

Impact of Vitamin K Antagonists on Quality of Life in a Prospective Cohort of 807 Atrial Fibrillation Patients

Hilde A.M. Kooistra, MD, PhD; Margriet Piersma-Wichers, MD;
Hanneke C. Kluin-Nelemans, MD, PhD; Nic J.G.M. Veeger, PhD; Karina Meijer, MD, PhD

Background—Vitamin K antagonists (VKA) use is challenging because of frequent blood monitoring and complex dosing. Therefore, many patients and physicians are reluctant to start VKA. However, it is unclear whether VKA use actually lowers quality of life. We aimed to determine the impact of VKA initiation on quality of life and to analyze the correlation between patient and treatment characteristics and VKA perception in atrial fibrillation patients.

Methods and Results—In a prospective cohort of 240 new and 567 long-term VKA users, general quality of life and VKA perception (satisfaction and convenience) were measured at inclusion and at 3 months by the validated Study Short-Form 36 and Perception of Anticoagulant Treatment Questionnaire. Scores were converted to a 0 to 100 scale. Higher scores are more favorable. In the new patients, Medical Outcomes Study Short-Form 36 scores improved during the initial 3 months to a level comparable with the general population. At 3 months, the median convenience score was 95 (Q1–Q3, 88–98) and was higher in older patients (regression coefficient, 0.47 per year; 95% confidence interval, 0.25–0.69) and lower after bleeding (regression coefficient, –12; 95% confidence interval, –20 to –4.7). The median satisfaction score was 64. For the long-term patients, VKA perception scores were highly comparable with the new patients. The convenience score mildly improved in patients with increased individual time in therapeutic range (regression coefficient, 0.03; 95% confidence interval, 0.01–0.05; $r^2=0.01$), and satisfaction scores decreased in patients with new comedication (regression coefficient, –7.0; 95% confidence interval, –12 to –1.9; $r^2=0.02$).

Conclusions—VKAs were well tolerated in real-life, and the influences of patient and treatment related factors on VKA perception were very limited. (*Circ Cardiovasc Qual Outcomes*. 2016;9:388–394. DOI: 10.1161/CIRCOUTCOMES.115.002612.)

Key Words: antagonist ■ anticoagulants ■ atrial fibrillation ■ epidemiology ■ quality of life ■ vitamin K

Atrial fibrillation (AF) increases the risk of embolic stroke 4 to 5 times.¹ Therefore, life-long thromboprophylaxis is indicated for patients with additional risk factors.² As most ischemic strokes cause long-term disability but are not fatal, thromboprophylaxis improves quality of life (QoL), rather than survival.^{3,4} Consequently, the clinical decision to anticoagulate is usually not only modeled as a balance between the thrombotic and the bleeding risk but also takes the burden of treatment into account.

Vitamin K antagonists (VKA) are still the most commonly used type of anticoagulant and are highly effective.^{5,6} However, their use is challenging because of complex dosing, common minor bleeding, and frequent blood monitoring.⁷ Therefore, many patients and physicians are reluctant to start VKA as they fear a negative impact on QoL.^{8–10}

Yet, it is uncertain whether VKA therapy actually is associated with a decline in QoL. Different studies had outcomes varying from no decline,¹¹ a small overall decline,¹⁰ or a profound decline in a minority of patients.¹² To optimize VKA

therapy, it is also important to identify the determinants of intraindividual changes in VKA perception. However, because of their cross-sectional design, none of the above-mentioned studies were able to analyze this.

The common assumption that VKA therapy lowers QoL plays a central role in clinical decision making, but is insufficiently supported by evidence. Therefore, we determined the impact of VKA initiation on QoL in a prospective cohort of newly referred AF patients. In addition, we analyzed in long-term VKA users whether intraindividual fluctuations in VKA perception were correlated to changes in patient and treatment characteristics.

Methods

Patients

From March to August 2013, we included 2 groups of AF patients: patients newly referred to Certe Thrombosis Service Groningen (new cohort), and a random selection of long-term (≥ 6 months) VKA users (long-term cohort). Patients were eligible if they were ≥ 18 years of age and were on regular anticoagulation care. The latter resulted in

Received November 5, 2015; accepted May 5, 2016.

From the Division of Hemostasis and Thrombosis, Department of Hematology (H.A.M.K., M.P.-W., H.C.K.-N., K.M.) and Department of Epidemiology (N.J.G.M.V.), University of Groningen, University Medical Center Groningen, Groningen, the Netherlands; and Certe Thrombosis Service Groningen, Groningen, the Netherlands (H.A.M.K., M.P.-W.).

The Data Supplement is available at <http://circoutcomes.ahajournals.org/lookup/suppl/doi:10.1161/CIRCOUTCOMES.115.002612/-/DC1>.

Correspondence to Hilde A.M. Kooistra, MD, Department of Hematology, University Medical Center Groningen, Anzeplein 1, 9713 GZ Groningen, The Netherlands. E-mail h.a.m.kooistra@umcg.nl

© 2016 American Heart Association, Inc.

