Comparison between Self-monitoring and Self-management and Standard Monitoring of Oral Anticoagulation

Objective: The safety and effectiveness of warfarin therapy is associated with the quality of anticoagulation control, which is often assessed by using the percentage time in therapeutic range (TTR). This study aimed to evaluate the variation in INR and TTR between individual and center-based measurements and to observe how this variation affects the effectiveness of oral anticoagulant therapy.

Materials and Methods: A total of 237 patients were selected in the current study. Patients were divided into two groups: The routine care group consisted of 179 subjects (75 men, with a median of 61 years), and the self-management group included of 58 age and sex-matched individuals (26 men, with a median of 64 years).

Results: The patients in self-management group had significantly higher levels of TTR (77 (63, 89) % vs. 46 (15, 75)), but the time below range (%) and the time above range (%)) were significantly lower than routine-care group (9 (0, 23) vs. 29 (15, 49), P=0.001, 12 (0, 23) vs. 20 (8, 44), P=0.006, respectively). Heart failure (HF) (3.281, %95 CI 1.561 -6.897, P=0.002), renal dysfunction (3.754, 95% CI 1.224-11.519, P=0.021), younger age (<65 years) (2.786, P=0.004), CHA2DS2-VASc (1.339, P=0.010), and routine-care management (8.113, P<0.001) were the independent predictors of having lower TTR.

Conclusion: Self-management strategy has good outcomes in terms of prevention of major thromboembolic and bleeding complications. The home testing devices may provide better management of being safe for long-term oral anticoagulation.

Key words: Warfarin, time in therapeutic range, anticoagulation

Introduction

Vitamin K antagonists (VKAs) have been used more than 60 years for the primary and secondary prevention of venous thromboembolism, for the prevention of systemic embolism in patients with prosthetic heart valves or atrial fibrillation. Moreover, their effectiveness has also been shown as an adjunct therapy in the prophylaxis of systemic embolism after myocardial infarction, and for reducing the risk of recurrent myocardial infarction. On the other hand, warfarin therapy has some consequences about narrow therapeutic range, drug and food interactions, and the need for continuous patient education and the routine international normalized ratio (INR) monitoring (1). The intensity of anticoagulation is measured as the INR, and it is proven that increased time in the therapeutic range (TTR) has a lower risk of thromboembolic events and bleeding risk in patients using VKA (2). Patients are expected to achieve TTR of >70 for...
preventing stroke, systemic embolism or bleeding, however, it was found that patients spent a weighted average 61% of their time in, 25% below and 15% above the target range of 2.0 to 3.0 (3, 4).

Recently investigators have examined the effectiveness of the individual based (self-monitoring and self-management) INR measurements rather than standard monitoring and care, including personal physicians and anticoagulation hospitals or clinics (5). Several portable devices have been approved by the Food and Drug Administration for self-usage (6, 7). However, there has been no detailed investigation of this new aspect in the Turkish population (8). Hence, the purpose of this study is to explore the variation in INR control and TTR between individual and center-based measurements and to observe how this variation affects the effectiveness of oral anticoagulant therapy.

Materials and Methods

In this single-center, retrospective study, we conducted a comprehensive search from January 1, 2016 to December 31, 2017 for patients using warfarin for any reason and attending routine INR monitoring. Demographic and clinical data including age, sex, medical history (the presence of hypertension, diabetes mellitus, hyperlipidemia, congestive heart failure, coronary artery disease, chronic renal failure, end-stage renal disease, cerebrovascular disease, pulmonary embolism, and deep venous thrombosis), smoking status were recorded (Table 1). Additionally, CHA2DS2-VASc (Congestive heart failure, Hypertension, Age ≥1 point, ≥75 = 2 points), Diabetes, and Stroke/TIA [2 points], vascular disease [peripheral arterial disease, previous myoccardial infarction, aortic atheroma] and female gender) (cutoff ≥2), and HAS-BLED (hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly >65 years), drugs/alcohol concomitantly (cutoff ≥3) were calculated using these data. The sample size was estimated based on the probable number of participants that could be recruited in a reasonable time with a 3:1 allocation ratio. A calculation of sample size revealed that at least 233 patients for all groups were needed to detect differences in a reasonable time with a 3:1 allocation ratio. A sample size was estimated based on the effectiveness of oral anticoagulant therapy.

