Annals of Internal Medicine | ARTICLE

Oral Vitamin K Versus Placebo to Correct Excessive Anticoagulation in Patients Receiving Warfarin

A Randomized Trial

Mark A. Crowther, MD, MSc; Walter Ageno, MD; David Garcia, MD; Luqi Wang, PhD; Dan M. Witt, PharmD; Nathan P. Clark, PharmD; Mark D. Blostein, MD; Susan R. Kahn, MD, MSc; Sara K. Vesely, PhD; Sam Schulman, MD; Michael J. Kovacs, MD; Marc A. Rodger, MD, MSc; Phillip Wells, MD, MSc; David Anderson, MD, MSc; Jeffery Ginsberg, MD; Rita Selby, MD, MSc; Sergio Siragusa, MD; Mauro Silingardi, MD; Mary Beth Dowd, PharmD; and Clive Kearon, MD, PhD

Background: Low-dose oral vitamin K decreases the international normalized ratio (INR) in overanticoagulated patients who receive warfarin therapy. Its effects on bleeding events are uncertain.

Objective: To see whether low-dose oral vitamin K reduces bleeding events over 90 days in patients with warfarin-associated coagulopathy.

Design: Multicenter, randomized, placebo-controlled trial. Randomization was computer-generated, and participants were allocated to trial groups by using sequentially numbered study drug containers. Patients, caregivers, and those who assessed outcomes were blinded to treatment assignment.

Setting: 14 anticoagulant therapy clinics in Canada, the United States, and Italy.

Patients: Nonbleeding patients with INR values of 4.5 to 10.0.

Intervention: Oral vitamin K, 1.25 mg (355 patients randomly assigned; 347 analyzed), or matching placebo (369 patients randomly assigned; 365 analyzed).

Measurements: Bleeding events (primary outcome), thromboembolism, and death (secondary outcomes).

Results: 56 patients (15.8%) in the vitamin K group and 60 patients (16.3%) in the placebo group had at least 1 bleeding complication (absolute difference, −0.5 percentage point [95% CI, −6.1 to 5.1 percentage points]); major bleeding events occurred in 9 patients (2.5%) in the vitamin K group and 4 patients (1.1%) in the placebo group (absolute difference, 1.5 percentage points [CI, −0.8 to 3.7 percentage points]). Thromboembolism occurred in 4 patients (1.1%) in the vitamin K group and 3 patients (0.8%) in the placebo group (absolute difference, 0.3 percentage point [CI, −1.4 to 2.0 percentage points]). Other adverse effects were not assessed. The day after treatment, the INR had decreased by a mean of 1.4 in the placebo group and 2.8 in the vitamin K group ($P < 0.001$).

Limitation: Patients who were actively bleeding were not included, and warfarin dosing after enrollment was not mandated or followed.

Conclusion: Low-dose oral vitamin K did not reduce bleeding in warfarin recipients with INRs of 4.5 to 10.0.

Funding: Canadian Institutes of Health Research and Italian Ministry of Universities and Research.

Ann Intern Med. 2009;150:293-300. www.annals.org

For author affiliations, see end of text.

ClinicalTrials.gov registration number: NCT00143715.

Warfarin is a remarkably effective drug for primary and secondary prevention of arterial and venous thromboembolism. Among commonly used medications, warfarin is unique because its dose–response characteristics are highly unpredictable, varying both among and within individuals over time. As a result, warfarin therapy requires ongoing monitoring using the international normalized ratio (INR), a value that reflects the degree to which warfarin has reduced coagulation factor levels and the coagulant potential of blood (1). For most indications, an INR range of 2.0 to 3.0 is targeted; INR values less than 2.0 are associated with an increased risk for thromboembolism, and INR values greater than 4.0 are associated with an increase in bleeding complications. The risk for bleeding, particularly intracranial bleeding, increases markedly as the INR exceeds 4.5 (1–3). Even in clinics dedicated to warfarin management, INRs are outside the therapeutic range one third to one half the time (4).

When managing a patient with an INR greater than 4.5 who is not bleeding, clinicians generally either withhold warfarin treatment and allow the INR to decrease to the desired value or administer vitamin K (orally or intravenously) to more rapidly reduce the INR (1, 5–10). Small randomized trials have shown that a single dose of low-dose oral vitamin K (for example, 1 to 2.5 mg) effectively reduces the INR in otherwise-stable overanticoagulated patients within 24 hours of its administration; however, these studies were not large enough to determine whether low-dose vitamin K reduces bleeding without increasing the risk for thromboembolism (11–15). A recent systematic review (16) supported this observation. To determine whether oral vitamin K is indicated in overanticoagulated

See also:

Print

Editors' Notes 294

Summary for Patients I-25

Web-Only

Conversion of graphics into slides

Context

Vitamin K decreases the international normalized ratio (INR) in overanticoagulated patients who receive warfarin therapy, but its effect on clinical outcomes is less clear.

Contribution

Trial investigators detected no differences in the frequency of bleeding, thromboembolism, or death among overanticoagulated patients who received warfarin therapy and were randomly assigned to receive low-dose vitamin K or placebo.

Caution

The study was underpowered to detect differences in major bleeding.

Implication

Low-dose vitamin K corrects the INR in overanticoagulated patients who received warfarin therapy, but it has little effect on clinical outcomes. Withdrawal of warfarin may be all that is necessary to manage elevated INRs.

