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A Retrospective Descriptive Analysis of Patient Adherence to Dabigatran at a Large Academic Medical Center

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ABSTRACT

BACKGROUND: Clinical trials evaluating the efficacy of dabigatran followed a very strict protocol, which included close monitoring and follow-up. Patients followed in this controlled environment had an average medication possession ratio (MPR) >0.95. However, very few studies have evaluated patient adherence to dabigatran in a real-world setting. Other studies of chronic medications indicate patients are not reliably adherent to twice daily regimens. Adherence to therapy is particularly important for direct thrombin inhibitors because there may be a risk of increased thromboembolic events associated with poor adherence to these agents.

OBJECTIVE: To identify the MPR for patients prescribed dabigatran at a large academic medical center and affiliated clinics.

METHODS: This retrospective descriptive study evaluated the MPR for patients prescribed dabigatran between January 1, 2012, and December 31, 2012. Patients included in this study had to receive dabigatran for a minimum of 3 months, have a primary care physician or cardiologist at the medical center or affiliated clinics, and must not use a mail order pharmacy. Patient MPR was calculated based on prescriptions picked up from the patient.

RESULTS: After screening 400 patients, 159 patients met eligibility criteria. The mean MPR for the patients in this study was 0.63. Overall, 43% of the patients had an MPR of <0.80, and the mean MPR for this subgroup was 0.39±0.27; 57% of the study population had an MPR of 0.80 or higher, with a mean MPR of 0.94±0.08. There was a significantly higher proportion of men (67.7%, $P=0.0112$) and a larger number of "as needed medications" prescribed (1.73 vs. 0.86, $P=0.0039$) in patients with an MPR<0.80. There were 5 patients hospitalized during the study period (3 for bleeding, 1 for confusion, and 1 death not related to dabigatran therapy).

CONCLUSIONS: The relatively low mean MPR seen in this study may indicate that there is a need for improved anticoagulation services and follow-up for patients taking dabigatran.

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What is already known about this subject

- Patients on warfarin (vitamin K antagonist therapy) are closely followed and monitored by their prescribers and/or anticoagulation clinics. There is strong evidence to support the management of patients on warfarin in this clinical environment.
- Dabigatran is a direct thrombin inhibitor approved for the prevention of thromboembolism in patients with atrial fibrillation, and no laboratory test has been validated to monitor drug levels. Patients on dabigatran are not routinely followed by an anticoagulation service.
- While clinical trial data indicate that patients taking dabigatran have a medication possession ratio (MPR) >0.95, claims data evaluating adherence indicate that 40% of patients taking dabigatran are nonadherent to therapy.

What this study adds

- This is the first study to evaluate adherence to dabigatran therapy as measured by prescriptions picked up at the local pharmacy from orders validated in the electronic medical record. The findings suggest that patients do not take dabigatran therapy consistently in a noncontrolled environment.
- The average MPR for all patients in this study was 0.63. Those with an MPR<0.80 (43%) had an average MPR of 0.39, and those with an MPR≥0.80 had an average MPR of 0.94. This MPR is far below that previously published in clinical trials.
- Despite the poor adherence to dabigatran in this study, no thromboembolic events were reported.

Dabigatran etexilate is a direct thrombin inhibitor approved in October 2010 for the prevention of stroke and systemic embolism in patients with nonvalvular atrial fibrillation. Dabigatran has predictable pharmacokinetics, fixed dosing, and fewer dietary and drug interactions than warfarin and does not require therapeutic monitoring. As a result, the use of dabigatran has many favorable properties compared with vitamin K antagonist (warfarin) therapy.[1] The 2012 American College of Chest Physicians Antithrombotic Therapy guidelines recommend dabigatran or adjusted dose vitamin K antagonist therapy as first-line agents for anticoagulation treatment of patients with atrial fibrillation.[2]

