Pharmacist Interventions Regarding the Appropriateness of Apixaban, Rivaroxaban, Dabigatran, and Warfarin in a University-Affiliated Outpatient Clinic

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Abstract

Background: Direct oral anticoagulants (DOACs) have become available recently as an alternative to warfarin in appropriate patients. Few studies have been conducted that evaluate pharmacist-managed services for the management of the DOACs. **Objective:** To review the appropriateness of DOAC therapy and warfarin therapy in adult patients in a university-affiliated outpatient clinic and the need for further monitoring of these agents. **Methods:** A retrospective chart review was conducted of patients receiving a DOAC or warfarin therapy. Indication, dose, duration, age, weight, adherence, drug interactions, bleeding risk/history, renal function, and hepatic function were evaluated for DOACs and warfarin. If prescribed warfarin, international normalized ratio readings were also obtained. The pharmacists made verbal recommendations to primary care prescribers regarding findings, and changes to therapy were reviewed and documented. **Results:** A total of 175 patient charts were reviewed (49% DOACs, 51% warfarin). Twenty-five percent of prescribed DOACs should have been avoided due to inappropriate indication or renal function. The majority of these were switched to warfarin after discussion with the primary care provider. Of patients prescribed DOACs, 22% had a history of poor adherence to therapy and half of these were switched to warfarin. An additional 24% of prescribed DOACs were inappropriate due to incorrect dosing, major drug interactions, and/or renal dosing; however, these medications could be appropriate if adjustments are made. Nineteen percent of patients on warfarin therapy would be a candidate for DOAC therapy. **Conclusion:** Although there were limitations to this analysis, the results demonstrate that additional intervention is needed to improve appropriate prescribing and monitoring of the DOACs. Pharmacists can meet this need by providing medication reviews of novel anticoagulants and educating physicians.

Keywords

anticoagulants, dabigatran, apixaban, rivaroxaban, warfarin, clinical pharmacy

Introduction

Anticoagulants are the most common drug class associated with preventable adverse drug events, with 80% of these potential adverse effects due to errors in the management of these medications.¹⁻⁴ Anticoagulants are commonly used for venous thromboembolism (VTE), atrial fibrillation (AFIB), protein S deficiency, protein C deficiency, stroke, factor V Leiden, antiphospholipid syndrome, or peripheral vascular disease.¹⁻³ Historically, clinicians have had little choice in oral anticoagulants to prescribe, with warfarin being the most common oral anticoagulant used in the outpatient setting.¹ Limitations to its use include the need for individualized dosing, multiple drug and food interactions, unpredictable pharmacokinetics, and a narrow therapeutic range, which leads to the need for frequent monitoring.² Direct oral anticoagulants (DOACs) have become available

within the past 6 years as an alternative to warfarin in appropriate patients. These novel agents include the factor Xa inhibitors apixaban, rivaroxaban, edoxaban, and the direct thrombin inhibitor dabigatran.

All of the DOACs are approved by the US Food and Drug Administration (FDA) for stroke prevention in nonvalvular AFIB and treatment of VTE. Additional FDA-approved

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Table 1. FDA-Labeled Indications and Dosing for DOACs⁵⁻⁹.

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban ^a
Stroke prevention in nonvalvular AFIB	CrCl >30 mL/min: 150 mg BID ^b CrCl 15 to 30 mL/min: 75 mg twice daily ^d CrCl < 15 mL/min or on dialysis: avoid	CrCl > 50 mL/min: 20 mg daily with evening meal CrCl 15 to 50 mL/min: 15 mg daily with evening meal	5 mg BID ^d	CrCl > 50 mL/min: 60 mg daily CrCl 15 to 50 mL/min: 30 mg once daily
VTE treatment	CrCl > 30 mL/min: 150 mg BID ^{*e,f} CrCl ≤ 30 mL/min or on dialysis: avoid	CrCl > 30 mL/min: 15 mg BID with food × 21 days, then 20 mg daily with evening meal CrCl ≤ 30 mL/min: avoid	10 mg BID × 7 days, then 5 mg BID	CrCl > 50 mL/min: 60 mg daily ^f CrCl 15 to 50 mL/min, weight <60 kg, or taking concomitant P-gp inhibitor medications: 30 mg once daily [*]
VTE extended		CrCl > 30 mL/min: 20 mg daily with evening meal CrCl < 30 mL/min: avoid	2.5 mg twice daily	
VTE prevention post TKR/THR		CrCl > 30 mL/min: 10 mg daily with evening meal CrCl < 30 mL/min: avoid	2.5 mg twice daily	

Abbreviations: FDA, Food and Drug Administration; DOAC, direct oral anticoagulant; AFIB, atrial fibrillation; CrCl, creatine clearance; BID, twice a day; VTE, venous thromboembolism; TKR, total knee replacement; THR, total hip replacement.

