

Analysis of Factors That Interrupt With INR Control in the First Anticoagulation Clinic Monitoring Jordanian Patients

Clinical and Applied
Thrombosis/Hemostasis
Volume 25: 1-9
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DOI: 10.1177/1076029619870252
journals.sagepub.com/home/cat



Nairooz H. Al-Momany, MSc¹, Zeid M. Makahleh, MD, MRCS¹,
Nadia A. Al-Omari, MSc², Hana A. Al-Sarayreh, BCs², and
Rawan O. Momani, MCs³

Abstract

Multiple factors such as vitamin K consumption, drug interactions, herbs interactions, disease states, and alcohol intake affect international normalized ratio (INR) values and thus warfarin dosing. These variables have been described in general and for all patients in the literature. In contrast, the factors that affect INR control in a specific population are rarely studied. Being aware of these factors contributes a lot in maintaining an INR control and avoiding the suprathreshold or subtherapeutic anticoagulation and the associated risks of hemorrhage or thromboembolism. The aim of this study is to recognize the specific population factors in Jordanian patients that interrupt INR control. Such recognition provides clinical pharmacists managing the anti-coagulation clinic (ACC) with necessary tools and predictors of dose adjustment, nontarget INR handling, and points to add on to the educational session. A total of 2788 patients were referred to the first clinical pharmacists managed ACC at Queen Alia Heart Institute—the only official referral hospital for cardiac patients in Jordan—for education and monitoring between November 1, 2013, and November 1, 2016. We evaluated specific population factors that interrupt INR control using a pre-tested, structured clinical data collection form. The patients were followed up regularly for achieving target INR (TINR). For patients who were not achieving TINR, the possible cause was examined thoroughly by reviewing the patient's medical file for recent medication intake, comorbidities, and laboratory results. Then the patients or their caregiver were asked direct questions regarding their diet, food supplements, cigarette smoking, shisha smoking, alcohol intake, herbs, and complementary medicine use and compliance, in addition to performing pharmacogenetic testing (polymorphisms of vitamin K-epoxide reductase complex [VKORC1] and cytochrome P450 2C9 [CYP2C9] genes) in special cases. For a total of 2788 patients, 89 488 INR values were included in the study. Of all, 20 365 (22.8%) were non-TINR values, 13 145 (14%) were subtherapeutic, and 7220 (8.1%) were suprathreshold. All patients included in the study had a non-TINR at least 3 times ($n = 65$, 2.3%) and as frequent as 50 times ($n = 21$, 0.8%) during the study period. Non-TINR values ranged from 1 to 11. Serious side effects reported in 7 patients with uncontrolled INR, 6 were bleeding, which required hospitalization (2 upper gastrointestinal [GI] bleeding, 3 nasal bleeding, and 1 eye bleeding), 1 was cerebrovascular accident (CVA thrombolytic). Factors that interrupted INR control in our population, arranged in descending sequence, were concurrent medication use 46.9% (mainly Salicylates and Amiodarone), smoking cigarettes and shisha 17% (represented the most frequent single factor that caused non-TINR in the present study), a nonbalanced dietary vitamin K intake 16.88% caused changes in INR (lower) was related to an increase in the intake of vitamin K-rich food, were noticed to be much more in the spring season in Jordan (end of March and April mainly), herbal supplements 15.02%; Hawthorn (Crataegus, الزعرور) is an herb that lives widely in Jordan, and shockingly we found that it is used very commonly in our ACC patients and corresponded to an elevated INR <8 in 11 patients, and serious bleeding events that required hospitalization in 2 cases), noncompliance 1.49%, comorbid diseases 1%, malabsorption 0.53%, alcohol intake

¹ Queen Alia Heart Institute, King Hussein Medical Center (KHMC), Royal Medical Services (RMS), Amman, Jordan

² Anti-Coagulation Clinic, Queen Alia Heart Institute, King Hussein Medical Center (KHMC), Royal Medical Services (RMS), Amman, Jordan

³ Prince Iman Center for Research and Laboratory Sciences, King Hussein Medical Center (KHMC), Royal Medical Services (RMS), Amman, Jordan

Corresponding Author:

Nairooz H. Al-Momany, Anti-Coagulation Clinic at Queen Alia Heart Institute, King Hussein Medical Center (KHMC), Royal Medical Services (RMS), Amman 11953, Jordan.

Email: nmomany@yahoo.com



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0.39%, and VKORC1 A/G and CYP2C9 *1*1 genotype 0.15%. The analysis of factors that interrupted with INR control in our patients were both predicted and distinctive; most of these factors were reported previously by other researchers. On the other hand, many of the previously reported factors were not frequently detected in our patients, and the frequency of each of the realized factors was contributed differently to non-TINR in our population. Alarming factors causing non-TINR detected in our study include smoking both cigarettes and shisha, herbal use (Hawthorn and Ginseng), increased intake of vitamin K rich food in the spring season, and concurrent medication use (Salicylates, Amiodarone, Ciprofloxacin, nonsteroidal anti-inflammatory drugs [NSAIDS], Azithromycin, Clarithromycin: although the use of these drugs is mandatory sometimes, it can be replaced by an alternative, eg, antibiotics or monitored closely together with warfarin).

Keywords

anticoagulants, INR control, factors affecting INR control, anti-coagulation clinic, warfarin, warfarin interactions

Date received: 9 May 2019; revised: 14 July 2019; accepted: 22 July 2019.

