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The prevalence of using direct oral anticoagulants (DOACs) versus warfarin in atrial fibrillation at King Abdullah Medical City (KAMC) in Makkah, Saudi Arabia

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ABSTRACT

Introduction: Atrial fibrillation is an irregular and can be a very rapid heart rate disorder. It is a type of arrhythmia that increases the risk of stroke and associated with increasing the risk of heart failure and all-cause mortality. Warfarin has been commonly prescribed in the treatment and prevention of different thromboembolic conditions including the atrial fibrillation. However, in recent years, several new oral anticoagulant medications with a direct and reversible inhibitory effect on the enzymatic activity of thrombin (dabigatran) or factor Xa (apixaban and rivaroxaban) in the coagulation cascade have been developed and approved by the FDA as an equivalent to warfarin or even more effective. We are doing this study to show the prevalence of those three drugs compared to warfarin and to estimate the patient's eligibility for using warfarin compared to the new oral anticoagulants. *Method:* Retrospective study, at Cardiology department at King Abdullah Medical city (KAMC) in Makkah. *Result:* We screened a total of 267 patients, out of 144 patients who were taking DOACs, 97 (74.6%) were included. And out of 123 patients who were taking warfarin, 33 (25.4%) of them were included. Patients were excluded because they don't have the right diagnosis, or do not have INR or serum creatinine results. Pregnant and lactating women were also excluded. *Conclusion:* Since FDA approval, apixaban and dabigatran use in AF has increased dramatically compared to warfarin which was diminished. In patients with AF, risks of stroke/SE and major bleeding were lower with DOACs versus warfarin. However, it is vital to perform continuous monitoring of these medication effectiveness.

Keywords: warfarin, dabigatran, apixaban and rivaroxaban, atrial fibrillation.

1. INTRODUCTION

Atrial fibrillation is a common thromboembolic condition through the worldwide (Pistoia et al., 2016). It is a type of arrhythmia that can increase the risk of stroke five folds, were one of five patients with stroke suffers from atrial fibrillation (AF) (Pistoia et al., 2016). Not only it increases the risk of stroke, but it is also associated with increasing the risk of heart failure and all-causes of mortality (Odutayo et al., 2016). After diagnosis, anticoagulation therapy is initiated to prevent stroke and other thromboembolic conditions and to decrease the risk of over-all morbidity and mortality (Kirchhof et al., 2016). The greatest risk factor of atrial fibrillation is age, there by the prevalence increases as the age increases (Kelly-Hayes, 2010; Da Silva, 2015). Warfarin has been commonly prescribed in the treatment and prevention of different thromboembolic conditions including the atrial fibrillation (January et al., 2014; Mayet, 2016). It has a narrow therapeutic index and is only effective when the therapeutic range is maintained (Mayet, 2016; Whalen et al., 2019). In warfarin treatment, patients require titration of the dose and the needed dose can differ largely among patients (Soff, 2012; Schulman, 2014; van den et al., 2018). A clot can form in the bloodstream if the dose is too low and a hemorrhage may occur if the dose is too high (Mayet, 2016; van den et al., 2018; Husted et al., 2014; Wadhera et al., 2014). Because of that, monitoring the International Normalized Ratio (INR) must be done frequently to adjust the dose (Wadhera et al., 2014; Harbrecht, 2011).

In recent years, several direct oral anticoagulant (DAOCs) medications with a direct and reversible inhibitory effect on the enzymatic activity of thrombin (dabigatran) or factor Xa (apixaban and rivaroxaban) in the coagulation cascade have been developed and approved by the FDA as an equivalent to warfarin or even more effective (Unger, 2015; Ahmed et al., 2016). They offer an easier way for long-term anticoagulation treatment since they don't need frequent INR monitoring and less frequent dose changes (van den et al., 2018; Wadhera et al., 2014; Avendano et al., 2019). These agents are effective alternatives to warfarin for the treatment and prevention of stroke in patients with atrial fibrillation, a meta-analysis study done on patients with atrial fibrillation showed that the direct oral anticoagulants significantly reduced the risk of stroke and systemic embolism by 19% compared to warfarin and showed an overall reduction in intracranial hemorrhage and all-cause mortality (Hindricks et al., 2021; Lip et al., 2017; Aguilar et al., 2013; De Caterina et al., 2012; Ruff et al., 2014; De souza et al., 2019). The eligibility of using warfarin or the direct oral anticoagulants may differ from patient to another depends on many reasons, the most common reason for the use of new oral anticoagulants ineligibility is renal dysfunction and the most common reason for warfarin ineligibility is bleeding (Dhillon et al., 2015).

