Comparison of Warfarin use in terms of efficacy and safety in two different polyclinics

Salih Kılıç, Hatice Soner Kemal[1], Elif İlkay Yüce[2], Evrim Şimşek[2], Burcu Yağmur[2], Nuray Memişoğlu Akgül[2], Cahide Soydaş Çınar[2], Mehdi Zoghi[2], Cemil Gürgün[2]

Department of Cardiology, Nizip State Hospital, Gaziantep-*Turkey*
[1]Department of Cardiology, Near East University Hospital, Nicosia-*Cyprus*
[2]Department of Cardiology, Faculty of Medicine, Ege University, İzmir-*Turkey*

Abstract

Objective: This study compared the efficacy and safety of warfarin in specialized international normalized ratio (INR) outpatient clinic (INR-C) and in general cardiology outpatient clinic (General-C).

Methods: Herein, 381 consecutive patients with a regular follow-up at INR-C (n=233) or General-C (n=148) for at least 1 year were retrospectively included. While INR-C patients were followed by a single experienced trained nurse, General-C patients were followed by a different cardiologist who worked in a rotational principle every month. During controls, demographic characteristics, INR levels, bleeding events, ischemic stroke, and transient ischemic attacks in the last 1 year were recorded. Primary endpoint was defined as the evaluation of the combined major bleeding and ischemic event, and secondary endpoint was defined as the evaluation of them separately.

Results: The mean age of the patients was 62±12.86 and 43.8% were male. Mean time in therapeutic range (TTR) level was statistically higher in INR-C than that in General-C (68.8%±15.88 and 51.6%±23.04, respectively; p<0.001). Primary outcomes were significantly higher in General-C than that in INR-C [13.5% (20) and 6.4% (15); respectively, p=0.020]. Overall, major bleeding was observed in 25 patients (6.5%) and (2.6%) ischemic event was observed in 10 patients. In General-C patients, both major bleeding (8.8% vs. 5.2%; p=0.163) and the ischemic event (4.7% vs. 1.3%; p=0.051) were more, and no statistically significant differences were detected between the two clinics.

Conclusion: The findings of our study demonstrate that patients followed in INR-C had higher TTR levels and lower bleeding and ischemic events rates that those followed in General-C. *(Anatol J Cardiol 2017; 18: 328-33)*

Keywords: warfarin, specific INR clinic, time in therapeutic range (TTR)

Introduction

Warfarin is one of the most commonly used effective oral anticoagulant in the prevention of thromboembolic events, particularly in atrial fibrillation (AF) and in patients with prosthetic valves. Compared to placebo, it reduces stroke rate by 64% in AF patients (1, 2). However, the efficacy and safety of warfarin is associated with the time elapsed in therapeutic range (time in therapeutic range, TTR) (3-6). A TTR lower than 70% is associated with an increased risk in all-cause morbidity and mortality (3, 5, 6). Approximately 60% of the patients in randomized clinical trials (RCT) have optimal TTR percentages; whereas in most observational studies and registries, only 50% of patients reach this value (7-9). Clinical follow-up is important in achieving the optimal TTR. Previous studies show that the best results were obtained with self-follow-up of patients; the results of specialized outpatient clinics were similar to randomized trials. In addition, studies in Turkey showed that TTR was far from optimal levels (9-12).

In the present study, the efficacy and safety of warfarin was compared in specialized international normalized ratio (INR) outpatient clinic (INR-C) and in general cardiology outpatient clinic (General-C). INR-C patients were followed by an experienced and trained nurse; and General-C patients were followed by a different cardiologist in our tertiary center.

Methods

We evaluated the INR data of the patients followed in INR-C and General-C in our tertiary center from January 2014 to January 2015. The study was designed retrospectively and complied with the principles of the Declaration of Helsinki, and the local Ethics Committee approved the study protocol.

