Effect of vitamin K administration on rate of warfarin reversal

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BACKGROUND: Vitamin K is reported to begin reversing warfarin within 6 to 12 hours, but this may occur sooner. We sought to determine the rate of international normalized ratio (INR) reversal following vitamin K and relationships with dose, route, and baseline INR.

METHODS: We evaluated adult patients receiving vitamin K monotherapy for warfarin reversal. Post–vitamin K INRs through 48 hours were collected. Relationships between vitamin K dose and route and baseline INR on rate of reversal and complete reversal (INR < 1.5) were evaluated. Assessment was performed graphically using scatter plots with a line of best fit and a counting process model to determine variables associated with achieving complete reversal.

RESULTS: A total of 469 post–vitamin K INRs from 235 patients were included. Time to first INR follow-up after vitamin K administration averaged 10.5 ± 4.2 hours. A significant decrease was detected in INR values in comparison to the baseline INR (3.0 ± 1.9 vs. 4.7 ± 2.2; $p < 0.01$). Rapid and steady INR change began immediately after vitamin K administration (0–4 hr). A high vitamin K dose and intravenous route were associated with rapid INR change and complete reversal (Vitamin K 10 mg [hazard ratio, 2.4; 95% confidence interval, 1.4–4.2] and IV route [hazard ratio, 1.8; 95% confidence interval, 1.3–2.6]); however, overall complete reversal at 24 and 48 hours was low (14.5% and 41.7%, respectively). Higher baseline INR was associated with rapid INR change and lower baseline INR with complete reversal.

CONCLUSION: Vitamin K alone starts to reverse warfarin immediately. High vitamin K doses and intravenous route are associated with faster INR reversal. Baseline INR also influences rate of correction and frequency of achieving complete reversal.

Despite the advent of direct oral anticoagulants, warfarin continues to be the most commonly used anticoagulant worldwide.[1] Warfarin confers its effects by inhibiting vitamin K epoxide reductase and preventing carboxylation of glutamic acid residues on vitamin K–dependent coagulation factors (II, VII, IX, and X) within hepatocytes. Warfarin is commonly reversed by exogenously repleting reduced vitamin K–dependent coagulation factors by fresh frozen plasma transfusion or prothrombin complex concentrate administration with or without vitamin K.[1] The intravenous (IV) route of vitamin K administration is reported to reverse international normalized ratio (INR) faster than the oral route, but the difference appears negligible beyond 24 hours.[2–5] Mixed results have been published regarding the association between vitamin K dose and rate of INR correction.[2,6,7] Baseline INR appears to be an independent variable, which influences post-vitamin K INRs.[2,6]

New studies indicate that vitamin K may begin reversing INR faster than previously described in the literature.[1,7] This has renewed the call for a conservative approach to reversing warfarin that includes reserving blood products or concentrated clotting factors for patients with life-threatening bleeding or a need for immediate surgery.[2,7] Although the effect of

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TABLE 1. Baseline characteristics (n = 235)

Age (y), mean ± SD	70.8 ± 15.2
Male, no. (%)	132 (56)
Weight (kg), mean ± SD	85.1 ± 24.4
Indication for warfarin anticoagulation, no. (%)	
Atrial fibrillation	132 (56)
DVT/PE	56 (24)
Mechanical heart valve	28 (12)
Stroke	4 (2)
Heart failure	4 (2)
Acute coronary syndrome (secondary prevention)	3 (1)
Unknown	8 (3)
Indication for warfarin reversal, no. (%)	
Upcoming/Emergent surgical procedure	98 (42)
Supratherapeutic INR > 4.5	99 (42)
Active bleeding	28 (12)
Unknown	10 (4)
Vitamin K administration	
Dose (mg), median (range)	5 (1–10)
Dose (mg), mean ± SD	5.4 ± 3.0
Dose, no. (%)	
Low (≤2.5 mg)	70 (30)
Medium (2.6–9.9 mg)	106 (45)
High (10 mg)	59 (25)
Route, no. (%)	
Intravenous	115 (49)
Oral	120 (51)

