Relationship between dietary vitamin K intake and the stability of anticoagulation effect in patients taking long-term warfarin

Kyun Hee Kim[1]; Won Suk Choi[1]; Jang Hoon Lee[1]; Hyejin Lee[2]; Dong Heon Yang[1]; Shung Chull Chae[1]

[1]Department of Internal Medicine, Kyungpook National University Hospital, Daegu, Republic of Korea; [2]Department of Public Health, Kyungpook National University, Daegu, Republic of Korea

Summary

Little study has been performed on the effect of vitamin K intake on the variability of warfarin's anticoagulant effects over long period of time. We estimated average vitamin K intake in the patients taking warfarin and evaluated its relation with the stability of anticoagulation effect. We estimated average daily vitamin K intake based on a three-day food diary in 66 patients taking warfarin regularly for ≥one year and divided them into three groups of equal number according to vitamin K intake. Stability of anticoagulant effect was compared in these groups using the coefficient of variation (CV) of the prothrombin time expressed in international normalised ratio (INR) and the CV of warfarin doses. Median daily vitamin K intake was 161.3 μg/day (31.3 μg/day – 616.6 μg/day). CVs of both INR and warfarin doses were negatively and independently correlated with dietary vitamin K intake (r=-0.293, p=0.017 and r= –0.350, p=0.004, respectively). CV of INR was significantly different among three groups of vitamin K intake (p<0.05 in ANOVA). High vitamin K intake (>195.7 μg/day) group had lower CV of INR than the low intake (<126.5 μg/day) group (19.2 ± 8.96 % vs. 25.5 ± 8.61 %, p<0.05). CV of warfarin doses was also significantly different among the groups (p<0.05 in Jonckheere-Terpstra test). However, the significance of difference between high and low vitamin intake groups was marginal (p=0.046 in Mann-Whitney test) In conclusion, long-term anticoagulation effect of warfarin is more stable in the patients who take greater than a certain amount of dietary vitamin K.

Keywords

Vitamin K, oral anticoagulant, stability

Correspondence to:
Shung Chull Chae, MD
Department of Internal Medicine, Kyungpook National University Hospital
50 Samduk 2-Ga, Daegu, 700–721, Republic of Korea
Tel.: +82 53 420 5527, Fax: +82 53 426 2046
E-mail: scchae@knu.ac.kr

Footnote: The content of this paper was submitted as partial fulfillment of the requirement for the degree of Master of Medical Science (Kim KH) to the Kyungpook National University.

Received: April 28, 2010
Accepted after minor revision: June 4, 2010
Prepublished online: July 20, 2010
doi:10.1160/TH10-04-0257
Thromb Haemost 2010; 104: ■■■

Introduction

Warfarin is an effective oral anticoagulant which is widely prescribed to treat or prevent thromboembolic disorders. Since warfarin has a narrow therapeutic range, clinicians should carefully monitor its dosage to minimise the bleeding complication and, at the same time, to get sufficient anti-coagulation effect Intra- and inter-individual variation of warfarin dose are influenced by variable clinical factors including nutritional status, liver function, intestinal malabsorption, genetic factors, ethnicity and dietary intake of vitamin K (1–5).

Influences of dietary vitamin K on anticoagulant effect of warfarin were reported in a few case reports and short-term studies (6–11). They were mostly about the effect of vitamin K intake on warfarin dose for achieving target prothrombin time or on achieved prothrombin time with a maintenance warfarin dose. However, the effect of dietary vitamin K on the variability of anticoagulant effects of warfarin over long period of time has rarely been studied.

We estimated dietary vitamin K intake of the patients who are taking warfarin for various indications and evaluated its influence on the stability of the anticoagulant effect and doses of warfarin.

Materials and methods

Patients who were taking warfarin regularly were invited to participate in this study. They used warfarin regularly for more than one year, gave informed consents, completed three-day food diaries and were interviewed with a dietitian. Patients were excluded if medications which were known to affect the prothromin time, including but not limited to torsemide and glimepirde, were stopped, added or changed in dosage during the previous one year. They had no symptoms of malabsorption and were taught to maintain their food habits after being involved in the study.

Patients were educated for writing a food diary by an experienced dietitian. To avoid intentional dietary control, patients were not educated about the vitamin K content of the various foods. The dietary intake of vitamin K was estimated by a daily food diary for the last three consecutive days before their visits. To maximise the accuracy of dietary records, we instructed the patients to describe their dietary intake in detail by using food models and photos of foods at the first interview. The second interview was performed on the next regular visit with their food diary to get more accurate information about food intake. We estimated vitamin K content of the patients' dietary diary using 7th Food Composition Table of Korea (12) and CAN PRO 3.0 software of the Korean Nutrition Society (13).

