

# HEALTH-RELATED QUALITY OF LIFE AND RELATED FACTORS OF OUTPATIENTS UNDERGOING WARFARIN THERAPY AT TWO HOSPITALS, BANGKOK, THAILAND

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**Abstract.** A cross-sectional study was conducted to investigate health-related quality of life (HRQoL) and related factors impacting outpatients ( $n = 206$ ) receiving at least 6-month warfarin treatment at Rajavithi Hospital and Prasat Neurological Institute, Bangkok from September 2019 and April 2020 employing a Thai EQ-5D-5L, a generic measure of HRQoL, personal and health questionnaires, and patients' medical records. Median (interquartile range) of utility (EQ index) and visual analogue (EQ VAS) score was 0.94 (0.87-0.97) and 80 (70-90) respectively. Patients with lower HRQoL score were  $\geq 60$  years of age, lived with spouse, completed at most primary school, unemployed, had a monthly income of  $\leq 10,000$  THB (USD330), received warfarin therapy  $\leq 3$  years, and had hypertension. In addition, patients receiving varying dosages of warfarin, taking  $\geq 5$  medications and with a history of bleeding had poorer HRQoL scores. In conclusion, outpatients on warfarin therapy attending two hospitals in Bangkok had overall good EQ index and EQ VAS scores, with the multifactorial causes of poorer HRQoL identified. These findings should lead to development of programs to improve HRQoL of those affected patients.

**Keywords:** EQ-5D-5L questionnaire, health-related quality of life, outpatient, Thailand, warfarin therapy

## INTRODUCTION

Quality of life (QoL) is an individual's

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perception of position in life in relation to personal goals, expectations, standards and concerns (WHOQOL Group, 1994). Currently, a primary goal of a country development is improvement of the populations' QoL and health constitutes one of the factors that has a great impact on the QoL, thus measurement of health-related quality of life (HRQoL) has emerged as an important parameter in determining the success of a holistic care

and patient-centered medicine (Moons *et al*, 2006).

Warfarin is an oral anticoagulant widely used for prophylaxis and treatment of thromboembolic disease (Harter *et al*, 2015). However, its high bioavailability but narrow therapeutic index can easily lead to adverse drug reactions, and effective dosage of warfarin has to be carefully monitored for each patient as many factors affect response to warfarin, such as vitamin K rich-food, alcohol, drug-drug interaction, comorbidity and other various conditions (Harter *et al*, 2015). As a number of patients need to receive warfarin treatment continuously over an extended period of time, such patients are advised to report any adverse effects and drug-drug reactions, follow dietary restrictions and place limitations on strenuous physical activities. Thus, warfarin therapy may negatively affect patients' HRQoL (Murawski and Bentley, 2001) as evidenced by a significantly poorer HRQoL in non-valvular atrial fibrillation patients younger than 65 years of age receiving warfarin compared to those not on warfarin therapy (Srinonprasert *et al*, 2019).

Several factors can adversely impact HRQoL in patients receiving warfarin, such as older age (Corbi *et al*, 2011; Montiel-Luque *et al*, 2017; Radaideh and Matalqah, 2018; Srinonprasert *et al*, 2019), female gender (Corbi *et al*, 2011; Montiel-Luque *et al*, 2017; Coban *et al*, 2018; Radaideh and Matalqah, 2018), poor education (Montiel-Luque *et al*, 2017; Radaideh and Matalqah, 2018), unemployment and/or failing financial situation (Montiel-Luque *et al*, 2017; Radaideh and Matalqah, 2018), history of bleeding brought about by warfarin therapy (Corbi *et al*, 2011; Radaideh and Matalqah, 2018; Srinonprasert *et al*, 2019),

existence of comorbidity (Montiel-Luque *et al*, 2017; Coban *et al*, 2018), multiple medication ( $\geq 3$ -5 drugs) (Montiel-Luque *et al*, 2017; Coban *et al*, 2018), first year of warfarin therapy (Corbi *et al*, 2011; Hasan *et al*, 2015; Montiel-Luque *et al*, 2017; Coban *et al*, 2018; Radaideh and Matalqah, 2018), and being prescribed warfarin in varying indications. (Corbi *et al*, 2011).

