Research Article

Safety Profile of Warfarin versus Dabigatran in Adult Patients with Non-valvular Atrial Fibrillation – A Prospective Cohort Study

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ABSTRACT

Context: Atrial fibrillation is the most commonly encountered sustained cardiac arrhythmia associated with extensive cardiovascular morbidity and mortality. Warfarin is the most recommended drug therapy for the prevention of thromboembolic events or stroke in patients with atrial fibrillation. Due to availability of newer drugs like dabigatran, the need for frequent PT/INR monitoring and bleeding risk has reduced drastically. Although, studies are lacking regarding its safety profile and therapeutic use in clinical practice. **Aim:** The main objective of the present study was to assess the safety profile of warfarin versus dabigatran in patients with non-valvular atrial fibrillation. **Materials and Methods:** This was a prospective cohort study carried out for a period of nine months. All adult patients, who were prescribed with either warfarin or dabigatran in non-valvular atrial fibrillation were included in the study. Patients were monitored initially for occurrence of adverse drug events and subsequently during their follow-up visits at 3 and 6 months. Reported ADEs were analyzed for various clinical characteristics and causality, severity and preventability using standard assessment scales. **Results:** A total of 75 patients (35 in warfarin and 40 in dabigatran cohort) were recruited. Out of 75, 38 patients experienced 70 ADEs (31 in warfarin and 39 in dabigatran cohort) which accounted for an overall incidence of 51%. Elevated coagulation profile (20%) followed by chest discomfort (10%), thrombocytopenia (7.14%), abdominal pain (7.14%), anemia (10%), gastritis (5.71%) and hematemesis (5.71%) were the most common reported ADEs among others. Dabigatran (55.71%) was associated with higher number but less severe ADEs as compared to warfarin (44.28%). Majority of ADEs were found to be probable (53%) in nature, moderate (57%) in severity, predictable (71%) and not preventable (40%). **Conclusion:** Dabigatran being a costly alternative appears to be safer than warfarin.

Key words: Adverse drug events, Anticoagulants, Dabigatran, Non-valvular atrial fibrillation, Safety profile, Warfarin.

Key Messages: Dabigatran appears to be safer than warfarin. Less frequent PT/INR monitoring, reduction in bleeding events and safer administration being the most probable reasons for preferring dabigatran in patients with non-valvular atrial fibrillation.

INTRODUCTION

Atrial Fibrillation (AF) is commonly associated with, or manifested alongwith other cardiovascular conditions which are usually characterized by "irregular" and "rapid heartbeat". The most common complaint in patients with AF is palpitations which results in rapid contraction rate which ranges from 100 to 160 beats/minute.[1]

The incidence rate of AF increases with age, as nearly 85% of patients diagnosed with AF are aged above 65 years old.[2] It increases the risk of stroke and therefore mortality rate in patients with AF.[3] It is estimated that an increase in the number of individuals with AF in 2010 was 33.5 million and expected to increase about 5 million new cases each year.[4]

Gulf SAFE is a study conducted in the Middle East Regions. It showed high prevalence of patients with AF, among 2043 recruited patients the primary reason for the emergency visit in 45% of patients was due to AF.[5]

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cardiology has a validated tool for the prediction of stroke risk in patients with AF as per CHADS2 to determine the initiation of anticoagulant therapy. CHA2DS2-VASC and HAS-BLED were used to assess the risk of bleeding along with introduction of anticoagulants. These scales used various risk factors such as congestive heart failure, age ≥ 75 years or older, hypertension, etc. and assigned points, further the risk is stratified into high, moderate and low, showing various drug treatment options.[6,7]

Until now, warfarin and other Vitamin-K antagonists were used as anticoagulant medications in AF to prevent the risk of thromboembolic events or stroke. However, warfarin is reported to have high bleeding risk which requires strict monitoring of Prothrombin Time (PT), International Normalized Ratio (INR), drug-drug and drug-food interactions. Due to these complications, Novel Oral Anticoagulants (NOACs), that are effective, safe and which don't require strict monitoring, are preferred over warfarin.[8] Dabigatran was introduced after the approval by Food and Drug Administration (FDA) on October 19, 2010 for the treatment of atrial fibrillation.[9] It is an oral direct thrombin inhibitor which is more efficacious than warfarin in reducing the risk of stroke, when given at a dose of 150 mg twice daily in patients with non-valvular atrial fibrillation; however, safety concerns are still controversial as it shows an increase in gastrointestinal bleeding. Often in the optimal clinical practice, information regarding the safety of newer medications is lacking relative to the existing medicines and comparative assessment is not available at the time of market authorization and initial use.[10,11] On February 14, 2011, the American College of Cardiology (ACC) Foundation and American Heart Association (AHA) recommended the addition of dabigatran to their guidelines for management of non-valvular atrial fibrillation as a class-I recommendation.[11]

