Pharmacokinetics and Dialytic Clearance of Apixaban During In Vitro Continuous Renal Replacement Therapy

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Abstract

Objective: To evaluate the transmembrane clearance (CL_{TM}) of apixaban during modeled *in vitro* continuous renal replacement therapy (CRRT), assess protein binding and circuit adsorption, and provide initial dosing recommendations.

Design: *In vitro* pharmacokinetic (PK) study.

Setting: University research laboratory.

Subjects: Not applicable.

Interventions: Apixaban was added to the CRRT circuit and serial, undiluted pre-filter bovine blood samples were collected along with analogous post-filter blood and effluent samples. All experiments were performed in duplicate using continuous veno-venous hemofiltration (CVVH) and hemodialysis (CVVHD) modes, with varying filter types (M150 and HF1400), flow rates (2 and 4 L/h), and point of CVVH replacement fluid dilution (pre, post, and pre/post filter). Concentrations of apixaban and urea were quantified via liquid chromatography-tandem mass spectrometry. Plasma PK parameters for apixaban were estimated via noncompartmental analysis in WinNonlin. CL_{TM} was calculated via the estimated area under the curve (AUC) and by the product of the sieving/saturation coefficient (SC/SA) and flow rate. Two and three-way ANOVA models were built to assess the effects of mode, filter type, flow rate, and point of dilution on CL_{TM} by each method. Optimal doses were suggested by matching the AUC observed *in vitro* to the systemic exposure demonstrated in Phase 2/3 studies of apixaban. Linear regression was then utilized to provide dosing estimations for flow rates from 0.5-5 L/h.

Measurements and Main Results: Mean adsorption to the HF1400 and M150 filters differed significantly at 38% and 13%, respectively, while mean (±SD) percent protein binding was 70.81±0.01%. Effect of CVVH point of replacement fluid dilution did not differ across filter types, although CL_{TM} was consistently significantly higher during CRRT with the HF1400 filter compared to the M150. The three-way ANOVA demonstrated improved fit when CL_{TM} values calculated by AUC were used (adjusted R^2 0.87 vs. 0.52), and therefore, these values were used to generate optimal dosing recommendations. Linear regression revealed significant effects of filter type and flow rate on CL_{TM} by AUC, suggesting doses of 5-10 mg BID may be needed for flow rates ranging from 0.5-5 L/h respectively.

Conclusion: CL_{TM} of apixaban during CRRT resulted in estimated dosing recommendations ranging from 5 mg BID for flow rates ≤3 L/h up to 7.5-10 mg BID for rates >3 L/h, depending on filter type, in order to match target systemic exposure thresholds. The safety and efficacy of these proposed dosing regimens warrants further investigation in clinical studies.

Introduction

Venous thromboembolism (VTE) and new-onset atrial fibrillation (NOAF) occur in up to 37% and 46% of critically ill patients, respectively, and are responsible for significant morbidity and mortality in the intensive care unit (ICU) [1–7]. Parenteral anticoagulation with unfractionated heparin (UFH) is the current mainstay therapy for VTE and NOAF in this population given its rapid onset of action and short half-life [8]. Due to the potential for serious adverse effects with UFH, activated thromboplastin time (aPTT) monitoring and dose titration are required to maintain exposures within a narrow therapeutic index [9]. Despite the assistance of dosing algorithms and decades of clinical experience, > 75% of hospitalized patients fail to achieve aPTTs within goal range during the first 24–48 hours after UFH initiation and only 29% are able to sustain them [10–12]. In the critically ill ICU population, only approximately 50% of patients achieve therapeutic aPTTs within this same time frame, largely secondary to pathophysiologic and pharmacokinetic (PK) derangements such as sepsis-induced acute kidney injury (AKI), which can necessitate renal replacement therapy (RRT) in up to 70% of patients [13–21]. Alternatively, despite minimal PK alterations, low molecular weight heparin (LMWH) has demonstrated detrimental pharmacodynamic (PD) properties, including increased thrombin generation time and an increased risk of bleeding in patients receiving RRT [22–25]. Given the challenges in optimizing the use of UFH and LMWH in the ICU setting, more reliable anticoagulation therapies are desperately needed for managing critically ill patients, especially those requiring extracorporeal organ support such as continuous RRT (CRRT).

Apixaban, a direct-acting oral anticoagulant (DOAC) agent, has emerged as a potential alternative therapy for the treatment of VTE and NOAF over UFH and LMWH in the ICU population due to its more reliable dose-exposure-response relationship, lack of required monitoring, decreased drug-drug interactions, and improved safety profile [8, 26–31]. Pharmacokinetic studies in otherwise healthy subjects with end stage renal disease (ESRD) on intermittent hemodialysis (HD) indicate that HD has a limited overall impact on the

clearance (CL) of apixaban [32–35]. However, data regarding CL by conventional HD cannot be accurately extrapolated to CRRT given the differences in modes, durations of therapy, types of hemofilters used, and blood, ultrafiltration, and dialysate flow rates. Unfortunately, robust PK data in patients receiving CRRT are scarce and often include only small numbers of critically ill patients on many different forms of CRRT with heterogeneous flow rates, filter types, dosing, and sampling schemes, making it difficult to draw meaningful conclusions [36–40]. As such, *in vitro* CRRT models are useful for generating precise assessments of sieving/saturation coefficients (SC/SA) across different modes, flow rates, filter types, and points of dilution while eliminating the variability introduced by the patient. As recognized by the U.S Food and Drug Administration (FDA), National Institutes of Health (NIH), and National Institute of Allergy and Infectious Diseases (NIAID), these models can be used to guide dosing in the absence of, or when combined with, *in vivo* data and have been shown to accurately predict *in vivo* total body clearance (CL_T) [41], allowing for data derived from *in vitro* investigations to be utilized in estimating clinical dosing regimens [42].

Although apixaban may represent a safer and more efficacious alternative to UFH and LMWH in ICU patients, the lack of PK data to inform appropriate dosing in patients undergoing CRRT currently precludes its use in a significant proportion of the critically ill population. As such, the objective of this study was to evaluate the PK and dialytic clearance of apixaban during *in vitro* CRRT in order to provide initial guidance on optimal dosing in this population.

Materials And Methods

Study design

In vitro **CRRT clearance model**

In vitro CRRT was simulated using a Prismaflex 7.2 control unit (Baxter Healthcare Corporation, Deerfield, IL, USA) in continuous veno-venous hemofiltration (CVVH) and continuous veno-venous hemodialysis (CVVHD) modes using fresh 1.4 m^2 polyarylethersulfone (PAES; Prismaflex HF1400) and 1.5 m^2 acrylonitrile (AN69; Prismaflex M150) hemofilter sets for each experiment. One liter of heparinized (20 units/mL) whole bovine blood (Densco Marketing Inc, Woodstock, IL, USA) was heated to 37 °C in a water bath and stirred continuously. The Prismaflex circuit was initially primed with 186 mL (HF1400) or 189 mL (M150) of 0.9% sodium chloride per the manufacturer's operating instructions [43, 44]. Prior to the start of each experiment, blood was then allowed to circulate throughout the system for at least 2 minutes to permit adequate exposure of the hemofilter to blood proteins. The blood flow rate was fixed at 200 mL/min for all experiments while CVVH replacement fluid (PrismaSOL® BGK 2/0; Baxter Healthcare Corporation, Deerfield, IL, USA) and CVVHD dialysate (PrismaSATE® BGK 2/0; Baxter Healthcare Corporation, Deerfield, IL, USA) rates of 2 L/h and 4 L/h were tested with each filter type. During CVVH at 2 L/h, replacement fluid was added 100% pre-filter, 100% post-filter, and at 50% pre-/50% post-filter. During CVVH at 4 L/h, replacement fluid was added at 50% pre-/50% post-filter. All experiments were performed in duplicate in each mode, at each rate, and with each filter for a total of 24 experiments (excluding adsorption experiments).

Apixaban (Eliquis®; Bristol-Myers Squibb, New York, NY, USA) was reconstituted per manufacturer's instructions [45] and added to the central blood reservoir at a concentration simulating the mean peak serum concentration (C_{max}) observed in healthy adult subjects following a single 5 mg dose of apixaban (~ 0.104 mg/L) [46]. Urea (Sigma-Aldrich, St. Louis, MO, USA) was also added at 75 mg/L to serve as the control solute.

After at least 1 minute of equilibration, serial undiluted pre-filter blood samples were collected in 3.2% sodium citrate tubes (Becton, Dickinson and Company, Franklin Lakes, NJ, USA) at 0, 10, 20, 30, 45, and 60 min post-dose with analogous post-filter blood and effluent samples collected at 10 and 30 min. Blood samples were centrifuged at 1,500 x *g* for 10 min and the resultant supernatant plasma and ultrafiltrate samples were frozen at -80 °C within 30 min of collection until analysis.

Adsorption experiments

To evaluate potential adsorption of apixaban to the hemofilters, the initial CRRT model was modified to create a closed-circuit system. Effluent was rerouted to the central blood reservoir, and 0.9% normal saline was exogenously pumped into the effluent bag via a Masterflex® Peristaltic pump (Cole-Parmer, Vernon Hills, IL, USA) at the same rate to prevent the Prismaflex system from aborting due to the patient blood loss/gain alarm. Serial blood samples were drawn from the central reservoir at 0, 10, 20, 30, 45, 60, 90, 105, 120, 150, and 180 min, centrifuged at 1,500 *x g* for 10 min, and supernatant plasma was frozen at -80 °C within 30 min of collection until analysis. This process was repeated twice in duplicate for a total of 4 experiments.

