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Warfarin Treatment: Home Health Services Versus Outpatient Clinics

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ABSTRACT

Objective: Warfarin use is difficult due to the necessity for regular international normalized ratio (INR) monitoring and drug–drug interaction. However, it is still the most widely preferred oral anticoagulant. This study aimed to assess the efficacy and reliability of warfarin use by patients attending outpatient clinics (OC) or who received home health services (HHS).

Materials and Methods: This study included 204 patients followed by OC and HHS and receiving warfarin treatment. Demographic and clinical characteristics and INR monitoring frequency were evaluated. Moreover, complications were retrospectively questioned. The interactions between warfarin use and other medications were assessed. Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile INR, Elderly, Drugs/alcohol (HAS-BLED) and Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA) scores were calculated in the atrial fibrillation (AF) group.

Results: The patients followed by HHS were older (78 vs. 68, p<0.001). Cerebrovascular disease was more frequent in the HSS group (51% vs. 29.4%, p=0.002) while AF was more common in the OC group (65.7% vs. 43.1%, p=0.001). Patients with an INR level in the subtherapeutic range were more common in the HHS group (42.2% vs. 24.5%, p=0.025), and thromboembolic complications were also observed more frequently (14.7% versus 10.8%, p=0.013). More than half of the individuals using drugs interacted with warfarin. In AF subgroup, the HAS-BLED and ATRIA scores were higher for HHS group compared with the OC group [HAS-BLED, 2 (1–4) vs. 2 (0–5); ATRIA, 5 (1–7) vs. 2 (0–7); p=0.032 and p<0.001, respectively].

Conclusion: The current study showed that HHS and OC staff should regularly monitor patients' INR levels and pay attention to drug–drug interactions to reduce complications.

Keywords: Warfarin, outpatient clinic, home health services, atrial fibrillation

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INTRODUCTION

Warfarin is one of the most commonly used oral anticoagulants. Moreover, warfarin's anticoagulant activity is associated with its reduction of vitamin K-dependent coagulation factors II, VII, IX, and X.

Warfarin use has a narrow therapeutic index range which is difficult to adjust. It is affected by many factors, including drug–drug interaction and diet and genetic variations. However, warfarin is the only oral anticoagulant medication that can be used by valvular atrial fibrillation (AF) and prosthetic valve patients (1). Moreover, medication doses should be set by the international normalized ratio (INR) which calculates within the time therapeutic range (TTR) for safety and efficiency. The risk of thromboembolism or hemorrhage increases if the INR value is lower or higher than the therapeutic range. Furthermore, the risk of total mortality and major hemorrhage increases with irregular follow-up, insufficient numbers of INR monitoring, and TTR <70%. The multicenter WARFARIN-TR study observed that the percentage of the therapeutic range in Turkey was 49.52%±22.93% (2).

Home health services (HHS) include the provision of examination, testing, treatment, and rehabilitation services for bedridden patients or individuals who cannot access healthcare services due to a variety of chronic diseases. Moreover, HHS staff perform blood sampling for INR values and regulate warfarin dose (3). HHS doctors assess INR levels. As a different method, the use of devices monitoring INR at home is recommended as an alternative route for frequent monitoring and reliable anticoagulation. Studies have observed a reduction in thromboembolic events with no difference in major hemorrhages for patients who are on self-monitored and self-managed anticoagulation treatment (4). Thus, this study aimed to assess the efficacy and reliability of warfarin use by patients attending outpatient clinics (OC) or who received HHS.

MATERIALS and METHODS

This study included 204 patients attending OCs or HHS run by Taksim Education-Research Hospital for routine INR monitoring. Patients aged <18 years old, whose who could not communicate verbally, and with a known psy-

chiatric disease were excluded from the study. Patients' age, gender, comorbidities, indications for warfarin use, durations of use, warfarin doses, INR levels, and INR monitoring frequencies were evaluated. The indication for warfarin therapy was classified as AF primary prophylaxis, cerebrovascular disease (secondary prophylaxis of AF), deep-vein thrombosis, and pulmonary thromboembolism.

