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Apixaban Concentrations in Routine Clinical Care of Older Adults with Non-valvular Atrial Fibrillation

Running Title: Apixaban Concentrations in Older Adults with NVAF

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ABSTRACT

Background: Direct-acting oral anticoagulants are first line agents for prevention of stroke in patients with non-valvular atrial fibrillation (NVAF) but data are limited for the oldest patients, and, with reduced dosing.

Objectives: To determine steady-state apixaban peak and trough concentrations during routine care of older adults with NVAF, compare concentrations to clinical trial concentrations, and explore factors associated with concentrations.

Methods: Cross-sectional study of medically stable older adults with NVAF (≥75 yr or ≥70 if Black) receiving apixaban. Peak (2-4.4 hours post-dose) and trough (before next dose) concentrations determined by anti-Xa activity calibrated chromogenic assay. Patient characteristics associated with concentrations determined by multivariate modelling.

Results: Patients (n=115) were aged 80 (77-84) y (median(IQR)), 46 women, 69 men; 98 White, 11 Black, 6 Asian. With 5mg twice daily per labelling (n=88), peak concentrations were higher in women: 248±105 vs. 174±67ng/mL in men (p<.001) and exceeded expected 95% range in 6/30 vs 0/55 men (p=.002). With 2.5mg twice daily per label (n=11), concentrations were <5mg twice daily (peak:136±87 vs. 201±90ng/mL, p=.026; trough: 65±28 vs. 109±56ng/mL, p<.001); but not different than 2.5mg twice daily without reduction criteria (n=13, peak: 132±88; trough:65±31ng/mL). Covariates associated with concentrations included sex, number daily medications and creatinine clearance.

Conclusions: Older women had higher than expected peak apixaban concentrations and 2.5mg twice daily produced lower concentrations than standard dosing. Factors not currently included in dosing recommendations affected concentrations. The impact of apixaban concentrations on outcomes needs evaluation.

KEY WORDS

Direct-acting oral anticoagulant, anti-Xa activity, anticoagulation, novel oral anticoagulant, geriatric cardiology

ABBREVIATIONS:

ACE inhibitor: Angiotensin converting enzyme inhibitor
ACCOuNT: African American Cardiovascular Pharmacogenomics Consortium
ADL: Activities of daily living
ARB: Angiotensin receptor blocker
AUC: Area under the concentration vs. time curve
DOACs: Direct-acting oral anticoagulants
IADL: Independent activities of daily living
Mis-T: Telephone-Memory Impairment Screen
P-gp: P-glycoprotein
T-MoCA: Telephone-Montreal Cognitive Assessment

INTRODUCTION

Clinical care guidelines currently recommend direct-acting oral anticoagulants (DOACs) as first-line anticoagulants for stroke prevention in patients with non-valvular atrial fibrillation (NVAF), in part due to improved safety shown in clinical trials when compared to vitamin K antagonists.[1-3] However, clinical trials often under-enroll the oldest patients, women, patients with multiple medical conditions, patients receiving multiple medications, patients with moderate renal impairment, and patients with reduced physical function.[4-8] The real world experience for DOACs in the decade after marketing approval in the U.S. has been accompanied by reports of higher rates of major bleeding compared to the pivotal clinical trials and substantial use of lower than labelled dosing for apixaban with potentially worse clinical outcomes for NVAF patients receiving lower than recommended doses. [9,10,11,12,13-15 ,16, 17-21] Both increased bleeding rates and reduced doses may have important relationships with DOAC concentrations. Peak concentrations reflect the maximal level of anticoagulation and would be expected to be related to bleeding risk. Trough levels reflect the minimum level of anticoagulation and some minimum threshold would be expected to be related to efficacy.

Our goal was to examine peak and trough steady-state concentrations of apixaban, the most commonly prescribed DOAC in older adults with NVAF, and compare concentrations during routine clinical care to reports from the pivotal efficacy trial.[1] We also explored whether patient level factors related to apixaban concentrations.

METHODS

We conducted a cross-sectional prospective study of medically stable older adults with NVAF taking stable doses of apixaban prescribed by healthcare providers and enrolled non-Black patients who were 75 years or older and self-identified Black patients who were 70 years or older to mirror the age distribution and prevalence of NVAF in clinical populations and the shorter average life expectancy in Blacks The study was approved by the Institutional Review Board (IRB) of the University of California, San Francisco (UCSF).

Study Population and Data Collection

Recruitment. Participants were recruited from UCSF Healthand the African American Cardiovascular Pharmacogenomics Consortium (ACCOuNT). [22] At UCSF Health, we identified patients with NVAF receiving apixaban by searching electronic medical records and research participant registries. Recruitment was via email or postal invitations and informed consent was obtained. Separately, we established a collaborative data sharing agreement through Northwestern University Medical School on behalf of the ACCOuNT Consortium. De-identified data from outpatients enrolled in protocols approved by the Northwestern University Feinberg School of Medicine IRB for the Consortium (Northwestern Medicine, University of Chicago Medical Center, University of Illinois Chicago, George Washington University Hospital and Medical Faculty Associates, and Washington DC VA Medical Center) was accessed and participant data meeting study criteria were included.