In our clinic, all the patients start administering warfarin after a standard training by physicians regarding its use. This training includes how to use warfarin, how often to have INR

Address for correspondence: Dr. Salih Kılıç, Nizip Devlet Hastanesi, Gaziantep-*Türkiye*
E-mail: kilicsalihhh@gmail.com
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Table 1. Basal characteristics of patients

Parameters	INR-C (n=233)	General-C (n=148)	*P*
Age, years, mean±SD	62±13.2	62±12.3	0.864¥
Sex, male, n, (%)	106 (45.5)	61 (41.6)	0.412
Warfarin use years, median (25^{th}-75^{th} percentiles)	6.5 (2.5-13)	3.5 (2.5-8.5)	<0.001 ¶
Life style, living alone, n, (%)	23 (9.9)	17 (11.5)	0.616
Heart failure, n, (%)	120 (51.7)	80 (54.1)	0.657
Hypertension, n, (%)	130 (56.3)	87 (58.8)	0.630
Diabetes mellitus, n, (%)	57 (24.6)	44 (29.7)	0.267
Vascular disease, n, (%)	50 (21.6)	36 (24.3)	0.529
Smoking, n, (%)	35 (15.1)	17 (11.5)	0.319
Alcohol consumption, n, (%)	4 (1.7)	3 (2.0)	0.830
Use of NSAID, n, (%)	14 (6.0)	25 (16.9)	0.001
Abnormal liver function, n, (%)	11 (4.7)	4 (2.7)	0.320
Labil INR, n, (%)	66 (28.4)	81 (54.7)	<0.001
History of bleeding, n, (%)	42 (18.1)	25 (16.9)	0.762
Anti-platelet use, n, (%)	65 (27.9)	39 (26.4)	0.741
Chronic kidney disease, n, (%)	18 (7.8)	4 (2.7)	0.040
eGFR	80.9±25	81.7±26	0.765
Reason of warfarin use			0.006
Atrial fibrillation, n, (%)	137 (59.1)	63 (42.6)	
Prosthetic valve, n, (%)	65 (28.0)	62 (41.9)	
Other reasons, n, (%)	30 (12.9)	23 (15.5)	
Education			0.388
İlliterate, n, (%)	22 (9.4)	17 (11.5)	
Complete primary school, n, (%)	119 (51.1)	78 (52.7)	
Complete high school, n, (%)	54(23.1)	39 (26.3)	
Complete university, n, (%)	38 (16.3)	14 (9.5)	

Data are presented as the means±standard deviations or median (25^{th}-75^{th} percentiles). or as numbers and percentages. ¥Student's t-test was performed. ¶Mann-Whitney U test was performed. Chi-square test was performed for other parameters. eGFR-estimated glomerular filtration rate, General-C-general cardiology outpatient clinic, INR-C-specific INR outpatient clinic, NSAID-non steroidal anti-inflammatory drugs, SD-standard deviation.

checked, food-drug interactions, and possible side effects. The INR follow-up is performed in INR-C and General-C in our clinic. All patients are informed about INR-C. Patients may have follow-ups in a polyclinic of their choice. The follow-ups are maintained by a nurse who is trained on the effects, follow-up principles, complications, and food-drug interactions of INR-C warfarin and who is working in the same polyclinic for nearly 5 years. The nurse knows the target INR range defined by the doctor and may increase or decrease the dosage according to the INR value checked. INR is checked at least once a month for each patient. When necessary, more frequent INR checks may be conducted according to the results of the INR-C and General-C patients. Each patient who is followed-up in INR-C receives an individualized chart including daily warfarin dose to be used and the next appointment date. The patients are given a list of foods that interact with warfarin. When INR is below the target value, the patient and nurse review the possible reasons for this situation (for example, new medication use and unsuitable diet). Each time a patient does not attend the scheduled appointment, they receive a telephone call from the nurse as a reminder.

A random cardiologist in the General-C follows the patients and gives training for the use of medication. The cardiologist works in a rotation principle in General-C. During the controls, INR dose is adjusted and a follow-up appointment is arranged. All consecutive patients who were followed-up in INR-C or General-C for at least 1 year were included in the present study. Because there could be exchange between clinics, only the patients followed in a single clinic for at least 1 year were included in the study. In addition, the inclusion criteria required that all INR controls took place in our institution in the last 1 year.

The demographical and clinical backgrounds of the patients were recorded during face-to-face INR checks on the case forms by the authors of the present study. All the INR values of the patients between the date they were included in the study and their first admission dates for follow-ups were recorded in the case forms in the digital recording system of the hospital, and the TTR values were computed. Major and minor bleeding events and ischemic strokes within the last 1 year were recorded on the basis of the declarations of the patients.

