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ORIGINAL ARTICLE

Vitamin K versus warfarin interruption alone in patients without bleeding and an international normalized ratio > 10

Georgina S. Farrow[1] | Thomas Delate[1,2] | Kelsey McNeil[3] | Aubrey E. Jones[4] | Daniel M. Witt[4] | Mark A. Crowther[5] | Nathan P. Clark[1]

[1]Pharmacy Department, Kaiser Permanente Colorado, Aurora, CO, USA

[2]Department of Clinical Pharmacy, Skaggs School of Pharmacy and Pharmaceutical Sciences, University of Colorado, Aurora, CO, USA

[3]Ambulatory Services, Boulder Community Health, Boulder, CO, USA

[4]Department of Pharmacotherapy, University of Utah College of Pharmacy, Salt Lake City, UT, USA

[5]Department of Medicine, McMaster University, Hamilton, ON, Canada

Correspondence
Thomas Delate, Pharmacy Department, Kaiser Permanente Colorado, 16601 East Centretech Parkway, Aurora, CO 80011, USA.
Email: tom.delate@kp.org

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Abstract

Background: Reversal of an international normalized ratio (INR) > 10 with vitamin K is recommended in patients experiencing bleeding; however, information on outcomes with reversal using vitamin K in non-bleeding patients is lacking.

Objective: To compare clinical and safety outcomes between non-bleeding patients receiving warfarin with an INR > 10 who did and did not receive a prescription for vitamin K.

Patients/Methods: This was a retrospective cohort study conducted in an integrated health-care delivery system. Adult patients receiving warfarin therapy who experienced an INR > 10 without bleeding between 01/01/2006 and 06/30/2018 were included. Patients were assessed for an outpatient dispensing or in-office administration of vitamin K on the day of or the day after an INR > 10 and then clinically relevant bleeding, thromboembolism, all-cause mortality, and time to INR < 4 within the next 30 days.

Results: A total of 809 patients was included with 332 and 477 who were and were not dispensed vitamin K, respectively. Overall, mean patient age was 71.7 years, 60.1% were female and the mean INR was 10.4 at presentation. There were no differences between groups in 30-day rates of bleeding or thromboembolism (both $P > .05$). Patients dispensed vitamin K had a higher likelihood of mortality (15.1% versus 10.1%, $P = .032$, adjusted odds ratio = 1.63, 95% confidence interval 1.03 to 2.57). Overall, time to an INR < 4 was similar between groups.

Conclusion: Vitamin K administration was not associated with improved clinical outcomes in asymptomatic patients with an INR > 10.

KEYWORDS

anticoagulation, bleeding, international normalized ratio, thromboembolism, warfarin

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1 | INTRODUCTION

The international normalized ratio (INR) is the most commonly utilized laboratory measure to monitor the safety and efficacy of warfarin with most patients targeted to an INR between 2.0 and 3.5. The risk of warfarin-related bleeding complications increases with higher INR values.[1,2] The management of excessive anticoagulation (ie, INR > 4.5) depends on the degree of INR elevation and whether bleeding is present.[3] Prompt reversal of the anticoagulant effect is warranted when serious or life-threatening bleeding is involved.[4] Treatment options for a patient presenting with an elevated INR but no bleeding include temporarily stopping warfarin and/or treatment with vitamin K. Available guidelines suggest administering vitamin K for an INR > 10 whereas warfarin interruption alone is sufficient for an INR between 4.5 and 10.[3]

Data informing the management of asymptomatic patients with an INR > 10 are limited. One prospective cohort study of asymptomatic patients with an INR > 10 identified low rates of 90-day major bleeding when patients were treated with oral vitamin K.[5] Another small, retrospective cohort study reported that patients who had an INR > 10 and received vitamin K were more likely to reach their in-range INR quicker than patients who only withheld warfarin.[6] Thus, the evidence supporting the current American College of Chest Physicians guidelines recommending treatment with oral vitamin K for asymptomatic patients presenting with an INR > 10 is of very low certainty.[3] The purpose of this study was to evaluate treatment outcomes in non-bleeding patients with an INR > 10 who did and did not receive prescription vitamin K. Information from this study will provide additional evidence of the effectiveness and safety of prescription vitamin K treatment in patients with an elevated INR.

