The Occurrence of Re-elevated INR During Hospitalization Following Reversal of Phenprocoumon with Prothrombin Complex Concentrate (PCC) and/or Phytomenadione: A Retrospective Study

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Abstract

Background: The long half-life of the oral vitamin K antagonist (VKA) phenprocoumon (72-720 h) presents challenges in managing anticoagulation, particularly during reversal with prothrombin complex concentrate (PCC) and/or phytomenadione. This study investigates the incidence of International Normalized Ratio (INR) re-elevation 48 hours post-reversal and identifies factors influencing this outcome.

Methods: We conducted a retrospective observational study on hospitalized patients receiving phenprocoumon, reversed with PCC and/or phytomenadione at the Dutch hospital Spaarne Gasthuis. Cox proportional hazards models were used to assess differences between patients with an INR ≥ 6 and < 6 at admission, as well as between patients in surgical versus non-surgical departments. A multivariate logistic regression analysis was performed to evaluate the contributions of various factors to the risk of re-elevated INR.

Results: Of the 2972 admissions, 498 were included in the final analysis. Re-elevated INR was observed in 86/498 (17.3%) of the study population. Re-elevated INR was particularly noted in patients with an INR at admission ≥ 6 (37.5% vs. 10.8%, $p < 0.01$), and those in non-surgical departments (11.2% vs. 6.0%, $p < 0.01$).

Conclusion: Our present study emphasizes that patients with an INR ≥ 6 upon admission or those treated in non-surgical departments face a higher risk of INR re-elevation 48 hours after reversal. Timely administration of additional doses of PCC or phytomenadione is essential to prevent this INR re-elevation and minimize the risk of potential (re)bleeding.

Introduction

Oral anticoagulation with vitamin K antagonists (VKAs) have been widely used for the prevention and treatment of thrombotic complications including atrial fibrillation and venous thromboembolism. They act by inhibiting the synthesis of functional vitamin K-dependent coagulation factors FII, FVII, FIX and FX (1,2). The intensity and quality of anticoagulation is monitored through the measurement of the International Normalized Ratio (INR). Target INR ranges, usually between 2.0 and 3.5, are adjusted according to the specific condition (3). The risk of bleeding increases when the INR exceeds this target range (4,5). The narrow therapeutic window and inter- and intra-individual variability in dosage response of VKAs presents substantial management challenges, especially in the context of bleeding or unplanned surgical procedures (2). In such circumstances reversal of VKAs is necessary to stop or prevent bleeding. Acute interventions to reverse the coagulopathy and lower the INR include administration of phytomenadione (vitamin K) and prothrombin complex concentrate (PCC) (6). PCC provides a rapid and efficient method to restore deficient clotting factors and normalize the INR. In contrast, phytomenadione induces a more slowly decrease of the INR. The maximal effect of vitamin K-dependent clotting factors is observed after 12 to 24 hours, as they must undergo carboxylation in the liver before becoming fully active (7,8). PCC (Cofact®) consists of the vitamin K-dependent clotting factors II, VII, IX, and X, as well as protein C and S. Among these, factor VII is the factor with the shortest half-life of 4 to 6 hours (9,10). As a result, the activity of PCC starts to diminish after 6 hours (11). The half-lives of the other coagulation factors, shown in table 1, are also significantly shorter compared to the half-life of phenprocoumon, which ranges from 72 to 720 hours (10).

Table 1: Half-life of the substances in Prothrombin Complex Concentrate (PCC) (9,10)

Substance	**Half-life**
Factor II	40-60 hours
Factor VII	4-6 hours
Factor IX	18-25 hours
Factor X	30-60 hours
Proteïn C	49.6 hours
Proteïn S	50.4 hours

VKAs with a long half-life, such as phenprocoumon provide greater stability of the INR and a higher proportion of INR measurements within the therapeutic range compared with the VKAs warfarin and acenocoumarol, which have half-lives of 36-42 and 8-10 h, respectively (12,13). However, the longer half-life of phenprocoumon is a disadvantage in the case of over-coagulation (12).

The RADOA study has highlighted that patients admitted to the hospital for acute bleeding or emergency surgery often exhibit intense VKA activity, with drug half-lives extending beyond five days (7). This prolonged action may result in the INR rising again over time despite reversal with phytomenadione and PCC, potentially leading to a recurrent bleeding event in some cases (6).

