Apixaban in patients on hemodialysis: a single dose pharmacokinetics study

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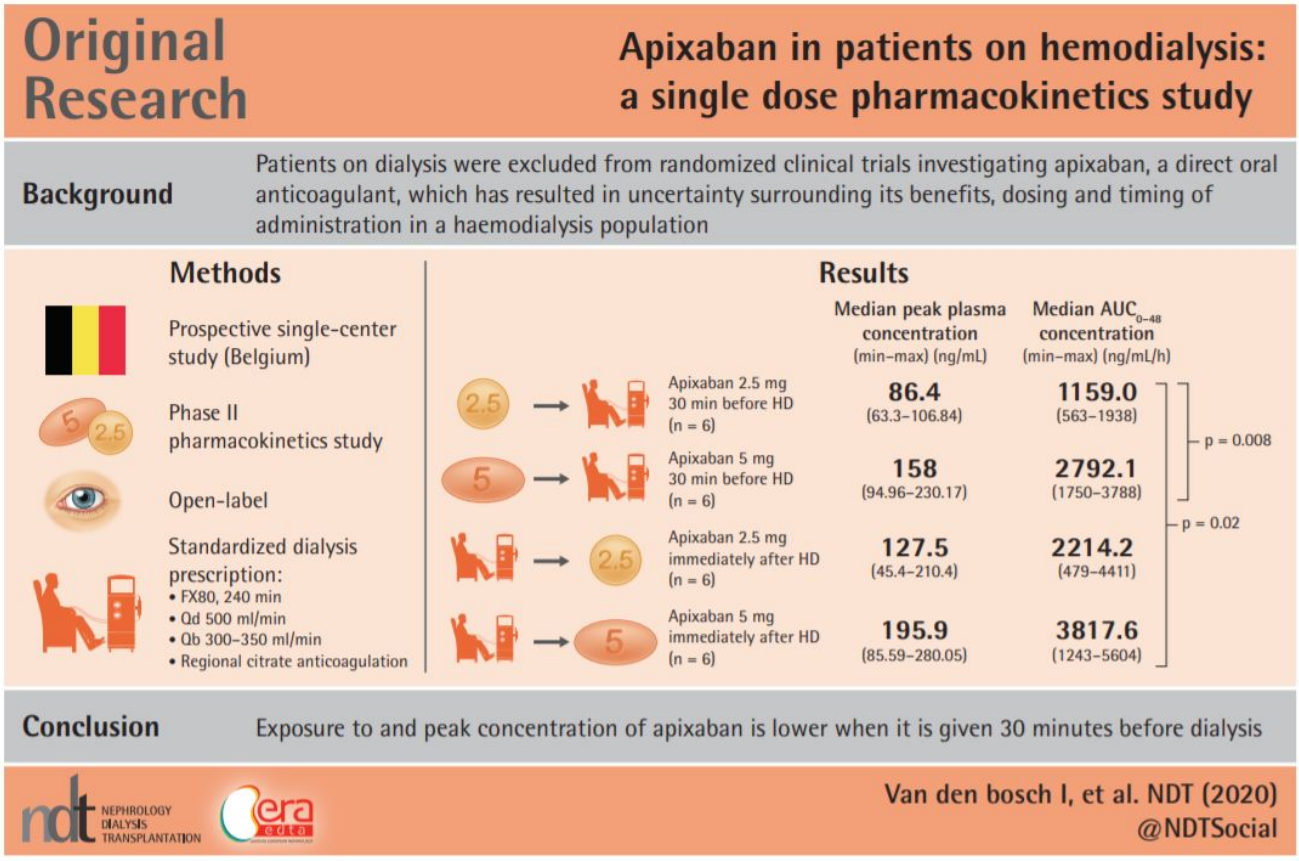
GRAPHICAL ABSTRACT



ABSTRACT

Background. Apixaban, a direct oral anticoagulant inhibiting factor Xa, has been proven to reduce the risk of atrial fibrillation-related stroke and thrombo-embolism in patients with mild to moderate renal insufficiency. Patients on renal replacement therapy, however, were excluded from randomized controlled trials. Therefore, uncertainty remains concerning benefits, dosing and timing of intake in hemodialysis population.

