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Original Article

ORIGINAL ARTICLE

Vitamin K antagonist has a higher impact than heparin in preventing circuit clotting in chronic haemodialysis patients

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ABSTRACT

Background. In dialysis sessions, some data suggest that decreasing or even avoiding additional anticoagulation by heparin is possible among patients already treated with oral anticoagulation. However, the required dose of heparin may actually depend on the pre-dialysis international normalized ratio (INR), which varies from one session to another. The aim of our study was to determine the respective role of INR and heparin dosing in the risk of circuit clotting during chronic haemodialysis.

Methods. From early 2012 to July 2016, we analysed the totality of dialysis sessions performed at Brest University Hospital among haemodialysis patients treated by vitamin K antagonists (VKA). We established a prediction of circuit clotting on the basis of a simplified score obtained by combining INR and heparin dosing.

Results. In total, 7184 dialysis sessions among chronic haemodialysis patients under VKA were identified, including 233 with clotting events. The mean INR without clotting events was 2.5 versus 1.8 with clotting events ($P < 0.001$). Frequencies of circuit clotting were different according to INR group (INR <2.0, INR 2.0–3.0, INR >3.0; $P < 0.0001$). The protective role of VKA was higher than heparin, as shown by discriminant factor analysis ($P < 0.0001$).

Conclusion. Our study established a predictive model of thrombosis risk of dialysis circuits in patients treated by VKA for a given heparin dose and a given INR. This model shows a marginal contribution of heparin to protect against the risk of thrombosis compared with VKA. Moreover, heparin would not appear to be necessary for patients with an INR >2.2.

Keywords: chronic haemodialysis, coagulation, heparin, vitamin K antagonist

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INTRODUCTION

Despite their controversial use [1–5], a substantial proportion of dialysis patients remains treated by oral anticoagulation, especially for atrial fibrillation [6, 7], with marked variation between countries (from 2% to as high as 26–37%) [8]. Oral anticoagulation exposes patients to an increased risk of haemorrhagic adverse effects [9–13] while these patients are already at risk of bleeding due to their platelet dysfunction linked to end-stage renal disease [14, 15]. Particularly, gastrointestinal and intracranial haemorrhages are most prominent [16] in this population and may lead to death [17]. In contrast, it is necessary to use heparin during dialysis sessions to prevent any circuit clotting [18], which may be responsible for insufficient dialysis or blood loss. However, in the literature, the necessity of additional anticoagulation by heparin among patients already treated by oral anticoagulation is still poorly studied. Although some data suggest that additional anticoagulation by heparin could be avoided [19] in these patients, this notion is not univocal [20].

In fact, the need for additional heparin may actually depend on the pre-dialysis international normalized ratio (INR) value, although no data formally support the correlation of INR and clotting event occurrence during dialysis. However, the variability of INR [21, 22] coupled with the fact that this analysis is not performed for each dialysis session complicates any adjustment concerning heparin dosage. Moreover, even if INR is determined for a given session, its result is not available immediately due to the technical time required; thus, most heparin is administered without knowledge of INR value. Thus, it is routinely difficult to appreciate the respective role of heparin or vitamin K antagonist (VKA) use on the risk of clotting events. The aim of our study was to evaluate the specific influences of INR value and heparin dosing on the clotting circuit risk among dialysis patients already treated by VKA. This study may lead to limited heparin use when thrombotic risk can be controlled by VKA alone, as heparin exposes patients to an increased risk of bleeding and side effects.

MATERIALS AND METHODS

Study design

The COAGHEMO study was a retrospective, observational study conducted in the Department of Nephrology of the University Hospital in Brest from early 2012 to July 2016. The study protocol was approved by the local Ethics Committee, and patients gave informed consent before the start of the study.

