SUPPLEMENTARY METHODS

Study Design

This study (EudraCT 2019-002353-29) was a single-center, investigator-driven, open-label cohort study. The study design is illustrated in Figure S1. A CONSORT diagram describing the flow of participants through the study (Figure S4) and a detailed protocol are also included as supplementary material. The study protocol was approved by the Research Ethics Committee of Hospital Bellvitge and registered at www.ClinicalTrials.gov (study identifier NCT 04952792). All the participants provided written informed consent.

Sample Size and Power Determination

We considered the study by Thomas Mavrakanas [3], which investigated the PK of apixaban at steady state in seven stable patients on HD at a dose of 2.5 mg BID. This study detected a substantial increase in the AUC of the drug between day 1 (298.6 ng h/mL, with a CV of 38%) and day 8 (1009.8 ng h/mL, with a CV of 30.7%). To determine the appropriate sample size with a significant level (α) of 0.05 and a statistical power (1-β) of 0.8, we used the formula: $n=((Z_{\alpha/2}+Z_{\beta})/\text{Effect size})^2$ x (variance/precision). Here, $Z_{\alpha/2}$ is the critical value for the desired level of significance (1.96 for 95% confidence interval); Z_{β} is the critical value for the desired power (0.84 for 80% power); Effect size is the differences of AUCs means divided by the standard deviation; Variance is the assumed common variance of the two groups; Precision is the allowable margin of error. Substituting the values, we obtained $n=((1.96+0.84)/1454.87)^2$ x (54546.3173/0.05). Therefore, a sample size of 5 patients will be sufficient, but we decided to recruit 10 patients for ensure that the calculated sample size was achieved.

Study Population

Eligible participants in the study included men and women (aged >18 years) on stable dialysis for at least three months and with non-valvular AF treated with oral VKA. Exclusion criteria included pregnant or lactating women, those not adhering to contraceptive methods, body weight <60 kg, liver diseases, thrombocytopenia (<100.000 platelets/mL), those who had experienced bleeding episodes within the last month, and patients currently undergoing treatment with other anticoagulants (e.g., heparins) or cytochrome P450 3A4 inhibitors or inducers.

Interventions

Each patient received a 2.5 mg oral dose of apixaban twice daily for a duration of four weeks. The first dose was initiated when the INR was <2, and apixaban achieved a steady state within 2-3 days of commencement.

Pharmacokinetics

Venous blood samples (4 mL) were collected in 3.2% sodium citrate tubes at various time points: before the morning dose (pre-dose) and at 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 h after the morning dose. Samples were obtained during mid-week dialysis, on the day before dialysis, and on the day after dialysis. For the pharmacokinetics (PK) analysis and Anti-FXa activity (AXA) determination, samples were collected on days 3, 4, 5, 12, 13, 14, 24, 25, and 26. We also monitored the elimination of apixaban by collecting dialysis effluent (prior to HDF, and at 15 min, 1, 2, 3, and 4 h after initiation), as well as 24-hour urine from patients with residual kidney function. The clearance of apixaban was calculated using the following formula: (24-hour volume of urine in mL)·(concentration of apixaban in urine in ng/mL)/C_{min} of apixaban in serum in ng/mL·1440 min. This

clearance was expressed in mL/min. To evaluate adherence to apixaban, study staff conducted pill counts at each visit. Blood samples were stored at -80 ºC until the assay. Apixaban concentration was measured using a previously validated method published by our group [7]. The primary outcome was the area under the plasma concentration-time curve (AUC) within the dosing interval. Initially, the AUC within one dosing interval (AUC_{0-12}) was calculated. Secondary outcomes included C_{max} (maximum observed plasma concentration within the dosing interval), C_{min} (minimum observed plasma concentration within the dosing interval), time to reach peak apixaban concentration (T_{max}), calculation of terminal half-life ($T_{1/2}$) following the last dose, and assessment of the accumulation index. We calculated the accumulation index from the first week (ratio of AUC_{0-12} at specific points, such as 2nd week or 4th week/ AUC_{0-12} at first week) and from the second week. In addition, the peak-to-trough ratios (C_{max}/C_{min}) of plasma concentration were calculated. These PK parameters were estimated using a non-compartmental method with PKsolver v2.0.

Anti-factor Xa activity.

Blood samples for the determination of anti-FXa activity (AXA) were collected at the same time points as PK samples. AXA was determined using an automated chromogenic assay with an Instrumentation Laboratory (IL) Coagulation System (ACL TOP 750). This assay employed HemosIL Liquid Anti-Xa Reagent, HemosIL Apixaban Calibrators and HemosIL Apixaban Controls (Low and High) from Instrumentation Laboratory Company (Bedford, MA, USA), following the manufacturer's instructions. The values of the calibrators and controls were determined using liquid chromatography-mass spectrometry. The normal calibration curve ranged from 0 to 520 ng/mL, and the high-calibrator curve extended from 0 to 1100 ng/mL. The AXA parameters assessed included

peak and trough plasma AXA, time-to-peak AXA (T_{peak}), area under the plasma AXA-time curve, and AXA half-life.

Statistical Analyses

Values are expressed as mean (standard deviation, SD). The coefficient of variation (CV) was defined as the SD divided by the mean and expressed as a percentage. We used a paired t-test to compare the PK parameters of each individual between the baseline and final time points. For comparisons across different dose-time intervals and to calculate intra-subject and inter-subject CV, we conducted an analysis of variance (ANOVA) with repeated measures on the log-transformed PK parameters. For comparisons across different dose-time intervals and to calculate intra-subject and inter-subject CV, we performed an independent mixed linear model with patient clusters for each log-transformed PK parameter and time as independent variables. The mixed linear models were adjusted for age. Individual PK and AXA parameters were estimated using noncompartmental methods with PKsolver v2.0. Terminal elimination rate constants were estimated using the PKsolver v2.0, and AUC parameters were calculated using the log-linear trapezoidal rule. Actual sampling times were employed for all parameter calculations. Descriptive statistics for the PK and AXA parameters are tabulated. A linear regression model was used to compare apixaban levels measured using AXA and LC-MS/MS. The measurement of AXA was validated against the gold standard method, LC-MS/MS using the Bland-Altman analysis. Statistical analysis was performed using R v 4.2.2 (R Foundation for Statistical Computing, http://www.r-project.org).

SUPPLEMENTAL MATERIAL

Table S1: **Population demographics.**

Sex, n (%)	
Male	9 (90%)
Female	1 (10%)
Age, years, mean (SD)	67.4 (6.6)
Weight, Kg, mean (SD)	82.6 (13.6)
Heith, cm, mean (SD)	170 (9.59)
BMI, mean (SD)	28.7 (5.23)
Systolic BP (mmHg)	131 (19)
Diastolic BP (mmHg)	69.4 (10.9)
Comorbidities	
Diabetes, n (%)	5 (50%)
Coronary Artery Disease, n (%)	3 (30%)
Laboratory Data	
Platelets, cells/mL; mean (SD)	177,000 (51,000)
Alanine AminoTransferase (ALT); mkat/L	14.8 (12.2)
Vascular access, n (%)	
Catheter	4 (40%)
FAV	6 (60%)
Residual kidney Function, n (%)	5 (50%)
Antiplatelet treatment, n (%)	3 (30%)
Phosphate Binders, n (%)	7 (70%)
Cation Exchange resins, n (%)	1 (10%)
Dialysis Prescription	
Duration of dialysis session; min	240
Blood Flow rate; mL/min	300

Dialyzer	VitaPES® 210 HF
Convection Volumen; mL/min	100

Abbreviations: BMI, body mass index; n, total number of subjects; SD, standard deviation.

