

## Original

# Does treatment guided by vitamin K in the diet alter the quality of life of anticoagulated patients?

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### Abstract

**Purpose:** To compare whether health-related quality of life (HRQoL) is altered in patients undergoing a treatment strategy guided by changes in dietary vitamin K.

**Methods:** This study is a randomized clinical trial carried out with chronic oral anticoagulation outpatients randomized into a control group (conventional dose adjustment of oral anticoagulants) (n = 66) and an intervention group (strategy based on changes in dietary vitamin K intake) (n = 66). HRQoL was measured using the Duke Anticoagulation Satisfaction Scale (DASS) at baseline and 90 days of follow-up.

**Results:** Patients with worse HRQoL were younger (p = 0.005) and were using a higher dose of baseline oral anticoagulants (p = 0.008), while those with better HRQoL scores had a higher level of education (p = 0.01). Both groups had significant improvements in HRQoL from baseline to 90 days in the global DASS score (p < 0.001), as well as in the negative and positive psychological impact (p < 0.001) domains. We did not observe differences in the variations of HRQoL scores in any of the DASS domains (p values > 0.05) between groups of interventions. Patients who achieved oral anticoagulation stability (n = 23) had significantly better HRQoL scores than patients who did not achieve stability (p = 0.003).

**Conclusion:** Patients receiving the treatment strategy based on changes in dietary vitamin K intake did not have better HRQoL scores; however, both treatment approaches to manage oral anticoagulation improved HRQoL. Patients with greater oral anticoagulation stability had better HRQoL scores.

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### ¿EL TRATAMIENTO GUÍADO POR LA VITAMINA K EN LA DIETA ALTERA LA CALIDAD DE VIDA DE LOS PACIENTES ANTICOAGULADOS?

### Resumen

**Objetivo:** Comparar si la calidad de vida relacionada a la salud (CVRS) se ve alterada en los pacientes sometidos a una estrategia de tratamiento guiado por cambios en la ingesta de vitamina K en la dieta.

**Métodos:** El estudio es un ensayo clínico aleatorizado llevado a cabo con pacientes ambulatorios crónicos de anticoagulación oral con asignación al azar o en un grupo control (ajuste de la dosis convencional de anticoagulantes orales) (n = 66) o en un grupo intervención (estrategia basada en los cambios en la ingesta de vitamina K) (n = 66). La CVRS se midió utilizando el instrumento Duke Anticoagulation Satisfaction Scale (DASS) al inicio y 90 días de seguimiento.

**Resultados:** Los pacientes con peor CVRS eran más jóvenes (p = 0,005) y estaban utilizando una dosis más alta de los anticoagulantes orales de referencia (p = 0,008), mientras aquellos con mejores puntajes de CVRS tenían un mayor nivel de educación (p = 0,01). Ambos grupos tuvieron mejoras significativas en la CVRS desde el inicio hasta 90 días en la puntuación global de DASS (p < 0,001), así como en el los dominios impacto psicológico positivo y negativo (p < 0,001). No se observaron diferencias en las variaciones de las puntuaciones de CVRS en cualquiera de los dominios DASS (valores de p > 0,05) entre los grupos de intervención. Los pacientes que lograron la estabilidad de la anticoagulación oral (n = 23) tuvieron significativamente mejores puntuaciones de CVRS que los pacientes que no lograron la estabilidad (p = 0,003).

**Conclusión:** Los pacientes tratados con la estrategia de tratamiento basada en los cambios en la ingesta de vitamina K no tuvieron mejores puntuaciones de CVRS, sin embargo, ambos enfoques al tratamiento para manejar la anticoagulación oral mejoró la CVRS. Los pacientes con una mejor estabilidad en la anticoagulación oral tuvieron mejores puntuaciones de CVRS.

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Palabras clave: *Vitamina K. Dieta. Anticoagulantes. Calidad de Vida. Ensayo Clínico.*

## Abbreviations

HRQoL: Health-related quality of life.  
INR: International Normalized Ratio.