^aAvoid use in patients with CrCl > 95 mL/min.

^bReduce dose to 75 mg twice daily if patient concomitantly taking dronedarone or systemic ketoconazole.

^c2.5 mg BID if patient has 2 of the following: ≥80 years, ≤60 kg, or SCr ≥ 1.5 mg/dL.

^dAvoid co-administration of P-gp inhibitors.

^eIf CrCl < 50 mL/min avoid co-administration of P-gp inhibitors.

^fInitiate after 5 to 10 days of parenteral anticoagulant.

indications for rivaroxaban and apixaban include VTE prophylaxis post knee or hip surgery, and for rivaroxaban include VTE extended treatment (Table 1). DOACs are not recommended for valvular AFIB, secondary stroke prevention, inherited thrombophilia (factor V Leiden, protein C or S deficiency), antiphospholipid syndrome, or peripheral vascular disease as these agents have not been studied in these populations.^{1,5-14}

The CHEST guidelines suggest oral anticoagulation in patients with AFIB and a CHADS₂ score of 1 or greater.¹ For patients with nonvalvular AFIB, the guidelines suggest dabigatran 150 mg twice daily rather than adjusted-dose vitamin K antagonist therapy.¹ The CHEST guidelines do not recommend the factor Xa inhibitors; however, at the time of the guideline publication the factor Xa inhibitors were not approved for use in patients with AFIB.¹ The American College of Cardiology, American Heart Association, and Heart Rhythm Society (AHA/ACC/HRS) guidelines also suggest that patients with nonvalvular AFIB with a prior stroke/transient ischemic attack, a CHA₂DS₂-VASc score of 2 or greater, or patients who are unable to maintain a therapeutic international normalized ratio (INR)

level on warfarin have the option of dabigatran, rivaroxaban, or apixaban.^{10,11} For patients with nonvalvular AFIB and moderate-to-severe chronic kidney disease with CHA₂DS₂-VASc scores of 2 or greater, treatment with reduced doses of dabigatran, rivaroxaban, or apixaban is suggested, but safety and efficacy have not been established.^{10,11} The guidelines do not recommend dabigatran, rivaroxaban, or apixaban be used in patients with nonvalvular AFIB and end-stage chronic kidney disease or in those patients on dialysis.^{1,10,11} For patients with AFIB and mechanical or tissue heart valves only warfarin is mentioned for use.^{1,10} Edoxaban therapy was not approved at the time of publication and was not included in the recommendations.

Studies evaluating dabigatran, rivaroxaban, apixaban, and edoxaban (RE-LY, ROCKET-AF, ARISTOTLE, and ENGAGE AF-TIMI 48) have all shown the DOACs to be noninferior when compared to warfarin therapy for the treatment of nonvalvular AFIB. Apixaban was also found to be superior when compared to warfarin therapy for the treatment of nonvalvular AFIB.¹⁵⁻¹⁸ All 4 agents were found to cause less intracranial bleeding when compared to

warfarin therapy; and the dabigatran 110 mg dose, apixaban 2.5 mg and 5 mg doses, and edoxaban 30 mg and 60 mg doses were all found to cause less major bleeding when compared to warfarin therapy.¹⁵⁻¹⁸ Dabigatran 150 mg and edoxaban 60 mg were both associated with increased gastrointestinal (GI) bleeding when compared to warfarin.^{15,16}

For the treatment of VTE in patients with no cancer, the CHEST guidelines suggest the DOACs over warfarin therapy.¹² Studies utilizing dabigatran (RE-COVER I, RE-COVER II), rivaroxaban (Einstein DVT, Einstein PE), apixaban (Amplify), and edoxaban (Hokusai-VTE) have all shown noninferiority when compared to warfarin therapy.¹⁹⁻²⁴ Rivaroxaban and apixaban showed a lower incidence of major bleeding when compared to warfarin therapy, and all 4 agents had a lower incidence of intracranial hemorrhage when compared to warfarin.¹⁹⁻²⁴ Dabigatran had a higher incidence of GI bleed when compared to warfarin therapy.^{19,24}

The DOACs have many advantages over warfarin including the lack of a requirement for routine laboratory monitoring. DOACs also have a faster onset of action versus warfarin, with a peak effect occurring within hours of administration versus 5 days for warfarin.⁵⁻⁹ Lastly, DOACs have fewer drug and food interactions versus warfarin. The main drug interactions with the DOACs include concomitant medications with metabolism via CYP3A4 or p-glycoprotein.⁶⁻⁹

