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Apixaban Concentrations with Lower than Recommended Dosing in Older Adults with Atrial Fibrillation

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Authors

Sukumar, Smrithi
Gulilat, Markus
Linton, Bradley
[et al.](#)

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1 Apixaban concentrations with lower than recommended dosing in older adults with
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5 Smrithi Sukumar ^a, Markus Gulilat, PhD ^b, Bradley Linton ^c, Steven E. Gryn, MD ^b,

6 George K. Dresser, MD ^b, Jeffrey E. Alfonsi, MD ^b, Ute I. Schwarz, MD, PhD ^b,

7 Richard B. Kim, MD ^b, Janice B. Schwartz, MD ^a

8 ^a University of California, San Francisco, San Francisco, CA

9 ^b Schulich School of Medicine and Dentistry, Western University, London, ON
10 Canada

11

12 ^c Pharmacy Services, London Health Sciences Centre, London, ON Canada

13

14 Corresponding Author: Janice B. Schwartz, MD

15 3333 California Street, UCSF Box 1265

16 San Francisco, CA 94143-1265

17 Email: Janice.schwartz@ucsf.edu phone: (415)502-3710

18 Alternate corresponding author: Smrithi Sukumar

19 Email Smrithi.Sukumar@ucsf.edu

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30

31

32 **ABSTRACT**

33

34 **Background/ Objectives**

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

39 **Design**

40 Convenience sample of patients receiving anticoagulation during 2017

41 **Setting**

42 Academic medical center

43 **Participants**

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

46 **Measurements**

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

48 **Results**

49 One hundred and ten older adults with NVAF (mean age of 80.4 years, range 66-
50 100 with 45% women) were studied. Forty-eight patients received recommended
51 dosing of 5 mg twice daily and 42 received lower-than-recommended dosing. One
52 patient in each category had concentrations below expected 5-95% range at time
53 of peak concentrations. Differences in proportion of apixaban concentrations within
54 or outside expected ranges were not significant between patients receiving lower-
55 than-recommended doses and those dosed-as-recommended at 5 mg twice daily

56(p=0.35). However, in patients dosed-as-recommended with 5 mg twice daily, four
57had concentrations above 5-95% range for peak levels expected at 3-4 hours after
58dosing; in two, this occurred around the midpoint of the dosing interval. Twenty
59patients received 2.5 mg twice daily as recommended. One third had apixaban
60concentrations higher than expected peak concentrations compared to the clinical
61trials and, over 2/3 had levels above the reported median for peak concentrations.

62**Conclusions**

63Apixaban concentrations in older adults with NVAF seen clinically were higher than
64expected based on clinical trial data. The findings raise questions about the
65optimal dosing of apixaban in older adults with NVAF encountered outside of
66clinical trials and suggest a role for monitoring of apixaban concentrations during
67care of patients that differ from those in randomized trials, or when considering
68dosing outside of published guidelines.

69

70Keywords: apixaban, direct-acting oral anticoagulant, non-valvular atrial fibrillation,
71dosing accuracy,

72

73INTRODUCTION

74Direct-acting oral anticoagulants (DOACs) are replacing vitamin K antagonists for
75anticoagulation due to fewer food and medication interactions and simplified dosing and
76monitoring regimens.¹ While DOACs have been shown to have equivalent or superior
77efficacy to prevent stroke or systemic emboli in patients with non-valvular atrial fibrillation
78(NVAF) with fewer intracranial hemorrhages in randomized trials,²⁻⁴ there are limited data
79on older adults with NVAF during routine clinical care. These patients are often older,
80more likely to be women, have more co-morbidities, falls, and higher bleeding risks than
81those enrolled in clinical trials. Possibly due to these factors, post-marketing analyses
82of DOAC use in patients with NVAF report prescribed doses often inconsistent with
83product labelling.¹ Lower-than-recommended dosing is more common than higher-
84than-recommended dosing, especially for apixaban in older patients.^{5,6 7,8}

85The consequences of under-dosing are currently uncertain. If under-dosing resulted in
86lower apixaban concentrations, increased stroke rates would be expected, as would lower
87bleeding rates. Analyses from administrative claims data lacking full assessment of
88dosing accuracy reported increased stroke rates without increased bleeding in patients
89with NVAF receiving apixaban classified as “under-dosed”.⁷ Under-dosing was also
90initially reported to result in worse outcomes in patients enrolled in The Outcomes
91Registry for Better Informed Treatment of Atrial Fibrillation II (ORBIT-AF) registry.⁹
92However, when the outcomes were adjusted for patient risk characteristics, no significant
93difference in outcomes between “under-dosed” patients compared to patients dosed as
94recommended was detected in the ORBIT-AF registry.¹⁰ These studies did not determine
95drug concentrations in relation to dosing or outcomes to investigate potential mechanisms
96for alterations in responses or outcomes.