CHA2DS2-VASc [congestive heart failure, hypertension, age >75 (doubled), diabetes, stroke (doubled), vascular disease, age 65–74 years, and sex (female)] and HAS-BLED [hypertension, abnormal liver/kidney function (1 point each), stroke, bleeding history, labile INR, age >65 years, and drugs/alcohol (1 point each)] scores were measured at the time of the interview (13). Therapeutic INR for mechanic aortic valve, AF, and other reason was accepted as 2–3 and for mechanic mitral valve and/or mechanical heart valves in both the aortic and mitral position as 2.5–3.5. TTR was calculated according to F. R. Roosendaal's algorithm with linear interpolation (14).

Ischemic stroke was defined as neurologist-confirmed symptomatic ischemic cerebral infarction with an apparent brain lesion on imaging studies. Transient ischemic attack was defined as a neurologist-confirmed transient episode of neurologic dysfunction without a brain lesion on imaging studies. BARC (bleeding academic research consortium) 3 and above was assessed as major bleeding (15). All other bleeding events were classified as minor bleedings. Primary endpoint was defined as the evaluation of major bleeding and ischemic event, and secondary endpoint was defined as the evaluation of them separately.

Statistical analysis

Continuous variables were presented as mean±standard deviation (mean±SD) or median (25%–75% percentiles), and the categorical variables were expressed as number and percentage

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Table 2. Efficacy and safety of warfarin in INR-C and General-C

Parameters	INR-C (n=233)	General-C (n=148)	*P*
TTR, mean±SD	68.8±15.88	51.6±23.04	<0.001¥
CHA2DS2-VASc score, (n=200)			
median (25th-75th percentiles)	4.0 (2.0-5.0)	3.0 (2.0-5.0)	0.762¶
HAS-BLED score,			
median (25th-75th percentiles)	2.0 (1.0-3.0)	2.0 (1.0-3.0)	0.981¶
Number of INR performed	13.8±2.89	14.6±4.63	0.076¥
in a year, mean±SD			
Primary outcomes, n, (%)			
(Ischemic events and	15 (6.4)	20 (13.5)	0.020*
major bleeding)			
Ischemic events, n, (%)	3 (1.3)	7 (4.7)	0.051ø
All bleeding events, n, (%)	56 (24)	37 (25)	0.831*
Major bleeding, n, (%)	12 (5.2)	13 (8.8)	0.163*

Data are presented as the means±standard deviations or median (25th-75th percentiles). or as numbers and percentages. ¥Student's t-test, *Chi-square test, øFisher's Exact test and ¶Mann-Whitney U test was performed. General-C-general cardiology outpatient clinic, INR-C- specific INR outpatient clinic, SD-standard deviation, TTR- time in therapeutic range,

(%). The continuous variables were compared across the groups using the Student's t-test or the Mann–Whitney U test. Normality of the data distribution was verified by the Kolmogorov–Smirnov test. Homogeneity of variance was assessed by the Levene's test. The categorical variables were compared using the chi-square or Fisher's exact test. *P* value <0.05 was considered to be statistically significant. Logistic regression analysis was performed to determine the independent correlates of the major event (major bleeding and ischemic event). A stepwise model with backward selection method was performed. The results were tabulated as odds ratio (OR) and 95% confidence intervals (CI). All the data were analyzed with SPSS (SPSS Inc., Chicago, IL, USA) software for Windows Version 20.0.

Results

Demographic characteristics

Overall, 381 (43.8%, n=167 male) patients were included in the study. The mean age of the patients was 62±12.86 years. The median warfarin use period was 4.5 (2.5–8.5) years and the usage time was longer in INR-C than that in General-C [6.5 (2.5–13.0) vs. 3.5 (2.5–8.5); respectively, p<0.001]. Majority of the patients in INR-C were on warfarin because of AF (59.1%). However, 42.6% of the patients in General-C were on warfarin for the same reason; it was statistically different between the groups (p=0.006). The basal characteristics of the patients are summarized in Table 1. There was no difference between the two groups regarding sex, education level, concomitant antiplatelet use, age, and lifestyle. While history of chronic kidney disease was higher in INR-C patients, labile INR and use of NSAID were significantly higher in General-C patients.