Adverse Drug Event (ADE) is a broad term which can arise from inappropriate prescribing of a medication (e.g., misdiagnosis, inappropriate medication, inappropriate dose, inappropriate regimen etc.), medication errors, self-medication, side effects, allergies, genetic predispositions, Drug-Drug Interaction (DDI), drug-disease interaction, or patient non-compliance (taking more or less of a drug than the prescribed amount).[12] Although ADEs and Adverse Drug Reactions (ADRs) are sometimes used interchangeably, they do not have the same meaning. An ADR refers to adverse effects of medications when they are used appropriately while ADEs in addition includes medication errors which are preventable. There are number of consequences, which range from mild allergic reaction to permanent harm, thereby causing morbidity and mortality as well as increase in the overall healthcare cost.[13] It is reported that each year more than 7,70,000 people die or are injured during hospital stay due to ADEs, which may cost $5.6 million of the overall healthcare costs.[14] The approval process of dabigatran took place in a large phase III clinical trial, which reported similar risk of bleeding with warfarin versus dabigatran in NVAF patients. In the trial, two doses 110 mg and 150 mg of dabigatran were compared which have been non-inferior to warfarin, in terms of efficacy and safety outcomes for the prevention of stroke, systemic embolism and reduction in the risk of intracerebral hemorrhage.[15] Another recent retrospective Medicare data analysis study on dabigatran's safety highlighted that the incidence of bleeding (33% versus 27%) was higher than with warfarin, major bleeding (9% versus 6%) and gastrointestinal bleeding (17% versus 10%). Intracranial hemorrhage occurred more often with warfarin than dabigatran (1.8% versus 0.6%).[16,17] Another study revealed higher hemorrhagic stroke rates in Asians due to warfarin compared to non- Asians despite similar blood pressure, age or INR value, however, dabigatran benefits were consistent among both the cohorts.[18] The cost associated with the use of dabigatran is another major concern and non-compliance issue in patients with low income financial status. In United Kingdom (UK), the estimated total costs were $143, 193 for warfarin, comparatively less than $164, 576 for low $168, 398 for high-dose dabigatran.[19,20] A study conducted in United Arab Emirates (UAE) and Kingdom of Saudi Arabia (KSA) recruited 157 and 152 patients respectively, the majority of which were diagnosed with chronic (persistent or permanent) AF (81% in UAE, 64% in KSA). The mean total annual costs per patient attributable to AF were $1,151 (standard deviation (SD): $1,796) per person in the UAE and $3,001 (SD: $3,502) per person in KSA, with monitoring costs being the largest contributor to costs in both countries (47% and 66%, respectively).[21]

Although, dabigatran has been recently introduced in UAE hospitals for its clinical use among the National and non-national population with diverse characteristics, no prospective studies have been conducted regarding its safety profile in atrial fibrillation patients. Hence, the main objective of the present study was to compare the safety profile of dabigatran with warfarin in patients with NVAF.

The main objective of the present study was to assess the safety profile of warfarin versus dabigatran in adult patients with non-valvular atrial fibrillation. Secondary objectives of the study were to monitor ADEs associated with warfarin or dabigatran in patients with non-valvular atrial fibrillation, characterize ADEs based on various parameters such as demographics, co-morbid conditions, organ system affected, type of ADE, individual reaction,

predisposing factors, management and outcome of ADEs, analyze the reported ADEs for causality, severity and preventability using standard assessment scales and estimate the direct cost attributable to ADEs.

MATERIALS AND METHODS

The present study was a prospective observational cohort, non-interventional study which was conducted in the cardiology department of a secondary care hospital, Ibrahim Bin Hamad Obaidallah Hospital, Ras Al-Khaimah, UAE for a period of nine months (Oct. 2015 to June 2016). This study was initiated after obtaining approval from the Research and Ethics committee of RAK Medical and Health Sciences University (RAKMHSU) and Ras Al-Khaimah (RAK) Research and Ethics Committee.

Patients were enrolled into the study by attending the clinical rounds with clinicians, clinical meetings and out-patient clinic visits. Prior information regarding the study was conveyed to the cardiology department and hospital pharmacy division for the better recruitment of eligible patients. All adult patients who were prescribed with either warfarin or dabigatran in NVAF for the prevention of stroke or systemic embolism were included in the study. Patients receiving anti-thrombotics for other clinical conditions were excluded.

Baseline data pertaining to their previous history, allergy, disease condition, investigations and medications was collected using the electronic patient medical records and documented in the patient profile forms, ADR notification and documentation forms designed for the study purpose. Patients were monitored for the occurrence of ADEs during hospital stay, at the time of discharge and on their subsequent follow-up visits at 3 months and 6 months.

The main outcome of the study was safety events like bleeding events and any other adverse drug events. Reported adverse drug events were analyzed for their causality, severity and preventability using standard assessment scales.

