The idea that mechanical intervention to close the left atrial appendage (LAA) might reduce complications from atrial fibrillation (AF) is at least 70 years old.1 Early attempts to test this idea in humans with surgical ligation were abandoned after only a few years for 2 reasons. First, proponents soon realized that they had no way to choose the candidates believed most likely to benefit without the ability to image the LAA preoperatively. Second, interest was rapidly growing in what appeared a much more promising new therapy, chronic oral anticoagulation.2 Fast forward about a half century. Transesophageal echocardiography provides excellent imaging data about the LAA, clinical risk scores are used to guide therapy, and major research efforts are underway to develop an effective pharmacological alternative to warfarin, which doctors really do not like using and patients really do not like taking. At the same time, some in the field think a better approach still might be to occlude the LAA, thereby eliminating the need for lifetime anticoagulation altogether.

See Article by Freeman et al

Even with transesophageal echocardiography and modern percutaneous device technology, the path to an approved LAA occlusion device for clinical use in the United States was not easy. The first catheter-based occlusion device for the LAA, the Percutaneous Left Atrial Appendage Transcatheter Occlusion (PLAATO) device (2001, Medtronic), was removed from the market because of safety concerns with implantation, despite early favorable evidence of stroke reduction.3 The Amplatz device (2002) was developed into the Amplatz Plug (2008, St Jude Medical) specifically for LAA occlusion, but no clinical trials of the device have yet been completed.4

The Watchman Device (2002) is the only percutaneously delivered LAA occlusion device to have its efficacy and safety measured in 2 randomized controlled trials5,6 and to receive Food and Drug Administration approval for the indication of reducing the risk of LAA thromboembolism in patients with nonvalvular AF. Achieving that approval took 6 years (2009–2015) and involved review by 3 advisory panels. The first advisory panel, in 2009, voted in favor of Watchman approval based on the PROTECT-AF (The Percutaneous Closure of the Left Atrial Appendage Versus Warfarin Therapy for Prevention of Stroke in Patients With Atrial Fibrillation) trial, which was a noninferiority efficacy study of 707 patients randomized 2:1 to Watchman versus warfarin with a composite primary end point of stroke, systemic embolism, or cardiovascular death.7 In the first report from that trial (mean follow-up 18 months), the Watchman device was noninferior to warfarin on efficacy but had more early, procedure-related, safety events.7 The Food and Drug Administration elected not to approve the device and asked for more data, particularly relating to safety and to device use by novice implanters.

The second advisory panel met in 2013 and also voted in favor of approval, based on longer-term follow-up from PROTECT-AF (mean follow-up of 2.3 years) and the new implantation safety data from PREVAIL (Prospective Randomized Evaluation of the Watchman LAA Closure Device in Patients with Atrial Fibrillation Versus Long Term Warfarin Therapy).5,6 The PREVAIL trial showed increased rates of successful device implantation relative to PROTECT-AF, and it met the prespecified safety event rate, although it missed its primary, noninferiority efficacy end point (composite of stroke, systemic embolism, and cardiovascular or unexplained death). In longer-term PROTECT-AF data, the primary efficacy end point continued to meet criteria for noninferiority, driven by lower rates of cardiovascular death and hemorrhagic stroke. Again, the Food and Drug Administration decided not to approve and called a third advisory panel in late 2014. With the third advisory panel approval and data from PROTECT-AF, PREVAIL, and the continuing access registry data from the trials (demonstrating efficacy data consistent with trial data),8 the Food and Drug Administration approved Watchman for stroke prevention in AF patients in March 2015.9

Based on a detailed evidence review that included the same trial data, the Centers for Medicare and Medicaid Services issued a Watchman national coverage decision in February 2016,10 which requires entry of patients into a new National Cardiovascular Data Registry and limits Watchman reimbursement to patients with a CHADS2 score ≥2 or CHA2DS2-VASc score ≥3 who are not suitable for long-term anticoagulation and have had a documented shared decision-making interaction with a noninterventional physician.10 US physicians, therefore, are in the odd situation of having regulatory approval for use of the Watchman device as an alternative to warfarin in warfarin-eligible patients based on 2 randomized trials but can only get reimbursed by Centers for Medicare and Medicaid Services when we use the device in a different population for which no relevant trial data exists.

