ORIGINAL RESEARCH

Evaluation of Dabigatran for Appropriateness of Use and Bleeding Events in a Community Hospital Setting

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Am Health Drug Benefits. 2014;7(7):376-384
www.AHDBonline.com

Received June 26, 2014
Accepted in final form August 14, 2014

Disclosures are at end of text

BACKGROUND: Warfarin has been the predominant anticoagulant for the prevention of stroke and systemic embolism in patients with nonvalvular atrial fibrillation (NVAF). Its disadvantages are well-known and include a narrow therapeutic index, drug interactions, and the need for frequent monitoring. Dabigatran etexilate, a direct thrombin inhibitor, presents less complexity in prescribing and has emerged as an alternate therapy to warfarin. Although dabigatran does not require routine monitoring, concerns associated with its use include the lack of a reversal agent, complex dose adjustments, and limited guidance to the management of drug interactions.

OBJECTIVES: The goals of this study are to describe and to evaluate the use of dabigatran at a community hospital to identify areas for improvement in its prescribing.

METHODS: This retrospective chart review of patients at a community hospital in St Louis, MO, included patients who received at least 1 dose of dabigatran between December 2010 and June 2012. The appropriateness of dabigatran was evaluated based on recommendations approved by the US Food and Drug Administration for stroke prophylaxis in the setting of NVAF. The composite end point of bleeding included hospital readmission within 1 year of receiving at least 1 dose of dabigatran at the study institution secondary to bleeding, bleeding associated with a decrease in hemoglobin level by ≥2 g/dL or transfusion of ≥2 units of blood, or a notation of bleeding in the patient's medical record.

RESULTS: Of the 458 patients included in the evaluation, 76 (16.6%) patients receiving dabigatran were using an inappropriate regimen of this drug, based on dose and frequency on the first day of therapy of dabigatran or the presence of valvular disease. Many patients (42.3%) received at least 1 dose of a concomitant parenteral anticoagulant. The composite end point for bleeding was reported in 66 (14.4%) patients, including 23 (5%) with confirmed gastrointestinal bleeding.

CONCLUSIONS: High-risk medications such as dabigatran require monitoring of prescribing habits to improve patient safety and outcomes. Various initiatives, such as pharmacist interventions, therapeutic interchanges, and obtaining appropriate patient parameters, can be implemented in the practice setting to ensure the appropriate use of oral anticoagulants and improved patient outcomes.

Oral anticoagulation has changed drastically in the past 4 years with the US Food and Drug Administration (FDA) approval of 3 new agents—dabigatran, rivaroxaban, and apixaban. Warfarin has had a primary role in oral anticoagulation therapy for many decades. Although its efficacy and safety have been established, therapy with warfarin is associated with significant challenges, including the need for frequent monitoring, drug interactions, a delayed time to onset, and a narrow therapeutic index.[1,2] The challenges associated with warfarin not only affect its efficacy, but they also impact patient satisfaction. These concerns have contributed to the development of novel oral anticoagulants, beginning with dabigatran etexilate.

Dabigatran etexilate, a direct thrombin inhibitor, was approved by the FDA in October 2010 and is the first novel oral anticoagulant approved to reduce the risk for stroke in patients with nonvalvular atrial fibrillation (NVAF).[3] Results from the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) study demonstrated the superiority of dabigatran 150 mg orally twice daily compared with warfarin for the prevention of stroke and systemic embolism in patients with NVAF.[4] In that study, the rate of major bleeding was similar between the agents; however, dabigatran demonstrated a

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lower risk for intracranial hemorrhage, but with an increased risk for major gastrointestinal (GI) bleeding, compared with warfarin.[4]

A recent analysis performed by the FDA confirmed these findings.[5,6] In this analysis, compared with warfarin, dabigatran demonstrated lower rates of ischemic stroke, intracranial hemorrhage, and death; however, dabigatran was associated with a significant increase in major GI bleeding.[5,6] In April 2014, dabigatran received new FDA indications for the treatment of patients with deep-vein thrombosis (DVT) and pulmonary embolism (PE) and for the risk reduction of recurrent DVT and PE in previously treated patients. Two studies, RE-COVER and RE-COVER II, compared dabigatran 150 mg twice daily with warfarin for the treatment of DVT and PE after 5 to 10 days of parenteral anticoagulation. Both studies demonstrated dabigatran's noninferiority to warfarin.[7,8] When the RE-COVER study was initiated, dabigatran was the only agent approved by the FDA for the risk reduction of recurrent venous thromboembolism (VTE).