Circ Cardiovasc Qual Outcomes is available at <http://circoutcomes.ahajournals.org>

DOI: 10.1161/CIRCOUTCOMES.115.002612

WHAT IS KNOWN

- VKA use is challenging because of frequent blood monitoring and complex dosing.
- Patients and physicians are reluctant to start VKA as they fear a negative impact on quality of life.

WHAT THE STUDY ADDS

- In this large real-world cohort study, VKA were well tolerated as patients reported a quality of life comparable with the general population.
- Treatment convenience was reported by patients to be very high.
- The associations of patient and treatment-related factors with patients' perceptions of VKA were limited.

the exclusion of patients on self-measurement or self-management, hospitalized patients, and patients not currently using VKA because of temporary discontinuation. Before inclusion started, the University Medical Center Groningen Institutional Review Board confirmed that this study did not require ethical review according to Dutch law. All participants provided written, informed consent.

Assessment Tools

We used the Medical Outcomes Study Short Form 36 (SF-36) health survey questionnaire to measure general QoL.^{13,14} In addition, the validated Perception of Anticoagulant Treatment Questionnaire (PACT-Q) was used.¹⁵ This PACT-Q exists of 2 parts. The first (PACT-Q1) can be administered at anticoagulant treatment initiation and assesses patients' expectations using 7 separate items. The second (PACT-Q2) is administered during anticoagulant treatment and measures treatment perception. The PACT-Q2 exists of 2 dimensions: satisfaction and convenience. The 8 SF-36 domains, and the convenience and satisfaction dimensions, were converted to a 0 to 100 scale. Higher scores are more favorable. The Dutch versions of the SF-36 and PACT-Q were previously validated.^{13,15}

Data Collection

New patients were asked to complete the PACT-Q1 (expectations) on the day of their first appointment (Figure). The PACT-Q2 (perception)

was sent by mail to a random selection of 900 long-term users. Three months thereafter, all participating patients (new and long term) were approached by mail for the second measurement (PACT-Q2). Every PACT-Q was accompanied by a SF-36 questionnaire. Not all new patients were approached for participation because employees of the Thrombosis Service sometimes forgot to provide the questionnaires. It was recorded whether patients were provided with questionnaires. Therefore, the response rate was calculated based on the number of actually approached patients.

Patient and treatment characteristics were collected from the patient records at the Thrombosis Service. Patient characteristics were age, sex, comedication with increased bleeding risk, new comedication, new comorbidity (minor, major, any severity), and invasive interventions (minor, major, and any severity). Treatment characteristics included prescribed type of VKA (acenocoumarol 1 mg or phenprocoumon 3 mg), individual time in the therapeutic range (iTTR), mean number of days between International Normalized Ratio (INR) measurements, mean dose in tablets per day, location of INR measurement (home versus outpatient clinic), comorbidity with increased bleeding risk at referral to the Thrombosis Service, bleeding events (minor, major, and any severity), and thromboembolic events. The therapeutic range was INR 2.0 to 3.5, as routinely applied in the Netherlands.¹⁶ Additional information on the definitions can be found in the [Data Supplement](#).

For the comparison with the general Dutch population, we used SF-36 data from 1742 patients randomly selected by the Netherlands Organization for Applied Scientific Research in 1996. These data were collected to generate normative data and were also used for the validation study of the Dutch version of the SF-36. Except for the proportion of participants aged 15 to 25 years and a somewhat larger percentage of men (56%), these data were representative for the total adult population of the Netherlands.¹³

Statistical Analysis

In the new cohort, we evaluated the impact of VKA initiation on general QoL. The SF-36 scores of the second measurement were compared with the first measurement and to data from the general population (matched for age category and sex).¹³ For this, the individual score of the first measurement was subtracted from the second measurement. In the second analysis, the mean score for the general population category with the same sex and age was subtracted from the individual scores of the included patients. The differences were analyzed using a 1-sample *t* test as data were normally distributed. Analyzing differences in this way takes the dependency of the measurements into account. Next, the mean difference (MD) was divided by the SD of the difference to determine effect sizes (ESs).

Subsequently, we determined whether the course of VKA treatment during the first 3 months was associated with changes in SF-36 scores, adjusting for changes in the above-mentioned patient characteristics. Furthermore, we analyzed whether patient and treatment characteristics were associated with convenience and satisfaction scores after 3 months.

The correlation between fluctuations in treatment characteristics and intraindividual changes in SF-36 scores was analyzed in the long-term cohort and corrected for changes in the above-mentioned patient characteristics such as new comorbidity. Moreover, we analyzed whether changes in patient and treatment characteristics were associated with intraindividual changes in PACT-Q2 scores. All correlations were analyzed using stepwise multivariable regression models with backward selection and were checked for interaction with age and sex. By analyzing the change within individual patients, we took into account that scores were repeatedly measured within patients.

Clinical relevance of differences was determined according to Cohen guidelines.¹⁷ Effects of 0.2, 0.5, and 0.8 SD correspond with a small, moderate, and large ES, respectively. The power analysis showed that we were able to identify small to moderate ESs in the new patients and small ESs in the long-term patients. We used SAS 9.3 statistical software package.