As there have been few studies on HRQoL of patients receiving warfarin in Thailand, most of which in atrial fibrillation patients and do not cover all indications of warfarin treatment, such as heart valve replacement and thromboembolic stroke (Srinonprasert *et al*, 2019), this study evaluated HRQoL and factors affecting HRQoL in outpatients receiving warfarin for all indications. HRQoL might be higher than those of patients with atrial fibrillation only and additional factors might be found lead to development of programs to improve HRQoL.

## MATERIALS AND METHODS

### Study design and enrollment of participants

This was a cross sectional study conducted between September 2019 and April 2020 at two hospitals in Bangkok, Thailand, namely, Rajavithi Hospital, a large tertiary hospital with about 2,000 patients per year or 50-60 per day receiving warfarin therapy (based on the Hospital database for 2019) and Prasat Neurological Institute, a hospital mainly treating the nervous system and brain, with more than 300 patients on warfarin treatment annually (from the Institute medical records). Participants were outpatients  $\geq 18$  years of age receiving warfarin for at least 6 months. Exclusion criteria were patients who could not provide complete information required due to

physical or mental impairment or other reasons and were unable to communicate in the Thai language. Sample size was estimated at 128 (including 10% drop-outs) (Ryan, 2013). The research protocol was approved by the Ethics Committees of Rajavithi Hospital (IRB no. 137/2562) and Prasat Neurological Institute (IRB no. 007/2563). Prior written consent was obtained from each participant.

### HRQoL assessment

HRQoL was assessed using an EQ-5D-5L questionnaire, a generic instrument for HRQoL measurement developed by EuroQol Group and translated into more than 150 languages including Thai, and widely used because of its ease of implementation and short time required to complete (Pattanaphesaj, 2014). The questionnaire has a good face validity, good test-retest reliability and has been used with a variety Thai groups, both adult and elderly, in households and hospitals (Pattanaphesaj and Thavorncharoensap, 2015; Charoensuksiri and Charoensuksiri, 2017). The questionnaire is divided into two parts. The first part consists of a five-item questionnaire on health status (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), with each domain having five levels of perception (no problem, slight problem, moderate problem, severe problem, and extreme problem), and their scores are converted into a utility index (EQ-index) score, higher score indicative of better HRQoL. The second part consists of a patient's self-rating of health status, with scores using a visual analogue (EQ-VAS) scale, best imaginable health state scoring 100 and worst imaginable health state scoring 0.

### Data collection

Demographic and clinical data were

collected by interviewing patients and from self-administered answers to the EQ-5D-5L questionnaire. Additional information on clinical data, such as indication of warfarin treatment, duration of warfarin therapy, warfarin dosage and regimen, international normalized ratio (INR) value and adverse drug reactions were collected from patients' medical records.

### Statistical analysis

Data were analyzed using PASW statistics for windows, version 18.0 (SPSS Inc, Chicago, IL). Demographic and HRQoL data are presented in form of descriptive statistics: frequency, percentage, mean  $\pm$  SD, or median and interquartile range (IQR). Factors significantly affecting HRQoL were analyzed using chi-square, independent t test, one-way ANOVA and Pearson's correlation or Mann-Whitney U test, Kruskal Wallis test and Spearman's rank correlation depending on the distribution of variables. A *p*-value <0.05 is considered significant.

## RESULTS

### Demographic and clinical profiles

Participants (*n* = 206) had a mean age of 59  $\pm$ 14 years old, 117 (57%) were female, 112 (54%) finished primary school education and 133 (65%) had a monthly income  $\leq$ 10,000 THB (USD330) (Table 1).

Forty-nine percent of patients received warfarin for prevention of thrombosis after heart valve replacement, 32% after atrial fibrillation and 26% after thromboembolic stroke (Table 1). Median (IQR) of duration and dose of warfarin was 48 (16-96) months and 21.5 (17.5-31.5) mg/week respectively. One hundred and sixty-five (80 %) patients prepared medication by themselves, 77

Table 1  
Demographic, clinical characteristics and health-related quality of life indices of outpatients receiving warfarin attending Rajavithi Hospital and Prasat Neurological Institute, Bangkok, Thailand (September 2019 and April 2020).