Direct cost attributable to ADEs was assessed at the time of discharge and subsequent follow-up visits at 3 months and 6 months. In case if the patient was unable to come for follow-up visit, a telephonic interview was conducted to ensure the safety of ongoing warfarin or dabigatran. Details pertaining to the same were recorded in the follow-up documentation form. The parameters which were considered for the estimation of direct cost include hospitalization cost, consultation and sub-consultation charges, bed charges, nursing charges, investigation charges and medication cost.

Statistical Analysis

Data collected from the present study was entered into the Microsoft Excel sheet for analysis using the Statistical Package for the Social Sciences (SPSS) Version 23.0. Descriptive statistics was presented in the form of frequency, percentage, mean and standard deviation (Mean ± SD). Independent t-test was used to compare the number of ADEs and variables in both cohorts. ANOVA and Chi-square tests were performed to find out the association between the ADEs and socio-demographic parameters, comorbid conditions and concurrent medications. Multivariate regression was applied for the dependent variable such as age, gender, nationality, comorbidities and polypharmacy to analyze the predictors of ADEs. *P*-value of less than 0.05 was considered as statistically significant.

RESULTS

A total of 75 patients, including 40 patients in dabigatran cohort and 35 patients in warfarin cohort, were enrolled in the present study.

The average length of hospital stay was observed to be 4.85 ± 11.5 days in the study.

Incidence of Adverse Drug Events

A total of 70 ADEs (31 in warfarin vs. 39 in dabigatran) were observed among 38 patients. At the time of follow-up, a total of 45 ADEs were observed among 24 patients. Eleven patients were observed as lost to follow-up during 3 months visit whereas 14 patients could not complete their six months follow-up during the study period. The overall incidence rate of ADEs was recorded as 50.67%. In 6 patients, ADE was the reason for hospital admission which accounted for an incidence of 8%.

Demographics- Age wise distribution

The age of patients ranged between 31 and 103 years with an average mean of 70 ± 14.6 years. The maximum number of ADEs [31 (44.28%) and 27 (38.5%)] were observed in elderly patients aged more than 65 years. The significant difference was observed in the age groups among both the cohorts (p-value=0.002) as dabigatran [35 (87.5%)] users were higher in number in the age group above 65 years as tabulated in Table 1.

Demographics- Gender wise distribution

Out of 75 patients, majority of patients were female (53.33%) as compared to male (46.67%). Among males, 19 (47.5%) patients were enrolled in dabigatran cohort whereas 16 (45.71%) patients in warfarin cohort. On the other hand, 21 (52.5%) female patients were enrolled in dabigatran cohort whereas 19 (54.28%) female patients in warfarin cohort. Female (53.33%) preponderance was observed over male (46.67%) in the present study (Table 1).

Male preponderance [11 (55%) in warfarin vs. 7 (54%) in dabigatran] was observed over female with respect to the occurrence of ADEs [9 (45%) in warfarin and 6 (46%) in dabigatran] in both the treatment groups (Table 1).

Nationality

Majority of patients [53 (70.67%)] included in the study were Emiratis [21 (60%) in warfarin vs 32 (80%) in Dabigatran] followed by expatriates (Table 2).

CHA_2DS_2-VASc and HAS-BLED score

For the assessment of risk factors and bleeding tendencies, the mean CHA_2DS_2-VASc score and mean HAS-BLED score was calculated and recorded as 3.7 ± 1.44 and 2 ± 1.02 respectively as represented in Table 3.

Associated co-morbidities and concurrent medications

On evaluation of concurrent medications among enrolled patients with multiple co-morbidities, significant numbers of ADEs (p=0.001) were recorded with clopidogrel (p=0.018) and NSAIDs (p=0.010) (Table 4 and 5).

Due to the presence of multiple co-morbidities, majority of patients were found to be on multiple medications (polypharmacy) as depicted in Table 6.

Table 1: Demographics (age and gender wise distribution).

Demographic characteristics	Warfarin cohort (n=35) No (%) of patients	Dabigatran cohort (n=40) No (%) of patients	Total (n=75) No (%) of patients	p-value
Age (in years)				
< 55	9 (25.71)	1 (2.5)	10 (13.33)	
55-64	6 (17.14)	4 (10)	10 (13.33)	
65-74	12 (34.28)	17 (42.5)	29 (38.67)	
≥ 75	8 (22.85)	18 (45)	26 (34.67)	
Subtotal	**35 (100)**	**40 (100)**	**75 (100)**	**0.002***
Mean ± SD	70 ± 14.6			
Age group < 65	14 (40)	5 (12.5)	19 (25.33)	
Age group ≥ 65	21 (60)	35 (87.5)	56 (74.67)	
Subtotal	**35 (100)**	**40 (100)**	**75 (100)**	
Gender				
Male	16 (45.71)	19 (47.5)	35 (46.67)	
Female	19 (54.28)	21 (52.5)	40 (53.33)	
Subtotal	**35 (100)**	**40 (100)**	**75 (100)**	**0.761**

n=number of patients, figure in the parenthesis represent percentage, *ANOVA test.