Anticoagulant therapy is optimized by providing specialized monitoring and management. Although regular INR monitoring may be different from patient to patient, INR should be measured daily until it is within the therapeutic range for at least two consecutive days when warfarin treatment is started. INR test monitoring can be extended for 2 weeks if the INR becomes stable. However, it needs to be extended for 4 or 6 weeks if it is still stable again.

Hemorrhage or thromboembolic complication history linked to warfarin was retrospectively questioned. Bleeding requiring hospitalization or an invasive procedure (gastrointestinal, retroperitoneal, cranial, intra-abdominal, and so on) was considered as major bleeding. Conversely, subconjunctival hemorrhage, hematuria, epistaxis, bleeding from mucous membranes, and ecchymosis were defined as minor bleeding (5). Transient ischemic attack, stroke, deep-vein thrombosis (DVT), and pulmonary thromboembolism (PTE) during warfarin therapy were evaluated as thromboembolic complications.

Drugs were evaluated for warfarin interaction. These included amiodarone, antibiotics (cephalosporin, fluoroquinolones, macrolides, penicillin, trimethoprim-sulfamethoxazole, and so on), statins, cimetidine, azole group antifungal drugs, proton pump inhibitors (PPI), nonsteroidal anti-inflammatory drugs (NSAIDs), and antidepressants (6).

When AF patients receiving warfarin treatment were analyzed separately, Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile INR, Elderly, Drugs/alcohol (HAS-BLED) (7) and the Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA) (8) scores were determined. The HAS-BLED hemorrhage score was calculated by giving 1 point for each of the following: hypertension (uncontrolled or systolic blood pressure ≥160 mmHg), abnormal liver function tests (aspartate aminotransferase; alanine aminotransferase; alkaline phosphatase, which was three times higher than normal values; or bilirubin values, which was two times higher than the normal or chronic liver disease), abnormal renal function tests (dialysis, renal transplantation, or creatinine >2.5 mg/dL), stroke, hemorrhage (anemia, bleeding history, or diathesis), labile INR (time in a therapeutic range <60%), age >65 years, and use of alcohol and medications (nonsteroidal anti-inflammatory drugs and antiplatelet medications). Those with a HAS-BLED score of ≥3 were assessed as high risk in terms of hemorrhage. The ATRIA hemorrhage risk score was assessed from 10 points: 3 points for anemia (hemoglobin <12 g/dL for women; <13 g/dL for men), 3 points for severe renal failure (glomerular filtration rate <30% mL/min or dialysis dependence), 2 points for ≥75 years, 1 point for previous hemorrhage history, and 1 point for hypertension. Patients with ATRIA score of ≥5 were determined to be high risk in terms of hemorrhage.

Ethical permission was approved by Taksim Education and Research Hospital Ethics Committee (number: 95, date: 29 November 2017).

Table 1. Demographic and clinical characteristics of patients

	Home health services (n=102)	Outpatient clinic (n=102)	p
Age	78 (18–95)	68 (22–97)	**0.001**
Gender (female)	75 (73.5%)	54 (52.9%)	**0.02**
AF	44 (43.1%%)	67 (65.7%)	**0.001**
CVD	52 (51%)	30 (29.4%)	**0.002**
DVT	3 (2.9%)	2 (2%)	0.651
PTE	3 (2.9%)	3 (2.9%)	1
HT	85 (83.2%)	70 (68.6%)	0.014
DM	28 (27.5%)	28 (27.5%)	1
CHF	45 (44.1%)	30 (29.4%)	**0.029**
Chronic kidney disease	6 (5.9%)	2 (2%)	0.149
Abnormal LFT	3 (2.9%)	3 (2.9%)	1

AF: Atrial fibrillation; CVD: Cerebrovascular disease; DVT: Deep vein thrombosis; PTE: Pulmonary thromboembolism; HT: Hypertension; DM: Diabetes mellitus; CHF: Congestive heart failure; LFT: Liver function tests

Statistical Analysis

Descriptive statistics were expressed as a mean±standard deviation for variables with normal distribution, as median (minimum–maximum) for variables with skew distribution, and as a percentage for categorical variables. In both groups, the t-test was used for normal distribution and the Mann–Whitney U-test was used for the skew distributed parameters. Results with $p<0.05$ were accepted as statistically significant. In addition, IBM SPSS 23 program was used for data analysis.