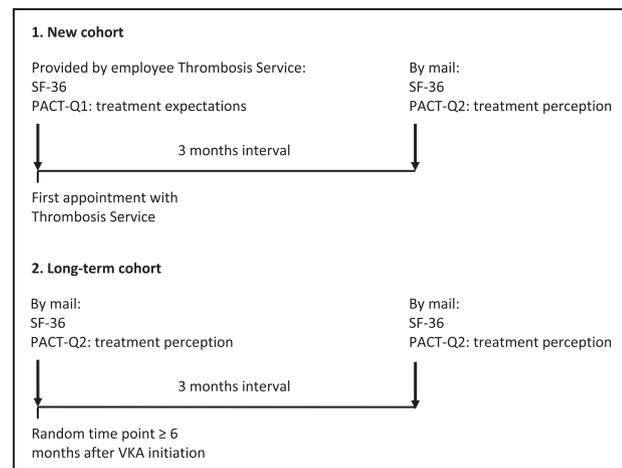


Figure. Study design for the new (1) and long-term cohort (2). PACT-Q indicates Perception of Anticoagulant Treatment Questionnaire; and SF-36, Short Form 36.

Results

We included 240 newly referred AF patients (inclusion rate 74%). During follow-up, 24 of these patients became ineligible to complete the second questionnaire: 2 patients died, 16 patients discontinued VKA treatment permanently, and 6 patients were not receiving regular VKA care anymore. Of the 16 patients who discontinued treatment at Certe Thrombosis Service Groningen, 1 patient migrated, 7 switched to an alternative treatment, 6 patients did not have an indication for anticoagulants anymore, 1 patient had side effects, and for 1 patient, the reason was unknown. Five of the 6 patients on nonregular VKA treatment switched to self-measurement. Of the remaining 216 patients, 186 completed the second questionnaire (86%).

Of the 900 randomly selected long-term patients, 7 became ineligible between selection and approach. Of the remaining 893 patients, 567 (63%) participated. The second questionnaire was not sent to 9 of them because of death (4), permanent discontinuation (2), and discontinuation of regular VKA care because of migration resulting in INR measurements by another health facility (3). Subsequently, 490 patients (88%) completed the second questionnaire.

New and long-term patients attending the outpatient clinic for INR measurement were one and a half times more likely to participate than patients visited at home. Other baseline characteristics were comparable for patients who were and were not included in this study (data not shown). Table 1 shows the baseline characteristics of the included patients.

New Patients: General QoL (SF-36)

Six of 8 domains of the SF-36 questionnaire showed a small to moderate improvement after 3 months (Table 2). However, only for 2 domains, changes were related to treatment characteristics. Bodily pain scores decreased with 18 points (95% confidence interval [CI], -34 to -2.6; $r^2=0.03$) in case of a major bleeding, indicating an increase in pain. Social functioning became less appreciated with every additional VKA tablet that the patient had to take (regression coefficient, -4.5; 95% CI, -8.3 to -0.67; $r^2=0.02$).

Compared with the general Dutch population, the scores of the second measurement for physical functioning, vitality, social functioning, and role emotional did not differ significantly (Table 2). General health (MD, -3.4; 95% CI, -6.2 to -0.51) and physical role (MD, -8.3; 95% CI, -15 to -1.7) scores were somewhat lower in the AF patients. In contrast, AF patients showed higher scores on mental health (MD, 4.7; 95% CI, 2.3-7.2) and bodily pain (MD, 5.0; 95% CI, 1.5-8.5) than the general Dutch population. The ESs of the differences in physical role (ES, 0.19) and general health scores (ES, 0.17) were not even small (<0.2). Thus, the general QoL of the VKA users was not clearly lower than the general population after 3 months of treatment.

New Patients: Treatment Expectations (PACT-Q1)

The majority of patients reported high treatment expectations. For the 7 individual PACT-Q1 items, this proportion varied between 46% and 86% of patients (Table 3). Most expectations were not related to any of the baseline characteristics, but for 2 items, a correlation with location was found. Patients at the outpatient clinic had more confidence in prevention of

Table 1. Baseline Characteristics

	New	Long Term
Patients, n (%)	240 (100)	567 (100)
Age, y, n (%)		
<56	19 (8)	5 (1)
56-65	41 (17)	55 (10)
66-75	94 (39)	198 (35)
≥76	86 (36)	309 (54)
Male sex, n (%)	136 (57)	303 (53)
Acenocoumarol, n (%)	238 (99)	554 (98)
Comedication with increased bleeding risk, n (%)	57 (24)	73 (13)
Comorbidity with increased bleeding risk at referral, n (%)	12 (5)	N/A
Location first INR measurement, n (%)		
At home	124 (52)	N/A
Outpatient clinic	116 (48)	N/A
Treatment characteristics 90 d preceding first measurement		
Location of INR measurements, n (%)		
At home	N/A	201 (35)
Outpatient clinic	N/A	337 (59)
Both	N/A	29 (5)
Time between INR measurements, d, median (Q1-Q3)	N/A	28 (17-40)
Tablets per day, mean (SD)	N/A	2.3 (1.0)
Time in therapeutic range (%), median (Q1-Q3)	N/A	87 (68-100)
Time since VKA treatment initiation, y, median (Q1-Q3)	N/A	4.3 (2.0-7.5)

Percentages may not total 100 because of rounding. N/A indicates not applicable; and VKA, vitamin K antagonists.

blood clots (odds ratio, 2.3; 95% CI, 1.3-3.9), and for the subgroup aged ≥ 65 years, independency was more important (odds ratio, 2.3; 95% CI, 1.2-4.4).