Table 2: Demographics (Nationality wise distribution).

Demographic characteristics	Warfarin cohort (n=35) No (%) of patients	Dabigatran cohort (n=40) No (%) of patients	Total (n=75) No (%) of patients	p-value
Nationality				
Emirati	21 (60)	32 (80)	53 (70.67)	
Non--Emirati	14 (40)	8 (20)	22 (29.33)	
Subtotal	35 (100)	40 (100)	75 (100)	0.261

n=number of patients, figure in the parenthesis represent percentage, *ANOVA test

Table 3: Risk score in both the treatment groups.

Risk Score	Warfarin cohort (n=35) No (%) of patients	Dabigatran cohort (n=40) No (%) of patients	Total (n=75) No (%) of patients
CHA2DS2-VASc score*			
0 - 1	5 (14.28)	1 (2.5)	6 (8)
2	5 (14.28)	3 (7.5)	8 (10.67)
3-4	19 (54.28)	18 (45)	37 (49.33)
5-6	6 (17.14)	18 (45)	24 (32)
Mean ± SD			3.7 ± 1.44
HAS – BLED score			
0-1	14 (40)	13 (32.5)	27 (36)
2-3	17 (48.57)	24 (60)	41 (54.67)
4-5	4 (11.43)	3 (7.5)	7 (9.33)
Mean ± SD			2 ± 1.02

n=number of patients, figure in the parenthesis represent percentage, *ANOVA test.

Table 4: Associated co-morbidities and distribution of patients in both the treatment groups.

Associated co-morbidities	Warfarin cohort (n=35) No (%) of patients	Dabigatran cohort (n=40) No (%) of patients	Total (n=75) No (%) of patients
Prior stroke, Transient Ischemic attack or systemic embolism	2 (5.71)	8 (20)	10 (13.33)
Hypertension a	26 (74.28)	38 (95)	64 (85.33)
Heart Failure	4 (11.43)	10 (25)	14 (18.67)
Diabetes Mellitus type (II)a	16 (45.71)	23 (57.50)	39 (52)
Myocardial Infarction a	11 (31.43)	13 (32.5)	24 (32)
Chronic Kidney Disease	6 (17.14)	5 (12.50)	11 (14.67)
Liver Disease	2 (5.71)	0	2 (2.67)
Others Thyroid disorders	4 (11.43)	3 (7.5)	7 (9.33)
Gastrointestinal disorders	2 (5.71)	2 (5)	4 (5.33)
Bronchial Asthma	2 (5.71)	3 (7.5)	5 (6.67)

n=number of patients, figure in the parenthesis represent percentage, aChi-square p-value =0.044.

Adverse drug events

The number of adverse drug events was significantly higher among inpatients (p-value=0.004). The most common suspected ADEs were elevated coagulation profile (20%), anemia (10%), chest discomfort (10%), gastritis (5.71%), hematemesis (5.71%), hematuria (5.71%), abdominal pain (7.14%) and thrombocytopenia (7.14%). In the warfarin cohort, majority of the ADEs were elevated coagulation profile (45.16%) and chest discomfort (13%) followed by anemia (9.68%), hemoptysis (6.45%), rectal bleeding (6.45%) and skin bruises and redness (6.45%). Dabigatran cohort presented with higher number of ADEs, especially anemia (10.26%), mild gastritis (10.26%), hematuria (10.26%), thrombocytopenia (10.26%), abdominal pain (10.26%) followed by chest discomfort (7.69%), hemoptysis (5.13%) and increased creatinine clearance (5.13%) as presented in Table 7. There was a significant association observed between the drug and type of ADEs (p value=0.002) with a strong positive association (φ=0.756).

Organ system affected by ADEs

The gastrointestinal (28.2%) and renal (16.6%) systems

Table 5: Concomitant drug therapy and distribution of patients in both the treatment groups.

Concomitant drug therapy	Warfarin cohort (n=35) No (%) of patients	Dabigatran cohort (n=40) No (%) of patients	Total (n=75) No (%) of patients
Aspirin	12 (34.28)	15 (37.5)	27 (36)
Clopidogrel b	4 (11.43)	1 (2.5)	5 (6.67)
NSAIDs b	1 (2.86)	4 (10)	5 (6.67)
ACEIs/ ARBs	18 (51.43)	36 (90)	54 (72)
Beta blockers	17 (48.57)	36 (90)	53 (70.67)
Calcium channel blocker	6 (17.14)	15 (37.5)	21 (28)
Statins	18 (51.43)	31 (77.5)	49 (65.33)
Proton pump inhibitors or H-2 receptor blockers	12 (34.28)	20 (50)	32 (42.67)

n=number of patients, figure in the parenthesis represent percentage, Angiotensin Converting Enzyme Inhibitors and Angiotensin Receptor-II Blockers (ACEI/ARB), Non-steroidal anti-inflammatory drugs (NSAIDs), Proton pump inhibitors (PPIs), Histamine receptor-II blockers (H_2 blocker); bANOVA test p-value 0.001; Post Hoc test, clopidogrel (p=0.018), NSAIDs (p=0.010); Independent t- test (p value =0.061).