Inclusion/exclusion criteria: Subjects were eligible if aged ≥70 years if self-identified as Black, otherwise if aged ≥ 75 years, taking a stable apixaban dose (≥1 month) for NVAF, and could provide informed consent. Patients were excluded if hospitalized, had medication changes in the past month, or had conditions that were exclusion criteria in the pivotal studies: renal dialysis or renal transplant, moderate or severe hepatic impairment (≥ Child-Pugh class B) or cirrhosis, or receiving strong combined CYP3A4/5 P-gp inhibitors or inducers. Moderate or severe cognitive impairment identified by modified telephone-Montreal Cognitive Assessment (T-MoCA) [23] and Telephone-Memory Impairment Screen (Mis-T) were also exclusion criteria.[24]

Data Collection. After informed consent, standardized video, in-person or telephone interviews were conducted and data entered into a REDCap database. Data included demographics, medical conditions, self-reported health status, self-report of activities and instrumental activities of daily living,[25] apixaban dosing, and use of prescription and non-prescription medications. Race was self-reported and categorized as American Indian or Alaska Native, Asian, Black/African American, Hispanic or Latino, Native Hawaiian or Other Pacific Islander, or White based on NIH Policy on Reporting Race and Ethnicity Data.[26] CHA_2DS_2-VASc

stroke risk score[27] and HAS-BLED bleeding risk[28] were calculated after medical record review. Clinical Frailty Score[29] was determined during interviews. Ethnicity, self-reported health status, activities of daily living, and Clinical Frailty Score were not available from the ACCOuNT consortium (n=11).

Venous blood was obtained at trough (immediately before next dose) and/or peak apixaban concentrations (2-4.4 hours after dosing) using mobile phlebotomy or hospital laboratory phlebotomy sites. Patients completed medication diaries of apixaban intake for two days prior to sampling for adherence assessment.

Laboratory measurements included apixaban concentrations by chromogenic anti-Xa assay (STA ® Liquid anti-Xa kit, Diagnostica Stago, Inc., Parsippany, N.J. USA) calibrated to apixaban, (analytical measurement range 29-554ng/mL) at UCSF Clinical laboratories or Northwestern Memorial Hospital Clinical Diagnostic Laboratory. Observed intra-day assay coefficient of variation (cv) is ≤3.8%; observed inter-day cv is ≤5.1%. Serum creatinine was measured, creatinine clearance (CrCL) estimated with Cockcroft and Gault formula using total weight,[30] and eGFR calculated by CKD-EPI formula.[31] Apixaban exposure was summarized as daily area under the concentration vs. time curve (AUC) calculated by trapezoidal rule for comparisons to ARISTOTLE.[32]

Classifying dosing concentrations, and concomitant medications. Apixaban dosing was classified as lower than label recommendation, in agreement, or higher than labelling per US Food and Drug Administration (FDA). Label recommendations for use of apixaban in NVAF are 5mg twice daily, reduced to 2.5mg twice daily if patients meet two of the following criteria (age≥80y, weight≤60kg, serum creatinine≥1.5mg/dL) or co-administration of a strong combined Pg-p/CYP3A4 inhibitor if otherwise qualifying for 5mg twice daily.[33] We identified moderate combined Pg-p/CYP3A4 inhibitors or inducers using the FDA-approved label [33] and drug interactions tables.[34] Expected concentration ranges for apixaban for stroke prevention in patients with NVAF were defined by International Council for Standardization in Hematology recommendations for measurement of DOACs by calibrated anti-Xa activity[35] and the literature.[36]

Statistical Methods. We compared baseline characteristics of patients by dosing group and by sex using χ^2 for proportions, unpaired two-sided t-tests for means of normally distributed variables and Wilcoxon rank-sum tests for non-normal continuous variables. Proportions of concentrations outside expected 5%-95% ranges were compared using χ^2 tests. Simple linear regression was used to assess univariate relationships between patient characteristics and apixaban concentrations. Separate multivariable regression analyses tested for relationships between peak and trough apixaban concentrations and factors expected to influence apixaban pharmacokinetics (age, sex, weight, health status, number daily medications, co-administration of moderate combined CYP3A4/5-Pg-p inhibitors, creatinine clearance, and frailty). Multivariable analyses were confined to the 5mg twice daily per labelling group due to small numbers receiving 2.5mg twice daily per label. Backward elimination was used for variable selection and the significance level at which variables were removed from the model was 0.05. Analyses were conducted using SAS 9.4 and R.[37]

RESULTS

Population. We enrolled 112 participants from UCSF Health and obtained data from 11 participants from the ACCOuNT consortium. Three withdrew, 4 became ineligible with intercurrent illness or sampling out of target timeframes, and 1 postponed participation (see **Supplemental Figure 1**). Demographic data for the final 115 participants are in **Table 1**. Median age was 80 years, 40% were women and 10% self-identified Black. Ninety-one received apixaban 5mg twice daily (3 at higher than labelling doses). Twenty-four received 2.5mg twice daily with 13 not meeting dose reduction criteria. Participants receiving 2.5mg twice daily were significantly older, weighed less, had a higher proportion of women, worse health status, lower creatinine clearance, and higher CHA_2DS_2-VASc Scores. Only weight and creatinine differed between men and women. Median number of daily oral medications was 5. Daily medications in >10% included: beta-blockers in 78 (68%), statins in 74 (64%), diuretics in 45 (39%), ACE inhibitors in 31 (27%), ARBs in 26 (23%), thyroid in 26 (23%), dihydropyridine calcium channel blockers in 23 (20%), proton pump inhibitors in 15 (13%),

