Vitamin K_1 supplementation to improve the stability of anticoagulation therapy with vitamin K antagonists: a dose-finding study

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Acknowledgments: the authors would like to thank to all nurses and employees of both the Leiden anticoagulation clinic and the Medial anticoagulation clinic. The authors would especially like to thank Désirée Verbeek – Janssen, head nurse, Leiden anticoagulation clinic; Marie Annet Zeegers, student assistant; Caroline Klopper, executive manager, Medial anticoagulation clinic and Marja Sukel, dosing physician Medial anticoagulation clinic. Special thanks from the authors to Manon Goddijn, data manager, Leiden University Medical Center, Department of Clinical Epidemiology, for her valuable assistance throughout the entire study.

Funding: this study was funded by the Netherlands Heart Foundation (number 2007B211).

Manuscript received on October 11, 2010. Revised version arrived on December 10, 2010. Manuscript accepted on December 15, 2010.

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ABSTRACT

Background

Poor anticoagulant stability in patients using vitamin K antagonists is a risk factor for both bleeding and thrombosis. In previous studies supplementation with low dose vitamin K_1 was shown to improve the stability of anticoagulant control. We set up a study to confirm earlier reports and to determine the optimal daily dose of vitamin K_1 in preparation of a large study with clinical endpoints.

Design and Methods

Four hundred patients from two anticoagulation clinics starting with vitamin K antagonists, independently of a possible history of instable anticoagulation, were randomized to receive either placebo or 100, 150 or 200 μg of vitamin K_1 together with their treatment with vitamin K antagonists. The treatment was administered for 6 to12 months. Anticoagulation stability, expressed as the percentage of time that the International Normalized Ratio was within the therapeutic range, was compared between the groups.

Results

After adjustment for age, sex, vitamin K antagonist used, anticoagulation clinic and interacting drugs as confounding factors the difference in percentage of time with the International Normalized Ratio within the therapeutic range between the placebo group and the vitamin K_1 groups was 2.1% (95% CI: -3.2% - 7.4%) for the group taking 100 μg, 2.7% (95% CI: -2.3% - 7.6%) for the group taking 150 μg and 0.9% (95% CI: -4.5% - 6.3%) for the group taking 200 μg vitamin K_1 group, in favor of the vitamin K_1 groups. The patients from both the 100 μg group and the 150 μg group had a 2-fold higher chance of reaching at least 85% of time with the International Normalized Ratio within the therapeutic range. There were no differences in thromboembolic or hemorrhagic complications between the groups.

Conclusions

In patients starting vitamin K antagonists, supplementation with low dose vitamin K_1 resulted in an improvement of time that anticoagulation was within the therapeutic range. Differences between doses were, however, small and the improvement is unlikely to be of clinical relevance. For future studies we recommend selecting only patients with instable anticoagulant control. *(This study was registered at www.isrctn.org as ISRCTN37109430)*

Key words: vitamin K_1, supplementation, anticoagulation stability, dose-finding, therapeutic range.

Citation: Gebuis EPA, Rosendaal FR, van Meegen E, and van der Meer FJM . Vitamin K_1 supplementation to improve the stability of anticoagulation therapy with vitamin K antagonists: a dose-finding study. Haematologica 2011;96(4):583-589. doi:10.3324/haematol.2010.035162

Introduction

Anticoagulant therapy with vitamin K antagonists is an effective treatment for both primary and secondary prevention of venous and arterial thrombosis.[1] Vitamin K antagonists do, however, have several serious disadvantages, such as a narrow therapeutic window, large intra- and interpersonal variability in required dose and interactions with other drugs and diet. Despite intensive monitoring, the percentage of time the International Normalized Ratio (INR) is within the therapeutic range (TTR) usually lies between 50% and 60%.[2-4] Improving the stability of anticoagulation therapy with vitamin K antagonists (i.e. maintaining the INR in the therapeutic range) would reduce the risk of both hemorrhage and thrombosis by decreasing time above and below the therapeutic range, respectively.[2,4,5]

