JHAS 2020; 10(2):40-48
DOI: https://doi.org/10.37107/jhas.154

Predictors of Oral Anticoagulants Utilization in Patients with Atrial Fibrillation

Sabina Sankhi,[1] Nirmal Raj Marasine,[1] Rajendra Lamichhane,[2] Nim Bahadur Dangi[1]
[1]Pharmaceutical Sciences Program, School of Health and Allied Sciences, Pokhara University, Kaski, Nepal
[2]Department of Public Health, Asian College for Advance Studies, Lalitpur, Nepal.

ABSTRACT

Introduction: Atrial fibrillation (AF) is the most common sustained cardiac rhythm disturbance, increasing in prevalence with age. It is often associated with structural heart disease, although a substantial proportion of patients with AF have no detectable heart disease. Hemodynamic impairment and thromboembolic events related to AF result in significant morbidity, mortality, and cost. Several factors are associated with the prescription of oral anticoagulants. This review predicts the overall factors that are associated with oral anticoagulant utilization in patients with AF.

Methods: Literatures that analyze the predictors of oral anticoagulant utilization in atrial fibrillation were searched using PubMed and Google Scholar published in journals from 2003 to 2019. Eligibility, data extraction and quality assessment were followed by a narrative synthesis of data. An extensive search of recent literature was performed.

Results: Older age, comorbidities like hypertension, diabetes, heart failure, coronary artery disease, peripheral artery disease, moderate to severe kidney disease, polypharmacy, higher stroke and bleeding risk, history of smoking and alcohol or substance abuse, and lower cost are predictors of warfarin utilization. Similarly, younger age, better kidney function with creatinine clearance at least 30 mL/min, no or lower risk of stroke and hemorrhage, no polypharmacy, less comorbidities, prescriptions by neurologists and cardiologist, people residing in countries with lower poverty rates, and high cost are potential predictors of non-vitamin K antagonist oral anticoagulants utilization.

Conclusion: Our study suggests that knowing the predictors for anticoagulation utilization can improve medication appropriateness in arterial fibrillation patients.

Keywords: *Predictors, Atrial fibrillation, Oral anticoagulants, Stroke risk*

INTRODUCTION

Atrial fibrillation (AF) is the most common sustained cardiac rhythm disturbance, increasing in prevalence with age. Its prevalence ranges from 0.1% in patients <55 years old to 8% in those ≥80 years age.[1-3] AF is often associated with structural heart disease, although a substantial proportion of patients with AF have no detectable heart disease. Patients with AF have a five-fold increased risk of stroke and account for approximately 15% of all strokes.[4] Strokes associated with AF are more severe with higher mortality, and greater disability requiring longer hospitalization and hence the increased health care cost.[5, 6] Oral anticoagulants (OAC) are highly effective, and principal therapy for atrial fibrillation patients with increased risk of stroke. OAC includes both Vitamin-K antagonists (VKAs) like warfarin, and recently introduced, non-vitamin K antagonist oral anticoagulants (NOAC) including both direct thrombin inhibitors (dabigatran) and direct factor Xa inhibitors (rivaroxaban, apixaban, and edoxaban).[7-9] NOACs are also called direct oral anticoagulants (DOAC). For more than 50 years, Warfarin was only available long-term anticoagulant therapy for the prevention of stroke in patients with atrial fibrillation (AF). NOACs are equally as effective as VKAs with less bleeding evidence like intracranial hemorrhage.[8-10] NOACs are easy to use for both patients and physicians, since they offer specific benefits, such as predictable pharmacologic profiles, rapid onset of action, wide therapeutic window favoring fixed dosing regimens, no need for routine coagulation monitoring, and fewer and better- defined food and drug interactions compared with warfarin.[11-13] In contrast, VKAs have narrow therapeutic index, more drug-drug and food-drug interactions, need regular coagulation monitoring, and dose adjustments.[14-16] Even after careful dose adjustment, the international normalized ratio (INR) goes frequently outside the target therapeutic range, which is associated with an increased risk of stroke (INR <2.0) and bleeding (INR >3.0).[17, 18] Despite their recognized limitations, warfarin are still regarded as

Correspondence: Sabina Sankhi, M.Pharm, Clinical Pharmacist, Pharmaceutical Sciences Program, School of Health and Allied Sciences, Pokhara University, Email: sabinasankhi03@gmail.com

the standard regimen for stroke prevention in many regions because of their low costs and established monitoring services, which makes easy for physicians to monitor anticoagulation adherence.[19-21]

