Profesional paper

# EFFECTIVENESS OF VITAMIN K ANTAGONISTS FOR SECONDARY PROPHYLAXIS OF BRAIN STROKE IN PATIENTS WITH ATRIAL FIBRILLATION IN ROUTINE PUBLIC CARE SETTINGS

Miftari, V.1, Vavlukis, M.2,3, Miftari, S.S.4, Ismani, E.1, Serafimov, A.3,5,

1 Clinical Hospital – Tetovo, Macedonia
2 University Clinic of Cardiology – Skopje, Macedonia
3 Medical faculty at the University "Goce Delchev" – Shtip, Macedonia
4 State University Tetovo, Department for Psychology, Macedonia
5 Clinical Hospital – Shtip, Macedonia

Medicus 2020, Vol. 25 (3): 413-419

## ABSTRACT

Intro : Vitamin K antagonists are the mainstay for prevention of strokes in patients with atrial fibrillation (AF) world-wide. Yet estimates on its effectiveness are heterogeneous and reveal stark differences between different health-care systems. The aim of the present study was to assess the laboratory parameters for achieving the goal of the therapy (Time in therapeutic range – TTR) and to describe the effectiveness of the therapy in real-time setting.

Methods : Patients treated in our clinic, with confirmed AF were considered in the study. The study was prospective observational study by design, where the participants were assessed at baseline for known risk factors for stroke, diagnosis for atrial fibrillation, use of anticoagulant medication and presence of identifiable ischemic lesions in the brain with non-contrast computed tomography (NCCT). The drug of choice was acenocoumarol, with planned monthly measurements of INR with the duration of 6 months, and the study was concluded with additional NCCT at the end, in order to assess for differences.

Results : 96 patients finished the observation. The mean age of the patients was 64.5 years (SD = 6.36), and 50 (52%) were male. Regarding the INR measurement, we collected data from 88.2% of the planed measurements; 69.7% of the patients achieved TTR above 60%. Cross-comparison between groups (TTR < 59% and TTR > 60%) revealed that the first group had statistically significant higher proportion of patients with newly registered lesions on NCCT (p-value < 0.05).

Conclusion: Acenocoumarol is the only therapeutic VKA option in our country, despite the availability of other VKA antagonists that show better indices for effectiveness. Our sample confirmed that the proper use of VKA significantly reduces the incidence of new NCCT ischemic lesions in conditions of routine public health care.

Authors keywords: atrial fibrillation, oral anticoagulants, stroke prevention, time in therapeutic range, vitamin-K antagonists, silent stroke, effectiveness;

## INTRODUCTION

Vitamin-K antagonists (VKA) represent the most utilized class of drugs in the secondary prophylaxis of thromboembolism and brain stroke in patients with atrial fibrillation on global level. They partake an important role in reducing the associated risks with atrial fibrillation (1,2), mainly regarding thromboembolic events in the brain (3–5). The use of VKA therapy has associated burdens – narrow therapeutic index (6) and sensitive pharmacokinetics (7,8), which necessitate regular laboratory monitoring and risk for complications, such as persistent bleeds from wounds or spontaneous bleeds. Some of these complications are predictable (9) by following a laboratory parameter - the international standardized ratio (INR) (10), a derivate of prothrombin time, which is used to express the targets of the therapy and to properly dose the VKA (11). As recommended, the best treatment effect of VKA therapy in this scenario is achieved when the value of INR is in the range 2-3 (11,12), while values below and above are associated with thromboembolic and hemorrhagic events, respectively (13). Recent studies report on the use of VKA in terms of serial INR measurements, finding out that in setting of regular care, patients achieve the targets of therapy in 30-75% of all measurements (14–16), which is less than in settings of randomized control trials.

The use of VKA at local level has not been subject to a systematic study. Previous study conducted in the Balkans (neighboring countries) revealed that patients achieved TTR of 49.5% (Potpara et al.) In Macedonia there is only one registered VKA, acenocoumarol (tablets, 4 mg), which is used in the secondary prophylaxis of stroke in patients with atrial fibrillation.

The aim of the present study is to analyze the correlation of time in therapeutic range in patients taking VKA and incident ischemic stroke (diagnosed with clinical and imaging modalities).

