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Cost Effectiveness of Rivaroxaban versus Warfarin to Prevent Stroke in Iranian Atrial Fibrillation Patients

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ABSTRACT

Background and Aims: Atrial fibrillation (AF) is the most common sustained arrhythmia in adults which need anti-coagulant to prevent stroke. Due to high cost of Rivaroxaban compared to Warfarin, it is not prescribed as much as Warfarin by physicians despite its superiority in intracranial hemorrhage. This study aimed to evaluate the cost-effectiveness of Rivaroxaban versus Warfarin in preventing stroke in AF patients.

Material and Methods: This study is a cost-utility analysis with cost-effectiveness assessed by the incremental cost per quality-adjusted life-year (QALY). Two strategies were used to obtain the costs; the first was from available resources, and the next was to collect data using a questionnaire. A total number of 98 patients who met the inclusion criteria had answered the questionnaire. Utility values for obtaining ΔQALYs originated from published data. Finally the cost-effectiveness of Warfarin versus Rivaroxaban was assessed using an incremental cost-effectiveness ratio (ICER), which was calculated as the incremental cost per QALY gained.

Results: Mean annually physician visits were 4 times in Rivaroxaban and 14 times in Warfarin group. The patients in Warfarin Group checked their INR (international normalized ratio) 15 times a year, while the patients in Rivaroxaban group did not check at all. The wasting time for each physician visit and doing Lab test was approximately 3 hours. Total cost of Rivaroxaban in both private (16,699,000 IRR) and governmental sector (15,755,000 IRR) were less than that for Warfarin; governmental sector 24, 233,700 & 20,345,600 IRR respectively. We analyzed the ΔQALYs of 7 different articles in which the mean ΔQALY was 0.21 (Variance: 0.0072). The incremental cost per QALY per patient for Warfarin in private versus governmental sector was 18,514,762 Rial /QALY, while the ICER between Rivaroxaban versus Warfarin in both private and governmental sectors was negative (-35,879,523.8 and -21,860,000 Rial/QALY). So the calculated threshold based on the per capita gross national product (GDP), which was 702,576,000 Rials (calculated at 42,000IRR/$), showed that Rivaroxaban is more cost-effective than Warfarin.

Conclusions: Use of Rivaroxaban versus Warfarin in both governmental and private sectors is a cost-effective choice. So, due to its economic and potential benefits, it is recommended to prescribe Rivaroxaban rather than Warfarin.

INTRODUCTION

Atrial fibrillation (AF) is the most common sustained arrhythmia in adults and its prevalence increases by age [1]. The incidence of AF ranges from 0.1% per year before the age of 40 years to higher than 1.5% per year in women and higher than 2% in men older than 80 years [2]. AF patients are five times more at risk of stroke and other thromboembolic events than age-matched individuals in sinus rhythm [3, 4]. Therefore, an

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anticoagulant is often recommended to decrease the risk. Both Warfarin and NOACs (Novel Oral Anticoagulants) are effective for stroke prevention in AF patients [5].

Until recently, Warfarin has been the selective anticoagulant, which reduces the risk of thromboembolism by two-thirds at minimum cost [6]. The limitations of Warfarin include the variety of food and drug interactions, slow onset of action, high discontinuation rates, therapeutic range limitation, and variable dose response in different patients, which require regular INR test (at least once a month according to latest guidelines) that have complicated the management of AF patients and encouraged the development of newer oral anticoagulants (NOACs) [7, 8]. In recent years, several NOACs (including Dabigatran, Rivaroxaban , Apixaban, and Edoxaban) have been approved as alternatives to Warfarin for stroke prevention in non-valvular AF patients. These newer agents do not require regular monitoring, have faster onset of action, less food and drug interactions than Warfarin, and provide more convenient oral anticoagulation (OAC) treatment [9]. In the ROCKET-AF study, Rivaroxaban was non-inferior to Warfarin for the prevention of stroke and systemic embolism in the intent-to-treat analysis, while the per-protocol on-treatment analysis achieved statistical superiority with a 21% reduction in stroke or systemic embolism compared to Warfarin ([HR] 0.79; 95 % CI 0.66–0.96; p=0.001). Rivaroxaban did not reduce the rates of mortality, ischemic stroke, or major bleeding events compared to Warfarin; gastrointestinal bleeding events were decreased, but there was no significant reduction in haemorrhagic stroke and intracranial haemorrhage with Rivaroxaban compared to Warfarin [10].

