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ORIGINAL ARTICLE

Assessment of novel oral anticoagulant use within a community teaching hospital[☆]

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KEYWORDS

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Abstract *Background:* Novel oral anticoagulants (NOACs) are considered to be at least as effective and safe as warfarin with several advantages such as predictable pharmacokinetics, allowing for standardized dosing without monitoring, a lack of food interactions and fewer drug interactions; however, their misuse could potentially result in patient harm. *Objective:* To evaluate the appropriate use of the NOACs within a community teaching hospital. *Setting:* A community teaching hospital in the United States. *Method:* A retrospective chart review of patients that were prescribed dabigatran, rivaroxaban, or apixaban at our institution from October 2012 through November 2014 was conducted. *Main outcome measure:* The primary objective was to determine the percentage of patients that were appropriately prescribed NOACs. Secondary objectives were to determine the number of patients who were inappropriately transitioned from warfarin or parenteral anticoagulants to a NOAC or vice versa, the number of incidents when a NOAC was held or discontinued inappropriately before a procedure and the number of bleeding or thrombotic events while taking a NOAC. *Results:* Of the 113 patients receiving therapy with an NOAC, appropriate prescribing was observed in 79.7%. Dabigatran, rivaroxaban, and apixaban were appropriately prescribed in 73.8%, 88.3%, and 85.8% of patients respectively. Lack of renal dose-adjustment in patients with reduced renal function was the most common reason for inappropriate use (8.8%). Ten out of 38 patients (26%) were inappropriately transitioned from/to other anticoagulants. Two out of six patients underwent a procedure without holding NOACs as recommended prior to surgery. Of all patients receiving NOACs, a total of 3 bleeding incidents were observed, one with each NOAC. *Conclusion:* The NOACs were appropriately prescribed

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for the majority of patients within our institution. Future efforts however should focus on ensuring appropriate dose adjustments for renal impairment, procedures for transitioning between NOACs and parenteral anticoagulants, and adequate withholding times for NOACs prior to surgery in order to optimize the management of NOACs usage within our institution.

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1. Introduction

Until recently warfarin has been the sole oral anticoagulant for the treatment and prevention of venous thromboembolism (VTE) and stroke prevention in atrial fibrillation (AF). Despite its efficacy, warfarin use is complicated by drug and food interactions, a narrow therapeutic index, and required monitoring to maintain an international normalized ratio (INR) within the target therapeutic range (Coumadin, 2011). The novel oral anticoagulants (NOACs), dabigatran, rivaroxaban, and apixaban, are currently approved for the prevention of stroke or systemic embolism in patients with nonvalvular AF and the prevention and treatment of VTE (Pradaxa, 2013; Xarelto, 2014; Eliquis, 2014). Apixaban and rivaroxaban are approved for VTE prevention post hip or knee replacement, and for VTE treatment or prevention of recurrence (Xarelto, 2014; Eliquis, 2014). Dabigatran is approved for treatment of VTE in patients who have been treated with a parenteral anticoagulant for 5–10 days, and to reduce the recurrence of VTE in patients who have been previously treated (Pradaxa, 2013). In general these agents are considered to be at least as effective and safe as warfarin with several advantages such as predictable pharmacokinetics, allowing for standardized dosing without monitoring, a lack of food interactions and fewer drug interactions (Connolly et al., 2009; Schulman et al., 2009; Patel et al., 2011; Turpie et al., 2011; Lopes et al., 2012; Bauersachs et al., 2010; Buller et al., 2012; Agnelli et al., 2013; Lassen et al., 2010a, 2010b).

Despite their advantages, these agents are nevertheless anticoagulants; therefore, their misuse could potentially result in patient harm (NSW, 2014). Dosing of the NOACs is based on indication and may require adjustments based on age, weight, concurrent medications and/or renal function. At our institution, initiation of the NOACs is performed by physicians while pharmacists are responsible for daily monitoring and usage. When initiating therapy, prescribers should take into consideration the patient's indication, renal function, age, and body weight in addition to concomitant medications. Changes in renal function and medication profile may necessitate either a dose reduction or the discontinuation of these agents during therapy. Furthermore, the transition between warfarin or parenteral anticoagulants and NOACs should be performed appropriately to avoid complications in addition to avoiding inappropriate duplication of therapy.