Background

Anticoagulation clinics (ACC) have been widely used since 5 decades for anticoagulation management in many countries. In 2013, the first ACC has been established in the Royal Medical Services (RMS) at Queen Alia Heart Institute (QAHI), Amman, Jordan. The beneficial outcomes of oral anticoagulation therapy are dependent on achieving and maintaining an optimal international normalized ratio (INR) therapeutic range, with minimal adverse events like bleeding and thrombosis. There is ongoing evidence that better outcomes are achieved when anticoagulation is managed by a pharmacist with expertise in anticoagulation management rather than usual care by physicians.¹⁻⁵ Our clinic protocol was prepared in consensus between the managing clinical pharmacists and the referring physicians and approved by the RMS higher medical committee (Online Appendix 1).

The main goals of the clinic were to assist physicians in improving the quality of care provided to their patients on anticoagulation therapy and assuring that these services improve patients' therapeutic outcomes, reduce complications of anticoagulation therapy, provide patient education on disease state and drug therapy, and reduce hospitalizations.

Since its establishment, the clinic has provided primary care of educational sessions and INR monitoring for about 3000 patients. This considerable number of patients served as a database for anticoagulation research in Jordan.

The American College of Chest Physicians recommends INR ranges between 2.0 and 3.0 for most indications and between 2.5 and 3.5 for patients with certain mechanical heart valves (MFVs).^{6,7} Multiple factors such as vitamin K consumption, drug interactions, herbs interactions, disease states, and alcohol intake affect INR values and thus warfarin dosing.⁸ These variables have been described in general and for all patients in the literature. In contrast, the factors that affect INR control in a specific population are rarely studied. Being aware of these factors highly contributes in maintaining INR control and avoiding the supratherapeutic or subtherapeutic anticoagulation and the associated risks of hemorrhage or thromboembolism.

The aim of this study is to recognize specific population factors (Jordanian patients) that interrupt INR control. Such recognition provides clinical pharmacists managing the ACC with the necessary tools and predictors of dose adjustment, nontherapeutic INR handling, and points to add to the educational session.

Methods

Patients, Setting, and Study Design

Patients enrolled in the present study were referred to our ACC by their treating physicians at QAHI between September 2013 and May 2017. Eligible patients were outpatients on maintenance warfarin dose for any indication. We excluded patients referred to the clinic for initialization of therapy (warfarin was not initialized at hospital mostly; atrial fibrillation [AF] patients) and patients post warfarin dose interruption (due to surgery, dental, or any invasive procedure that requires dose interruption) until they achieved target INR. Queen Alia Heart Institute is the only official referral hospital for cardiac patients in Jordan performing all types of interventional catheterization and cardiac surgeries for all age groups. Patients were enrolled in the study if informed consent was obtained from the patient or his/her representative. The study was approved by the Career Ethics Committee, the equivalent of an institutional review board in Jordan, in the RMS.

Data Collection

Generally, the study evaluated specific population predictors that interrupt INR control. Data were collected from the patients' verbal self-reports, files, medication sheets, and prescriptions. The deduced causes were documented in a special excel form prepared by researchers (Table 1). The form had been pretested on a small pilot scale ($n = 10$) and subsequently modified to ensure that the data would provide valid information. The entire clinical data collection form is available from the authors upon request.

All parts of the form were completed by the authors (N.H. A.-M., a clinical pharmacist; N.A.A.-O., a clinical pharmacist;

Table 1. Summary of Clinical Data Collection Form.

Patient's name	Age	Gender	Comorbidities	Warfarin indication	Target INR	Non TINR value/values	Possible cause/causes of non-TINR value

and Z.M.M., a cardiac surgeon) who work at QAHI. For all patients who were monitored in the clinic, an INR test was performed on each visit (frequency of visits is determined according to the clinic protocol; Online Appendix 1).

Detection of Specific Population Factors That Interrupt INR Control

On their first clinic appointment, all patients or their caregivers received a 45-minute educational session and printed booklet regarding warfarin indication, mechanism of action, target INR, INR monitoring, side effects, drug-warfarin interactions, food-warfarin interactions, and duration for treatment.

The patients were followed up regularly for achieving target INR (TINR). For patients who were not achieving TINR, the possible causes were examined thoroughly by

- (1) Reviewing patients medical file for recent medication intake, comorbidities, and laboratory results
- (2) Asking the patients or their caregiver direct questions regarding their diet or food supplements, cigarette smoking, shisha smoking, alcohol intake, herbs and complementary medicine use, and compliance
- (3) For warfarin-resistant or warfarin-sensitive patients
 - (a) Those with frequent supratherapeutic INR plus recurrent bleeding (considered Warfarin sensitive if they required a warfarin dose of ≤ 21 mg/week to achieve TINR value)
 - (b) Those with frequent subtherapeutic INR despite dose increase (considered Warfarin resistant if they required a warfarin dose of >105 mg/week without achieving TINR value)

We considered going further by performing pharmacogenetic testing (polymorphisms of vitamin K-epoxide reductase complex [VKORC1] and cytochrome P450 2C9 [CYP2C9] genes) for both (a) and (b) groups and by adopting Osinbowale et al algorithm (Figure 1) as a reference to determine the type of resistance pattern for group (b).⁹ For patients who were not achieving TINR, we did dose adjustment according to Figures 2 and 3.

Laboratory Devices and Methods

Oral anticoagulant therapy was mandated by the prothrombin time, that is, evaluated using an automated method over STAGO coagulometric unit in the QAHI laboratory. To calculate INR, there was a blood coagulation (clotting) test.