Many researchers have attempted to demonstrate the factors for the utilization of oral anticoagulants and their consistent use in patients with AF. Evidence suggest that, old age, race, patient-related, and provider-related factors determines the utilization of OAC, i.e. either VKA or NOAC.[22, 23] Older patients at an elevated stroke and low bleeding risk may be associated with a higher prescription of OAC. However, younger age, higher bleeding risk, perceived low stroke risk, and personal preference were reported to be associated with lower OAC prescription. In addition, the presence of antiplatelet use was common and was associated with a four-fold increased odds of OAC non-prescription.[24] There are limited studies on the widespread activity of NOACs and so on the predictors leading to the choice of oral anticoagulants in patients with AF in clinical practice. Identification of factors associated with anticoagulant selection and use could lead to an improvement in patient care. Inappropriate use or selection of OAC may lead to inadequate stroke prevention and adverse effects in patients with AF.[25] Hence, the objective of this analysis was to conduct a literature review summarizing the results of studies dealing with the predictors of OACs i.e. VKA and NOACs utilization in patients with AF.

METHODS

Data Sources, Searches, and selection

An extensive search of recent literature was performed using PubMed and Google Scholar to identify relevant study to this topic published in journals from 2003 to 2019. The following search terms were used: anticoagulants, prescription pattern, anticoagulant utilization, predictors, atrial fibrillation, oral anticoagulants, vitamin K antagonist, warfarin, and NOACs. The search was limited to the English language. Articles listed in the author's reference lists and those listed in other systematic reviews were also included on the basis of relevancy, and irrelevant studies were eliminated.

Data screening and extraction

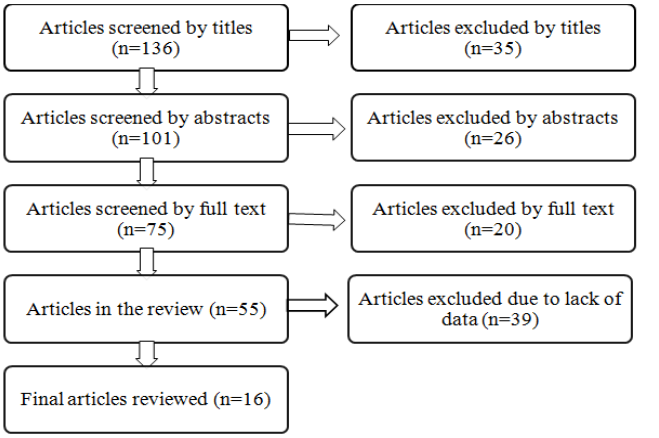

Figure 1: Data screening and extraction

Study selection

For inclusion in our review, studies need to be:

1. Of varying methodologies i.e. observational, prospective, cross-sectional, and retrospective, that analyze the predictors of oral anticoagulant utilization in patients with AF.
2. Reported on a population of patients aged ≥ 18 years with atrial fibrillation receiving at least one anticoagulant.
3. Published in English language only, and
4. Published no earlier than 2003.

Our study outcomes were the possible factors that predict the utilization of oral anticoagulants that may be either VKA (warfarin) or any NOACs in patients with AF. Studies that did not meet our criteria were excluded during the review. Studies were discarded if they were clinical trials, reviews, protocols, and case reports.

RESULTS

The studies included were published from 2003 to 2019. One hundred and thirty-six articles were selected by title/abstract, and finally sixteen were included. The total sample size was 8, 80, 213 patients. One study was performed in Germany,[26] one in Italy,[27] four in Canada,[28, 29, 32, 36] nine in the United States,[30, 31, 33-35, 37, 38, 40, 41] and one in Israel [39]. Sample sizes were less than 1000 in five of the studies, 1000-15,000 in five of the studies, 20,000-75,000 in five of the studies, and more than 5,00,000 in one of the studies. Table 1 shows the main findings of these studies.

Table 1: Study, objective, methods, and major findings of the studies

Study	Objective	Methods	Major findings
Haas et al (2019)[26]	To explore the predictors of NOAC vs VKA use for stroke prevention in patients with AF.	Cross-sectional study GARFIELD-AF registry n=24,137 age: ≥18 years (April 2013 and August 2016)	Predictors of NOAC prescription: elderly patients with acute coronary syndrome, paroxysmal AF, normotensive patients, and with moderate alcohol consumption. Predictors of VKA prescription: patients with permanent AF, moderate to severe kidney disease, heart failure, vascular disease, and diabetes and with concomitant use of antiplatelet.