Table 3. Comparison of patients with and without major event

Parameters	Major Event (n=35)	Non-Major Event (n=346)	*P*
Age, years, mean±SD	62.3±13.2	62.3±8.8	0.965¥
INR-C, n, (%)	15 (6.4)	218 (93.6)	0.020
General-C, n, (%)	20 (13.5)	128 (86.5)	
Male, n, (%)	21 (60)	146 (42.2)	0.043
TTR, mean±SD	53.5±23.41	63.1±20.27	0.009¥
Number of INR	15.4±4.42	14±3.57	0.086¥
performed in a year			
HAS-BLED score,			
median (25th-75th percentiles)	3.0 (2.0-4.0)	2.0 (1.0-3.0)	<0.001¶
Warfarin use years,			
median (25th-75th percentiles)	4.5 (2.5-13.5)	4.5 (2.5-8.5)	0.940¶
Life style, living alone, n, (%)	2 (5.7)	38 (11.0)	0.560ø
Heart failure, n, (%)	14 (40)	186 (53.9)	0.116
Hypertension, n, (%)	26 (74.3)	191 (55.5)	0.033
Diabetes mellitus, n, (%)	8 (22.9)	92 (27)	0.601
Vascular disease, n, (%)	8(22.9)	78 (22.6)	0.973
Chronic kidney disease, n, (%)	5 (14.3)	17 (4.9)	0.041ø
Smoking, n, (%)	9 (25.7)	43 (12.5)	0.039ø
Alcohol consumption, n, (%)	2 (5.7)	5 (1.4)	0.129ø
History of bleeding, n, (%)	29 (82.9)	64 (18.5)	<0.001
Labil INR, n, (%)	21 (60)	126 (36.5)	0.007
Antiplatelet use, n, (%)	8 (22.9)	96 (27.7)	0.536
Use of NSAID, n, (%)	5 (14.3)	34 (9.9)	0.384ø

Data are presented as the means±standard deviations or median (25th-75th percentiles). or as numbers and percentages. ¥Student's t-test was performed.¶Mann-Whitney U test was performed. øFisher's exact test was performed. Chi-square test was performed for other parameters. General-C-general cardiology outpatient clinic, INR-international normalized ratio, INR-C- specific INR outpatient clinic, SD-standard deviation, TTR-time in therapeutic range,

Risk scores

CHA2DS2-VASc scores were measured for patients with Non-valvular atrial fibrillation (NVAF) (n=200). The median CHA2DS2-VASc scores score was 3.0 (2.0–5.0), and there was no significant difference between two clinics [INR-C 4.0 (2.0–5.0) and General-C 3.0 (2.0–5.0); p=0.762]. HAS-BLED scores were also measured to compare the groups for bleeding risks. Median HAS-BLED score was 2.0 (1.0–3.0), and there was no significant difference between two clinics [INR-C 2.0 (1.0–3.0) and General-C 2.0 (1.0–3.0); p=0.981] (Table 2).

INR and time in therapeutic range

Mean TTR level of all study groups was 62.1%±20.73, and the

Table 4. Characteristic of patients with major bleeding event

Parameters	Bleeding (n=25)	Non- bleeding (n=356)	P
Age, years, mean±SD	62.6±8.76	62.2±13.11	0.906¥
Male, n, (%)	15 (60)	152 (42.7)	0.092
TTR, mean±SD	56.2±22.92	62.5±20.54	0.142¥
HAS-BLED score, median (25^{th}-75^{th} percentiles)	3.0 (2.0-4.0)	2.0 (1.0-3.0)	<0.001¶
Warfarin use <3 years, n, (%)	12 (48)	122 (34.3)	0.165
Life style, living alone, n, (%)	2 (8.0)	38 (10.7)	0.673
Heart failure, n, (%)	10 (40)	190 (53.5)	0.191
Hypertension, n, (%)	19 (76)	198 (55.9)	0.050
Diabetes mellitus, n, (%)	4 (16)	97 (27.3)	0.215
Vascular disease, n, (%)	5 (20)	81 (22.8)	0.745
Chronic kidney disease, n, (%)	4 (16)	18 (5.1)	0.024
Smoking, n, (%)	4 (16)	48 (13.5)	0.727
Alcohol consumption, n, (%)	2 (8.0)	5 (1.4)	0.018
History of bleeding, n, (%)	20 (80)	47 (13.2)	<0.001
Labil INR, n, (%)	15 (60)	132 (37.2)	0.024
Antiplatelet use, n, (%)	4 (16)	100 (28.1)	0.191
Use of NSAID, n, (%)	3 (12)	36 (10.1)	0.767

