The Promise of Pharmacoepidemiology in Helping Clinicians Assess Drug Risk

Jerry Avorn, MD

Case Presentation: A 63-year-old accountant with long-standing atrial fibrillation presents for a routine visit. He is asymptomatic and reports complying fairly well with his regimen of warfarin 5 mg/d and atenolol 100 mg/d for rate control. He has had regular international normalized ratio monitoring, with results within the therapeutic range (2.0–3.0) ≈ 75% of the time. His chief complaint is that he has seen television commercials for new oral anticoagulants and wants to know why he is still being prescribed a 59-year-old drug when newer treatments are now available that are probably safer and more effective.

Physical examination revealed a blood pressure of 130/80 mmHg and an irregularly irregular pulse at a rate of 96 bpm; it was otherwise unremarkable. His international normalized ratio was 1.7. On further questioning, he noted that his wife has put him on a kale-rich diet to promote weight loss.

His physician explains that the novel oral anticoagulants (NOACs) performed well in the clinical trials in which they were compared with warfarin but noted that although such drugs have been in use in the United States since October 2010, there is still little information available defining their benefits and risks in typical patient care or directly with each other. The patient observes that such an absence of relevant data would not be tolerated in the corporation for which he works.

Three NOACs have been approved over the last 3 years for the management of atrial fibrillation or deep vein thrombophlebitis: dabigatran (Pradaxa) in 2010, rivaroxaban (Xarelto) in 2011, and apixaban (Eliquis) in 2012. In considering their clinical role as alternatives to warfarin, these drugs illustrate the growing pains, vulnerabilities, and promise of 2 related, younger disciplines: pharmacoepidemiology and pharmacoconomics. This Clinician Update considers the role of pharmacoepidemiology in informing the therapeutic choice presented above; a subsequent article will discuss the drugs from the perspective of pharmacoeconomics.

Pharmacoepidemiology is the discipline that seeks to evaluate the benefits and risks of medications as they are used in routine practice. It draws on observational analysis of the medications taken by large numbers of patients (often in the millions) and the subsequent clinical courses of each of these individuals. The recent growth of the field has been made possible by several factors: the advent of electronic databases describing medication use and clinical events in enormous populations of (anonymized) patients in commercial or public insurance systems, the rapid maturation of powerful computational hardware and software needed to analyze such large volumes of data, and emerging methodological expertise for addressing confounding.

The rising prominence of pharmacoepidemiology has also been driven by growing awareness of the limits of randomized, clinical trials on which initial drug approvals are based. Although a rigorous method for assessing efficacy, randomized clinical trials also have important limitations that...
can compromise their clinical validity and generalizability, as noted in Table 1. These have led to important clinical problems for thousands of patients; some cardiovascular-related examples are presented in Table 2.

The NOAC-warfarin decision represented in the case presentation illustrates both the promise and the growing pains of modern pharmacoepidemiology. Because the only published clinical trials of the NOACs compare each of them with warfarin, no head-to-head studies of the new agents are yet available, allowing only limited indirect comparisons based on the published trials.

In 2007, concerned that the nation had had no mechanism to detect the substantial cardiovascular toxicity of rofecoxib (Vioxx) during its 5 years on the market, Congress instructed the Food and Drug Administration (FDA) to develop a drug safety surveillance Sentinel system. It was to systematically tap into the terabytes of clinical information continuously generated by electronic health records and subject that information to rigorous observational analysis to assess the adverse effects of drugs used in routine practice. The agency was told to develop such a system by 2012 to access data on 100 million Americans. In an impressive organizational and informatics tour de force, that goal was met last year. However, the use of this approach to help clinicians understand the risks and benefits of the NOACs illustrates the challenges the FDA has faced in using that system (which it calls the Mini-Sentinel Pilot Project) to fulfill its mission.

