A cost comparison of warfarin vs enoxaparine or new oral anticoagulants used for the treatment of patients with pulmonary embolism

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SUMMARY

A cost comparison of warfarin vs enoxaparine or new oral anticoagulants used for the treatment of patients with pulmonary embolism

Introduction: *Recently, novel oral anticoagulants (rivaroxaban, dabigatran, apixaban) have been approved for pulmonary embolism (PE) treatment. Each anticoagulant used during initial and maintenance therapy has direct and indirect costs for healthcare systems. Demonstrating the costs of treatment with different anticoagulants in a specific patient group will be helpful for clinicians determining treatment strategies.*

Materials and Methods: *Retrospective data of 118 patients with PE who were hospitalized and treated with warfarin for at least 3 months were evaluated. Direct medical and nonmedical costs were calculated. True costs with warfarin and modeled costs with rivaroxaban, dabigatran, apixaban and enoxaparine were calculated and compared for maintenance therapy. Estimated costs of initial and maintenance treatment with different anticoagulants were compared for the 49 patients with low complication risk.*

Results: *The average total cost of maintenance treatment with warfarin was found to be higher than the novel oral anticoagulants (€286.5 for warfarin, €233.3 for rivaroxaban, €231.7 for dabigatran, and €229.6 for apixaban). In patients with low complication risk, who could be treated without hospitalization, alternative treatment regiments were found to cost less than warfarin treatment (€883.1 for warfarin, €254.3 for rivaroxaban, €238 for apixaban, and €810.6 for enoxaparine).*

Conclusion: *Maintenance therapy with novel oral anticoagulant costs less than warfarin treatment. In patients with lower complication risks, alternative regimens that do not require hospitalization could cost less.*

Key words: *Economics, pharmaceutical, pulmonary embolism, new oral anticoagulants*

ÖZET

Akut pulmoner embolide varfarin ile enoksaparin veya yeni oral antikoagülanların kullanımının maliyetlerinin karşılaştırılması

Giriş: *Yeni nesil oral antikoagülanlar (rivaroksaban, dabigatran, apiksaban) yakın zamanda pulmoner emboli (PE) tedavisi için onay almış ilaçlardır. Başlangıç ve idame tedavisinde kullanılan*

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ilaçların doğrudan ve dolaylı maliyetleri bulunmaktadır. Spesifik bir hasta grubunda ortaya çıkan bu maliyetlerin gösterilmesi, klinisyenlere tedavi seçimlerinde yardımcı olabilecektir. Bu çalışmada PE tedavisinde kullanılabilecek farklı antikoagülanlarla ortaya çıkan maliyetlerin karşılaştırılması amaçlanmıştır. Ayrıca düşük komplikasyon riski bulunan hasta grubu belirlenerek bu grupta başlangıç (ilk 5-10 gün) ve idame (başlangıç tedavisinin bitiminden itibaren) tedavi maliyetleri analiz edilmiştir.

Materyal ve Metod: PE tanısı ile hastane yatışı yapılan ve en az 3 ay varfarin tedavisi alan 118 hastanın verileri retrospektif olarak değerlendirildi. Doğrudan medikal ve nonmedikal maliyetler belirlendi. İdame tedavide varfarin kullanımına bağlı gerçek maliyetler ve rivaroksaban, dabigatran, apiksaban ve enoksaparin kullanımına bağlı tahmini maliyetler belirlendi ve karşılaştırıldı. Düşük komplikasyon riski bulunan 49 hastada ortaya çıkabilecek tahmini başlangıç ve idame tedavi maliyetleri belirlenerek karşılaştırıldı.

Bulgular: Varfarin ile idame tedavisine devam eden hastalarda ortaya çıkan ortalama toplam maliyet, yeni nesil oral antikoagülanlara göre yüksek bulundu (varfarin için 286.5 €, rivaroksaban için 233.3 €, dabigatran için 231.7 € ve apiksaban için 229 €). Hastane yatışı olmadan tedavi edilebilecek olan düşük komplikasyon riskine sahip hastalarda kullanılabilecek alternatif tedavi seçenekleri ile ortaya çıkan maliyetler, varfarin tedavisine göre daha düşük bulundu (varfarin için 883.1 €, rivaroksaban için 254.3 €, apiksaban için 238 € ve enoksaparin için 810.6 €).

