomic considerations have been evaluated in several series.^{16,46,47} In a study of 31 autopsy hearts, important considerations included the LAA length, its angulation, and the presence and number of lobes.⁴⁶ Su et al⁴⁶ found substantial variability in LAA wall thickness, and found that approximately half of the specimens had pits or troughs that might be sources of clot. Some

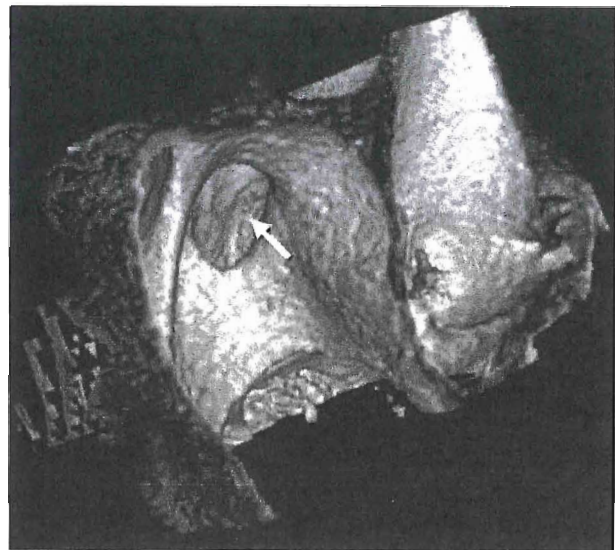


Figure 2. Cardiac computed tomographic angiography from a normal patient showing view from the atrial septum looking toward the orifice of the left atrial appendage. The depth and recesses, along with the elliptical orifice shape, are evident.

regions had shallow pits, whereas others contained narrow troughs occurring in isolated regions and sometimes in clusters. The typical pit or trough diameter was 3.6 mm (range 0.5 to 10.3 mm). These were typically located to the anterolateral or lateral left atrial wall. Most important was that the mean atrial wall thickness was only 1 mm (range 0.4 to 1.5 mm). This marked thinning may be responsible for perforations that have been documented with LAA catheter manipulation. A further consideration is the LAA orifice shape, which is consistently elliptical (Figure 2). This has implications for occlusive device configuration. A round implant in an oval orifice may result in incomplete orifice sealing.

Several approaches have been applied to LAA exclusion, though limited data exist on which are best. Most data come from single or multicenter registries, and these used historical patient cohorts as comparators. In these studies, the CHADS₂ score is often used, and these studies estimated what the stroke risk would have been in a similar group of patients not treated with the device.

LAA obliteration/exclusion is recommended in the American College of Cardiology/American Heart Association Guidelines for patients undergoing mitral valve surgery, and it is performed during surgical approaches for ablation of atrial fibrillation (maze procedures). A pilot randomized trial of exclusion of the LAA at the time of coronary artery bypass graft surgery has been published,⁴⁸ with 77 randomized patients. Fifty-two patients underwent attempted occlusion of the LAA, whereas 25 served as controls. During surgery, 9 patients developed LAA appendage laceration. Obliteration was achieved in 45% of patients closed with suture compared with success in 72% of patients where a surgical staple was

used. During a mean follow up of 13 ± 7 months, 2.6% of patients had embolic events; both occurring in the perioperative period. Continued technological improvements are being made to make these open surgical approaches easier, more reliable, and safer.

Catheter-Based LAA Obliteration

The transcatheter approach to LAA obliteration has recently become feasible.^{49–55} This approach uses a standard transseptal technique for percutaneous access to the left atrium. A specialized guiding catheter is advanced into the LAA. This may be performed using angiographic, intracardiac echocardiographic, or transesophageal echocardiography guidance. Angiography of the LAA is performed to optimize visualization of the ostium of the appendage and to document angulation, length, number of lobes of the appendage and, in particular, the size of the ostium. This latter measurement is important for selection of a specific device size. After this, the occluding device is advanced to cover the ostium of the appendage. This is typically performed using echocardiographic guidance. If the position is satisfactory and stable, the device is released. Great care must be taken to avoid damage to the appendage wall either during intubation or device positioning, as pericardial effusion may result.