From January 2012 to July 2016, the totality of the dialysis sessions performed in our department was inventoried, and those performed in patients treated by VKA were selected. In our department, in order to minimize the bleeding risk, we systematically tried to reduce or stop heparin injection in patients under VKA. In most cases, however, it became necessary to reintroduce and maintain heparin, due to the outcome of a clotting event. During this period, this approach led us to obtain sessions with and without heparin in the same patients. The data collection was performed using Sined Medware® software (SINED, Bologna, Italy). The characteristics of each dialysis session, including heparin dosing (unfractionated heparin), INR values [automated measurements performed in central hospital laboratory—STAGO STA-R Evolution analyser (STAGO, Asnières, France)—STAGO Neoplastine CI Plus] and dialysis incidents were exhaustively analysed. For INR measurement, a heparin inhibitor was systematically used, in order to avoid a potential risk of interference from the presence of heparin (particularly with the use of heparin locks in patients with two-lumen-tunnelled central venous catheter).

The INR target range was similar for all patients (2.0–3.0), except for one whose indication was catheter dysfunction (1.8–2.5) [23]. Guidelines recommend that patients under VKA (for which indication is atrial fibrillation) with stable INR should undergo INR every 4 weeks [24]. Due to variability of INR, and increased risk of haemorrhagic effects in dialysis patients, the monitoring in our department is weekly. Blood samples were drawn at the beginning of the dialysis session from the blood arterial line to determine INR value and adapt VKA dose. The average time to obtain the INR value from the laboratory was 1 h. According to recommendations [18], heparin injection was devised into a loading dose (50 IU/kg) followed by a continuous infusion (800–1500 IU/h). The heparin injection was performed on the blood venous line. The maintenance dose was continued upon receipt of INR value, except in case of VKA overdose (INR >3), where the heparin was stopped. We excluded dialysis sessions conducted during a hospital stay and those for patients who presented a contraindication to heparin.

A flow diagram has been designed to summarize the process of included patients (Figure 1).

Definition of the clotting incident

Two types of clotting incidents were defined: the existence of a total coagulation of the circuit, attested by the need of a premature restitution to the patient, or the visual observation of clots in the extracorporeal circuit at any time during the session. Data were entered by the nurses during each session using the Sined Medware® software. For sessions where both events were traced, we retained only the most serious event (total coagulation of the circuit with immediate restitution).

Statistical analysis

The frequencies of clotting events according to three groups of INR ranges, <2.0, 2.0–3.0 and >3.0, were compared using a Chi-square test. The mean INRs were compared between groups presenting a clotting incident or not using a Mann–Whitney test. We also compared the previous mean INR (i.e. during session immediately preceding the one considered), depending on the outcome of a clotting event during the following session or not. A Chi-square test was also performed to determine if the type of vascular access could promote the outcome of clotting event. A P-value <0.05 was considered significant.

A factorial discriminant analysis (including Wilks' lambda estimation) was performed to design a prediction model of clotting events, which was dependent on the INR value and heparin dosing. Sensibility, specificity and receiver operating characteristics (ROC) curves were calculated. A cross-validation was then used to confirm the robustness of the predictive model (XLSTAT, Addinsoft, France).

RESULTS

General characteristics of dialysis patients

From the beginning of 2012 to July 2016, >37 000 sessions of dialysis were performed in our department. In totality, 32 chronic dialysis patients under VKA were included (22 under warfarin and 10 under fluindione), with 7184 dialysis sessions performed. The characteristics of the 32 patients are presented in Table 1. Twenty-nine patients were dialysed on arteriovenous fistula