Protein binding determination

To assess apixaban protein binding in bovine plasma, 4 contrived samples were centrifuged at 2,000 x *g* for 30 minutes using a Centrifree® Ultrafiltration Device (Merck Millipore Ltd. Tullagreen, Carrigtwohill, Co. Cork, Ireland) with resulting bound and unbound plasma samples frozen at -80 °C within 30 min until analysis. This process was repeated twice in duplicate for a total of 4 experiments.

Bioanalytical procedures

Concentrations of apixaban and urea in bovine plasma and effluent were quantified via liquid chromatography-tandem mass spectrometry (Keystone Bioanalytical, North Wales, PA, USA) as previously described [47]. The calibration range of the assay was linear from 0.001-0.2 mg/L ($r \geq 0.999$). The precision and accuracy acceptance criteria for the quality control (QC) samples and calibration standards were ≤ 15% coefficient of variance (CV) and ± 15% relative error (RE) determined at each concentration level.

Pharmacokinetic procedures

Pharmacokinetic parameters for apixaban were estimated from observed pre-filter, pre-dilution plasma concentrations via noncompartmental analysis in Phoenix WinNonlin Version 8.1 (Certara USA Inc., Princeton, NJ, USA). Reported parameters included: C_{max}, last observed plasma concentration (C_{last}), elimination rate constant (K_e), half-life ($t_{1/2}$), apparent volume of distribution (V_d), clearance (CL), and the area under the concentration-time curve ($AUC_{0-\infty}$ and AUC_{0-last}) as determined via the linear up-log down method. As *in vitro* experiments were performed over a period of one hour, AUC_{0-last} was multiplied by 24 to demonstrate proportional AUC_{0-24}. Calculations for the estimation of apixaban and urea removal from the CRRT circuit were as follows:

- sieving coefficient (SC) = (C_{uf} / C_{pre})
- saturation coefficient (SA) = (2 * $C_{dialysate}$) / (C_{pre} + C_{post})

Where C_{uf} is the concentration in the ultrafiltrate, C_{pre} is the concentration from an undiluted pre-filter sampling port, $C_{dialysate}$ is the concentration in the dialysate, and C_{post} is the concentration from the post-filter sampling port [48–50].

Clearance by CRRT was then estimated by two distinct methods to ensure accuracy and allow for comparison. The primary method of estimating CL_{TM} was estimated using the AUC_{0-24} determined via noncompartmental analysis (CL_{TM} by AUC), as previously described. The secondary method, CL_{TM} by sieving/ saturation coefficients (SC/SA), utilized the following equations:

- CL_{CVVH} = (SC * Q_{uf} * Q_b) / (Q_b + Q_{rep})
- CL_{CVVHD} = (SA * Q_d)

Where Q_{uf} is the ultrafiltrate or replacement fluid rate flow rate and Q_d is the dialysate flow rate. In experiments where replacement fluid was added pre-filter, a dilutional correction factor was incorporated into the clearance equation, with Q_b representing blood flow rate and Q_{rep} being the pre-filter replacement fluid rate [50, 51].

Adsorption was calculated as the difference between the total amount of apixaban added to the system and the total amount recovered in the dialysate and plasma after 180 min using the following equation at each sampling time point:

- Adsorption (%) = 1- [(dose of apixaban added at time zero) / (concentration of apixaban * volume in central reservoir)] [52].

Optimal dosing determination

Optimal dosing was calculated to provide a comparable mean AUC value to that achieved following the administration of apixaban 5 mg twice daily for 7 days in healthy subjects (2103.8 mg · h/L) via the equation AUC = Dose / CL_T; where CL_T = CL_{TM} + CL_{NR} [53]. Here, CL_T represents total body clearance, CL_{TM} represents CL via CRRT, and CL_{NR} is non-renal clearance. The value for CL_{NR} (2.52 L/h) was imputed from Phase 2 and 3 studies evaluating apixaban for the treatment or prevention of recurrent VTE and assumed to be constant [54, 55]. Additionally, residual renal function was assumed to be negligible as the majority of critically ill patients with AKI on CRRT have no appreciable residual renal function [51].

Statistical analysis

Data are presented as mean (± SD) or with 95% confidence intervals (95% CI). Continuous data were compared via Student's t-test. Additionally, one- and two-way ANOVA models with Tukey's post-hoc tests were built to evaluate statistically significant differences in

mean CL_{TM} according to CVVH point of dilution within and between each filter type, respectively. Then, three-way ANOVA models were fit using CL_{TM} as the outcome to evaluate the interaction between CRRT mode, filter type, and flow rate. ANOVA-generated means and 95% CI of CL_{TM} were then used to estimate AUC and optimal total daily doses (TDD) of apixaban during CRRT. Finally, multiple linear regression via backwards stepwise analysis was used to correlate flow rate with mean CL_{TM} while adjusting for covariates (CRRT mode, filter type, point of dilution, and flow rate) and predict optimal dosing regimens across flow rates from 0.5-5 L/h. Model performance was assessed via the adjusted R^2 value. Collinearity was assessed via tolerance and variance inflation factor. A P value of ≤ 0.05 was considered statistically significant in the final model. All statistical analyses were performed using SPSS® Version 26 (IBM Corp, Armonk, NY, USA).

Results

In vitro **CRRT clearance model**

Mean (± SD) pre-filter PK parameters of apixaban in bovine plasma during CRRT as estimated via noncompartmental analyses are summarized in Table 1, and respective plasma concentration-time profiles are shown in Fig. 1. The mean (± SD) C_{max} value observed across the 24 experiments was 0.106 ± 0.014 mg/L (< 2% difference from target value of 0.104 mg/L). Notably, CL_{TM} by AUC did not scale proportionally with flow rate, with increases in CL_{TM} ranging from 1.3-1.8-fold as flow rate increased from 2 to 4 L/h.

Table 2 displays the observed SC, SA, and CL_{TM} by SC/SA values of apixaban and urea during CVVH and CVVHD stratified by CRRT mode, filter type, flow rate, and point of replacement fluid dilution. As expected, CL_{TM} by SC/SA values scaled roughly proportional to increases in flow rate from 2 to 4 L/h during CVVH (1.86–2.34 L/h) and CVVHD (1.94 L/h). The mean apixaban SC value during CVVH with the M150 filter was 0.584 and 0.594 with HF1400 (P = 0.726) and mean SA during CVVHD was 0.587 with M150 and 0.612 with HF1400 (P = 0.543). The average SC across CVVH was 0.589 and SA across CVVHD was 0.599 (P = 0.628). The overall mean SC/SA for apixaban was 0.594 across all CRRT modes, filter types, flow rates, and points of replacement fluid dilution tested, while overall mean CL_{TM} by SC/SA at 2 and 4 L/h were 1.2 and 2.4 L/h, respectively. Urea SC, SA, and CL_{TM} values were comparable to previously established parameters obtained in analogous experimental conditions [56].

Effect of CVVH point of dilution

Within the HF1400 filter group, there were no significant differences in CL_{TM} by AUC across any of the 3 points of dilution at 2 L/h (P = 0.641), however, when evaluated as CL_{TM} by SC, there were significant differences noted between the 50/50% and both the 0/100% (P = 0.009) and 100/0% modes (P = 0.014). Within the M150 group, point of replacement fluid addition also did not affect CL_{TM} by AUC (P = 0.420), but again demonstrated significant differences between the 50/50% and both the 0/100% (P = 0.003) and 100/0% (P = 0.004) groups by SC.

Effect of filter type

At 2 L/h, filter type did significantly affect CL_{TM} by AUC where the mean CL_{TM} was 1.80 L/h (95% CI 1.56–2.05) for the HF1400 filter vs 1.12 L/h (95% CI 0.87–1.37) for the M150 filter (P = 0.001). No difference was observed at 4 L/h: 3.30 L/h (95%CI 0.63–5.97) for HF1400 and 2.07 L/h (95%CI -2.12-6.26) for M150 (P = 0.088), although there were only 2 experiments per group at this rate. Including both flow rates, mean CL_{TM} values by AUC differed significantly between filters (HF1400 2.18 L/h, 95% CI 1.57–2.78 vs. M150 1.36 L/h, 95% CI 0.93–1.79, P = 0.021).

For CL_{TM} by SC/SA at 2 L/h, filter type did not have a significant effect with mean CL_{TM} values of 1.44 L/h (95% CI 0.97–1.91) for HF1400 and 1.51 L/h (95% CI 0.97–2.04) for M150 (P = 0.810). There was also no difference observed at 4 L/h: 2.49 L/h (95% CI 0.58–4.39) for HF1400 and 2.16 L/h (95% CI 0.89–3.43) for M150 (P = 0.209). Including both flow rates, mean CL_{TM} values by SC/SA remained similar between filters (HF1400 1.70 L/h, 95% CI 1.18–2.22 vs. M150 1.67 L/h, 95% CI 1.23–2.11, P = 0.915).