In recent years it has become clear that diet, and especially the intake of vitamin K_1, plays an important role as a cause of the variability of the INR.[6-9] The amount of dietary vitamin K_1 intake correlates with warfarin sensitivity, the actual INR level and the variability of the INR.[6-8] Furthermore, patients with a low intake of dietary vitamin K_1 were found to be at a higher risk of unstable anticoagulant control than those with normal intake.[8,9] This led to the hypothesis that increasing the vitamin K_1 intake by supplementation would improve the stability of the INR control. Several scientific studies did indeed show that vitamin K_1 supplementation improved anticoagulant control, both in healthy volunteers,[10] and in patients on anticoagulant therapy[11-13] without necessitating a large increase of the dose of vitamin K antagonists required to maintain a therapeutic INR.[14] Sconce *et al*. investigated whether supplementation with 150 μg vitamin K_1 in a group of 70 patients with a history of unstable INR values was able to increase the stability of the anticoagulant control.[11] They found that the standard deviation of the mean INR improved by 0.24 in patients using vitamin K_1 in comparison to an improvement of 0.11 in the patients using placebo. Furthermore, a 13% improvement in the TTR in favor of the vitamin K_1 group was observed.[11] Rombouts *et al.* performed a study in 200 patients who had already been on anticoagulant treatment for at least 1 year. These patients were assigned to either 100 μg vitamin K_1 or a placebo. A difference of 3.6% in the TTR (95% CI: -0.8–8.0%) was seen in favor of the vitamin K_1 group.[12] Several questions remain in this regard. First, it is unclear whether all patients benefit from vitamin K_1 supplementation or only a subgroup of patients with unstable anticoagulation control. Secondly, the most effective dose of vitamin K_1 is unknown because different dosages were used in the previous studies. Sconce *et al*. used 150 μg and Rombouts *et al.* used 100 μg.[11,12] Thirdly, the type of vitamin K antagonist that is used might influence the effect of vitamin K_1 supplementation on the achieved stability, because longer acting vitamin K antagonists result in more stable control *per se*.[15-19] Finally, supplementation with vitamin K_1 would only be useful in the clinic if the frequency of clinical endpoints, such as the number of hemorrhages or thrombotic events, is reduced.

We planned a large study to investigate the effect of vitamin K_1 supplementation on anticoagulation stability and clinical endpoints. Before starting this large study with clinical endpoints we set up a dose-finding study to investigate the effect on anticoagulation stability of 100, 150 and 200 μg of vitamin K_1 in comparison to placebo. The results of this dose-finding study are presented here.

Design and Methods

Study design

We set up a double-blind, randomized, placebo-controlled clinical trial. Four hundred patients starting with oral anticoagulant therapy with vitamin K antagonists were randomized into four equal groups, receiving either a placebo or 100 μg, 150 μg or 200 μg vitamin K_1 once daily together with their vitamin K antagonists. Patients were treated with either adjusted-dose phenprocoumon or acenocoumarol. The study medication was used for at least 6 months and was stopped: (i) when the anticoagulant therapy ended, or (ii) when a patient had participated for a period of 12 months or, (iii) when the study ended, which was 6 months after the last patient had been included. Patients who continued vitamin K antagonists after the study ended were monitored at weekly intervals for at least 4 weeks to adjust for possible instability as a result of stopping the vitamin K_1.

The study started at the Leiden anticoagulation clinic (Leiden, the Netherlands) and was subsequently extended to the Medial anticoagulation clinic (in the region of Haarlem/Hoofddorp, the Netherlands). Permission for this study was received from the local Medical Ethics Committee at Leiden University Medical Center. Written informed consent was obtained from all patients willing to participate in the study.

Participants

Participants were recruited from the Leiden and Medial anticoagulation clinics. All patients between 18 and 85 years old who were starting low intensity oral anticoagulant therapy for at least 6 months were eligible. Stability or instability was not a criterion for inclusion or exclusion. The target INR range was that recommended in the guidelines of the Federation of Dutch Anticoagulation Clinics, i.e. between 2.0 and 3.5 with a target INR level of 3.0. Patients were only eligible for inclusion in the study within the first 4 weeks after the start of anticoagulant therapy.