Despite the advent of Sentinel, the FDA still relies heavily on evaluating individual case reports of adverse events submitted spontaneously by clinicians, patients, and manufacturers through its Adverse Event Reporting System. Possible side effects of newer drugs are known to be reported far more frequently than those involving established treatments, so it is not surprising that the FDA received a growing number of reports of patients who bled while taking drugs such as dabigatran, even though its rate of hemorrhage was found to be lower than that for warfarin in the Randomized Evaluation of Long-term Anticoagulant Therapy (RE-LY) randomized trial. The agency alerted clinicians to this high volume of spontaneous case reports in December 2011, causing considerable concern. In an attempt to go beyond the anecdotal, the FDA announced in November 2012 that it had used the Mini-Sentinel Pilot Project to systematically assess the rate of gastrointestinal and intracranial hemorrhage in populations of patients who began taking dabigatran or warfarin through December 2011, a data cutoff date nearly a year earlier. An important worry for clinicians had been that bleeding caused by dabigatran could be more serious because of the absence of an antidote such as is available for warfarin, but the FDA’s analyses considered only the occurrence of these events, not their outcomes (such as death).

In its follow-up advisory announcement, the FDA presented clinicians with only the conclusion: that such bleeding events were 1.8 to 3.0 times more frequent for warfarin than for dabigatran. The underlying data on which this conclusion was based were not initially made available, nor were its confidence intervals. Most important, the agency noted that this analysis was not adjusted for age, sex, or any clinical differences between the patients taking the 2 drugs, even though age and gender are independent risk factors for bleeding with anticoagulant use and the kind of atrial fibrillation patients in whom physicians would start the new drug could well have been different from those in whom they chose to continue using warfarin. If the FDA’s conclusions were correct, beyond exculpating dabigatran from concern over excess bleeding risk, the finding could have been a signal that the newer drug might be up to 3 times safer than warfarin—surely a potentially important finding for physicians and patients. However, the absence of any adjustment for possible confounding and the paucity of actual data made the analysis unsuitable for informing the care of patients such as the case example above.

In February 2013, the FDA released slightly more information. Using the same pre-2012 data set, it produced 3 pages of bar graphs depicting the incidence of both kinds of hemorrhage for each drug, again without controlling for patient age and sex or any clinical differences at baseline. As before, the bar graphs showed markedly higher rates of bleeding with warfarin compared with dabigatran. Tables with data for different strata of age groups were later depicted on 6 additional pages and for sex separately on 6 other tables, but no summary analyses adjusted for both age and sex or for any other potential confounders. A few of these unadjusted

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<tr>
<th>Table 1. Limitations of Randomized Clinical Trials That Can Be Addressed by Follow-Up Pharmacoepidemiological (Observational) Analyses</th>
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<td>Omission or underrepresentation of key populations (complex elderly, pregnant women, children)</td>
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<td>Other inclusion/exclusion criteria</td>
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<td>Limited size</td>
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<td>Atypical physicians, study setting, highly protocoted care</td>
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<td>Short duration (sometimes just 8–16 wk, even for long-term medications)</td>
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<td>Use of a surrogate measure of efficacy</td>
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<td>Comparator may be placebo</td>
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<th>Table 2. Important Medication Problems That Came to Widespread Notice After Marketing</th>
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<td>Medication</td>
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<tr>
<td>Cerevastatin (Baycol)</td>
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<td>Dextenfluramine (Redux)</td>
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<td>Rofecoxib (Vioxx)</td>
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Notice After Marketing

Problems That Came to Widespread Notice After Marketing

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<tr>
<td>Cerevastatin (Baycol)</td>
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<tr>
<td>Dextenfluramine (Redux)</td>
<td>Pulmonary hypertension, valvulopathy</td>
</tr>
<tr>
<td>Rofecoxib (Vioxx)</td>
<td>Nearly doubling of the risk of myocardial infarction or stroke</td>
</tr>
<tr>
<td>Rosiglitazone (Avandia)</td>
<td>Increase in the risk of myocardial infarction</td>
</tr>
<tr>
<td>Ezetemibe (Zetia, Vytorin)</td>
<td>Uncertain clinical effectiveness resulting from the use of a surrogate measure (low-density lipoprotein) for approval</td>
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numbers appeared in a commentary written by 3 FDA scientists in the New England Journal of Medicine in April 2013,12 by then 15 months after the last observational data had been collected. The FDA authors again concluded simply that bleeding rates with dabigatran did not appear to be higher than those seen with warfarin.

