BMC Nephrology

RESEARCH

Open Access

Apixaban dosing in hemodialysis - can drug level monitoring mitigate controversies?

Simeon Schietzel[1*], Andreas Limacher[2], Matthias B. Moor[1], Cecilia Czerlau[3], Uyen Huynh-Do[1], Bruno Vogt[1], Fabienne Aregger[1] and Dominik E. Uehlinger[1]

Abstract

Background Inconsistent study results and contradictory recommendations from health authorities regarding the use of apixaban in patients on hemodialysis have generated considerable uncertainty among clinicians, making investigations of appropriate dosing an unmet need.

Methods We analyzed pre-dialysis apixaban drug levels from a tertiary care dialysis unit, comparing 2.5 mg once versus twice daily dosing. We applied mixed-effects models including dialysis modality, adjusted standard Kt/V, ultrafiltration, and dialyzer characteristics. We included an exploratory analysis of bleeding events and compared the drug levels of our dialysis patients to those from non-CKD reference populations taking the standard dose of 5 mg twice daily.

Results We analyzed 143 drug levels from 24 patients. Mean (SD) age at first drug level measurement was 64.7 (15.9) years (50 % female), median (IQR) follow-up was 12.5 (5.5 – 21) months. For the apixaban 2.5 mg once and twice daily groups, median (IQR) drug levels were 54.4 (< 40 – 72.1) and 71.3 (48.8 – 104.1) ng/mL respectively ($P < 0.001$). Levels were below the detection limit in 30 % (with 2.5 mg once daily) and 14 % (with 2.5 mg twice daily) respectively. Only dosing group (twice versus once daily) was independently associated with higher drug levels ($P = 0.002$). Follow-up did not suggest accumulation. The 95th percentile of drug levels did not exceed those of non-CKD populations taking 5 mg twice daily. Median (IQR) drug levels before a bleeding (8 episodes) were higher than those without a subsequent bleeding: 111.6 (83.1 – 129.3) versus 54.8 (< 40 – 77.1) ng/mL ($P < 0.001$). Concomitant antiplatelet therapy was used in 86% of those with bleeding events versus 6% without bleeding events ($P < 0.001$).

Conclusions Drug monitoring may be a contributory tool to increase patient safety. Despite non-existing target ranges, drug levels on both edges of the spectrum (e.g. below detectability or beyond the 95th percentiles of reference populations) may improve decision-making in highly individualized risk-benefit analyses.

Keywords Anticoagulation, Apixaban, Dialysis, Drug, Level

Background

Apixaban has emerged as a safe and practicable alternative to vitamin K antagonists. In patients on hemodialysis however, use and dosing of apixaban are controversial.

The U.S. Food and Drug Administration (FDA) has approved apixaban for use in patients on hemodialysis [1]. The European Medicines Agency (EMA) [2] and the European Society of Cardiology (ESC) [3] vote against its use in this population. Other authorities like the American College of Cardiology and the Heart Rhythm Society

*Correspondence:
Simeon Schietzel
simeon.schietzel@insel.ch
[1] Division of Nephrology and Hypertension, Inselspital, Bern University Hospital, University of Bern, Freiburgstrasse 18, Bern 3010, Switzerland
[2] CTU Bern, University of Bern, Bern, Switzerland
[3] Division of Nephrology, Central Hospital Biel, Biel, Switzerland

(AHA/ACC/HRS) [4] or the Association of the Scientific Medical Societies of Germany (AWMF) [5] take intermediate positions refraining from a contraindication but referring to the moderate quality of evidence.

Pharmacokinetic properties that encourage the use of apixaban in patients on hemodialysis are considerable non-renal excretion (73 %) [6] lack of active metabolites [7] and partial removal by hemodialysis [8, 9]. However, high plasma protein binding (87 %) [10] and a large volume of distribution (21 L) [6] limit effective clearance increasing the risk of accumulation.

Results from cohort studies [11–14] and from the AXADIA-AFNET 8 trial [15] showed superiority and non-inferiority respectively, comparing apixaban to vitamin K antagonists in patients on hemodialysis. However, the evidence regarding appropriate dosing is contradictory with suggestions of 5 mg twice daily [11, 14, 16], 2.5 mg twice daily [15, 17], or no respective difference [13, 18, 19]. In addition, even 2.5mg once daily might be considered, as inter-individual variability of drug level is high [6], serious bleedings do occur with 2.5 mg twice-daily [20] and prophylactic indications (e.g. access flow difficulties) are known challenges.

As a result, clinicians are faced with the conundrum of implementing a promising therapy without indubitable evidence regarding efficacy, dosing and safety. This is reflected by frequent off-label under-dosing [21] making investigations regarding appropriate dosing and risk of accumulation an unmet need.

Drug monitoring is a legitimate approach to approximate a patient's risk of an overtly strong or rather weak exposure to anticoagulant effect under a given dose [2]. However, only three studies with very few patients have been providing apixaban trough levels in patients on hemodialysis so far with none of them investigating a dose of 2.5 mg once daily [19, 22, 23].

Here we provide results from a 5 years apixaban drug-monitoring program. We investigated drug levels from different dosing regimens, associated factors, risk factors for accumulation, bleeding risk and we provide comparative data from non-chronic kidney disease (CKD) reference populations.

Methods

Population

Chronic hemodialysis patients from a tertiary care center at the university hospital of Bern, Switzerland.

Study type

Retrospective analysis of 5 years health-related data, available from routine clinical practice.

In- and exclusion criteria

We included all adult patients under apixaban treatment at the initiation of the study that gave their informed consent to further use of health-related data. Inclusion was independent of apixaban dosing or indication. We excluded patients on peritoneal dialysis and those on home hemodialysis. Only scheduled apixaban drug level measurements were included. We excluded drug levels that had been taken in other departments, during emergencies or before surgical procedures.

Measurement of apixaban

The unit`s drug monitoring program was set to measure apixaban drug levels on a regular base targeting measurements every three to six months allowing for individual measurements according to the treating physician. Measurements were performed before the start of the dialysis treatment at the beginning of the week (after two days without dialysis - long interval). The time of drug level monitoring after not one but two days without dialysis was chosen to detect overtly high drug level assuming only partial dialyzability.

