The search for a safer and more tolerable anticoagulant alternative to warfarin has been the holy grail of thromboembolic research for decades. With its capacity to reduce the risk of ischemic stroke by nearly two thirds in patients with atrial fibrillation, warfarin remains one of the most powerful preventive tools in all of medicine. But in the 57 years since the drug was introduced, generations of clinicians and patients have become all too familiar with the difficulty of establishing and maintaining an adequate level of the international normalized ratio (INR) in the face of intercurrent illnesses, the use of myriad interacting drugs, and dietary changes. Partly as a result, anticoagulation remains woefully underused in patients for whom it could do enormous good. Sensitive to problems that result from commission more than from omission, physicians often overestimate the likelihood of hemorrhagic complications and underestimate the consequences of failing to prevent embolic events.

This is especially true in older patients, whom prescribers excessively perceive to be poor risks for anticoagulation, because they are frail or more likely to fall—even though these are the very patients at highest risk for preventable atrial fibrillation-induced stroke. Although there is good evidence that well-run anticoagulation clinics can help patients to hit the sweet spot of an INR of 2 to 3 consistently, most receive warfarin without benefit of such services. As a result, the average patient prescribed warfarin spends a distressingly high proportion of time either over or under the safe INR range. The prospect that pharmacogenetic testing could guide warfarin dosing, although now enshrined in the official labeling for the drug, has not been borne out as a compelling clinical or economic strategy.

The search for a better alternative to warfarin has had several false starts and blind alleys. One of the most notable of these was ximelagatran, a direct thrombin inhibitor. It had been in use in Europe, but marketing plans in the United States were suspended when it was found to cause potentially fatal hepatotoxicity. In 2010, the Food and Drug Administration approved a new direct thrombin inhibitor, dabigatran, which arrived with a major clinical trial credential. Its single large published study, the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY), demonstrated in an unblinded design that patients randomly assigned to 150 mg BID of the new drug in comparison with warfarin had a significantly lower rate of ischemic stroke, and no higher risk of major bleeding. Several other prespecified outcomes added additional nuances of the sort that make clinical decision making in this realm so multifaceted and challenging: in comparison with warfarin, dabigatran caused significantly fewer intracerebral hemorrhages and deaths from vascular causes, although the risk of major bleeding was similar overall. It had a nearly significant (P=0.051) advantage for all-cause mortality as well. Yet, the new drug also led to significantly more symptomatic dyspepsia. A statistically significant 38% increase in the risk of myocardial infarction with dabigatran was initially reported; when 30 new myocardial infarctions were found on closer inspection of trial data, that incidence remained elevated at a 27% increase, but fell below the conventional level of statistical significance. Overall, however, the findings indicated that the net clinical risk-benefit balance for the 2 drugs favored dabigatran, at least as far as the data from RE-LY went.

That trial was not designed to take into account the drug’s cost; now that it is marketed in the United States, we know that this is $3000 per year. The price of warfarin is $48 per year in many pharmacies, in addition to the modest expense of INR testing and physician time for dose adjustment, which do not come close to matching the cost of the new product.

Ignoring such large annual costs may or may not have been a reasonable perspective in the days when health expenditures did not approach 18% of the gross domestic product and the nation had budget surpluses as far as the eye could see. But at present, as the cost of medical care, especially through Medicare, looms as the single largest threat to the US economy, attention must be paid. The argument is most starkly obvious in considering the plight of the nation’s strapped state Medicaid programs. Adding several tens of millions of dollars to a Medicaid program’s costs will not simply strain its budget; with little likelihood of increasing appropriations, it will mean that other expenses will have to be foregone—for other services, for payments to providers, or for maintenance of program eligibility for many indigent patients.