Table 6: Polypharmacy and distribution of patients in both the treatment groups.

Categories	Warfarin cohort (*n*=35) No (%) of patients	Dabigatran cohort (*n*=40) No (%) of patients	Total (*n*=75) No (%) of patients	*p*-value
Polypharmacy (≥ 6 drugs)	21 (60)	23 (57.5)	44 (58.67)	0.061
Major polypharmacy (≥ 11drugs)	6 (17.14)	12 (30)	18 (24)	
Excessive polypharmacy (≥ 21 drugs)	-	-	-	

n=number of patients, figure in the parenthesis represent percentage, remaining patients were on less than 6 drugs, Independent t- test.

Table 7: Suspected adverse drug events.

Suspected ADEs#	Warfarin cohort (*n*=31) No (%) of ADEs	Dabigatran cohort (*n*=39) No (%) of ADEs	Total (*n*=70) No (%) of ADEs
Elevated Coagulation Profile (INR, PT, APTT)	14 (45.16)*	0	14 (20)
Anemia	3 (9.68)	4 (10.26)	7 (10)
Mild Gastritis	0	4 (10.26)*	4 (5.71)
Hematemesis (Malena)	1 (3.22)	3 (7.69)	4 (5.71)
Rectal Bleeding	2 (6.45)	0	2 (2.86)
Hematuria	0	4 (10.26)	4 (5.71)
Thrombocytopenia	1 (3.22)	4 (10.26)	5 (7.14)
Abdominal pain	1 (3.22)	4 (10.26)	5 (7.14)
Chest discomfort	4 (13)	3 (7.69)	7 (10)
Hemoptysis	2 (6.45)	2 (5.13)	4 (5.71)
Increased Creatinine Clearance	0	2 (5.13)	2 (2.86)
Skin bruise and redness	2 (6.45)	0	2 (2.86)
Epistaxis	0	1 (2.56)	1 (1.43)
Gum bleeding	0	1 (2.56)	1 (1.43)
Elevation of Hepatic enzymes (ALT)	0	1 (2.56)	1 (1.43)
Dizziness	0	1 (2.56)	1 (1.43)
Hypotension	0	1 (2.56)	1 (1.43)
Tachycardia	0	2 (5.13)	2 (2.86)
Palpitations	1 (3.22)	2 (5.13)	3 (4.28)
Subtotal	31 (100)	39 (100)	70 (100)

n=number of ADEs, figure in the parenthesis represent percentage, *Independent t-test (p-value=0.004), Chi-square (p-value=0.002), Phi value (0.756), #ADEs- Adverse drug events.

were mainly affected in dabigatran cohort as compared to less number in warfarin cohort (Table 7).

All the dependent variables were analyzed statistically by multivariate regression analysis and results revealed that age, gender, nationality, polypharmacy and number of comorbidities were not significant (p >0.05) predictors for ADEs (Table 8).

Management of ADEs

Most of the ADEs were managed by altering the dose (54.28%) monitoring the patient without any change in drug therapy (35.71%) and withdrawing the drug in 7 (10%) ADEs. Suspected drug was de-challenged in 22 patients [39 (55.7%)] and then re-challenged, of whom in 4 cases [7 (10%)], reaction reappeared (Table 3). Few adverse drug events were managed by either specific treatment (Injection protamine sulphate) or symptomatic therapy (*Inj.* pantaprazole given for gastritis, *Inj.* hyoscine for abdominal pain, etc) in both the treatment groups [warfarin (8, 26%) and (15, 38.5%) dabigatran cohort]. Majority of cases [54 (77.14%)] had recovered in both the groups [26 (83.87%) in warfarin cohort and 28 (71.79%) in dabigatran cohort] (Table 9).

Assessment of ADEs

Causality assessment by WHO probability scale

Adverse drug events were analyzed using WHO probability scale for the causality assessment. Majority of the suspected ADEs were probable (52.86%), followed by certain (12.86%), possible (21.43 %) and unlikely (12.86%) in both the groups (Table 10).

Severity assessment by Hartwig *et al*. scale

Severity assessment of ADEs revealed both moderate (57.14%) and mild (37.14%) type of ADEs, but none of the ADE was fatal (Table 10).

Predictability assessment

Table 8: Multivariate regression analysis of the dependent variables and ADEs.

Dependent Variables	B	Beta	t	P
Gender	-0.186	-0.089	-0.746	0.458
Age	-0.13	-0.132	-0.948	0.346
Nationality	0.037	0.016	0.133	0.894
Polypharmacy	0.391	0.142	1.082	0.283
No. of comorbidities	0.146	0.191	1.469	0.146

Table 9: Management, treatment and outcome of ADEs in both the treatment groups.