Blood samples were obtained before administration of anticoagulants. After discarding the first 5-10 mL of blood, around 3 mL of blood were drawn using 4.3 mL citrate-plasma tubes and sent for analyses within 1 hour. The central laboratory of University Hospital Bern used the BIOPHEN^{TM} Heparin LRT Anti-Xa chromogenic assay and the BIOPHEN^{TM} Apixaban Calibrator, both HYPHEN BioMed®. Anti-Xa activity is determined via an accredited chromogenic substrate method and a proportional concentration output is provided in ng/mL via a serial dilution calibration process. Hereby, drug concentration is measured indirectly.

Patients were under apixaban 2.5 mg once or twice daily. In patients were times of prescribed drug intake (morning, midday or evening) matched starting times of their dialysis sessions (2 sessions were offered at our center, morning or midday), trough level could be determined: For once daily dosing, trough level could be determined if drug intake and dialysis sessions both took place in the morning or at midday. For twice daily dosing (morning and evening), trough level could be determined if dialysis sessions started in the morning. If no trough level determination was possible (e.g. once daily drug intake in the evening and start of dialysis session in the morning or twice daily drug intake and start of dialysis session at midday), level were regarded as random. In a few instances, drug levels were taken after the dialysis session to obtain post-dialysis trough level (e.g. twice daily dosing, dialysis at midday). Whenever possible, the treating physician tried to align medication and dialysis

schedules to enable regular apixaban trough level monitoring. We decided against time-based analyses, as it was impossible to retrospectively figure out exact timing of drug intake. Whenever trough level obtainment was possible (24 hours level in once daily dosing, 12 hours level in twice daily dosing), the dialysis care team routinely instructed patients in advance to postpone drug intake until blood had been sampled.

Baseline characteristics, dialysis parameters and covariates

We obtained age, BMI (applying post-dialysis weight) and dialysis vintage at first drug level measurement as well as indication for apixaban use as baseline characteristics. We obtained number and length of dialysis session, pre- and post-dialysis weight and machine-calculated single pool Kt/V as further dialysis parameters. We obtained apixaban dosing, age, sex, BMI, ultrafiltration-adjusted standard Kt/V, dialysis modality (hemodialysis or hemodiafiltration, the latter being defined as a treatment with an exchange volume of ≥ 12 L per session), dialyzer surface area, dialyzer brand/material, episodes of bleeding (via chart review) and antiplatelet therapy as covariates for the analyses.

Calculation of Ultrafiltration-adjusted standard Kt/V

1. We took machine-calculated single pool Kt/V (spKt/V) from the week before drug level monitoring (3 sessions) and calculated mean weekly spKt/V.
2. We calculated equilibrated Kt/V (eKt/V) from spKt/V by using the equation suggested by Tattasall [24] with a slightly modified time constant (30.7 instead of 35 minutes) suggested by Daugirdas [25] based on results from the HEMO study [26, 27].
3. We applied the Leypoldt equation [28] to calculate fixed-volume standard Kt/V (fv stdKt/V).
4. We adjusted fv stdKt/V for volume removal (ultrafiltration adjusted standard Kt/V; UF adj. stdKt/V) by using the Frequent Hemodialysis Network (FHN) equation [29] and estimated volume of urea distribution as 90% of the sex-adjusted Watson volume of total body water.

Statistical analyses

We used STATA, version 17.0. We characterized population and results by mean/SD (age, BMI, dialysis dosage), median/IQR/range (drug level) or number/% (sex, dialysis modality, dialyzer brand, dialyzer surface). We calculated number of drug level measurements overall, per dosing group and per patient. We analyzed drug levels for the total population, for the two dosing groups and for the time points after intake (trough and random). Drug levels below the detection limit of < 40 ng/mL were replaced with the value of 40 ng/mL. For between-group comparisons, we applied mixed-effects models to account for repeated measures within patients. We performed mixed effects multivariable linear regression analyses with drug level as dependent variable. For the independent variables, we sequentially added anthropometrics (age, sex, BMI) and dialysis parameters (UF-adjusted standard Kt/V, dialysis modality [HD or HDF], dialyzer surface area [continuous variable, 1 - 2.5m^2] and dialyzer brand/material [Baxter Nephral, Fresenius CorDiax, Braun Xevonta or Fresenius CorAl; Table 3). Individual participants were included as random effect parameter. We log-transformed drug level values to achieve normal distribution of residuals and an improved fit of the model. To study the drug levels among patients with and without bleeding events, we performed additional mixed effects multivariable linear regression analyses with log-transformed drug level as dependent variable and bleeding status as independent variable. Bleeding episodes according to concomitant anti-platelet therapy were evaluated using Fisher's exact test. Due to the low number of participants and bleeding events, we refrained from investigating bleeding episodes in Cox or logistic models.

Ethics

The study was approved on July 27, 2022 by the Cantonal Ethics Committee for Research of the Health, Social and Integration Directorate Bern, Switzerland. The project-ID is 2022-00981. At all stages, the study was executed according to the principles defined in the Declaration of Helsinki. All patients gave their informed consent to further use of health-related data.

Results

Characteristic of study population

We analyzed results from 24 patients. Mean (SD) age was 64.7 (15.9) years, 50 % were female and mean (SD) BMI was 28.1 (7.2) kg/m^2. One participant (4%) self-identified as Hispanic, 23 participants (96%) self-identified as White. All patients dialyzed thrice weekly with a mean (SD) UF-adjusted standard Kt/V of 2.12 (0.26), using 5 different dialyzers and a wide range of dialyzer surface areas (Table 1).