tamsulosin in 14 (12%), aspirin in 16 (14%), antidepressants in 13 (11%), gabapentin in 13 (11%). Anti-arrhythmics were taken by 19 (17%) (flecainide in 8, dofetilide in 5, propafenone in 4, digoxin in 3). Three participants took NSAIDs. A minority (17%) took combined moderate CYP3A4/5-Pg-p inhibitors (9 on amiodarone, 10 on diltiazem, 1 on verapamil, 1 on ciprofloxacin); none took inducers. One hundred and four subjects completed medication diaries (noACCOuNT participants) and reported 100% apixaban adherence for 2 days prior to sampling.

Outcomes

Apixaban concentrations. Peak concentrations were measured at a mean of 3 hours after apixaban in all groups. Trough concentrations were immediately before dosing (mean of 12 hours after dosing in participants dosed per labelling and 11 hours in those taking 2.5mg lower than label recommendation). Mean and median apixaban concentrations by dose and sex for patients dosed per labelling are in the **Central Illustration** and as box plots in **Supplemental Figure 2**. Peak and trough apixaban concentrations for all dosing regimens are in **Figure 1** and in **Table 2** by dose, sex, and in comparison to expected 5-95% concentration ranges. **Table 3** presents peak and trough data by dose, sex, and patient characteristics.

Patients taking apixaban 5mg twice daily. Mean peak concentrations were 248±105ng/mL in women vs. 174±67ng/mL in men ($p<.001$); trough concentrations were 128±70ng/mL in women vs. 100±47ng/mL in men receiving recommended doses ($p<.041$). Six participants (7%) had peak concentrations > expected 95% range (>321ng/mL) withlabelled dosing; all were women (6/30; $p=.002$). One weighed <60kg, one received a combined CYP3A4/5-P-gp moderate inhibitor, 3 had CrCL <50mL/min (and eGFR <60mL/min/1.73M^2). Trough concentration was <5% range in 1 man. The 3 subjects taking 5mg twice daily at higher than labelling had peak and trough concentrations within the expected 5%-95% range.

Patients taking apixaban 2.5mg twice daily. Patients receiving 2.5mg twice daily per label had concentrations similar to expected ranges for 2.5mg twice daily. Compared to expected ranges for 5mg twice daily, peak

concentrations were >95% for one woman dosed per label (CrCL of 38mL/min. eGFR of 56ml/min/1.73M^2,) and one man dosed < label, CrCL 30mL/min, eGFR 52ml/min/1.73M^2). Trough concentrations were <5% range in 2 women (dosed per label) and 1 man (dosed lower than label). No differences in peak or trough concentrations were detected between patients receiving 2.5mg twice daily per labelling versus lower than label dosing. **Supplemental Figure 3** presents peak and trough data for individuals for all dosing regimens.

Dosing regimen comparisons. Both mean peak and trough concentrations, and daily exposure as area under the concentration vs. time curve (AUC), were 32-41% lower in patients receiving recommended 2.5mg twice daily compared to those receiving recommended 5mg twice daily (p=.026 for peak, p<.001 for trough, and p=.003 for AUC).

Characteristics associated with apixaban concentrations. On univariate testing for dosing with 5mg twice daily, significant associations between apixaban concentrations andsex, number of daily medications, and CrCLwere identified. **(Table 3)** Associations were also seen with co-administration of moderate CYP3A4/5 inhibitors. No associations were detected for age, weight, race, self-reported health status, or Clinical Frailty Score. **Figure 2** presents estimated mean and 95% CI for concentrations defined by variables in multivariate analysis. The final multivariable model of peak concentrations included sex, number of daily medications and CrCL (R^2= 0.34, see **Table 4**). Adjusted average peak apixaban concentrations were 65.9ng/mL (95% CI 31.5,100.2ng/mL) higher in women than in men, increased by 11.0ng/mL (95% CI: 4.4,17.6ng/mL) for each additional daily medication, and increased by 13.8ng/mL (95% CI: 5.0,22.7ng/mL) for every 10 mL/min decrease in CrCL. Estimated peak concentrations for patients with CrCL of 40 mL/min were 217.0±17.4ng/mL for a man and 283.0±17.3ng/mL for a woman.

The final multivariable model of trough concentrations also included sex, number of daily medications, and CrCL (R^2= 0.17). The adjusted average trough concentrations were 25.9ng/mL (95% CI: 0.2,51.5ng/mL) higher in women than men, increased by 6.4ng/mL (95% CI: 1.5,11.3ng/mL) for each additional daily

medication, and increased by 7.0ng/mL (95% CI: 0.2,13.8ng/mL) for every 10 mL/min decrease in CrCL. Estimated trough concentrations for patients with CrCL of 40mL/min were 121±12.9ng/mL for a man and 147±13.5ng/mL for a woman.

