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Utilization for Warfarin Therapy Among Jordanian People and Its Relation with International Normalized Ratio Control- Cross-Sectional Study at Queen Alia Heart Institution

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Abstract—Background*: Oral anticoagulant therapy (OAT) has demonstrated a reduction in morbidity and mortality of thromboembolic complications. Universally, the management of anticoagulant therapy is a great challenge for laboratory and clinical services. Warfarin is associated with a number of adverse drug reactions and complications which could be decreased by better anticoagulation control. Treatment with it requires proper and regular monitoring to prevent thromboembolic complications as well as to prevent over anticoagulation state. International normalized ratio (INR) is an easily distinguished clinical parameter associated with a moderate degree of increased risk of thromboembolism in warfarin patients. Many factors are responsible for INR fluctuation in warfarin treatment, these include aging, dosage error, laboratory error, poor compliance, concomitant use with other drugs, concomitant illness, kidney and liver dysfunction, and dietary interaction. In spite of the guidelines that outline the benefits of using warfarin clearly, it remains to be underutilized. This has resulted in increased mortality and morbidity among affected patients. Anticoagulant underutilization risk factors are: old age, female sex, vascular disease presence, limited options of anticoagulant, and having insurance medical aid. The aim of the study was to provide the first national utilization of warfarin among their users as well as to evaluate the therapeutic INR monitoring for it in Jordan*. ***Methods****: A prospective observational cross-sectional study was conducted on 133 patients during a period of six weeks: (from 24th of December 2018 to 29th of January 2019) at the Anticoagulation Clinic at Queen Alia Heart Institute, who were on warfarin therapy.* ***Results****: Among 133 patients who completed the study, the majority of patients (48.12%) had good control with safe warfarin management with a total frequency of sixty-four patients, while thirty-five patients (26.32%) had a safe warfarin management approach only, and almost an equal number of patients (25.56%) had un-safe warfarin management with almost sixty percent; an average TTR score. This study found that ninety-six percent of patients received warfarin for three major indications which are: Atrial fibrillations, aortic valve replacement, and mitral valve replacement. Interestingly, the study found that eighty-one percent of warfarin users had at least one DDI. Also, this study, found that approximately fifty-six percent of patients were receiving furosemide medication, while, forty-eight percent of them were receiving atorvastatin medication, and almost thirty-seven percent of them were receiving bisoprolol medication.* ***Conclusion****: This observational study called for strategies to enhance INR control, by the following probable solutions; maintenance and monitoring of the (INR) to be within the optimal therapeutic target range in order to reduce the possibility of bleeding episodes, and encourage patients who are smoking to quit it at every possible visit to the clinic.*

Keywords— *DDI, INR, TTR, Oral anticoagulant therapy, Warfarin*.

I. BACKGROUND

Thrombosis is a considerable contributor to the universal disease burden and death rate. It accounts worldwide for about one in every four deaths (Sonuga, et al., 2016). Oral anticoagulant therapy is influenced by: co-administered drugs, anticoagulation intensity, physician's experience, laboratory testing, patient compliance, and their education (Joshua, and Kakkar, 2015).

Warfarin is characterized by: a narrow therapeutic window, underutilization, and multiple drug and food interactions, these factors are responsible for an inconstant dosage response relationship with the hazard of deficient protection and/or increased risk of bleeding (Ewen, et al., 2014).

Warfarin requires close monitoring if used on a long-term basis and in an outpatient setting (Shrestha, et al., 2015). The significance of therapeutic INR monitoring is emphasized by the fact that warfarin treatment is contraindicated in conditions where INR monitoring is not appropriate (Sonuga, et al., 2016).

Because most patients respond widely to warfarin dose (Mahtani, et al., 2014). Implications of poor administration of warfarin treatment are of great importance for both the clinician and patient since poor International Normalized Ratio (INR) control can lead to bleeding, toxicity, and enhanced mortality (Sonuga, et al., 2016).

Warfarin is a widely used oral anticoagulant since it has a large body of clinical experience and has been used in many clinical settings (Hull, Garcia, and Vazquez, 2018). It has been used to treat and prevent thromboembolic complications related to vascular conditions such as atrial fibrillation (AF), and events such as myocardial infarction (Menzin, et al., 2012). It is also used in the prevention of thromboembolism conditions like deep vein thrombosis (DVT), pulmonary embolism (PE), and stroke (Kotirum, et al., 2007).