Exclusion criteria were: dialysis (both hemodialysis and peritoneal dialysis); pregnancy or current pregnancy wish; a life expectancy of less than 6 months due to any known condition; an expected interruption of anticoagulant therapy for more than 1 week and patients enrolling in the self-management program.

We argued that a 10% improvement in TTR would be clinically relevant and achievable. The standard deviation of the TTR was estimated at 23%. With a power of 80% and a significance level of 5% we calculated that 84 patients were needed in each group. Allowing a loss of 15% of patients in each group we included a total of 400 patients over the four groups.

Procedures

Patients were treated according to the standard protocols of both anticoagulation clinics with either acenocoumarol or phenprocoumon, which are both registered and used in the Netherlands, at the referring physicians' discretion. The anticoagulation clinics use integrated information databases and dosage algorithms, with routine recording of the dosages of vitamin K antagonists, along with relevant clinical information such as complications (both thromboembolic and hemorrhagic), hospital admissions, surgery and co-medication. After the treatment period ended the required data were extracted from these databases and analyzed. No specific dietary recommendations were given.

The study capsules, placebo and vitamin K_1, were manufactured by Numard B.V. (Lelystad, the Netherlands). The vitamin K_1

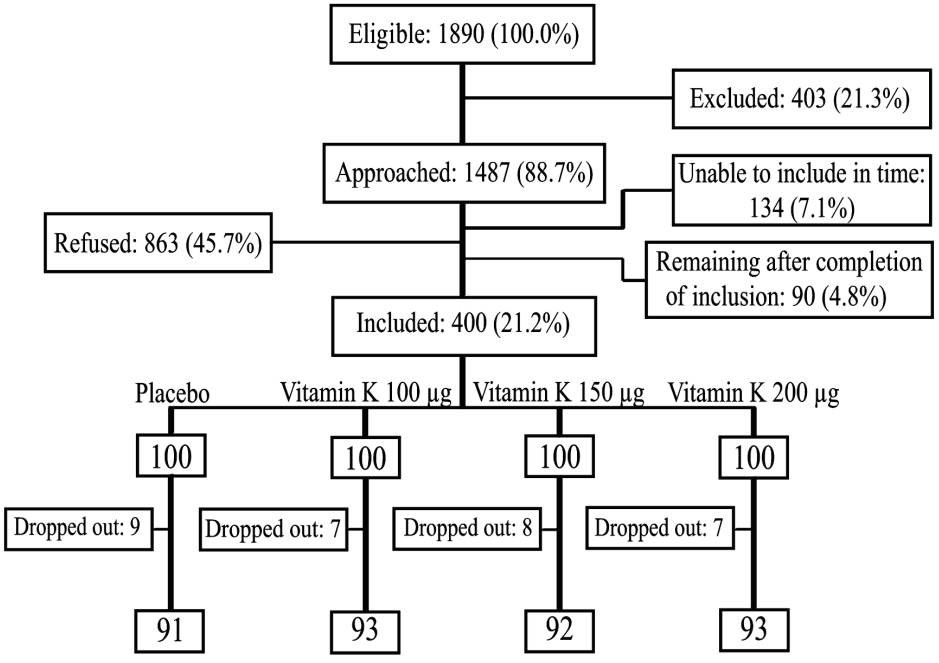

Figure 1. Flow of patients through the trial. Patients were considered to have dropped out if they participated in the study for less than 4 weeks. Out of the 1487 patients who were approached to participate in our study 90 were not included after 400 patients (the number of patients needed) had agreed to participate.

capsules were made from 5% dry vitamin K1 (Acatris, Londerzeel, Belgium) in three different dosages: 100 µg, 150 µg and 200 µg.