## Introduction

Despite the exponential increase in studies evaluating health-related quality of life (HRQoL) as an important outcome in patients with several chronic diseases, data in an anticoagulated patient population are still scarce in the relevant literature. The evidence currently available has shown that monitoring these patients in specialized clinics leads to more chronic oral anticoagulation stability, lower incidence of bleeding and ischemic events and improved HRQoL.<sup>1-3</sup> On the other hand, patients treated in general clinics are at higher risk of bleeding and thrombosis, therefore impacting on HRQoL.<sup>4,6</sup>

Among the existing strategies to control oral anticoagulation, anticoagulant dose adjustment has been the first method of choice of most professionals. However, recently, changes in vitamin K intake in the diet have emerged as an attractive option to manage patients outside the therapeutic target based on the *International Normalized Ratio* (INR) of the prothrombin time. Our group has recently demonstrated through a randomized clinical trial that management guided by modulation of vitamin K in the diet improves the stability of oral anticoagulation when compared to patients treated conventionally. Moreover, this dietary based strategy seems to be safer, demonstrating a strong tendency for a lower occurrence of adverse events inherent in oral anticoagulation, such as bleeding or thrombosis.<sup>7</sup>

Despite evidence showing that the HRQoL of anticoagulated patients followed up in specialized clinics is improved,<sup>1,7</sup> the impact of different management strategies of anticoagulation on specific scales of HRQoL, and whether there is a significant association between HRQoL parameters and oral anticoagulation stability and/or adverse events, are unknown. The present study was performed to evaluate the variation of HRQoL scores measured by the *Duke Anticoagulation Satisfaction Scale*, a novel and specific instrument for anticoagulated patients, according to two different strategies to manage oral anticoagulation.

## Methods

### *Patients and study design*

Data on INR values and HRQoL used for the present analysis were derived from a randomized clinical trial in which 132 patients were evaluated from the anticoagulation clinic of a university tertiary care hospital in Porto Alegre, Brazil. Patients were randomized into a

control group (a strategy treatment based on conventional dose adjustment of oral anticoagulants) and an intervention group (a strategy treatment based on pragmatic changes in dietary vitamin K intake according to INR values). The protocol was registered at ClinicalTrials.gov (<http://clinicaltrials.gov>) as NCT00355290. The study was approved by the Research Ethics Committee of our institution, and complies with the Declaration of Helsinki. Detailed data from the study protocol described in the original publication<sup>7</sup>. Briefly, prospective and sequential data on INR values and HRQoL were collected at baseline and 90 days after randomization. For atrial fibrillation, the INR target was 2.5 (from 2.0 to 3.0), and patients were considered to be eligible if the observed INR was 1.5 to 1.99 or 3.01 to 4.0. For valvular prosthesis, the INR target for most patients was 3.0 (from 2.5 to 3.5), and they were considered to be eligible if the observed INR was 1.5 to 2.49 or 3.51 to 4.0. For inclusion in the study, patients had to have been using oral anticoagulants for more than three months, and the last INR had to be outside the therapeutic target, with no definite cause for instability. Patients with the following criteria were excluded: extreme values of INR (< 1.5 or > 4.0) and evidence of bleeding or thrombosis. In this study, stability was defined as the number of times that the INR was in therapeutic range in the follow-up phase.

### *Instrument for quality of life*

HRQoL was measured in both groups through the instrument *Duke Anticoagulation Satisfaction Scale*, a specific instrument for assessing HRQoL for anticoagulated patients,<sup>8</sup> at baseline (randomization visit) and at the final study visit, which occurred 90 days after inclusion. This instrument was adapted to and validated for the Portuguese variant spoken in Brazil featuring adequate reliability (Cronbach's alpha of 0.79). It consists of 25 items covering three dimensions related to oral anticoagulation: *limitation* (Cronbach's alpha 0.72), *task/burden* (Cronbach's alpha 0.76), and *positive* (Cronbach's alpha 0.67) and *negative* (Cronbach's alpha 0.38) *psychological impact*<sup>9</sup>. With respect to descriptive analysis, studies of construction and validation present *Duke Anticoagulation Satisfaction Scale* scores in two ways: the sum of the responses to 25 items (possible range 25 to 175) or by averaging the responses to 25 items (possible range 1 to 7). For the current analysis, we opted to use the averaging system.