Characteristic	Number (%) ( <i>n</i> = 206)	Median (IQR)	
		EQ VAS	EQ index
Gender			
Male	89 (43)	80 (65-90)	0.94 (0.86-1.00)
Female	117 (57)	80 (70-90)	0.93 (0.87-0.97)
Age in years, mean ± SD	59 ± 14		
<60	104 (50)	80 (70-90)	0.96 (0.90-1.00)*
≥60	102 (50)	80 (70-90)	0.91 (0.83-0.96)*
Marital status			
Single	37 (18)	80 (60-80)	0.96 (0.93-1.00)†
Married/lived with a partner	124 (60)	80 (70-90)	0.93 (0.87-0.97)†
Widowed/divorced/separated	45 (22)	80 (70-90)	0.90 (0.83-0.96)†
Education			
No formal education/primary school	120 (58)	80 (70-90)	0.93 (0.86-0.96)*
Higher than primary school	86 (42)	80 (70-90)	0.96 (0.89-1.00)*
Employment status			
Unemployed	47 (23)	80 (70-95)	0.89 (0.79-0.95)†
Employed	144 (70)	80 (70-90)	0.96 (0.89-1.00)†
Retired	15 (7)	80 (65-80)	0.89 (0.82-0.92)†
Monthly income (THB\$)			
≤10,000	133 (65)	80 (60-90)*	0.92 (0.83-0.96)*
>10,000	73 (35)	80 (70-90)*	0.96 (0.93-1.00)*
Indication for warfarin therapy (more than one indication)			
Atrial fibrillation	66 (32)	80 (70-90)	0.93 (0.85-0.97)
Heart valve replacement	101 (49)	80 (70-85)	0.94 (0.88-0.97)
Thromboembolic stroke	53 (26)	80 (60-95)	0.91 (0.85-0.96)
Duration of warfarin therapy			
≤3 years	95 (46)	80 (70-95)	0.91 (0.85-0.96)*
>3 years	111 (54)	80 (70-82.5)	0.96 (0.90-1.00)*
Dosage of warfarin			
≤21 mg/week	103 (50)	80 (70-90)	0.94 (0.83-0.96)
>21 mg/week	103 (50)	80 (70-90)	0.94 (0.88-1.00)
Dividing warfarin before taking			
Yes	77 (37)	80 (60-90)	0.93 (0.87-0.96)
No	129 (63)	80 (70-90)	0.94 (0.87-1.00)
Prescribed warfarin >1 strength			
Yes	77 (37)	80 (70-95)	0.93 (0.87-0.97)
No	129 (63)	80 (70-90)	0.94 (0.87-0.97)

Table 1 (Continued)

Characteristic	Number (%) ( <i>n</i> = 206)	Median (IQR)	
		EQ VAS	EQ index
Warfarin regimen in each day			
Different dosage on certain days	70 (34)	80 (70-95)	0.92 (0.78-0.96)*
Same dosage each day	136 (66)	80 (70-90)	0.94 (0.88-1.00)*
Medicines preparation			
By patient	165 (80)	80 (70-90)	0.94 (0.89-1.00)*
By relative/caregiver	41 (20)	80 (75-90)	0.87 (0.77-0.94)*
Within INR target			
Yes	139 (68)	80 (70-90)	0.94 (0.87-0.97)
No	67 (32)	80 (70-90)	0.93 (0.87-0.96)
History of bleeding			
No	134 (65)	80 (70-90)*	0.94 (0.87-0.97)
Yes	72 (35)	80 (60-90)*	0.93 (0.87-0.97)
Comorbidity			
Yes	68 (33)	80 (70-90)	0.96 (0.90-1.00)*
No	138 (67)	80 (70-90)	0.93 (0.86-0.96)*
Comorbidity (more than one disease)			
Hypertension	90 (44)	80 (70-90)	0.93 (0.85-0.96)‡
Diabetes mellitus	44 (21)	80 (65-90)	0.94 (0.87-0.98)
Hyperlipidemia	41 (20)	80 (70-90)	0.90 (0.85-0.96)
Kidney disease	14 (7)	60 (50-80)‡	0.89 (0.83-1.00)
Gout/rheumatoid arthritis	13 (6)	70 (50-80)‡	0.88 (0.85-0.94)
Number of medications, median (IQR)	5 (3 to 7)		
<5	94 (46)	80 (70-90)	0.96 (0.90-1.00)*
≥5	112 (54)	80 (67.5-90)	0.93 (0.85-0.96)*
Alternative supplement			
Yes	19 (9)	80 (67.5-82.5)	0.94 (0.91-0.96)
No	187 (91)	80 (70-90)	0.93 (0.87-0.97)