Essentials

- Reversal of an INR >10 with vitamin K is recommended in patients with bleeding.
- Outcomes of vitamin K in non-bleeding patients with INR >10 are lacking.
- Non-bleeding patients who did and did not receive vitamin K were assessed.
- Vitamin K was not associated with improved outcomes in this cohort study.

2 | METHODS

2.1 | Study design and setting

This was a retrospective cohort study conducted at Kaiser Permanente Colorado (KPCO), an integrated health-care delivery system providing medical care to more than 630,000 members in Colorado. Anticoagulation services for patients receiving warfarin therapy at KPCO are provided by the Clinical Pharmacy Anticoagulation Service (CPAS).[7] Patients with an INR > 10 are contacted by a clinical pharmacist on the same day as the INR result regardless of time of day. The patient is assessed over the phone for symptoms of bleeding and referred to the appropriate care setting if bleeding is suspected. For non-bleeding patients, a decision is made whether to prescribe vitamin K according to the judgment of the managing clinical pharmacist. If vitamin K is prescribed, the order is sent to a pharmacy either the same day or the following morning. Documentation of anticoagulation interventions and care is collated in a centralized electronic database (DAWN-AC; 4S Systems, Ltd). In addition, KPCO utilizes an outpatient electronic health record that provides e-prescribing capabilities and interfaces with the internal pharmacy and laboratory systems. Coded and free-text medical, pharmacy, laboratory, emergency department, hospitalization, and membership information from within the integrated health-care delivery system, as well as from other contracted and affiliated facilities, are captured in KPCO's administrative and claims databases. All study activities were reviewed and approved by the KPCO Institutional Review Board.

2.2 | Study population

Patients ≥ 18 years of age who were receiving chronic warfarin therapy and experienced an INR > 10 between January 1, 2006 and June 30, 2018 were eligible for study inclusion. Included patients also had: (a) continuous KPCO health plan membership for at least 180 days prior to the index date; (b) to be asymptomatic (ie, no known bleeding) at the time of index date (defined as the day of the INR > 10); (c) no serum creatinine levels > 4 mg/dL or a diagnosis of end stage renal disease within the previous 180 days prior to index date; (d) no dispensing or in-office administration of vitamin K during the 180 days prior to index date; and (e) no hospitalization or emergency department visit on the index date or the day after. Patients were assigned to the *Vitamin K* group if they had a dispensing or in-office administration of prescription vitamin K within 24 hours of the index date (ie, the same day or the day after the INR > 10). Patients were assigned to the *No Vitamin K* group if they had no prescription vitamin K dispensing or in-office administration within 24 hours of the index date (ie, no dispensing or in-office administration of prescription vitamin K on the same day or the day after the INR > 10). Patients in both groups could receive vitamin K beyond 24 hours of the index date.

2.3 | Study outcomes

The primary outcome was the 30-day rate of clinically relevant bleeding. Secondary outcomes include the rates of 30-day major

bleeding, thrombosis, and all-cause mortality, and a composite of clinically relevant bleeding, thrombosis, and all-cause mortality. In addition, time to INR < 4 for patients with an INR measured during the 30 days after the index date was assessed. Clinically relevant bleeding was defined as any symptomatic or clinically overt bleeding leading to an emergency department visit or hospitalization regardless of severity. Major bleeding was a subset of clinically relevant bleeding defined according to the criteria of the International Society for Thrombosis and Haemostasis: fatal and/or symptomatic bleeding requiring transfusion of two or more units of red blood cells and/or involves a decrease in hemoglobin of greater than or equal to 2 g/dL and/or occurs in a critical area (intracranial, intraspinal, intraocular, retroperitoneal, intra-articular, pericardial, or intramuscular with compartment syndrome).[8] A subanalysis of the outcomes was conducted by (a) restricting the Vitamin K group to include only those patients who received vitamin K on the index date compared to the No Vitamin K group; (b) restricting the No Vitamin K group to patients who did not receive vitamin K at any time during the 30-day follow-up; (c) performing 1:1 propensity matching of Vitamin K patients to No Vitamin K patients; and (d) restricting the Vitamin K and No Vitamin K groups to patients with a high HAS-BLED score (ie, ≥ 3).[9,10]