The first technology developed for LAA obliteration was the Percutaneous Left Atrial Appendage Transcatheter Occlusion (PLAATO) device^{52–54} (Figure 3A). It was a self-expanding nitinol cage covered with an impermeable expanded polytetrafluoroethylene membrane. Anchors prevented device embolization, and it was made in a variety of sizes. Although this device is no longer available, valuable lessons emerged from clinical trials. Ostermayer reported on 2 prospective multicenter trials in which LAA closure was attempted in 111 patients with nonvalvular atrial fibrillation. All patients had at least 1 additional risk factor for stroke, and all patients had a clinical contraindication for anticoagulant therapy. The primary end point was a composite of stroke, cardiac or neurologic death, myocardial infarction, and/or requirement for procedural-related cardiovascular surgery within 30 days. The patients had a mean CHADS score of 2.5.⁵³ Of 111 patients, 38% had prior stroke or transient ischemic attack. LAA obliteration was successful in 108 patients. After device placement, 92.6% of patients received aspirin and 75.9% received clopidogrel. Of the 111 enrolled patients, 2 experienced stroke, 1 at 173 days and 1 at 215 days (1.8%, 95% CI 0.2% to 6.4%). Additionally, 3 transient ischemic attacks occurred in 2 patients. There were 6 deaths, of which 4 were cardiac or neurological. The annual stroke rate in these studies was 2.2%. When compared with a patient population with a similar CHADS₂ score, a stroke rate of 6.3% would be anticipated. Assuming a comparable patient population taking only aspirin, the PLAATO device was associated with a stroke reduction of 65%. However, this was a nonrandomized study, and follow-up was limited to a maximum of 17 months. Accordingly, firm conclusions on

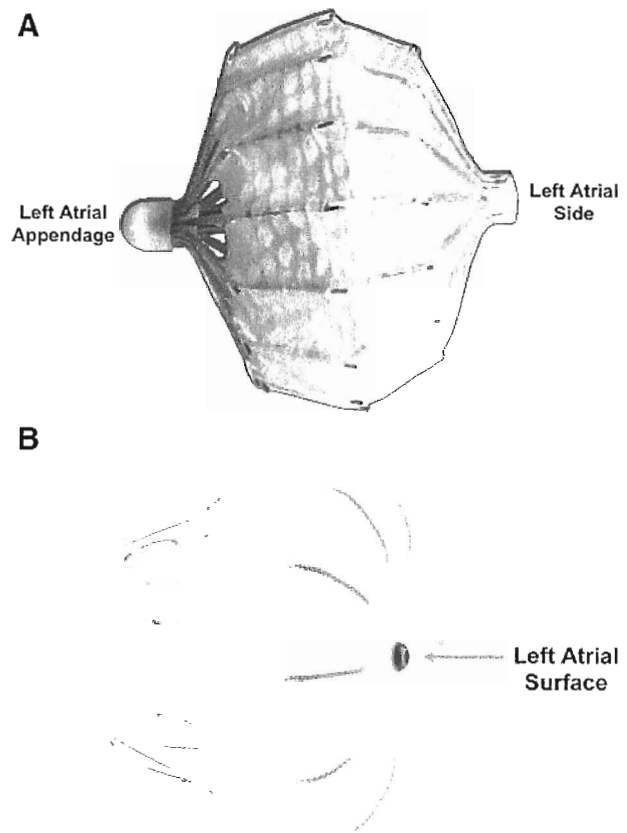


Figure 3. A, PLAATO left atrial appendage occlusion device is composed of a nitinol frame with expanded polytetrafluoroethylene membrane. Anchors on the frame provide stability for the device. B, Atritech WATCHMAN (Plymouth, Minn) device is a nitinol frame with barbs for anchoring. The membrane is initially permeable until it becomes endothelialized.

the statistical significance of an anticipated 6.3% to an observed 2.2% are difficult. Irrespective of this, initial results from this approach seem promising.