Data are presented as the means±standard deviations or median (25^{th}-75^{th} percentiles).or as numbers and percentages. ¥Student's t-test was performed.¶Mann-Whitney U test was performed. Chi-square test was performed for other parameters. INR-international normalized ratio, TTR-time in therapeutic range.

Table 5. Characteristic of patients with ischemic event

Parameters	Ischemic qevent (n=10)	Non-ischemic event (n=371)	P
Age, years, mean±SD	61.8±9.48	62.3±12.95	0.870¥
Male, n, (%)	6 (60)	161 (43.4)	0.296¥
TTR, mean±SD	46.5±24.47	62.5±20.50	0.016
HAS-BLED score, median (25^{th}-75^{th} percentiles)	3.0 (2.0-4.0)	2.0 (1.0-3.0)	0.173
Warfarin use years, median (25^{th}-75^{th} percentiles)	4.0 (2.5-8.5)	4.5 (2.5-8.5)	0.844¶
Life style, living alone, n, (%)	0 (0)	40 (10.8)	0.272
Heart failure, n, (%)	4 (40)	196 (53)	0.418
Hypertension, n, (%)	7 (70)	210 (56.9)	0.409
Diabetes mellitus, n, (%)	4 (40)	97 (26.2)	0.330
Vascular disease, n, (%)	7 (70)	287 (77.6)	0.573
Chronic kidney disease, n, (%)	1 (10)	21 (5.7)	0.563
Smoking, n, (%)	5 (50)	47 (12.7)	0.001
Alcohol consumption, n, (%)	0 (0)	7 (1.9)	0.661
History of bleeding, n, (%)	3 (30)	64 (17.3)	0.298
Labil INR, n, (%)	6 (60)	141 (38.1)	0.161
Antiplatelet use, n, (%)	4 (40)	100 (27)	0.361
Use of NSAID, n, (%)	2 (20)	37 (10)	0.304

Data are presented as the means±standard deviations or median (25th-75th percentiles) or as numbers and percentages. ¥Student's t-test was performed. ¶Mann-Whitney U test was performed. Fisher's exact test was performed for other parameters. INR-international normalized ratio, NSAID-non steroidal anti-inflammatory drugs, SD-standard deviation, TTR-time in therapeutic range.

patients in INR-C groups had significantly better TTR levels than those in General-C group (68.8%±15.88 and 51.6%±23.04, respectively; p<0.001) (Table 2). The number of INR tests performed in 1 year was 14.1±3.67, and there was no difference between the two groups (INR-C, 13.8±2.89 and General-C, 14.6±4.63; p=0.076).

Safety of warfarin

Primary outcomes (major bleeding and ischemic events) were significantly higher in General-C than in INR-C [13.5% (20) and 6.4% (15); respectively, p=0.020]. Patients with major events had lower TTR levels than those without major events (53.5%±23.41 and 63.1%±20.27; respectively, p=0.009). In addition, hypertension, chronic kidney disease, smoking, history of bleeding, and labile INR rates were higher in patients with major events (Table 3). To find the independent predictors of the major events, the multiple logistic regression analysis was performed. History of bleeding (OR, 14.620; 95% CI, 6.614-22.316; p<0.001) and follow-up in General-C (OR, 2.855; 95% CI, 1.296-6.287; p=0.009) were found as independent predictors of the primary outcomes.

