Original Article

A comparison between warfarin and apixaban: A patient's perspective

Abdullah U. Althemery, Abdullah A. Alfaifi, Abdulrahman Alturaiki[1,2,3], Maha A. L. Ammari[1,2,3], Khizra Sultana[1,2,3], Leanne Lai[4]

Department of Clinical Pharmacy, College of Pharmacy, Prince Sattam bin Abdulaziz University, Al-Kharj 11942, [1]Department of Pharmaceutical Care, Ministry of the National Guard - Health Affairs, [2]King Abdullah International Medical Research Center, [3]King Saud bin Abdulaziz University for Health Sciences, Riyadh, Saudi Arabia, [4]Sociobehavioral Administrative Pharmacy, Nova Southeastern University, College of Pharmacy 3200 S. University Drive, Ft. Lauderdale, FL, USA

Address for correspondence:
Dr. Abdullah U. Althemery, Prince Sattam Bin Abdulaziz University, P. O. Box 173, Al-Kharj 11942, Saudi Arabia.
E-mail: a.althemery@psau.edu.sa

Submission: 26-11-2019
Accepted: 23-01-2020
Published: 03-04-2020

Access this article online

Quick Response Code:

Website: www.thoracicmedicine.org

DOI: 10.4103/atm.ATM_352_19

Abstract:

BACKGROUND: Novel oral anticoagulants (NOACs) were developed as alternatives to warfarin. However, the patients' preference regarding warfarin or the NOACs has not been established. Quality-of-life (QOL) surveys are a well-established method for determining the patients' preference for a treatment route.

AIMS: This study compared the patients' perspectives on treatment with warfarin versus apixaban using the QOL measures.

SETTINGS AND DESIGN: This cross-sectional study was conducted in 2019 for patients treated with either warfarin or apixaban at King Abdulaziz Medical City, Riyadh, Kingdom of Saudi Arabia.

METHODS: We used a series of descriptive statistics to examine the differences in sociodemographic characteristics among patients. A propensity score-matching approach was employed to reduce the effect of confounding variables that often influence treatment selection. Greedy matching approach was used to analyze the QOL.

RESULTS: A total of 388 patients were identified, of which 124 were matched between the two groups (62 patients in each group). Most of the patients were female, married, below the sufficiency level, educated, and nonsmokers. The patients using warfarin had a significantly better health state ($M = 69.64$, standard deviation [SD] = 16.52) than those using apixaban ($M = 66.33$, SD = 23.17), $P = 0.011$.

CONCLUSIONS: Future studies should explore why patients using apixaban showed lower QOL scores and improve health-care providers' awareness of these issues.

Keywords:

Apixaban, EuroQoL, oral anticoagulants, patient-reported outcomes, propensity score matching, warfarin

According to the 2014 World Health Organization (WHO) report, 50% of mortalities in the Kingdom of Saudi Arabia (KSA) were related to cardiovascular (CVS) diseases.[1] Stroke, a common condition associated with CVS mortality, has an estimated prevalence of 29/100,000 people in the KSA each year.[2] Moreover, the prevalence of CVS in the Kingdom is projected to increase three-fold, along with its direct and indirect costs, reaching up to $3.7 billion.[3]

Anticoagulants, also called blood thinners, treat and prevent blood clots by interfering with the natural blood-clotting mechanism. Ultimately, these medications prevent or minimize strokes and CVS diseases.[4] For decades, warfarin was the most prescribed anticoagulant agent.[4] However, warfarin has some limitations: requires frequent monitoring of the international normalized ratio (INR) due to its narrow therapeutic window, shows inconsistent responses, and is involved in a variety of food and drug interactions.[5]

Recently, the new oral anticoagulants, known as novel oral anticoagulants (NOACs), were

How to cite this article: Althemery AU, Alfaifi AA, Alturaiki A, Ammari MA, Sultana K, Lai L. A comparison between warfarin and apixaban: A patient's perspective. Ann Thorac Med 2020;15:84-9.