\**p*-value <0.05 by Mann-Whitney U test; †*p*-value <0.05 by Kruskal Wallis test; ‡*p*-value <0.05 by Mann-Whitney U test compared with patients with these diseases; §: THB30 is approximately USD1. EQ index: utility index score; EQ VAS: visual analogue scale; INR: international normalized ratio; IQR: interquartile range.

(37%) divided warfarin tablets before taking them, 77 (37%) received warfarin of >1 strength and 70 (34%) had different dosage regimens of warfarin, such as different dose on alternate days or on weekends. Sixty-seven (32%) patients did not achieve INR target and 72 (35%)

had a history of bleeding resulting from warfarin therapy.

#### HRQoL evaluations

Forty-six percent of patients reported problem of pain/discomfort, 46% regarding mobility, and 31% of anxiety /

depression; however, the majority reported levels of problem perception as slight. Ninety-three percent of patients had no problem of self-care (Table 2).

Median (IQR) of EQ index and EQ VAS score was 0.94 (0.87-0.97) and 80 (70-90) respectively and with a small but significant correlation between the two scores ( $r = 0.362$ ,  $p$ -value  $<0.001$  using Spearman's rank correlation). Factors that impacted HRQoL were divided in two main categories, namely, demographic and clinical. Demographic factors that has a negative impact on EQ index score were age ( $\geq 60$  years old), with small but significant correlation with increase in age ( $r = 0.295$ ,  $p$ -value  $<0.001$  using Spearman's rank correlation; data not shown), marital status (married/living with a partner or widowed/divorced/separated), education (no formal or completed primary education), employment (retired or unemployed), and monthly income ( $\leq 10,000$  THB or USD330) (Table 1). Clinical factors that significantly differed with lower EQ index scores were duration of warfarin therapy ( $<3$  years), warfarin dosage (dosage on alternate days

or different dosage during weekend), patients whom caregivers prepared medication, comorbidity [hypertension, with small but significant correlation with number of comorbidities ( $r = 0.184$ ,  $p$ -value = 0.008 using Spearman's rank correlation)] (data not shown), and number of medications [ $\geq 5$ , with small but significant correlation with number of medications ( $r = 0.232$ ,  $p$ -value = 0.001 using Spearman's rank correlation)] (data not shown) (Table 1). Achieving INR target did not significantly affect HRQoL (both EQ index and EQ VAS scores); however, patients with history of bleeding from warfarin therapy had a significant lower EQ VAS score compared to those without this complication ( $p$ -value = 0.047) (Table 1).

On closer examination of frequencies of patients who significantly more reported in each of the five domains of the EQ-5D questionnaire, problems facing the following groups of patients stood out: mobility problems in those receiving  $\geq 5$  medications, problems in mobility and usual activities in those  $\geq 60$  years of age, with monthly income  $\leq 10,000$  THB

Table 2

Levels of problem perception from EQ-5D questionnaire by outpatients on warfarin therapy attending Rajavithi Hospital and Prasat Neurological Institute, Bangkok, Thailand (September 2019 and April 2020).