The purpose of this study was to evaluate the appropriate use of the NOACs (rivaroxaban, dabigatran, and apixaban) within a community teaching hospital.

2. Methodology

A retrospective chart review of patients that were prescribed dabigatran, rivaroxaban, or apixaban from October 2012

through November 2014 was conducted. Patients initiated on a NOAC as well as those on a NOAC continued as a home medication were included. Patients were excluded if there was insufficient history or laboratory data to determine the appropriateness of therapy or if they were seen in the emergency department without an admission.

The primary objectives of the trial were to determine (1) percentage of patients that were appropriately prescribed NOACs (rivaroxaban, dabigatran, and apixaban), and (2) the percentage of patients who received the correct dose of each agent based on the specific indication, renal function, age and/or body weight and concomitant medications. The use of each NOAC was considered appropriate based on the criteria listed in Appendix A.

The secondary objectives were to determine (1) the number of patients who were inappropriately transitioned from warfarin or parenteral anticoagulants to a NOAC or vice versa, (2) the number of incidents when a NOAC was held or discontinued inappropriately before a procedure, (3) the number of orders for prothrombin time, aPTT, or INR obtained for the purpose of assessing NOAC therapy, and (4) the number of bleeding and thrombotic events in patients receiving a NOAC.

Data collected included the following: demographic data, NOAC received, indication, dose, serum creatinine, any known medications or concurrent disease states that may affect the pharmacokinetics of NOACs and consideration for dosing, coagulation laboratory results including INR values for appropriate transition between NOACs and warfarin or parenteral anticoagulants, any incidence of bleeding or thromboembolism, and any held, discontinued, or adjusted doses in the NOAC during therapy.

3. Results

Of the 133 patients who received a NOAC from October 2012 through November 2014, a total of 113 patients were included in the study. Twenty patients were excluded: fifteen due to insufficient data available to evaluate the appropriateness of use and five that were seen in the emergency department without an admission. Sixty-five patients received dabigatran, 34 rivaroxaban and 14 apixaban. The majority received NOACs for stroke prevention in atrial fibrillation. The mean age of patients was 70 years. For dabigatran, the majority of patients were receiving therapy as a continuation of therapy upon admission. For apixaban, more patients were initiated on therapy during hospitalization and the number of patients on rivaroxaban was more evenly split between the continuation of home therapy and initiation during hospitalization. A small portion of patients received antiplatelet therapy concurrently with NOACs for post-cardiac stent placement, post-myocardial infarction, or cerebral vascular accident (Table 1).

Table 1 Baseline characteristics.

	Dabigatran (<i>n</i> = 65)	Rivaroxaban (<i>n</i> = 34)	Apixaban (<i>n</i> = 14)
Mean ± SD age, yr	71 ± 11	70 ± 15	70 ± 14
Gender, n			
Male	28	16	6
Female	37	18	8
Indication, n			
Stroke prevention	64	21	9
VTE prophylaxis/treatment	1	13	5
Status of NOACs, n			
Home medication	51	18	4
New start	14	16	10
Cancer, <i>n</i>	2	4	1
Concurrent use of antiplatelets, n			
Aspirin 325 mg	3	0	0
Aspirin 81 mg	18	9	4
Clopidogrel 75 mg	1	1	1

VTE = venous thromboembolism, NOACs = novel oral anticoagulants.

Collectively the NOACs were prescribed appropriately in 79.7% (*n* = 90) of the patients (Fig. 1). Dabigatran, rivaroxaban, and apixaban were prescribed appropriately in 73.8% (48 of 65), 88.3% (30 of 34), and 85.8% (12 of 14) respectively (Fig. 2). Regarding inappropriate use, the dose of NOACs was unadjusted (for specific indication, renal function, age and/or weight) in 8.8% (*n* = 10) of patients collectively. All cases were due to unadjusted doses in patients with renal impairment and occurred in 9.2% (*n* = 6) of patients receiving dabigatran, 8.8% (*n* = 3) of patients receiving rivaroxaban, and 7.1% (*n* = 1) of patients receiving apixaban. NOAC drug interactions without considering dose adjustment or medication discontinuation were identified in 3.5% (*n* = 4) of patients. All drug interactions were identified in the dabigatran group (6.2%). Concurrent administration of NOACs with other anticoagulants was identified in 8% (*n* = 9) of patients collectively; 10.8% (*n* = 7) in the dabigatran group, 2.9% (*n* = 1) in the rivaroxaban group, and 7.1% (*n* = 1) in the apixaban group. Most were given concurrently with enoxaparin (*n* = 6). Two patients were started on a NOAC while receiving warfarin, and one patient received two NOACs concurrently.