developed as an alternative to warfarin. However, the use of these NOACs is not without consequences. The main disadvantage is the absence of a medication that counteracts major bleeding related to NOACs' utilization. In addition, NOACs are relatively new and may have unknown side effects.[6]

The WHO described the quality of life (QOL) as a subjective indicator of how people view the lives, objectives, prospects, and concerns generated from assessments and is therefore predisposed to bias caused by a person's values and environment.[7] Conversely, health-related QOL (HRQoL) and its indicators involve aspects of overall QOL, specifically related to health, and reflect people's perceived physical and mental health. It is a crucial measure in our study because it evaluates the treatment effect on patients' well-being along with mental functioning.[8]

Several pharmacoeconomic studies have compared the two groups' experience with regard to the effectiveness, benefits, and side effects; however, they were limited to the payers' or prescribers' perspectives or these relationships were never explored in the Middle East, mainly in the KSA.[4,5,9,10] The aim of the current study was to compare patients' perspectives on taking warfarin versus apixaban using QOL measures.

Methods

The study was conducted in 2019 and employed a cross-sectional design. A total of 388 patients taking warfarin or apixaban at King Abdulaziz Medical City (KAMC), Riyadh, KSA, were enrolled in the study at three clinic sites – cardiac thrombosis clinic, arrhythmia clinic, or anticoagulant clinic. From the sample size, a total of 124 patients were matched into two groups: warfarin (62 patients) or apixaban (62 patients), as prescribed by the physician, clinical pharmacist, or both for the treatment of atrial fibrillation. These two groups were compared and tested accordingly. Patients who used treatment for less than a month or were diagnosed with dementia, cognitively impairment, deafness, or mutism were excluded from the study.

Institutional Review Board (IRB) permission was submitted, and approval was granted in December 2018 by the KAMC and the King Abdullah International Medical Research Center IRB. The permission to use the EuroQOL five-dimension (EQ-5D) scale was obtained from the EQ Research Foundation in 2017.[11] All patients provided informed consent prior to the inclusion in the study.

The initial sample size was determined by adopting the recommendations from the WHO's STEPS Sample Size Calculator, which requires the anticipated population proportion, confidence intervals, and statistical precision.[12] Local population proportion was estimated from a previously published work.[13] The primary independent variable was the type of anticoagulant agent used and was classified into warfarin group and apixaban group.

Most of the variables – including age, gender, marital status, education attainment, smoking, monthly income, and employment status – were derived from the patients' medical records and self-reports. Age, taken at the time of the interview and similar to the previous literature, was classified into patients 65 years of age and older and those younger than 65.[14] Marital status was classified into married patients and others. The unmarried group included patients who were single, divorced, and widowed. The education level variable was categorized into educated versus noneducated patients, with educated defined as patients who finished any type of degree: primary, secondary, bachelor's, or master's or above. The family income level was classified into above and below sufficiency level. The sufficiency line was set at $599 a week, as suggested by a report from the King Khalid Foundation.[15]

One of the most employed tools to assess HRQOL is the EQ5D questionnaire. It captures five domains, with reflective levels for each domain: mobility, self-care, normal activities, pain, and anxiety. Moreover, the EQ-5D evaluates the patients' perception of their health through EQ-visual analog scale (EQ-VAS) using a score ranging from 1 to 100.[11] The EQ-5D has been translated into Arabic and validated for use in Arab countries.[16] Moreover, an Arabic version of the EQ-5D was specifically designed to be appropriate for Saudis.[17] This study employed the EQ-5D survey to estimate HRQOL for patients taking the anticoagulant therapy.

A series of Student's *t*-tests were performed to assess the differences in data obtained from patients taking warfarin and those taking apixaban. These comparisons were applied after matching the two groups based on propensity scores. The propensity score matching (PSM) is the conditional probability of medication assignment based on observed features.[18] Rosenbaum and Rubin asserted that the effects of patients' characteristics could be aggregated into a propensity score which could then be used to balance the case and control groups. Thus, the propensity score evens the distribution between the study and control individuals based on chosen baseline characteristics.[19] The propensity score, in our study, was therefore estimated using a logistic regression model with a binary variable representing the probability of taking either warfarin or apixaban regressed on measured baseline characteristics. The

independent variables considered for the PSM model show statistically significant differences affecting treatment assignment or outcomes to increase the accuracy of estimates for treatment effect.[20] All data analyses were conducted using SAS software version 9.4, (Institute Inc., Cary, NC, USA).