—The Editors

patients who are not bleeding, we did a randomized trial in which we allocated oral vitamin K or placebo, 1.25 mg, to patients who presented with an INR of 4.5 to 10.0. The primary outcome measure was the frequency of all forms of bleeding events during the first 90 days. Our hypothesis that bleeding events would be reduced was based on our previously published, smaller studies of low-dose oral vitamin K administered to various patient groups. In these studies, we found a consistent and rapid decrease in the INR after low-dose vitamin K was administered (13, 15, 17–22).

METHODS

Study Patients

We identified patients with INRs of 4.5 to 10.0 in participating outpatient anticoagulant therapy clinics. We screened patients as they presented for routine INR assessment and considered them for eligibility if they were receiving warfarin therapy with a target INR of 2.0 to 3.5, their most recent INR was between 4.5 and 10.0 in the past 24 hours, and they were not bleeding. We excluded patients if discontinuation of warfarin therapy was scheduled and if they were younger than 18 years, had a life expectancy less than 10 days, had an indication for acute normalization of their INR (such as imminent surgery), had a known severe liver disease, had a history of a major bleeding event within 1 month, had a known bleeding disorder, had received thrombolytic therapy within 48 hours, had a platelet count less than 50×10^9 cells/L, could not take oral medications, had a known allergy to vitamin K, or could not return for laboratory or clinical monitoring. Study staff at each participating anticoagulant therapy clinic approached patients who met inclusion criteria for consent to participate.

This study ran in parallel with a cohort study in which patients with INRs greater than 10.0 received oral vitamin K, 2.5 mg. Patients were otherwise identical to those enrolled in this study, and we followed them for similar outcome events. The results of the concurrent cohort study will be presented in a subsequent paper.

Randomization and Treatment

We instructed all eligible, consenting patients to withhold warfarin for 1 day and randomly assigned them to receive a capsule containing either vitamin K, 1.25 mg, or placebo. Randomization was done by using a computer-generated random-number table at the coordinating and methods center and was stratified by clinical center. Vitamin K capsules were compounded from 5-mg vitamin K tablets (Merck & Co., Whitehouse Station, New Jersey) by a commercial pharmacy with Health Canada approval (Clinical Trials Application control number 092635). Placebo capsules contained inert filler and were indistinguishable from the capsules that contained vitamin K. Random allocation of patients was accomplished when site-specific study personnel dispensed the next numbered study drug container at each clinical center; thus, patients, treating clinicians, and research coordinators were unaware of treatment allocation.

In 2 centers, we monitored the INR of outpatients in clinics or laboratories outside the clinical center. In such centers, we obtained consent for the study by telephone, and the study drug was shipped within hours to the patient's home by using a courier service. In all cases, we confirmed receipt and consumption of the study drug on the day of randomization by telephone. In the remaining centers, in which patients were seen in person, consent and study drug administration occurred at the same time that the elevated INR was detected.

Follow-up and Outcome Measures

At enrollment, we advised patients to promptly seek medical evaluation if they developed signs or symptoms of bleeding or thromboembolism. At minimum, we assessed patients by telephone or in person on days 1, 3, 7, 14, 28, and 90 after randomization. Additional contact and INR sampling necessary to manage the patient's anticoagulant therapy were done at the discretion of the patient's physician. At each follow-up, we sought signs and symptoms of bleeding and thromboembolism and collected details about all such events. We asked patients a focused series of questions to help them recall these events. We reviewed and abstracted medical records of all suspected bleeding episodes, thromboembolism, and deaths.

Our primary outcome measure was the frequency of bleeding events during the 90 days after randomization. We defined "major bleeding" as fatal bleeding, bleeding

requiring transfusion of 2 or more units of packed red blood cells, bleeding resulting in a therapeutic intervention (such as endoscopy), or objectively confirmed bleeding into an enclosed space. We defined "minor bleeding" as bleeding resulting in a medical assessment that did not meet criteria as a major bleeding event. We defined "trivial bleeding" as all patient-reported bleeding events that did not result in a medical assessment. We combined all reported bleeding events (major, minor, and trivial) for this analysis. We chose to combine these events because our clinical experience suggested that reducing medically unimportant but bothersome bleeding, such as epistaxis, bruising, and menorrhagia, was a clinically important goal for our patients; patients with a minor or trivial bleeding event may be at greater risk for subsequent major bleeding; and the frequency of major bleeding was likely to be very low, calling into question the feasibility of a study powered to detect differences in major bleeding events.

Secondary outcome measures included the frequency of major bleeding events, objectively confirmed venous or arterial thromboembolism, and death during the 90 days after randomization. We chose the 90-day period on the basis of our previous studies wherein we found a significant reduction in bleeding events (90 days) after the administration of similar doses of oral vitamin K (13). We hypothesized that low-dose oral vitamin K might influence a bleeding event during this extended period, because even small doses of this highly lipophilic drug might have an extended influence on INR control (and thus the risk for bleeding and thrombosis). In post hoc analyses, we examined the frequency of all bleeding and major bleeding events in the first 7 days and the number of clinical events in patients who were older than 70 years at enrollment.

An independent adjudication committee, blinded to treatment allocation and not otherwise involved in the study, reviewed all bleeding events, thromboembolism, and deaths. Confirmation of venous thromboembolism required a nononcompressible venous segment on ultrasonography, an intraluminal filling defect on venography or computed tomographic pulmonary angiography, or a segmental (or larger) mismatch defect on ventilation–perfusion lung scan. Arterial thromboembolism required either direct surgical visualization of thrombus; an intraluminal filling defect on angiography; or clear evidence of a new ischemic event on an objective test, such as electrocardiography, computed tomography, or magnetic resonance imaging.