## METHODS AND POPULATION

This was prospective, observational cohort study, conducted at the Neurology Department of the University Clinic – Tetovo, Macedonia. All registered patients in the last six months and patients in the period from January 2019 to April 2019 with findings of atrial fibrillation were considered in the study, based on their informed consent. The patient population is representative of the northwestern part of the country, as the overall majority of the citizens use the public health service. Patients were evaluated for indication for oral anticoagulant therapy use (and previous OAT use). Inclusion criteria were: EGC-evidenced atrial fibrillation (2) and diagnosis set by cardiologist (ICD-10 code I-48), CHA2DS2Vasc-Score above 1 (or above 0 for males) (17), actual use of acenocoumarol or willing to start with prescribed therapy with acenocoumarol (in accordance with treatment guidelines), and consent to attend regular INR monitoring on monthly basis and undergo native computed tomography scan of the brain on two occasions, six months apart. As exclusion criteria we used concurrent use of/or indication for antiplatelet drug, presence of contraindications for acenocoumarol (active bleeding or previous major bleeding due to acenocoumarol, previous major surgery). All patients signed informed consent to participate in the study.

## MEASUREMENTS

At study enrollment, patients underwent native non-contrast computed tomography (NCCT) of the brain and measurement of the international standardized ratio (INR). Their previous health records were checked for previous/actual conditions of the vasculature, heart, thromboembolic events, diabetes mellitus, presence of implants and rheumatological conditions and targets for INR other than 2-3. All of the measurements were done at the Clinical hospital – Tetovo. For performing CT of the brain, we used SOMATOFORM SIEMENS CT, with generating 1.6 mm axial slices. All of the CT-scans of the brain were evaluated for the presence of fields of ischemic sequelae in the brain by trained radiologist and neurologist. As findings of interest were CT-hypo-intense signals with Handsfield unit (HU) values approximating the HU values of the cerebrospinal liquor in the same case which were localized in single arterial territory and were not consequence of known trauma or bleeding, including both cortical and lacunar infarctions. At the end of the observation period patients were scanned again, and the second NCCT-scan of the brain was used for comparison, in order to register new lesions. Patients came regularly at three-month visit for follow-up, with monthly check of the INR at the transfuziology unit at our hospital with the use of Hymanclot Analyzer. The time in therapeutic range was determined individually under the assumption that patients performed monthly INR measurements as number of INR measurements in range of 2-3 over number of total INR measurements,

with projected 7 measurements during the 6 months of observation. Patients with less than 4 measurements were not included in the analysis, as their TTR could not be reliably determined.

CHA2DS2Vasc score (18) represents a quantitative tool for determining future stroke risk in patients with diagnosed atrial fibrillation. It takes into account the age (>= 75 years – 2 points, 65-75 years – 1 point), presence of arterial hypertension (1 point), presence of congestive heart failure or left-ventricular systolic dysfunction (1 point), diabetes mellitus (1 point), prior stroke, transient ischemic attack or embolic event (2 points), vascular disease (1 point), female sex (1 point), with 9 points in total, with projected annual risks for incident disease rising significantly above 1 point. It's use has entered the practice as clinical tool for risk assessment (19), making compound measure of risk factors for thromboembolism in patients with AF.

Table 1. Descriptive statistics on patient sample characteristics (n = 96)

| Variable | Patient sample |
|---|---|
| Age (x, SD) | 64.5 (6.36) |
| Gender (% males) | 50 (52%) |
| Previous VKA use (%) | 67 (69.7%) |
| Past/current thromboembolic conditions | 56 (55.2%) |
| Arterial hypertension (%) | 70 (72.9%) |
| Diabetes mellitus (%) | 26 (27.1%) |
| INR measurements (x, SD) | 6 (0.6) |

INR – International Normalized Ratio

## ANALYSIS

In order to describe the patient group, demographic characteristics on age, gender, ethnicity, previous OAT use, CHA2DS2-Vasc score, presence of arterial hypertension and diabetes mellitus are presented in terms of mean (with standard deviation) for continuous and proportions for categorical variables. The values regarding time in therapeutic range, presence of NCCT-identifiable lesions at enrollment and follow-up are derived from individual patient data and were described with mean, SD, median. In order to test for differences in NCCT-incident lesions between patients with TTR above and below 60%, the Fischer's exact test for comparison of proportions was used. The analysis of data employs intention-to-treat analysis. Statistical significance was determined at the level of 0.05.