The limitation domain has nine items, the task domain has eight items, the positive psychological impact domain has five items, and the negative psychological impact has three items. Obtaining the numerical values of the total scale is possible by averaging the responses to items, as well as obtaining the numerical values of the sub-scales. Lower values of scales depict improved HRQoL.

## Data analysis

Variables were assessed according to their characteristics and distribution, using parametric or nonparametric tests in the assessment of absolute or percentage differences between dependent samples. To compare clinical and demographic characteristics, patients were divided into quartiles according to the score on the *Duke Anticoagulation Satisfaction Scale* and grouped into two major groups: upper (HRQoL scores above 1.88) and lower (scores below 1.52). For comparison of HRQoL scores over time in the group guided by dietary vitamin K changes and in the control group (conventionally managed), a paired t-test was used for comparing different moments. To assess whether the difference ( $\Delta$ ) in HRQoL scores was attributable to the type of intervention, the presence or absence of bleeding, stability and adherence, an interaction variable between the groups was created, obtained from the difference between the baseline HRQoL score (Pre) and the final HRQoL score (Post). For this analysis, we used ANOVA for repeated measures to compare the two groups over time, as well as to evaluate the final scores of HRQoL in both groups

when comparing bleeding (presence or absence), stability and adherence. P values < 0.05 (two-tailed) were considered statistically significant. Data were analyzed using the statistical PASW application *Statistics* 18.0 (IBM SPSS software).

## Results

132 patients (66 in each group) who met the inclusion criteria and consented to participate in the protocol were included. Detailed data of the enrolled patients were previously described.<sup>7</sup> Demographic and clinical characteristics of patients were compared by stratifying the studied population into two groups according to extremes of HRQoL scores at baseline (upper and lower quartiles). We observed that patients with worse HRQoL were younger ( $p = 0.005$ ) and were using a higher dose of baseline oral anticoagulant ( $p = 0.008$ ). On the other hand, those with a higher level of education had improved HRQoL ( $p = 0.01$ ) (table I).

Comparing baseline and the post-intervention period, the group guided by vitamin K in the diet had improvements in the total HRQoL score ( $p < 0.001$ )

**Table I**  
Comparison of demographic and clinical variables among patients with scores of quality of life in the upper and lower quartile

Clinical variables	QoL score, upper quartile (> 1.88) (n = 33)	QoL, score, lower quartile ( $\leq$ 1.52) (n = 29)	P
Age, in years	53.3 $\pm$ 13	62.8 $\pm$ 12	0.005
Male	21 (63.6)	17 (58.6)	0.68
Group			0.07
Intervention	20 (60.6)	11 (37.9)	
Control	13 (39.4)	18 (62.1)	
Income, minimum wages*	3.4 $\pm$ 2.5	4.1 $\pm$ 2.4	0.26
Education			0.01
Elementary school	2 (6.1)	4 (13.8)	
High school	0 (0)	1 (3.4)	
Comorbidities			
Heart failure	3 (9.1)	8 (27.6)	0.19
Diabetes mellitus	2 (6.1)	4 (13.8)	0.55
Ischemic heart disease	4 (12.1)	6 (20.7)	0.35
COPD	0 (0)	1 (3.4)	0.16
Indications for OAC			0.36
Chronic AF Fibrillation	9 (28.1)	17 (63)	
Mitral Prosthesis	10 (31.3)	3 (11.1)	
Aortic Prosthesis	13 (40.6)	5 (18.5)	
Others	0 (0)	2 (7.4)	
Duration of OAC, months	24 (8.5-54)	36 (12-78)	0.56
Dose of anticoagulation	37.8 $\pm$ 28	25.8 $\pm$ 13.1	0.008
Baseline INR	2.3 $\pm$ 0.7	2.4 $\pm$ 0.8	0.63
Anticoagulant drugs			0.37
Warfarin	28 (84.8)	22 (75.9)	
Phenprocoumon	5 (15.2)	7 (24.1)	

Values expressed as mean  $\pm$  standard deviation, n (%) or median (25<sup>th</sup> percentile, 75<sup>th</sup> percentile). QoL: Quality of Life; COPD: Chronic obstructive pulmonary disease; AF: Atrial fibrillation; OAC: Oral anticoagulation.