Numerous studies have reported INR rebound rates for VKAs, with estimates ranging from 18% to 36% (8,14–16). However, these studies often involved small populations and predominantly focused on warfarin. Our study aims to fill this gap by investigating the incidence of INR rebound in hospitalized patients using phenprocoumon. Given phenprocoumon's considerably longer half-life compared to warfarin, the likelihood of INR rebound is expected to be higher (12). Additionally, most studies regarding the reversal of phenprocoumon and its monitoring have been conducted in a prospective setting. These studies mainly evaluate the effectiveness and safety of PCC in reversing phenprocoumon, with INR being monitored (11,17). A retrospective study is valuable as it reflects real-world clinical setting and includes a larger, more diverse population. Preventing repeated elevation of INR after reversal of phenprocoumon by early and intensified INR monitoring allows for additional doses of PCC or phytomenadione to be administered when the target INR is not achieved. This critical phase in monitoring contributes to improving anticoagulation management in clinical practice and helps prevent complications such as bleeding (18).

The aim of this study was to determine the prevalence of re-elevated INR values 48 hours after reversal treatment with PCC and/or phytomenadione in hospitalized patients using phenprocoumon as an oral anticoagulant, and to analyze the factors that may play a role in the occurrence of a re-elevated INR after reversal.

Methods

Study design and patients

This retrospective observational study was performed at Spaarne Gasthuis (formerly Kennemer Gasthuis and Spaarne Hospital). The merger took place on March 22, 2015. The database consists of patients from Spaarne Hospital in the time period January 2009 until March 2015 and from Spaarne Gasthuis in the time period March 2015 until January 2024. Permission for the data extraction was given by the Advisory Committee for Local Feasibility (ACLU) and informed consent was not required given the retrospective study design.

The study cohort consisted of all patients older than 18 years admitted to the Spaarne Gasthuis within the specified time period who used phenprocoumon as an oral anticoagulant before admission and received at least one dose of phytomenadione (oral or intravenous) and/or PCC. The cohort was stratified into two groups, surgical and non-surgical. This stratification was based on the department where the patient was admitted during hospitalization, and it was necessary due to the application of different cutoff values for elevated INR in surgical and non-surgical patients. For the non-surgical group, an elevated INR is considered as higher than 2, while for the surgical group, it is higher than 3.5, 48 hours after reversal. Within each department group, patients were further categorized based on the method of phenprocoumon reversal therapy, PCC and phytomenadione, PCC only, or phytomenadione only.

Patients were reversed depending on the severity of bleeding or the nature of the procedure based on the Spaarne Gasthuis protocols for coagulation and bridging around surgeries. The Spaarne Gasthuis uses the Hospital Information System Epic, data for the analyses were obtained from this system. The following data were collected: demographic information, admission and discharge data, medication order data of PCC (Cofact ®) and phytomenadione (dosage, route of administration, administration date and time, MTR status) and the measured INR value(s) with the corresponding date and time. The INR measurements included in the dataset are the INR prior to administration of phytomenadione or PCC, the first INR after reversal and the lowest INR within 48 hours after reversal. Additionally, INR measurements taken 48 hours after reversal include the highest INR value and the first INR values higher than 2 and 3.5.

The follow-up period of the patients is defined as the time from the initial administration of phytomenadione or PCC until the occurrence of one of the following events, in the specified order: an elevated INR 48 hours after administration of PCC or phytomenadione, restart of phenprocoumon and discharge from the hospital or death.

Patients who never achieved an INR of 2 or lower within 48 hours after reversal with phytomenadione or PCC were excluded from the analyses to prevent incorrect inclusion in the group of patients with re-elevated INR post-reversal. In addition, patients whose department was unknown, those with a follow-up of less than 48 hours, or those without an INR measurement 48 hours after reversal were excluded from the analyses.