In November 2011, rivaroxaban, a factor Xa inhibitor, was the second novel oral anticoagulant to receive FDA approval to reduce the risk for stroke in patients with NVAF.[9] Results from the ROCKET AF trial demonstrated the noninferiority of rivaroxaban to warfarin for the first occurrence of stroke or systemic embolism.[10] In November 2012, rivaroxaban received an additional indication for the treatment of and reduction in the risk for recurrent VTE. Two studies, EINSTEIN-DVT and EINSTEIN-PE, compared rivaroxaban (at an initial dose of 15 mg twice daily for 3 weeks, followed by 20 mg once daily) with enoxaparin 1 mg/kg twice daily for at least 5 days with warfarin and then continued with warfarin after the target international normalized ratio (INR) of 2.0 to 3.0 was reached.[11,12] Both studies demonstrated the noninferiority of rivaroxaban to warfarin in time to first recurrent DVT or PE event.[11,12]

In December 2012, the factor Xa inhibitor apixaban was the newest novel oral anticoagulant to receive FDA approval to reduce the risk for stroke in patients with NVAF.[13] The ARISTOTLE trial compared apixaban 5 mg twice daily (or 2.5 mg twice daily in select patients) with warfarin.[14] Apixaban was superior to warfarin for the primary end point of reducing the risks for stroke and systemic embolism. Superiority to warfarin was primarily attributable to reductions in hemorrhagic stroke and ischemic stroke with hemorrhagic transformation compared with warfarin.[14]

In AVERROES, patients with NVAF who were not candidates for therapy with warfarin were randomized to treatment with apixaban 5 mg twice daily (or 2.5 mg twice daily in select patients) or to aspirin 81 mg to 324 mg once daily.[15] The primary objective of the study was to determine if apixaban was superior to aspirin for preventing the outcomes of stroke or systemic embolism. This trial was stopped early on the basis of a prespecified interim analysis that showed significant reductions in stroke and systemic embolism with apixaban compared with aspirin, but apixaban was associated with a modest increase in major bleeding.[15]

The current guidelines for the treatment of atrial fibrillation provide a class I recommendation for warfarin (level of evidence A) and dabigatran, rivaroxaban, and apixaban (level of evidence B) for the prevention of thromboembolism in patients with a CHA_2DS_2-VAS_c score of ≥2.[16]

Dabigatran provides an effective alternative therapy to warfarin. It offers a predictable pharmacokinetic profile, which eliminates the need for routine monitoring of serum drug concentrations. Approximately 80% of dabigatran is excreted renally and requires dose reductions for patients with reduced creatinine clearance.[17] Although dabigatran addresses some of the challenges asso-

KEY POINTS

- Anticoagulation has changed drastically in the past 4 years in the United States with the FDA approval of novel oral anticoagulants, starting with dabigatran in 2010, rivaroxaban in 2011, and apixaban in 2012.
- These new anticoagulants present a safe alternative to warfarin for the prevention of stroke and systemic embolism in the setting of nonvalvular atrial fibrillation (NVAF).
- However, although anticoagulation has been simplified with the novel oral drugs, many safety issues must be considered when prescribing these agents.
- This retrospective chart review at a community hospital analyzed the appropriateness use of dabigatran, the first novel anticoagulant to receive FDA approval for the treatment of NVAF.
- Of the 458 patients included in this study, 76 patients were prescribed an inappropriate, mostly too high, dose of dabigatran.
- Although dabigatran is only approved for the treatment of NVAF, 13 patients had valvular disease.
- The majority of the patients were also receiving concomitant medications that are known to have drug interactions with dabigatran.
- These results indicate that high-risk medications require better monitoring of prescribing habits to improve patient safety and outcomes.