Results

Descriptive results for original and matched patients

The descriptive findings showed that about two-third of patients taking anticoagulants were below the age of 65 years. A frequency analysis showed that the majority of these patients were female (53.19%), married (73.7%), below the sufficiency level (73.6%), educated (71.6%), and nonsmokers [84.1%; Table 1]. A Chi-square test of independence examined the relationship between age and all patients taking anticoagulants. The relationship between these variables was significant, χ^2 (1, n = 388) = 41.29, $P < 0.0001$. Educated patients were more likely to use warfarin than uneducated patients, χ^2 (1, n = 388) = 19.65, $P < 0.0001$). A Chi-square test of independence showed that there was a significant association between gender and the type of anticoagulant used, χ^2 (1, n = 388) = 7.67, P = 0.0056. The Chi-square tests of the null hypothesis of equal proportions for both groups of patients taking anticoagulants were not significant for marital status or income level. PSM was used to control for differences in the two treatment groups before conducting further analyses. To estimate the propensity score for each observation, logistic regression was applied using medication type as the dependent variable and all significant sociodemographic and clinical characteristics as independent variables.

Table 1: Descriptive statistics for patients taking anticoagulants (before matching)

Characteristics	Warfarin (*n*=326), *n* (%)	Apixaban (*n*=62), *n* (%)	*P*
Age			
<65	79.64	40.32	<0.0001
≥65	20.36	59.68	
Gender			
Male	43.77	62.90	0.0056
Female	56.23	37.10	
Marital status			
Married	73.31	75.81	0.6827
Never/previously married	26.69	24.19	
Income			
Above sufficiency level	26.46	26.23	0.9699
Below sufficiency level	73.54	73.77	
Educational attainment			
Educated	76.07	48.39	<0.0001
Uneducated	23.93	51.61	
Smoking			
Yes	17.70	6.56	0.0123
No	82.30	93.44	
Employment			
Employed	17.65	3.28	0.0013
Unemployed	82.35	96.72	

The results demonstrated adequate discriminative power (C-statistic = 0.81), indicating the ability of the logistic model to differentiate between warfarin and apixaban users. The predicted probabilities represented the relationship between the sociodemographic characteristics examined and the dependent variable. Apixaban users had a higher propensity score average than the warfarin users [Table 2].

A greedy matching algorithm was used to match patients from the warfarin group to the patients from the apixaban group to produce equivalent groups. The goal was to create matched sets of case and control subjects with similar estimated propensity scores. This process was repeated until the nearest control subject had been matched to a case subject or until the list of case subjects for whom a matched untreated subject could be found had been exhausted. The greedy matching algorithm showed that both the groups exhibited similar propensity score averages [Table 3].

In the matched-pair sampling, observed baseline-confounding variables (age, gender, education level, smoking status, and employment) were balanced between the two groups [Table 4].

Inferential results for matched patients

Warfarin users reported more problems in all dimensions of usual activities, anxiety, and depression, but the effect was not strong enough to warrant a statistically significant difference. In terms of pain/discomfort, there was a significant difference in the scores for warfarin (M = 4.68, standard deviation [SD] = 0.91) and apixaban (M = 4.38, SD = 1.26) groups, P = 0.01. The patients were asked to rate how good or bad their health was that day. A scale numbered from 0 to 100, with 0 meaning the worst health imaginable and 100 meaning the best health imaginable, was employed. An independent t-test was conducted to compare the health scores. It revealed that patients on warfarin had a significantly better health state than those on apixaban [Table 5].