Disadvantages of the DOAC include higher cost, less labeled indications versus warfarin, and no individualized dosing for patients with extreme body weights, major drug interactions, and/or high bleed risk. Due to the short half-life of these agents, premature discontinuation and/or non-adherence is associated with increased risk of thrombotic events.⁶⁻⁹ Lastly, while there are no reversal agents for the factor Xa inhibitors, idarucizumab was approved in October 2015 for the reversal of dabigatran for patients presenting with life-threatening or uncontrolled bleeding or if they require emergency surgery or urgent procedures.²⁵⁻²⁷ Further development of a reversal agent(s) for the DOACs is in the pipeline and necessary for their widespread use and for scenarios such as life-threatening bleeding or the need of an urgent surgical procedure.^{25,28}

For the DOACs to be utilized appropriately, multiple factors such as indication, age, renal function, weight, history of GI or intracranial bleeding, and adherence must be considered.^{6-9,29} As an example, all of the DOACs have adjustments for renal impairment, and certain agents such as dabigatran and apixaban have specific warnings or dosage adjustments in the elderly.⁶⁻⁹ While pharmacist-managed anticoagulation services are proven to be beneficial in improving anticoagulation management and reducing warfarin-related complications when compared to traditional monitoring by physicians, few studies have been conducted that evaluate specialized anticoagulation services for the

management of the DOACs.^{30,31} The objective of this study is to review the appropriateness of apixaban, rivaroxaban, dabigatran, and warfarin therapy in adult patients in a university-affiliated outpatient clinic and the need of further monitoring of novel oral anticoagulants.

Methods

A retrospective chart review was conducted of all patients receiving apixaban, rivaroxaban, dabigatran, or warfarin therapy January 1, 2014, through May 1, 2015, in a university-affiliated outpatient clinic to assess the appropriateness of therapy as well as the need for further monitoring in the management of the DOACs. Edoxaban was not evaluated in this study due to the lack of FDA approval at the time of the study. Indication, dose, duration, age, weight, blood pressure control, adherence, drug interactions, bleeding risk/history, renal function, and hepatic function were all evaluated based on documentation in the patient's chart. INR readings were also recorded if available for warfarin patients. Two separate specified data collection forms (one for DOACs and one for warfarin) were used to review all patient charts. After completion of analysis, inappropriate use identified through the analysis was verbally communicated to clinic physicians and adjustments were made through usual course of practice. Institutional review board approval was obtained.

DOAC therapy was considered inappropriate if the agent was prescribed for an indication that was not FDA approved, if a history of nonadherence was noted in the patient chart, if the patient was estimated to have a creatinine clearance (CrCl) < 15 mL/min, or if the patient was prescribed dabigatran or rivaroxaban therapy for the treatment of VTE and their estimated CrCl was < 30 mL/min. Appropriate dosing for each agent was reviewed to assess dose adjustments needed for indication, renal impairment, weight, age, and major drug interactions. Strong P-gp inhibitors and inducers were considered major drug interactions with all DOACs.⁶⁻⁹ Strong CYP 3A4 inhibitors and inducers were considered major drug interactions with rivaroxaban and apixaban.^{7,8} Manufacturer's guidelines for the DOACs recommend avoiding these interactions when possible.⁶⁻⁹

Patients were considered to have inappropriate laboratory monitoring for DOAC therapy if the criteria for monitoring the complete blood count (CBC), renal function, and liver function were not met: yearly in patients with normal renal function, every 6 months for patients with estimated CrCl 30 to 50 mL/min or if on dabigatran and >75 years, every 3 months for patients with estimated CrCl 15 to 30 mL/min or if considered high bleed risk.³

Patients were considered candidates for a switch from warfarin to a DOAC if they were unable to comply with routine laboratory monitoring of INR or if they had labile INRs

Table 2. Results: Patient Demographics and Indications^a.