RESULTS

The study included 102 patients attending the OC and 102 accepting HHS. HHS controlled patients were older than the OC group [mean age, 78 (18–95) versus 68 (22–97) years; $p<0.001$]. The HHS group has a higher number of female patients [75 (73.5%) versus 54 (52.5%); $p=0.02$]. Warfarin indications for the HHS group were patients with cerebrovascular disease (CVD; 52, 51%), AF (44, 43.1%), DVT (3, 2.9%), and PTE occurrence 3 (2.9%). The indications in the OC group were patients with CVD (30, 29.4%), AF (67, 65.7%), PTE (3, 2.9%), and DVT occurrence (2, 2%). While CVD was more frequent ($p=0.002$) in the HHS group, AF was more commonly diagnosed in the OC group ($p=0.001$). Also, 11 (26.8%) and 18 (50%) patients had valvular and nonvalvular AF in the HHS group, respectively. Furthermore, 30 (73.2%) and 18 (50%) patients had valvular and nonvalvular AF in the OC group, respectively. Although 16 (53.3%) patients received warfarin due to prosthetic valve in the HHS group, only 14 (46.7%) patients received it in the OC group ($p=0.008$).

While hypertension was more common in the HHS group [85 (83.2%) versus 70 (68.6%) patients; $p=0.014$], congestive heart failure was more common in the OC group [45 (44.1%) versus 30 (29.4%) patients; $p=0.029$]. The two groups were similar in terms of diabetes mellitus, chronic kidney disease, and abnormal liver function tests (Table 1).

Of the patients in the HHS and OC groups, 91 (89.2%) and 80 (78.4%) had been receiving warfarin medication for more than 1 year (p=0.036), respectively. The median warfarin dose in HHS and OC patients was 3.5 mg/day (1.2–8 mg/day) and 5 mg/day (1.2–10 mg/day) in the OC patients (p<0.001). However, regular INR controls could not be performed for one (1%) and eight (7.8%) HHS and OC patients, respectively. The number of patients without INR monitoring was more frequent in outpatient follow-up (p=0.035).

INR monitoring frequency was examined wherein one (1%), 16 (15.8%), and 84 (83.2%) HHS patients was monitored every 2–3 days, every 2 weeks, and 84 once a month, respectively. In addition, eight (8.5%), nine (30.9%), 52 (55.3%), and five (5.3%) OC patients were monitored every 2–3 days, every 2 weeks, once a month, and every time, respectively. However, the number of HHS patients monitored once a month was statistically significant compared with the OC group (p<0.001).

In the HHS group, 43 (42.2%), 43 (42.2%), 16 (15.7%) patients had targeted therapeutic range of INR, decreased, and increased values, respectively. Moreover, 59 (57.8%) OC patients had a targeted therapeutic range of INR values. However, 25 (24.5%) and 18 (17.6%) patients had decreased and increased values, respectively. The number of patients with INR levels below the therapeutic range was higher in the HHS group (p=0.025). Table 2 summarizes the warfarin levels and INR monitoring frequency of patients.

During warfarin use, 31 (30.4%) and 41 (40.2%) HHS and OC patients had a bleeding history (p=0.143), respectively. Moreover, 13 (6.4%), two (1%), and 61 (29.9%) had bleeding in the gastrointestinal system, intracranial hemorrhage, and bleeding in other parts of their bodies, respectively. Five and one HHS patient had gastrointestinal and intracranial hemorrhage, respectively, whereas eight and one OC patients had gastrointestinal and intracranial hemorrhage, respectively.