Prothrombin time was measured with the Automated Blood Coagulation Analyzer (CA-7000, Sysmex corporation, Kobe, Japan). The coefficient of variation (CV) of prothromin time expressed in international normalised ratio (INR) of our institution, accredited by the College of American Pathologists, was less than 2%.

To evaluate the variability of anticoagulation, we used the CVs of INR and warfarin doses. The CVs of INR and warfarin doses were calculated as standard deviation (SD) divided by the average of the INRs and warfarin doses for one year, respectively.

This protocol was approved by the Institutional Review Board of Kyungpook National University Hospital.

Data were expressed in mean ± SD or median value (range) for continuous variables and % for categorical variables. The amount of vitamin K intake was log-transformed due to their skewed distribution. Correlations between vitamin K intake and indexes of anticoagulation stability, CVs of INR and warfarin doses, were analysed by standard techniques.

We divided the subjects into three groups of equal number in the order of the amount of dietary vitamin K intake; "low intake (<126.5 μg/day, n=22)", "medium intake (126.5 μg/day – 195.7 μg/day, n=22)", and "high intake (>195.7 μg/day, n=22)". CV of INR was compared among three groups by the analysis of variance (ANOVA) with post hoc analysis by Bonferroni test. CV of warfarin doses was compared by Jonckheere-Terpstra test with post hoc analysis by Mann-Whitney test, since it was not distributed normally.

Two-tailed $p < 0.05$ ($p < 0.017$ for post hoc Mann-Whitney test after Jonckheere-Terpstra test) was regarded as statistically significant. All statistical analyses were performed using SPSS 17.0 for windows (SPSS Inc., Chicago, IL, USA).

Table 1: Baseline characteristics of study subjects. Data are expressed in mean ± standard deviation or number (percentage). * Systemic embolism included deep vein thrombosis, pulmonary embolism, renal infarction, intracardiac thrombus and cerebrovascular embolism.

	n=66
Age (year-old)	59.5 ± 11.1
Female (%)	24 (36.4)
Height (cm)	164.2 ± 8.5
Weight (kg)	64.0 ± 12.5
Body mass index (kg/m^2)	23.6 ± 3.4
Duration of warfarin intake (months)	87.2 ± 53.9
Indications for warfarin	
Atrial fibrillation (%)	36 (54.5)
Valve Replacement (%)	18 (27.3)
Systemic embolism (%)*	11 (16.7)
Dilated cardiomyopathy (%)	1 (1.5)

Table 2: State of anti-coagulation and dietary vitamin K intake. INR, international normalised ratio of prothrombin time; CV, coefficient of variation.

	n=66
Warfarin daily dose (mg)	4.1 ± 1.5
INR	2.2 ± 0.3
Median vitamin K intake (range) (μg/day)	161.3 (31.3 – 616.6)
Log dietary vitamin K (μg/day)	5.0 ± 0.6
CV of INR (%)	22.3 ± 8.3
Median CV of warfarin doses (range) (%)	5.4 (0.0 – 26.0)

Results

Sixty-six patients were included in the study. The baseline characteristics of the patients were showed in ▶Table 1. Mean age of the patients was 59.5 ± 11.1 years and 36% were female. The clinical indications for warfarin therapy, as expected, were atrial fibrillation in 36 (54.5%), valve replacement surgery in 18 (27.3%), systemic embolism in 11 (16.7%), and dilated cardiomyopathy in one patient (1.5%). Systemic embolism included deep-vein thrombosis, pulmonary embolism, renal infarction, intracardiac thrombus and cerebrovascular embolism. Duration of anticoagulation with warfarin was 87 ± 53.9 months, ranging 15 to 243 months. The state of anticoagulation and dietary vitamin K intake are shown in ▶Table 2. Mean dose of warfarin was 4.1 ± 1.5 mg (1.5 mg-9.2 mg). Eighteen (27.3%) patients were on moderate intensity anticoagulation (INR 2.5–3.5), whereas the others were on low intensity (INR 2.0–3.0). Their INRs were 2.61 ± 0.34 and 2.10 ± 0.21 for moderate and low intensity anticoagulations, respectively. Median daily vitamin K intake was 161.3 μg/day (31.3 μg/day – 616.6 μg/day). There was no gender difference in mean warfarin dose, mean INR, vitamin K intake and CVs of both INR and warfarin doses. There were no significant differences in both CVs of INR and warfarin doses in terms of target intensity of anticoagulation.