Although warfarin is available as a generic drug, which is significantly less costly than dabigatran, the management of patients on warfarin creates significant labor costs because patients must be closely monitored. Anticoagulation clinics routinely educate patients on warfarin and emphasize the importance of adhering to the prescribed dosing regimen. The close follow-up allows for frequent discussions about other potentially important issues such as changes in health status, medication reconciliation, drug-drug interactions, changes in diet, or problems filling prescriptions. Organized

anticoagulation clinics have been shown to improve clinical outcomes and reduce the risk of bleeding for patients on warfarin therapy.[3-6]

In contrast to warfarin, dabigatran does not require routine laboratory monitoring and is marketed as being less burdensome for patients; however, the lack of regular monitoring may be a limitation. Absence of regular contact with health care providers who monitor adherence and other issues may increase the likelihood of transiently missing or skipping anticoagulant doses, thereby increasing the risk of a thromboembolic event.

In clinical trials evaluating dabigatran, regular follow-up was part of the study protocol.[7-8] Patients in the Randomized Evaluation of Long Term Anticoagulation Therapy (RE-LY) trial had follow-up visits at 14 days, 1 month, and every 3 months thereafter. Dabigatran was placed in dated bubble packs that were counted by the research coordinator.[7-8] Although adherence was not reported in the RE-LY trial, the RE-COVER trial reported 98% adherence and used a similarly rigorous protocol.[9]

There are several calculations used to measure patient adherence to therapy. The measurement accepted by the International Society for Pharmacoeconomics and Outcomes Research is medication possession ratio (MPR).[10] MPR is calculated by determining the number of doses dispensed (known as the quantity in possession) over a defined dosing period (time), with an MPR of ≥ 0.80 generally accepted as "adherent." Several studies have evaluated adherence to twice daily treatment schedules and reported that patients are only adherent to their scheduled dosing 30%-80% of the time in a nonclinical trial environment.[11-17] A recent claims database review found that nearly 40% of patients on dabigatran were nonpersistent to dabigatran during a 180-day time period.[18] However, a major limitation of this study was the inability to determine if the prescriber discontinued dabigatran and the use of a retrospective claims database without validation that the patient picked the prescription up at the pharmacy. Adherence to warfarin therapy is determined by measuring international normalized ratio (INR) and calculating the "time in the therapeutic range (TTR)." The TTR for patients on warfarin remains between 46%-78% despite being dosed once daily.[19] Although this range indicates a wide variability in achieving therapeutic INR for patients on warfarin, a TTR of > 58% appears to be an effective target associated with a reduced number of thromboembolic events.[19] To date, there has not been a similar measure proposed to quantify the adequacy of dabigatran therapy.

The purpose of this study was to determine adherence (using MPR) to the prescribed dabigatran dose in patients with atrial fibrillation who were not followed by an anticoagulation clinic. We hypothesized that adherence to dabigatran for patients not followed by an anticoagulation clinic is much lower than that reported in clinical trials.

Methods

Study Design

This was a retrospective descriptive study evaluating electronic medical and pharmacy records for patients seen within the University of California (UC) Davis Medical Center. Study protocol was approved by the UC Davis Medical Center Institutional Review Board with expedited approval. Patients prescribed dabigatran were identified using an electronic medical record (EMR) report generated by clinical decision support. Medical and pharmacy records were evaluated between January 1, 2012, and December 31, 2012. All prescription records were obtained directly from the dispensing pharmacies.

