Clinical utility of dabigatran in United Arab Emirates

A pharmacovigilance study

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ABSTRACT

الأهداف: نهدف إلى توفير البيانات في وقت مبكر عن الفائدة السريرية من دابيقاترن في العين، دولة الإمارات العربية المتحدة.

الطريقة: دراسة مقطعية بأثر رجعي موافق عليها. تمت الدراسة على مجموعه 76 مريضاً تستخدم دابيقاترن من سبتمبر الى ديسمبر 2014 في عيادة أمراض القلب بمستشفى العين، العين، الإمارات العربية المتحدة. وقد تم تصميم التحليل الأساسي لاختبار وتيرة النزيف (المعدل) مع دابيقاترن 75، 110، و150 ملغ.

النتائج: كان متوسط العمر 1.5 ± 67.9 سنة (المدى 29-98 سنة). وتألفت هذه من الذكور (52.6%) مع متوسط العمر 66.3 ± 1.7 سنوات والإناث (47.4%) مع متوسط العمر 69.6 ± 1.1 سنوات. وكانت أعلى فئة عمرية تلك التي بين 80-61 سنة (60.5%)، حيث شكلت الفئة العمرية 75≥ سنة الأكثرية>. كان مؤشر استخدام دابيقاترن في مرضى الرجفان الأذيني. كان معدل النزيف مع دابيقاترن 18/76 (23.7%)، وميلينا هي سبب النزيف الرئيسي 8/76 (10.7%). وكان معدل دخول المستشفى 67.1%، معدل وقف استخدام الدابيقاترن 0.01%، ومعدل الوفيات 6.5%. لقد بحثت الدراسة سلامة دابيقاترن. أظهر مرضى الدراسة بعض حالات النزيف مع حالة واحدة لنزيف رئيسي قاتلة. أظهر المرضى وجود حالات مرضية مصاحبة عالية، ودخول وإعادة دخول للمشفى التي لا ترتبط مباشرة مع دابيقاترن ولكن نسبة إلى الرجفان الأذيني غير المنضبط. لم نجد أي علاقة للوفاة بسبب دابيقاترن.

الخاتمة: دابيقاترن بديل مناسب للوارفارينتنت في الحاجة إلى رصد النسب المطبعة الدولية المتكررة، ومع ذلك، قد تحتاج إلى رصد الدواء بالبلازما.

Objectives: To provide early data regarding clinical utility of dabigatran in Al-Ain, United Arab Emirates (UAE).

Methods: This was an ethics approved retrospective cross sectional study. We retrieved a total of 76 patients who were using dabigatran from September to December 2014 in the Cardiology Clinic at Al-Ain Hospital, Al-Ain, UAE. The primary analysis was designed to test the frequency of bleeding events (rate) with dabigatran 75, 110, and 150 mg.

Results: The mean age ± standard deviation of cohort was 67.9 ± 1.5 years (range; 29-98 years), composed of males (52.6%) with mean age of 66.3 ± 1.7 years, and females (47.4%) with mean age of 69.6 ± 1.1 years. The highest age group was those between 61-80 years (60.5%). Most comprised the age strata of ≤75 years (73.7%). The main indication for dabigatran use was atrial fibrillation. The rate of bleeding with dabigatran was 18/76 (23.7%), and melena was the leading cause of bleeding 8/76 (10.7%). The hospitalization rate was 67.1%, dabigatran withdrawal rate was 0.01%, and mortality rate was 6.5%. The cohort had exhibited incidences of minor bleeding with one fatal major bleeding, high co-morbidities, admission, and readmission, which was not directly linked to dabigatran. We did not identify any relation of death due to dabigatran.

Conclusion: Dabigatran is a suitable alternative to warfarin obviating the need for repetitive international normalized ratio monitoring, however, it may need plasma drug monitoring.