Discussion

The study adds new evidence to the research on QOL, as the majority of the published articles explore QOL in Western countries.[21] Studies with similar goals but focused on Saudi Arabia are needed. The Saudi culture, social life, health-care settings, and availability of treatment differ from those of Western societies. Thus,

Table 2: Propensity score finding for prematched studied participants

Propensity score	Warfarin	Apixaban
Mean (95% CI)	0.86 (0.85-0.88)	0.68 (0.63-0.73)
Minimum-maximum	0.30-0.99	0.30-0.96

CI=Confidence interval

Table 3: Propensity score finding for matched studied participants

Propensity score	Warfarin	Apixaban
Mean (95% CI)	0.70 (0.65-0.74)	0.70 (0.65-0.74)
Minimum-maximum	0.30-0.96	0.30-0.96

CI=Confidence interval

Table 4: Descriptive statistics for matched indivudualss (after matching)

Characteristics	Warfarin (*n*=62), *n* (%)	Apixaban (*n*=62), *n* (%)	*P*
Age			
<65	43.33	41.67	0.8535
≥65	56.67	58.33	
Gender			
Male	63.33	61.67	0.8504
Female	36.67	38.33	
Marital status			
Married	86.44	75.00	0.1140
Never/previously married	13.56	25.00	
Income			
Above sufficiency level	27.12	27.12	1.0000
Below sufficiency level	72.88	72.88	
Educational attainment			
Educated	51.72	50.00	0.8514
Uneducated	48.28	50.00	
Smoking			
Yes	6.78	6.78	0.2832
No	93.22	93.22	
Employment			
Employed	3.39	3.39	0.3815
Unemployed	96.61	96.61	

Table 5: EuroQOL mean scores for individuals taking anticoagulants (after matching)

	Mean scores (SD)		*P*
	Warfarin	Apixaban	
Mobility	4.23 (1.21)	4.30 (1.09)	0.43
Self-care	4.68 (0.91)	4.38 (1.26)	0.01
Usual activities	4.35 (1.19)	4.35 (1.28)	0.55
Pain/discomfort	4.41 (0.88)	4.58 (0.96)	0.54
Anxiety/depression	4.60 (0.80)	4.53 (0.89)	0.44
VAS	69.64 (23.17)	66.33 (16.52)	0.01

EQ-VAS=EuroQOL-visual analog scale, QOL=Quality of life, SD=Standard deviation

the results of this study bring a much-needed insight into culture and society. The findings of this analysis pertained to patients attending KAMC, Riyadh, KSA, and established the prominent use of warfarin among patients (84%). However, the updated atrial fibrillation treatment guidelines recommend NOACs as the preferred alternative to warfarin for reducing the risk of stroke and for enhanced bleeding outcomes.[22]

In terms of QOL measures, the study's results showed that the majority of patients in both the groups reported slight to no problem in self-caring (for example, in performing daily activities). Self-care is increasingly becoming an important topic among patients due to the introduction of self-testing and point-of-care devices and their positive correlation with therapeutic outcomes.[23-25] A comparison of the two groups revealed a higher and significant difference associated with warfarin therapy versus apixaban groups in terms of self-care. This result contradicted a previous study in which Benzimra *et al*. (2018) could not detect significant differences across oral anticoagulant therapy.[26] Altogether, this finding indicated that clinicians preferred to prescribe apixaban to patients prone to poor self-management and used warfarin for patients who self-managed well.[27]

Patients on apixaban showed deterioration in the QOL based on EQ-VAS scores. Apixaban users scored significantly lower in EQ-VAS than those on warfarin. The EQ-VAS for the patients on warfarin was consistent with a previous study that measured EQ-VAS among treated patients.[28] However, when interpreting these differences, it is important to consider that these patients showed a decline in the EQ-VAS, although the only difference between the groups was the type of medication used; thus, the intrinsic differences among patients that were not measured and matched in the propensity score model could also have resulted in differences in EQ-VAS scores.[29] In fact, one of the limitations of this study was uncaptured data on comorbid conditions and INR levels in patients on anticoagulant therapy and the absence of important elements influencing bleeding management and outcomes from the study's analysis. Nevertheless, the study was able to match the patients based on their age, gender, marital status, income, education level, smoking, and employment.

