Direct Oral Anticoagulant (DOAC) to Warfarin Transitions in a Pharmacist-led Anticoagulation Clinic

Ashley G. Woodhouse, PharmD, BCACP, CACP, CDTM; Madeline J. Burke, PharmD; Anne D. Misher, PharmD, BCACP, BC-ADM, CDE

Abstract

Purpose

Patients with non-valvular atrial fibrillation or venous thromboembolism have historically been treated with vitamin-k antagonist therapy; however, due to well-documented limitations, direct oral anticoagulant (DOAC) use has been increasing. The convenience and clinical utility of DOACs is not applicable to all patients, and some must be transitioned to warfarin therapy. Despite practice recommendations, suggestions from package inserts, and clinical trial evidence, there remains a lack of literature describing real-world examples of patient transition from DOACs to warfarin.

Summary

All patients who were transitioned from a DOAC to warfarin from January to December 2016 and were managed by the clinic were included. Patients were excluded if the transition to warfarin did not include ≥ 2 days of DOAC overlap or if DOAC therapy was used as a bridge to surgery or procedure. St. Joseph’s/Candler Health System IRB granted expedited approval and waived informed consent. Four elderly, Caucasian patients met the inclusion criteria. Four patients were successfully transitioned from a DOAC to warfarin for their atrial fibrillation, 3 were transitioned from apixaban and 1 was transitioned from rivaroxaban.

Conclusion

Overall the purpose of this retrospective, observational study was to highlight real-world management of the transition of DOACs to warfarin in an outpatient, pharmacist-led clinic.

Keywords:

pharmacist; anticoagulation; transitions; warfarin

Introduction

Patients with non-valvular atrial fibrillation (NVAF) or venous thromboembolism (VTE) have historically been treated with vitamin-k antagonist therapy; however, due to well-documented limitations, direct oral anticoagulant (DOAC) use has been increasing. The convenience and clinical utility of DOACs is not applicable to all patients, and some must be transitioned to warfarin therapy.

Atrial fibrillation is the most common arrhythmia in the general population, and its incidence increases with age. Patients with atrial fibrillation are at a higher risk for stroke and are often placed on anticoagulation. The American Heart Association (AHA)/American College of Cardiology (ACC) Atrial Fibrillation guidelines recommend warfarin, dabigatran, rivaroxaban or apixaban as appropriate anticoagulation therapy options for patients with non-valvular atrial fibrillation. Of note, edoxaban was approved by the Food and Drug Administration (FDA) after these guidelines were released and is anticipated to be included in future guideline recommendations.

Patients with a history of, or at high risk for, venous thromboembolism may also be started on warfarin or DOAC therapy. The 2016 CHEST guideline update recommends dabigatran, rivaroxaban, apixaban or edoxaban over warfarin for the treatment of deep vein thrombosis (DVT) or pulmonary embolism (PE) in patients without cancer for at least 3 months.

Little information is available to guide evidence-based transitions from DOAC therapy to warfarin, and current guidelines acknowledge the need for further research. Additionally, DOAC package inserts do not provide specific recommendations for switching these agents to or from warfarin, but do give some suggestions. When switching to warfarin from rivaroxaban or apixaban, package inserts suggest starting parenteral anticoagulation and warfarin at the time patients would take their next dose. These package inserts note that rivaroxaban and apixaban may affect international normalized ratio (INR) results with concomitant use of DOAC and warfarin therapies. For transition to warfarin from edoxaban, the manufacturer suggests the use of a parenteral anticoagulant or reducing the dose of edoxaban by one half. Warfarin should be started, and monitoring the INR should occur weekly until a stable INR ≥ 2 is reached. When switching from dabigatran to warfarin, renal function must be taken into account, and again the effect on INR is acknowledged. Additionally, the European Heart Rhythm Association recommends clinic visits every 3 to 6 months for DOAC patients.

In the ROCKET-AF trial, rivaroxaban was found non-inferior to warfarin for preventing stroke and systemic embolism in NVAF with moderate to high stroke risk. However, this trial led to a black box warning of increased thrombotic events after discontinuation of rivaroxaban and transition to open-label warfarin at the end of the study. Significantly more major bleeds and strokes were found in patients who were transitioning from rivaroxaban to warfarin at the end of the trial compared to those who continued on warfarin.