CV of INR was negatively correlated with dietary vitamin K intake (r= –0.293, p=0.017) (▶Fig. 1) and mean INR (r= –0.270, p=0.028). CV of warfarin doses was negatively correlated with dietary vitamin K intake (r= –0.350, p=0.004) (▶Fig. 2). In multiple regression analysis, log-transformed vitamin K intake was independently correlated with the CVs of INR (regression coefficient

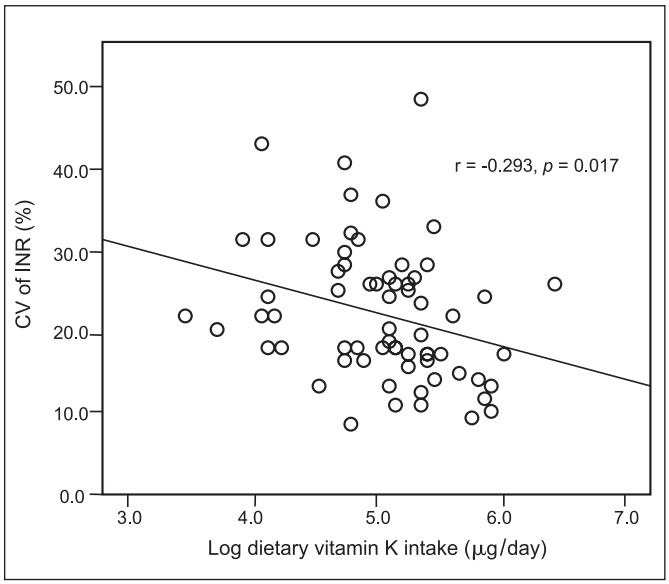

Figure 1: Correlation between dietary vitamin K and coefficient of variation (CV) of INR.

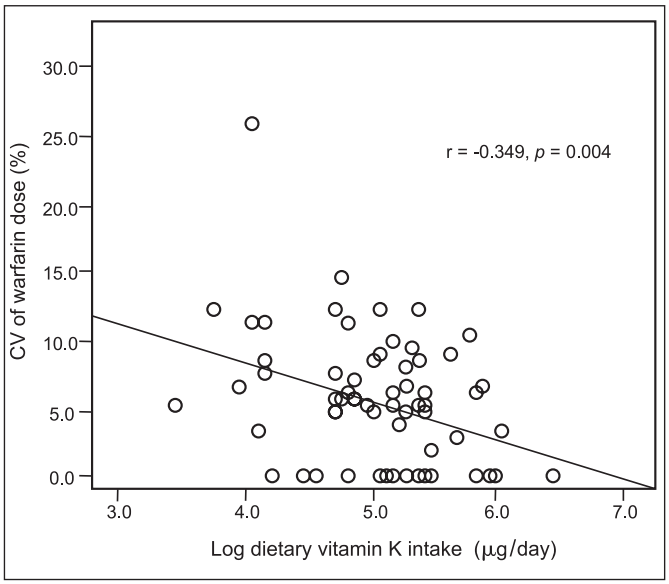

Figure 2: Correlation between dietary vitamin K intake and coefficient of variation (CV) of warfarin doses.

beta= –4.745, p<0.01) and warfarin doses (regression coefficient beta= –2.900, p<0.01), after adjusting age, gender, body surface area, body mass index, mean INR, mean dose of warfarin and duration of anticoagulation (▶Table 3). The CV of INR was significantly different among three groups of vitamin K intake (p<0.05 in ANOVA); The CV of INR in the high vitamin K intake group was lower than in the low intake group (19.2 ± 8.96% vs. 25.5 ± 8.61%, p<0.05) (▶Fig. 3). The CV of warfarin doses was also significantly different among three groups (p<0.05 in Jonckheere-Terpstra test). However, statistical significance of the difference between the high- and low-intake groups was marginal (4.2 ± 4.04 % vs. 7.6 ± 5.97 %, p=0.046 in Mann-Whitney test) (▶Fig. 4).

Discussion

Vitamin K is a cofactor for the carboxylation of glutamate residues to γ- carboxyglutamates on the N-terminal regions of vitamin K-dependent coagulation factors II, VII, IX, and X. These coagulation factors require γ-carboxylation by vitamin K for their biological activity. Warfarin inhibits vitamin K epoxide reductase, resulting in insufficient generation of vitamin K hydroquinone to support full carboxylation and therefore full function of the vitamin K-dependent coagulation factors (1–3).