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In this issue of *Circulation Arrhythmia and Electrophysiology*, Freeman et al use the available trial data in a Markov model to consider the cost-effectiveness of the Watchman device.11 Interestingly, the economics of LAA occlusion therapy using the Watchman device relative to both warfarin and novel oral anticoagulants (NOACs) has been the subject of several prior economic analyses.12–14 When examining model-based economic analyses of medical care involving chronic disease therapies (such as AF), 2 points are worth keeping in mind. First, before considering any cost data, attention should be directed to the clinical effectiveness story reflected in the model and how that relates to the understanding of effectiveness based on empirical trial data. Extrapolating from the empirical trial outcomes to the lifetime outcomes needed for economic analysis is done with one of several types of models (eg, statistical models, Markov models). To varying degrees, use of these models creates a black box problem where a lot of complicated data goes in and a putative answer comes out, but the intervening steps are largely invisible. Confidence in the analysis results is enhanced when multiple independent analyses reach the same result or the investigators demonstrate that their model predictions are in close agreement with empirical trial data or other useful benchmarks. To facilitate interpretation and benchmarking in economic analyses, clinical outcomes (the effectiveness part) must be translated into incremental life years (LYs) or incremental quality-adjusted LYs (QALYs). Ideally, one should examine both to clarify how much the value story of the therapy being produced by some model is caused by projected enhanced survival (and how persuasive are the empirical data for this) and how much is caused by assumptions about enhanced quality of life (QOL).

The second, related, issue to keep in mind when reviewing an economic analysis of a clinical care strategy is that economic analysis is not discovery science. In other words, the analysis should not create some new, previously unrecognized story about the clinical effectiveness of the care in question. Instead, it should clarify and amplify understanding about the consequences of care evident in empirical data (ideally high-quality randomized clinical trial data) together with clear and plausible assumptions about what happens in the period beyond where the empirical data currently end.

What expectations for cost-effectiveness of the Watchman device relative to warfarin therapy are plausible based on clinical trial evidence? To answer this question, we need to identify survival benefits from trial data that should translate into extra life expectancy and QOL benefits that might enhance QALYs. If we use the PROTECT-AF data to answer the survival/life expectancy question, the case is fairly easy to make as long as we are willing to assume that the substantial all-cause mortality benefits evident at 5 years (about 7 per 100 more survivors in the Watchman arm) are preserved over the longer term.15 The most recent survival data from PROTECT-AF actually show curves that diverge, implying that the benefits may amplify further, which would make the case for cost-effectiveness even easier. The assumption that the 5-year benefits are at least preserved without attenuation seems reasonable but needs empirical verification.

If the PROTECT-AF long-term survival data are sufficient to support a cost-effectiveness analysis for Watchman, how do the PREVAIL data affect the case? As noted earlier, PREVAIL was performed primarily to generate additional safety data about device implantation, and it was not designed to confirm or modify the effectiveness story of PROTECT-AF. The evidence for improved survival and an improved primary efficacy end point with the Watchman device took 6 to 12 months to begin to emerge in PROTECT-AF. Therefore, PREVAIL was neither large enough nor did it have enough follow-up to permit more precise estimation of the long-term outcome differences between Watchman and warfarin.