Study Population

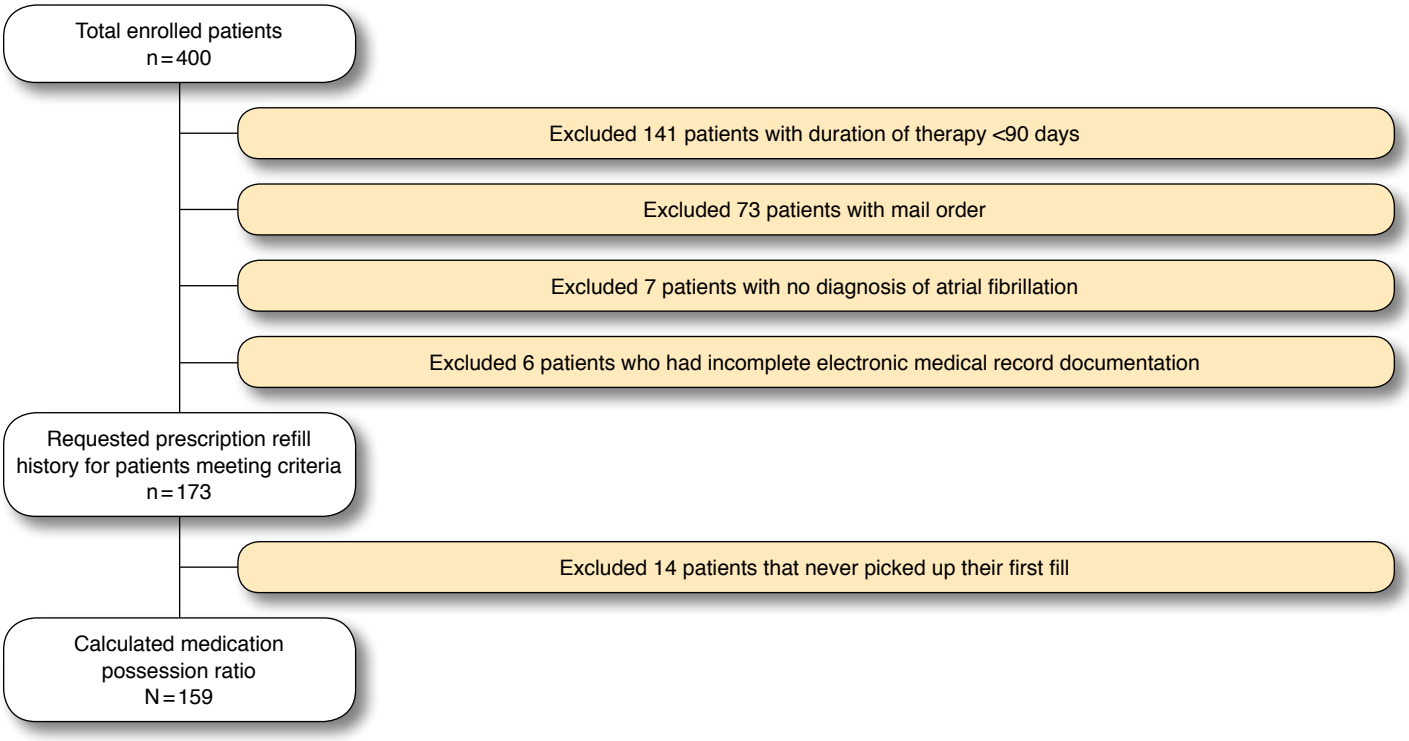
Patients were consecutively evaluated for this study until a total of 400 eligible patients were identified. Patients that were at least aged 18 years, had a UC Davis primary care physician or cardiologist, had an active medication order for dabigatran documented in the EMR, had a diagnosis of atrial fibrillation documented in the EMR, and had at least 1 dabigatran prescription filled during the study period were included in the MPR analysis. Cases with the following criteria were excluded from the analysis: (a) discontinuation of dabigatran by the prescribing physician within 90 days of the index (first fill) prescription, (b) refusal of the patient's pharmacy to share refill records, (c) transfer of care to a non-UC Davis clinician during the study period, and (d) use of a mail order pharmacy.