Thirty-eight patients were transitioned from a NOAC to another anticoagulant or vice versa (Fig. 3). Ten of the 38 patients (26%) were inappropriately transitioned. The majority of inappropriate transition was associated with the transition from enoxaparin to a NOAC (*n* = 7). The NOACs were administered sooner than recommended after the discontinuation of enoxaparin. Two were transitioned from a heparin infusion and another from argatroban. In each situation, administration of the NOAC was delayed for several hours past the recommended time of transition. Of all patients included in the study, six patients underwent a procedure while they were on a NOAC, 3 patients on dabigatran and 3 on rivaroxaban. In 2 of the dabigatran patients, surgery was initiated prior to dabigatran being held for the recommended duration. None of the surgeries were urgent in nature. Of all patients who received NOACs, a total of 3 bleeding incidents

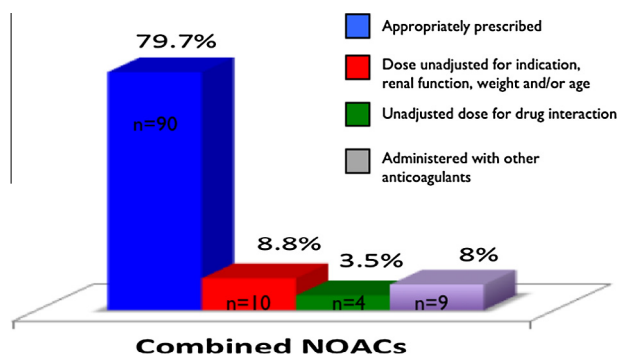


Figure 1 Appropriate use of combined novel oral anticoagulants (NOACs).

were observed: one bleeding incident with each NOAC. None of these bleeding incidents appear to have been associated with inappropriate use of the NOACs.

4. Discussion

The majority of patients were appropriately prescribed dabigatran, rivaroxaban, and apixaban within our community teaching hospital. The most common reason for inappropriate use identified in this study was the absence of dose-adjustment in patients with reduced renal function. There have been several case reports of epistaxis, gastric hemorrhage, or other bleeding events with dabigatran use in patients with impaired renal function (Feinberg et al., 2014; Cano and Miyares, 2012; Felows et al., 2013; Freshour et al., 2012; Maddry et al., 2013; Schaeffer and Conway, 2013). Due to this concern and from the results of our study, the addition of the NOACs to the renal dose adjustment protocol at our institution will be recommended. This will allow the pharmacist to automatically adjust the dose of these agents based on the patient's renal function.

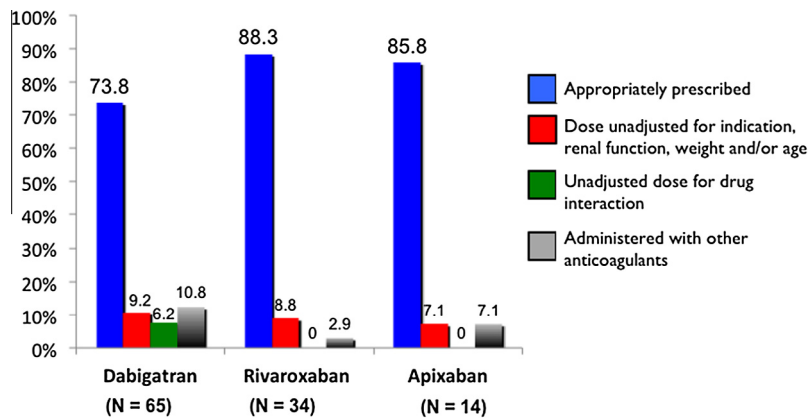


Figure 2 Appropriate use of individual novel oral anticoagulants (NOACs).

