

Original Research Article

Knowledge, attitude and practice of physicians towards oral anti-coagulants in Taif city, Saudi Arabia

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ABSTRACT

Background: Thromboembolism is a common phenomenon of major significance. Oral anticoagulants have been used for decades, however, they were associated with many complications and different monitoring techniques. Therefore, novel oral anticoagulants (NOACs) with better efficacy, lower adverse events, superior pharmacokinetic and pharmacodynamic profile were developed. Unfortunately, many of the physicians are still hesitant to prescribe these agents.

Methods: This was a cross-sectional study conducted in Taif city on 61 physicians from King Abdulaziz Specialist Hospital and King Faisal Hospital in Taif. A questionnaire was given to participants to answer questions related to knowledge, attitude, and practice of prescription of KA and NOACs, indications of prescription, reasons for non-use, follow up methods adopted, follow up frequency, common adverse events encountered, awareness of new guidelines of NOACs, and providing patients with health education about their medications.

Results: Only 69% of participants used NOACs on regular basis, whilst 100% used warfarin. Half of those who didn't prescribe NOACs attributed this to the non-availability of an antidote and fear of toxicity. Twenty-five% considered the NOACs new medications with inadequate clinical trials that make them trustable., and 17% did not prescribe them because of their non-availability at the hospital pharmacy. Only 66% used NOACs in treatment of non-valvular atrial fibrillation. Regarding knowledge, 71% of participants were aware of the new guidelines of NOACs, and 69% of institutions provided educational programs about these new agents. Major life-threatening bleeding was reported in 47.3% and 10.8% of patients on warfarin and NOACs, respectively.

Conclusions: Physicians at Taif city in Saudi Arabia had a fairly good knowledge of NOACs. They prescribed them frequently and they were aware with the new guidelines and proper follow-up methods. However, more educational activities are recommended to encourage the rest of physician to use these agents and to correct their defective information about safety issues, pharmacokinetic and pharmacodynamic properties of NOACs, and adverse events.

Keywords: Attitude, Knowledge, Oral anticoagulants, NOACs, Practice, Warfarin

INTRODUCTION

Thromboembolism is a common phenomenon of major significance, and the use anticoagulants for its prevention

and management has been used for decades. Despite the presence of various parenteral and oral anticoagulants, the management of arterial and venous thromboembolism remains challenging.¹ Oral anticoagulants currently

available are of two types: vitamin K antagonists (such as warfarin) and novel oral anticoagulants (such as dabigatran, rivaroxaban, apixaban, and edoxaban).² Vitamin K antagonists have been commonly used during the past sixty years and, therefore, they are widely known and prescribed by many physicians worldwide. Physicians tend to use them frequently because they have a long adequate experience with their usage, side effects, monitoring strategies, and approaches of management of potential complications.³ Novel oral anticoagulants (NOACs), on the other hand, have been developed during the last decade and they are not well-known and commonly prescribed among physicians despite their approved efficacy and safety profile.⁴⁻⁶ Whilst vitamin K antagonists act through inhibiting synthesis and action of vitamin K-dependent coagulation factors, NOACs act on specific factors in the coagulation cascade. Dabigatran inhibits thrombin (factor IIa), whereas Rivaroxaban, apixaban, and edoxaban act on activated factor X (Xa).^{7,8}

The main differences of clinical significance between vitamin K antagonists and NOACs are the side effects, monitoring techniques, drug-drug interaction, drug food interaction, and therapeutic window. NOACs have a lower incidence of adverse events particularly major bleeding, a wider therapeutic window, and a lower incidence of drug-drug and drug-food interactions. Furthermore, they do not necessitate laboratory monitoring or complex dose adjustment regimens.² Thus, NOACs are more convenient for use in most of cases. However, their novelty sometimes makes them a second option among many physicians.

The aim of this study was to study the knowledge, attitude, and practice among physicians at Taif city in Saudi Arabia towards both types of oral anticoagulants i.e. vitamin K antagonists and NOACs.

METHODS

This was a descriptive cross-sectional study conducted in King Abdulaziz Specialist hospital and King Faisal hospital in Taif city in Saudi Arabia during a period of 6 months from October 2017 until March 2018. A prepared written questionnaire was given to physicians from Internal Medicine Department in the previously mentioned hospitals to be filled.