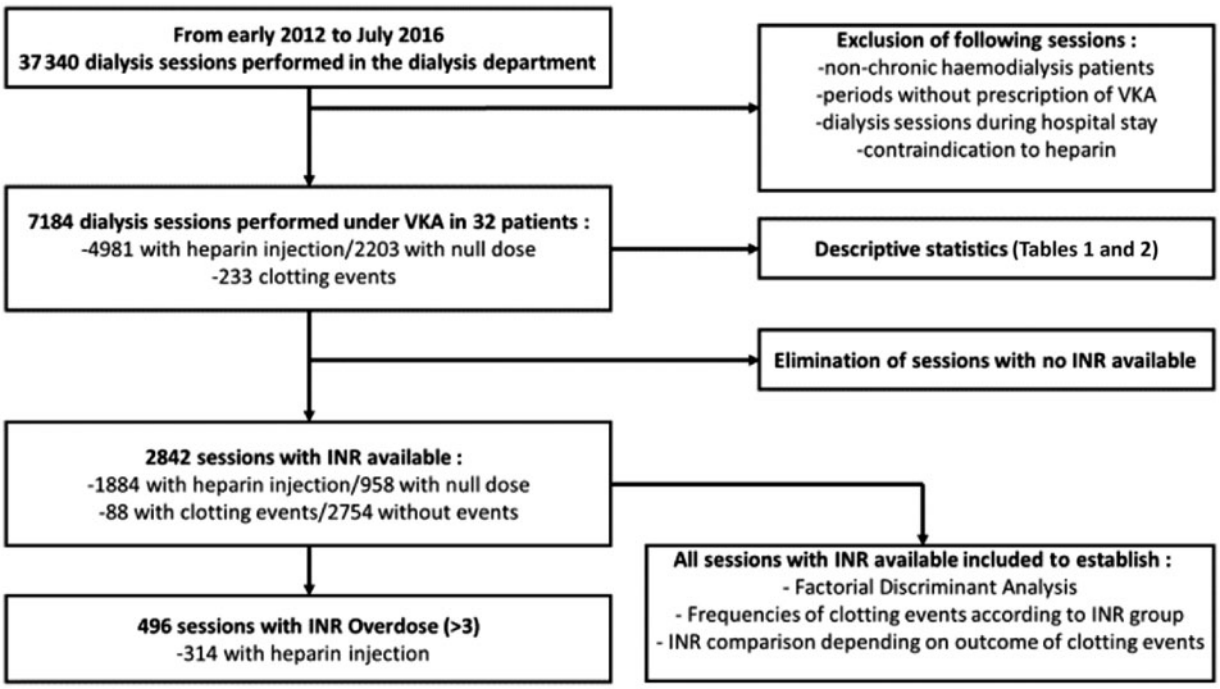

FIGURE 1: Inclusion process of dialysis sessions performed under VKA and analysis conducted according to the availability of INR.

Table 1. Clinical characteristics of chronic dialysis patients under VKA

Variables	Total ($n = 32$)
Sex female/male, *n*/*n*	19/13
Age (years), mean ± SD	72.3 ± 11.5
Type of nephropathy, *n* (%)	
Vascular nephropathy	7 (21.9)
Autosomic dominant polycystic	4 (12.5)
Glomerulopathy	11 (34.3)
Tubulointerstitial nephropathy	2 (6.3)
Unknown	8 (25.0)
Indication of VKA, *n* (%)	
Atrial fibrillation	22 (68.8)
Venous thromboembolism	7 (21.9)
Catheter dysfunction	1 (3.1)
Arteriopathy	1 (3.1)
Nephrotic syndrome	1 (3.1)

and three on a two-lumen-tunnelled central venous catheter. The main indication of anticoagulation was atrial fibrillation (68.8%).

General characteristics of dialysis sessions

Almost half of the sessions were performed with haemodiafiltration (Table 2). The duration of each dialysis session was almost 4 h, according to recommendations. Mean dose of heparin delivered per session was 1844 units and among the membranes used in our centre at the date of the study, the majority (85%) was polycarbonate with grafted heparin.

Clotting events, INR and heparin administration

Of the 7184 dialysis sessions under VKA, heparin was administered in 69.3% of the cases. In total, 233 clotting events were observed, including 124 total coagulations of circuits and 109 observations of clots in circuits. A total number of 2842 sessions with INR available were then analysed, with 17.5% exceeding the INR value of 3 reflecting an overdose of VKA. An INR was available in 88 sessions with clotting event (40 sessions with clots in circuits, 48 with total occlusions). Given the absence of INR result at the beginning of the dialysis session, the frequencies of injection of heparin were not different according to INR group (Figure 2). However, the frequencies of clotting events were lower as the INR range increased (Figure 2). In the almost 500 sessions with an INR value >3, only one clotting event was observed. Figure 3 represents the difference in mean INR according to the outcome of a clotting event during the current session (Figure 3A) or the next one (Figure 3B). The mean INR during sessions without an event was 2.48 versus 1.81 in sessions with clotting events ($P < 0.001$).