Outcomes

The primary outcome assesses the frequency of re-elevated INR 48 hours after the reversal of phenprocoumon with PCC and/or phytomenadione, expressed as percentages. As secondary outcomes, this study investigates the influence of various factors contributing to re-elevated INR following reversal. Specifically, exploratory endpoints will characterize the relationships between department type (surgical/non-surgical) and the frequency of re-elevated INR, as well as the reversal method used (PCC, phytomenadione, or a combination of both). Additionally, we will evaluate how age, gender, total dosages of PCC and phytomenadione, and the number of INR measurements within 48 hours post-reversal affect the likelihood of experiencing a re-elevated INR. Finally, we will examine the impact of baseline INR at admission on the incidence of re-elevated INR after reversal, comparing the frequency of elevated INR between two cohorts stratified by baseline INR (INR < 6 and INR ≥ 6). By analyzing these factors, the study aims to provide a comprehensive understanding of the dynamics influencing re-elevated INR levels after reversal in phenprocoumon users.

Statistical Analysis

For the primary and secondary endpoints, frequencies, means, and standard deviations will be calculated using descriptive statistics. Frequencies will be expressed as percentages, and continuous variables will be presented as the mean with the standard deviation. The frequencies (in percentages) and mean values were compared with the independent sample t-test or the chi-squared test to evaluate the statistical significance. The time to achieve the endpoint (re-elevated INR after reversal) will be presented for both the surgical and non-surgical groups using Kaplan-Meier curves. Furthermore, Kaplan-Meier curves will be used to compare the difference in achieving the endpoint between the group with an INR > 6 and the group with an INR < 6 at admission, combining both surgical and non-surgical groups. The endpoint is considered reached if the INR re-increases after 48 hours.

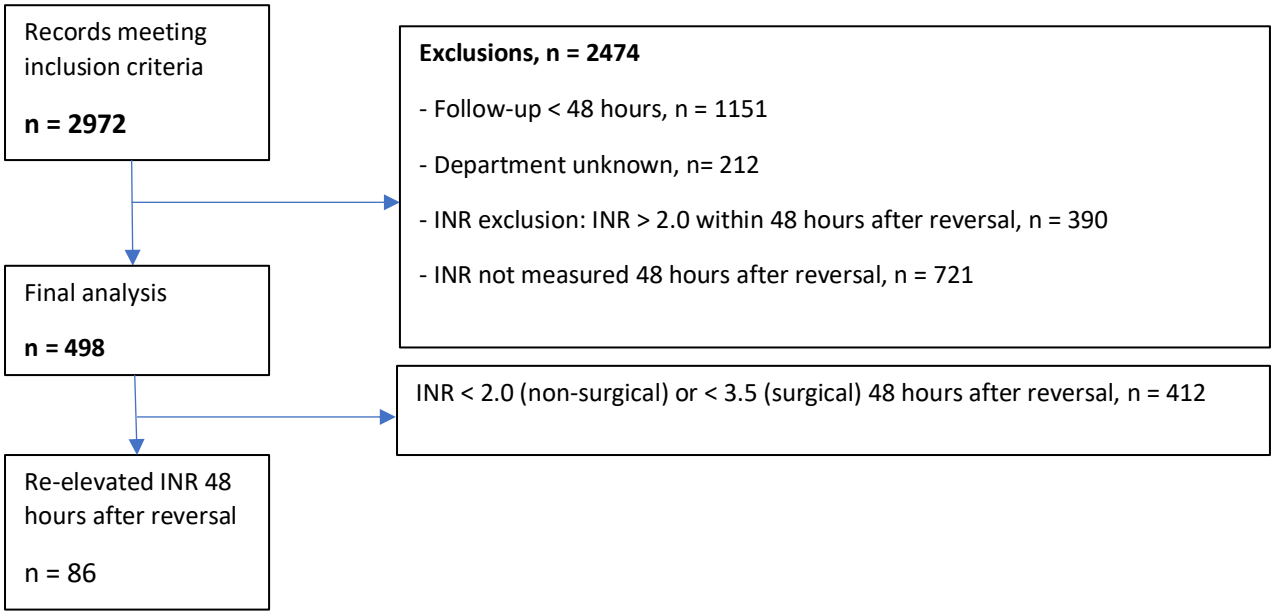
The Cox proportional hazards model is used to compare the Kaplan-Meier survival curves and calculate the hazard ratio (HR) to quantify the difference in risk of reaching a re-elevated INR between the two groups. A multivariate logistic regression was used to explore the relationship between the occurrence of re-elevated INR and potential determinants including age, gender, the number of INR measurements within 48 hours, the total phytomenadione dosage (in mg) within 48 hours and the total PCC dosage (in IE/kg) within 48 hours. All analyses were considered statistically significant with a p-value < 0.05. Analyses were conducted in R using RStudio (version 4.2.2).