Effect of point of dilution and filter type

CVVH

These results were confirmed via a two-way ANOVA which demonstrated that the interaction between point of dilution and filter type was not significant on CL_{TM} by AUC (P = 0.292) or by SC (P = 0.519) at 2 L/h. An analysis of the main effects of each variable indicated

that there was a significant difference in CL_{TM} by AUC according to filter type ($P = 0.003$) but not point of dilution ($P = 0.922$), as previously described (Fig. 2). Conversely, CL_{TM} by SC again differed significantly by point of dilution ($P < 0.001$) but not by filter type ($P = 0.304$). As only one point of dilution (50/50%) was tested at the 4 L/h rate (2 experiments), two-way ANOVAs were not performed. Ignoring flow rate generated similar results with a non-significant interaction between filter type and point of dilution for CL_{TM} by AUC ($P = 0.648$) and by SC ($P = 0.792$) while main effects continued to differ according to filter type for CL_{TM} by AUC ($P = 0.049$) but not point of dilution ($P = 0.238$) and vice versa for CL_{TM} by SC ($P = 0.904$ for filter type and $P < 0.001$ for dilution).

CVVHD

Similarly for CVVHD at 2 L/h, there was a significant difference in mean CL_{TM} by AUC based on filter type (HF1400 1.67 L/h, 95% CI 0.08–3.25 vs. M150 0.91 L/h, 95% CI 0.46–1.35, $P = 0.028$). This difference remained at 4 L/h with mean CL_{TM} by AUC values of 2.17 L/h (95% CI 0.96–3.37) for HF1400 and 1.63 L/h (95% CI 0.99–2.27) for M150 ($P = 0.038$). For CL_{TM} by SA, mean values did not differ at 2 L/h (HF1400 1.25 L/h, 95% CI 0.93–1.56 vs. M150 1.24 L/h, 95% CI 0.73–1.75, $P = 0.925$) or 4 L/h (HF1400 2.41 L/h, 95% CI 1.71–3.10 vs. M150 2.23 L/h, 2.16–2.29, $P = 0.083$). Ignoring flow rate, mean CL_{TM} by AUC values remained significantly higher for HF1400 (1.92 L/h, 95% CI 1.41–2.42) compared to the M150 (1.27 L/h, 95% CI 0.60–1.94, $P = 0.049$) but did not differ significantly for CL_{TM} by SA (HF1400 1.83 L/h, 95% CI 0.76–2.89 vs. M150 1.73 L/h, 95% CI 0.83–2.64, $P = 0.841$).

Effect of CRRT mode, filter type, and flow rate

Ignoring point of dilution, the three-way ANOVA for the effect of CRRT mode, filter type, and flow rate on CL_{TM} by AUC demonstrated no significant two-way interactions between CRRT mode and filter ($P = 0.176$) or filter and flow rate ($P = 0.475$), while CRRT mode and flow rate was significant at $P = 0.013$ (Fig. 3). The three-way interaction between CRRT mode, filter, and flow rate was also non-significant ($P = 0.098$) with an adjusted R^2 of 0.869. For the CL_{TM} by SC/SA model, all two-way interactions were non-significant (CRRT mode*filter, $P = 0.914$, filter*flow rate, $P = 0.427$, and CRRT mode*flow rate, $P = 0.540$) along with the three-way interaction (CRRT mode*filter*flow rate, $P = 0.755$, adjusted $R^2 = 0.516$). The estimated marginal means for CL_{TM} by AUC and SC/SA generated from these ANOVAs as a function of CRRT mode, filter type, and flow rate are displayed in Table 3.

Adsorption experiments

The extent of apixaban adsorbed to the CRRT circuit was evaluated across two duplicate experiments; 2 with each filter type in CVVH mode at a flow rate of 2 L/h with a 50/50% dilution scheme. The intra-assay CV% within the HF1400 filter experiments was 5.55% and 10.05% for the M150 filter. Overall, the mean (± SD) percent adsorption differed significantly between the HF1400 and M150 filter types at 38.1 ± 13.4% and 12.8 ± 11.2% ($P < 0.001$).

Protein binding

The protein binding of apixaban has been previously explored in the serum of rats, dogs, chimpanzees, and humans but never in bovine plasma [57]. Protein binding in these species has ranged from 87% in humans to 96% in rats and varied slightly by concentration. Given its impact on drug clearance during CRRT, the protein binding of apixaban to bovine plasma from 4 contrived plasma samples with a measured bovine albumin concentration of 3.597 mg/dL (Biologic Resources Laboratory, University of Illinois at Chicago, Chicago, IL, USA) was evaluated. Samples were spiked at the human simulated C_{max} and 0.5x C_{max} concentration [46]. Overall, the mean (± SD) percent protein binding in bovine plasma was 70.81 ± 0.01% with an intra-assay CV% of 4.2% at C_{max} and 1.2% at 0.5x C_{max}.

Optimal CRRT dose determination

Given the increased precision of CL_{TM} by AUC compared to SC/SA [58], lack of influence by point of dilution, and improved model fit (adjusted R^2 0.87 vs. 0.52), these values were used to generate optimal dosing recommendations generalizable across varying CRRT modalities. All 4 applicable covariates (CRRT mode, filter type, flow rate, and point of dilution) were entered into the multiple linear regression model (Table 4). Filter type and flow rate were significant, and therefore, retained in the final model demonstrating a decrease of 0.821 L/h (95% CI -1.13 to -0.509, $P < 0.001$) in CL_{TM} when switching from the HF1400 to M150 filter and an increase of 1.224 L/h (95% CI 0.864–1.585, $P < 0.001$) in CL_{TM} for every 1 L/h increase in flow rate with excellent correlation (adjusted $R^2 = 0.849$). This regression equation was then used to make predictions for CL_{TM} and estimate optimal dosing recommendations for apixaban during CRRT across filter types and simulated flow rates from 0.5-5 L/h (Table 5). Although renal excretion (CL_R) typically only accounts for approximately 27% of the CL_T of apixaban [45], mean observed CL_{TM} values account for up to 67% of CL_T at the highest flow rates simulated in this model (Table 5). As such, the recommended doses of apixaban ranged from the labeled dose of 5 mg BID up to

7.5 mg BID for flow rates > 3 L/h. If the average filter adsorption was also considered, especially for the HF1400 filter (38%), doses of 10 mg BID would likely be needed once flow rates exceed 3 L/h. Given the direct correlation between apixaban concentrations and its pharmacodynamic activity along with its well-established safety profile, including doses up to 50 mg daily for 3–7 days and AUC values up to 6045 ng · h/mL [45, 59], we feel these doses are appropriate to maximize the efficacy and safety of apixaban and match the desired systemic exposure in patients with increased CL_T due to high CRRT flow rates. Maintaining single doses ≤ 10 mg also ensures that its linear PK properties are preserved, and that dissolution-limited absorption and decreases in bioavailability are avoided.

Discussion

To our knowledge this is the first study to evaluate the CL_{TM} of apixaban during CRRT and provides the first set of PK information for which to guide optimal dosing. Our data demonstrate that although it is considered highly protein bound (87%) and minimally renally excreted (27%), the estimated removal of apixaban during CRRT secondary to CL_{TM} and filter adsorption is significant and may necessitate doses as high as 7.5–10 mg BID to achieve target therapeutic AUC values at high flow rates (> 3 L/h). These results underscore the need to thoroughly evaluate the extracorporeal removal of drugs in tightly controlled, rigorous *in vitro* settings rather than estimating the potential removal using drug- and/or CRRT-specific factors, which has shown to be misleading in previous investigations [60], or by extrapolating from data generated from patients on intermittent hemodialysis [59, 61]. This is especially true as the use of apixaban for therapeutic anticoagulation continues to increase among critically ill ICU patients [8, 62–64], many if not most of whom will require CRRT at some point during their hospitalization.

In addition to providing clinicians with the first set of data for which to guide dosing of apixaban during CRRT, our study has several other notable strengths. Primarily, our methodology for assessing true CL_{TM} employed a rich PK sampling scheme allowing for calculation of the AUC which significantly improved our ability to accurately estimate drug removal during CRRT. The majority of previous studies employ a single sample design and attempt to estimate CL_{TM} by multiplying SC or SA derived from a single time point by the flow rate [65–68]. These methods assume SC and SA are static over time and that CL_{TM} is directly proportional to flow rate across the continuum of CRRT settings. Moreover, the methods for calculating SC and SA have varied dramatically throughout the literature, even among the same authors/groups across different studies [49, 69–72], resulting in an up to 28% difference in SC/SA values based solely on calculation differences. Through rigorous analysis and thorough statistical justification in this study, along with our previous work [58], we have demonstrated that calculation of CL_{TM} by AUC via noncompartmental analyses provides more robust and precise estimations of drug removal by CRRT, and therefore, more reliable dosing recommendations.

Additionally, our study utilized the cutting edge Prismaflex 7.2 System (Baxter International, Deerfield, IL, USA) which holds over 55% of the dialysis market share and allows for the collection and measurement of spent effluent such that all drug administered into the circuit can be accurately accounted for [73]. Antiquated machinery often require the formation of a closed-loop system whereby the effluent is returned to the blood as replacement fluid [74]. This closed system requires the blood to recirculate through the system, where virtually all of the drug in the blood continuously encounters the hemofilter and CRRT circuit, therefore precipitating the maximal degree of drug-filter interaction and adsorptive loss [75].

