Over-the-counter vitamin $K_1$-containing multivitamin supplements disrupt warfarin anticoagulation in vitamin $K_1$-depleted patients

A prospective, controlled trial

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Summary
Most multivitamin supplements contain far less vitamin $K_1$ than thought to affect warfarin anticoagulation. Having described 3 patients with multivitamin-warfarin interactions, we hypothesized that vitamin $K_1$-depleted patients are sensitive to even small increments. Therefore, we compared the effect of a vitamin $K_1$-containing multivitamin on warfarin anticoagulation between patients with low versus normal vitamin $K_1$ status. We screened 102 warfarin-treated patients and recruited nine with "low" (< 1.5 mcg/L, 10th percentile) (group 1) and 7 with "normal" (>4.5 mcg/L, median) (group 2) total vitamin $K_1$ plasma levels (vitamin $K_1$ + vitamin $K_1$ 2,3-epoxide). Patients received one multivitamin tablet containing 25 mcg of vitamin $K_1$ daily, for 4 weeks (period 1). A predefined algorithm was used to adjust warfarin doses if the INR was outside the therapeutic range. Patients requiring warfarin increments were then switched to 4 weeks of a vitamin $K_1$-free multivitamin supplement (period 2). During period 1, subtherapeutic INRs occurred in 9/9 and 1/7 patients in group 1 and 2, respectively ($p < 0.001$). In group 1, INR decreased by a median of 0.51 ($p < 0.01$), and warfarin dose had to be raised by 5.3% ($p < 0.01$), whereas INR and warfarin dose did not change significantly in group 2. During period 2 (7 patients), there were trends towards decreased total vitamin $K_1$ and rising INRs associated with significantly lower warfarin doses. We conclude that vitamin $K_1$-containing multivitamins reduce INR in patients with low vitamin $K_1$ status. Our study suggests that vitamin $K_1$-depleted patients are sensitive to even small changes in vitamin $K_1$ intake.

Keywords
Clinical trials, oral anticoagulants, vitamin K-dependent factors, clinical / epidemiological studies

Introduction
Despite a lack of clear health benefits (1-3) about 20% of the American adult population consume daily multivitamin supplements (4, 5). Unfounded health beliefs, lack of adverse effects, and aggressive marketing result in increasing self-medication with these over-the-counter products. Most over-the-counter multivitamin supplements contain small amounts (10-25 mcg) of vitamin $K_1$, a far lesser amount than the daily 250 mcg (either from dietary intake or from supplementation) known to affect anticoagulant control in patients treated with vitamin K-antagonists (warfarin and other coumarins) (6-9). Accordingly, such multivitamins are generally considered safe in anticoagulated patients. However, we recently described three stable anticoagulated patients in whom the unreported use, or discontinuation, of a multivitamin supplement containing 25 mcg of vitamin $K_1$ caused major changes in the international normalized ratio (INR), with severe clinical complications in two (10).
Considering that about 10% of our anticoagulation clinic cohort manifests low dietary intake (7) and low plasma levels of vitamin K₁ (10), we hypothesized that this subgroup of patients may be particularly sensitive even to the small increment in vitamin K₁ intake provided by such daily multivitamin supplements (10). To test this hypothesis we designed a prospective, open-label, controlled trial of multivitamin supplementation with a typical vitamin K₁-containing product in anticoagulated patients with low versus normal vitamin K₁ status.

**Methods**

**Patient screening**

Non-fasting morning total vitamin K₁ plasma levels, the sum of vitamin K₁ (hydroquinone and quinone) and vitamin K₁ 2,3-epoxide, were determined between October 2001 and January 2002 in 102 consecutive consenting patients on stable chronic warfarin anticoagulation attending the Sheba Medical Center anticoagulation clinic, an outpatient clinic in a tertiary care center serving about 400 patients. Stability was defined as therapeutic INRs attained with stable warfarin doses (weekly maintenance dose ± 5%) during the 3 previous months (at least 3 clinic visits) and absence of any intercurrent factor known to affect anticoagulation (illness, change of concomitant medication or diet, questionable compliance). The individual therapeutic range for INR was defined by indication (2.0-3.0 for atrial fibrillation, thromboembolic disease, mechanical aortic valve, or 2.5-3.5 for mechanical mitral valve and antiphospholipid antibody syndrome) (11). Dietary vitamin K₁ intake was assessed by semiquantitative counts of weekly green leafy vegetable portions during a structured interview with a trained pharmacist (12).