The only randomized clinical trial with a percutaneous device is the WATCHMAN Left Atrial Appendage System for Embolic Protection in Patients with Atrial Fibrillation (PROTECT AF) trial^{56,57} (Figure 3B), which randomized patients with nonvalvular atrial fibrillation in a 2:1 scheme to either the WATCHMAN device (Atritech Inc, Plymouth, Minn) or control (conventional) treatment with warfarin. Both groups had to be eligible for warfarin therapy. The WATCHMAN device is a self-expanding nitinol frame with fixation barbs. It has a permeable polyethylene membrane and comes in several sizes to accommodate variations in LAA anatomy. It seals the LAA ostium, resulting in a smooth endocardial lining (Figure 4). The primary trial end point was a composite efficacy end point of freedom from all stroke, cardiovascular death, and systemic embolization. Safety end points were major bleeding, pericardial effusion, and device embolization.



Figure 4. Gross pathology in a dog of an LAA successfully sealed using a percutaneous WATCHMAN device. Note the complete LAA ostial coverage with glistening endocardium. Animal models suggest such coverage is complete by 60 days after implantation.

Candidates for the trial are characterized in the Table.⁵⁶ Both clinical and echocardiographic inclusion and exclusion criteria were used. Patients randomized to device implantation received warfarin for 45 days until follow-up transesophageal echocardiography; if the device was well seated and the LAA was sealed without significant leak, then warfarin was discontinued and the patient then received acetylsalicylic acid and clopidogrel.

The initial experience with the WATCHMAN device has been reported on 66 patients treated successfully with a mean follow-up of 740 ± 341 days.⁵¹ In this group at 45 days, 93% of patients had successful sealing, and 91.7% were able to discontinue warfarin treatment. No patient had ischemic stroke during follow-up, and there were no instances of systemic embolization. Two patients developed a transient ischemic attack. This incidence is generally comparable to that of the PLAATO system, where patients receiving the device had a lower stroke rate compared with that predicted by CHADS₂ score.

The initial results of PROTECT AF were presented as an American College of Cardiology Late-Breaking Clinical Trial in 2009 and included information on 800 patients enrolled from February 2005 to June 2008.⁵⁷ There was a 2:1 allocation ratio of device to control. This trial included a 45-day transesophageal echocardiography to assess the device and LAA. At 45 days, 87% of the patients with the device were able to discontinue warfarin. As mentioned, the primary efficacy end point was a composite of freedom from all stroke, cardiovascular death, and systemic embolization. The primary safety end point was a composite of device embolization, pericardial effusion requiring intervention, intracranial hemorrhage, gastrointestinal bleeding, or any bleeding requiring ≥ 2 units of red blood cells. Using an intent-to-treat noninferiority analysis, at 900 patient-years of follow-up, the event-free probability was better with the

Table. Enrollment Criteria for PROTECT AF Trial

Inclusion criteria	
Age	≥ 18 years
	Paroxysmal, persistent, or permanent nonvalvular AF
	Eligible for long-term warfarin therapy
	Eligible to come off warfarin therapy if the LAA is sealed
	CHADS ₂ score of ≥ 1
Exclusion criteria	
Clinical exclusion criteria	
	New York Heart Association class IV congestive heart failure
	Myocardial infarction within 3 months
	ASD or atrial septal repair or closure device
	Single occurrence of AF
	Cardioversion or ablation procedure planned within 30 days
	Resting heart rate > 110
	Transient case of AF
	Implanted mechanical valve prosthesis
	Obliteration of LAA
	Heart transplantation
	Symptomatic carotid disease
	Prior embolic stroke or TIA within the last 30 days
	Long-term warfarin therapy required
	Contraindicated for warfarin therapy
	Thrombocytopenia or anemia
	Contraindicated for aspirin
	Enrolled in another IDE or IND investigation of a cardiovascular device or an investigational drug
	Pregnant or pregnancy is planned during the course of the investigation
	Active infection of any kind
	Terminal illness with life expectancy < 2 y
Echocardiographic exclusion criteria	
	LVEF $< 30\%$
	Intracardiac thrombus or dense spontaneous echo contrast as visualized by TEE within 2 days before implant
	Patent foramen ovale
	Significant mitral valve stenosis (ie, MV < 1.5 cm ²)
	Complex aortic atheroma with mobile plaque of the descending aorta and/or aortic arch
	Cardiac tumor
	Maximum LAA ostium width is > 32 or < 17 mm
	Maximum LAA length is less than maximum ostium width

ASD indicates atrial septal defect; AF, atrial fibrillation; CHADS₂ score, congestive heart failure, hypertension, age > 75 years, diabetes, and stroke or prior transient ischemic attack; IDE, investigational device exemption; IND, investigational new drug; LVEF, left ventricular ejection fraction; MV, mitral valve; TEE, transesophageal echocardiography; and TIA, transient ischemic attack.