The questionnaire included questions about the gender and nationality of the participating physician and questions about the general knowledge, attitude and practice among those physicians towards oral anticoagulants. Questions about oral anticoagulants included the frequency of prescription of warfarin and novel oral anticoagulants (NOACs), the reasons behind not using NOACs (when present), the indications of anticoagulants prescription, the need for a clinical pharmacologist when prescribing oral anticoagulants, the NOAC agent most often prescribed, the frequency of follow-up, the follow-up method, the regular need for

renal follow-up, and whether the age of the patient affect their decision of oral anticoagulation prescription or not. The questionnaire also reviewed the physicians' knowledge of the new guidelines of NOACs, their experience with switching from warfarin to NOACs, providing information to patients about oral anticoagulants, whether institutional medical education is provided about NOACs, and whether the physicians attend this activity or not. The participants were also asked about the frequency of documented adverse events experienced with warfarin and NOACs particularly bleeding and the severity and location of bleeding.

All data were fed to a computer and analysed using SPSS version 22.0. Quantitative variables were expressed in terms of frequencies.

RESULTS

Sixty-one physicians participated in this study with males constituting 80.3% of them. Non-Saudi participants constituted more than half (54.1%) of the recruited physicians. All participants reported that they were regularly prescribing warfarin, whereas only 68.9% reported regular use of NOACs. The main reasons behind the less frequent use of NOACs were the non-availability of an antidote (50%), the novelty of the drugs and the few available studies about them (25%), and the non-availability of these agents in the hospital pharmacy (16.7%). None of the physicians reported the cost or the renal dysfunction as causes for not prescribing NOACs (Table 1).

Table 1: Different basic characteristics of study participants.

Variables	N (%)	
Age: Mean (SD)	2.38 (0.71)	
Gender	Male	49 (80.3)
	Female	12 (19.7)
Nationality	Saudi	28 (45.9%)
	Non-Saudi	33 (54.1%)
Prescribing oral anticoagulant	Yes	61 (100)
	No	0
Prescribing NOACs	Yes	42 (68.9)
	No	6 (9.8)
	Sometimes	13 (21.3)

N: number, NOACs: Novel oral anticoagulants, SD: standard deviation

The main indications for prescribing oral anticoagulants in the study questionnaire included prevention and treatment of deep venous thrombosis (DVT) and/or pulmonary embolism (PE), prophylaxis before certain surgeries particularly hip or knee replacement, and treatment of non-valvular atrial fibrillation (AF). Among the studied participants, 86.9% reported use of NOACs and 13.1% reported the use of warfarin for treatment of DVT and/or PE. For prevention of DVT or PE, 80.3% of participants used NOACs and 19.7% used warfarin.

About 65.6% of participants used NOACs and 32.8% used warfarin in treatment of non-valvular AF (Table 2 and Figure 1).

Table 2: Attitude of doctors in prescribing new oral anticoagulants.

Variables	Causes	N (%)
Different Causes of not prescribing new oral anticoagulants		
Why don't prescribe NOACs	Still new, no enough studies	3 (25)
	The cost	0
	Not available in their pharmacy	2 (16.7)
	No antidote	6 (50)
	Renal dysfunction	0
	Other	1 (8.3)
Different causes of prescribing new oral anticoagulants		
Treatment of PE/DVT	NOACS	53 (86.9)
	VKA	8 (13.1)
	Not my specialty	0
	Prevention PE/DVT	NOACS
VKA		12 (19.7)
not my specialty		0
Atrial fibrillation		NOACS
	VKA	20 (32.8)
	not my specialty	1 (1.6)

DVT: deep venous thrombosis, NOACs: Novel oral anticoagulants, PE: pulmonary embolism, VKA: vitamin K antagonists.

