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Quality of life in patients with venous thromboembolism and atrial fibrillation treated with coumarin anticoagulants

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ABSTRACT

Introduction: Little is known about the overall quality of life (QOL) in patients newly diagnosed with venous thromboembolism (VTE) and atrial fibrillation (AF).
We studied QOL in patients with VTE and AF immediately after the start of anticoagulant therapy, and after three months of treatment. Furthermore we identified whether QOL was affected by age, gender and nationality.
Materials and Methods: The European pharmacogenetics of anticoagulant therapy (EU-PACT) study was a multicentre, randomized controlled trial of patients aged >18 years diagnosed with VTE or AF. QOL was assessed using EuroQol 5 dimensions (EQ-5D) questionnaires.
Results: The EQ-5D questionnaires were completed by 187 patients with VTE and 660 patients with AF. The QOL in patients diagnosed with VTE or AF was significantly impaired, however, during a 3 months treatment period, patients experienced an improvement ($p < 0.05$). The QOL in patients diagnosed with VTE improved with increasing age, with similar effects seen in men and women. Men and women diagnosed with AF differed in QOL (respectively 0.84 and 0.74, $p < 0.05$), and QOL decreased with age. Comparison between countries showed significant differences in the EQ-Index score at follow-up of patients with VTE, and in both EQ-Index score and EQ-VAS of patients with AF.
Conclusions: The QOL in patients with VTE and AF is strongly reduced directly after the start of anticoagulant treatment, but improves within 3 months. Moreover, QOL is influenced by demographic and disease-specific variables. These findings provide useful information for future cost-effectiveness studies.

Introduction

Venous thromboembolism (VTE) is a cardiovascular disorder, which most commonly manifests itself in the veins of the legs, known as deep venous thrombosis and pulmonary embolism, which occurs when a part of the thrombus detaches and enters the lungs [1,2]. Atrial fibrillation (AF) is the most common heart rhythm disorder, affecting 1.5-2% of the general population in the developed world [3].

Quality of life (QOL) is considered an increasingly important outcome measure in clinical care and research, since it provides information about the patient's view on his or her health and disease burden, which cannot be solely captured by clinical measures of morbidity or mortality [4,5]. This is particularly relevant in conditions which are not immediately life-threatening but substantially impair QOL [6]. QOL often differs among patients, and individual patients fulfilling the same clinical criteria can rate their QOL completely differently. QOL measurements also enable researchers to calculate quality adjusted life years, which are an important outcome measure in pharmacoeconomic research [7].

Several studies have examined the impact of VTE on QOL [8–14]. However, none of these focused on QOL in newly diagnosed patients with VTE at the start of anticoagulant therapy and in 3 months following the initiation of treatment using the EQ-5D questionnaire. Additionally, potential determinants of QOL such as age, gender and nationality were

Abbreviations: AF, Atrial fibrillation; EQ-VAS, EuroQol visual analogue scale; EQ-5D, EuroQol 5 dimensions; EU-PACT, European pharmacogenetics of anticoagulant therapy; IQR, Interquartile range; SD, Standard deviation; VTE a, Venous thromboembolism; QOL, Quality of life.

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studied in depth. The impact of AF on QOL has in greater extent been studied previously [15–26], however, this study contributes to current scientific knowledge, particularly as a result of the detailed analysis of how patients' age and nationality influence QOL.

Study Population and Methods

Participants

The study design and results of the European pharmacogenetics of anticoagulant therapy (EU-PACT) trial have been described elsewhere [27,28]. The EU-PACT study was designed and conducted according to the Helsinki declaration, and all patients have signed written informed consent before inclusion in the EU-PACT study.

In brief, 1,003 patients with VTE or AF were enrolled in 11 different centres (general practices, anticoagulation clinics and hospitals) in four European countries (The Netherlands, Sweden, United Kingdom, and Greece). Inclusion criteria were: 18 years or older, recently diagnosed with VTE or AF requiring anticoagulation for at least 12 weeks, and a target international normalized ratio in the lower intensity range (2.0-3.0). Patients were treated with warfarin, acenocoumarol or phenprocoumon and randomized to genotype-guided dosing or non-genotype-guided dosing, and had not previously received treatment with coumarins.