However, since the costs of NOACs are considerably higher than the costs of Warfarin, it is important to investigate their cost effectiveness carefully. The economic-pharmacological aspects of NOACs were analyzed for many countries, all of which demonstrated to be cost-effective for the health care system [11]. Rivaroxaban is the most common prescribed NOACs in Iran. The cost of Rivaroxaban is significantly higher than Warfarin and most of the Iranian Insurance Organizations (Governmental & Private) do not cover it. Therefore, this study aimed to investigate the cost effectiveness of Rivaroxaban compared to Warfarin in Islamic Republic of Iran.

MATERIAL AND METHODS

This cross-sectional study was a cost-utility analysis with cost-effectiveness assessed by the incremental cost per quality-adjusted life-year (QALY) [12].

Among the patients referred to the cardiac clinics in Tehran (governmental clinics included Taleghani & Loghman Hospital clinics and private clinics included Parsian Hospital and other private clinics), we chose all the patients who had the inclusion criteria, suffering from non-valvular AF and were at moderate-to-high risk for stroke (CHADS2 score of 2 or more), for participating in our study. We get our ethical approval from shahid Beheshti University of medical sciences ethical center with ethical code 1397,585.

Utility values were derived from published data on whether the patients experienced an event (MI, stroke, PE, TIA, ICH, and extra cranial hemorrhage) in the current cycle and their event history [13]. Since there was no significant difference in calculated ΔQALYs (the difference between Rivaroxaban & Warfarin QALYs) in other studies between Warfarin and Rivaroxaban , we estimated ΔQALYs according to these studies using their utility values on treatment [14-16].

We used two strategies to obtain costs: the first was obtaining them from the drug manufacturer, drugstores, medical Laboratories and any other available resources, the second was to collect data using a questionnaire. The questionnaire consisted of two sections: the first section included identity and medical records of patients and the second part included the direct and indirect cost of treatment. The intangible costs were not collected. The patients treated with Warfarin were recommended to visit their physician regularly to maintain the target INR of 2.5 (typical target range is 2.0–3.0) for at least 12 times per year according to new Guidelines [17]. We asked the patients "How many times a month do you visit your doctor?" and "How many times per month do you take the INR test?" and "how much did you pay?", We asked them whether these visits had any positive impact on their income or not and in case of positive answer we asked how long it took (wasting time) to visit their doctor and about the duration of their departure from the laboratory to get home. The costs of transition to doctor's office and Laboratory were also asked. We asked them about their transportation vehicle (Personal Car, governmental transportation, Charter Taxi). The wasting time and transportation costs were calculated using a parallel study for non-AF patients not only to increase the accuracy and power of our study due to the limited population of our patients with AF disease, but also for assessing the validity and reliability of questionnaire and the patient answers. Since the Iranian Medical Health System has two types of governmental and private sectors and the cost of these two sectors are different, so we distributed our questionnaires in both governmental and private Health Centers. Also, some questionnaires were filled by phone calls; patients' phone numbers were obtained from Taleghani & Loghman Hospitals as the public databases, and Parsian Hospital and private clinics as the private databases. All costs of medical procedures, doctors' visit and laboratory were extracted from web site of Ministry of Health and Medical Education based on tariffs specified on 2019 [18]. The minimum wage was obtained from Ministry of Labor and Social Welfare based on tariffs specified on 2019 [19].

Model Analyses

Patients suffering from non-valvuar AF who were at moderate-to-high risk for stroke (CHADS2 score of 2 or more) particINTRODUCTION

Atrial fibrillation (AF) is the most common sustained arrhythmia in adults and its prevalence increases by age [1]. The incidence of AF ranges from 0.1% per year before the age of 40 years to higher than 1.5% per year in women and higher than 2% in men older than 80 years [2]. AF patients are five times more at risk of stroke and other thromboembolic events than age-matched individuals in sinus rhythm [3, 4]. Therefore, an

Table 1. Baseline characteristics of participants

	Total	Rivaroxaban	Warfarin	P value
Numbers	98	39 (40%)	59 (60%)	
Age	68	67.64 ± 12.57	68.25 ± 12.51	0.813
Sex (Male%)	56 (58%)	23 (59%)	33 (56%)	0.791
Visit (Mean) (per year)		4	14	0.001
INR checking (per year)		0	15	0.001
Wasting time (per hour)	3h			

anticoagulant is often recommended to decrease the risk. Both Warfarin and NOACs (Novel Oral Anticoagulants) are effective for stroke prevention in AF patients [5].

