JACC: CARDIOVASCULAR INTERVENTIONS
VOL. 8, NO. 15, 2015

ISSN 1936-8798/$36.00
PUBLISHED BY ELSEVIER INC.
http://dx.doi.org/10.1016/j.jcin.2015.08.034

EDITORIAL COMMENT

Closing the Oval Door*

David R. Holmes, Jr, MD, Douglas L. Packer, MD

As is widely appreciated by all medical and surgical specialties, atrial fibrillation is the most common significant cardiac arrhythmia seen in practice; approximately 5 to 7 million patients in the United States have atrial fibrillation, with the numbers expected to increase to approximately 16 million by 2050 (1), and there are 200,000 to 250,000 new cases each year. Although symptoms vary widely, the most concerning one relates to thromboembolism with stroke and/or transient ischemic attack.

For many patients, as well as for individuals without known medical problems, stroke is the most feared medical catastrophe. From a societal standpoint, strokes are also extremely concerning. Direct annual stroke-related medical costs are predicted to increase dramatically from $72 billion to $183 billion between 2012 and 2030 (2). In addition, many survivors of stroke remain significantly limited. In the setting of atrial fibrillation, the risk of stroke has been well studied and is increased by approximately 5-fold. The relationship between increasing age, increasing incidence of atrial fibrillation, and increasing incidence of stroke has also been well studied (3-5). A variety of stroke risk scores have been developed to identify those at highest risk of stroke. The most common currently used is the CHADS2-VASc score (6). Such scores are used increasingly for patient education and decision making, and form an important part of professional guidelines. Such scores are particularly useful in identifying patients at very low risk of stroke as well as those at the other end of the spectrum.

In the past, anticoagulation with vitamin K antagonists (VKA) or novel factor Xa or direct thrombin inhibitors have been found to be effective for stroke prevention, reducing its incidence by approximately two-thirds, and have become the new standard of care (7). However, although very effective, a substantial number of patients at risk for stroke are not treated because of increased risk of bleeding, previous bleeding episodes, patient frailty, inability to consistently follow medication recommendations, drug-drug interactions, patient discontinuation of drugs during follow-up, and managing physician uncertainties as to the required treatment for their patients (8). In the highest-risk patients, including elderly patients, a substantial number, and in some practices even a majority of the elderly patients, are not treated.

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This, plus the information that, in the setting of nonvalvular atrial fibrillation, thromboembolic events typically arise from the left atrial appendage, has led to the development of local, directed site-specific therapy for stroke prevention with a variety of surgical and catheter-based techniques. Such local site-specific therapy could prevent left atrial appendage thromboembolic events without the need for long-term anticoagulant agents. Closing the oval door (or the left atrial appendage orifice, which is actually oval in most patients) is the approach studied in the paper by Dr. Wiebe et al. (9) in this issue of *JACC: Cardiovascular Interventions*. It is focused on

*Editorials published in *JACC: Cardiovascular Interventions* reflect the views of the authors and do not necessarily represent the views of *JACC: Cardiovascular Interventions* or the American College of Cardiology.

From the Cardiovascular Diseases, Department of Medicine, Mayo Clinic, Rochester, Minnesota. Dr. Holmes, along with Mayo Clinic, receive royalties from Boston Scientific for technology related to this research. Dr. Packer has received research funding from the American Heart Association Foundation, Biosense Webster, Boston Scientific/EPT, CardioInsight Technologies, CardioFocus, Endosense, EpiEP, EP Rewards, Hansen Medical, Medtronic, CryoCath LP, NIH, St. Jude Medical, Siemens, and Thermedical; has been a consultant, without compensation, for Abbott Laboratories, Abiomed, Biosense Webster, Boston Scientific, CardioFocus, CardioInsight Technologies, Johnson & Johnson Healthcare Systems, Johnson & Johnson, MediaSphere Medical, Medtronic CryoCath, Siemens, and St. Jude Medical; has received royalties from Blackwell Publishing, and Oxford Royalty; and along with Mayo Clinic, receives annual royalties >$10,000 from St. Jude Medical for mapping technology.

the only U.S. Food and Drug Administration-approved device for stroke prevention in the setting of nonvalvular atrial fibrillation, namely the Watchman device, and adds significant information to the published data. This device has been well described and has been the focus of 2 completed randomized clinical trials, 2 post-market approval registries and multiple meta-analyses (10–12). This current specific paper includes a single-center experience with a relatively large number of patients (N = 102) who were at high stroke risk but also had high bleeding risk with a mean CHA2DS2-VASc score of 4.3 ± 1.7 and HAS-BLED score of 2.9 ± 1.2, respectively.

