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

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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=0.061) 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 than 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
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, food-drug interactions, and possible side effects. 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.
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.

#### 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 (2.5–13.5) 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
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, 21.057; 95% CI, 12.413-35.366; p<0.001) were found as independent predictors of the major events.

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

| 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 (25th-75th 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) | 0.181 |
| History of bleeding, n, (%) | 20 (80) | 47 (13.2) | <0.001 |
| Labil INR, n, (%) | 15 (60) | 132 (37.2) | 0.024 |
| Unplatelet 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 (25th-75th 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 event (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 (25th-75th percentiles) | 3.0 (2.0-4.0) | 2.0 (1.0-3.0) | 0.173 |
| Warfarin use years, median (25th-75th 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 |
| Unplatelet 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.
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 anticoagu-
lants, 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 fol-
lowed for 22 months in average, Türk et al. (11) reported that
the mean TTR level was 42.3±18. Erttaş 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 con-
ducted 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 phy-
sician 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 aware-
ness, 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 monitoization of the patients with INR-C, their
being followed by the same nurse, reminding missed appoint-
ments through phone, repeating the warfarin trainings when
needed, and their spending more time in the clinic when com-
pared with the General-C patients may have caused high average
TTR values and less major events.

The safety and efficacy of warfarin therapy depends criti-
cally 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 fol-
low-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 re-
member the exact events they experienced in the past year, in
which case, the patients may have provided incomplete or incor-
correct 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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