Until recently, Warfarin has been the selective anticoagulant, which reduces the risk of thromboembolism by two-thirds at minimum cost [6]. The limitations of Warfarin include the variety of food and drug interactions, slow onset of action, high discontinuation rates, therapeutic range limitation, and variable dose response in different patients, which require regular INR test (at least once a month according to latest guidelines) that have complicated the management of AF patients and encouraged the development of newer oral anticoagulants (NOACs) [7, 8]. In recent years, several NOACs (including Dabigatran, Rivaroxaban , Apixaban, and Edoxaban) have been approved as alternatives to Warfarin for stroke prevention in non-valvular AF patients. These newer agents do not require regular monitoring, have faster onset of action, less food and drug interactions than Warfarin, and provide more convenient oral anticoagulation (OAC) treatment [9]. In the ROCKET-AF study, Rivaroxaban was non-inferior to Warfarin for the prevention of stroke and systemic embolism in the intent-to-treat analysis, while the per-protocol on-treatment analysis achieved statistical superiority with a 21% reduction in stroke or systemic embolism compared to Warfarin ([HR] 0.79; 95 % CI 0.66–0.96; p=0.001). Rivaroxaban did not reduce the rates of mortality, ischemic stroke, or major bleeding events compared to Warfarin; gastrointestinal bleeding events were decreased, but there was no significant reduction in haemorrhagic stroke and intracranial haemorrhage with Rivaroxaban compared to Warfarin [10].

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Table 2. Costs of Rivaroxaban versus Warfarin (in Rials) [cost of Drug , visit, Laboratory, transportation, time wasting.]

	Rivaroxaban		Warfarin	
	Private	Governmental	Private	Governmental
Drug Cost				
Per pill	35,000		1200	
Per year	12,775,000		438,000	
Visit Cost				
Per visit	384,000	148,000	384,000	148,000
Per year	1,536,000	592,000	5,376,000	2,072,000
Lab Cost (INR)	0	0	1,106,700	522,600
Transportation Cost				
per visit	387,000		387,000	
Per year	1,548,000		11,223,000	
Time Wasting cost				
visit (per year)	840,000		2,940,000	
INR checking (per year)	-		3,150,000	
Total Cost	16,699,000	15,755,000	24,233,700	2,0345,600

from Ministry of Labor and Social Welfare based on tariffs specified on 2019 [19].

Model Analyses

Patients suffering from non-valvuar AF who were at moderate-to-high risk for stroke (CHADS2 score of 2 or more) participating in the model receiving chronic treatment with either a fixed dose Rivaroxaban (20 mg daily or 15 mg daily in patients with a creatinine clearance of 15 to 49 ml per minute) or adjusted-dose of Warfarin (with target international normalized ratio [INR], 2.0 to 3.0) [10, 20].

The cost-effectiveness of Warfarin compared to Rivaroxaban was assessed using the incremental cost-effectiveness ratio (ICER), which was calculated as the incremental cost per QALY (Quality-adjusted life years). The threshold value in other cost effectiveness studies conducted in other countries was $20,000 to $50,000. For developing countries such as Iran, World Health Organization (WHO) has recommended a cost-effectiveness threshold indicating that the ICER is less than three times the GDP (Gross Domestic Production) per capita [21]. So while the Iranian GDP is 5576$ (based on WHO recommendation), the ICER in Iran is less than 16,728$ indicating the cost-effectiveness, converting to 702,576,000IRR.

The analysis of collected data was done by SPSS software version 22 and Microsoft Excel 2003. We used the two Independent sampling T Test to examine differences between the two treatment groups. A P value of <0.05 was considered significant.