Data analysis

The main objective of the study was to investigate the dose-dependent improvement of the quality of anticoagulation treatment with vitamin K antagonists in patients receiving vitamin K1 in comparison with patients receiving placebo. Quality of anticoagulation therapy was measured with the TTR calculated using the linear interpolation method of Rosendaal *et al.*[20] After calculating individual time in therapeutic range (iTTR) for each patient separately we calculated an average and a weighted average per group by taking the time each patient participated in the study into account, or, in other words, we calculated the proportion of person-time in range over the total person-time of the cohort. The first 4 weeks of participation in the study were not included in the analysis since this period is used to find the right dosage of vitamin K antagonist in a patient starting with anticoagulant therapy.

One secondary endpoint was the chance of reaching stability, expressed as the odds ratio (OR) of reaching a high TTR in the vitamin K1 group compared to the placebo group. Another secondary endpoint was the number of complications, both thromboembolic and hemorrhagic. Major hemorrhage was defined according to the classification of Schulman *et al.*[21] In this classification, bleeding is defined as major hemorrhage if: (i) the hemorrhage is fatal; (ii) the hemorrhage is symptomatic in a critical area or organ (such as intracranial bleeding or intramuscular bleeding with compartment syndrome); or (iii) the hemorrhage causes the hemoglobin level to drop by 20 g/L (1.24 mmol/L) or more, or leads to a transfusion of two or more units of whole blood or red cells. All other hemorrhages were considered to be minor.

We considered age, sex, use of co-medications known to interact with vitamin K antagonists, the type of vitamin K antagonist used and the anticoagulation clinic in which the patient was treated as potential confounders for which we adjusted our results by linear regression.

Results

Inclusion of patients started on June 1st, 2008 and was completed by July 1st, 2009. Figure 1 shows a flow chart of the patients' participation in the study.

Out of 1890 eligible patients receiving an invitation to participate 400 were randomized in the four groups. Data from 369 patients were analyzed. The number of patients, follow-up time of each group of patients and the patients' characteristics are shown in Table 1. The group receiving 150 µg vitamin K1 included more patients using phenprocoumon and more patients from the Leiden anticoagulation clinic. The groups receiving 150 µg and 200 µg vitamin K1 included more patients treated for atrial fibrillation and fewer for other treatment indications than the other two groups.

The results of the primary study outcome, weighted TTR, are presented in Table 2A-C. The unadjusted differences in weighted TTR between the placebo and the treatment groups were 2.2% (95% CI: –3.3% - 7.7%), 3.9% (95% CI: –3.2% - 11.0%) and 0.3% (95% CI: –5.3% - 5.9%) for the 100 µg, 150 µg and 200 µg vitamin K1 groups, respectively. Adjustment for age, sex, vitamin K antagonist used, anticoagulation clinic and the use of interacting drugs resulted in a difference of 2.1% (95% CI: –3.2% - 7.4%), 2.7% (95% CI: –2.3% - 7.6%) and 0.9% (95% CI: –4.5% - 6.3%) for the 100 µg, 150 µg and 200 µg vitamin K1 groups, respectively, all in reference to the values in the placebo group. The unweighted adjusted differences were 3.3% (95% CI: –1.4% - 7.9%) for the vitamin K1 100 µg group, 4.5% (95% CI: 0.1% - 9.0%) for the 150 µg group and 4.2% (95% CI: –0.5% - 8.8%) for the 200 µg group, again all in reference to the values in the placebo group.

Table 3 shows the odds ratios comparing the chance of reaching stable anticoagulation when using vitamin K1 supplementation with that when using a placebo. For both the vitamin K1 100 µg and 150 µg groups the adjusted odds ratio for reaching more than 85% of TTR was higher than in the placebo group (2.1; 95% CI: 1.1-4.1 and 2.2; 95% CI 1.2-4.2, respectively). In the vitamin K1 200 µg group no clear difference was found (odds ratio 1.7; 95% CI: 0.9-3.3).