## RESULTS

From the initial 126 patients enrolled at the beginning, 96 (76%) patients finished the observation period. The resulting sample of 96 patients had average age of 64.5 years (SD = 6.36) and 50 (52%) were male. 29 patients were newly prescribed VKA users while the remaining 67 patients had continued VKA use in the last 3 months. The descriptive statistics on the patient sample are available in table 1.

From 96 patients and planned 672 measurements, we collected data from 593 of the measurements (88.2%). The mean time in therapeutic range was 0.65 (SD = 0.15), ranging from 0.28 to 1 (3 cases). The corresponding distribution is presented with histogram in figure 1. Patients that did not show up during the study had an average of 3.1 INR measurements, insufficient for calculating the time in therapeutic range. The resulting sample revealed that 67 patients (69.7%) achieved TTR above 60%, while 29 patients achieved TTR below that threshold.

The results from the first NCCT-scan revealed that 59 patients were free of identifiable lesions while 37 patients had at least one identifiable lesion that could be attributed to ischemic event in the brain. From the 37 patients with CT findings, 2 patients had 2 lesions registered on the NCCT-scan. The results from the second NCCT-scan revealed that 42 patients had NCCT-registered lesions in the brain, out of which 5 patients had 2 lesions, while 54 patients did not have any finding.

Cross-comparison between the patients with TTR above 60% and the other group revealed that 2 patients (3%) of the first group had NCCT-findings consistent with new ischemic lesion, while 5 patients (17.2%) in the second group had NCCT-findings for new lesion.

Differences between the two groups in terms of incident CT-lesions were assessed by the Fisher's exact test, which revealed statistically significant differences in proportions of 0.142, with p-value of 0.025 (figure 2). The odds ratio for incident CT lesion was 5.78 higher in the group that did not maintain TTR above 60% (95%CI 1.189 – 28.067) (Figure 2).

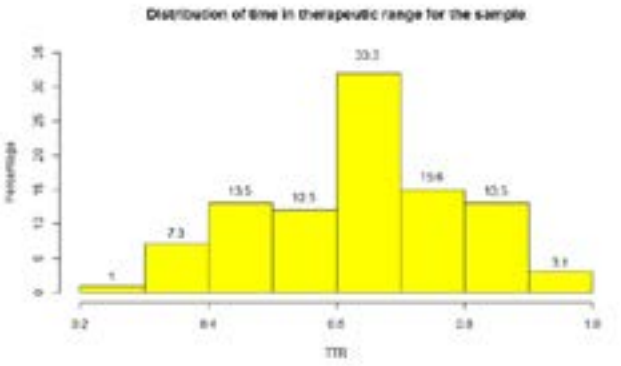


Figure 1. Histogram of individual time in therapeutic range (TTR) of the patient sample (n = 96). Numbers above bars denote percentages.

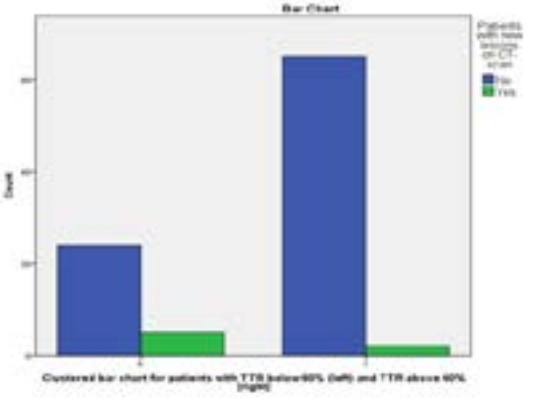

Figure 2. Comparison between proportion of patients with new CT-lesions between patients that achieved TTR above 60% and patients that achieved TTR below 60%.

Legend: TTR- time in therapeutic range

## DISCUSSION

The present study is the first study to investigate the importance of maintaining time in therapeutic range for prophylaxis of incident brain strokes in Macedonia. Given the fact that 38% of the patients had identifiable lesion that can be attributed to ischemic event in the brain on the baseline computed tomography reflects the patient base drawn from neurological practice.