	Dabigatran (n = 24)	Rivaroxaban (n = 48)	Apixaban (n = 13)	Warfarin (n = 90)
Male	13 (54%)	16 (33%)	9 (69%)	44 (49%)
Female	11 (46%)	32 (67%)	4 (31%)	46 (51%)
Indication				
VTE	9 (38%)	30 (63%)	5 (38%)	40 (44%)
Nonvalvular AFIB	14 (58%)	15 (31%)	7 (54%)	37 (41%)
Valvular AFIB ^b	0 (0%)	2 (4%)	1 (8%)	1 (1%)
Mitral/atrial valve replacement without AFIB ^b	0 (0%)	0 (0%)	0 (0%)	11 (12%)
Stroke ^b	0 (0%)	0 (0%)	0 (0%)	2 (2%)
Protein S deficiency ^b	0 (0%)	1 (2%)	0 (0%)	4 (4%)
Factor V Leiden ^b	0 (0%)	1 (2%)	0 (0%)	2 (2%)
Antiphospholipid syndrome ^b	0 (0%)	0 (0%)	0 (0%)	2 (2%)
Peripheral vascular disease ^b	0 (0%)	0 (0%)	0 (0%)	2 (2%)
Coronary artery disease ^b	1 (4%)	1 (2%)	0 (0%)	0 (0%)

Abbreviations: VTE, venous thromboembolism; AFIB, atrial fibrillation; DOAC, direct oral anticoagulant.

^aPatients could have >1 indication for anticoagulation.

^bInappropriate indication for DOAC therapy.

Table 3. Results: Appropriateness of DOAC Prescribing.

	Dabigatran	Rivaroxaban	Apixaban	Warfarin
Number of patients reviewed (N = 175)	24	48	13	90
Therapy inappropriate due to				
Indication not approved	1 (4%)	5 (10%)	1 (8%)	0 (0%)
Avoid due to renal impairment				
CrCl 16-30 mL/min	5 (21%)	6 (13%)	0 (0%)	N/A
CrCl ≤15 mL/min	0 (0%)	1 (2%)	2 (8%)	N/A
Inappropriate therapy needing adjustments				
Nonadherence	6 (25%)	9 (19%)	4 (31%)	33 (37%)
Dosing adjustment needed	6 (25%)	12 (25%)	2 (15%)	N/A
Major drug interaction	3 (13%)	4 (8%)	1 (8%)	34 (38%)
Recent major GI bleed (within 90 days)	2 (8%)	4 (8%)	0 (0%)	3 (3%)

Abbreviations: DOAC, direct oral anticoagulant; CrCl, creatine clearance; GI, gastrointestinal.

(frequent supratherapeutic INRs or time in therapeutic range <60%) despite warfarin adherence.^{2,3} Patients were not considered a good candidate for switching from warfarin to a DOAC if they could not afford the higher cost of the DOAC, if they reported nonadherence with medications, if they had end-stage renal disease or on dialysis, or if they had a history of recent GI bleeding (within 90 days).^{6-10,16,18}

Results

A total of 175 patients were reviewed in this retrospective analysis, and the number of patients prescribed each medication along with the indication are listed in Table 2. Twenty-one (25%) prescribed DOACs should have been avoided due to inappropriate indication or impaired renal function (Table 3, Figure 1).

After discussion with the patient's primary care provider, 19 patients were switched to warfarin therapy, including 5 patients prescribed a DOAC for valvular AFIB or CAD, 3 patients with a CrCl < 15 mL/min, and 11 patients prescribed dabigatran or rivaroxaban for VTE treatment and had a CrCl < 30 mL/min. The 2 patients who were diagnosed with protein S deficiency and factor V Leiden were continued on rivaroxaban therapy. It was uncertain if the protein S deficiency diagnosis was accurate due to timing of the test.

Nineteen (22%) of the patients prescribed DOACs were reported to have poor adherence to therapy. Ten patients were continued on the prescribed DOAC after adherence education was provided, and it was recommended to switch the other 9 patients to warfarin therapy. Twenty (24%) patients were prescribed an inappropriate dose

Figure 1. Results.

based on their renal impairment, indication, and/or major drug interactions; however, these agents could be appropriate if appropriate adjustments were made. Six patients in the nonvalvular AFIB group were prescribed dabigatran 150 mg twice daily; however, this dose should have been reduced to 75 mg twice daily due to CrCl > 30 mL/min and co-administration of dronedarone, verapamil, and/or amiodarone. All 6 of these patients were switched to the dabigatran 75 mg twice daily dose. Nine patients prescribed rivaroxaban 20 mg daily for the treatment of nonvalvular AFIB should have been prescribed the 15 mg daily dose due to CrCl 15 to 50 mL/min. These patients were switched to the rivaroxaban 15 mg daily dose. Three patients in the VTE treatment rivaroxaban group were inappropriately prescribed 15 mg daily instead of the 20 mg daily dose. All 3 patients had a CrCl > 30 mL/min. These patients were switched to the 20 mg daily dose of rivaroxaban. Two patients in the nonvalvular AFIB group were prescribed apixaban 5 mg twice daily; however, these patients met at least 2 of the 3 criteria requiring a dose reduction to 2.5 mg twice daily. Both patients were switched to the apixaban 2.5 mg twice daily dose.

