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INR Response to Low-Dose Vitamin K in Warfarin Patients

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Abstract

Background: Literature suggests that 2 mg of vitamin K intravenously (IV) provides a similar effect as 10 mg to reverse warfarin. Doses <5 mg haven't been studied in depth. **Objective**: The objective was to determine the international normalized ratio (INR) reduction effect of ultra low-dose (ULD) IV vitamin K. **Methods**: This retrospective, observational cohort study compared IV vitamin K doses of 0.25-0.5 mg (ULD) versus 1-2 mg (standard low dose [SLD]). The primary outcome assessed ΔINR at 36 hours; secondary outcomes assessed ΔINR at 12 hours and 30-day venous thromboembolism (VTE) and mortality rates. **Results:** Of 88 patients identified (median baseline INR [IQR], 5.1 [3.1, 7.3] vs 4.5 [2.8, 8.2], ULD vs SLD, respectively), 59 had an INR at 12 hours. The ULD had fewer 12-hour INR values <2, with no statistical difference in the ΔINR at 12 hours between the ULD and SLD cohorts (median ΔINR, 2.2 [1.1, 3.4] vs 2.2 [1.1, 6.3]; $P = 0.54$; median INR, 2.3 vs 1.8). A total of 41 patients had both a 12- and 36-hour INR. No significant difference in the ΔINR between the 12- and 36-hour values occurred (median ΔINR, 0.52 [0.2, 0.91] vs ΔINR, 0.46 [0.18, 0.55]; $P = 0.61$), suggesting no rebound or excessive reversal and no difference in 30-day rates of VTE ($P > 0.99$) or death ($P = 0.38$). **Conclusion and Relevance:** ULD IV vitamin K reversed INR similarly to doses of 1-2 mg without rebound. A ULD strategy may be considered in patients requiring more cautious reversal.

Keywords

warfarin, anticoagulation, INR, international normalized ratio, vitamin K, intravenous, ultralow dose, low dose, reversal

Background

Warfarin is a commonly used anticoagulant that is utilized for a variety of indications, including thromboembolism prevention in patients with atrial fibrillation, mechanical heart valves, durable left-ventricular assist device thromboprophylaxis, and the treatment and prophylaxis of venous and arterial thrombosis. Warfarin is a vitamin K antagonist that blocks the action of vitamin-K-epoxide reductase (VKORC) to prevent the formation of functional vitamin-K-dependent clotting factors.[1] Administration of vitamin K can bypass warfarin's inhibition of VKORC and allow for the production of fully carbonylated coagulation factors. Patients on warfarin require close monitoring of the international normalized ratio (INR) to reduce the risk of both thrombosis and bleeding.[2,3] The risk of bleeding increases as the INR increases, with the risk increasing markedly with INR values exceeding 5.0; the risk of bleeding also increases with prolonged high values.[4] Therefore, in acutely ill patients who present with supratherapeutic INR values, goals of therapy often involve decreasing the extent and duration of the INR elevation to reduce bleeding risk. Agents that have been known to help reduce the INR include vitamin K, fresh frozen plasma, prothrombin complex concentrates (PCCs), activated PCCs (aPCCs), and recombinant factor VIIa.[5-7] Withholding anticoagulation in expectation of the return of a therapeutic INR is another approach, though it tends to be time-consuming and potentially increases the duration patients are exposed to a higher bleed risk.[8,9]

Vitamin K has classically been utilized for the reversal of supratherapeutic INRs associated with warfarin use. It promotes the formation of clotting factors II, VII, IX, and X and can be administered in a variety of ways, including enterally, intravenously (IV), and subcutaneously. The onset of IV vitamin K effects can be seen within 4 to 6 hours

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postadministration and reaches maximum effect within 24 to 36 hours.[10]