Source: American Heart Association.

device and met noninferiority criteria. The composite of efficacy events occurred at a rate of 3.4% (95% CI 2.1% to 5.2%) within the device group compared with 5.0% (95% CI 2.8% to 7.6%) in the control group. Hemorrhagic stroke was

significantly less in the device group, and there were fewer deaths. On the safety side, there was an imbalance, with more safety events occurring in the device group. The majority of these were periprocedural, consisting of pericardial effusion requiring intervention, which occurred overall in 5% of patients. Although there was no mortality related to the effusion, these patients had prolonged hospital stays. There was a learning curve for this event, which documented a reduction in event rate over the course of the study.

Other technologies such as the Amplatzer device have also been used in off-label indications for LAA obliteration. However, the number of patients involved is very small.

A crucial consideration involves the risk-benefit ratio of either the device or long-term anticoagulation approaches. With LAA device therapy, periprocedural risk must be weighed against long-term warfarin or anticoagulant therapy, either bleeding or embolic stroke from lack of efficacy or poor therapeutic control. Potential procedural risks include air embolism from the placement of large sheaths, device embolization, pericardial effusions, and vascular access events. Air embolism has been well documented with atrial septal defect and patent foramen ovale devices but can be minimized by technical approaches, such as continuous flushing during catheter advancement. Device embolization has been rare given the presence of fixation barbs. Meticulous attention to implantation criteria such as the "tug" test (the operator exerts traction on the device to ascertain its solid fixation within the LAA) will further minimize device embolization. Perhaps the most common significant complication is pericardial effusion, which rarely causes tamponade. This may occur during transseptal catheterization or may be the result of damage to the thin LAA wall. This complication can be minimized by enhanced operator experience, device design improvements, and using guided imaging techniques. The most important finding from early study is that these complications are limited to the perioperative period. Risk falls dramatically to very low levels over time, though will likely never be zero.

Early data suggest that procedural and device risk is indeed concentrated early. However, there is limited long-term device follow-up to assess continued stability and integrity in comparison to the risk associated with anticoagulation, which continues to grow over the time a patient is anticoagulated. This continued incremental risk with anticoagulant therapy will likely be true for both conventional warfarin or for new agents under development.

Conclusions

Though available data are scarce, several tentative conclusions can be proposed for transcatheter LAA obliteration: (1) Atrial fibrillation is increasing in incidence and prevalence as the population ages. The relationships among age, atrial fibrillation, and stroke have been studied extensively. Atrial fibrillation, embolic stroke, and complications from warfarin anticoagulation all are progressively more frequent and dangerous with increasing age. (2) Cardiac emboli in patients


with nonvalvular atrial fibrillation originate in the LAA in >90% of cases. (3) Warfarin anticoagulation reduces embolic stroke in atrial fibrillation but is underused, is difficult to maintain in a therapeutic range, and is associated with increased bleeding, problems that become greater over time. (4) LAA obliteration by novel transcatheter methods are under evaluation and may find clinical use if they effectively reduce stroke and mortality without warfarin use in selected patients, such as those with nonvalvular atrial fibrillation. Invasive transcatheter therapeutic approaches will always carry with them at least some early procedural risk. Although this may be minimized with new improved technology and expanded operator experience and training, it will not be completely abolished. The risk-benefit ratio of these early periprocedural events must be balanced by the long-term risks of warfarin anticoagulation.


Disclosures

Both the Mayo Clinic and Dr Holmes have a financial interest in technology related to this research. That technology has been licensed to Atritech, and the Mayo Clinic and Dr Holmes have contractual rights to receive future royalties from this license. To date, no royalties have been received by either the Mayo Clinic or Dr Holmes. Dr Schwartz is a shareholder in Atritech.

