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Apixaban concentrations with lower than recommended dosing in older adults with atrial fibrillation

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ABSTRACT

Background/ Objectives

Lower-than-recommended doses of direct-acting oral anticoagulants are often prescribed to older adults with non-valvular atrial fibrillation (NVAF). Our goal was to determine the consequences of lower-than- recommended dosing on plasma apixaban concentrations during clinical care of older adults with NVAF.

Design

Convenience sample of patients receiving anticoagulation during 2017

Setting

Academic medical center

Participants

Stable adults over age 65 years with non-valvular atrial fibrillation receiving apixaban on a chronic basis

Measurements

Patient age, weight, creatinine, co-medications, apixaban concentrations

Results

One hundred and ten older adults with NVAF (mean age of 80.4 years, range 66-100 with 45% women) were studied. Forty-eight patients received recommended dosing of 5 mg twice daily and 42 received lower-than-recommended dosing. One patient in each category had concentrations below expected 5-95% range at time of peak concentrations. Differences in proportion of apixaban concentrations within or outside expected ranges were not significant between patients receiving lower-than-recommended doses and those dosed-as-recommended at 5 mg twice daily

(p=0.35). However, in patients dosed-as-recommended with 5 mg twice daily, four had concentrations above 5-95% range for peak levels expected at 3-4 hours after dosing; in two, this occurred around the midpoint of the dosing interval. Twenty patients received 2.5 mg twice daily as recommended. One third had apixaban concentrations higher than expected peak concentrations compared to the clinical trials and, over 2/3 had levels above the reported median for peak concentrations.

Conclusions

Apixaban concentrations in older adults with NVAF seen clinically were higher than expected based on clinical trial data. The findings raise questions about the optimal dosing of apixaban in older adults with NVAF encountered outside of clinical trials and suggest a role for monitoring of apixaban concentrations during care of patients that differ from those in randomized trials, or when considering dosing outside of published guidelines.

Keywords: apixaban, direct-acting oral anticoagulant, non-valvular atrial fibrillation, dosing accuracy,

INTRODUCTION

Direct-acting oral anticoagulants (DOACs) are replacing vitamin K antagonists for anticoagulation due to fewer food and medication interactions and simplified dosing and monitoring regimens. [1] While DOACs have been shown to have equivalent or superior efficacy to prevent stroke or systemic emboli in patients with non-valvular atrial fibrillation (NVAF) with fewer intracranial hemorrhages in randomized trials,[2-4] there are limited data on older adults with NVAF during routine clinical care. These patients are often older, more likely to be women, have more co-morbidities, falls, and higher bleeding risks than those enrolled in clinical trials. Possibly due to these factors, post-marketing analyses of DOAC use in patients with NVAF report prescribed doses often inconsistent with product labelling. [1] Lower-than-recommended dosing is more common than higher-than-recommended dosing, especially for apixaban in older patients.[5,6] [7,8]

The consequences of under-dosing are currently uncertain. If under-dosing resulted in lower apixaban concentrations, increased stroke rates would be expected, as would lower bleeding rates. Analyses from administrative claims data lacking full assessment of dosing accuracy reported increased stroke rates without increased bleeding in patients with NVAF receiving apixaban classified as “under-dosed”. [7] Under-dosing was also initially reported to result in worse outcomes in patients enrolled in The Outcomes Registry for Better Informed Treatment of Atrial Fibrillation II (ORBIT-AF) registry. [9] However, when the outcomes were adjusted for patient risk characteristics, no significant difference in outcomes between “under-dosed” patients compared to patients dosed as recommended was detected in the ORBIT-AF registry. [10] These studies did not determine drug concentrations in relation to dosing or outcomes to investigate potential mechanisms for alterations in responses or outcomes.