Vitamin K is not an innocuous agent. Historically, it has been associated with anaphylaxis or thrombosis resulting from warfarin resistance.[9,11,12] The optimal dose of IV vitamin K to administer without over- or undershooting a target INR range is not completely elucidated. If the INR drops below the established target, the potential risk of thrombosis may increase, and the patient may require anticoagulation bridging therapies, which can create additional management challenges, increase monetary costs, and potentially increase hospital length of stay among other factors. If insufficient reversal of the INR occurs, the risk for bleeding may persist. Current guidelines endorse the utility of both IV and enteral vitamin K.[13] For stable patients on warfarin with INRs between 4.5 and 10 without evidence of bleeding, the routine use of vitamin K is discouraged.[13] For patients with INRs greater than 10 and with no evidence of bleeding, oral vitamin K is recommended.[13] For patients with warfarin-associated bleeding, the use of IV vitamin K at a dose of 5 to 10 mg should be administered via slow injection rather than the use of coagulation factors alone.[13] Current data describing the optimal dose of IV vitamin K are limited, though lower dosing strategies have been studied in more recent years. Data suggest that INR reduction is similar for IV vitamin K doses of 2 mg or greater and can lead to full reversal and, typically, no additional INR lowering, but prolonged effects occur at doses greater than 2 mg.[14] However, the role of doses lower than 2 mg is not completely elucidated.

Based on the paucity of data concerning the use of low-dose vitamin K for the treatment of supratherapeutic INRs in patients at high risk of hemorrhage, the primary objective of this trial was to investigate the differences in the effect of INR reduction between ultralow doses (ULDs; 0.25-0.5 mg) and more standard low doses (SLDs; 1-2 mg) of IV vitamin K to prevent excessive INR reversal, specifically regarding the INR change between baseline and at 36 hours post–IV vitamin K administration. Secondary objectives were to describe the change in INR from baseline to 12 hours post–IV vitamin K administration and the incidence of new 30-day venous thromboembolism (VTE) and 30-day all-cause mortality.

Methods

This was an institutional review board–approved, single-center, retrospective cohort study of the effect of ULD versus SLD IV vitamin K on INR. ULD IV vitamin K was defined as doses of 0.25 or 0.5 mg; SLD IV vitamin K was defined as doses of 1 or 2 mg. This analysis was conducted at a tertiary care academic medical center designated as a level 1 trauma center. Patients were included in this study if they were at least 18 years old, were admitted to the hospital, were on warfarin therapy, and received IV vitamin K at a dose of 0.25, 0.5, 1, or 2 mg. Patients were excluded for the following reasons: (1) less than 18 years of age; (2) prisoner; (3) pregnant; (4) received aPCC, PCC, recombinant factor VIIa, fresh frozen plasma, or any other doses of vitamin K in the 48 hours before or after the study where IV vitamin K dose was given; and (5) no baseline INR or no repeated INR within 48 hours post–IV vitamin K.

A total of 500 patients who received IV vitamin K between January 1, 2010, and July 1, 2018, were reviewed for inclusion. The cohort was identified using a pharmacy-generated medication administration record on the electronic medical record (EMR). Pertinent information, including age, weight, sex, height, serum creatinine, care unit (eg, intensive care vs ward care), primary service (medical versus surgical), anticoagulation indication, INR goal, weekly warfarin dose, diagnosis of heart failure, total bilirubin, and whether or not they were hemodialysis dependent, was also collected. Baseline characteristics such as heart failure and renal dysfunction were included to better describe the weekly warfarin dosing requirements in these individuals because both renal impairment and heart failure have been shown to make patients more sensitive to the effects of warfarin and require lowing dosing.[15,16] Furthermore, factors such as body mass index (BMI) have also shown correlation to the required weekly dose of warfarin.[17] INR readings (Analyzer: ACL TOP analyzer [Instrumentation Labs]; reagent: Innovin [Siemens]) were included in specified time ranges if they were collected within 6 hours before or after the specified time period (eg, INR readings listed as 12 hours could range from 6 to 18 hours after the administration of IV vitamin K). Prior-to-admission warfarin dose information was collected from the medication reconciliation records, pharmacist chart notes, and outpatient anticoagulation records.