2.4 | Data collection

Integrated electronic medical, pharmacy, membership, and laboratory administrative records and the anticoagulation database were used to identify patients, treatments, and outcomes for this study. The DAWN-AC database was used to collect information on INR values, indication for anticoagulation, and patient date of birth. Patient characteristics were collected during the 180 days prior to the index date (baseline). The KPCO pharmacy database was used to identify baseline warfarin and concomitant medication therapy as well as prescription vitamin K dispensings. The KPCO procedures database was used to identify in-office administrations of vitamin K. The KPCO laboratory database was used to collect baseline serum creatinine levels. Other KPCO administrative databases were used to identify KPCO membership, sex, death date, race, ethnicity, health plan type, and baseline comorbidities. Bleeding and thromboembolic events were identified from inpatient, emergency, and outpatient administrative ambulatory and claims databases using International Classification of Disease, Ninth and Tenth Revisions diagnosis codes and confirmed by manual chart review by at least two study team members (GSF and NPC) who were blinded to study group assignment. Disagreements between reviewers were resolved

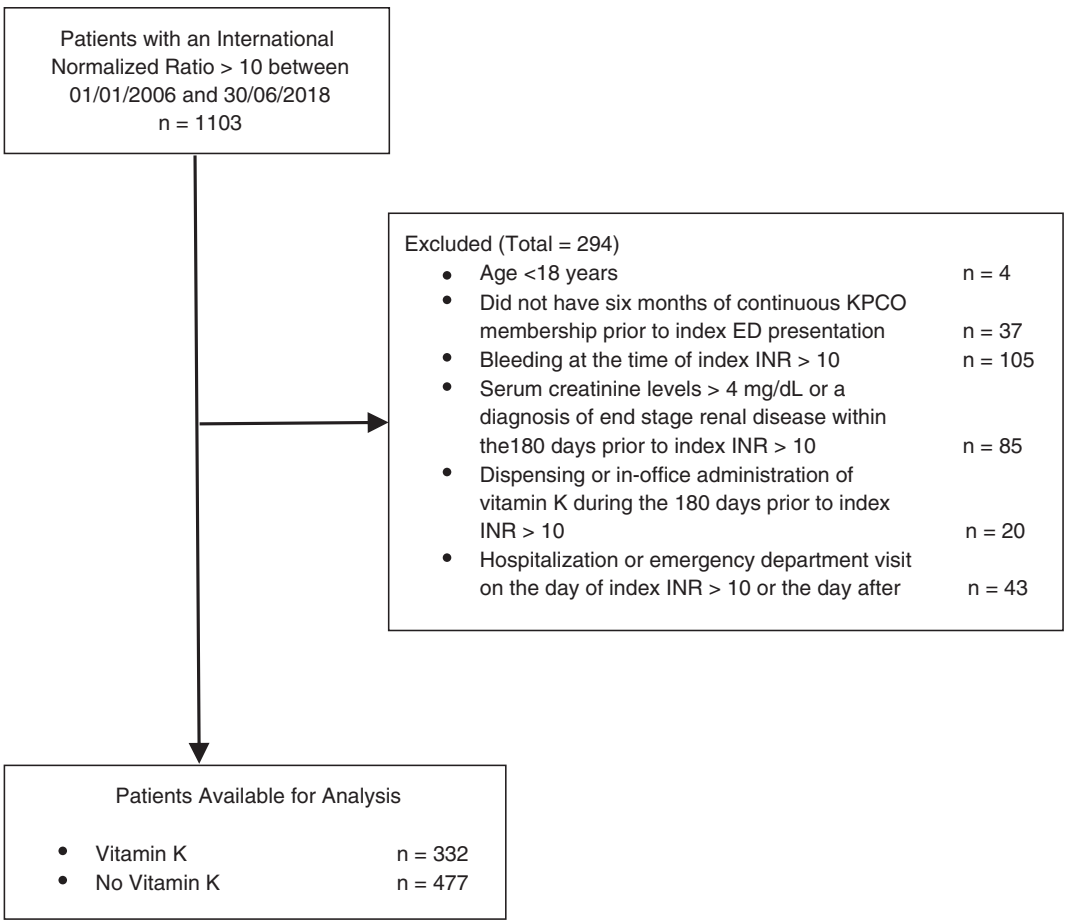

FIGURE 1 Patient dispositions. Abbreviations: ED, emergency department; INR, International Normalized Ratio; KPCO, Kaiser Permanente Colorado

by a third reviewer (TD). There was no loss to follow-up as KPCO is an integrated health-care delivery system. If a patient died or was hospitalized for bleeding or thrombosis at any point within 30 days of the index date, the event would be captured in an administrative database.

