RESEARCH ARTICLE / *Araştırma Makalesi*

Treatment Cost Analysis Study in Patients with Atrial Fibrillation Using Warfarin or New Generation Oral Anticoagulant

Varfarin veya Yeni Nesil Oral Antikoagülan Kullanan Atriyal Fibrilasyonlu Hastalarda Tedavi Maliyetinin Analiz Çalışması

Ercan Aydın[1], Aydın Kant[2], Altuğ Ösken[3], Salih Şahinkuş[4], Selçuk Yaylacı[5]

[1] Vakfıkebir State Hospital, Department of Cardiology, Trabzon
[2] Vakfıkebir State Hospital, Departmant of Chest Diseases, Trabzon
[3] Siyami Ersek Chest Cardiovascular Surgery Training and Research Hospital, Department of Cardiology, İstanbul
[4] Sakarya Education and Research Hospital, Department of Cardiology, Sakarya
[5] Sakarya Education and Research Hospital, Department of İnternal Medicine, Sakarya

Yazışma Adresi / *Correspondence:*
Ercan Aydın
Çarşı Mah. Gülbahar Hatun Sk. No:35 Kat:6 Vakfıkebir / Trabzon
T: **+90 530 527 61 28** E-mail **: ercanaydin112@yahoo.com**

Geliş Tarihi / Received : **21.12.2020** Kabul Tarihi / Accepted : **03.04.2021**

Orcid :
Ercan Aydın https://orcid.org/0000-0001-8743-3762
Aydın Kant https://orcid.org/0000-0003-2914-2478
Altuğ Ösken https://orcid.org/0000-0003-3018-3331
Salih Şahinkuş https://orcid.org/0000-0003-1558-5761
Selçuk Yaylacı https://orcid.org/0000-0002-6768-7973

(Sakarya Tıp Dergisi / ***Sakarya Med J*** **2021, 11(2-):322-327) DOI: 10.31832/smj.844292**

Abstract

Objective — We compared the cost analysis of warfarin and new-generation oral anticoagulant (NOAC) treatment in patients with atrial fibrillation.

Materials and Methods — Four hundred and ninety-four patients diagnosed with atrial fibrillation at the cardiology outpatient clinic (OC) and using warfarin or NOAC therapy were retrospectively included in the study.Comparison of the total cost of OC and examination fees paid by the social security institution; Fees related to hospitalizations due to hemorrhage caused by anticoagulants and anticoagulant drug cost were compared.

Results — In the study group, 18.8% of the anticoagulant drug users were using warfarin, and 81.2% were using NOACs. The average number of admission to OC is more prevalent in patients using warfarin. No statistical difference was observed in gender between patients, but patients using NOAC had a higher mean age ($p<0.026$).The costs of OC examination and hospitalization were higher in patients receiving warfarin medication but the total costs were higher in NOAC patients ($p<0.001$).

Conclusion — Hemorrhagic complications of NOAC drugs and hospitalization frequency are low, and the cost of OC examination is beneficial. If the NOAC prices are lower, the total cost will be reduced and these drugs will be more favorable than warfarin.

Keywords — New-generation oral anticoagulant; warfarin; cost analysis

Öz

Amaç — *Atriyal fibrilasyonu olan hastalarda varfarin ve yeni nesil oral antikoagülan (NOAC) tedavisinin maliyet analizini karşılaştırdık.*

Gereç ve Yöntemler — *Kardiyoloji polikliniğinden atriyal fibrilasyon tanısı alan, varfarin veya NOAC tedavisi kullanan 494 hasta retrospektif olarak çalışmaya dahil edildi. Poliklinik hizmet ücreti ,antikoagülanların neden olduğu kanama nedeniyle hastaneye yatış ücretleri ve antikoagülan ilaç maliyeti dahil edilerek Sosyal Güvenlik Kurumunca ödenen ücretlerin karşılaştırılması yapıldı.*