References

- Rosamond W, Flegal K, Furie K, Go A, Greenland K, Haase N, Hailpern SM, Ho M, Howard V, Kissela B, Kittner S, Lloyd-Jones D, McDermott M, Meigs J, Moy C, Nichol G, O'Donnell C, Roger V, Sorlie P, Steinberger J, Thom T, Wilson M, Hong Y, for the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics 2008 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation*. 2008;117:e25–e146.
- Miyasaka Y, Barnes ME, Gersh GJ, Cha SS, Bailey KR, Abhayaratna WP, Seward JB, Tsang TSM. Secular trends in incidence of atrial fibrillation in Olmsted County, Minnesota, 1980–2000, and implications on the projections for future prevalence. *Circulation*. 2006;114:119–125.
- Benjamin EJ, Levy D, Vaziri SM, D'Agostino RB, Belanger AJ, Wolf PA. Independent risk factors for atrial fibrillation in a population-based cohort: the Framingham Heart Study. *JAMA*. 1994;271:840–844.
- Psaty BM, Manolio TA, Kuller LH, Kronmal RA, Cushman M, Fried LP, White R, Furberg CD, Rautaharju PM. Incidence of and risk factors for atrial fibrillation in older adults. *Circulation*. 1997;96:2455–2461.
- Stewart S, Hart CL, Hole DJ, McMurray JJ. Population prevalence, incidence, and predictors of atrial fibrillation in the Renfrew/Paisley study. *Heart*. 2001;86:516–521.
- Ruigomez A, Johansson S, Wallander MA, Rodriguez LA. Incidence of chronic atrial fibrillation in general practice and its treatment pattern. *J Clin Epidemiol*. 2002;55:358–363.
- Lloyd-Jones DM, Wang TJ, Leip EP, Larson MG, Levy D, Vasan RS, D'Agostino RB, Massaro JM, Beiser A, Wolf PA, Benjamin EJ. Lifetime risk for development of atrial fibrillation: the Framingham Heart Study. *Circulation*. 2004;110:1042–1046.
- Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. *Stroke*. 1991;22:983–988.
- Lin HJ, Wolf PA, Kelly-Hayes M, Beiser AS, Kase CS, Benjamin EJ, D'Agostino RB. Stroke severity in atrial fibrillation. The Framingham Study. *Stroke*. 1996;27:1760–1764.
- Garcia DA, Hylek E. Reducing the risk for stroke in patients who have atrial fibrillation. *Cardiol Clin*. 2008;26:267–275.