Genomic DNA was extracted within 1 week of blood collection using the commercially available Wizard GenomicDNA Purification Kit (Promega Corporation, Madison, Wisconsin) according to the manufacturer's instructions. After extraction, the DNA was diluted in 96-well plates using an automated robotic system to achieve concentrations of 20 ng/L (50-500 L). Concentrations were confirmed with the Nano-Drop ND-100 (Thermo Scientific, Wilmington, Delaware). Genotyping was carried out by means of the MassARRAY[®] system (iPLEX GOLD; Sequenom, San Diego, California).

Statistical Analysis

All data were coded, entered, and analyzed using SPSS for Windows, version 14.0 (SPSS Inc, Chicago, Illinois). Frequency and percentages were calculated and presented.

Results

Between November 1, 2013, and November 1, 2016, 2788 patients were referred to our ACC for education and monitoring. During the study period, 95 260 INR values were obtained for all patients referred to the clinic. After the application of inclusion and exclusion criteria, 89 488 INR values were included in the study; 20 365 (22.8%) were non-TINR values; 13 145 (14%) were subtherapeutic; 7220 (8.1%) were supratherapeutic. All patients included in the study had a non-TINR at least 3 times ($n = 65$, 2.3%) and as frequent as 50 times ($n = 21$, 0.8%) during the study period. Non-TINR values ranged from 1 to 11. Serious side effects reported in 7 patients with uncontrolled INR, 6 were bleeding that required hospitalization (2 upper GI bleeding, 3 nasal bleeding, and 1 eye bleeding), 1 was CVA (thrombolytic). Patients' characteristics are presented in Table 2.¹⁰

Factors that interrupt INR control were stratified and coded. Then the frequency of each factor was calculated. Factors that interrupted INR control in our population arranged in descending sequence are concurrent medication use 46.9% (mainly

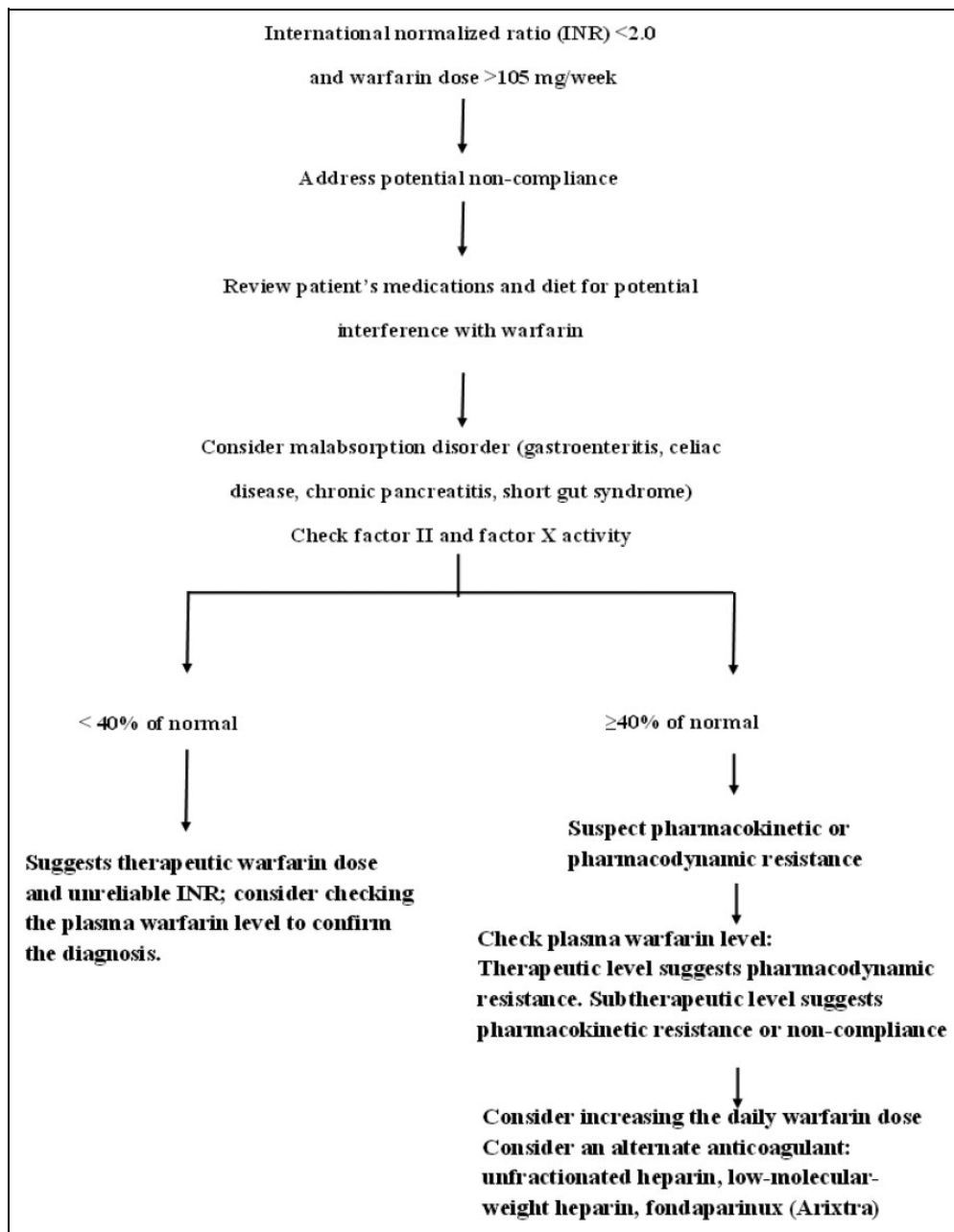


Figure 1. Algorithm for evaluating suspected warfarin resistance modified from Osinbowale et al.