Methods. We conducted a phase II pharmacokinetics study in which twenty-four patients on maintenance hemodialysis were given a single dose (2.5 mg or 5 mg) of apixaban, either 30 minutes before or immediately after dialysis on the mid-week dialysis day.

Results. Apixaban 5 mg resulted in higher $AUC_{0\text{-}48}$ in comparison to 2.5 mg, although significance could only be reached for dosing pre-dialysis (2.5 mg vs. 5 mg, P = 0.008). In line, peak concentrations (C_{max}) after dosing pre-dialysis were significantly higher in the 5 mg than in the 2.5 mg groups (P = 0.02). In addition, dialysis resulted in significant reduction of drug exposure. $AUC_{0\text{-}48}$ pre-dialysis were on average 48 percent (2.5 mg) and 26 percent (5 mg)

lower than the AUC_{0-48} post-dialysis, in line with C_{max}. As a result, a dose of 2.5 mg post-dialysis and a dose of 5 mg pre-dialysis resulted in similar AUC_{0-48}. In contrast, significant differences were found between the 5 mg group post-dialysis and the 2.5 mg group pre-dialysis (P = 0.013).

Conclusions. Our data suggest that exposure to apixaban in patients in maintenance hemodialysis is not only dependent on drug dose but also on timing of intake relative to the hemodialysis procedure

Keywords: apixaban, DOAC, dose-finding, hemodialysis, pharmacokinetics

KEY LEARNING POINTS

What is already known about this subject?

Non-vitamin K oral anticoagulants are the treatment of choice for non-valvular atrial fibrillation in patients with mild to moderate chronic kidney disease. Patients with end-stage kidney disease have been excluded from randomized controlled trials. The optimal dosing of apixaban in patients on hemodialysis is unknown and timing of intake vs. timing of dialysis is not taken into account.

What this study adds?

This single dose pharmacokinetics study demonstrates that drug exposure to apixaban is lower when taken just before dialysis.

What impact this may have on practice or policy?

Apixaban dosing in hemodialysis patients should take into account timing of dialysis relative to timing of apixaban intake.

INTRODUCTION

Chronic kidney disease (CKD) is an independent risk factor for atrial fibrillation (AF) [1] with reported prevalence of AF exceeding 20 percent [2;3]. In patients with preserved kidney function, vitamin K antagonists (VKA) have been shown to reduce AF-related thromboembolic risk by up to 60 percent[4]. Uncertainty, however, remains about the clinical benefit and safety of VKA in patients on maintenance dialysis[5].

Direct oral anticoagulants (DOAC) have become the recommended alternative to VKA in patients with AF and preserved kidney function[6]. In patients with reduced kidney function, the level of evidence to support the use of DOACs varies across the stages of CKD[7]. Patients on dialysis were excluded from randomized controlled trials. Current labeling of apixaban (FDA 2014), however, endorses its use in hemodialysis population. While some observational data support the use of standard (5 mg twice daily) dose apixaban[8], others advocate the use of reduced-dose (2.5 mg twice daily) apixaban[9]. A recent observational study was unable to demonstrate clear benefits of apixaban vs. no anticoagulation, as no reduction of the risk for new stroke, transient ischemic attack, or systemic thromboembolism was found [10].

The pharmacokinetics (PK) of apixaban during dialysis is not studied in detail and almost all patients are on a fixed dose (2.5 mg or 5 mg) twice-daily dosing regimen. Mavrakanas et al. found a 4% reduction in exposure to apixaban when taken before hemodialysis [9]. Preclinical studies in humans found that total protein binding amounted to 87%, with about 70% bound to human albumin and about 10% bound to α1-acidic glycoprotein [11]. The reported near-negligible impact of hemodialysis has been attributed to the high degree of protein-binding. These data, however, are at odds with kinetics of protein-bound molecules during dialysis. Indoxyl sulfate an p-cresol sulfate are two metabolites with a comparable bound fraction (around 90%) [12]. The reduction rate of these solutes during hemodialysis approximates 25-30% [13;14]. Using kinetics models to model the removal of protein-bound uremic toxins, and assuming the distribution volume to be close to the extracellular volume, the reduction rate of a molecule with a protein binding between 85 and 90% will be close to or even exceeding 50% (personal communication, T.W. Meyer, Stanford). The actual dialytic clearance of apixaban might differ, as the distribution volume is not known. Whether timing of intake relative to dialysis will influence pharmacokinetics is unclear. We therefore conducted a phase

II pharmacokinetics study to determine inter-dialytic and intra-dialytic pharmacokinetics of apixaban.