Table 1 Dabigatran Dosing Recommendations

Indication	Creatinine clearance	Dose
Reduction in risk for stroke and systemic embolism in NVAF	>30 mL/min	150 mg orally twice daily
	15-30 mL/min	75 mg orally twice daily
	<15 mL/min or dialysis	Dosing recommendation cannot be provided
	30-50 mL/min + dronedarone or systemic ketoconazole	75 mg orally twice daily
	15-30 mL/min + dronedarone or systemic ketoconazole	Avoid use

NVAF indicates nonvalvular atrial fibrillation.
Used with permission from Pradaxa (dabigatran etexilate mesylate) capsules [prescribing information]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc; September 2014.

Table 2 Drugs Interacting with Dabigatran

Pharmacodynamic interactions	
LMWH (enoxaparin, dalteparin)	Prasugrel
Fondaparinux	Ticagrelor
Heparin	Aspirin
Clopidogrel	NSAIDs (ibuprofen, naproxen, diclofenac, ketorolac)

Pharmacokinetic interactions		
P-gp/ABCB1 inhibitors (increase concentration)		**P-gp/ABCB1 inducers (decrease concentration)**
Amiodarone	Nicardipine	Carbamazepine
Atorvastatin	Progesterone	Dexamethasone
Carvedilol	Propranolol	Prazosin
Clarithromycin	Quinidine	Rifampin
Cyclosporine	Quinine	St John's wort
Dipyridamole	Ranolazine	Trazodone
Dronedarone	Ritonavir	
Erythromycin	Tacrolimus	
Itraconazole	Tamoxifen	
Ketoconazole (systemic)	Verapamil	

LMWH indicates low-molecular-weight heparin; NSAIDs, nonsteroidal anti-inflammatory drugs; P-gp, P-glycoprotein.
Source: Lexicomp. www.lexi.com (access requires fee payment).

ciated with warfarin, there are remaining issues regarding the use of dabigatran.

Warfarin interacts with numerous medications, disease states, and a variety of foods containing vitamin K; however, there is a great deal of clinical experience and resources available to effectively manage many of warfarin's interactions.[1] Unlike warfarin, dabigatran is not metabolized by cytochrome P450 enzymes and has fewer drug interactions. Although several drug interactions with dabigatran and P-glycoprotein inducers and inhibitors have been identified, little guidance has been provided on how to address them in practice.[18]

Additional concerns surrounding dabigatran include the lack of a reversal agent and the lack of availability of laboratory testing to determine its degree of anticoagulation activity. Dabigatran prolongs markers of coagulation, such as the activated partial thromboplastin time (aPTT) and ecarin clotting time, and may potentially impact INR values. The aPTT can only provide an approximation of the anticoagulation effect of dabigatran, and the INR is relatively insensitive to the degree of anticoagulation. The ecarin clotting time is a more specific parameter to determine the effect of anticoagulation[19]; however, most laboratories are not adequately equipped to perform the laboratory test. Without laboratory parameters to guide dosing adjustments, it is unclear how to balance the drug interactions that have been identified to potentially increase or decrease dabigatran serum concentrations. The lack of monitoring also makes it difficult to manage special populations that typically require dosage adjustments (eg, the elderly, obese patients, underweight patients, and those with renal dysfunction).

Since dabigatran became the first oral anticoagulant to be introduced to the US market, and the first to be included on hospital formularies, there has been a dramatic shift in the approach to anticoagulation. Laboratory markers of anticoagulation effect are no longer reliable, drug interactions require significantly less dose adjustments, and renal function continually needs to be addressed.[20] The purpose of this study was to evaluate the use of dabigatran at a community hospital between December 2010 and June 2012 and to identify prescribing areas that can be improved to ensure appropriate use and patient outcomes.

Methods

Participants and Design

This retrospective chart review was performed at a 489-bed community hospital in St Louis, MO. Institutional Review Board approval was obtained before the start of data collection for the study. Data for patients who received at least 1 dose of dabigatran between December 2010 and May 2012 were evaluated. Patients

without available data on serum creatinine, height, or weight were excluded from the evaluation.