DVT = deep vein thrombosis; INR = international normalized ratio; PE = pulmonary embolism.

vitamin K on INR during warfarin reversal has been elucidated in previously published research, many studies do not record the effect of vitamin K monotherapy on INR within the first few hours of administration or observe complete INR reversal as an endpoint.[2,3,5,6]

The purpose of this study was to characterize the rate of INR correction when vitamin K is used as monotherapy in a cohort of patients with elevated INR requiring warfarin reversal. Additionally, we examined the relationship between vitamin K dose, route, baseline INR, and patient-specific characteristics on the rate of INR reversal and achievement of complete reversal.

MATERIALS AND METHODS

This was a retrospective, observational study of adult patients who received vitamin K for warfarin reversal at a large, academic medical center between January and December 2014. The primary objective was to assess response of INR to vitamin K monotherapy over the first 48 hours. Secondary objectives were to evaluate vitamin K dose, route of administration, baseline INR, and patient characteristics on INR response over time and frequency of achieving complete reversal (INR < 1.5). Approval for this study was obtained from the institutional review board.

Patients were included if they were age 18 years or older, received vitamin K for warfarin reversal and had both a baseline INR (before vitamin K administration) and at least one post–vitamin K INR drawn within 48 hours. Patients were excluded if they received a procoagulant such as fresh frozen plasma, recombinant factor VIIa, three- or four-factor prothrombin complex concentrate or factor IX complex concentrates between baseline and follow-up INR; had a known coagulation disorder (factor deficiencies, lupus anticoagulants, disseminated intravascular coagulation); or had liver dysfunction. Patients who were reversed with vitamin K more than once during the study period had their repeat administration(s) excluded. Patients receiving multiple doses of vitamin K had any INR values recorded after the second administration of vitamin K excluded.

A complete medical record review was conducted by one abstractor using a standardized abstraction tool and data dictionary. Data collection included demographic information, warfarin indication, reversal indication (bleeding, procedure/surgery, high INR), vitamin K dose and route, pre–vitamin K INR and post–vitamin K INR (may be multiple) up to 48 hours, and timing of INR in relation to vitamin K administration. Our laboratory detection limit for INR is up to 8.8; any higher values are reported as greater than 8.8. For the statistical analysis of our data we used 8.8 for any INR values of greater than 8.8.

Descriptive statistics were used to characterize the study sample. Patterns and time-varying trends in the effect of vitamin K dose and route on INR reversal over time were assessed graphically using scatter plots with a line of best fit applied across individual data points (0 to 24 hours and 0 to 48 hours). To test primary associations between dose and route of vitamin K, we modeled whether dose, route, or the interaction between dose and route was associated with complete INR reversal at the time of the first post–vitamin K INR. A logistic regression model was constructed in which each primary independent variable (dose and route), as well as the interaction between dose and route, were entered into the model separately to assess significance. Potential confounding variables including weight and baseline INR level were assessed. Given the nonuniform nature in which the time to INR reversal was collected, traditional time-to-event analyses were not possible. Thus, to assess whether vitamin K dose or route or baseline INR was associated with time to INR reversal, a counting process model was constructed. This is a modification of Cox proportional hazards regression, which accounts for the nonuniform timing of repeat INR assessments across study subjects.