We advised clinics to reinstitute warfarin therapy once the INR was within the therapeutic reference interval after administration of the study drug. The clinicians who cared for the patients determined the warfarin dose when the drug was readministered. Target INR ranges for individual patients did not change as a result of the elevated INR that led to enrollment.

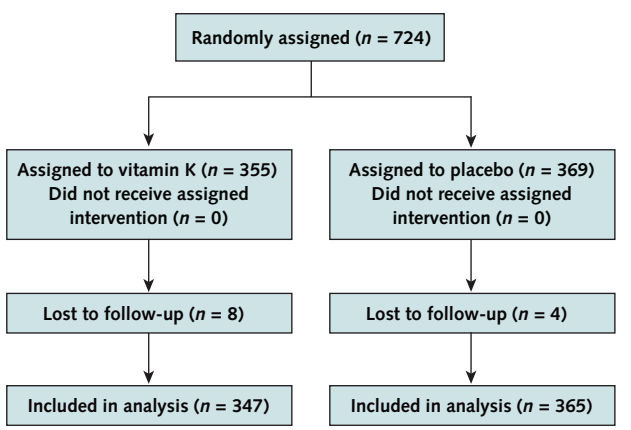
Statistical Analysis

Our primary analysis was an intention-to-treat comparison of the proportions of patients in the 2 study groups who had at least 1 bleeding episode. The study was powered to detect an absolute 5% reduction in the frequency of all bleeding events with vitamin K, with the assumption that the frequency of bleeding would be 8% in the placebo group. This reduction was based on previous studies (13, 23) and the assumption that clinicians will treat 20 patients to prevent 1 bleeding episode. To have 80% power to detect this difference with a 2-sided P value of 0.05, a sample size of 330 patients per group was required.

We calculated proportions with 95% CIs and risk differences with 95% CIs by using Microsoft Excel (Microsoft, Redmond, Washington). We used a template prepared by 1 of the authors to calculate the exact 95% CI for a single proportion and the 95% CI for the difference between 2 independent sample proportions by using Yates correction for continuity (24). For proportion analysis and the Mantel–Haenszel analysis, we used EpiInfo, version 6 (Centers for Disease Control and Prevention, Atlanta, Georgia), and SAS statistical software, version 9.1 for Windows (SAS Institute, Cary, North Carolina). We compared means of continuous variables by using Microsoft Excel (t test function).

An independent data safety monitoring board that externally supervised the study reviewed events after we enrolled approximately 50% of patients. This committee ensured the safety of the study by examining the frequency of major bleeding events, thromboembolisms, and deaths and comparing these frequencies with our a priori expectations.

Figure. **Study flow diagram.**



Patients were screened from large anticoagulant therapy clinics by using the inclusion and exclusion criteria to assess eligibility. Because of the high throughput of such clinics, the numbers of patients screened, ineligible patients, and eligible but not enrolled patients are unknown. We attempted to enroll consecutive eligible patients; however, on many days, research personnel would not have been able to accommodate all eligible patients because of their number.

Table 1. **Baseline Characteristics**

Characteristic	Vitamin K Group (*n* = 355)	Placebo Group (*n* = 369)
Mean age (SD), *y*	69.5 (14.2)	68.5 (13.5)
Men, *n (%)*	188 (53.0)	195 (52.8)
Mean INR at enrollment (range)	6.0 (4.5–9.9)	5.8 (4.5–9.5)
Indication for warfarin therapy, *n (%)**		
Treatment of arterial or venous thromboembolism	138 (38.9)	148 (40.1)
Primary prevention of venous thromboembolism	29 (8.2)	26 (7.0)
Atrial fibrillation	150 (42.3)	165 (44.7)
Artificial heart valve	82 (23.1)	76 (20.6)
Risk factors for a bleeding event at enrollment, *n (%)*		
Previous bleeding event	63 (17.7)	65 (17.6)
Renal insufficiency	16 (4.5)	21 (5.7)
Cancer	30 (8.5)	30 (8.1)
Target INR range, *n (%)*		
2.0–3.0†	273 (76.9)	289 (78.3)
2.5–3.5‡	82 (23.1)	80 (21.7)
Country, *n (%)*		
United States	112 (31.5)	125 (33.9)
Italy	69 (19.4)	68 (18.4)
Canada	174 (49.1)	176 (47.7)

INR = international normalized ratio.
* Patients may have had ≥1 indication for warfarin therapy.
† One patient with a target INR range of 1.8 to 2.5 was included in the placebo group.
‡ One and 3 patients with a target INR range of 3.0 to 4.0 were inadvertently included in the vitamin K group and placebo group, respectively. These patients were retained throughout the analysis.

Role of the Funding Source

The Canadian Institutes of Health Research and the Italian Ministry of Universities and Research provided funding for the study. Vitamin K tablets were provided at no cost by Merck & Co. Neither Merck & Co. nor the funding sources had a role in study design, implementation, data collection, interpretation, and analysis of the study, or preparation of the manuscript or in the decision to submit the manuscript for publication. The authors had complete access to all data. The study was coordinated through the Thromboembolism Unit at St. Joseph's Healthcare, Hamilton, Ontario, Canada.

RESULTS

From September 2004 to June 2006, we enrolled 724 patients at 14 clinical centers in Canada, the United States, and Italy. In total, 355 patients received vitamin K and 369 received placebo (all patients received therapy as allocated) (**Figure**). Patient characteristics were similar in the 2 groups (**Table 1**). Twelve patients (1.7%) were lost to follow-up. The last days of follow-up in these patients were day 2 (1 patient), day 8 (1 patient), and day 29 (6 patients) in patients who received vitamin K and day 29 (4 patients) in patients who received placebo. All other patients were followed until death or for the full 90 days. **Table 2** shows clinical outcomes in all patients and subgroups, and **Table 3** shows clinical outcomes by INR at presentation.