A total of 237 patients had a primary warfarin indication. TTR was calculated according to F.R. Roosendaal’s algorithm with linear interpolation (2). An interpolated INR value was assigned to each follow-up day. TTR was the mean percentage of days that the INR for an individual patient as in the therapeutic range of 2.0–3.0 or 2.5–3.5.

The target of INR was 2.5 (range 2.0–3.0) in patients with a mechanical aortic valve, non-valvular AF, and the other reasons. The target of INR was 3 (range 2.5–3.5) in patients with a mechanical mitral valve and mechanical heart valves in both the aortic and mitral position (9). We recorded the patients mean warfarin dosages as ≤2.5 mg, 2.5–5 mg, 5–10 mg, or ≥10 mg daily and we also calculated the proportion of time below the therapeutic INR range, proportion of time above the therapeutic range.

Major bleeding was defined as a reduction in the hemoglobin level of at least 20 g/L or requiring transfusion of at least 2 units packed blood cells, or hemorrhage into a critical anatomical site (e.g. intracranial, retroperitoneal, intracranial, intraspinal, intracoarcal, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome) (10). Minor bleeding was defined any non-major bleeding. Thromboembolic events were stroke, arterial embolism, symptomatic deep-vein thrombosis, or pulmonary embolism (11).

Statistical analyses were performed using SPSS software version 22 (SPSS Inc, Chicago, IL, USA). The variables were investigated using visual (histograms, probability plots) and analytical methods (Kolmogorov Smirnov/Shapiro-Wilk test) to determine whether or not they are normally distributed. Continuous variables were presented as a mean ± SD or medians (interquartile ranges), whereas categorical variables were summarized as the number of cases with the percentage (%). Overall comparisons of categorical variables were performed using Pearson’s χ2 test and Fisher’s exact test. Student t-test was used for normally distributed parameters, whereas Mann Whitney U test was used for the parameters not distributed normally. The study population was also divided into two groups: Poor
control and good control group. The cut-off point for TTR 55% (defined by Nelson et al. (12) and Baker et al. (13) was used for the discrimination of the groups.

Logistic regression was used to determine which variables were associated with poor control. Candidate variables were those that showed significance in the bivariate analysis or those that had been reported to show an association with control of INR in previous studies: sex, age, hypertension, type 2 diabetes mellitus, renal failure, CHA2DS2-VASc, HAS-BLED, and staff charged with validating the INR (routine care or self-management strategy). Hosmer-Lemeshow goodness of fit statistics was used to assess model fit. In the graphical representation of pie charts were used. A p value less than 0.05 was considered statistically significant.

Results

The baseline demographic and clinical data are presented in Table 1. The study population was divided into two groups which were similar regarding sex distribution, age, risk factors including hypertension, diabetes mellitus, hyperlipidemia, congestive heart failure, coronary artery disease, chronic renal failure, end-stage renal disease, cerebrovascular disease, pulmonary embolism, deep venous thrombosis, and smoking status. No significant differences were found in the time of warfarin usage (75.4±56.2, 70.2±64.1, P=0.582, respectively) and the number of INR monitoring within a year (12.0±2.6, 12.3±3.5, P=0.498, respectively) between groups. However, there was significantly differences between groups based on warfarin usage (5.2% of patients used ≤2.5 mg/daily of warfarin, 63.8% used 2.5–5 mg/daily, 29.3% used 5–10 mg/daily, and 1.7% used ≥10 mg/daily in self-management group, and 15.6% of patients used ≤2.5 mg/daily of warfarin, 49.2% used 2.5–5 mg/daily, 27.4% used 5–10 mg/daily, and 7.8% used ≥10 mg/daily in routine care group) (P=0.044).

