Evaluating Appropriate Dosing of Direct Oral Anticoagulants in a Family Medicine Practice

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Abstract

Objective: To determine if patients are prescribed appropriate doses of direct oral anticoagulants (DOACs) in a large, family medicine, teaching practice.

Methods: This study was an institutional review board approved retrospective chart review. Patients 18 or older who were prescribed dabigatran, rivaroxaban, apixaban, or edoxaban were included. Patients were excluded if these agents were prescribed by outside providers, actively monitored elsewhere, or cared for in a skilled nursing facility. Appropriate doses were determined based on manufacturer prescribing information. The primary outcome was the percentage of patients prescribed inappropriate doses of DOACs. Secondary outcomes included reasons for inappropriate dosing, percentage of patients taking appropriate doses but were borderline for dose change, and number of patients taking interacting medications.

Results: Sixty-four patients taking DOACs met inclusion criteria: 9 taking dabigatran, 37 taking rivaroxaban, 18 taking apixaban, and none taking edoxaban. Fifteen of 64 patients (23%) were found to be on incorrect doses. Of patients taking appropriate doses, 15 of 49 (31%) were considered borderline for dose change. One of 64 patients was found to be taking interacting medications.

Conclusion: DOAC use was suboptimal when prescribed within our family medicine practice. Efforts to improve safe use of these medications are warranted.

Keywords: direct oral anticoagulant, target-specific oral anticoagulant, novel oral anticoagulant, monitoring

Introduction

The use of direct oral anticoagulants (DOACs) has steadily increased in recent years as an alternative to warfarin for multiple indications. Use of these medications, dabigatran, rivaroxaban, apixaban, and edoxaban, continues to grow due to the convenience of lack of anticoagulation monitoring. However, the need for management of these high risk medications, including but not limited to regular monitoring of renal function, liver function, bleeding, adherence and adverse events, has been recognized by several national organizations. The Institute of Safe Medication Practices (ISMP) issued a medication safety alert for DOACs in 2012 due to reports of higher incidence of hemorrhagic death from dabigatran and rivaroxaban compared with warfarin. Conversely, the ISMP also reported higher incidence of thromboembolic events with rivaroxaban compared to dabigatran, the only other DOAC marketed at the time, when used for prophylaxis in orthopedic surgery. Additionally, the Joint Commission has recognized the need for safe use of these medications with National Patient Safety Goal 03.05.01, which aims to “reduce the likelihood of patient harm associated with the use of anticoagulant therapy.” Internationally, the European Heart Rhythm Association (EHRA) developed a practical guide to DOAC monitoring in 2013 and numerous Canadian health care groups collectively endorsed ongoing active management of DOACs in 2015.

Several studies have demonstrated that establishing regular monitoring and follow-up for patients taking these medications improves patient adherence, appropriate dosing, and promotes cost-savings. However, there are currently no consensus guidelines for management of these drugs in

the United States. The purpose of this study was to establish a baseline in prescribing practices of these medications in a primary care setting to better determine if there is a need for such protocols.

Methods

This study used comprehensive electronic health records (EHR) maintained by the Mountain Area Health Education Center (MAHEC), a large family medicine practice providing care for over 15,000 patients in western North Carolina. MAHEC is recognized as a Level 3 Patient-Centered Medical Home with 19 faculty physicians, 31 family medicine residents, 5 faculty pharmacists, 4 pharmacy residents, and 4 behavioral medicine faculty. This study was an institutional review board approved retrospective chart review to determine the prevalence of inappropriately dosed DOACs in family medicine.

Patients were included if they had dabigatran, rivaroxaban, apixaban, or edoxaban as an active medication listed in the MAHEC EHR as of June 1, 2015. Patients were excluded if these medications were prescribed by outside providers, were actively monitored elsewhere, or were cared for in a skilled nursing facility. Charts were reviewed for appropriateness of DOAC dose as recorded in their medication lists. Each chart was independently reviewed by one of two authors. In any cases of uncertainty regarding inclusion or appropriateness of dose, the chart was reviewed by two additional authors and discussed to reach a consensus.