For all patients meeting the inclusion criteria, a study investigator called the pharmacy associated with the dabigatran prescription and obtained the following information: (a) the date the patient picked up a completed prescription for dabigatran between January 1, 2012, and December 31, 2012, (b) the prescribed directions for use, and (c) the number of tablets dispensed at each fill date. If the pharmacy reported that the prescription was transferred to another pharmacy, that next pharmacy was contacted, and the necessary information was obtained. If the transferred prescription could not be located, the patient was excluded from analysis.

Outcome

The principal outcome was the MPR, which is the sum of the number of days that the daily dose of dabigatran was dispensed, divided by the number of days elapsed until the next prescription was filled. For instance, if 60 tablets (a 30-day supply) were prescribed on day 0, and the next prescription is filled on day 40, the MPR was 30/40 or 0.75. The MPR can be > 100% if the prescription is picked up early. For purposes of this study, the MPR was calculated based on the time between the date that the index prescription was filled and the date that the medication was discontinued or December 31, 2012, defaulting to the earlier of the 2 dates. The maximum number of days in the study period was 366, since 2012 was a leap year.

FIGURE 1 Study Population



Because there is no evidence-based definition of adherence for dabigatran, adherence was defined as MPR of 0.80 or greater, and patients were categorized into adherent and nonadherent groups (MPR ≥ 0.80 and MPR < 0.80, respectively).

In order to determine if the length of time from initiation of therapy affected MPR rates, varying durations of therapy were also evaluated (1-90 days, 91-180 days, 181-270 days, and 271-360 days). This quarterly MPR was calculated for consecutive 90-day intervals by using the first fill as the index date. Each subsequent quarterly MPR was determined from that index date. Not all patients generated all 4 of the possible quarterly interval MPRs, since this was dependent on the date of the first dabigatran fill.

Statistical Analysis

Descriptive statistics were performed on all study variables. Continuous variables were summarized as means ± standard deviations, medians, and ranges. Categorical variables were summarized as frequency distributions and percentages. Two-tailed t-tests with equal variance were used for comparisons between 2 groups of continuous variables with normal distribution. Wilcoxon rank-sum tests were used for comparisons between 2 groups of continuous variables that did not meet normality criteria. Two-tailed z-tests were used for comparisons between 2 groups of frequency distributions. One-way analysis of variance (ANOVA) and repeated measures ANOVA tests were used for comparisons between 3 or more groups of frequency distributions. No data points were substituted or filled in for repeated measures ANOVA tests. All statistical analyses were performed in VassarStats: Website for Statistical Computation (Richard Lowry, PhD, Vassar College, Poughkeepsie, NY).

Results

A total of 400 consecutive patients were identified through an EMR report as being prescribed dabigatran and underwent chart review. As shown in Figure 1, a total of 159 patients met eligibility criteria and had their prescription fill histories collected from their respective pharmacies and MPR calculated.

The average age of patients included in the analysis was 70.7 ± 10.9, and 60% were men. Patients in the study population were prescribed an average of 8.64 ± 4.36 chronic medications, and the overall average calculated creatinine clearance was 77 milliliter per minute (Table 1).

The average MPR for all 159 patients was 0.63 ± 0.35; the median MPR was 0.75 (Table 1). Overall, 43% of the patients had an MPR of < 0.80, and the mean MPR for this subgroup was 0.39 ± 0.27; 57% of the study population had an MPR of 0.80 or