RESULTS

Study population

A total number of 98 patients who met the inclusion criteria responded to the questionnaire. 60% of participants (n=59) were in Warfarin group, while 40% were in Rivaroxaban group (n=39). Mean age of patients was 68 years (SD= 12.32) in both Warfarin and Rivaroxaban groups. Most of the patients (58% of them) were male (56 persons) ([59% of patients in Warfarin group were male (n=33), 56% of patients in Rivaroxaban group were male(n=23)] and 42% of them were Female (n=42) [41 % of patients in Warfarin group were Female (n=26) ,44% of patients in Rivaroxaban group were Female (n=16)). Mean physician visits were 14 (SD= 0.93) times per year in Warfarin group and 4 (SD= 0.25) times in Rivaroxaban group. The patients treated with Warfarin had checked their INR on average 15 times per year for anticoagulation to maintain the target INR of 2.5 (typical target range is 2.0–3.0), while the patients in Rivaroxaban group did not require an INR test. The time wasted for each doctor visit and taking Lab test was 3 hours. (Table1)

Costs

All of the related costs are summarized in Table 2. The cost of one year consumption of Rivaroxaban was 12,775,000IRR and in case of Warfarin was 438,000IRR. The annual costs of doctor visits were significantly lower in Rivaroxaban than in Warfarin group for both private and governmental Health Sectors. The cost of INR test in Warfarin group was 1,106,700IRR per year in private sector and 522,600IRR in governmental sector. The mean Transportation Cost per visit or lab tests was 387,000R, while transportation cost for Warfarin group was significantly higher than Rivaroxaban group (11,223,000 vs 1,548,000IRR). Assuming 70,000R for each hour wasted (according to minimum basic salary), the cost of time spent on doctor visit was (840,000IRR) in Rivaroxaban group and (2,940,000IRR) in Warfarin group, while this cost for INR checking was (3,150,000IRR) just in Warfarin group. Finally, our study showed that total costs of Rivaroxaban in both private (16,699,000R) and governmental sector (15,755,000R) were less than Warfarin in both private and governmental sector (24,233,700 & 20,345,600 IRR).

Utility Values

We analyze the ΔQALYs (difference between Rivaroxaban & Warfarin QALY) of 7 different articles using Markov models

Table 3. Delta QALYs of different article

		Rivaroxaban	Warfarin	Delta QALY
Lee S et al [24]		10.03	9.81	0.22
Anuj Shah et al [25]		9.24	9.02	0.22
Talitha L et al [26]	NL	9.791	9.625	0.166
	UK	8.262	7.966	0.296
Ying Zheng et al [23]		7.68	7.36	0.32
Joris Kleintjens et al [22]		8.213	8.119	0.094
Amanda R et al [27]		8.26	7.97	0.29
Martin Krejczy et al [11]		7.67	7.59	0.08
Mean				0.21075
Variance				0.00729

Table 4: Calculated ICER

	Cost		ICER (Rial/QALY)
	Warfarin	Rivaroxaban	
rivate	24,233,700	16,699,000	-35,879,523.81
governmental	20,345,600	15,755,000	-21,860,000
ICER (Rial/QALY)	18,514,761.9	4,495,238.095	

with different periods and countries which are summarized in table 3. The mean ΔQALY was 0.21 (Variance: 0.0072), and there were no significant differences between ΔQALY`s of these articles. So we used this mean ΔQALY to calculate The ICER of our study.

ICER

The Incremental cost per QALY per patient for Warfarin group in Private versus governmental sector was 18,514,762 Rial / QALY, while the ICER in Rivaroxaban group in both private & Governmental sector was negative compared to Warfarin group (-35,879,523.8 and -21,860,000 Rial/QALY) (Table 4). The negative ICER means that the use of Rivaroxaban is more cost effective than the use of Warfarin in both governmental and private sector.

DISCUSSION

Despite the more expensive cost of Rivaroxaban pills compared to Warfarin especially in IRAN, the present study showed that using Rivaroxaban can reduce the costs in both governmental and private sector than Warfarin; therefore, it is more cost effective.

One of the most important differences between the costs of governmental and private sector in Iran is the cost of doctor's visits, meaning that the costs will significantly decrease, if the patients use the governmental sector. Another important parameter that directly influences the Warfarin cost is the frequent INR test, so its decreased frequency can reduce the costs. The most significant cost in this study was Transportation cost. This means that we can reduce the costs considering this factor. For example, using governmental transportation, referring to nearest clinics and Laboratories, using mobile or social communication applications for sending the results of INR to their physicians can reduce the transportation costs.

