IVYSPRING INTERNATIONAL PUBLISHER

International Journal of Medical Sciences

2014; 11(7): 680-684. doi: 10.7150/ijms.8916

Research Paper

New Oral Anticoagulants vs Vitamin K Antagonists: Benefits for Health-Related Quality of Life in Patients with Atrial Fibrillation

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Received: 2014.02.24; Accepted: 2014.04.01; Published: 2014.05.01

Abstract

New oral anticoagulants (NOAC) have demonstrated their efficacy as an alternative to vitamin K antagonists (VKA) in the prophylaxis of cardioembolic events in patients with atrial fibrillation (AF). However, evidence on the benefits of NOAC in health-related quality of life (HRQoL) is lacking.We evaluated changes in HRQoL related to oral anticoagulation therapy employing a specific questionnaire in a cohort of 416 patients with AF undergoing electrical cardioversion. In terms of HRQoL, we observed a progressive adaptation to treatment with VKA; satisfaction with NOAC remained constant. Older age, higher left ventricular ejection fraction and NOAC were associated with better HRQoL.

Key words: vitamin K antagonists; dabigatran; health-related quality of life; new oral anticoagulants; ribaroxaban.

Introduction

Treatment with vitamin K antagonists (VKA) is complex and requires frequent analytical work-ups and visits to monitor the international normalized ratio (INR). This treatment can affect patients' assessment of health-related quality of life (HRQoL) in that it requires changes in lifestyle and not provide relief from symptoms [1]. Results from clinical trials have demonstrated the usefulness of new oral anticoagulants (NOAC) (dabigatran, rivaroxaban, and apixaban) as an alternative to conventional treatment with VKA in the prophylaxis of cardioembolic events in patients with AF [2-4]. NOAC have shown also its benefits in specific settings as electrical cardioversion [5] and catheter ablation of AF [6]. One of the benefits of therapy with NOAC is that it obviates the periodical monitoring required for VKA. Consequently, assessment of HRQoL in patients with AF treated with NOAC could improve. However, evidence of the superiority of NOAC over VKA in HRQoL is lacking.

In the present study, we compared the impact of NOAC on HRQoL with that of conventional treatment based on VKA in a group of patients with AF undergoing electrical cardioversion who had recently initiated anticoagulant treatment.

Methods

Patients

HRQoL was evaluated at cardioversion (baseline) and 6 months later in 416 patients included in the CARDIOVERSE study. The CARDIOVERSE study

was designed to monitor the clinical practice of elective electrical cardioversion in Spain by prospectively recording all patients with persistent AF who underwent the procedure between 1st Feb and 30th June 2012 in 67 Spanish hospitals. Patients were recruited consecutively. The inclusion criteria were age >18 years, duration of AF >7 days, and absence of AF precipitating conditions (e.g., hyperthyroidism, fever, and pericarditis). No instructions for the use of anticoagulant treatment had been recommended. For the current analysis, we selected those patients who had initiated anticoagulant therapy in the 4 months before electrical cardioversion (N=528) and who completed a questionnaire on HRQoL (N=416). Two patients with disabling embolic or hemorrhagic events during follow-up were excluded. We divided patients into 2 groups, depending on whether they had received NOAC (n=65) or VKA (n=351). At the beginning of the study, the only NOAC approved in Spain for the prophylaxis of embolisms in AF was dabigatran; rivaroxaban was approved at the end of the recruitment period. Fifty-nine patients were treated with dabigatran and 6 patients were treated with rivaroxaban. Apixaban was not approved for this indication in Spain during the present study.