After the study ended 227 patients continued treatment with vitamin K antagonists (59 patients in the placebo

group, 51 in the 100 μg vitamin K1 group, 60 in the 150 μg vitamin K1 group and 57 in the 200 μg vitamin K1 group). The differences between the mean daily doses of vitamin K antagonists over the last four dosages prior to the end of the study and the mean daily dose calculated over the first four dosages after the end of the study were –0.117 mg per day (95% CI: –0.492 - 0.257) in the placebo group (–4.4%), –0.097 mg per day (95% CI: –0.446 - 0.267) in the 100 μg vitamin K1 group (–3.6%), –0.156 mg per day (95% CI: –0.578 - 0.267) in the 150 μg vitamin K1 group (–5.8%) and –0.162 mg (95% CI: –0.508 - 0.183) in the 200 μg vitamin K1 group (–6.5%).

Table 1. Patients' baseline characteristics.

	Placebo (n=91)	Vitamin K1 100 μg (n=93)	Vitamin K1 150 μg (n=92)	Vitamin K1 200 μg (n=93)
Age (median with spread)	62 (26 - 85)	63 (31 - 85)	66.5 (20 - 84)	64 (23 - 84)
Female, n (%)	31 (34.1)	29 (31.2)	36 (39.1)	36 (38.7)
Indication				
Atrial fibrillation, n (%)	56 (61.5)	58 (62.4)	68 (73.9)	67 (72.1)
Venous thromboembolism, n (%)	32 (35.2)	31 (33.3)	21 (22.8)	22 (23.7)
Other, n (%)	3 (3.3)	4 (4.3)	3 (3.3)	4 (4.3)
Vitamin K antagonist				
Phenprocoumon, n (%)	78 (85.7)	76 (81.7)	86 (93.5)	70 (75.3)
Acenocoumarol, n (%)	13 (14.3)	17 (18.3)	6 (6.5)	23 (24.7)
Anticoagulation clinic				
Leiden, n (%)	79 (86.8)	83 (89.2)	87 (94.6)	79 (84.9)
Medial, n (%)	12 (13.2)	10 (10.8)	5 (5.4)	14 (15.1)
Patient-years	56.3	52.5	60.3	57.5
Interacting medication				
Yes, n (%)	46 (50.5)	44 (47.3)	50 (54.3)	43 (46.2)
No , n (%)	45 (49.5)	49 (52.7)	42 (45.7)	50 (53.8)

Table 2A. Weighted TTR compared between placebo group and vitamin K1 100 μg group.

	Placebo (n = 91)	Vitamin K1 100 μg (n = 93)	Difference (95% CI)	Adjusted difference[1] (95% CI)
Time in therapeutic range (%)	84.3 (80.2-88.4)	86.5 (82.9-90.1)	2.2 (-3.3-7.7)	2.1 (-3.2-7.4)
Time above therapeutic range (%)	10.9 (7.8-14.1)	9.3 (6.7-12.0)	-1.6 (-5.8-2.6)	-1.8 (-6.0-2.5)
Time below therapeutic range (%)	4.8 (2.4-7.1)	4.2 (1.8-6.5)	-0.6 (-4.0-2.8)	-0.4 (-3.5-2.8)

Table 2B. Weighted TTR compared between placebo group and vitamin K1 150 μg group.

	Placebo (n = 91)	Vitamin K1 150 μg (n = 92)	Difference (95% CI)	Adjusted difference[1] (95% CI)
Time in therapeutic range (%)	84.3 (80.2-88.4)	88.2 (85.4-91.1)	3.9 (-3.2-11.0)	2.7 (-2.3-7.6)
Time above therapeutic range (%)	10.9 (7.8-14.1)	8.2 (5.5-10.8)	-2.7 (-6.9-1.4)	-2.4 (-6.7-1.8)
Time below therapeutic range (%)	4.8 (2.4-7.1)	3.6 (6.3-11.5)	-1.2 (-4.0-1.6)	-0.2 (-2.9-2.5)

Table 2C. Weighted TTR compared between placebo group and vitamin K1 200 μg group.