Since the insurance system in Iran covers 70% of the costs of some drugs like Warfarin (while Rivaroxaban is not covered) and 70% of doctor visits in governmental hospitals, we found out that if the insurance institutes support the cost of Rivaroxaban pills, then it would be more cost effective than Warfarin in all situations. Because one of the most important reasons that in some circumstances the Rivaroxaban is not cost effective, is that insurance institutes do not cover Rivaroxaban, so the cost of this drug is significantly higher than Warfarin.

Most of the studies in different countries show the similar results as the present study that using the Rivaroxaban is more cost effective than Warfarin. Jurys Clinton et al. in their study evaluated the efficacy of Rivaroxaban compared to Warfarin in preventing stroke in AF patients in the Belgian Health System. They concluded that Rivaroxaban was more cost effective than Warfarin [22]. In another study, Anuj Shah et al. evaluated the effectiveness of NOACS compared to Warfarin in non-valvular AF patients. They concluded that all NOACS were more cost effective than Warfarin [22]. Amanda et al. evaluated the efficacy of Rivaroxaban compared to Warfarin in preventing stroke in non-valvular patients, and concluded that prescription of Rivaroxaban 20 mg is more cost effective than Warfarin [23].

The significant difference between Rivaroxaban and Warfarin's cost in private sector was one of the most important results of this study. It can be concluded that prescription of Rivaroxaban is suggested for patients who want to use private sector, due to its approved benefits like faster onset of action, fewer food and drug interactions, and more convenient oral anticoagulation (OAC) treatment instead of limitation of Warfarin especially the need for routine laboratory monitoring. Therefore, Rivaroxaban is a suitable suggestion in governmental sectors.

There were some limitation in our study. The first one was the actual estimation of transportation costs, because some patients used their own car for medical purposes and some others used the governmental transportations, so it was difficult to estimate the actual transportation cost. The second limitation was the cost of hospitalization for titrating the INR to its Therapeutic Range for the first prescription of Warfarin (concomitant injection of Heparin or Enoxaparin), which was not calculated in our study and hence may increase the costs for this group. The next limitation was calculating the cost and probability of events for determining QALY; so due to the lack of a database in Iran, we used the ΔQALY instead of calculating the QALY that was estimated by other studies to determine the ICER. Finally, since there was no significant threshold in Iranian literature for ICER and the calculated threshold based on the per capita gross national product (GDP) was 702,576,000 Rials (calculated at 42,000IRR/$); which seemed to be far from the reality; we could only calculate the ICER and suggest that the use of Rivaroxaban is more cost effective than Warfarin.

CONCLUSION

As a conclusion, the present study showed that use of Rivaroxaban is more cost-effective in both the governmental and private

sectors than Warfarin, so it is recommended to prescribe Rivaroxaban for the majority of patients given its potential benefits and cost-effectiveness compared to Warfarin.

CONFLICT OF INTERESTS

Our study has no relationship with industry.

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REFRENCES

1. Krahn AD, Manfreda J, Tate RB, Mathewson FA and Cuddy TE.The natural history of atrial fibrillation: incidence, risk factors, and prognosis in the Manitoba Follow-Up Study.The American journal of medicine.1995;98(5):476-84.

2. Morady F and Zipes DP. Atrial Fibrillation: Clinical Features. Mechanisms, and Management. Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine2018.

3. Hart RG, Pearce LA and Aguilar MI.Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation.Annals of internal medicine.2007;146(12):857-67.

4. Pharmacy Drug Pricing [Available from: http://www.medicaid.gov/Medicaid-CHIP-Program-Information/By-Topics/Benefits/Prescription-Drugs/Pharmacy-Pricing.html.

5. Ruff CT, Giugliano RP, Braunwald E, Hoffman EB, Deenadayalu N, Ezekowitz MD, et al.Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials.The Lancet.2014;383(9921):955-62.

6. Hart RG, Benavente O, McBride R and Pearce LA.Antithrombotic therapy to prevent stroke in patients with atrial fibrillation: a meta-analysis.Annals of internal medicine.1999;131(7):492-501.

7. Thomson R, Parkin D, Eccles M, Sudlow M and Robinson A.Decision analysis and guidelines for anticoagulant therapy to prevent stroke in patients with atrial fibrillation.The Lancet.2000;355(9208):956-62.

8. January CT, Wann LS, Alpert JS, Calkins H, Cigarroa JE, Cleveland JC, et al.2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society.Journal of the American College of Cardiology.2014;64(21):e1-e76.