Thromboembolic complications which were below the therapeutic interval due to anticoagulant treatment were seen in 15 (14.7%) and 11 (10.8%) HHS and OC patients (p=0.013), respectively. Moreover, thromboembolic complications were more frequent in the HHS group.

When the frequency of warfarin and incompatible medication use was assessed, 58 (56.9%) and 56 (54.9%) HHS and OC patients, respectively, appeared to be using incompatible medication (p=0.778). Among these, 84 (41.2%), 20 (9.8%), 14 (6.9%), 13 (6.4%), 5 (2.5%), and each one (0.5%) were using PPI, NSAID, statin, tricyclic antidepressants, antibiotics, and antifungals, cimetidine, and amiodarone, respectively.

Of the patients, 111 using warfarin treatment due to AF were assessed according to the HAS-BLED and ATRIA hemorrhage risk scores. The HAS-BLED and ATRIA hemorrhage scores were higher in HHS patients compared with the OC group [HAS-BLED: 2 (1–4) versus 2 (0–5) points, p=0.032; ATRIA: 5 (1–7) versus 2 (0–7) points, p<0.001]. In addition, 23 (52.3%) and seven (10.6%) high-risk patients had ATRIA hemorrhage scores ≥5 in the HHS and OC groups (p<0.001), respectively. For the HAS-BLED score, 16 (36.4%) and 17 (25.4%) high-risk patients had a score of ≥3 in the HHS and OC group, (p=0.215), respectively.

Table 2. Warfarin doses and INR monitoring frequency

	Home health services (n=102)	Outpatient clinic (n=102)	p
Warfarin dose (mg)	3.5 (1.2–8)	5 (1.2–10)	**0.001**
Treatment duration (>1 year)	91 (89.2%)	80 (78.4%)	**0.036**
No regular INR monitoring	1 (1%)	8 (7.8%)	**0.035**
INR monitoring frequency			**<0.001**
Every 2–3 days	1 (1%)	8 (8.5%)	
Every 2 weeks	16 (15.8%)	9 (30.9%)	
Once a month	84 (83.2%)	52 (55.3%)	
When attending the doctor	0 (0%)	5 (5.3%)	
INR value			**0.025**
Subtherapeutic INR values	43 (42.2%)	25 (24.5%)	
Therapeutic INR value	43 (42.2%)	59 (57.8%)	
Supratherapeutic INR value	16 (15.7%)	18 (17.6%)	

INR: International normalized ratio

DISCUSSION

This study assessed the efficacy and reliability of warfarin use by patients monitored by HHS and in OCs. Moreover, patients evaluated by HHS had more comorbidities with INR levels below the therapeutic range and had more frequent thromboembolic complications. Furthermore, more than 50% of patients monitored by HHS in the OC were determined to use medication that is incompatible with warfarin.

Warfarin is still the most commonly used anticoagulant medication despite its increased usage as a non-vitamin K antagonist oral anticoagulants (NOAC) for both stroke prevention in nonvalvular AF and venous thromboembolism treatment. Thus, performing frequent and regular INR monitoring is very important to avoid insufficient anticoagulation during warfarin use. Many patients are considered to have little information about warfarin monitoring due to the exchange of warfarin with NOAC treatment (9). In the current study, eight OC patients were evaluated and one HHS patient did not have regular INR monitoring. Furthermore, the National Institute for Health and Care Excellence guidelines recommend INR monitoring daily or every second day until INR levels are within the therapeutic range twice consecutively. After achieving this target, monitoring every 12 weeks is recommended if INR values remain stable after INR is measured twice a week for 1 or 2 weeks (10). In the current study, 83.2% and 55.3% of HHS and OC patients, respectively, had INR monitoring once a month. A study assessing 10,922 patients in New Zealand observed that the INR monitoring frequency varied according to TTR level. The INR test frequency was 13–14 days if patients had TTR of 20%–70%. However, this duration extended up to 23 days among those with a TTR of 90%–100% (11).