In this group, treated at a very experienced center, procedural success was excellent (96.1%). Procedure-related complications occurred in 8.8% of the entire group, typically the result of a pericardial effusion. There was some trend toward a learning curve, with 11.8% complications in the first half of the experience, decreasing to 5.8% in the second half, although this was not statistically significant.

Post-procedural medications varied. That is of great importance in terms of assessing the results. Conventionally, with the Watchman device, VKA is administered following implantation for 45 days; however, in this series, 24.5% of patients were not eligible for anticoagulant agents. Accordingly, dual antiplatelet therapy (DAPT) was administered for 6 months in 41.8%, whereas the remaining patients (58.2%) received VKA for 45 days followed by DAPT until 6-month follow-up.

Follow-up was available in 96 patients for a mean of 3.1 ± 1.6 years; the longest follow-up was out to 5 years. Assessment of the follow-up is of major importance with this technology. Both echocardiographic and clinical follow-up data were available. A single patient had residual flow around the device because of an uncovered lobe at the time of implantation; during follow-up, no other patient had a significant peri-device leak (≥5 mm). Major clinical events were infrequent: 2 patients had an ischemic stroke occurring >12 months post-implantation, whereas 2 additional patients had a transient ischemic attack. Accordingly, the rate of transient ischemic attack/stroke was 1.4% per year. Although no control group was included, on the basis of the CHADS2-VASc score, the annual stroke risk would have been substantially greater. Using this score for CHADS2-VASc patients with a score of 4, the predicted annual stroke risk is 4%, whereas for those with a CHADS2-VASc score of 5, the predicted annual risk of stroke is 6.7%. Intracerebral hemorrhage occurred in 3 patients: 1 patient on VKA and aspirin, 1 on aspirin and clopidogrel, and 1 on aspirin alone. Accordingly, the combined rate of ischemia and intracerebral hemorrhage was 2.5 per year. Severe bleeding requiring hospitalization occurred in 6 patients with an annual rate of 2.1%. Seven additional patients died during follow-up; in 5 of these, mortality was not related to stroke, atrial fibrillation, or bleeding, whereas in 2 patients, the cause was uncertain.

The investigators concluded that left atrial appendage "closure with the Watchman device is safe and feasible for stroke protection in patients with atrial fibrillation. Low ischemic event rates demonstrated its effectiveness during long-term follow-up." (9). In addition to these conclusions, there are other important pieces of information. A particularly important one relates to the fact that despite the current recommendation that all Watchman patients be treated with VKA for 45 days, in this study only 58.2% received this treatment for 45 days, whereas in 41.8%, DAPT was administered instead for 6 months. Despite that, although the numbers are very low, event rates were not felt to be different between both groups in regard to ischemic events, cerebral bleeding, or thrombus on the left atrial appendage occlusion device. However, again, the numbers of patients with this are small. This, however, would be consistent with the ASAP (ASA Plavix Feasibility Study With Watchman Left Atrial Appendage Closure Technology) trial of 150 patients who had a contraindication to anticoagulation (13).

This left atrial appendage occlusion technology is transformational; closing the oval door offers the potential for treatment of patients who have very limited options for stroke prevention by virtue of associated conditions or patient or physician preference that limit the use of anticoagulant agents. As such, it meets a substantial clinical need. There are issues that continue to be evaluated in closing the oval door. 1) What is the best device to close the door, which is actually oval in most patients? This does have important implications because the current devices are circular, and when placed in an oval orifice may lead to persistent leaks; 2) What is the relative role of this device in preventing ischemic versus hemorrhagic stroke? It is obvious that local site-specific therapy will not prevent stroke related to noncardiac sources. However, in the published meta-analysis (10), there is a dramatic reduction in hemorrhagic stroke, which is the most severe type of stroke and is associated with the worst outcome; and 3) The observation that there is a substantial survival advantage in patients treated with the device needs to be confirmed in larger studies. Such a dramatic improvement in survival has major implications in terms of patient and physician decision making.

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DECEMBER 28, 2015:1922–4

The story continues to develop. Closing the oval door remains transformational with technology documented to be, as the investigators conclude, safe and feasible for stroke protection in patients with atrial fibrillation with low ischemic event rates during long-term follow-up.

REPRINT REQUESTS AND CORRESPONDENCE: Dr. David Holmes, Jr., Cardiovascular Diseases and Internal Medicine, Mayo Clinic, 200 First Street, SW, MB 4-523, Rochester, Minnesota 55905. E-mail: holmes.david@mayo.edu.

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KEY WORDS left atrial appendage occlusion, nonvalvular atrial fibrillation, stroke prevention