**Study sample for interventional study**

Based on the estimated prevalence of low vitamin K status in our patient population (7, 10), patients within the 10th percentile (≤1.5 mcg/L) of the total plasma vitamin K₁-distribution were eligible for recruitment into the low vitamin K₁-group (group 1) of the interventional study. The control group (group 2) consisted of an equal number of consecutive age-matched patients with normal total vitamin K₁ levels (above the median (> 4.5 mcg/L) of the total plasma vitamin K₁-distribution).

The study was approved by the Sheba Medical Center review board, and all patients gave written informed consent.

**Interventions**

**Study period 1**

Patients were instructed to take 1 tablet of a multivitamin supplement containing 25 µg vitamin K₁ (Centrum Plus®, Lederle, Neopharm, Israel), daily, at 8:00 p.m., together with their daily warfarin dose, over 4 weeks. Other concomitant medication, if any, was continued unchanged. At recruitment and at every follow-up, patients were instructed to maintain their regular dietary habits, especially with respect to green leafy vegetables.

Blood for INR measurement was drawn at 8:00-9:00 a.m. on the first study day, twice during the first week, and at weekly intervals thereafter (and, at the study physician’s discretion, more often if required to ensure anticoagulant control). If an INR measurement was outside the individual’s therapeutic range warfarin dose was changed according to a predetermined algorithm (appendix).

Non-fasting morning total vitamin K₁ plasma levels were measured between 8:00-9:00 a.m. twice at baseline (at the screening examination and on the first study day) and 3-4 times during the study period. Adverse events and compliance with both tablet intake and dietary instructions were assessed by weekly personal interviews and pill counts.

**Study period 2**

After completing period 1, patients with a subtherapeutic INR at any point during period 1 were switched to a vitamin K₁-free multivitamin supplement. These patients were instructed to take 1 tablet daily of Geriatric Pharmaton® (Pharmaton Ltd, Lugano-Bioggio, Switzerland), a vitamin K-free multivitamin supplement similar to Centrum® with respect to all other ingredients, together with their daily warfarin dose for an additional 4 weeks. Patient follow-up, INR- and vitamin K₁-measurements were performed as outlined for study period 1. Warfarin was continued at the last weekly dose given in period 1, and subsequent doses were adjusted according to INR following the same algorithm.

**Laboratory measurements**

INR was determined from citrated (0.5 ml of 109 mmol/L sodium citrate) blood within 90 minutes from collection in our institution’s coagulation laboratory using the same coagulometer (MLA Electra 1000 Coagulation Analyzer, Medical Laboratory Automation Inc., Pleasantville, NY, USA) and the same batch of thromboplastin (Innovin®, Dade, Miami, FL, USA) with an International Sensitivity Index (ISI) of 1.02. The laboratory operates under the UK National External Quality Assessment Scheme for Blood Coagulation (UK NEQAS). Blood samples for vitamin K₁ measurements were kept at 4°C, protected from light, immediately after collection, centrifuged within 30 min, and plasma aliquots were frozen at -70°C until assayed. Except for the first screening sample, all samples from a given patient were assayed in the same batch. Plasma vitamin K₁ 2,3-epoxide and vitamin K₁ (quinone and hydroquinone) were determined by high-performance liquid chromatography using postcolumn quantitative reduction on a zinc/zinc ++ column (13).

**Outcome measures**

INR values, daily warfarin doses, and vitamin K₁ levels were averaged for every patient per period and compared between
baseline (day 0 and 3 preceding clinic visits during the previous 3 months) and the two study periods. The primary outcome measure was the need for a warfarin dose change due to non-therapeutic INRs at any point during the study period. Other outcome measures were (a) change in mean INR and (b) change in mean warfarin dose between baseline and study periods.