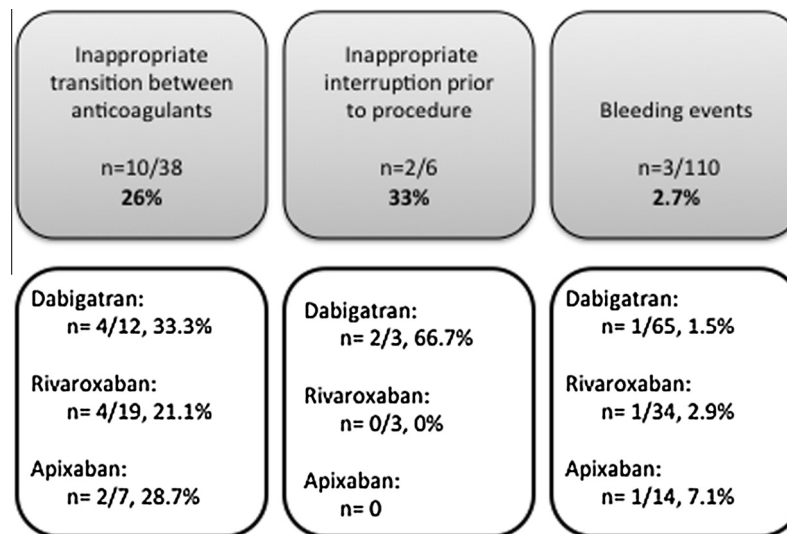


Figure 3 Secondary outcomes.

Although there are fewer drug interactions with the NOACs, they are not obsolete. Interactions between the NOACs and CYP3A4 inducers/inhibitors or P-glycoprotein inducers/inhibitors have been reported. Cases resulting in patient death, gastrointestinal bleeding, and pulmonary embolism with rivaroxaban have been reported when given concurrently with rifampin, protease inhibitors and carbamazepine respectively (Atlena et al., 2014; Lakatos et al., 2014; Risselada et al., 2013). In our trial, concomitant administration of dabigatran with P-glycoprotein inducers was seen in two cases with carbamazepine, one case with both phenytoin and phenobarbital, and one case with phenytoin. In addition, the NOACs are contraindicated in patients with prosthetic heart valves due to an increased risk of thrombosis seen with dabigatran in clinical trials. Despite this contraindication, patients with mechanical valves have received dabigatran with resultant valve thrombosis (Atar et al., 2013; Kuwauchi et al., 2013; Price et al., 2012). None of the patients in our study had a prosthetic heart valve. Coagulation tests such as prothrombin time or activated partial thromboplastin time are often obtained as an indicator of anticoagulation response or used to guide dose adjustments with the NOACs; however, this

practice is both inappropriate and costly (Deremer et al., 2011). A total of 21 coagulation tests were ordered for our patients in the study to assess therapy with the NOACs.

It is essential to understand the importance of discontinuing these agents prior to surgery and when to do so. A resultant patient death due to stroke has been reported in the literature when dabigatran was ceased inappropriately prior to a procedure (NSW, 2014). Although two patients in our study underwent surgical procedures without the NOAC being held for the recommendation duration, neither of these cases resulted in bleeding. There have also been cases in which patients received an additional anticoagulant such as warfarin or heparin while receiving one of the NOACs, resulting in significant bleeding. The concurrent administration of NOACs with other anticoagulants was observed in 9 cases in our study, most received enoxaparin along with the NOAC. None of these cases resulted in a bleeding incidence during hospitalization. The inappropriate transition between NOACs and other anticoagulants may also put a patient at risk of bleeding and/or thrombosis. We found that most patients being transitioned were being transitioned from another anticoagulant to a NOAC and there was a delay or advance in the administration

of the NOAC once the other anticoagulant was discontinued. Therefore, developing a formalized guide for transitioning between NOACs and other anticoagulants, and providing additional education to physicians, nurses, and pharmacists appear to be warranted.