Results

Patient demographics

A total of 2972 received PCC and/or phytomenadione for the reversal of phenprocoumon during the specified time period. After exclusion, 498 were included in the final analysis (Figure 1). Patient demographics are summarized in Table 1. The mean follow-up time was 200 hours (± 167), and the mean age was 79 years (± 9). The most common department for patient admissions was the non-surgical department (56.6%), and the most prevalent method of reversing phenprocoumon was with phytomenadione (70.4% in the surgical department and 52.1% in the non-surgical department).

Figure 1: Records included in final analysis and the reasons for exclusions



The INR was measured on average 2.36 times after reversal in the surgical (± 1.22) and non-surgical (± 1.10) group. The mean INR measured after phenprocoumon was reversed (1.4) was significantly lower than the mean INR measured on admission (4.9, $p < 0.01$) in the entire study population. Although patients in the non-surgical group presented slightly higher INR values at admission compared to patients in the surgical group, no significant differences between both groups were found ($p = 0.07$).

Table 1 Baseline characteristics of the study population

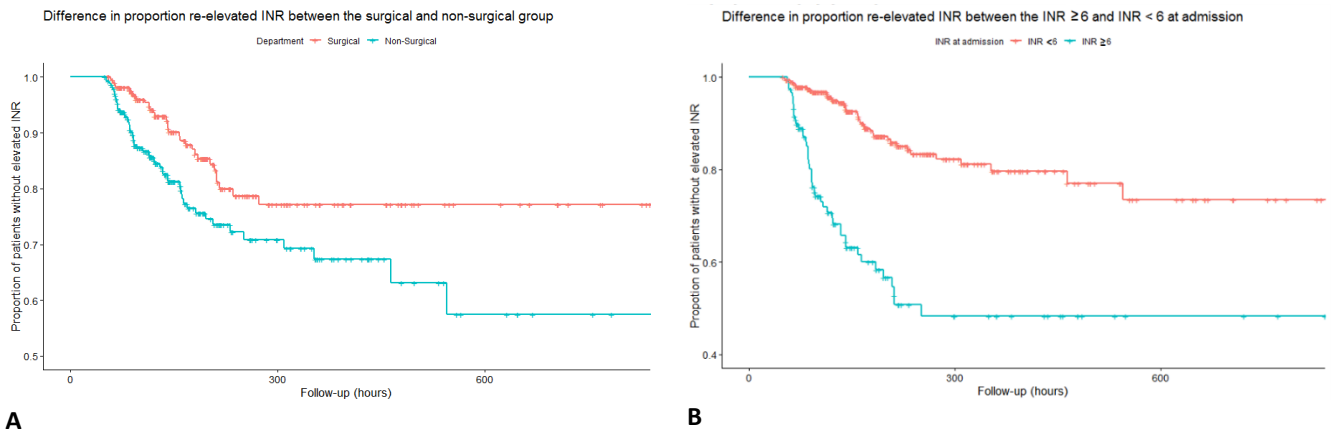
Characteristic (mean ± SD) ***n (%)***	*Total* *n = 498*	*Surgical* *n = 216 (43.4%)*	*Non-surgical* *n = 282 (56.6%)*
Age (years)	79 ± 9	78.9 ± 9.5	79.3 ± 8.8
Weight (kg)	77.8 ± 16.5	77.2 ± 17.6	78.4 ± 15.8
INR on admission	4.9 ± 3.1	4.6 ± 3.0	5.1 ± 3.2
Lowest INR after reversal	1.4 ± 0.3	1.5 ± 0.2	1.4 ± 0.3
Highest INR 48 h after reversal	2.1 ± 2.0	2.3 ± 2.2	2.0 ± 1.9
Gender (n (%))			
Female	217 (43.6%)	102	115
Male	281 (56.4%)	114	167
Phytomenadione (mg)*	13.7 ± 10.1	14.8 ± 10.8	12.9 ± 9.4
Reversal used ***n (%)***	***Total*** ***n = 498***	***Surgical*** ***n = 216 (43.4%***	***Non-surgical*** ***n = 282 (56.6%)***
Phytomenadione + PCC	158 (31.7%)	50 (23.1%)	108 (38.3%)
PCC	41 (8.2%)	14 (6.5%)	27 (9.6%)
Phytomenadione	299 (60.0%)	152 (70.4%)	147 (52.1%)