Our primary goal was to measure plasma apixaban concentrations during routine clinical care of older adults with NVAF and compare apixaban concentrations between patients receiving recommended vs. lower-than-recommended dosing relative to concentrations reported from the pivotal trial on which marketing approval was granted (ARISTOTLE trial). [11] We found that older adults with NVAF receiving lower than recommended dosing of apixaban had the same proportion of concentrations within the ranges reported from patients receiving recommended doses, and, only patients receiving recommended doses had concentrations in excess of those observed in clinical trials.

METHODS

Patients and Data Collection. Clinically stable older adults with NVAF taking apixaban and seen at least once at an anticoagulation clinic during 2017 were invited to participate in the study. Written informed consent was obtained per protocol approved by the Health Sciences Research Ethics Board of the University of Western Ontario (London, Ontario, Canada). Patient age, sex, weight, height, apixaban dose regimen, concomitant use of moderate (amiodarone, diltiazem, fluconazole, verapamil) to strong (clarithromycin, ketoconazole, ritonavir) P-gp/CYP3A4 inhibitors and P-gp/CYP3A4 inducers (carbamazepine, phenytoin, phenobarbital, rifampin) , most recent serum creatinine, and date/time of last apixaban dose were collected when single steady-state blood samples were obtained. Blood samples were immediately stored at -4ºC before centrifugation at 2000g for 10 minutes for plasma isolation. Plasma samples were stored at -80ºC until further analysis. Apixaban concentrations were determined by liquid

chromatography tandem mass spectrometry as previously reported. [12] Lower limit of quantitation is 5 ng/mL. Assay performance across the 25, 250, and 1000 ng/mL quality controls were 1.5% and 8.5%, intraday bias and precision was 1.3% and 5.1%.

Data analysis. Dosing was categorized as recommended, higher-than, or lower-than-recommended. Recommended apixaban dosing in 5 mg twice daily reduced to 2.5 mg twice daily with two of the following present: age $\geq$ 80 y, weight $\leq$ 60 kg, serum creatinine $\geq$ 1.5 mg/dL, or a strong CYP3A4/P-gp inhibitor is co-administered without 2 of the 3 dose reduction criteria. (https://packageinserts.bms.com/pi/pi_eliquis.pdf). For patients meeting recommendations for 5 mg twice daily, apixaban concentrations were categorized as being within, higher, or lower than the expected 5-95% percentile at peak (91-321 ng/mL, median =171 ng/mL) or trough (41-230 ng/mL, median =103 ng/mL) compared to patients receiving 5 mg twice daily in the pivotal ARISTOTLE trial. [11] For patients receiving 2.5 mg twice daily as recommended, concentrations were similarly categorized in reference to patients receiving 2.5 mg twice daily in ARISTOTLE (peak: 69-221 ng/mL, 123 median; trough: 34-162 ng/mL, median 79 ng/mL). Concentrations were analyzed in relation to dosing accuracy by Chi Square

RESULTS

One hundred ten patients were studied (see Table 1 for characteristics). No patients received higher- than-recommended dosing. Sixty-eight patients received recommended dosing: 5 mg twice daily in 48 (26 had one dose reduction criteria: age in 16, weight in 3, creatinine in 7), and 2.5 mg twice daily in 20 (age criteria in

all; creatinine criteria in 13, weight criteria in 9 (two patients met all 3 dose reduction criteria). Forty-two received lower-than-recommended dosing of 2.5 mg twice daily (29 had one dose reduction criteria: age in 21, weight in 2, creatinine in 6). No patients received strong CYP3A4/5 P-gP inhibitors.

Apixaban concentrations after dosing in patients receiving the recommended dose of 5 mg twice daily and those receiving lower than recommended dosing at 2.5 mg twice daily are shown in Figure 1. One dosed as recommended and one dosed lower than recommended patient had concentrations below the expected 5-95% range at expected time of peak concentrations (91-321 ng/ml). In patients dosed-as-recommended with 5 mg twice daily, four (two older than age 90) had concentrations above expected 5-95% range at peak that occurred later than the reported 3-4 hours after dosing time of peak concentrations in two. Few patients were sampled at trough (12 hours after dosing) but none had concentrations below expected 5-95% range at trough in either group. No significant differences in proportion of apixaban concentrations within or outside expected ranges were detected between patients receiving lower-than-recommended doses and those dosed as recommended ($p=0.35$).