Treatment strategies	Warfarin Cohort (*n*=31) No (%) of ADEs	Dabigatran Cohort (*n*=39) No (%) of ADEs	Total (*n*= 70) No (%) of ADEs
Management			
Drug withdrawn	1 (3.22)	6 (15.38)	7 (10)
Dose altered/ reduced	22 (70.97)	16 (41.02)	38 (54.28)
No change	8 (25.81)	17 (43.59)	25 (35.71)
Treatment Given			
Nil	18 (58.06)	24 (61.54)	42 (60)
Symptomatic	8 (25.81)	15 (38.46)	23 (32.86)
Specific	5 (16.13)	0	5 (7.14)
Outcome of ADEs			
Recovered	26 (83.87)	28 (71.79)	54 (77.14)
Continuing	2 (6.45)	7 (17.95)	9 (12.86)
Unknown	3 (9.68)	4 (10.26)	7 (10)

n= number of ADEs, figure in the parenthesis represent percentage.

Predictability analysis showed that 71.43% of ADEs were predictable while 28.57% were not predictable (Table 10).

Preventability assessment by Modified Schumock and Thornton scale

Preventability of reported ADEs was assessed using the modified Schumock and Thornton scale. On preventability assessment, 28 (40%) ADEs were found to be not preventable, followed by 21 (30%) probably preventable and definitely preventable ADEs respectively (Table 10).

Direct cost attributable to adverse drug events

The direct cost incurred to manage these ADEs was also calculated and compared between the two treatment groups. The estimated total direct cost was AED 19,023 (USD 5179), of which cost was observed to be higher in dabigatran group (AED 11, 932; USD 3248) as compared with warfarin group (AED 7,091; USD 1930). The average cost per patient was estimated to be AED 652 ± 703 (USD 177 ± 191) in dabigatran group as compared

Table 10: Common Assessment of adverse drug events.

Categorical Classification				
Causality@	**Certain**	**Probable**	**Possible**	**Unlikely**
No (%) of ADEs (*n*=70)	9 (12.86)	37 (52.86)	15 (21.43)	9 (12.86)
Severity#	**Mild**	**Moderate**	**Severe**	
No (%) of ADEs (*n*=70)	26 (37.14)	40 (57.14)	4 (5.71)	
Preventability*	**Definitely Preventable**	**Probably preventable**	**Not preventable**	
No (%) of ADEs (*n*=70)	21 (30)	21 (30)	28 (40)	
Predictability	**Predictable**	**Not predictable**		
No (%) of ADEs (*n*=70)	50 (71.43)	20 (28.57)		

n= number of ADEs, figure in the parenthesis represent percentage; @WHO probability scale; #Hartwig et al. scale, *Modified Schumock and Thornton scale.

to AED 442.6 ± 278 (USD 120 ± 75.69) in warfarin group and the difference was observed to be statistically insignificant.

DISCUSSION

The present study was carried out in cardiovascular patients suffering from non-valvular atrial fibrillation and receiving at least one anti-thrombotic agent either warfarin or dabigatran as prophylaxis. This was a safety monitoring study which involved primary assessment of ADEs in out-patient clinics or during hospital stay followed by assessment of safety events on follow-up visits at 3 months and 6 months respectively.

Patients prescribed with dabigatran were older in age than the warfarin-treated patients and associated with significantly higher number of co-morbid conditions (p=0.044) and concurrent medications. The present findings are comparable to that of a study conducted earlier.[17]

Male preponderance was observed over female with respect to incidence of ADEs. This could be attributed to clinical condition, atrial fibrillation, which is prevalent among males and advanced age.

In the present study, large number of patients were observed to be on multiple medications signifying polypharmacy. As majority of patients belongs to elderly age group having multiple co-morbidities, they are likely to be on multiple medications.

Patients who were taking concurrent medications, clopidogrel (p=0.018) and non-steroidal anti-inflammatory drugs [NSAIDs] (p=0.010) along with the medications under study, showed significant association with the ADEs (p=0.001). These drugs are likely to precipitate ADRs when given along the anticoagulants. However, no significant difference was observed among patients who were using 81 mg aspirin in the present study,[22] unlike that of a study which showed significant risk of bleeding.[15]

On risk assessment, patients were found to have CHA_2DS_2-VASC score more than 1 which showed the appropriateness of receiving anticoagulant therapy. The present findings are comparable with the findings of a previous study carried out by Shehab A, *et al.* (3.54 ± 1.82 and 3.46 ± 1.205).[17] The mean score of HAS-BLED was recorded as 2 ± 1.02 which indicates that most of the patients were at low risk of bleeding unlike that of a study conducted earlier.[18] Further statistical analysis revealed that these predisposing factors were not significantly associated with ADEs.

