Dabigatran and Postmarketing Reports of Bleeding

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In the months following the approval of the oral anticoagulant dabigatran (Pradaxa, Boehringer Ingelheim) in October 2010, the Food and Drug Administration (FDA) received through the FDA Adverse Event Reporting System (FAERS) many reports of serious and fatal bleeding events associated with use of the drug. Because dabigatran is an anticoagulant, reports of bleeding were anticipated, but the rate of reported incidents was unusually high and was greater than the concurrent rate of reported bleeding incidents with warfarin, which had been the anticoagulant of choice for nearly 60 years before dabigatran was approved. In contrast, the controlled trial that supported the approval of dabigatran (Randomized Evaluation of Long-Term Anticoagulation Therapy [RE-LY]), which compared warfarin with dabigatran in patients with nonvalvular atrial fibrillation,[1] showed that the two drugs conferred a similar risk of bleeding.

The postmarketing reports of bleeding with dabigatran led to discussions in medical publications as well as the mainstream media about the agency's approval of the drug. Many of these discussions cited the large numbers of reports of bleeding events in FAERS as a reason to question the benefit–risk profile of dabigatran as described in its labeling. But important factors that could have affected reporting rates, such as the novelty of dabigatran (relative to the well-established warfarin) and the coverage of novel drugs in the media, which can greatly influence how and when adverse events are reported, were not generally considered.

The RE-LY trial enrolled patients with nonvalvular atrial fibrillation and at least one risk factor for stroke. Dabigatran at a dose of 150 mg twice daily was shown to be superior to warfarin for reducing the combined rate of stroke and systemic embolism (1.1 vs. 1.7 per 100 patient-years) among these patients. Dabigatran resulted in a lower rate of both thrombotic and hemorrhagic strokes than warfarin, and the mortality rate was lower in the dabigatran group than in the warfarin group (3.6 vs. 4.1 per 100 patient-years). The level of the primary risk, bleeding, was similar among the patients who received dabigatran at a dose of 150 mg and those who received warfarin (for major bleeding, the rates were 3.3 and 3.6 per 100 patient-years, respectively). (Major bleeding in the RE-LY study was defined as a reduction in hemoglobin concentration of at least 2 g per deciliter, the need to transfuse at least 2 units of blood or packed cells, or symptomatic bleeding in a critical area or organ.) Although major gastrointestinal bleeding events were more frequent in the dabigatran group than in the warfarin group (1.6 vs. 1.1 per 100 patient-years), the rate of intracranial bleeding events was lower for dabigatran than for warfarin (0.3 vs. 0.8 per 100 patient-years). The superiority of dabigatran (at the 150-mg dose) over warfarin for reducing the rates of stroke and systemic embolism with a similar rate of clinically significant bleeding led to FDA approval of dabigatran.

Because the RE-LY trial had clearly shown that bleeding was a serious side effect of dabigatran, it was expected that bleeding events would be reported after the product was approved, but the number of reports was sufficiently high to prompt the FDA to initiate a review of the spontaneous reports received by FAERS. We were concerned that postmarketing use of dabigatran might be different from its use in the RE-LY trial (e.g., different patient populations, dosing, concomitant medications, and degree of renal impairment) or that adjustments for renal function had not been made correctly.

As is often the case with spontaneous reports, the reports of bleeding generally did not include information on patients' risk factors, age, renal function, or cause of death. In a small number of cases, the dabigatran dose had not been reduced for a patient who had impaired renal function. Overall, however, the case review did not identify any unrecognized risk factors for bleeding, and there was generally no indication that dabigatran was not being used in accordance with its labeled directions.

Consequently, we considered the possibility that the unexpectedly high rate of reported bleeding events in patients who had received dabigatran might have reflected a greater likelihood of reporting a bleeding event in a patient receiving dabigatran than in one receiving warfarin — a tendency driven by awareness due to published case reports and safety communications from regulatory authorities outside the United States and by the fact that dabigatran was new to the market. We know that publications about an adverse event or legal activity involving a drug can increase reporting rates. We also know that newly

Intracranial and Gastrointestinal Bleeding Events in New Users of Dabigatran and Warfarin from the Mini-Sentinel Distributed Database, October 2010 through December 2011.*

Analysis	Dabigatran			Warfarin		
	No. of Patients	No. of Events	Incidence (no. of events/ 100,000 days at risk)	No. of Patients	No. of Events	Incidence (no. of events/ 100,000 days at risk)
Gastrointestinal hemorrhage						
Analysis with required diagnosis of atrial fibrillation	10,599	16	1.6	43,541	160	3.5
Sensitivity analysis without required diagnosis of atrial fibrillation	12,195	19	1.6	119,940	338	3.1
Intracranial hemorrhage						
Analysis with required diagnosis of atrial fibrillation	10,587	8	0.8	43,594	109	2.4
Sensitivity analysis without required diagnosis of atrial fibrillation	12,182	10	0.9	120,020	204	1.9

* Patients were included in the cohorts if, in the 183 days before the index dispensing of dabigatran or warfarin, they were enrolled in plans for drug and medical coverage and had been given a diagnosis of atrial fibrillation in any care setting. Patients were excluded from the cohorts if, in the 183 days before the index dispensing, they had a claim for an event of interest in an inpatient or emergency department setting or a claim for dispensing of dabigatran or warfarin. Events were assessed during drug exposure, from inpatient or emergency department settings only.

marketed products, by virtue of their novelty alone, may elicit adverse-event reports at high rates; reporting rates tend to decrease over time (the Weber effect[2]). Thus, warfarin, having been marketed for almost 60 years and being well known to cause bleeding, would be far less likely to elicit adverse-event reports than would a newer drug with a similar risk. Although the agency thought it most likely that the unexpectedly high number of reports of bleeding associated with dabigatran was the result of these factors, we issued a drug-safety communication in December 2011[3] to convey the information on bleeding to health care practitioners and patients, in accordance with standard FDA practice.