Concentrations from patients receiving appropriately reduced doses were compared to data from ARISTOTLE participants receiving appropriately reduced doses. Concentration vs. time data for these twenty patients receiving 2.5 mg twice daily as recommended are shown in Figure 2. Concentrations above the 5-95% range for expected peak from ARISTOTLE data (69-221 ng/mL) were seen in 7

of the 20 as late as 7 hours after dosing. Seventeen of the twenty had concentrations from 3 to 8.5 hours after dosing that were above the expected median peak level at 3-4 hours (123 ng/mL).

DISCUSSION

Our goal was to determine apixaban concentrations in older and very old adults in the community being treated with apixaban for the prevention of stroke in the presence of non-valvular atrial fibrillation. The mean age of patients studied in this report is 80.4 years (range 66-100), women represented 45% of the group, and one third received lower than recommended dosing. There are several key observations from our study. One is that patients receiving reduced dosages without meeting criteria for dosage reduction had apixaban concentrations within the ranges reported for the recommended doses. A second point is that a low and similar proportion of concentrations below expected peak concentrations was seen in patients receiving 2.5 mg twice daily without meeting criteria for dose reductions compared to patients receiving the recommended 5 mg twice daily. Third, only patients receiving recommended 5 mg twice daily dosing had concentrations far in excess of the expected 5-95% range for peak concentrations Numbers were small and the trend was not significant but raises concern as increasing apixaban concentrations produce greater anticoagulation and older adults are at higher basal risk for bleeding. Fourth, patients receiving

appropriately reduced doses of 2.5 mg twice daily had concentrations greater than patients receiving the 2.5 mg twice daily in the clinical trials. Finally, the data also suggest that clinicians recognize characteristics of patients that may warrant dosage reductions from recommendations based on randomized clinical trials.

Current clinical dosing recommendations for DOACs reflect the regimens that were used in the efficacy trials on which marketing approval was granted. For apixaban, recommended standard dosing is 5 mg twice daily reduced to 2.5 mg twice daily if the patient has two of the following characteristics: 80 years or older, weight of 60 kg or below, creatinine of 1.5 mg/dL or above; or, is co-administered a strong CYP3A4/5 P-gP inhibitor. (https://packageinserts.bms.com/pi/pi_eliquis.pdf). Dosing with 2.5 mg twice daily in the absence of 2 of the 3 criteria represents a 50% reduction from recommendations. The algorithm appears to have been selected to account qualitatively for possible changes in drug distribution or clearance (without more precise estimates of creatinine clearance) or the increased risk of bleeding in the very elderly. Most pivotal pre-marketing trials of DOACs did not report measurement of concentrations or anticoagulant effects and thus prescribing guidelines do not advocate laboratory monitoring of either DOAC concentrations or effects. However, DOAC concentrations are directly related to factor Xa inhibition and anticoagulation. Data recently published from the earlier trials show dabigatran and edoxaban have a direct relationship between drug concentrations, factor Xa inhibition and efficacy as well as bleeding outcomes for the treatment of patients with NVAF. [13-15] Apixaban concentration data from NVAF

clinical trials have recently been analyzed and published but have not been related to clinical outcomes. [16,17] Clinical laboratories are establishing DOAC assays and report the concentration

data from the clinical trials as reference ranges.

