The evolution of left atrial appendage occlusion: EWOLUTION and the WATCHMAN in practice

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This editorial refers to ‘Implant success and safety of left atrial appendage closure with the WATCHMAN device: peri-procedural outcomes from the EWOLUTION registry’, by L.V.A. Boersma et al. on page 2465.

Randomized clinical trials (RCTs) are considered the standard for determining the benefit–risk balance of medical treatments due to the strength of their internal validity, or the validity of the results in the enrolled population. However, they are often limited in terms of their external validity, or their applicability to the larger patient populations who will receive the treatment in practice. Trials traditionally enrol highly specified patients, employing relatively strict criteria that exclude medically complex individuals either explicitly or implicitly, resulting in populations that can differ substantially from those treated in practice. While clinicians may feel comfortable applying the results of trials to patients who meet these enrolment criteria, clinical decision-making becomes more challenging in proportion to the patient’s complexity.

Trials of technologies have an additional potential limitation: operators involved and the centres in which they practise may be recruited because of their experience, and thus may have greater success with the procedure. Assuming that procedural outcomes in RCTs can be extrapolated to all centres and operators can be hazardous. Because of the restricted populations and operators involved in traditional randomized trials, other sources of data are helpful in understanding the procedural and clinical outcomes of medical technologies in the ‘real world.’

Observational data are critical complements to RCTs because they provide this broader perspective (Figure 1). Registries have evolved to serve as a critical component of post-market device surveillance in practice. In this issue of the journal, Boersma and colleagues present a report of short-term outcomes of an evolving technology—left atrial appendage (LAA) occlusion—in 1025 patients treated in 47 centres in 13 countries with the WATCHMAN device and enrolled in the EWOLUTION registry. The patients studied in this manufacturer-sponsored cohort study differed from those enrolled in the RCTs of the WATCHMAN in important respects: for example, the estimated risks of both stroke and bleeding using the CHA2DS2-VASc and HAS-BLED scores, respectively, were substantially higher. The operators and centres also had varying degrees of experience with the WATCHMAN.

Given the diversity of patients and operators in EWOLUTION, the results are somewhat surprising. Specifically, the procedure was successful in nearly all patients (98.5%); 28 [2.8%, 95% confidence interval (CI) 1.6–3.6%] serious adverse events (SAEs) deemed related to the procedure at 7 days occurred in 23 patients, and 79 SAEs (7.9%, 95% CI 6.3–9.8%) occurred within 30 days in 73 patients; 36 of which were deemed related to the procedure. Three patients died within 30 days of causes that appear unrelated to the device. The rates of procedural success and 7-day device-related SAEs were both nominally more favourable than those found in the randomized Protection in patients with atrial fibrillation (PROTECT-AF) and Prospective Randomized Evaluation of the WATCHMAN LAA Closure Device (PREVAIL) trials comparing the WATCHMAN with anticoagulation. These short-term results are encouraging in terms of the safety of the device.

The study also provides an opportunity to assess the indications for the WATCHMAN in participating centres. The majority (61.8%) of patients were considered ineligible for chronic anticoagulation therapy. Both PROTECT-AF and PREVAIL restricted enrolment to patients deemed suitable for anticoagulation. Although the current European Society of cardiology guidelines for atrial fibrillation recommend consideration of LAA occlusion in patients with a high stroke risk and contraindications to long-term anticoagulation (a relatively weak Class IIb, level of evidence B recommendation), data in this subgroup treated with the WATCHMAN have until now been limited to a small cohort study. EWOLUTION thus demonstrates how the diffusion of a technology in practice may often expand beyond the patients for whom RCT evidence is available.

The study has important strengths. The study cohort is relatively large, providing reasonable statistical power, which is important given the relatively low rates of complications that would have been expected based upon the trials. The patients were those

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deemed eligible for the WATCHMAN based upon local and international guidelines, and procedures were performed at sites with varied experience. Source documents for SAEs were reviewed by a Sponsor Medical Safety group. These design features contribute to the broader representativeness of the patients and operators, as well as the clinical precision of the results. Additional follow-up of the cohort is planned, which will provide a longer-term perspective on outcomes after WATCHMAN implantation.