The results of the current study showed that 42.2% and 57.8% patients in the HHS and OC groups had INR values in the therapeutic range. Moreover, the AF in Turkey: Epidemiologic Registry study revealed that oral anticoagulant therapy was used by 40% of

all patients with 37% having effective INR (12). Furthermore, warfarin dose adjustment should be made in patients admitted to HHS to achieve effective INR value and patients should be evaluated for frequent INR monitoring.

Studies showed that patients with AF were more dependent on instrumental activities of daily living, falling more frequently, and frailty which was correlated with symptom severity score (13). The median age in the current study was >65 in both home healthcare services and OCs. Thus, evaluation and treatment of geriatric syndromes in home healthcare services can improve the quality of life of patients.

The rates were 30.4% and 40.2% for HHS and OC cases, respectively, when major and minor hemorrhage rates were examined in the current study. The rate for gastrointestinal and intracranial hemorrhage was 6.4% and 2%, respectively. The WARFARIN-TR study in Turkey identified the hemorrhage rate as 20.1% in 1 year. The same study identified the gastrointestinal and intracranial hemorrhage rates as 10% and 5.8%, respectively (14). A possible reason for lower hemorrhage complications in the current study was that the INR levels were below the therapeutic range, especially in HHS patients.

Guidelines recommend the calculation of hemorrhage risk with hemorrhage scores before beginning anticoagulant treatment for AF patients. Moreover, age is the most significant and unchangeable risk factor for both ischemic stroke and hemorrhage. Modifiable risk factors may be listed as hypertension, labile INR, medications (e.g., antiplatelet and NSAIDs), and alcohol use (15). The current study assessed two hemorrhage risk scores recommended in the guidelines for patients with AF. Moreover, the HHS group had higher hemorrhage risk scores compared with the OC group. The reason for this is that HHS patients are older and have a more frequent cerebrovascular disease and hypertension. The TREAT-AF study assessing 167,190 patients found increased stroke and hemorrhage risk with poor INR control despite similar INR monitoring (16). Thus, high hemorrhage risk should not be a reason to stop anticoagulant treatment and assessment, as a modifiable risk factor for every patient, is important (17).

A meta-analysis showed that thromboembolic events increased 3.5 times for INR <2 when compared with INR values from 2 to 3 (RR, 3.5; 95% CI, 2.8–4.4) (18). A study assessing 201 patients attending the emergency room indicated that thromboembolic complication rate was 2% and half of these patients had subtherapeutic INR levels (19). A nationwide cohort study in Denmark demonstrated that the thromboembolism risk was 4.6% and 2.6% in patients receiving warfarin for mitral stenosis 1 year after AF diagnosis and those using warfarin for aorta stenosis or new generation oral anticoagulants (20). In the current study, the INR levels were at subtherapeutic levels in HHS patients and thromboembolic complications were observed more frequently in this group.

In the current study, more than half of the patients used medications interacting with warfarin. PPI, nonsteroidal anti-inflammatory drugs, and statins were the most common interacting medications with warfarin.

The outcomes for drug–drug interaction between warfarin and PPI are controversial. Both warfarin and PPI are metabolized by cytochrome p450 2C19. Thus, the intake of these medications together is considered to increase INR and hemorrhage risk. A study assessing 4494 patients receiving warfarin treatment revealed that the patients taking PPIs had a significantly higher incidence of minor bleedings compared with patients who did not take PPIs (21). Additionally, studies show that the addition of PPI to warfarin treatment does not cause any changes to INR. According to a retrospective cohort study, co-treatment of warfarin with PPI was beneficial to reduce upper gastrointestinal system hemorrhage, especially in patients using warfarin with antiplatelets or NSAIDs. This benefit was not observed in the group with only warfarin treatment (22). According to Turkish Inappropriate Medication Use in the Elderly criteria, choosing an agent other than omeprazole is recommended if patients have indications for PPI use (23).