The case for cost-effectiveness of the Watchman device relative to warfarin can thus be made on survival differences alone (using PROTECT-AF but not PREVAIL), subject to the caveats noted, but what effects might we expect QOL to have on the analysis? In a cost-effectiveness analysis, QOL weights (called utilities) serve 2 different purposes: as a discount factor on life expectancy and as a separate pathway to reflect treatment-specific benefits. When we calculate cost-effectiveness in terms of added (incremental) LYs only, we make the assumption that the added time provided by the therapy is spent in full health; however, in chronic disease therapy, that assumption is often implausible. The PROTECT-AF cohort had a mean age of 72 years at study enrollment along with the usual portfolio of comorbidities. Is an added year of life for these patients to be valued the same as an added LY for a 35-year-old? Asking such questions opens a Pandora’s Box of unresolvable ethical questions. The perspective that economic analysis holds as normative is that of the rational utility maximizer, an individual who will make self-interested decisions to maximize satisfaction (utility). If we are forced to provide relative values for a LY for a 35-year-old and a 75-year-old, both of whom are healthy and neither of whom are known to us, the rational choice would generally be to pick the 35-year-old LY, meaning that the 75-year-old LY does not have equal value, and QALY utility weight may be used to express this preference quantitatively. The question of whether it is ethical to value health benefits provided to younger, healthier people over older ones or those who have some chronic disability lies outside the realm of economic analysis, but it is critical for policy makers. Comparing incremental LYs and incremental QALYs in an economic analysis, one can gain useful insights into how much discounting of this type is built into the analysis.

The second way QOL (utility) can enter into a cost-effectiveness analysis is as an indicator of differential therapeutic benefit. Three different versions of therapeutic benefit can be observed and incorporated into economic models. In the context of the Watchman versus warfarin comparison, one generally would not expect implanting a Watchman device to affect AF symptom status. Not having to take long-term warfarin might seem like a benefit with important QOL effects, but prior efforts to measure such an effect empirically have found only very small effects. The prevention of major non-fatal events might seem like an important source of QOL benefits until one examines the mathematics of the situation. In PROTECT-AF, implantation of the Watchman device was associated with ≈1 per 100 more ischemic strokes. Although the effect of such an event on the individual patient involved may be profound, the effects on average QALYs of the overall
treatment group are minimal because 99 of 100 patients did not have such an event. Unless the treatment in question is preventing a large number of nonfatal major adverse events relative to the control therapy, the absolute effect of this aspect of the therapeutic benefit (even with a large relative benefit) is often too small to influence the results in a meaningful way.

Even if the Watchman device does nothing at all to the patients’ disease or disease-related symptoms, patients are aware the device is being implanted for the postulated benefits, and beliefs developed in this process can result in measurably improved QOL. A QOL substudy from PROTECT-AF reported a relatively large QOL benefit for the Watchman device, too large to be plausibly tied to direct health benefits of the device, and the investigators postulated that the reassurance factor was most likely the cause.

With those caveats in mind, we can examine and compare some of the details of the 2 previous cost-effectiveness models of the Watchman device together with the one published in this issue. Singh et al created a Markov model examining Watchman LAA occlusion versus warfarin (based on PROTECT-AF) and versus dabigatran (using RE-LY) from the perspective of the Ontario Ministry of Health. Life expectancy for the Watchman patients was increased by 0.10 LYs and 0.13 QALYs relative to warfarin therapy. The authors acknowledged that they may have underestimated the benefits of the Watchman device because they only had access to the earliest PROTECT-AF results (which did not show the large statistically significant mortality benefit that became evident later). The price for the device was assumed to be $8500 (about half of the current US price), and the incremental lifetime costs for the device arm relative to warfarin were $5600 (discounted). The resulting cost-effectiveness ratio for Watchman device therapy relative to warfarin was $42,000 per QALY, and the analysis did not report a sensitivity analysis on the device costs.

Reddy et al published a second cost-effectiveness model of Watchman versus warfarin and versus NOACs as a class, also using the PROTECT-AF data together with NOAC trial data and meta-analyses in a Markov model, with costs reflecting a US Centers for Medicare and Medicaid Services perspective. This model projected 0.51 LY and 0.64 QALY gains with Watchman, but the drivers for those projected benefits in the model are not easily identified. The authors assigned a procedure cost for the device plus implantation of $16,109 using relevant DRG codes. The lifetime discounted costs with the Watchman device was projected to be almost $19,000 lower than that for warfarin therapy. This result is unexpected. The most plausible source of a $35,000 cost reversal seems likely because of modeling assumptions about warfarin discontinuation rates, but these are not reported. The Watchman Device’s maintenance free feature (implant it and it works indefinitely without additional cost) may be a major source of clinical and economic benefit over drug therapy in situations where high discontinuation rates occur. The case for this, of course, would be much stronger if this could be empirically demonstrated in a comparative effectiveness context. In PROTECT-AF, adherence in the warfarin group was high (time in therapeutic range =70%).