From the planned measurements for INR, patients that finished the study managed to attend at the 89% of the monthly regular measurements. In our sample, 67% of the patients maintained TTR of at least 60%, and the mean TTR was 0.65. This finding is slightly different than the results from another regional study, where the measure of TTR was secondary objective, reports that TTR was available for 18.7% of the analyzed patients, with reported mean TTR of 49.5% (95%CI 20-90%), while the most recent measurement of INR was available for 79% of the patients, where 55.2% of the patients were in therapeutic range (20). Of note is that patients treated with VKA's were not exclusively on monotherapy and this was not the primary objective of the study, which could explain the differences in comparing the results for TTR (0.65 vs 0.52) and availability of past INR measurements (89% vs 79%).

One of the earliest meta-analysis on the topic from Walraven (21) revealed differences of achieving good anticoagulation control in the setting of RCT, anticoagulation clinic and community follow-up. For instance, the mean unadjusted mean of TTR followed in clinic or RCT was 65.4% (95%CI 63.7-67.7%) and 66.4% (95%CI - 59.4%-73.3%) respectively, while TTR measured in community practice was estimated at 56.7% (95%CI - 51.5%-62%), giving statistically significant difference, while the conclusions of the study revealed that self-monitoring of INR could increase TTR in selected populations, an option that is still not employed in the health systems in Macedonia. The findings of the study are comparable to our results, taking into account that the INR measurements were conducted at the transfusiology department of Clinical Hospital – Tetovo. Still, of note is one curious finding, albeit statistically insignificant (p = 0.08) – the metanalysis compared TTR in studies conducted before 1998, finding out that studies conducted later reported slightly better anticoagulation control, which might be indicative of the gained experience of the health systems in prescribing therapy with VKA and follow-up. The reported results are in line with the findings of other studies conducted at European level (22)

Another consideration in this study is the choice of the anticoagulant drug. Currently, our market has only one registered drug, acenocoumarol. Recent observational study from PREFER IN AF Registry reports that patients on monotherapy with acenocoumarol achieved the lowest TTR (65.9%), in comparison to warfarin (69.3%), fluindione (72.7%), phenprocoumon (80.4%) (22) Another recent observational study from Spain, where the most utilized drug is acenocoumarol, conducted on older sample than ours (mean age = 73.8 +- 9.4 years), estimated that the mean TTR was 63.77%, while 54% of the patients exhibited poor control (TTR < 65%) ((23). Regarding the long-term stability of this parameter, it has been found that most of the patients show stable trajectory after the first 6 months of measurement (Pokorney et al.; Witt et

al.; McAlister et al.).

Although 37 patients did have previous findings on CT scan, additional 19 patients had either recorded finding in the past for transient ischemic attack, acute myocardial infarction or deep venous thrombosis. Additionally, 67 of the patients had already been put on routine Vitamin-K antagonists, while during the recruitment, 32 patients started treatment with VKA. The results of the study confirm the finding of effectiveness of VKA antagonist with regard to strokes as registered on NCCT.

The variability of the findings in the reported studies are due to factors regarding the patients, the drug used in the study, but also due to the different health care setting among different countries. The last has been investigated in a cost-benefit analysis, comparing the use of NOACs vs the traditional VKAs – for instance, where three NOACs have been calculated as cost-effective alternative of coumarins in Great Britain, while two of them were significantly better in terms of cost-effectiveness in The Netherlands. The findings of the study emphasize the quality of INR control, which is main determinant of effectiveness of this therapy (24). This finding is in line with other studies on cost-effectiveness, where the importance of maintaining INR is highlighted (25).

The limitations of our study might stem from the sample population, which is drawn from population that utilize public health services. Next, the possibility for information bias is present since the outcome is derived from inferior imaging method (CT in comparison to MRI). CT in this scenario has lower sensitivity than advanced imaging techniques, such as the computed-tomography perfusion (CTP), computed tomography angiography (CTA) (26) and magnetic resonance imaging (MRI) (27). Although the analysis was done in intention-to-treat manner, the study assumes that the INR measurements are indicative of real use of the medication by the patients.