*INR = Internal Normalized Ratio, PCC = prothrombin complex concentrate, *total dosage within 48 hours after reversal*

Incidence of re-elevated INR

The incidence of re-elevated INR 48 hours after reversal of phenprocoumon with PCC and/or phytomenadione was assessed as the primary endpoint in this study. Overall, re-elevated INR occurred in 86 admissions, which represents 17.3% of the entire study population. In these 86 admissions, the measured INR 48 hours after reversal was on average 5.5 (± 3.0).

Fig. 2: Kaplan Meier curves



A **B**

INR = International Normalized Ratio

Factors associated with re-elevated INR

Kaplan-Meier curves were generated to provide a visual representation of the time to re-elevation of the INR 48 hours after reversal of patients in the surgical and the non-surgical department (Fig. 2A). The comparison between the surgical and non-surgical groups using the Cox proportional hazards model estimated a HR of 1.85 (95% CI: 1.19-2.89, $p < 0.01$). This analysis revealed that patients in the non-surgical group had a statistically significant higher risk (11.2% vs. 6.0%) of reaching the endpoint compared to those in the surgical group.

To investigate whether the used reversal method affects reaching the endpoint, we compared the different reversal treatments within the surgical and non-surgical groups (Table 2). Patients treated with phytomenadione alone experienced significantly fewer re-elevations of INR compared to those treated with phytomenadione and PCC (11.2% vs. 26.0%, $p = 0.01$). Conversely, in the non-surgical group, there were no statistically significant differences in the percentages of re-elevated INR between the different reversal methods.

Table 2: Mean baseline INR and percentages of re-elevated INR within the surgical and non-surgical department per reversal method

Department (n)	Reversal used (n)	Baseline INR (mean ± SD)	p-value	Re-elevated INR 48 hours after reversal n (%)	p-value
Surgical (216)	Phytomenadione + PCC (50)	5.8 ± 3.8	Ref.	13 (26%)	Ref.
	PCC (14)	2.8 ± 1.0	0.002*	0 (0%)	0.98
	Phytomenadione (152)	4.4 ± 2.7	0.008*	17 (11.2%)	0.01*
Non-surgical (282)	Phytomenadione + PCC (108)	5.1 ± 3.2	Ref.	21 (19.4%)	Ref.
	PCC (27)	3.8 ± 2.4	0.07	3 (11.1%)	0.32
	Phytomenadione (147)	5.4 ± 3.4	0.39	32 (21.8%)	0.65

*INR = International Normalized Ratio, PCC = prothrombin complex concentrate, * significant difference compared to reference*

A multivariate logistic regression was conducted to examine the relationship between the likelihood of re-elevated INR and several predictors: age, gender, the number of INR measurements within 48 hours, the total phytomenadione dosage (in mg) within 48 hours and the total PCC dosage (in IE/kg) within 48 hours. None of these predictors were found to be statistically significant.

Kaplan-Meier curves were generated to provide a visual representation of the time to re-elevation of the INR 48 hours after reversal of patients with an INR < 6 and those with INR ≥ 6 at admission (Fig. 2B). A statistically significant difference between the two groups was found. In the INR < 6 group 41/378 (10.8%) events (re-elevation of INR) were observed compared to 45/120 (37.5%) events in the INR ≥ 6 group ($p < 0.01$). The HR was 4.1 (95% CI: 2.72-6.34), indicating that patients with an INR of 6 or higher at admission had a 4.1 times higher risk of reaching the endpoint compared to those with an INR below 6 at admission. Of the 120 patients in the INR ≥ 6 group, 43 were in the surgical group and 77 in the non-surgical group. The mean baseline INR was 9.4 in the INR ≥ 6 group and 3.2 the INR < 6 group.