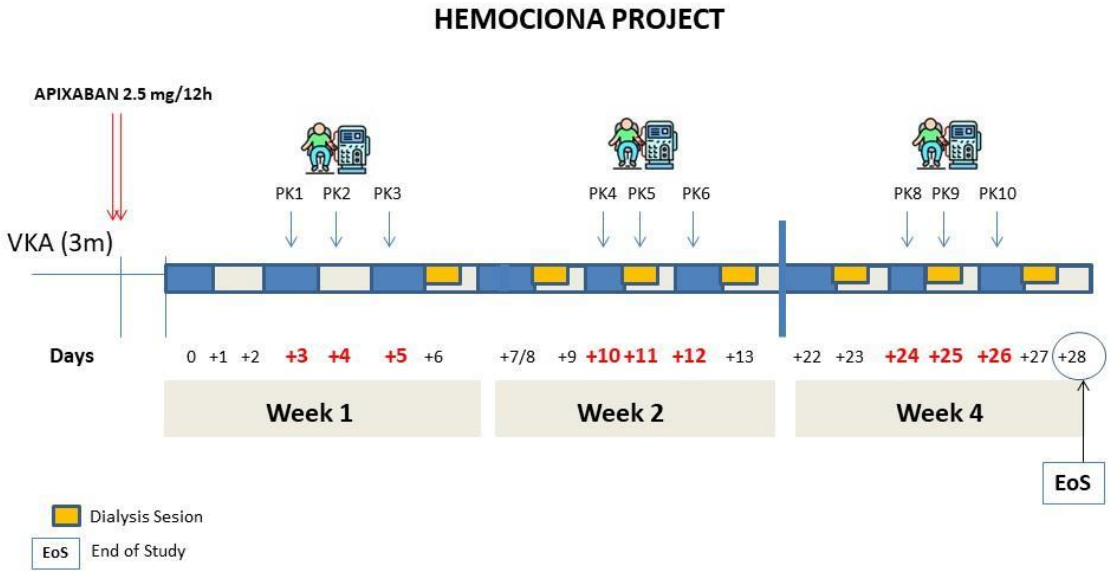
Table S2: Unadjusted marginal means and 90% confidence interval for the log-transformed PK parameters.

	Dose_time	Cmax	Tmax	T1/2
D3 - D4_DHF	-0.152[-0.314, 0.011]	-0.028[-0.211, 0.154]	-0.099[-0.918, 0.719]	-0.264[-0.695, 0.167]
D3 - D5	-0.145[-0.308, 0.018]	-0.041[-0.223, 0.142]	-0.15[-0.969, 0.668]	-0.541[-0.972, -0.109]
D3 - D10	-0.098[-0.26, 0.065]	-0.018[-0.2, 0.165]	0.65[-0.169, 1.469]	-0.305[-0.736, 0.127]
D3 - D11_HDF	-0.068[-0.231, 0.094]	-0.005[-0.187, 0.178]	-0.197[-1.016, 0.621]	-0.246[-0.69, 0.199]
D3 - D12	-0.198[-0.36, -0.035]	-0.091[-0.273, 0.092]	-0.248[-1.067, 0.57]	-0.456[-0.887, -0.024]
D3 - D24	-0.071[-0.234, 0.092]	0.014[-0.169, 0.196]	-0.069[-0.888, 0.749]	-0.273[-0.705, 0.158]
D3 - D25_HDF	-0.099[-0.261, 0.064]	-0.004[-0.187, 0.178]	-0.092[-0.91, 0.727]	-0.363[-0.794, 0.068]
D3 - D26	-0.175[-0.337, -0.012]	-0.102[-0.285, 0.08]	0.022[-0.796, 0.841]	-0.339[-0.77, 0.092]
D4_DHF - D5	0.007[-0.156, 0.169]	-0.012[-0.195, 0.17]	-0.051[-0.87, 0.768]	-0.277[-0.708, 0.155]
D4_DHF - D10	0.054[-0.109, 0.217]	0.01[-0.172, 0.193]	0.75[-0.069, 1.568]	-0.04[-0.472, 0.391]
D4_DHF - D11_HDF	0.083[-0.079, 0.246]	0.023[-0.159, 0.206]	-0.098[-0.917, 0.721]	0.018[-0.426, 0.463]
D4_DHF - D12	-0.046[-0.209, 0.117]	-0.063[-0.245, 0.12]	-0.149[-0.968, 0.67]	-0.191[-0.623, 0.24]
D4_DHF - D24	0.081[-0.082, 0.243]	0.042[-0.141, 0.224]	0.03[-0.789, 0.849]	-0.009[-0.441, 0.422]
D4_DHF - D25_HDF	0.053[-0.11, 0.216]	0.024[-0.159, 0.206]	0.008[-0.811, 0.826]	-0.099[-0.53, 0.332]
D4_DHF - D26	-0.023[-0.186, 0.14]	-0.074[-0.257, 0.108]	0.122[-0.697, 0.94]	-0.075[-0.506, 0.356]
D5 - D10	0.047[-0.115, 0.21]	0.023[-0.16, 0.205]	0.801[-0.018, 1.619]	0.236[-0.195, 0.668]
D5 - D11_HDF	0.077[-0.086, 0.239]	0.036[-0.147, 0.218]	-0.047[-0.866, 0.772]	0.295[-0.149, 0.739]
D5 - D12	-0.053[-0.215, 0.11]	-0.05[-0.233, 0.132]	-0.098[-0.917, 0.721]	0.085[-0.346, 0.517]
D5 - D24	0.074[-0.088, 0.237]	0.054[-0.128, 0.237]	0.081[-0.738, 0.9]	0.267[-0.164, 0.699]
D5 - D25_HDF	0.047[-0.116, 0.209]	0.036[-0.146, 0.219]	0.059[-0.76, 0.878]	0.178[-0.254, 0.609]
D5 - D26	-0.029[-0.192, 0.133]	-0.062[-0.244, 0.121]	0.173[-0.646, 0.992]	0.202[-0.23, 0.633]
D10 - D11_HDF	0.029[-0.133, 0.192]	0.013[-0.169, 0.196]	-0.848[-1.666, -0.029]	0.059[-0.385, 0.503]
D10 - D12	-0.1[-0.263, 0.063]	-0.073[-0.255, 0.11]	-0.899[-1.718, -0.08]	-0.151[-0.582, 0.28]
D10 - D24	0.027[-0.136, 0.19]	0.032[-0.151, 0.214]	-0.72[-1.538, 0.099]	0.031[-0.4, 0.462]
D10 - D25_HDF	-0.001[-0.164, 0.162]	0.014[-0.169, 0.196]	-0.742[-1.561, 0.077]	-0.058[-0.49, 0.373]
D10 - D26	-0.077[-0.24, 0.086]	-0.085[-0.267, 0.098]	-0.628[-1.447, 0.191]	-0.035[-0.466, 0.397]
D11_HDF - D12	-0.129[-0.292, 0.033]	-0.086[-0.268, 0.097]	-0.051[-0.87, 0.768]	-0.21[-0.654, 0.234]
D11_HDF - D24	-0.003[-0.165, 0.16]	0.019[-0.164, 0.201]	0.128[-0.691, 0.947]	-0.028[-0.472, 0.417]
D11_HDF - D25_HDF	-0.03[-0.193, 0.133]	0.001[-0.182, 0.183]	0.106[-0.713, 0.925]	-0.117[-0.562, 0.327]
D11_HDF - D26	-0.106[-0.269, 0.056]	-0.098[-0.28, 0.085]	0.22[-0.599, 1.039]	-0.093[-0.538, 0.351]
D12 - D24	0.127[-0.036, 0.29]	0.105[-0.078, 0.287]	0.179[-0.64, 0.998]	0.182[-0.249, 0.613]
D12 - D25_HDF	0.099[-0.064, 0.262]	0.087[-0.096, 0.269]	0.157[-0.662, 0.976]	0.093[-0.339, 0.524]
D12 - D26	0.023[-0.14, 0.186]	-0.012[-0.194, 0.171]	0.271[-0.548, 1.09]	0.116[-0.315, 0.548]
D24 - D25_HDF	-0.028[-0.19, 0.135]	-0.018[-0.2, 0.164]	-0.022[-0.841, 0.796]	-0.09[-0.521, 0.342]
D24 - D26	-0.104[-0.266, 0.059]	-0.116[-0.299, 0.066]	0.092[-0.727, 0.91]	-0.066[-0.497, 0.366]
D25_HDF - D26	-0.076[-0.239, 0.087]	-0.098[-0.281, 0.084]	0.114[-0.705, 0.933]	0.024[-0.407, 0.455]
Intra-subject variability (ICC)	84.22%	78.14 %	3.92 %	38.15 %
Inter-subject variability	15.78%	21.86 %	96.08 %	61.85 %

Table S3: Adjusted by age marginal means and 90% confidence interval for the log-transformed PK parameters.