Statistics

All analyses were conducted with SAS (version 9.4 [TS1M5]; SAS Institute Inc, Cary, NC). All continuous variables were evaluated for normality using the Shapiro-Wilk test, the Kolmogorov-Smirnov test, and visual inspections of histograms. Both age and height were found to have a normal distribution. As such, between-cohort comparisons were made using a *t*-test. All other continuous variables were found to be nonnormal; thus, all between-cohort comparisons were made using the Mann Whitney *U* test. Continuous variable results are presented as mean (SD) or median (interquartile range) as appropriate. Between-cohort comparisons of categorical variables were evaluated using a χ^2 or Fisher exact test as appropriate. Results of categorical variables are presented as count (proportion of cohort). The null hypothesis of no difference is rejected if between-cohort comparisons *P* values are less than 0.05.

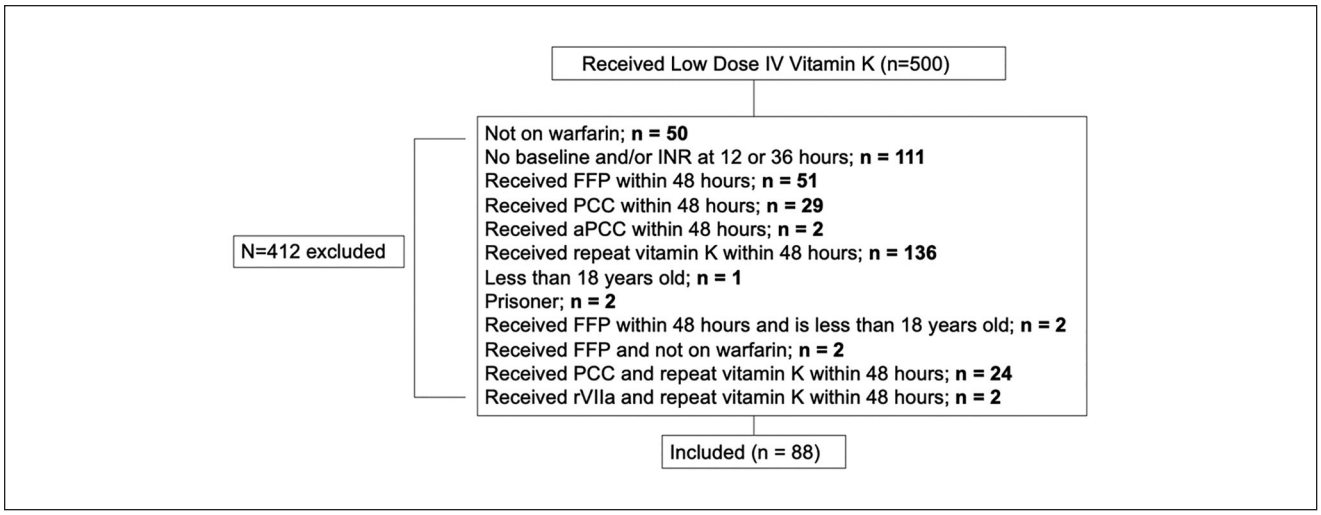

Figure 1. Flowchart of patient selection.
Abbreviations: aPCC, activated prothrombin complex concentrate; FFP, fresh frozen plasma; INR, international normalized ratio; IV, intravenous; rVIIa, recombinant factor VIIa.