Guerriero et al (2018)[27]	To assess predictors of new oral anticoagulants vs warfarin in elderly adults.	Retrospective observational study n=967 age: ≥75 years (January 2014 to December 2014)	Predictor of NOAC initiation: Prior exposure to platelet aggregation inhibitors. Age>75 years, severe renal disease, and multiple concomitant medications (five to nine drugs) were associated with a low rate of NOAC initiation.
Miller et al (2018)[28]	To identify factors associated with OAC prescription in patients presenting to the emergency department with atrial fibrillation or atrial flutter.	Retrospective cohort study n=663 age: >18 years (January 2015 to December 2015)	Factors associated with high rates of OAC initiation: hospitalization, atrial fibrillation/atrial flutter presented as a primary diagnosis and increased risk of stroke.
Mclntyre et al (2018)[29]	To identify patient, physician, and temporal factors associated with the stroke-prevention strategy in Patients With AF.	Observational cross-sectional study GLORIA AF-Registry n=3,320 age: ≥18 years (November 2011 to February 2014)	Predictors of OAC non-prescription: use of antiplatelet drugs, a history of falling, prior bleeding, and paroxysmal AF. Factors associated with VKA: heart failure, diabetes mellitus, and additional therapy with antiplatelet drugs. Predictors for lower OAC use: patients at higher risk of stroke (CHADS2 score ≥2), and high risk of bleeding (HAS-BLED score ≥3).
Lubitz et al (2018)[30]	To identify factors associated with the lack of OAC prescription in an outpatient sample of AF patients with elevated stroke risk.	Longitudinal study PINNACLE registry n=6,74,841 age: ≥18 years (January 2008 to December 2014)	Diverse factors related with OAC non-prescription: female sex, liver, renal or vascular disease, physician versus non-physician providers, and concomitant use of antiplatelet. OAC prescription: Older patients at elevated stroke and low bleeding risk. Lower prescription of OAC: younger age, lower stroke risk, and higher bleeding risk.
Fohtung et al (2017)[31]	To examine changes in anticoagulation prescribing practices for older adults with AF, and trends in the uptake of NOACs.	Retrospective observational study n=6,568 age: ≥75 years (October 2010 to September 2015)	Younger age, white race, female gender, higher hemoglobin, higher creatinine clearance, being on medical service, history of stroke, no history of intracranial hemorrhage increased the use of NOACs.
Brais et al (2017)[32]	To assess clinical predictors associated with the use of DOACs over warfarin among new users of OAC for AF.	Retrospective cross-sectional study n=439 age: ≥18 years (October 2011 to October 2014)	Predictors of DOACs prescription: younger age, history of stroke, no peripheral artery disease, estimated creatinine clearance of at least 30mL/min, no polypharmacy and OAC prescription by a neurologist. Predictors of warfarin prescription over DOACs: Older age (≥75 years), comorbidities (hypertension, diabetes), CHADS2 score of 2 or more, coronary artery disease, peripheral artery disease, polypharmacy and concomitant use of clopidogrel.
Efird et al (2017)[33]	To determine the prevalence of novel anticoagulant use in patients with AF and venous thromboembolism.	Retrospective cross-sectional study n=5,632 age: ≥75 years (April 1, 2012 to April 3, 2013)	Predictors of novel anticoagulant use in AF: younger age, lowest stroke risk (CHADS2 score of 0 or 1) and people residing in countries with lower poverty rate. Lower prescribing of novel agents was seen in patients with heart failure and diabetes.