The effects of vitamin K intake on the anticoagulant effect of warfarin have been studied in small group of patients or in short-term studies. Schurgers et al. controlled vitamin K intake and increased content of dietary vitamin K weekly (6). As the dose of vit-

Table 3: Multiple regression analysis for stability indexes of anticoagulation. Multiple r = 0.532 (p<0.05) for CV of INR and 0.488 (p<0.05) for CV of warfarin doses. BS,= body surface area; BMI, body mass index. Other abbreviations are as in Table 2.

Clinical variables	CV of INR (%)			CV of warfarin dose (%)		
	Regression coefficient	Standardised regression coefficient	P-value	Regression coefficient	Standardised regression coefficient	P-value
Age (year-old)	0.043	0.057	0.654	–0.062	–0.142	0.285
Sex	2.373	0.139	0.425	2.195	0.219	0.224
BSA (m^2)	–7.673	–0.179	0.458	–1.054	–0.042	0.866
BMI (kg/m^2)	–0.079	–0.032	0.860	–0.172	–0.119	0.526
Log dietary vitamin K (μg/day)	–4.745	–0.338	0.005	–2.900	–0.352	0.005
Mean INR	–5.148	–0.212	0.142	1.781	0.125	0.399
Mean warfarin dose (mg)	0.871	0.161	0.265	–0.151	–0.048	0.749
Duration of anticoagulation (month)	–0.043	–0.276	0.058	–0.021	–0.227	0.129

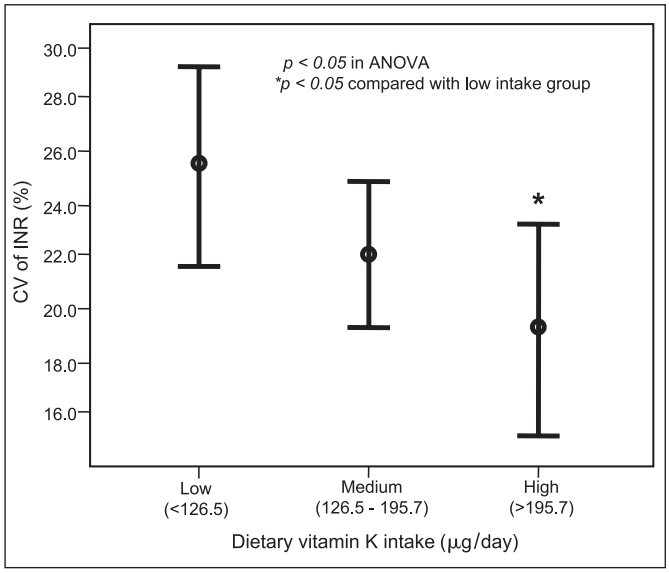

Figure 3: Comparison of coefficient of variation (CV) of INR among three groups according to dietary vitamin K intake. The difference was statistically significant among three groups (p<0.05 in ANOVA test).

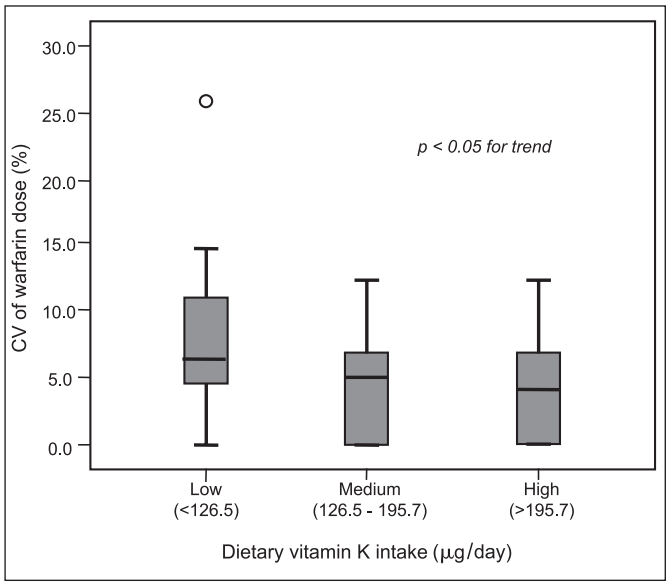

Figure 4: Comparison of coefficient of variation (CV) of warfarin doses among three groups according to dietary vitamin K intake. The difference was statistically significant among three groups (p<0.05 in Jonckheere-Terpstra test). Significance of the difference between high and low vitamin K intake groups was marginal (p = 0.046 in Mann-Whitney test).