DISCUSSION

Our findings challenge the current consensus regarding apixaban dosing in older patients with NVAF in several important ways. We found that women on average had higher peak and trough concentrations than men. Mean peak concentrations were 43% higher in older women with NVAF receiving recommended doses of 5mg twice daily compared to older men receiving recommended doses of 5mg twice daily. This was associated with daily apixaban exposure, or daily area under the concentration vs. time curve (AUC), that was 36% higher in women compared to men. These differences are larger than the 15% higher daily apixaban exposure seen in women compared to men in the pivotal clinical trial (ARISTOTLE)[1] that informed labelling recommendations.[32] Perhaps more important than average differences between women and men, was that 20% of these older women receiving 5mg twice daily according to labelling had peak concentrations above the upper 95% range estimated from ARISTOTLE.[36] Apixaban has a slow absorption rate producing broad peaks suggesting these women had high concentrations for a significant fraction of a dosing interval. Concentrations observed in these women and the apixaban daily exposure as AUC were associated with the highest major bleeding rates in analyses from ARISTOTLE.[32] Observational studies have reported higher than expected single apixaban concentrations at varying timepoints after dosing in older Caucasian patients with NVAF,[38-41] have related higher concentrations to bleeding ,[42,43] and reported that trough concentrations that are high on one measurement are high on repeated measurement.[44] The aggregate data suggests that higher apixaban concentrations are a contributing and potentially modifiable factor to higher bleeding rates in older patients,[45] especially older women.

The second finding with important clinical implications is the lower concentrations with reduced dosing of apixaban. Even with label-recommended dosing, 2.5mg twice daily produced 32%-41% lower apixaban

exposure compared to 5mg twice daily. This is a larger difference than the 25% lower exposure observed in ARISTOTLE. [1] Only 4.7% of those randomized to apixaban in ARISTOTLE received 2.5mg twice daily (with 15% not meeting study-defined reduction criteria). Thus, conclusions regarding the efficacy of apixaban for stroke prevention in NVAF are based on the 95% of NVAF patients receiving 5mg twice daily and concentrations associated with those doses. Curvilinear relationships have been modelled for stroke prevention as well as bleeding for dabigatran and edoxaban.[46,47] Across the range of apixaban concentrations analyzed in subgroups of ARISTOTLE and in AVERROES, relationships were detected for bleeding and concentrations but not stroke, although events were low in the limited numbers of patients with concentrations measured.[1,48] One observational study examining DOAC concentrations and stroke/thrombotic events in 565 AF patients (208 on apixaban) found thromboembolic complications only in patients with concentrations in the lowest quartile for each drug.[49] Estimates are that 25-40% of NVAF patients are prescribed 2.5mg twice daily and outcomes may be worse when dosed lower than label recommendations[11,12] Until stroke prevention efficacy of 2.5mg twice daily apixaban is demonstrated, it would seem logical that evidence-based goals in patients with NVAF would be to approximate concentrations shown to be efficacious for stroke prevention with 5mg twice daily dosing.

Important differences exist between clinical trial populations and patients receiving apixaban during routine clinical care. Patients receiving DOACs during routine clinical care are on average older with 25-40% over the age of 80 years compared to the mean age of 70 in the pivotal clinical trial, Renal clearance on average is lower with only 15% with moderate renal impairment enrolled inARISTOTLE compared to 26% in this study, and the number of co-morbidities and co-medications are higher in real world patients with NVAF treated with DOACs. Routine monitoring of DOAC or apixaban concentrations or anti-Xa activity is not currently recommended, and a number of experts advocate for strict adherence to the doses used in ARISTOTLE. [50-52] We found significant associations between apixaban concentrations and the number of daily medications and

with CrCLin this study focused exclusively on older adults. To date, polypharmacy has not been a consideration in dosing guidelines. Most DOAC doses are adjusted for estimated renal clearance, but criteria for apixaban dosage reduction are based on age, body weight, and serum creatinine (or co-medications). Measurement of creatinine alone to estimate renal clearance is recognized as suboptimal in older adults. Our data suggest CrCL may have a role in estimating apixaban dosing as recommended by at least one European Society. [53]

Study Limitations

Our study has limitations as a prospective observational study with dosing prescribed by healthcare providers. The sample was moderately sized yet may not reflect the entire target patient population. However, the age and sex distribution and proportion of patients receiving each dosage match real world data from large databases,[9,13,14,19] unlike the pivotal ARISTOTLE trial.[1] We did not assess outcomes. We sampled at the time of estimated peak concentrations and our results may be underestimates. Fewer patients were prescribed apixaban 2.5mg twice daily limiting our analyses for this regimen. Finally, the study was conducted during the COVID-19 pandemic that limited a broader or more diverse population sample.

CONCLUSIONS

In this prospective cross-sectional study of older adults with NVAF, we found female sex, number of daily medications, and creatinine clearance to be associated with apixaban concentrations. Our data suggest that current dosing recommendations may not provide concentrations shown to be associated with safety or efficacy in patients with AF. While data using monitored DOAC concentrations to improve clinical outcomes is currently lacking, our findings support a practice of ensuring that apixaban concentrations in older women and those on 2.5mg twice daily are within expected ranges. The role of concentration measurements to improve clinical outcomes with apixaban warrants evaluation.

CLINICAL PERSPECTIVES

Clinical Competency in Patient Care: Routine monitoring of DOAC concentrations is not currently recommended during care of patients with NVAF, but current dosing recommendations may not provide apixaban concentrations previously shown to be safe and effective. Concentrations may lie outside expected ranges in older women, patients with reduced creatinine clearance, and those receiving polypharmacy or moderate CYP3A4/5 inhibitors.