Patients were excluded if they were pregnant, lactating, had severe cognitive impairment that could affect the ability to participate in the study, or if the treating physician felt that the patient was not eligible for clinical reasons.

The patients who did not complete the EuroQol 5 dimensions (EQ-5D) and EuroQol visual analogue scale (EQ-VAS) at both the start of therapy (baseline) and after three months of treatment (follow-up) were not included in the present analysis.

Methods

EuroQol is a self-administered generic instrument comprising two parts. In the first part, patients classify themselves to be in one of three levels of health – no problems, some problems, extreme problems – in each of five dimensions of health - mobility, self-care, usual activities, pain/discomfort and anxiety/depression [29]. This generates 3^5 (equals 243) possible health states. For statistical analysis, the EQ-5D health state can be converted into a single summary index of QOL by applying scores from a standard set of preference weights derived from general population samples [30]. In this study, the York A1 tariff, derived from a survey of the UK general population, was used to obtain QOL values for the health states in all populations [30,31]. The use of a single value set, such as the UK EQ-5D index tariff, is recommended when comparing QOL across countries [32].

Both the health states and the summary EQ-Index score were used for this analysis.The second part is the EuroQol Visual Analogue Scale (EQ-VAS) which is used to rate the perceived health state of the patients by assessing their health on a scale from 100 (best imaginable health) to 0 (worst imaginable health).

Statistical Methods

The statistical analyses were performed using SPSS v. 20.0.

Categorical variables were summarized using counts and percentages, while for the continuous variables the mean and standard deviation (SD)/median and interquartile range (IQR) was calculated. Baseline characteristics were analysed to assess the association with EQ-5D outcomes and detect differences among patient groups. Because the EQ-Index score and EQ-VAS have skewed distributions, nonparametric methods were used to analyse these data.

Changes from baseline to follow-up for EQ-5D Index score and EQ-VAS were tested for statistical significance using Wilcoxon signed-rank tests.

Mann-Whitney U tests and Kruskal-Wallis tests were used to test for median differences between gender, age groups, and nationalities. The statistical significance level was set at 0.05 in all statistical analyses.

Results

Patient Characteristics

A total of 1,003 patients were included in the EU-PACT study. 184 of 222 patients diagnosed with VTE completed the EQ-VAS (82.9%) and 187 patients (84.2%) completed the EQ-5D questionnaire. More than half of these patients were male (respectively 56.5% and 56.1%), with a mean age of 57 years (range 22-90 years) (Table 1). Patients enrolled in the study who did not complete the QOL questionnaire were more likely to be female (61.8%)($p < 0.05$).

Table 1
Baseline characteristics of the study participants.

Venous thromboembolism			Atrial fibrillation		
	EQ-5D	EQ-VAS		EQ-5D	EQ-VAS
All patients, n	187	184	**All patients, n**	660	664
Gender, n			**Gender, n**		
Male	105 (56.1%)	104 (56.5%)	**Male**	412 (62.4%)	414 (62.3%)
Age, years			**Age, years**		
Male, SD	59.6 (14.7)	59.4 (14.5)	**Male, SD**	70.7 (10.2)	70.7 (10.2)
Female, SD	54.8 (18.6)	54.4 (18.6)	**Female, SD**	74.2 (8.5)	74.2 (8.6)
Mean	57.5 (16.6)	57.2 (16.5)	**Mean**	72.0 (9.7)	72.0 (9.8)
Range	22-90	22-90	**Range**	32-93	32-93
Age, interval, n			**Age, interval, n**		
22-39	30 (16.0%)	30 (16.3%)	**32-59**	68 (10.3%)	68 (10.3%)
40-49	32 (17.1%)	32 (17.4%)	**60-69**	187 (28.3%)	188 (28.3%)
50-59	34 (18.2%)	33 (17.9%)	**70-79**	238 (36.1%)	238 (35.8%)
60-69	46 (24.6%)	45 (24.5%)	**80+**	167 (25.3%)	170 (25.6%)
70+	45 (24.1%)	44 (23.9%)			
Country, n			**Country, n**		
Greece	13 (7.0%)	13 (7.1%)	**Greece**	154 (23.3%)	154 (23.2%)
The Netherlands	66 (35.3%)	67 (36.4%)	**The Netherlands**	235 (35.6%)	233 (35.1%)
Sweden	55 (28.3%)	53 (28.8%)	**Sweden**	35 (5.3%)	30 (4.5%)
United Kingdom	53 (29.4%)	51 (27.7%)	**United Kingdom**	236 (35.8%)	247 (37.2%)