2.5 | Data analysis

All patients meeting inclusion and exclusion criteria were included in the study and no a priori sample size or power calculation was performed. Patients were categorized as *Vitamin K* and *No Vitamin K* based on prescription vitamin K dispensing or in-office administration within 24 hours or not, respectively.

Age was calculated as of the index date. A chronic disease score, an indicator of a patient's burden of chronic illness and predictor of future health-care utilization,[11] was calculated from each patient's baseline prescription dispensing history. The presence of specific comorbidities was determined using the Quan adaptation of the Charlson comorbidity index (CCI).[12] The algorithm was applied to diagnoses during the baseline period to provide a 30-point comorbidity score. A HAS-BLED score was calculated using seven parameters from each patient's comorbidity history.[9] The score assesses the 1-year risk of bleeding and ranges between 0 and 9.

Patient characteristics and outcomes were reported as means and standard deviations for continuous variables and percentages for categorical variables. Characteristics and outcomes were compared between groups using *t*-tests or the Wilcoxon two-sample test, as appropriate based on the underlying distribution, for continuous variables and chi-square tests of association for categorical variables. Multivariable logistic and linear regression modeling was used to adjust the outcomes for potential confounders. Based on statistical and clinical judgment, all models were adjusted for age, sex, index INR, aspirin use, hypertension and renal disease comorbidities, CCI, chronic disease score, and HAS-BLED score.

A propensity score (PS) for a prescription vitamin K dispensing or in-office administration was estimated for each eligible patient with a logistic regression logit model.[13] Characteristics in the model included age; sex; index INR; previous hemorrhage history; indication for anticoagulation; race; ethnicity; Medicare status; Medicaid status; alcohol abuse; aspirin use; cerebrovascular disease, chronic pulmonary disease, diabetes, hypertension, liver disease, and renal disease comorbidities; amiodarone, azole antifungal, metronidazole, non-steroidal antiinflammatory, and sulfamethoxazole ± trimethoprim dispensings; CCI; chronic disease score; and HAS-BLED score. Patients in the Vitamin K group were matched 1:1 to patients in the No Vitamin K group using the Greedy method with a ± 0.5 standard deviation (SD) (0.04) of the mean (0.410) PS caliper.[14] Outcomes were compared between groups using conditional logistic and linear regression models with adjustment for the PS and intercorrelations of the matched pairs. All tests were two-tailed and the alpha was set at 0.05.

3 | RESULTS

A total of 809 patients was included with 332 (41%) and 477 (59%) assigned to the Vitamin K and No Vitamin K groups, respectively (Figure 1). Overall, included patients were primarily 65 years or older and white and with a high burden of chronic disease, an indication for warfarin therapy of atrial fibrillation/flutter or venous thromboembolism (VTE), and a mean index INR of 10.4 (Table 1). Patient characteristics were balanced between the groups with no statistically significant differences. The mean initial dose of vitamin K received by the Vitamin K group was 3.1 mg (SD ± 1.7) with 260 (78.3%) and 46 (13.9%) patients having received a 2.5 mg and 5 mg dose, respectively. Thirty-two patients (9.6%) required a second vitamin K dose and two patients (0.6%) received a third. Overall, 95.4% of vitamin K doses were administered orally.

Clinically-relevant and major bleeding and thromboembolism outcomes were infrequent and there were no unadjusted or adjusted differences (all $P > .05$) between groups during the 30-day follow-up (Table 2). The 30-day rate of all-cause mortality was higher in the Vitamin K group (15.1% versus 10.1%, $P = .032$; adjusted odds ratio = 1.63, 95% confidence interval 1.03 to 2.57). Nevertheless, there was no unadjusted or adjusted differences between the groups in the rate of the composite outcome. Similarly, there was no unadjusted or adjusted difference between the groups in the mean time to an INR < 4.

