



# Time in Therapeutic Range (TTR) and the Efficacy of Anticoagulant Therapy in Preventing Thromboembolism in Cardiac Patients Receiving Warfarin at Shifa Medical Complex: A Cross-Sectional Study

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Received 09 September 2021;

Accepted 25 September 2021;

Published 29 October 2021

## Abstract

**Background:** Anticoagulant control is assessed by Time in Therapeutic Range (TTR). For a given patient, TTR is defined as the duration of time in which the patient's International Normalized Ratio (INR) values were within a desired range. **Aim:** To assess TTR in patients receiving anticoagulant treatment and the efficacy of Anticoagulant therapy in preventing Thromboembolism in Cardiac Patients receiving Warfarin for atrial fibrillation and with high CHADS VASC score, valvular and non-valvular heart disease at a referral center for cardiovascular diseases at Gaza Shifa Medical Complex, Palestine. **Materials and Method:** Over 8 months, we enrolled eligible patients presenting to Shifa Medical Complex in Gaza for regular INR testing. Demographic data, medical history, and current medications were determined for all participants. TTR was assessed by both tradition and cross-sectional methods. **Results:** A total of 46 patients (mean age  $57.15 \pm 12.6$  years, 50% women) underwent 230 INR measurements. The mean TTR was calculated as  $50.86 \pm 21.37\%$ . Participants of this study were assessed for their risk of having stroke using CHADS VASC score and risk of bleeding using HAS BLED score. Risk of stroke was significantly higher for females ( $P=0.031$ ). Of the sample patients, 47.8% were in the good control category (TTR  $>60\%$ ), and 52.2% were in the poor control category (TTR  $<60\%$ ). The mean TTR of the studied patients (54.9%) was below the good control range. There were 12 participants had thromboembolism of patients with low traditional TTR. This was statistically significant, TTR with occurrence of thromboembolism, ( $P=0.001$ ). **Conclusion:** We found a mean TTR of 50.86% among study patients diagnosed with atrial fibrillation and high CHADS VASC score, valvular and non-valvular heart disease who were receiving warfarin therapy. None of the risk factor was significantly related to low TTR values among study participants. The study showed the low TTR was associated with increased risk of thromboembolism among participants in this study. Moreover, showed the superiority of tradition TTR over cross-sectional TTR in evaluating anticoagulant therapy.

**Keywords:** Anticoagulant, Time in Therapeutic Range, International Normalized Ratio, Cardiac Disease, Gaza, Palestine

## Introduction

Thrombosis prevention is a top priority in managing patients with a high risk of thromboembolic events, such as patients with atrial fibrillation (AF), valvular prostheses, and venous or pulmonary embolism venous thromboembolism (VTE) [1-2]. The vitamin K antagonist warfarin is widely used compared to non-vitamin K antagonist oral anticoagulant (NOAC) agents, especially for elders and patients with comorbidities [3]. A major problem of warfarin therapy is the narrow therapeutic index that requires close monitoring of the international normalized ratio (INR).

Maintaining INR values within a narrow target range (INR: 2.0-3.0) requires frequent blood tests to ensure the safety and efficacy of warfarin used [4]. Maximizing the time in the therapeutic range (TTR) within the optimal INR range provides the greatest benefit for the prevention of embolic or thrombotic events and avoidance of severe side effects [5-6]. The TTR is a good indicator of anticoagulation control and the best predictor for patients' quality outcomes [6].

The target TTR in clinical trials may be different than the target TTR achieved in community practice. The Thrombosis Canada Guidelines State that good INR control is defined

arbitrarily as a TTR >60% [5]. Low TTRs reflect poor anticoagulation control and are associated with thromboembolic or bleeding events. High TTRs provide a better quality of life and health outcomes with fewer adverse events [7].

Few studies have examined the quality of anticoagulation clinics in high-load centers in our region. We conducted this study to evaluate the quality of an anticoagulation clinic in a tertiary hospital and identify factors affecting the TTR and its relation to different complications.