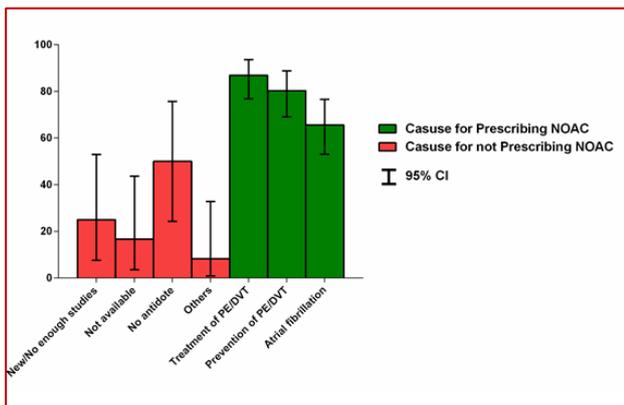


Figure 1: Attitude of physicians in prescribing new oral anticoagulants.

Among recruited patients, only 23% reported that they need clinical pharmacists for prescribing oral anticoagulants. The most often prescribed NOACs among the recruited physicians was rivaroxaban (72.4%) followed by Dabigatran (24.1%). Apixaban was prescribed by only 3.4% of the participants. About three-fourths (70.5%) of the participating physicians were regularly following the renal profile of patients on NOACs. The frequency of follow ups visits ranged from monthly to every six months-based visits with more than

half of the cases (46.7%) being followed up every 2-3 months (Table 3).

Table 3: Knowledge of doctors in prescribing new oral anticoagulants.

Questions	Answers	N (%)
Need a clinical pharmacist when starting NOAC	Yes	14 (23)
	No	47 (77)
Regular renal follow up for patient on NOACs	Yes	43 (70.5)
	No	18 (29.5)
Often prescribed NOACS	Rivaroxaban	42 (72.4)
	Apixaban	2 (3.4)
	Dabigatran	14 (24.1)
	Never	0
Frequency of follow up	Once	0
	Monthly	28 (46.7)
	Every 2-3 months	31 (51.7)
	Every 6 months	1 (1.7)
Follow up method	Annually	0
	Clinically	20 (33.3)
	Creatinine	34 (56.7)
	CBC	4 (6.7)
Does age affect choice	liver enzymes	2 (3.3)
	Yes	43
	No	18

NOACs: Novel oral anticoagulants, CBC: complete blood count.

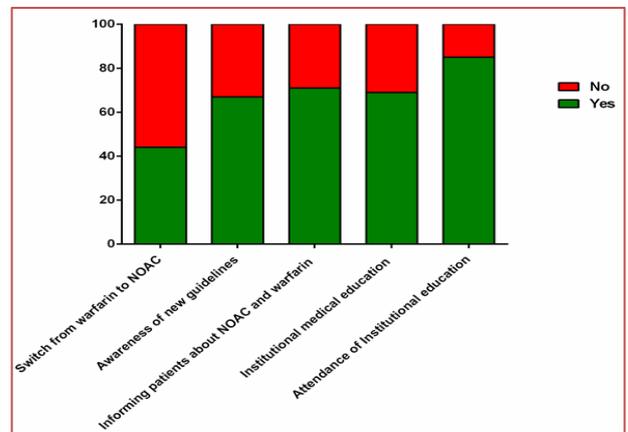


Figure 2: Practice of physicians in prescribing new oral anticoagulants.

The most common follow up methods were laboratory follow up of creatinine level (56.7%), clinical follow-up (33.3%), follow-up of CBC (6.7%), and follow-up of liver enzymes (3.3%). Age was reported to affect the decision of oral anticoagulants among 70.5% of the participating physicians (Table 3). Regarding the clinical practice towards oral anticoagulants, 44.3% reported that they switched patients from warfarin to NOACs. The vast majority of them (67.2%) stated that they were aware of the latest guidelines of using NOACs, and about 70%

were providing information about the oral anticoagulants to their patients. Almost 69% of participating physicians reported that their institutions were providing medical

education of NOACs, and more than 85% of them were attending these activities (Figure 2).

Table 4: Frequency of documented adverse effects.