- 
11. Onalan O, Crystal E. Left atrial appendage exclusion for stroke prevention in patients with nonrheumatic atrial fibrillation. *Stroke*. 2007;38:624–630.
 12. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation: a major contributor to stroke in the elderly: The Framingham Study. *Arch Intern Med*. 1987;147:1561–1564.
 13. Henriksson KM, Farahmand B, Johansson S. Survival after stroke: the impact of CHADS₂ score and atrial fibrillation. *Int J Cardiol*. January 12, 2009. DOI: 10.1016/j.ijcard.2008.11.122. Available at: [http://www.internationaljournalofcardiology.com/article/S0167-5273\(08\)01278-3/fulltext](http://www.internationaljournalofcardiology.com/article/S0167-5273(08)01278-3/fulltext). Accessed August 15, 2009.
 14. 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;285:2864–2870.
 15. Watson T, Shantsila E, Lip GYH. Mechanisms of thrombogenesis in atrial fibrillation: Virchow's triad revisited. *Lancet*. 2009;373:155–166.
 16. Goldsmith I, Kumar P, Carter P, Blann AD, Path MR, Patel RI, Lip GYH. Atrial endocardial changes in mitral valve disease: a scanning electron microscopy study. *Am Heart J*. 2000;140:777–784.
 17. Pollick C, Taylor D. Assessment of left atrial appendage function by transesophageal echocardiography. Implications for the development of thrombus. *Circulation*. 1991;84:223–231.
 18. Blackshear JL, Odell JA. Appendage obliteration to reduce stroke in cardiac surgical patients with atrial fibrillation. *Ann Thorac Surg*. 1996;61:755–759.
 19. Go AS, Hylek EM, Borowsky LH, Phillips KA, Selby JV, Singer DE. Warfarin use among ambulatory patients with non valvular atrial fibrillation: the AnTicoagulation and Risk factors In Atrial fibrillation (ATRIA) study. *Ann Intern Med*. 1999;131:927–934.
 20. Optimal oral anticoagulant therapy in patients with nonrheumatic atrial fibrillation and recent cerebral ischemia: The European Atrial Fibrillation Trial Study Group. *N Engl J Med*. 1995;333:5–10.
 21. The effect of low-dose warfarin on the risk of stroke in patients with nonrheumatic atrial fibrillation: The Boston Area Anticoagulation Trial for Atrial Fibrillation Investigators. *N Engl J Med*. 1990;323:1505–1511.
 22. Stroke Prevention in Atrial Fibrillation study: final results: The Stroke Prevention in Atrial Fibrillation Investigators. *Circulation*. 1991;84:527–539.
 23. Connolly SJ, Laupacis A, Gent M, Roberts RS, Cairns JA, Joyner C. Canadian Atrial Fibrillation Anticoagulation (CAFA) Study. *J Am Coll Cardiol*. 1991;18:349–355.
 24. Ezekowitz MD, Bridgers SL, James KE, Carliner NH, Colling CL, Gornick CC, Krause-Steinrauf H, Kurtzke JF, Nazarian SM, Radford MJ. Warfarin in the prevention of stroke associated with nonrheumatic atrial fibrillation: Veterans Affairs Stroke Prevention in Nonrheumatic Atrial Fibrillation Investigators. *N Engl J Med*. 1992;327:1406–1412.
 25. 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.
 26. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. *Ann Intern Med*. 2007;146:857–867.
 27. Go AS, Hylek EM, Chang Y, Phillips KA, Henault LE, Capra AM, Jensvold NG, Selby JV, Singer DE. Anticoagulation therapy for stroke prevention in atrial fibrillation: how well do randomized trials translate into clinical practice? *JAMA*. 2003;290:2685–2692.
 28. Albers GW, SPORTIF Investigators. Stroke prevention in atrial fibrillation: pooled analysis of SPORTIF III and V trials. *Am J Manag Care*. 2004;10:S462–S469.
 29. ACTIVE Writing Group of the ACTIVE Investigators, Connolly S, Pogue J, Hart R, Pfeffer M, Hohnloser S, Chrolavicius S, Pfeffer M, Hohnloser S, Yusuf S. Clopidogrel plus aspirin versus oral anticoagulation for atrial fibrillation in the Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE W): a randomised controlled trial. *Lancet*. 2006;367:1903–1912.
 30. Gage BF, Boechler M, Doggett AL, Fortune G, Flaker GC, Rich MW, Radford MJ. Adverse outcomes and predictors of underuse of anti-thrombotic therapy in medicare beneficiaries with chronic atrial fibrillation. *Stroke*. 2000;31:822–827.
 31. Fang MC, Go AS, Hylek EM, Chang Y, Henault LE, Jensvold NG, Singer DE. Age and the risk of warfarin-associated hemorrhage: the anticoagulation and risk factors in atrial fibrillation study. *J Am Geriatr Soc*. 2006;54:1231–1236.
 32. Hylek EM, Evans-Molina C, Shea C, Henault LE, Regan S. Major hemorrhage and tolerability of warfarin in the first year of therapy among elderly patients with atrial fibrillation. *Circulation*. 2007;115:2689–2696.
 33. Waldo AL, Becker RC, Tapson VF, Colgan KJ, for the NABOR Steering Committee. Hospitalized patients with atrial fibrillation and a high risk of stroke are not being provided with adequate anticoagulation. *J Am Coll Cardiol*. 2005;46:1729–1736.
 34. Bungard TJ, Ghali WA, Teo KK, McAlister FA, Tsuyuki RT. Why do patients with atrial fibrillation not receive warfarin? *Arch Intern Med*. 2000;160:41–46.
 35. Gage BF, van Walraven C, Pearce P, Hart RG, Koudstaal PJ, Boode BS, Petersen P. Selecting patients with atrial fibrillation for anticoagulation: stroke risk stratification in patients taking aspirin. *Circulation*. 2004;110:2287–2292.
 36. Fang MC, Go AS, Chang Y, Hylek EM, Henault LE, Jensvold NG, Singer DE. Death and disability from warfarin-associated intracranial and extracranial hemorrhages. *Am J Med*. 2007;120:700–705.
 37. Flaberty M, Haverbusch M, Sekar P, Kissela BM, Kleindorfer D, Moomaw CJ, Broderick JP, Woo D. Location and outcome of anticoagulant-associated intracerebral hemorrhage. *Neurocrit Care*. 2006;5:197–201.
 38. Levine MN, Raskob G, Landefeld, Kearon C. Hemorrhagic complications of anticoagulant treatment. *Chest*. 2001;119:108S–121S.
 39. Palareti G, Leali N, Coccheri S, Poggi M, Manotti C, D'Angelo A, Pengo V, Erba N, Moia M, Ciavarella N, Devoto G, Berrettini M, Musolesi S. Bleeding complications of oral anticoagulant treatment: an inception-cohort, prospective collaborative study (ISCOAT). Italian Study on Complications of Oral Anticoagulant Therapy. *Lancet*. 1996;348:423–428.
 40. Connolly SJ, Pogue J, Eikelboom J, Flaker G, Commerford P, Franzosi MG, Healey JS, Yusuf S, ACTIVE W Investigators. Benefit of oral anticoagulant over antiplatelet therapy in atrial fibrillation depends on the quality of international normalized ratio control achieved by centers and countries as measured by time in therapeutic range. *Circulation*. 2008;118:2029–2037.
 41. Parker CS, Chen Z, Price M, Gross R, Metlay JP, Christie JD, Brensinger CM, Newcomb CW, Samaha FF, Kimmel SE. Adherence to warfarin assessed by electronic pill caps, clinician assessment, and patient reports: results from the IN-RANGE study. *J Gen Intern Med*. 2007;22:1254–1259.
 42. Levine MN, Raskob G, Beyth RJ, Kearon C, Schulman S. Hemorrhagic complications of anticoagulant treatment: The Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest*. 2004;126:287S–310S.
 43. Albers GW, Diener HC, Frison L, Grind M, Nevinson M, Partridge S, Halperin JL, Horrow J, Olsson SB, Petersen P, Vahanian A, SPORTIF Executive Steering Committee for the SPROTIF V Investigators. Ximelagatran vs warfarin for stroke prevention in patients with nonvalvular atrial fibrillation: a randomized trial. *JAMA*. 2005;293:690–698.
 44. Olsson SB, Executive Steering Committee of the SPORTIF III Investigators. Stroke prevention with the oral direct thrombin inhibitor ximelagatran compared with warfarin in patients with non-valvular atrial fibrillation (SPORTIF III): randomized controlled trial. *Lancet*. 2003;362:1691–1698.
 45. Blackshear JL, Odell JA. Appendage obliteration to reduce stroke in cardiac surgical patients with atrial fibrillation. *Ann Thorac Surg*. 1996;61:755–759.
 46. Su P, McCarthy KP, Ho SY. Occluding the left atrial appendage: anatomical considerations. *Heart*. 2008;94:1166–1170.
 47. Kerut EK. Anatomy of the left atrial appendage. *Echocardiography*. 2008;25:669–673.
 48. Healey JS, Crystal E, Lamy A, Teoh K, Semelhalgo L, Hohnloser SH, Cybulsky I, Abouzahr L, Sawchuck C, Carroll S, Morillo C, Klein P, Chu V, Lonn E, Connolly SJ. Left atrial appendage occlusion study (LAAOS):