Questionnaire and assessment of HRQoL

We analyzed the scores of a specific questionnaire designed to assess HRQoL in patients treated with oral anticoagulants. The questionnaire used was a validated Spanish adaptation [7] of the Sawicki questionnaire [8], an original questionnaire that has been used in several studies [9-11]. The questionnaire includes 32 items grouped in 5 dimensions. Patients estimated the impact of each item on their self-perceived treatment-related quality of life on a scale of 1 (total disagreement) to 6 (total agreement). The 5 dimensions are general treatment satisfaction, self-efficacy, strained social network, daily hassles, and distress. The self-efficacy dimension was not analyzed in the present study owing to the characteristics of NOAC. A higher score in the dimensions indicates greater impact and, therefore, worse situation of the individual patient. Finally, we obtained a global score by adding up the score of each dimension. A lower score indicates higher HRQoL and a higher score indicates lower HRQoL. The questionnaire was self-completed.

Continuous variables are expressed as mean±SD, and comparisons between groups were made using the *t* test (for independent values when comparing both groups at baseline and at 6 months and for paired values when comparing the same group at both time points). Categorical variables are expressed as percentages and were analyzed using the chi-square test. Stepwise multiple linear regression models were developed to find independent factors related to the global score of HRQoL. Gender, age, left ventricular ejection fraction, diabetes mellitus, NYHA, congestive heart failure, CHADS2, CHA2DS2VASc, HAS-BLED and NOAC were included in the analysis. The internal reliability of the questionnaire was assessed using the Cronbach alpha coefficient. Differences were considered statistically significant if $p<0.05$. The statistical analysis was performed using SPSS Inc. Released 2009. PASW Statistics for Windows, Version 18.0. Chicago: SPSS Inc.

The study was approved by the Institutional Review Boards (Clinical Ethics Committee) of each participating hospital. Written informed consent was obtained from all the patients who participated in this study.

Results

The baseline characteristics of the 416 patients analyzed are presented in Table 1. No significant differences were detected between patients treated with VKA and patients treated with NOAC in terms of duration of therapy, maintenance of sinus rhythm, or other characteristics potentially related to HRQoL.

Table 2 shows the questionnaire scores. At baseline, the general treatment satisfaction score was significantly lower and the daily hassles score tended to be significantly lower in the NOAC group (better HRQoL). In addition, the global score tended to be lower in the NOAC group (also indicating a better HRQoL) (10.3±3.5 COA vs 9.6±3.7 NOAC; p=0.17). Six months after cardioversion, 252 patients continued to receive oral anticoagulant therapy and completed the questionnaire (215 in the VKA group and 37 in the NOAC group). Scores for general treatment satisfaction, daily hassles, distress, and strained social network improved in the VKA group with respect to baseline and did not show significant changes in the NOAC group (Table 3). When we compared thescores for both groups at 6 months, we did not observe significant differences in any dimension (Table 2). The global score was similar in both groups at 6 months (9.5±3.5 VKA vs 9.4±3.0 NOAC; p=0.88).

The internal reliability was acceptable as indicated by the Cronbachα values. A ceiling effect (more than 15% of maximum value for a dimension) was only observed in strained social network at baseline (19%).

We applied multiple linear regressions to investigate those variables independently associated with the global score at baseline. Older age (β= -0.05 x year; p=0.009), higher left ventricular ejection fraction (β= -0.05 x %; p=0.002), and NOAC (β= -0.56; p=0.03) were associated with a lower global score (better HRQoL).

Table 1. Characteristics of patients.