Several studies investigating the prevalence of warfarin have been done and the results showed an overall decline in the prescribing rate of warfarin, a study showed that the usage of warfarin in atrial fibrillation decreased from 69.8% in 2008 to 42.2% in 2014 and another showed a significantly decrease from 72.2% to 42.1% over a 5-year period from 2013 to 2017 (Alalwan et al., 2017; Shields et al., 2019). However, in Saudi Arabia the extent to which the DOACs have been used is unknown. Thus, we are aiming in this current study to investigate the prevalence of DOACs usage in atrial fibrillation at King Abdullah Medical City in Makkah.

2. METHODOLOGY

Study design and setting

We conducted a retrospective study at King Abdullah Medical City (KAMC) in Makkah. Data from 267 patients were obtained from January 2018 through November 2022 based on patient's medication records obtained from an electronic database medical record (EMRs).

Data collection and assessment

Data were collected from the electronic medical records in KAMC in Makkah. Data collection forms which are not showing any nominative information. Patient was identified by medical record number (MRN) and initials. These were linked to patient's name and MRN in a separate identification log sheet which was kept in a safe locked place. Data entry was performed by two different researchers. After verification, data was transferred directly to statistical database. The data collection form was filled with patient demographics (age, weight, etc.,) clinical diagnosis of atrial fibrillation, medications (warfarin or apixaban or dabigatran or rivaroxaban) for at least 48 hours, laboratory results (INR, Scr, CrCl) and adverse events (occurrence of atrial fibrillation, stroke, venous thromboembolism, valvular heart disease and bleeding such as intracranial hemorrhage or major gastrointestinal bleeding).

Inclusion and exclusion criteria

Patients who were above 18 years old and taking warfarin, dabigatran, rivaroxaban or apixaban for atrial fibrillation treatment or stroke prevention were included in this study. We excluded pregnant and lactating women, patients who can't take oral medication and patients who have undocumented INR.

Outcomes and measurement

The primary outcome was the prevalence of using the direct oral anticoagulants (DOACs) including dabigatran, rivaroxaban or apixaban compared to warfarin as they were prescribed by physicians between the 1 January 2018 to 31 December 2020. The secondary outcomes were assessing the patients' eligibility for using either warfarin or the new oral anticoagulants by measuring the creatinine clearance and INR levels and appropriateness of dosing and drug interaction in poly pharmacy patients.

Statistical Analysis Plan

All variables were analyzed using SPSS Var 23.0 software 2015. Descriptive statistics were calculated and presented as means and standard deviations or percentages. Comparison between two groups was made using Mann Whitney test or Student's t-test. The P-value <0.005 was considered statistically significant.

Ethical part & confidentiality

Ethical approval was obtained from KAMC IRB. No King Abdulaziz City for Science and Technology on 14-07-1433 (Registration no. H-02-K-001) and is following the GCP-ICH regulations (OHRP Registration no. IORG0007625).

3. RESULTS

Patients included in this study were predominantly female (52.8%, no=121). The mean age was 65.39 (SD ± 13.16) and mean BMI was 33.68 (SD ± 28.29). Other demographic characteristic of patients who were involved in this study are summarized in table 1.

Table 1 Demographic characteristic, Table represents demographics; data presented in actual patient's numbers and percentage (%).

Demographic characteristic	Actual patients' numbers (Percentage %)
Gender	
Male	108 (47.2)
Female	121 (52.8)
Nationality	
Saudi	208 (90.8)
Non-Saudi	21 (9.2)
Diagnosis	
AF	207 (90.4)
Paroxysmal AF	22 (9.6)