The primary outcome was the percentage of patients prescribed inappropriate doses of DOACs. Appropriate doses of each medication were determined based on manufacturer recommendations for indication, interacting medications, and renal function. In the case of dabigatran, appropriate dosing was also based on age, and in the case of apixaban, age and body weight. No patients were taking DOACs for venous thromboembolism (VTE) prophylaxis after orthopedic surgery. Across all DOACs, drug interactions were identified and evaluated at the time of data collection and where defined as those requiring a dose change in the DOAC. Manufacturer recommended dose adjustments that were made based on interactions were categorized as appropriate doses.

Secondary outcomes included reasons for inappropriate dosing, percentage of patients taking appropriate doses but were borderline for dose change, and the number of patients taking interacting medications. The secondary outcome classifying patients as “borderline” for dose change was created to capture the cohort of patients who may benefit from more frequent monitoring based on their higher potential need for dose adjustment. The parameters for this classification were designated based on clinical judgement. Patients were categorized as borderline if they had no serum creatinine between June 1, 2014 and June 1, 2015, or had a serum creatinine or creatinine clearance within 0.2 mg/dl (apixaban, edoxaban) or 5 ml/min (dabigatran, rivaroxaban) of dose adjustment cutoffs, respectively. Creatinine clearance was calculated using the most recent serum creatinine and the Cockcroft-Gault equation. In renal function calculations, ideal body weight was used unless it exceeded total body weight. Adjusted body weight was used if total body weight was more than 30% above the ideal body weight. Descriptive statistics are used to present the data.

For patients taking dabigatran with atrial fibrillation, doses were considered appropriate if 150 mg twice daily was prescribed with a creatinine clearance ≥ 30 ml/min, or 75 mg twice daily with creatinine clearance of 15-30 ml/min. For atrial fibrillation, dabigatran was considered inappropriate, at any dose, if creatinine clearance was less than 15 ml/min. For patients taking dabigatran for VTE treatment or prophylaxis who had a creatinine clearance ≥ 30 ml/min, a dose of 150 mg twice daily was considered appropriate. For VTE, dabigatran was considered inappropriate, at any dose, if creatinine clearance was less than 30 ml/min. Additionally, given increased risk of bleeding evident in elderly patients, and based on international recommendations to reduces doses to 110 mg twice daily for dabigatran (not available in the United States), patients older than 80 years taking dabigatran were considered to be on an inappropriate dose.
For patients taking rivaroxaban with atrial fibrillation, doses were considered appropriate if 20 mg daily was prescribed with a creatinine clearance ≥ 50 ml/min, or 15 mg daily with creatinine clearance of 15-50 ml/min. For atrial fibrillation, rivaroxaban was considered inappropriate at any dose if creatinine clearance was less than 15 ml/min. For patients taking rivaroxaban for any VTE purpose and had a creatinine clearance ≥ 30 ml/min, a dose of 15 mg twice daily was considered appropriate during the first 3 weeks of treatment, and 20 mg daily was appropriate greater than 3 weeks from initiation. For VTE, rivaroxaban was considered inappropriate, at any dose, if creatinine clearance was less than 30 ml/min.

For apixaban in patients with atrial fibrillation, doses were considered appropriate if 5 mg twice daily was prescribed for normal renal function or for patients on hemodialysis. Apixaban 2.5 mg twice daily was appropriate if 2 out of 3 of the following criteria were met: weight < 60 kg, serum creatinine > 1.5 mg/dl, and age > 80 years. For patients taking apixaban for any VTE purpose, a dose of 10 mg twice daily was considered appropriate during the first 7 days of treatment, 5 mg twice daily between 7 days and 6 months of initiation, and 2.5 mg twice daily was appropriate if greater than 6 months from initiation. Apixaban at any dose was inappropriate, regardless of indication, in patients with creatinine clearance < 25 ml/min or serum creatinine > 2.5 mg/dl and not on hemodialysis.