		VKA n=351	NOAC n=65	*p*
Age, years		63.1 ± 10.1	61.0 ± 9.5	0.13
Male gender, n (%)		285 (81)	58 (89.2)	0.09
BMI, kg/m²		29.0 ± 4.3	29.3 ± 4.2	0.70
LA, mm		44 ± 6	43 ± 5	0.61
LVEF - quantitative		58 ± 11	60 ± 9	0.12
LVEF - qualitative, n (%)	Normal (≥50%)	260 (80)	54 (89)	0.30
	Slightly depressed (49-41%)	32 (9)	5 (8)	
	Moderately (40-31%)	22 (7)	1 (2)	
	Severely (≤30%)	13 (4)	1 (2)	
Hypertension, n (%)		206 (57)	39 (60)	0.79
Diabetes mellitus, n (%)		58 (17)	16 (25)	0.11
Pulmonary disease, n (%)		38 (11)	6 (9)	0.72
Congestive heart failure, n (%)		42 (12)	12 (19)	0.15
Previous electrical CV, n (%)		45 (13)	5 (8)	0.25
Antiplatelet therapy, n (%)		45 (13)	7 (11)	0.66
$CHADS_2$, n (%)	Low risk (score=0)	113 (32)	18 (28)	0.70
	Medium risk (score=1)	146 (42)	26 (40)	
	High risk (score≥2)	92 (26)	21 (32)	
CHA_2DS_2VASc, n (%)	Low risk (score=0)	68 (19)	13 (20)	0.98
	Low-medium risk (score=1)	96 (27)	17 (26)	
	Medium-high risk (score≥2)	187 (53)	35 (54)	
HAS-BLED, n (%)	Low-medium risk (score<3)	335 (95)	60 (92)	0.66
	High risk (score≥3)	16 (5)	5 (8)	
Duration of AF, n (%)	8 days - 1 month	15 (4)	4 (6)	0.66
	1 - 3 months	131 (37)	22 (34)	
	3 - 12 months	122 (35)	19 (29)	
	> 12 months	25 (7)	7 (11)	
	Unknown	58 (17)	13 (20)	
Symptoms related to AF, n (%) (EHRA scale)	I	145 (41)	33 (51)	0.18
	II	183 (52)	26 (40)	
	III	17 (5)	5 (8)	
	IV	1 (0.5)	1 (1)	
	Unknown	5 (1.5)	0 (0)	

Values represent mean ± SD or n (%). AF, atrial fibrillation; BMI, body mass index; VKA, vitamin K antagonists; CV, cardioversion; EHRA, European Heart Rhythm Association; LA, left atrium; LVEF, left ventricle ejection fraction; NOAC, new oral anticoagulant.

Table 2. Comparison of questionnaire scores at baseline and at 6 months in relation to the type of oral anticoagulant treatment.

	Baseline					Follow-up (6 months)				
	Cronbach α	VKA	NOAC	Difference	*p*	Cronbach α	VKA	NOAC	Difference	*p*
General treatment satisfaction	0.75	2.5 ± 1.0	2.2 ± 1.1	-0.3	< 0.01	0.75	2.3 ± 1.0	2.2 ± 1.0	-0.1	0.80
Distress	0.84	3.3 ± 1.1	3.2 ± 1.0	-0.1	0.46	0.84	3.1 ± 1.0	3.1 ± 0.9	0	0.86
Daily hassles	0.81	2.3 ± 1.0	2.2 ± 1.1	-0.1	0.13	0.78	2.1 ± 1.0	2.0 ± 0.9	-0.1	0.91
Strained social network	0.72	2.0 ± 1.0	1.9 ± 1.0	-0.1	0.23	0.68	1.9 ± 0.9	2.0 ± 0.8	0.1	0.29

VKA, vitamin K antagonists; NOAC, new oral anticoagulant.

Table 3. Changes in the questionnaire scores between baseline and at 6 months depending on the type of oral anticoagulant treatment.

	VKA				NOAC			
	Baseline	6 months	Difference	*p*	Baseline	6 months	Difference	*p*
General treatment satisfaction	2.5 ± 1.0	2.3 ± 1.0	-0.2	< 0.01	2.4 ± 1.2	2.2 ± 1.0	-0.2	0.48
Distress	3.3 ± 1.1	3.1 ± 1.0	-0.2	< 0.001	3.3 ± 1.1	3.1 ± 0.9	-0.2	0.24
Daily hassles	2.3 ± 1.1	2.1 ± 1.0	-0.2	< 0.005	2.2 ± 1.1	2.0 ± 0.9	-0.2	0.45
Strained social network	2.1 ± 1.0	1.9 ± 0.9	-0.2	< 0.05	1.9 ± 2.0	2.0 ± 0.8	0.1	0.43

VKA, vitamin K antagonists; NOAC, new oral anticoagulant.