There were several limitations to our study. This was a retrospective review conducted at only one institution. All data were collected from patients' electronic medical records; therefore, there was the potential for missing information. Other limitations include a limited follow-up period, and the majority of patients were receiving dabigatran rather than the newer NOACs, rivaroxaban and apixaban.

5. Conclusion

The novel oral anticoagulants were appropriately prescribed for the vast majority of patients in our retrospective review of patients receiving therapy at a community teaching hospital. Efforts appear to be warranted to address areas such as dose adjustment for renal impairment, transitioning between NOACs and parenteral anticoagulants, and withholding NOACs prior to surgery to optimize the management of NOACs usage at our institution.

Acknowledgments

This work was presented at Southeastern Residency Conference in Athens, Georgia, and as grand rounds presentation in Columbus, Georgia.

Appendix A. Criteria of appropriate use of NOACs

Apixaban

The use of apixaban was considered appropriate if

- (1) The dose was 5 mg BID for nonvalvular AF or 2.5 mg BID if two of the following were present: age 80 years or older, weight 60 kg or less, serum creatinine (SCr) 1.5 mg/dl or greater⁴
- (2) The dose was 2.5 mg BID for VTE prevention post-hip or knee replacement
- (3) The dose was 10 mg BID for one week followed by 5 mg BID for 6 months for patients diagnosed with DVT or PE after August 21st, 2014
- (4) The patient was not receiving a strong inducer of both CYP3A4 and P-glycoprotein
- (5) Dose reduction with concomitant use of strong inhibitors of both CYP3A4 and P-glycoprotein
- (6) Apixaban was discontinued 24 to 48 h in patients with CrCl > 15 ml/min or 36–48 h in patients with CrCl < 15 ml/min prior to a procedure
- (7) The INR was < 2 if switched from warfarin to apixaban or apixaban was discontinued once an INR of 2–3 was achieved in those being converted from apixaban to warfarin or apixaban was discontinued once parenteral anticoagulation was initiated

Dabigatran

The use of Dabigatran was considered appropriate if

- (1) The dose was 150 mg BID for nonvalvular AF or 75 mg BID if the CrCl was 15–30 ml/min²
- (2) The dose was 150 mg BID for treatment of DVT or PE after April 7th, 2014
- (3) The patient was not on any strong inducers of both CYP3A4 and P-glycoprotein
- (4) Dose reduction was considered with concomitant use of strong inhibitors of both CYP3A4 and P-glycoprotein
- (5) Dabigatran was discontinued with CrCl < 15 ml/min in AF or < 30 ml/min in the treatment of VTE
- (6) Dabigatran was discontinued 24–48 h with CrCl > 50 ml/min or 48–96 h with CrCl 30–50 ml/min prior to a procedure
- (7) The INR was < 2 if the patient was switched from warfarin to dabigatran or dabigatran was discontinued once an INR of 2–3 was achieved in those being converted from dabigatran to warfarin or dabigatran was discontinued once parenteral anticoagulation was initiated

Rivaroxaban

The use of rivaroxaban was considered appropriate if

- (1) The dose was 20 mg daily with nonvalvular AF, or 15 mg daily with a CrCl of 15–50 ml/min³
- (2) The dose was 10 mg daily for VTE prevention post-hip or knee replacement
- (3) The dose was 15 mg BID for three weeks followed by 20 mg daily for the treatment of DVT or PE
- (4) The patient was not on any strong inducers or inhibitors of both CYP3A4 and P-glycoprotein
- (5) Rivaroxaban was discontinued in patients with CrCl < 15 ml/min in AF and < 30 ml/min in VTE prevention or treatment
- (6) Rivaroxaban was discontinued 24–48 h with CrCl > 15 ml/min or 36–48 h with CrCl < 15 ml/min prior to a procedure
- (7) The INR was < 3 if the patient was switched from warfarin to rivaroxaban or rivaroxaban was discontinued once an INR of 2–3 was achieved in those being converted from rivaroxaban to warfarin or rivaroxaban was discontinued once parenteral anticoagulation was initiated

AF = atrial fibrillation; SCr = serum creatinine; VTE = venous thromboembolism; DVT = deep vein thrombosis; PE = pulmonary embolism; CrCl = creatinine clearance; INR = International normalized ratio.

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