9. Katsnelson M, Sacco RL and Moscucci M.Progress for stroke prevention with atrial fibrillation: emergence of alternative oral anticoagulants.Circulation.2012;125(12):1577-83.

10. Patel M, Mahaffey K, Garg J, Pan G, Singer D, Hacke W, et al.Investigators: Rivaroxaban versus warfarin in nonvalvular atrial fibrillation.N Engl J Med.2011;365(10):883-91.

11. Krejczy M, Harenberg J, Marx S, Obermann K, Froelich L and Wehling M.Comparison of cost-effectiveness of anticoagulation with dabigatran, rivaroxaban and apixaban in patients with non-valvular atrial fibrillation across countries.Journal of thrombosis and thrombolysis.2014;37(4):507-23.

12. Drugs CAf and Health Ti.Ottawa, Canada: Canadian Agency for Drugs and Technologies in Health; 2006.Guidelines for the economic evaluation of health technologies 3rd edition[Google Scholar].

13. Coyle D, Coyle K, Cameron C, Lee K, Kelly S, Steiner S, et al.Cost-effectiveness of new oral anticoagulants compared with warfarin in preventing stroke and other cardiovascular events in patients with atrial fibrillation.Value in health.2013;16(4):498-506.

14. Gage BF, Cardinalli AB and Owens DK.The effect of stroke and stroke prophylaxis with aspirin or warfarin on quality of life. Archives of internal medicine.1996;156(16):1829-36.

15. Sullivan PW, Arant TW, Ellis SL and Ulrich H.The cost effectiveness of anticoagulation management services for patients with atrial fibrillation and at high risk of stroke in the US.Pharmacoeconomics.2006;24(10):1021-33.

16. Freeman JV, Zhu RP, Owens DK, Garber AM, Hutton DW, Go AS, et al.Cost-effectiveness of dabigatran compared with warfarin for stroke prevention in atrial fibrillation.Annals of internal medicine.2011;154(1):1-11.

17. Clinical Practice Guideline for Anticoagulation Management [Available from: https://www.mahealthcare.com/pdf/practice_guidelines/Anticoagulation.pdf.

18. Ministry of Health and Medical Education Report [Available from: http://behdasht.gov.ir.

19. Ministry of Cooperatives Labour and Social Welfare Report [Available from: https://www.mcls.gov.ir/.

20. 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.European journal of cardio-thoracic surgery.2016;50(5):e1-e88.

21. WHO. World Health Organisation. Choosing interventions that are cost effective (WHO-CHOICE) Tables of costs and prices used in WHO-CHOICE analysis. [Available from: http://www.who.int/choice/costs/CER_levels/en/index.html.

22. Kleintjens J, Li X, Simoens S, Thijs V, Goethals M, Rietzschel ER, et al.Cost-effectiveness of rivaroxaban versus warfarin for stroke prevention in atrial fibrillation in the Belgian healthcare setting.Pharmacoeconomics.2013;31(10):909-18.

23. Zheng Y, Sorensen SV, Gonschior A-K, Noack H, Heinrich-Nols J, Sunderland T, et al.Comparison of the cost-effectiveness of new oral anticoagulants for the prevention of stroke and systemic embolism in atrial fibrillation in a UK setting.Clinical therapeutics.2014;36(12):2015-28. e2.

24. Lee S, Anglade MW, Pham D, Pisacane R, Kluger J and Coleman CI.Cost–effectiveness of rivaroxaban compared to warfarin for stroke prevention in atrial fibrillation.The American journal of cardiology.2012;110(6):845-51.

25. Shah A, Shewale A, Hayes CJ and Martin BC.Cost-effectiveness of oral anticoagulants for ischemic stroke prophylaxis among nonvalvular atrial fibrillation patients. Stroke.2016;47(6):1555-61.

26. Verhoef TI, Redekop WK, Hasrat F, de Boer A and Maitland-van der Zee AH.Cost effectiveness of new oral anticoag-

ulants for stroke prevention in patients with atrial fibrillation in two different European healthcare settings.American Journal of Cardiovascular Drugs.2014;14(6):451-62.

27. Harrington AR, Armstrong EP, Nolan Jr PE and Malone DC.Cost-effectiveness of apixaban, dabigatran, rivaroxaban, and warfarin for stroke prevention in atrial fibrillation. Stroke.2013;44(6):1676-81.