Salicylates and Amiodarone), diet and herbal supplements 31.9%, smoking 17%, noncompliance 1.49%, comorbid diseases 1%, malabsorption 0.53%, alcohol intake 0.39%, and VKORC1 A/G and CYP2C9 *1*1 genotype 0.15%. Realized factors are presented in Table 3.

Discussion

The present study identified the most common factors that interrupt INR control in our population. All of our patients experienced non-TINR values during the study period either sub- or supratherapeutic. Warfarin dose was adjusted

according to the ACC protocol. Generally, the identified factors are well known from previous studies. But its frequency in causing non-TINR was specific to our population. Concurrent medication use represented the most frequent cause for non-TINR (46.9%), particularly Salicylates and Amiodarone (16.5%, 12%). The use of both drugs is very common among our patients, since most of them are cardiac patients; AF and MHV (Table 2). The aspirin-warfarin interaction is well known and described thoroughly in the literature.^{11–13} In a meta-analysis of randomized controlled trials, the risk of major bleeding was calculated to be about 1.5 times higher in combination therapy with aspirin and warfarin than with

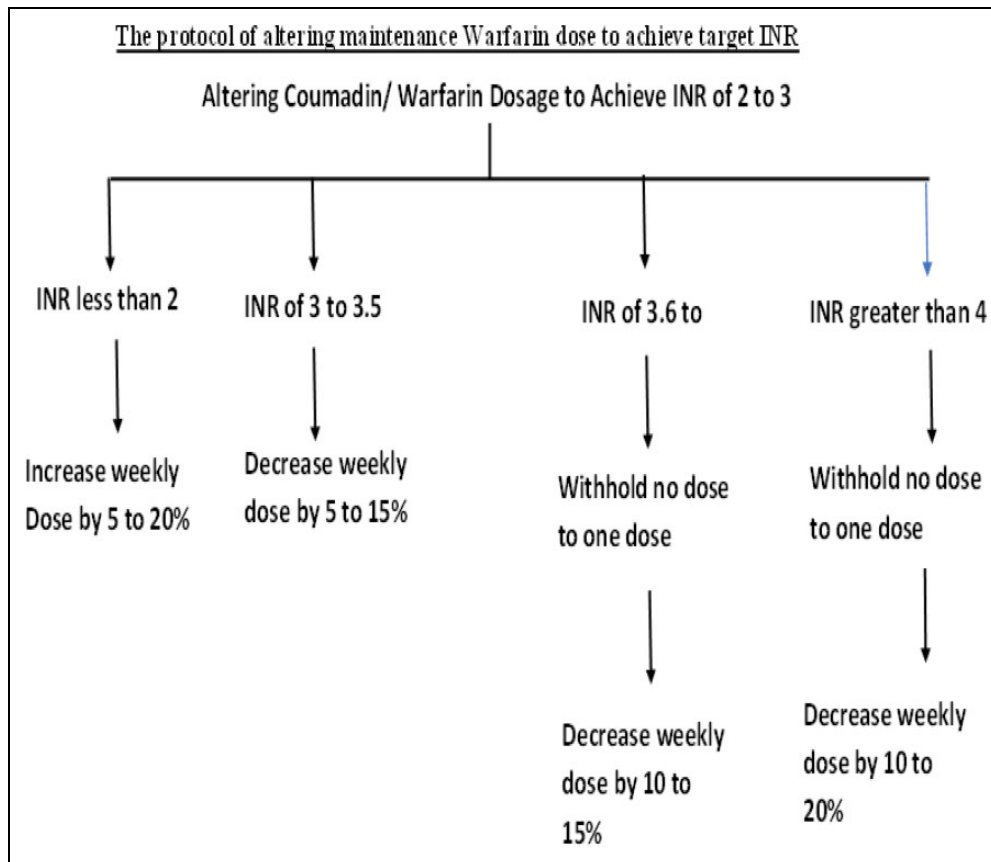


Figure 2. The protocol of altering maintenance warfarin dose to achieve target INR. Altering Coumadin/warfarin dosage to achieve INR of 2 to 3.

warfarin alone.¹³ In such cases, we have 2 options (to take in consensus with the treating physician): either to stop aspirin for individual cases such as patients with stable coronary artery disease or at risk of coronary disease, where the benefit of adding aspirin is not substantial and continuing warfarin alone may be the preferred strategy; or to keep both aspirin and warfarin if the cardiovascular benefit outweighs the increased risk of bleeding in patients presenting with an acute coronary syndrome or those with MHVs or coronary stents.¹⁴ If the decision is to continue on both drugs, then based on the results of the current study, the dose of warfarin should be decreased before starting aspirin and then titrated accordingly. Patients should also be educated for the interaction and the need to do dose adjustment (under the monitoring of ACC) if aspirin is interrupted. Similarly, the warfarin amiodarone interaction represented a main factor of non-TINR. This is a well-known interaction as well.^{15,16} Saleh found in his study that Amiodarone use was associated with 3.29-fold increases the likelihood of receiving a low warfarin dose.¹⁶ The findings of our study encouraged extra precautions in dealing with patients on warfarin–amiodarone combination such as, alarming the patient regarding the interaction, the need to adjust warfarin dose while changing amiodarone dose or before discontinuing it, and the need to comply to both medications as any noncompliance to amiodarone may interrupt INR control.