	AUC	Cmax	Tmax	T1/2
D3 - D4_DHF	-0.152[-0.314, 0.011]	-0.028[-0.211, 0.154]	-0.099[-0.918, 0.719]	-0.264[-0.695, 0.167]
D3 - D5	-0.145[-0.308, 0.018]	-0.041[-0.223, 0.142]	-0.15[-0.969, 0.668]	-0.541[-0.972, -0.109]
D3 - D10	-0.098[-0.26, 0.065]	-0.018[-0.2, 0.165]	0.65[-0.169, 1.469]	-0.305[-0.736, 0.127]
D3 - D11_HDF	-0.068[-0.231, 0.094]	-0.005[-0.187, 0.178]	-0.197[-1.016, 0.621]	-0.247[-0.691, 0.198]
D3 - D12	-0.198[-0.36, -0.035]	-0.091[-0.273, 0.092]	-0.248[-1.067, 0.57]	-0.456[-0.887, -0.024]
D3 - D24	-0.071[-0.234, 0.092]	0.014[-0.169, 0.196]	-0.069[-0.888, 0.749]	-0.273[-0.705, 0.158]
D3 - D25_HDF	-0.099[-0.261, 0.064]	-0.004[-0.187, 0.178]	-0.092[-0.91, 0.727]	-0.363[-0.794, 0.068]
D3 - D26	-0.175[-0.337, -0.012]	-0.102[-0.285, 0.08]	0.022[-0.796, 0.841]	-0.339[-0.77, 0.092]
D4_DHF - D5	0.007[-0.156, 0.169]	-0.012[-0.195, 0.17]	-0.051[-0.87, 0.768]	-0.277[-0.708, 0.155]
D4_DHF - D10	0.054[-0.109, 0.217]	0.01[-0.172, 0.193]	0.75[-0.069, 1.568]	-0.04[-0.472, 0.391]
D4_DHF - D11_HDF	0.083[-0.079, 0.246]	0.023[-0.159, 0.206]	-0.098[-0.917, 0.721]	0.017[-0.427, 0.462]
D4_DHF - D12	-0.046[-0.209, 0.117]	-0.063[-0.245, 0.12]	-0.149[-0.968, 0.67]	-0.191[-0.623, 0.24]
D4_DHF - D24	0.081[-0.082, 0.243]	0.042[-0.141, 0.224]	0.03[-0.789, 0.849]	-0.009[-0.441, 0.422]
D4_DHF - D25_HDF	0.053[-0.11, 0.216]	0.024[-0.159, 0.206]	0.008[-0.811, 0.826]	-0.099[-0.53, 0.332]
D4_DHF - D26	-0.023[-0.186, 0.14]	-0.074[-0.257, 0.108]	0.122[-0.697, 0.94]	-0.075[-0.506, 0.356]
D5 - D10	0.047[-0.115, 0.21]	0.023[-0.16, 0.205]	0.801[-0.018, 1.619]	0.236[-0.195, 0.667]
D5 - D11_HDF	0.077[-0.086, 0.239]	0.036[-0.147, 0.218]	-0.047[-0.866, 0.772]	0.294[-0.15, 0.738]
D5 - D12	-0.053[-0.215, 0.11]	-0.05[-0.233, 0.132]	-0.098[-0.917, 0.721]	0.085[-0.346, 0.517]
D5 - D24	0.074[-0.088, 0.237]	0.054[-0.128, 0.237]	0.081[-0.738, 0.9]	0.267[-0.164, 0.699]
D5 - D25_HDF	0.047[-0.116, 0.209]	0.036[-0.146, 0.219]	0.059[-0.76, 0.878]	0.178[-0.253, 0.609]
D5 - D26	-0.029[-0.192, 0.133]	-0.062[-0.244, 0.121]	0.173[-0.646, 0.992]	0.202[-0.23, 0.633]
D10 - D11_HDF	0.029[-0.133, 0.192]	0.013[-0.169, 0.196]	-0.848[-1.666, -0.029]	0.058[-0.386, 0.502]
D10 - D12	-0.1[-0.263, 0.063]	-0.073[-0.255, 0.11]	-0.899[-1.718, -0.08]	-0.151[-0.582, 0.28]
D10 - D24	0.027[-0.136, 0.19]	0.032[-0.151, 0.214]	-0.72[-1.538, 0.099]	0.031[-0.4, 0.462]
D10 - D25_HDF	-0.001[-0.164, 0.162]	0.014[-0.169, 0.196]	-0.742[-1.561, 0.077]	-0.058[-0.49, 0.373]
D10 - D26	-0.077[-0.24, 0.086]	-0.085[-0.267, 0.098]	-0.628[-1.447, 0.191]	-0.035[-0.466, 0.397]
D11_HDF - D12	-0.129[-0.292, 0.033]	-0.086[-0.268, 0.097]	-0.051[-0.87, 0.768]	-0.209[-0.653, 0.235]
D11_HDF - D24	-0.003[-0.165, 0.16]	0.019[-0.164, 0.201]	0.128[-0.691, 0.947]	-0.027[-0.471, 0.417]
D11_HDF - D25_HDF	-0.03[-0.193, 0.133]	0.001[-0.182, 0.183]	0.106[-0.713, 0.925]	-0.116[-0.561, 0.328]
D11_HDF - D26	-0.106[-0.269, 0.056]	-0.098[-0.28, 0.085]	0.22[-0.599, 1.039]	-0.092[-0.537, 0.352]
D12 - D24	0.127[-0.036, 0.29]	0.105[-0.078, 0.287]	0.179[-0.64, 0.998]	0.182[-0.249, 0.613]
D12 - D25_HDF	0.099[-0.064, 0.262]	0.087[-0.096, 0.269]	0.157[-0.662, 0.976]	0.093[-0.339, 0.524]
D12 - D26	0.023[-0.14, 0.186]	-0.012[-0.194, 0.171]	0.271[-0.548, 1.09]	0.116[-0.315, 0.548]
D24 - D25_HDF	-0.028[-0.19, 0.135]	-0.018[-0.2, 0.164]	-0.022[-0.841, 0.796]	-0.09[-0.521, 0.342]
D24 - D26	-0.104[-0.266, 0.059]	-0.116[-0.299, 0.066]	0.092[-0.727, 0.91]	-0.066[-0.497, 0.366]
D25_HDF - D26	-0.076[-0.239, 0.087]	-0.098[-0.281, 0.084]	0.114[-0.705, 0.933]	0.024[-0.407, 0.455]
Intra-subject variability (ICC)	80.87%	73.59 %	2.58 %	29.63 %
Inter-subject variability	19.13%	26.41 %	97.42 %	70.37 %

Figure S1: Study Design.



Each day is shown in boxes, and the HDF is shown in yellow boxes. Arrows indicate the days of FC/AXA.

Abbreviations: AVK: antagonists vitamin K, HDF: Hemodiafiltration.

Figure S2: CONSORT diagram describing the flow of participants through the study.