There are 3 methods for assessing TTR in patients taking warfarin: 1) Calculating the fraction of INRs that are in range, which is the conventional method; 2) Evaluating a cross-section of the patient's files; and 3) using the Rosendaal method [7-8]. Assessing TTR allow physicians to estimate the success of warfarin therapy in patients, because it is a major determinant of warfarin's efficacy and safety, with the maximum benefits evident when TTR is >70% [6,9]. In this study, we used the first two methods to assess the TTR.

Age, sex, socioeconomic status, smoking status, comorbid medical and psychiatric conditions, alcohol abuse, polypharmacy, and frequent hospitalizations are correlated with TTR [3,12-15]. Screening tools to predict nonadherence to warfarin demonstrate promise in secondary care settings [16]; the strongest associations are with those who are currently smoking, disabled, or cognitively impaired [17]. In this study, authors aim to evaluate TTR in patients with valvular and non-valvular heart disease patients who were receiving anticoagulant therapy at a referral hospital for cardiovascular diseases in Gaza, Palestine.

## Methods

### Study design

This was a descriptive, correlational cross-sectional study to evaluate TTR in cardiac patients. Since the aim of the study was to assess TTR in patients receiving anticoagulant treatment for valvular or non-valvular heart disease at a referral center for cardiovascular diseases in Gaza, Palestine, this is the suitable design for this research.

### Study setting

The study was carried out at cardiology outpatient department at Shifa Medical Complex. The data were collected prospectively from the patients and medical records. The data collection process was completed during a period from February to September 2021.

### Sampling and sample

Participants were chosen via non-probability convenient sampling technique according to cardiac patients presenting to the cardiology outpatient department.

### Inclusion criteria:

1. Patients must be at least 18 years old, presenting to Shifa Medical Complex for INR follow-up, have been on Warfarin for at least 3 months.

2. The INRs of patients were collected during their referral to the clinic where every patient had at least 5 INR measurements taken in total for 8 months.
3. Patients with a high CHADS VASC score and persistent atrial fibrillation.
4. Patients with prosthetic hearts valves.
5. Patients with non-valvular heart disease who are being treated with warfarin (PE, DVT).

### Exclusion criteria:

Patients were excluded if they had a life expectancy of below 8 months or were not capable of at least 5 months of follow-up.

### Data collection

Data were collected by a resident cardiologist at cardiology outpatient department in Shifa Medical Complex. Demographic data such as age, sex, medical history and current medications were determined for all participants.

### Instruments

Data collection tool was self-designed and base on latest literature. It contained the following information: (1) basic information about participants, (2) medical history, (3) drug history, (4) INR laboratory results, (5) CHADS VASC score and (6) HAS BLED score.