\*1 Brazilian minimum wage = \$349.80.

**Table II**  
*Difference of scores of quality of life and its domains between baseline (Pre) and the end of the follow-up (Post) according to the intervention group (treatment guided by vitamin K in diet) or control group (conventional treatment)*

Domains of quality of life	Intervention group Dietary Vitamin K Guided				Control group Conventionally Managed				P*
	Pre	Post	Δ	P	Pre	Post	Δ	P	
Total score	1.78 ± 0.3	1.63 ± 0.3	-0.15	<0.001	1.69 ± 0.3	1.59 ± 0.2	-0.10	0.02	0.41
Limitation	1.52 ± 0.6	1.38 ± 0.5	-0.14	0.04	1.31 ± 0.5	1.25 ± 0.5	-0.60	0.43	0.44
Task	1.4 ± 0.39	1.29 ± 0.3	-0.10	0.02	1.35 ± 0.2	1.31 ± 0.1	-0.03	0.23	0.24
Psychological impact (PI)	2.44 ± 0.4	2.23 ± 0.4	-0.20	<0.001	2.51 ± 0.5	2.26 ± 0.4	-0.25	<0.001	0.61
Positive PI	3.04 ± 0.4	2.68 ± 0.5	-0.35	<0.001	3.11 ± 0.6	2.72 ± 0.5	-0.39	<0.001	0.76
Negative PI	1.45 ± 0.6	1.48 ± 0.5	0.03	0.69	1.51 ± 0.6	1.49 ± 0.5	-0.02	0.81	0.65

Values expressed as mean ± standard deviation. Δ = Difference in quality of life score between Pre and Post periods.

\* P values refer to the comparison for the intervention.

and in the limitation ( $p = 0.04$ ), task ( $p = 0.02$ ), negative ( $p < 0.001$ ) and positive psychological impact ( $p < 0.001$ ) domains. For the control group, there was an improvement in the total HRQoL score ( $p = 0.02$ ), as well as in the negative ( $p < 0.001$ ) and positive psychological impact ( $p < 0.001$ ) domains (table II).

When assessing whether differences in HRQoL scores could be attributable in part to differences between interventions (dietary vitamin K guided versus conventional management), we found no significant difference between the variations of HRQoL in the groups: total HRQoL score ( $p = 0.41$ ) and limitation ( $p = 0.44$ ), task ( $p = 0.24$ ), psychological impact ( $p = 0.61$ ), positive ( $p = 0.76$ ) and negative psychological impact ( $p = 0.65$ ) domains (last column of table II).

We did not observe any significant interaction of HRQoL scores and the presence ( $n = 7$ ) or absence ( $n = 119$ ) of bleeding and adherence ( $n = 105$ ) or not to treatment ( $n = 21$ ) (fig. 1A e 1B). However, HRQoL scores were higher in patients who achieved oral anticoagulation stability ( $n = 23$ ) [100% of INRs within the therapeutic range], when compared to patients with lower oral anticoagulation stability ( $p = 0.003$ ) (fig. 1C).

## Discussion

In the present study, we have confirmed that HRQoL scores improve over a relatively short period of follow-up. This improvement had a similar magnitude in both groups regardless of allocation (dietary change versus anticoagulant dose adjustment). Notably, patients who achieved oral anticoagulation stability during follow-up showed, at the end of the study, significantly higher HRQoL scores. No interaction of HRQoL scores was observed between the presence of bleeding and treatment adherence. These findings corroborate previous data indicating that anticoagulated patients under multidisciplinary follow-up in specialized clinics can improve HRQoL.<sup>10,11</sup>