Within each of the two groups (INR < 6 and INR ≥ 6), further analysis was conducted to assess the influence of the baseline INR on the percentage of patients with a re-elevated INR 48 hours after reversal among the three different reversal treatments (Table 3). The difference in the re-elevated INR percentage was only significant in the group with a baseline INR < 6 when comparing PCC reversal treatment with the combination treatment (0% vs. 13.6%, $p = 0.04$).

Table 3: Mean baseline INR and percentages of re-elevated INR within the baseline INR ≥ 6 and < 6 group per reversal method

Baseline INR (n)	**Reversal used (n)**	**Baseline INR (mean ± SD)**	**p-value**	**Re-elevated INR 48 hours after reversal n (%)**	**p-value**
INR ≥ 6 (120)	Phytomenadione + PCC (40)	10.0 ± 2.2	Ref.	18 (45%)	Ref.
	PCC (3)	9.1 ± 2.2	0.50	3 (100%)	0.22
	Phytomenadione (77)	9.1 ± 2.8	0.03*	24 (31.1%)	0.20
INR < 6 (378)	Phytomenadione + PCC (118)	2.9 ± 1.6	Ref.	16 (13.6%)	Ref.
	PCC (38)	2.7 ± 1.5	0.36	0	0.04*
	Phytomenadione (222)	2.6 ± 1.3	0.28	25 (11.3%)	0.66

*INR = International Normalized Ratio, PCC = prothrombin complex concentrate, * significant difference compared to reference*

Discussion

The primary endpoint of our study was to determine the incidence of re-elevated INR during hospitalization following phenprocoumon reversal using prothrombin complex concentrate (PCC) and/or phytomenadione. Our data indicate that 17.3% of phenprocoumon-treated patients experienced re-elevated INR after reversal. Patients with an INR of 6 or higher at admission and those admitted to non-surgical departments were at higher risk. The measured INR was on average 5.5 (± 3.0) in the 86 (17.3%) admissions where the INR was re-elevated 48 hours after reversal. This indicates that in this group of patients, the risk of bleeding is significantly increased. Though bleeding is not always associated solely with high INR values and also depends on patient-specific characteristics, several studies have shown that the risk of bleeding becomes exponential for INR values greater than 4.5 (5,19,20).

The incidence of INR elevation after 48 hours post-reversal was significantly higher in the non-surgical group compared to the surgical group (11.2% vs. 6.0%, $p < 0.01$). A retrospective study ($n = 82$) also observed a trend on increasing INR after reversal of warfarin with PCC in bleeding (non-surgical) patients and patients with a high baseline INR, this trend was not seen in the surgery patients (15). This observation aligns with our findings. Several hypotheses were considered to explain the observed differences between surgical and non-surgical patients in our study. Initially, it was assumed that surgical patients might be more closely monitored after their procedures, potentially accounting for the lower incidence of INR rebound. However, our data showed that both groups had similar monitoring frequencies post-intervention, with a mean number of INR measurements being identical for surgical (2.36 ± 1.22) and non-surgical (2.36 ± 1.10) patients. Further analysis revealed that non-surgical patients presented with a higher baseline INR (mean 5.1 vs. 4.6 in surgical patients; $p = 0.07$). This difference in baseline INR, although not statistically significant, may indicate that non-surgical patients are at a higher risk of experiencing a re-increased INR following reversal. Previous studies have shown that groups experiencing reversal failure or INR rebound after reversal often present with higher INR values. In these studies, reversal failure was defined as an INR ≥ 1.5 after PCC or phytomenadione administration and INR rebound as an INR ≥ 1.5 within 24 hours after decrease of the INR (6,8,21,22). Moreover, non-surgical patients received a statistically significant lower dosage of phytomenadione compared to surgical patients ($p = 0.04$). Given the role of phytomenadione in facilitating clotting factor synthesis, this could contribute to more effective long-term reversal and prevention of re-elevated INR in the surgical patients 48 hours after reversal (16). This suggests a need for intensified long-term reversal treatment in the non-surgical group. One potential approach could be to increase the dosage of phytomenadione. Alternatively, administering an additional small dose of phytomenadione on the second day could

also be considered (6). Another plausible explanation is that non-surgical patients require hospitalization for medical reasons rather than surgical procedures, such as treatment for an infection. Panneerselvam et al. investigated the risk factors for over-anticoagulation with the VKA warfarin. They demonstrated that intercurrent illnesses, such as infections, particularly when antibiotics are prescribed, significantly increased the risk of elevated INR compared to the control group (23). This finding supports our hypothesis and could correlate with the higher incidence of the re-elevated INR in the non-surgical group. However, it should be noted that if a lower threshold value (<3.5) had been chosen for defining a re-elevated INR in the surgical group, the percentage of patients with a re-elevated INR might have been higher, thereby potentially reducing the difference between the surgical and non-surgical department.