(AF) is a relatively common disease worldwide (Kubota, et al., 2018). Importantly, it is associated with significant

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economic and medical burden. AF elevates the risk of ischemic stroke by four to fivefold (Baker, et al., 2009). The literature reports consistently oral anticoagulation underutilization in AF patients having a modest to highest risk for stroke (Casciano, et al., 2013).

Using anticoagulants can result in a decline in systemic embolism and stroke risk by two-thirds approximately relative to non-therapy (Obamiro, et al., 2018). Despite the recommendation of using anticoagulant therapy in the prevention of systemic embolism, and stroke anticoagulant therapy remains underused in AF patients (Kubota, et al., 2018).

In one study underutilization of anticoagulants in patients with a high risk for stroke was reported to decrease from 68% to 62.5% (Choi, Lee, and Je, 2016).

Despite the evidence-based current guidelines that recommend strongly antithrombotic treatment in ischemic stroke (IS) patients, underutilization of it has been reported worldwide in clinical practice. Warfarin and anti-platelets therapy compared to no therapy, were associated significantly with declined death risk during one year beyond stroke onset (Wang, et al., 2015).

Universally, a mechanical valve is predominant as replacement therapy for young and adolescent adults having rheumatic heart disease (RHD), which necessitates life-long warfarin management (Mangnall, et al., 2016). This therapy can prohibit serious complications so that it increases the quality of patient life and post-operative survival rate (Wang, et al., 2018). The incidence of valve-associated death was higher significantly with greater anticoagulation variability relative to low and intermediate variability for both: mitral valve replacement (1.5% versus 0.5% per year) (Butchart, et al., 2002).

The risk for venous thromboembolism (VTE) is highest in patients with complications including PE, and DVT, within the previous three months and individuals with having VTE history with an associated high risk of inherited thrombophilia (Lip and Douketis, 2018). An acute VTE, is common, affecting up to five percent of the population, given that DVT is associated with a lower short-term death rate than PE (Bungard, et al., 2018). Early risk in VTE recurrence without anticoagulation was approximately fifty percent, but one month of treatment with warfarin therapy reduced the risk to 8-10%, while treatment for three months with warfarin therapy reduced the risk to 4-5% (Coon and Willis, 2018; Douketis, et al., 2018; Kearon and Hirsh, 2018).

Therapy's duration varies from six months in VTE, to lifelong in cardiac conditions or recurrent thromboembolism. The main goal of treatment is the reduction in thromboembolic disease risk, and minimizing bleeding risk in the same interval of time (Sonuga, et al., 2016).

Anticoagulation with warfarin can be measured through INR. The recommended INR value is between 2.0–3.0 for most of the indications (Kotirum, et al., 2007), between 2.5–3.5 for patients having cardiac prosthesis valve to be optimal or in the therapeutic target range (Sonuga, et al., 2016), and lower target INR range for aortic valve relative to the mitral valve, (Kuruvilla and Gurk-Turner, 2001; Vaughan and Waterworth, 2005).

At the minimum having one probable Drug–Drug interaction (DDI) increases the possibility of visits to the Emergency Room as well as the number of outpatient visits (Feng, et al., 2018). Drugs such as beta-lactam antibiotics, sodium valproate, anti-ulcer medications, and non-steroidal anti-inflammatory drugs (NSAIDs) have appeared to make alterations in warfarin response (Sonuga, et al., 2016).

With warfarin the patient needs to attain an efficient anticoagulation control (Ababneh, et al., 2016). Monitoring for INR is costly because it is associated with using laboratory resources, nurse and physician time, and making dose adjustments accordingly (Nelson, et al., 2015). A recommended measurement of the outcomes, as well as a good way to evaluate the quality of the management of oral anticoagulation provided by the clinic of anticoagulation, is the Time in the Therapeutic Range (TIR) (Sonuga, et al., 2016).

American College of Chest Physicians Antithrombotic Guidelines and The British

The Committee for Standards in Hematology (BCSH) recommends that at least sixty percent of the time, readings of the INR should be within the therapeutic target range (Sonuga, et al., 2016). Realizing why patients adhere to INR monitoring or not has the potential to detect useful targets to improve adherence or use alternative strategies for treatment (Kauffman, Schroeder, and Witt, 2015).

II. METHODS

Design

A prospective observational cross-sectional study was carried out at the Anticoagulation Clinic at Queen Alia Heart Institute (QAHI), at King Hussein Medical Center (KHMC). The purpose of this clinic is to monitor individuals receiving anticoagulant medication.