In clinical studies, elevated INR levels and hemorrhage were observed as a result of taking atorvastatin, fluvastatin, rosuvastatin, and simvastatin with warfarin (24). In the current study, nearly 7% of patients were using warfarin with statin treatment. Analgesic medications are frequently used with warfarin and increasing hemorrhage risk. A meta-analysis observed that the use of warfarin with paracetamol increased INR by 0.62 times (95% CI=0.46–0.78) compared with placebo. Considering polypharmacy and drug–drug interactions especially in older patients and stopping medications without indications are important (25).

This is the first study in Turkey to compare warfarin use monitored by HHS and in OCs. The limitation of this study is that it is a single-center and observational study. Additionally, patient complications were assessed retrospectively, AF stroke risk scores were not calculated, and drug–drug interactions did not assess unprescribed over-the-counter medications.

CONCLUSION

In the current study, patients in HHS were older, TTR was lower, and bleeding risk scores were higher. In addition, more than half of the patients on both HHS and OC were using drugs that could interact with warfarin.

In conclusion, focusing attention to drug–drug interactions and performing regular INR monitoring for patients is essential to keep the INR level within the therapeutic range in both HHS and OCs.

Ethics Committee Approval: The Gaziosmanpaşa Taksim Training nad Research Hospital Clinical Research Ethics Committee granted approval for this study (date: 29.11.2017, number: 95).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