The incidence of ADEs was high among dabigatran cohort as compared to warfarin cohort which constituted for an overall incidence of 50.6%. These findings are consistent with that of a study conducted earlier by Aslan O *et al.*[23] At the time of follow up, the incidence of ADEs was recorded as 29.6% at 3 months and 8.1% at 6 months. This could be due to less intensive monitoring of ADEs post-discharge.

Adverse drug events observed among in-patients during hospital stay were found to be statistically significant. The present findings are comparable to that of a study conducted earlier.[24] This could be due to intensive monitoring of ADEs and efficient reporting by healthcare professionals.

In the present study, 75 mg and 110 mg dosage strengths of dabigatran were mainly preferred as prophylactic treatment as a part of hospital protocol. Safety events

were monitored while using these strengths in patients on dabigatran. Dabigatran users were found to have more gastrointestinal bleeding events as compared to warfarin users.

The safety profile was further explored in the patients having tendency to bleed. There were no major bleeding events reported in the present study. However, minor bleeding events were observed in dabigatran cohort as compared to warfarin cohort which is inconsistent with that of a study conducted earlier. Similar profile of bleeding events was observed in a study carried out by Shehab *et al*.[17]

Gastrointestinal bleeding was the most frequent adverse event among the dabigatran cohort reported earlier in a study which is similar to the present study findings.[25] One logical reason for increased gastric irritation could be use of a different formulation which is capsule which contains dabigatran-coated pellets with a tartaric acid core. This may partly explain the increased incidence of dyspeptic symptoms with both strengths of dabigatran.[26] Therefore, the use of gastro-protective agents is advisable prior to dabigatran use.

Dissimilar findings were observed in a previous study.[15] Another literature revealed elevated liver profile as an adverse effect among dabigatran users which was comparable to that of present study findings. Though less frequent but there was one patient who had experienced elevated alanine aminotransferase (ALT) levels of three times than the upper normal limit.[26] This initiates discussion about having standard recommendations for monitoring liver function tests (LFTs) prior to and after using dabigatran.

Elevated coagulation profile was the most common ADE observed among warfarin cohort followed by anemia, rectal bleed, hemoptysis and skin bruises. These findings were dissimilar to that of a study conducted earlier by Aslan O *et al*. where dyspepsia (18.3%), headache (16.4%), nausea/vomiting (11.9%) and dizziness (10%) were reported.[24] Another study by Hanlon *et al*. on monitoring ADRs in elderly patients, the common ADRs with anticoagulants (i.e., warfarin) observed were gastrointestinal bleeding, epistaxis and hematuria.[25] The type of ADEs observed with dabigatran was mild gastritis like symptoms (dyspepsia) apart from ADEs related to bleeding which was common in both the groups. The present findings of both cohorts were comparable to studies carried out by Hori *et al*. (16.1%), Connolly *et al*. (11.8%) and Ansal *et al*. (21.9%).[18,22,23]

In terms of management of ADEs, majority of the reactions were managed by dose reduction and without any change in treatment. Drug was withdrawn in some cases. The finding observed in the present study was in contrast with that of a study conducted by Gholmai *et al*. where 65% of the ADEs were managed by without change in the treatment schedule.[27] Further observation in a previous study showed that the management of ADEs was done by withdrawal of a suspected drug (47.28% vs. 47.5%).[28] However, few ADEs were treated by administering the specific antidotes (Vitamin K) in case of warfarin induced bleeding (7.14%) while there was no antidote recommended for patients receiving dabigatran.

In dabigatran cohort, symptomatic treatment was given in almost one third of ADEs with pantoprazole 40 mg, hyoscine bromide 10 mg, fresh frozen plasma and Prothrombin Coagulation Complex (PCC). These findings are in par with the study of M.A. Smythe *et al*. where the authors used the same treatment for the management of bleeding. Idarucizumab is a recently introduced drug in Europe and USA for the reversal of anticoagulant effects of dabigatran in life-threatening situations which is currently not available in UAE.[29]

The outcome of ADEs suggested that majority of cases completely recovered, however, reaction continued in few patients. The outcome was unknown in few cases. This finding could be due to their premature death or inability to come for follow-up. The mortality observed during the study was not associated with adverse drug events as the patient died due to complications of the existing medical condition which can be further supported by studies.[17,24]

In the present study, suspected drugs were suspended or withheld in 22 patients which showed resolution of ADEs which is in line with that of a previous study.[30] Re-challenge was considered among these patients in view of their ongoing treatment but in 4 patients, the ADE reappeared, thereby confirming the evidence of causal relationship.