Recently our group published the results of a randomized clinical trial which evaluated the role of changes in dietary vitamin K intake in the management of chronic oral anticoagulation instability (patients with minor changes of INR).<sup>7</sup> In this study we found that patients who were managed with pre-defined modifications in oral vitamin K intake were more likely to reach the desired target INR when compared to the conventional management (increases and decreases in oral anticoagulant dose). These results substantiate the interaction between dietary vitamin K and the effect of coumarin derived anticoagulants, and indicate that this strategy is feasible, safe and efficacious. However, such an approach could theoretically impact HRQoL in different ways. If oral anticoagulation stability could be more easily achieved over time, patients would suffer less adverse events and need less frequent blood controls, impacting positively on HRQoL scores. On the other hand, active changes in dietary patterns can be potentially troublesome for many patients. The dietary recommendations defined by the suggested protocol could be perceived as a major interference in routine food ingestion and impact negatively on HRQoL parameters. Our results indicate that the final net effect of both strategies (conventional adjustment and dietary adjustment) on the *Duke Anticoagulation Satisfaction Scale* overall score was similar over time. The lack of greater improvement in HRQoL parameters in the dietary adjustment strategy could be attributed, in part, to the relatively short period of follow-up during the protocol, besides the pre-specified blood drawings for INR measurement which were part of the original research protocol.

Qualitative studies have confirmed that frequent monitoring of blood tests and visits to the clinic, anxiety related to adverse events, patient autonomy, alcoholic and dietary restrictions and the impact of anticoagulant medication on physical activities have a negative impact on the HRQoL.<sup>12-14</sup> Lancaster<sup>15</sup> in a randomized clinical trial carefully analyzed the impact

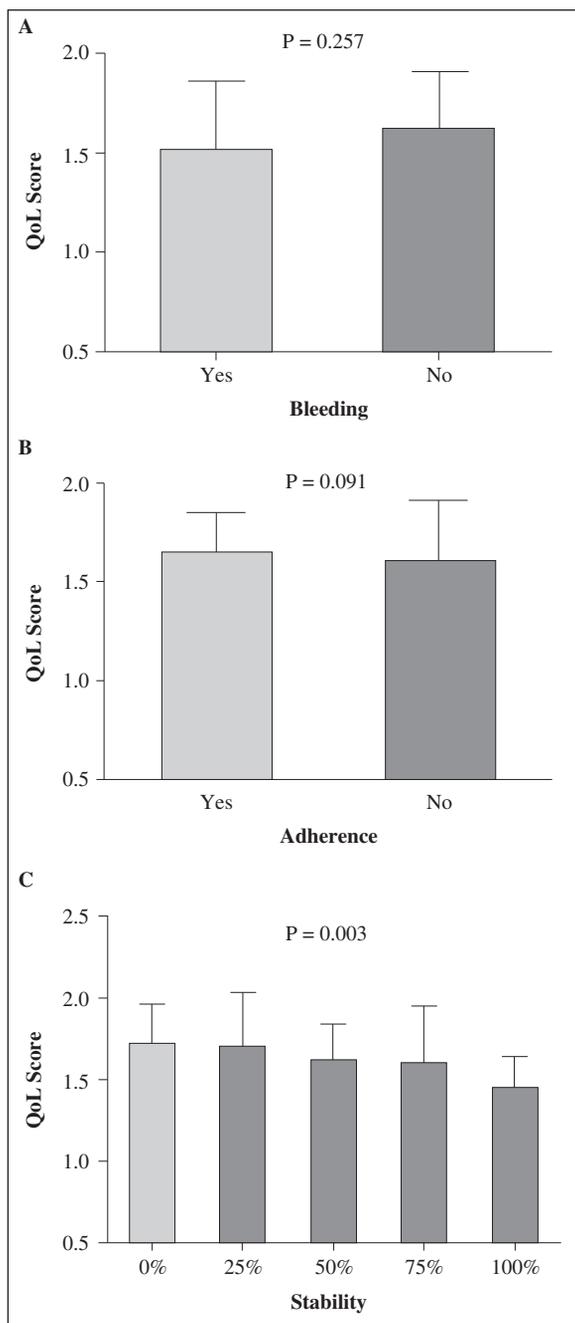


Fig. 1.—Total Quality of Life (QoL) score at the end of the study between patients with presence or absence of bleeding (A), adherence or not to treatment (B) and oral anticoagulation stability (C).

of long-term warfarin therapy in the HRQoL. This study randomized patients with non-rheumatic atrial fibrillation to warfarin treatment *versus* conventional management without anticoagulants. Patients were observed for two years and regularly had their HRQoL evaluated with validated scales which measure functional status, to “feel good” and health perception. Overall, there was no significant difference in measures of HRQoL between groups of patients treated with warfarin or not. However, patients with a

bleeding episode had a significant reduction in perceived health.

