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The Watchman Saga — Closure at Last?

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Atrial fibrillation is a critical public health issue, and its clinical burden and related costs will only grow as the aging of the U.S. population increases its prevalence and the risk of resulting stroke and systemic embolism. Several investigators have tried to prevent complications of atrial fibrillation using medical devices designed to prevent embolization of clots formed in the left atrial appendage. Although such devices have been available for nearly a decade in Europe, they are not yet approved in the United States. Examination of the review conducted by the Food and Drug Administration (FDA) of one device for closure of the left atrial appendage provides insight into differences in medical-device regulation between the United States and the European Union (EU) and highlights the urgency of monitoring devices in a coordinated and rigorous manner.

Recent clinical trials have broadened the pharmacologic options for thromboembolic prophylaxis in patients with nonvalvular atrial fibrillation. But device-based strategies targeting thromboembolism from the left atrial appendage may be an alternative to anticoagulation. The most intensely studied device has been the Watchman Left Atrial Appendage Closure System, designed by Atritech (which was later acquired by Boston Scientific) and first implanted in human subjects in 2002. It earned EU marketing authorization in 2005, although information on the exact data used for that decision is not publicly available. The EU directives on medical devices empower “notified bodies,” private entities accredited by their home countries, to evaluate the performance of investigational devices. However, individual countries cannot impose additional requirements for either premarketing or postapproval study. A 2007 report describing the results of “initial worldwide experience” with the Watchman provided data on 75 patients, 66 of whom had received the device, including 53 who had received a second-generation system featuring design modifications.¹

The Watchman was still an investigational product in the United States in April 2009 when an FDA advisory committee reviewed the findings from manufacturing, bench, and clinical testing of the device. The committee did not review any data accrued from pilot studies conducted between 2002 and 2005, and if there were any reports describing the EU experience from 2005 to 2009, they were not presented to the committee. Rather, the review

focused on the results of the Embolic Protection in Patients with Atrial Fibrillation (PROTECT-AF) study, in which 707 patients were randomly assigned in a 2-to-1 ratio to receive the device or pharmacotherapy with warfarin.² The noninferiority margin for the composite effectiveness end point was met, though adverse events were more common in the device group.

The committee voted seven to five in favor of approval of the Watchman system, with conditions such as on-site surgical backup.³ The FDA — which is not bound by committee recommendations — instead requested additional data. The agency was concerned about procedural complications, as well as reports of suboptimal warfarin management in the control group in PROTECT-AF.³

After the 2009 FDA decision, the manufacturer of the Watchman sponsored the PREVAIL study, in which 407 patients were randomly assigned in a 2-to-1 ratio to receive the device or warfarin. Both the composite effectiveness end point and adverse events were to be evaluated at 18 months. In the new study, the procedural complication rates were lower than those in PROTECT-AF, but at 18 months, the prespecified end point for noninferiority had not been met.⁴ In December 2013, another advisory committee reviewed both PREVAIL and longer-term follow-up from PROTECT-AF and a nonrandomized registry of similar patients, which also showed improved implantation success and reductions in procedural complications. This committee voted 13 to 1 in favor of approval, but again the FDA requested further data with more patients having reached 18 months of follow-up. These data, presented to a third committee in October 2014, now suggested higher rates of ischemic stroke in the Watchman-treated patients. Nevertheless, the committee voted unanimously that the device was safe — but were closely divided on its effectiveness and the favorability of the overall risk–benefit profile. As of the end of February, the device had not been approved in the United States.

This story illustrates a few key problems related to the systems for medical-device approval in the United States and the EU. First, the lack of global coordination and the lower barriers to entry into the EU market create an environment in which important opportunities for generating scientifically meaningful data on safety and effectiveness are missed. Device manufacturers will naturally gravitate toward the regulatory system with the lowest barriers to entry. Although EU patients have had access to the Watchman device since 2005, the accumulated clinical experience in Europe apparently contributed no relevant scientific information to subsequent FDA deliberations. Only in October 2013 did the manufacturer launch a proposed 1000-patient prospective study in the EU, with planned follow-up of only 2 years.

This lost decade represents a missed opportunity for collaboration among the manufacturer, U.S. and EU regulators, and payers. An integrated approach to postapproval monitoring might have included, for example, careful review of procedural information and evaluation of short-term safety outcomes or best practices for periprocedural anticoagulation and antiplatelet use. Identification of matched controls who received anticoagulant therapy alone might have supported comparative effectiveness analyses, which in turn might have

informed the design of pivotal U.S. clinical trials, and perhaps stronger evidence would have been brought to bear sooner on the FDA's review of the device.

The EU experience also demonstrates that unless required to do so, manufacturers are unlikely to pursue the costly, time-consuming clinical trials from which the highest-quality evidence emerges. Advocates who highlight the results of PROTECT-AF and PREVAIL in arguing for the Watchman's approval should recognize that these studies were probably conducted only because they were necessary for access to the U.S. market. EU policymakers continue to consider raising the bar for approval of devices based on potentially disruptive technology. These reforms may strengthen the evidence that is generated before market authorization. Whether stronger evidence at the time of EU market entry would enhance clinical uptake of a new device is unknown, but theoretically such reforms could provide an incentive for manufacturers to develop higher-quality data. At the same time, the United States may be moving in the opposite direction, as Congress in 2015 considers legislation lowering the levels of evidence needed to demonstrate device safety and effectiveness.

The next chapter in the Watchman story will soon be written. If the FDA approves the device, questions will remain about its clinical role, and the agency will remain responsible for ensuring its safety and effectiveness in real-world use. The pivotal studies enrolled fewer than 2000 patients in total, and we lack a complete understanding of rare or late-appearing adverse effects and effectiveness over the long clinical life anticipated for this high-stakes device — a permanent implant, aimed at preventing life-threatening complications of a condition affecting millions of patients.

Although a registry that engaged professional societies, the manufacturer, and clinicians could provide real-world outcomes data, prospective postapproval trials of the device will also be needed in order to answer questions such as its comparative effectiveness versus novel anticoagulants. Unfortunately, the current system provides limited incentives to complete required postapproval trials in a timely fashion. One approach to motivating manufacturers to undertake such studies would be for Congress to authorize the FDA to grant marketing approval lasting only 5 years for high-risk devices.⁵ After that period, the manufacturer could be required to present data accumulated since the initial approval and to again make its case for reasonable assurance of safety and effectiveness — a process that might lead to revision of the labeled indications. If mandated postapproval studies were not complete by that time, the manufacturer would risk having the device removed from the market.

We believe that clinicians and regulators worldwide should expect timely data on real-world experience to complement clinical-trial evidence — both are essential for understanding new technology such as Watchman and its potential for improving public health. Whatever the FDA decides for Watchman, closure may remain elusive.

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