97Our primary goal was to measure plasma apixaban concentrations during routine
98clinical care of older adults with NVAF and compare apixaban concentrations
99between patients receiving recommended vs. lower-than-recommended dosing
100relative to concentrations reported from the pivotal trial on which marketing
101approval was granted (ARISTOTLE trial).¹¹ We found that older adults with NVAF
102receiving lower than recommended dosing of apixaban had the same proportion of
103concentrations within the ranges reported from patients receiving recommended doses,
104and, only patients receiving recommended doses had concentrations in excess of those
105observed in clinical trials.

106**METHODS**

107 **Patients and Data Collection.** Clinically stable older adults with NVAF taking
108apixaban and seen at least once at an anticoagulation clinic during 2017 were
109invited to participate in the study. Written informed consent was obtained per
110protocol approved by the Health Sciences Research Ethics Board of the University
111of Western Ontario (London, Ontario, Canada). Patient age, sex, weight, height,
112apixaban dose regimen, concomitant use of moderate (amiodarone, diltiazem,
113fluconazole, verapamil) to strong (clarithromycin, ketoconazole, ritonavir) P-
114gp/CYP3A4 inhibitors and P-gp/CYP3A4 inducers (carbamazepine, phenytoin,
115phenobarbital, rifampin) , most recent serum creatinine, and date/time of last
116apixaban dose were collected when single steady-state blood samples were
117obtained. Blood samples were immediately stored at -4°C before centrifugation at
1182000g for 10 minutes for plasma isolation. Plasma samples were stored at -80°C
119until further analysis. Apixaban concentrations were determined by liquid

120chromatography tandem mass spectrometry as previously reported.¹² Lower limit
121of quantitation is 5 ng/mL. Assay performance across the 25, 250, and 1000
122ng/mL quality controls were 1.5% and 8.5%, intraday bias and precision was 1.3%
123and 5.1%.

124**Data analysis.** Dosing was categorized as recommended, higher-than, or lower-
125than-recommended. Recommended apixaban dosing in 5 mg twice daily reduced
126to 2.5 mg twice daily with two of the following present: age \geq 80 y, weight \leq 60
127kg, serum creatinine \geq 1.5 mg/dL, or a strong CYP3A4/P-gp inhibitor is co-
128administered without 2 of the 3 dose reduction criteria.

129(https://packageinserts.bms.com/pi/pi_eliquis.pdf). For patients meeting
130recommendations for 5 mg twice daily, apixaban concentrations were categorized
131as being within, higher, or lower than the expected 5-95% percentile at peak (91-
132321 ng/mL, median =171 ng/mL) or trough (41-230 ng/mL, median =103 ng/mL)
133compared to patients receiving 5 mg twice daily in the pivotal ARISTOTLE trial.¹¹
134For patients receiving 2.5 mg twice daily as recommended, concentrations were
135similarly categorized in reference to patients receiving 2.5 mg twice daily in
136ARISTOTLE (peak: 69-221 ng/mL, 123 median; trough: 34-162 ng/mL, median 79
137ng/mL). Concentrations were analyzed in relation to dosing accuracy by Chi Square

138RESULTS

139One hundred ten patients were studied (see Table 1 for characteristics). No
140patients received higher- than-recommended dosing. Sixty-eight patients received
141recommended dosing: 5 mg twice daily in 48 (26 had one dose reduction criteria:
142age in 16, weight in 3, creatinine in 7), and 2.5 mg twice daily in 20 (age criteria in

143all; creatinine criteria in 13, weight criteria in 9 (two patients met all 3 dose
144reduction criteria). Forty-two received lower-than-recommended dosing of 2.5 mg
145twice daily (29 had one dose reduction criteria: age in 21, weight in 2, creatinine in
1466). No patients received strong CYP3A4/5 P-gP inhibitors.

147

148Apixaban concentrations after dosing in patients receiving the recommended dose
149of 5 mg twice daily and those receiving lower than recommended dosing at 2.5 mg
150twice daily are shown in Figure 1. One dosed as recommended and one dosed
151lower than recommended patient had concentrations below the expected 5-95%
152range at expected time of peak concentrations (91-321 ng/ml). In patients dosed-
153as-recommended with 5 mg twice daily, four (two older than age 90) had
154concentrations above expected 5-95% range at peak that occurred later than the
155reported 3-4 hours after dosing time of peak concentrations in two. Few patients
156were sampled at trough (12 hours after dosing) but none had concentrations below
157expected 5-95% range at trough in either group. No significant differences in
158proportion of apixaban concentrations within or outside expected ranges were
159detected between patients receiving lower-than-recommended doses and those
160dosed as recommended ($p=0.35$).