Steinberg et al (2017)[34]	To describe pattern and factors associated with selection of a NOAC versus warfarin.	Prospective, observational cohort study ORBIT-AF II design n=11,603 age: ≥21 years (February 2013 to January 2016)	Factors for NOAC selection: renal function, prior stroke or valve replacement, rhythm control, AF management strategy, treatment by a cardiologist, and higher patient education level. NOACs users: younger patients (<71 years), were less likely to have prior stroke, prior bleeding, had better kidney function and low stroke risk.
Durham et al (2017)[35]	To describe the time from AF diagnosis to the initiation of an OAC, characteristics associated with treatment, and the incidence of switching OACs.	Retrospective cohort study n=23,018 age: ≥18 years (2010 to 2014)	OAC non-prescription was associated with severe dementia or psychosis. OAC prescription was associated with a history of stroke or transient ischemic attack.
Ha et al (2015)[36]	To explore patterns of and factors associated with the use of oral anticoagulation for stroke prevention of AF patients.	Retrospective Cross-sectional analysis SPRINT-AF registry n=782 age: ≥18 years (December 2012-July 2013)	Factors associated with warfarin use (vs. NOAC use): older age, history of smoking, coronary artery disease, non-paroxysmal AF, treatment with concomitant antiplatelet and lower cost.
Lauffenburer et al (2015)[37]	To assess the factors associated with anticoagulant selection in patients with AF.	Retrospective cohort study n=70,498 age: ≥ 18 years (October 2010 to December 2012)	Predictors of warfarin selection (vs NOACs): Patients with high ischemic stroke risk (CHADS2≥2) and high bleeding risk (ATRIA≥5).
AbuDagga et al (2014)[38]	To identify patient, healthcare provider, and health plan factors associated with dabigatran versus warfarin use among non-valvular AF patients.	Retrospective analysis n=20,320 age: ≥ 18 years (October 2009-April 2012)	Dabigatran users: young age (<70 years), females, prescription by a cardiologist, high cost, lower CHADS2 risk scores, lower ATRIA scores, fewer comorbidities and history of ischemic stroke.
Melamed et al (2011)[39]	To assess the level of anticoagulation control achieved in patients with AF, and the factors influencing it.	Retrospective cross-sectional study n=906 age: 18-85 years (November 2006 to October 2007)	Factors associated with poor control (warfarin): female sex, advancing age (age ≥75 years), and comorbid conditions (diabetes mellitus, hypertension, heart failure, or prior stroke). Independent predictors of poor control: Heart failure and having a non–board-certified physician.
Agarwal et al (2010)[40]	To evaluate clinical factors that could influence warfarin use or other anticoagulant use in hospitalized patients with AF.	Retrospective observational study n=24,820 age: ≥40 years (November 2003 to October 2004)	Predictors for lower warfarin treatment: Older age (≥75 years), female sex, and certain risk factors for bleeding, including hepatic disease, renal disease, aspirin use, and fractures. Higher stroke risk (CHADS2 scores 2 and 3) was associated with a higher likelihood of warfarin treatment.
Johnston et al (2003)[41]	To find predictors of warfarin use among patients with new-onset non-valvular atrial fibrillation.	Retrospective cohort analysis n=11,699 age: ≥18 years (January 1998-December 2000)	Independent factors associated with warfarin use: Hypertension and Congestive Heart Failure. Predictors of lower warfarin use: older age (≥85years), younger age (<55years), prior intracranial hemorrhage, alcohol or other drug abuse and renal impairment.