Ethical considerations

The study was approved by the scientific committee of the School of Pharmacy, as well as the School of Postgraduate Studies at the University of Jordan. Ethical approval was obtained from the ethics committee at Royal Medical Services (RMS) to perform it at QAHI.

Participants

The study included adult patients (18 years old or older), who were receiving warfarin therapy for any clinical indication for four months or more. Each patient had at least four previous INR readings in the medical records for the last sixteen weeks and gave verbal consent to participate. Patients who were unable to give verbal consent or who refused to participate in the trial were not allowed to participate.

Sampling and Data collection

In the data collection process, the data collection sheet form was used to collect baseline demographic data and clinical characteristics of the patients, including patient lifestyle: (mainly smoking), patient medical history, and

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patient medications, as well as data regarding their warfarin medication such as:

1. Dose of warfarin:(strength, and frequency),
2. Indication for warfarin use,
3. Duration of the medication i.e. when it starts, and target INR.
4. INR results during previous most recent consecutive four visits

Research Instruments

Identification of potential drug-drug interaction was done by an online interactive analysis program: Drug Interaction Checker www.https://www.drugs.com/interactions-check.php. Accessed on 1st February 2019. we highlighted the moderate to major drug interactions Calculation of INR control was done through count (number) of percentage when INR readings are in the optimal therapeutic range (Shilbayeh, et al., 2018), among the most recent visits.

The "safe warfarin management" approach is when the stability of INRs, is greater than or equal to fifty percent, which means an INR in an optimal range of more than half tested times, (Shilbayeh, et al., 2018). While, the "Good control" of INR had been defined by Time in Therapeutic Range (TTR), calculated using the Rosendaal method. A TTR greater than seventy-five percent is considered controlled (Rosendaal, et al., 1993).

In the procedure of interpretation for TTR score data, we categorized our patients into three groups: unsafe warfarin management, safe warfarin management, or safe warfarin management with good control.

Statistical analysis

Data were coded, entered, and analyzed using the IBM Statistical Package for Social Sciences (IBM SPSS®, Version 22). The Nonparametric test was used if the data were not normally distributed. The Normality of the data was determined by the Shapiro-Wilk test with a P-value > 0.05 indicating a normally distributed continuous variable. The features of the patient were described using descriptive statistics. Frequencies and percentages were used to describe the categorical data. For continuous data, the appropriate reporting units were the mean ± standard deviation (SD) or the median and interquartile range (IQR). Responses to each item in the questionnaire were expressed as frequencies and corresponding percentages. When comparing baseline variables the non-parametric statistical tests were used accordingly. Mann–Whitney, Kruskal–Wallis H, Pearson Chi-square tests.

Individuals who were more satisfied with warfarin therapy were expected to be positively associated and to have a better anticoagulation control status. The correlation between satisfaction scores, and INR control parameters was assessed using bivariate analysis by Chi-square tests. P-values below 0.05 were regarded as statistically significant.

III. RESULTS

One hundred sixty-four patients were invited to participate in our study. From them One hundred forty-three patients accepted to participate, with a response rate of 87.2%. Out of these 143 one hundred thirty-three patients were included with a drop-out rate of 7.0. The demographic data and clinical characteristics of the study participants are presented in (Tables 1, and 2).

TABLE 1: Demographic Data

Characteristics	N (%)
Place of residence	
Capital city	**89(66.9)**
Outside the capital city	**44(33.1)**
Age	
(18-35) years	**17(12.7)**
(36-53) years	**40(29.9)**
(54-71) years	**55(41.0)**
>71years	**20(14.9)**
Educational level	
Low (non- educated/ primary)	**26(19.5)**
Middle (12-18 years of education)	**77(57.9)**
High (> 18 years of education)	**30(22.6)**
Gender	
Female	**83(62.4)**
Male	**50(37.6)**
Insurance	
Exemption*	**61(45.9)**
Military	**72(54.1)**
Marital status	
Single	**15(11.3)**
Married	**89(66.9)**
Other	**29(21.8)**
Monthly Income	
Low (0 - 249)	**82(61.7)**
Middle (250 - 500)	**33(24.8)**
High (>500)	**18(13.5)**
Nationality	
Jordanian	**118(88.7)**
Others **	**15(11.3)**

*: Either patients had an endorsement form from the Royal Court or they paid instead of the service.
**: one Syrian, and the remaining are Palestinians.