161Concentrations from patients receiving appropriately reduced doses were
162compared to data from ARISTOTLE participants receiving appropriately reduced
163doses. Concentration vs. time data for these twenty patients receiving 2.5 mg
164twice daily as recommended are shown in Figure 2. Concentrations above the 5-
16595% range for expected peak from ARISTOTLE data (69-221 ng/mL) were seen in 7

166of the 20 as late as 7 hours after dosing. Seventeen of the twenty had
167concentrations from 3 to 8.5 hours after dosing that were above the expected
168median peak level at 3-4 hours (123 ng/mL).

169

170**DISCUSSION**

171

172Our goal was to determine apixaban concentrations in older and very old adults in
173the community being treated with apixaban for the prevention of stroke in the
174presence of non-valvular atrial fibrillation. The mean age of patients studied in this
175report is 80.4 years (range 66-100), women represented 45% of the group, and
176one third received lower than recommended dosing. There are several key
177observations from our study. One is that patients receiving reduced dosages
178without meeting criteria for dosage reduction had apixaban concentrations within
179the ranges reported for the recommended doses. A second point is that a low and
180similar proportion of concentrations below expected peak concentrations was seen
181in patients receiving 2.5 mg twice daily without meeting criteria for dose
182reductions compared to patients receiving the recommended 5 mg twice daily.
183Third, only patients receiving recommended 5 mg twice daily dosing had
184concentrations far in excess of the expected 5-95% range for peak concentrations
185Numbers were small and the trend was not significant but raises concern as
186increasing apixaban concentrations produce greater anticoagulation and older
187adults are at higher basal risk for bleeding. Fourth, patients receiving

188appropriately reduced doses of 2.5 mg twice daily had concentrations greater than
189patients receiving the 2.5 mg twice daily in the clinical trials. Finally, the data also
190suggest that clinicians recognize characteristics of patients that may warrant
191dosage reductions from recommendations based on randomized clinical trials.

192

193Current clinical dosing recommendations for DOACs reflect the regimens that were used
194in the efficacy trials on which marketing approval was granted. For apixaban,
195recommended standard dosing is 5 mg twice daily reduced to 2.5 mg twice daily if
196the patient has two of the following characteristics: 80 years or older, weight of 60
197kg or below, creatinine of 1.5 mg/dL or above; or, is co-administered a strong
198CYP3A4/5 P-gP inhibitor. (https://packageinserts.bms.com/pi/pi_eliquis.pdf). Dosing
199with 2.5 mg twice daily in the absence of 2 of the 3 criteria represents a 50%
200reduction from recommendations. The algorithm appears to have been selected to
201account qualitatively for possible changes in drug distribution or clearance
202(without more precise estimates of creatinine clearance) or the increased risk of
203bleeding in the very elderly. Most pivotal pre-marketing trials of DOACs did not
204report measurement of concentrations or anticoagulant effects and thus
205prescribing guidelines do not advocate laboratory monitoring of either DOAC
206concentrations or effects. However, DOAC concentrations are directly related to
207factor Xa inhibition and anticoagulation. Data recently published from the earlier
208trials show dabigatran and edoxaban have a direct relationship between drug
209concentrations, factor Xa inhibition and efficacy as well as bleeding outcomes for
210the treatment of patients with NVAf. ¹³⁻¹⁵ Apixaban concentration data from NVAf

211clinical trials have recently been analyzed and published but have not been related
212to clinical outcomes.^{16,17} Clinical laboratories are establishing DOAC assays and
213report the concentration

214data from the clinical trials as reference ranges.

215Importantly, pivotal non-valvular atrial fibrillation trials enrolled patients with mean
216age of 70 years, fewer women than men, almost no racial minorities, no patients
217on dialysis, resulting in only about 5% receiving the reduced dose.¹⁸ This leaves a
218critical deficiency of data on use of apixaban in the complex and heterogeneous
219population of older adults with NVAF. Post-marketing registry studies or analyses
220of claims data have attempted to address this gap, and in general report equal
221efficacy in clinical populations to that seen during clinical trials.^{7,9,10,19-22} However,
222major extracranial and GI bleeding rates were similar for warfarin and DOACs in
223NVAF trials. Rates for major bleeding of 2.6-3.3% were reported for patients over
224age 75y in ARISTOTLE and were 4.5% per year for major and clinically relevant
225nonmajor bleeding in patients unsuitable for warfarin in AVERROES.^{2,23,24} Major
226bleeding rates reported from administrative claims data are on the order of 4% -5%
227per year for major bleeding^{7,10 7 10,25} but range from 2.6 -10%.^{7,10,26,27 28} No post-
228marketing studies have analyzed either drug concentrations or factor Xa inhibition
229in relation to dosing or outcomes. When doses are higher than recommended,
230major bleeding rates rise⁷ and have been reported as 6.9%⁹. We recognize our
231data are preliminary. Our sample was not random and patients receiving 2.5 mg
232twice daily not meeting dose reduction criteria were likely oversampled. Patients
233were seen or followed in a specialized anticoagulation clinic at a tertiary care