New Patients: Convenience and Satisfaction (PACT-Q2)

The median convenience was 95 (Q1-Q3, 88-98). It was lower after bleeding (regression coefficient, -12; 95% CI, -20 to -4.7) in patients aged <65 years and increased with age (regression coefficient, 0.47 per year; 95% CI, 0.25-0.69) (Table 3). The r^2 of the model was only 0.11, and there was no correlation with other treatment-related factors. This agreed with the answers to the individual questions: the majority of patients did not have any (79%) or only few difficulties (18%) with dose adjustments. The same applied to the interaction of VKA treatment with dietary intake (74% and 22%, respectively), and the burden of follow-up appointments associated with VKA treatment (74% and 21%, respectively). So, patients' convenience was very high and only weakly correlated with age and bleeding.

Table 2. SF-36 Scores of New Patients

SF-36 domains	SF-36 Scores		Difference (Second–First)		Determinants Difference (Second–First)		Difference (Second–General Population)	
	Median (Q1–Q3)		Mean (95% CI)	Effect Size	Variable	RC (95% CI)	Mean (95% CI)	Effect Size
	First Measurement	Second Measurement						
Physical functioning	55 (30–85)	65 (40–90)	5.7 (2.8 to 8.7)	0.29	–2.6 (–6.7 to 1.6)	0.09
Role physical	25 (0–100)	50 (0–100)	13 (7.4 to 19)	0.33	–8.3 (–15 to –1.7)	0.19
Bodily pain	62 (41–100)	74 (52–100)	7.1 (3.2 to 11)	0.27	Major bleeds	–18 (–34 to –2.6)	5.0 (1.5 to 8.5)	0.21
General health	57 (42–67)	57 (45–67)	1.6 (–0.6 to 3.9)	0.11	–3.4 (–6.2 to –0.5)	0.17
Vitality	60 (40–70)	65 (50–75)	6.9 (4.2 to 9.7)	0.37	–1.7 (–4.6 to 1.3)	0.08
Social functioning	75 (50–88)	81 (63–100)	7.7 (4.3 to 11)	0.33	No. of tablets	–4.5 (–8.3 to –0.67)	–1.4 (–4.6 to 1.9)	0.06
Role emotional	100 (33–100)	100 (33–100)	4.3 (–2.7 to 11)	0.09	–4.6 (–11 to 1.3)	0.11
Mental health	80 (64–88)	80 (68–92)	3.9 (1.8–6.1)	0.27	4.7 (2.3 to 7.2)	0.29

CI indicates confidence interval; Q1–Q3, interquartile range; RC, regression coefficient; SF-36, Short-Form 36.

The median satisfaction was 64 (Q1–Q3, 57–71) and did not correlate with any of the patient or treatment characteristics (Table 3). The vast majority was satisfied with their independency (87%) and also with patient management (92%). However, the majority of patients (65%) experienced no or little symptom decrease, and little reassurance was felt by 43% of patients. Sixty-four percent of patients reported good and 25% very good overall satisfaction when asked directly (last item), which reflects a higher satisfaction than the total satisfaction scores. As VKA treatment does not induce symptom relieve in AF patients, this discrepancy could be partly explained by the poor scores on the question about symptom decrease.

Long-Term Patients: Differences in General QoL (SF-36)

For the total group, the median SF-36 scores were highly comparable between the first and second measurements. However,

scores varied remarkably within patients, indicated by SDs of the MD ranging from 7.0 to 39 for the 8 domains. These differences were significantly related to treatment factors for 4 of the 8 domains (Table 4).

A decrease in iTTR was associated with better physical functioning, but r^2 was small (0.02). An increase in major bleeding events was associated with more pain ($r^2=0.01$), ie, a lower bodily pain score. The correlation between major bleeds and social functioning depended on age. For patients aged <65 years, an increase in bleeding was associated ($r^2=0.13$) with less appreciation of social functioning. Surprisingly, for older patients, a decrease in bleeding was associated ($r^2=0.02$) with a lower social functioning score, but only 6 patients had decreased bleeding. The same was observed for general health perception; the 8 patients with a decrease in bleeding also had lower scores ($r^2=0.02$). Shorter intervals between INRs were associated ($r^2=0.01$) with a better general health score.