Bleeding Events

In the 90 days after enrollment, 56 of 355 patients (15.8% [95% CI, 12.1% to 20.0%]) allocated to vitamin K and 60 of 369 patients (16.3% [CI, 12.6% to 20.4%]) allocated to placebo had a bleeding event (absolute difference, −0.5 percentage point [CI, −6.1 to 5.1 percentage points]). Major bleeding events occurred in 9 patients (2.5% [CI, 1.2% to 4.8%]) allocated to vitamin K and 4 patients (1.1% [CI, 0.3% to 2.8%]) allocated to placebo (absolute difference, 1.5 percentage points [CI, −0.8 to 3.7 percentage points]). Within 7 days, 28 patients (7.9%) allocated to vitamin K and 34 patients (9.2%) allocated to placebo had bleeding events (absolute difference, −1.3 percentage points [CI, −5.7 to 3.0 percentage points]).

Table 2. **Major Clinical Outcomes**

Outcome	Day 90				Day 30			
	Vitamin K Group [95% CI], *n (%)*	Placebo Group [95% CI], *n (%)*	Risk Difference (95% CI), *percentage points*	*P* Value	Vitamin K Group [95% CI], *n (%)*	Placebo Group [95% CI], *n (%)*	Risk Difference (95% CI), *percentage points*	*P* Value
Any bleeding event	56 (15.8 [12.1 to 20.0])	60 (16.3 [12.6 to 20.4])	−0.5 (−6.1 to 5.1)	0.86*	41 (11.5 [8.4 to 15.3])	47 (12.7 [9.5 to 16.6])	−1.2 (−6.2 to 3.8)	0.63†
Major bleeding event	9 (2.5 [1.2 to 4.8])	4 (1.1 [0.3 to 2.8])	1.5 (−0.8 to 3.7)	0.22‡	–	–	–	–
Thromboembolism	4 (1.1 [0.3 to 2.9])	3 (0.8 [0.2 to 2.4])	0.3 (−1.4 to 2.0)	0.72‡	2 (0.6 [0.1 to 2.0])	1 (0.3 [0.0 to 1.5])	0.3 (−0.9 to 1.5)	0.62†
Death	7 (2.0 [0.8 to 4.0])	7 (1.9 [0.8 to 3.9])	0.1 (−2.2 to 2.4)	0.94‡	1 (0.3 [0.0 to 1.6])	5 (1.4 [0.4 to 3.1])	−1.1 (−2.7 to 0.5	0.22†

* Prespecified primary outcome.
† Post hoc exploratory analysis.
‡ Prespecified secondary outcome.

Table 3. **Main Study Outcomes in the First 7 Days, by INR at Presentation**

Outcome	INR Range at Presentation					
	4.5–6.0		6.1–8.0		8.1–10.0	
	Vitamin K Group (*n* = 226), *n*	Placebo Group (*n* = 261), *n*	Vitamin K Group (*n* = 103), *n*	Placebo Group (*n* = 82), *n*	Vitamin K Group (*n* = 26), *n*	Placebo Group (*n* = 26), *n*
Major bleeding event	0	2*	0	0	1†	0
Any bleeding event	12	22	9	8	7	4
Death	0	0	0	1‡	0	0
Thromboembolism	0	0	1	1	0	0

INR = international normalized ratio.
* Day 1 and 5.
† Day 1.
‡ The patient died of septicemia on day 5 after enrollment.

Three of these events were major, and 2 of the 3 occurred in patients allocated to placebo.

The primary analysis assumed that patients who were lost to follow-up did not have bleeding outcomes after their censoring event. We did 2 sensitivity analyses to explore the effect of losses during follow-up. In the first (worst-case) scenario, we assumed that all 8 patients in the vitamin K group and none of the 4 patients in the placebo group lost to follow-up had bleeding events. In the second (best-case) scenario, we assumed the converse. In the worst-case scenario, the risk difference was 1.8 percentage points (CI, −4.0 to 7.5 percentage points) favoring placebo, and in the best-case scenario, the risk difference was −1.6 percentage points (−7.3 to 4.0 percentage points) favoring vitamin K. The results of this analysis are consistent with the frequency of events found in our primary analysis.

Our results were not affected by an analysis stratified by center. Estimated relative risks for all bleeding events were similar by using a Mantel–Haenszel stratified analysis (relative risk, 0.97 [CI, 0.71 to 1.33) and an unstratified analysis (relative risk, 0.97 [CI, 0.69 to 1.35]).

Table 2—**Continued**

Day 7			
Vitamin K Group [95% CI], *n (%)*	Placebo Group [95% CI], *n (%)*	Risk Difference (95% CI), *percentage points*	*P* Value
28 (7.9 [5.3 to 11.2])	34 (9.2 [6.5 to 12.6])	−1.3 (−5.7 to 3.0)	0.52†
–	–	–	–
1 (0.3 [0.0 to 1.6])	1 (0.3 [0.0 to 1.5])	0.0 (−1.0 to 1.1)	1.00†
0 (0.0 [0.0 to 1.0])	1 (0.3 [0.0 to 1.5])	0.3 (−1.1 to 0.5)	1.00†

Thromboembolism

Over 90 days, 4 patients (1.1%) allocated to vitamin K and 3 patients (0.8%) allocated to placebo had thromboembolism (risk difference, 0.3 percentage point [CI, −1.4 to 2.0 percentage points). Two of these events, 1 in a patient allocated to placebo, occurred within 7 days of enrollment.