Results

Baseline Characteristics

Of the 500 patients evaluated for inclusion, 88 patients met the inclusion criteria (Figure 1). Table 1 compares the baseline characteristics of patients who received ULD as compared with SLD IV vitamin K. There were no statistically significant differences between cohorts in terms of height, weight, BMI, or unit of care. The majority of patients in this study were given IV vitamin K while on a general medicine floor, though a large proportion of patients (n = 21, 42% ULD, vs n = 13, 34.2% SLD) were in the intensive care unit. The majority of patients within each cohort were being managed by a medical service. When assessing indication for warfarin, there was a statistically higher proportion of patients in the ULD cohort who were anticoagulated for the presence of a left-ventricular assistance device. The SLD cohort had a statistically significantly higher rate of mechanical heart valves and presence of a hypercoagulable state. The most common indications for warfarin therapy were atrial fibrillation, history of deep-vein thrombosis, and history of pulmonary embolism. It should be noted that some patients were on warfarin for multiple indications (eg, history of pulmonary embolism and atrial fibrillation), and Table 1 reflects each individual indication. SLD patients had a higher median weekly warfarin dose than ULD patients (ULD 20.5 mg vs SLD 35 mg). Bridge therapy was defined as therapeutic anticoagulation—either with therapeutic IV unfractionated heparin infusion or therapeutic enoxaparin given subcutaneously. There was no statistically significant difference in patients who required bridge therapy, nor in days of bridge therapy that were required.

Change in INR at 36 Hours

A total of 28 patients in the ULD cohort and 13 in the SLD cohort had both 12-hour and 36-hour INR levels drawn. At 36 hours, the median INR was statistically higher in the ULD cohort at 1.7 (1.5, 2.6) versus 1.5 (1.2, 1.8) in the SLD cohort ($P = 0.0354$; Figure 2). There was no statistically significant difference in the magnitude of median change in INR between the 2 cohorts (ΔINR, 0.52 [0.2, 0.91] vs 0.46 [0.18, 0.55]; $P = 0.607$). Figure 3 shows a representation of the actual INR values between cohorts.

Change in INR at 12 Hours

There were 59 patients with an INR at 12 hours with 33 in the ULD cohort and 26 in the SLD cohort. At 12 hours, the median INR in the ULD remained in the target at 2.3 (1.8, 3.4) compared with 1.8 (1.6, 2.3) in the SLD cohort (Figure 2). When comparing those in the ULD cohort versus the SLD cohort, there was no statistical difference in the magnitude of change in the median INR 12 hours after administration of vitamin K (ΔINR, 2.2 [1.1, 3.4] vs 2.2 [1.1, 6.3]; $P = 0.5488$).

30-Day VTE

There was no statistical difference in the 30-day VTE rates between cohorts (ULD, n = 2 [4%], vs SLD, n = 1 [2.6%]; >0.999).

30-Day Mortality

Of the 86 patients with information concerning death within 30 days, 49 were in the ULD cohort and 37 were in the SLD cohort. When comparing those who received ULD and

Table 1. Baseline Characteristics of Patients Receiving Ultralow-Dose Versus Standard-Low-Dose IV Vitamin K.