In the subanalysis restricting the Vitamin K group to include only those patients who received vitamin K on the same day as the index INR > 10, there were no unadjusted or adjusted differences in the 30-day clinically relevant and major bleeding, all-cause mortality, and composite outcomes compared to No Vitamin K group patients (all $P > .05$; Table 3). The rate of thromboembolism was nearly three-fold higher in the prescription Vitamin K group, but this difference was not statistically significant. The mean time to an INR < 4 was shorter in the Vitamin K group (1.8 days versus 2.4 days) in both the unadjusted ($P = .002$) and adjusted ($P = .002$) analyses.

In the No Vitamin K group, 51 (10.7%) patients received vitamin K > 24 hours after the index date. In the subanalysis restricting the No Vitamin K group to patients who did not receive vitamin K at any time during the 30-day follow-up (n = 426), there were no unadjusted or adjusted differences in the 30-day clinically relevant (4.8% versus 6.1%) and major bleeding (3.0% versus 3.5%), thromboembolism (1.8% versus 0.9%), all-cause mortality (15.1% versus 10.6%), composite outcome (20.2% versus 16.7%) rates between Vitamin K and No Vitamin K groups (all $P > .05$). The time to an INR < 4 was numerically lower in the Vitamin K group (2.2 days versus 4.4 days) but this did not reach statistical significance in the unadjusted ($P = .420$) or adjusted ($P = .130$) analysis.

In the subanalysis performing 1:1 propensity matching of Vitamin K patients to No Vitamin K patients, 332 (100%) Vitamin K patients were matched to 332 (69.6%) No Vitamin K patients. There were no unadjusted or adjusted differences in the 30-day clinically relevant

TABLE 1 Baseline patient characteristics by vitamin K status (N = 809)

Demographic	Vitamin K (n = 332)	No Vitamin K (n = 477)	*P*-value
Mean age[a] (years, SD)	71.8 (15.1)	71.7 (14.9)	.570
Aged ≥ 65 years (n, %)	245, 73.8%	346, 72.5%	.692
Female sex (n, %)	190, 57.2%	296, 61.1%	.168
Race (n, %)			
Other	32, 9.6%	44, 9.2%	.547
White	240, 72.3%	360, 75.5%	
Undeclared/unknown	60, 18.1%	73, 15.3%	
Hispanic ethnicity (n, %)	29, 8.7%	41, 8.6%	.945
High deductible health plan (n, %)	2, 0.6%	5, 1.1%	.501
Medicare beneficiary (n, %)	262, 78.9%	383, 80.3%	.632
Medicaid beneficiary (n, %)	18, 5.4%	31, 6.5%	.528
Anticoagulation			
Mean index INR (SD)	10.4 (0.9)	10.4 (1.0)	.534
Indication (n, %)			
Atrial fibrillation/flutter	121, 36.5%	143, 30.0%	.279
Prosthetic heart valve	17, 5.1%	29, 6.0%	
Stroke/systemic embolism	22, 6.6%	44, 9.2%	
Venous thromboembolism	102, 30.7%	170, 35.6%	
Venous thromboembolism prophylaxis	32, 9.6%	43, 9.0%	
Other	38, 11.5%	48, 10.1%	
Outpatient medication[b]			
Amiodarone (n, %)	21, 6.3%	24, 5.0%	.430
Azole antifungal (n, %)	14, 4.2%	19, 4.0%	.869
Metronidazole (n, %)	17, 5.1%	19, 4.0%	.440
Aspirin (n, %)	103, 31.0%	123, 25.8%	.102
Non-steroidal anti-inflammatory (n, %)	15, 4.5%	21, 4.4%	.938
Sulfamethoxazole ± trimethoprim (n, %)	14, 4.2%	14, 2.9%	.327
Comorbidity[c]			
Alcohol abuse (n, %)	9, 2.7%	17, 3.6%	.499
Cerebrovascular disease (n, %)	55, 16.6%	76, 15.9%	.810
Chronic pulmonary disease (n, %)	128, 38.6%	194, 40.7%	.545
Diabetes (n, %)	71, 21.4%	111, 23.3%	.528
Previous hemorrhage (n, %)	66, 19.9%	80, 16.8%	.258
Hypertension (n, %)	195, 58.7%	311, 65.2%	.062
Liver disease (n, %)	16, 4.8%	26, 5.5%	.691
Renal disease (n, %)	84, 25.3%	151, 31.7%	.050
Risk scores			
Mean charlson comorbidity index (SD)	3.4 (3.2)	3.6 (3.3)	.170
Mean chronic disease score (SD)	7.7 (3.5)	7.2 (3.2)	.183
Mean HAS-BLED score (SD)	3.4 (1.3)	3.4 (1.3)	.511

Abbreviations: INR, International Normalized Ratio; SD, standard deviation.