A predictive model of clotting events

Factorial discriminant analysis was performed on the totality of the 2842 sessions where both INR and heparin dosing (possibly null dose in case of non-injection of heparin) were available. Eighty-eight of those sessions were conducted with an outcome of clotting event, while no clotting event was observed in the remaining 2754 sessions. The factorial discriminant analysis was designed as a predictive score for clotting events, based on a linear combination of INR and heparin dosing ($P < 0.001$).

The function is represented as follows:

$$F = -3.7 + 1.66 \times \text{INR} + 0.1 \times \text{heparin dose}$$

where INR is the current value of INR at the beginning of the session, and heparin dose is the total volume of heparin administered (bolus and infusion) in thousands of units of unfractionated heparin.

If $F > 0$, the predicted outcome is the absence of a clotting event.

If $F < 0$, the predicted outcome is a clotting event (total coagulation or clots in the circuit).

With the range of INR (2.0–3.0) and heparin dosing (50 IU/kg + 800–1500 IU/h) usually administered, the term of the function (1.66 × INR) (magnitude of 5) is ∼10 times superior to the term containing the heparin dosing (0.1 × heparin dosing) (magnitude of 0.5), demonstrating the superior efficiency of VKA to protect against clotting events compared with heparin.

The predictive model established by this linear function has an area under the ROC curve (AUC) of 0.781 (Figure 4), and the optimal sensitivity and specificity are, respectively, 80% and 65%.

Considering a null value of the function to switch to one issue or the other, we can report that a value of INR <2.2 could correctly classify 80% of thrombosis issues if no heparin dose is used. In contrast, an INR >2.2 would correctly classify 66% of non-thrombotic events.

The cross-validation gives a sensibility and specificity that are similar, respectively 79% and 65%, indicating the quality of our model.

Of note, among 1602 sessions with an INR >2.2 in our data, heparin injection was performed in 67.1%. Based on our model, these injections could have been avoided.

Table 2. Characteristics of dialysis sessions among chronic patients under VKA

Variables	Total ($n = 32$)
Number sessions (per patient), mean ± SD	225 ± 239
Number sessions (per patient and per week), mean ± SD	2.9 ± 1
Duration of each session (min), mean ± SD	231 ± 23
Heparin delivered per session (units), mean ± SD	1844 ± 1950
Blood flow rate (mL/min), mean ± SD	301 ± 33
Dialysis method, *n* (%)	
Haemodiafiltration	3505 (48.8)
Standard haemodialysis	2700 (37.6)
Acetate-free biofiltration	979 (13.6)
Dialysis membrane, *n* (%)	
Polycarbonate with grafted heparin	6107 (85)
Polysulphone	585 (8.1)
Polymethylmethacrylate	275 (3.9)
Other	217 (3)

Comparison depending on the vascular access

The characteristics of the dialysis sessions according to the vascular access are presented in Table 3. No significant difference in the frequencies of clotting event was observed between sessions with catheter and arteriovenous fistula. This fact was noted, even if a tendency to a lower dose of heparin and a significantly lower blood flow rate were found in patients with catheter.

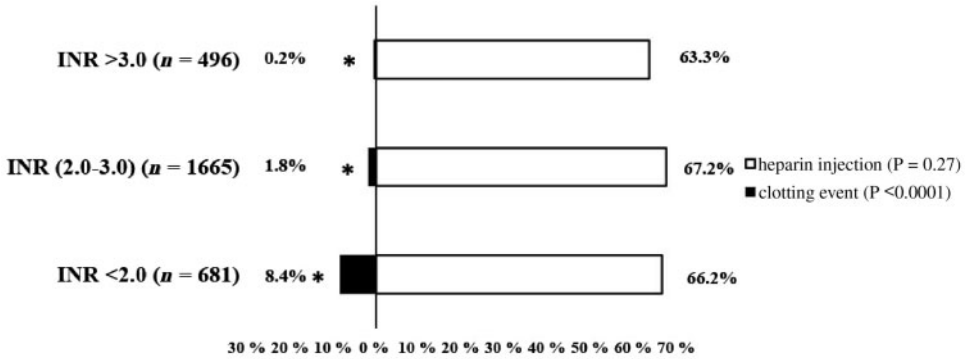

FIGURE 2: Frequencies of heparin injection and clotting events according to INR range. *P < 0.05 sessions with INR <2.0 versus INR 2.0–3.0 or INR >3.0, and sessions with INR 2.0–3.0 versus INR >3.0.