MATERIALS AND METHODS

Study design

This was a prospective single-center phase II open-label PK study, registered on clinicaltrials.gov (NCT03456648). The study was conducted according to the Helsinki Declaration for medical research in humans, with approval of the Ethics Committee of the University Hospitals Leuven.

Patients providing written informed consent and fulfilling in- and exclusion criteria were given a single tablet of either 2.5 mg or 5 mg of apixaban, either 30 minutes before or immediately after dialysis.

Patients were excluded from participation if they received treatment with oral vitamin K antagonists, recent (< 4 weeks prior to informed consent) major surgery, recent (< 4 weeks prior to informed consent) severe bleeding episode requiring blood transfusion and/or hospitalization, concurrent moderate to severe liver dysfunction, pregnancy or participation in an interventional study with investigational medication. Patients were allowed to take a low ($\leq$ 100 mg) dose of aspirin, but dual anti-platelet therapy was not allowed.

Conventional hemodialysis sessions were carried out using a high flux membrane (FX80 CorDiax, membrane surface area 1.8 m², Fresenius Medical Care, Bad Homburg, Germany). Treatment modality (hemodialysis), dialyzer and dialysis duration (240 min) were standardized for all patients and sessions during the study period. Dialysate flow rate was 500 ml/min and blood flow rate ranged from 300-350 ml/min. To exclude interference of anticoagulation with the chromogenic anti-Xa activity assay, routine anticoagulation during dialysis (unfractionated heparin or low molecular weight heparins) was switched to regional citrate anticoagulation (RCA) according to local protocol during the study period, starting from three sessions before administration of apixaban [15]. RCA is performed by infusing citrate into the arterial line of the dialysis tubing. This reduces ionized calcium concentrations to very low levels to prevent clotting. Blood calcium is restored by using a calcium-containing dialysate. During dialysis ionized calcium is monitored according to local protocol.

In part A, inter-dialytic kinetics were studied. A single dose of apixaban 2.5 mg (n = 6) or 5 mg (n = 6) was ingested immediately post-dialysis. We collected blood samples at start and end of the midweek dialysis (t = 0), and at t = 0.5, 1, 2, 4, 8, 24 hours post-dialysis, at start of next dialysis (t = 44 hours) and at end of next dialysis (t = 48 hours). In part B, the intra- plus inter-dialytic pharmacokinetics were studied. A single dose of apixaban 2.5 mg (n = 6) or 5 mg (n = 6) was taken 30 minutes pre-dialysis. We collected blood samples at time of administration, at start of dialysis, t = 0.25, 0.5, 1, 1.5, 2, 3, 4 hours after start of dialysis, at end of dialysis (post, t = 0) and at t = 0.5, 1, 2, 4, 24 hours post-dialysis, at start of next dialysis (t = 44 hours) and at end of next dialysis (t = 48 hours). After centrifugation, plasma samples were initially stored at -20 °Celsius, and less than 2 weeks after collection stored at -80 °Celsius until batch analysis. Apixaban concentrations in plasma samples were measured using an ACL-TOP 500 (Werfen, Brussels, Belgium), with the Coamatic® Heparin kit (Werfen) according to the manufacturer's protocol. The calibration curves were generated with Biophen® Apixaban Calibrator (Nodia, Boom, Belgium). The assays was controlled with human plasma spiked with Apixaban at various concentrations (Biophen™ Apixaban control; Nodia). Both the calibrators and the controls were titrated by the manufacturer relative to a Reference Internal Standard, whose qualification is linked to the reference method by LC-MS/MS. The levels of Apixaban measured in the controls were within the range defined by the manufacturer. The inter-run CVs for the 24 ng/ml, 75 ng/ml and 191 ng/ml Apixaban controls were 7.7, 4.6 and 1.5%, respectively. The LOD and LOQ of the assay were 10 and 21 ng/ml Apicaban, respectively. The FXa assay is carried out according to the manufacturer's instruction with a buffer containing EDTA. Accordingly, the small variations of ionized calcium concentrations in the patients' plasma [16] cannot interfere with the FXa activity in the assay and the measurement of apixaban concentration.