Side effects	Answers	N (%)
Facing bleeding while the patient on warfarin	Yes	54 (88.5)
	No	7 (11.5)
Severity of bleeding from warfarin	Minor	29 (52.7)
	Life threatening	26 (47.3)
Bleeding site when the patient on warfarin	Epistaxis	19 (34.5)
	Hematoma	3 (5.5)
	Gastrointestinal bleeding	29 (52.7)
	Intracranial bleeding	4 (7.3)
	Abdominal bleeding	0
	Other	0
Facing bleeding while the patient on NOACs	Yes	37 (62.7)
	No	22 (37.3)
Severity of bleeding from NOACs	Minor	33 (89.2)
	Life threatening	4 (10.8)
Bleeding site when the patient on NOACs	Epistaxis	29 (78.4)
	Hematoma	1 (2.7)
	Gastrointestinal bleeding	5 (13.5)
	Intracranial bleeding	2 (5.4)
	Abdominal bleeding	0
	Other	0

NOACs: Novel oral anticoagulants

When asked about the adverse events of oral anticoagulants, 88.5% and 62.7% of participants reported that they saw cases of bleeding with warfarin and NOACs, respectively. Life-threatening bleeding was reported among 47.3% and 10.8% of patients on warfarin and NOACs, respectively. The most common bleeding sites reported among patients who received warfarin were gastrointestinal bleeding (52.7%), epistaxis (34.5%), intracerebral haemorrhage (7.3%), and subcutaneous hematomas (5.5%), respectively (Table 4). Among patients with NOACs, epistaxis was the most common reported bleeding site occurring in 78.4% of cases. Next came the gastrointestinal bleeding, the intracerebral haemorrhage, and subcutaneous hematomas occurring in 13.5%, 5.4%, and 2.7% of patients on NOACs.

DISCUSSION

Novel oral anticoagulants are increasingly used for prevention and treatment of thromboembolism. Despite their higher efficacy, better safety profile, lower incidence of drug-drug interaction and drug-food interaction, and easier monitoring strategies, some physicians are still conservative about their prescription.² This might be due to their novelty and the less experience with their usage. In this study, authors aimed to study the knowledge, attitude, and practice of physicians at Taif

city in Saudi Arabia towards using the conventional oral anticoagulants i.e. warfarin and NOACs. Of note, all participants (100%) reported that they used to prescribe warfarin regularly, whilst only two-thirds (68.9%) of them used NOACs on regular basis. However, this number is still promising especially when compared to the percentage of physicians using NOACs for treatment of atrial fibrillation in 2015 that was roughly 19%.⁹ Conversely, Bami et al, in this survey investigating the physicians' attitudes towards prescribing new oral anticoagulants, reported that the vast majority of them accepting referring patients for clinical trials of new oral anticoagulants, with values of 81%, 81%, 94%, and 100% among physicians in Netherlands, Switzerland, Canada, and Denmark, respectively.⁹ The percentage of prescribing NOACs in our study was also higher than this reported in Europe in 2016 where only 33% of patients were on NOACs and 67% were on vitamin K antagonists.¹⁰

Upon investigating the reasons behind non-prescribing NOACs among the participating physicians, the main reason was the non-availability of an antidote in case of toxicity (among 50% of participants not using NOACs). The second cause was the absence of adequate studies about these agents reported among 25% of participants. Non-availability of NOACs in the hospitals was the third

cause for not prescribing them. The physicians' fears about the absence of antidote and the inadequate available studies about NOACs is probably attributed to novelty of these agents and it would be reduced over time. The Saudi hospitals are recommended to supply the pharmacies with NOACs to provide the physicians with the chance to build up an experience with NOACs efficacy and adverse events. Of interest, none of the patients reported the high cost of the NOACs or the potential renal dysfunction as a barrier against usage of NOACs. In agreement with this, the high financial host was not a barrier against shifting patients from conventional oral anticoagulants to NOACs in Europe after the recommendations of UK National Institute of Health and Care Excellence (NICE) 2014 guidelines.³ This shift placed a significant burden on health budget with the expenditure on oral anticoagulants rising by £400 million in 2017.¹¹