### Statistical analysis

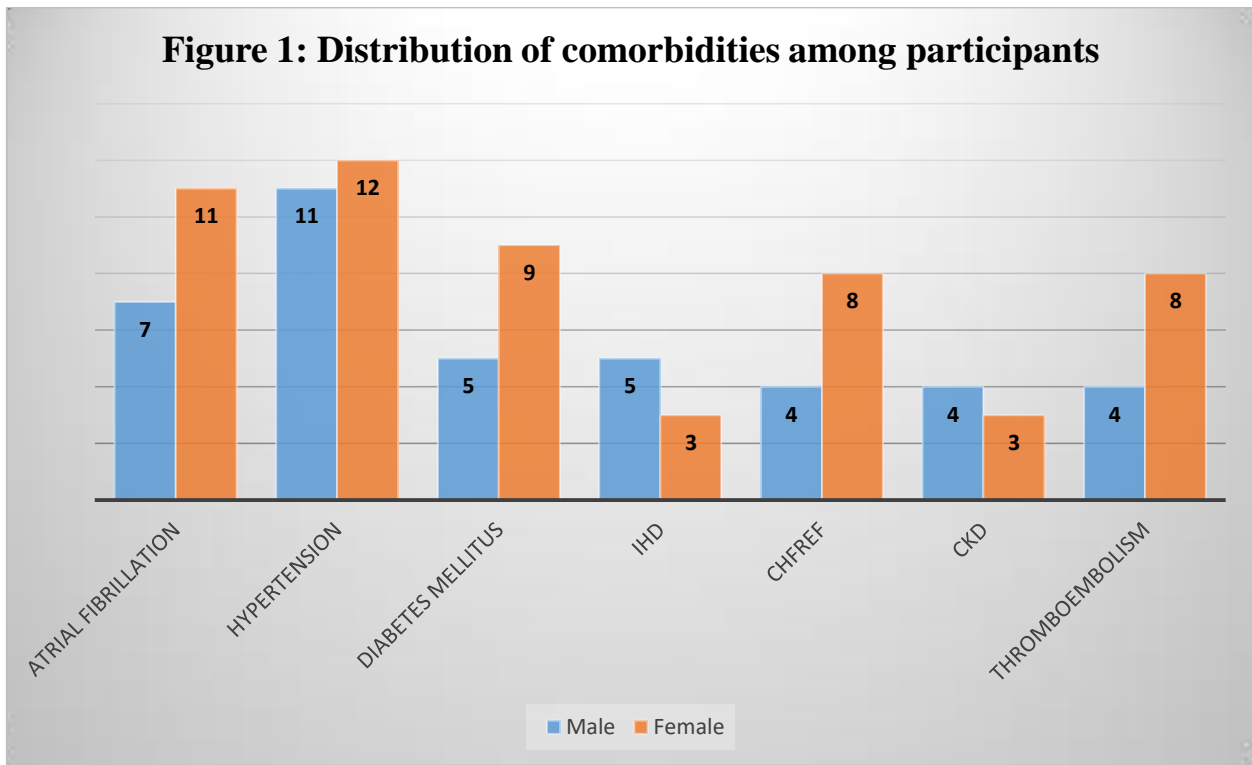
Data obtained from questionnaire were entered and analyzed using SPSS program version 23 computer software. Sociodemographic data are presented using descriptive statistics as means, median, percentages and standard deviation. Independent T test and one-way Anova are used to show statistical significance among patients' characteristics and tool scores. Chi square test is used to show relationship between categorical variables.

### Permission and ethical considerations

An approved permission was gained from Helsinki committee and Human Resources in Gaza Strip to collect data from the pediatric ward at Nasser Medical Complex.

## Results

The study included 46 cardiac patients during the study period. The mean age of participants was 57.15 ± 12.6 years with median age of 60 years. The youngest patient included in this study was 17 years old and the oldest patient was 81. Gender was equally distributed in this study, as half of participants was males and the other half was females. There were 18 patients ((39.1%) diagnosed with atrial fibrillation. Among them, 11 of the AF patients were females. Other comorbidities are presented in figure 1. It is noticed that comorbidities are more prevalent among females more than males except for IHD and CKD. No statistically significance was found between gender and comorbidities.



Some patients underwent valve repair surgery. Mitral valve repair was performed among 11 males and 13 females (n= 24, 52.2%). On the other hand, aortic valve repair was performed among 8 males and one female(n= 9, 19.6%). P value for valve repair was

significant (0.009). Some of these patients had atrial fibrillation and the other hadn't (table 1). There was statistically significant relationship between the diagnosis of atrial fibrillation and valve repair surgery (P= 0.004).

**Table 1: Distribution of valve surgery repair among atrial fibrillation patients by gender**

Valve surgery repair		Atrial fibrillation	
		Yes	No
Mitral valve	Male	3	8
	Female	5	8
Aortic valve	Male	1	7
	Female	0	1

INR test was done 5 times for each patient during 8 months for all study participants. Mean values, standard deviation and median values for all tests are presented in table 2 separately for males and

females. All patients received warfarin while only 7 patients took baby aspirin (15.2%) and none of the patients was on new oral anticoagulants.