TABLE 1 Baseline Characteristics

Age (years)	
Mean ± SD	70.69 ± 10.86
Range	31 - 91
Weight (kg)	
Mean ± SD	88.17 ± 22.04
Range	42.60-149.32
Male sex, n (%)	95 (59.7)
Chronic medications prescribed per patient	
Mean ± SD	8.64 ± 4.36
Range	0-22
PRN medications prescribed per patient	
Mean ± SD	1.35 ± 1.96
Range	0-10
Total medications prescribed per patient	
Mean ± SD	9.99 ± 5.41
Range	0-30
Dabigatran dose, n (%)	
75 mg twice daily	26 (16.4)
150 mg twice daily	133 (83.6)
Mean MPR	
Mean ± SD	0.63 ± 0.35
Median	0.75
Range	0.00-1.12
MPR cut-offs, n (%)	
≥ 0.80	69 (43.4)
< 0.80	90 (56.6)
$CHADS_2$[a]	
Mean ± SD	1.93 ± 1.21
Range	0-6
$CHADS_2$ scoring break down, n (%)	
0	19 (11.9)
1	38 (23.9)
2	57 (35.8)
3	30 (18.9)
4	11 (6.9)
5	3 (1.9)
6	1 (0.6)
Creatinine clearance (mL/min)	
Mean ± SD	77.33 ± 32.48
Range	8.86-193.88
Creatinine clearance cut-offs, n (%)	
Unknown	6 (3.8)
< 30 mL/min	2 (1.3)
≥ 30 mL/min	151 (95.0)

[a]*The $CHADS_2$ score is a measure of the risk of stroke in which congestive heart failure, hypertension, an age of 75 years or older, and diabetes mellitus are each assigned 1 point, and previous stroke or transient ischemic attack is assigned 2 points; the score is calculated by summing all the points for a given patient.*

kg = kilogram; mg = milligram; mL/min = milliliter per minute; MPR = medication possession ratio; PRN = prescribed as needed; SD = standard deviation.

higher, with a mean MPR of 0.94 ± 0.08. The most commonly prescribed dose of dabigatran was 150 milligrams twice daily (84% of patients). The $CHADS_2$ score for patients on dabigatran therapy ranged from 0-6, with the majority of patients having a $CHADS_2$ score of 2 or greater (64.2% of patients).

The demographic characteristics of the "more adherent" (MPR > 0.80) patients were compared with "less adherent" (MPR < 0.80) patients (Table 2). The mean MPR, as needed (PRN) medications prescribed per patient, and total medications prescribed per patient variables were not normally distributed, and the Wilcoxon rank-sum test was used for statistical analyses. The less adherent group had significantly more men (67.7% compared with 47.8% in the more adherent group, $P = 0.0112$) and were prescribed a larger number of PRN medications (1.73 compared with 0.86 in the more adherent group, $P = 0.0039$). There was no statistically significant difference detected between groups in mean age, weight, $CHADS_2$ score, or number of chronic medications prescribed.

The MPR in each successive quarter following the index prescription fill date (Day 1) did not vary significantly between patients on therapy in the first 90 days (MPR 0.62), 91-180 days (MPR 0.66), and 181-270 days (MPR 0.66). There were not enough patients who took dabigatran for 271-360 days to make this between-group comparison (Table 3).

Table 4 describes the adverse events in patients in the study population. There was 1 death that was not related to the study drug. Three patients had an emergency department encounter or hospital admission for bleeding. One patient was hospitalized for confusion, and a computerized topography of the brain was negative for acute infarction (magnetic resonance imaging was not performed).

Discussion

The major finding of this study was that, in a cohort of patients starting dabigatran for the first time at an academic medical center, more than 40% had an MPR of less than 0.80. Overall, the mean MPR for the entire study population was 0.63 (possession of dabigatran 63% of the time), which is much lower than the adherence rate reported in the RE-COVER trial (98%). However, the adherence rate in our study population was similar to the values reported in a recent retrospective claims review and other studies that have evaluated adherence rates for twice daily medications.[11-18] Medication adherence has been shown to be inversely proportional to the frequency of dosing, and the reported rates of adherence for twice daily medications vary between 30%-80%.[11-17] This is the first study to evaluate adherence in a real-world environment validated by prescription pickup and EMR review.

