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.

KEYWORDS: Direct oral anticoagulants; DOACs; Nonvalvular atrial fibrillation; Postmarketing studies; Safety

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). 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. Dabigatran was also approved for treatment and prevention of DVT and PE for the prophylaxis of DVT and PE in patients who have undergone hip replacement surgery. 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.

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.
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. 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] or Global Anticoagulant Registry in the FIELD-Atrial Fibrillation [GARFIELD] 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. 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%. Validation studies have also demonstrated good positive predictive values with these codes for identifying the presence and location of GI bleeding. 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). 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.

To date, the U.S. Medicare study reported by Graham et al 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, in 2 privately administered U.S. patient databases, and in a Danish national database (Table). 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. 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
### Table: Bleeding and Myocardial Infarction Risk with DOACs vs Warfarin Given for Stroke Prevention in Atrial Fibrillation in RCTs and Large-Scale Observational Studies (Hazard Ratios and Relative Risks are Adjusted Unless Indicated)

<table>
<thead>
<tr>
<th>Study</th>
<th>Mean Age</th>
<th>Follow-Up</th>
<th>Adjustment</th>
<th>Major Bleeding Risk (95% CI)</th>
<th>Intracranial Bleeding Risk (95% CI)</th>
<th>GI Bleeding Risk (95% CI)</th>
<th>Myocardial Infarction Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran etexilate</td>
<td>71 y</td>
<td>Median 2.0 y</td>
<td>Cox proportional-hazards models</td>
<td>RR 0.93 (0.81-1.07)</td>
<td>RR 0.40 (0.27-0.60)</td>
<td>RR 1.50 (1.19-1.89)</td>
<td>RR 1.38 (1.00-1.91)</td>
</tr>
<tr>
<td>RE-LY5,* (150 mg BID)</td>
<td>&gt;65 y</td>
<td>Total 37,587 patient-years</td>
<td>PSM</td>
<td>HR 0.97 (0.88-1.07)</td>
<td>HR 0.34 (0.26-0.46)</td>
<td>HR 1.28 (1.14-1.44)</td>
<td>HR 0.92 (0.78-1.08)</td>
</tr>
<tr>
<td>U.S. Medicare1</td>
<td>74 y</td>
<td>Mean 297 ± 259 d</td>
<td>PSM</td>
<td>HR 0.87 (0.74-1.03)</td>
<td>Unadjusted HR 0.49† (0.30-0.79)</td>
<td>Unadjusted HR 1.13† (0.94-1.37)</td>
<td>Unadjusted HR 0.65† (0.45-0.95)</td>
</tr>
<tr>
<td>U.S. Department of Defense15 (75 mg and 150 mg)</td>
<td>68 y</td>
<td>Mean 5 mo</td>
<td>PSM</td>
<td>HR 0.75 (0.65-0.87)</td>
<td>HR 0.31 (0.17-0.54)</td>
<td>HR 0.97 (0.79-1.18)</td>
<td>HR 0.89 (0.57-1.38)</td>
</tr>
<tr>
<td>MarketScan/Clinformatics16 (dose not specified)</td>
<td>71 y</td>
<td>Median 10.5 mo‡</td>
<td>PSM</td>
<td>HR 0.66 (0.36-1.14)</td>
<td>HR 0.08 (0.01; 0.40)</td>
<td>HR 1.12 (0.67-1.83)</td>
<td>HR 0.40 (0.21-0.70)</td>
</tr>
<tr>
<td>Danish Registry of Medicinal Product Statistics17 (150 mg)</td>
<td>Median 73 y</td>
<td>Median 707 d</td>
<td>Cox proportional-hazards models</td>
<td>HR 1.04 (0.90-1.20)</td>
<td>HR 0.67 (0.47-0.93)</td>
<td>RR 1.46 P &lt; .001†</td>
<td>HR 0.81 (0.63-1.06)</td>
</tr>
<tr>
<td>Rivaroxaban 20 mg QD</td>
<td>78 y</td>
<td>Total 455 d</td>
<td>None</td>
<td>IR 2.86 (2.61-3.13)</td>
<td>IR 0.22 (0.15-0.30)</td>
<td>IR 2.53 (2.30-2.78)</td>
<td>NR</td>
</tr>
<tr>
<td>ROCKET AF6,*</td>
<td>78 y</td>
<td>Total 2 y</td>
<td>None</td>
<td>IR 2.89 (2.71-3.08)§ Incidence 0.2% (79 of 39,052)</td>
<td>Incidence 2.2% (846 of 39,052)</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Apixaban 5 mg BID</td>
<td>70 y</td>
<td>Median 1.8 y</td>
<td>Cox proportional-hazards models</td>
<td>HR 0.69 (0.60-0.80)</td>
<td>HR 0.42 (0.30-0.58)</td>
<td>HR 0.89 (0.70-1.15)</td>
<td>HR 0.88 (0.66-1.17)</td>
</tr>
<tr>
<td>ARISTOTLE7,*</td>
<td>Median 707 d</td>
<td>Total 180 d</td>
<td>Cox proportional-hazards models</td>
<td>HR 0.75 (0.63-0.88)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