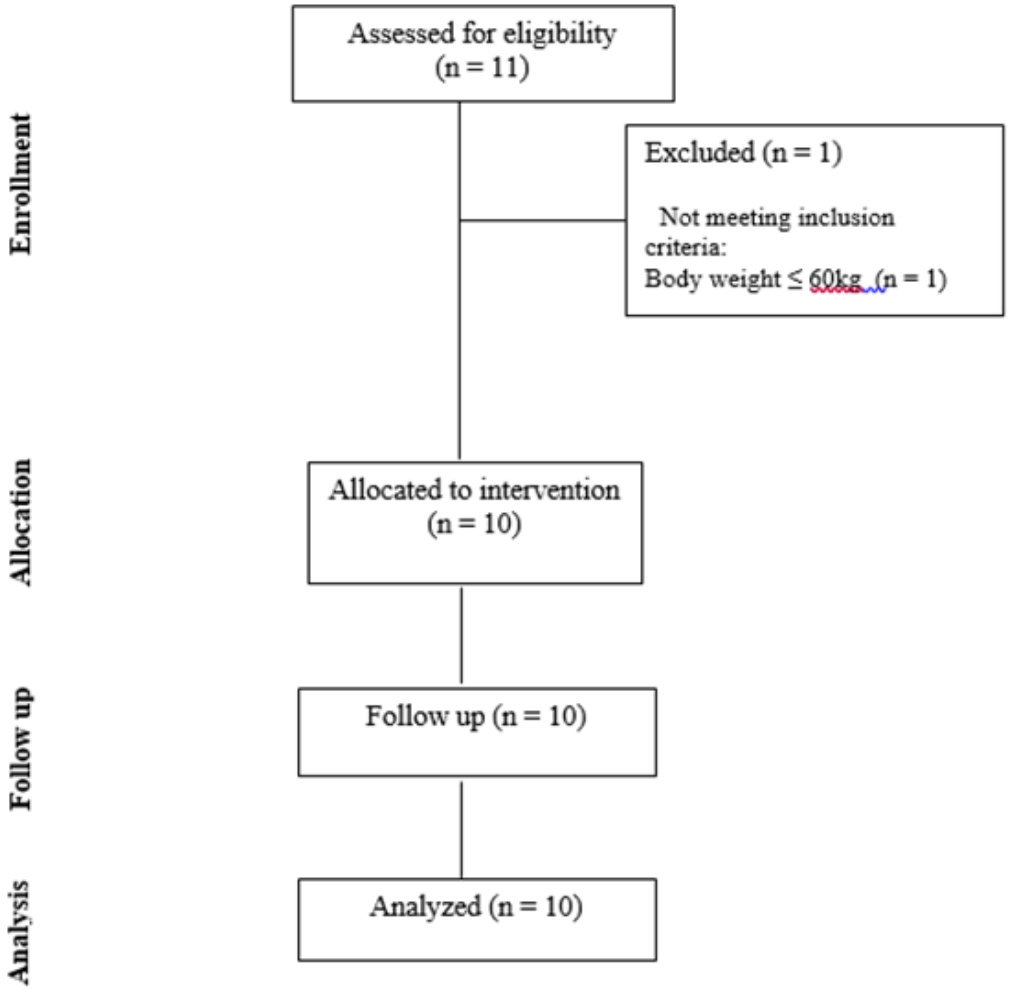
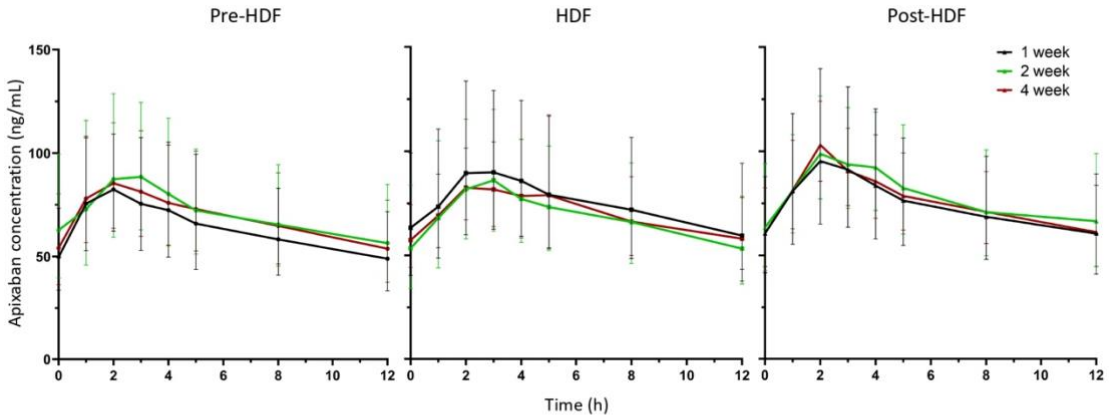
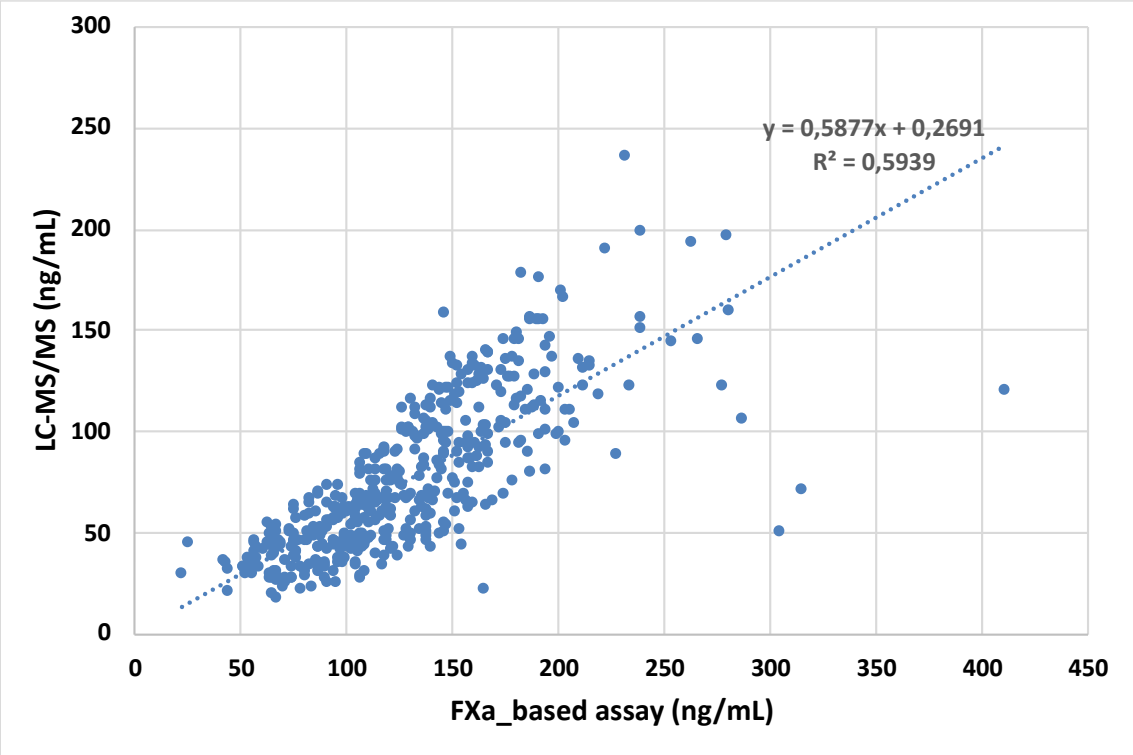


Figure S3: Arithmetic means apixaban plasma concentration over time during the first, second, and fourth week.



Each panel shows the plasma apixaban concentration versus time profiles on the non-dialysis day before HDF (Pre-HDF), during mid-week dialysis (HDF), and the non-dialysis day after HDF (post-HDF), throughout the first, second and 4 weeks. The data revealed that apixaban concentration remained similar and was not reduced during HDF treatment.

Figure S4: Linear regression model showing apixaban levels measured using AXA and LC-MS/MS.



We considered FXa-based assay (AXA) as an independent variable to predict the actual value measured by LC-MS/MS (dependent variable). This approach allows us to calibrate the estimation apixaban levels with AXA. To validate the FXa-based assay against the gold standard LC-MS/MS, we used the Bland-Altman analysis, which is considered the most appropriated method for determining the limits of agreement (LOA) between measurements.

DETAIL PROTOCOL

Phase II Clinical Trial of Apixaban Pharmacokinetics, Pharmacodynamics and Safety in Hemodiafiltration Patients.

1 METHODS/DESIGN {6b}

1.1 OBJECTIVES {7}:

Primary Objective:

The main objective of the HEMOCIONA Project is to determine the plasma concentrations of apixaban in patients on hemodialysis and non-valvular atrial fibrillation before, during and after renal replacement techniques: hemodialysis or hemodiafiltration (HDF).

Secondary objectives:

Our secondary objectives are:

1-. Clinical objectives:

- Pharmacodynamics (PD): Determine the anti-Factor Xa activity of apixaban before, during and after renal replacement techniques (HD or HDF).
- Safety: Determine the short-term safety (4 weeks) of apixaban in patients on dialysis.