Variable	Ultralow dose (n = 50)	Standard low dose (n = 38)	*P* value
Age, years[a]	63.7 (15.3)	62.9 (16.1)	0.8269
Female[b]	27 (54)	20 (52.6)	0.8986
Height, cm[a] (n = 49, n = 38)	170 (10.7)	170.6 (9.7)	0.7998
Weight, kg[c]	79.7 (63.5, 104.3)	83.5 (66.6, 99.2)	0.7656
BMI, kg/m^2 (n = 49, n = 38)[c]	26.8 (23.0, 33.0)	28.5 (22.3, 33.2)	0.7685
Unit of care[b]			0.4573
ICU care	21 (42)	13 (34.2)	—
Ward care	29 (58)	25 (65.8)	—
Medical service[b]			0.5315
Medical	36 (72)	25 (65.8)	—
Surgical	14 (28)	13 (34.2)	—
Warfarin indication[b]			
Atrial fibrillation	29 (58)	21 (55.3)	0.7974
Deep-vein thrombosis	14 (28)	8 (21.1)	0.4560
Pulmonary embolism	8 (16)	8 (21.1)	0.5427
Left-ventricular assist device	9 (18)	0 (0)	0.0090
Mechanical heart valve	1 (2)	5 (13.2)	0.0397
Stroke	3 (6)	1 (2.6)	0.6307
Hypercoagulable state	0 (0)	4 (10.5)	0.0317
Other	11 (22)	8 (21.1)	0.9148
History of heart failure[b]	18 (36)	10 (26.3)	0.3340
Hemodialysis dependent[b]	10 (20)	7 (18.4)	0.8526
Serum creatinine, mg/dL[c]	1.4 (0.98, 2.3)	1.4 (1, 3.3)	0.8304
Weekly warfarin dose, mg[c] (n = 38, n = 35)	20.5 (15, 28)	35.0 (28, 45)	0.0002
Total bilirubin ≥1.5 mg/dL[a] (n = 37, n = 28)	27 (73.0)	24 (85.7)	0.2159
IV vitamin K dose, mg[c]	0.5 (0.25, 0.5)	1 (1, 2)	<0.0001
INR goal[b]			0.8238
<2	2 (4)	3 (7.9)	—
2 to 3	43 (86)	30 (79.0)	—
2.5 to 3.5	2 (4)	2 (5.3)	—
>3.5	0 (0)	0 (0)	—
Other	3 (6)	3 (7.9)	—
Days warfarin was held prior to IV vitamin K dose[c]	2 (0, 2)	0.5 (0, 2)	0.0507
INR prior to vitamin K dose[c]	5.1 (3.1, 7.3)	4.5 (2.8, 8.2)	0.7496
INR 12 hours after vitamin K dose[c] (n = 33, n = 26)	2.3 (1.8, 3.4)	1.8 (1.6, 2.3)	0.0445
Received bridge therapy[b]	12 (24)	8 (21.1)	0.7438
Days of bridge therapy[c] (n = 11, n = 6)	6 (3, 10)	5 (4, 5)	0.3225
Restarted warfarin[b]	39 (78)	28 (73.7)	0.6380

Abbreviations: BMI, body mass index; ICU, intensive care unit; INR, international normalized ratio; IV, intravenous.
[a]Mean (SD).
[b]Number of participants (%).
[c]Median (interquartile range).

those who received SLD, there was no statistical difference in the occurrence of death at 30 days (ULD, n = 4 [8.2%] vs SLD, n = 1 [2.7%]; $P = 0.3853$).

Discussion

This study sought to investigate the difference between the ability of ULD and SLD of IV vitamin K to prevent excessive INR reversal. This may be a consideration in situations where lowering of the INR is desired, but not to values below the target range, to allow continued anticoagulation without the need to initiate bridge therapy, especially with high thrombosis risks, such as hypercoagulable conditions, mechanical mitral valves, and ventricular assist devices. There was no detectable difference in the ULD and SLD groups with regard to INR reversal at 36 hours. At the minimum, this study suggests that ULD provides no more reversal than the SLD cohort.