Bulgular — *Çalışma grubunda antikoagülan ilaç kullanıcılarının %18.8'i varfarin, %81.2'si NOACs kullanıyordu. Varfarin kullanan hastalarda poliklinik muayene hizmet sayısı daha yüksekti. Hasta grupları arasında cinsiyet açısından istatistiksel bir fark görülmedi fakat NOAC kullanan hastalarda ortalama yaş daha yüksekti ($p<0.026$). Varfarin kullanan hastalarda poliklinik muayene hizmet ve hastaneye yatış ücretleri daha yüksek fakat NOAC hastalarında toplam maliyetler daha yüksekti ($p<0.001$).*

Sonuç — *NOAC ilaçlarının hemorajik komplikasyonları ve hastaneye yatış sıklığı düşüktür ve poliklinik muayene ücretleri açısından daha avantajlıdır. NOAC ilaçlarının fiyatları daha düşük olsa, toplam maliyet azalacak ve bu ilaçlar varfarin'e göre toplam maliyet açısından daha avantajlı olacaktır.*

Anahtar Kelimeler — *Yeni nesil oral antikoagülan; varfarin; maliyet analizi*

INTRODUCTION

Atrial fibrillation (AF) is a leading cause of major cardiovascular events worldwide, including mortality and fatal stroke. However, AF is one of the main indications for anticoagulant theraphy.[1] According to the Turkey Adult Risk Factor results, the prevalence of AF in Turkey is 1.25%, and the incidence is 1.35/1000, and rheumatic valve disease was determined as a predisposing factor in only 6.0% of the AF population.[2] Anticoagulant therapy is the mainstay of stroke prevention in non-valvular atrial fibrillation (NVAF). The evaluation of AF patients with the CHA2DS-2VASC score is recommended for regulating anticoagulant therapy.[3] Conventional preventive AF strategies, such as appropriate anticoagulants and rate-limiting therapeutic agents are crucial to prevent complications. For more than 50 years, vitamin K antagonists (VKAs) such as warfarin, phenprocoumon, and acenocoumarol have been the only oral anticoagulants. These drugs have a narrow target therapeutic range, general food, and drug interactions, and their use requires repeated blood tests to determine the target international normalized rate (INR). These common problems of VKAs have led to the search for more effective and safer anticoagulants. New-generation oral anticoagulants (NOAC) are the result of these studies and have become widely used in treatment. Dabigatran (direct thrombin inhibitor), rivaroxaban, apixaban, and edoxaban (factor Xa inhibitors) are NOACs that are approved in Turkey. NOACs are approved for non-valvular AF and deep vein thrombosis and pulmonary embolism. The main purpose of the study was to make a cost analysis of warfarin and NOACs. We also wanted to show which of these drugs, covered by the government, are more profitable in the long term.

MATERIALS and METHODS

Our study was carried out as a cross-sectional descriptive study between November 2016 and December 2018 at Vakfikebir Hospital, Trabzon, Turkey. The data of 93 patients who were treated with VKAs and followed up with INR regularly and 401 patients who used NOAC regularly and patients who were followed up with the diagnosis of atrial fibrillation and regularly taking anticoagulant medication for 2 years by examining social security institution-drug records were included in the study.Edoxaban was not included in the study because the drug fee was not paid by the Social Security institution.Baseline characteristics and in-hospital clinic data of 494 patients were analyzed, retrospectively.

The costs of the OACs whose prices are determined by the social security institution for each year are shown in the table. The polyclinic fee paid for the treatment of patients was 7.75$ (dollars) between the years 2016–2018 by the social security institution. The total unit price of complete blood count and INR test is 3.25 $ in patients receiving warfarin treatment and those who use warfarin visit the outpatient clinic for regular complete blood count and INR test every month. Patients using NOAC visit the outpatient clinic for prescription and control four times in a year. The number of admissions of patients to the polyclinic between the specified dates was examined, and the total amount paid for the drugs and the prices paid by the social security institution for hospitalization due to atrial fibrillation or bleeding were calculated and analyzed.The work protocol was designed in accordance with the principles of the Helsinki Declaration and approved by the Ethics Committee of Trabzon Kanuni Education and Research Hospital (17.6.2020 protocol no:2020/26).