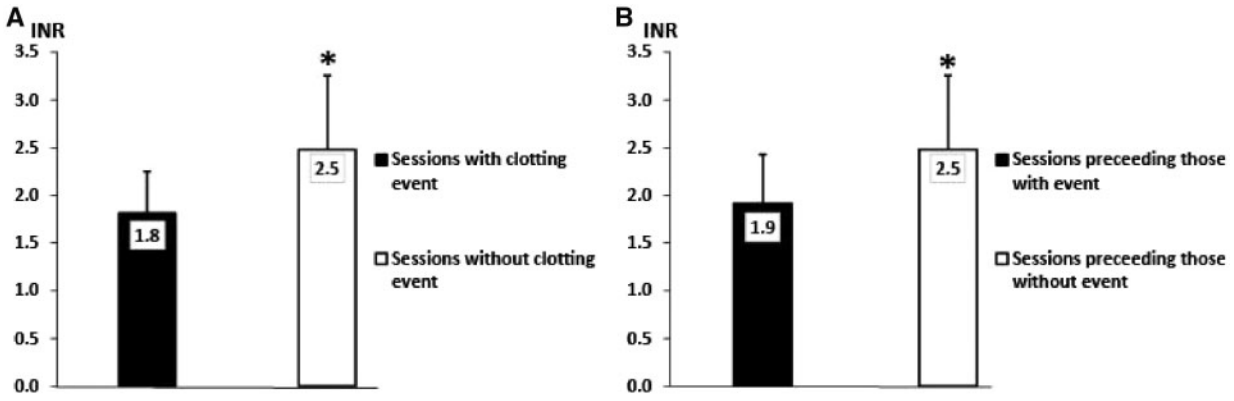

FIGURE 3: Comparisons of mean INR according to the outcome of clotting or not. (**A**) Sessions with clotting event versus sessions without clotting event; (**B**) according to the outcome of the sessions that immediately followed those with INR measurement. *P < 0.001.

DISCUSSION

Our study raises the question of heparinization during haemodialysis in patients already treated by oral anticoagulation. Our data demonstrate the impact of INR value on the risk of clotting events, with a lower effect of heparin, which not seems to be necessary, for circumstances when INR is >2.2. This work also offers a model fir prediction of a clotting event for a given INR value and heparin dose. Although limiting the risk of bleeding in haemodialysis patients under VKA remains a crucial issue, little research has investigated the question of the need for heparinization during dialysis. In this regard, the study of Krummel *et al.* [19] is of particular interest. In their prospective work, they found that heparin-free haemodialysis could be performed, provided that the oral anticoagulation was adequate (INR 2.2–2.77), while no additional benefit was found with heparin grafted membrane. In our study, we found that the higher the INR value, the lower the risk of clotting events. This finding is also supported by the discriminant analysis, as an INR of 2.2 (without heparin) could be considered as a threshold that can predict 80% of thrombosis events if the current INR is lower than this value. This notion is fully consistent with the results of Krummel *et al.*, as the lower limit of the range found in their work (2.2) is identical to our threshold. Interestingly, we also noted that for patients with clotting events, the mean INR in the previous haemodialysis session was also lower than the mean INR prior to sessions without event. This may reflect that, despite an adaptation of VKA dose (during an under-dosage for example), a delay of correction might be responsible for a clotting event the following session. In the study of Krummel *et al.*, they also observed a low rate of sessions that ended prematurely, as they ensured during the session preceding the study that patients had an INR within the target range (2.0–3.0). Given the retrospective nature of our study, it has been possible to study an extended period, which allowed us to identify a large number of dialysis sessions and thereby clotting events, especially total occlusion of dialysis circuits.