Other warfarin drug interactions were also detected as factors that interrupted INR control in our study (Table 3). Ciprofloxacin was remarkably the cause of non-TINR (4.6%) and levofloxacin to a less extent (1%), but it caused a serious bleeding event in 1 of the 6 bleeding cases that required hospitalization. This high percentage is explained by the considerable number of cardio-surgical patients who were discharged on ciprofloxacin. This interaction has been reported by previous studies to be clinically significant.^{16–19} Based on the findings of our study, the infection control team at QAHI restricted the prescription of ciprofloxacin (or other quinolones) and warfarin to cases where ciprofloxacin (or quinolones) is the only antibiotic option and advised to monitor patients on this drug combination more frequently.

Out of 6 serious bleeding events that were detected in the study, 4 were related to drug combination: 2 cases (warfarin, aspirin, NSAID) for at least 6 days and lead to upper GI bleeding, 1 case (warfarin, aspirin, clopidogrel), and lead to eye and continuous nasal bleeding and the above mentioned (warfarin, levofloxacin) lead to recent surgical site bleeding. Smoking represented the most frequent single factor that caused non-TINR in the present study.

A systematic review and meta-analysis of 13 studies assessing the interaction between smoking and warfarin reported that smoking may potentially increase warfarin clearance,

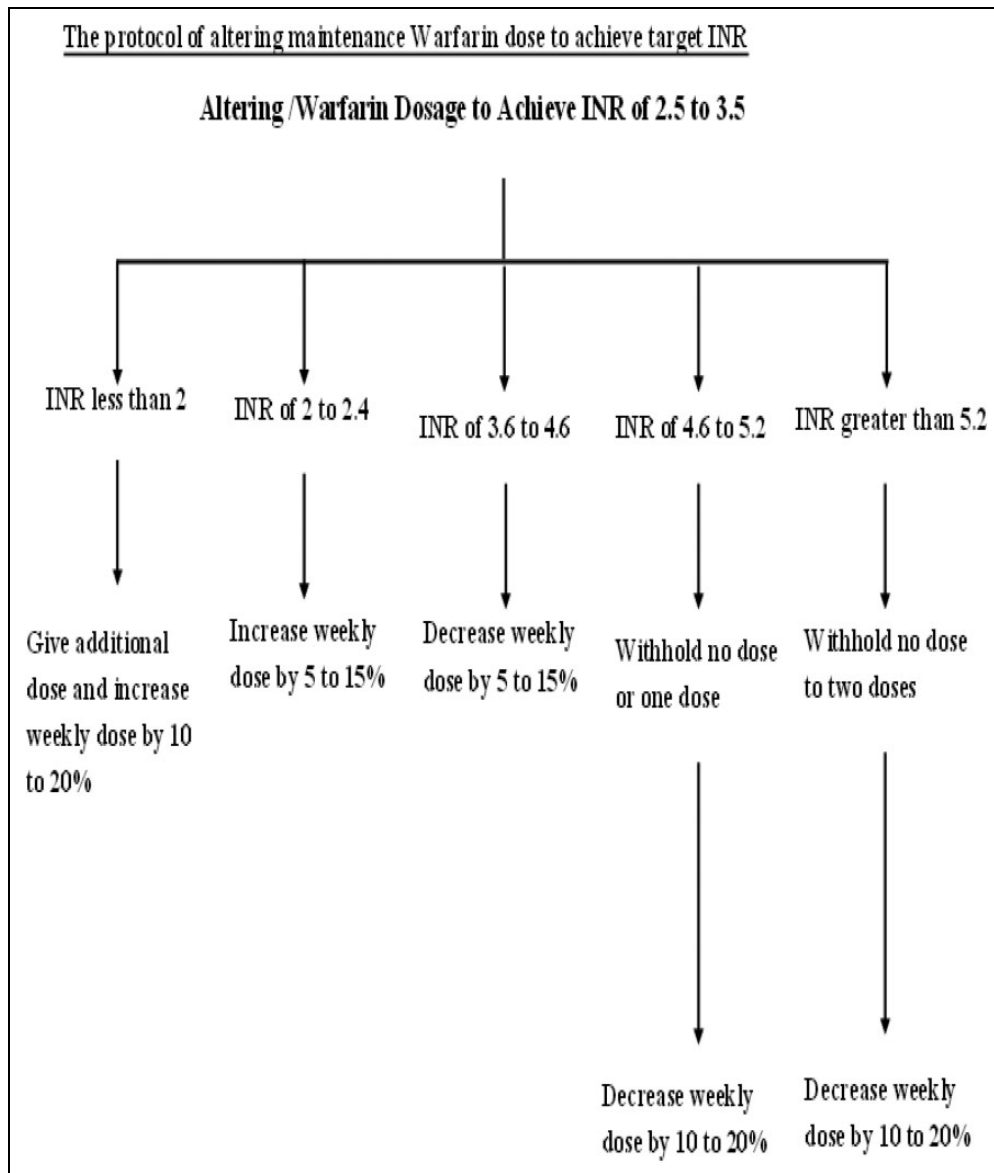


Figure 3. The protocol of altering maintenance warfarin dose to achieve target INR. Altering warfarin dosage to achieve INR of 2.5 to 3.5.