The vehicle used for drug delivery to the hemodialyzer is also an essential consideration during *in vitro* CRRT studies [76]. Saline or lactated Ringer's solutions, with or without albumin, or a mixture of blood and crystalloids, are often used as they are easily accessible and inexpensive [77–79]. Importantly, these solutions lack blood proteins vital for facilitating drug-protein binding and their viscosity is different from that of blood, which can alter the hydrostatic pressure within the extracorporeal circuit. The influence of blood proteins on a drug is a critically important aspect of drug disposition during CRRT, as only the unbound fraction of the drug is readily dialyzable. Furthermore, the use of a blood vehicle allows for the formation of a protein and fibrin layer on the extracorporeal circuit and hemodialyzer membrane during the first 20–30 minutes of CRRT.

Finally, we also assessed protein binding, adsorption, and the effects of point of replacement fluid dilution on drug removal. Although protein binding is known to be one of the most important factors affecting drug removal during CRRT [80], exceedingly few agents have available data regarding binding to bovine plasma as these animals are not typically utilized in the drug development process [81]. As such, it is crucial to directly measure this for appropriate clinical translation of *in vitro* results. Our protein binding results differed significantly from those seen in other mammalian species and humans. Albeit the use of modern, highly biocompatible hemofilters has often made drug adsorption negligible compared to the effect of filtration, it is critical to evaluate this component of removal from the circuit especially for moderately water soluble, lipophilic drugs like apixaban. In our study, we observed degrees of filter adsorption high

enough to potentially effect drug dosing during CRRT in addition to filtration, particularly for the HF1400 filter. Although the effect of point of replacement fluid dilution during CVVH is largely ignored from CRRT dosing recommendations [80, 82], the impact can be significant, especially at high flow rates [52], and warrants thorough evaluation such as ours during *in vitro* studies.

Despite these strengths, our study is not without limitations. First, although as many different CRRT machines, filter types, dilution points, and flow rates as possible were included in this study, the results may not be representative of all modalities of CRRT. Second, we assumed non-renal drug clearance to be stable when estimating dosing recommendations. Although there are some data to suggest AKI may affect non-renal clearance [83], there are currently no practical methods or useful biomarkers to assess changes in non-renal clearance. Third, the lower protein binding of apixaban in bovine plasma compared to humans may have led to increased CRRT clearance and subsequently increased dosing recommendation, although hypoalbuminemia is a common phenomenon among ICU patients underdoing CRRT [84]. Fourth, as mentioned, the necessity of forming a closed system may falsely inflate the degree of filter adsorption observed *in vitro* as virtually all of the drug in the blood continuously encounters the hemofilter and CRRT circuit, therefore precipitating the maximal degree of drug-filter interaction and adsorptive loss [75]. Lastly, as the PK of apixaban has already been extensively described [85], our 1-hour PK sampling scheme in this study was designed to evaluate the CL_{TM} of apixaban during CRRT, and therefore, the half-lives reported should be interpreted in light of this.

Conclusion

As recognized by the FDA, NIH, and NIAID, non-clinical PK/PD models play a critical role in designing human dosage regimens and are essential tools for drug development and dose optimization in special populations [42]. This study thoroughly explored the PK and dialytic clearance of apixaban during CRRT during tightly controlled *in vitro* experimentation. Apixaban was approximately 70% bound to bovine plasma and demonstrated variable adsorption to the HF1400 and M150 filters at approximately 38% and 13%, respectively. Clearance of apixaban during CRRT was most accurately estimated via calculation of CL_{TM} through noncompartmental estimation of AUC, as opposed to utilizing the product of SC/SA and flow rate. Transmembrane clearance during CRRT was significantly higher than predicted based on the known drug properties of apixaban and resulted in estimated dosing recommendations ranging from 5 mg BID for flow rates $\leq$ 3 L/h up to 7.5–10 mg BID for flow rates > 3 L/h, depending on filter type, in order to match target systemic exposure thresholds. The safety and efficacy of these proposed dosing regimens warrants further investigation in *in vivo* studies of critically ill patients undergoing CRRT.

Declarations

Ethics approval and consent to participate:

Not applicable

Consent for publication:

Not applicable

Availability of data and materials:

The datasets generated and/or analyzed during the current study are not publicly available due confidentiality agreements with the study sponsor but may be available from the corresponding author on reasonable request.

Competing interests:

E.W. serves on the speaker's bureau for Allergan Plc, Melinta Therapeutics, and Astellas Pharma and on the advisory board for GenMark Diagnostics and Shionogi. All other authors declare that they have no competing interests.

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Author contributions:

E.W. and S.B. conceptualized and designed the study, provided study oversight, and assisted with data analysis and manuscript writing. L.A. and X.T. performed the experiments and drafted the initial versions of the manuscripts. All authors contributed significantly and read and approved the final version of the manuscript.

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References

1. Kaplan D, Casper TC, Elliott CG, Men S, Pendleton RC, Kraiss LW, Weyrich AS, Grissom CK, Zimmerman GA, Rondina MT: **VTE Incidence and Risk Factors in Patients With Severe Sepsis and Septic Shock**. *Chest* 2015, **148**(5):1224-1230.
2. Khanna R, Maynard G, Sadeghi B, Hensley L, Medvedev S, Danielsen B, White RH: **Incidence of hospital-acquired venous thromboembolic codes in medical patients hospitalized in academic medical centers**. *J Hosp Med* 2014, **9**(4):221-225.
3. Malhotra AK, Goldberg SR, McLay L, Martin NR, Wolfe LG, Levy MM, Khiatani V, Borchers TC, Duane TM, Aboutanos MB *et al*: **DVT surveillance program in the ICU: analysis of cost-effectiveness**. *PLoS One* 2014, **9**(9):e106793.
4. Duarte PAD, Leichtweis GE, Andriolo L, Delevatti YA, Jorge AC, Fumagalli AC, Santos LC, Miura CK, Saito SK: **Factors Associated with the Incidence and Severity of New-Onset Atrial Fibrillation in Adult Critically Ill Patients**. *Crit Care Res Pract* 2017, **2017**:8046240.
5. Klein Klouwenberg PM, Frencken JF, Kuipers S, Ong DS, Peelen LM, van Vught LA, Schultz MJ, van der Poll T, Bonten MJ, Cremer OL *et al*: **Incidence, Predictors, and Outcomes of New-Onset Atrial Fibrillation in Critically Ill Patients with Sepsis. A Cohort Study**. *Am J Respir Crit Care Med* 2017, **195**(2):205-211.
6. Moss TJ, Calland JF, Enfield KB, Gomez-Manjarres DC, Ruminski C, DiMarco JP, Lake DE, Moorman JR: **New-Onset Atrial Fibrillation in the Critically Ill**. *Crit Care Med* 2017, **45**(5):790-797.
7. Sibley S, Muscedere J: **New-onset atrial fibrillation in critically ill patients**. *Can Respir J* 2015, **22**(3):179-182.
8. Rali P, Gangemi A, Moores A, Mohrien K, Moores L: **Direct-Acting Oral Anticoagulants in Critically Ill Patients**. *Chest* 2019, **156**(3):604-618.
9. Tapson VF, Shirvanian S: **Anticoagulation**. In: *Critical Care*. Edited by Oropello JM, Pastores SM, Kvetan V. New York, NY: McGraw-Hill Education.
10. Hyers TM: **Management of venous thromboembolism: past, present, and future**. *Arch Intern Med* 2003, **163**(7):759-768.
11. Hylek EM, Regan S, Henault LE, Gardner M, Chan AT, Singer DE, Barry MJ: **Challenges to the effective use of unfractionated heparin in the hospitalized management of acute thrombosis**. *Arch Intern Med* 2003, **163**(5):621-627.
12. Smith SB, Geske JB, Maguire JM, Zane NA, Carter RE, Morgenthaler TI: **Early anticoagulation is associated with reduced mortality for acute pulmonary embolism**. *Chest* 2010, **137**(6):1382-1390.
13. Aarab R, van Es J, de Pont AC, Vroom MB, Middeldorp S: **Monitoring of unfractionated heparin in critically ill patients**. *Neth J Med* 2013, **71**(9):466-471.
14. Bagshaw SM, George C, Dinu I, Bellomo R: **A multi-centre evaluation of the RIFLE criteria for early acute kidney injury in critically ill patients**. *Nephrol Dial Transplant* 2008, **23**(4):1203-1210.
15. Khwaja A: **KDIGO clinical practice guidelines for acute kidney injury**. *Nephron Clin Pract* 2012, **120**(4):c179-184.
16. Ostermann M, Chang RW: **Acute kidney injury in the intensive care unit according to RIFLE**. *Crit Care Med* 2007, **35**(8):1837-1843; quiz 1852.
17. Ricci Z, Cruz D, Ronco C: **The RIFLE criteria and mortality in acute kidney injury: A systematic review**. *Kidney Int* 2008, **73**(5):538-546.
18. Thakar CV, Christianson A, Freyberg R, Almenoff P, Render ML: **Incidence and outcomes of acute kidney injury in intensive care units: a Veterans Administration study**. *Crit Care Med* 2009, **37**(9):2552-2558.
19. Hoste EA, Bagshaw SM, Bellomo R, Cely CM, Colman R, Cruz DN, Edipidis K, Forni LG, Gomersall CD, Govil D *et al*: **Epidemiology of acute kidney injury in critically ill patients: the multinational AKI-EPI study**. *Intensive Care Med* 2015, **41**(8):1411-1423.
20. Bagshaw SM, Uchino S, Bellomo R, Morimatsu H, Morgera S, Schetz M, Tan I, Bouman C, Macedo E, Gibney N *et al*: **Septic acute kidney injury in critically ill patients: clinical characteristics and outcomes**. *Clin J Am Soc Nephrol* 2007, **2**(3):431-439.