Translational Outlook: Higher than expected peak concentrations of apixaban with in older women may be a modifiable risk factor for bleeding that warrants consideration and investigation. Reduced dosing with apixaban was infrequent in randomized trials and the lower concentrations seen with reduced dosing suggests that reduced dosing regimens need further evaluation.

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FIGURE LEGENDS

Figure 1: Peak and Trough Apixaban Concentrations for 5 and 2.5mg Twice Daily

Apixaban concentrations after dosing in patients receiving 5mg twice daily (on left) or 2.5mg twice daily (on right). Pink indicates data from women and blue indicates data from men. Squares and vertical lines indicate mean±SE. Larger closed circles indicate higher than labeled dosing and open circles indicate lower than labeled dosing. Shaded rectangles indicate the 5-95% range modeled and reported from the pivotal clinical trial (ARISTOTLE) at the time of peak (2.6-4.4hr) or trough (9.6-14.4hr) concentrations for 5mg twice daily and vertical striped rectangles indicate the reported 5-95% range for 2.5mg twice daily. [36]

Figure 2: Forest Plot of Multivariate Results for 5mg Apixaban Twice Daily per Label. The estimated mean and 95% confidence interval for peak and trough apixaban concentrations defined by variables in the multivariate analysis: sex, number of daily medications, clinical frailty category, co-administrations of moderate CYP3A-Pgp inhibitors, and dichotomized for creatinine clearance, weight, and number of daily medications. The dashed vertical lines represent the average for 5mg twice daily per label.

CENTRAL ILLUSTRATION: Apixaban Concentrations: Dose and Sex Effect

Mean±SE apixaban concentrations with 5mg (green) or 2.5mg (orange) twice daily per labelling are in the left panel and model-derived average concentrations ±SE for women and men receiving 5mg twice daily per label are on the right.

Supplemental Figures:

Figure S1: **CONSORT Diagram**

Flowchart of subject recruitment, enrollment, and data enrichment from the ACCoUNT Consortium. Mean age±SD and sex are provided at each step. Final analyses included 115 subjects with full demographic details in Table 1.

Figure S2: Box Plot of Apixaban Concentrations for Dose and Sex Categories

Apixaban concentrations with 5mg (green) and 2.5mg (orange) twice daily per labelling are on the left and concentrations with 5mg twice daily per label for women and men are shown on the right. Boxes shown the median and IQ, whiskers indicate highest and lowest quartiles, circles are outliers (x=mean).

Figure S3: Peak and Trough Apixaban Concentrations for Individual Patients

Dosing per labelling is indicated for 5mg twice daily in blue and 2.5mg twice daily in black. Red lines represent data for patients receiving 5mg twice daily higher than labelling. Dotted gold lines represent data from patients receiving reduced dosing of 2.5mg twice daily without meeting dose reduction criteria.

Table 1. Patient Characteristics and Apixaban Dosing

					5 mg twice daily			2.5 mg twice daily		
	Total	**5 mg twice daily**	**2.5 mg twice daily**	***P* Value**	**Women**	**Men**	***P* Value**	**Women**	**Men**	***P* Value**
Total	115	91 (79)	24 (21)		31 (34)	60 (66)		15 (63)	9 (38)	
Age (y)	80 (77-84)	79 (76-82)	86 (82-87)	<0.001[a]	78 (76-80)	80 (76-82)	0.590[a]	84 (80-88)	87 (84-87)	0.352[a]
Weight (kg)	77 (67-86)	80 (72-91)	58 (54-74)	<0.001[a]	70 (62-80)	81 (77-93)	<0.001[a]	56 (51-58)	76 (73-83)	0.002[a]
BMI (kg/M^2)	25 (23-28)	26 (23-29)	23 (20-25)	0.002[a]	24 (22-28)	26 (24-29)	0.233[a]	22 (19-24)	25 (24-28)	0.008[a]
Sex (Men)	69 (60)	60 (66)	9 (38)	0.011[b]						
Race										
Asian	6 (5)	3 (3)	3 (13)	0.134[b]	0 (0)	3 (5)	0.118[b]	3 (20)	0 (0)	0.525[b]
Black or African American	11 (10)	8 (9)	3 (13)		5 (16)	3 (5)		2 (13)	1 (11)	
White	98 (85)	80 (88)	18 (75)		26 (84)	54 (90)		10 (67)	8 (89)	
Ethnicity										
Hispanic or Latino	0 (0)	0 (0)	0 (0)	0.696[b]	0 (0)	0 (0)	0.116[b]	0 (0)	0 (0)	0.533[b]
Not Hispanic or Latino	104 (90)	83 (91)	21 (88)		26 (84)	57 (95)		14 (93)	7 (78)	
Not Reported	11 (10)	8 (9)	3 (13)		5 (16)	3 (5)		1 (7)	2 (22)	
Self-reported health	105[d]	83	22		26	57		14	8	
Excellent	8 (8)	8 (10)	0 (0)		3 (12)	5 (9)		0 (0)	0 (0)	
Very good	45 (43)	39 (47)	6 (27)	0.042[b]	8 (31)	31 (54)	0.238[b]	3 (21)	3 (38)	0.046[b]
Good	38 (36)	28 (34)	10 (45)		12 (46)	16 (28)		9 (64)	1 (13)	
Fair	14 (13)	8 (10)	6 (27)		3 (12)	5 (9)		2 (14)	4 (50)	
ADL	6 (6-6)[d]	6 (6-6)	6 (6-6)	0.623[a]	6 (6-6)	6 (6-6)	0.516[a]	6 (6-6)	6 (6-6)	>0.999[a]
IADL	8 (8-8)[d]	8 (8-8)	8 (8-8)	0.727[a]	8 (8-8)	8 (8-8)	0.387[a]	8 (8-8)	8 (8-8)	0.188[a]