About the indications of oral anticoagulants, physicians in Taif hospital tended to use NOACs for treatment more than for prevention of deep venous thrombosis and/or pulmonary embolism (86.9% and 80.3%, respectively). They also used NOACs only in two-thirds (65.6%) of patients with non-valvular atrial fibrillation (AF). The use of NOACs in treatment rather than prevention of DVT and/or PE may indicate that physicians in Taif city perceive that the NOACs are potent and more superior to conventional vitamin K antagonists in treatment of these condition. However, various clinical trials proved that NOACs are superior to vitamin K antagonists in both prophylaxis against and treatment of deep venous thrombosis and pulmonary embolism.¹²⁻¹⁴ This point should be a focus for future educational programs about oral anticoagulants to physicians at different Saudi health institutions. The use of NOACs in AF is comparable to literature, however, it is still recommended that the educational institutions provide more programs about safety and efficacy of these agents.^{15,16}

The attitude towards using NOACs among physicians participating in this study was generally positive. More than two-thirds of them reported that they were prescribing NOACs without a need to clinical pharmacists reflecting their good knowledge about the pharmacokinetics and pharmacodynamics of these agents. The main NOACs prescribed in Taif city were Rivaroxaban, Dabigatran, and Apixaban, respectively. Rivaroxaban inhibits activated factor X that was shown to be superior to warfarin in efficacy.⁴ In agreement with many of the literature studies, Rivaroxaban was the most common NOAC agent used especially for elderly above the age of 65 years.¹⁷ It carries the advantages of having a rapid onset of action, a higher oral bioavailability, and a lower renal metabolism in comparison to apixaban and dabigatran.¹⁸ Other studies reported a preference of Dabigatran over other NOACs¹⁰, and Apixaban was the novel oral anticoagulant of choice for many physicians particularly in young age.^{10,17} Dabigatran is a thrombin (factor IIa) inhibitor that was the first NOACs licensed.¹⁹

It has the advantage of having an available antidote, i.e. idarucizumab, in cases of toxicity. However, idarucizumab is very expensive.²⁰

Physicians' knowledge about frequency of follow-up and the follow-up methods was fair. NOACs are metabolized in liver and eliminated by kidneys. NOACs require a creatinine clearance levels of more than 50 mL/min to be prescribed.²¹ Regular follow up of renal functions is essential on annual basis in patients with intact renal profile and more frequent follow up in patients with reduced creatinine clearance.²² In this study, more than 97% of them were following up their patients every 1-3 months. The main follow-up method utilized among the participating physicians was laboratory follow-up of creatinine level. Clinical follow-up was reported in one third of patients, and other laboratory tests were used in only 10% of cases. Age is an important factor to decide the NOAC agent and dosage to be used. Patients above the age of 75 years, particularly with weight below 50 kilograms, should be administered slower dose escalation of NOACs and should be monitored carefully. Rivaroxaban is preferred among this age group due to its safer profile, lower renal elimination, and lower hepatic metabolism. Elderly individuals have reduced renal function and therefore longer elimination time of NOACs exposing them to higher rates of toxicity.^{23,24} In the present study, the vast majority of participants reported that the patient age did not affect their decision of prescribing NOACs. This is another point of concern to be considered during educational programs in Saudi Arabia.

Saudi institutions were found to provide fair educational programs for more than two thirds of the physicians working in its hospitals, and the vast majority of them were consequently aware of the latest guidelines of using NOACs. More than 85% seemed to be keen on attending these educational activities and almost half of them reported that they shifted their patients from warfarin to NOACs. However, it seems that certain points should be repetitively emphasized at these educational about the pharmacokinetics, pharmacodynamics, and efficacy of NOACs.

The incidence rates of adverse events associated with warfarin and NOACs reported in this study were closely similar to what was reported in various literature researches. Bleeding rates reported with warfarin were higher than those reported with NOACs, and life-threatening bleeding was reported in almost half of the patients on warfarin versus only 10% of patients on NOACs. This was closely similar to what has been reported in many literature studies.^{25,26} Warfarin was particularly associated with gastrointestinal bleeding and epistaxis, whereas NOACs were associated with higher incidence of epistaxis, occurring in more than three fourths of patients with bleeding complications. Gastrointestinal bleeding was reported in 13.5% of cases. In disagreement with these results, Graham et al, reported

higher incidence of major gastrointestinal bleeding with Dabigatran when used in treatment of AF in elderly.²⁷

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