Death

Over 90 days, 7 patients (2.0%) allocated to vitamin K and 7 patients (1.9%) allocated to placebo died (risk difference, 0.1 percentage point [CI, −2.2 to 2.4 percentage points]). No deaths were adjudicated as being due to thromboembolism.

INR Response

The INR decreased more rapidly in the patients allocated to vitamin K. In patients who received vitamin K, the mean INR was 5.95 (CI, 5.83 to 6.07) at enrollment and 3.17 (CI, 3.06 to 3.28) the day after the study drug was administered. In patients allocated to placebo, the corresponding values were 5.75 (CI, 5.64 to 5.86) and 4.40 (CI, 4.24 to 4.54). The average INR decrease (1.4 INR units in the placebo group and 2.8 INR units in the vitamin K group) was significantly greater in the vitamin K group ($P < 0.001$). The INR values the day after the study drug was administered were available for 333 of 355 patients (93.8%) allocated to vitamin K and 343 of 369 patients (93.0%) allocated to placebo. The day after the study drug was administered, 3 patients (0.9%) allocated to placebo and 25 patients (7.6%) allocated to vitamin K had an INR less than 2.0; 34 (10.1%) in the placebo group and 136 (41.6%) in the vitamin K group had an INR between 2.0 and 3.0 ($P < 0.001$ for both comparisons of proportions).

Influence of Age on Outcomes

Two hundred patients allocated to vitamin K and 188 patients allocated to placebo were 70 years or older at enrollment. Of these patients, 195 in the vitamin K group and 184 in the placebo group were followed until death or day 90. The number of bleeding events (28 vs. 28), thromboembolisms (2 vs. 2), or deaths (2 vs. 5) did not signifi-

cantly differ between the vitamin K and placebo groups. Major bleeding events seemed to be more common in patients older than 70 years: Of the 13 major bleeding events reported in the study, 10 (77% [CI, 46% to 95%]) occurred in patients older than 70 years.

Interim Analysis

We did an interim analysis after 50% of patients were enrolled. The study's data safety monitoring board compared global and unadjudicated rates of major bleeding events, thromboembolism, and death combined for the 2 study groups with the rates predicted in the study design. The committee found the overall rates to be consistent with our expectations and recommended continuation of the study.

DISCUSSION

We found no differences in the frequency of overall or major bleeding events when we compared low-dose vitamin K with placebo for patients who received warfarin therapy and had INRs of 4.5 to 10.0, suggesting that vitamin K does not effectively reduce bleeding in overanticoagulated patients. However, our finding of no effect was consistent with an absolute increase of 5.1% in the frequency of overall bleeding events with vitamin K or an absolute reduction of 6.1%. Despite this negative primary finding, we detected no between-group differences in the frequency of stroke or thromboembolism, suggesting that vitamin K is at least safe, and confirmed previous observations that a low dose of oral vitamin K more rapidly returns the INR toward the therapeutic range.

Our finding of no difference in the frequency of bleeding events has several potential explanations. First, our study may have missed a vitamin K effect because we followed patients for 90 days after study drug administration. The 90-day period was based on our previous study in which we saw a significant reduction in bleeding events when low-dose oral vitamin K was administered (13). In retrospect, this observation was probably due to chance. However, in post hoc analyses of this study, we did not observe any differences in bleeding events at 7 and 30 days, suggesting that, although the INR is corrected by vitamin K, this correction is not accompanied by important changes in the propensity of patients to have a bleeding event during shorter follow-up. Second, any effect of vitamin K on bleeding events may have been obscured by our careful collection of details of all types of bleeding events: The frequency of bleeding events (15.8% in patients allocated to vitamin K and 16.3% in patients allocated to placebo) was higher than that predicted in our sample size calculation. This increase in the frequency is probably due to our extended duration of follow-up and our frequent and protocol-directed inquiries into all types of bleeding complications at each contact between research personnel and study participants. Third, our study was underpowered to detect important differences in major bleeding events (although major bleeding events were a secondary outcome measure). Major bleeding events actually occurred less frequently than previously reported for patients who presented with markedly prolonged INR values. We believe that the low number of observed bleeding events (especially in the placebo group) is important because it is consistent with previous work (10). Although the absolute number of major bleeding events was small (9 in patients allocated to vitamin K and 4 in patients allocated to placebo), there was no significant imbalance in major bleeding events that favored placebo. The small number of major bleeding events explains the wide CIs about our estimates of bleeding rates. Consistent with previous reports, **Table 3** demonstrates that bleeding within 7 days of enrollment occurred more often in patients with INRs of 8.1 to 10.0 than in those with INRs of 4.5 to 6.0 (34 of 487 vs. 11 of 52 patients who had a bleeding event; $P < 0.001$). Thus, although many potential explanations for the observed lack of reduction in bleeding events can be proposed, our results cannot satisfactorily explain this observation.

Death and thromboembolism occurred infrequently and were balanced between study groups. This observation suggests that vitamin K is safe and, when used at the doses we used in this study, does not cause thrombosis because of inadvertent overcorrection of the INR.

Strengths of our study include randomization with concealed allocation; blinding of clinicians, patients, and outcome adjudicators; intention-to-treat analysis; and complete follow-up in almost all patients. These characteristics minimize bias. Enrollment of a representative, heterogeneous sample of patients who present with warfarin-associated coagulopathy enhances the generalizability of our findings. We chose not to use a composite outcome measure for our analysis because the relative weight that should be afforded to bleeding events, thrombosis, and death remains controversial.