The secondary outcome was different between groups for major bleeding and ischemic event rates separately. The characteristic of patients with major bleeding and ischemic events are demonstrated in Table 4 and Table 5, respectively. During the study period, 24.4% (n=93) of the patients had a bleeding complication. The 26.9% of bleedings (n=25) were major bleedings, and there was no statistically significant difference between the two clinics for overall bleeding events and major bleeding events [INR-C 5.2% (n=12) and General-C 8.8% (n=13); p=0.163] (Table 2). In addition, 2.6% of the patients (n=10) had ischemic events (3 ischemic strokes and 7 transient ischemic attacks). Ischemic events were higher in patients followed in General-C but did not reach a statistically significant level [4.7% (n=7) vs. 1.3% (n=3); p=0.051] (Table 2). Three patients who were followed in INR-C died because of non-cardiac reasons.

Discussion

Mean TTR levels of the patients followed in INR-C were significantly higher than those in the patients followed in General-C. In addition, the rates of combined major bleeding and ischemic events were lower in INR-C than that in General-C. These

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results show the importance of following the warfarin patients in a specialized single clinic with an experienced staff.

Despite the growing use of new-generation oral anticoagulants, warfarin is still the only choice in mechanical prosthetic valve and valvular AF. Although the incidence of rheumatic heart disease is decreasing, valvular AF is still a serious problem in many developing countries like Turkey (16). Furthermore, many studies in Turkey have shown that the TTR level is far from the desirable levels in patients using warfarin (10-12). In their study with 572 patients who were using warfarin for AF and were followed for 22 months in average, Türk et al. (11) reported that the mean TTR level was 42.3%±18. Ertaş et al. (10) conducted a study that included 2242 patients with at least one AF episode and reported that only 41.3% of all patients had effective INR level. Similarly, in their study that included 4987 patients with all-cause warfarin use, Çelik et al.(12) showed that the mean TTR level was 49.5%±22.9 in Turkey (12). INR monitoring can be conducted in hospitals, general outpatient clinics, and specialized INR outpatient clinics and also by self-monitoring. The highest TTR is reached with self-monitoring (17-19). However, the most significant limitation is the patient's compatibility, the ability of device use, and the consciousness to set the required drug dose (19, 20). RCTs have shown that significantly higher TTR level is reached with INR-C rather than with General-C and general practitioner follow-up (21, 22). There are a few advantages of INR-C, for example, closer follow-up of patients by a single physician or nurse results in closer monitoring of the disease status and reduces the number of missed appointments, and frequent reminding of food and drug interaction results in better TTR (21, 22). Patient compliance, regular follow-up, training and awareness, education level, etc. play roles in reaching the effective TTR levels. It has been demonstrated that the educational level of patients play roles in the efficacy and safety of warfarin (23-26). In the present study, nearly half of the patients were primary school-graduates, and no significant differences were detected between the groups. This shows that the results are better in patients with INR-C despite low educational levels, which also shows the importance of these clinics.

In our study, the TTR level of the General-C follow-up patients were similar to other studies conducted in Turkey, whereas the TTR level of INR-C conducted by trained nurse were at targeted levels (10-12). This result is important for our country where TTR average is lower. Many factors may have affected this result. In our study, longer monitorization of the patients with INR-C, their being followed by the same nurse, reminding missed appointments through phone, repeating the warfarin trainings when needed, and their spending more time in the clinic when compared with the General-C patients may have caused high average TTR values and less major events.

The safety and efficacy of warfarin therapy depends critically on maintaining the INR within the therapeutic range (27-30). Many studies found that a vast number of thromboembolic and bleeding events occurred when the INR was outside the therapeutic range. The risk of bleeding increases when the INR is higher than the upper limit of the therapeutic range, and the risk of thromboembolism increases when the INR falls below the lower limit of the therapeutic range (30, 31). In the present study, we found that mean TTR level of the patients with major events (major bleeding and ischemic events) was lower than that in the patients without major events. In addition, we showed that follow-up clinic is an independent predictor of major events.

Study limitations

First, ours is a single-center study and we only assessed the INR data in previous 1 year. Second, the patients may not remember the exact events they experienced in the past year, in which case, the patients may have provided incomplete or incorrect information.

Conclusion

To the best of our knowledge, this is the first study in Turkey to compare the follow-up of patients in INR-C and in General-C. Patients followed at INR-C had higher TTR levels and lower bleeding and ischemic events rates. By increasing the number of INR-C in Turkey, a better quality of INR follow-up could be achieved resulting in less morbidity.

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