Data Collection

A total of 533 eligible patients were identified from the pharmacy information system. The baseline demographic information was collected, including age, sex, race, length of stay, height, weight, serum creatinine, and creatinine clearance at the initiation of dabigatran therapy. The appropriateness of the initial regimen ordered was assessed based on the presence of valvular disease, dose, and frequency (**Table 1**).[3]

The concomitant use of antithrombotic therapies as well as P-glycoprotein inhibitors was documented to determine the potential for any association with increased risk for bleeding (**Table 2**). Patients were screened for readmission within 1 year to a system hospital secondary to any type of bleeding. Other bleeding parameters assessed included decreased hemoglobin level by ≥2 g/dL, transfusion of at least 2 units of blood, or notation of bleeding in the medical record; the composite end point of bleeding included these 4 criteria.

Although patients might have met more than 1 bleeding criterion, each patient was only included once in the composite bleeding analysis, unless therapy with dabigatran was reinitiated after the initial bleeding event.

Statistical Analysis

The parameters that were evaluated in this analysis based on the data collected from the patients' electronic medical records included demographic data, clinical indication for dabigatran use, concomitant medication use that could potentially interact with dabigatran (all medications listed in Table 2 plus warfarin), and bleeding. Descriptive statistics were used to characterize the prescribing patterns of dabigatran. Differences in baseline demographics and concomitant medications between patients who experienced a bleeding event and those who did not were analyzed using the Student's *t*-test for continuous data, the chi-square test, or the Fisher's exact test for categorical data.

Results

Of the 533 eligible patients identified for the study, 75 were excluded because of the inability to assess their renal function (ie, they had no record of serum creatinine level, height, or weight). Baseline demographics were collected on the 458 patients included in the analysis (**Table 3**). Of note, 12 (2.6%) patients weighed <50 kg and 124 (27.1%) patients weighed >100 kg.

The indications for patients' dabigatran use are listed in Table 3. During the specified study time frame, dabigatran had not yet been approved for the treatment of or the reduction of risk for recurrent VTE. Therefore, those indications were considered off-label for this analysis.

Table 3 Patient Demographics

Demographics	Patients (N = 458)
Age, yrs, mean (± SD)	73 (± 13.1)
Male sex, N (%)	247 (54)
Race	
Caucasian, N (%)	419 (91.5)
Black, N (%)	18 (3.9)
Native American, N (%)	2 (0.4)
Other, N (%)	5 (1.1)
Unknown, N (%)	14 (3.1)
Mean length of hospital stay, days (± SD)	4.9 (± 5.3)
Mean BMI, kg/m^2 ± SD (median)	29.9 ± 7.32 (29)
Mean weight, kg, mean ± SD (median)	88.5 ± 26 (85)
Weight	
<50 kg, N (%)	12 (2.6)
>100 kg, N (%)	124 (27.1)
AST 3 × upper limit of normal, N (%)	7 (1.5)
ALT 3 × upper limit of normal, N (%)	8 (1.7)
Past medical history of liver disease, N (%)	12 (2.6)
Indication for dabigatran	
Atrial fibrillation, N (%)	426 (93)
VTE, N (%)	18 (3.9)
Aortic thrombus, N (%)	3 (0.65)
Pulmonary embolism, N (%)[a]	6 (1.3)
Cerebrovascular accident, N (%)	1 (0.22)
Renal artery infarct, N (%)	1 (0.22)
Femoral-popliteal bypass, N (%)	1 (0.22)
Orthopedic surgery prophylaxis (total knee replacement), N (%)	1 (0.22)
Factor V Leiden, N (%)	1 (0.22)
Outpatient prescribing	
Dabigatran home medication, N (%)	208 (45.4)
Warfarin home medication, N (%)	32 (7)
Dabigatran continued at discharge, N (%)	397 (86.7)

[a]Only 1 patient received 5-10 days of parenteral anticoagulant overlap.

ALT indicates alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; SD, standard deviation; VTE, venous thromboembolism.

Table 4 Assessment of Initial Dabigatran Regimen Appropriateness

Dabigatran regimen	Patients, N (%)
Inappropriate regimen	76 (16.6)
Home medication inappropriately continued	41 (9)
Medication inappropriately initiated in hospital	35 (7.6)
Contraindicated due to renal function	8 (1.7)
Inappropriate dose	66 (14.4)
Inappropriate frequency	13 (2.8)
Bioprosthetic valve	12 (2.6)
Moderate or severe mitral stenosis	1 (0.2)

Of note, although dabigatran is only approved for the treatment of NVAF, 13 patients were deemed to have valvular disease, as defined by the presence of moderate or severe mitral stenosis on echocardiogram, or had a prosthetic heart valve. Taking these factors into consideration, along with creatinine clearance, 76 (16.6%) patients were treated with inappropriate regimens (**Table 4**).