Table 3. PACT-Q1 and PACT-Q2 Scores of New Patients

	High Expectations	Second Measurement	Determinants	
	n/Completed (%)	Median (Q1–Q3)		OR (95% CI)
PACT-Q1				
1: High confidence in prevention of blood clots	155/235 (66)	N/A	Outpatient clinic	2.3 (1.3 to 3.9)
2: High expectations of symptom relief	105/226 (46)	N/A
3: Low expectations of side effects	120/233 (52)	N/A
4: Much importance of ease of use	135/232 (58)	N/A
5: Few worries about making mistakes	202/236 (86)	N/A
6: Much importance of independency	161/232 (69)	N/A	Patients ≥65 y: Outpatient clinic	2.3 (1.2 to 4.4)
7: Few worries about costs	142/236 (60)	N/A
PACT-Q2				RC (95% CI)
Convenience	N/A	95 (88–98)	Age (per y)	0.47 (0.25 to 0.69)
	Patients <65 y: bleeds of any severity	–12 (–20 to –4.7)
Satisfaction	N/A	64 (57–71)

CI indicates confidence interval; OR, odds ratio; N/A, not applicable; PACT-Q, Perception of Anticoagulant Treatment Questionnaire; and Q1–Q3, interquartile range.

Table 4. SF-36 and PACT-Q2 Scores of Long-Term Patients

	First Measurement	Difference (Second–First)		Determinants Difference	
	Median (Q1–Q3)	Mean (95% CI)	Effect Size		RC (95% CI)
SF-36 domains					
Physical functioning	55 (30–80)	–0.9 (–2.3 to 0.5)	–0.06	Change iTTR (per %)	–0.07 (–0.12 to –0.02)
Role physical	50 (0–100)	–1.9 (–5.4 to 1.6)	–0.05
Bodily pain	72 (51–100)	0.0 (–2.0 to 1.9)	0.00	Increase major bleeds	...
	vs no change	–12 (–22 to –1.3)
General health	57 (42–70)	0.0 (–1.3 to 1.3)	0.00	Change interval (per day)	–0.11 (–0.22 to –0.002)
	Decrease bleeds of any severity	...
	vs no change	–10 (–16 to –4.5)
	vs increase	–12 (–19 to –4.3)
Vitality	65 (47–75)	0.1 (–1.3 to 1.5)	0.01
Social functioning	88 (63–100)	–0.7 (–2.7 to 1.2)	–0.03	Patients <65 y: increase major bleeds	...
	vs no change	–41 (–68 to –14)
	vs decrease	–48 (–87 to –10)
	Patients ≥ 65 y: decrease major bleeds	...
	vs no change	–28 (–46 to –10)
	vs increase	–27 (–48 to –6.7)
Role emotional	100 (33–100)	0.0 (–3.4 to 3.5)	0.00
Mental health	80 (68–88)	–0.4 (–1.5 to 0.8)	–0.03
PACT-Q2 dimensions					
Convenience	96 (90–100)	0.0 (–0.7 to 0.6)	–0.01	Change iTTR (per %)	0.03 (0.01–0.05)
Satisfaction	64 (57–71)	–0.2 (–1.6 to 1.2)	–0.01	Increase new medication	...
	vs no change	–4.6 (–8.7 to –0.42)
	vs decrease	–7.0 (–12 to –1.9)

CI indicates confidence interval; iTTR, individual time in the therapeutic range; PACT-Q, Perception of Anticoagulant Treatment Questionnaire; Q1–Q3, interquartile range; RC, regression coefficient; and SF-36, Short Form 36.

In summary, there were large fluctuations in patients' SF-36 scores, but only a very small part of it was correlated with treatment-related factors.

Long-Term Patients: Differences in Convenience and Satisfaction (PACT-Q2)

The median convenience score was 96, and did not change between the first and second measurement (MD, 0.0; 95% CI, –0.7 to 0.6; Table 4). iTTR was the only factor associated with intraindividual changes in convenience; patients with an increased iTTR reported more convenience (regression coefficient, 0.03; 95% CI, 0.01–0.05; $r^2=0.01$). The lack of correlation with other treatment-related factors was in line with the responses to the individual items (second measurement), as patients reported no or few difficulties on follow-up appointments (98%), dose adjustments (97%), interactions with other drugs (95%), and interactions with diet (97%). Thus, convenience scores were very high, and changes were only weakly related to iTTR and independent from any other treatment factor or patient characteristic.

The median satisfaction score was 64, and again no difference was seen between the first and second measurement

(MD, –0.2; 95% CI, –1.6 to 1.2; Table 4). An increase in new medication was the only factor related with intraindividual changes in satisfaction: patients with an increase in new medication experienced a decrease in satisfaction, $r^2=0.02$. In line with the new patients, 70% of the long-term patients reported to be satisfied and another 25% to be very satisfied when asked directly. So, median satisfaction scores were moderate, and new medication was the only factor that was associated with intraindividual changes.