Serious Adverse Events (SAEs) that occurred following the subject's written consent to participate in the study through 30 days of discontinuation were recorded and reported to BMS Worldwide Safety.

Pharmacokinetic analyses:

Apixaban concentration-time profiles were generated and observed values for the descriptive PK parameters C_{max} (peak plasma concentration) and time to C_{max} (T_{max}) were determined directly from these profiles. PK profiles were analyzed with non-compartmental analysis (NCA)

using non-parametric Mann-Whitney statistics. The area under the curve (AUC_{0-48}) between administration (time 0) and the last measurable data point was calculated with the trapezoidal method.

RESULTS

Twenty-four volunteers with end-stage renal disease on maintenance hemodialysis were enrolled into four groups of six patients each. Demographic characteristics are provided in *Table 1*. We administered a single dose of 2.5 mg or 5 mg of apixaban on the mid-week dialysis day. Apixaban was taken either immediately after dialysis (part A), or 30 minutes before dialysis (part B). Blood was sampled up until the end of the next four-hour dialysis session of the week (*see methodology for sampling time-points*).

The primary endpoint of this study was the comparison of the area under the curve (AUC) from time to ingestion up until last measurable time-point (AUC_{0-48}). As expected, 5 mg of apixaban resulted in higher AUC_{0-48} (*table 2*) in comparison to 2.5mg, although significance could only be reached for dosing pre-dialysis (2.5 mg vs. 5 mg, P = 0.008). The AUC_{0-48} of apixaban pre-dialysis were on average 48 percent (2.5 mg) and 26 percent (5 mg) lower than the AUC_{0-48} post-dialysis (*Figure 1*). Although differences did not reach significance for the 2.5 mg groups, results were bordering on significance for the 5 mg groups (P = 0.09). The impact of dialysis is better illustrated when comparing different doses (*Figure 1E-F*). A dose of 2.5 mg post-dialysis and a dose of 5 mg pre-dialysis result in similar AUC_{0-48}, whereas a dose of 2.5 mg taken before dialysis and a dose of 5 mg taken immediately after dialysis results in significantly different AUC_{0-48} (P = 0.02). These results suggest that exposure is not only dependent on drug dose but also on timing of administration.

We observed similar findings in peak concentrations (C_{max}) (*Table 2*). A significant difference of C_{max} was observed between the 5 mg and 2.5 mg pre-dialysis groups (P = 0.02) and, in line with AUC_{0-48}, between the 5 mg group post-dialysis and the 2.5 mg group pre-dialysis (P = 0.013). C_{max} was 32 percent higher in the post- versus pre-dialysis group for 2.5 mg, and 19 percent for apixaban 5mg.

Concerning safety and tolerability we report one episode of transient elevation of liver function tests (ALT and AST >3xULN), 18 days after drug administration. Further diagnostic work-up revealed heart failure, which improved after percutaneous coronary intervention. A second patient was re-admitted to hospital for recurrent respiratory infection. A third patient developed high fever and inflammation less than 24 hours after intake of the study drug. None of these adverse events were considered likely to be attributed to intake of apixaban.

DISCUSSION

We evaluated single-dose inter-dialytic and intra-dialytic pharmacokinetics of apixaban in patients treated with maintenance hemodialysis. The main finding is that exposure to apixaban (AUC_{0-48}) as well as C_{max} are lower when apixaban is administered 30 minutes before dialysis. Our data suggest that hemodialysis has a non-negligible effect on drug exposure.

Observed pharmacokinetics are in line with previous studies[9]. When compared with PK data from healthy volunteers [17;18], C_{max} and exposure (AUC_{0-48}) were higher in dialysis population. The C_{max} after a single-dose of 2.5 mg apixaban in dialysis patients is similar to the C_{max} after a 5 mg apixaban in healthy individuals. T_{max} was reached after median 3 hours, similar to healthy volunteers.

In our study, timing of intake of apixaban relative to dialysis had a significant effect on drug exposure. Wang et al [19] observed a 14 percent decrease in apixaban exposure in function of the timing of apixaban pre- versus post-dialysis. In our study, apixaban taken pre-dialysis also resulted in lower drug exposure. Differences, however, are more marked, with a 48 percent (2.5 mg) and 26 percent (5 mg) lower AUC in comparison with the post-dialysis groups. As a result, apixaban 5 mg taken 30 minutes pre-dialysis resulted in similar drug exposure as apixaban 2.5 mg taken post-dialysis.