234medical center capable of monitoring apixaban concentrations as part of a
235research program. We did not have outcomes data to relate the concentrations to
236either efficacy or adverse bleeding events but used the surrogate marker of drug
237concentration ranges reported from the clinical trials as the reference range by
238clinical laboratories that perform DOAC assaysWe also did not have information on
239reasons physicians prescribed lower than recommended dosing. Nonetheless, the
240data suggest that concentration responses to doses of apixaban in older patients
241encountered during routine clinical care may differ from the somewhat limited data
242reported from clinical trials.

243There is a need for more information about prescribing, outcomes, as well as risks
244and benefits of DOAC use in the older patients with NVAF. ²⁹Until such data are
245available, the clinician is faced with balancing the high risk of embolic stroke from
246NVAF with the high risk of bleeding. Clinical laboratories are establishing DOAC
247assays and laboratory monitoring may provide helpful information.

248

249**CONCLUSION**

250Our findings raise questions about optimal dosing of apixaban in older adults with
251NVAF outside of clinical trials. Drug concentrations were higher than expected
252based on clinical trial data and should caution those who advocate that lower than
253recommended dosing be a target for correction.³⁰ Clinical laboratories are
254establishing DOAC assays and report the concentration data from the clinical trials
255as reference ranges. Our data support a role for monitoring factor Xa inhibition or

Patents		x		x		x		x
Personal Relationship		x		x		x		x

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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
Patents		x		x		x		x

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272 Author Name: ___ Smrithi Sukumar _____

273

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274

275 Author Name: ___ Markus Gulilat, PhD _____

276

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277

278 Author Name: ___ Bradley Linton _____

279

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280

281 Author Name: ___ Steven E. Gryn, MD _____

282

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283

284 Author Name: ___ George K Dresser, MD _____

285

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286

287 Author Name: ___ Jeffrey Alfonsi, MD _____

288

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289

290 Author Name: Ute I. Schwarz, MD _____

291

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-----------------------	---	------------------------------------

292

293

294 Author Name: Richard Kim MD _____

295

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409 LEGENDS

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

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

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

421 Apixaban concentrations after dosing are shown from patients receiving
422 recommended dosing of 2.5 mg twice daily Dashed vertical lines indicate expected
423 5-95% range (and median) at peak (69-221 ng/mL, median;123 ng/mL at 3-4hrs
424 after dosing) and trough (34-162 ng/mL, median 79 ng/mL at 12hrs after dosing).