In this issue of the Journal, using the same PROTECT-AF published data, Freeman et al project an incremental benefit of Watchman device therapy over warfarin of 1.98 QALYs (versus 0.638 for Reddy and 0.13 for Singh). This is a huge treatment difference that reflects a core model assumption of amplifying survival benefits past where the empirical data end (ie, the model sees survival curves that continue to diverge after 5 years). Cost for the Watchman device together with implantation costs were estimated from 2014 Centers for Medicare and Medicaid Services reimbursements as $24,000 (current US costs for the device alone are $14,000 to $18,000). The lifetime incremental cost of the Watchman arm over warfarin therapy was $40,654, and the cost-effectiveness ratio was $20,486 per QALY.

Thus, we have 3 model-based cost-effectiveness analyses comparing the Watchman LAA occlusion device with warfarin using much of the same data but arriving at substantially different estimates of incremental costs and incremental QALYs. Because all 3 models also consider a NOAC treatment option, it is instructive to examine some of those results to judge model performance from a different perspective. Singh projected discounted life expectancies and QALYs to be close between warfarin (6.71 years and 4.55 QALYs, respectively) and dabigatran (6.79 years and 4.64 QALYs), both of which were slightly lower than that for Watchman (6.81 years and 4.68 QALYs). Thus, the model of Singh estimates that the outcomes between Watchman and dabigatran would likely be a virtual tie, probably too small to measure in a clinical trial.

The Reddy model projects moderate benefits for pooled NOACs against warfarin (7.68 QALYs versus 7.39 QALYs, a difference of 0.29 QALYs that is plausible given the analyses already conducted by other research teams on the NOAC trials). However, the same model projects that the Watchman device will have an advantage over NOACs larger than the advantage NOACs have over warfarin (8.03 QALYs versus 7.68 QALYs for a difference of 0.35 QALYs). This part of the modeling seems implausible.

The Freeman model projects 8.28 QALYs for dabigatran versus 7.96 for warfarin, a difference of 0.32 QALYs, again within the ballpark of what the NOAC trial economic analyses have reported. However, that same model projects that the Watchman device would add 1.66 QALYs over dabigatran therapy. Thus, both the Reddy and the Freeman models project the warfarin–NOAC differences plausibly but project some implausibly large benefits for the Watchman device over NOACs. To achieve these results, their models must be assuming facts not in evidence, to borrow a legal phrase.

We still have much to learn about the use of LAA occlusion devices, such as Watchman. There have been 732 patients randomized to Watchman versus 382 warfarin comparator patients, resulting in 36 strokes or systemic emboli in Watchman patients versus 21 among warfarin patients. In comparison, 42,411 patients have been randomized to NOAC versus 29,272 warfarin comparator patients, resulting in 911 strokes or systemic emboli in NOAC patients versus 1,107 among warfarin patients. Concluding that the Watchman device substantially improves survival over the best modern NOAC therapy based on current evidence is beyond what cost-effectiveness models are suited to do.

Given these considerations, what can be concluded about the cost-effectiveness of LAA occlusion therapy with...
the Watchman device? As we noted at the beginning of this editorial, the case for cost-effectiveness usually rests heavily on the absolute improvements produced in health outcomes expressed as incremental LYs and QALYs. Based on PROTECT-AF, the Watchman device relative to high-quality warfarin therapy produces enough incremental QALYs to be cost-effective under most plausible scenarios. The proposition that the device is cost saving over the long run relative to warfarin (as in the Reddy analysis) is not supported by any empirical evidence. Neither is the assertion that the Watchman device will produce a substantial survival advantage over NOAC therapy.

Cost-effectiveness analysis can be a useful clinical policy tool, in part because it forces us to be explicit about what incremental benefits and costs we think will be produced by a given therapy. But cost-effectiveness models cannot discover new therapeutic stories for which no empirical evidence exists. Because the models do not come with guiderails to warn of an impending off-road adventure, those who create economic models and those who use them must stay ever mindful of the evidence on which the models are based.

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