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Safety of Direct Oral Anticoagulants: Insights from Postmarketing Studies

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ABSTRACT

Direct oral anticoagulants (DOACs) have been marketed in the United States since 2010. While numerous large-scale prospective phase 3 outcomes studies have documented the effectiveness of DOACs for the prevention of stroke and systemic embolism in patients with nonvalvular atrial fibrillation, the primary safety concern with all of these drugs—as it is with the more established oral anticoagulant warfarin—is the risk of major bleeding. Postmarketing surveillance studies (PMSS) provide the opportunity to evaluate the safety of these recently approved drugs across a spectrum of patients that may be broader than those included in randomized controlled trials. This review will summarize the safety findings of numerous recently performed, large-scale PMSS evaluations, and consider the currently available evidence regarding the risks for bleeding in patients treated with DOACs, in order to give providers and patients additional evidence regarding the safety of DOACs.

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Direct oral anticoagulants (DOACs) have been marketed in the United States since 2010, when the U.S. Food and Drug Administration (FDA) approved the direct thrombin inhibitor dabigatran etexilate for prevention of stroke and systemic embolism in patients with nonvalvular atrial fibrillation (NVAF).[1] The oral direct factor Xa (FXa) inhibitors rivaroxaban and apixaban were subsequently approved for treatment and prevention of deep vein thrombosis (DVT) and pulmonary embolism (PE) (including in patients who have undergone hip or knee replacement surgery) and for reduction in risk of stroke and systemic embolism in patients with NVAF.[2,3] Dabigatran was also approved for treatment and prevention of DVT and PE and for the prophylaxis of DVT and PE in patients who have undergone hip replacement surgery.[1] Additionally, the FXa inhibitor edoxaban has been approved in the United States to reduce the risk of stroke and systemic embolism in patients with NVAF and for the treatment of DVT and PE.[4]

The primary safety concern with all of these drugs—as it is with the older, more established oral anticoagulant warfarin—is the risk of bleeding as a complication of deliberate anticoagulation aimed at preventing pathologic thrombosis. Although statistically rare, an intracranial hemorrhage (ICH) is the most feared adverse event associated with all oral anticoagulants because of its devastating clinical sequelae and high rate of mortality. Anticoagulant-associated gastrointestinal hemorrhages are more common, but are less often likely to be fatal adverse events.

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In recent years, researchers have reported the findings of postmarketing surveillance studies (PMSS) of adverse events associated with the DOACs. These studies followed the publication of randomized controlled trials (RCTs) that established the foundational evidence for the comparative safety and efficacy of DOACs vs warfarin and formed the basis for FDA approval.[5-7] Postmarketing surveillance may take the form of independent studies, evaluations performed by regulators, or as part of phase 4 research performed by the drug manufacturers. These studies are observational in nature. Postmarketing surveillance is typically conducted in retrospect from large databases (eg, those maintained by Medicare, the FDA Adverse Event Reporting System [FAERS], private health-maintenance organizations, health benefits provider roles, health insurance company), or obtained from ongoing prospective registries (eg, Global Registry on Long-Term Oral Antithrombotic Treatment in Patients with Atrial Fibrillation [GLORIA-AF][8] or Global Anticoagulant Registry in the FIELD-Atrial Fibrillation [GARFIELD][9] for patients with NVAF).

Postmarketing research, therefore, attempts to assess the effectiveness and safety of the drug in a "real-world" setting that is representative of how it is being prescribed and used in clinical practice.[10,11] The most common methodology in these studies utilizes International Classification of Diseases (ICD) coding data to identify patients, determine baseline demographics and clinical characteristics, and assess outcomes or parameters of interest. The positive predictive value of using ICD-9 and ICD-10 codes for identification of patients with strokes has been validated at 80% to 97%.[12,13] Validation studies have also demonstrated good positive predictive values with these codes for identifying the presence and location of GI bleeding.[14] Because ICD-10 for inpatient hospital procedures was recently adopted in the United States, published studies are based on ICD-9 coding.

Study cohorts in PMSS are not randomized, but researchers may control for differences in patient characteristics by using multivariable modeling or propensity score matching. Observational research, such as PMSS, has inherent limitations because of its uncontrolled, nonrandomized nature. The compared populations are potentially subject to confounding factors that may have been excluded in RCTs. Modeling or propensity score matching can reduce or eliminate these factors, but some residual confounding variables may remain. As a consequence of potential for bias, the assessment of effectiveness—while performed and reported—should be interpreted with caution.

These studies may consider treatment in larger and more variable populations over greater periods of time than would be feasible in a phase 3 RCT, and thus have the potential to reveal more rare adverse events or provide more information about anticipated adverse event rates. Postmarketing research may also provide information on parameters that RCTs are unable to evaluate due to ethical considerations (eg, time delay to treatment or the management of rare intentional overdoses). In addition, PMSS can provide information about the treatment of patients who would be excluded from RCTs or complex therapeutic scenarios (eg, multiple conflicting comorbidities, extremes of age/body habitus, or lifestyle consequences related to complications of the drug in question).

PUBLISHED STUDIES

Dabigatran

As the first FDA-approved DOAC, dabigatran has been the most frequent subject of PMSS (a PubMed literature search in October 2015 found 21 completed observational studies with dabigatran and 10 with rivaroxaban) in this therapeutic area. Since the drug was introduced in 2010, several observational studies have provided insights into the risk of bleeding in patients treated with dabigatran vs the vitamin K antagonist (VKA) warfarin (**Table**).[1,5-7,15-20] The findings of these studies have been broadly consistent with the results of the Randomized Evaluation of Long-term anticoagulation therapY (RE-LY) trial, which compared dabigatran with warfarin in patients with NVAF.[5]

To date, the U.S. Medicare study reported by Graham et al[1] evaluated the largest cohort of patients taking dabigatran. These researchers compared bleeding risk in a propensity score matching population of patients with NVAF who were naïve to anticoagulation and were prescribed either warfarin or dabigatran etexilate (n = 67,207 in each group). In the Medicare cohort, the risk for major bleeding with dabigatran was similar to warfarin (adjusted hazard ratio [HR] 0.97; 95% confidence interval [CI], 0.88-1.07). Risk for ICH was significantly reduced with dabigatran (HR 0.34; 95% CI, 0.26-0.46), but risk for major GI bleeding was increased (HR 1.28; 95% CI, 1.14-1.44). The risk of GI bleeding was highest in women aged 75-84 years (HR 1.50; 95% CI, 1.20-1.88) and in men and women ≥85 years (HR 1.55; 95% CI, 1.04-2.32) and (HR 2.18; 95% CI, 1.61-2.97), respectively. There was no difference in the rate of acute myocardial infarction between the groups (HR 0.92; 95% CI, 0.78-1.08).

Several additional studies assessed safety outcomes of dabigatran as compared with warfarin users among patients with NVAF in the U.S. Department of Defense database,[3] in 2 privately administered U.S. patient databases,[16] and in a Danish national database (**Table**).[17,21] These studies reported similar findings as compared with the Medicare analysis, extending PMSS data to non-Medicare patient cohorts. These authors also found no increased risk of myocardial infarction among dabigatran users vs patients taking warfarin. In addition to these studies, researchers for the FDA published a postmarketing bleed comparison using data from the FAERS for the first year that dabigatran was available.[22] Their data showed that despite initial concerns about bleeding adverse events with dabigatran, incidence rates were not higher than concurrent incidence rates with warfarin.

Rivaroxaban

Postmarketing data for the FXa inhibitors (rivaroxaban and apixaban) have also been published. Two noncomparative