leading to reduced warfarin effects.²⁰ Smoking cigarettes can have a significant impact on warfarin therapy. Although there is no reported interaction between nicotine and warfarin, the other chemical compounds that are absorbed into the body from the smoke have an effect on the liver. The liver makes more enzymes to eliminate the toxic substances and, in the process, eliminates more warfarin. The end result of this process is an increase in warfarin requirements for someone who has started smoking. Warfarin management can also be problematic in patients who stop smoking. Ex-smokers should be monitored carefully after quitting because their warfarin requirements will likely be lower. Patients with a known recent smoking history who develop an unstable INR pattern should be questioned about smoking relapses, since starting and stopping smoking can cause warfarin requirements to vary.²¹

Besides cigarettes smoking there is shisha smoking that has emerged as a significant cause of non-TINR in the present study. Generally, shisha smoking is considered as dangerous as cigarette smoking or even more. But its effect on warfarin dosing is not studied yet. We found that monitoring patients smoking shisha is even worse than cigarettes smoking; patients who smoke shisha occasionally consider themselves nonsmokers unless they are asked directly about shisha. In addition, the nonconsistent pattern of smoking shisha makes it very difficult to maintain TINR, moreover smoking shisha the day just before performing INR test caused a sharp drop in the test (much more than smoking cigarettes). Smoking generally is an alarming phenomenon in Jordanian population, and the high percentage of smoking in our cardiac patients study sample (20.0%) rings the bell for the urgent need of a national awareness program and smoking cessation strategies.

Table 2. Characteristics for Patients Enrolled in the Study.

Characteristic	N = 2788
Mean [SD] (range) age in years	46 [29.3] (5-81)
Male, % (n)	65% (1812)
Patient weight ^a	
Underweight (BMI ≤ 18.5)	4.4% (122)
Normal weight (BMI = 18.5–24.9)	40.3% (1123)
Overweight (BMI = 25–29.9)	38% (1059)
Obese (BMI ≥ 30)	17.4% (484)
Current smoking, % (n)	20.0% (557)
Diabetes mellitus, % (n)	38.3% (1068)
3 medical diagnoses or more, % (n)	29.5% (822)
Indication of warfarin	
AF	15.4% (430)
MHV	83% (2314)
Others ^b	1.6% (45)

Abbreviations: AF, atrial fibrillation; SD, standard deviation.

^aBMI (Body Mass Index) = weight in kilograms divided by height in squared meters.¹⁰

^bDeep vein thrombosis, pulmonary embolism, recurrent stroke.

Diet and herbal supplements were responsible for 31.9% of non-TINR during the study period. Non balanced dietary vitamin K intake corresponded to 16.88% of non-TINR despite the detailed educational session and the printed booklet that shows the daily allowed amount of vitamin K-rich food in serving size and that stresses on the need to take a consistent amount of vitamin K daily. The changes in INR (low) that is related to increased intake of vitamin K-rich food were noticed to be much more in the spring season in Jordan (end of March and April mainly), which is due to the increased consumption of seasonal leafy vegetables in spring such as spinach, hibiscus, hedge mustard, and parsley.

The effect of gross changes in vitamin K intake on anticoagulation is a classic. Since the early years of warfarin use, countless case reports and case series have described decreased anticoagulant response due to sudden excessive vitamin K intake. The causes were usually vitamin K rich, vegetable-based, weight reducing diets and food supplements or multivitamins.^{22–25} Excessive anticoagulation has also been described after unrecorded dietary modification or discontinuation of multivitamin use.^{25,26}

Herbal supplements corresponded to 15.02% of non-TINR—mainly high. Hawthorn (*Crataegus*, الزعرور) is an herb that lives widely in Jordan. It is well known in traditional and alternative medicine, and it is claimed to be a treatment for cardiovascular diseases and to prevent heart attacks and clots. Shockingly, we found that it is used very commonly in our ACC patients. It was corresponded to an elevated INR <8 in 11 patients, and serious bleeding events that required hospitalization in 2 cases. Ginseng use was also associated with elevated INR <8 in 2 patients. Herbs–warfarin interactions are well studied, and many herbs are well known to interact with warfarin. Ge et al in their updates on the clinical evidenced herb–warfarin interactions found that among 38 herbs, Cannabis, Chamomile, Cranberry, Garlic, Ginkgo, Grapefruit,

Table 3. Factors Interrupt With INR Control.

Realized cause of non-TINR value	Frequency, (n/20365), %
Concurrent medication use	(9550/20 365), 46.9%
Salicylates	(3361/20 365), 16.5%
Amiodarone	(2447/20 365), 12%
Ciprofloxacin	(927/20 365), 4.6%
NSAIDS	(705/20 365), 3.5%
Azithromycin	(609/20 365), 3%
Clarithromycin	555/20 365, 2.7%
Carbamazepine	413/20 365, 2%
Levofloxacin	215/20 365, 1 %
Metronidazol	120/20 365 0.6%
Multivitamins (containing Vit K)	100/20 365, 0.49%
Allopurinol	50/20 365, 0.25%
Thyroxin	22/20 365, 0.1%
Phenytoin	18/20 365, 0.09%
Fluconazole	8/20 365, 0.04%
Smoking	3466/20 365, 17%
Cigarettes	3005/20 365, 14.7%
Shisha	461, 2.3%
Diet and herbal supplements	6495/20 365, 31.9%
Nonbalanced vitamin K diet	3437/20 365, 16.88%
Herbal supplements	3058/20 365, 15.02%
Hawthorn (<i>Crataegus</i> , الزعرور)	866/20 365, 4.25%
Ginseng	732/20 365, 3.59%
Garlic	602/20 365, 2.96%
Ginger	466/20 365, 2.29%
Fish oil	236/20 365, 1.16%
Tamarind (التمر الهندي)	95/20 365, 0.47%
Liquorice	31/20 365, 0.15%
Green tea	30/20 365, 0.15%
Noncompliance	303/20 365, 1.49%
Comorbid diseases (cerebrovascular, renal, gastrointestinal, and duodenal ulcers)	203/20 365, 1.00%
Malabsorption	107/20 365, 0.53%
Alcohol intake	80/20 365, 0.39%
Genetic polymorphism	30/20 365, 0.15%
Unknown	131/20 365, 0.64%

Abbreviations: INR, international normalized ratio; NSAIDS, nonsteroidal anti-inflammatory drug; TINR, target INR.

