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

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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*

Oral Antikoagülasyonun Bireysel ve Standart İzlem ve Yönetim ile Karşılaştırılması

Amaç: Warfarin tedavisinin güvenliği ve etkinliği antikoagülasyon kontrolünün kalitesi ile ilişkili olup genellikle terapötik aralıkta (TTR) geçen süre kullanılarak değerlendirilir. Bu çalışma, bireysel ve merkezi tabanlı ölçümler arasındaki INR ve TTR'deki varyasyonu değerlendirmeyi ve bu varyasyonun oral antikoagülan tedavisinin etkinliğine etkisini gözlemlemeyi amaçlamıştır.

Gereç ve Yöntem: Mevcut çalışmada toplam 237 hasta seçildi ve iki gruba ayrıldı: rutin bakım grubu 179 denekten (75 erkek, ortanca 61 yaş) ve yaş ve cinsiyetle eşleşen 58 bireyi (26 erkek, 64 yaş arası bir medyan) içeren, kişilerin ölçümlerini kendilerinin üstlendiği öz-yönetim grubundan oluşuyordu.

Bulgular: Öz-yönetim grubundaki hastalarda TTR (77 (63, 89)% vs. 46 (15, 75), %P<0.001) anlamlı olarak daha yüksek seviyelerde bulundu, ancak aralık altında(%) ve aralık üzerinde (%) geçen süre rutin bakım grubuna göre anlamlı olarak daha düşük bulundu (sırasıyla (9 (0, 23) ve. 29 (15, 49), P<0.001, 12 (0, 23) ve 20 (8, 44), P=0.006). Kalp yetersizliği (3.281, %95 CI 1.561 -6.897, p=0.002), böbrek fonksiyon bozukluğu (3.754, %95 CI 1.224 -11.519, P=0.021), genç yaş (<65 yaş) (2.786, P=0.004), CHA2DS2-VASc (1.339, P=0.010) ve rutin bakım yönetimi (8.113, P<0.001), düşük TTR'nin bağımsız belirleyicileri olarak saptandı.

Sonuç: Öz yönetim stratejisi, major tromboembolik komplikasyonlar ve kanama komplikasyonlarının önlenmesi açısından iyi sonuçlara sahiptir. Ev test cihazları, güvende geçirilecek uzun süreli oral antikoagülasyon için daha iyi yönetim sağlayabilir.

Anahtar Kelimeler: *Warfarin, terapötik aralıktaki zaman, antikoagülasyon*

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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 showed 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 [≥65 = 1 point, ≥75 = 2 points], Diabetes, and Stroke/TIA [2 points], vascular disease [peripheral arterial disease, previous miyocardial 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 between results with a statistical power (1-β value) of 95% allowing for a type i (α) error of 0.05. Of those 233 patients, 175 should be placed in the the routine care group and 58 should be placed in the self-management group with an actual power. 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 (51 to 68) years), and the self-management group included of 58 age and sex-matched individuals (26 men, with a median of 64 (56 to 70) years).

In the self-management group, patients' INR results gathered from the CoaguChek XS (Roche Diagnostics, Basel, Switzerland) which is a whole blood sampling point-of-care testing (POCT) device using strips containing a human thromboplastin (ISI=1). In the routine care group, patients' INR results gathered from Stago Star Evolution (electromechanical cloth detection after addition of a rabbit brain thromboplastin-STA Neoplastin) in the central lab at hospital or at an anticoagulation clinic. Self-management group received a structured educational series given by the nurse or physician responsible for care. Also, they received training in self-testing with the portable device, instructions to prevent bleeding or thromboembolic complications and were educated diet and medication.

Patients were excluded if anticoagulant treatment had been interrupted during these 12 months or if the patients had a severe psychiatric disease or terminal illness. Patients were informed by their physician of their individually defined INR therapeutic target ranges. Informed consent was obtained from the control group involved in this study. The study was approved by the Institutional Ethics Committee.