[a]As of index INR > 10 date.

[b]Recorded during the 6 months prior to index INR > 10 date.

[c]Diagnosis recorded during the 6 months prior to index INR > 10 date.

TABLE 2 Outcomes by vitamin K status (N = 809)

Outcome[a]	Vitamin K (n = 332)	No Vitamin K (n = 477)	*P*-value
Clinically relevant bleeding (n, %)	16, 4.8%[b]	32, 6.7%	.263
Major bleeding (n, %)	10, 3.0%[c]	18, 3.8%	.560
All-cause mortality (n, %)	50, 15.1%[d]	48, 10.1%	.032
Thromboembolism (n, %)	6, 1.8%[e]	4, 0.8%	.332
Composite of clinically relevant bleeding, all-cause mortality, and thromboembolism (n, %)	67, 20.2%[f]	80, 16.8%	.216
Mean time to INR < 4 in days (SD)	2.2 (1.8)[g]	2.4 (2.3)	.911

Abbreviations: INR, International Normalized Ratio; SD, standard deviation.

[a]During the 30 days after index INR > 10.

[b]Odds ratio adjusted for age, sex, index INR, over-the-counter aspirin, hypertension and renal disease comorbidities, Charlson comorbidity index, chronic disease score, and HAS-BLED score (adjusted odds ratio [AOR]) = 0.69, 95% confidence interval (CI) 0.37 to 1.28.

[c]AOR = 0.75, 95% CI 0.34 to 1.65.

[d]AOR = 1.63, 95% CI 1.03 to 2.57.

[e]AOR = 2.24, 95% CI 0.60 to 8.36.

[f]AOR = 1.23, 95% CI 0.85 to 1.79.

[g]p = 0.140 with adjustment for age, sex, index INR, over-the-counter aspirin, hypertension and renal disease comorbidities, Charlson comorbidity index, chronic disease score, and HAS-BLED score.

TABLE 3 Outcomes for patients who received prescription vitamin K on same day as their INR > 10 versus patients who received no prescription vitamin K (N = 574)

Outcome[a]	Vitamin K (n = 97)	No Vitamin K (n = 477)	*P*-value
Clinically relevant bleeding (n, %)	5, 5.2%[b]	32, 6.7%	.570
Major bleeding (n, %)	3, 3.1%[c]	18, 3.8%	.745
All-cause mortality (n, %)	14, 14.4%[d]	48, 10.1%	.206
Thromboembolism (n, %)	3, 3.1%[e]	4, 0.8%	.065
Composite of clinically relevant bleeding, all-cause mortality, and thromboembolism (n, %)	22, 22.7%[f]	80, 16.8%	.165
Mean time to INR < 4 in days (SD)	1.8 (1.6)[g]	2.4 (2.3)	.002

Abbreviations: INR, International Normalized Ratio; SD, standard deviation.

[a]During the 30 days after INR > 10.

[b]Odds ratio adjusted for age, sex, index INR, over-the-counter aspirin, hypertension and renal disease comorbidities, Charlson comorbidity index, chronic disease score, and HAS-BLED score (adjusted odds ratio [AOR]) = 0.77, 95% confidence interval (CI) 0.29 to 2.07

[c]AOR = 0.88, 95% CI 0.28 to 3.12.

[d]AOR = 1.37, 95% CI 0.67 to 2.81.

[e]AOR = 2.92, 95% CI 0.55 to 15.53.

[f]AOR = 1.31, 95% CI 0.75 to 2.30.

[g]*P* = .002 with adjustment for age, sex, index INR, over-the-counter aspirin, hypertension and renal disease comorbidities, Charlson comorbidity index, chronic disease score, and HAS-BLED score.