Sonuç: İdame tedavide yeni nesil oral antikoagülanlarla ortaya çıkabilecek maliyetler daha düşük bulunmuştur. Hastane yatışı yapılmayabilecek düşük komplikasyon riskine sahip hastalarda tercih edilecek alternatif tedavi seçenekleri daha düşük maliyetler ortaya çıkacaktır.

Anahtar kelimeler: İlaç maliyetleri, pulmoner emboli, yeni oral antikoagülanlar

INTRODUCTION

Pulmonary embolism (PE) is a common clinical condition with high mortality and morbidity unless treated with appropriate therapy. It has a mortality of 25%-30% when untreated compared with 2%-8% in treated cases. Initial treatment requires therapeutic dosages of unfractionated heparin (UFH), low molecular weight heparin (LMWH), fondaparinux or new oral anticoagulants (rivaroxaban, apixaban) (1-3). Dabigatran is also approved for the treatment of PE, it requires 7 to 10 days of UFH or LMWH treatment initially. In clinical practice, initial treatment (first 5-10 days) with parenteral anticoagulants following hospitalization, bridging to warfarin as maintenance therapy (from end of initial treatment), is the mostly preferred treatment option (4,5). Current guidelines suggest that patients with an in-hospital mortality risk less than 1% can also be treated in outpatient settings (4,6).

Each therapy used during initial or maintenance treatment periods causes direct and indirect costs for the healthcare system, the majority of which are due to hospitalization. In a study using US data, the average cost per patient for hospitalization due to PE and 12 months of follow-up was found to be $16.644, and hospital expenses were reported to make 87.5% of the costs (7).

In this study, we aimed to determine and compare the costs of initial and maintenance therapy of PE with different anticoagulant strategies. In order to evaluate these costs, we modeled a group of patients that were hospitalized and treated with warfarin for PE. In a group of patients with low risk of complications (those with low simplified pulmonary embolism severity index score) who could be treated without hospitalization, we also compared true and estimated costs for hospitalization and outpatient clinic follow-up.

MATERIALS and METHODS

Patient Selection

Data of 636 patients who were followed up in a university hospital between February 2004 and January 2014 were retrospectively evaluated. In total, 118 patients that were hospitalized and treated for PE, who were treated with warfarin for at least 3 months on maintenance therapy, who had no kidney diseases or active malignancy, and whose INRs were controlled only at our clinic, at regular intervals, were included in the study (Figure 1). Any patient whose treatment was discontinued for reasons other than clinically important minor bleeding or high INR, or who had major bleeding, were excluded from the study.