Apixaban drug levels

One hundred forty-three drug levels were obtained during August 2017 and January 2023. From 24 patients, 7 patients changed dosing during the observation period providing data to both dosing regimens. Seventeen patients were on 2.5 mg once daily providing 87 levels

Table 1 Characteristics of study participants, indication of apixaban and dialysis parameters

	Total **24 patients[a]** **143 measurements**	**2.5mg once daily** **17 patients** **87 measurements**	**2.5mg twice daily** **14 patients** **56 measurements**
Age at first sample mean (SD), min-max	64.7 (15.9), 29-90	65.8 (16.6), 29-90	62.2 (13.9), 39-83
Women %	50	47	43
BMI at first sample (Kg/m^2) mean (SD)	28.1 (7.2)	27.9 (7.1)	27.9 (6.7)
Indication for apixaban n (%)			
- Permanent catheter	9 (38)	8 (47)	4 (29)
- Atrial fibrillation	6 (25)	4 (24)	4 (29)
- Pulmonary embolism	2 (8)	1 (6)	2 (14)
- Deep vein thrombosis	2 (8)	1 (6)	1 (7)
- Other	5 (21)	3 (18)	3 (21)
Dialysis vintage (years) at first sample	1.3 (0.6; 3.3.8)	0.8 (0.7; 6.2)	2.4 (0.7; 3.6)
median (IQR), min-max	0.01 - 23.1	0.01 - 26.5	0.02 - 23.1
HD/HDF/changed n patients	18/3/3	12/3/2	6/0/1
HD/HDF % of treatments	78/22	70/30	91/9
UF-adj. std. Kt/V mean (SD)	Mean 2.12 (0.26)	Mean 2.11 (0.07)	Mean 2.14 (0.26)
Dialyzer type n (%)			
- Baxter Nephral	13 (9)	10 (12)	3 (5)
- Fresenius CorDiax	48 (34)	32 (37)	16 (39)
- Braun Xevonta	38 (27)	23 (26)	15 (27)
- Fresenius CorAL	40 (28)	19 (22)	21 (38)
- Nipro Elisio	4 (3)	3 (4)	1 (2)
Dialyzer surface area n (%)			
- 1.0 - 1.8m^2	24 (30)	19 (39)	5 (16)[b]
- 1.9 - 2.5 m^2	119 (70)	68 (61)	51 (84)[c]

[a] Of 24 patients, 7 patients changed dosing providing data to both dosing groups

[b] 1.6 – 1.8 m^2

[c] 1.9 – 2.3m^2

with a median (range) of 4 (1–17) measurements per case. Fourteen patients were on 2.5 mg twice daily providing 56 levels with a median (range) of 2 (1–11) measurements per case (Table 2). Median (IQR) follow-up defined as time between first and last drug level measurement was 12.5 (5.5 – 21) months with a maximum follow-up of 51 months.

Median (IQR) apixaban drug levels were 54.1 (< 40 – 72.1) ng/mL in the 2.5 mg once daily and 71.3 (45.8 – 104.1) ng/mL in the twice-daily group, $P < 0.001$ (Table 2, Fig. 1a). The highest levels that we found were 157.6 ng/mL and 223.7 ng/mL respectively. Thirty percent of drug levels in the once daily and 14 % in the twice-daily dosing group were below our assays detection limit of < 40 ng/mL (Table 2). Drug level pre and post hemodialysis did not differ from each other. However, with only 8 post hemodialysis levels from 5 cases of the apixaban 2.5 mg once daily dosing group and 4 levels from 3 cases of the apixaban twice daily dosing group, this analysis has to be regarded as purely explorative. For both dosing groups, trough level (24 hours after once daily and 12 hours after twice daily dosing) compared to random drug level were not significantly different from each other (Fig. 1b).

Mixed-effects models analysis

Only dosing group (2.5 mg twice daily higher than once daily) was significantly and independently associated with log apixaban drug levels (Table 3). Sensitivity - analyses including dialyzers specificity (crylonitrile versus PES plus PSU or acrylonitrile versus PES versus PSU) or adding dialyzer surface, as a dichotomous variable (1 – 1.8 versus 1.9 – 2.5 m^2) did not change results.

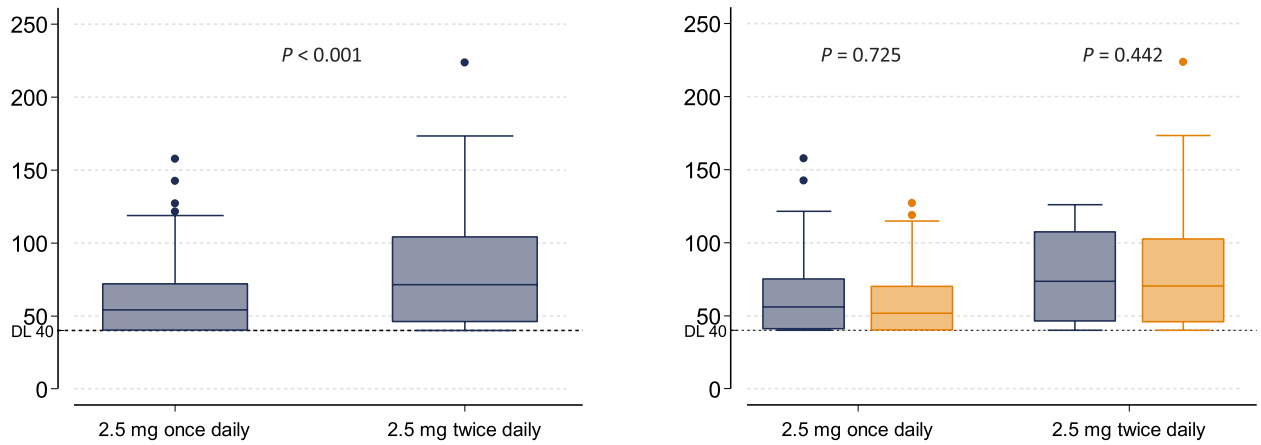
Bleeding events

In 7 out of 24 patients (29 %) a bleeding event was documented (8 bleeding events in total, one patient had two