The mean TTR levels of all patients were found to be 54.1±32.1 (median, 60%). When compared to routine care group, the patients in self-management group had significantly higher levels of TTR (72.7±22.8% vs. 44.9±31.6%, P<0.001), but the time below range (%) and the time above range (%) were significantly lower (14.1±16.5 vs. 32.7±23.5, P<0.001, 16.4±18.8 vs. 26.4±23.6, P=0.004, respectively) (Table 1, Figure 1).

Table 1. Patients’ anticoagulation characteristics

<table>
<thead>
<tr>
<th>INR and TTR Range</th>
<th>Self-management Group (n: 58)</th>
<th>Routine Care Group (n: 179)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of INR monitoring within a year</td>
<td>12.0 ± 2.6</td>
<td>12.3 ± 3.5</td>
<td>0.498</td>
</tr>
<tr>
<td>TTR (%)</td>
<td>77 (63, 89)</td>
<td>46 (15, 75)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Time below range (%)</td>
<td>9 (0, 23)</td>
<td>29 (15, 49)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Time above range (%)</td>
<td>12 (0, 23)</td>
<td>20 (8, 44)</td>
<td>0.006</td>
</tr>
<tr>
<td>CHA2DS2-VASc</td>
<td>2.8 ± 1.7</td>
<td>2.7 ± 1.8</td>
<td>0.845</td>
</tr>
<tr>
<td>HAS-BLED</td>
<td>1.58 ± 1.1</td>
<td>1.7 ± 1.2</td>
<td>0.347</td>
</tr>
</tbody>
</table>

Values are median (IQR), mean ± SD, or n (%)
CHA2DS2-VASc, congestive heart failure, hypertension, age, diabetes, stroke, vascular disease, sex; HAS-BLED, hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly (> 65 years), drugs/alcohol concomitantly; INR, international normalized ratio; TTR, time in the therapeutic range
**Comparison between Self-monitoring and Self-management.**

**Table 2. Odds ratios of significant and independent risk variables associated with low time in therapeutic range in stepwise logistic regression analysis**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Odds Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart Failure</td>
<td>3.281 (1.561 – 6.897)</td>
<td>0.002</td>
</tr>
<tr>
<td>Renal dysfunction</td>
<td>3.754 (1.224 – 11.519)</td>
<td>0.021</td>
</tr>
<tr>
<td>Age (&lt; 65 years)</td>
<td>2.786 (1.379 – 5.631)</td>
<td>0.004</td>
</tr>
<tr>
<td>CHADS2-VASc score</td>
<td>1.339 (1.071 – 1.673)</td>
<td>0.010</td>
</tr>
<tr>
<td>Routine care management</td>
<td>8.113 (3.593 – 18.321)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

CI: confidence interval; CHADS2-VASc: Congestive heart failure, Hypertension, Age: Diabetes, Stroke, Vascular disease, Sex

**Discussion**

This study designed to compare routine care management and self-monitoring and self-management strategies for oral anticoagulation. In terms of oral anticoagulation, the prevention of major thromboembolic complications, and bleeding complications, findings have revealed that the patients with the self-management of oral anticoagulation therapy are superior to the routine care managed group. The present study showed that 6.9% vs. 17.9% thromboembolic and 29.9% vs. 8.6% bleeding events within a year. These findings are consistent with the previous systematic reviews, in which patients who self-monitor and, or self-management could improve the high rate of time in therapeutic range and the quality of their oral anticoagulation therapy (7, 14, 15). Indeed, current practice guidelines suggest the strategy of self-management for patients treated with vitamin K antagonists who are motivated and can demonstrate competency in self-management strategies, including the self-testing equipment (Class IIb) (16).

In a multicenter study of anticoagulation control, Abenhaima et al. (4) demonstrated a biphasic relationship with age, TTR peaking around 77% at 70-75 years, being weaker in females than in males, and home monitored patients than those attending the clinic.