21. Uchino S, Kellum JA, Bellomo R, Doig GS, Morimatsu H, Morgera S, Schetz M, Tan I, Bouman C, Macedo E *et al*: **Acute renal failure in critically ill patients: a multinational, multicenter study**. *JAMA* 2005, **294**(7):813-818.
22. Brophy DF, Carr ME, Jr., Martin EJ, Venitz J, Gehr TW: **The pharmacokinetics of enoxaparin do not correlate with its pharmacodynamic effect in patients receiving dialysis therapies**. *J Clin Pharmacol* 2006, **46**(8):887-894.
23. Tsai TT, Maddox TM, Roe MT, Dai D, Alexander KP, Ho PM, Messenger JC, Nallamothu BK, Peterson ED, Rumsfeld JS *et al*: **Contraindicated medication use in dialysis patients undergoing percutaneous coronary intervention**. *JAMA* 2009, **302**(22):2458-2464.
24. Kearon C, Akl EA, Ornelas J, Blaivas A, Jimenez D, Bounameaux H, Huisman M, King CS, Morris TA, Sood N *et al*: **Antithrombotic Therapy for VTE Disease: CHEST Guideline and Expert Panel Report**. *CHEST* 2016, **149**(2):315-352.
25. Shaikh SA, Regal RE: **Dosing of Enoxaparin in Renal Impairment**. *P T* 2017, **42**(4):245-249.
26. Agnelli G, Buller HR, Cohen A, Curto M, Gallus AS, Johnson M, Masiukiewicz U, Pak R, Thompson J, Raskob GE *et al*: **Oral apixaban for the treatment of acute venous thromboembolism**. *N Engl J Med* 2013, **369**(9):799-808.
27. Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, Al-Khalidi HR, Ansell J, Atar D, Avezum A *et al*: **Apixaban versus warfarin in patients with atrial fibrillation**. *N Engl J Med* 2011, **365**(11):981-992.
28. Levy JH, Faraoni D, Spring JL, Douketis JD, Samama CM: **Managing new oral anticoagulants in the perioperative and intensive care unit setting**. *Anesthesiology* 2013, **118**(6):1466-1474.
29. Garg VP, Halperin JL: **Novel antiplatelet and anticoagulant agents in the cardiac care unit**. *Cardiol Clin* 2013, **31**(4):533-544, viii.
30. Johnson SA, Yarbrough PM, Rose RS, Lanspa MJ: **Prescribing patterns of target-specific oral anticoagulants: an academic hospital perspective**. *Blood Coagul Fibrinolysis* 2015, **26**(7):767-771.
31. **ELIQUIS (apixaban) package insert. Princeton, NJ and New York, NY: Bristol-Myers Squibb Company and Pfizer Inc.; Revised 2019 Nov. https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/202155s000lbl.pdf**.
32. Kimachi M, Furukawa TA, Kimachi K, Goto Y, Fukuma S, Fukuhara S: **Direct oral anticoagulants versus warfarin for preventing stroke and systemic embolic events among atrial fibrillation patients with chronic kidney disease**. *Cochrane Database Syst Rev* 2017, **11**:CD011373.
33. Mavrakanas TA, Samer CF, Nessim SJ, Frisch G, Lipman ML: **Apixaban Pharmacokinetics at Steady State in Hemodialysis Patients**. *J Am Soc Nephrol* 2017, **28**(7):2241-2248.
34. Siontis KC, Zhang X, Eckard A, Bhave N, Schaubel DE, He K, Tilea A, Stack AG, Balkrishnan R, Yao X *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):1519-1529.
35. Wang X, Tirucherai G, Marbury TC, Wang J, Chang M, Zhang D, Song Y, Pursley J, Boyd RA, Frost C: **Pharmacokinetics, pharmacodynamics, and safety of apixaban in subjects with end-stage renal disease on hemodialysis**. *J Clin Pharmacol* 2016, **56**(5):628-636.
36. Beumier M, Roberts JA, Kabtouri H, Hites M, Cotton F, Wolff F, Lipman J, Jacobs F, Vincent JL, Taccone FS: **A new regimen for continuous infusion of vancomycin during continuous renal replacement therapy**. *The Journal of antimicrobial chemotherapy* 2013, **68**(12):2859-2865.
37. Roberts JA, Udy AA, Bulitta JB, Stuart J, Jarrett P, Starr T, Lassig-Smith M, Roberts NA, Dunlop R, Hayashi Y *et al*: **Doripenem population pharmacokinetics and dosing requirements for critically ill patients receiving continuous venovenous haemodiafiltration**. *The Journal of antimicrobial chemotherapy* 2014, **69**(9):2508-2516.
38. Roberts DM, Liu X, Roberts JA, Nair P, Cole L, Roberts MS, Lipman J, Bellomo R: **A multicenter study on the effect of continuous hemodiafiltration intensity on antibiotic pharmacokinetics**. *Critical care (London, England)* 2015, **19**:84.
39. Jamal JA, Udy AA, Wallis SC, Ranganathan D, McWhinney BC, Ungerer JP, Lipman J, Roberts JA: **Can we use an ex vivo continuous hemofiltration model to describe the adsorption and elimination of meropenem and piperacillin?** *Int J Artif Organs* 2015, **38**(8):419-424.
40. Roger C, Wallis SC, Muller L, Saissi G, Lipman J, Bruggemann RJ, Lefrant JY, Roberts JA: **Caspofungin Population Pharmacokinetics in Critically Ill Patients Undergoing Continuous Veno-Venous Haemofiltration or Haemodiafiltration**. *Clin Pharmacokinet* 2017, **56**(9):1057-1068.
41. Churchwell MD: **Use of an in vitro model of renal replacement therapy systems to estimate extracorporeal drug removal**. *J Clin Pharmacol* 2012, **52**(1 Suppl):35s-44s.

42. Bulitta JB, Hope WW, Eakin AE, Guina T, Tam VH, Louie A, Drusano GL, Hoover JL: **Generating Robust and Informative Nonclinical In Vitro and In Vivo Bacterial Infection Model Efficacy Data To Support Translation to Humans**. *Antimicrob Agents Chemother* 2019, **63**(5).
43. **PRISMAFLEX System M60/M100/M150 Hemofilter Sets** [https://econnect.baxter.com/assets/downloads/products_expertise/renal_therapies/PRISMAFLEX_System_M60_M100_M150.pdf]
44. **PRISMAFLEX System HF1000/HF1400 Hemofilter Sets** [https://econnect.baxter.com/assets/downloads/products_expertise/renal_therapies/Prismaflex_HF_Spec_Sheet.pdf]
45. Charlson F, Degenhardt L, McLaren J, Hall W, Lynskey M: **A systematic review of research examining benzodiazepine-related mortality**. *Pharmacoepidemiol Drug Saf* 2009, **18**(2):93-103.
46. Frost C, Wang J, Nepal S, Schuster A, Barrett YC, Mosqueda-Garcia R, Reeves RA, LaCreta F: **Apixaban, an oral, direct factor Xa inhibitor: single dose safety, pharmacokinetics, pharmacodynamics and food effect in healthy subjects**. *Br J Clin Pharmacol* 2013, **75**(2):476-487.
47. Pursley J, Shen JX, Schuster A, Dang OT, Lehman J, Buonarati MH, Song Y, Aubry AF, Arnold ME: **LC-MS/MS determination of apixaban (BMS-562247) and its major metabolite in human plasma: an application of polarity switching and monolithic HPLC column**. *Bioanalysis* 2014, **6**(15):2071-2082.
48. Churchwell MD, Pasko DA, Mueller BA: **Daptomycin clearance during modeled continuous renal replacement therapy**. *Blood Purif* 2006, **24**(5-6):548-554.
49. Golper TA, Wedel SK, Kaplan AA, Saad AM, Donta ST, Paganini EP: **Drug removal during continuous arteriovenous hemofiltration: theory and clinical observations**. *Int J Artif Organs* 1985, **8**(6):307-312.
50. Schetz M: **Drug dosing in continuous renal replacement therapy: general rules**. *Curr Opin Crit Care* 2007, **13**(6):645-651.
51. Choi G, Gomersall CD, Tian Q, Joynt GM, Freebairn R, Lipman J: **Principles of antibacterial dosing in continuous renal replacement therapy**. *Crit Care Med* 2009, **37**(7):2268-2282.
52. Sime FB, Pandey S, Karamujic N, Parker S, Alexander E, Loutit J, Durso S, Griffith D, Lipman J, Wallis SC *et al*: **Ex Vivo Characterization of Effects of Renal Replacement Therapy Modalities and Settings on Pharmacokinetics of Meropenem and Vaborbactam**. *Antimicrob Agents Chemother* 2018, **62**(10).
53. Frost C, Nepal S, Wang J, Schuster A, Byon W, Boyd RA, Yu Z, Shenker A, Barrett YC, Mosqueda-Garcia R *et al*: **Safety, pharmacokinetics and pharmacodynamics of multiple oral doses of apixaban, a factor Xa inhibitor, in healthy subjects**. *Br J Clin Pharmacol* 2013, **76**(5):776-786.
54. Byon W, Sweeney K, Frost C, Boyd RA: **Population Pharmacokinetics, Pharmacodynamics, and Exploratory Exposure-Response Analyses of Apixaban in Subjects Treated for Venous Thromboembolism**. *CPT Pharmacometrics Syst Pharmacol* 2017, **6**(5):340-349.
55. Byon W, Garonzik S, Boyd RA, Frost CE: **Apixaban: A Clinical Pharmacokinetic and Pharmacodynamic Review**. *Clin Pharmacokinet* 2019, **58**(10):1265-1279.
56. Troyanov S, Cardinal J, Geadah D, Parent D, Courteau S, Caron S, Leblanc M: **Solute clearances during continuous venovenous haemofiltration at various ultrafiltration flow rates using Multiflow-100 and HF1000 filters**. *Nephrol Dial Transplant* 2003, **18**(5):961-966.
57. He K, Luettgen JM, Zhang D, He B, Grace JE, Xin B, Pinto DJP, Wong PC, Knabb RM, Lam PYS *et al*: **Preclinical pharmacokinetics and pharmacodynamics of apixaban, a potent and selective factor Xa inhibitor**. *European Journal of Drug Metabolism and Pharmacokinetics* 2011, **36**(3):129-139.
58. Bunnell K, Wenzler E, Rodvold K: **1362: EVALUATION OF CLEARANCE EQUATIONS IN CONTINUOUS RENAL REPLACEMENT THERAPY WITH AN IN VITRO MODEL**. *Critical Care Medicine* 2018, **46**(1):664.
59. Mavrakanas TA, Samer CF, Nessim SJ, Frisch G, Lipman ML: **Apixaban Pharmacokinetics at Steady State in Hemodialysis Patients**. *J Am Soc Nephrol* 2017, **28**(7):2241-2248.
60. Vilay AM, Shah KH, Churchwell MD, Patel JH, DePestel DD, Mueller BA: **Modeled Dalbavancin Transmembrane Clearance during Intermittent and Continuous Renal Replacement Therapies**. *Blood Purification* 2010, **30**(1):37-43.
61. Westermann H, Choi TN, Briggs WM, Charlson ME, Mancuso CA: **Obesity and exercise habits of asthmatic patients**. *Ann Allergy Asthma Immunol* 2008, **101**(5):488-494.