An additional 8 (16%) prescribed DOACs were found to be prescribed in combination with other agents considered to be major drug interactions (strong CYP3A4 and p-glycoprotein inhibitors); however, specific dosing recommendations were not available for these interactions. All 8 patients with major drug drug interactions were switched to drugs that did not interact with their prescribed DOAC. Two patients in the dabigatran group were lost to follow-up and adjustments were not made.

Dabigatran and rivaroxaban have both shown a potential increased risk of GI bleeding when compared to warfarin therapy; however, 6 patients were initiated or reinitiated on these agents after experiencing a GI bleed while on dabigatran, rivaroxaban, or warfarin therapy.^{8,9} Two patients in the dabigatran AFIB group were initiated on dabigatran therapy after developing a GI bleed while on warfarin therapy. Both of these patients were also taking antiplatelet therapy and nonsteroidal anti-inflammatory drug therapy. One patient in the rivaroxaban VTE group was initiated on rivaroxaban therapy after developing a GI bleed while on warfarin therapy. This patient was also taking dual antiplatelet therapy. Three patients on rivaroxaban therapy developed a GI bleed while taking rivaroxaban therapy and were reinitiated on therapy. One of the patients' rivaroxaban dose was too high based on their estimated CrCl and the other 2 patients were taking nonsteroidal anti-inflammatory drug therapy and antiplatelet therapy. None of the patients with recent GI bleeds were prescribed a GI protectant agent (proton pump inhibitor, H-2 antagonist, misoprostol, etc) prior to the bleed or after the bleed. INRs were not available for the 3 patients that developed a GI bleed while on warfarin therapy. All 6 patients with a history of recent GI bleed were

switched to either apixaban or warfarin therapy and a GI protectant was added.

Seventeen (19%) patients on warfarin therapy would be a candidate for DOAC therapy. Nine of these patients were switched to a DOAC. The most common reason for not switching warfarin to a DOAC were adherence concerns and/or cost/formulary concerns. Only 11 (13%) of patients taking a DOAC had appropriate labs for monitoring therapy (CBC, renal function, and liver function) ordered. Sixty-eight (76%) patients taking warfarin therapy had appropriate labs ordered.

Discussion

The results of this study demonstrate that pharmacists can provide needed monitoring of DOACs and educate providers on appropriate use of DOAC therapy. A study by Shore et al found that pharmacist-physician collaboration, pharmacist-led management of high-risk patients, and longer duration of follow-up were associated with greater adherence to dabigatran therapy.³² The study by Shore et al also highlighted the role of pharmacists in selecting appropriate patients for DOACs based on evaluation of indication, ruling out contraindications, patient adherence, and developing comprehensive monitoring strategies.³²

Just as pharmacist-managed anticoagulation services have been proven to be beneficial in improving anticoagulation management and reducing warfarin-related complications, the results of this study indicate that these anticoagulation services should be expanded to include DOACs. At initiation of anticoagulation therapy, pharmacists can assist other health care providers with determining the appropriate choice and dosing of DOACs based on indication, renal function, concomitant medications, age, weight, concomitant disease states, and patient adherence. Pharmacists can also assess if concurrent proton pump inhibitor or histamine antagonist should be considered based on the patient's GI bleed risk; ensure appropriate lab monitoring is obtained (baseline CBC, renal function, and hepatic function tests); provide patient education; and schedule follow-up visit for continued monitoring.³ Ideally, pharmacists should follow-up after 1 month of initiating therapy to assess patient adherence, efficacy (assessment of thromboembolic events), tolerability, and adverse events (signs and symptoms of bleeding). Afterwards, patients should be monitored by the pharmacist every 6 to 12 months to assess adherence, efficacy, tolerability, bleeding, and kidney function to determine if therapy needs to be adjusted.⁷

There were limitations to this review. Medication adherence and incidence of bleeding had to be assessed through physician notes and was not always recorded in patient charts. INR values were not available for all patients

receiving warfarin; therefore, it is unknown how many patients were within therapeutic range and if dose adjustments with warfarin were warranted.

Conclusion

Although there were limitations to this retrospective analysis, the results of this study demonstrate that additional intervention is needed to improve appropriate prescribing and monitoring of the DOACs. These results also demonstrate the importance of medication reviews of novel anti-coagulants by a pharmacy team.

Authors' Note

Institutional review board approval was obtained.

Declaration of Conflicting Interests

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