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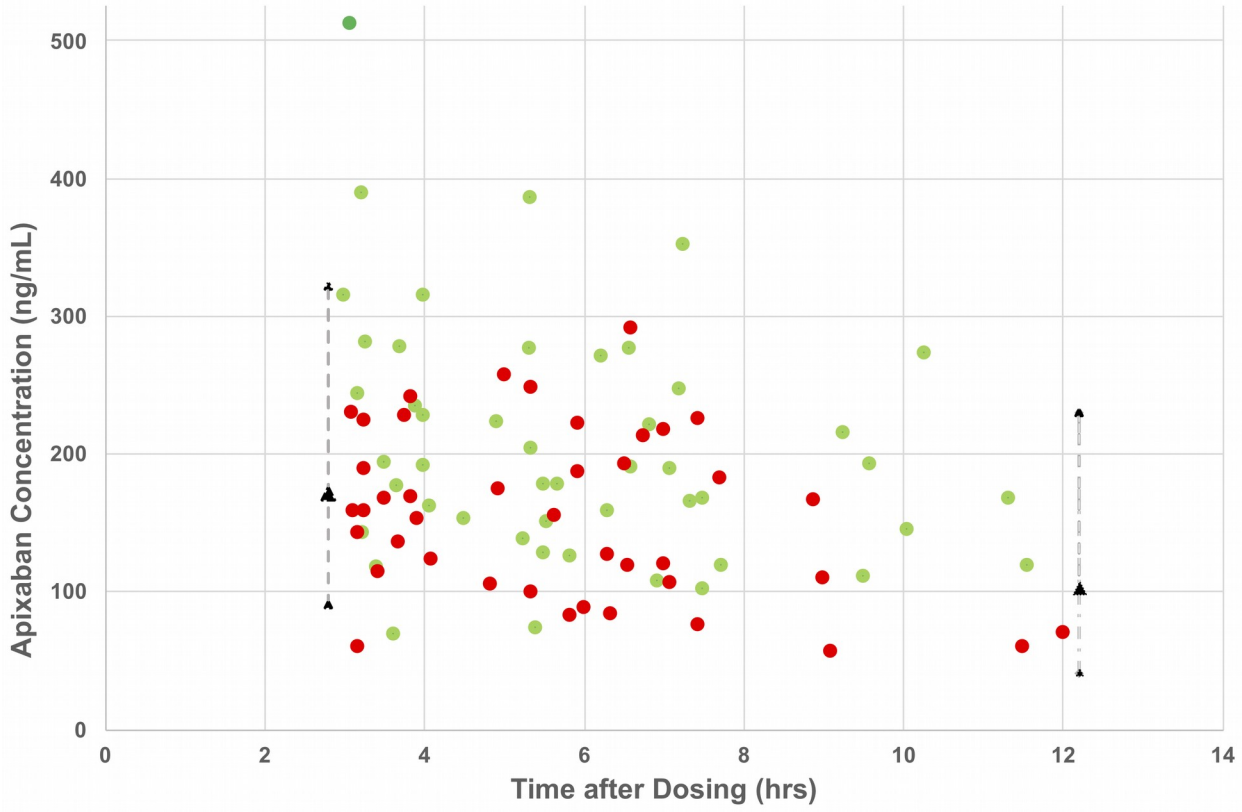
426Table 1. Patient Characteristics and Apixaban Dosing

		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

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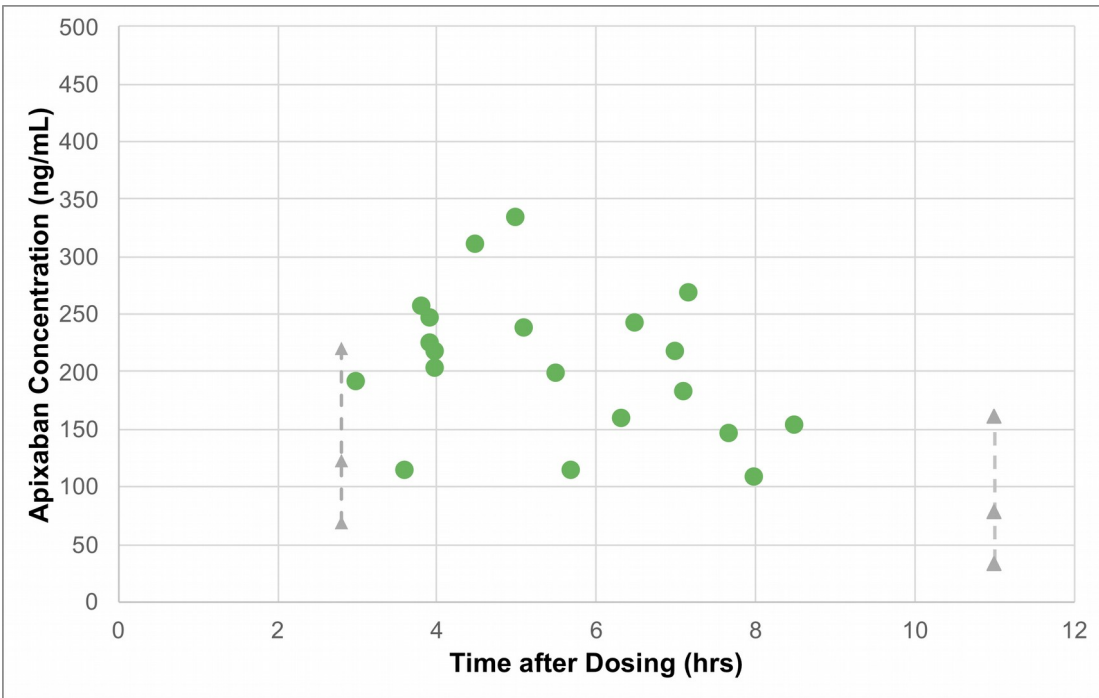
428*Data are mean ± SD, (range). [^] No dose adjustment recommended for moderate
429inhibitors.

430



431

432Figure 1.



433

434Figure 2.