Of the patients with an inappropriate dose of dabigatran, 50 were receiving too high of a dose based on their renal function. Nearly 8% of the patients had an inappropriate dabigatran regimen continued at home that had been initiated on admission to the hospital. Although there is no FDA-approved regimen that includes once-daily dosing of dabigatran, 13 patients received once-daily dosing.

Patients receiving dabigatran for an off-label indication were not evaluated in this study for appropriateness of use. Despite not having an FDA-approved indication for these conditions at the time this review was conducted, 18 (3.9%) patients received dabigatran treatment for VTE and 6 (1.3%) patients received dabigatran for PE. Furthermore, based on the RE-COVER and RE-COVER II trials and FDA-approved indication, patients should receive 5 to 10 days of a parenteral anticoagulant before the initiation of dabigatran.[7,8] However, only 1 of the 6 patients receiving treatment for PE was appropriately treated with parenteral anticoagulation before initiating dabigatran therapy. Other off-label indications are listed in Table 3.

Table 2 includes all the potential drug interactions with dabigatran that were documented in this review. Many patients were receiving at least 1 medication interacting with dabigatran; 204 (44.5%) patients were receiving at least 1 P-glycoprotein inhibitor, and 13 (2.8%) patients were receiving at least 1 P-glycoprotein inducer (**Table 5**). In addition, many patients received concurrent antithrombotic therapy while receiving dabigatran (Table 5).

Table 5 Use of Concomitant Medications in Patients Receiving Dabigatran

Concomitant medication	Patients, N (%)
Warfarin	9 (1.9)
Enoxaparin	120 (26.2)
Dalteparin	0
Fondaparinux	1 (0.2)
Heparin	73 (15.9)
Clopidogrel	44 (9.6)
Prasugrel	0
Ticagrelor	0
Aspirin	
81 mg	181 (39.5)
162 mg	90 (19.7)
325 mg	2 (0.44)
Triple therapy (clopidogrel + aspirin)	35 (7.6)
Ibuprofen	6 (1.3)
Naproxen	0
Diclofenac	0
Ketorolac	1 (0.2)
Drug with interactions	
Amiodarone	81 (17.7)
Atorvastatin	41 (9)
Carvedilol	21 (4.6)
Dronedarone	15 (3.3)
Propranolol	1 (0.2)
Ranolazine	2 (0.4)
Verapamil	2 (0.4)
Trazodone	12 (2.6)
2 drug interactions	41 (9)
3 drug interactions	2 (0.4)

Overall, 42.3% of patients were administered at least 1 dose of heparin or enoxaparin concomitantly with dabigatran. For patients receiving concomitant heparin, the average number of doses administered was 7. Antiplatelet therapy was used in the majority of patients, and 60% of patients received a daily aspirin. Of note, 7.6% of the patients received "triple therapy" with aspirin, clopidogrel, and dabigatran.

For the composite end point of bleeding, 66 (14.4%) unique patients experienced at least 1 bleeding event (**Table 6**). The most common confirmed source of bleed-

ing was GI, which is consistent with data from the RE-LY trial.[4]

Patients who had a bleeding event were significantly more likely than patients who did not have bleeding to have an INR value of >1.1 (40.9% vs 22.7%, respectively; $P = .002$), a lower body weight (82.7 kg vs 89.6 kg; $P = .016$), and a longer length of stay (174 hours vs 108.3 hours; $P < .005$).

The length of hospital stay was most likely increased as a result of the treatment of active bleeding, or it could be attributed to more medically complex patients with comorbid conditions that are associated with an increased risk for bleeding. Other factors hypothesized to increase the risk for bleeding were also examined, including appropriate dosing in renal disease, drug interactions, concomitant anticoagulant use, and low body weight. Those patients not receiving appropriate dosing of dabigatran for renal disease were not more likely to experience bleeding (16.7% patients were receiving excessive doses; $P = .208$), as observed in this analysis.