2-. Pharmaco-economics objectives: To estimate the economic impact of anticoagulation therapy with apixaban compared to warfarin in dialysis patients.

1.2 HYPOTHESES {7}:

1-. Apixaban is a safe oral anticoagulant in hemodialysis patients.

2-. Considering that severe renal dysfunction increases the AUC of apixaban by 36% and the hemodialysis treatment only decreases drug exposure by 14%, the recommended dose of apixaban for patients on hemodialysis or hemodiafiltration is 2.5 mg twice daily [6-10].

3-. Apixaban is an effective oral anticoagulant in patients with CKD (on HD or HDF) and NVAF:

a. Plasma apixaban concentrations are stable in patients with CKD (on HD or HDF) and NVAF.

b. The anti-Factor Xa activity of apixaban is not altered in patients with CKD (on HD or HDF) and NVAF.

1.3 TRIAL DESIGN {8}:

This is a single-center, phase II clinical trial to evaluate pharmacokinetics, pharmacodynamics and safety, with multiple doses (4 weeks), with a single experimental group, in patients with CKD on hemodialysis and NVAF.

Patients included in the clinical trial will be treated with apixaban 5 mg/day (2.5 mg twice daily), the dose recommended in the apixaban data sheet.

Men and women patients (ages ≥18 years old) with ESRD on hemodialysis (three weekly sessions of 4 hours each) for at least 3 months from the Dialysis Unit at Bellvitge University Hospital and nonvalvular AF were eligible for this study. Patients waiting to enter the transplant list or who have been excluded as candidates for this list will be also eligible.

1.4 SETTING OF THE STUDY {9}:

HEMOCIONA Project will carried out at the Bellvitge University Hospital (HUB), located at L'Hospitalet de Llobregat, Spain.

1.5 CARACTERISTICS OF PARTICIPANTS {10}:

Inclusion Criteria:

- Men and women (18 years or older).
- Body weight ≥ 60kg.
- ESRD patients on hemodialysis (at least 3 months), clinically stable, and non-valvular atrial fibrillation in treatment VKA treatment.
- Patient candidate to change the anticoagulant treatment.
- Negative pregnancy test (absence of HCG in urine) in childbearing age women.
- Written informed consent.

Exclusion Criteria:

- Pregnant or lactating women.
- Women of childbearing age (period of time from menarche to postmenopausal status defined as 12-month absence of menstruation without other medical cause) who do not follow contraceptive methods recommended by the Clinical Trial Facilitation Group (www.hma.eu/fileadm/dateien/Human_Medicines/01): hormonal contraceptives associated

with ovulation inhibitors, intrauterine devices, surgical methods (tubal ligation, vasectomy), abstinence and barrier methods.

- Body weight ≤ 60kg.
- Liver disease (increased liver enzyme levels ALT / AST> 2x the upper limit of normal, or total bilirubin> 1.5 ULN).
- Thrombocytopenia (<100,000 platelets / mL).
- Treatment with other anticoagulants (heparins) or antiplatelet drugs.
- Treatment with enzyme inhibitors (such as azole antifungals or HIV protease inhibitors) or enzyme inducers (such as rifampin, phenobarbital, carbamazepine, or phenytoin) of cytochrome P450 3A4.
- Bleeding episodes in the last month.
- Clinical or analytical alterations not caused by kidney disease.
- Participation in another clinical trial.

1.6 DESCRIPTION OF ALL PROCESSES, INTERVENTIONS AND COMPARISONS

1.6.1 INTERVENTION DESCRIPTION {11a}:

Patients will be screened from the Hemodialysis unit. Patients enrolled on the trial will be followed up until 28 days (1 month) after starting treatment with apixaban (see Figure 1).

At visit 1 (Day 0, patient inclusion). A complete clinical evaluation will be performed to confirm that the patient meets all the inclusion criteria and none of the exclusion criteria. Participants will be informed about the study and sign a written informed consent before enrolling in the trial. Demographic parameters, medical history, concomitant medication and adverse events will be recorded.

Patients will receive an oral dose of 2.5 mg of apixaban twice daily for 4 consecutive weeks. The first day of drug administration will be a dialysis-free day, 3 days before the first dialysis of the week to ensure that apixaban is at steady state after completing 6 apixaban half-lives. PK analysis will be performed at week 1 (first HD of the study), week 2 (second HD of the study) and week 4 (third HD of the study). During these 4 weeks the patient will attend their scheduled HD sessions and will be given instructions on how to correctly take the apixaban.

The day of initiation of treatment with apixaban will be considered day 0 of the clinical trial. Switching from VKA to apixaban will be performed according to the technical data sheet, section "4.2 Dosage and

method of administration: “Switching from treatment with parenteral anticoagulants to apixaban (and vice versa) can be performed at the next scheduled dose. These drugs should not be administered simultaneously. Switching from VKA therapy to apixaban: When switching from VKA therapy to apixaban, warfarin or other VKA therapy should be discontinued and apixaban therapy initiated when the international normalized ratio (INR) is <2.”

Visit 2, 3 and 4 will be divided into 3 days, comprising pre-HD day, HD day and post-HD day (see Table 1):

Visit 2 (first study hemodialysis)

At visit 2.1 (Day 3 - pre-1st HD day). This is the third day after starting the apixaban: This visit corresponds to the day before the midweek dialysis day of the first week. The patient will be admitted to the Clinical Research Support Unit (CRSU) for 12.5 hours to perform the first PK study. A physical examination will be performed and the correct intake of apixaban will be verified. Concomitant medication will also be recorded, including dose, route of administration, and start and end date. In addition, it will be confirmed that patient does not present any criteria for discontinuation of apixaban. Venous blood samples (4 cc) will be collected immediately before (0) and 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8 and 12 hours after apixaban administration for PK analysis. In patients with residual diuresis, 2 urine aliquots (urine collected during the 12 hours of the PK study) will be collected. Blood, and urine samples will be stored at -80ºC until assay.

Visit 2.2 (Day 4 - 1st HD day). A venous blood samples (4 cc) will be collected immediately before (0) and 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8 and 12 hours after apixaban administration for PK analysis during the midweek dialysis. Patient will receive 2.5 mg apixaban immediately before starting hemodialysis and 12 h after the preceding dose. Blood samples will be collected prior to dialysis and then at 0.5, 1, 1.5, 2, 2.5, 3, 4 hours. In addition, aliquots of dialysis fluid will be collected immediately before dialysis, at 0.15 h and then hourly until the end of the dialysis session. In patients with residual diuresis, 2 urine aliquots (urine collected during the 12 hours of PK study) will be collected. Blood, urine and dialysis liquid samples will be stored at -80ºC until assay.

Visit 2.3 (Day 5 – post-1st HD day). This visit corresponds to the day after the first hemodialysis session of the study. The patient will be admitted to the CRSU for 12.5 hours for the PK study. Physical examination, correct apixaban intake, concomitant medication and study stop criteria will be checked.

Visit 3 (second study hemodialysis)

The correspondence scheme for these visits will be as follows:

Visit 3.1 (Day 10 – pre-2nd HD day) tenth day after starting the medication: This visit corresponds to the day before the second hemodialysis session of the study.

Visit 3.2 (Day 11 – 2nd HD day) eleventh day after starting the medication corresponding to the second midweek hemodialysis session.

Visit 3.3 (Day 12 – post-2nd HD day) twelfth day after starting the medication corresponding after the second midweek hemodialysis session

In each of the visits the same procedures and collection of samples are carried out as in the visits 2.1, 2.2 and 2.3.

Visit 4 (third study hemodialysis)

The correspondence scheme for these visits will be as follows:

Visit 4.1 (Day 24 – pre-3rd HD day) twenty-fourth day after starting the medication: This visit corresponds to the day before the third midweek hemodialysis session.

Visit 4.2 (Day 25 – pre-3rd HD day) twenty-fifth day after starting the medication: This visit corresponds to the day the third midweek hemodialysis session.

Visit 4.3 (Day 26 – post-3rd HD day) twenty-sixth day after starting the medication: This visit corresponds to the day after the third midweek hemodialysis session.