Table 2
Median (IQR) of EQ-Index scores and EQ-VAS, and positive change from baseline to follow-up by age and gender of patients diagnosed with VTE.

	EQ-Index				EQ-VAS			
	Baseline	Follow-up			Baseline	Follow-up		
	Median (`IQR)	Median (IQR)	Positive change*	P-value*	Median (IQR)	Median (IQR)	Positive change*	P-value*
All	0.68 (0.62-0.85)	0.82 (0.73-1.0)	63.6%	0.000	65.7 (50.8-80.0)	75.6 (70.0-90.0)	62.5%	0.000
Age, years								
22-39	0.55 (0.34-0.80)	0.78 (0.62-1.0)	76.7%	0.001	56.5 (40.0-71.3)	75.4 (70.0-86.3)	90%	0.000
40-49	0.58 (0.42-0.80)	0.80 (0.80-1.0)	81.3%	0.000	59.0 (50.0-70.0)	70.0 (60.0-90.0)	71.9%	0.004
50-59	0.73 (0.68-0.80)	0.86 (0.72-1.0)	64.7%	0.001	65.6 (60.0-79.0)	75.9 (67.0-87.5)	54.5%	0.000
60-69	0.75 (0.69-1.0)	0.87 (0.80-1.0)	56.5%	0.000	73.5 (69.0-88.0)	77.4 (70.0-90.0)	46.7%	0.153
70+	0.73 (0.69-0.94)	0.79 (0.69-1.0)	48.9%	0.032	69.0 (60.0-80.0)	77.6 (70.0-90.0)	59.1%	0.002
P-value**	0.006	0.472			0.000	0.702		
Gender								
Male	0.70 (0.64-0.85)	0.83 (0.74-1.0)	61.9%	0.000	66.6 (53.5-80.0)	75.1 (65.0-90.0)	58.7%	0.000
Female	0.66 (0.59-0.80)	0.82 (0.71-1.0)	65.9%	0.000	64.5 (50.0-75.0)	76.1 (70.0-90.0)	67.5%	0.000
P-value***	0.173	0.418			0.341	0.870		

* Wilcoxon signed-rank test. Positive change was calculated based on the number of patients having a positive change from baseline to follow-up (EQ-Index score at baseline < EQ-Index score at follow-up). P-values indicate significant difference from baseline to follow-up.
** Kruskal-Wallis test. P-values indicate significant difference between age groups.
*** Mann-Whitney U test. P-values indicate significant difference between gender.

Of the patients diagnosed with AF, 664 out of 781 patients (85%) completed the EQ-VAS and 660 (84.5%) completed the EQ-5D questionnaire. Of these patients, 62.3% and 62.4% respectively were male, and the mean age was 72 years (range 32-93 years) (Table 1). There were no statistically significant differences in patient characteristics between patients who did or did not fill in the QOL questionnaires.

Not all patients answered both the EQ-5D questionnaire and the EQ-VAS; however, there were no significant differences in patient characteristics between these patients.