Table 1. Patient Characteristics and Apixaban Dosing Continued

					5 mg twice daily			2.5 mg twice daily		
	Total	**5 mg twice daily**	**2.5 mg twice daily**	***P* Value**	**Women**	**Men**	***P* Value**	**Women**	**Men**	***P* Value**
Creatinine (mg/dL)	1.00±0.30, 1.00	1.00±0.30, 1.00	1.00±0.30, 1.00	0.835[c]	0.90±0.30, 1.00	1.10±0.30, 1.00	0.005[c]	0.90±0.30, 1.00	1.20±0.20, 1.00	0.010[c]
Range	0.50-2.10	0.50-2.10	0.50-1.50		0.50-2.10	0.70-2.00		0.50-1.40	0.80-1.50	
Creatinine Clearance (mL/min)	63±20, 61	68±19, 67	47±12, 46	<0.001[c]	63±20, 57	70±18, 68	0.095[c]	44±13, 43	51±11, 49	0.207c[c]
Range	25-122	28-122	25-75		28-106	30-122		25-75	38-69	
eGFR CKD-EPI (mL/min/1.73 m^2)	69 (55-80)	70 (58-81)	60 (50-77)	0.105[a]	70 (52-82)	70 (58-80)	0.741[a]	66 (52-78)	57 (46-59)	0.387[a]
CHA_2DS_2-VASc Score	4 (3-5)	4 (3-5)	5 (3-6)	0.041[a]	4 (4-5)	4 (3-5)	0.055[a]	5 (4-6)	4 (3-5)	0.143[a]
HAS-BLED Score	2 (1-2)	2 (1-2)	2 (1-2)	0.607[a]	2 (1-2)	2 (1-2)	0.732[a]	2 (1-2)	2 (1-2)	0.793[a]
Clinical Frailty Score[d]	3 (2-3)	2 (2-3)	3 (2-3)	0.400[a]	3 (2-4)	2 (1-3)	0.106[a]	3 (2-3)	3 (1-4)	0.619[a]
Charlson Co-morbidity Score	5 (4-6)	4 (4-6)	6 (5-7)	0.012[a]	4 (3-6)	5 (4-6)	0.100[a]	6 (4-6)	6 (5-7)	0.624[a]
Co-administration moderate CYP3A4/5-P-gp Inhibitors (No Inhibitors)	95 (83)	76 (84)	19 (79)	0.762[b]	26 (84)	50 (83)	1.00[b]	12 (80)	7 (78)	1.00[b]
Number of daily medications	5 (4-7)	5 (4-7)	5 (4-7)	0.953[a]	5 (4-8)	6 (4-7)	0.889[a]	5 (4-6)	5 (4-8)	0.832[a]

Values are n (%), median (IQR), or mean±SD, median; percentages may not add to 100 due to rounding

[a]Wilcoxon rank-sum tests

[b]χ^2 tests

[c]Unpaired two-sided t-tests

[d]Not assessed in 10 subjects included from ACCOuNT Consortium: Total (N=105), 5 mg twice daily (N=83, Women N=26, Men N=57), 2.5 mg twice daily (N=22, Women N=14, Men N=8)

Table 2. Peak and Trough Apixaban Concentrations by Dosing Regimen

	5 mg twice daily (n=91)		2.5 mg twice daily (n=24)	
	Dosed per label	**Dosed Higher than label**	**Dosed per label**	**Dosed Lower than label**
Total	88 (97)	3 (3)	11 (46)	13 (54)
Men, Women	58, 30	2, 1	2, 9	7, 6
Peak Concentrations (ng/mL)				
	83 (94)	3 (100)	11 (100)	13 (100)
	201±90	233±53	136±87	132±88
	Compared to range for 5 mg twice daily[a]			
Above 95% range	6 (7)	0 (0)	1 (9)	1 (8)
Women	6	0	1	0
Below 5% range	5 (6)	0 (0)	4 (36)	5 (38)
Men	5	0	0	4
			Compared to range for 2.5 mg twice daily[b]	
Above 95% range	-	-	*2 (18)*	*2 (15)*
Women			*2*	*1*
Below 5% range	-	-	*1 (9)*	*1 (8)*
Men			*0*	*1*
Trough Concentrations (ng/mL)				
	80 (91)	3 (100)	10 (91)	11 (85)
	109±56	163±48	65±28	65±31
	Compared to range for 5 mg twice daily[a]			
Above 95% range	4 (5)	0 (0)	0 (0)	0 (0)
Women	2	0	-	-
Below 5% range	1 (1)	0 (0)	2 (20)	2 (18)
Men	1	0	0	2
			Compared to range for 2.5 mg twice daily[b]	
Above 95% range	-	-	*0 (0)*	*0 (0)*
Below 5% range	-	-	*2 (20)*	*1 (9)*
Men			*2*	*1*
Daily AUC (ng*hr/mL)[c]				
	75 (85)	3 (100)	10 (91)	11 (85)
	3643±1540	4784±1015	2138±905	2056±1072