Interestingly, some investigators have suggested that there is no association between oral anticoagulation stability and HRQoL, as demonstrated by Davis et al.<sup>6</sup> In their study, anticoagulated patients with the worst perception of their HRQoL did not have worse stability of oral anticoagulation. However, this study had a relatively small sample size, and used a simple non-validated instrument to evaluate HRQoL (the 4-item Morisky survey). Recent studies indicate that patients under an oral anticoagulation self-management strategy using portable devices (*Point of Care CoaguChek*) to measure INRs also have better stability of oral anticoagulation, less bleeding episodes and improved HRQoL.<sup>16-18</sup> In a randomized clinical trial comparing self-management strategy versus laboratory monitoring in which researchers used the *Duke Anticoagulation Satisfaction Scale* instrument, the results were similar to those obtained in the present study regarding the magnitude of HRQoL score variation, and better scores for HRQoL were found in patients with self-management of oral anticoagulation.<sup>19</sup>

In a randomized study of INR self-control *versus* conventional INR control there were significant improvements in HRQoL for patients in the domains of self-satisfaction and self-efficacy. Similarly to our findings, INR stability was associated with higher HRQoL in this last report.<sup>20</sup>

A potential limitation of the present study is that we used an instrument to evaluate quality of life related to health-specific anti-coagulated patients. This can be an advantage to capture changes in health status over time, but on the other hand, does not assess the broader areas which could also be affected by a chronic condition or by specific interventions. Casais et al.<sup>4</sup> evaluated HRQoL of anticoagulated patients using the *Medical Outcomes Survey 36-Item Short Form (SF-36)*,<sup>21</sup> considered to be a generic instrument for assessing HRQoL. They found that anticoagulated patients with more negative perceptions about their treatment achieved the lowest score in the SF-36 survey (which means the worst HRQoL). This instrument includes eight domains, including pain, general health and social aspects which are not included in the *Duke Anticoagulation Satisfaction Scale*, and may also have been affected by the type of management adopted for anticoagulation therapy.

## Conclusion

This study showed that both strategies for oral anticoagulation improved HRQoL scores. Treatment guided by vitamin K in the diet did not substantially alter the improvement observed in the conventional treatment. Importantly, oral anticoagulation stability was directly associated with improvement in HRQoL scores, reinforcing the need to strengthen the efforts

being made to pursue INRs within the therapeutic target.