Data Collection

Demographic features (sex, age, marital status, and occupation), comorbidities, and follow-up data were recorded. For every patient, the number of admissions during their follow-up period was established. For those patients whose treatment was planned to be life long, data were recorded for a 1-year period. Clinically important minor bleedings were recorded.
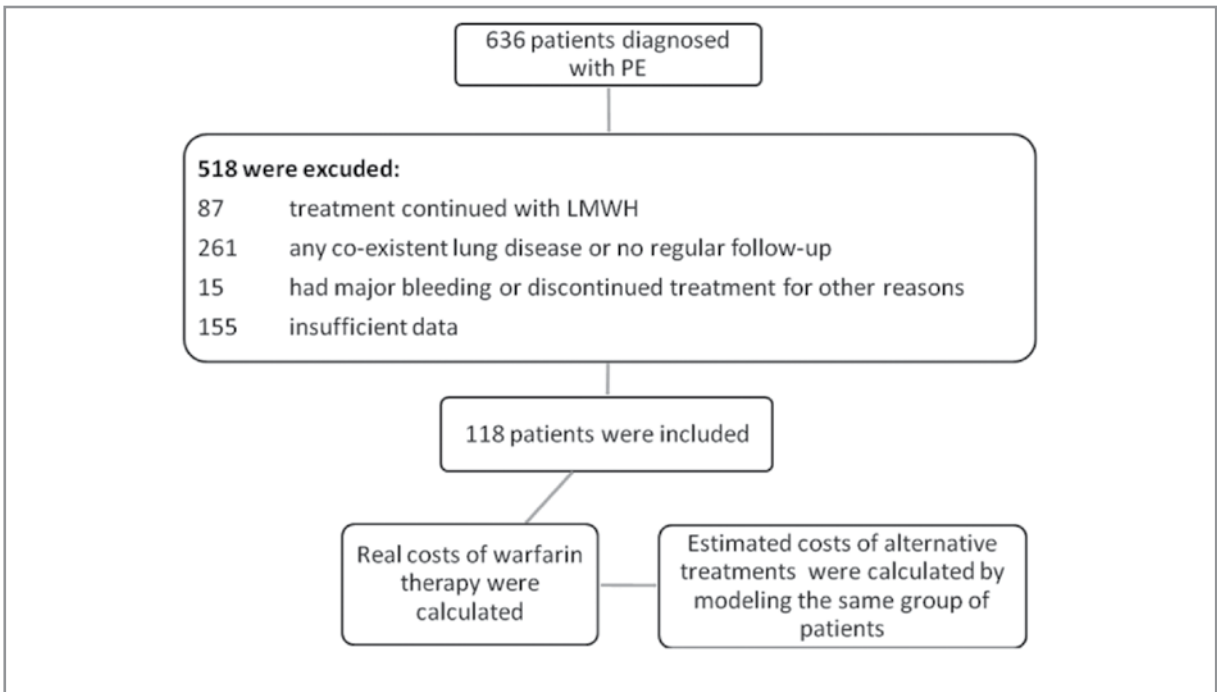
Figure 1. Patient selection and modeling.

Costs Analysis and Model Assumptions

Direct medical and nonmedical costs were calculated based on up-to-date values for cost estimation. The cost of hospitalization at the time of diagnosis was derived from the statistics unit in our hospital. Current pharmacy costs were derived from data of the "Turkish Ministry of Health, General Directorate of Pharmaceuticals and Pharmacy"; costs of admission to outpatient clinic for chest diseases were derived from data of "Application Statement on Health" and transportation costs were derived from the schedule of prices of the "Ankara Chamber of Minibus Drivers." In order to exchange Euro (€) to Turkish Lira (TL) for hospitalization expenses, exchange rates at the time of patient admission were used; for other costs, the exchange rate of €1 = TL 2.8521 was used. Quality-adjusted life-years and costs related to productivity loss were not calculated. Instead, average absences from work per year secondary to outpatient clinic admissions were calculated for working patients.

Pharmacy costs were based on the Coumadin® 5 mg tablet for warfarin, the Xarelto® 15 mg/20 mg tablets for rivaroxaban, the Pradaxa® 150 mg 60 tablet for dabigatran, the Eliquis® 5 mg 60 tablet for apixaban and the Clexane® 6000 anti-Xa IU/0.6 mL injector for enoxaparine.

Maintenance treatment costs

The estimated costs of maintenance treatment with rivaroxaban, dabigatran, apixaban or enoxaparine in a population with the same clinical features were calculated and compared by modeling the 118 patients under warfarin treatment. Since no complications occurred in selected patient group and no other hospitalization or routine controls were needed, only pharmacy costs were calculated for rivaroxaban, dabigatran, apixaban and enoxaparine.

Initial and maintenance treatment costs with low sPESI score

Hospitalization, pharmacy, admissions to outpatient clinics, and transportation costs were calculated for the warfarin therapy group. For all patients, simplified PE severity index (sPESI) scores were calculated. Subgroup analysis was performed for those patients who could be treated in outpatient setting without hospitalization according to sPESI scores (sPESI= 0). For the modeled alternative anticoagulation strategies, estimated pharmacy costs for rivaroxaban (Initial treatment: 2 x 15 mg for 21 days; maintenance treatment: 1 x 20 mg), apixaban (Initial treatment: 2 x 10 mg for 10 days; maintenance treatment: 2 x 5 mg) and enoxaparine (Initial treatment: 2 x 0.6 mL for 5 days; maintenance treatment; 1 x 0.6 mL) were

calculated and compared because no hospitalization or routine follow-up was required in this selected patient population. Since 7 to 10 days of dual therapy with UFH or LMWH is needed for dabigatran initially, it was not included in this calculation.