Results

Of the 83 patients that were identified as being actively prescribed DOACs, 64 met inclusion criteria. Nineteen patients were excluded on the basis of having DOACs prescribed by outside physicians, DOACs actively monitored by another clinic, or receiving care in a skilled nursing facility (Figure 1). Demographics of the included patients are described in Table 1.
Table 1. Baseline characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Included Patients (N = 64)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age – mean (SD)</td>
<td>73.0 (13.1)</td>
</tr>
<tr>
<td>Female – no. (%)</td>
<td>39 (60.9)</td>
</tr>
<tr>
<td>Race – no. (%)</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>53 (82.8)</td>
</tr>
<tr>
<td>Non-White</td>
<td>11 (17.2)</td>
</tr>
<tr>
<td>Prescribed DOAC – no. (%)</td>
<td></td>
</tr>
<tr>
<td>Dabigatran</td>
<td>9 (14.1)</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>37 (57.8)</td>
</tr>
<tr>
<td>Apixaban</td>
<td>18 (28.1)</td>
</tr>
<tr>
<td>Edoxaban</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Indication – no. (%)</td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>44 (68.7)</td>
</tr>
<tr>
<td>VTE</td>
<td>17 (26.6)</td>
</tr>
<tr>
<td>Other</td>
<td>3 (4.7)</td>
</tr>
</tbody>
</table>

In this study population, 15 of 64 (23%) patients prescribed a DOAC by a MAHEC provider were on an incorrect dose based on prescribing information. Of patients prescribed appropriate doses, 15 of 49 (31%) were borderline for dose change. In total, 30 of 64 (46%) patients were either on an incorrect dose or were classified as borderline for dose change (Figure 2). This sum represents patients that were potentially at higher risk for adverse events, either from being incorrectly dosed or from being only a slight change in renal function away from the dose adjustment cutoff. Only one patient was identified as being prescribed an interacting medication. The interaction, between apixaban and ritonavir, had already been managed appropriately through dose reduction of apixaban after consultation with the pharmacotherapy team.

Figure 2. Number of patients on appropriate and incorrect doses of DOACs

![Diagram showing the number of patients on incorrect and appropriate doses of DOACs.](image)

Reasons for incorrect dosing in the 15 patients that were identified as being inappropriately dosed are described in Figure 3. The most common reason for incorrect dosing was inappropriate dose.
adjustment for renal function. This included lack of dose adjustment for poor renal function as well as dose reduction despite adequate creatinine clearance. Of the 15 patients that were on appropriate doses but were borderline for dose change, 14 were classified as borderline based on a lack of serum creatinine level within the last 12 months. One patient, who was prescribed dabigatran, had a creatinine clearance within 5 mL/min of the dose adjustment cutoff. All 3 patients who lacked an FDA-approved indication for DOAC use were receiving rivaroxaban: one was being treated for anticardiolipin antibody syndrome without history of clot, one for atherosclerotic cardiovascular disease, and one for “very high risk of VTE” despite never having had a clotting event.

![Fig 3. Reasons for incorrect dosing of DOACs](image)

The frequency of inappropriate dosing among patients receiving each DOAC is displayed in Figure 4. The DOAC most commonly dosed incorrectly was dabigatran; of the 9 patients receiving the drug, 4 were over 80 years old. Apixaban and rivaroxaban were dosed correctly 83% and 78% of the time, respectively.

![Fig 4. Percentage of patients on each DOAC that were receiving inappropriate doses](image)
Discussion

Currently, little evidence has been published on whether or not monitoring of DOACs is warranted. The limited existing data is in small sample sizes and in one instance, conflicting with the overall body of work. This small study adds to the literature in support of the need for regular monitoring of these agents, specifically in our large, family medicine teaching clinic, based on the imperfect prescribing practices of DOACs at baseline.