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REFERENCES

1. Pirmohamed M. Warfarin: the end or the end of one size fits all therapy? J Pers Med 2018; 8(3): 22. [CrossRef]
2. Kılıç S, Çelik A, Çakmak HA, Afşin A, Tekkeşin Aİ, Açıksarı G, et al. The time in therapeutic range and bleeding complications of warfarin in different geographic regions of Turkey: A subgroup analysis of WARFARIN-TR study. Balkan Med J 2017; 34(4): 349–55. [CrossRef]
3. Çayır Y. Home health services in primary care: What can we do? Dicle Med J 2013; 40(2): 340–4. [CrossRef]
4. Heneghan CJ, Garcia-Alamino JM, Spencer EA, Ward AM, Perera R, Bankhead C, et al. Self-monitoring and self-management of oral anticoagulation. Cochrane Database Syst Rev 2016; 7(7): CD003839.
5. Ozturk M, Ipekci A, Kiyak SK, Akdeniz YS, Aydin Y, Ikizceli I, et al. Bleeding complications in Warfarin-Treated patients admitted to the emergency department. J Clin Med Res 2019; 11(2): 106–13. [CrossRef]
6. Vazquez SR. Drug-drug interactions in an era of multiple anticoagulants: a focus on clinically relevant drug interactions. Hematology Am Soc Hematol Educ Program 2018; 2018(1): 339–47. [CrossRef]
7. Pisters R, Lane DA, Nieuwlaat R, de Vos CB, Crijns HJ, Lip GY. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. Chest 2010; 138(5): 1093–100. [CrossRef]
8. Fang MC, Go AS, Chang Y, Borowsky LH, Pomernacki NK, Udaltsova N, et al. A new risk scheme to predict warfarin-associated hemorrhage: The ATRIA (Anticoagulation and Risk Factors in Atrial Fibrillation) Study. J Am Coll Cardiol 2011; 58(4): 395–401. [CrossRef]
9. Teruel RS, Thue G, Fylkesnes SI, Sandberg S, Kristoffersen AH. Warfarin monitoring in nursing homes assessed by case histories. Do recommendations and electronic alerts affect judgements? Scand J Prim Health Care 2017; 35(3): 299–306. [CrossRef]
10. National Institute for Health and Care Excellence (NICE). Atrial fibrillation and heart valve disease: self-monitoring coagulation status using pointof-care coagulometers (the CoaguChek XS system and the INRatio2 PT/INR monitor). Available from: URL: https://www.nice.org.uk/guidance/dg14/resources/atrial-fibrillation-and-heart-valve-disease-selfmonitoring-coagulation-status-using-pointofcare-coagulometers-the-coaguchek-xs-system-pdf-1053629789893. Accessed, 19 December, 2017.
11. McAuliffe GN, De Silva F, Upton A, Chan G. International normalised ratio monitoring in the community populations of the Auckland and Northland regions of New Zealand: time in therapeutic range and frequency of testing. Intern Med J 2018; 48(12): 1487–91. [CrossRef]
12. Ertas F, Eren NK, Kaya H, Aribas A, Acar G, Kanadasi M, et al; AFTER Investigators. The atrial fibrillation in Turkey: Epidemiologic Registry (AFTER). Cardiol J 2013; 20(4): 447–52. [CrossRef]
13. Koca M, Yavuz BB, Tuna Doğrul R, Çalışkan H, Şengül Ayçiçek G, Özsürekçi C, et al. Impact of atrial fibrillation on frailty and functionality in older adults. Ir J Med Sci 2020; 189(3): 917–24. [CrossRef]
14. Çelik A, İzci S, Kobat MA, Ateş AH, Çakmak A, Çakıllı Y, et al; WARFARIN-TR Study Collaborates. The awareness, efficacy, safety, and time in therapeutic range of warfarin in the Turkish population: WARFARIN-TR. Anatol J Cardiol 2016; 16(8): 595–600. [CrossRef]
15. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, et al; ESC Scientific Document Group. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Eur Heart J 2016; 37(38): 2893–962. [CrossRef]
16. Hellyer JA, Azarbal F, Than CT, Fan J, Schmitt SK, Yang F, et al. Impact of baseline stroke risk and bleeding risk on warfarin international normalized ratio control in atrial fibrillation (from the treat-af study). Am J Cardiol 2017; 119(2): 268–74. [CrossRef]
17. Shoeb M, Fang MC. Assessing bleeding risk in patients taking anticoagulants. J Thromb Thrombolysis 2013; 35(3): 312–9. [CrossRef]
18. Oake N, Jennings A, Forster AJ, Fergusson D, Doucette S, van Walraven C. Anticoagulation intensity and outcomes among patients prescribed oral anticoagulant therapy: a systematic review and meta-analysis. CMAJ 2008; 179(3): 235–44. [CrossRef]
19. Anthony CJ, Karim S, Ackroyd-Stolarz S, Fry A, Murphy NG, Christie R, et al. Intensity of anticoagulation with warfarin and risk of adverse events in patients presenting to the emergency department. Ann Pharmacother 2011; 45(7-8): 881–7. [CrossRef]
20. Melgaard L, Overvad TF, Jensen M, Lip GYH, Larsen TB, Nielsen PB. Thromboembolism and bleeding complications in anticoagulated patients with atrial fibrillation and native aortic or mitral valvular heart disease: a descriptive nationwide cohort study. Eur Heart J Cardiovasc Pharmacother 2021; 7(FI1): f101–10. [CrossRef]
21. Bertram V, Yeo K, Anoopkumar-Dukie S, Bernaitis N. Proton pump inhibitors co-prescribed with warfarin reduce warfarin control as measured by time in therapeutic range. Int J Clin Pract 2019; 73(11): e13382. [CrossRef]
22. Ray WA, Chung CP, Murray KT, Smalley WE, Daugherty JR, Dupont WD, et al. Association of proton pump inhibitors with reduced risk of warfarin-related serious upper gastrointestinal bleeding. Gastroenterology 2016; 151(6): 1105–12.e10. [CrossRef]
23. Bahat G, Ilhan B, Erdogan T, Halil M, Savas S, Ulger Z, et al. Turkish inappropriate medication use in the elderly (TIME) criteria to improve prescribing in older adults: TIME-to-STOP/TIME-to-START. Eur Geriatr Med 2020; 11(3): 491–8. [CrossRef]
24. Shaik AN, Bohnert T, Williams DA, Gan LL, LeDuc BW. Mechanism of drug-drug interactions between warfarin and statins. J Pharm Sci 2016; 105(6): 1976–86. [CrossRef]
25. Merel SE, Paauw DS. Common drug side effects and drug-drug interactions in elderly adults in primary care. J Am Geriatr Soc 2017; 65(7): 1578–85. [CrossRef]