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. 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. Data from the Framingham study suggest a high incidence of atrial fibrillation. 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. The overall rate of ischemic stroke among patients with nonrheumatic atrial fibrillation averages 5% per year, and this rate increases with age. 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. Moreover, cardioembolic strokes are associated with the worst long-term prognosis. Henricksson et al 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. Henricksson also evaluated the utility of the CHADS2 score, 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, 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,
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. Oral anticoagulation is superior to placebo and aspirin, though hemorrhage is clearly increased in the anticoagulated patient. Hart et al 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. 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. Hylek 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. Fang 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, Flaherty 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] \( \leq 2 \)), 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. 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. Fewer than 60% of those treated have therapeutic INR values. 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, Connolly summarized recently by Watson. 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. Goldsmith 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 Taylor 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 Odel 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

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. Extra cardiac factors such as mobile aortic atherosclerosis or carotid arterial disease may also cause stroke in atrial fibrillation.
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 anticoagulant 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 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) device52–54 (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 CHADS$_2$ 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 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) trial56,57 (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 barbs for anchoring. The membrane is initially permeable until it becomes endothelialized.
Candidates for the trial are characterized in the Table.\textsuperscript{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\textsuperscript{341} days.\textsuperscript{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 CHADS\textsubscript{2} 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.\textsuperscript{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 \( \geq 2 \) 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 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

### Table. Enrollment Criteria for PROTECT AF Trial

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ( \geq 18 ) years</td>
</tr>
<tr>
<td>Paroxysmal, persistent, or permanent nonvalvular AF</td>
</tr>
<tr>
<td>Eligible for long-term warfarin therapy</td>
</tr>
<tr>
<td>Eligible to come off warfarin therapy if the LAA is sealed</td>
</tr>
<tr>
<td>CHADS\textsubscript{2} score of ( \geq 1 )</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical exclusion criteria</td>
</tr>
<tr>
<td>New York Heart Association class IV congestive heart failure</td>
</tr>
<tr>
<td>Myocardial infarction within 3 months</td>
</tr>
<tr>
<td>ASD or atrial septal repair or closure device</td>
</tr>
<tr>
<td>Single occurrence of AF</td>
</tr>
<tr>
<td>Cardioversion or ablation procedure planned within 30 days</td>
</tr>
<tr>
<td>Resting heart rate ( &gt; 110 )</td>
</tr>
<tr>
<td>Transient case of AF</td>
</tr>
<tr>
<td>Implanted mechanical valve prosthesis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Echocardiographic exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEF ( \leq 30% )</td>
</tr>
<tr>
<td>Intracardiac thrombus or dense spontaneous echo contrast as visualized by TEE within 2 days before implant</td>
</tr>
<tr>
<td>Patent foramen ovale</td>
</tr>
<tr>
<td>Significant mitral valve stenosis (ie, MV ( &lt; 1.5 ) cm(^2))</td>
</tr>
<tr>
<td>Complex aortic atheroma with mobile plaque of the descending aorta and/or aortic arch</td>
</tr>
<tr>
<td>Cardiac tumor</td>
</tr>
<tr>
<td>Maximum LAA ostium width is ( &gt; 32 ) or ( &lt; 17 ) mm</td>
</tr>
<tr>
<td>Maximum LAA length is less than maximum ostium width</td>
</tr>
</tbody>
</table>

Source: American Heart Association.

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.
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 peri-procedural, 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, peri-procedural 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 bars. 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 trans-septal 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


---

Response to Holmes and Schwartz

Richard P. Whitlock, MD, MSc; Jeff S. Healey, MD; Stuart J. Connolly, MD

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.
Left Atrial Appendage Occlusion Eliminates the Need for Warfarin
David R. Holmes, Jr and Robert S. Schwartz

Circulation. 2009;120:1919-1926
doi: 10.1161/CIRCULATIONAHA.108.844761
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2009 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://circ.ahajournals.org/content/120/19/1919

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/