Values are n (%), mean ±SD. Percentages may not add to 100% due to rounding.
[a]Compared to estimated 5-95% range for apixaban 5 mg twice daily[35]
[b]Italics are compared to estimated 5-95% range for apixaban 2.5 mg twice daily per labelling[35]
[c]Participants with both peak and trough concentrations

Table 3. Univariate Analyses of Apixaban Concentration Data for 5 mg Twice Daily per Label

	Peak Concentration (ng/mL)				Trough Concentration (ng/mL)			
Characteristic			**Difference in Means (95% CI)**	***P* Value[a]**			**Difference in Means (95% CI)**	***P* Value[a]**
Categorical								
Sex								
Male	53 (64)	174±67	Reference Group	<0.001	55 (69)	100±47	Reference Group	0.041
Female	30 (36)	248±105	74.9 (37.3, 112.4)		25 (31)	128±70	27.5 (1.1, 54.0)	
Race								
White	74 (89)	196±78	Reference Group		76 (95)	107±57	Reference Group	
Black or African American	7 (8)	222±182	26.0 (-44.5, 96.5)	0.330	1 (1)	109±NA	1.8 (-111.1, 114.8)	0.489
Asian	2 (2)	282±45	86.1 (-41.6, 213.8)		3 (4)	147±47	39.8 (-26.2, 105.9)	
Self-reported health status								
Very good or Excellent	43 (57)	192±67	Reference Group		44 (56)	102±46	Reference Group	
Good	25 (33)	209±81	16.6 (-22.9, 56.1)	0.698	27 (34)	117±63	15.1 (-12.6, 42.7)	0.522
Fair or Poor	8 (11)	203±123	10.5 (-50.0, 71.0)		8 (10)	116±85	13.5 (-30.0, 56.9)	
Clinical Frailty Score								
Very fit or Well	38 (50)	196±75	Reference Group		40 (51)	104±51	Reference Group	
Managing well	22 (29)	189±66	-7.7 (-49.5, 34.2)	0.492	23 (29)	100±36	-4.6 (-33.7, 24.5)	0.147
Vulnerable or Mildly frail	16 (21)	219±100	22.4 (-24.2, 68.9)		16 (20)	133±85	28.9 (-4.0, 61.8)	
Combined CYP3A4/5-P-gp moderate inhibitors								
No inhibitors	69 (83)	191±83	Reference Group	0.032	69 (86)	107±57	Reference Group	0.600
Inhibitors	14 (17)	247±110	56.0 (4.9, 107.2)		11 (14)	117±49	9.7 (-26.8, 46.1)	
Continuous								
1 Additional Daily Medication			11.1 (3.4, 18.7)	0.005			5.5 (0.4, 10.6)	0.036
Age (per 5 years)			5.8 (-17.6, 29.2)	0.624			7.7 (-7.3, 22.7)	0.310
10 mL/min decrease in CrCL			17.7 (7.9, 27.6)	<0.001			7.5 (0.5, 14.5)	0.035
Weight (per 5 kg)			-1.4 (-7.4, 4.7)	0.654			-0.3 (-4.0, 3.4)	0.886
Charlson Comorbidity Score			0.4 (-11.0, 11.8)	0.949			3.5 (-3.6, 10.6)	0.332

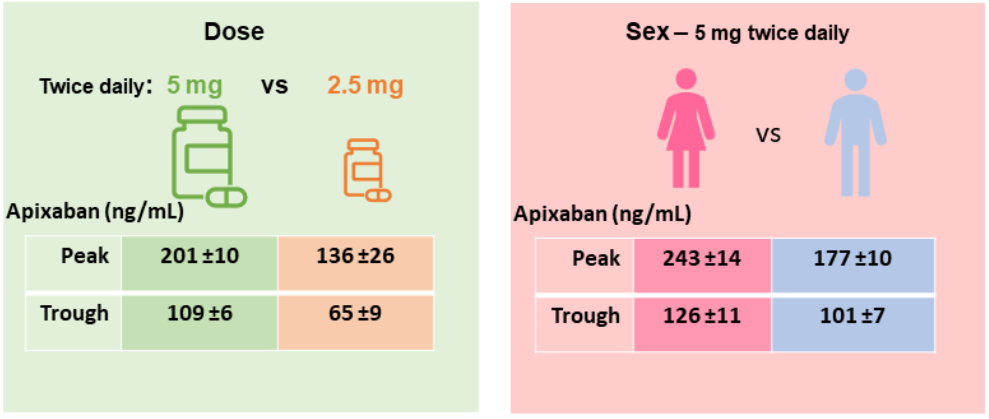
Values are n (%) or mean±SD

[a]P value is based on overall F-test of univariate linear regression of concentration on selected characteristic.