Leaving aside the contentious issue of why dabigatran costs $3000 per year, this is the reality that patients, clinicians, and payers must face. Given all the competing ways we can spend our increasingly scarce healthcare dollars, is it a
good buy? It could be, if its clinical benefit exceeds that of warfarin by a significant margin. (It is important to point out that cost-effective is not the same as cost-saving. It simply means that the incremental expenditure required for a particular intervention is generally in the range that we are used to spending for a given increment in health benefit. Very few interventions in medicine actually reduce overall expenditures; aspirin for the secondary prevention of ischemic cardiovascular events is one of the few exceptions.)

The cost-effectiveness analysis (CEA) by Shah and Gage in this issue of Circulation seeks to address this question.10 The authors analyze clinical and fiscal inputs and outcomes based on the RE-LY trial, and assign to each a value, in terms of both quality of life and cost, viewed from the societal perspective. An advantage of their analysis over previous work on this question is that they go on to rigorously do what good physicians intuitively do all the time: they stratify patients in terms of their risks to determine the most appropriate regimens for different groups. Using a well documented score (CHADS2) that assesses stroke risk, they confirm that for a patient with atrial fibrillation with low risk of stroke (CHADS2 score of 0), the best outcome, highest safety, and lowest cost treatment is aspirin.11 For those at higher stroke risk (CHADS2 score of 1 or 2), they further stratify patients along 2 additional dimensions that make sound clinical sense: the risk of bleeding and the likely adequacy of warfarin management. In these cases, warfarin is the best choice unless the likelihood of good INR control is low, or the risk of hemorrhage is high. Finally, for those at high stroke risk, they report that dabigatran would be the most cost-effective choice, unless INR management is expected to be excellent.

A strength of the Shah and Gage CEA attempts to assess the benefits and risks of different anticoagulation strategies in light of a particular patient’s clinical situation, an approach that also makes sense beyond the economic dimension of this analysis. Whereas RE-LY concluded that overall, dabigatran 150 mg BID conferred greater stroke protection than warfarin at comparable bleeding risk, and a prior study concluded that it was likely to be more cost-effective,12 the Shah and Gage CEA takes the assessment to a more detailed level in also considering preexisting risk of hemorrhage, stroke risk, and likelihood of adequate INR control.

Cost-effectiveness analyses are easy to perform and simple to evaluate—with the exception of the parts dealing with cost and effectiveness, which are notoriously difficult. To begin with costs, Shah and Gage conducted a survey of pharmacies and used an average annual cost of dabigatran of $3240—at $9 per day ($270 per month), a price close to that listed on at least one widely used Internet pharmacy site. In this regard, they fared better than a prior CEA conducted by Freeman et al11 before the drug was marketed. Those authors had to guess at the eventual price of dabigatran, which they overestimated at $390 per month. When the actual retail price turned out to be closer to $240 per month, they had to revise their analysis; the new findings suggested that the drug’s incremental cost-effectiveness ratio was nearly 4 times better than it had been thought to be in the original calculations, demonstrating the exquisite (though obvious) sensitivity of such calculations to drug price.13

If any CEA of this question can be so distorted by problems with the estimation of the cost of the new drug, what about the cost of the old drug? Using a 2003 price listing, Shah and Gage assume that the retail cost of warfarin (not including testing) is $15 per month, even though it is now routinely available all over the United States at discount pharmacies for $4 per month. In this, they replicate the error of Freeman et al, who used the same source (the Drug Topics Red Book) to come up with an excessively high monthly medication-only cost for warfarin of $32. (In both analyses, the additional costs of INR testing were considered separately.) This approach of relying on the so-called average wholesale price of a drug is highly problematic, because such published figures are not average, not wholesale, and not actual prices. In neither study do they consider the cost of INR testing. In this, they replicate the error of Freeman et al, who used the same source (the Drug Topics Red Book) to estimate the price of warfarin. In this regard, they replicate the error of Freeman et al, who used the same source (the Drug Topics Red Book) to come up with an excessively high monthly medication-only cost for warfarin of $32. (In both analyses, the additional costs of INR testing were considered separately.) This approach of relying on the so-called average wholesale price of a drug is highly problematic, because such published figures are not average, not wholesale, and not actual prices.