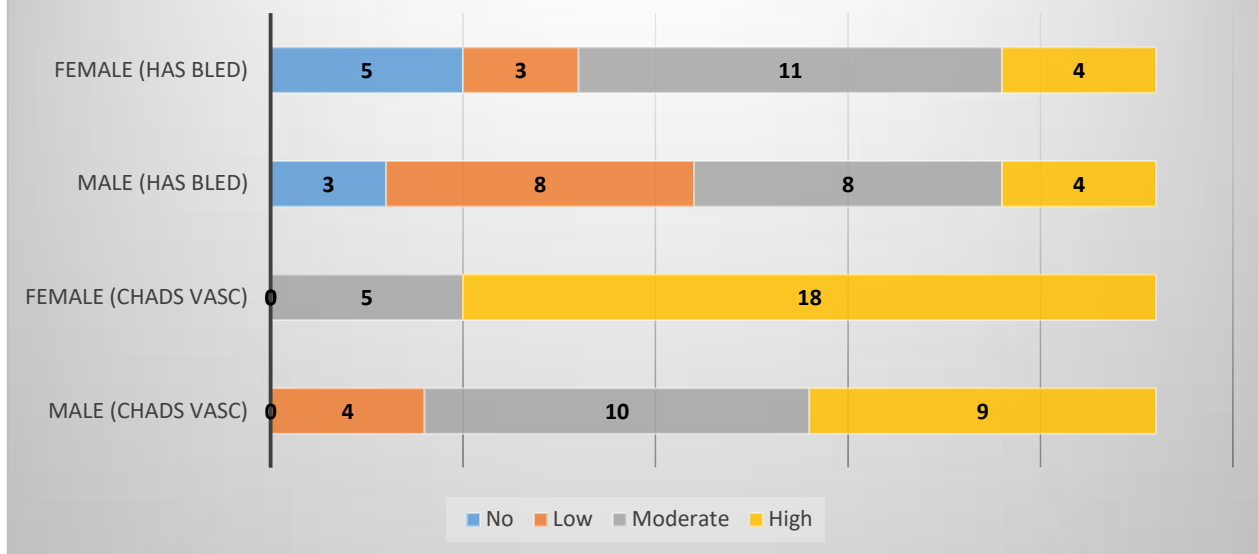
**Table 2: INR laboratory test results among study participants distributed by gender**

INR test	Mean ± SD (min – max)	Median	Student T test (t)	P value
First and last INR	2.26 ± 0.76 (1.00 – 4.20)	2.25	0.172	0.165
Second INR	2.19 ± 0.80 (1.00 – 6.00)	2.05	-0.710	0.261
Third INR	2.35 ± 0.79 (1.30 – 4.10)	2.10	-0.698	<b>0.012</b>
Fourth INR	2.23 ± 0.58 (1.30 – 4.00)	2.05	0.223	0.436
Fifth INR	2.41 ± 0.67 (1.20 – 4.30)	2.30	-0.215	0.924

Participants of this study were assessed for their risk of having stroke using CHADS VASC score and risk of bleeding using HAS BLED score. The risk for both stroke and bleeding is demonstrated

in figure 2. Risk of stroke was significantly higher for females (P= 0.031).

**Figure 2: Risk of stroke and risk of bleeding among study participants by gender**



TTR was calculated using two methods. First is the traditional method. Results of traditional TTR is presented in table 3. Traditional TTR above target was defined as more than 60% while below target means less than 60%. It is noticed that 24 participants (52.2%) has low TTR target which means high risk for thromboembolism. The mean value for traditional TTR was 50.86 + 21.37 with median value of 40. The least traditional TTR was 20 and the highest was 100. There were 12 participants had thromboembolism of patients with low traditional TTR. This was statistically significant, TTR with occurrence of thromboembolism, (P= 0.001).