Table 2 Apixaban drug levels for the total population and the two dosing groups

	Total	2.5mg Once daily	2.5mg Twice daily
No of patients n	24[a]	17	14
No of samples n	143	87	56
No of samples per case median (range)	3 (1-17)	4 (1-17)	2 (1-11)
% of samples pre/post dialysis	92/8	91/9	93/7
Drug level, ng/mL (all)			
- Median (IQR)	56.0 (40.9 - 82.4)	54.1 (< 40 - 72.1)	71.3 (45.8 - 104.1)
- 5/95 percentile	< 40/127.1	< 40/118.7	< 40/140.5
- Min. - Max.	< 40 - 223.7	< 40 - 157.6	< 40 - 223.7
- % Below detection limit	26.0	29.9	14.3
Drug level, ng/ml, (trough) n	85	52	33
- Median (IQR)	54.1 (40.0 - 78.6)	51.8 (< 40 - 70.0)	70.4 (45.5 - 102.7)
- 5/95 percentile	< 40/133.4	< 40/114.8	< 40/173.4
- Min. - Max.	< 40 - 223.7	< 40 - 127.1	< 40 - 223.7
- % Below detection limit	27.1	36.5	12.1

[a] Total number of patients is 24. Total number of cases is 31 as 7 patients are in both dosing group as dosing was changed during treatment period. Drug levels (all) of twice daily dosing are significantly higher than those of the once daily dosing. Trough level and non-through level within each dosing group were not significantly different from each other



a. Drug levels (all) per dosing group **b.** Random (blue) vs. trough levels (yellow).

Fig. 1 Apixaban drug levesl. Comparisons of dosing groups and random versus trough levels

Legend: DL, Detection Limit

episodes). Bleedings with 2.5 mg once daily occurred in the masseter, the spleen (hemorrhagic shock), the upper gastrointestinal tract and pericardial (hemodynamic impairment) as well as with 2.5 mg twice daily from the lower gastrointestinal tract, from prostate varicose veins (recurrence without apixaban), and rectal condyloma. All but the pericardial bleeding occurred with concomitant antiplatelet therapy.

Median (IQR) apixaban levels of patients with a bleeding event where not significantly different from those without a bleeding event: 68.1 (41.2 – 98.0) versus 54.1 (40.7 – 74.4) ng/mL; $P = 0.09$. However, median (IQR) apixaban drug levels measured before the bleeding event were significantly higher compared to drug levels without a subsequent bleeding: 111.6 (83.1 – 129.3) versus 54.8 (< 40 – 77.1) ng/mL; $P < 0.001$. From 7 patients with a bleeding, 6 patients (86%) took concomitant antiplatelet therapy whereas from 17 patients without a bleeding only one patient (6%) was under additional antiplatelet therapy ($P < 0.001$).

Table 3 Mixed-effects model with 2 level of multivariate adjustments

Log apixaban drug level	Model 1		Model 2	
	Coefficient (95% CI)	***P***	**Coefficient (95% CI)**	***P***
Dosing 0 = 1 x 2.5 mg, 1 = 2 x 2. 5mg	.164 (.091 to -.24)	**<0.001**	.161 (0.089 to 0.232)	**<0.001**
Age (y)	-0.002 (-0.005 to 0.001)	0.30	-.002 (-0.005 to 0.001)	0.19
Sex 0 = female, 1 = male	.001 (-0.091 to 0.093)	0.98	.033 (-0.053 to 0.12)	0.45
BMI (Kg/m^2)	.000 (-0.005 to 0.006)	0.93	.004 (-0.002 to 0.01)	0.22
UF-adj. standard Kt/V			.108 (-0.016 to 0.233)	0.09
Dialysis modality 0 = HD, 1 = HDF			.057 (-0.025 to 0.14)	0.17
Dialyzer surface area (1 - 2.5 m2)			-.031 (-0.141 to 0.08)	0.59
Dialyzer Brand / Material				
1 = Baxter Nephral/Actyl[a]			Reference	
2 = Fresenius CorDiax/PES[b]			-.015 (-0.154 to 0.123)	0.83
3 = Braun Xevonta/PSU[c]			-.09 (-0.223 to 0.045) -.09	0.2
4 = Fresenius CorAL/PSU-PVP[d]			(-0.229 to 0.045)	0.19
Ultrafiltration per week L			-.003 (-0.012 to 0.007)	0.58
Wald Chi2	21.8		30.7	
No participants	24		24	
No observations	143		143	

[a] Acrylonitrile and Sodium methallyl sulfonate blend

[b] Polyethersulfone

[c] Polysulfone

[d] Polysulfone + increased polyvinylpyrrolidone

Change of apixaban dosing due to drug level

In 6 out of 24 patients (25 %), the treating physicians decided to change apixaban-dosing regimen due to drug level results. In three patients, 2.5 mg once daily dosing was increased, with resulting median (IQR) drug level changes from 46.2 (43.1 – 49.3) to 48 (46.4 – 57), < 40 to 94.9 (79.8 – 115.4) and 48 (46.4 – 57) to 40 (40 – 45.1) ng/mL. In two patients, 2.5 mg twice daily dosing was reduced, with resulting median (IQR) drug level changes from 78.6 (64.3 – 92.9) to 65.6 (53.7 – 76.7), and from 109.6 (89.4 – 166.7) to 56.4 ng/mL. In one further patient, median (IQR) drug level with 2.5 mg once daily dosing were 74.5 (56.3 – 109.5) ng/mL. An increase to twice daily dosing resulted in a drug level of 173.4 ng/mL whereupon the dosing was reduced to 2.5 mg once daily again with resulting median (IQR) drug level of 95.3 (70.4 – 107.3) ng/mL.

Change of apixaban dosing due to bleeding

Due to 3 out of the 8 bleeding episodes, the attending physician decided to adjust the apixaban treatment: In one episode, apixaban was reduced from 2.5 mg twice to once daily dosing. This resulted in a mean (SD) drug level change from 118 (117 – 121.6) to 51.9 (45.9 – 58.8) ng/mL. In the remaining 2 bleeding episodes, the attending physician decided to stop the apixaban treatment.