Statistical analysis

Statistical analysis was performed using SPSS 22.0 computer program. Categorical variables were expressed as number or percentage, and continuous variables as mean ±standard deviation. A chi-square test was used to compare categorical variables. For the comparison of continuous variables, the suitability of the parameters to normal distribution was examined by the Kolmogorov-Smirnov test.An independent sample's t-test was used to compare the normal distribution data. A p-value below 0.05 was considered statistically significant.

RESULTS

A total of 93 patients (56 women [60.2%], 37 men [39.8%]) received warfarin, and the mean age was 71 years. A total of 401 patients (mean age of 76 years) used NOACs (243 women [60.6%], 158 men [39.2%]). There was no statistical difference in gender between the patients but those using NOAC had a higher mean age and it was statistically significant (p<0.026). In our study, 93 patients were using warfarin 5 mg, 108 patients using rivaroxaban 15 mg twice daily (QD) (26.9%), 123 patients using rivaroxaban 20 mg QD (30.7%), 57 patients using dabigatran 110 mg BID, 32 patients using dabigatran 150 mg BID (8%), 39 patients using apixaban 2.5 mg BID (9.7%), and 42 patients using apixaban 5 mg BID (10.5%) (Figure 1).

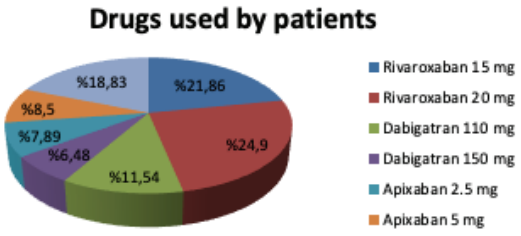

Figure 1. The rates of drugs used by patients

The age ratio of women using NOAC was statistically significant compared with that of men using NOAC. Women using NOACs were older than men. There was no gender difference between them.

During the period 2016–2018, the two years average total cost of all healthcare and medicines was 457±196 $ for NOACs and 377±91$for the patients using warfarin, and the cost of healthcare was higher for patients using NOACs and was statistically significant (p<0.001) (Table 1).

The average number of admission to the outpatient clinic is more meaningful in patients using VKAs because they visit the clinic regularly for INR follow-up (Table 1). Gastrointestinal bleeding occurred in two patients using dabigatran 110 mg. The use of warfarin caused hematuria in 2 patients and gastrointestinal system bleeding in 15 patients. Cerebrovascular stroke was not observed in any patient using anticoagulants.

Table 1. Comparison of the characteristics and costs of the patients between warfarin and NOAC groups

Parameters	WARFARIN (n=93)	NOAC (n=401)	P value
Gender	Female: n:56 Male: n:37	Female: n:243 Male: n:158	P > 0.05
Age	71 ±10 Female: 73 ±10 Male: 69 ±10	76 ±9 Female: 77 ±9 Male: 75 ±9	P= 0.026
Average Number of OC Admissions	28 ±4	5 ±1	P < 0.001
OC and Examination Fees (USD)	273 ±15	38 ±18	P < 0.001
Average SSI Drug and OC costs (USD)	320 ± 34	456 ± 188	P < 0.001
Frequency of hospitalization	0.22±0.05	0.01±0.06	P < 0.001
Hospitalization cost (USD) Included Total Cost (USD)	377 ± 90	457 ± 196	P < 0.001

NOAC: New-generation Oral Anticoagulant, OC: Outpatient Clinic; SSI: Social Security Institution, USD: American dollar