QOL in Patients Diagnosed with VTE

The QOL in patients diagnosed with VTE improved in the three months after initiation of oral anticoagulant therapy (EQ-Index score improved from 0.68 (0.62-0.85) to 0.82 (0.73-1.0), $p < 0.001$ and EQ-VAS score improved from 65.7 (50.8-80.0) to 75.6 (70.0-90.0), $p < 0.001$). For all age groups, QOL scores improved between baseline and follow-up measurements ($p < 0.05$), with the exception of the EQ-VAS score of the patients aged 60-69 years.

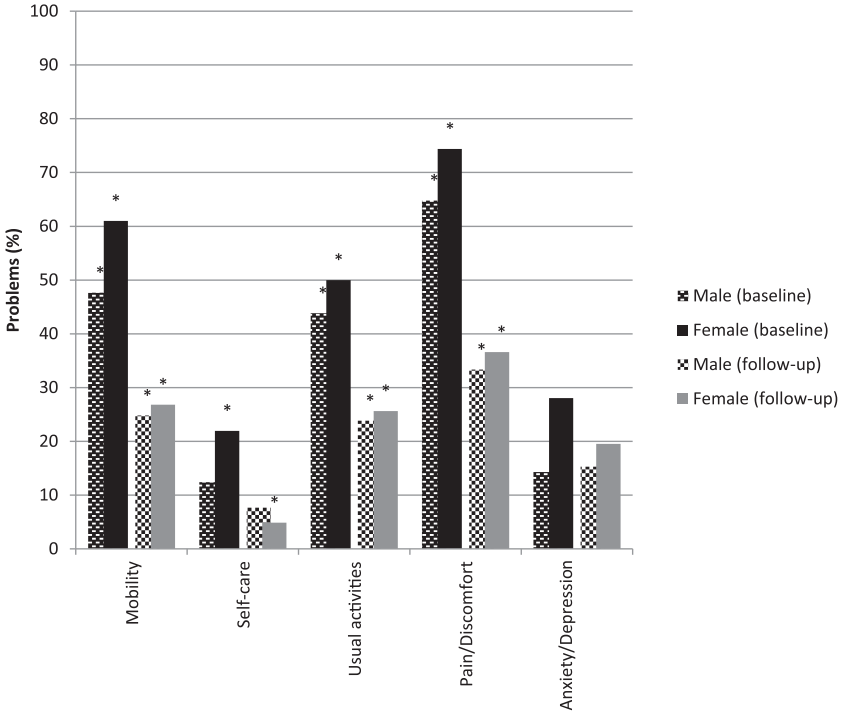

Fig. 1. Percentage of responders reporting any problems at baseline and follow-up by gender of patients diagnosed with VTE (*P < 0.05 between baseline and follow-up).

Table 3
EQ-Index scores at baseline and follow-up by nationality of the patients diagnosed with VTE.

	Greece		The Netherlands		Sweden		United Kingdom		P-value*	
	Baseline	Follow-up	Baseline	Follow-up	Baseline	Follow-up	Baseline	Follow-up	Baseline	Follow-up
EQ-Index	0.66	0.67	0.69	0.87	0.73	0.89	0.62	0.74	0.321	0.008
P-value**		0.674		0.000		0.000		0.000		
EQ-VAS	73.9	78.5	66.5	75.1	65.7	78.0	62.6	72.9	0.405	0.520
P-value**		0.233		0.000		0.000		0.003		

* Kruskal-Wallis test. P-values indicate significant difference between countries at baseline and at follow-up.
** Wilcoxon signed-rank test. P-values indicate significant difference between baseline and follow-up of each country.

The younger patients (aged 22-49) had a lower EQ-Index score and EQ-VAS at baseline, compared with the older age groups ($p < 0.05$). The score was still lower at the follow-up measurement, but the difference was no longer statistically significant (Table 2). The oldest patients (aged 70+) had the smallest change in EQ-Index score between baseline and follow-up (48.9%). Furthermore they had a lower EQ-Index score compared to the patients aged 60-69 years (respectively 0.79 (0.69-1.0) and 0.87 (0.80-1.0)), and the differences were not statistically significant. However, there was a trend toward a decreasing EQ-index score starting from the age of 70 (Table 2).