If the patients had more than one indication of anticoagulation treatment with warfarin, the main reason was selected as the 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, intraocular, 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 $\chi 2$ 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/day, 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/day, and 7.8% used ≥10 mg/day 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).

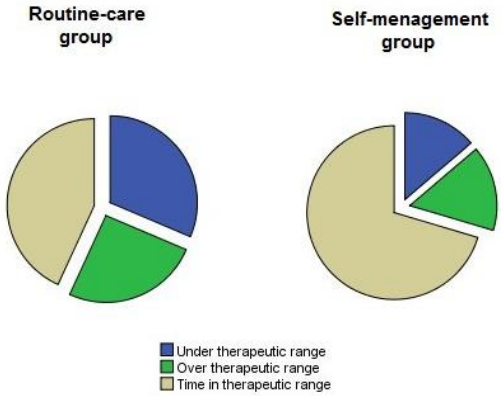

Figure 1. The evaluation of time in therapeutic range of groups

Although analysis of the thrombotic risk scales (CHA2DS2-VASc) and bleeding risk scales (HAS-BLED score) did not show statistically significant differences between the 2 groups (P=0.845, P=0.342, respectively), routine care group showed higher number of thromboembolic and bleeding events (P=0.029, P<0.001, respectively). It was observed that 29.9% of the patients had a bleeding event [major bleeding 5.6%, minor bleeding 25.7%] in routine care group and 8.6% of the patients had a bleeding event [major bleeding 3.4 %, minor bleeding 5.2 %] in self-management group within a year.

The multivariate logistic regression analysis to predict patient's probability of poor control (TTR<55) entered the variables of sex, age (≥65years/ <65 years), hypertension, type 2 diabetes mellitus, renal failure, CHA2DS2-VASc, HAS-BLED, and staff charged with validating the INR (routine care or self-management strategy). 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, 95% CI 1.379–5.631, P=0.004), CHA2DS2-VASc (1.339, 95% CI 1.071-1.673, P=0.010), and routine-care management (8.113, 95% CI 3.593–18.321, P<0.001) rather than self-management strategy were the independent predictors of having lower TTR.

Table 1. Patients' anticoagulation characteristics

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

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

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

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

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, Abohelaika 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, Kantito 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