62. Boutin-Foster C, Charlson ME: **Do recent life events and social support explain gender differences in depressive symptoms in patients who had percutaneous transluminal coronary angioplasty?** *J Womens Health (Larchmt)* 2007, **16**(1):114-123.
63. Neuman HB, Charlson ME, Temple LK: **Is there a role for decision aids in cancer-related decisions?** *Crit Rev Oncol Hematol* 2007, **62**(3):240-250.
64. Groetzinger LM, Miller TJ, Rivosecchi RM, Smith RE, Gladwin MT, Rivera-Lebron BN: **Apixaban or Rivaroxaban Versus Warfarin for Treatment of Submassive Pulmonary Embolism After Catheter-Directed Thrombolysis**. *Clin Appl Thromb Hemost* 2018, **24**(6):908-913.
65. Chaijamorn W, Shaw AR, Lewis SJ, Mueller BA: **Ex vivo Ceftolozane/Tazobactam Clearance during Continuous Renal Replacement Therapy**. *Blood Purification* 2017, **44**(1):16-23.
66. Lewis SJ, Switaj LA, Mueller BA: **Tedizolid Adsorption and Transmembrane Clearance during in vitro Continuous Renal Replacement Therapy**. *Blood Purif* 2015, **40**(1):66-71.
67. Kesner JM, Yardman-Frank JM, Mercier RC, Wong CS, Walker SE, Argyres DP, Vilay AM: **Trimethoprim and sulfamethoxazole transmembrane clearance during modeled continuous renal replacement therapy**. *Blood Purif* 2014, **38**(3-4):195-202.
68. Jang SM, Hough G, Mueller BA: **Ex vivo Rezafungin Adsorption and Clearance During Continuous Renal Replacement Therapy**. *Blood Purif* 2018, **46**(3):214-219.
69. Akers KS, Rowan MP, Niece KL, Stewart IJ, Mende K, Cota JM, Murray CK, Chung KK: **Colistin pharmacokinetics in burn patients during continuous venovenous hemofiltration**. *Antimicrobial agents and chemotherapy* 2015, **59**(1):46-52.
70. Uchino S, Cole L, Morimatsu H, Goldsmith D, Bellomo R: **Clearance of vancomycin during high-volume haemofiltration: impact of pre-dilution**. *Intensive Care Medicine* 2002, **28**(11):1664-1667.
71. Janssen PK, Foudraine NA, Burgers DM, Neef K, le Noble JL: **Population Pharmacokinetics of Cefuroxime in Critically Ill Patients Receiving Continuous Venovenous Hemofiltration With Regional Citrate Anticoagulation and a Phosphate-Containing Replacement Fluid**. *Ther Drug Monit* 2016, **38**(6):699-705.
72. Tegeder I, Bremer F, Oelkers R, Schobel H, Schüttler J, Brune K, Geisslinger G: **Pharmacokinetics of imipenem-cilastatin in critically ill patients undergoing continuous venovenous hemofiltration**. *Antimicrobial agents and chemotherapy* 1997, **41**(12):2640-2645.
73. Doherty SJ, Anderson TL, Charlson RJ: **Measurement of the lidar ratio for atmospheric aerosols with a 180 degrees backscatter nephelometer**. *Appl Opt* 1999, **38**(9):1823-1832.
74. Jang SM, Hough G, Mueller BA: **Ex vivo Rezafungin Adsorption and Clearance During Continuous Renal Replacement Therapy**. *Blood Purification* 2018, **46**(3):214-219.
75. Lewis SJ, Switaj LA, Mueller BA: **Tedizolid Adsorption and Transmembrane Clearance during in vitro Continuous Renal Replacement Therapy**. *Blood Purification* 2015, **40**(1):66-71.
76. Churchwell MD: **Use of an In Vitro Model of Renal Replacement Therapy Systems to Estimate Extracorporeal Drug Removal**. *The Journal of Clinical Pharmacology* 2012, **52**(S1):35S-44S.
77. Sime FB, Pandey S, Karamujic N, Parker S, Alexander E, Loutit J, Durso S, Griffith D, Lipman J, Wallis SC *et al*: **Ex Vivo Characterization of Effects of Renal Replacement Therapy Modalities and Settings on Pharmacokinetics of Meropenem and Vaborbactam**. *Antimicrobial Agents and Chemotherapy* 2018, **62**(10):e01306-01318.
78. W TPW, Guerra Valero Y, Choi GYS, Ordóñez Mejia JL, Wallis SC, Joynt GM, Lipman J, Gomersall CD, Roberts JA: **In-vitro adsorption and sieving coefficient of ticarcillin-clavulanate during continuous haemofiltration**. *Int J Antimicrob Agents* 2019, **54**(2):261-264.
79. Roehr AC, Frey OR, Koeberer A, Fuchs T, Roberts JA, Brinkmann A: **Anti-Infective Drugs during Continuous Hemodialysis –Using the Bench to Learn What to do at the Bedside**. *The International Journal of Artificial Organs* 2015, **38**(1):17-22.
80. Hoff BM, Maker JH, Dager WE, Heintz BH: **Antibiotic Dosing for Critically Ill Adult Patients Receiving Intermittent Hemodialysis, Prolonged Intermittent Renal Replacement Therapy, and Continuous Renal Replacement Therapy: An Update**. *Annals of Pharmacotherapy* 2020, **54**(1):43-55.
81. Charlson ME, Peterson JC, Krieger KH, Hartman GS, Hollenberg JP, Briggs WM, Segal AZ, Parikh M, Thomas SJ, Donahue RG *et al*: **Improvement of outcomes after coronary artery bypass II: a randomized trial comparing intraoperative high versus customized mean arterial pressure**. *J Card Surg* 2007, **22**(6):465-472.
82. Heintz BH, Matzke GR, Dager WE: **Antimicrobial dosing concepts and recommendations for critically ill adult patients receiving continuous renal replacement therapy or intermittent hemodialysis**. *Pharmacotherapy* 2009, **29**(5):562-577.

83. Vilay AM, Churchwell MD, Mueller BA: **Clinical review: Drug metabolism and nonrenal clearance in acute kidney injury**. *Critical care (London, England)* 2008, **12**(6):235-235.

84. Wu X, Clancy CJ, Rivosecchi RM, Zhao W, Shields RK, Marini RV, Venkataramanan R, Nguyen MH: **Pharmacokinetics of Intravenous Isavuconazole in Solid-Organ Transplant Recipients**. *Antimicrobial Agents and Chemotherapy* 2018, **62**(12):e01643-01618.