**Notes:**
- RE-LY = Randomized Evaluation of Long-term anticoagulation therapy
- ROCKET AF = Rivaroxaban Once daily oral direct factor Xa inhibition Compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation
- ARISTOTLE = Apixaban for Reduction In StROKE and Other Thromboembolic Events in Atrial Fibrillation

*These studies are phase 3 RCTs in patients with NVAF.
†Following propensity score matching, the unadjusted and adjusted hazard ratios were almost all identical. For secondary bleeding end points, unadjusted hazard ratios were reported.
‡Median follow-up includes 110-mg and 150-mg patients.
§No warfarin group.
††IRR was calculated from data reported in the primary publication.
studies have assessed rivaroxaban using the U.S. Department of Defense database (Table). Tamayo et al performed a noncomparative pharmacovigilance study of records for 27,467 patients with NVAF taking rivaroxaban. They observed an incidence rate for major bleeding of 2.86 (95% CI, 2.61-3.13) per 100 person-years, and for fatal bleeding events of 0.08 (95% CI, 0.05-0.14) per 100 person-years. Overall, of the bleeding population, the vast majority of bleeding events were GI (88.5%), and fatalities were rare in this cohort. Conversely, the ICH rate was very low (36 of 478 major bleeding cases), but 50% of all fatalities in the study were recorded in patients with ICH. A subsequent postmarketing assessment of 39,052 NVAF patients on rivaroxaban confirmed these findings, reporting an incidence rate for major bleeding of 2.89 (95% CI, 2.71-3.08) per 100 person-years. The most common site for major bleeding was GI (87.2%). Intracranial bleeds made up 8.1% of the overall incidence. These findings show that “real-world” routine clinical care is consistent with the safety profile observed in the Rivaroxaban Once daily oral direct factor Xa inhibition Compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF). 

Apixaban
To date, we have one preliminary report of “real-world” use of apixaban in comparison with warfarin. Using records of patients with NVAF (2038 on apixaban and 24,872 on warfarin) from a Humedica (Boston, Mass.) medical record database, the investigators found a higher rate of bleeds with warfarin than with apixaban (HR 1.34; 95% CI, 1.13-1.58).

All DOACs
Recently a group of researchers presented abstracts at the 2015 European Society of Cardiology meeting from 3 observational studies comparing bleeding outcomes with apixaban vs dabigatran, rivaroxaban, or warfarin. In the first, using data from the MarketScan Early View health insurance claims database, they evaluated major bleeding in 60,277 patients with NVAF (n = 8785 apixaban, n = 20,963 dabigatran, and n = 30,529 rivaroxaban). They reported that rivaroxaban increased the risk for major bleeding (adjusted HR 1.36; 95% CI, 1.23-1.52) compared with apixaban, while dabigatran had a risk similar to that of apixaban for major bleeding (adjusted HR 0.99; 95% CI, 0.88-1.10). Similar findings were reported in the other 2 abstracts concerning patients with NVAF who newly initiated oral anticoagulant therapy. Comparing Cox proportional-hazards model adjusted HRs for inpatient and outpatient bleeding events, they found increased risk with warfarin or rivaroxaban compared with apixaban (adjusted HRs: warfarin 1.62; 95% CI, 1.20-2.18; rivaroxaban 1.70; 95% CI, 1.26-2.29), but not with dabigatran compared with apixaban (adjusted HR 1.28; 95% CI, 0.92-1.79).

In a study of patients in the Cerner Health Facts hospital database, Deitelzweig et al compared rates of bleeding-related hospitalization readmissions among those previously hospitalized for NVAF and treated with apixaban, dabigatran, or rivaroxaban. After adjusting for baseline differences in stroke and bleeding risks, they found increased risk of bleeding-related 30-day hospitalizations with rivaroxaban vs apixaban (OR 1.6; P = .04) but no differences with dabigatran vs apixaban (OR 1.3; P = .30). Analyses of all-cause hospitalization, length of all-cause hospital stay, and costs related to all-cause hospitalization also showed apixaban to be better than rivaroxaban and comparable to dabigatran.

