

## EDITORIAL COMMENT

# Left Atrial Appendage Closure for Stroke Prevention in AF

## The Quest for the Holy Grail\*

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Strokes resulting from embolization of left atrial appendage (LAA) thrombi in patients with atrial fibrillation (AF) account for up to 25% of the 700,000 cerebrovascular accidents occurring annually in the United States. LAA, a complex structure with considerable anatomic variability, has been appropriately described as the “most lethal human attachment” (1). Stasis, hypercoagulability, and endothelial dysfunction (Virchow triad) contribute to LAA thrombus formation in AF patients. This pathophysiological process results in a 5-fold increased risk for cerebral embolization (2). Stroke is currently the major cause of disability and the third leading cause of death in the United States (2). The age-adjusted prevalence of AF is projected to increase 3-fold by 2050. Accordingly, strokes related to AF are expected to markedly increase unless effective prevention strategies are identified.

Currently, optimal clinical approaches for stroke prevention in AF patients remain under investigation. The dominant therapeutic approach is systemic anticoagulation (3). Evidence-based medicine from large, prospective, randomized controlled trials of oral anticoagulants, including warfarin, factor Xa inhibitors, and direct thrombin inhibitors, support oral anticoagulants as the standard of care to reduce the risk of stroke (3). However, multiple limitations to anticoagulant therapy with warfarin and the novel oral anticoagulants (NOAC) remain (3).

Underutilization, compliance, bleeding, and expense all contribute to a substantial gap between those patients needing and those receiving anticoagulant therapy. This treatment gap grows in those most vulnerable to embolic stroke: the elderly. Many patients with AF who might benefit from anticoagulation have unfavorable risk profiles with relative or absolute contraindications to anticoagulation. Others are unable or unwilling to adhere to long-term anticoagulation therapy. Thus, there remains a clinical need to develop alternatives to anticoagulant therapy to reduce the risk of embolization from the LAA.

Alternative approaches include LAA excision, ligation, or closure (1,3,4). These rely on the fundamental premise that procedures to exclude the LAA should prevent strokes while eliminating the disadvantages of systemic anticoagulation. Since the original report of surgical LAA excision over 6 decades ago, a variety of surgical techniques have evolved. Unfortunately, the evidence supporting these is severely limited by the absence of appropriately controlled prospective randomized trials, variable surgical techniques, and lack of standardized outcomes measurements (4). Current American College of Cardiology/American Heart Association guidelines limit surgical LAA excision to a Class IIB recommendation (Level of Evidence: C) as an adjunctive procedure in patients undergoing cardiac surgery (3).

Recently, meaningful progress has been made in developing minimally invasive percutaneous transcatheter techniques to exclude the LAA and thereby prevent strokes in AF (5,6). Avoidance of the morbidity of surgery for LAA excision has driven development of multiple, less-invasive approaches. To date, the U.S. Food and Drug Administration has

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approved 1, the Watchman device (Boston Scientific, Marlborough, Massachusetts), for clinical use (5). This device has been evaluated in multiple trials compared with anticoagulant therapy (5,6). After a regulatory odyssey, Watchman was recently approved for use in the United States by the Food and Drug Administration as an alternative to warfarin for stroke prevention (5). The approval specified indications for use in patients with nonvalvular AF who are: 1) at increased risk of stroke and systemic embolism on the basis of CHADS<sub>2</sub> (Congestive Heart Failure History, Hypertension History, Age  $\geq$ 75 Years, Diabetes Mellitus History, Stroke or Transient Ischemic Attack Symptoms Previously) or CHA<sub>2</sub>DS<sub>2</sub>-VASc (Congestive Heart Failure, Hypertension, Age  $\geq$ 75 Years, Diabetes Mellitus, Prior Stroke or Transient Ischemic Attack or Thromboembolism, Vascular Disease, Age 65 to 75 Years, Sex Category) scores; 2) deemed by their physicians to be suitable for warfarin therapy; and 3) have an appropriate rationale to seek a non-pharmacological alternative to warfarin, taking into account the safety and efficacy of the device compared with warfarin (5). With availability of this device for clinical use, percutaneous LAA closure now provides a clinically available alternative to oral anticoagulation or surgery for stroke prevention in selected patients with AF.