Finally, it is important to recognize that the older population in our study likely experienced a reduced intake of vitamin K upon admission, possibly due to decreased food intake due to illness or diarrhea (24,25). Studies on warfarin have identified factors such as malnutrition, diarrhea, and malignancy as influencing INR levels (24,26,27). These factors may also contribute to the increases in INR after reversal observed in our study.

We also compared the different reversal treatments within the non-surgical group and the surgical group, but the substantial differences between the reversal treatment groups and the presence of other unknown risk factors in our population, combined with the retrospective nature of our study, prevent us from drawing definitive conclusions about the differences in the percentage of re-elevated INR between the treatment groups based on the available data.

Interestingly, the incidence of INR rebound is 0% in the group baseline INR < 6 treated solely with PCC, which is unexpected given the short half-life of PCC compared to phenprocoumon (10,11,16). As highlighted by Yasaka et al., PCC administration without phytomenadione resulted in a rapid decrease of INR but a subsequent re-increase of INR 12–24 hours after PCC administration in 2 out of 17 patients, one of whom developed an enlargement of an intracerebral hematoma (16). This finding was also seen in two other studies (8,11). In the study by Vigue et al., all patients who received phytomenadione and PCC maintained normal coagulation throughout the study. By contrast, a re-increase in INR values was observed in the five patients for whom oral phytomenadione had been omitted (11). In the study by Sin et al., among patients on warfarin who experienced INR rebound after reversal with 4F-PCC, 57.1% did not receive in parallel phytomenadione (8). Both studies considered an INR re-increase to be significant at a threshold of 1.5 or higher after reversal (8,11). A potential explanation for the unexpectedly low INR rebound in the PCC subgroup is that the baseline INR in the surgical group treated with PCC alone is significantly lower compared to those treated with the combination (2.8 vs. 5.8, p = 0.002). It is likely that,

especially in the surgical group, physicians administered PCC due to its faster action compared to phytomenadione in cases of acute surgical procedures (8,28). Additionally, because the INR at admission in the surgical group was still within the therapeutic range, it is logical that no re-increase was observed after reversal with PCC. A potential direction for future research could involve excluding patients with an admission INR still within the therapeutic range of 2.0-3.5 (29). By focusing only on patients with INR values above the therapeutic range, the study could provide more definitive insights into the risks of re-increased INR values after reversal. This approach would focus on the actual reversal of VKA due to over-anticoagulation rather than minor adjustments for surgery-related purposes.

One of the secondary endpoints of this study compared the percentage of INR elevation after reversal between patients with an INR < 6 and those with an INR ≥ 6 at admission. The results suggest that patients presenting with a higher baseline INR (≥ 6) have a highly significant increased risk (HR = 4.1, $p < 0.01$) of INR rebound following reversal therapy. As Pagano et al. also suggests in a retrospective analysis among patients receiving warfarin, the reversal therapy for hospitalized patients with an INR greater than 9 must be carefully chosen. Due to other comorbidities such as liver disease and concurrent treatments that may prolong the INR, hospitalized patients may not respond to withholding the VKA or administering phytomenadione and PCC as effective as might be expected from studies involving carefully selected patients (30). Therefore, it may be highly beneficial to monitor INR levels earlier and more frequently in patients with a higher baseline INR (≥ 6), given the high percentage (37.1%) of INR re-elevation in this group. Increased monitoring would allow for the timely administration of additional doses of PCC or phytomenadione as necessary, thereby preventing significant INR rebounds and minimizing potential bleeding risks (5,18).