TABLE 2: Clinical Characteristics

Characteristics	N (%)
Major bleeding history of Patients*	
Negative	**105(78.9)**
Positive	**28(21.1)**
Concurrent medical conditions	
None	**67(50.4)**
DM and/or HTN	**50(37.6)**
Other£	**16(12.0)**
Indication of Warfarin	
AF	**49(36.8)**
AVR	**34(25.6)**
MVR	**45(33.8)**
Other€	**5(3.8)**
Smoking status	
None	**117(88.0)**
Yes	**16(12.0)**

DM: Diabetes mellitus, HTN: Hypertension, AF: Atrial fibrillation, AVR: Aortic valve replacement, MVR: Mitral valve replacement
**: within the previous four months to enrollment*
£: Asthma, Benign Prostatic Hypertension, Coronary Artery Disease, Coronary Heart Disease, Chronic Kidney Disease, Colon cancer, Dyslipidemia, Gout, Hepatitis C, Hyper and hypothyroidism, Migraine, Neurodisorders, Osteoarthritis, Osteoporosis, Pulmonary Embolism, Ulcerative colitis, and Vascular Heart Disease.
€: Antiphospholipid Syndrome, Deep Vein Thrombosis, Senning, and Thrombophilia.

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IV. DISCUSSION

Among 133 patients who were available for the statistical analysis of the study, forty nine patients received warfarin for AF indication, with a therapeutic target INR (2-3), for most of cases. The average weekly dose of warfarin was (33.15 mg). Thirty four patients received warfarin for AVR indication, with a therapeutic target INR (of 2.5-3.5), for approximately half of the cases, also with an average weekly dose of 36.68 mg. Forty five patients received warfarin for MVR indication, with a therapeutic target INR of 2.5-3.5, for most of the cases, also with an average weekly dose of 42.72 mg. While the minority of them (3.7%) received warfarin for four minor indications which are: APS, DVT, Senning, and Thrombophilia (Table 3).

Also, Among 133 patients who completed the study a total of 109 major DDIs was found, and 61moderate DDIs (Table 4). Approximately 83% of major DDIs were for aspirin users. While 62% of moderate DDIs were for omeprazole users (Table 5).

TABLE 3: Utilization Review of Indications, Doses, and INR ranges

Indication	Number	Weekly Dose (average , range) (mg)	Target INR
Major	128		
AF	49 (36.8%)	33.15	(2-3) (48)
		(8.75-92.5)	(2.5-3.5) (1)
AVR	34 (25.6%)	36.68	(2-3) (20)
		(8.75-67.5)	(2.5-3.5) (14)
MVR	45 (33.8%)	42.72	(2-3) (2)
		(16.25-105.0)	(2.5-3.5) (43)
Minor	5		
APS	1 (20%)	25	(2-3)
DVT	2 (40%)	48.75	(2-3)
		(17.5 - 80)	(2.5-3.5)
Senning	1 (20%)	22.5	(2-3)
Thrombophilia	1 (20%)	26.25	(2-3)

A.F: Atrial fibrillation, AVR: Aortic valve replacement, MVR: Mitral valve replacement, A.P.S: Antiphospholipid syndrome, DVT: Deep vein thrombosis.

TABLE 4: Utilization Review of Drug-Drug Interactions (DDIs)

DDI	N (%)
None	25(18.8)
DDIs	108(81.2)
Major	58(43.6)
1 major	53(91.4)
2 major	4(6.9)
3 major	1(1.7)
Moderate	14(10.5)
1 moderate	12(85.7)
3 moderate	2(14.3)
Major and Moderate	36(27.1)
1 Major, 1 Moderate	29(80.6)
2 Major, 1 Moderate	3(8.3)
2 Major, 2 Moderate	1(2.8)
2 Major, 3 Moderate	2(5.6)
3 Major, 1 Moderate	1(2.8)

Major: Highly clinically significant. Avoid combinations; the risk of the interaction outweighs the benefit.
Moderate: Moderately clinically significant. Usually avoid combinations; use it only under special circumstances.

Among 133 patients who completed the study, approximately 50% of warfarin users had at least one concurrent medical condition. The highest percentages of concurrent medical condition were HTN, and DM TYPE 2 (Table 6).