Drug level over time

We did not see signs of accumulation in 25 cases that provided at least 2 measurements (Fig. 2). In these patients, first drug level measurement took place at a median (IQR) of 14 (8 - 30) days after initiation of apixaban (available data for 15 cases) with a total follow-up time of median (IQR) 12 (2 – 16) and a range of 1 – 51 months intake (available data for all cases).

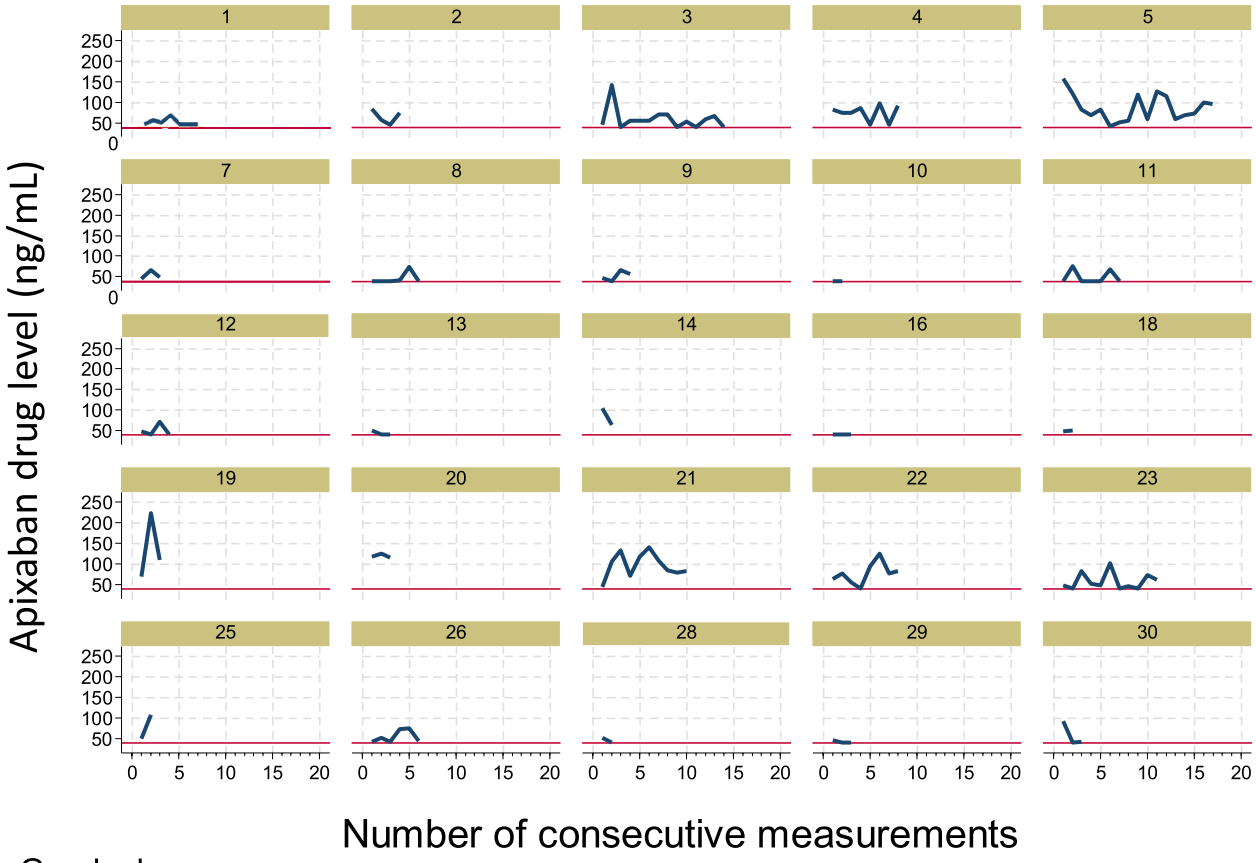


Fig. 2 Apixaban level (all) of each participant over time. Legend: Serial drug level monitoring from 25 hemodialysis patients each providing between 2 and 17 drug levels. First drug level measurement took place at a median (IQR) of 14 (8 – 30) days after initiation of apixaban (available data for 15 cases) with a total follow-up time of 12 (2 – 16) months intake (available data for all cases)

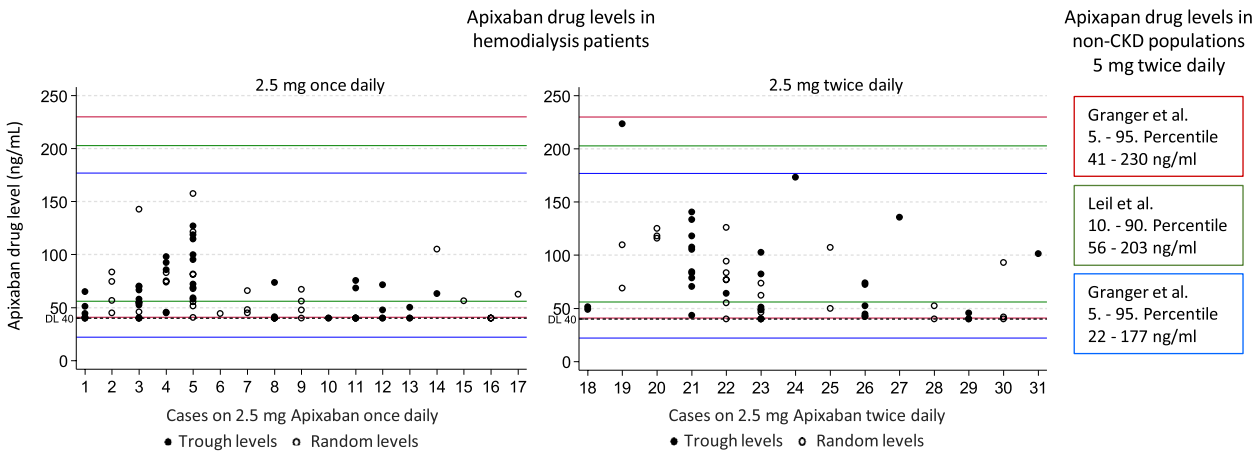


Fig. 3 Comparison of measured apixaban levels in our study with those from non-CKD patients taking therapeutic doses of 5 mg twice daily. Legend: Cases 1 – 17 were on 2.5 mg once daily, cases 18 – 31 were on 2.5 mg apixaban twice daily. Apixaban levels were measured pre-dialysis at the beginning of the week. From 143 samples, 85 were trough levels and 58 were random levels. Trough and random levels were not significantly different from each other. The lower detection limit of our assay was 40 ng/mL. Comparative confidence intervals (boxes on the right side as well as reference lines in red, green and blue) are derived from apixaban trough levels from non-CKD populations [30–32] provided by the European Union summary of product characteristics [2]