No statistically significant differences between men and women were detected in the overall result of EQ-Index score and EQ-VAS. As shown in Fig. 1, women experienced a statistically significant change between baseline and follow-up measurements in all dimensions, except anxiety/depression; a similar picture was found with men. For both men and women, the largest difference was in the dimensions of pain/discomfort. Male patients improved from 64.8% at baseline to 33.3% at three-month follow-up, while the females changed from 74.4% to 36.6% ($p < 0.05$).

When comparing QOL in patients from the four countries, the patients from Greece did not have a significant change in EQ-Index score or EQ-VAS between baseline and follow-up ($p > 0.05$).

The EQ-Index scores were highest for the Swedish and Dutch patients at follow-up, being significantly higher than the scores from the Greek and English patients (see Table 3).

QOL in Patients Diagnosed with AF

The QOL in patients with AF improved in the three months after starting anticoagulant treatment (EQ-Index score improved from 0.78 (0.69-1.0) to 0.80 (0.73-1.0), $p < 0.001$ and EQ-VAS improved from 69.5 (60.0-80.0) to 73.3 (65.0-83.0), $p < 0.001$). The EQ-VAS improved in all age groups, while the EQ-Index score only improved in patients aged 60-79 ($p < 0.05$), Table 4. The EQ-Index score decreased with age both at baseline ($p = 0.001$) and follow-up ($p = 0.001$), whereas the data of EQ-VAS did not show statistically significant differences between the age groups.

Male patients had a higher EQ-Index score and EQ-VAS compared to females at both baseline and follow-up ($p < 0.05$)(Table 4). The EQ-VAS for men and women, and the EQ-Index score for men improved from baseline to follow-up ($p < 0.05$).

The male and female patients reported most problems in the dimension pain/discomfort (Fig. 2). This was also the only question where the women reported a change from baseline to follow-up ($p = 0.015$) (Fig. 2).

Comparison of the four countries showed a statistically significant difference in EQ-Index score and EQ-VAS at baseline and follow-up (Table 5). The English patients were the only ones to change significantly in both EQ-Index score and EQ-VAS from baseline to follow-up. The Swedish patients did not show significant change in either outcome, but this might be due to the small number of respondents.

Table 4
Median (IQR) of EQ-Index scores, EQ-VAS, and positive change from baseline to follow-up by age and gender of patients diagnosed with AF.

	EQ-Index				EQ-VAS			
	Baseline	Follow-up			Baseline	Follow-up		
	Median (IQR)	Median (IQR)	Positive change*	P-value*	Median (IQR)	Median (IQR)	Positive change*	P-value*
All	0.78 (0.69-1.0)	0.80 (0.73-1.0)	33.9%	0.000	69.5 (60.0-80.0)	73.3 (65.0-83.0)	50.3%	0.000
Age, years								
32-59	0.84 (0.80-1.0)	0.85 (0.80-1.0)	25%	0.687	66.4 (55.0-80.0)	72.7 (60.0-84.0)	48.5%	0.030
60-69	0.80 (0.73-1.0)	0.82 (0.75-1.0)	33.2%	0.015	71.1 (60.0-82.3)	75.1 (70.0-85.0)	46.8%	0.002
70-79	0.77 (0.69-1.0)	0.80 (0.73-1.0)	34.5%	0.006	69.3 (60.0-80.0)	72.5 (60.0-80.0)	50.8%	0.002
80+	0.73 (0.69-1.0)	0.76 (0.69-1.0)	37.7%	0.110	69.1 (60.0-80.0)	72.6 (60.0-85.0)	52.9%	0.001
P-value**	0.001	0.001			0.158	0.229		
Gender								
Male	0.81 (0.73-1.0)	0.84 (0.80-1.0)	32.5%	0.000	70.8 (60.0-80.0)	74.8 (70.0-85.0)	50.2%	0.000
Female	0.72 (0.66-0.88)	0.74 (0.66-1.0)	36.3%	0.065	67.3 (55.0-80.0)	70.7 (60.0-80.0)	49.6%	0.001
P-value**	0.000	0.000			0.014	0.004		

* Wilcoxon signed-rank test. Positive change was calculated based of patients having a positive change from baseline to follow-up (EQ-Index score at baseline < EQ-Index score at follow-up). P-values indicate significant difference from baseline to follow-up.
** Kruskal-Wallis test. P-values indicate significant difference between age groups and between gender.