Importantly, pivotal non-valvular atrial fibrillation trials enrolled patients with mean age of 70 years, fewer women than men, almost no racial minorities, no patients on dialysis, resulting in only about 5% receiving the reduced dose. [18] This leaves a critical deficiency of data on use of apixaban in the complex and heterogeneous population of older adults with NVAF. Post-marketing registry studies or analyses of claims data have attempted to address this gap, and in general report equal efficacy in clinical populations to that seen during clinical trials. [7,9,10,19-22] However, major extracranial and GI bleeding rates were similar for warfarin and DOACs in

NVAF trials. Rates for major bleeding of 2.6-3.3% were reported for patients over age 75y in ARISTOTLE and were 4.5% per year for major and clinically relevant nonmajor bleeding in patients unsuitable for warfarin in AVERROES. [2,23,24] Major bleeding rates reported from administrative claims data are on the order of 4% -5% per year for major bleeding [7,10 7 10,25] but range from 2.6 -10%. [7,10,26,27 28] No post-marketing studies have analyzed either drug concentrations or factor Xa inhibition in relation to dosing or outcomes. When doses are higher than recommended, major bleeding rates rise [7]and have been reported as 6.9% [9]. We recognize our data are preliminary. Our sample was not random and patients receiving 2.5 mg twice daily not meeting dose reduction criteria were likely oversampled. Patients were seen or followed in a specialized anticoagulation clinic at a tertiary care

medical center capable of monitoring apixaban concentrations as part of a research program. We did not have outcomes data to relate the concentrations to either efficacy or adverse bleeding events but used the surrogate marker of drug concentration ranges reported from the clinical trials as the reference range by clinical laboratories that perform DOAC assaysWe also did not have information on reasons physicians prescribed lower than recommended dosing. Nonetheless, the data suggest that concentration responses to doses of apixaban in older patients encountered during routine clinical care may differ from the somewhat limited data reported from clinical trials.

There is a need for more information about prescribing, outcomes, as well as risks and benefits of DOAC use in the older patients with NVAF. [29]Until such data are available, the clinician is faced with balancing the high risk of embolic stroke from NVAF with the high risk of bleeding. Clinical laboratories are establishing DOAC assays and laboratory monitoring may provide helpful information.

CONCLUSION

Our findings raise questions about optimal dosing of apixaban in older adults with NVAF outside of clinical trials. Drug concentrations were higher than expected based on clinical trial data and should caution those who advocate that lower than recommended dosing be a target for correction.[30] Clinical laboratories are establishing DOAC assays and report the concentration data from the clinical trials as reference ranges. Our data support a role for monitoring factor Xa inhibition or

apixaban concentrations when treating patients that differ from those in randomized trials, or when considering dosing outside of published guidelines.

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Employment or Affiliation		x		x		X		x
Grants/Funds		x		X		x		x
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		x						
Speaker Forum				x		x	z	
Consultant		x		x		x	z	
Stocks		x		x		x		x
Royalties		x		x		x		x
Expert Testimony		x		x		x		x
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Employment or Affiliation		X		x		x		x
Grants/Funds		x		x		x		x
Honoraria	y			x		x		x
Speaker Forum		x		x		x		x
Consultant		x		x		x		x
Stocks		x		x		x		x
Royalties		x		x		x		x
Expert Testimony		x		x		x		x
Board Member		x		x		x		x
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LEGENDS

Figure 1. Apixaban concentrations after dosing in patients with recommended dosing of 5 mg twice daily.

Apixaban concentrations after dosing are shown from patients receiving lower than recommended dosing of 2.5 mg twice daily in red and those receiving recommended dosing of 5 mg twice daily in green. Dashed vertical lines indicate expected 5-95% range (and median) at peak (91-321 ng/mL at 3-4hrs after dosing, median 171 ng/ml) and trough (41-230 ng/mL, median 103 ng/mL at 12hrs after dosing).