**Table 3: Results of traditional TTR distributed by gender**

TTR	Gender	
	Male	Female
TTR 20%	3	5
TTR 40%	8	8
TTR 60%	7	5
TTR 80%	5	4
TTR 100%	0	1
TTR below target	11	13
TTR above target	12	10

The second method was cross-sectional TTR. Table 4 shows the results of cross-sectional TTR distributed by gender. We notice that 13 participants (28.3%) had low cross-sectional TTR. However, there was no significance with either gender or the occurrence of thromboembolism.

**Table 4: Results of cross-sectional TTR distributed by gender**

TTR	Gender	
	Male	Female
Below target	7	6
Above target	16	17

**Discussion**

The current study aimed to assess TTR in patients receiving anticoagulant treatment for valvular and non-valvular heart disease at a referral center for cardiovascular diseases in Gaza, Palestine.

To the best of our knowledge, this is the first study to fulfill this purpose.

Warfarin have been shown to be effective in the treatment and prevention of thromboembolic events; however, they possess many drug- drug and drug-food interactions, as well as a narrow therapeutic window [18]. The efficacy and safety of oral vitamin K antagonists such as warfarin depend strongly on the percentage of TTR, with the maximum benefits being evident when the TTR is >70% [19-20]. It is well-known that poor control of anticoagulant intensity increases the risks of thrombotic and hemorrhagic events [9].

The consistency of an effective INR is reflected by the TTR, which is a measure of the period in which the patient was in an optimal INR range. Cotte et al., evaluated the TTRs of 6250 patients in four European countries (France, Germany, Italy, and United Kingdom) with atrial fibrillation who had been prescribed vitamin K antagonists. They concluded that 47.8%, 44.2%, 46.1%, and 65.4% of the evaluated patients had TTRs >70% in France, Germany, Italy, and the United Kingdom, respectively [21]. Our results showed that the percentage of good control patients (47.8%) was comparable to each European country as discussed by Cotte et al., [21]. Sample size has an effect as our sample is markedly less than the sample size in Cotte et al.

Mark et al., [22] recently analyzed data from 272 patients with non-valvular atrial fibrillation in a hospital in Hungary. They did not classify their patients into different TTR categories and only reported the mean TTR, which was found to be 64%. The mean TTR in our study (50.86%) was lower than that reported by Mark et al. It seems that Gaza patients have poorer control of warfarin dosing compared to the patients in European studies [22].

Our results were similar to those from recent research by Zubaid et al., in Kuwait. They evaluated the quality of warfarin therapy for 369 patients with non-valvular atrial fibrillation and estimated TTRs by the Rosendaal method. They reported a mean TTR of 52.6% in their sample, which is close to the mean TTR determined in the present study (50.86%) [23]. Pharmacogenetic and dietary regimens are two important factors to be considered in relation to warfarin [24-26]. Gaza, Palestine and Kuwait are located in western Asia and have similar dietary regimens, cultures and may be genetic patterns, which may provide reasons for why our

results and those in Zubaid's study are similar. Zubaid et al., had concluded that females and patients with no history of hypertension were more likely to have poor anticoagulation (expressed as Rosendaal TTR < 58%). Unlike Zubaid et al., we did not see any tendencies of poor control among females or patients without hypertension.

Melamed et al., [27] studied TTR in 906 patients diagnosed with atrial fibrillation in the United States who were treated with warfarin for at least 6 months. They concluded that poor control (TTR < 60% in their study) was significantly associated with females, advanced age (>75 years), and heart failure [27]. However, in our study, there were no significant differences in TTR between male and females ( $p = 0.68$ ), patients <75 years, those >75 years ( $p = 0.31$ ), and patients with and without heart failure ( $p = 0.35$ ). Previous studies have not referred to the relationship between TTR and the number of patient's medications and this was a drawback in our study as well.

Zulling et al., evaluated adherence barriers among patients with cardiovascular risk factors. The most commonly reported medication barrier was having too many medications to take (31%), in their study [28].