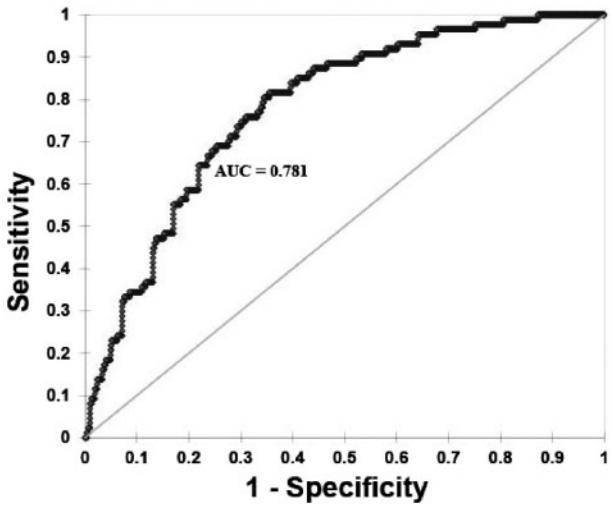

FIGURE 4: ROCs curve for the model designed by the factorial discriminant analysis. The grey diagonal lines indicate the area of 0.500, corresponding to no informative discrimination.

An unrecognized finding is this work was the marginal impact of heparin on clotting events in opposition to VKA. First, due to the lack of awareness of INR value before each session, there was no difference in heparin administration according to INR group, while we observed a difference in outcome of clotting events. Secondly, as evidenced by discriminant analysis, the term containing heparin dosing was of lower value than the one including INR value. However, these findings must be compared with those of Ziai *et al.* [20]. In their study, 10 dialysed patients under oral anticoagulation were randomized to either no additional anticoagulation or to additional low-dose dalteparin (40 IU/kg body weight). The authors underline that an oral anticoagulation with a median INR of 2.2 was not sufficient to prevent clotting during haemodialysis. Two main reasons could explain the differences between our results. First, we reported a larger number of sessions, particularly those involving total occlusions of dialysis circuit. Secondly, the Ziai *et al.* study used low-permeability membranes, which are potentially more prone to activate coagulation [25], while we used mainly high-permeability membranes. Despite this difference, their work also notes that heparin could be reduced during dialysis while patients were already under VKA. This notion does not completely contradict our result; based on our model, the lower the INR value, the higher the dose of heparin that is needed. Thus, we can also consider the anticoagulation needed as a continuous digital variable, rather than a binary one (absence/presence). A sufficiently high INR makes it possible to avoid the use of heparin during dialysis sessions. Conversely, based on our function, an INR <2.2 will require the use of heparin, the dosing of which depends on the INR value. The minimal dosing of heparin (Hep) is given by the following formula: Hep = 37 – 16.66 × INR (in thousands of units of unfractionated heparin). Our model has a satisfactory ROC curve (0.781). Furthermore, sensitivity and specificity were similar after cross-validation, demonstrating reliability. One reason for the lower impact of heparin than VKA might be the type of dialysis membranes used in our department. In our study, most of the membranes (85%) used are impregnated with heparin on their surface (grafted membranes). This fact could minimize the impact of heparin in the risk of clotting, as the injected heparin might play a marginal role that is weak compared with to the heparin grafted on the membranes. However, the effectiveness of these

Table 3. Characteristics of dialysis sessions according to vascular access

Variables	Arteriovenous fistula	Catheter	P-value
Total dialysis session, *n* (%)	6607 (92)	577 (8)	
Clotting event, *n*	211	22	
Frequency of clotting (%)	3.2	3.8	0.45
Total coagulation, *n*	114	10	
Clots in circuit, *n*	97	12	
Heparin delivered per session (units), mean ± SD	1854 ± 2000	1715 ± 1300	0.054
Blood flow rate (mL/min), mean ± SD	306 ± 27	272 ± 43	<0.001

grafted membranes in patients under VKA is not universal, as we see from the study of Krummel *et al.* [19]. In their study, no benefit was found regarding the effect of membranes with grafted heparin on the risk of clotting while patients were already under VKA. Interestingly, Sagedal *et al.* [26] demonstrated that, in spite of clinically effective anticoagulation obtained by heparin during haemodialysis, a potentially thrombophilic state persisted, with an impact of warfarin on both clinical clot formation and activation of coagulation, as evidenced by biomarkers. In their study, the increase in prothrombin fragment and thrombin–antithrombin complex, which are correlated to clotting events, was lower with VKA compared with dalteparin. This finding suggests that VKA could overcome the anticoagulation induced by only heparin.