In ARISTOTLE, analysis was conducted to assess and understand occurrence of clinical events after blinded study drug was discontinued and during transition to open-label warfarin. When the blinded study drug was discontinued, patients were transitioned to open-label warfarin (knowing that half of these patients would be continuing warfarin) with a 2-day (4 dose) bridging of apixaban or its matching placebo. Events per year in patients who were treated with apixaban during the trial were higher (4.02%/year stroke or systemic embolism and...
4.97%/year major bleeding) when transitioned to warfarin at end of trial than those who continued on warfarin (0.99%/year for stroke or systemic embolism and 1.97%/year major bleeding). Rate of events was similar between groups in the early permanent discontinuation groups. However, those who were warfarin-naive at the beginning of ARISTOTLE were at a higher risk of stroke or systemic embolism during transition period (5.41%/year) compared to those who had been on warfarin prior to the trial (1.42%/year). Apixaban events were similar regardless of warfarin-naive or experienced at the beginning of the study. As a result of this post-hoc analysis, authors concluded that transition from a DOAC to warfarin should be avoided, but if necessary a transition should be similar to warfarin-naive initiation.

**Rationale**

Despite practice recommendations, suggestions from package inserts, and clinical trial evidence, there remains a lack of literature describing real-word examples of patient transition from DOACs to warfarin. Overall the purpose of this observational study is to shed light on real-world management of the transition of DOACs to warfarin in an outpatient, pharmacist-led clinic. While many patients and prescribers may want to switch from a DOAC to warfarin due to cost, side effects, prescriber preference, or new medical diagnosis, there is minimal data on transitioning from DOACs to warfarin. This lack of data leaves a gap in knowledge of how patients are currently being managed in clinical practice. It is currently unknown how practitioners implement current recommendations and outcomes of DOAC to warfarin transitions. Our goal is to add more evidence for future recommendations on safe transition from a DOAC to warfarin.

**Methodology**

The St. Joseph’s/Candler Center for Medication Management serves over 900 patients in Savannah, Georgia, and its surrounding areas. Pharmacists and nurse practitioners provide anticoagulation services to patients. Clinical personnel include 4 pharmacists, 3 nurse practitioners, and 2 medical assistants.

The nature of pharmacist intervention for DOAC to warfarin transitions varied based upon the timing of the physician’s referral to the clinic. In most cases, the pharmacist would meet face-to-face with or call the patient. Evaluation of proper dosing was performed utilizing patient-specific information prior to patient visits. Pharmacists utilized previously published literature from clinical trials and package inserts to guide dosing recommendations as guideline recommendations are not yet available. Counseling including specific dosing instructions, proper follow-up and disease state education was provided to the patient. Minimum intervention by pharmacists occurred when physicians referred patients to the clinic after they had been given instructions for transitioning DOAC to warfarin. In these cases, the pharmacist reviewed the physician instructions for effectiveness, proper dosing and safety. Physicians and/or patients were contacted if interventions were necessary.

A retrospective, observational study of all patients who were transitioned from a DOAC to warfarin from January to December 2016 was conducted. All patients managed by the clinic were eligible for inclusion unless exclusion criteria were met. Patients were excluded if the transition to warfarin did not include ≥ 2 days of DOAC overlap or if DOAC therapy was used as a bridge to surgery or procedure. Two days or longer of overlap was deemed necessary as this was done in previous clinical trials. Outcomes included the number of days with overlapping therapy, INR (point-of-care or venous) at discontinuation of DOAC, time to reach target INR range, creatinine clearance (CrCl) at time of transition and adverse events thought to be associated with transition in therapy for a follow-up period of 4 weeks. Descriptive statistics were used to report results. The Institutional Review Board of St. Joseph’s/Candler Health System granted expedited approval and waived informed consent.

**Results**

All patients were Caucasian with an average age of 82.75 years (see Table 1). Patient 1 was an elderly male whose indication for anticoagulation was atrial fibrillation and a history of transient ischemic attacks (TIAs). His comorbidities were hypertension and hyperlipidemia (see Table 2 for more details about this patient). Previous clots included TIAs and patient and no previous bleeds. INR was not recorded when the rivaroxaban was discontinued, but 2 days of overlap were given.

Patient 2 was an elderly male whose indication for anticoagulation was atrial fibrillation and a history of cerebrovascular accident (CVA). His comorbidities included hypertension, hyperlipidemia, glaucoma, benign prostatic hypertrophy, and vertigo (see Table 2 for more details about this patient). He had no previous history of bleeding, and only the history of clot was his CVA in 1993. Patient had 2 days of overlap with both apixaban and warfarin, and his point-of-care INR was 1.4 when the apixaban was discontinued.

Patient 3 was an elderly male whose indication for anticoagulation was atrial fibrillation. His comorbidities included heart failure, chronic obstructive pulmonary disease (COPD), hypertension, stroke in 1984, and prostate cancer (see Table 2 for more details about this patient). Patient had 3 days of overlap with both apixaban and warfarin, and his point-of-care INR was 1.7 when the apixaban was discontinued.