Discussion

In the newly referred AF patients, QoL improved during the initial 3 months of VKA treatment to a level comparable with the general population. Bleeding events and a higher number of tablets were negatively correlated with this improvement. VKA perception scores of the new patients did not differ from the long-term patients; the convenience was high, and the satisfaction was moderate. The convenience was, in particular, high in older patients and in patients without bleeding events. Only a very small part of the intraindividual changes in VKA perception and general QoL could be explained by alterations in patient or treatment characteristics. The responses to the

individual items of the PACT-Q affirmed that the vast majority of new and long-term patients did not have any or few difficulties with VKA-specific treatment characteristics, such as diet restrictions, follow-up appointments, and dose adjustments.

This study confirmed, in a real-life population of AF patients, the findings of Lancaster et al¹¹ that VKA use was not associated with lower QoL after 3 months. The contrary results in a minority of patients found by Barcellona et al¹² could be explained by their inclusion of younger patients with a mix of indications and the lack of home testing service. The initial lower QoL in the current study could have been related to the temporary distress associated with the diagnosis of AF, symptoms related to AF, and also to any comorbidity leading to the discovery of AF and the burden of VKA initiation. The SF-36 scores at ≥ 3 months of treatment in our cohorts were comparable with the findings in a previous Dutch AF study conducted between 1998 and 2001 by Hagens et al.¹⁸

The literature showed a relation between QoL while on VKA and age,¹² quality of VKA control,¹⁹ and bleeding events.¹¹ However, none of these studies could appropriately address confounding because of the cross-sectional design. After careful adjustment in our longitudinal study, changes in QoL were only weakly related to bleeding events, the interval between INR measurements, and iTTR. The sometimes counterintuitive relations we observed, such as improving physical functioning as the iTTR deteriorated, may result from a causal relationship in the opposite direction or a chance finding. Both explanations would support that general QoL is hardly influenced by the course of VKA treatment.

The median convenience scores and their increase with age were in line with the validation study of the PACT-Q.¹⁵ Our somewhat lower satisfaction scores probably resulted from the lack of venous thromboembolism patients, as these patients score naturally better on symptom decrease. We were the first to identify a weak correlation between iTTR and intra-individual changes in convenience, which is not surprising as we needed a very large cohort for this. No prior study analyzed whether changes in treatment perception were related to alterations in the course of VKA treatment other than iTTR and thrombotic events.

There are some limitations to this study. First, the results may not be generalizable to patients with other indications, other kinds of anticoagulation, and patients who refused to use VKA, as these patients were not represented in this study. Also, the majority of patients used acenocoumarol, but there is no reason to assume that this is less burdensome than other kinds of VKA. Second, participation in the study might not have been random. However, we have shown that location of INR measurement was the only difference between patients who did and did not participate in the study. Yet, patients visited at home were still sufficiently represented in this study. Also, the cohort of new patients did not only differ from the general population on the use of VKA, but naturally also on the presence of AF, which is associated with a lower QoL.²⁰ However, this makes it even more unlikely that VKA negatively impact QoL.

The strengths of our study include the real-life setting with large numbers of new and long-term AF patients, the use of validated questionnaires, the very complete treatment

data, and the prospective longitudinal design. The latter provided the opportunity to analyze changes within patients. With this strategy, we were able to control for many known and unknown confounders. The inclusion of both new and long-term patients created the possibility to analyze the impact of VKA initiation on general QoL, and furthermore to identify factors influencing the perception of chronic VKA treatment. The large number of patients and the very complete data enabled us to identify relatively weak correlations. Therefore, we are confident that we did not miss any clinically relevant correlation. Finally, patients with AF do not experience symptom relief from anticoagulants. Therefore, this was the optimal population to study the burden of prophylactic anticoagulation treatment.

Our data provided more insight in the perception of VKA treatment and showed that VKA did not negatively influence general QoL after 3 months of use. This could possibly help to persuade the large group of AF patients who are at risk for stroke but are afraid to start VKA treatment.^{21,22} The very high convenience scores imply that for the general group of AF patients, no relevant improvement in convenience can be expected from switching to alternative treatments such as aspirin or the non-vitamin K oral anticoagulants. Possibly, this does not apply to younger patients, as their convenience with VKA was relatively low. This study also demonstrated no or very limited impact of the regular visits that characterize VKA on patients' well-being. To achieve better adherence, instead of decreasing the number of visits,²³ it would probably be more effective to inform patients on the good tolerability of VKA.

Conclusions

In contrast to the common assumption that VKA have a negative impact on QoL, VKA were well tolerated by AF patients in real-life. They reported a very high convenience and a QoL comparable with the general population. Changes in QoL and VKA perception were mostly independent from the course of VKA treatment.

Disclosures

Dr Kooistra reports travel support from Bayer Healthcare, outside the submitted work. Dr Piersma reports speaker fees from Boehringer Ingelheim, speaker fees from GlaxoSmithKline, travel support from Bayer Healthcare, speaker fees from Pfizer, travel support from Leo Pharma, outside the submitted work. Dr Meijer reports grants and travel support from Baxter, grants, travel support and speaker fees from Bayer, grants, travel support and speaker fees from Sanquin, travel support from Pfizer, and speaker fees from Boehringer Ingelheim, outside the submitted work.