One potential explanation for this clinically relevant finding might be that the clearance of apixaban during dialysis is more important than previously reported. We aimed to measure apixaban in the dialysate to measure dialytic clearances. Dialysate concentrations of apixaban, however, were below the limit of detection. Our study differs from the Wang study [19], in that intake pre-dialysis was 30 minutes vs. 2 hours pre-dialysis. Perhaps more importantly, our study is the first to study PK data of apixaban using regional citrate anticoagulation (RCA).

Previous studies have used saline infusion in order to avoid use of heparin or LMWH, as these interfere with measurement of anti-Xa activity. It is however well known that saline infusion results in frequent clotting of the dialyzer and is associated with a lower dialysis adequacy in contrast to RCA [20].

An alternative hypothesis is that the dialysis procedure interferes with splanchnic perfusion. The predominant site of absorption of apixaban are the small intestines [21] and entero-enteric recirculation contributes to overall pharmacokinetic profiles of apixaban [22]. Reduced splanchnic perfusion theoretically might reduce absorption of apixaban and lower C_{max}. Since all dialysis sessions except one were morning sessions, previously reported diurnal variation in AUC[23] is unlikely to be a factor of significance.

Our study has several limitations and strengths. The current data are not paired, evidently reducing statistical power to determine the impact of timing of dosing relative to dialysis treatment. A second limitation is that we studied single-dose PK, and did not perform steady-state PK. Interpretation of PK results is hampered by the absence of well-studied therapeutic concentration target ranges. In contrast to previous studies in hemodialysis patients, we took timing of dosing into account, and all dialysis sessions except one took place in the morning. A major strength over previously PK studies in HD patients is that we used RCA, which has been shown to be highly efficacious at maintaining dialyzer patency[16]. As a result, our study provides more reliable estimates of the impact of dialytic clearance on PK of apixaban.

How to translate the current data into clinical practice, as currently patients almost always are prescribed a fixed twice daily dosing regimen for patients on maintenance hemodialysis. The current study corroborates a previous PK study in HD patients promoting 2.5 mg twice daily dosing of apixaban [9]. Indeed, a single-dose of 2.5 mg in patients on maintenance dialysis results in drug exposure measured as AUC_{0-48} and C_{max} that is comparable to apixaban 5 mg in healthy volunteers. A retrospective cohort study however, seems to support the use of standard (5 mg twice daily) dose of apixaban in patients with ESKD since it was associated with less major bleeding, less thromboembolic events and a lower mortality risk in comparison to matched patients on VKA [8]. This study however did not investigate timing of intake of apixaban relative to hemodialysis sessions, nor did it correct for hemodialysis anticoagulation. Taking into account our current PK/PD data, one may consider prescribing a dose of 2.5mg twice daily

on non-dialysis-days and dialysis days. For patients being dialyzed during morning hours and taking apixaban shortly before dialysis, a morning dose of 5mg on dialysis days may be considered. It seems prudent to await prospective data comparing VKA and Apixaban in patients on hemodialysis (RENAL-AF NCT02942407, AXADIA NCT02933697) for definite dosing recommendations.

In conclusion, this open-label single-dose phase II study evaluated the inter-dialytic and intra-dialytic pharmacokinetics of apixaban after a single-dose of 2.5 mg or 5 mg in hemodialysis patients. Our data suggest that timing of intake relative to dialysis could be relevant in choice of dosing of apixaban.

CONFLICT OF INTEREST STATEMENT

B. Meijers reports to have received a restricted grant from Bristol-Myers Squibb Company and Pfizer Inc. during the conduct of the study; P. Verhamme reports to have received grants and personal fees from Bristol-Myers Squibb Company, grants and personal fees from Daiichi-Sankyo Europe, personal fees from Johnson & Johnson, grants and personal fees from Pfizer, Inc., and grants and personal fees from Bayer AG, outside the submitted work.

The results presented in this paper have not been published previously in whole or part, except in abstract format.

AUTHORS' CONTRIBUTIONS

B. Meijers and P. Verhamme designed the study. I. Van den bosch, together with study nurses H. Wielandt, J. De Vis and V. Verbeek collected the clinical data. B. Meijers, I. Van den bosch, T. Bouillon and M. Coemans analyzed the data. B. Meijers and I. Van den bosch drafted the manuscript. All authors revised and approved the final version of the manuscript.