Other, more subtle issues also cloud the cost issue in these studies, including the potentially undermeasured extra physician time required to monitor INR levels and adjust doses accordingly, the hard-to-measure disutility for the patient of repeated phlebotomies and dose changes, and the possibility that major bleeding events on dabigatran may be more costly than those on warfarin because of the lack of an available specific antidote.

One solution to all these problems would be for authors of published CEAs to make their models available online, so that analysts who would like to insert their own figures for costs, probabilities, or utilities could do so. In an ideal world, this would be the routine practice for such studies.

Problems can also bedevil the assessment of outcomes in any CEA, because a thorough consideration of the clinical and policy choices at hand must confront the difference between efficacy and effectiveness. Efficacy assesses the performance of a drug (or test, or procedure) under the ideal but atypical circumstances of the randomized clinical trial. But effectiveness takes into account how well something works in the actual context of everyday practice. These can differ substantially, and are quite likely to do so in the case of anticoagulation, for several reasons:

- Dabigatran is administered twice a day and has a relatively short half-life; there is evidence that a medication that must be taken twice a day is more likely to have doses missed than a drug (like warfarin) taken once a day.
- An even greater potential cause of poor adherence is the drug’s cost; we know that patients adhere less well to expensive drugs than to their more affordable alternatives,14 and at $3000 per year (or with a correspondingly high co-payment) this could be an enormous concern for many patients. Stretching out doses of a costly drug will, in this case, mean that patients who try this strategy will be more likely to have their anticoagulation drop to nonprotective levels, increasing their risk of stroke.
• When a patient taking warfarin veers above or below the ideal range of anticoagulation, it can be detected with an INR test; but no such testing is available for dabigatran.

• If a patient bleeds while taking warfarin, there are well-documented ways of reversing its effect on the coagulation cascade; for dabigatran, no such well-tested antidote is available.

• We have generations of experience with cessation of warfarin before planned surgery, as well as correction of the INR in the face of emergency procedures or trauma; no such experience is available for the new drug.

• Dabigatran has far less of a track record of adverse events, because it was introduced into use so recently. When ximelagatran was approved for widespread use in Europe, it too was a new, safe direct thrombin inhibitor alternative to warfarin—until it was not.

• Patients in the unblinded RE-LY study were in an acceptable INR range only 64% of the time. Although this is comparable to or better than many clinical settings, it is far from ideal, especially for a well-resourced clinical trial. What would be the effect of spending part of the incremental cost of >$2000 per patient per year on hiring legions of anticoagulation nurses or pharmacists to achieve better control with warfarin?

More experience will be needed before we can really understand the actual benefit-risk relationships inherent in dabigatran as used routinely, and, therefore, its cost-effectiveness, as well. In addition to better estimation of the actual costs of treatment, this will require assiduous postmarketing surveillance of its use in the real world of routine patient care. This will have to include data on the patients chosen for treatment (and how many have renal insufficiency, despite labeled warnings), the way in which patients and doctors will use the drug outside the trial setting, and any unexpected adverse events that arise. A variety of tools for postmarketing surveillance of drug effects have emerged to provide data on this key aspect of real-world medication utilization and outcomes, including the Food and Drug Administration’s new Sentinel system, which tracks such events in millions of ordinary patients in routine care.15

A key next step will be to see how dabigatran fares in the bumpy, messier setting of typical patient care, where it may well perform differently than RE-LY would suggest. For many of those with atrial fibrillation, over time it may prove to be a safer alternative to warfarin, even if its economic value in this comparison has yet to be measured adequately. But for many other patients, until we know more about its track record in this more demanding but far more relevant setting, there is merit to the recent joint professional society recommendation of the American College of Cardiology and the American Heart Association that for those who are currently stable and doing well on warfarin until we learn more, staying the course with that annoying old standby may be a prudent—and certainly affordable—course of action for the near future for many other patients.16

Disclosures

None.

References


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The Relative Cost-Effectiveness of Anticoagulants: Obvious, Except for the Cost and the Effectiveness
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