	Placebo (n = 91)	Vitamin K1 200 μg (n = 93)	Difference (95% CI)	Adjusted difference[1] (95% CI)
Time in therapeutic range (%)	84.3 (80.2-88.4)	84.6 (81.6-88.9)	0.3 (-5.3-5.9)	0.9 (-4.5-6.3)
Time above therapeutic range (%)	10.9 (7.8-14.1)	9.4 (6.3-11.5)	-1.5 (-5.7-2.7)	-1.7 (-5.9-2.6)
Time below therapeutic range (%)	4.8 (2.4-7.1)	6.0 (3.6-8.1)	1.2 (-2.0-4.5)	0.8 (-2.0-3.6)

Mean percentages with 95% confidence interval (CI) of time in -, above – and below therapeutic range, weighted for treatment time of the individual patients. [1]Adjusted for age, sex, vitamin K antagonist used, anticoagulation clinic and interacting drugs. TTR: time in therapeutic range.

Among the 47 complications seen, there were two thromboembolic events and one major hemorrhage. Of the two thromboembolic events, one was a recurrent deep venous thrombosis in the leg in a patient in the 100 μg vitamin K1 group (INR 2.6; the recurrence took place 5 weeks after inclusion and 8 weeks after the start of anticoagulant treatment) and the other was recurrent pulmonary embolism in a patient in the 150 μg group (INR 1.3; the recurrence took place 1 day after inclusion and 3 weeks after the start of anticoagulant treatment, INR at inclusion date was 1.4). The major hemorrhage was an intra-ocular hemorrhage in a patient in the 200 μg vitamin K1 group (INR 2.8; the hemorrhage occurred 10 weeks after inclusion and 12 weeks after the start of anticoagulant treatment). All other complications were minor hemorrhages. No clear differences were found between the study groups.

Six patients died during the trial. In the placebo group one patient died of myocardial infarction after interruption of treatment because of elective surgery. In the 100 μg group three patients died: one of malignancy, one of intracranial hemorrhage 1 day after inclusion in the trial and one of an unknown cause. In both the 150 μg and 200 μg groups one patient each died of pneumonia.

Several patients reported having trouble swallowing the study capsules and at least one patient withdrew from the study for this reason. No other side effects of the study capsules were reported.

Discussion

We performed a randomized, placebo-controlled trial in two Dutch anticoagulation clinics. In 400 patients using vitamin K antagonists we examined the effect of supplementation with three different dosages of vitamin K1. In comparison to the placebo group the adjusted difference in weighted TTR, as a measure of stability of the anticoagulant effect, was 2.1%, 2.7 % and 0.9 % in the groups taking 100 μg, 150 μg and 200 μg vitamin K1, respectively. Patients taking either 100 μg vitamin K1 or 150 μg vitamin K1 had a better chance of reaching a high TTR of at least 85% (odds ratios over 2). There was no difference in the number and severity of complications (thromboembolic and hemorrhagic) between the four groups.

Our study is the fourth study of its kind. The three previous studies, one pilot study and two trials, also showed a positive effect of vitamin K1 supplementation on the stability of anticoagulant therapy.[11,12,14] The first trial, published by Sconce *et al.*,[11] compared two groups of 35 patients with unstable anticoagulation receiving 150 μg vitamin K1 or placebo once daily. Instability was defined as having a standard deviation of the INR values in the 6 months prior to the study of more than 0.5 and three or more dose changes of warfarin in the same period. After using the study medication for 6 months the standard deviation of INR values had decreased by 0.24 in the vitamin K1 group and 0.11 in the placebo group while the TTR improved 13% in the vitamin K1 group in which regression to the mean may have to be taken into account.

After a pilot study, Rombouts *et al.* published the results of the second trial[12] in which 100 patients who received 100 μg vitamin K1 once daily were compared with 100 patients who received a placebo. All patients used phenprocoumon and were treated with the vitamin K antagonist for at least 1 year before being included in the study. These patients were not selected on the basis of a measure of anticoagulant stability. Only a small adjusted difference in TTR of 3.6% (95%CI: –0.8% - 8.0%) was found.