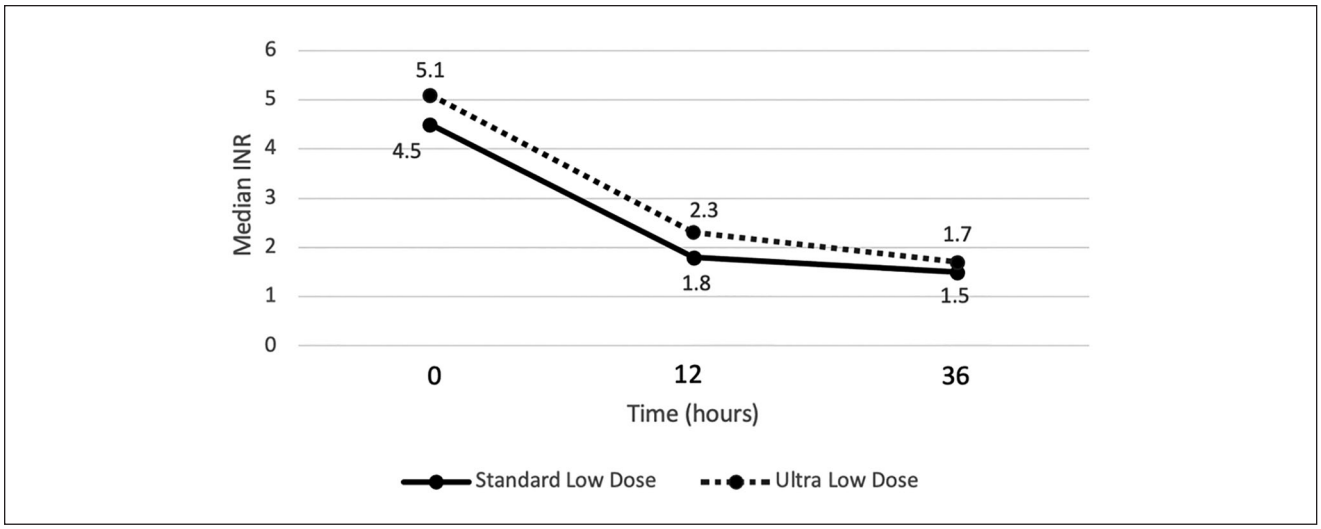

Figure 2. Change in median INR at 12 and 36 hours post–IV vitamin K administration.
Abbreviations: INR, international normalized ratio; IV, intravenous.

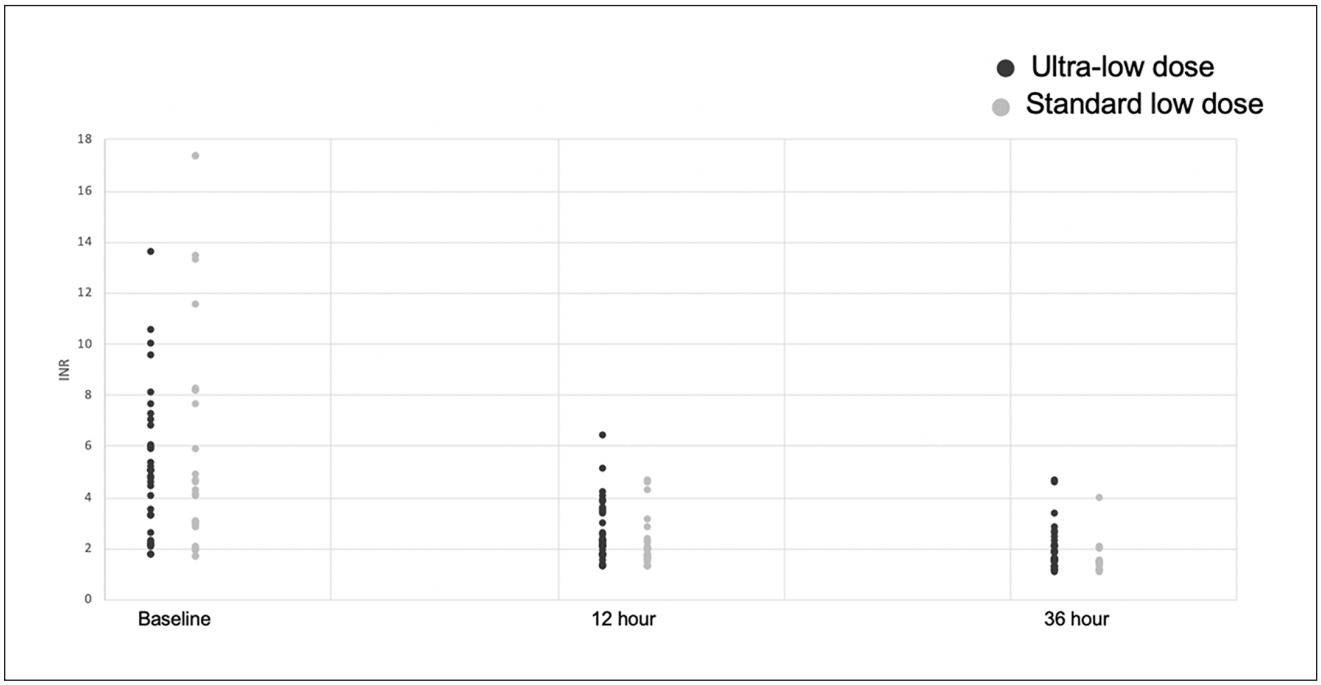

Figure 3. INR values at baseline, 12 hours, and 36 hours after the administration of IV vitamin K between ultralow-dose versus standard low-dose cohorts.
Abbreviations: INR, international normalized ratio; IV, intravenous.