Clearly, the FDA's mission of providing meaningful pharmacovigilance must be informed by an understanding of multiple factors, many of which may be unrelated to pharmacology per se but nevertheless affect postmarketing reporting of adverse events. In the case of dabigatran, we sought to determine whether the large number of bleeding reports reflected a true increased bleeding risk relative to warfarin in the postmarketing setting. We compared bleeding rates for dabigatran and warfarin using insurance-claim data and administrative data from the FDA Mini-Sentinel database, a pilot program of the Sentinel Initiative.[4] This database enables estimation of the incidence rates for bleeding diagnoses and drug use within chosen populations. We queried the database for the period from October 19, 2010 (the date of dabigatran approval), to December 31, 2011, to identify inpatient diagnosis codes for intracranial and gastrointestinal hemorrhages associated with new use of dabigatran or warfarin (see table). We found that bleeding rates associated with dabigatran use during the period of interest did not appear to be higher than those associated with warfarin.

There are limitations to the Mini-Sentinel analysis, including lack of adjustment for confounding variables and lack of a detailed medical record review (to verify whether the claim code reflected an actual bleeding occurrence). To address some of these limitations, we are now conducting two protocol-based assessments, using claims data from Mini-Sentinel and other claims databases, in which adjustments will be made for confounding factors.

We believe that the large number of reported cases of bleeding associated with dabigatran provides a salient example of stimulated reporting. In this case, such reporting provided a distorted estimate of the comparative bleeding rates associated with dabigatran and warfarin in clinical practice. The Mini-Sentinel assessment suggests that bleeding rates associated with dabigatran are not higher than those with warfarin, a finding that is consistent with the results of RE-LY.

Although some have noted the lack of an available reversal agent for the anticoagulant effects of dabigatran as an important limitation of its use, data from RE-LY are reassuring with respect to bleeding. We believe that dabigatran provides an important health benefit when used as directed.

Further analysis of the Mini-Sentinel and other claims databases is ongoing, as is routine postmarketing surveillance through FAERS.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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HISTORY OF MEDICINE

Something New under the Sun? The Mediterranean Diet and Cardiovascular Health

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Related article, p. 1279

Increasingly, the Mediterranean diet has become the standard for healthy eating. Adherence to it appears to reduce the risk of cardiovascular disease, cancer, Alzheimer's disease, and Parkinson's disease, as well as the risk of death due to cardiovascular disease or cancer and even premature death overall.[1] Largely plant-centered, with high intakes of olive oil, fruit, nuts, and whole-grain cereals, moderate consumption of fish and poultry, low intakes of dairy, red meat, and sweets, and often moderate drinking of red wine, the "classic" Mediterranean diet is younger than the region's history suggests. In fact, this dietary pattern was first observed in Greece, Italy, and Spain in the decade after World War II — an artifact of postwar impoverishment that proved beneficial to health. Unfortunately, it is currently under siege in southern Europe from the globalization of fast foods rich in refined carbohydrates, sweets, and red meat.

In this issue of the *Journal*, Estruch et al. (pages 1279–1290) report the positive results of PREDIMED (Prevención con Dieta Mediterránea), a randomized trial of the Mediterranean diet (supplemented with either extra-virgin olive oil or nuts) for the primary prevention of cardiovascular events. The data are impressive and seem to support the high ranking of the Mediterranean diet and its constituent foods among various cardioprotective vegetable- and fruit-rich regimens, such as DASH (Dietary Approaches to Stop Hypertension) and Japanese and traditional vegetarian diets. Yet in many ways, that is old news. The history of dietary guidelines for heart health — a project begun in the 1950s when the United States felt threatened by a perceived "epidemic" of heart attacks — reveals that the Mediterranean diet's cardiovascular benefits have been recognized for decades. As early as 1948, the Rockefeller Foundation assessed the health, economic, and social status of Cretan Greeks and noted that their "impoverished" diet was rich in cereal grains, legumes, wild greens and herbs, and fruits, paired with limited meat, milk, and fish. Meals were said to be "swimming" in olive oil and prepared simply in ways that "preserved the nutritive value of the food rather well."[2]

The first epidemiologic data supporting the Mediterranean diet came from the Seven Countries Study (SCS), a prospective investigation of diet and other cardiovascular-disease risk factors in 16 cohorts totaling nearly 13,000 men in the United States, Italy, Greece, Yugoslavia, Finland, the Netherlands, and Japan, which began in 1958. The PREDIMED results would come as little surprise to the man behind the SCS, American physiologist and epidemiologist Ancel Keys, who advanced the low-fat diet and the low-saturated-fat Mediterranean diet for the primary and secondary prevention of heart disease. Keys "discovered" the Mediterranean diet's health benefits in the early 1950s, when visiting the region as a medical scientist concerned about the widely reported increase in heart attacks in the United States. After spending several years exploring the dietary patterns and cardiovascular status of men in Italy, Spain, and Crete, Keys launched the SCS. Study data (which are still being collected from elderly "survivors") offered strong population-level support for the effects of dietary fat and fatty acids on serum cholesterol levels and cardiovascular disease risk.

The still-unfolding story of dietary fat has proven more complicated than Keys envisioned, but his observations about dietary pat-