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Watching, but not waiting: vascular neurology perspective on the disparate regulatory pathways for stroke

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Vascular neurologists have keenly watched the Watchman device (Atritech, Plymouth, Minnesota, USA) regulatory approval process. We are, as always, searching for additional options in the prevention and treatment of stroke to better care for our patients, and new approaches to the management of atrial fibrillation play a large part in this effort. Recently, a Food and Drug Administration (FDA) panel voted 13:1 in favor of the Watchman device for the prevention of ischemic stroke in nonvalvular atrial fibrillation.[1] The panelists came to this decision after reviewing data from large randomized trials that compared anticoagulation with warfarin, the standard of care at the time, with antiplatelet therapy plus occlusion of the left atrial appendage with the Watchman device.[2 3] The studies found that the approach incorporating the Watchman device was non-inferior to warfarin in the prevention of stroke or systemic embolism, with an acceptable periprocedural safety profile. Therefore, the panel, mostly without stroke experience, gave near unanimous support for the device. Although the device offers an intriguing new approach to stroke prevention in this high-risk group of patients, the decision also underscores the seemingly disparate process for development of stroke therapies and the disengagement of the stroke community from recent cardiology-driven stroke trials.

While designed as cardiology device trials to treat complications of a cardiac arrhythmia, studies examining thromboembolism from atrial fibrillation are, in fact, stroke prevention studies. The most relevant endpoint in these trials is the prevention of stroke, and it will be predominantly vascular neurologists, not cardiologists, who will ultimately manage, treat, and counsel those people later affected by stroke. It is particularly striking, therefore, that the examination, assessment, and strong endorsement of a device designed to prevent stroke could be undertaken with only minimal involvement of vascular neurologists.

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In clinical studies in which stroke is the primary endpoint, or part of a composite primary endpoint, vascular neurologists should be involved in trial design and regulatory approval. In the particular case of the Watchman device, increased stroke expertise in the design and reporting of the trial might have called for improved characterization of the events ultimately diagnosed as stroke, such as transient ischemic attack versus infarction, as well as their etiologies, whether large vessel, small vessel and, ultimately, cardioembolic or otherwise. Similarly, further investigation and evaluation of concurrent and potentially confounding diseases, such as extracranial carotid disease or intracranial stenosis, might have been included.

Apart from the details of the trial, the differences in perception between the two fields are particularly poignant when comparing the evidence considered to be sufficient to endorse the use of a device in stroke. The studies that led to the support of the Watchman device were designed as non-inferiority studies, and were adjudged by the panel, consisting primarily of cardiologists, as adequate to endorse its use.[2] Recent devices under examination by vascular neurologists, particularly endovascular clot retrieval devices, have undergone trials testing superiority over existing treatments.[4-6] And while the non-inferiority of these devices, as compared with IV tissue plasminogen activator (tPA) at time points unsuitable for intravenous thrombolysis, has already been suggested in the recent SYNTHESIS Expansion study, the perception of vascular neurologists is that these therapies remain unproven.[6 7] Perhaps as a result, despite evidence that a non-inferiority endpoint may be attainable, subsequent endovascular stroke trials have continued to aim for superiority. Such perceptions have not persisted in acute cardiac interventions, where non-inferiority designs are routinely used for both pharmacologic and procedure-driven trials in myocardial infarction.[8-13] Thus, while non-inferiority has been considered ‘negative’ data by vascular neurologists, it has been thought of as ‘positive’ in cardiology trials. The willingness of the FDA to approve devices for stroke has followed this double standard, with a non-inferiority design seemingly sufficient in stroke trials coordinated by cardiology, whereas this level of evidence has not been regularly attempted by vascular neurology. There remain no FDA-approved devices for the treatment of acute ischemic stroke.

The larger question is whether vascular neurologists should accept a noninferiority trial design for devices in stroke. In the absence of compelling superiority data, is the additional cost and potential for harm justified? While a rich topic for debate, there is precedence for a non-inferiority design in acute stroke treatment, in the form of the SWIFT and TREVO2 studies.[14 15] The SWIFT study was designed as non-inferiority trial to compare the performance of an existing Merci device with the Solitaire device for arterial recanalization in acute ischemic stroke. The study was stopped early owing to the apparent benefit achieved with the Solitaire device, and shortly thereafter led to FDA clearance for the device as a means of revascularization. Similarly, TREVO2 compared the ability of the Trevo device to recanalize occluded cerebral vessels in acute ischemic stroke with that of the Merci device, with a non-inferiority endpoint. This device was also awarded FDA clearance following the results of the trial. By comparing two devices and obviating the need for a medical arm, these trials benefitted from not needing to randomize against IV tPA and thereby avoided a potential obstacle in non-inferiority approaches, but suggest a methodology that may prove successful.

The complexities of successful clinical trial design are manifold and should not be oversimplified. The methods involved in trials focusing on stroke prevention are radically different from those evaluating acute treatments. Each new trial must be placed in the context of the trials that preceded it, the level of evidence they provided, and the standard of care at the time. Cardiology has historically been far more successful than vascular neurology in coordinating large, multicenter, multinational clinical trials, which have resulted in tremendous power to detect efficacy in their interventions. As vascular neurologists, it is our responsibility to advocate for our involvement in trials concerning stroke, and thus blend our approaches with the different techniques and standards currently in use, in terms of not only trial design but also effective outcome measures, maximizing our ability to accurately evaluate our interventions and provide evidence for their use. Doing so is the only means of creating a level regulatory landscape for drugs and devices in the treatment and prevention of stroke. In many ways, the story of atrial fibrillation and stroke should highlight the success of harmonious partnership between the cardiovascular and neurological specialties. Unraveled in concert by luminaries in both fields, this arrhythmia that was once viewed as only relevant to rheumatic heart disease was shown to pose a radical risk for stroke from cerebral thromboembolism.[16-18] From these initial observations grew a mechanistic understanding, and countless strokes were prevented with the therapies then developed.

From the fundamentals of their biology, stroke and cardiovascular disease are inextricably linked. As clinicians, it is our duty to rigorously assess disease not merely from the viewpoint of our field of interest, but from the perspective of how best to treat our patients. For stroke and atrial fibrillation, as our approach to this disorder becomes increasingly sophisticated, a closer understanding between cardiologists and vascular neurologists will advance our ability to provide complete care for the patients that depend upon us.

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