Analysis of the more adherent and less adherent subgroups indicated that the adherent patients had a very high mean MPR of 0.94, whereas the less adherent patients had a mean MPR of 0.39, with a wide standard deviation, indicating that some patients were extremely nonadherent. $CHADS_2$ scores, number of chronic medications prescribed, age, and length of dabigatran therapy did not appear to predict adherence. Although we can only speculate about the possible reasons for nonadherence in this study population, it is known that several factors other

TABLE 2 Comparison of Adherent and Nonadherent Patients Taking Dabigatran

	Adherent (MPR ≥ 0.80) N = 69 (43.4%)	Nonadherent (MPR < 0.80) N = 90 (56.6%)	*P* Value
MPR, mean ± SD	0.94 ± 0.08	0.39 ± 0.27	< 0.0001
Mean age (years), mean ± SD	72.00 ± 11.0	69.69 ± 10.67	0.18
Weight (kg), mean ± SD	87.68 ± 20.53	88.55 ± 23.24	0.81
$CHADS_2$ score, mean ± SD[a]	2.12 ± 1.33	1.79 ± 1.09	0.14
Male sex, n (%)	33 (47.8)	61 (67.7)	0.0112
Chronic medications prescribed per patient, mean ± SD	8.37 ± 3.89	8.83 ± 4.69	0.51
PRN medications prescribed per patient, mean ± SD	0.86 ± 1.17	1.73 ± 2.33	0.0039
Total medications prescribed per patient, mean ± SD	9.23 ± 4.42	10.57 ± 6.03	0.1159

[a]The $CHADS_2$ score is a measure of the risk of stroke in which congestive heart failure, hypertension, an age of 75 years or older, and diabetes mellitus are each assigned 1 point and previous stroke or transient ischemic attack is assigned 2 points; the score is calculated by summing all the points for a given patient

kg = kilograms; MPR = medication possession ratio; PRN = prescribed as needed; SD = standard deviation.

TABLE 3 Mean MPR from Initiation of Dabigatran (Day 1)

	All Patients (N = 159)	1-90 Days (N = 60)	91-180 Days (N = 47)	181-270 Days (N = 33)	*P* Value
Mean MPR ± SD	0.63 ± 0.35	0.62 ± 0.36	0.66 ± 0.42	0.66 ± 0.41	0.27

MPR = medication possession ratio; SD = standard deviation.

than the dosing frequency are associated with decreased adherence. These include the patient's perception of the medication's benefit, the provider-patient relationship, lower socioeconomic class, cost, and the lack of a support system.[20] It is possible that a high copayment for dabigatran may have contributed to expense-related nonadherence. Other potential contributors to the nonadherence observed in the current study include the requirement to refill the medication monthly, the total cost of the medications, and the symptoms of gastrointestinal upset or gastritis frequently reported by patients prescribed dabigatran.

Another important factor that might explain the relatively low degree of adherence to dabigatran was the absence of close monitoring by the prescribing health professionals. A study by Shulman et al. (2013) evaluated adherence to dabigatran among patients who were followed in an anticoagulation clinic.[21] In this study, the patients were educated at the time the medication was first prescribed, were scheduled for a 3-month follow-up appointment, and then had annual appointments thereafter (similar to the RE-COVER trial). After follow-up, Shulman et al. reported a median "estimated adherence" of 99.7% with MPR ≥ 0.80 in 88% of the study population (N = 103). Of note, 16% of the participants in this study were also participants in the RE-LY trial. A small Veterans Administration study evaluated adherence to dabigatran in patients followed by a pharmacist in an anticoagulation clinic at defined intervals (2 weeks, 1 month, and 3 months) versus patients receiving care from their primary care physician without anticoagulation clinic intervention.[22] This study showed no appreciable difference in the adherence rates as measured by the MPR between the pharmacist and usual care groups. However, the study was not powered to determine differences between groups, and the baseline MPR was very high in each group (greater than 0.80). This was likely because the patients were part of the Veterans Administration system and received mail order refills at little to no cost. Regardless, little is known about dabigatran adherence monitoring by primary care physicians and/or subspecialty clinics. The studies just mentioned demonstrated high adherence rates in patients that were closely and actively followed; however, dabigatran monitoring protocols have yet to become standard practice.