The main limitation of our study is that it was not powered to detect small differences in the frequency of major bleeding events. However, our findings suggest that it is very unlikely that administering vitamin K would reduce the absolute frequency of major bleeding events by as much as 1%, and in absolute terms, more major bleeding events occurred in patients allocated to vitamin K. This unexpected increase was probably due to chance; however, it might be a real observation. For example, in selected patients, even low-dose vitamin K might produce short-term increases in average warfarin requirements. As time passes and the vitamin K effect is lost, the warfarin dose might not be appropriately reduced, resulting in overanticoagulation and an increased risk for a bleeding event. An additional limitation is our inability to rule out administration of open-label vitamin K to patients with new or persistent INR elevation during the 90 days after enrollment. To our knowledge, this occurred rarely and usually in the setting of a bleeding event. Because this study was designed to be pragmatic, we did not dictate or monitor the frequency of INR testing or warfarin dosing after enrollment. For example, we did not mandate INR measurement the day after the study drug was administered, and

thus, this value was not available for 6.6% of patients. We made this decision to simplify the study and reduce the likelihood that study-recording requirements (outside the administration of the study drug) influenced INR control and therefore the likelihood of bleeding or other outcome events. A secondary limitation of our study is that we used a dry powder form of vitamin K. In many jurisdictions, only liquid forms of vitamin K are available; whether our results apply to other forms of vitamin K is unknown.

Our results are important because they inform day-to-day clinical practice. We chose to administer oral vitamin K, 1.25 mg, because this dose is one quarter of the most widely available vitamin K tablet. Although a 2.5-mg dose (one half of a "standard" tablet in the United States) may have been more practical, our anecdotal experience suggested that this dose was excessive and would have overcorrected the INR in many patients. Our results support the practice of treating patients with INRs between 4.5 and 10.0 with simple warfarin therapy withdrawal and reinstitution once the INR has decreased into the desired range. This approach to management produced rates of bleeding events similar to those seen with the more complex approach of actively decreasing the INR with oral vitamin K and was associated with a low frequency of major bleeding events. The low frequency of major bleeding events in patients allocated to placebo during the first 7 days of this study is very similar to that reported in 2 cohort studies of similar patients who were managed without active reversal of the INR by using vitamin K in community practice settings (10, 25), but it is lower than that in a smaller study in a largely urban population that may have had additional risk factors for bleeding events (23). The results of this trial should not be applied to patients who present with active bleeding, those who require acute normalization of their INR, or those with INRs greater than 10.0.

In conclusion, although a small dose of oral vitamin K helped to correct supratherapeutic INR values, it did not substantially reduce the frequency of bleeding events. Furthermore, major bleeding was uncommon in such patients, regardless of whether vitamin K was administered.

From McMaster University, Hamilton, Ontario, Canada; University of Insubria, Varese, Italy; University of New Mexico, Albuquerque, New Mexico; Kaiser Permanente, Denver, Colorado; McGill University, Montreal, Quebec, Canada; University of Western Ontario, London, Ontario, Canada; University of Ottawa, Ottawa, Ontario, Canada; Dalhousie University, Halifax, Nova Scotia, Canada; University of Toronto, Toronto, Ontario, Canada; University of Palermo, Palermo, Italy; Reggio Emilia Hospital, Reggio Emilia, Italy; and University of Oklahoma, Oklahoma City, Oklahoma.

Grant Support: By the Canadian Institutes of Health Research and the Italian Ministry of Universities.

Potential Financial Conflicts of Interest: *Employment:* L. Wang (McMaster University). *Consultancies:* M.A. Crowther (Anton Pharmaceuticals).

Reproducible Research Statement: *Study protocol*: Available from www.clinicaltrials.gov. *Statistical code and data set*: Available from Dr. Crowther (e-mail, crowthrm@mcmaster.ca) after approval by the steering committee.

Requests for Single Reprints: Mark A. Crowther, MD, MSc, Division of Hematology and Thromboembolism, McMaster University Faculty of Health Sciences, Room L208, St. Joseph's Hospital, 50 Charlton Avenue East, Hamilton, Ontario L8N 4A6, Canada; e-mail, crowthrm@mcmaster.ca.

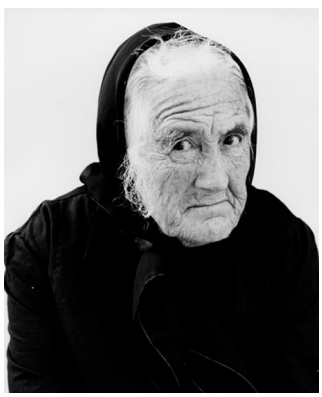
Current author addresses and author contributions are available at www.annals.org.