DISCUSSION
Randomized and controlled clinical trials with DOACs established their efficacy and safety, and provided the basis for FDA approval for the prevention of stroke and systemic embolism in patients with NVAF and for the prevention or treatment of VTE. In the years since these drugs became available to health-care providers and their patients, observational studies with data involving more than 250,000 patients have provided additional information on safety end points, particularly bleeding—an adverse effect of all anticoagulation agents.

The primary advantage of postmarketing surveillance is that it provides information not available in RCTs. Randomized trials generally represent a small segment of the overall population, one that is selected based on precise entry and exclusion criteria. These trials are performed in a cohort that excludes patients likely to be noncompliant, the terminally ill, and those with advanced age or suffering multiple comorbidities. Furthermore, PMSS analyses allow the evaluation of physician bias in selecting the intervention population. As physicians commonly opt to treat only the lowest-risk patients when there are perceived therapeutic risks, the PMSS study methodology thus allows the evaluation of any potential alterations in a drug’s risk-to-benefit relationship that may occur as a result.

The primary limitation of all PMSS is their retrospective nature and their (typically) relatively short duration of follow-up when considering the currently available data involving DOACs. The currently available PMSS are limited in that efficacy and safety outcomes have been evaluated over mean follow-up durations of <1 year and are not designed to select comparable groups at treatment onset. Warfarin patients, for example, may have substantial clinical and demographic differences in comparison with patients treated with the DOACs. Sophisticated statistical modeling techniques can attempt to adjust for baseline differences in order to (hopefully) approximate the effects of randomization in cohort preparation, but the risk of residual confounding always persists. The strength of PMSS data is that they are based on large cohorts using well-established coding extraction methods from reliable data sources. They constitute evidence from “real-world” prescribing and
use, and they may be performed independently of the drug makers (eg, the FDA dabigatran Medicare study). As such, PMSS data function as a “real-world” effectiveness translation of the efficacy and safety results of RCTs.

Findings from PMSS with DOACs have, in general, supported the findings of the phase 3 clinical trials that provided evidence of their efficacy and tolerability for regulatory agencies. The potential for uncontrolled bleeding has long been a concern with warfarin (especially when taken with certain drugs or food), and similar concerns arose at the onset of the availability of the first DOAC, dabigatran. However, surveillance of the FAERS database demonstrated no differences in reported bleeding during the first year of availability of dabigatran.

That assurance was borne out in the Medicare and Department of Defense studies that confirmed the initial safety evidence of dabigatran in the RE-LY trial. More recently, additional PMSS have provided clarification of bleeding risks for rivaroxaban and apixaban. Pharmacovigilance studies with rivaroxaban found similar rates of bleeding to the FDA registration ROCKET AF trial. Importantly, these studies confirmed that the vast majority of major bleeding with rivaroxaban was GI rather than intracranial in location. Recently, PMSS data comparing apixaban with warfarin or other DOACs have provided further insights.

An interim analysis of the GLORIA-AF patient registry has shown that the introduction of DOACs has influenced patient treatment patterns, with a substantial increase in appropriate anticoagulation among patients compared with a prior evaluation. The GLORIA-AF (N = 56,000) data show that DOACs are already more commonly prescribed than warfarin in newly diagnosed patients with NVAF. In North America in 2015, overall OAC use was distributed as follows: VKA 26.1%, dabigatran 25%, rivaroxaban 20.5%, and apixaban 6.6%. When all DOACs are grouped, they represent more than half of all antithrombotic prescriptions—including antiplatelet agents or aspirin.

Investigators researching the GARFIELD registry database (N = 17,184) recently confirmed suboptimal thromboprophylaxis with oral anticoagulants by both female and male patients with newly diagnosed NVAF, and observed that perceived bleeding risk was the main reason for not giving VKAs (female, 14.7%; male, 17.8%). However, just 1.9% of either female or male patients cited a previous bleeding incident.

In addition to GLORIA-AF, GARFIELD, and the RE-LY AF Registry, thromboprophylaxis for patients with NVAF is being prospectively evaluated in ongoing registry studies, including the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF) registry study and the Euro Heart Survey on Atrial Fibrillation. Findings from these studies will provide enhanced information on the incorporation of DOACs into the atrial fibrillation and VTE therapeutic regimens. Robust PMSS evaluations of DOACs used for the prevention of VTE are also needed to further understand the safety of these agents.

CONCLUSION
Data from PMSS evaluations of DOACs provide assurance that the risks associated with their use are manageable and in line with the results seen in RCTs. As expected, overall risks for major bleeding are similar to warfarin, although the risk for intracranial hemorrhage is significantly reduced, and risk for GI hemorrhage slightly increased. While all instances of major bleeding are a concern, oral anticoagulation therapy is aimed at preventing potentially debilitating or fatal thromboembolic events. The risks of bleeding must be balanced against the benefits of reduced risk for stroke or venous thromboembolism.

References