Lycium, Red clover, and St. John's wort were evaluated to have major severity interaction with warfarin.²⁷

Therefore, we provide our patients with a printed table of the herbs to avoid or the maximum amount they can use. Hawthorn was not among the list in the beginning, but since we reported the bleeding events and the elevated INR, we added it to the list of herbs to avoid and we now ask patients routinely if they use it.

Noncompliance, comorbid diseases, malabsorption, alcohol intake, genetic polymorphism were also corresponded to the causes of non-TINR values in our study population. Those factors are well studied previously, and our results are consistent with previous studies.^{28,29}

Although genetic variants in both CYP2C9 and VKORC1 enzymes are known to affect INR control, we did not do genetic-guided therapy routinely since it is a burden on the system; instead we did it for selected patients (n = 2) in whom

we could not achieve therapeutic INR control despite the high warfarin dose (105 and 122.5 mg). Warfarin-sensitive patients with increased bleeding risk may also be candidates for genetic study. In a study that has been done at our ACC by other genetics researchers, Al-Eitan et al confirmed a genetic association of the CYP2C9*3 and VKORC1 rs10871454, rs8050894, rs9934438, and rs17708472 single-nucleotide polymorphisms with warfarin sensitivity. This study also found an association between CYP2C9 and VKORC1 genetic haplotype blocks and warfarin sensitivity.³⁰

The genetic report for our 2 warfarin resistance patients suggested that the VKORC1-1639 GG and the wild-type CYP2C9*1*1 genotypes are associated with the high-dose requirement for warfarin therapy, and that VKORC1-1639 GG is responsible for warfarin resistance and failure in our patients.

In 2007, the Food and Drug Administration (FDA) added pharmacogenetic information to the warfarin package insert, presumably in recognition of the fact that genetic variations in the CYP2C9 and VKORC1 genes contribute significantly to the variability in dose requirements for warfarin. However, the FDA did not propose a specific method for using genetic information to predict the dose required in individual patients.³¹ The review by Limdi et al³² did not find supporting evidence to suggest that genotype-guided therapy will improve anticoagulant control and prevent or reduce the risk of hemorrhagic or thromboembolic complications. In any case, it would be both reasonable and prudent to use CYP2C9 and VKORC1 genotypes as part of diagnostic efforts to understand unusual responses to standard medical care.³³

Limitations

The realized factors corresponded to non-TINR depended to some extent on a patient's story and explanations regarding their lifestyle. So some factors may be missed out or not told or exaggerated. In the future, one can consider finding more reliable tools of detecting factors related to patient's behavior and practice.

Conclusion

The analysis of the realized factors that interrupted with INR control in our patients were both predicted and distinctive; most of these factors were reported previously by other researchers. On the other hand, many of the previously reported factors were not frequently detected in our patients and the frequency of each of the realized factors was contributed differently to non-TINR in our population. Alarming factors causing non-TINR detected in our study include smoking both cigarettes and shisha, herbal use (Hawthorn and Ginseng), increased intake of vitamin K-rich food in the spring season, and concurrent medication use (Salicylates, Amiodarone, Ciprofloxacin, NSAIDS, Azithromycin, Clarithromycin; although the use of these drugs is mandatory sometimes, it can

be replaced by an alternative, eg, antibiotics or monitored closely together with warfarin).

Authors' Note

All authors contributed equally to concept and design, data collection and interpretation, and writing and revision of the manuscript.

Acknowledgments

The authors would like to thank all the physicians and nurses working at Queen Alia Heart Institute (QAHI) who helped us in patient recruitment and data collection.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This study was funded by the Royal Medical Services.

Supplemental Material

Supplemental material for this article is available online.

References

1. Baker WL, Cios DA, Sander SD, Coleman CI. Meta-analysis to assess the quality of warfarin control in atrial fibrillation patients in the United States. *J Manag Care Pharm.* 2009;15(3):244–252.
2. Chamberlain MA, Sageser NA, Ruiz D. Comparison of anticoagulation clinic patient outcomes with outcomes from traditional care in a family medicine clinic. *J Am Board Fam Pract.* 2001;14(1):16–21.
3. Chiquette E, Amato MG, Bussey HI. Comparison of an anticoagulation clinic with usual medical care: anticoagulation control, patient outcomes, and health care costs. *Arch Intern Med.* 1998;158(15):1641–1647.
4. van Walraven C, Jennings A, Oake N, Fergusson D, Forster AJ. Effect of study setting on anticoagulation control, a systematic review and meta regression. *Chest.* 2006;129(5):1155–1166.
5. Levi M, Richard Hobbs FD, Jacobson AK, et al. Improving antithrombotic management in patients with atrial fibrillation: current status and perspectives. *Sem Thromb Hemost.* 2009;35(6):527–542.
6. Ansell J, Hirsh J, Hylek E, Jacobson A, Crowther M, Palareti G. Pharmacology and management of the vitamin k antagonists: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest.* 2008;133(suppl 6):160S–198S.
7. Salem DN, O'Gara PT, Madias C, Pauker SG. Valvular and structural heart disease: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest.* 2008;133(suppl 6):593S–629S.
8. Neel S. Essential warfarin knowledge. In: Gulseth M, ed. *Managing Anticoagulation Patients in the Hospital: The Inpatient Anticoagulation Service.* Bethesda, MD: American Society of Health-System Pharmacists; 2007;133–175.