References

1. **Ansell J, Hirsh J, Hylek E, Jacobson A, Crowther M, Palareti G; American College of Chest Physicians.** Pharmacology and management of the vitamin K antagonists: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest. 2008;133:160S-198S. [PMID: 18574265]
2. **Odén A, Fahlén M.** Oral anticoagulation and risk of death: a medical record linkage study. BMJ. 2002;325:1073-5. [PMID: 12424167]
3. **Palareti G, Leali N, Coccheri S, Poggi M, Manotti C, D'Angelo A, et al.** Bleeding complications of oral anticoagulant treatment: an inception-cohort, prospective collaborative study (ISCOAT). Italian Study on Complications of Oral Anticoagulant Therapy. Lancet. 1996;348:423-8. [PMID: 8709780]
4. **Witt DM, Sadler MA, Shanahan RL, Mazzoli G, Tillman DJ.** Effect of a centralized clinical pharmacy anticoagulation service on the outcomes of anticoagulation therapy. Chest. 2005;127:1515-22. [PMID: 15888822]
5. **Ageno W, Garcia D, Libby E, Crowther MA.** Managing oral anticoagulant therapy in patients with mechanical heart valves undergoing elective surgery: results of a survey conducted among Italian physicians. Blood Coagul Fibrinolysis. 2004;15:623-8. [PMID: 15613916]
6. **Garcia DA, Ageno W, Libby EN, Bibb J, Douketis J, Crowther MA.** Perioperative anticoagulation for patients with mechanical heart valves: a survey of current practice. J Thromb Thrombolysis. 2004;18:199-203. [PMID: 15815882]
7. **Libby EN, Garcia DA.** A survey of oral vitamin K use by anticoagulation clinics. Arch Intern Med. 2002;162:1893-6. [PMID: 12196089]
8. **Oh D, Kim S, Lim CY, Lee JS, Park S, Garcia D, et al.** Perioperative anticoagulation in patients with mechanical heart valves undergoing elective surgery: results of a survey conducted among Korean physicians. Yonsei Med J. 2005;46:66-72. [PMID: 15744807]
9. **Dentali F, Ageno W, Crowther M.** Treatment of coumarin-associated coagulopathy: a systematic review and proposed treatment algorithms. J Thromb Haemost. 2006;4:1853-63. [PMID: 16961594]
10. **Garcia DA, Regan S, Crowther M, Hylek EM.** The risk of hemorrhage among patients with warfarin-associated coagulopathy. J Am Coll Cardiol. 2006;47:804-8. [PMID: 16487849]
11. **Pengo V, Banzato A, Garelli E, Zasso A, Biasiolo A.** Reversal of excessive effect of regular anticoagulation: low oral dose of phytonadione (vitamin K_1) compared with warfarin discontinuation. Blood Coagul Fibrinolysis. 1993;4:739-41. [PMID: 8292723]
12. **Cosgriff SW.** The effectiveness of an oral vitamin K_1 in controlling excessive hypoprothrombinemia during anticoagulant therapy. Ann Intern Med. 1956;45:14-22. [PMID: 13340565]
13. **Crowther MA, Julian J, McCarty D, Douketis J, Kovacs M, Biagoni L, et al.** Treatment of warfarin-associated coagulopathy with oral vitamin K: a randomised controlled trial. Lancet. 2000;356:1551-3. [PMID: 11075768]
14. **Yiu KH, Siu CW, Jim MH, Tse HF, Fan K, Chau MC, et al.** Comparison of the efficacy and safety profiles of intravenous vitamin K and fresh frozen plasma as treatment of warfarin-related over-anticoagulation in patients with mechanical heart valves. Am J Cardiol. 2006;97:409-11. [PMID: 16442406]
15. **Ageno W, Garcia D, Silingardi M, Galli M, Crowther M.** A randomized trial comparing 1 mg of oral vitamin K with no treatment in the management of warfarin-associated coagulopathy in patients with mechanical heart valves [Letter]. J Am Coll Cardiol. 2005;46:732-3. [PMID: 16098445]
16. **Dezee KJ, Shimeall WT, Douglas KM, Shumway NM, O'Malley PG.** Treatment of excessive anticoagulation with phytonadione (vitamin K): a meta-analysis. Arch Intern Med. 2006;166:391-7. [PMID: 16505257]
17. **Crowther MA, Douketis JD, Schnurr T, Steidl L, Mera V, Ultori C, et al.** Oral vitamin K lowers the international normalized ratio more rapidly than subcutaneous vitamin K in the treatment of warfarin-associated coagulopathy. A

randomized, controlled trial. Ann Intern Med. 2002;137:251-4. [PMID: 12186515]
18. **Woods K, Douketis JD, Kathirgamanathan K, Yi Q, Crowther MA.** Low-dose oral vitamin K to normalize the international normalized ratio prior to surgery in patients who require temporary interruption of warfarin. J Thromb Thrombolysis. 2007;24:93-7. [PMID: 17380255]
19. **Whitlock RP, Crowther MA, Warkentin TE, Blackall MH, Farrokhyar F, Teoh KH.** Warfarin cessation before cardiopulmonary bypass: lessons learned from a randomized controlled trial of oral vitamin K. Ann Thorac Surg. 2007; 84:103-8. [PMID: 17588394]
20. **Gunther KE, Conway G, Leibach L, Crowther MA.** Low-dose oral vitamin K is safe and effective for outpatient management of patients with an INR > 10. Thromb Res. 2004;113:205-9. [PMID: 15140584]
21. **Ageno W, Crowther M, Steidl L, Ultori C, Mera V, Dentali F, et al.** Low dose oral vitamin K to reverse acenocoumarol-induced coagulopathy: a randomized controlled trial. Thromb Haemost. 2002;88:48-51. [PMID: 12152676]
22. **Crowther MA, Donovan D, Harrison L, McGinnis J, Ginsberg J.** Low-dose oral vitamin K reliably reverses over-anticoagulation due to warfarin. Thromb Haemost. 1998;79:1116-8. [PMID: 9657434]
23. **Hylek EM, Chang YC, Skates SJ, Hughes RA, Singer DE.** Prospective study of the outcomes of ambulatory patients with excessive warfarin anticoagulation. Arch Intern Med. 2000;160:1612-7. [PMID: 10847254]
24. **Fleiss JL, Levin B, Paik MC.** Statistical Methods for Rates and Proportions. 3rd ed. Hoboken, NJ: J Wiley; 2008.
25. **Lousberg TR, Witt DM, Beall DG, Carter BL, Malone DC.** Evaluation of excessive anticoagulation in a group model health maintenance organization. Arch Intern Med. 1998;158:528-34. [PMID: 9508231]coagulation. Ann Intern Med. 2007;147;I-38.