References

1. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. *Stroke*. 1991;22:983-988.
2. European Heart Rhythm Association, European Association for Cardio-Thoracic Surgery, Camm AJ, Kirchhof P, Lip GY, Schotten U, Savelieva I, Ernst S, Van Gelder IC, Al-Attar N, Hindricks G, Prendergast B, Heidbuchel H, Alfieri O, Angelini A, Atar D, Colonna P, De Caterina R, De Sutter J, Goette A, Gorenek B, Haldal M, Hohloser SH, Kolh P, Le Heuzey JY, Ponikowski P, Rutten FH, ESC Committee for Practice Guidelines. Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). *Europace*. 2010;12:1360-1420.

3. Nydevik I, Eller B, Larsen L, Milton A, Wall B, Hulter-Asberg K. Functional status of stroke patients in long-term care—a basis for development of rehabilitation and care. *Scand J Caring Sci*. 1993;7:85–91.
4. Dennis MS, Burn JP, Sandercock PA, Bamford JM, Wade DT, Warlow CP. Long-term survival after first-ever stroke: the Oxfordshire Community Stroke Project. *Stroke*. 1993;24:796–800.
5. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. *Ann Intern Med*. 2007;146:857–867.
6. Lauffenburger JC, Farley JF, Gehi AK, Rhoney DH, Brookhart MA, Fang G. Factors driving anticoagulant selection in patients with atrial fibrillation in the United States. *Am J Cardiol*. 2015;115:1095–1101. doi: 10.1016/j.amjcard.2015.01.539.
7. Ansell J, Hirsh J, Hylek E, Jacobson A, Crowther M, Palareti G. Pharmacology and management of the vitamin K antagonists: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest*. 2008; 133:160S–198S.
8. Ingelgård A, Hollowell J, Reddy P, Gold K, Tran K, Fitzmaurice D. What are the barriers to warfarin use in atrial fibrillation?: Development of a questionnaire. *J Thromb Thrombolysis*. 2006;21:257–265. doi: 10.1007/s11239-006-5633-2.
9. Scott PA, Pancioli AM, Davis LA, Frederiksen SM, Eckman J. Prevalence of atrial fibrillation and antithrombotic prophylaxis in emergency department patients. *Stroke*. 2002;33:2664–2669.
10. Gage BF, Cardinalli AB, Owens DK. The effect of stroke and stroke prophylaxis with aspirin or warfarin on quality of life. *Arch Intern Med*. 1996;156:1829–1836.
11. Lancaster TR, Singer DE, Sheehan MA, Oertel LB, Maraventano SW, Hughes RA, Kistler JP. The impact of long-term warfarin therapy on quality of life. Evidence from a randomized trial. Boston Area Anticoagulation Trial for Atrial Fibrillation Investigators. *Arch Intern Med*. 1991;151:1944–1949.
12. Barcellona D, Contu P, Sorano GG, Pengo V, Marongiu F. The management of oral anticoagulant therapy: the patient's point of view. *Thromb Haemost*. 2000;83:49–53.
13. Aaronson NK, Muller M, Cohen PD, Essink-Bot ML, Fekkes M, Sanderman R, Sprangers MA, te Velde A, Verrips E. Translation, validation, and norming of the Dutch language version of the SF-36 Health Survey in community and chronic disease populations. *J Clin Epidemiol*. 1998;51:1055–1068.
14. Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care*. 1992;30:473–483.
15. Prins MH, Guillemin I, Gilet H, Gabriel S, Essers B, Raskob G, Kahn SR. Scoring and psychometric validation of the Perception of Anticoagulant Treatment Questionnaire (PACT-Q). *Health Qual Life Outcomes*. 2009;7:30. doi: 10.1186/1477-7525-7-30.
16. Bezemer ID, Roemer WH, Penning-van Beest FJ, van Eekelen E, Kramer MH. INR control calculation: comparison of Dutch and international methods. *Neth J Med*. 2013;71:194–198.
17. Cohen J. *Statistical Power Analysis for the Behavioral Sciences*. New York: Academic Press; 1977.
18. Hagens VE, Ranchor AV, Van Sonderen E, Bosker HA, Kamp O, Tijssen JG, Kingma JH, Crijns HJ, Van Gelder IC; RACE Study Group. Effect of rate or rhythm control on quality of life in persistent atrial fibrillation. Results from the Rate Control Versus Electrical Cardioversion (RACE) Study. *J Am Coll Cardiol*. 2004;43:241–247.
19. Jaffary F, Khan T, Kamali F, Hutchinson M, Wynne HA. The effect of stability of oral anticoagulant therapy upon patient-perceived health status and quality of life. *J Am Geriatr Soc*. 2003;51:885–887.
20. Thrall G, Lane D, Carroll D, Lip GY. Quality of life in patients with atrial fibrillation: a systematic review. *Am J Med*. 2006;119:448.e1–448.19. doi: 10.1016/j.amjmed.2005.10.057.
21. ACTIVE Investigators, Connolly SJ, Pogue J, Hart RG, Hohnloser SH, Pfeffer M, Chrolavicius S, Yusuf S. Effect of clopidogrel added to aspirin in patients with atrial fibrillation. *N Engl J Med*. 2009;360:2066–2078.
22. Connolly SJ, Eikelboom J, Joyner C, Diener HC, Hart R, Golitsyn S, Flaker G, Avezum A, Hohnloser SH, Diaz R, Talajic M, Zhu J, Pais P, Budaj A, Parkhomenko A, Jansky P, Commerford P, Tan RS, Sim KH, Lewis BS, Van Mieghem W, Lip GY, Kim JH, Lanas-Zanetti F, Gonzalez-Hermosillo A, Dans AL, Munawar M, O'Donnell M, Lawrence J, Lewis G, Afzal R, Yusuf S; AVERROES Steering Committee and Investigators. Apixaban in patients with atrial fibrillation. *N Engl J Med*. 2011;364:806–817. doi: 10.1056/NEJMoa1007432.
23. Schulman S, Parpia S, Stewart C, Rudd-Scott L, Julian JA, Levine M. Warfarin dose assessment every 4 weeks versus every 12 weeks in patients with stable international normalized ratios: a randomized trial. *Ann Intern Med*. 2011;155:653–9, W201. doi: 10.7326/0003-4819-155-10-201111150-00003.