Domain	Level of problem perception				
	None	Slight	Moderate	Severe	Extreme
Mobility	112 (54)	57 (28)	24 (12)	9 (4)	4 (2)
Self-care	191 (93)	7 (3)	3 (1)	1 (<1)	4 (2)
Usual activities	181 (88)	15 (7)	4 (2)	1 (<1)	5 (2)
Pain/discomfort	111 (54)	81 (39)	12 (6)	2 (1)	0 (0)
Anxiety/depression	143 (69)	42 (20)	10 (5)	10 (5)	1 (<1)

(USD330) and hypertension, problems of mobility, self-care and usual activities in those receiving warfarin  $\leq 3$  years, and anxiety and depression problems in those with monthly income  $\leq 10,000$  THB (USD330) and with history of bleeding (Table 3).

## DISCUSSION

Patients receiving warfarin have to be careful regarding adverse effects of the drug, contraindications from other medications and too strenuous physical activities, and regular visits to physicians for monitoring INR level are advised. This survey of HRQoL of outpatients on warfarin medication attending two hospitals in Bangkok using a Thai version of an EQ-5D-5L questionnaire shows median EQ index higher than that previously reported (EQ

index of 0.72-0.84) (Srinonprasert *et al*, 2019). This may be due to that the latter study collected data from 24 hospitals located across Thailand while our study collected data in Bangkok, which is better in terms of the access to medical care and health services. In addition, indication for warfarin in the present study was not limited only to atrial fibrillation, patients with which have lower HRQoL compared to patients receiving warfarin for other indications (Corbi *et al*, 2011).

Problems of pain/discomfort (46%) and mobility (46%) were most reported in the present study, consistent with previous studies (Radaideh and Matalqah, 2018; Casais *et al*, 2005), which suggest impaired HRQoL domains were related to physical functioning and pain. Older patients ( $\geq 60$  years of age) had worse HRQoL regarding mobility and usual activities than younger

Table 3

Patients reported problem on each EQ-5D domains in the significant characteristic groups of outpatients on warfarin therapy attending Rajavithi Hospital and Prasat Neurological Institute, Bangkok, Thailand (September 2019 and April 2020).

Patients' characteristic	EQ-5D domain				
	EQ1	EQ2	EQ3	EQ4	EQ5
Age $\geq 60$ years ( $n = 102$ )	64 (63)*	10 (10)	20 (20)*	44 (43)	33 (32)
Primary school education or lower ( $n = 120$ )	60 (50)	10 (8)	19 (16)	59 (49)	43 (36)
Monthly income $\leq 10,000$ THB ( $n = 133$ )	72 (54)*	12 (9)	22 (16)*	67 (50)	50 (38)*
Duration of warfarin therapy $\leq 3$ year ( $n = 95$ )	57 (60)*	13 (14)*	19 (20)*	40 (42)	27 (28)
Bleeding arising from warfarin therapy ( $n = 72$ )	33 (46)	4 (6)	9 (12)	31 (43)	29 (40)*
Hypertension ( $n = 90$ )	50 (56) <sup>†</sup>	7 (8)	16 (18) <sup>†</sup>	47 (52)	28 (31)
Medication $\geq 5$ items ( $n = 112$ )	62 (55)*	10 (9)	18 (16)	55 (49)	39 (38)

\* $p$ -value  $< 0.05$  by Chi-square test; <sup>†</sup> $p$ -value  $< 0.05$  by Chi-square test compared to patients without hypertension.

EQ1: mobility; EQ2: self-care; EQ3: usual activities; EQ4: pain/discomfort; EQ5: anxiety/depression.

patients as previously observed (Almeida *et al*, 2011; Corbi *et al*, 2011; Balci *et al*, 2016; Montiel-Luque *et al*, 2017; Radaideh and Matalqah, 2018; Srinonprasert *et al*, 2019), highlighting the importance of the role of two factors in compromising HRQoL among this group of patients.

Several studies found patients living alone had worse HRQoL than patients who were married or lived with a partner (Zamora-Sánchez *et al*, 2012; Montiel-Luque *et al*, 2017; Radaideh and Matalqah, 2018), while the present survey noted patients living alone had better HRQoL. This difference may be due to patients living alone in the present study had a lower average age than the other groups, suggesting the former group's better physical status allowed greater ability for self-care, and without live-in family obligations would have fewer financial problems. Although previous studies found female patients have poorer HRQoL and lower health perspectives than males (Corbi *et al*, 2011; Montiel-Luque *et al*, 2017; Coban *et al*, 2018; Radaideh and Matalqah, 2018), this was not observed in the present study. This may reflect differences in family structure and culture among the study groups.