Table 6 Bleeding Events in Patients Receiving Dabigatran

Bleeding	Patients/events, N (%)
Readmission for bleeding within 1 year	19 (4.1)
Bleeding noted during admission resulting in discontinuation	11 (2.4)
≥2 g/dL decrease in hemoglobin	38 (8.3)
Transfusion ≥2 units PRBC	18 (3.9)
Unique patients experiencing any bleeding	66 (14.4)
Confirmed bleeding source: GI	23 (5)

GI indicates gastrointestinal; PRBC, packed red blood cells.

Discussion

The third goal of the Hospital National Patient Safety Goals relates to the safe use of medications in the hospital.[21] Reducing harm from anticoagulants is specifically highlighted within this goal.[21] Although novel oral anticoagulants are not specifically mentioned, the complexity of anticoagulant dosing can be extrapolated to these agents. Many hospitals have well-established monitoring systems for patients receiving warfarin, including requirements for measuring daily INR values. Although there are no daily laboratory tests available to monitor these agents, there are important parameters to consider when initiating or continuing these drugs in the hospital. To ensure the appropriate dosing of dabigatran, current, patient-specific data to calculate creatinine clearance[22] are necessary.

In this analysis, 75 patients were excluded as a result of a lack of complete data to calculate creatinine clearance to assess the appropriateness of dabigatran dosing. This illustrates one challenge pharmacists and other healthcare professionals may encounter when assessing the safety of dabigatran dosing. The dosing recommendations for dabigatran in the setting of renal disease are fairly complex and must take into consideration the indication and the concomitant use of P-glycoprotein inhibitors, such as dronedarone.

A 2013 article demonstrated the positive impact of a pharmacist-managed anticoagulation service.[23] Physicians placed an electronic order delegating authority to the pharmacists for the management of dabigatran while the patient is in the hospital. During the review period, 46% of the patients required pharmacist intervention.[23] This illustrates one method to improve the safe use of anticoagulation in an inpatient setting. Another frequently used method is therapeutic interchange. These therapeutic interchanges are often approved by the institution's Pharmacy & Therapeutics Committee. Such policies would allow pharmacists to adjust the dosing of anticoagulants without contacting a physician for a verbal order.

Anticoagulation has changed drastically in the United States in the past 4 years, starting with the approval of dabigatran in 2010, rivaroxaban in 2011, and apixaban in 2012. Ensuring that agents are prescribed based on their indications with supporting efficacy and safety data is another important factor. Novel oral anticoagulants are often approved by the FDA for a single indication and later receive added indication approvals as the drug is studied in additional clinical trials. It is important that prescribers and pharmacists are aware of all current indications or utilize supporting clinical trials when prescribing novel oral anticoagulants.

During the time of this analysis, the treatment of VTE was not an approved indication for dabigatran, although, as is shown in this analysis, it was prescribed for this indication. Although dabigatran can now be used for the treatment of VTE, it requires an initial 5 to 10 days of parenteral anticoagulation, which was not implemented in routine practice at this institution. One example of the risk of using dabigatran off-label is the Randomized, Phase II Study to Evaluate the Safety and Pharmacokinetics of Oral Dabigatran Etexilate in Patients After Heart Valve Replacement (RE-ALIGN), which was terminated early because of an excess number of thromboembolic and bleeding events in the cohort receiving dabigatran.[24] The use of dabigatran in the patients with mechanical heart valves (before the results of this study were available) could have caused significant harm to patients.

The complexity of anticoagulation management increases because many hospitals have more than 1 novel

oral anticoagulant on their formulary. Each agent varies in renal adjustment requirements, with rivaroxaban dosing varying even between indications. Apixaban recently received FDA approval for use in patients receiving hemodialysis; however, this was not part of the drug's initial approval.[13] It can be difficult to not only be aware of evolving indications, but to provide appropriate dosing recommendations as well.

Another prescribing concern highlighted by this analysis is the use of concomitant parenteral anticoagulation. DVT prophylaxis is important for the reduction of morbidity and mortality in hospitalized patients. However, it is not necessary to use parenteral anticoagulants in addition to novel oral anticoagulants because of the quick onset of an anticoagulant effect. This is an important screening step when initiating a novel oral anticoagulant or when continuing home medications once patients are admitted to the hospital. Alerts incorporated into physician order entry or during pharmacy verification represent 1 step that could help to prevent concomitant anticoagulant use.