On causality assessment, majority of ADEs were observed as probable in nature as per WHO probability scale. The findings observed in the present study are similar to that of a previous study carried out by Davis *et al*.[31]

According to this study, majority of suspected ADEs were found to be moderate in nature. Moderate reactions, that were frequent, resulted in the extension of hospital stay by more than 2 days. This finding is inconsistent with that of a study conducted earlier which reported more number of mild reactions [mild reactions: (53% vs.79.23%)].[30]

Predictability assessment showed that most of the ADEs were predictable and well documented with incidence rate greater than 10 % in the literature. This finding is comparable to that of a previous study.[32] The observed ADEs were assessed for preventability using modified Schumock and Thornton scale which revealed that majority were not preventable whereas the rest of them were probably preventable and definitely preventable. This observation is similar to that of a study carried out by Wadhwa *et al*. where 83.84% ADEs were not preventable.[30]

The overall direct cost was estimated to be AED 19,023, which is inclusive of cost in both the treatment groups (warfarin: AED 7,091; dabigatran: AED 11,932). Higher cost in dabigatran was observed probably due to the use of prothrombin complex concentrate which is a costly product (approx. 3000 dirhams). This product was used to manage life threatening situation in the present study. There is no published data available in the Middle-Eastern countries regarding the cost burden due to ADEs. A study performed by Gyllensten *et al*. in Europe reported that the average direct cost per patient was 444.9 US dollars among 596 patients.[33] In the present study, the average cost per patient was estimated to be AED 652±703 in dabigatran group and AED 442.6±278 in warfarin group which was not statistically significant. There were four severe ADE cases observed which were treated intensively in critical care unit (CCU). This might have further contributed for the increment of direct cost in both the treatment groups.

Various studies that are carried out before to compare the safety and efficacy of dabigatran and warfarin in atrial fibrillation patients had demonstrated superiority of dabigatran over warfarin.[15,16,22] The results of these studies have also highlighted safety issues associated with dabigatran such as gastrointestinal effects and bleeding tendencies. Among elderly population low-dose dabigatran was associated with high risk of gastrointestinal bleeding compared to warfarin, however, no difference was seen in the treatment outcome.[34,35] Shehab *et al*. studied the clinical utility of dabigatran among the UAE population showed that 23.7% patients had bleeding events.[17] Apart from clinical trials, most of the studies were performed retrospectively by retrieving the data from registries. However, the only available prospective study comparing these two drugs on the Danish population which has followed up the enrolled patients for a duration of ≥1 year.[15] Hence, the present study is the first of its kind performed in the Gulf region population to evaluate the safety of dabigatran over warfarin.

The present study was a non-randomized study which was carried out at a single center for short duration. Study design and duration restrict to generalize the findings. Furthermore, studies are required to be conducted at multicenter involving large population and extending the follow-up duration to more than six months. Less number of reactions were observed during 3-months or 6-months follow up period. Monitoring long term effects of drugs over extended period (more than one year) can provide better insight about the safety of ongoing treatment.

In the present study, emphasis has been given to data reported for out-patients as well as in-patients during study period. Follow-up data cannot be presented due to inadequate information about ADEs. However, utmost care was taken to avoid drop-outs and lost to follow-up cases.

Medication Errors (ME) were not monitored during the study period. Awareness regarding the importance of monitoring and reporting ADEs can improvise the ADE reporting practices in a hospital setting.

Language was one of the barriers while interacting with patients as most of them were locals. It was overcome by taking proper support from nurses in translating the terms and conveying information to patients.

CONCLUSION

In the present study, dabigatran appears to be safer than warfarin. Less frequent PT/INR monitoring, reduction in bleeding events and safer administration being the most probable reasons for preferring dabigatran in non-valvular atrial fibrillation patients. Dabigatran being a costly alternative is most commonly preferred by healthcare professionals for the prevention of thrombotic stroke in NVAF. Dabigatran is associated with gastro intestinal adverse effects and therefore, utmost care should be exercised to prevent gastrointestinal (GI) adverse effects and ensure patient compliance. Patients who are at high risk of developing adverse effects especially bleeding events should be encouraged for voluntary reporting and be critically reviewed for their medication regimen during hospitalization and in the outpatient setting.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

ABBREVIATIONS

ACC: American College of Cardiology; **ADEs:** Adverse Drug Events; **ADRs:** Adverse Drug Reactions; **AF:** Atrial Fibrillation, **AHA:** American Heart Association; **ALT:** Alanine Aminotransferase; **DDI:** Drug-Drug Interaction; **FDA:** Food and Drug Administration; **GI:** Gastrointestinal; **INR:** International Normalized Ratio; **KSA:** Kingdom of Saudi Arabia; **LFTs:** Liver Function Tests; **NOACs:** Novel Oral Anti-coagulants; **NSAIDs:** Non-Steroidal Anti-Inflammatory Drugs; **NVAF:** Non-valvular Atrial Fibrillation; **PCC:** Prothrombin Coagulation Complex; **PT:** Prothrombin time; **UAE:** United Arab Emirates; **WHO:** World Health Organization.

SUMMARY

Dabigatran being a costly alternative is most commonly preferred by healthcare professionals for the prevention of thrombotic stroke in NVAF. Dabigatran appears to be safer than warfarin. Less frequent PT/INR monitoring, reduction in bleeding events and safer administration being the most probable reasons for preferring dabigatran in non-valvular atrial fibrillation patients.

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