Table 4. Multivariate Analyses of Apixaban Concentration Data for 5 mg twice daily per Label

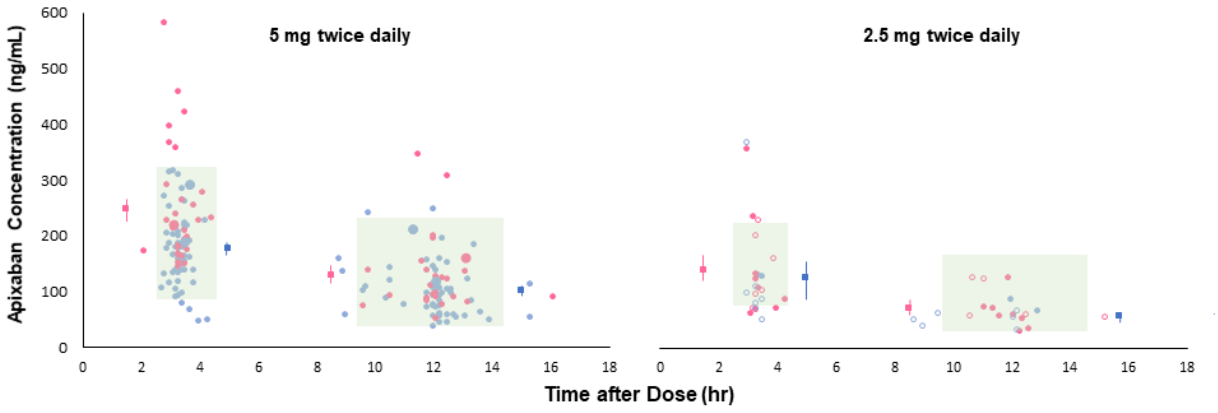
	Peak Concentration			Trough Concentration		
Parameter	**Estimate (ng/mL)**	**(95% CI)**	**R^2**	**Estimate (ng/mL)**	**(95% CI)**	**R^2**
Female v. Male	65.9	(31.5, 100.2)		25.9	(0.2, 51.5)	
1 Additional Daily Medication	11.0	(4.4, 17.6)	0.34	6.4	(1.5, 11.3)	0.17
Per 10 mL/min decrease Creatinine Clearance	13.8	(5.0, 22.7)		7.0	(0.2, 13.8)	

CENTRAL ILLUSTRATION: Apixaban Concentrations, Dose and Sex Differences



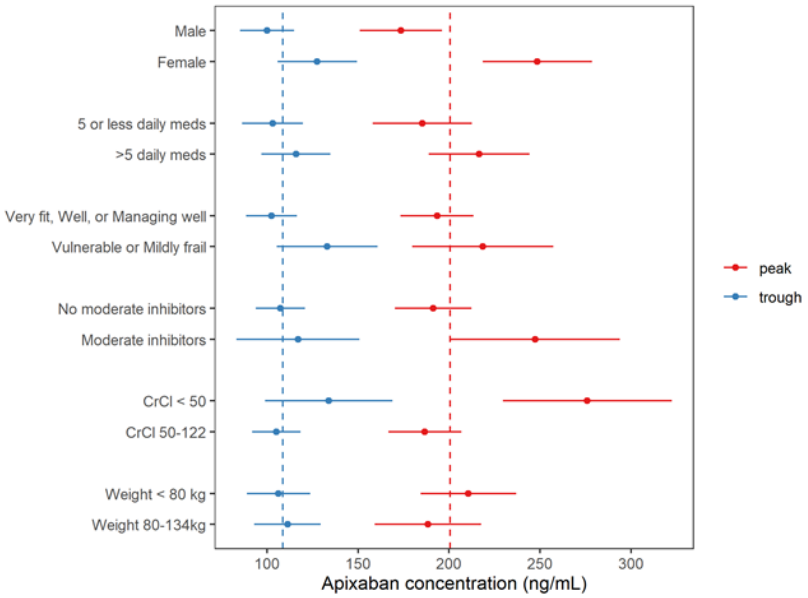
Mean ± SE apixaban concentrations with 5mg (green) or 2.5mg (orange) twice daily per labelling are in the left panel and model-derived average concentrations ± SE for women and men receiving 5 mg twice daily per label are on the right.

Figure 1. Peak and Trough Apixaban Concentrations for 5 and 2.5mg Twice Daily



Apixaban concentrations after dosing in patients receiving 5mg twice daily (on left) or 2.5mg twice daily (on right). Pink indicates data from women and blue indicates data from men. Squares and vertical lines indicate mean±SE. Larger closed circles indicate higher than labeled dosing and open circles indicate lower than labeled dosing. Shaded rectangles indicate the 5-95% range modeled and reported from the pivotal clinical trial (ARISTOTLE) at the time of peak (2.6-4.4 hr) or trough (9.6-14.4 hr) concentrations for 5mg twice daily and vertical striped rectangles indicate the reported 5-95% range for 2.5mg twice daily. [35]

Figure 2: Forest Plot of Multivariate Results of 5mg Apixaban Twice Daily per Label



The estimated mean and 95% confidence interval for peak and trough apixaban concentrations defined by variables in the multivariate analysis: sex, number of daily medications, clinical frailty category, co-administrations of moderate CYP3A-Pgp inhibitors, and dichotomized for creatinine clearance, weight, and number of daily medications. The dashed vertical lines represent the average for 5mg twice daily per label.