Additionally, Siebenhofer et al. (17) concentrated on elderly patients and found a definite improvement in general treatment satisfaction after participation in the self-management program (17). Along with these studies, current results come up with the same observation in terms of TTR increased with increasing age (>65 years) and individual management, however, in the present study there were no statistical differences between genders. It could be explained by the increasing level of the awareness of warfarin usage and compliance of the elderly patients in self-management strategy.

On the other hand, the findings of the current study are contrary to the previous research which have suggested lack of superiority of self-testing over clinic testing in reducing the risk of stroke, major bleeding episode, and death among patients taking warfarin therapy. A possible explanation for this might be high-quality clinic testing of the INR which included assigned, competent staff responsible for patients’ visits and follow-up, the use of a standard procedure at each site for anticoagulation management; and the performance of regular INR testing about once a month. However, in accordance to the current study, they observed that home monitoring improved secondary outcomes (time in target INR range, general quality of life, and patient satisfaction with anticoagulation therapy (6)).

Furthermore, multivariate analysis revealed that patients with heart failure (HF), renal dysfunction, younger age (<65 years), CHA2DS2-VASc score and routine care rather than self-management strategy were the independent predictors of having lower TTR (TTR< 55%). It is showed that chronic diseases such as HF and renal dysfunction are associated with polypharmacy which may affect the pharmacodynamics of the warfarin, cause drugs interactions with warfarin and promote poor quality of warfarin therapy. Additionally, the findings highlighted the in compliance of the young patients to the warfarin therapy. These results reflect those of Macedo et al. (18) who also have demonstrated that poor anticoagulation control driven by time spent under INR range was observed in younger patients, underweight patients, and in AF patients with an increased number of hospitalizations in their large-scale study. Similar to the current study (19), the VARIA investigators concluded that age less than 55 years repeat hospitalizations, chronic diseases such as cancer and chronic liver disease negatively affected TTR.

Cost-effectiveness is one of the most critical issues for patients, especially in low-income countries. Although there is no clear evidence for the costs comparing self-management and anticoagulation clinics in Turkey, a review concluded that patient self-management is unlikely to be more cost-effective than the currently specialized anticoagulation clinics in the UK (20). On the other hand, Canadian study suggested that self-management is a cost-effective strategy for patients receiving long-term oral anticoagulation therapy for atrial fibrillation or a mechanical heart valve (21). Additionally, Matchar et al. (6) reported that costs were higher in the self-testing group but not significantly different from those in the clinic-testing group (difference = $1.249; P=0.32). Recently, Kanito et al. (22) stated that

The cost-effectiveness of Patient Self-testing (PST) to other different care approaches for anticoagulation therapy in Thailand, a low-to-middle income country (22). Furthermore, It has been observed
the patients either treated with non-vitamin K antagonist oral anticoagulants (NOACs) and treated with warfarin with high TTR (mean TTR was 70%) have similar benefits regarding preventing bleeding, stroke or systemic embolism (3, 23). NOACs are considered to be inevitable alternatives for the patients with poor control. However, the high prevalence of valvular atrial fibrillation and the high cost of NOACs in developing countries limit their use.

Overall, the findings of the present study should be interpreted with caution because of the limited sample size, retrospective origin and the selection of eligible patients for self-monitoring and self-management which may overestimate the actual effects of treatment with self-monitoring and self-management; therefore, prospective randomized studies in a larger population are required to confirm our results.

Conclusion, this study has been one of the first attempts to thoroughly examine the efficacy of self-management of oral anticoagulation and evaluate its effects on outcomes in the Turkish population. Since achieving high-quality anticoagulation control with warfarin in real-world clinical practice is rather difficult (24), efforts are required to identify warfarin patients who require closer monitoring or innovative management strategies to optimize the outcomes of oral anticoagulant therapy. This study provides evidence that self-management strategy has good outcomes in terms of prevention of major thromboembolic complications and bleeding complications. Hence, the use of home testing devices to measure INR may be a potential way to improve the comfort and the compliance of the patients and their families, to control the frequency of monitoring, to reach cost-effective status and, as a result, to provide better management of being safe for long-term oral anticoagulation.

References