One of the strengths of this study was its use of PSM to identify and control the effect of confounding variables. Case and control groups were well defined from the beginning and not randomly assigned. PSM was used to avoid the internal validity threat of nonequivalent groups and account for selection bias between the treatment and EQ outcomes. The findings of the PSM analysis showed a reduction in bias for all confounding variables.

The study produced significant findings on decision-making in clinical settings. Health-care practitioners should consider patients' preferences, besides the risks, benefits, and costs of all treatment

options before prescribing them to patients. Information on QOL for patients with chronic conditions is greatly needed. This study aids clinical decision-makers in determining the best treatment options while aiming to improve patients' overall QOL. These data provide new information by comparing the QOL measures for two comparable treatment options.

Conclusions

The findings of this study indicate a need to form a policy to enhance the HRQOL outcomes of patients using anticoagulant therapy. Moreover, further studies should explore why patients using apixaban showed lower EQ-VAS scores and seek to improve health-care providers' awareness of these issues.

Acknowledgments

We would like to thank King Abdullah International Medical Research Center and Prince Sattam Bin Abdulaziz University for their administrative and financial support during this project.

Financial support and sponsorship

This project was supported by the Deanship of Scientific Research at Prince Sattam bin Abdulaziz University through the research proposal No 2017/03/6915.

Conflicts of interest

There are no conflicts of interest.