amin K increased, INR values decreased dose dependently. When the K1 supplement dose had reached 150 μg/day in women and 200 μg/day in men, the change in INR from baseline became statistically significant. However, this threshold for the effect of vitamin K intake does not seem to be applicable to patients in clinical practice, since participants were asked to refrain from consuming foods known to be rich in vitamin K and their calculated daily K1 intake was somewhat lower than what has been reported (8–10). Franco et al. put 12 patients, in a randomised crossover protocol, either on a 500% increased vitamin K intake or on a 80% decreased vitamin K intake relative to the baseline level. Both vitamin K-enriched and -depleted diets affected INR stability; the former more quickly than the latter (7). Lubetsky et al. investigated correlation of vitamin K intake and sensitivity to warfarin in 50 patients commencing warfarin therapy and consuming their regular diets (8). They used warfarin sensitivity index (WSI, INR/warfarin dose) as an index of stability of anticoagulation and found that, in 32% of their patients under usual dietary conditions, sensitivity to warfarin is decreased by vitamin K intake ≥250 μg/day. Sconce et al. reported on improvement of stability of anticoagulation by vitamin K supplementation (150 μg/day) in patients with unexplained variability in response to warfarin (11). Recently, de Assis et al. showed that the patients on vitamin K-guided strategy achieve target range of INR more frequently than those on conventional approach in a 90-day trial (14). However, its clinical applicability for longer term therapy needs to be further evaluated, since self-adjusting vitamin K intake every month seems to be cumbersome and difficult to adhere to than conventional adjustment of anticoagulation prescription.

In this study, the daily intake of vitamin K was similar to a Western diet in other studies (7, 8, 10). We found that stability of anticoagulant effect increased as dietary intake of vitamin K increased. Log-transformed vitamin K was the strongest determinant for both CVs of INR and warfarin doses, although the multiple regression models explain them only modestly. Patients in the highest tertile of vitamin K intake showed the most stable anticoagulant effects over long periods of time. We used the CVs of INR and warfarin doses as parameters that represent the stability of anticoagulation. In our opinion, there is a limitation in using WSI for the estimation of stability of warfarin's anticoagulation effect. Since WSI is calculated with the INR and warfarin at one time after stabilisation, it does not reflect the variability, i.e. stability, of anticoagulation. However, CV, defined as SD divided by mean value, has been commonly used for testing precision of laboratory tests. It includes a series, not one point value, of INR and warfarin doses. We adopted this value to compare INR range and warfarin dose fluctuations, in other words, the stability of anticoagulation effect. Our finding suggests that, with the large reservoir of daily vitamin K intake, a certain amount of change in vitamin K intake does not significantly affect the anticoagulant effect of warfarin. Interestingly, the cut-off value at large in this study, 196 μg/day of vitamin K intake for the high intake group is similar to its "threshold dose" for the effect of warfarin in the previous reports (6, 8, 15) and a little higher than the "stabilising vitamin K supplementation dose" by Sconce et al. (11).

Limitations

Vitamin K is synthesised by normal flora of human intestine (16). Therefore, there can be some discrepancy between actual vitamin

What is known about this topic?

- As the dose of vitamin K intake increases, anticoagulation effect decreases dose dependently.
- Vitamin K supplementation improves the stability of warfarin's effect in the patients with unexplained variability of anticoagulation.

What does this paper add?

- Taking a certain amount (>195 μg/day) of vitamin K regularly may help maintain the stability of warfarin's anticoagulant effects.
- As the dietary vitamin K intake increases, stability of warfarin's anticoagulation effect over long periods of time increases.

K content in human body and estimated vitamin K measured by food diary. Secondly, we regarded the average vitamin K intake derived from a three-day food diary as the usual vitamin K intake of individuals. Problems with using food diaries over a longer time period have been reported in the elderly. Gersovitz et al. questioned the validity of using a seven-day food record in assessing the usual intakes of the elderly, arguing that the accuracy of recording deteriorates as the days go by (17). In addition, no significant seasonal variations in vitamin K_1 were found in a study from the United Kingdom (18). Therefore, although it may not be the best option, using a three-day food diary, which in fact is commonly used in nutrition surveys (19), seems to be a practical option for the estimation of average nutrient uptake in our patients with mean age of 60 years. Thirdly, although the differences in CVs of INR and warfarin doses were statistically significant among vitamin K intake groups, their magnitudes were only modest with overlap in SDs. Therefore, our results may not be directly applied in daily clinical practice. Finally, we could not evaluate simultaneously the effect of mutation in the genes which takes part in the metabolism of vitamin K (20, 21).