Impact of Vitamin K Antagonists on Quality of Life in a Prospective Cohort of 807 Atrial Fibrillation Patients

Hilde A.M. Kooistra, Margriet Piersma-Wichers, Hanneke C. Kluin-Nelemans, Nic J.G.M. Veeger and Karina Meijer

Circ Cardiovasc Qual Outcomes. 2016;9:388-394; originally published online June 21, 2016;
doi: 10.1161/CIRCOUTCOMES.115.002612

Circulation: Cardiovascular Quality and Outcomes is published by the American Heart Association, 7272
Greenville Avenue, Dallas, TX 75231

Copyright © 2016 American Heart Association, Inc. All rights reserved.
Print ISSN: 1941-7705. Online ISSN: 1941-7713

The online version of this article, along with updated information and services, is located on the
World Wide Web at:

<http://circoutcomes.ahajournals.org/content/9/4/388>

Data Supplement (unedited) at:

<http://circoutcomes.ahajournals.org/content/suppl/2016/06/22/CIRCOUTCOMES.115.002612.DC1>

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Circulation: Cardiovascular Quality and Outcomes* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the [Permissions and Rights Question and Answer](#) document.

Reprints: Information about reprints can be found online at:
<http://www.lww.com/reprints>

Subscriptions: Information about subscribing to *Circulation: Cardiovascular Quality and Outcomes* is online at:
<http://circoutcomes.ahajournals.org//subscriptions/>

SUPPLEMENTAL MATERIAL

Supplemental methods:

Patient characteristics:

List: age, sex, comedication with increased bleeding risk, new comedication, new comorbidity (minor, major, any severity), and invasive interventions (minor, major, any severity).

Definitions:

Comedication with increased bleeding risk:

- Platelet aggregation inhibitors
- Low molecular weight heparin (LMWH)
- Non-steroidal anti-inflammatory drugs (NSAIDs)

New comorbidity (without invasive interventions):

- Scored as major if the patient was admitted to a hospital or if the patient was treated for cancer (including melanoma but excluding other types of skin cancer).
- Scored as minor if the comorbidity did lead to a medical intervention, but did not meet the criteria for major.

Invasive interventions:

- Scored as major if the intervention did not meet the criteria for minor.
- Scored as minor in case of invasive procedures restricted to the skin or dentition, endoscopies or coronary angiography.

Treatment characteristics:

List: prescribed type of VKA (acenocoumarol 1 mg or phenprocoumon 3 mg), individual time in the therapeutic range (iTTR), mean number of days between INR measurements, mean dose in tablets per day, location of INR measurement (home versus outpatient clinic), comorbidity with increased bleeding risk at referral to the Thrombosis Service, thromboembolic events, and bleeding events (minor, major, any severity).

Definitions:

Comorbidity with increased bleeding risk at time of referral to the Thrombosis Service:

- Insufficiently controlled hypertension
- Recent bleeding lesion in digestive tract
- Increased bleeding tendency
- Recent intracerebral hemorrhage
- Diabetic retinopathy with hemorrhages and/or neovascularisation
- Malabsorption syndrome
- Liver insufficiency
- Renal insufficiency
- Varying degree of heart failure
- Malignancy

Bleeding events

- Scored as minor if the bleeding did not meet the criteria for major.
- Scored as major in case of a:
 - o Fatal bleeding
 - o Symptomatic bleeding in a critical organ
 - o Bleeding causing a fall in hemoglobin level of 20 g/L or more
 - o Bleeding leading to transfusion of whole blood or red blood cells, a medical intervention, unscheduled contact with a physician and/or temporary cessation of anticoagulant therapy

Thromboembolic events

- Ischemic stroke

- Venous thromboembolism
- Myocardial infarction