Table 4 Apixaban level in comparison to the literature in HD and non-CKD populations

Author year (no. patients), prospective pharmacokinetic study = P	Hemodialysis		Non-CKD		Author year Observed (o), predicted (p)
	Apixaban levels (ng/mL)		Apixaban levels (ng/mL)		
	Median ([1]mean)	5/95[th] percentile ([2]range, [3]2 SD)	Median	5/95[th] percentile ([2]range, [4]10/90[th])	
	2.5 mg once daily		**2.5 mg once daily**		
Our data 2023 (14)	54	<40/119			
	2.5 mg twice daily		**2.5 mg twice daily**		
Roberge 2017 (1)	NA	58/84	NA	16/27	Yamahira 2014 (o)
Mavrakanas 2017 (7), P	58[1]	22/94[3]	56	24/103[4]	Leil 2010 phase II (o)
Our data 2023 (17)	71	<40/141	63	11/90	Byon 2017 (p)
			79	34/162	Cirincione 2018 phase I-III (p)
			85	41/200[2]	Mavri 2021 (o)
	5 mg twice daily		**5 mg twice daily**		
Mavrakanas 2017 (5), P	218	91/337[2]	NA	49/78	Yamahira 2014 (o)
Pokorney 2022 (42), P[a,b]	142	NA	103	41/230	Cirincione 2018 phase I-III (p)
Pokorney 2022 (21), P[a,c]	168	NA	107	56/203[2]	Leil 2010 Phase II (o)
			117	63/291[2]	Mavri 2021 (o)
			120	22/177	Byon 2017 (p)
	10 mg twice daily		**10 mg twice daily**		
			NA	104/114	Yamahira 2014 (o)
			120	41/335	Byon 2017 (p)

P prospective pharmacokinetic study, *o* observed, *p* predicted

[a] The cohort with pharmacokinetic data comprised in total 63 patients. 43 patients took 5 mg twice daily. 20 patients took 2.5 mg twice daily of which 14 met dose reduction criteria of age ≥ 80 years and/or weight ≤ 60 Kg

[b] Group (42 patients) without major or clinically relevant non-major bleeding

[c] Group (21 patients) with major or clinically relevant non-major bleeding

Drug levels in comparison

In Fig. 3 and Table 4 scatter plots of our drug levels are compared to 10th to 90th and 5th to 95th percentiles of drug level from non-CKD patients taking 5 mg apixaban twice daily [20–22].

Discussion

We provided results from apixaban drug level monitoring in hemodialysis patients on different dosing regimens. We investigated risk factors for increased drug level, an analysis with regard to bleeding events and provided a literature comparison to non-CKD populations.

With regard to a 2.5 mg twice daily dosing in patients on hemodialysis, our median drug levels were comparable to those from non-CKD-populations, taking the same reduced dose [30–32], published among others by the European Union summary of product characteristics [2]) although with a larger 5[th] – 95[th] percentile range (71 [< 40 – 141] versus 56 [24 – 103], 79 [34 – 162], 63 [11 – 90] ng/mL). However, our median (5[th] – 95[th] percentiles) drug levels appeared considerably lower in comparison to non-CKD-reference populations taking the standard dose of 5 mg twice-daily [30–32]. Hence, looking at drug level data only, our results suggest, that 2.5 mg twice daily is not associated with overtly increased drug exposition compared to non-CKD patients for whom licensure studies were performed. On the contrary, our results rather suggest, that with 2.5 mg twice daily (14 % below detection limit), and even more so with 2.5 mg once daily dosing (30 % below detection limit), individual patients are probably under-dosed, arguing for more routine drug monitoring. It is worth mentioning however, that some patients on 2.5 mg once daily dosing showed comparable drug level to other patients on 2.5 mg twice-daily schedules. In addition, 2.5mg once daily dosing might still confer valuable prophylactic benefits e.g. for long-term patency of venous accesses.

Our analysis did not include a patient on a 5 mg twice-daily dosing schedule. Pokorney et al. found AUC0-12 values of patients on hemodialysis with 5 mg twice daily significantly higher compared to non-CKD participants from the ARISTOTLE trial (2475 ng/mL×h versus 1374 ng/mL×h) taking the same standard dose [19]. Interestingly, values in patients on hemodialysis were comparable to ARISTOTLE participants with an eGFR of 15 - 59

ml/min/1.73m^2. These results again argue for contributory drug monitoring.

It needs to be emphasized, that target ranges for apixaban drug levels are not established and that existing literature does not support valid assessment of efficacy or bleeding risk via drug monitoring [19, 33, 34]. However, risk-benefit analysis regarding anticoagulation in hemodialysis is challenging and recommendations regarding apixaban are contradictory. Thus, drug level monitoring does provide clinicians with valuable information for improved individual decision making, especially if drug levels are at the edges of the spectrum (e.g. below detection limit or beyond the 95th percentile of non-CKD reference populations). Here, our study provides valuable practical guidance to improve patient safety.

Trough levels did not differ from random levels. An important factor here is the retrospective nature of the study with substantial inaccuracies regarding the time point of drug intake. E.g. if the treating team forgot to inform the patient to wait with the apixaban intake until trough level measurement had taken place, or if the patient did not comply with the agreed schedules, measurements labeled as trough could provide levels shortly after or even days after the last intake. These inaccuracies have to be considered for the interpretation of all drug levels. In cases of overtly low or overtly high drug levels, missing intakes or accidental peak level ascertainments should be ruled out. Furthermore, there is considerable intra- and inter-individual variability of drug levels, a well-known challenge of apixaban drug level monitoring [6, 33]. However, even under the real-live conditions of our investigation, no exacerbation of drug levels was seen.