Our work also points out that despite a lower blood flow rate in sessions with a catheter, which is usually more prone to generate clots in the extracorporeal circuit [27], the frequency of clotting event was not different than in patients with an arteriovenous fistula. This notion is of particular interest, as this may suggest that VKA could protect against clotting events, irrespective of the vascular access used.

Despite the fact that this study provided interesting results, it suffers from several limitations.

First, the multivariate analysis was based on retrospective sessions. This fact can be justified by the frequency of clotting events (3.2% in our series), which remains a relatively rare event. However, it cannot be excluded that the close monitoring of INR value (on a weekly basis) may have decreased the frequency of under-dosage and consequently affected the outcome of clotting events. As a result, the total number of clotting events did not allow us to test the efficiency of the predictive function for new patients, even if the cross-validation shows a good reliability of our model.

Secondly, our model shows good performance: the AUC is 0.78 (between 0.7 and 0.87), but not high enough to be classified as discriminating (AUC >0.87). This is most likely because the presence of clots in the dialysis circuit is not only due to the degree of anticoagulation. Several others mechanisms also contribute to the risk of clotting events, such as inflammation, blood flow and the quality of the vascular access. Hence, this model reminds the clinician not to omit that the clotting circuit is a multifactorial occurrence, which requires assessing all of the risk factors. In this sense, our model must be considered a simplified tool to help in promptly evaluating the risk of clotting events and should not replace the global evaluation of the clinician. However, by using this predictive function with only two adjustable factors, its application is simplified and makes it usable in many chronic haemodialysis patients under VKA.

Thirdly, our approach was based exclusively on clotting events, without taking into consideration possible haemorrhagic complications. Avoiding heparin anticoagulation when not needed might minimize bleeding events among chronic dialysis patients under VKA. It also would have been interesting to analyse bleeding events in this study.

Fourthly, unlike previous studies [19, 20] and given the retrospective characteristics of our study, we did not use a visual scale of clotting to grade more precisely the clot formation. Moreover, we did not analyse blood coagulation markers, such as D-dimers, fibrin monomers, antithrombin or fibrinogen.

Finally, a remaining problem is obtaining the INR value at the beginning of each session to adjust the heparin dose. Mostly, the INR value is not available at the beginning of the dialysis session because assays are frequently performed in the central laboratory and an set amount of time is needed for this. This fact is even more important considering the high frequency of heparin administration in situations of overdose in VKA in our study. A possible solution could be the use of point-of-care INR, which has previously been considered in dialysis patients [28]. This device allows a rapid evaluation (a few minutes) of the INR value. Its use at the beginning of each dialysis session could provide heparin dose adjustments. Nevertheless, based on our work, obtaining an INR value by classical methods would still disrupt the heparin initiated previously during the session, provided the value is >2.2.

CONCLUSION

Our study shows a significant impact of INR on the risk of clotting circuits in dialysis patients treated by VKA. We also established a predictive model of thrombosis risk for dialysis circuits in patients treated by VKA for a given heparin dose and a given INR. This model shows a low marginal contribution of heparin to protect against the risk of thrombosis compared with VKA, which does not appear necessary in sessions with an INR >2.2. Heparin may even increase the haemorrhagic risk, particularly in cases of unknown overdose in VKA. Point-of-care INR may represent an alternative solution to address this risk, but additional work is needed to confirm an interest in this device to prevent the use of heparin in this situation.

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AUTHORS' CONTRIBUTIONS

All of the authors fulfil the authorship criteria. P.-Y.C. and T.T. contributed to the study design and performed study follow-up. P.-Y.C. was responsible for data collection. H.G. was responsible for data analysis. P.-Y.C. and H.G. contributed to data interpretation. P.-Y.C., T.T., Y.L.M. and H.G. were responsible for drafting the manuscript. P.-Y.C., T.T., Y.L.M. and H.G. contributed to revising manuscript content. P.-Y.C., Y.L.M., T.T. and H.G. were responsible for approving the final version of the manuscript. P.-Y.C. and H.G. took responsibility for the integrity of the data analysis.

CONFLICT OF INTEREST STATEMENT

None declared.

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