For the clinician and patient facing the prescribing choice in the case above, these unadjusted findings are compatible with any of the following possibilities: that dabigatran is far safer than warfarin, that there is no difference in bleeding risk between the 2 drugs, or that dabigatran might have been found to be riskier if the analysis had been done more carefully. Yet, over 2 years since the release of the drug, the FDA’s pharmacoepidemiological analysis as of summer 2013 allowed only 1 conclusion for clinicians, familiar to all medical test takers: “Not enough information is provided to answer the question.” This is surprising, given the enormous analytic potential of the Sentinel system and the epidemiological expertise available to the FDA from around the country, which was apparently not fully tapped for these analyses. In fact, the Sentinel project already has in place a simple computer program to adjust for age and sex. (Such an automated approach was described by Rothman and Boice in 197413 and the underlying epidemiological approach by Farr in 1839.14) Additional automated approaches to address other potential clinical confounders have also been developed for potential use in such large-scale surveillance data sets.15

If the patients in the Sentinel observational datasets who were prescribed dabigatran were younger or less likely to be female compared to those who were prescribed warfarin, an analysis unadjusted for age or gender could make dabigatran appear to be safer than it is, a finding that would be useless or misleading. Review of the FDA’s own data on age and sex originally posted on the Mini-Sentinel website in February 2013 reveals that this is indeed the case. Its summary analyses were re-issued and labeled as “complete” in May 2013, still without integrating this basic demographic information.15

Further analyses are ongoing within the Sentinel system, but it is unclear when they will be completed. Additional studies are also being conducted by other researchers using other databases, including our own group. Through 1 or more of these sources, pharmacoepidemiological investigations will no doubt produce vital information for clinicians in the coming months to address this question. Given the low likelihood of a very large randomized, controlled trial of routine care testing the NOACs against warfarin and against each other, such future pharmacoepidemiological data are likely to be the only source of this information for some time to come. When those more rigorous observational studies are published, the NOAC-warfarin bleeding question will need not doubt become a case study of the clinical utility of this discipline in quantifying the actual risks and benefits of medications as used in typical practice.

This clinical question arises at a pivotal time in the evolution of post-approval drug safety surveillance. Enormous databases of real-world medication use are growing, and computational and methodological techniques are poised to use them to provide nearly real-time data on medication outcomes. The systems envisioned in the 2007 post-Vioxx legislation have been impressively constructed and put in place, even if their full activation by regulatory authorities has lagged. The good news is that with the growing ubiquity of such data, hardware, and expertise, groups around the world will be able to address this and related questions with rigor and efficiency in a variety of settings and systems, whether through regulatory authorities or independently of them.16 At the same time, the new Patient Centered Outcomes Research Institute plans to accelerate the funding of pharmacoepidemiological methods to assess drug risks and benefits in ways that can substantially supplement the information available from preapproval trials, even if the comparative effectiveness aspect of its work has gotten off to a slow start.17,18

Case Conclusion: Despite the enormous potential of pharmacoepidemiological methods and the Sentinel system to address precisely these issues, 2½ years after the introduction of the first NOAC to treat atrial fibrillation, the patient’s physician was not able to answer the question, “In routine use, is dabigatran safer or more efficacious than warfarin?” As a result, both patient and physician elected to follow the American College of Cardiology/American Heart Association recommendation that patients with atrial fibrillation who are reasonably well controlled on warfarin need not change therapy.19 The physician also recommended that the patient use kale in moderation.

As the tools of pharmacoepidemiology are applied more effectively and rigorously in the coming years in both the academic and public sectors, it is likely that clinicians and their patients will not have to wait so long to determine whether such a decision was correct.

Disclosures
In 2012, the author spent 20 hours as a member of the Sentinel Safety Science Committee advising about statistical issues concerning the reuse of data from large data sets in multiple analyses. A small payment (under $3000) was provided by the Harvard Pilgrim HealthCare Institute to the Brigham and Women’s Hospital for this work, representing about 1% of his salary. The author received no other support for this work. He accepts no personal compensation of any kind from any pharmaceutical manufacturer. Other faculty members in the author’s division receive support to study the safety of dabigatran from the Food and Drug Administration and from Boehringer-Ingelheim, but he is not involved in any of this work and receives no funding from it.

References

 supplementary


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