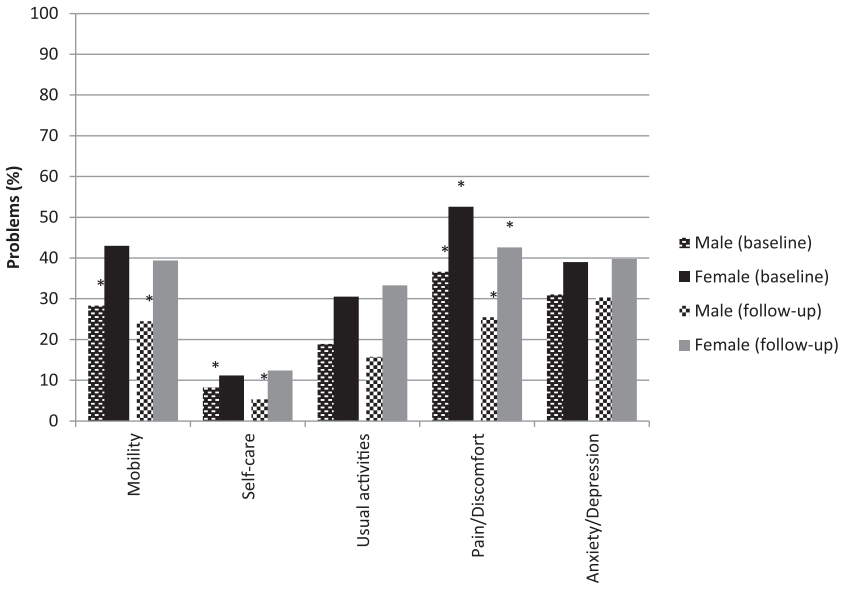

Fig. 2. Percentage of responders reporting any problems at baseline and follow-up by gender of patients diagnosed with AF (*P < 0.05 between baseline and follow-up).

Finally the EQ-Index score and EQ-VAS between patients receiving genotype-guided dosing or non-genotype-guided dosing were compared, and no significant differences were detected (data not shown).

Discussion

The QOL in patients diagnosed with AF and VTE improved over a period of three months after the start of coumarin treatment. The lower QOL at the start of treatment may have been caused by the acute onset of disease prior to the start of treatment (especially for the VTE patients), which will have caused both physical discomfort and psychological stress. The improvement of QOL three months later might be influenced by the patient's acceptance of the diagnosis as well as the benefits of treatment. Younger patients (aged 22-49) diagnosed with VTE in particular had a low QOL at baseline and experienced a large improvement.

The same trend was not seen amongst patients diagnosed with AF. This suggests that a diagnosis of VTE has a higher impact on QOL in younger patients, since younger patients may have more difficulty to accept a disease such as VTE, while older people might accept disease as one of the aspects of aging. Other studies have shown similar results; for example Langelaan et al. identified the same trend among patients with visual impairment [33]. In contrast, patients diagnosed with AF showed a decrease in EQ-Index score by age. Similar, to what one would expect in a general population due to old age [34]. Data collected as part of the BAFTA study, also showed that AF per se does not appear to have a significant negative effect on QOL in patients aged 75 years and over compared with the general age-matched population [18].

Further comparison between the two patient groups also showed that patients with AF had a lower improvement in QOL than patients with VTE (being approximately 34% in EQ-Index score of AF and 63% for VTE). The data on the EQ-5D dimensions showed that both patient groups reported most problems in the dimension of pain/discomfort, however, while patients with VTE improved significant in most dimensions, women with AF only reported significant change in the dimension pain/discomfort. Neither of the patient groups reported significant change in the dimension anxiety/depression.