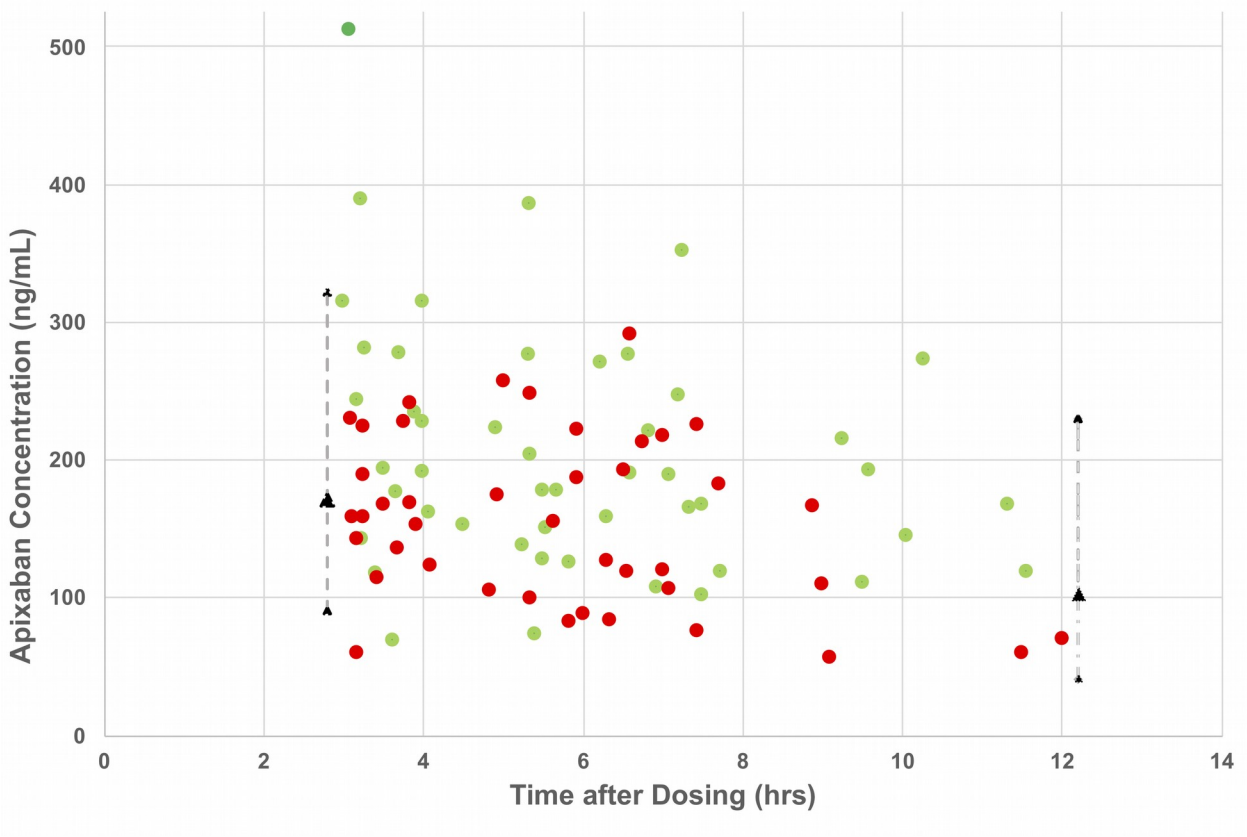
Figure 2. Apixaban concentrations after dosing in patients receiving recommended 2.4 mg twice daily.

Apixaban concentrations after dosing are shown from patients receiving recommended dosing of 2.5 mg twice daily Dashed vertical lines indicate expected 5-95% range (and median) at peak (69-221 ng/mL, median;123 ng/mL at 3-4hrs after dosing) and trough (34-162 ng/mL, median 79 ng/mL at 12hrs after dosing).