Statistical Analysis

SPSS 17.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. Central tendency and dispersion of data were shown as mean ± standard deviation or median (interquartile range). In addition, the 95% confidence interval was calculated for cost data. As the numerical values related to costs did not have a normal distribution, unless stated otherwise, they were expressed as median (interquartile range) or percent.

When comparing continuous variables, an independent sample t test was used for parametric values and the Mann-Whitney U test for nonparametric values. The p value of < 0.05 was considered to be significant.

This study was approved by the institutional review board of Gazi University (26.205.2014/272).

RESULTS

Patient Population

Median age of the whole population was 61.5 years (19-86) and women represented 51.7% of patients (Table 1). The treatment period related to PE was 205.5 (172.8-325) days. During this treatment period, the average number of outpatient clinic admissions was 15.4 ± 5.9 per patient. During follow-up, INR results were in the therapeutic range (2.0-3.0) for only 50.5% of time in the whole group. There were seven clinically significant minor bleeding episodes, including three hemoptyses, three superficial echymoses, and one epistaxis. Medical therapy was discontinued by the doctor for a short time as the bleeding continued.

Costs Analysis

Costs on maintenance treatment

The median pharmacy cost for warfarin usage was calculated as €15.9 (10.5-22.4) for the maintenance period. The cost of outpatient clinic admission was €240.5 (189-326.4) per patient (Table 2). Sex, age, comorbidity and its type, complications, and occupation had no effect on the average number of outpatient clinic admissions, so changes in these

Table 1. General characteristics and follow-up data of all patients

	n= 118
Median age (min-max)	61.5 (19-86)
Gender, n (%)	
Female	61 (51.7)
Comorbid disease, n (%)	
Yes	65 (55.6)
No	52 (44.4)
Comorbidities, n (%)	
Cardiac	50 (42.7)
Endocrine	19 (16.2)
Neurological	2 (1.7)
Respiratory	6 (5.1)
Rheumatological	3 (2.6)
Malignancy *	4 (3.4)
Median duration of treatment, days (25-75% IQR)	205.5 (172.8-325)
Number of outpatient clinic admissions	15.4 ± 5.9

Min= Minimum, Max= Maximum, IQR interquartile range.
* Those without active malignancy.

variables caused no significant difference to the average annual cost of outpatient clinics (p> 0.05). At the outpatient clinic, the total transportation cost was €19.6 (15.4-26.6) per patient (Table 2). The total cost of pharmacy, admission to outpatient clinic, and transportation for warfarin maintenance treatment was €286.5 (225-369.2).

Considering the alternative treatments, the estimated cost per patient of maintenance treatment was calculated as €233.3 (196-368.9) with rivaroxaban, €231.7 (194.8-366.5) with dabigatran, €229.6 (193.1-363.2) with apixaban and €800.9 (673.2-1266.6) with enoxaparine (Table 2). Only pharmacy costs were calculated for these treatment options that did not require routine follow-up and showed no complications in the selected group of patients. For patients under maintenance treatment with warfarin, alternative therapies with rivaroxaban, dabigatran or apixaban significantly decreased the costs approximately by 19%, and therapy with enoxaparin significantly increased the cost approximately by 180%.

Costs on initial and maintenance treatment for low sPESI score

There were 49 patients with sPESI= 0. The mean true hospitalization cost of initial treatment for these

Table 2. True and estimated costs of maintenance treatment in the whole patient population

n= 118	True costs based on maintenance treatment, €		
	Mean ± SD	Median (IQR)	95% CI
Warfarin pharmacy	17.4 ± 11	15.9 (10.5-22.4)	15.4; 19.5
Outpatient clinic admission	263.8 ± 100.7	240.5 (189-326.4)	245.5; 282.2
Transportation	21.5 ± 8.2	19.6 (15.4-26.6)	20; 23
Total	306.1 ± 113.9	286.5 (225-369.2)	284.8; 327.5
	Estimated costs based on maintenance treatment, €		
Rivaroxaban pharmacy*	258.8 ± 106.3	233.3 (196-368.9)	239.4; 278.2
Dabigatran pharmacy**	257.1 ± 105.6	231.7 (194.8-366.5)	237.9; 276.36
Apixaban pharmacy***	254.8 ± 104.6	229.6 (193.1-363.2)	235.7; 273.9
Enoxaparine pharmacy ****	888.5 ± 364.9	800.9 (673.2-1266.6)	822; 955.1

