Devices to Prevent Stroke in Patients with Atrial Fibrillation: Fuzzy Logic or Thoughtful Innovation

In this issue of Innovations in Cardiac Rhythm Management Joel A. Lardizabal and Sanjiv Sharma\(^1\) present a succinct review of interventional approaches solely aiming to exclude the LAA from the cardiac circulation. They highlight the important challenges that remain before we can claim success in eliminating the most disabling sequelae of atrial fibrillation (AF)—cardioembolic stroke. The plurality of approaches that have been attempted to reach this goal and the fact that there is no existing device with an indication for use to prevent AF-related stroke available to our patients despite these efforts, legitimately leads us to wonder whether the premise on which this area of cardiac innovation is sound. Medical practitioners who chose to embark on the innovation track to improve patient care are frequently confronted by this question: Is our out-of-the-box thinking simply unclear logic or necessary fuzziness that eventually allows a major step forward?

Innovative thought: picking the right target

Not so long ago, for a patient with AF and stroke risk, a straightforward decision-making process existed for the clinician since the only available option was warfarin anticoagulation. Three separate streams of rapidly evolving discovery have now led to multiple potential avenues of pursuit to direct the innovative process. Data now clearly support the alarming increase in risk for stroke when AF is recorded even in asymptomatic patients.\(^2\) Therefore, an appropriate target to decrease stroke would be to eliminate AF. Given the remarkable advent of pulmonary vein isolation in decreasing symptomatic AF,\(^3,4\) we could think the stroke problem is solved or, with further innovative thought, will be. However, initial optimism has given way to the realistic acceptance that ablation is probably a palliative treatment option, particularly in patients with persistent forms of AF. In addition, the comorbidities present in many patients with AF may independently enhance stroke risk.

The last few years have also given us for the first time in decades new effective antithrombotic drug therapy.\(^5,6\) We could therefore reasonably focus innovation to even better and safer antithrombotic regimens. However, the underlying paradox presented as a result of the fact that patients who need anticoagulation the most are the same patients who are at the most bleeding risk makes it difficult to imagine a pharmacological innovation that will solve this dilemma and the problem with stroke in AF as well.

The third area of rapid innovative growth is the subject of Lardizabal and Sharma’s review\(^1\)—devices for AF. Perhaps the least explored at present and with appreciation that the above two approaches may never produce a complete solution for the most devastating complication of the most prevalent human arrhythmia drives innovation in picking this target.

Innovative thought: avoiding complications

Although every advance in clinical medicine attempts to decrease complications while improving efficacy, stroke prevention in AF perhaps highlights this principle more than others. As Lardizabal and Sharma note,\(^1\) procedural complications with existing appendage closure devices are significant, ranging from 1% to nearly 8%. They also point out a striking observation that in one of the device trials, 27% of the patients available for follow-up had died with just 5 years’ follow-up,\(^7\) and, in addition, 12.5% had strokes despite the device. Although the authors clarify that these deaths or strokes were not the result of the device itself, we do learn from this that the patient population being targeted for stroke prevention have simultaneously poor long-term survival and high non-appendage-related stroke
In this light, it becomes paramount to avoid complications since these are “front loaded,” and if high cannot be offset advantageously by cumulative incremental stroke reduction over many years.

Innovative thought: individualized patient care

A major impetus in health-care policy is individualized patient care. However, this concept with regard to cardiac devices has not gathered commensurate attention. While titrating doses of drugs, adjusting filters on monitoring equipment, or finding a gene profile-directed therapeutic approach works well in some therapeutic arenas, how do we individualize device approaches?