9. Osinbowale O, Al Malki M, Schade A, Bartholomew JR. An algorithm for managing warfarin resistance. *Cleve Clin J Med*. 2009;76(12):724–730. (published Online First: Epub Date) [PubMed]
10. Lacy CF, Armstrong LL, Goldman MP, Lance LL. *Drug Information Handbook 2006-2007*. 15th ed. Washington, D.C.: The American Pharmaceutical Association; 2006.
11. Steinberg BA, Kim S, Piccini JP, et al. Use and associated risks of concomitant aspirin therapy with oral anticoagulation in patients with atrial fibrillation: insights from the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF) Registry. *Circulation*. 2013;128(7):721–728.
12. Rothberg MB, Celestin C, Fiore LD, Lawler E, Cook JR. Warfarin plus aspirin after myocardial infarction or the acute coronary syndrome: meta-analysis with estimates of risk and benefit. *Ann Intern Med*. 2005;143(4):241–250.
13. Dentali F, Douketis JD, Lim W, Crowther M. Combined aspirin-oral anticoagulant therapy compared with oral anticoagulant therapy alone among patients at risk for cardiovascular disease: a meta-analysis of randomized trials. *Arch Intern Med*. 2007;167(2):117–124.
14. Madhwal S, Lincoff AM, Rolston DDK. Should patients on long-term warfarin take aspirin for heart disease? *Clev Clin J Med*. 2008;75(3):206–208.
15. Heimark LD, Wienkers L, Kunze K, et al. The mechanism of the interaction between amiodarone and warfarin in humans. *Clin Pharmacol Ther*. 1992;51(14):398–407.
16. Saleh MI. Clinical predictors associated with warfarin sensitivity. *Am J Ther*. 2015;23(6):e1690–e1694. <http://dx.doi.org/10.1097/MJT.0000000000000248>.
17. Bayer Corporation. *Product Information: Cipro (Ciprofloxacin)*. West Haven, Conn: Bayer Corporation;1997.
18. Jolson HM, Tanner LA, Green L, Grasela TH Jr. Adverse reaction reporting of interaction between warfarin and fluoroquinolones. *Arch Intern Med*. 1991;151(5):1003–1004.
19. Bianco TM, Bussey HI, Farnett LE, Linn WO, Roush MK, Wong YW. Potential warfarin-ciprofloxacin interaction in patients receiving long-term anticoagulation. *Pharmacotherapy*. 1992;12(6):435–439.
20. Nathisuwan S, Dilokthornsakul P, Chaiyakunapnik N, et al. Assessing evidence of interaction between smoking and warfarin: a systematic review and meta-analysis. *Chest*. 2011;139(5):1130–119.
21. Anna DG. Smoking affects warfarin therapy. pharmacytimes.com/publications/issue/2007-05-6496.
22. Qureshi GD, Reinders TP, Swint JJ, Slate MB. Acquired warfarin resistance and weight-reducing diet. *Arch Intern Med*. 1981;141(4):507–509.
23. Walker FB. 4th Myocardial infarction after diet-induced warfarin resistance. *Arch Intern Med*. 1984;144(10):2089–2090.
24. Oren B, Shvartzman P. Unsuspected source of vitamin K in patients treated with anticoagulants: a case report. *Fam Pract*. 1989;6(2):151–152.
25. Kurnik D, Lubetsky A, Loebstein R, Almog S, Halkin H. Multi-vitamin supplements may affect warfarin anticoagulation in susceptible patients. *Ann Pharmacother*. 2003;37(11):1603–1606.
26. Chow WH, Chow TC, Tse TM, Tai YT, Lee WT. Anticoagulation instability with life-threatening complication after dietary modification. *Postgrad Med J*. 1990;66(780):855–857. PMC free article.
27. Ge B, Zhang Z, Zuo Z. Updates on the clinical evidenced herb-warfarin interactions. *Evid Based Complement Alternat Med*. 2014;2014:957362.
28. Dharmarajan L, Dharmarajan TS. Prescribing warfarin appropriately to meet patient safety goals. *Am Health Drug Benefits*. 2008;1(6):26–32.
29. Ageno W, Gallus AS, Wittkowsky A, Crowther M, Hylek EM, Palareti G. Oral anticoagulant therapy: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;141(suppl 2):e44S–e88S.
30. Al-Eitan LN, Almasri AY, Khasawneh RH. Impact of CYP2C9 and VKORC1 polymorphisms on warfarin sensitivity and responsiveness in Jordanian cardiovascular patients during the initiation therapy. *Genes (Basel)*. 2018;9(12):E578. doi:10.3390/genes9120578.
31. The International Warfarin Pharmacogenetic Consortium; Klein TE, Altman RB, Eriksson N, et al. Estimation of the warfarin dose with clinical and pharmacogenetic data. *N Engl J Med*. 2009;360:753–764.
32. Limdi NA, Veenstra DL. Warfarin pharmacogenetics. *Pharmacotherapy*. 2009;28:1084–1097.
33. Yenny Y. Warfarin: do we need genotype-based dose prediction? *Univ Med*. 2010;29(3):1–3.