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- results of a randomized controlled pilot study of left atrial appendage occlusion during coronary bypass surgery in patients at risk for stroke. *Am Heart J*. 2005;150:288–293.
49. Bayard YL, Ostermayer SH, Hein R, Skowasch M, Buscheck F, Baranowski A, Heinisch C, Sievert H. Percutaneous devices for stroke prevention. *Cardiovasc Revasc Med*. 2007;8:216–225.
 50. Meier B. Left atrial appendage closure: Amplatzer devices. Abstract book of the 7th International Workshop, Catheter Interventions in Congenital Heart Disease and Other Non-coronary Interventions, Frankfurt am Main, Germany, June 17–19, 2004.
 51. Sick PB, Schuler G, Hauptmann KE, Grube E, Yakubov S, Turi ZG, Mishkel G, Almany S, Holmes DR. Initial worldwide experience with the WATCHMAN left atrial appendage system for stroke prevention in atrial fibrillation. *J Am Coll Cardiol*. 2007;49:1490–1495.
 52. El-Chami MF, Grow P, Eilen D, Lerakis S, Block PC. Clinical outcomes three years after PLAATO implantation. *Catheter Cardiovasc Interv*. 2007;69:704–707.
 53. Ostermayer SH, Reisman M, Kramer PH, Matthews RV, Gray WA, Block PC, Omran H, Bartorelli AL, Della Bella P, DiMario C, Pappone C, Casale PN, Moses JW, Poppas A, Williams DO, Meier B, Skanes A, Teirstein PS, Lesh MD, Nakai T, Bayard Y, Billinger K, Trepels T, Krumdordf U, Sievert H. Percutaneous left atrial appendage transcatheter occlusion (PLAATO System) to prevent stroke in high-risk patients with non-rheumatic atrial fibrillation: results from the international multicenter feasibility trials. *J Am Coll Cardiol*. 2005;46:9–14.
 54. Sievert H, Lesh MD, Trepels T, Omran H, Bartorelli A, Della Bella P, Nakai T, Reisman M, DiMario C, Block P, Kramer P, Fleschenberg D, Krumdordf U, Scherer D. Percutaneous left atrial appendage occlusion to prevent stroke in high-risk patients with atrial fibrillation: early clinical experience. *Circulation*. 2002;105:1887–1889.
 55. Bayard Y, Omran H, Kramer P, Matthew R, Reisman M, Block P, Ostermayer S, Leetz M, Fischer E, Sievert H, for the PLAATO Investigators. Worldwide experience of percutaneous left atrial appendage transcatheter occlusion (PLAATO). *J Neurol Sci*. 2005;238:S70.
 56. Fountain RB, Holmes DR, Chandrasekaran K, Packer D, Asirvatham S, Van Tassel R, Turi Z. The PROTECT AF (WATCHMAN Left Atrial Appendage System for Embolic PROTECTion in patients with atrial fibrillation) trial. *Am Heart J*. 2006;151:956–961.
 57. Holmes DR Jr, Reddy VY, Turi Z, Doshi SK, Sievert H, Buchbinder M, Mullin CM, Sick P for the PROTECT AF Investigators. Percutaneous closure of the left atrial appendage versus warfarin therapy for prevention of stroke in patients with atrial fibrillation: a randomized non-inferiority trial. Late Breaking Clinical Trial presented at American College of Cardiology i2 Summit; March 28, 2009; Orlando, Fla.