None of the dialysis-associated parameter were independently associated with drug levels. This was somewhat unexpected. Apixaban has a molecule size of 459.5 Dalton, a protein binding of 87 % and a distributional volume of 21 L [1]. Thus, a fractional removal by hemodialysis is expected. Small prospective pharmacokinetic studies show a reduction in AUC by hemodialysis of -14 % (pre/post) [8] and -26 % (AUC-48h) [9] for a 5 mg dose and a AUC-48h reduction of -48 % for a 2.5 mg dose [9]. Potentially, our inter-individual differences in dialysis dose were too small. However, in light of low sample numbers and retrospective analyses, interpretation of multivariable regression results is limited. Intake of a second dose of 2.5 mg of apixaban per day was consistently associated with higher drug level. This highlights at least a rough relationship between amount of intake and steady state drug level, again supporting drug monitoring as an additional mean for individual dose finding.

Our analysis does not suggest drug accumulation over time independent of dosing regimen and length of follow-up. In contrast, pharmacokinetic analyses revealed significant accumulation in hemodialysis patients during the first 8 days [23]. Our data did not allow valid analyses of drug levels within the first few days after starting the drug. However, with regard to our follow-up period (IQR 5.5 - 21 months), our data clearly support the picture of a non-accumulating steady state.

Our study has several strengths. It is the second largest analysis of apixaban drug levels in hemodialysis to date with the longest follow-up. It is the only investigation incorporating apixaban drug levels from 2.5 mg once daily dosing and comprehensive dialysis-related covariates. In addition, we provide a comparative review to drug levels from non-CKD populations facilitating interpretation of drug levels and supporting sensible decision making regarding appropriate dosing.

The main limitations of our study are its retrospective nature, limiting precise specification of timing of drug intake and a reliable integration of residual kidney function. Drug levels of our study however, do picture long-term results from a tertiary care real-life setting. The analysis of bleedings must be considered exploratory as drug level measurements were infrequent and number of patients and bleeding events were small. The selection of covariates is overly inclusive. However, selected dialysis-associated factors represent important confounders, which have not been comprehensively investigated in studies of apixaban in patients on hemodialysis.

Conclusions

Our investigation provides evidence, that drug levels from hemodialysis patients taking 2.5 mg apixaban twice daily are approximately comparable to those from non-CKD populations taking the same reduced dose; but are lower compared to non-CKD populations taking the standard dose of 5 mg twice daily. Individual under-dosing needs to be considered, with 2.5 mg twice daily and even more so with 2.5 mg once daily dosing. There is considerable inter- and intra-individual variability. Higher drug levels and concomitant antiplatelet therapy might result in higher risks of bleeding.

Target ranges for apixaban drug levels do not exist and the correlation between drug levels and bleeding is poor. However, in light of contradictory recommendations and challenging risk-benefit analyses regarding anticoagulation in patients on hemodialysis, drug level monitoring can be a contributory tool. This applies in particular to the detection of drug levels at the edges of the spectrum (e.g. below detection limit or beyond the 95th percentile of non-CKD reference populations). Here, our

study provides valuable practical guidance to improve safety and appropriate dosing in hemodialysis patients on apixaban.

Acknowledgments
Special thanks to the dialysis care team of the department of nephrology and hypertension of the University Hospital of Bern for their invaluable contribution to the apixaban drug level monitoring program.

Authors' contributions
S.S.: Conceptualization, methodology, funding acquisition, formal analysis, visualization, writing of manuscript. A.L.: Methodology, formal analysis, validation, review of manuscript. M.M.: Supervision, review of manuscript. C.C.: Conceptualization, review of manuscript. U.H.: Review of manuscript. B.V.: Supervision, review of manuscript. Fabienne Aregger: Supervision, review of manuscript. D.U.: Supervision, review of manuscript.

Funding
The project was funded by the Swiss Kidney Foundation. Confirmation was given by the Foundation Board on September 26, 2022.

Availability of data and materials
Additional data supporting the findings of this study will be made available upon reasonable request to the corresponding author.

Declarations

Ethics approval and consent to participate
The study was approved on July 27 2022 by the Health, Social and Integration Directorate Cantonal Ethics Committee for Research of the Canton of Bern, Switzerland, project-ID 2022-00981. Every participant gave his/her written informed consent before data analysis.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Received: 10 February 2024 Accepted: 27 September 2024
Published online: 09 October 2024