References

1. World Health Organization. Global Status Report on Noncommunicable Diseases 2014. Available from: https://www.who.int/nmh/publications/ncd-status-report-2014/en. [Last accessed on 2019 Jul 09].
2. Robert AA, Zamzami MM. Stroke in Saudi Arabia: A review of the recent literature. Pan Afr Med J 2014;17:14.
3. Gagnon-Arpin I, Habib M, Al Ayoubi F, Sutherland G, Dobrescu A, Villa G, *et al*. Modelling the burden of cardiovascular disease in Saudi Arabia and the impact of reducing modifiable risk factors. J Saudi Heart Assoc 2018;30:365.
4. Wadhera RK, Russell CE, Piazza G. Warfarin versus novel oral anticoagulants: How to choose? Circulation 2014;130:e191-3.
5. Biondi-Zoccai G, Malavasi V, D'Ascenzo F, Abbate A, Agostoni P, Lotrionte M, *et al*. Comparative effectiveness of novel oral anticoagulants for atrial fibrillation: Evidence from pair-wise and warfarin-controlled network meta-analyses. HSR Proc Intensive Care Cardiovasc Anesth 2013;5:40-54.
6. Shehab A, Elnour AA, Bhagavathula AS, Erkekoglu P, Hamad F, Al Nuaimi S, *et al*. Novel oral anticoagulants and the 73rd anniversary of historical warfarin. J Saudi Heart Assoc 2016;28:31-45.
7. Development of the World Health Organization WHOQOL-BREF quality of life assessment. The WHOQOL Group. Psychol Med 1998;28:551-8.
8. Honeycutt AA, Hoerger T, Hardee A, Brown L, Smith K. An Assessment of the State of the art for Measuring Burden of Illness: Final Report. Washington, DC: U.S. Department of Health and Human Services; 2011.
9. Wanat MA. Novel oral anticoagulants: A review of new agents. Postgrad Med 2013;125:103-14.
10. Coyle D, Coyle K, Cameron C, Lee K, Kelly S, Steiner S, *et al*. Cost-effectiveness of new oral anticoagulants compared with warfarin in preventing stroke and other cardiovascular events in patients with atrial fibrillation. Value Health 2013;16:498-506.
11. van Reenen M, Janssen B. EQ5D5L User Guide Basic Information on How to Use the EQ5D5L Instrument. Rotterdam Euro Qol Res Found; 2019. Available from: https://euroqol.org/wp-content/uploads/2019/09/EQ-5D-5L-English-User-Guide_version-3.0-Sept-2019-secured.pdf. [Last cited on 2019 Nov 10].
12. World Health Organization. STEPS Sample Size Calculator and Sampling Spreadsheet 2016. Available from: https://www.who.int/nmh/publications/ncd-status-report-2014/en. [Last accessed on 2018 Jul 09].
13. ALammari M, Alturaiki A, Althemery A, Alfaifi A. Factors associated with the use of warfarin and the risk of bleeding: Cross-sectional study. Indo Am J Pharm 2019;6:7284-91.
14. Cavallari I, Patti G. Efficacy and safety of oral anticoagulation in elderly patients with atrial fibrillation. Anatol J Cardiol 2018;19:67-71.
15. King Khalid Foundation. Determining Poverty Line and Sufficiency Line; 2017. Available from: https://kkf.org.sa/media/qfahczvz/1-determining-poverty-line-and-sufficiency-line-2017.pdf. [Last accessed on 2019 Jul 19].
16. Khoudri I, Belayachi J, Dendane T, Abidi K, Madani N, Zekraoui A, *et al*. Measuring quality of life after intensive care using the Arabic version for Morocco of the EuroQol 5 Dimensions. BMC Res Notes 2012;5:56.
17. Bekairy AM, Bustami RT, Almotairi M, Jarab A, Katheri AM, Aldebasi TM, *et al*. Validity and reliability of the Arabic version of the the EuroQOL (EQ-5D). A study from Saudi Arabia. Int J Health Sci (Qassim) 2018;12:16-20.
18. Rosenbaum PR, Rubin DB. The central role of the propensity score in observational studies for causal effects. Biometrika 1983;70:41-55.
19. Austin PC. An introduction to propensity score methods for reducing the effects of confounding in observational studies. Multivariate Behav Res 2011;46:399-424.
20. Faries D, Leon AC, Haro JM, Obenchain RL, editors. Analysis of Observational Health Care Data Using SAS. North Carolina: SAS Institute Inc.; 2010.
21. Briasoulis A, Inampudi C, Akintoye E, Alvarez P, Panaich S, Vaughan-Sarrazin M. Safety and efficacy of novel oral anticoagulants versus warfarin in medicare beneficiaries with atrial fibrillation and valvular heart disease. J Am Heart Assoc 2018;7:e008773.
22. January CT, Wann LS, Calkins H, Chen LY, Cigarroa JE, Cleveland JC Jr., *et al*. 2019 AHA/ACC/HRS focused update of the 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: A report of the American College Of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart R. Circulation 2019;140:E125-51.
23. Siebenhofer A, Jeitler K, Horvath K, Habacher W, Schmidt L, Semlitsch T. Self-management of oral anticoagulation. Dtsch Arztebl Int 2014;111:83-91.
24. Grove EL, Skjøth F, Nielsen PB, Christensen TD, Larsen TB. Effectiveness and safety of self-managed oral anticoagulant therapy compared with direct oral anticoagulants in patients with atrial fibrillation. Sci Rep 2018;8:15805.
25. Yiu A, Bajorek B. Patientfocused interventions to support vulnerable people using oral anticoagulants: A narrative review. Ther Adv Drug Saf 2019;10:1-27.
26. Benzimra M, Bonnamour B, Duracinsky M, Lalanne C, Aubert JP, Chassany O, *et al*. Real-life experience of quality of life, treatment satisfaction, and adherence in patients

receiving oral anticoagulants for atrial fibrillation. Patient Prefer Adherence 2018;12:79-87.

27. Garkina SV, Vavilova TV, Lebedev DS, Mikhaylov EN. Compliance and adherence to oral anticoagulation therapy in elderly patients with atrial fibrillation in the era of direct oral anticoagulants. J Geriatr Cardiol 2016;13:807-10.
28. Marvig CL, Verhoef TI, de Boer A, Kamali F, Redekop K, Pirmohamed M, *et al*. Quality of life in patients with venous thromboembolism and atrial fibrillation treated with coumarin anticoagulants. Thromb Res 2015;136:69-75.
29. Sarkar S. Treatment of AF in the very old patient: Do comorbidities play a role in drug choice? e-Journal Cardiol Pract 2019;17:8-15.