For both the logistic regression and counting process models, we used a manual model building process to assess for potential confounders and effect measure modifiers. Vitamin K doses were defined as low (<2.6 mg), medium (2.6–9.9 mg) or high (10 mg) and baseline INR was defined as low (<2), medium (2–6), or high (>6). Any variable found to be significantly associated with the outcome ($p < 0.05$) and confounders that appreciably changed (>10%) the beta coefficient for the primary independent variable or statistically significant predictors of the outcome were retained in the final model. Complete reversal of INR was established

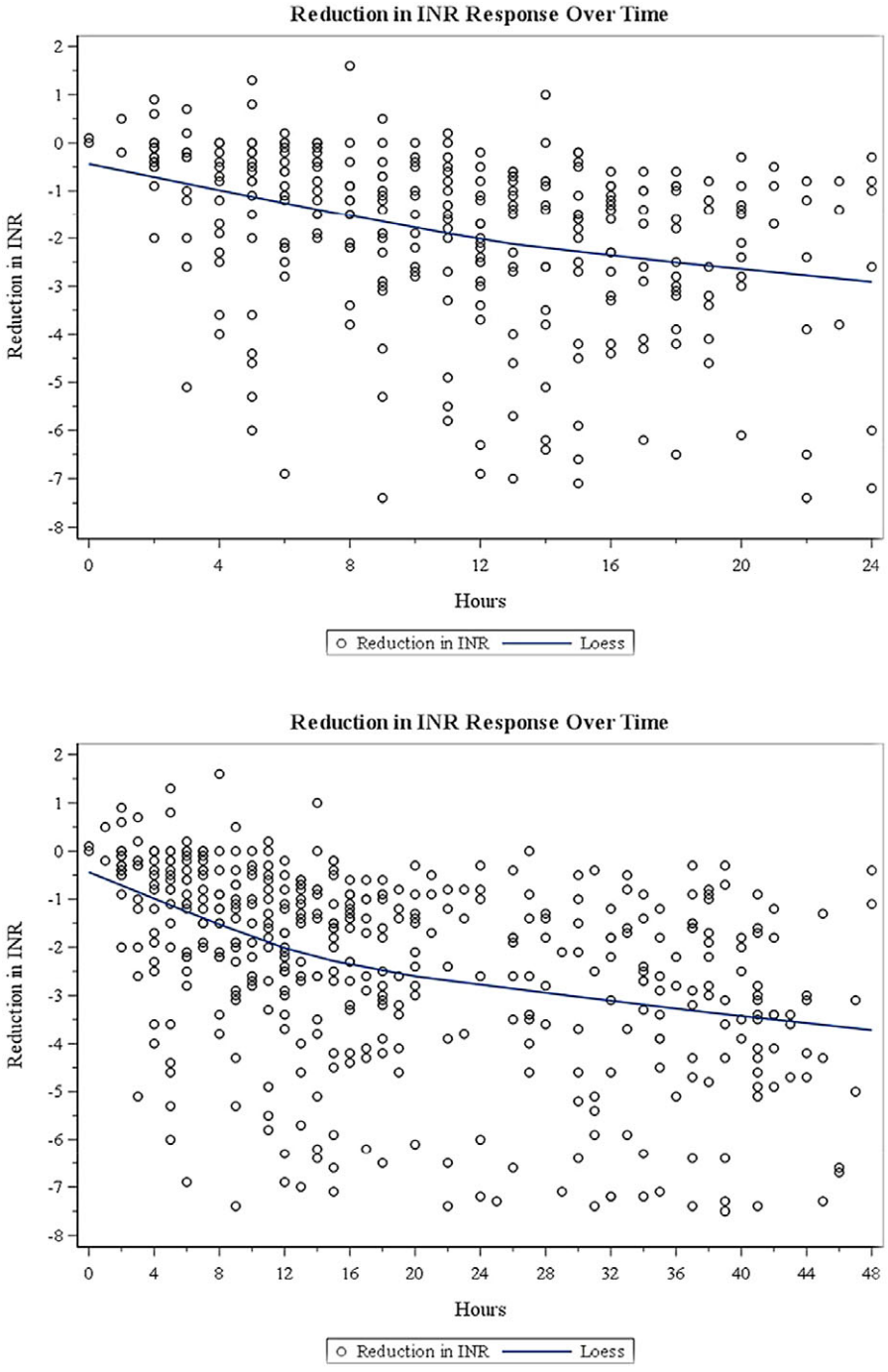

Fig. 1. Reduction in INR response over 24 and 48 hours. [Color figure can be viewed at wileyonlinelibrary.com]

a priori (INR <1.5) and p values less than 0.05 were considered statistically significant.