There are several differences in the studies by Sconce *et al.* and those from our institution which may or may not explain why Sconce *et al.* found a larger effect than either Rombouts *et al.* (13% *versus* 3.6% improvement in TTR) or we did. Firstly, Sconce *et al.* investigated patients who proved to have unstable anticoagulation control while Rombouts *et al.* did not take anticoagulation stability into account. In our trial we selected patients who were starting anticoagulant treatment and stability was not a selection criterion. We thought that probably all patients would benefit from supplementation with vitamin K1 and unstable patients would profit the most. It is well known that patients are more unstable in the starting phase and the advantage of vitamin K1 supplementation might, therefore, be greatest if started directly at the initiation of treatment with a vitamin K antagonist.

Secondly, the type of vitamin K antagonist used may be of importance. In the trial by Sconce *et al.* all patients used warfarin while in the trial by Rombouts *et al.* all patients were on phenprocoumon. In our trial most patients were using phenprocoumon and a small number of patients used acenocoumarol. These three vitamin K antagonists have different half-lives and previous studies showed that the stability of anticoagulant therapy was better with the longer-acting phenprocoumon than with acenocoumarol.[15-19] A recent study showed better stability in patients treated with warfarin than in patients using phenprocoumon.[22] We performed a subgroup analysis in the group of patients treated with acenocoumarol. The difference became more marked between the placebo group and the vitamin K1 150 μg group, but with wide confidence intervals due to the small number of acenocoumarol users (9.5% difference in TTR; 95% CI: –61.8% - 80.9%). After pooling all three vitamin K1 groups for the acenocoumarol users the difference between the pooled vitamin K1 groups

Table 3. Chance of reaching anticoagulant stability.

	Placebo (n=91)	Vitamin K1 100 μg (n=93)	OR (95%CI)	Adjusted OR[1] (95%CI)	Vitamin K1 150 μg (n=92)	OR (95%CI)	Adjusted OR[1] (95%CI)	Vitamin K1 200 μg (n = 93)	OR (95%CI)	Adjusted OR[1] (95%CI)
At least 65% TTR, n (%)	76 (83.5)	83 (89.2)	1.6 (0.7-3.9)	1.9 (0.7-5.0)	86 (93.5)	2.8 (1.0-7.7)	2.3 (0.8-6.5)	82 (88.2)	1.5 (0.6-3.4)	1.9 (0.7-4.8)
At least 85% TTR, n (%)	45 (49.5)	59 (63.4)	1.8 (1.0-3.2)	2.1 (1.1-4.1)	64 (69.6)	2.3 (1.3-4.3)	2.2 (1.2-4.2)	55 (59.1)	1.5 (0.8-2.7)	1.7 (0.9-3.3)

OR are for dosages of vitamin K1 compared to placebo. [1]OR adjusted for age, sex, vitamin K antagonist used, anticoagulation clinic and interacting medication.

and the placebo group was consistent with the overall outcome of the study (3.5% difference in TTR; 95% CI: –15.8% - 22.8%). So, in our study we could not demonstrate that the effectiveness of vitamin K_1 supplementation differed between patients receiving phenprocoumon and those receiving acenocoumarol. Considering half-life as the discriminating factor it is unlikely that a different effect of vitamin K_1 supplementation would be shown in patients using warfarin, with a half-life between that of phenprocoumon and acenocoumarol. Other differences between the various vitamin K antagonists cannot, however, be excluded in this regard.

Thirdly, the absolute level of anticoagulant control may be of importance. In our study the TTR in the placebo group was 84.3% which is far higher than that in most other studies and might be difficult to improve upon by vitamin K_1 supplementation.[2-4] One explanation for this higher TTR is the use of the Dutch therapeutic range, INR 2.0 - 3.5, which is wider than the generally used INR range from 2.0 to 3.0, which was used by Sconce *et al.* We also performed the analyses using the therapeutic range of 2.0 - 3.0. This resulted in an overall TTR similar to the TTR reported in the international literature. However, in our opinion these results are not comparable since 2.0 - 3.0 is not the therapeutic range we aimed at. Indeed, when the INR is above 3.0 but below 3.5 the dose is not changed. Another explanation might be the use of phenprocoumon and acenocoumarol in our studies while Sconce *et al.* used warfarin. This has been discussed in the previous paragraph. A third explanation for the higher TTR might be a difference in the skills of dosage prescribing between our center and that of Sconce *et al*. However, as we know that the center of Sconce *et al.* has long-standing interest and experience in anticoagulant control we do not think this is a realistic possible explanation.