1. Ansell J, Hirsh J, Hylek E, et al. Pharmacology and management of the vitamin K antagonists: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2008; 133: 160S-98S.
2. Rosendaal F, Cannegieter SC, Van der Meer FJ, Briet E. A method to determine the optimal intensity of oral anticoagulant therapy. Thromb Haemost 1993; 69: 236-239.
3. Sjögren V, Byström B, Renlund H, et al. Non-vitamin K oral anticoagulants are non-inferior for stroke prevention but cause fewer major bleedings than well-managed warfarin: A retrospective register study. PloS one 2017; 12: e0181000.
4. Abohelaika S, Wynne H, Avery P, et al. Individual and monitoring centre influences upon anticoagulation control of AF patients on warfarin: A longitudinal multi-centre UK-based study. 2018; 101: 486-495.
5. Grove EL, Skjøth F, Nielsen PB, Christensen TD, Larsen TB. Effectiveness and safety of self-managed oral anticoagulant therapy compared with direct oral anticoagulants in patients with atrial fibrillation. Scientific Reports 2018; 8: 15805.
6. Matchar DB, Jacobson A, Dolor R, et al. Effect of home testing of international normalized ratio on clinical events. New England Journal of Medicine 2010; 363: 1608-1620.
7. Bloomfield HE, Krause A, Greer N, et al. Meta-analysis: Effect of patient self-testing and self-management of long-term anticoagulation on major clinical outcomes. Annals of Internal Medicine 2011; 154: 472-482.
8. Nieuwlaat R, Connolly BJ, Hubers LM, et al. Quality of individual INR control and the risk of stroke and bleeding events in atrial fibrillation patients: A nested case control analysis of the ACTIVE W study. Trombosis Research 2012; 129: 715-719.
9. Guyatt GH, Akl EA, Crowther M, Gutterman DD, Schuünemann HJJC. Executive summary: Antithrombotic therapy and prevention of thrombosis: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2012; 141(2 Suppl): 7S.
10. Roskell NS, Samuel M, Noack H, Monz BUJE. Major bleeding in patients with atrial fibrillation receiving vitamin K antagonists: A systematic review of randomized and observational studies. Europace 2013; 15: 787-797.
11. Schulman S, Kearon C, Scientific SoCoAot, Thrombosis SCotISo, Thrombosis HJJo, Haemostasis. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. Journal of Thrombosis and Haemostasis 2005; 3: 692-694.
12. Nelson WW, Choi JC, Vanderpoel J, et al. Impact of co-morbidities and patient characteristics on international normalized ratio control over time in patients with nonvalvular atrial fibrillation. The American Journal of Cardiology 2013; 112: 509-512.
13. Baker WL, Cios DA, Sander SD, Coleman CIJJoMCP. Meta-analysis to assess the quality of warfarin control in atrial fibrillation patients in the United States. Journal of Managed Care Pharmacy 2009; 15: 244-252.
14. Heneghan C, Ward A, Perera R, et al. Self-monitoring of oral anticoagulation: Systematic review and meta-analysis of individual patient data. Lancet 2012; 379: 322-334.
15. Siebenhofer A, Ulrich L-R, Mergenthal K, et al. Primary care management for patients receiving long-term antithrombotic treatment: A cluster-randomized controlled trial. PloS one 2019; 14: e0209366.
16. Holbrook A, Schulman S, Witt DM, et al. Evidence-based management of anticoagulant therapy: Antithrombotic therapy and prevention of thrombosis: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2012; 141: e152S-e84S.
17. Siebenhofer A, Hemkens LG, Rakovac I, Spat S, Didjurgeit U, research SSGJT. Self-management of oral anticoagulation in elderly patients–Effects on treatment-related Quality of Life 2012; 130: e60-e6.
18. Macedo AF, Bell J, McCarron C, et al. Determinants of oral anticoagulation control in new warfarin patients: Analysis using data from Clinical Practice Research Datalink. Thrombosis Research 2015; 136: 250-260.

19. Rose AJ, Hylek EM, Ozonoff A, et al. Patient characteristics associated with oral anticoagulation control: Results of the Veterans AffaiRs Study to Improve Anticoagulation (VARIA). Journal of Thrombosis and Haemostasis 2010; 8: 2182-2191.

20. Connock M, Stevens C, Fry-Smith A, et al. Clinical effectiveness and cost-effectiveness of different models of managing long-term oral anticoagulation therapy: A systematic review and economic modelling. Health technology assessment 2007; 11: ii-iv, ix-66.

21. Regier DA, Sunderji R, Lynd LD, Gin K, Marra CAJCMAJ. Cost-effectiveness of self-managed versus physician-managed oral anticoagulation therapy. CMAJ: Canadian Medical Association Journal 2006; 174: 1847-52.

22. Kantito S, Saokaew S, Yamwong S, et al. Cost-effectiveness analysis of patient self-testing therapy of oral anticoagulation. Journal of Thrombosis and Thrombolysis 2018; 45: 281-290.

23. Wallentin L, Yusuf S, Ezekowitz MD, et al. Efficacy and safety of dabigatraompared with warfarin at different levels of international normalised ratio control for stroke prevention in atrial fibrillation: An analysis of the RE-LY trial. The Lancet 2010; 376: 975-983.

24. Pokorney SD, Simon DN, Thomas L, et al. Patients' time in therapeutic range on warfarin among US patients with atrial fibrillation: Results from ORBIT-AF registry. American Heart Journal 2015; 170: 141-148.