Congratulations to Federico R. Justiniani, MD, winner of the 2008 *Annals* Personae prize. Dr. Justiniani's photograph was published on the cover of the 21 October 2008 issue (vol. 149, no. 8) and is reprinted below.



For more information on the *Annals* Personae Prize and to view a list of past winners, go to www.annals.org/shared/aim_personae.shtml.

Current Author Addresses: Dr. Crowther: Division of Hematology and Thromboembolism, McMaster University Faculty of Health Sciences, Room L208, St. Joseph's Hospital, 50 Charlton Avenue East, Hamilton, Ontario L8N 4A6, Canada.
Dr. Ageno: Department of Internal Medicine, Universita Degli Studi Dell'Insubria-Varese, Via Speroni 5, Varese, Italy 21100.
Dr. Garcia: University of New Mexico, 5th Ambulatory Care Center, 2211 Lomas Boulevard NE, Albuquerque, NM 87131.
Dr. Wang: St. Joseph's Healthcare, 50 Charlton Avenue East, Hamilton, Ontario L8S 2G9, Canada.
Drs. Witt, Clark, and Dowd: Kaiser Permanente Colorado Region, 280 Exempla Circle, Lafayette, CO 80026.
Dr. Blostein: McGill University, 3755 Côte Sainte-Catherine, Montreal, Quebec M3T 1E2, Canada.
Dr. Kahn: Jewish General Hospital 3755 Côte Sainte-Catherine, A-127, Montreal, Quebec H3T 1E2, Canada.
Dr. Vesely: The University of Oklahoma, Health Sciences Centre, P.O. Box 26901, Oklahoma City, OK 73126-0901.
Dr. Schulman: McMaster University, Hamilton General Hospital, 237 Barton Street East, Hamilton, Ontario L8L 2X2, Canada.
Dr. Kovacs: Hematology Division, London Health Sciences Centre, 800 Commissioners Road East, London, Ontario N6A 4G5, Canada.
Dr. Rodger: The Ottawa Hospital, 1812, Ebox 201, 501 Smyth Road, Ottawa, Ontario K1H 8L6, Canada.
Dr. Wells: The Ottawa Hospital, Civic Site, Suite F649, 1053 Carling Avenue, Ottawa, Ontario K1Y 4E9, Canada.
Dr. Anderson: Dalhousie University, Halifax, Nova Scotia B3H 3J5, Canada.
Dr. Ginsberg: McMaster University, 1200 Main Street West, HSC 3X28, Hamilton, Ontario L8N 3Z5, Canada.
Dr. Selby: Sunnybrook Health Sciences Centre, Room 0675a, 2075 Bayview Avenue, Toronto, Ontario M4N 3M5, Canada.
Dr. Siragusa: Cattedra ed U.O. di Ematologia con trapianto, Azienda Ospedaliera Universitaria Policlinico P. Giaccone, via del Vespro 127, I-90127 Palermo, Italy.
Dr. Silingardi: Arcispedale S. Maria Nuova, Azienda Ospedaliera, Viale Risorgimento 80, 42100 Reggio Emilia, Italy.
Dr. Kearon: McMaster University, Henderson General Hospital, 711 Concession Street, 40 Wing, Ground Floor, Room 115, Hamilton, Ontario L8V 1C3, Canada.

Author Contributions: Conception and design: M.A. Crowther, W. Ageno, D. Garcia, S. Schulman, P. Wells, J. Ginsberg, R. Selby, C. Kearon.
Analysis and interpretation of the data: M.A. Crowther, W. Ageno, L. Wang, D.M. Witt, N.P. Clark, S.K. Vesely, S. Schulman, M.A. Rodger, D. Anderson.
Drafting of the article: M.A. Crowther, W. Ageno, D.M. Witt, N.P. Clark, P. Wells, D. Anderson.
Critical revision of the article for important intellectual content: M.A. Crowther, W. Ageno, D. Garcia, D.M. Witt, N.P. Clark, S.R. Kahn, S. Schulman, M.J. Kovacs, M.A. Rodger, P. Wells, D. Anderson, J. Ginsberg, R. Selby, S. Siragusa, C. Kearon.
Final approval of the article: M.A. Crowther, W. Ageno, D. Garcia, M.D. Blostein, S.R. Kahn, S. Schulman, M.J. Kovacs, P. Wells, D. Anderson, J. Ginsberg, R. Selby, S. Siragusa, C. Kearon.
Provision of study materials or patients: M.A. Crowther, W. Ageno, D. Garcia, D.M. Witt, N.P. Clark, M.D. Blostein, S.R. Kahn, S. Schulman, M.J. Kovacs, P. Wells, D. Anderson, J. Ginsberg, R. Selby, M. Silingardi, M.B. Dowd, C. Kearon.
Statistical expertise: M.A. Crowther, L. Wang, S.K. Vesely, M.A. Rodger.
Obtaining of funding: M.A. Crowther, W. Ageno, M.J. Kovacs, M.A. Rodger, P. Wells, R. Selby.
Administrative, technical, or logistic support: M.A. Crowther, D. Garcia, S.R. Kahn, M.B. Dowd.
Collection and assembly of data: M.A. Crowther, L. Wang, D.M. Witt, N.P. Clark, S. Siragusa, M.B. Dowd.