Further research including more risk factors and other characteristics of patients is warranted to confirm the current observation. Researchers are encouraged to spot light on this topic as it is highly important for such patients.

## Conclusion

There are no reports in the literature regarding TTR values among patients in Gaza and this is the first study that evaluates TTR among Gaza population. We found a mean TTR of 50.86% among study patients diagnosed with either valvular or non-valvular cardiac disease who were receiving warfarin therapy. None of the risk factor was significantly related to low TTR values among study participants. In the future, we recommend evaluating factors that could possibly affect INR values and TTR rates, such as drug-warfarin interactions, food-warfarin interactions, number of medications and patients' treatment adherence. The study showed the low TTR was associated with increased risk of thromboembolism among participants in this study. Moreover, showed the superiority of tradition TTR over cross-sectional TTR in evaluating anticoagulant therapy.

## Competing Interest

Authors declare that they have no competing interests.

## Funding

None

## Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

## References

[1] Caldeira D, Cruz I, Morgado G, Stuart B, Gomes C, Martins C, et al. Evaluation of time in therapeutic range in anticoagulated patients:a single-center, retrospective, observational study. *BMC Res Notes*. 2014;7:891.

[2] Wigle P, Hein B, Bloomfield HE, Tubb M, Doherty M. Updated guidelines on outpatient anticoagulation. *Am Fam Physician*. 2013;87:556–566.

[3] Zhu J, Alexander GC, Nazarian S, Segal JB, Wu AW. Trends and variation in oral anticoagulant choice in patients with atrial fibrillation 2010–2017. *Pharmacotherapy*. 2018;38:907–920.

[4] Hirsh J, Fuster V, Ansell J, Halperin JL. American heart association/American college of cardiology foundation guide to warfarin therapy. *Circulation*. 2013;107:1692–1711.

[5] Gateman D, Trojnar ME, Agarwal G. Time in therapeutic range:warfarin anticoagulation for atrial fibrillation in a community-based practice. *Can Fam Physician*. 2017;63:e425–e431.

[6] Farsad BF, Abbasinazari M, Dabagh A, Bakshandeh H. Evaluation of time in therapeutic range (TTR) in patients with non-valvular atrial fibrillation receiving treatment with warfarin in Tehran, Iran:a cross-sectional study. *J Clin Diagn Res*. 2016;10:FC04–FC06.

[7] Lip GYH, Banerjee A, Boriani G, Chiang CE, Fargo R, Freedman B, et al. Antithrombotic therapy for atrial fibrillation:CHEST guideline and expert panel report. *Chest*. 2018;154:1121–1201.

[8] Rosenstein R, Parra D. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med*. 2011;365(24):2334–5.

[9] Meyer BJ. Time in therapeutic range for warfarin—a European success story. *J Watch Cardiol*. 2011 Oct 19; Available from: [www.jwatch.org/jc201110190000001/2011/10/19/time-therapeutic-range-warfarin-european-success](http://www.jwatch.org/jc201110190000001/2011/10/19/time-therapeutic-range-warfarin-european-success). Accessed 2021Oct19.

[10] Van Walraven C, Jennings A, Oake N, Fergusson D, Forster AJ. Effect of study setting on anticoagulation control. *Chest*. 2016;129(5):1155–66.

[11] Connolly S, Pogue J, Eikelboom J, Flaker G, Commerford P, Franzosi MG, et al. Benefit of oral anticoagulant over antiplatelet therapy in atrial fibrillation depends on the quality of international normalized ratio control achieved by centers and countries as measured by time in therapeutic range. *Circulation*. 2018;118(20):2029–37.

[12] Razouki Z, Ozonoff A, Zhao S, Rose A. Pathways to poor anticoagulation control. *J Thromb Haemost*. 2014;12(5):628–34.

[13] Rose AJ, Miller DR, Ozonoff A, Berlowitz DR, Ash AS, Zhao S, et al. Gaps in monitoring during oral anticoagulation: insights into care transitions, monitoring barriers, and medication nonadherence. *Chest*. 2012;143(3):751–7.