Abbreviation: CHADS2: incorporates congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke/transient ischemic attack; ATRIA: incorporates anemia, severe renal disease, age ≥75 years, previous hemorrhage, and hypertension; HAS-BLED: hypertension, abnormal renal and liver function, stroke, bleeding history or predisposition, labile INR, elderly age (>65 years)

DISCUSSION

This review describes the predictors of warfarin and NOAC utilization in patients with atrial fibrillation. From this review, it is revealed that NOACs were more likely to be prescribed in younger patients,[31-34, 38] while warfarin was mostly used in older patients (≥75 years), except in patients ≥85 years.[27, 30, 32, 36] In older patients, extra precautions should be followed while administering the drug, and they might have a higher incidence of contraindications with increasing age. Increased risk of both ischemic stroke and major hemorrhage (including intracranial hemorrhage) might be associated with old age.[42] But the benefits provided by warfarin in terms of decreasing the stroke rates might be the reason for considering the use of warfarin in older AF patients.[43] Lower use of warfarin in younger patients might be due to physicians considering younger people to be at lower risk of thromboembolic and stroke events. During the literature review, it was found that women were less likely to receive warfarin than men.[30, 40] A study by Melamed et alshowed poor coagulation control in women using warfarin.[39] Other two studies by Fohtung et al. and AbuDagga et al pointed out that NOACs were more prescribed in women than men.[31, 38] This might be due to women being on lower risk of AF-associated stroke.[44] The difference might also be associated with a physician prescribing habit and belief that the benefits of warfarin use in men are higher than those in women, as men are at higher risk of stroke than women.[45] A study by Steinberg et al demonstrated socioeconomic factors like education level driving NOAC selection.[34] NOACs were found to be used in more educated patients, since they are more concerned about safety and efficacy of medications. A number of studies have demonstrated that patients with a high stroke risk (CHADS2 ≥2 and high bleeding risk (ATRIA≥5 or HAS-BLED score ≥3) were more likely to use warfarin than NOACs.[28, 30, 37] Patients treated with NOACs (dabigatran) have a lower risk of stroke and bleeding. Therefore, a history of stroke and low stroke risk (CHADS2 score 0 or 1) were found to be the predictors of NOACs use.[31-34, 38] Warfarin, being a narrow therapeutic index drug, requires close monitoring with frequent blood tests and counseling about drug and dietary interactions, which might have contributed to poor anticoagulation control and low utilization rates.[39, 40, 46] It was also found that patients with comorbid conditions like hypertension, coronary artery disease (CAD), peripheral artery disease (PAD), diabetes, and heart failure were more likely to be prescribed warfarin than NOACs.[26, 29, 32, 39-41] Relatively, reduction in anticoagulant prescription is associated with fewer conditions. A wide range of cardiac disorders are associated with an increase in the utilization of anticoagulants, which might be due to increased visit of patients with physicians who are more inclined to start anticoagulants. According to the findings of our review, polypharmacy is an important factor that influences the choice of VKA over NOAC.[27, 32] Patients with AF who are exposed to moderate (five to nine drugs) to extensive polypharmacy (more than ten drugs) were less likely to use an NOAC compared to warfarin.[2] Interestingly, concomitant use of clopidogrel, aspirin, and other anti-platelets were negatively associated with NOAC initiation, as per the studies conducted in Canada in the years 2018 and 2015, respectively.[29, 32, 36] This could be due to the interaction of such drugs with NOACs, resulting in an increase in the risk of bleeding complications. Additionally, limited evidence on the safety of NOAC-antiplatelet association and lack of knowledge on NOACs induced drug interactions may also have limited their use.[28, 33, 47] It reflects that clinicians are aware of NOACs and had a better understanding of indications for their use along with their use on antiplatelet therapy.[31, 32] In contrast, antiplatelet use, paroxysmal AF, history of bleeding, history of falls, dementia, psychosis, liver disease, and use of antiplatelet were pointed as the potential reasons for OAC non-prescription by two of the studies.[29, 35] Similarly, patients at higher risk of stroke who are at high risk of bleeding were found less likely to receive OAC.[29] The net benefit of OAC in AF patients is demonstrated in those who have additional risk factors for stroke, including higher bleeding score.[48, 49] Another factor associated with NOAC initiation was prior exposure to platelet aggregating inhibitors (PAI). Concomitant use of PAI and OAC is required in AF patients with drug-eluting stent implantation or acute coronary syndrome. These patients are likely to use NOACs more than three times compared to warfarin. The concomitant use of PAI and NOAC is related to the easier management of therapy in terms of bleeding risk.[27, 50] Moreover, three of the studies [31, 32, 34] demonstrated that an estimated creatinine clearance of at least 30mL/min is a predictor of NOACs use. They demonstrated better renal function in patients on NOACs than those on warfarin.[32, 51] A 75 mg twice daily dose of dabigatran was approved by the Food and Drug Administration of the United States, for individuals with severe renal impairment (creatinine clearance: 15 to 30 mL/min).[51]Nevertheless, two of the studies showed that VKAs are advantageous for patients with severe renal diseases where creatinine clearance is ≤15 mL/min, in contrast to NOAC.[26, 27, 52] Another predictor of NOAC utilization found was prescription by neurologists and cardiologists.[32, 34] This could be due to NOACs associated with a lower risk of intracranial hemorrhage and being effective in stroke prevention.[53-55] NOACs are superior in efficacy and costlier than warfarin. The cost of