RESULTS

According to our pharmacy records, a total of 1355 patients received vitamin K during the study period. Of these patients, 235 (17%) met inclusion criteria. Nutritional use of vitamin K (n = 589; 43%) accounted for the majority of exclusions, followed by liver dysfunction or coagulopathy (n = 355; 26%), non–vitamin K procoagulant administration (n = 136; 10%), repeat vitamin K administration(s) (n = 22; 2%), and missing INR data (n = 18; 1%). Patient and vitamin K characteristics are shown in Table 1.

A total of 469 post–vitamin K INR data points were collected in 235 patients. Average time from vitamin K administration to first follow-up INR was 10.5 ± 4.2 hours. Overall

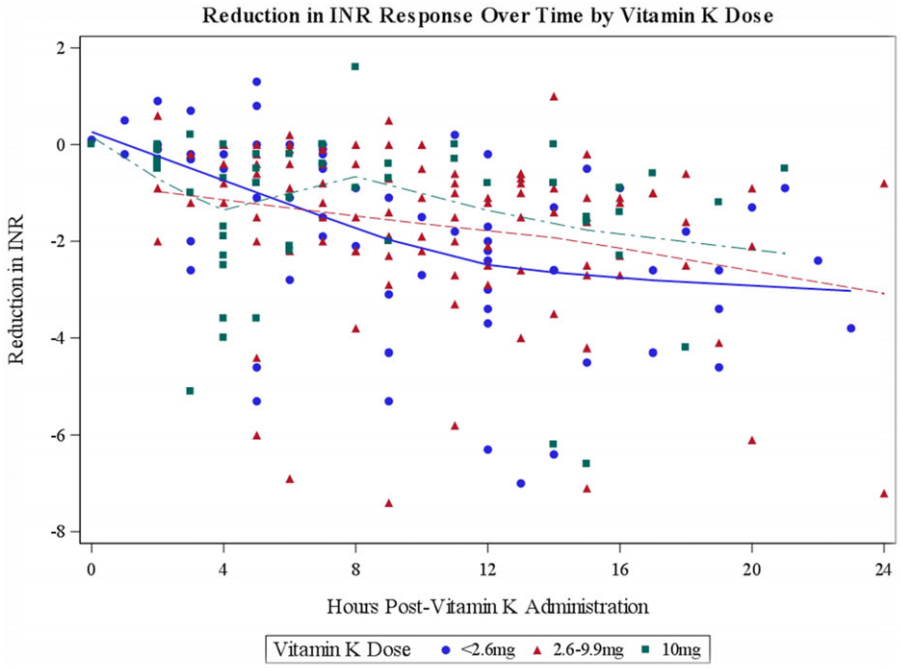

Fig. 2. Reduction in INR over 24 hours by vitamin K dose. [Color figure can be viewed at wileyonlinelibrary.com]