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## References

1. Matchar DB, Samsa GP, Cohen SJ, Oddone EZ, Jurgelski AE. Improving the quality of anticoagulation of patients with atrial fibrillation in managed care organizations: results of the managing anticoagulation services trial. *Am J of Med* 2002; 113 (1): 42-51.
2. Cromheecke ME, Levi M, Colly LP, de Mol BJ, Prins MH, Hutten BA et al. Oral anticoagulation self-management and management by a specialist anticoagulation clinic: a randomized cross-over comparison. *Lancet* 2000; 356 (8): 97-102.
3. Gadsisseur AP, Breukink-Engbers WG, van der Meer FJ, van den Besselaar AM, Sturk A, Rosendaal FR. Comparison of the quality of oral anticoagulant therapy through patient self-management and management by specialized anticoagulation clinics in the Netherlands. *Arch Intern Med* 2003; 163: 2639-46.
4. Casais P, Meschengieser SS, Sanchez-Luceros A, Lazzari MA. Patients' perceptions regarding oral anticoagulation therapy and its effect on quality of life. *Curr Med Res Opin* 2005; 21 (7): 1085-90.
5. Gadsisseur AP, Kaptein AA, Breukink-Engbers WG, van der Meer FJ, Rosendaal FR. Patient self-management of oral anticoagulant care vs. management by specialized anticoagulation clinics: positive effects on quality of life. *J Thromb Haemost* 2004; 2 (4): 584-91.
6. Davis NL, Billett HH, Cohen HW, Arnsten JH. Impact of adherence, knowledge, and quality of life on anticoagulation control. *Ann Pharmacother* 2005; 39: 632-6.
7. De Assis MC, Rabelo ER, Avila CW, Polanczyk CA, Rohde LE. Improved oral anticoagulation after a dietary vitamin k-guided strategy: a randomized controlled trial. *Circulation* 2009; 120 (12): 1115-22.
8. Samsa G, Matchar DB, Dolor RJ, Wiklund I, Hedner E, Wygant G et al. A new instrument for measuring anticoagulation-related quality of life: development and preliminary validation. *Health Qual Life Outcomes* 2004; 2: 22-33.
9. Pelegrino FM, Dantas RA, Corbi IS, da Silva Carvalho AR, Schmidt A, Filho AP. Cross-cultural adaptation and psychometric properties of the Brazilian-Portuguese version of the Duke Anticoagulation Satisfaction Scale. *J Clin Nurs* 2011; 1: 1-9.
10. Blaise S, Satger B, Fontaine M, Yver J, Rastel D, Toffin L et al. Evaluation of an education program for patients taking oral anticoagulants: Experience of the GRANTED network in Isère. *J Mal Vasc* 2009; 34 (5): 346-53.
11. Ansell J, Hirsh J, Dalen J, Bussey H, Anderson D, Poller L et al. Managing oral anticoagulant therapy. *Chest* 2001; 119: 22S-33S.
12. Prins MH, Marrel A, Carita P, Anderson D, Bousser MG, Crijns H et al. Multinational development of a questionnaire assessing patient satisfaction with anticoagulant treatment: the "Perception of Anticoagulant Treatment Questionnaire" (PACT-Q). *Health Qual Life Outcomes* 2009; 7 (9): 9-22.
13. Dantas GC, Thompson BV, Manson JA, Tracy CS, Upshur RE. Patients' perspectives on taking warfarin: qualitative study in family practice. *BMC Fam Pract* 2004; 5: 15.
14. Kneeland PP, Fang MC. Current issues in patient adherence and persistence: focus on anticoagulants for the treatment and prevention of thromboembolism. *Patient Prefer Adherence* 2010; 4: 51-60.
15. Lancaster TR, Singer DE, Sheen MA, Oertel LB, Maravento SW, Hughes RA et al. The impact of long-term warfarin therapy on quality of life. Evidence from a randomized trial. *Arch Intern Med* 1991; 151 (10): 1944-9.
16. Soliman Hamad MA, van Eekelen E, van Agt T, van Straten AH. Self-management program improves anticoagulation control and quality of life: a prospective randomized study. *Eur J Cardiothoracic Surg* 2009; 35 (2): 265-9.
17. Bloomfield HE, Krause A, Greer N, Taylor BC, Macdonald R, Rutks I et al. Meta-analysis: effect of patient self-testing and self-management of long-term anticoagulation on major clinical outcomes. *Ann Intern Med* 2011; 154 (7): 472-82.
18. Fitzmaurice DA, Murray ET, Gee KM, Allan TF, Hobbs FD. A randomized controlled trial of patient self management of oral anticoagulation treatment compared with primary care management. *J Clin Pathol* 2002; 55 (11): 845-9.
19. Matchar DB, Jacobson A, Dolor R, Edson R, Uyeda L, Phibbs CS et al. Effect of home testing of international normalized ratio on clinical events. *N Engl J Med* 2010; 363: 1608-20.
20. McCahon D, Murray ET, Murray K, Holder RL, Fitzmaurice DA. Does self-management of oral anticoagulation therapy improve quality of life and anxiety? *Fam Pract* 2011; 28 (2): 134-40.
21. Ware JE Jr, Sherbourne CD. The MOS 36-item short-form healthy survey (SF-36). I. Conceptual framework and item selection. *Med Care* 1992; 30 (6): 473-83.