FUNDING

This study was funded by a restricted grant of Bristol-Myers Squibb Research and Development, in alliance with Pfizer.

Tables

Table 1. Demographic characteristics

Characteristic	Part A 2.5 mg	Part A 5 mg	Part B 2.5 mg	Part B 5 mg	% of all patients
Median Age (y)	70,5 (64-77)	72,8 (66-84)	59,3 (33-85)	71,7 (63-85)	
Sex					
Female	4	3	1	2	41.6
Male	2	3	5	4	58.3
Caucasian race	6	6	6	6	100
Diabetes mellitus	0	2	1	3	24
Liver disease	0	0	0	0	0
Urinary output / 24 h					
< 300 ml	4	5	5	4	75
300-600 ml	2	0	1	2	20.8
> 600ml	0	1	0	0	4.2
IDWG (kg)	1.1	1.8	1.7	2.0	
Kt/V	1.80	1.65	1.39	1.53	
Albumin (g/L)	34.9	33.7	41.1	39.9	
Hemoglobin (g/dL)	9.6	8.9	11.5	11.0	

Table 2

Timing	*Part*	*Dose (mg)*	*Median T_{max} (h)*	*Median C_{max} (ng/ml)*	*Median AUC_{0-48} (ng/ml/h)*	*P-value AUC (<0.05)*
Pre-dialysis	B	2.5	3.5 (1.5 – 5.5)	86.4 (63.3-106.84)	1159.0 (563-1938)	* 0.02, ^ 0.0082
Pre-dialysis	B	5	2,75 (1 - 3,8)	158 (94,96 -230,17)	2792,1 (1750-3788)	^ 0.0082
Post-dialysis	A	2.5	3.33 (1 – 3.5)	127.5 (45.4-210.4)	2214.2 (479-4411)	
Post-dialysis	A	5	2.83 (1 – 4)	195.9 (85.59-280.05)	3817.6 (1243-5604)	* 0.02

Table 2. Pharmacokinetics of the four patient groups. Cmax and AUC_{0-48} of apixaban are given as median (minimum-maximum), * significant difference between AUC_{0-48} of part B 2.5 mg and Part A 5 mg, ^significant difference between AUC_{0-48} of part B 2.5 mg and Part B 5 mg

Legends to figures

FIGURE 1: Concentration-time profiles of apixaban; A: 2.5 mg pre-dialysis, B: 5mg pre-dialysis, C: 2.5mg post-dialysis, D: 5mg post-dialysis, E: comparison of 5 mg pre-dialysis and 2.5 mg post-dialysis, F: comparison of 2.5mg pre-dialysis and 5 mg post-dialysis

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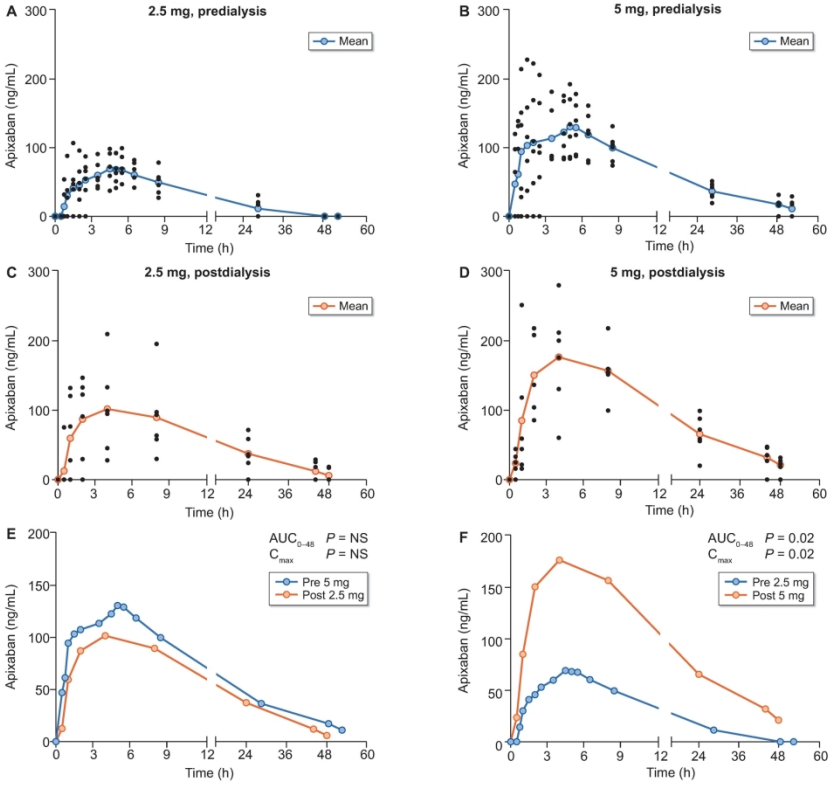