SD= Standard deviation, IQR= Interquartile range, CI= Confidence interval.
   * Rivaroxaban 1 x 20 mg,
  ** Dabigatran 2 x 150 mg,
 *** Apixaban 2 x 5 mg,
**** Enoxaparine 1 x 0.6mL.

patients was €577.3 (442.7-888.3) per patient. These patients can also be treated at outpatient settings without hospitalization, so they were assumed to be treated with rivaroxaban 2 x 15 mg for 21 days as initial and 1 x 20 mg as maintenance treatment, apixaban 2 x 10 mg for 10 days as initial and 2 x 5 mg as maintenance treatment or enoxaparine 2 x 0.6 mL for 5 days as initial and 1 x 0.6 mL as maintenance treatment. The estimated costs were calculated (Table 3) and compared for these groups (Figure 2). In this group of patients with sPESI= 0, initial and maintenance treatment (without hospitalization) with rivaroxaban, apixaban and enoxaparine decreased the costs significantly by ~71%, 73%, and 8%, respectively, compared with warfarin.

Work Absences During the Follow-Up With Warfarin

Forty-one patients who were actively working were admitted to outpatient clinics 574 times during their treatment period. From 2004 to 2014, working days comprised approximately 71% of a year; assuming that these patients took a half-day off, they were found to be absent from work for 4.7% of the year.

DISCUSSION

Our study demonstrated that, in Turkish healthcare settings, new oral anticoagulants are the most economical choices in maintenance therapy for PE. For patients who could be treated without hospitalization, costs of initial and maintenance treatment with rivaroxaban, apixaban or enoxaparine could cost lower than warfarin. In patients who were hospitalized for PE, hospitalization was found to constitute approximately 75% of all costs from diagnosis to the end of treatment. In patients receiving warfarin treatment, outpatient clinic admissions were found to be responsible for approximately 90% of costs related solely to maintenance therapy.

Table 3. Costs of initial and maintenance therapy in patients with sPESI= O with different anticoagulants

Anticoagulants n= 49	Mean ± SD	Median (IQR)	95% CI
Warfarin*	996.7 ± 507.5	883.1 (623.3-1234.4)	847.7; 1145.7
Rivaroxaban **	283 ± 102.8	254.3 (228.7-347.9)	253.5; 312.6
Apixaban***	266.4 ± 101.2	238 (212.9-330.2)	237.3; 295.4
Enoxaparin ****	909.4 ± 353.1	810.6 (722.9-1132.1)	797.6; 1006.2