## CONCLUSIONS

As important finding of this study is the high rate of INR control in our sample. The differences between the patients that achieve TTR > 60% had significantly lower number for new ischemic lesions as registered on CT. One realization of the present study is the unavailability of other drugs from the same class on our market. The use of acenocoumarol provides certain benefits with regard to its short half-life, which is convenient as therapy before anticipated invasive or semi-invasive procedures. The absence of other VKA antagonists in our health-care system should be reconsidered, as it has been found out that acenocoumarol achieves lowest TTR, as provided from the literature, and showed similar TTR to the studies that pointed out this difference. This necessity is emphasized for countries in development, where the health care systems cannot afford to provide the NOACs which are much more expensive and where the use of anticoagulant therapy in the patients with risk is underutilized.

## BIBLIOGRAPHY


1. Mcallen PM, Marshall J. CARDIAC DYSRHYTHMIA AND TRANSIENT CEREBRAL ISCHÆMIC ATTACKS. Lancet [Internet]. 1973 Jun 2 [cited 2019 Sep 27];301(7814):1212–4. Available from: https://www.sciencedirect.com/science/article/pii/S0140673673905278
2. Fuster V, Rydén LE, Cannom DS, Crijns HJ, Curtis AB, Ellenbogen KA, et al. ACC/AHA/ESC 2006 guidelines 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 European Society of Cardiology Committee for practice [Internet]. Vol. 114, Circulation. 2006 [cited 2018 Oct 15]. p. e257-354. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16908781
3. Granger CB, Alexander JH, McMurray JJV, Lopes RD, Hylek EM, Hanna M, et al. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med [Internet]. 2011 Sep 15 [cited 2019 Sep 27];365(11):981–92. Available from: http://www.nejm.org/doi/10.1056/NEJMoa1107039
4. Prystowsky EN, Padanilam BJ, Fogel RI. Treatment of Atrial Fibrillation. JAMA [Internet]. 2015 Jul 21 [cited 2019 Sep 27];314(3):278. Available from: http://jama.jamanetwork.com/article.aspx?doi=10.1001/jama.2015.7505
5. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: The framingham study. Stroke [Internet]. 1991 Aug [cited 2019 Sep 27];22(8):983–8. Available from: https://www.ahajournals.org/doi/10.1161/01.STR.22.8.983
6. Katzung BG, Trevor AJ. Basic and Clinical Pharmacology 13 E : Bertram G. Katzung : 9780071825054. McGraw-Hill Education - Europe. 2015.
7. Shoeb M, Fang MC. Assessing bleeding risk in patients taking anticoagulants. In: Journal of Thrombosis and

Thrombolysis [Internet]. NIH Public Access; 2013 [cited 2018 Oct 15]. p. 312–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23479259