Taking all the information together, it seems that the type of vitamin K antagonist used and the high level of anticoagulant control are less likely explanations for the differences in the effect of vitamin K_1 supplements between the study by Sconce *et al.* and that carried out in our institution. The most likely explanation for this difference does, therefore, seem to be the selection of patients with unstable anticoagulant control, as done by Sconce *et al.*

Based on the studies by Sconce *et al.*[11] and Rombouts *et al.*[12] we hypothesized that the improvement of stability of anticoagulation control might increase when higher dosages of vitamin K_1 supplementation are used. However, the results for both the TTR and the chance of reaching stability (Table 3) do not support this hypothesis, because supplementation with 200 μg vitamin K_1 did not result in a higher TTR or a greater chance of stability. At the moment we have no clear explanation for this observation. It may however be determined by the relative concentrations of vitamin K epoxide and the vitamin K antagonists at presentation to the vitamin K epoxide reductase (VKORC1) enzyme system in the liver. Another possible factor might be the relative affinity of the various vitamin K antagonists for VKORC1.

The total number of complications (47, of which two were thromboembolic, and only one categorized as a major hemorrhage) was low in our study population. We did not find any difference in either the number of complications (both thromboembolic and hemorrhagic) or their severity between the various groups.

One concern could be that the patients we approached for the trial and were willing to participate represented a (self-)selection of highly stable patients. We think this is unlikely since the TTR in our placebo group (84.3%) was similar to that of all patients treated for mid- to long-term indications by both anticoagulation clinics.

We believe the time a person participated in the study should be taken into account in calculating the TTR and, therefore, used the primary endpoint as weighted TTR. We cannot, however, exclude the possibility there is, for example, an unknown patient factor partially responsible for reaching stability which would make an evaluation of unweighted time in range preferable. We, therefore, decided to report the outcomes of both the weighted and unweighted analyses.

Although the study was set up as a double-blind trial, blinding may not have been entirely complete because of the changes in dose-requirements in patients receiving vitamin K_1. To minimize this potential unblinding the main researcher did not prescribe dosages of anticoagulant therapy to participating patients.

Unfortunately, we were unable to collect reliable data on patient compliance. We cannot, therefore, exclude that poor compliance may have resulted in a lower estimate of the effect of vitamin K_1 supplementation. If patients participating in a clinical trial were not motivated to take the vitamin K_1 supplementation it is unlikely that patients in routine clinical practice would do better. Furthermore, it is very unlikely that compliance differed between the study groups. We are, therefore, convinced that compliance did not influence either the comparison between the groups or our final conclusion that low dose vitamin K1 supplementation does not result in a clinically relevant improvement of TTR.

In conclusion we found that daily supplementation with 150 μg vitamin K_1 improved the stability of oral anticoagulant therapy with a 2.7% increase in TTR. In addition there was a 2-fold increase in the chance of reaching a TTR of at least 85%. This result is in agreement with that of a previous study from our institution and we are convinced that the effect, for all patients, is around this figure. To be clinically relevant we think an improvement of at least 10% in the TTR is necessary and, therefore, in our opinion there is no place for vitamin K_1 supplementation in general practice of oral anticoagulant control. For the same reason we decided against performing the large trial to compare clinical endpoints as originally intended. The effect of vitamin K_1 supplementation may be greater in selected patients who have unstable anticoagulant control and do not respond to other measures. A previous study by Sconce *et al*. showed an improvement of TTR of 13% in unstable patients, which would be clinically relevant. We, therefore, recommend that future studies of vitamin K_1 supplementation be limited to patients with unstable anticoagulation control.

Authorship and Disclosures

The information provided by the authors about contributions from persons listed as authors and in acknowledgments is available with the full text of this paper at www.haematologica.org.

Financial and other disclosures provided by the authors using the ICMJE (www.icmje.org) Uniform Format for Disclosure of Competing Interests are also available at www.haematologica.org.

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