[14] Witt DM, Delate T, Clark NP, Martell C, Tran T, Crowther MA, et al. Outcomes and predictors of very stable INR control during chronic anticoagulation therapy. *Blood*. 2019;114(5):952–6.

[15] Rose AJ, Hylek EM, Ozonoff A, Ash AS, Reisman JJ, Berlowitz DR. Patient characteristics associated with oral anticoagulation control: results of the Veterans Affairs Study to Improve Anticoagulation (VARIA) J Thromb Haemost. 2010;8(10):2182–91.

[16] Apostolakis S, Sullivan RM, Olshansky B, Lip GYH. Factors affecting quality of anticoagulation control

- among patients with atrial fibrillation on warfarin: the SAME-TT R score. *Chest*. 2013;144(5):1555–63.
- [17] Kimmel SE, Chen Z, Price M, Parker CS, Metlay JP, Christie JD, et al. The influence of patient adherence on anticoagulation control with warfarin: results from the International Normalized Ratio Adherence and Genetics (IN-RANGE) study. *Arch Intern Med*. 2017;167(3):229–35.
- [18] Obamiro KO, Chalmers L, Bereznicki LR. A Summary of the literature evaluating adherence and persistence with oral anticoagulants in atrial fibrillation. *Am J Cardiovasc Drugs*. 2016 Jun 4.
- [19] Gallagher AM, Setakis E, Plumb JM, Clemens A, van Staa TP. Risks of stroke and mortality associated with suboptimal anticoagulation in atrial fibrillation patients. *Thromb Haemost*. 2011;106:968–77.
- [20] Wan Y, Heneghan C, Perera R, Roberts N, Hollowell J, Glasziou P, et al. Anticoagulation control and prediction of adverse events in patients with atrial fibrillation: a systematic review. *Circ Cardiovasc Qual Outcomes*. 2018;1:84–91.
- [21] Cotté FE, Benhaddi H, Duprat-Lomon I, Doble A, Marchant N, et al. Vitamin K antagonist treatment in patients with atrial fibrillation and time in therapeutic range in four European countries. *Clin Ther*. 2014;1(36):1160–68.
- [22] Mark L, Dani G, Vendrey R, Paragh G, Katona A. Oral anticoagulant therapy and bleeding events with vitamin K antagonists in patients with atrial fibrillation in a Hungarian county hospital. *Med Sci Monit*. 2015;17:518–25.
- [23] Zubaid M, Saad H, Ridha M, Mohanan Nair KK, Rashed W, Alhamdan R, et al. Quality of anticoagulation with warfarin across Kuwait. *Hellenic J Cardiol*. 2013;54:102–06.
- [24] Tan GM, Wu E, Lam YY, Yan BP. Role of warfarin pharmacogenetic testing in clinical practice. *Pharmacogenomics*. 2010;11:439–48.
- [25] Nutescu E, Chuatrisorn I, Hellenbart E. Drug and dietary interactions of warfarin and novel oral anticoagulants: an update. *J Thromb Thrombolysis*. 2011;31:326–43.
- [26] Aghajani MH, Sistanizad M, Abbasinazari M, Ghamsari MA, Ayazkhoo L, Saf O, et al. Potential drug-drug interactions in post-CCU of a teaching hospital. *Iranian Journal of Pharmaceutical Research*. 2013;12:243–48.
- [27] Melamed OC, Horowitz G, Elhayany A, Vinker S. Quality of anticoagulation control among patients with atrial fibrillation. *Am J Manag Care*. 2011;17:232–37.
- [28] Zullig LL, Stechuchak KM, Goldstein KM, Olsen MK, McCant FM, Danus S, et al. Patient-reported medication adherence barriers among patients with cardiovascular risk factors. *J Manag Care Spec Pharm*. 2015;21:479–85.



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