Statistical analysis
Since some data were skewed, continuous variables are presented as medians and interquartile ranges (IQR). Comparisons between baseline and the study periods were performed by Friedman’s repeated measures 2-way analysis of variance (ANOVA) with pairwise multiple comparisons by Dunnet’s method, or Wilcoxon Signed-Rank test, where appropriate. Comparison between the two patient groups were performed by Mann-Whitney U test (for continuous variables) or Fisher’s exact test (for categorical variables), and a Kaplan-Meier cumulative survival analysis was used to compare the time to subtherapeutic INR. All tests were two-tailed, and p-values < 0.05 were considered significant. All analyses were performed using GBSTAT statistical software (version 8.0, Dynamic Microsystems Inc., Silver Spring, MD, USA).

Sample size calculations
Assuming a standard deviation of 0.4 for the change in INR values (10), and considering a 0.5 change in INR units as clinically relevant, a sample size of 9 patients in each group was calculated to provide a power of 90% (1-β) at the usual level of significance (α = 0.05).

Results
Study population and baseline characteristics
Among 10 patients with total vitamin K1 levels <1.5 mcg/L identified during the cross-sectional screening examinations, 9 consented to participate in the interventional study and were recruited into study group 1. Accordingly, 9 age-matched, consecutive consenting patients with levels >4.5 mcg/L were recruited into study group 2. Of the latter, two discontinued the study (one due to infectious gastroenteritis, another due to onset of dyspepsia which she attributed to the multivitamin supplement). These two patients had therapeutic INRs during the study period. Demographic and baseline clinical details (Table 1) as well baseline anticoagulation parameters (Table 2) did not differ significantly between the two study groups.

Repeat baseline total vitamin K1 determination at day 0 of the intervention study did not differ significantly from the screening results (data not shown). Vitamin K1 status, averaged from the screening and day 1 visit, was significantly lower in group 1 compared to group 2, both by total vitamin K1 plasma levels and by assessment of dietary intake (Table 2).

Study period 1
All patients in group 1 required at least one single warfarin dose supplement after a mean of 8.6 (95% CI, 4.0-13.1) days, and 6 required repeated warfarin supplements (mean, 2.8; 95% CI, 1.4-4.2), compared to only one out of 7 patients in group 2 requiring a single dose supplement at day 24 (p < 0.0001) (Figure 1). The odds ratio for a subtherapeutic INR at any visit during the study period 1 was 15.9 (95% CI, 2.0-127.5) for patients in group 1 vs. group 2. One patient in group 2 required a single dose reduction due to supratherapeutic INR.

In group 1, INR dropped significantly by a median of -0.51 units (IQR, -0.59 to -0.20), and warfarin daily doses had to be raised by a median of 0.4 mg (IQR, 0.1 to 1.3 mg), a median relative rise of 5.3% (IQR, 3.4 to 13.7%) (Table 3). In contrast, INR and warfarin doses did not change significantly in group 2.

Total vitamin K1 plasma levels increased significantly in group 1 (median rise, 2.0-fold (IQR: 1.5-3.6), but did not
change significantly in group 2 (Table 3). This increase was attributable to an increase in vitamin K₁ 2,3-epoxide, whereas vitamin K₁ (quinone / hydroquinone) remained unchanged.

The number of visits during period 1 was equal for patients in the low vs. normal TVK group (median (IQR), 5 (5-5.5) and 5 (5-5), respectively). No thromboembolic complications, bleeding, or other adverse events were recorded.

Study period 2

Among 10 patients with subtherapeutic INRs during study period 1, nine (all in group 1) consented to switch to a vitamin-K₁ free multivitamin supplement, and 7 completed the second 4-week-period (one patient was hospitalized for exacerbation of congestive heart failure at therapeutic INR-values, and another patient received antibiotic treatment (cefuroxime) for sinusitis; both were excluded from analysis). Continuing the last weekly dose given in study period 1, three patients reached supratherapeutic INRs, but the rise in median INR between period 1 and 2 did not reach statistical significance (p = 0.12) (Table 3). Median warfarin daily dose declined significantly and approached baseline values (Table 3). The decline in total vitamin K₁ levels during period 2 [median decline (IQR) = 39% (17-84%)] did not reach statistical significance (p = 0.13) (Table 3). No bleeding or thrombembolic events or other adverse effects were recorded during a median (IQR) of 4 (4-5) visits.