A strength of this study is its retrospective design, which provides a realistic depiction of clinical practice compared to prospective studies where interventions may be altered by the awareness of study protocols. However, this study has several limitations. Firstly, there is a subgroup for which no INR measurement was taken 48 hours after reversal of phenprocoumon. Due to the lack of data, this subgroup was excluded from the analyses. It is possible that some individuals within this group experienced undetected re-elevated INR after the reversal of phenprocoumon, potentially resulting in a higher total percentage of elevated INR than 17.3%. Conversely, this percentage may have been overestimated, as INR measurements might have been selectively performed in patients exhibiting symptoms of bleeding. This subgroup is quite significant, comprising 721 patients. Secondly, we did not differentiate between surgical procedures with high, intermediate, or low bleeding risks when determining cutoff values for the surgical group. We opted for an upper limit (> 3.5), which is applicable to procedures with a low bleeding risk. If data on bleeding risk and type of

procedure were available, we could have applied different cutoff values to more accurately define the endpoint, thereby providing a more nuanced understanding of the percentages of patients reaching the endpoint in the surgical group. The cut-off value of 3.5 might have led to an underestimation of the endpoint achievement in the surgical group. If lower cutoff values were used (e.g., INR < 2.1 or < 1.5), more patients would have reached the endpoint. Conversely, the number of patients reaching the endpoint in the non-surgical group might have been overestimated, as we used the lower limit of the low-intensity therapeutic range. Given that various studies have demonstrated that an INR > 1.5 significantly increases the risk of intracranial hemorrhage (ICH), particularly in an older population, we opted for the lower limit of the low-intensity range (18,29). This decision was also influenced by the possibility that some non-surgical patients may have already been admitted due to bleeding, necessitating a lower cutoff value than the upper limit. Although the lower limit of the high-intensity range is not much higher (2.5), using a cutoff value of 3 (the upper limit of the low-intensity range) might have resulted in fewer patients overshooting the INR. Additionally, because this study involves an older population, who are at higher risk of bleeding, it is prudent to use stricter cutoff values (31–33). A limitation here is the lack of data on whether these patients were admitted for bleeding or other reasons. For future research, knowing the reason for admission would be valuable, as different cutoff values for a re-elevated INR could then be applied. We also lack information on concomitant medications, which could influence INR levels (2,19). Future research should consider concomitant medications to account for potential interactions with phenprocoumon that may cause an increase in INR (19,34).

Finally, this study utilized a re-increase in INR as the primary indicator, rather than bleeding events, which may be a more clinically relevant outcome. An elevated INR does not necessarily imply the occurrence of bleeding and conversely, bleeding can occur even with a low INR (19). The RADOA study, which assessed anticoagulation related outcomes in patients treated with phenprocoumon, also identified a significant INR rebound (>1.5) in 27.6% of patients (n = 115) following initial reversal treatment. This rebound was associated with higher bleeding rates (22% vs. 4.2%, p = 0.012) (7). We did not record data on bleeding events in our study, it would be relevant for future research to include this information to better understand the complications resulting from re-elevated INR levels after reversal. Moreover, additional data is required to conclusively determine the risk factors for INR rebound. The review by Palareti et al. analyzed various treatment- and patient-associated risk factors for bleeding during VKA treatment, such as the timing from the initiation of anticoagulation, comorbid conditions, and co-medication (19). Incorporating these risk factors in future analyses could help assess their contribution to INR rebound after phenprocoumon reversal. Additional

prospective comparative research including these clinical details would further validate the findings of this study.

In conclusion, this study, which included 498 patients who underwent phenprocoumon reversal with PCC and/or phytomenadione, found that 86 patients (17.3%) experienced a re-elevation of INR 48 hours after reversal. In this subgroup, the mean measured INR was 5.5. The re-elevated INR particularly occurred in patients with an INR ≥ 6 at admission or those admitted to non-surgical departments. To prevent this INR re-elevation and minimize the risk of potential (re)bleeding, it is crucial to timely administer additional doses of PCC or phytomenadione, thereby maintaining INR reduction and minimizing the risk of INR re-elevation due to the long half-life of phenprocoumon after reversal. Future research should aim to involve larger cohorts and include additional patient-specific risk factors that may influence INR re-elevation after reversal of phenprocoumon. Such studies can aid in the development of more refined reversal protocols for VKAs.

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