medication is often an important limiting factor for patients in the selection of better treatment. NOAC use was found higher in patients with higher incomes and those who reside in the country with a lower poverty rate.[33, 36] Some studies have shown a negative association between some adverse sociodemographic factors like smoking, alcohol consumption, and substance abuse with OAC use.[26, 36, 41]

CONCLUSION

This review suggests that knowing the predictors for anticoagulation utilization can improve medication appropriateness in arterial fibrillation patients. Though the predictors varied, and had potential for mortality reduction and cost savings but its impact on quality of life was not clear. The good use of oral anticoagulant treatment influence greatly the response of patients with atrial fibrillation, and the indication for oral anticoagulant treatment is important point in that use. Thus, clinical practice is important to improve good use, and hence the response to treatment.

ACKNOWLEDGMENT

We acknowledge all the authors of the retrieved original articles.

CONFLICTS OF INTEREST

The authors declare that they have no competing interests.

REFERENCES

1. Go AS, Hylek EM, Phillips KA, Chang Y, Henault LE, Selby JV, Singer DE. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. Jama. 2001; 285(18): 2370-5.
2. Misayaka Y, Barnes ME, Gersh BJ, Cha SS, Bailey KR, Abhayaratna WP. Secular trends in incidence of atrial fibrillation in Olmsted county Minnesota, 1980 to 2000 and implications on the projection for future prevalence. Circulation. 2006; 114:119-25.
3. Naccarelli GV, Varker H, Lin J, Schulman KL. Increasing prevalence of atrial fibrillation and flutter in the United States. The American journal of cardiology. 2009; 104(11):1534-9.
4. Fuster V, Rydén LE, Cannom DS, Crijns HJ, Curtis AB, Ellenbogen KA, Halperin JL, Le Heuzey JY, Kay GN, Lowe JE, Olsson SB. ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation. Europace. 2006; 8(9):651-745.
5. Conen D, Chae CU, Glynn RJ, Tedrow UB, Everett BM, Buring JE, Albert CM. Risk of death and cardiovascular events in initially healthy women with new-onset atrial fibrillation. Jama. 2011 May 25; 305(20): 2080-7.
6. Patel NJ, Deshmukh A, Pant S, Singh V, Patel N, Arora S, Shah N, Chothani A, Savani GT, Mehta K, Parikh V. Contemporary trends of hospitalization for atrial fibrillation in the United States, 2000 through 2010: implications for healthcare planning. Circulation. 2014; 129(23): 2371-9.
7. Authors/Task Force Members, Camm AJ, Lip GY, De Caterina R, Savelieva I, Atar D, Hohnloser SH, Hindricks G, Kirchhof P, ESC Committee for Practice Guidelines (CPG), Bax JJ. 2012 focused update of the ESC Guidelines for the management of atrial fibrillation: an update of the 2010 ESC Guidelines for the management of atrial fibrillation Developed with the special contribution of the European Heart Rhythm Association. European heart journal. 2012; 33(21):2719-47.
8. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, Castella M, Diener HC, Heidbuchel H, Hendriks J, Hindricks G. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. European journal of cardio-thoracic surgery. 2016; 50(5):e1-88.
9. Guidelines for pharmacotherapy of atrial fibrillation (JCS 2013). Circulation Journal. 2014; 78(8): 1997-2021.
10. Giugliano RP, Ruff CT, Braunwald E, Murphy SA, Wiviott SD, Halperin JL, Waldo AL, Ezekowitz MD, Weitz JI, Špinar J, Ruzyllo W. Edoxaban versus warfarin in patients with atrial fibrillation. New England Journal of Medicine. 2013; 369(22): 2093-104.
11. Gorst□Rasmussen A, Skjøth F, Larsen TB, Rasmussen LH, Lip GY, Lane DA. Dabigatran adherence in atrial fibrillation patients during the first year after diagnosis: a nationwide cohort study. Journal of Thrombosis and Haemostasis. 2015; 13(4): 495-504.
12. Di Minno MN, Russolillo A, Di Minno A, Camera M, Parolari A, Tremoli E. Direct anticoagulant drugs to overcome limitations of vitamin K antagonists. A critical appraisal of data in atrial fibrillation patients. Expert Opinion on Emerging Drugs. 2013; 18(1):9-23.
13. Safavi-Naeini P, Saeed M. Target-specific oral anticoagulants: should we switch from warfarin?. Texas Heart Institute Journal. 2015; 42(3):229-33.
14. Zirlik A, Bode C. Vitamin K antagonists: relative strengths and weaknesses vs. direct oral anticoagulants for stroke prevention in patients with atrial fibrillation. Journal of thrombosis and thrombolysis. 2017; 43(3):

365-79.