The appendage occlusion options reviewed by Lardizabal and Sharma focus on endocardial approaches that involve transseptal puncture and circulatory occlusion of the LAA. Recent studies and presently non-investigational patient procedures are performed with an approach that involves both transseptal puncture and subxiphoid epicardial access. Other epicardial approaches have involved minimally invasive thoracoscopic surgery or stand-alone subxiphoid epicardial appendage ligation. Further, regardless of the approach to reach the appendage, whether circulatory occlusion or ligation with eventual appendage necrosis is the goal or byproduct of the innovation also lends uniqueness. As mentioned in their review, the appendage anatomy itself is variable and the structure’s location relative to other cardiac structures also may vary. Thus, an opportunity exists for innovation not only to remove the appendage as a source of stroke but to tailor the exact approach and device based on the patient. Factors that can be considered in computing the ideal approach for a specific patient would include risks of endocardial catheter manipulation, appropriateness of temporary anticoagulation, prior cardiac surgery, and the exact appendage morphology. The nature of innovation itself, however, makes it difficult for device approaches to be patient specific. Limited capital resources, time, and the intellectual property protection process make collaborative innovation difficult, and by itself an innovative approach! Such advances in how we think about new devices may, however, be necessary in order to get the best fit for our patients and avoid complications that may arise during the development of new device-based technology.

Innovative thought: getting the product to our patients

Perhaps understandably the regulatory process involved in allowing new products to get to our patients is complex, circuitous, and laced with multiple layers of difficulty. Traditional approaches that involve design and prototyping of the device, acute and chronic animal studies, the first in-human use after obtaining an investigational device exemption, followed by a larger trial, and then a Food and drug Administration-approved device with a specific clinical indication have now become the exception rather than the rule with device innovation. To obtain an IDE in order to conduct a human trial, it may be necessary to have human data! This has led to initial trials being conducted outside the United States, a phenomenon by itself representing a logistical and ethical quagmire. Recently, one of the devices has become rapidly and increasingly used for clinical appendage closure using the 5 to 10 K approval process. Here, a specific clinical indication, such as for AF-related stroke reduction, is absent with the approval of the device specifically for a technical component of a procedure, such as occlusion of a hollow viscus, etc. The decision-making process behind a company as to whether such an approval process or the more traditional approach is better is complex and beyond the scope of this commentary. However, innovative thinking as to how we can more rapidly yet safely get products to our patients after performing scientifically rigorous and ethically tenable experiments is needed.

Innovative thought: why should it matter?

A more basic underlying question in the device-related appendage closure field is why should appendage closure matter at all? Lardizabal and Sharma clearly outline for us that a significant number of strokes that occur in AF patients do so even when the appendage is occluded. Although the majority of thrombi in the atrium when found with transesophageal echocardiography are in the left atrial appendage, it is only a minority of patients with AF who present with stroke that any thrombus is found at all. Further, the same clinical arrhythmia, AF, has a completely different stroke risk based on non-arrhythmia patient characteristics, such as diabetes mellitus, hypertension, structural heart disease, prior stroke, etc. Given this background, is it logical to anticipate stroke reduction with appendage occlusion? The innovative thought underlying the continued widespread interest in device-based appendage closure has to do with appreciating that anticoagulation works! In other words, warfarin does not treat diabetes, hypertension, age, and more importantly also does not prevent atheroembolic stroke. Thus, the critical
The hypothesis being tested as these devices are developed is not whether appendage occlusion prevents stroke, but whether appendage occlusion is an alternative to warfarin in preventing the same strokes that warfarin prevents.

As we read and benefit from Lardizabal and Sharma’s informative review1 and as we await the results of progress with various innovative approaches for stroke reduction in AF, we do so appreciating that for the most part progress and discovery in this field is less fuzzy logic and, hopefully, more thoughtful innovation.

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References
1. Lardizabal JA, Sharma S. Mechanical approaches to stroke prevention in atrial arrhythmias. Innov Cardiac Rhythm Manage 2012.

The author discloses that he is a co-inventor of two non-surgical left atrial appendage (LAA) occlusion systems and has been involved in the development of these devices, as well as an investigator participating in the implantation and evaluation of an endocardial LAA system.