The evidence of clinical effectiveness and safety of this LAA closure device has been established in a series of well-performed clinical trials and registries that were recently analyzed in a patient-level meta-analysis (6). Although the evidence for approval for clinical use is robust, multiple issues remain unresolved. Safety and efficacy alone are insufficient to cause a paradigm shift toward LAA closure for stroke prevention in AF patients (6,7). In the current health care environment, economic analyses assessing comparative costs over time are also needed. In this issue of the *Journal*, Reddy et al. (7) address this increasingly important issue with a cost-effectiveness analysis of warfarin, NOAC, and LAA closure with the Watchman device in patients with nonvalvular AF. These investigators conclude that compared with warfarin, LAA closure is cost-effective at 7 years, whereas NOAC are cost effective at 16 years. LAA closure becomes the dominant strategy over NOAC by year 5 and warfarin by year 10 (7). On the basis of their assumptions and model, they conclude that the Watchman device is cost-effective compared with warfarin and offered better value relative to NOAC (7).

Because cost-effectiveness modeling enables cost, clinical effectiveness, and patient outcomes to be taken into account, this novel analysis represents an important analytic approach for evaluating stroke

prevention strategies in AF (7). However, clinicians should be mindful of the limitations of this cost-effectiveness model. Out of necessity, the analysis was performed using indirect comparison methodology, with warfarin as the common control. The best available data from controlled clinical trials support the notion that the NOAC have a favorable risk/benefit ratio compared with warfarin. Watchman has not yet been compared directly to NOAC in prospective randomized trials. Whether LAA closure provides a clear benefit when compared with factor Xa inhibitors or direct thrombin inhibitors should be determined by head-to-head comparisons in future trials.

The clinical inputs for this cost-effectiveness analysis were on the basis of clinical trial data with experienced centers implanting LAA closure devices (7). As acknowledged by the investigators, treatments in clinical practice rarely achieve the outcomes observed in clinical trials (7). Clinical trials enroll selected patients, have lower procedural complication rates, achieve higher levels of medication adherence, and monitor patients more intensively. The high compliance achieved in the Watchman, NOAC, and warfarin trials have not been and are unlikely to be achieved in clinical practice. All of the data used in the analysis had variable time horizons and were extrapolated to 20 years (7). The conclusions are also highly dependent on assumptions regarding increases in costs of treatment and monitoring over time. It is evident that only prospective trials of LAA closure devices will give data for an evidence-based analysis of cost-effectiveness over a patient's lifetime.

The approval of Watchman as the initial minimally invasive percutaneous transcatheter technique to exclude the LAA as an alternative for stroke prevention in AF brings to the forefront additional issues beyond safety, efficacy, and cost-effectiveness (6-8). Among them are selection and training of implanting centers and mechanisms for rigorous assessment of outcomes (8). The identification of patient cohorts with the most favorable risk/benefit and cost-effectiveness analysis, as well as those with the most unfavorable characteristics, remains an important objective of clinical registries (8). Mechanisms are needed for extension of this technology to the treatment of other groups of patients not studied in the randomized and observational clinical studies (8). As future technologies become available as alternatives to anticoagulation for stroke prevention in AF, centers with proper resources and training should oversee deployment into clinical practice. Furthermore, registries to rigorously evaluate short- and

long-term safety, comparative effectiveness, and cost-effectiveness are needed (8). Despite these unanswered questions, the evidence from the Watchman clinical trials and this analysis represent meaningful progress in the quest for LAA closure as a clinical strategy for stroke prevention in AF patients.

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