SD= Standard deviation, IQR= Interquartile range, CI= Confidence interval.
   * Includes hospitalization, outpatient clinic admission, pharmacy and transportation.
  ** Rivaroxaban 2 x 15 mg 21 days as initial and 1 x 20 mg as maintenance treatment.
 *** Apixaban 2 x 10 mg 10 days as initial and 2 x 5 mg as maintenance treatment.
**** Enoxaparine sodium 2 x 0.6 mL 5 days as initial and 1 x 0.6 mL as maintenance treatment.
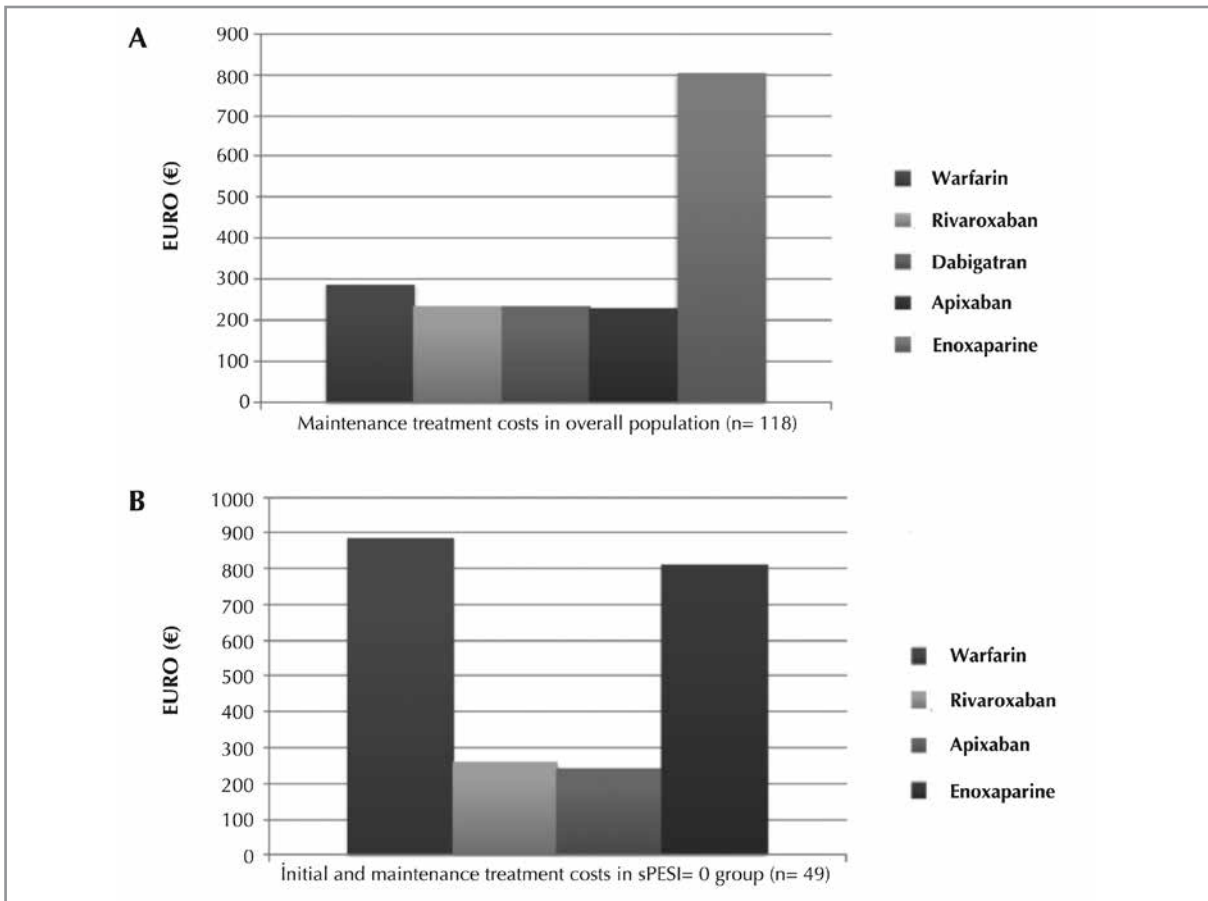
Figure 2. (A) Maintenance treatment costs of different anticoagulants in all patients. Rivaroxaban, dabigatran and apixaban cost lesser and enoxaparine costs higher than warfarin (p< 0.05). There was no significant difference between costs of all three new oral anticoagulants. **(B)** Initial and maintenance treatment costs of different anticoagulants in patients with sPESI= 0. Rivaroxaban and apixaban cost lesser than (p< 0.05), enoxaparine costs similar with warfarin (p> 0.05).

Warfarin, although cheap, requires regular clinic controls and INR follow-up; hence, it has nonpharmacy costs. In contrast, its alternatives, rivaroxaban, dabigatran, apixaban and enoxaparine, cause much higher pharmacy costs but they do not require routine follow-up. Based on our findings, changing warfarin treatment to alternative regimens other than enoxaparine in the maintenance period costs less in our country. When planning treatment, factors such as patient characteristics and preferences, as well as costs, are primarily important. Weitz and Gross provided a table to assist physicians in selecting anticoagulants based on patient characteristics (8). It stated that changing regimen is unnecessary in patients under warfarin treatment who are stabilized and had INR results in the therapeutic range. They showed that for patients with dyspepsia or upper gastrointestinal symptoms, creatinine clearance between 30 and 50 mL/min, and requests for a once-daily regimen, rivaroxaban can be chosen.