Low education level impacted HRQoL to a greater extent compared to patients with better education. Montiel-Luque *et al* (2017) and Radaideh and Matalqah (2018) also reported patients lacking fundamental education had poorer HRQoL than those more educated owing to the latter advantage in accessing and understanding information on their disease, medication and precautionary measures to prevent undesirable complications. Similarly, patients with regular employment and higher monthly income have access to better medical care and health services (Montiel-Luque *et al*,

2017; Radaideh and Matalqah, 2018), and hence would be less prone to anxiety/depression.

The observation patients receiving warfarin  $\leq 1$  year had no significant difference in HRQoL compared with those who received warfarin  $> 1$  year was consistent with report of Das *et al* (2007) but contrary to studies of Corbi *et al* (2011), Hasan *et al* (2015), Montiel-Luque *et al* (2017), Coban *et al* (2018), and Radaideh and Matalqah (2018). One possible explanation is that in our study more patients were on warfarin therapy for longer than 12 months and thereby obscuring any statistical difference. However, it was noticeable patients on warfarin treatment  $> 3$  years had higher HRQoL, suggesting this group had time to adjust to the lifestyle more fitting with their medical condition, such restrictions to diet and daily activities (Casais *et al*, 2005; Corbi *et al*, 2011). Patients prescribed a fixed daily dosage of warfarin had a higher HRQoL than those taking a more complicated drug regimen, possibly due to poorer compliance in the latter situation (Holt *et al*, 2010; Ludt *et al*, 2011; Saleh *et al*, 2014; Montiel-Luque *et al*, 2017). In addition, taking of several medications reduced patients' HRQoL, with a small but significant correlation with the number of medications, probably as the result of adverse drug reactions and drug-drug interactions, which unnoticed especially in the more elderly patients manifested in a HRQoL assessment (Agostini *et al*, 2004; Franic and Jiang, 2006; Hamilton *et al*, 2009; Henderson *et al*, 2006; Montiel-Luque *et al*, 2017; Coban *et al*, 2018).

Among comorbidities, patients with hypertension reported poorer HRQoL, particularly related to mobility and usual activities, than those without this condition. Coban *et al* (2018) noted

patients with hypertension or diabetes mellitus have a negative perception of QoL possibly owing to dietary restrictions and constraints to daily activities, or arising from complications due to this particular comorbidity (Montiel-Luque *et al*, 2017). As expected patients with a history of bleeding stemming from warfarin medication reported low EQ VAS score with more anxiety / depression, as have been recently reported (Radaideh and Matalqah, 2018; Srinonprasert *et al*, 2019)

A major weakness of the present study was that patients were recruited from those who received warfarin at least six months prior to HRQoL assessment, *ie* patients on chronic warfarin use, and the findings were not representative of patients who have recently been placed on warfarin medication.

In summary, determination of health-related quality of life using a Thai version of an EQ-5D-5L questionnaire among outpatients ( $n = 206$ ) on long-term warfarin therapy attending two hospitals in Bangkok demonstrates the majority of participants had high health-related quality of life as evidenced by median (interquartile range) of utility (EQ index) and visual analogue (EQ VAS) score of 0.94 (0.87-0.97) and 80 (70-90) respectively. Demographic features associated with low health-related quality of life were elderly age ( $\geq 60$  years old), family life, poor education, unemployment or retirement, and insufficient monthly income; while clinical factors were warfarin therapy  $\leq 3$  years, hypertension comorbidity, history of bleeding from warfarin medication, non-consistent daily warfarin dosage, and the taking of multiple drugs. Knowledge of these impediments to maintaining a high health-related quality of life should allow development of programs specifically

targeting this high-risk group of patients through appropriate adjustment to their medication, provision of psychological counseling, assistance in improving their physical environment and (if possible) financial needs, as well as ensuring patients have adequate knowledge of their health condition and the required changes to their lifestyle.

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#### CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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