Discussion

In its reduced form (hydroquinone), vitamin K₁ serves as the essential cofactor for the activation of clotting factors II, VII, IX, X, (and protein C and S) by post-translational gamma-glutamyl carboxylation. During this reaction, vitamin K₁ is oxidized to the inactive vitamin K₁ 2,3-epoxide, and must be regenerated in a redox-cycle by the microsomal enzyme vitamin K 2,3-epoxide reductase (VKOR). Coumarins exert their anticoagulant effect as vitamin K-antagonists. By inhibiting VKOR, they partially block the vitamin K₁ redox cycle, resulting in accumulation of inactive vitamin K₂ 2,3-epoxide, and depletion of reduced vitamin K₁, and, thus, active clotting factors (11).

Conversely, dietary vitamin K₁ can replenish depleted stores of reduced vitamin K₁ and thus antagonize warfarin effect (7-9, 14-16). A number of case reports demonstrated that an inadvertent substantial increase in dietary vitamin K₁ intake may result in subtherapeutic INRs in stable anticoagulated patients (17-21). In two small prospective studies, in which baseline vitamin

![Figure 1: Kaplan-Meier analysis of time to subtherapeutic INR by vitamin K₁-status. The graph depicts percentage of patients above the lower therapeutic INR limit during supplementation with a vitamin K₁-containing multivitamin supplement (period 1). The solid and dotted lines represent the low (group 1) and normal (group 2) vitamin K₁ group, respectively.](https://www.thrombosis-online.com)

**Table 3: Vitamin K₁ status and anticoagulation parameters by vitamin K₁-status during baseline and multivitamin supplementation.** All values represent medians (interquartile ranges). *p <0.05, **p <0.01 for comparison with baseline, p <0.05 for comparison with baseline among the 7 patients in study period 2. Group 1 (n = 9): low total vitamin K₁ plasma level; Group 2 (n = 7): normal total vitamin K₁ plasma levels. In study period 2, group 1 comprised only 7 patients. Study period 1 = multivitamin supplementation including 25 mcg of vitamin K₁; study period 2 = vitamin K₁-free multivitamin supplementation

<table>
<thead>
<tr>
<th>INR</th>
<th>Baseline period</th>
<th>Study period 1 (n=7)</th>
<th>Study period 2 (n=7)</th>
<th>Comparison between periods</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td>2.59 (2.44-3.01)</td>
<td>2.08 (1.96-2.65)**</td>
<td>2.66 (2.14-2.85)*</td>
<td>p=0.01, p=0.74</td>
</tr>
<tr>
<td>Group 2</td>
<td>2.82 (2.63-2.88)</td>
<td>2.72 (2.27-3.06)</td>
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</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Warfarin dose (mg/d)</th>
<th>Baseline period</th>
<th>Study period 1 (n=7)</th>
<th>Study period 2 (n=7)</th>
<th>Comparison between periods</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td>6.0 (3.9-9.2)</td>
<td>4.3 (1.9-9.2)</td>
<td>4.3 (1.9-10.9)</td>
<td>p&lt;0.01, p=0.65</td>
</tr>
<tr>
<td>Group 2</td>
<td>7.2 (4.1-10.6)**</td>
<td>4.2 (1.9-8.2)</td>
<td>6.8 (6.0-10.0)**</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Total Vitamin K₁ (mcg/L)</th>
<th>Baseline period</th>
<th>Study period 1 (n=7)</th>
<th>Study period 2 (n=7)</th>
<th>Comparison between periods</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td>1.5 (1.0-2.2)</td>
<td>2.6 (2.4-5.2)**</td>
<td>2.1 (0.9-2.2)</td>
<td>p&lt;0.01, n.s.</td>
</tr>
<tr>
<td>Group 2</td>
<td>7.8 (5.0-9.7)</td>
<td>7.5 (5.4-8.4)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Vitamin K₂ 2,3-epoxide (mcg/L)</th>
<th>Baseline period</th>
<th>Study period 1 (n=7)</th>
<th>Study period 2 (n=7)</th>
<th>Comparison between periods</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td>1.3 (0.9-1.8)</td>
<td>2.4 (1.6-4.8)*</td>
<td>0.9 (0.5-1.45)</td>
<td>p=0.01, n.s.</td>
</tr>
<tr>
<td>Group 2</td>
<td>6.2 (4.5-8.9)</td>
<td>6.2 (4.7-7.8)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Vitamin K₁ (mcg/L)</th>
<th>Baseline period</th>
<th>Study period 1 (n=7)</th>
<th>Study period 2 (n=7)</th>
<th>Comparison between periods</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td>0.4 (0.3-1.0)</td>
<td>0.5 (0.3-0.6)</td>
<td>0.4 (0.3-0.8)</td>
<td>n.s., n.s.</td>
</tr>
<tr>
<td>Group 2</td>
<td>0.8 (0.5-1.1)</td>
<td>1.0 (0.6-1.3)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
K status was not assessed, daily oral supplements of 100 mcg did not affect INRs, whereas doses of 250-1,000 mcg daily significantly reduced warfarin effect (8, 9). In fact, oral doses between 500 and 5,000 mcg are used therapeutically to antagonize warfarin in patients with excessive anticoagulation (22). In a recent prospective trial, a 5-fold increase or decrease of vitamin K1 intake led to a significant reciprocal change in INR within 4 and 7 days, respectively (16).