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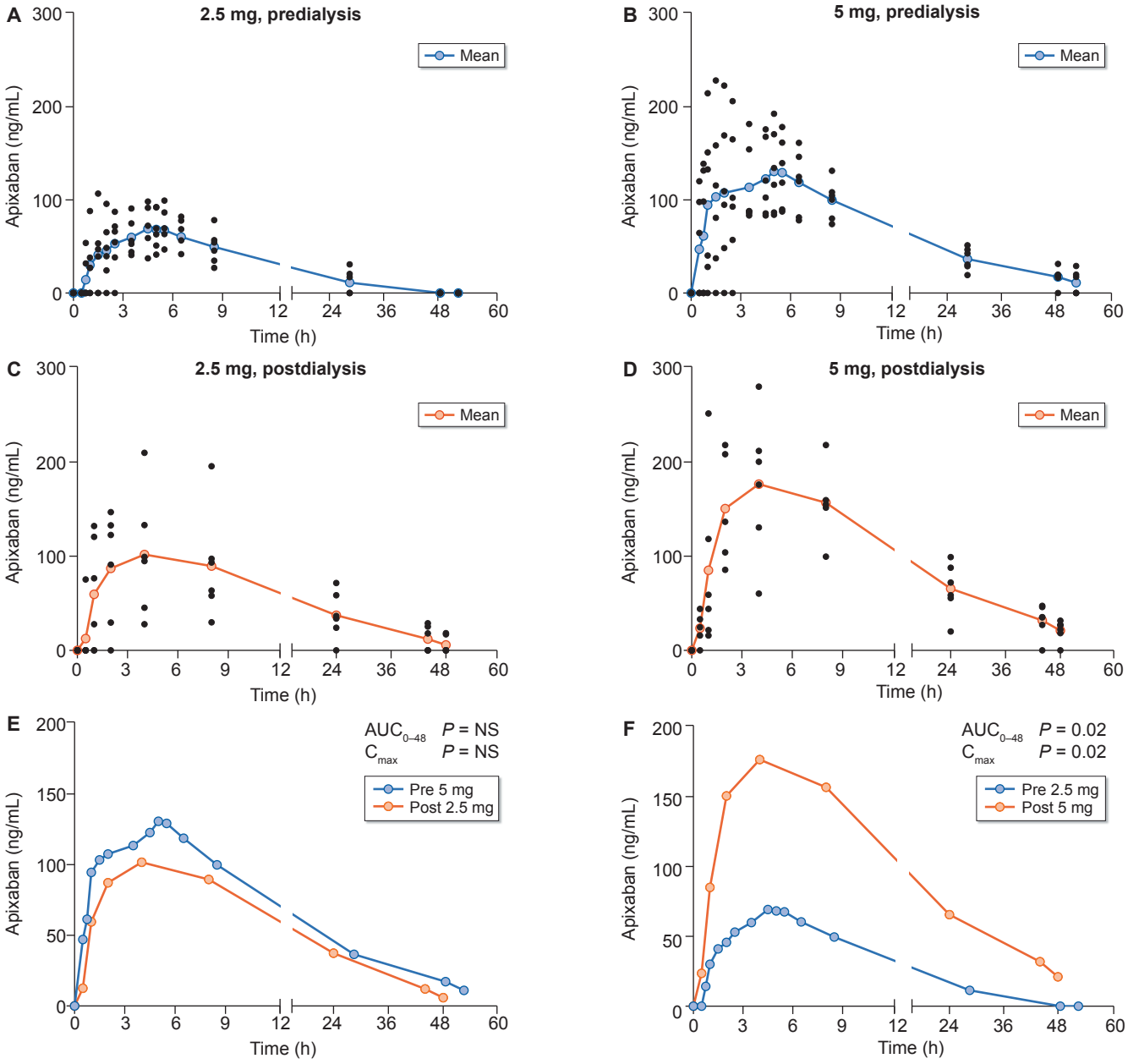

