Predictors of Oral Anticoagulants Utilization in Patients with Atrial Fibrillation

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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

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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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.

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,\textsuperscript{26} one in Italy,\textsuperscript{27} four in Canada,\textsuperscript{28, 29, 32, 36} nine in the United States,\textsuperscript{30, 31, 33-35, 37, 38, 40, 41} and one in Israel.\textsuperscript{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.
| Source                        | Aim                                                                 | Study Design and Details                                                                 | Key Findings                                                                 |
|-------------------------------|----------------------------------------------------------------------|-----------------------------------------------------------------------------------------|------------------------------------------------------------------------------|
| Guerriero et al (2018)⁷       | 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)⁸          | 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. |
| McIntrye et al (2018)⁹        | 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)⁸          | 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)¹¹        | 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. |
| Bras et al (2017)¹²           | 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)¹¹          | 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. |
| Study (Year) | Purpose | Study Design | Study Sample | Factors for NOAC selection | Factors for Warfarin Use |
|-------------|---------|--------------|--------------|----------------------------|--------------------------|
| Steinberg et al (2017) | 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) | 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) | 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. |
| Lauffenburger et al (2015) | 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) | 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) | 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) | 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) | 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 (≥85 years), younger age (<55 years), 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, while warfarin was mostly used in older patients (≥75 years), except in patients ≥85 years. 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.4 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 al showed 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, 32 This might be due to women being on lower risk of AF-associated stroke.4 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.44 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 In contrast, patients with paroxysmal AF, a 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, 31 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, 30 Moreover, three of the studies 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 75mg 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. Some studies have shown a negative association between some adverse sociodemographic factors like smoking, alcohol consumption, and substance abuse with OAC use.

**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.

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**CONFLICTS OF INTEREST**

The authors declare that they have no competing interests.

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