Response to Holmes and Schwartz

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After summarizing the evidence, Holmes and Schwartz arrive at 4 conclusions. We agree that in the context of an aging population, stroke related to atrial fibrillation (AF) is becoming increasingly important. However, the second conclusion that cardiac emboli originate from the left atrial appendage (LAA) in >90% of cases is overstated. Echocardiographic and anatomic studies demonstrate that when thrombus is observed in the left atrium, it is located in the LAA in >90% of cases. This does not mean that the LAA is the source of emboli in 90% of AF cardiac embolic strokes. Among patients with nonvalvular AF and completed ischemic stroke, sources of embolism other than the LAA have been identified in up to 50% of patients. It is at least possible that many strokes in AF are not related to the LAA, which would make it less likely that LAA occlusion will be viable as a sole intervention for stroke prevention. Further research is needed. We also agree that warfarin is an effective therapy for stroke reduction in AF, but it is underused because of bleeding risk. This highlights the importance of pursuing alternatives to warfarin such as dabigatran, rivaroxaban, and apixaban. Finally, along with Holmes and Schwartz, we are encouraged by their recent trial results indicating that LAA obliteration can provide satisfactory patient outcomes. We also agree with their final conclusion that the results with LAA occlusion are still “tentative.” Therefore, antithrombotic medications, warfarin in particular, remain the standard for stroke prophylaxis in AF patients at elevated risk.