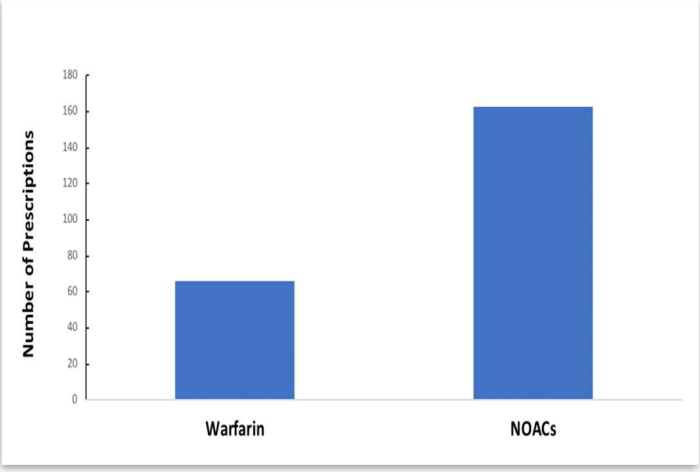

Figure 1 The prescribing prevalence of DOACs versus Warfarin

We screened a total of 267 patients. Around 163 (71%) patients were taking DOACs, while 66 (40%) patients were taking warfarin. We excluded patients who don't have atrial fibrillation, recorded INR or serum creatinine results. Pregnant and lactating women were excluded too. Figure 1 demonstrates the prescription prevalence of warfarin 66 (25.4%) versus DOACs 163 (74.6%), while Figure 2 shows the prescription prevalence of different DOACs. Majority of patients were receiving Apixaban (150 prescriptions, 65.5%) and some received dabigatran (13 prescriptions, 5.7%). However, rivaroxaban was not prescribed among our patients.

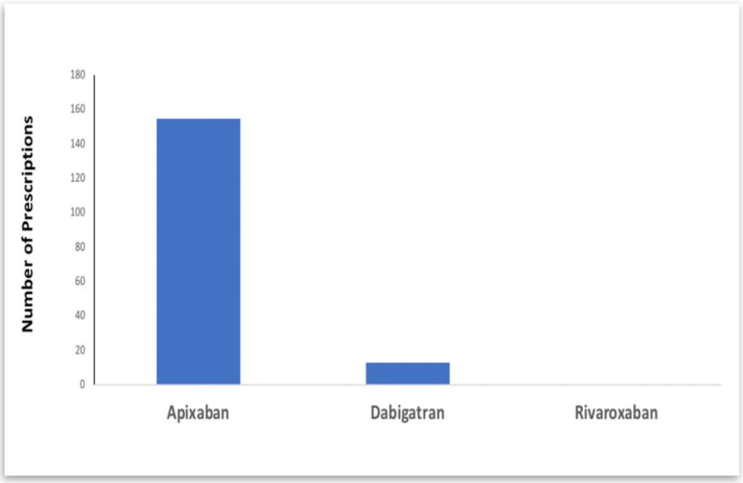

Figure 2 The prescribing prevalence of different DOACs: Apixaban, Dabigatran and Rivaroxaban

Comorbidity burden of congestive heart failure (CHF), hypertension, older age, diabetes, and stroke was very high in subjects prescribed Dabigatran as shown in table 2

Table 2 Comorbidity burden of DOACs and warfarin, data presented in actual patient's numbers and percentage (%).

	DOACs		
	Apixaban	Dabigatran	Warfarin
CHF	49 (32.6%)	5 (38%)	16 (24.2%)
Hypertension	128 (85.3%)	12 (92.3%)	40 (60%)
Age > 75	45 (30%)	9 (69.2%)	11 (16.6%)
Age > 65	85 (56.6%)	11 (84.6%)	28 (42.4%)
DM	96 (64%)	9 (69.2%)	26 (39.3%)
Stroke	23 (15.3%)	3 (23%)	10 (15%)
Vascular Disease	12 (8%)	1 (4%)	10 (15%)
Abnormal liver or renal functions	80 (53.3%)	9 (69.2%)	38 (57.5%)

Table 3 Comparison between the DOACs and Warfarin on Age, Poly Pharmacy, CHADSVASc scores, HAS BLEED scores, Creatinine Clearance

	DOAC	Warfarin
Age		
Mean	55 years	65 years
St. Deviation	12.613	13.809
Polypharmacy		
Mean	6 medications/month	5 medications/month
%	79.4%	57.6%
CHADSVASc Score		
Mean	4.07	2.66
St. Deviation	1.8722	1.8143
HAS BLEED scores		

Mean	2.52	2.12
St. Deviation	1.1555	1.4309
Creatinine Clearance		
Mean	81.09 ml/min	86.46 ml/min
St. Deviation	35.263	50.566

As shown in Table 3, CHADSVASc scores were higher among patients receiving DOACs compared to patients receiving warfarin (P-value, 0.05). In which the average CHADSVASc score in DOACs group is 4.07, where in warfarin group is 2.66. However, HAS-BLED scores between the two groups were quite similar, the average score in DOACs group was 2.52, where in warfarin group was 2.12. Moreover, 79.4% of the DOACs patients had poly pharmacy, which mean that they were taking more than 5 medications a month, whereas 57.6% of those on warfarin are considered to have poly pharmacy. Around 8 patients suffered adverse event while on Warfarin that made them switch to DOACs, those adverse events include (Bleeding, stroke and Subsegmental PE).