TABLE 4 Adverse Events Identified in Study Population

Patient	Adverse Event	Summary
A	Death	Cause of death: sepsis, urinary tract infection
B	Rectal bleeding	Patient on dabigatran at time of ED visit. Upper gastroendoscopy performed 2 weeks later with only gastritis noted in report. Patient continued on dabigatran.
C	Upper gastrointestinal bleed	Patient on dabigatran at time of admission and required 2-day ICU stay.
D	Mild hematuria and urinary tract infection	Patient was admitted for urosepsis. No correlation to dabigatran noted.
E	Confusion, mild hematuria	Head computerized topography scan noted only old CVA infarction but no acute infarctions.

CVA = cerebral vascular accident; ED = emergency department; ICU = intensive care unit.

For anticoagulants, nonadherence poses potentially significant health risks, specifically thromboembolic events that can result in death, major disability, functional decline, and/or major bleeding. In addition, researchers have theorized that there may be a rebound prothrombotic state that develops after abruptly discontinuing an anticoagulant.[23] In the ROCKET atrial fibrillation study, discontinuation of another new oral anticoagulant, rivaroxaban, without overlap or "bridging" to warfarin was associated with a very high stroke rate, which has led to a black box warning by the U.S. Food and Drug Administration.[24] The package insert for dabigatran also includes a black box warning cautioning against abrupt discontinuation without adequate continuous anticoagulation.[1] This is particularly relevant to the findings of the present study because dabigatran also has a relatively short half-life. Although the current study was small, there were no documented strokes, and only 3 bleeding episodes were identified during the study period. The risk of stroke in patients with atrial fibrillation and a $CHADS_2$ score of 2 without anticoagulation is 4 events per 100 patient years.[25] Therefore, the absence of stroke may have been observed in this study because of the small study population and short duration of the study. Therefore, a longer and larger study is needed to evaluate the risks associated with periodic nonadherence to dabigatran.

Limitations

There are several limitations to this study. First, our study sample was from a single academic institution and may not be generalizable to smaller, nonacademic institutions. Second, there were several assumptions used in the MPR calculations. For example, it was assumed that dabigatran was continued until the order to discontinue dabigatran was placed in the EMR. However, it is possible that some patients were told to "hold" their dabigatran for a procedure or were verbally told to discontinue the medication without entering a note into the EMR. We also assumed that all patients were supposed to take dabigatran as prescribed and that the only source of dabigatran was from their pharmacies. Third, patients may have been hospitalized, which would have led to an underestimation of adherence. Fourth, because patients were not contacted, direct pill counts were not made, and we did not inquire if patients ever used pharmacies that were not linked to the prescription orders that were listed in their medical charts.

Conclusions

Other studies evaluating twice daily chronic medications have shown poor rates of adherence.[11-17] This is the first study to evaluate patient adherence to dabigatran in a real-world setting that included validated prescription pickup and EMR documentation. Patients in this study had no oversight or surveillance by nurses, pharmacists, or anticoagulation clinic staff. The major finding was that approximately 40% of the patients had an MPR of less than 0.80, which is similar to that seen in a retrospective database review.[18] Although the observed number of adverse events in this study population was low with no strokes identified, the gaps in dabigatran adherence that we observed were quite striking. Further, only gender and number of PRN medications differed between patients that were more adherent to dabigatran versus those that were less adherent. The findings suggest that closer monitoring of patients on newer oral anticoagulants should be provided by the prescriber or by allied health personnel, such as the staff in an anticoagulation clinic. Further research is needed to determine the reasons for poor adherence in this group and to evaluate the outcomes of poor adherence to dabigatran. Additionally, studies are needed to determine the optimal method of monitoring medication adherence among patients prescribed dabigatran or any of the other newer oral anticoagulants.

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