85. Byon W, Garonzik S, Boyd RA, Frost CE: **Apixaban: A Clinical Pharmacokinetic and Pharmacodynamic Review**. *Clinical Pharmacokinetics* 2019, **58**(10):1265-1279.

Tables

Table 1.

Bovine plasma pharmacokinetic parameters of apixaban during in vitro CRRT as determined via noncompartmental analyses[a]

	C_{max} (ng/mL)	C_{last} (ng/mL)	K_e (hr^{-1})	$t_{1/2}$ (h)	V_d (L)	CL_{TM} (L/h)	$AUC_{0-\infty}$ (ng · h/mL)	AUC_{0-last} (ng · h/mL)	AUC_{0-24} (ng · h/mL)
CVVH					HF1400				
2 L/h, 50/50%	106.5 ± 0.7	23.4 ± 1.6	0.9 ± 0.0	0.8 ± 0.0	2.2 ± 0.0	1.9 ± 0.1	66.8 ± 2.7	39.3 ± 0.2	943.6 ± 4.9
2 L/h, 100/0%	113.3 ± 21.2	21.2 ± 4.5	0.9 ± 0.2	0.8 ± 0.2	2.0 ± 0.0	1.7 ± 0.4	78.2 ± 18.5	44.5 ± 5.0	1068.9 ± 120.5
2 L/h, 0/100%	108.5 ± 3.2	24.3 ± 2.0	1.0 ± 0.2	0.7 ± 0.2	1.9 ± 0.2	1.9 ± 0.2	66.9 ± 7.2	42.1 ± 0.3	1009.8 ± 6.8
4 L/h, 50/50%	86.5 ± 4.5	13.1 ± 1.2	1.3 ± 0.1	0.5 ± 0.0	2.6 ± 0.4	3.3 ± 0.3	38.2 ± 3.4	27.9 ± 3.1	669.4 ± 73.5
CVVHD									
2 L/h	117.7 ± 1.9	26.9 ± 1.8	0.9 ± 0.1	0.8 ± 0.1	1.9 ± 0.0	1.7 ± 0.2	75.7 ± 8.1	44.1 ± 2.2	1058.0 ± 52.2
4 L/h	119.1 ± 7.4	20.5 ± 1.6	1.2 ± 0.2	0.6 ± 0.1	1.9 ± 0.2	2.2 ± 0.1	58.1 ± 3.5	40.1 ± 0.4	962.7 ± 9.7
CVVH					M150				
2 L/h, 50/50%	107.9 ± 16.2	31.0 ± 10.2	0.9 ± 0.3	0.9 ± 0.3	1.8 ± 0.4	1.6 ± 0.7	92.5 ± 37.0	49.6 ± 11.8	1191.0 ± 283.3
2 L/h, 100/0%	90.4 ± 13.8	34.3 ± 9.9	0.7 ± 0.3	0.9 ± 0.2	1.8 ± 0.3	1.3 ± 0.6	97.1 ± 25.6	50.6 ± 10.8	1214.3 ± 259.3
2 L/h, 0/100%	108.4 ± 13.3	40.3 ± 9.5	0.7 ± 0.3	1.0 ± 0.2	1.5 ± 0.3	1.1 ± 0.6	117.6 ± 28.6	60.8 ± 10.7	1458.6 ± 256.9
4 L/h, 50/50%	94.9 ± 15.1	23.2 ± 9.9	1.2 ± 0.3	0.6 ± 0.2	1.7 ± 0.4	2.1 ± 0.7	62.2 ± 29.9	42.1 ± 11.8	1009.3 ± 283.1
CVVHD									
2 L/h	117.3 ± 14.2	46.2 ± 10.4	0.7 ± 0.2	1.1 ± 0.2	1.4 ± 0.4	0.9 ± 0.7	139.2 ± 32.6	69.0 ± 12.8	1656.1 ± 307.5
4 L/h	121.4 ± 14.3	26.9 ± 9.7	1.3 ± 0.3	0.5 ± 0.2	1.3 ± 0.3	1.6 ± 0.6	77.2 ± 29.3	56.1 ± 11.2	1346.3 ± 269.0

Data are presented as mean ± SD

[a]n=2 experiments in each mode, at each flow rate, point of dilution, and filter type (24 total experiments)

Table 2.
Transmembrane clearance of apixaban and urea during in vitro CRRT as determined by SC or SA * flow rate[a]

	Apixaban		Urea	
	SC	CL_{TM} (L/h)	SC	CL_{TM} (L/h)
CVVH	HF1400			
2 L/h, 50/50%	0.608 ± 0.08	1.22 ± 0.16	1.00 ± 0.03	2.00 ± 0.06
2 L/h, 100/0%	0.531 ± 0.06	1.06 ± 0.11	0.99 ± 0.08	1.98 ± 0.15
2 L/h, 0/100%	0.614 ± 0.03	1.23 ± 0.06	1.09 ± 0.03	2.17 ± 0.06
4 L/h, 50/50%	0.622 ± 0.04	2.49 ± 0.17	1.12 ± 0.03	4.47 ± 0.11
CVVHD	SA	CL_{TM} (L/h)	SA	CL_{TM} (L/h)
2 L/h	0.622 ± 0.12	1.24 ± 0.24	1.23 ± 0.08	2.46 ± 0.16
4 L/h	0.601 ± 0.11	2.40 ± 0.43	1.38 ± 0.17	5.53 ± 0.67
CVVH	M150			
2 L/h, 50/50%	0.612 ± 0.03	1.22 ± 0.06	1.08 ± 0.10	2.15 ± 0.19
2 L/h, 100/0%	0.581 ± 0.07	1.16 ± 0.14	1.01 ± 0.07	2.02 ± 0.14
2 L/h, 0/100%	0.603 ± 0.02	1.21 ± 0.04	1.08 ± 0.05	2.16 ± 0.09
4 L/h, 50/50%	0.540 ± 0.04	2.16 ± 0.17	1.00 ± 0.07	3.98 ± 0.29
CVVHD	SA	CL_{TM} (L/h)	SA	CL_{TM} (L/h)
2 L/h	0.619 ± 0.01	1.24 ± 0.03	1.19 ± 0.05	2.38 ± 0.10
4 L/h	0.555 ± 0.05	2.22 ± 0.20	1.27 ± 0.17	5.09 ± 0.66

Data are presented as mean ± SD

[a]n=2 experiments in each mode, at each flow rate, point of dilution, and filter type (24 total experiments)

Table 3.
Three-way ANOVA-generated marginal means of CL_{TM} by CRRT mode, filter type, and flow rate

CL_{TM} by SC or SA					
CRRT mode	Filter type	Flow rate (L/h)	CL_{TM} (L/h)	95% CI	SE
CVVH	HF1400	2	1.438	1.105-1.772	0.157
		4	2.490	1.913-3.067	0.272
	M150	2	1.507	1.173-1.840	0.157
		4	2.160	1.583-2.737	0.272
CVVHD	HF1400	2	1.245	0.668-1.822	1.245
		4	2.405	1.828-2.982	2.405
	M150	2	1.240	0.663-1.817	0.272
		4	2.225	1.648-2.802	0.272
CL_{TM} by AUC					
CVVH	HF1400	2	1.803	1.596-2.011	0.980
		4	3.300	2.941-3.659	0.170
	M150	2	1.118	0.911-1.326	0.098
		4	2.070	1.711-2.429	0.170
CVVHD	HF1400	2	1.665	1.306-2.024	0.170
		4	2.165	1.806-2.524	0.170
	M150	2	0.905	0.546-1.264	0.170
		4	1.630	1.271-1.989	0.170

SE, standard error

Table 4.
Multiple linear regression between tested covariates and CL_{TM} by AUC

Variable	Unstandardized β	95% CI	*P* value
Constant	1.469	0.800 – 2.137	<0.001
Filter type[a]	-0.821	-1.133 - -0.509	<0.001
Flow rate (L/h)	1.224	0.864 – 1.585	<0.001

[a]HF1400=1, M150=2
Variables entered: CRRT mode, filter type, flow rate, and point of dilution
Adjusted R^2 = 0.849
Regression equation: CL_{TM} = 1.469 L/h + (-0.821 * filter type) + (1.224 * flow rate (L/h))

Table 5.

Optimal dosing recommendations of apixaban by filter type and CRRT flow rate

	Mean CL_{TM} (L/h)			Mean CL_T (L/h)			Optimal total daily dose (mg)[a]		
CRRT flow rate (L/h)	HF1400 Filter	M150 Filter	Mean CL_{NR} (L/h)	HF1400 Filter	M150 Filter	Target AUC (ng · h/mL)	HF1400	M150	Optimal dosing regimen
0.5	1.36	0.60	2.52	3.88	3.12	2103.8	8.2	6.6	5 mg BID
1	1.80	1.04	2.52	4.32	3.56	2103.8	9.1	7.5	5 mg BID
1.5	2.24	1.47	2.52	4.76	3.99	2103.8	10.0	8.4	5 mg BID
2	2.67	1.91	2.52	5.19	4.43	2103.8	10.9	9.3	5 mg BID
2.5	3.11	2.35	2.52	5.63	4.87	2103.8	11.8	10.2	5 mg BID
3	3.54	2.78	2.52	6.06	5.30	2103.8	12.7	11.2	5 mg BID
3.5	3.98	3.22	2.52	6.50	5.74	2103.8	13.7	12.1	7.5 mg BID
4	4.42	3.66	2.52	6.94	6.18	2103.8	14.6	13.0	7.5 mg BID
4.5	4.86	4.10	2.52	7.38	6.62	2103.8	15.5	13.9	7.5 mg BID
5	5.30	4.53	2.52	7.82	7.05	2103.8	16.5	14.8	7.5 mg BID

[a]To achieve comparable mean AUC achieved in 6 patients administered apixaban 5 mg BID for 7 days, the observed AUC_{0-12} (1051.9 ng · h/mL) was multiplied by two to estimate AUC_{0-24} to solve for dose via the equation AUC=total daily dose/CL_T. Target AUC from Frost et al. *Br J Clin Pharmacol* 2013;76:776-786.