In each of the visits the same procedures and collection of samples are carried out as in the visits 2.1, 2.2 and 2.3.

Visit 5: End of study (EoS - 28 ± 1 days after starting treatment with apixaban): A physical examination will be performed and correct apixaban intake will be verified. Concomitant medication will be also recorded, including dose, route of administration, and start and end date. In addition, it will be confirmed that patient does not present any criteria for discontinuation of apixaban. At the end of the clinical trial, the patient will be proposed to continue in the extension study (to assess long-term safety, 9 months). If the patient does not agree to participate in the extension study, the apixaban will be withdrawn and the previous VKA will be reintroduced as indicated in the apixaban technical data sheet[7].

1.6.2 PARTICIPANT TIMELINE {13}

			1st Study Hemodialysis			2nd Study Hemodialysis			3rd Study Hemodialysis			
	Baseline Visit		**Pre-hemodialysis**	**Hemodialysis (HD)**	**Post-hemodialysis**	**Pre-hemodialysis**	**Hemodialysis (HD)**	**Post-hemodialysis**	**Pre-hemodialysis**	**Hemodialysis (HD)**	**Post-hemodialysis**	**EoS Visit**
	Visit 1: Patient inclusion	**Start of medication**	**Visit 2.1**	**Visit 2.2**	**Visit 2.3**	**Visit 3.1**	**Visit 3.2**	**Visit 3.3**	**Visit 4.1**	**Visit 4.2**	**Visit 4.3**	**Visit 5**
Day		**Day 0**	day 3 with apixaban	day 4 with apixaban	day 5 with apixaban	day 10 with apixaban	day 11 with apixaban	day 12 with apixaban	day 24 with apixaban	day 25 with apixaban	day 26 with apixaban	**Day 28**±1
Inclusion / Exclusion criteria	✓											
Informed consent signature	✓											
Demographic data	✓											
Vitals signs (BP, HR, BT, SpO2, RR)	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Physical examination	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Electrocardiogram (ECG)	✓											✓
Blood test (1)	✓		✓			✓			✓			✓
Urine sample collection			✓	✓	✓	✓	✓	✓	✓	✓	✓	
Dialysis fluid collection				✓			✓			✓		
Medication delivery		✓	✓			✓			✓			

PK/PD (2)			✓	✓	✓	✓	✓	✓	✓	✓	✓	
Chest X-ray	✓											✓
AE log	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Concomitant medication record	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

Table 1: During the study, tests and other complementary tests will be performed according to the clinical criteria of the responsible team. (1) Blood count, ionogram, kidney and liver function, coagulation (2) Collection of 4 cc at 0 (predose valley concentration, Cmin), 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8 and 12 (predose valley concentration, Cmin) hours after apixaban administration.

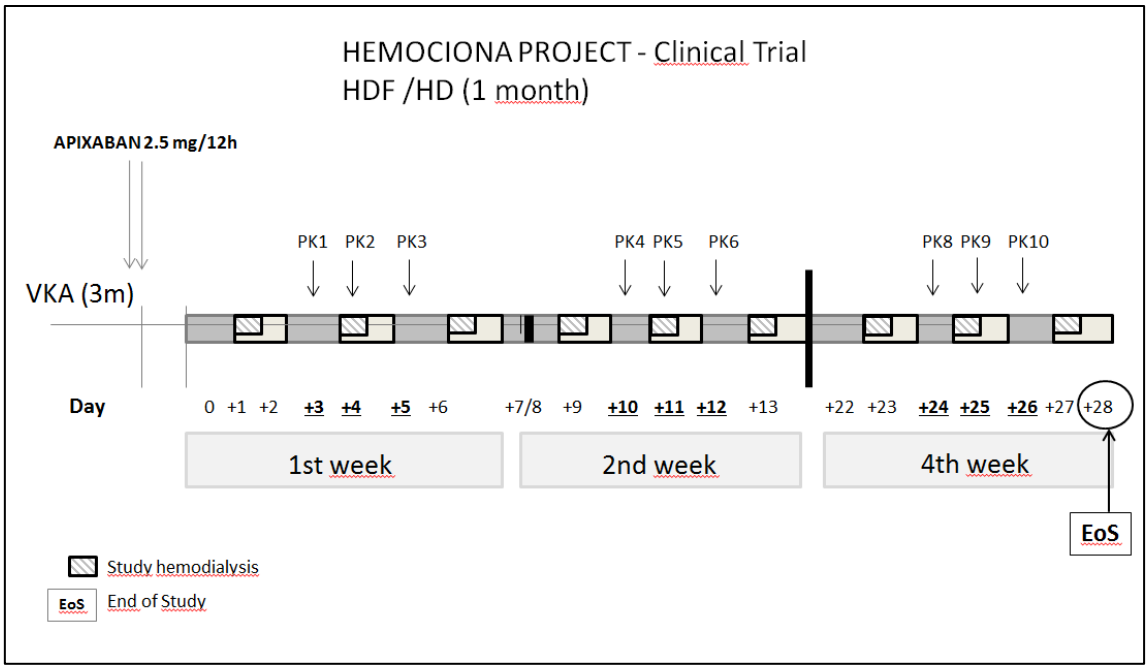


Fig 1: Study timeline

1.6.3 CRITERIA FOR DISCONTINUING OR MODIFYING ALLOCATED INTERVENTIONS {11b}

Participants may voluntarily discontinue apixaban and/or prematurely end their participation in the trial for any reason at any time. The investigator may also decide at any time during the course of the trial, to temporarily interrupt or permanently suspend trial treatment if it is considered that continuation would be harmful, or not in the participant's best interest. Similarly, the sponsor, Ethics Committee or authorized regulatory authority may decide to discontinue or prematurely terminate the trial when new information becomes available that would no longer ensure the rights, safety and well-being of trial participants, when the integrity of the trial has been compromised, or when the scientific value of the trial has become obsolete and/or unjustifiable.

Circumstances requiring premature discontinuation of treatment or discontinuation of the trial include, but are not limited to, the following (1) safety concerns related to investigational product or unacceptable intolerability (potentially life-threatening reaction during treatment), (2) violation of the inclusion and/or exclusion criteria and (3) pregnancy or the intention of become pregnant. In any case of early termination of the trial and/or interruption/discontinuation of treatment, the investigator will continue to closely monitor the participant's condition and ensure appropiate medical care and follow-up. Additionally, these

patients will continue to be followed for the secondary outcome and their data will be included in intention-to-treat analyses.

1.6.4 STRATEGIES TO IMPROVE ADHERENCE TO INTERVENTIONS {11c}

From the start of treatment with apixaban, correct compliance with the study medication will be verified by interviewing the patient about the number of tablets ingested and the schedule. In addition, throughout the 4 weeks of the study, the amount of medication remaining in the blister pack provided to the patient will be verified.

Although, patients included in this clinical trial 'a priori' will only meet one of the criteria of dose reduction criteria mentioned in the technical data sheet (serum creatinine ≥ 1.5 mg/dL), in this clinical trial the included patients will be treated with 2.5 mg administered twice daily for 28 days, according to the recommendations of the hemostasis and thrombosis department of the Bellvitge University Hospital. Patients will be advised to take the medication at 8:00 am and 8:00 pm. The PK study ensures that the included patients will not present under-therapeutic doses. The adjusted apixaban dose targets a mean trough concentration (Cmin) of 79 ng/mL (34-162 ng/mL) and mean antiXa activity of 1.5 IU/mL (0.61-3.4 IU/mL), according to clinical practice.

1.6.5 RELEVANT CONCOMITANT CARE PERMITTED OR PROHIBITED DURING THE TRIAL {11d}

Concomitant Treatment: According to the summary of product characteristics (SmPC) items 4.2. Posology and method of administration; 4.3. Contraindications; 4.4. Special warnings and precautions for use; and 4.5. Interaction with other medicinal products and other forms of interaction, apixaban should not be administered concomitantly with any other anticoagulant agent e.g., unfractionated heparin (UFH), low molecular weight heparins (enoxaparin, dalteparin, etc.), heparin derivatives (fondaparinux, etc.), oral anticoagulants (warfarin, rivaroxaban, dabigatran, etc.). Apixaban cannot be administered in the study simultaneously with CYP3A4 or P-gp inhibitors or inducers. Accordingly, the use of any drug will be allowed if deemed necessary for clinical management. Any concomitant medication will be recorded in the electronic health record (detailing product, dose, route, days of administration and reason for treatment). All this information will be recorded on the electronic case report forms (e-CRF).