Our findings show that a daily multivitamin supplement containing as little as 25 mcg of vitamin K1 results in subtherapeutic INRs in patients with low vitamin K1 status. A number of reasons implicate the small vitamin K1 component of the multivitamin in the observed effect. Firstly, it was seen almost exclusively in patients with low vitamin K1 status (group 1). Secondly, it seems biologically plausible: patients with very low total plasma vitamin K1-levels have dietary intake below the recommended daily allowance of 1 mcg/kg (23). Accordingly, a 25 mcg supplement may easily amount to a substantial relative increase (e.g. 50-100%) in dietary vitamin K1 intake (10). In fact, in group 1, the multivitamin supplement resulted in a median 2.0-fold increase in TVK plasma levels, a magnitude likely to disrupt the warfarin/vitamin K1 steady state equilibrium and thus reduce warfarin effect. Thirdly, when a vitamin K1-free multivitamin supplement was given in period 2, falling vitamin K1 plasma levels were associated with a trend towards rising INR levels, resulting in a significant decrease in warfarin requirements. Of note, although other multivitamin ingredients (vitamin A, D, E, and C at much higher doses) have been implicated as possibly interacting with warfarin, they potentiated rather than inhibited warfarin effect (6).

Anticoagulated patients are usually instructed to avoid fluctuations in dietary vitamin K1 intake exceeding 250 mcg/d (6), which may be easily misinterpreted as a request to reduce dietary vitamin K1 content altogether (24-26). Therefore, low vitamin K1 status could be more prevalent in anticoagulated patients than in the general population (10, 16). Based on previous studies in our cohort (7, 10), we chose to study a small patient sample at the lower extreme (<10th percentile) of the total plasma vitamin K1 distribution to test our hypothesis that small vitamin K1 supplements disrupt warfarin anticoagulation in vitamin K1-depleted patients. Yet, it is possible that less depleted patients (e.g. at the 15-20th percentile) could still be affected by small vitamin K1 supplements, albeit to a lesser degree. However, our study was not designed to address this question.

Our results suggest that vitamin K1 depletion, present in an important minority of anticoagulated patients, confers sensitivity to even small changes in dietary vitamin K1 intake, affecting their anticoagulant stability. Thus, if confirmed in larger studies, our findings have important practical implications for physicians caring for anticoagulated patients. Firstly, dietary recommendations regarding vitamin K intake should be reviewed with the patient to prevent exaggerated avoidance of vitamin K containing foods resulting in vitamin K depletion. Secondary, in patients with very low vitamin K intake, otherwise unexplained changes in INR may be attributable to only minor changes in vitamin K1 intake that were thus far considered negligible. In line with this observation, chronic low-dose vitamin K1 supplementation for warfarin patients has been suggested as a means to improve anticoagulant control (25). However, this approach has yet to be tested prospectively.

We chose non-fasting total vitamin K1 plasma levels as the marker for vitamin K1 status. In the absence of coumarins, VKOR readily reduces vitamin K1, 2,3-epoxide to vitamin K1, resulting in unmeasurably low plasma epoxide levels. Thus, in normal individuals, vitamin K1 plasma levels adequately represent vitamin K1 status (23). In warfarin-treated patients, however, epoxide levels are usually much higher than vitamin K1 levels as a result of warfarin’s inhibitory effect on vitamin K1 reconstitution (15, 26). Thus, in such patients, vitamin K1 status is best expressed as total plasma vitamin K1, namely the sum of vitamin K1 and the epoxide. In fact, the rise in total body vitamin K1 in group 1 was evident only in the epoxide fraction, with vitamin K1 levels unchanged, presumably reflecting increased warfarin dose and effect, required to maintain therapeutic INRs.