In the assessment of the participants within this study, it was determined by both the physician and managing team that doses of 2 mg or more given IV or by mouth risked full reversal and that holding alone was determined in clinical assessment to not be desirable. Furthermore, subsequent days of elevated INR values could create a higher level of anticoagulation independent of the INR based on the further reduction of factor II. Based on the data by Tsu et al[14] and White et al,[18] doses of 2 mg or more of vitamin K (both IV and oral) do not produce further reversal, but just how low to dose to titrate to certain INR values has not been explored, which is what this study provides insight into.

The primary strength of this study was that major confounders that would have affected the change in INR were accounted for. This included the administration of fresh frozen plasma, aPCCs, prothrombin complex concentrations, recombinant factor VIIa, and repeat doses of IV vitamin K. This is also the first study of its kind to study the comparative effect of IV vitamin K doses as low as 0.25 to 0.5 mg. Although the study by Tsu et al[14] first elucidated that IV vitamin K over 2 mg did not further reverse the INR, the effect of these ULDs was still unknown prior to our study. This study fills an important void in the literature—to date, the CHEST guidelines still only address IV vitamin K doses of 5 mg or more, which can potentially lead to overreversal in many patients. The rates of 30-day VTE and mortality in our study were also similar to that found in previous low-dose vitamin K studies, which increases confidence that our study was well designed and could be replicated.[11]

This study had several limitations. First, the retrospective, observational design of this study contains all inherent limitations of this type of design—notably, interpretation of outcomes as an association and not cause and effect. Second, data were not collected in real time, and therefore, investigators had to rely on the accuracy of what was charted. It is possible, though highly unlikely, that blood products and other medications may have been administered to patients that may have influenced INR but that were not charted because our EMR combines this all together in reports. This is because at the institution where the study was conducted, medications and blood transfusions must be scanned and charted prior to administration. Additionally, another limitation was the falloff in the number of patients in the baseline INR measurement and subsequent measurements. This trial also seemed relatively small, with 88 patients. However, our study is the largest to date evaluating IV vitamin K doses less than 2 mg used to correct supratherapeutic INR values caused by warfarin. Third, other factors influencing INR, such as diet, were not controlled for in this trial, and patients had a variety of different INR goals. Elevations in INR could have been multifactorial and could have been a result of liver impairment, degree of illness, or nutritional deficiencies apart from vitamin K antagonist use; therefore, the effects that IV vitamin K could have had may be variable among patients. However, these limitations are also a strength in our study because these data lend to broad clinical application because our patient population was very diverse.

Conclusion and Relevance

Ultimately, this study gives credence to the idea that ULDs of IV vitamin K such as 0.25 or 0.5 mg may provide substantial INR-lowering effect, with a potential not to overreverse the INR. This study may be hypothesis generating for further studies to assess whether the vitamin K dose can be titrated to effect, with the idea that multiple ULDs could be given to a patient to prevent overreversal while still getting the benefit of partially reversing a supratherapeutic INR to a near-therapeutic value. Although there is always a risk of thrombosis with the overcorrection of the INR, in certain populations, such as those with left-ventricular assistance devices or mechanical heart valves, thrombosis can be catastrophic and contribute to significant morbidity and mortality. The use of ULD over SLD IV vitamin K in these select patient populations may be considered because these doses still arguably produce a clinically significant INR reduction while potentially avoiding overcorrection. More studies need to be conducted in this specialized field.

Declaration of Conflicting Interests

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