Rescue Therapy: For situations where reversal of anticoagulation is necessary due to life-threatening or uncontrolled bleeding, administration of prothrombin complex concentrates (PCCs) or recombinant

factor VIIa may be considered. In case of bleeding (overdose or accidental ingestion), treatment will be discontinuated, activated charcoal will be administered orally and, if the patient life is at risk, fresh plasma, prothrombin complex or recombinant Factor VIIa will be administered. Note that the elimination half-life of apixaban is 13.4 h [7].

1.6.6 CRITERIA FOR THE DISCONTINUATION OF THE STUDY TREATMENT

As specified in the SmPC of Eliquis® it is contraindicated in case of hypersensitivity to the active substance or to any of its excipients. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this drug [7].

1.6.7 OUTCOMES {12}

Primary Outcomes:

Pharmacokinetics:

- Plasma concentration of apixaban will be determined by tandem chromatography with mass spectrometry (LC-MS / MS) (ACQUITY UPLC ©)[11].

Secondary outcomes:

Pharmacokinetics:

- Concentration in urine and in dialysis liquid from apixaban. Concentrations will be determined by tandem chromatography with mass spectrometry (LC-MS / MS) (ACQUITY UPLC ©) [11].

Pharmacodynamics:

- Anti-Factor Xa activity of apixaban. The anti-FXa (AXA) activity of apixaban will be determined according to a chromogenic technique previously described [12].

Security: Safety will be assessed by estimating the incidence of adverse events according to their severity and relationship with treatment.

- Number of patients with medical complications not directly related to chronic kidney disease or dialysis treatment.
- Total number of adverse events.
- Number of adverse events related to apixaban.

1.6.8 SAMPLE SIZE {14}

Although, no formal sample size calculation has been performed, 8 patients with ESKD were included in the clinical trial cited in the SmPC, and 7 in the steady-state PK of apixaban in Hemodialysis patients[8]. Thus, it is planned to include a total 20 consecutive patients who meet the inclusion/exclusion criteria, 10 patients on HD and 10 patients on hemodiafiltration.

1.6.9 RECRUITMENT {15}

The target population of this clinical trial are patients with clinically stable chronic kidney disease on hemodialysis (with a minimum of 3 months of treatment) and non-valvular atrial fibrillation on VKA therapy.

The study subjects will be recruited in the hemodialysis unit of the Bellvitge University Hospital.

1.6.10 ASSIGNMENT OF INTERVENTIONS: ALLOCATION AND BLINDING

SEQUENCE GENERATION {16a}, CONCEALMENT MECHANISM {16b} AND IMPLEMENTATION {16c}

This does not apply because this is an open-label study and in a single group of patients, and no randomization or blinding will be performed.

WHO WILL BE BLINDED? {17a} PROCEDURE FOR UNBLINDING IF NEEDED {17b}

This does not apply because this is an open-label study and in a single group of patients, and no randomization or blinding will be performed.

1.6.11 DATA COLLECTION AND MANAGEMENT {18a} {18b} {19}

For this study, an electronic case report form (e-CRF) based on the REDCap platform (Research Electronic Data Capture software, REDCap Consortium), will be created *ad hoc* in coordination with the Biostatistics Unit of the IDIBELL (UBiDi). It does not collect data that would allow patient identification.

Demographics, clinical data and hematological and biochemical analysis, as well as data on administered doses of the apixaban and any other treatments, will be collected.

1.6.12 OVERSIGHT AND MONITORING

COMPOSITION OF THE DATA MONITORING COMMITTEE, ITS ROLE AND REPORTING STRUCTURE {21a}

Not applicable

INTERIM ANALYSES {21b}

Not applicable.

1.6.13 ADVERSE EVENT REPORTING AND HARMS {22}

Adverse events recorded during the study will be coded according to the latest available version of the MedDRA dictionary and will be described by absolute and relative frequencies per study group, according to severity and their causal relationship with treatment.

In all the visits planned in the HEMOCIONA project, possible new-onset symptoms will be asked, as well as special attention will be paid to bleeding episodes of any cause.

The investigator will systematically monitor and collect adverse events (AEs) from the first use of the investigational medical device until the subject's last follow-up visit. AEs will be recorded in the patient's medical record, remarking the causal relationship to the trial treatment. Any AE, or any abnormal laboratory result that is considered clinically relevant, will be followed until a satisfactory resolution is reached and clinical judgment indicates that no further evaluation is necessary. All serious adverse events (SAEs), including death, regardless of its cause and regardless of their relationship with Investigational Medicines, will be notified as soon as possible, and no later than 24 hours after becoming aware of the event presentation, to the person or department responsible for pharmacovigilance.

The sponsor or the team designated by the sponsor to perform these tasks will notify the local authorities of all adverse events and other undesirable effects of the trial intervention in accordance with current regulations on clinical trials (Spanish Agency for Medicines and Health Products, AEMPS: Agencia Española de Medicamentos y Productos Sanitarios).

1.6.14 FREQUENCY AND PLANS FOR AUDITING TRIAL CONDUCT {23}

The Investigator will allow direct access to trial data and documents for monitoring, audits and/or inspections by authorized entities such as, but not limited to, the sponsor or its representatives and appropriate regulatory or health authorities. Therefore, e-CRFs, source records and other trial-related documentation (*e.g.*, the Trial Master File, pharmacy records) will be kept current, complete and accurate at all times. Auditors will be independent from the clinical trial and its conduct.

1.6.15 PLANS FOR COMMUNICATING IMPORTANT PROTOCOL AMENDMENTS TO RELEVANT PARTIES (*e.g.*, TRIAL PARTICIPANTS, ETHICAL COMMITTEES) {25}

In accordance with good clinical practice, trial participants will be informed of any significant changes during the trial. Major protocol changes will be submitted for Institutional Review Board (IRB) for approval and minor findings will be reported to the IRB.

1.6.16 WHO WILL TAKE INFORMED CONSENT? (26a)

Potential participants will be screened in the dialysis unit and in the Nephrology department. One of the physicians involved in the study will perform the first assessment to determine if the patient is interested in participating in the study. If interested in participating, the investigators of the HEMOCIONA project team will recheck the eligibility criteria and contact the patient to provide further information and obtain the signed written informed consent.

The informed consent form includes a brief and understandable summary of the rationale of the trial, the trial design and the study drug. This is followed by a detailed form, explaining all study-related procedures, the collection of clinical data (e.g., clinical scores and vital signs), the collection of biological samples (e.g., blood, urine and dialysis fluid samples), and the potential risks (adverse events) and benefits (potential individual positive effects of the intervention, contribution to knowledge production) of the study. In addition, data management and ethical approval as well as the insurance policy are detailed. The investigator will also verbally explain this consent form and will be available to answer any study-related questions that may arise, before asking the patient to sign the consent form.

Additional consent provisions for collection and use of participant data and biological specimens {26b}

Not applicable.

1.6.17 CONFIDENTIALITY {27}

The results of this clinical trial will be kept confidential and will not be transferred to any third party in any form or manner without written permission from the Sponsor. All persons participating in the clinical trial are bound to this confidentiality clause in line with REGULATION (EU) 2016/679 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of April 27th, 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, as well as all other laws and regulations in force and applicable, such as the 'Ley Orgánica 3/2018, de 5 de diciembre, de Protección de Datos Personales y garantía de los derechos digitales' [Organic Law 3/2018, of 5 December, on the Protection of Personal Data and guarantee of Digital Rights]. Therefore, the patient's data will be pseudonymized. At the same time that the signature of the Informed written Consent is obtained, the Investigator will request written permission from the patient to directly access his/her data. With this permission granted, the patient's data may be examined, analyzed, verified and reproduced for the evaluation of the clinical trial. The data will be anonymized and the corresponding patient will not be identified. Patient data will also be dissociated. Patients will be assigned consecutive numbers as they

enroll in the study, and these identification numbers (or codes) will be used in the e-CRF; the patient's full name will not be included in the e-CRFs. The investigator will maintain a current patient identification, list containing the patient's name, medical record number and patient identification number (or code) for the clinical trial.