(4.8% versus 5.7%) and major bleeding (3.0% versus 3.3%), thromboembolism (1.8% versus 1.2%), all-cause mortality (15.1% versus 12.1%), composite outcome (20.2% versus 18.1%) rates, and mean time to an INR < 4 (2.2 days versus 3.4 days) between Vitamin K and No Vitamin K groups (all $P > .05$).

There were 239 patients the Vitamin K group and 335 patients in the No Vitamin K group with a HAS-BLED score of 3 or greater. Analysis of this high bleeding risk group revealed no unadjusted or adjusted differences in the 30-day thromboembolism (1.3% versus 0.3%), all-cause mortality (16.7% versus 11.6%), composite outcome (20.1% versus 18.5%) rates, and mean time to an INR < 4 (2.2 days versus 3.5 days) between Vitamin K and No Vitamin K groups (all $P > .05$). The 30-day rates of clinically relevant bleeding (3.8% versus 7.2%) and major bleeding (2.1% versus 4.2%) were numerically lower in the Vitamin K group but did not reach statistical significance in the unadjusted or adjusted analyses (all $P > .05$).

4 | DISCUSSION

This retrospective analysis of more than 800 patients who experienced an INR > 10 while receiving chronic warfarin therapy identified no association between use of prescription vitamin K and improved clinical outcomes. We did identify a shorter mean time to an INR < 4 in a subset of the Vitamin K group patients who received prescription vitamin K on the same day as their elevated INR; however, a corresponding reduction in bleeding was not identified. In addition, the likelihood of experiencing a thromboembolism during the 30-day follow-up increased nearly three-fold in these patients. Our findings are important as there have been no studies comparing prescription vitamin K to warfarin interruption alone in non-bleeding patients with an INR > 10 that were adequately powered to compare clinical outcomes.

A prospective cohort study of 107 asymptomatic patients who received oral vitamin K 2.5 mg for an INR > 10 found major bleeding occurred in 2.0% of patients within 30 days.[5] These results are comparable to the major bleeding rates of 3.0% and 3.8% in our main analysis of the Vitamin K and No Vitamin K groups, respectively. Based on these observations, it appears that the absolute 30-day rate of subsequent major bleeding in asymptomatic patients presenting with an INR > 10 is low. As a result, the opportunity for prescription vitamin K to reduce the major bleeding risk by returning the INR to a safer level over the first 1 or 2 days after an initial INR > 10 is small. Thus, it is perhaps unsurprising that our analysis failed to identify any reduction in bleeding associated with the use of prescription vitamin K in this setting.

Vitamin K is generally safe when given in low doses. Concerns regarding refractoriness to warfarin reinstitution and subsequent thrombosis were likely related to high vitamin K doses (eg, > 10 mg)

that are no longer commonly used.[15] Nevertheless, the burden of vitamin K administration should not be discounted particularly in an older anticoagulated population who often have physical barriers that make repeated trips to the clinic, laboratory, or pharmacy to obtain prescription vitamin K a hardship. In addition, the cost of prescription vitamin K (Mephyton® [phytonadione]) tablets has risen substantially over the past decade and Medicare beneficiaries are often required to pay the cash price at the pharmacy because vitamin K is excluded from coverage by Medicare as a vitamin rather than a medication.[16]

Our finding that vitamin K did not impact the rate of INR correction conflicts with prior research including a randomized, placebo-controlled trial that found oral vitamin K 1.25mg decreased INR more rapidly than placebo for patients presenting with an INR 4.5 to 10.[17] In addition, a meta-analysis of prospective studies of patients with excessive anticoagulation reported that 52% of patients who had an INR > 10 returned to an INR between 1.8 and 4.0 within 24 hours after vitamin K administration compared to just 20% in the observation/placebo group.[18] While the meta-analysis included 105 patients receiving vitamin K (either oral, intravenous, or subcutaneous), they were compared to only six control patients receiving no vitamin K. We believe these small numbers underscore the importance of our large sample size.