Table 1. Patient Characteristics and Apixaban Dosing

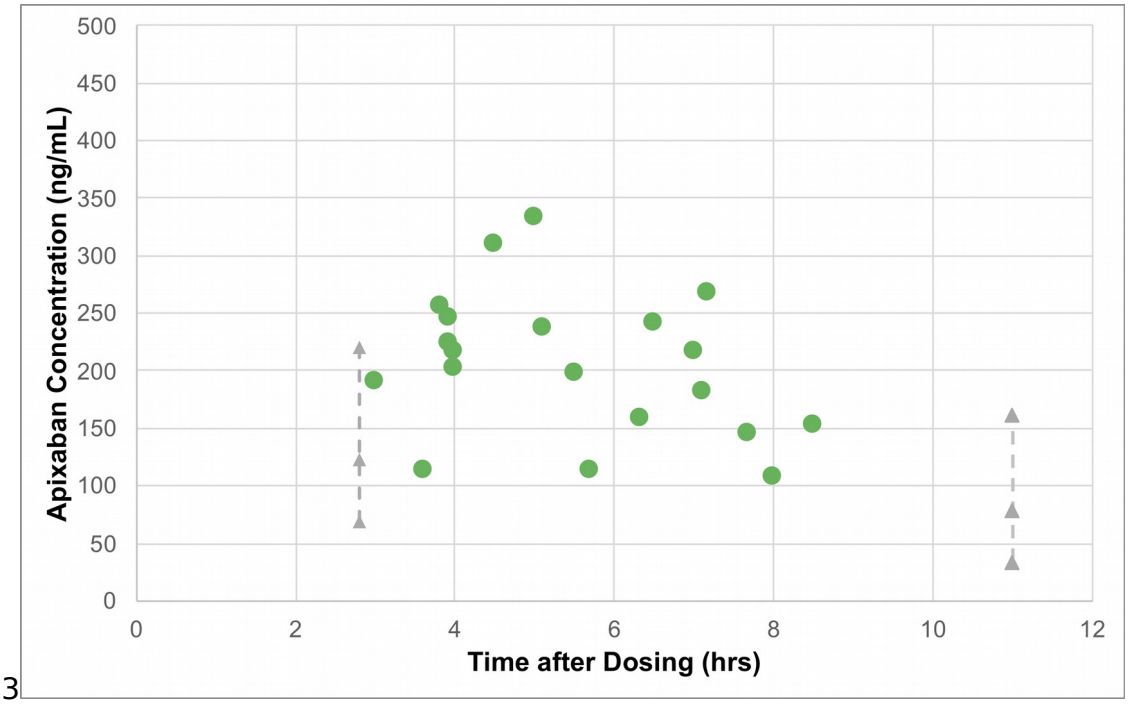
		Dosed as Recommended		Dosed lower than Recommended
		2.5 mg twice daily	5 mg twice daily	2.5 mg twice daily
N	110	20	48	42
Age (y) (range)	80.4± 7.8* (66-100)	88.6 ±5.3 (80-100)	77.8 ±7.2 (66-96)	79.4 ±6.9 (67-96)
Sex (men, women)	60, 50	5, 15	33, 15	22, 20
Race	White	White	White	White
Weight (kg)	86.4 ±21.4 (44-140.3)	71.1±22.2 (45.8-123.1)	94.6 ±19.7 (58-140.3)	83.9±18.6 (44-118.4)
Creatinine (mg/dL)	1.2±0.5 (0.6-2.7)	1.6 ±0.4 (0.8-2.7)	1.1 ±0.3 (0.6-2.0)	1.2±0.5 (0.6-2.7)
Creatinine Clearance (ml/min)	59 ± 27 14-143)	31 ± 15 (14-77)	68 ± 26 (35-143)	62 ± 24 (18-121)
Strong CYP3A4/5 P-gP Inhibitors	0	0	0	0
Moderate CYP3A4/5 P-gP Inhibitors^	20	6	6	8
Amiodarone	7	3	1	3
Diltiazem	13	3	5	5
Strong Inducer (carbamazepine)	1	0	0	1

*Data are mean ± SD, (range). ^ No dose adjustment recommended for moderate inhibitors.



431

432Figure 1.



433

434Figure 2.