8. Leite PM, Martins MAP, Castilho RO. Review on mechanisms and interactions in concomitant use of herbs and warfarin therapy [Internet]. Vol. 83, Biomedicine and Pharmacotherapy. 2016 [cited 2019 Oct 12]. p. 14–21. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27470545
9. Schulman S, Beyth RJ, Kearon C, Levine MN. Hemorrhagic Complications of Anticoagulant and Thrombolytic Treatment. Chest [Internet]. 2008 Jun [cited 2019 Sep 28];133(6):257S-298S. Available from: http://www.ncbi.nlm.nih.gov/pubmed/18574268
10. Mann K. Biochemistry and Physiology of Blood Coagulation. Thromb Haemost [Internet]. 1999 Dec 9 [cited 2019 Sep 11];82(08):165–74. Available from: http://www.thieme-connect.de/DOI/DOI?10.1055/s-0037-1615780
11. Ageno W, Gallus AS, Wittkowsky A, Crowther M, Hylek EM, Palareti G. Oral anticoagulant therapy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest [Internet]. 2012 Feb [cited 2019 Sep 11];141(2 Suppl):e44S-e88S. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22315269
12. Pengo V, Denas G. Optimizing quality care for the oral Vitamin K antagonists (VKAs). Hematology [Internet]. 2018 [cited 2019 Dec 21];2018(1):332–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/30504329
13. Witt DM, DelatE T, ClarK NP, Martell C, Tran T, Crowther MA, et al. Twelve-month outcomes and predictors of very stable INR control in prevalent warfarin users. J Thromb Haemost [Internet]. 2010 Apr [cited 2019 Sep 11];8(4):744–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20398186
14. McAlister FA, Wiebe N, Hemmelgarn BR. Time in therapeutic range and stability over time for warfarin users in clinical practice: a retrospective cohort study using linked routinely collected health data in Alberta, Canada. BMJ Open [Internet]. 2018 Jan 29 [cited 2018 Oct 12];8(1):e016980. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29382672
15. Park H-S, Kim Y-H, Kim JS, Oh Y-S, Shin D-G, Pak H-N, et al. Status of international normalized ratio control and treatment patterns in patients with nonvalvular atrial fibrillation taking vitamin K antagonist with or without antiplatelet therapy: Results from KORAFII registry. J Arrhythmia [Internet]. 2019 Aug [cited 2019 Sep 26];35(4):593–601. Available from: http://www.ncbi.nlm.nih.gov/pubmed/31410229
16. White HD, Gruber M, Feyzi J, Kaatz S, Tse HF, Husted S, et al. Comparison of outcomes among patients randomized to warfarin therapy according to anticoagulant control results from SPORTIF III and V. Arch Intern Med. 2007;
17. 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 [Internet]. Vol. 37, European Heart Journal. 2016 [cited 2018 Oct 15]. p. 2893–962. Available from: https://academic.oup.com/eurheartj/article-lookup/doi/10.1093/eurheartj/ehw210
18. Lip GYH, Nieuwlaat R, Pisters R, Lane DA, Crijns HJGM. Refining Clinical Risk Stratification for Predicting Stroke and Thromboembolism in Atrial Fibrillation Using a Novel Risk Factor-Based Approach. Chest [Internet]. 2010 Feb [cited 2020 Jan 13];137(2):263–72. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0012369210600670
19. January CT, Wann LS, Calkins H, Chen LY, Cigarroa JE, Cleveland JC, et al. 2019 AHA/ACC/HRS focused update of the 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 Clinical Practice Guidelines and the Heart R. Hear Rhythm [Internet]. 2019 Aug 1 [cited 2019 Aug 13];16(8):e66–93. Available from: http://www.ncbi.nlm.nih.gov/pubmed/30703530
20. Potpara TS, Dan G-A, Trendafilova E, Goda A, Kusljugic Z, Manola S, et al. Stoke prevention in atrial fibrillation and real world adherence to guidelines in the Balkan Region - The BALKAN-AF Survey. Sci Rep [Internet]. 2016 Feb 12 [cited 2019 Oct 13];6:20432. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26869284
21. Van Walraven C, Jennings A, Oake N, Fergusson D, Forster AJ. Effect of study setting on anticoagulation control: A systematic review and metaregression. Chest. 2006;
22. Le Heuzey JY, Ammentorp B, Darius H, De Caterina R, Schilling RJ, Schmitt J, et al. Differences among western European countries in anticoagulation management of atrial fibrillation: Data from the PREFER IN AF Registry. Thromb Haemost. 2014;111(5):833–41.
23. Bertomeu-González V, Anguita M, Moreno-Arribas J, Cequier Á, Muñiz J, Castillo-Castillo J, et al. Quality of

Anticoagulation with Vitamin K Antagonists. Clin Cardiol [Internet]. 2015 Jun [cited 2019 Dec 21];38(6):357–64. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25962838

24. Verhoef TI, Redekop WK, Hasrat F, de Boer A, Maitland-van der Zee AH. Cost Effectiveness of New Oral Anticoagulants for Stroke Prevention in Patients with Atrial Fibrillation in Two Different European Healthcare Settings. Am J Cardiovasc Drugs [Internet]. 2014 Dec 18 [cited 2019 Dec 21];14(6):451–62. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25326294
25. Janzic A, Kos M. Cost Effectiveness of Novel Oral Anticoagulants for Stroke Prevention in Atrial Fibrillation Depending on the Quality of Warfarin Anticoagulation Control. Pharmacoeconomics [Internet]. 2015 Apr 16 [cited 2019 Dec 20];33(4):395–408. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25512096
26. Shen J, Li X, Li Y, Wu B. Comparative accuracy of CT perfusion in diagnosing acute ischemic stroke: A systematic review of 27 trials. PLoS One [Internet]. 2017 [cited 2019 Dec 6];12(5):e0176622. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28520753
27. Mitomi M, Kimura K, Aoki J, Iguchi Y. Comparison of CT and DWI findings in ischemic stroke patients within 3 hours of onset. J Stroke Cerebrovasc Dis [Internet]. 2014 Jan [cited 2019 Sep 22];23(1):37–42. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23040956