DISCUSSION

The use of NOACs in elderly patients was shown to be as safe as warfarin in the REGIstry of patients on Non-vitamin K oral Anticoagulants (REGINA) study.[4] NOACs are used more in elderly patients because the INR is more difficult to follow up in this population. As similar in our study, we found that NOAC was used more often than warfarin, especially in the elderly group of patients, and there were fewer complications. Rohit et al. determined that for patients with unstable INR the cost of warfarin administration is more than three times that of fixed INR over time. The authors also found that warfarin is cheaper than NOACs and reported that NOAC treatment may not be more expensive than warfarin treatment management for NVAF patients with unstable INR monitoring.[5] Shannon L. Reynolds et al. found that dabigatran (NOAC) users did not significantly differ in total cause costs compared to warfarin users.[6] In our study, hospital admission and examination costs are less, but NOACs cost more than warfarin; therefore, NOACs are statistically more costly. In our country, NOACs cannot be started directly in anticoagulant therapy in NVAF patients. Warfarin treatment is started first, and if the patient is compatible with INR follow-up and the INR is stable, treatment with warfarin is continued. However, if the INR is unstable, one of the NOACs will be switched.

To assess the efficiency of warfarin treatment in follow-up patients, TTR (Time in Therapeutic Range) is another method used to evaluate efficient INR levels. There are many studies in the literature evaluating warfarin efficacy with INR and TTR values.[7,8] In these studies, since the risk of stroke and systemic embolism was higher at low TTR rates.[9] It would be a more rational solution to use NOACs in groups where TTR targets were not achieved.

We considered hospitalizations due to complications and add them to the cost analysis. More complications in the warfarin groupincreased the cost;however, even in thiscondition, the NOAC group was more costly in the whole cost analysis. The pharmacokinetic profile of warfarin is variable and the drug has multifaceted drug-food and drug-drug interactions. This results in poor INR control, which is often observed in real-world clinical practice. Furthermore, extremely high INR causes major bleeding, including intracranial hemorrhage, and extremely low INR causes thromboembolic events, or the patient may not be compatible with treatment.[10] These clinical conditions requiring hospitalization and mortality may increase the costs associated with warfarin.

Although the hospital OC examination and hospitalization costs of the warfarin group were significantly higher than those of the NOAC group, the total costs increased because of the high cost of NOACs and were significantly higher in NOAC patients. If the cost of NOACs is reduced, the total cost would be similar in both groups, patients will use the drug more comfortably, and the cost will be less to the state. Although NOAC patients have to come to the hospital less frequently for examination and the incidence of complications is very low, the total cost is higher for the state because of the high drug price. Canestaro et al. found that all NOACs were more disadvantaged in terms of cost, although they produce more quality-adjusted life expectancy than warfarin.[11]

According to Lip et al, the NOACs had lower rates of stroke/systemic embolism and comparative variable rates of major bleeding versus warfarin.[12] The studies with NOACs have shown that the effectiveness is at least as much as warfarin, while safety data is better than warfarin. It will help reduce the morbidity and mortality associated with thromboembolism in AF and ensure that patients with AF have a better quality of life.[13] It is expected that NOACs will also be used in patients at high risk of bleeding, with the introduction of NOACs approved for use in bleeding from side effects (idaricuzimab for Dabigatran and andexanet Alpha for Factor Xa inhibitors).[14] This is another reason why the government must support the cost of NOACs instead of warfarin.

According to the results of our study, the cost of warfarin is 12% of the total cost. In the NOAC group, the cost of the drug itself is 92% of the total cost. There is a significant difference between the costs of both drugs, but the costs associated with complications and hospitalization in the warfarin group is 88% of the total cost compared with only 8% in the NOAC group.

Limitations

Despite the strengths of the current study, we are well of aware of certain limitations: Our study was a descriptive study of the cross-sectional typeand retrospective analysis of the prospectively recorded data can ascertain bias. Clearly, larger studies are needed to more conclusively evaluate factors that compare total costs of warfarin and NOACs.