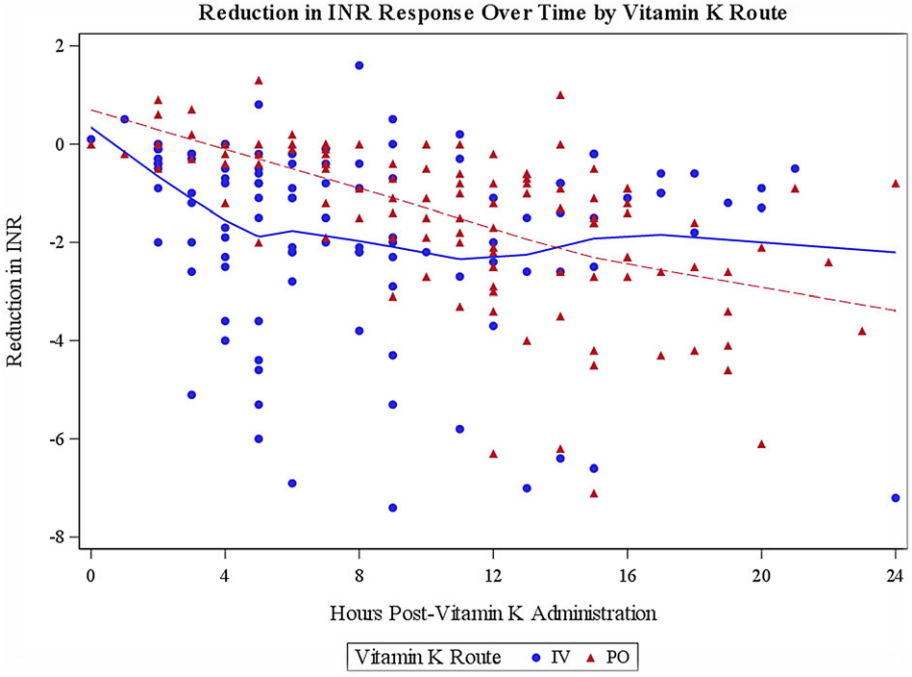

Fig. 3. Reduction in INR over 24 hours by vitamin K route. [Color figure can be viewed at wileyonlinelibrary.com]

INR was reduced by an average of 1.7 ± 1.8 (mean baseline INR 4.7 ± 2.2 to first follow-up INR 3.0 ± 1.9; $p < 0.01$). Certain patients experienced a dramatic initial change in INR, while others appeared to be resistant to reversal. Despite these outliers, the immediate and steady change in INR over time following vitamin K administration is reported in Fig. 1.

Figures 2–4, respectively, depict the relationship between vitamin K dose, route, and baseline INR as it relates to change in the first post–vitamin K INR over 24 hours. Visual interpretation of the best-fit line identified that the 10-mg dose and IV route cause a more rapid change in INR at 0 to 4 hours than lower doses or the oral

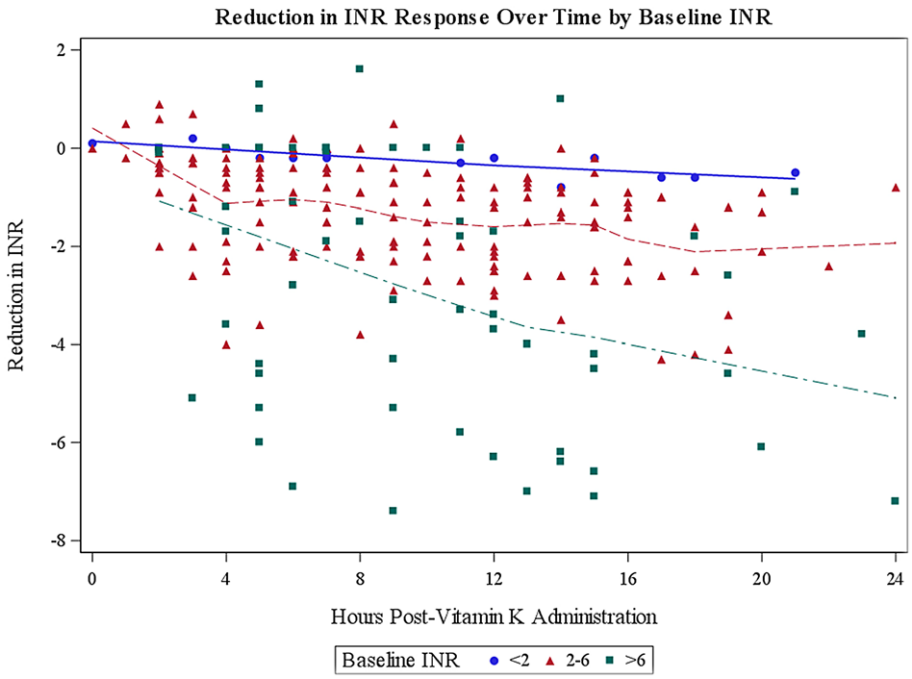

Fig. 4. Reduction in INR over 24 hours by baseline INR. [Color figure can be viewed at wileyonlinelibrary.com]

route, respectively (Figs. 2 and 3). Additionally, baseline INRs greater than 2 appear to be associated with a more rapid initial rate of reversal (Fig. 4).