References

1. FDA Full Prescribing Information 12/2012 Reference ID: 3237516. https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/202155s000lbl.pdf.
2. European Medicines Agency. https://www.ema.europa.eu/en/documents/product-information/eliquis-epar-product-information_en.pdf.
3. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): Supplementary Data. https://academic.oup.com/eurheartj/article/42/5/373/5899003#supplementary-data.
4. January CT, Wann LS, Calkins H, et al. 2019 AHA/ACC/HRS focused update of the 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: A report of the american college of cardiology/american heart association task force on clinical practice guidelines and the heart rhythm society. J Am Coll Cardiol. 2019;74(1):104–32.
5. Linnemann B, Blank W, Doenst T, Erbel C, Isfort P, Janssens U, Kalka C, Klamroth R, Kotzerke J, Ley S, Meyer J, Mühlberg K, Müller OJ, Noppeney T, Opitz C, Riess H, Solomayer EF, Volk T, Beyer-Westendorf J. Diagnostik und Therapie der tiefen Venenthrombose und Lungenembolie – AWMF-S2k-Leitlinie. Stand: 11.01.2023. Verfügbar unter: https://register.awmf.org/de/leitlinien/detail/065–002. Zugriff am: 10.12.2023.
6. Byon W, Garonzik S, Boyd RA, et al. Apixaban: a clinical pharmacokinetic and pharmacodynamic review. Clin Pharmacokinet. 2019;58(10):1265–79.
7. Raghavan N, Frost CE, Yu Z, et al. Apixaban metabolism and pharmacokinetics after oral administration to humans. Drug Metab Dispos. 2009;37(1):74–81.
8. Wang X, Tirucherai G, Marbury TC, et al. Pharmacokinetics, pharmacodynamics, and safety of apixaban in subjects with end-stage renal disease on hemodialysis. J Clin Pharmacol. 2016;56(5):628–36.
9. Van den Bosch I, Bouillon T, Verhamme P, et al. Apixaban in patients on haemodialysis: a single-dose pharmacokinetics study. Nephrol Dial Transplant. 2020;36(5):884–9.
10. He K, Luettgen JM, Zhang D, et al. Preclinical pharmacokinetics and pharmacodynamics of apixaban, a potent and selective factor Xa inhibitor. Eur J Drug Metab Pharmacokinet. 2011;36(3):129–39.
11. Siontis KC, Zhang X, Eckard A, et al. Outcomes associated with apixaban use in patients with end-stage kidney disease and atrial fibrillation in the United States. Circulation. 2018;138(15):1519–29.
12. Wetmore JB, Herzog CA, Yan H, et al. Apixaban versus warfarin for treatment of venous thromboembolism in patients receiving long-term dialysis. Clin J Am Soc Nephrol. 2022;17(5):693–702.
13. Ionescu F, Cooper C, Petrescu I, et al. Safety of apixaban compared to warfarin in hemodialysis patients: Do antiplatelets make a difference? Eur J Haematol. 2021;106(5):689–96.
14. Reed D, Palkimas S, Hockman R, et al. Safety and effectiveness of apixaban compared to warfarin in dialysis patients. Res Pract Thromb Haemost. 2018;2(2):291–8.
15. Reinecke H, Engelbertz C, Bauersachs R, et al. A randomized controlled trial comparing apixaban with the vitamin k antagonist phenprocoumon in patients on chronic hemodialysis: The AXADIA-AFNET 8 study. Circulation. 2023;147(4):296–309.
16. FDA Prescribing information 08/2014 Reference ID: 3608558. https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/202155s009lbl.pdf
17. Mavrakanas TA, Garlo K, Charytan DM. Apixaban versus no anticoagulation in patients undergoing long-term dialysis with incident atrial fibrillation. Clin J Am Soc Nephrol. 2020;15(8):1146–54.
18. Miao B, Sood N, Bunz TJ, et al. Rivaroxaban versus apixaban in non-valvular atrial fibrillation patients with end-stage renal disease or receiving dialysis. Eur J Haematol. 2020;104(4):328–35.
19. Pokorney SD, Chertow GM, Al-Khalidi HR, et al. Apixaban for patients with atrial fibrillation on hemodialysis: a multicenter randomized controlled trial. Circulation. 2022;146(23):1735–45.
20. Kufel WD, Zayac AS, Lehmann DF, et al. Clinical application and pharmacodynamic monitoring of apixaban in a patient with end-stage renal disease requiring chronic hemodialysis. Pharmacotherapy. 2016;36(11):e166–71.
21. Zhuo M, Paik JM, Tsacogianis TN, et al. Use of anticoagulants and dosing appropriateness of apixaban for new-onset atrial fibrillation among hemodialysis patients. Am J Kidney Dis. 2022;79(6):909–12.
22. Roberge G, Wells PS. Apixaban anti-Xa level monitoring in treatment of acute upper extremity deep vein thrombosis for patient on chronic hemodialysis: a case report. Thromb J. 2021;19(1):23.
23. Mavrakanas TA, Samer CF, Nessim SJ, et al. Apixaban pharmacokinetics at steady state in hemodialysis patients. J Am Soc Nephrol. 2017;28(7):2241–8.
24. Tattersall JE, DeTakats D, Chamney P, et al. The post-hemodialysis rebound: predicting and quantifying its effect on Kt/V. Kidney Int. 1996;50(6):2094–102.
25. Daugirdas JT, Blak PG, Ing TS. Handbook of dialysis. 5th ed. 2015.
26. Daugirdas JT, Depner TA, Greene T, et al. Solute-solver: a web-based tool for modeling urea kinetics for a broad range of hemodialysis schedules in multiple patients. Am J Kidney Dis. 2009;54(5):798–809.
27. Daugirdas JT, Leypoldt JK, Akonur A, et al. Improved equation for estimating single-pool Kt/V at higher dialysis frequencies. Nephrol Dial Transplant. 2013;28(8):2156–60.
28. Leypoldt JK, Jaber BL, Zimmerman DL. Predicting treatment dose for novel therapies using urea standard Kt/V. Semin Dial. 2004;17(2):142–5.
29. Daugirdas JT, Depner TA, Greene T, et al. Standard Kt/Vurea: a method of calculation that includes effects of fluid removal and residual kidney clearance. Kidney Int. 2010;77(7):637–44.
30. Cirincione B, Kowalski K, Nielsen J, et al. Population pharmacokinetics of apixaban in subjects with nonvalvular atrial fibrillation. CPT Pharmacometrics Syst Pharmacol. 2018;7(11):728–38.

31. Leil TA, Feng Y, Zhang L, et al. Quantification of apixaban's therapeutic utility in prevention of venous thromboembolism: selection of phase III trial dose. Clin Pharmacol Ther. 2010;88(3):375–82.
32. Byon W, Sweeney K, Frost C, et al. Population pharmacokinetics, pharmacodynamics, and exploratory exposure-response analyses of apixaban in subjects treated for venous thromboembolism. CPT Pharmacometrics Syst Pharmacol. 2017;6(5):340–9.
33. Mavri A, Vene N, Božič-Mijovski M, et al. Apixaban concentration variability and relation to clinical outcomes in real-life patients with atrial fibrillation. Sci Rep. 2021;11(1):13908.
34. Jakowenko N, Nguyen S, Ruegger M, et al. Apixaban and rivaroxaban anti-Xa level utilization and associated bleeding events within an academic health system. Thromb Res. 2020;196:276–82.

Publisher's Note