There are many situations during a hospitalization that can further increase a patient's bleeding risk. Acute renal failure can increase drug concentrations. Many patients in this analysis were receiving dabigatran that was continued from home. Although the dose may be appropriate in the outpatient setting, it should be reassessed when patients present to the hospital. Patients also frequently undergo procedures while admitted to the hospital. Each novel oral anticoagulant has unique recommendations to consider when discontinuing therapy because of a medical procedure. Although it may appear anticoagulation has been simplified by avoiding the complexities of warfarin, there are still many factors to consider for the safe use of novel oral anticoagulants.

Finally, it is also important to note that there is a significant increase in drug costs to hospitals, as well as to patients, as a result of the introduction of the novel oral anticoagulants. However, these costs may be offset by the savings in costs of laboratory monitoring, as well as the time saved by clinicians who monitor and adjust warfarin dosing based on daily INR values. The relative cost-effectiveness of dabigatran compared with warfarin is supported by a recent economic analysis evaluating data from the RE-LY trial.[25]

Limitations

There are several limitations to this study. This is a retrospective chart review that only focuses on the use of dabigatran at a single community hospital. Dabigatran was the first novel oral anticoagulant to be introduced to hospital formulary and was in use for about 1 year before rivaroxaban was added to the formulary. Characterizing prescribing patterns and evaluating the appropriateness of rivaroxaban are currently being conducted at the same institution; rivaroxaban was not included in this analysis because of a limited number of patients at the time of the Institutional Review Board's approval of this research.

The retrospective nature of this study allows for error in data abstraction from the patients' charts. Because the patients were not prospectively being observed during their hospital stay, documentation by nurses and physicians was heavily relied on. This leaves room for bias in the interpretation of medical records, as well as allows for error in documentation at the time of patient hospitalization. Some patient data (eg, serum creatinine, height, weight) and a complete medical history for each patient were unable to be obtained.

In addition, the retrospective nature of the study makes it difficult to use similar bleeding criteria as a prospective analysis, especially when assessing decreases in hemoglobin and identifying sources of bleeding or rationale for drug discontinuation.

It should also be noted that 91.5% of the patients included in this study were Caucasian, which may limit the validity of these data for other institutions.

Conclusions

The findings in this retrospective review highlight the difficulties of using dabigatran in patients admitted to the hospital. Potential future studies should include the continued review of dabigatran, as well as rivaroxaban and apixaban, once enough data are available to characterize prescribing patterns. When utilized appropriately, dabigatran has demonstrated superiority over warfarin for the prevention of systemic stroke and embolism in the setting of NVAF without having to monitor serum drug concentrations. However, with improved efficacy comes increased medication cost, various dosing regimens, and new challenges with maintaining safety in a hospital resulting from acute situations, such as changes in renal function, the initiation of novel medications, and the use of medical procedures.

Although dabigatran was the only novel oral anticoagulant included in this evaluation, similar process improvement plans can be extrapolated to rivaroxaban and apixaban, such as therapeutic interchanges for renal function, ensuring that appropriate patient data are collected at the time of admission, and physician education about new agents and indications as they are approved by the FDA. As the area of anticoagulation continues to evolve, it is imperative that hospitals institute monitoring systems to ensure the appropriate use of these high-risk medications. Although methods are well-established for safely monitoring warfarin, newer agents (eg, dabiga-

tran) also pose a safety risk to patients and thus require careful monitoring by competent clinicians. ■

Acknowledgments

JNT, TC, KMS, HCL, BKS, and PSC were responsible for writing the manuscript. JNT and TC validated the data. JNT is the guarantor of the quality and validity of this report. PSC provided clinical consultation.

Funding Source

This study was supported by a Faculty Research Incentive Fund Grant from St Louis College of Pharmacy.

Author Disclosure Statement

Dr Buehler participated in Pfizer's Midwest Atrial Fibrillation Advisory Board meeting; Dr Armbruster, Dr Min, Dr Riley, and Dr Daly reported no conflicts of interest.