Our subanalysis comparing only patients who received prescription vitamin K on the day of the index INR > 10 to patients who only withheld warfarin revealed that vitamin K treatment returned INR to < 4 more quickly. Our findings paired with the prospective data discussed above indicate that in a controlled environment in which vitamin K is administered on the same day as the INR > 10 and the INR follow-up is within 24 or 48 hours, treatment with prescription vitamin K likely is associated with a more rapid correction in the INR than withholding warfarin alone. Nevertheless, in a "real-world" environment in which INR results are reported, typically, late in the day and patients may not receive vitamin K until the following day, there appears to be no meaningful effect on INR correction compared to withholding warfarin alone. In any case, correction of the INR is a surrogate outcome and the associated rates of major bleeding we identified were low and comparable between the groups.

We did identify a higher rate of 30-day all-cause mortality in the Vitamin K group in both unadjusted and adjusted main analyses. The mortality difference did not appear to be explained by higher risk of thromboembolism, which was numerically higher in the vitamin K group, but not statistically significant. Baseline characteristics were balanced in the two groups with age, indication for warfarin, drug interactions, as well as estimates of comorbidity and bleeding risk equivalent in the two groups. It is possible that unmeasured characteristics or residual confounding influenced the mortality outcome. However, we did not identify a higher rate of 30-day all-cause mortality in the Vitamin K group in our restriction of the No Vitamin K group to patients who did not receive vitamin K and PS matching subanalyses. These analyses contained a smaller number of patients, which may have affected our power to discern statistical differences.

Our study was strengthened by its large sample size, rigid inclusion and exclusion criteria, robust data collection and validation, and adjusted analysis of clinical outcomes. Nevertheless, there are limitations that should be considered when interpreting the results. We relied on administrative data for initial identification of bleeding and thromboembolic outcomes and it is possible that some events may have been missed if not appropriately coded at the institution where they occurred.[19,20,21] We had small counts of outcomes (ie, major bleeding n = 10 for Vitamin K patients versus n = 18 for No Vitamin K patients and thromboembolism n = 6 for Vitamin K patients versus n = 4 for No Vitamin K patients); thus, our results may have been driven by these small numbers. A lack of statistically significant differences in outcomes, thus, may have been attributable to the small counts resulting in a Type II error. While we adjusted for clinically and statistically important characteristics, confounding by indication may have resulted in sicker patients receiving vitamin K preferentially and these patients may have been more likely to have adverse outcomes or delayed INR correction. We estimated a PS for receiving vitamin K and performed PS matching analysis to lessen the potential of confounding by indication and identified similar outcomes between the matched groups. The use of vitamin K was at the discretion of the clinical pharmacist managing the INR result and was not protocolized according to patient characteristics. We were unable to quantify the reasons for vitamin K nonuse in this analysis. The assessment of time to INR < 4 was limited by the timing of subsequent INR measurements, which could lead to overestimation of the amount of time it took to achieve an INR < 4. We were unable to control for use of non-prescription sources of vitamin K and it is possible that patients in either group may have consumed vitamin K from dietary or over-the-counter sources. It is possible that this occurred more frequently in patients in the No Vitamin K group or in those Vitamin K group patients who could not obtain vitamin K prescriptions until the day following the index INR. This may also in part explain the lack of difference in the mean time to INR < 4 between groups in this "real world" sample of patients.

5 | CONCLUSIONS

Use of vitamin K for asymptomatic patients presenting with an INR > 10 was not associated with reduced bleeding or increased thromboembolism during the 30 days after the elevated INR. These findings require confirmation from a sufficiently powered, randomized, placebo-controlled trial of vitamin K for non-bleeding patients presenting with an INR > 10 to establish the definitive effect of vitamin K on clinical outcomes in this setting.

AUTHOR CONTRIBUTIONS

Georgina Farrow (GF), Thomas Delate (TD), Kelsey Palmer (KP), Nathan Clark (NC), Aubrey Jones (AJ), Daniel Witt (DW), and Mark Crowther (MC) designed the research, interpreted the analysis, and revised the manuscript; TD extracted information from electronic data sources and performed the statistical analysis; GF, TD, and NC drafted the initial version of the manuscript; and GF, TD, KP, NC, AJ, DW, and MC approved the version of the manuscript for submission. Preliminary results were presented at Mountain States Conference

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CONFLICTS OF INTEREST

DW has received research support from and served on an advisory board for Roche Diagnostics. The other authors state that they have no conflicts of interest.

ORCID

Thomas Delate https://orcid.org/0000-0002-6530-8415

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