15. Ageno W, Gallus AS, Wittkowsky A, Crowther M, Hylek EM, Palareti G. Oral anticoagulant therapy: antithrombotic therapy and prevention of thrombosis: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2012; 141(2): e44S-88S.
16. Amouyel P, Mismetti P, Langkilde LK, Jasso-Mosqueda G, Nelander K, Lamarque H. INR variability in atrial fibrillation: a risk model for cerebrovascular events. European journal of internal medicine. 2009; 20(1): 63-9.
17. Fontana P, Robert-Ebadi H, Bounameaux H, Boehlen F, Righini MP. Direct oral anticoagulants: a guide for daily practice. Swiss medical weekly. 2016; 146: w14286.
18. White HD, Gruber M, Feyzi J, Kaatz S, Tse HF, Husted S, Albers GW. Comparison of outcomes among patients randomized to warfarin therapy according to anticoagulant control: results from SPORTIF III and V. Archives of internal medicine. 2007; 167(3): 239-45.
19. De RC, Husted S, Wallentin L, Andreotti F, Arnesen H, Bachmann F, Baigent C, Huber K, Jespersen J, Kristensen SD, Lip GY. Vitamin K antagonists in heart disease: current status and perspectives (Section III). Position paper of the ESC Working Group on Thrombosis--Task Force on Anticoagulants in Heart Disease. Thrombosis and haemostasis. 2013; 110(6): 1087-107.
20. Björck F, Renlund H, Lip GY, Wester P, Svensson PJ, Själander A. Outcomes in a warfarin-treated population with atrial fibrillation. JAMA cardiology. 2016; 1(2): 172-80.
21. Huisman MV, Rothman KJ, Paquette M, Teutsch C, Diener HC, Dubner SJ, Halperin JL, Ma C, Zint K, Elsaesser A, Bartels DB. Antithrombotic treatment patterns in patients with newly diagnosed nonvalvular atrial fibrillation: the GLORIA-AF registry, phase II. The American journal of medicine. 2015; 128(12): 1306-13.
22. Tulner LR, Van Campen JP, Kuper IM, Gijsen GJ, Koks CH, Mac Gillavry MR, van Tinteren H, Beijnen JH, Brandjes DP. Reasons for undertreatment with oral anticoagulants in frail geriatric outpatients with atrial fibrillation. Drugs & aging. 2010; 27(1): 39-50.
23. Waldo AL, Becker RC, Tapson VF, Colgan KJ, NABOR Steering Committee. Hospitalized patients with atrial fibrillation and a high risk of stroke are not being provided with adequate anticoagulation. Journal of the American College of Cardiology. 2005; 46(9): 1729-36.
24. Hsu JC, Maddox TM, Kennedy K, Katz DF, Marzec LN, Lubitz SA, Gehi AK, Turakhia MP, Marcus GM. Aspirin instead of oral anticoagulant prescription in atrial fibrillation patients at risk for stroke. Journal of the American College of Cardiology. 2016; 67(25): 2913-23.
25. Xu Y, Holbrook AM, Simpson CS, Dowlatshahi D, Johnson AP. Prescribing patterns of novel oral anticoagulants following regulatory approval for atrial fibrillation in Ontario, Canada: a population-based descriptive analysis. CMAJ open. 2013; 1(3): E115.
26. Haas S, Camm AJ, Bassand JP, Angchaisuksiri P, Cools F, Corbalan R, Gibbs H, Jacobson B, Koretsune Y, Mantovani LG, Misselwitz F. Predictors of NOAC versus VKA use for stroke prevention in patients with newly diagnosed atrial fibrillation: Results from GARFIELD-AF. American heart journal. 2019; 213: 35-46.
27. Guerriero F, Orlando V, Monetti VM, Colaccio FM, Sessa M, Scavone C, Capuano A, Menditto E. Predictors of new oral anticoagulant drug initiation as opposed to warfarin in elderly adults: a retrospective observational study in Southern Italy. Therapeutics and clinical risk management. 2018; 14: 1907.
28. Miller RJ, Chew DS, Rezazadeh S, Klassen S, Pournazari P, Lang E, Quinn FR. Factors influencing oral anticoagulation prescription for patients presenting to emergency departments with atrial fibrillation and flutter. Canadian Journal of Cardiology. 2018; 34(6): 804-7.
29. McIntyre WF, Conen D, Olshansky B, Halperin JL, Hayek E, Huisman MV, Lip GY, Lu S, Healey JS. Stroke prevention strategies in North American patients with atrial fibrillation: The GLORIA AF registry program. Clinical cardiology. 2018; 41(6): 744-51.
30. Lubitz SA, Khurshid S, Weng LC, Doros G, Keach JW, Gao Q, Gehi AK, Hsu JC, Reynolds MR, Turakhia MP, Maddox TM. Predictors of oral anticoagulant non-prescription in patients with atrial fibrillation and elevated stroke risk. American heart journal. 2018; 200: 24-31.
31. Fohtung RB, Novak E, Rich MW. Effect of new oral anticoagulants on prescribing practices for atrial fibrillation in older adults. Journal of the American Geriatrics Society. 2017; 65(11): 2405-12.
32. Brais C, Larochelle J, Turgeon MH, Blais L, Farand P, Perreault S, Letemplier G, Beauchesne MF. Predictors of direct oral anticoagulants utilization for thromboembolism prevention in atrial fibrillation. Journal of Pharmacy & Pharmaceutical Sciences. 2017; 20: 8-14.
33. Efird LE, Chasler J, Alexander GC, Mcguire M. Prescribing patterns of novel anticoagulants within a statewide multispecialty practice. American Journal of Pharmacy Benefits. 2016; 8(3): 97-102.
34. Steinberg BA, Shrader P, Thomas L, Ansell J, Fonarow GC, Gersh BJ, Hylek E, Kowey PR, Mahaffey KW, O'Brien EC, Singer DE. Factors associated with non–vitamin K antagonist oral anticoagulants for stroke