TABLE 5: Utilization Review for Interacting Medications

Medication	(%)
Major	N: 109(64.1)
Amiodarone	7(6.4)
Aspirin	90(82.6)
Clopidogrel	7(6.4)
Gemfibrozil	4(3.7)
Tamoxifen	1(1.0)
Moderate	n: 61(35.9)
Allopurinol	3(4.9)
Esomeprazole	2(3.3)
Glibenclamide	3(4.9)
Glimepiride	2(3.3)
Lansoprazole	1(1.6)
Levothyroxine	5(8.2)
Mesalamine	1(1.6)
Omeprazole	38(62.3)
Phenytoin	1(1.6)
Prednisolone	2(3.3)
Sodium-Valproate	1(1.6)
Tramadol	2(3.3)

ACE: Angiotensin II converting enzyme, ARBs: Angiotensin II receptor blockers, B: Beta, CCB: Calcium channel blockers H: Histamine,

TABLE 6: Utilization Review for Concurrent Medical Conditions in Warfarin Users

Diseases	N(%)
Asthma	3(4.5)
BPH	6(9.0)
CAD	2(3.0)
CHD	1(1.5)
CKD	1(1.5)
Colon cancer	1(1.5)
DM (TYPE 1)	5(7.5)
DM (TYPE 2)	22(32.8)
Dyslipidemia	5(7.5)
Gout	5(7.5)
Hepatitis C	1(1.5)
HTN	43(64.2)
Hyperthyroidism	2(3.0)
Hypothyroidism	6(9.0)
Migraine	1(1.5)
Neurodisorders	3(4.5)
Osteoarthritis	1(1.5)
Osteoporosis	3(4.5)
PE	1(1.5)
Ulcerative colitis	1(1.5)
VHD	11.5)

BPH: Benign prostatic hypertension, CAD: Coronary artery disease, CHD: Coronary heart disease, CKD: Chronic kidney disease, DM: Diabetes mellitus, HTN: Hypertension, PE: Pulmonary embolism, VHD: Vascular heart disease

Among 133 patients who completed the study, (24.0%) from concurrent medications was for the Diuretics group, with a great percentage (64.3%) of them receiving furosemide medication. While, 20.6% of concurrent medications were given to medications from the B-blockers group, with about half (48.5%) of them receiving bisoprolol medication. Also, 15.6% of concurrent medications were from the statins group, with a great percentage (85.3%) of them receiving atorvastatin medication (Table 7).

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TABLE 7: Utilization Review of Concurrent Medications

Medication (480)	N (%)
ACE-inhibitors	**38(7.9)**
Captopril	2(5.3)
Enalapril	36(94.7)
ARBs	**22(4.6)**
Candesartan	1(4.5)
Telmisartan	2(9.1)
Valsartan	14(63.6)
Valsartan + hydrochlorothiazide	5(22.7)
Anti-arrhythmic	
Flecainide	2(0.4)
Anti- diabetic	**25(5.2)**
Insulin	5(20.0)
Metformin	20(80.0)
Anticonvulsant	
Gabapentin	1(0.2)
Anti-gout	
Colchicine	1(0.2)
Anti- spastic	
Lioresal	1(0.2)
B 2-agonists	
Salbutamol	2(0.4)
B-blockers	**99(20.6)**
Atenolol	6(6.1)
Bisoprolol	48(48.5)
Carvedilol	17(17.2)
Metoprolol	22(22.2)
Propranolol	6(6.1)
Bisphosphonate	
Alendronate	1(0.2)
CCB	**19(4.0)**
Amlodipine	17(89.5)
Diltiazem	2(10.5)
Cardiac glycosides	
Digoxin	34(7.1)
Centrally acting agents	**8(1.7)**
Doxazosin	4(50.0)
Tamsulosine	4(50.0)
Corticosteroids	**2(0.4)**
Beclomethasone	1(50.0)
Fluticasone	1(50.0)
Diuretics	**115(24.0)**
Amiloride+ hydrochlorothiazide	2(1.7)
Furosemide	74(64.3)
Hydrochlorothiazide	12(10.4)
Spironolactone	27(23.5)
H2- Antagonists	
Famotidine	26(5.4)
Statins	**75(15.6)**
Atorvastatin	64(85.3)
Simvastatin	11(14.7)
Vasodilators	
Isosorbidedinitrate	9(1.9)

ACE: Angiotensin II converting enzyme, ARBs: Angiotensin II receptor blockers, B: Beta, CCB: Calcium channel blockers H: Histamine,

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