Conclusion

Long-term anticoagulation effect of warfarin is more stable in the patients who take more than a certain amount of dietary vitamin K.

Acknowledgement

The authors appreciate Ms Young Ji Cho, a dietitian, for her effort to analyse patients' food diary, Won Kee Lee, PhD, for statistical consultation and Min Ji Chae, MA, for her English-language editing.

References

1. Hirsh J, Fuster V, Ansell J, et al. American Heart Association/American College of Cardiology Foundation guide to warfarin therapy. Circulation 2003; 107: 1692–1711.
2. Breckenridge A. Oral anticoagulant drugs: pharmacokinetic aspects. Semin Hematol 1978; 15: 19–26.
3. Shearer MJ, Newman P. Metabolism and cell biology of vitamin K. Thromb Haemost 2008; 100: 530–547.
4. Greenblatt DJ, von Moltke LL. Interaction of warfarin with drugs, natural substances, and foods. J Clin Pharmacol 2005; 45: 127–132.
5. Dang MT, Hambleton J, Kayser SR. The influence of ethnicity on warfarin dosage requirement. Ann Pharmacother 2005; 39: 1008–1012.
6. Schurgers LJ, Shearer MJ, Hamulyák K, et al. Effect of vitamin K intake on the stability of oral anticoagulant treatment: dose-response relationships in healthy subjects. Blood 2004; 104: 2682–2689.
7. Franco V, Polanczyk CA, Clausell N, et al. Role of dietary Vitamin K intake in chronic oral anticoagulation: Prospective evidence from observational and randomized protocols. Am J Med 2004; 116: 651–656.
8. Lubetsky A, Dekel-Stern E, Chetrit A, et al. Vitamin K intake and sensitivity to warfarin in patients consuming regular diets. Thromb Haemost 1999; 81: 396–399.
9. Khan T, Wynne H, Wood P, et al. Dietary vitamin K influences intra-individual variability in anticoagulant response to warfarin. Br J Haematol 2004; 124: 348–354.
10. Cushman M, Booth SL, Possidente CJ, et al. The association of vitamin K status with warfarin sensitivity at the onset of treatment. Br J Haematol 2001; 112: 572–577.
11. Sconce E, Avery P, Wynne H, et al. Vitamin K supplementation can improve stability of anticoagulation for patients with unexplained variability in response to warfarin. Blood 2007; 109: 2419–2423.
12. Rural Resource Development institute, National Academy of Agricultural Science. Food composition table, 7th Ed. Seoul: Rural Development Administration (Korea); 2006.
13. The Korean Nutrition Society. CAN PRO 3.0. Seoul, 2006.
14. de Assis MC, Rabelo ER, Avila CW, et al. Improved oral anticoagulation after a dietary vitamin K-guided strategy : a randomized controlled trial. Circulation 2009; 120: 1115–1122.
15. Johnson MA. Influence of vitamin K on anticoagulant therapy depends on vitamin K status and the source and chemical forms of vitamin K. Nutr Rev 2005; 63: 91–97.
16. Shearer MJ, Newman P. Metabolism and cell biology of vitamin K. Thromb Haemost 2008; 100: 530–547.
17. Gersovitz M, Madden JP, Smiciklas-Wright H. Validity of the 24-hr. dietary recall and seven-day record for group comparisons. J Am Diet Assoc 1978; 73: 48–55.
18. Price R, Fenton S, Shearer MJ, et al. Daily and seasonal variation in phylloquinone (vitamin K_1) intake in Scotland. Proc Nutr Soc1996; 55: 244A.
19. Wiens L, Schulzer M, Chen C, et al. Reliability and validity of the SmartDiet Canadian version questionnaire. J Am Diet Assoc 2010; 110: 101–105.
20. The International Warfarin Pharmacogenetics Consortium. Estimation of the warfarin dose with clinical and pharmacogenetic data. N Engl J Med 2009; 360: 753–764.
21. Scott SA, Edelmann L, Kornreich R, et al. Warfarin pharmacogenetics: CYP2C9 and VKORC1 genotypes predict different sensitivity and resistance frequencies in the Ashkenazi and Sephardi Jewish populations. Am J Hum Genet 2008; 82: 495–500.