Figures

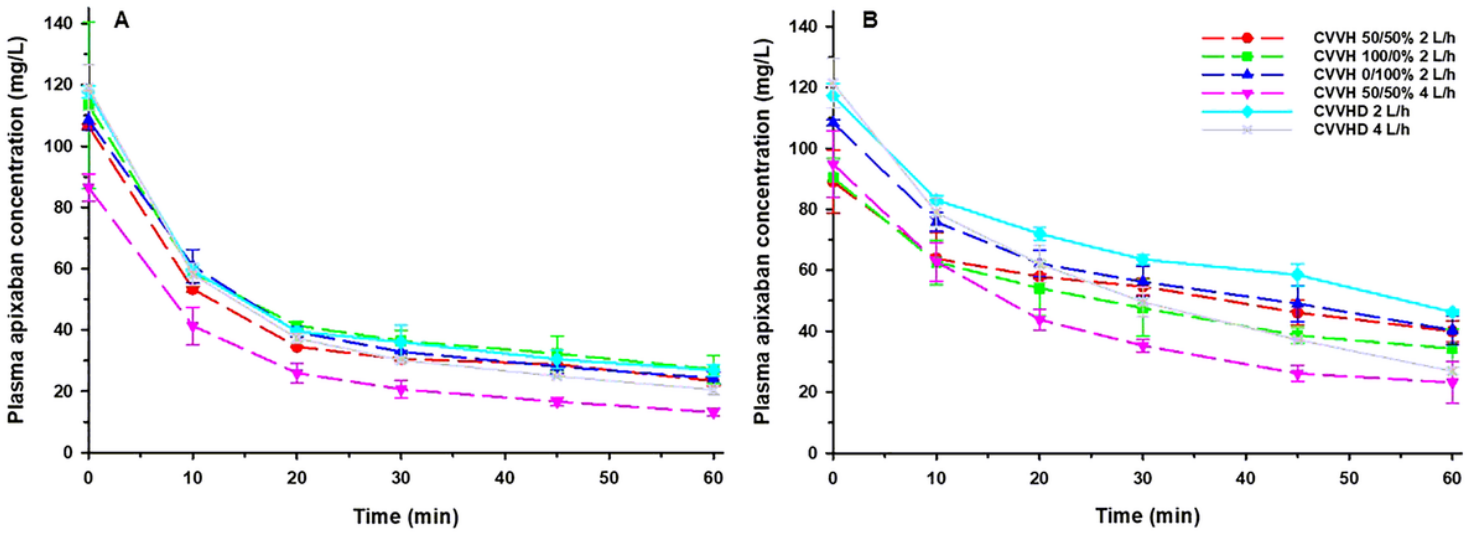

Figure 1

Pre-filter plasma concentration-time profiles of apixaban during CVVH and CVVHD at each rate and point of dilution with the HF1400 filter (A) and M150 filter (B). Mean values are displayed with error bars representing standard deviations.

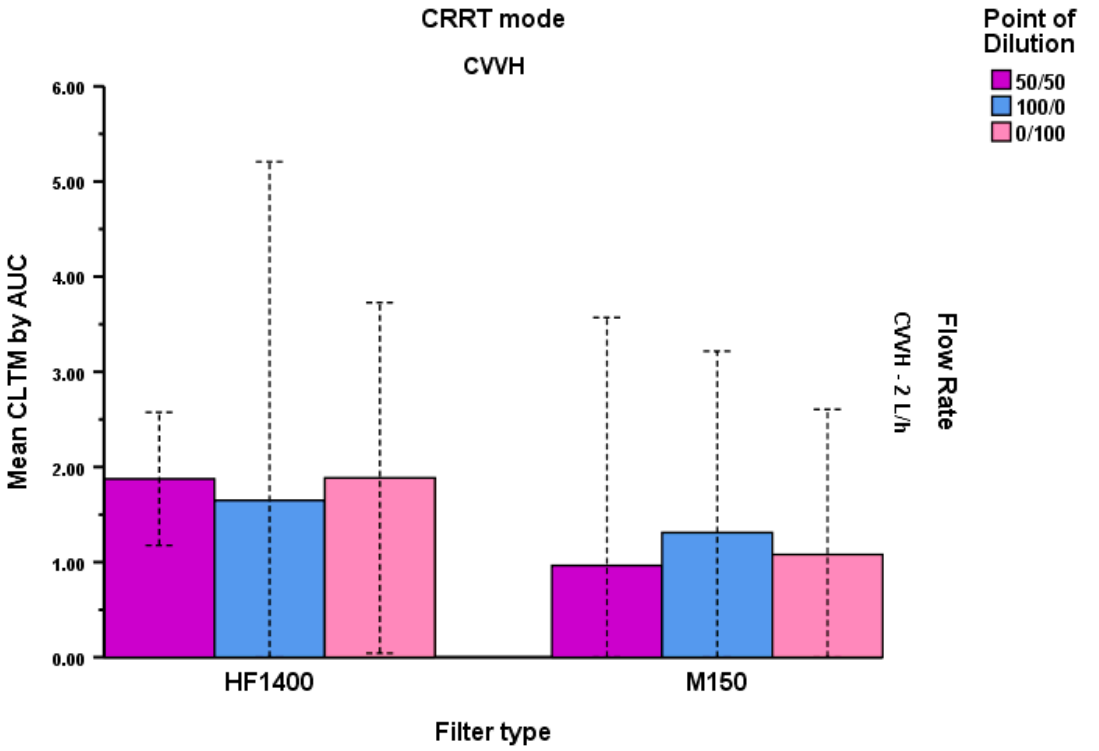

Figure 2

Mean CLTM by AUC of apixaban during CVVH at 2 L/h according to point of dilution and filter type. Bars represent mean values with 95% confidence intervals displayed as dashed lines.

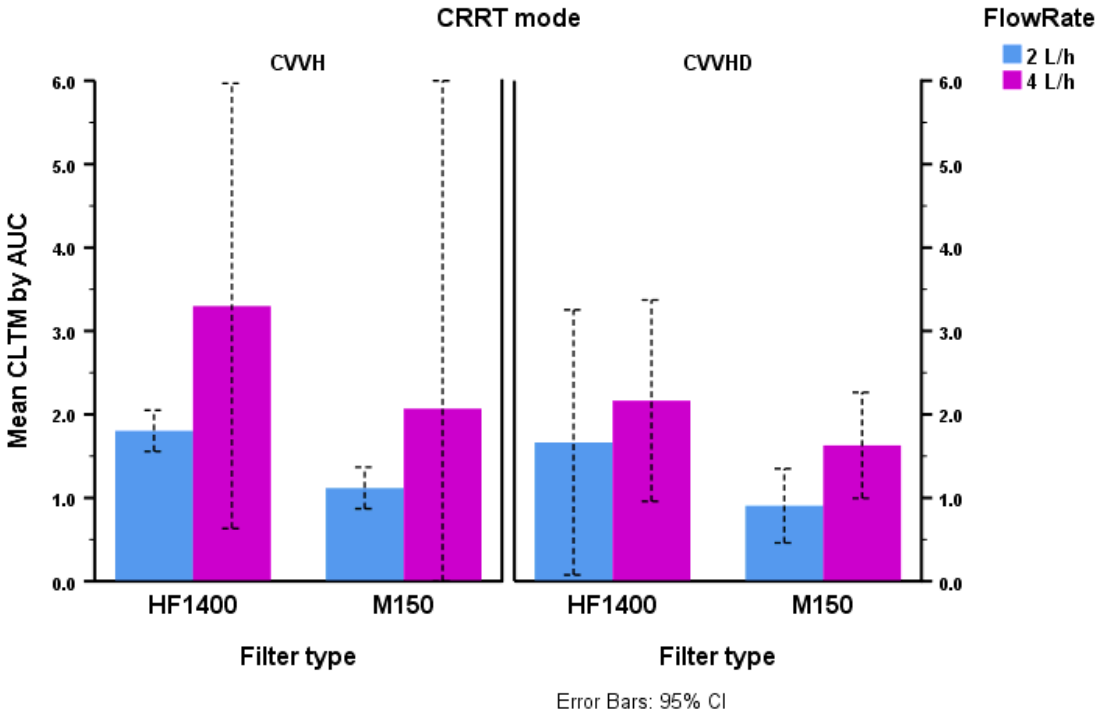

Figure 3

Mean CLTM by AUC of apixaban during in vitro CRRT according to mode, flow rate, and filter type. Bars represent mean values with 95% confidence intervals displayed as dashed lines.