Discussion

At initiation of anticoagulant therapy in patients with AF, we observed a worse HRQoL in some dimensions in patients treated with conventional VKA than in patients treated with NOAC. However, these differences disappeared 6 months later. We identified age, left ventricular ejection fraction, and treatment with NOAC as factors independently associated with better HRQoL.

The greatest differences in HRQoL were observed in the general treatment satisfaction dimen-

sion. The lower perception of HRQoL during the first months of VKA treatment with respect to NOAC may be explained by the higher number of visits required at the beginning of therapy and the frequent difficulties in achieving adequate INR levels [12-14]. The subsequent lower requirement for visits and more stable levels of INR could justify the improvement in the assessment of HRQoL and the lack of differences between the NOAC and VKA groups at 6 months.

Some variables were associated with perception of HRQoL. A worse left ventricular function was associated with worse HRQoL, probably because anticoagulation therapy created more problems for patients with an already reduced HRQoL. Aging was directly related to the HRQoL level. Younger patients showed lower levels of HRQoL related to anticoagulation treatment than older patients. Independence in daily social and working activities and avoidance of medical visits seem to be of particular concern to younger patients receiving anticoagulant therapy. This is especially true for employed persons. Our results show that NOAC improves these restrictions with respect to conventional treatment with VKA. Although we included patients undergoing electrical cardioversion, we believe that our results could be applied in other groups, such as patients undergoing catheter ablation of AF and patients for whom a rate control strategy is chosen.

Our study is subject to a series of limitations. First, the questionnaire used was originally designed for assessment of HRQoL associated with VKA treatment. Consequently, other aspects related to HRQoL in AF may be not detected. HRQoL affected by damage arising from disabling embolic or hemorrhagic events was not assessed in this questionnaire. In fact, 2 patients who had experienced these types of events were excluded from the analysis. In a sub-group of patients participating in the RE-LY trial, Monz*et al*. used a general non-specific disease questionnaire, the EQ-5D, and a visual analog scale to compare the impact of dabigatran on HRQoL with that of warfarin [15]. They found no significant differences in HRQoL between patients treated with dabigatran and patients treated with warfarin. In contrast, our objectives were different, the focus of our study being the association between HRQoL and anticoagulant therapy itself. Our findings suggest that our approach is more realistic for detection of differences in HRQoL associated with NOAC. Second, there is a clear imbalance in the number of patients included in the treatment groups. This distribution is coherent with the current use of the anticoagulation treatment in Europe [16]. The decrease in the number receiving NOAC at 6 months limits the possibility of establishing significant differences. Third, our study was not randomized. However, it included consecutive patients included in different hospitals and it reflects real-life assessment of HRQoL. Finally, patients treated with NOAC received mainly dabigratan. Therefore, these conclusions should be applied strictly to this drug. The potential advantages of rivaroxaban over dabigatran include once-daily dosing (compared with dabigatran, which is administered twice daily) and lower non-bleeding upper gastrointestinal side effects (recorded in 16.9% of individuals receiving dabigatran in the RE-LY trial [RR vs warfarin = 1.81; p <0.001])[17]. These advantages could have a favorable effect on HRQoL, although the small number of patients included prevents analysis. Our study did not analyze other aspects related to patient preferences, such as drug price.

In conclusion, in terms of HRQoL, we observed a progressive adaptation to VKA. Satisfaction with NOAC remained unchanged. Older age, higher left ventricular ejection fraction and NOAC were associated with better HRQoL.

Supplementary Material

List of centers and investigators participating in the study. http://www.medsci.org/v11p0680s1.pdf

Acknowledgment

Authors would acknowledge Almudena Gonzalez Amo and Raúl Beltrán-Debón for their invaluable administrative assistance.

Competing Interests

This study was funded by Bayer Health Care, Spain.

JMA has not added conflict of interest to declare. XV has exerted as consultant for Bayer. MAA has participated in conferences for Bayer. AM-R has received research grants, and has participated in advisory boards and conferences for Bayer, Boehringer Ingelheim and Pfizer. PR has not added conflict of interest to declare. CR is employee of Bayer.

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