CONCLUSION

In summary, concerning the use of oral anticoagulant drugs, drug use, and easy to adapt the treatmentof NOAC patients and the cost balance of drugs, if the prices of NOACs are reduced to a certain extent, the total cost difference between warfarin treatment and NOAC treatment is eliminated. Patients experience fewer complications with NOACs and have easy access to drugs that are easier to use and follow-up. This also reduces the outpatient workload of hospitals. If these regulations are put in place, the use of NOAC will be more beneficial for patients and government expenditures in the long run.

Ethics Committee Approval

Ethics Committee Approval of the study was obtained from the Ethics Committee of Trabzon Kanuni Education and Research Hospital (17.6.2020 protocol no:2020/26).

References

1. *Pistoia F, Sacco S, Tiseo C, Degan D, Ornello R, Carolei A. The Epidemiology of Atrial Fibrillation and Stroke. Cardiol Clin 2016;34(2):255-68.*
2. *Uyarel H, Onat A, Yüksel H, Can G, Ordu S, Dursunoğlu D. Incidence, prevalence and mortality estimates for chronic atrial fibrillation in Turkish adults. Arch Turk Soc Cardiol 2008;36:214–22.*
3. *Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Eur J Cardiothorac Surg 2016;50(5):e1-e88.*
4. *Cavallari I, Patti G. Efficacy and safety of oral anticoagulation in elderly patients with atrial fibrillation. Anatol J Cardiol 2018;19(1):67–71.*
5. *Bobade RA, Helmers RA, Jaeger TM, Odell LJ, Haas DA, Kaplan RS. Time-driven activity-based cost analysis for outpatient anticoagulation therapy: direct costs in a primary care setting with optimal performance. Journal of Medical Economics 2019;22(5):471–477.*
6. *Reynolds SL, Ghate SR, Sheer R,Gandhi PK, Moretz C, Wang C,et al, Healthcare utilization and costs for patients initiating Dabigatran or Warfarin .DisclaimerHealth Qual Life Outcomes 2017;15:128.*
7. *Varim P, Varim C, Ergenç H, Uyanık M, Yaylacı S, Vatan M, et al. Assessment of Warfarin Treatment Efficacy by means of Using Coagulation Test Results Within The Therapeutic Range. Georgian Med News 2016;255:62-6.*
8. *Kaya H, Ertaş F, Kaya Z, Kahya Eren N, Yüksel M, Köroğlu B, Köse N,et al. Epidemiology, anticoagulant treatment and risk of thromboembolism in patients with valvular atrial fibrillation: Results from Atrial Fibrillation in Turkey: Epidemiologic Registry (AFTER). Cardiol J 2014;21:158-62.*
9. *Nieuwlaat R , Connolly BJ,Hubers LM, Cuddy SM, Eikelboom JW, Yusuf S, et al. Active Investigators. 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. Thromb Res 2012;129: 715-719*
10. *Sorensen SV, Dewilde S, Singer DE, Goldhaber SZ, Monz BU, Plumb JM. Cost-effectiveness of warfarin: Trialversus"real-world" stroke prevention in atrial fibrillation. American HeartJournal 2009; 157(6):1064-73.*
11. *Canestaro WJ, Patrick AR, Avorn J, Ito K, Matlin OS, Brennan TA, et al. Cost-effectiveness of oral anticoagulants for treatment of atrial fibrillation. Circ Cardiovasc Qual Outcomes 2013;6:724-731.*
12. *Lip G, Keshishian A, Li X, Hamilton M, Masseria C, Gupta K, et al. Effectiveness and safety of oral anticoagulants among nonvalvular atrial fibrillation patients. Stroke 2018; 49(12):2933-2944.*
13. *Mezue K,,Obiagwu C, John J, Sharma A, Yang F,Shani J.Novel Oral Anticoagulants in Atrial Fibrillation. Update on Apixaban. Curr Cardiol Rev. 2017; 13(1): 41–46.*
14. *Başarıcı İ, Kılınc AY. New Oral Anticoagulants.Turkiye Klinikleri 2019:.90-100*