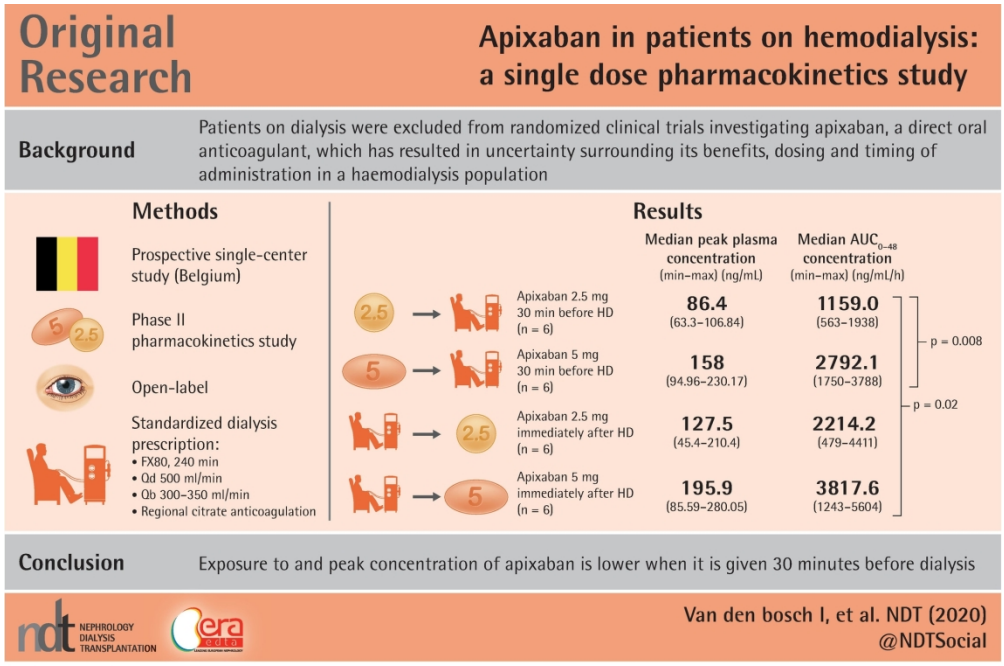

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Original Research

Apixaban in patients on hemodialysis: a single dose pharmacokinetics study

Background

Patients on dialysis were excluded from randomized clinical trials investigating apixaban, a direct oral anticoagulant, which has resulted in uncertainty surrounding its benefits, dosing and timing of administration in a haemodialysis population

Methods

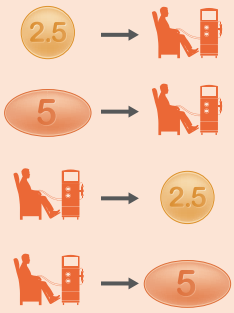
Prospective single-center study (Belgium)

Phase II pharmacokinetics study

Open-label

Standardized dialysis prescription:
- FX80, 240 min
- Qd 500 ml/min
- Qb 300–350 ml/min
- Regional citrate anticoagulation

Results



	Median peak plasma concentration (min–max) (ng/mL)	Median AUC_{0-48} concentration (min–max) (ng/mL/h)	
Apixaban 2.5 mg 30 min before HD (n = 6)	**86.4** (63.3–106.84)	**1159.0** (563–1938)	p = 0.008
Apixaban 5 mg 30 min before HD (n = 6)	**158** (94.96–230.17)	**2792.1** (1750–3788)	
Apixaban 2.5 mg immediately after HD (n = 6)	**127.5** (45.4–210.4)	**2214.2** (479–4411)	p = 0.02
Apixaban 5 mg immediately after HD (n = 6)	**195.9** (85.59–280.05)	**3817.6** (1243–5604)	

Conclusion

Exposure to and peak concentration of apixaban is lower when it is given 30 minutes before dialysis

NEPHROLOGY DIALYSIS TRANSPLANTATION

Van den bosch I, et al. NDT (2020)
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