The study monitor will have access to patient identity and data related to study monitoring procedures. Anyone with direct access to the data (regulatory authorities, trial monitors and auditors) will take every precaution to maintain the confidentiality of patient's identities.

It is the Investigator's responsibility to obtain written informed consent from the study patients. It is the trial monitor's responsibility to ensure that each patient has given written consent to allow this direct access.

The Investigator will ensure that the documents provided to the sponsor do not contain the patient's name or any identifiable information.

1.6.18 PROVISIONS FOR POST-TRIAL CARE {30}

Once the end-of-study visit is reached, the treating physician will perform an individualized assesment to decide whether to return the patient to VKA treatment or continue treatment with apixaban.

The investigator team intends to conduct a 9-month safety extension study with the cohort of patients included in this clinical trial. A specific protocol will be drafted for this extension study. The conduct of this extension study will depend on obtaining financial resources.

1.6.19 DISSEMINATION PLANS {31a}

The results will be published in a peer-reviewed journal and presented at international medical meetings.

1.6.20 PLANS TO GIVE ACCESS TO THE FULL PROTOCOL, PARTICIPANT LEVEL-DATA AND STATISTICAL CODE {31c}

The full protocol is available on clinicaltrials.gov (NCT NCT04952792). There are no plans at this time to provide public access to the patient dataset. Dr. Cristian Tebé, from the Biostatistics Unit, will be in charge of the dataset and granting access to this information will be evaluated on a case-by-case basis and upon request.

1.6.21 PLANS FOR COLLECTION, LABORATORY EVALUATION AND STORAGE OF BIOLOGICAL SPECIMENS FOR GENETIC OR MOLECULAR ANALYSIS IN THIS TRIAL/FUTURE USE {33}

Blood samples will be collected at the baseline visit to monitor the INR. Blood for PK study, urine, and dialysis fluid samples will be routinely collected.

1.7 STATISTICAL METHODS FOR PRIMARY AND SECONDARY OUTCOMES {20a}

All data collected in the study will be summarized using related statistics. Likewise, 95% confidence intervals will be calculated to report the characteristics of the target population.

Descriptive analysis: Continuous variables will be described as means and standard deviation (SD) or as median and range; and categorical variables as absolute frequencies and percentages.

Pharmacokinetic analysis: The pharmacokinetic parameters (Cmax, AUC0-12, Tmax) of apixaban will be calculated for each study period (the day before hemodialysis, the day of hemodialysis and the day after hemodialysis). Changes in PK analysis between days within a period and between the 3 periods under study will be analyzed. An exploratory comparative analysis will be performed between the 2 dialysis techniques: HD and HDF.

Pharmacodynamic analysis: The anti-Factor Xa activity of apixaban will be analyzed in each study period (the day before hemodialysis, the day of hemodialysis and the day after hemodialysis). Changes in Factor Xa activity between days within a period and between the 3 periods under study will be analyzed. An exploratory comparative analysis will be performed between the 2 dialysis techniques.

Safety analysis: A tabulated analysis by organs and systems, and a description of adverse events (number of patients with adverse events, number of events) will be performed. In addition, a tabulated analysis will be performed using dialysis techniques.

Data analysis will be performed using the R statistical package for Windows (R Foundation for Statistical Computing, http://www.r-project.org).

METHODS FOR ADDITIONAL ANALYSES (*e.g.,* SUBGROUP ANALYSES) {20b}

It is not planned to perform subgroup additional analysis.

METHODS IN ANALYSIS TO HANDLE PROTOCOL NON-ADHERENCE AND ANY STATISTICAL METHODS TO HANDLE MISSING DATA {20c}

In the case of missing data, the imputation will be performed considering that the treatment effect estimator is not biased and that an increase in type I error has been avoided.

NCT03987711 **(https://clinicaltrials.gov/ct2/show/record/NCT03987711?cond=NCT03987711&draw=2&rank=1)**	**NCT02933697** **(https://clinicaltrials.gov/ct2/show/record/NCT02933697?term=02933697&draw=2&rank=1)**
Study Sponsor: Unity Health Toronto Study Phase: Phase 2	Study Sponsor: Atrial Fibrillation Network Study Phase: Phase 3
Study Arms: -Experimental: Warfarin Individuals randomized to this arm will be exposed to dose-adjusted daily warfarin targeting an INR of 2.0-3.0. Intervention: Drug: Warfarin -Active Comparator: Apixaban Individuals randomized to this arm will receive apixaban 5 mg twice daily (a reduced dose of 2.5 mg twice daily will be given to selected participants). Intervention: Drug: Apixaban -Active Comparator: No oral anticoagulation Individuals in this arm will be exposed to a treatment strategy in which no oral anticoagulation is prescribed. Intervention: Other: No oral anticoagulation	Study Arms: -Active Comparator: Apixaban 2.5 mg apixaban twice daily for 6 to 60 months Intervention: Drug: Apixaban -Active Comparator: Vitamin-K antagonists (Phenprocoumon) Phenprocoumon by INR (Target: 2.0-3.0) treatment for 6 to 60 months Intervention: Drug: Phenprocoumon

Table 1

LIST OF ABBREVIATIONS

- AE / AEs: Adverse Event (s)
- AF: Atrial Fibrillation
- AEMPS: Spanish Agency for Medicinal Products and Medical Devices
- AUC: Area Under the Curve

- BP: Blood Pressure
- BT: body Temperature
- CKD: Chronic Kidney Disease
- Cmax: Peak concentration of a drug in the blood
- Cmin: Trough concentration
- CRSU: Clinical Research Support Unit
- DOACs: Direct Oral Anticoagulants
- e-CRF: Electronic Case Report Form
- EU: European Union
- ESKD: End-Stage Kidney Disease
- HD: Hemodialysis
- HDF: Hemodiafiltration
- HCG: Human Chorionic Gonadotropin
- HR: Heart Rate.
- HUB: Hospital Universitario de Bellvitge.
- IDIBELL: Bellvitge Institute for Biomedical Research
- INR: International Normalized Ratio
- MedDRA: Medical Dictionary for Regulatory Activities
- NVAF: Non-Valvular Atrial Fibrilation
- PCCs: Prothrombin Complex Concentrates
- PD: Pharmacodynamic
- PK: Pharmacokinetic
- PT: Prothrombin Time
- REDCap: Research Electronic Data Capture software, REDCap Consortium.
- RR: Respiratory Rate
- SAE: Serious Adverse Event
- SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2
- SD: Standard deviation

- SmPC: Summary of Product Characteristics for the investigational medicinal product
- SpO2: Oxygen Saturation
- Tmax: Time of Maximum concentration observed
- UBiDi: Biostatistics Unit of the IDIBELL
- ULN: Upper Limit of Normal
- VKAs: Vitamin K Antagonists

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1 NA
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	2,3
Objectives	3	State specific objectives, including any prespecified hypotheses	3, S13
Methods			
Study design	4	Present key elements of study design early in the paper	3, S1, S14
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	3 S1, S14
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (*b*) For matched studies, give matching criteria and number of exposed and unexposed	3, S2, S14-S19
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	S2-S4 S14-S17
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	3, S2-S4 S15
Bias	9	Describe any efforts to address potential sources of bias	S2, S20, S21
Study size	10	Explain how the study size was arrived at	S1
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	S2-S4
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding (*b*) Describe any methods used to examine subgroups and interactions (*c*) Explain how missing data were addressed (*d*) If applicable, explain how loss to follow-up was addressed (*e*) Describe any sensitivity analyses	S4
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	3,

		(b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	S10
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	3, S5-S6 S10
Outcome data	15*	Report numbers of outcome events or summary measures over time	4

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	3, 5
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	3-5
Discussion			
Key results	18	Summarise key results with reference to study objectives	7
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	6
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	5-7
Generalisability	21	Discuss the generalisability (external validity) of the study results	7
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	8

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.