Patient 4 was an elderly female whose indication for anticoagulation was atrial fibrillation. Her comorbidities included gastroesophageal reflux disease, dizziness, irritable bowel syndrome, COPD, hypertension, and hypothyroidism (see Table 2 for more details about this patient). Patient had 2 days of overlap with both apixaban and warfarin. Her point-of-care INR was 1.9 on day 6 of warfarin.

Overall, 4 patients were successfully transitioned from a DOAC to warfarin for their atrial fibrillation. Of these patients, 3 were transitioned from apixaban and 1 was transitioned from rivaroxaban. Three patients were transitioned from the DOAC due to cost, and 1 was transitioned due to adverse events associated with the DOAC. No thromboembolic or bleeding events were observed in patients in the 4 weeks following transition. Our results provide insight to successful transitions from DOAC to warfarin; however, further studies are needed to further evaluate the efficacy and safety of these transitions. Although our patients did not experience any thrombotic or bleeding events, previous trials have demonstrated patients may be at increased risk during this transition period.
### Table 1.

<table>
<thead>
<tr>
<th>Average Age</th>
<th>Race/Ethnicity</th>
<th>Average Height (in)</th>
<th>Average Weight (kg)</th>
<th>Average BMI (kg/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>82.75</td>
<td>100% Caucasian</td>
<td>68.5</td>
<td>76.8</td>
<td>25.1</td>
</tr>
</tbody>
</table>

### Table 2.

<table>
<thead>
<tr>
<th></th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
<th>Patient 4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td>Male</td>
<td>Male</td>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td><strong>Indication</strong></td>
<td>AFib and TIA</td>
<td>AFib and CVA in 1993</td>
<td>AFib</td>
<td>AFib</td>
</tr>
<tr>
<td><strong>DOAC being discontinued</strong></td>
<td>Rivaroxaban</td>
<td>Apixaban</td>
<td>Apixaban</td>
<td>Apixaban</td>
</tr>
<tr>
<td><strong>Reason for transition from DOAC</strong></td>
<td>Cost</td>
<td>Cost</td>
<td>Cost</td>
<td>“Weakness”</td>
</tr>
<tr>
<td><strong>Target INR</strong></td>
<td>2 - 3</td>
<td>2 - 3</td>
<td>2 - 3</td>
<td>2 - 3</td>
</tr>
<tr>
<td><strong>CrCl by Cockcroft-Gault</strong></td>
<td>71 mL/min</td>
<td>80 mL/min</td>
<td>27 mL/min</td>
<td>31 mL/min</td>
</tr>
<tr>
<td><strong>CHA²DS²-VASC</strong></td>
<td>4</td>
<td>3</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td><strong>HAS-BLED</strong></td>
<td>3</td>
<td>2</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td><strong>Days to Therapeutic INR</strong></td>
<td>17</td>
<td>12</td>
<td>11 days</td>
<td>11 days</td>
</tr>
<tr>
<td><strong>Adverse Events in First 4 Weeks after Transition</strong></td>
<td>Mild bruise under fingernail after trauma on day 24 of warfarin (NR 50)</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
</tbody>
</table>


Limitations

A limitation with the case series presented includes the fairly homogenous patient population and small sample size, with elderly Caucasian patients with atrial fibrillation in Savannah, Georgia. Other limitations included delay in INRs drawn at the time of transition, due to lag time with referrals and patient appointments. The patient data presented is limited in scope and duration; however, it provides initial evidence for treatment transitions from DOAC to warfarin therapy.

Conclusions

Overall the purpose of this retrospective, observational study was to highlight real-world management of the transition of DOACs to warfarin in an outpatient, pharmacist-led clinic. As current practice allows pharmacist monitoring to be interventional in promoting best patient outcomes, there is a need to provide evidence of strategic anticoagulant conversions.

About the Authors

Ashley G. Woodhouse, PharmD, BCACP, CACP, CDTM graduated from The University of Georgia COP in 2008 and continued her career in retail pharmacy before accepting a position with SJ/C Center for Medication Management in 2010. She completed a non-traditional PGY1 residency with SJ/C healthcare system in 2015, currently holds an Ambulatory Care board certification through the Board of Pharmacy Specialties, an anticoagulation board certification through the National Certification Board of Anticoagulation Providers, and a CDTM license with the state of Georgia. Dr. Woodhouse has no bias to report.

Madeline J. Burke, PharmD was a fourth year pharmacy student at the University of Georgia College of Pharmacy when this case report was completed. She is currently a PGY-1 Pharmacy Practice Resident at Central Arkansas Veterans Healthcare System in Little Rock, AR. Dr. Burke has no bias to report.

Anne D. Misher, PharmD, CDE, BC-ADM is a Clinical Assistant Professor at University of Georgia College of Pharmacy. Dr. Misher has been involved in research in the field of anticoagulation, diabetes and transitions of care. Dr. Misher has no bias to report.

References