In 2015, Shore et al. examined monitoring practices of Veterans Affairs sites for management of dabigatran. Sites varied greatly in services offered, ranging from pharmacist assistance with appropriate patient selection to pharmacist-led education and ongoing monitoring. Notably, there was an association between pharmacist-assisted patient selection services and pharmacist-led monitoring with improved patient adherence. This study was the first and largest study to date to demonstrate that offering monitoring services of any kind could be beneficial. However, how these services should be replicated in civilian patient care remains uncertain, especially given that within each intervention, there are significant differences across sites.

Another small study investigating interventions made by an existing DOAC monitoring service estimated a cost-savings of $162,388 for monitoring 80 patients taking dabigatran or rivaroxaban for 9 months. This service was completed in a specialized anticoagulation clinic in which many referrals for care originate from a local cardiology practice. The algorithm used was adapted from existing recommendations from the EHRA. An additional study conducted by the same institution explored patients admitted to the hospital for bleeding events, and identified the potential need for monitoring with 60% of patients taking DOACs also taking interacting medications, and 15.6% on inappropriate doses based on their renal function.

Conversely, preliminary results of the AEGEAN trial showed no improvement in adherence to apixaban with focused counseling. However, patients in the control group who received standard of care in education demonstrated a very high rate of adherence, which left little room for improvement with educational intervention. Both groups showed adherence of around 88%.

In this study, a large proportion of patients were taking incorrect doses which served as a surrogate marker for poor efficacy and safety outcomes that may be incongruent to those expected based on clinical trial results. In addition to the 15 patients found to be on incorrect doses, another 15 were identified as borderline for dose change. Together, these 30 patients represent a subset of the study population that may be at higher risk for poor outcomes. Patients that are borderline for dose change could easily be on an incorrect dose with only a minor change in renal function, further highlighting the need for routine monitoring in patients on DOACs. Without appropriate monitoring of these agents, it is exceedingly difficult to determine the cause of any potential treatment failures or bleeding events. Additionally, the reasons identified for incorrect dosing (i.e. inappropriate renal dose adjustments, lack of FDA approved indication) are those that can be easily corrected with more intentional laboratory monitoring and follow-up. Furthermore, our finding of one patient taking an interacting medication was attenuated by collaboration with the pharmacotherapy department at MAHEC to appropriately adjust the dose of his DOAC.

There are several limitations with our study. First, appropriate dosing of DOACs served as a surrogate marker for safety and efficacy; the correlation between inappropriate dosing of DOACs and bleeding or thromboembolic events remains unknown. Additionally, DOAC dosing was assessed at a single point in time, which may not accurately reflect other clinical factors impacting the patient’s DOAC dosing. Data were also collected from our practice medical record alone, and laboratory values from hospital admissions or outside providers were not captured. Outcomes such as “borderline for dose change” were defined arbitrarily in the absence of national guidelines for monitoring of these agents, and may not necessarily correlate with clinical outcomes. For this reason, interpretation of this finding in particular should be considered primarily for academic purposes rather than for clinical
application. Finally, this was a small, single-center, retrospective study that may not be generalizable to other practices.

Despite limitations, our study results indicate that prescribing practices of DOACs in a family medicine practice are suboptimal, resulting in a large proportion of patients taking incorrect doses of these medications. Given the relative newness of these agents and lack of consensus guidelines for use in the United States, it is understandable that results of our study as well as existing data show that there is room for improvement in prescribing accuracy for these high risk medications. In conjunction with literature describing improved adherence, dosing, and cost-savings with monitoring of these agents, this study suggests that structured guidance on management of DOACs is necessary.

At MAHEC, results of this quality improvement study have prompted focused efforts in creating a standardized monitoring protocol for DOACs. The protocol has been developed based on laboratory monitoring and counseling as recommended by the EHRA. A phone counseling component was developed based on the results of Shore, et al. which indicated phone follow-up with patients taking DOACs was as effective as face-to-face follow-up. Implementation and evaluation of this protocol is ongoing.

References
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Leah Herity, PharmD Candidate: Data collection, entry and management, analysis and interpretation of data, drafting the article, critical revision of the article
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