During study period 2, the decline in total vitamin K1 levels did not reach statistical significance. This could reflect a carryover effect from the first study period due to the lack of a washout period, an effect of the decreased sample size secondary to the exclusion of 2 patients, or a small, systematic increase in dietary vitamin K1 intake. However, there was still a trend for a reciprocal rise in INR and a significant, albeit small reduction in warfarin requirements, supporting the association between small changes in vitamin K1 intake and warfarin sensitivity in vitamin K1-depleted patients.

Counterintuitively, at similar INR values, patients in group 1 had (nonsignificantly) higher baseline warfarin doses than patients in group 2 (Table 3). This could be explained by the small sample size, or by differences in genotypes of the warfarin-metabolizing cytochrome CYP2C9, an important variable in explaining inter-individual differences in warfarin requirement (27) which was not assessed in our study.

Our study’s main limitations are the small sample size, precluding the generalization of its findings to other patient populations, and its unblinded design. However, in order to prevent systematic changes in dietary vitamin K1 intake during the study period, patients were regularly reminded to adhere to their normal diet, and compliance was ascertained by weekly dietary interviews. Moreover, physician bias was minimized by applying predefined algorithms for warfarin dose adjustments.

We conclude that in anticoagulated patients with very low vitamin K1-plasma status, over-the-counter vitamin K1-containing multivitamin supplements significantly reduce warfarin effect. Our study suggests that such patients could be sensitive to even small changes in vitamin K1 intake, jeopardizing the stability of their anticoagulation.
Appendix

Warfarin dosing adjustment algorithm.

<table>
<thead>
<tr>
<th>INR</th>
<th>Warfarin dosing</th>
<th>INR</th>
<th>Warfarin dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.5-3.5</td>
<td>Dose unchanged</td>
<td>2.0-3.0</td>
<td>Dose unchanged</td>
</tr>
<tr>
<td>3.6-4.0</td>
<td>Withhold warfarin for 1 day</td>
<td>3.1-3.5</td>
<td>Withhold warfarin for 1 day</td>
</tr>
<tr>
<td>4.1-4.5</td>
<td>Withhold warfarin for 1 day. Decrease weekly maintenance dose by 10%</td>
<td>3.6-4.0</td>
<td>Withhold warfarin for 1 day. Decrease weekly maintenance dose by 10%</td>
</tr>
<tr>
<td>4.6-5.0</td>
<td>Withhold warfarin for 2 days. Decrease weekly maintenance dose by 15%</td>
<td>4.1-5.0</td>
<td>Withhold warfarin for 2 days. Decrease weekly maintenance dose by 15%</td>
</tr>
<tr>
<td>&gt; 5.1</td>
<td>Stop MVS, withdraw patient from study</td>
<td>&gt; 5.1</td>
<td>Stop MVS, withdraw patient from study</td>
</tr>
<tr>
<td>2.0-2.4</td>
<td>Add 10% of weekly dose to single daily dose</td>
<td>1.8-1.9</td>
<td>Add 10% of weekly dose to single daily dose. Add LMWH for high risk patients</td>
</tr>
<tr>
<td>1.5-1.9</td>
<td>Add 10% of weekly dose to daily dose on 2 consecutive days. Add LMWH for high risk patients</td>
<td>1.6-1.7</td>
<td>Add 10% of weekly dose to daily dose on 2 consecutive days. Add LMWH for high risk patients.</td>
</tr>
<tr>
<td>&lt; 1.5</td>
<td>Stop MVS, withdraw patient from study</td>
<td>&lt; 1.5</td>
<td>Stop MVS, withdraw patient from study</td>
</tr>
</tbody>
</table>

Comments:
- Repeat INR 3-4 days after every dose change
- LMWH = subcutaneous low-molecular weight heparin; MVS=multivitamin supplement; high risk patients = patients with prosthetic heart valves or thromboembolic event within preceding month.

References
effectiveness, and optimal therapeutic range. Chest 2001; 119: 8S-21S.