The majority of costs related to initial treatment are revealed to be hospital expenses, so shortening length of stay (LOS) or decreased need for hospitalization may considerably decrease the burden on health expenses. The EINSTEIN-PE study demonstrated a 1-day decrease in median LOS for rivaroxaban compared to the low molecular weight heparin + warfarin regimen (9). In a study by Beckman et al., PE monotherapy with enoxaparine was shown to cause a 2-day decrease in the median LOS compared with the standard regimen (10). In a study in which Markov modeling was constructed based on the EINSTEIN-PE study, Lefebvre et al. (11) showed that rivaroxaban therapy costs $2.448 per

patient less than enoxaparine + warfarin therapy. In a similar study, Mody et al. stated $2,742 less per patient (12).

Even though there has been no published study about the diagnosis and treatment costs of PE in our country, studies comparing these three pharmaceuticals for deep-vein thrombosis, PE, stroke, nonvalvular atrial fibrillation treatment, and orthopedic postoperative prophylaxis demonstrated that new oral anticoagulants were more cost-effective than warfarin and enoxaparine (11-16). However, it should be remembered that costs related to hospitalization and complications are also included in these studies. For example, Mody et al. showed an economic gain of 17.1% with rivaroxaban compared with other agents and pointed out that approximately 90% of this gain was caused by the decreased LOS (12). When interpreting our results, one must consider that hospital costs are significantly lower in Turkey than in the US and EU. Our study showed an average hospitalization cost for PE of $717 per patient compared with Spyropoulos et al. estimate of $14.146 per patient in the US (7).

There are numerous scoring systems one can use in order to assess the complication risk related to PE and disease prognosis. Among these, the PESI or sPESI is the best validated (17,18). Patients at low risk of serious complications according to the scoring system are accepted to be suitable for treatment without hospitalization (4,17). An open-label randomized study by Aujesky et al. on outpatient treatment of low-risk patients diagnosed with PE showed that well-selected patients with a low PESI score can safely be treated at outpatient clinics (19). The ACCP guideline (The Updated 2012 American College of Chest Physicians Evidence-Based Clinical Practice Guidelines) and ESC 2014 guideline similarly state that well-selected patients can be treated at outpatient clinics, resulting in fewer unnecessary hospitalizations and up to 50% economical gain (4,6). In a multicenter study, low-risk patients were found to constitute 29.9% of patients with PE in our country (20). Thus, outpatient treatment can be considered in one-third of patients with PE, improving not only patient comfort but also economical gain.

In this study, costs related to productivity loss were not calculated because of a lack of data. Only loss of work days was calculated based on outpatient clinic admissions for INR control, and a loss of 4.7% per year (~17 days) was found. In a study by Page et al. (21), short-term disability per patient with PE was 56.4 ± 3 days, long-term disability 363.9 ± 26.1 days. The mean estimated lost wage per disability claim for PE was $18.514 ± 1476. The costs we have described will be a lot higher with the addition of these parameters.

Our study had some limitations; most importantly, we had data only for the group treated with warfarin and the other treatment results were calculated using assumptions based on the same group of patients. Because patients treated with enoxaparine were not regularly followed-up, real data could not be included in the study. Also, rivaroxaban and dabigatran had only recently been lisenced for PE treatment in our country at the time of the study, so there were no follow-up data about these drugs. Second, the results of this retrospective and single-centered study that included only noncomplicated patients may not reflect real-world settings. Third, costs related to productivity loss were not included. In the future, studies also including these costs can calculate the true costs more accurately.

Finally, the costs used were derived from Turkish health-system data, making them lower compared with similar studies in the US or EU because healthcare is much cheaper in our country.

CONCLUSIONS

Cost data calculated in our study will be a guide for clinicians planning PE treatment. The findings suggest new oral anticoagulants cost less in maintenance therapy. We emphasize that anticoagulation choice in PE must be patient tailored. Increased referral to sPESI and similar scoring systems in clinical practice and outpatient treatment of patients with low risk for complications will provide up to 73% economical gain.

AUTHORSHIP and CONTRIBUTORSHIP

Murat Türk designed the study, analyzed data and drafted manuscript, Yağmur Aldağ collected data and drafted the manuscript, İpek Kıvılcım Oğuzülgen designed the study and edited the manuscript, Numan Ekim participated in the planning of the manuscript and critical review.

CONFLICT of INTEREST

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