prevention in patients with new-onset atrial fibrillation: results from the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation II (ORBIT-AF II). American heart journal. 2017; 189: 40-7.
35. Durham TA, Lich KH, Viera AJ, Fine JP, Mukherjee J, Weinberger M, Dusetzina SB. Utilization of standard and target-specific oral anticoagulants among adults in the United Kingdom with incident atrial fibrillation. The American journal of cardiology. 2017; 120(10): 1820-9.
36. Ha AC, Singh N, Cox JL, Mancini GJ, Dorian P, Fournier C, Gladstone DJ, Lockwood E, Shuaib A, Kajil M, Tsigoulis M. Oral anticoagulation for stroke prevention in Canadian practice: stroke prevention and rhythm interventions in atrial fibrillation (SPRINT-AF) registry. Canadian Journal of Cardiology. 2016; 32(2): 204-10.
37. Lauffenburger JC, Farley JF, Gehi AK, Rhoney DH, Brookhart MA, Fang G. Factors driving anticoagulant selection in patients with atrial fibrillation in the United States. The American journal of cardiology. 2015; 115(8): 1095-101.
38. AbuDagga A, Stephenson JJ, Fu AC, Kwong WJ, Tan H, Weintraub WS. Characteristics affecting oral anticoagulant therapy choice among patients with non-valvular atrial fibrillation: a retrospective claims analysis. BMC health services research. 2014; 14(1): 310.
39. Melamed OC, Horowitz G, Elhayany A, Vinker S. Quality of anticoagulation control among patients with atrial fibrillation. The American journal of managed care. 2011; 17(3): 232-7.
40. Agarwal S, Bennett D, Smith DJ. Predictors of warfarin use in atrial fibrillation patients in the inpatient setting. American journal of cardiovascular drugs. 2010; 10(1): 37-48.
41. Johnston JA, Cluxton RJ, Heaton PC, Guo JJ, Moomaw CJ, Eckman MH. Predictors of warfarin use among Ohio medicaid patients with new-onset nonvalvular atrial fibrillation. Archives of internal medicine. 2003; 163(14): 1705-10.
42. Choudhry NK, Soumerai SB, Normand SL, Ross-Degnan D, Laupacis A, Anderson GM. Warfarin prescribing in atrial fibrillation: the impact of physician, patient, and hospital characteristics. The American journal of medicine. 2006; 119(7): 607-15.
43. Fitzmaurice DA, Blann AD, Lip GY. Bleeding risks of antithrombotic therapy. Bmj. 2002; 325(7368): 828-31.
44. Fuster V, Rydén LE, Cannom DS, Crijns HJ, Curtis AB, Ellenbogen KA, Halperin JL, Le Heuzey JY, Kay GN, Lowe JE, Olsson SB. 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 guidelines (writing committee to revise the 2001 guidelines for the management of patients with atrial fibrillation): Developed in collaboration with the european heart rhythm association and the heart rhythm society. Circulation. 2006; 114(7): e257-354.
45. Frost L, Johnsen SP, Pedersen L, Toft E, Husted S, Sørensen HT. Atrial fibrillation or flutter and stroke: a Danish population□based study of the effectiveness of oral anticoagulation in clinical practice. Journal of internal medicine. 2002; 252(1): 64-9.
46. Hankey GJ, Eikelboom JW. Dabigatran etexilate: a new oral thrombin inhibitor. Circulation. 2011; 123(13): 1436-50.
47. Trikha R, Kowey PR. Practical considerations for the nonvitamin K antagonist oral anticoagulants. Cardiology. 2017; 136(2): 115-24.
48. Friberg L, Rosenqvist M, Lip GY. Evaluation of risk stratification schemes for ischaemic stroke and bleeding in 182 678 patients with atrial fibrillation: the Swedish Atrial Fibrillation cohort study. European heart journal. 2012; 33(12):1500-10.
49. Olesen JB, Lip GY, Lindhardsen J, Lane DA, Ahlehoff O, Hansen ML, Raunsø J, Tolstrup JS, Hansen PR, Gislason GH, Torp-Pedersen C. Risks of thromboembolism and bleeding with thromboprophylaxis in patients with atrial fibrillation: a net clinical benefit analysis using a 'real world'nationwide cohort study. Thrombosis and haemostasis. 2011; 106(10): 739-49.
50. Task Force Members, Lip GY, Windecker S, Huber K, Kirchhof P, Marin F, Ten Berg JM, Haeusler KG, Boriani G, Capodanno D, Gilard M. Management of antithrombotic therapy in atrial fibrillation patients presenting with acute coronary syndrome and/or undergoing percutaneous coronary or valve interventions: a joint consensus document of the European Society of Cardiology Working Group on Thrombosis, European Heart Rhythm Association (EHRA), European Association of Percutaneous Cardiovascular Interventions (EAPCI) and European Association of Acute Cardiac Care (ACCA) endorsed by the Heart Rhythm Society (HRS) and Asia-Pacific Heart .... European heart journal. 2014; 35(45): 3155-79.
51. Steinberg BA, Holmes DN, Piccini JP, Ansell J, Chang P, Fonarow GC, Gersh B, Mahaffey KW, Kowey PR, Ezekowitz MD, Singer DE. Early adoption of dabigatran and its dosing in US patients with atrial fibrillation: results from the outcomes registry for better informed treatment of atrial fibrillation. Journal of the American

Heart Association. 2013; 2(6): e000535.

52. Andreotti F, Rocca B, Husted S, Ajjan RA, Ten Berg J, Cattaneo M, Collet JP, De Caterina R, Fox KA, Halvorsen S, Huber K. Antithrombotic therapy in the elderly: expert position paper of the European Society of Cardiology Working Group on Thrombosis. European heart journal. 2015; 36(46): 3238-49.
53. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, Pogue J, Reilly PA, Themeles E, Varrone J, Wang S. Dabigatran versus warfarin in patients with atrial fibrillation. New England Journal of Medicine. 2009; 361(12):1139-51.
54. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, Breithardt G, Halperin JL, Hankey GJ, Piccini JP, Becker RC. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. New England Journal of Medicine. 2011; 365(10):883-91.
55. Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, Al-Khalidi HR, Ansell J, Atar D, Avezum A, Bahit MC. Apixaban versus warfarin in patients with atrial fibrillation. New England Journal of Medicine. 2011; 365(11):981-92.