At 24 and 48 hours, 31 (14.5%) and 98 (41.7%) patients achieved complete reversal (INR <1.5). When reviewing all INR data points, both high-dose and IV route of administration were associated with a higher complete reversal rate at first INR and 24 and 48 hours (Table 2). However, although those that had a high baseline INR had a quicker rate of INR reversal, fewer achieved complete reversal compared to patients with a lower baseline INR (Fig. 4 and Table 2).

Multivariate analysis of the influences of dose, route of administration, baseline INR, and the combination of these on achieving complete reversal were assessed using the pre–vitamin K and first post–vitamin K INR values only (Table 3). All other patient variables including weight were not found to be significant confounders. In the unadjusted and partially adjusted models, hazard ratios significantly favored medium and high doses compared to low doses for achieving complete reversal. In the fully adjusted model, high doses of vitamin K conferred a 2.4 times greater hazard of achieving complete reversal compared to low doses (95% confidence interval, 1.4–4.2). The IV route of administration resulted in a significantly greater hazard of achieving complete reversal across all models. Additionally, the IV route conferred a 1.8 times greater hazard to achieving complete reversal compared to the oral route in the fully adjusted model (95% confidence interval, 1.3–2.6).

DISCUSSION

To our knowledge this is the largest study of patients receiving vitamin K monotherapy for reversal of warfarin and evaluation of INR over time. We found that INR correction begins almost immediately, and rate of change over time is steady through 48 hours. Our results support the findings of previous studies showing an INR response to vitamin K sooner than 12 hours.[2,3,5] We also found that higher vitamin K dose, IV route of administration compared to oral, and a higher baseline INR significantly influence INR reversal rate. The route and baseline INR relationships have been previously reported in the literature; however, analyses of vitamin K dose have been contradictory.[2,3,5,6] Variability in clinical practice and these results may be related to inconsistent or incomplete guideline recommendations.[8–10]

Guidelines fail to fully address INR reversal in the setting of an upcoming surgical procedure or other non–life-threatening bleeding indications.[8–10] Using blood products or procoagulants for these indications, despite cost and risk, is common. These reversal interventions may be unnecessary, as our results support that vitamin K monotherapy begins to reverse INR immediately after administration. One study found vitamin K 3 mg IV was effective at lowering therapeutic INR values to less than 1.5 in 94% of patients when given 12 to 18 hours before a planned surgery.[11] Additionally, Sahai et al. reported vitamin K 5 mg IV provided adequate hemostasis within 5 hours for patients with non–life-threatening bleeding.[7]

Although our study results differed in that the most aggressive reversal regimens (high vitamin K dose and IV

TABLE 2. Percentage of patients reaching complete reversal (INR < 1.5)

	Study Cohort	Dose*			Route		Baseline INR†			High Dose/IV	Procedure/Surgery
No. (%)	235	Low 70	Med 106	High 59	IV 115	PO 120	Low 14	Med 159	High 62	40	98
At First INR	21 (9.0)	2 (2.9)	9 (8.5)	10 (16.9)	15 (13.0)	6 (5.0)	8 (57.1)	10 (6.3)	3 (4.8)	9 (22.5)	10 (10.2)
Within 24 hours	34 (14.5)	2 (2.9)	16 (15.1)	16 (27.1)	29 (25.2)	5 (4.2)	9 (64.3)	21 (13.2)	4 (6.5)	15 (37.5)	20 (20.4)
Within 48 hours	98 (41.7)	18 (25.7)	46 (43.4)	34 (57.6)	58 (50.4)	40 (33.3)	11 (78.6)	73 (45.9)	14 (22.6)	24 (60.0)	53 (54.1)