4. DISCUSSION

Our main aim of this research was to investigate the prevalence of using the Direct Oral Anticoagulants versus Warfarin therapy in the therapy and prophylaxis of atrial fibrillation at King Abdullah Medical City in Makkah. In Saudi Arabia the majority of people lifestyle, health and eating habits differ than western countries. Therefore, it was recommended that DAOCs is better than Warfarin to decrease the risk of stroke and the rate of bleeding (Yiu and Bajorek, 2019). In our study we concluded that the prevalence of using DAOCs was very high especially in older patients which shows a good management in following the guideline in Saudi Arabia as this will help in increasing patients' safety and low adverse effects from the other medications. Moreover, we found that patients were receiving Apixaban and dabigatran. However, rivaroxaban was not prescribed among our patients, this drug might be unavailable in this hospital. Our results were like a study that was done in the USA they concluded that Rivaroxaban and Apixaban were both used to treat VTE versus the use of Warfarin (Lutsey et al., 2019). Another similar analysis of the Danish Nationwide Cohort study they also showed the same shift from warfarin to the use of new oral anticoagulant medications as Rivaroxaban, Apixaban and Dabigatran (Sindet-Pedersen et al., 2017).

On the other hand, we found that patients with low creatinine clearance their physicians prescribe Warfarin for them despite the vital adverse effect that occurs from it. There is a study was done in Saudi Arabia to assess the quality of life in patients using apixaban versus Warfarin and they found a significant difference between the two groups in the form of self-care (Dhillon et al., 2015). Explaining that their physicians used Warfarin in patients who had well self-management (Alalwan et al., 2017). HAS-BLED is scoring system to assess bleeding risk in patient with atrial fibrillations based on factors such as hypertension, abnormal renal and liver function, stroke, bleeding tendency, labile INR in patients taking warfarin, elderly age and the use of other medications (Shields et al., 2019). HAS-BLED has been found to predict hemorrhage risk better compared with another score (Hart et al., 2007). In our study there was no difference between the group using Warfarin and the group using DAOCs. This was different from a study found that patients took Warfarin had higher Has-Bled versus patients taking rivaroxaban (Alkhotani et al., 2020).

On the contrary, our study showed a significant difference in the CHADSVASc score found that patient using DAOCs had higher scores than using Warfarin. Our results showed also that the average creatinine clearance in the warfarin group was higher than the average in the DOACs group. Moreover, our patients in this study with AF, risks of stroke/SE and major bleeding were lower with DOACs versus warfarin. This result was in parallel with a systematic review assessing the efficacy and safety of DOACs analysis that showed bleeding risk was reduced for Apixaban and Rivaroxaban versus Warfarin (Sterne et al., 2017). Evidence from Pair wise meta-analysis showed that Apixaban had lower risk for GI bleeding compared to Rivaroxaban (Mamas et al., 2022), this can be an explanation of our results as the major drug was Apixaban which showed low risk of bleeding. In addition, patients on DOACs had more comorbidities than patients on Warfarin. Therefore, using DOACs is much safer with lower side effects than Warfarin this is supported by our results that showed patients on Warfarin were shifted to DOACs.

Our study possesses several limitations of inherent to its retrospective, observational design and one central analysis with small sample size. Moreover, we did not have the exact information about the reason to select the DOAC, also that we did not measure the quality of life and assess it in patients using Warfarin versus DAOCs in those patients, but we are considering this in the future investigations. However, one of our major strengths that this is the first investigation to be done in Makkah, Saudi Arabia.

5. CONCLUSION

Our findings support data from the real-world. Since FDA approval, apixaban and dabigatran use in AF has increased dramatically compared to warfarin which was diminished. Given widespread usage of dabigatran and apixaban, it is essential to continue to monitor how effective the DOAC therapies in real-world settings. In patients with AF, the risk of any emboli, stroke and major bleeding were lower with NOACs versus warfarin. Our findings need conformation by large prospective multicentral study.

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Conflict of interest

The authors declare that there is no conflict of interests.

Data and materials availability

All data sets collected during this study are available upon reasonable request from the corresponding author.

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