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STAKEHOLDER PERSPECTIVE

Accurate Prescribing Key to Safe Use of Anticoagulants in Patients with Nonvalvular Atrial Fibrillation

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Atrial fibrillation (AF) is the most common arrhythmia in patients aged ≥65 years and is associated with a significant risk for thromboembolic stroke. Nonvalvular AF (NVAF) imposes a 5-fold increased risk for stroke compared with the overall population.[1]

PATIENTS: Warfarin is the most frequently prescribed antithrombotic medication for patients with NVAF. Warfarin is inexpensive and is well-tolerated; however, its use is associated with an increased risk for bleeding complications and must be constantly monitored. Moreover, patients taking warfarin must watch their diets, because many foods and medications interact with warfarin, which can impact its anticoagulation effect.

In the past few years, novel oral anticoagulants have

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STAKEHOLDER PERSPECTIVE *Continued*

been approved by the US Food and Drug Administration (FDA) as safe and effective alternatives to warfarin, including dabigatran, rivaroxaban, and apixaban. These drugs are direct thrombin and/or factor Xa inhibitors that do not require anticoagulation monitoring—as measured by prothrombin time and reported as an international normalized ratio—and are not associated with food or medication interactions.[2] Early randomized, double-blind clinical trials suggest that these drugs may be more effective than warfarin for the prevention of stroke in patients with NVAF.[3,4]

In their retrospective claims analysis, Armbruster and colleagues discuss the use of dabigatran in 1 hospital setting.[5] Of the 458 patients included in this analysis, 76 patients were prescribed dabigatran inappropriately, and many patients were receiving concomitant medications that interact with this anticoagulant, placing patients at unnecessary risk for potentially serious adverse events, and/or adversely affecting dabigatran's efficacy.[5]

Although the newer oral anticoagulants are easier to manage, they are also substantially more expensive than warfarin and may not be covered by the patient's insurance plan, which is a particular concern for patients with Medicare or Medicaid coverage. In addition, although the half-life of these drugs can be as little as 5 to 14 hours, patients need to understand that there are no antidotes for these drugs. Patients may be apprehensive about taking a drug that cannot be reversed even in an emergency setting. Patients must weigh the benefits and risks of antithrombotic medication for the treatment of NVAF.

PAYERS: Although the newer agents are easier to prescribe and to monitor, the costs of these drugs remain high. Payers will need to balance the cost of these drugs with their safety profiles, efficacy, cost of monitoring, and most of all, the evidence for clinical superiority. Payers, too, must weigh the benefits and risks of antithrombotic medication for the treatment of NVAF in particular patients, in addition to cost.

PROVIDERS: As is clear from this present article by Armbruster and colleagues, providers, including pharmacists who monitor patients using anticoagulants, must ensure that patients are properly receiving these medications according to treatment guidelines and FDA drug labeling information.[5] They must carefully ensure that these anticoagulants do not interact with other drugs their patients are using, and that the dose is prescribed correctly.[5]

Furthermore, although risk stratification schemes, such as $CHADS_2$, CHA_2DS_2-VAS_c, and HAS-BLED, are beyond the scope of this perspective, they represent scoring guidelines that have been validated in many patients with NVAF. Based on these scores, a patient can be stratified as low, intermediate, or high risk for a thromboembolic event, and therefore be properly evaluated for the initiation of antithrombotic medication.[1,6] In patients aged ≥65 years, it would be rare to have a $CHADS_2$ or CHA_2DS_2-VAS_c of zero, and therefore the majority of patients will be treated. Furthermore, studies indicate that all women aged ≥65 years with NVAF should be treated, even with a score of zero, because of their observed increased risk for stroke.[1,6]

To reduce the risk for bleeding, providers must offer proper education and timely, consistent, and accurate monitoring to patients who are receiving antithrombotic medications. The education should include the importance of drug compliance, dietary restrictions, medication interactions, and lifestyle changes. Many thromboembolic and bleeding complications occur as a result of inconsistent monitoring and poor communication.

Because of the simplicity of monitoring, many providers prefer to use the newer oral antithrombotic agents as first-line therapy for patients with NVAF. However, cost can be an issue with these newer agents for patients whose insurance does not cover these medications. The lack of an antidote, too, may be a concern for the patient, and should be carefully considered by the provider. ■

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