* Dose: Low, ≤2.5 mg; medium, 2.6–9.9 mg; high, 10 mg.
† Baseline INR: low, <2; medium, 2–6; high, >6.
INR = international normalized ratio.

route) resulted in less than 50% of patients achieving complete reversal within 24 hours, this would still correlate to a large number of patients for whom risks and costs from blood products or concentrated clotting factors could be avoided. Also, we postulate that the higher baseline INR, nonstandardized timing of repeat INR values, possible differences in clinical acuity, and unclear reversal goals of our patient population may account for the difference in our results compared to these studies. It is important to note that even with aggressive doses of vitamin K, patients who require complete reversal may need more frequent INR monitoring and escalation of vitamin K dose to ensure that reversal goals are met, as significant interpatient variability may exist in terms of INR response.

There are several limitations to our study. This review was retrospective, with inherent unaccounted biases in terms of the decision to administer vitamin K and the choice of dose and route. Although it may not be crucial for this INR-based analysis, we were not able to record the patient's warfarin dose or the time between the last dose and vitamin K administration. Additionally, the timing of post–vitamin K INRs was not standardized. Due to this and varying sample sizes across the time points, we were unable to calculate the slope of the best-fit lines depicted in Figs. 1–4. We attempted to account for this with visual interpretation, and counting process regression modeling. Furthermore, we were not able to record actual INR values greater than 8.8; 26 values met this criterion. It is likely that the actual mean baseline INR of our cohort was higher than reported, and our results may actually underestimate the rate of change in INR

TABLE 3. Multivariate analysis of dose, route, baseline INR, or combination of these on achieving complete reversal

	Unadjusted*	Adjusted†	Fully Adjusted ‡
	HR (95% CI)	HR (95% CI)	HR (95% CI)
Dose			
≤2.5 mg	1.0 (Ref.)	1.0 (Ref.)	1.0 (Ref.)
2.6–9.9 mg	2.0 (1.2–3.3)	1.8 (1.1–3.1)	1.6 (0.9–2.7)
10 mg	3.5 (2.1–3.9)	2.8 (1.7–4.8)	2.4 (1.4–4.2)
Route			
PO	1.0 (Ref.)	1.0 (Ref.)	1.0 (Ref.)
IV	2.4 (1.7–3.4)	2.0 (1.4–2.9)	1.8 (1.3–2.6)
Baseline INR			
<2	…	…	1.0 (Ref.)
2–6	…	…	0.3 (0.2–0.4)
>6	…	…	0.1 (0.0–0.2)

* Unadjusted does not account for influences of dose, route, or baseline INR – the effect estimates presented are crude associations between dose and INR reversal or route and INR reversal. Each primary independent variable was modeled separately.
† Adjusted for either route or dose depending on the primary independent variable being assessed.
‡ Adjusted model accounts for either route or dose and baseline INR, as a categorical value.
CI = confidence interval; HR = hazard ratio; INR = international normalized ratio; IV = intravenous; PO = oral.

after vitamin K administration. We also stratified vitamin K doses and baseline INR into three groups (low, medium, and high), and it is unknown if there are statistical differences within these groups. Finally, we do not know how many patients had a goal of achieving a complete reversal versus therapeutic range. In an attempt to minimize this factor, we did evaluate patients with a known indication for reversal in anticipation of an upcoming surgery or procedure, but these results were not significantly different.

We conclude that vitamin K monotherapy begins to reverse INR immediately, and high doses of vitamin K, IV route of administration, and baseline INR are associated with the rate of INR change and complete reversal.

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CONFLICT OF INTEREST

The authors have disclosed no conflicts of interest.

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