The study also has limitations. Although the centres were encouraged to enrol consecutive patients—an important condition to reduce selection bias—it is not noted that consecutive enrolment was verified. Although reported events were adjudicated, and sites were visited at least once before completion of the 30-day follow-up data, there was no reported secondary mechanism to identify SAEs beyond self-report by the clinical centre. Both of these factors could result in an underestimation of adverse event rates. Finally, the number lost to follow-up is not reported, and although adverse events were adjudicated, procedural success was not. The issue of the centre- and operator-level experience is particularly important given the existing data that strongly suggest a ‘learning curve’ with the WATCHMAN device observed in the randomized trials. Although the investigators reportedly enrolled sites and operators with varied experience, this variation is not quantified in the report. All operators underwent training and certification. The details of this process and the extent to which this process can be replicated efficiently is important to determine whether the EWOLUTE results have broader applicability.

The study highlights broader issues with registries. First, as is often the case with populations selected because they were treated with a device, there is no control group with which to assess effectiveness. Even when control groups are available, comparative studies between non-randomized groups must still be interpreted with great caution because of the risks of confounding by indication. Although sophisticated statistical methods have been developed to optimize adjustment for measured variables, it is not possible to exclude the influence of unmeasured confounders. Secondly, the quality of the results is only as strong as that of the underlying data. Data quality programmes of registries are variable, and relatively few apply robust approaches including outlier analysis and audits of medical records. Finally, ascertaining exposures and outcomes after hospital discharge is resource intensive. In some cases, administrative (billing) data are used as a relatively economical method of ascertaining vital status and the diagnoses associated with hospitalizations. In the case of LAA occlusion, the subsequent use of anticoagulant and antiplatelet agents is important. Ascertaining longitudinal use of medications is challenging in the absence of the availability of robust electronic pharmacy records.

The recent approval of the WATCHMAN in the USA by the Food and Drug Administration (FDA) was conditional upon the conduct of two post-market cohort studies by the manufacturer, reflecting the growing importance of observational data in the FDA surveillance strategy. The first of these studies will be a single-arm study of 1000 patients followed clinically for 2 years and with linked

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**Figure 1** Randomized controlled trials (RCTs) and observational studies provide complementary data to inform clinical decision-making.
insurance claims data for an additional 3 years for the three co-primary outcomes defined in the PREVAIL trial and secondary endpoints of procedural success, safety, and strokes of all causes. The second is a single-arm study of an additional 1000 patients enrolled in a registry with clinical surveillance for a year and claims follow-up for 5 years, with a focus on procedural success, safety, and strokes. The American College of Cardiology’s National Cardiovascular Data Registry (NCDR) will be supporting these studies with the Left Atrial Appendage Occlusion (LAAO) Registry.

Rigorous observational data are particularly important in the area of LAA occlusion because several approaches are in use despite substantially less evidence than that supporting the WATCHMAN. In these cases, robust surveillance for safety issues could have important implications for patients. For example, reports from the FDA voluntary reporting system identifying several serious adverse events with the LARIAT device are concerning. However, without data on all patients receiving the device, neither a complete numerator of adverse events nor an accurate denominator with which to calculate rates is available. The NCDR LAAO Registry is designed to collect data for percutaneous LAA occlusion regardless of the device used. As has been previously mentioned, however, registries are not substitute for establishing the efficacy of therapies, and indeed many of the technologies used in practice for LAA occlusion have not yet been proven efficacious, without which the use of even the safest device is difficult to justify.

Despite their limitations, observational data such as those from EWOLUTION are becoming increasingly important as pieces in a complex puzzle of evidence to guide clinical decision-making and ensure patient safety. While they will never be substitutes for randomized trials in determining therapeutic efficacy, well-designed observational registries—those that enrol consecutive patients, have the capacity to ascertain outcomes over long time periods, and that employ rigorous data quality programmes—can play a central role in understanding patient selection, procedural safety, and outcomes after treatment in contemporary clinical practice.

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