The male patients diagnosed with AF had a statistically significant higher QOL compared with the women. Also, women reported a higher incidence of problems in all dimensions. This trend was also identified by other studies comparing men and women diagnosed with AF [15,17,18,35], and studies analysing the general population also show that women have a tendency of having lower QOL [32,36–38].

In contrast, amongst patients diagnosed with VTE, there was no statistically significant difference between male and female patients in either the EQ-Index score or EQ-VAS. This was notable since other studies in patients with VTE showed a lower reported score among women [9–11].

The study of Hoeymans et al. and König et al. compared their results with other European studies and reported differences in the percentage of people with problems between nationalities [36,37]. These differences can be explained by various factors, such as different response style, reference levels, external factors, but especially cultural differences. This is confirmed by the results of our study, and might explain why differences between the four countries were seen. Furthermore this emphasizes the importance of taking the response of the different nationalities into consideration when studying QOL across countries.

Our study had a number of strengths. The study inclusion criteria were broad, and the response rate was high making this study generalizable to the general population with AF and VTE. Also, patients

Table 5
EQ-Index score at baseline and follow-up by nationality of the patients diagnosed with AF.

	Greece		The Netherlands		Sweden		United Kingdom		P-valuea*	
	Baseline	Follow-up	Baseline	Follow-up	Baseline	Follow-up	Baseline	Follow-up	Baseline	Follow-up
EQ-Index	0.72	0.74	0.83	0.83	0.81	0.84	0.75	0.80	0.001	0.001
P-value**		0.132		0.393		0.348		0.000		
EQ-VAS	67.2	71.8	73.0	75.0	68.3	63.8	67.7	73.6	0.021	0.031
P-value**		0.000		0.020		0.206		0.000		

* Kruskal-Wallis test. P-values indicate significant difference between countries at baseline and at follow-up.
** Wilcoxon signed-rank test. P-values indicate significant difference between baseline and follow-up of each country.

were not excluded if they had comorbid conditions, as long as the practitioners did not find them non-eligible for the trial for clinical reasons. Other studies often tend to focus on a very specific and hereby limited patient population, which means that the outcome cannot be interpreted as general for patients with AF. Studies representing the general patient population has therefore been requested [19].

Furthermore, the study examined a large number of patients and was performed in different countries, allowing us to compare different health systems.

When interpreting the results of this study, some limitations should be taken into consideration. QOL was measured using a generic questionnaire and one of the primary weaknesses of this type of measurement is that it reflects general health and daily function, which are strongly influenced by other factors, such as age and comorbid medical conditions, and thus not only by the patient's disease. This could cause the generic measure to be less sensitive to change in older patients that have multiple health problems [17]. A combination of generic- and disease-specific instruments is recommended when measuring QOL, in order to identify more aspects of the QOL and detect key dimensions of QOL for the specific disease.

However, the EQ-5D questionnaires were used for the analysis since these allow comparisons across populations of patients with different diseases, as it was intended for use in population health surveys [39]. Additionally the results enable comparisons of the health benefits of various types of treatments for various types of diseases.

Conclusion

The findings of this study indicated that QOL in patients newly diagnosed with VTE or AF was significantly impaired and the illness had an impact on QOL in both VTE and AF.

Furthermore this study showed that QOL at baseline and over time is influenced by demographic and disease specific variables, in particular gender, age, and nationality. These findings can provide useful information on the effect of VTE and AF on QOL and input for economic evaluations of treatments for these diseases. Furthermore the identified differences in QOL due to age and gender might be helpful in identifying ways to improve clinical practice. Differences between countries might lead to different cost-effectiveness results and clinical approach, which should be taken into consideration in future studies.

Given the observed impact of VTE and AF on QOL, assessment of QOL should be included in future studies on the outcomes of VTE and AF, however the study also specify the need to adjust for population differences, and to consider other potential determinants impact on QOL. For clinical care, our results indicate that clinicians should be sensitive about the influence of VTE and AF on the wellbeing of their patients.

Disclosure of Conflict of Interests

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