Atrial fibrillation (AF) is the most common cardiac arrhythmia that affects 1-1.5% of population worldwide.[1] Atrial fibrillation prevalence increases with age, and rises from 0.7% in those between 55-59 years to 17.8% in those ≥85 years. Nearly 85% of patients with AF are aged >65 years old.[2] The lifetime risk for the development of AF as demonstrated in the Framingham study was one in 4 for men and women aged ≥40 years,[3] which pose certain concerns in countries with aging populations.[4,5] In addition to this, hospitalization related to AF is alarmingly increasing.[6] The risk of stroke in patients with AF is 5 folds, and systemic thromboembolism is 3 folds.[7,8] Banerjee, et al[9] has deployed stroke prevention score in patients with AF, however, the predictive value is of less magnitude. The European Society of Cardiology set estimation of stroke risk in patients with AF as per CHA_2DS_2-VASc score to determine the recommendation for initiating an oral anticoagulant,[10] whereas in patients with CHA_2DS_2-VASc ≥2, HAS-BLED score can be used to assess the risk of bleeding, and commencement of anticoagulant.[11]

Warfarin (vitamin K antagonist [VKA]) has proven efficacy in reducing the risk of stroke in patients with AF, however, it poses high bleeding incidences, emergency hospitalizations, unpredictable therapeutic effect, and multiple international normalized ratio (INR) tests leading to many limitations in its clinical utility.[12] Novel oral anticoagulants (NOACs) are proved as effective anticoagulants in prevention of stroke in patients with AF. Novel oral anticoagulants were preferred in non-valvular AF, and do not require coagulation monitoring, however, strict adherence to approved indication is highly warranted.[13] Dabigatran (Pradaxa®), a competitive inhibitor of thrombin was approved in October 2010 by the United States of America Food and Drug Administration to reduce the risk of stroke, and systemic embolism in patients with non-valvular AF.[14] A systematic review incorporated 6 economic reviews from diverse healthcare systems (USA, Canada, and United Kingdom) utilizing different economic models. It has suggested the benefit of dabigatran in patients with high-risk of stroke, high-risk of intra-cerebral hemorrhage, or suboptimal use of warfarin. The review outlined concerns on tolerability of dabigatran, adherence issues, and adverse consequences.[15]

Disclosure. Authors have no conflict of interest, and the work was not supported or funded by any drug company.

In comparison with warfarin, dabigatran 150 mg has shown low rates of stroke, and systemic embolism (dabigatran $p<0.001$ for superiority). However, both drugs exhibited comparable rates of major hemorrhage.[16-18] Greater fatal, and non fatal bleeding events were reported with dabigatran than warfarin.[19,20] A recent (2015) retrospective Medicare data analysis study[20] on dabigatran's safety highlighted that the incidence of bleeding was higher than with warfarin (33% versus 27%), 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%).[20] It has been documented that risks of major bleeding from dabigatran is high for patients with chronic kidney disease, and in African Americans.[20] The Randomized Evaluation of Long-term Anticoagulant Therapy: Dabigatran versus warfarin-RE-LY studies[18] have showed similar risk of bleeding with warfarin versus dabigatran in patients with non-valvular AF. This dictated the importance of age sub-group analysis in studies. In real clinical practice, patients from different countries may have more co-morbid conditions than those in the RE-LY study.[21] The current available data around bleeding incidences from dabigatran is relevant to populations with diverse characteristics. Revealing the clinical utility of dabigatran in our Emirati population may demonstrate different perspectives. Therefore, we intend to provide early data around the clinical utility of dabigatran in United Arab Emirates (UAE) Emirati population.

Methods. *Ethical clearance.* The study protocol was approved by the Al-Ain Hospital Ethics Committee, and ratified by Al-Ain Medical District Human Research Ethics Committee, Al-Ain, UAE. A retrospective cross-sectional cohort study was conducted from September to December 2014 in the Cardiology Clinic at Al-Ain Hospital, Al-Ain City, UAE. Patients receiving dabigatran from the time of first prescription from January 2011 to March 2014 were retrieved from the electronic database using Cerner® registry. All patients using dabigatran irrespective of age, were included in our study.

Power and sample size. Taking into account our retrospective study design, we performed a confirmatory power calculation for our sample estimation. We used 5% precision, 5% prevalence of overall bleeding, and 95% confidence level (CI) (95% actual mean falls within our CI), at one tailed analysis (due to expected small sample size). The minimum sample required was 73 patients. Since we have 76 patients on dabigatran, we

have exceeded the calculated target sample. Therefore, 76 patients were considered sufficient to detect the study main outcome. We utilized readily available data for dabigatran users.

Patient selection. This study was conducted on selected group of patients using dabigatran. The selection of patients was performed from the electronic database (Cerner®), which has yielded 76 patients on dabigatran during the study period.

Inclusion and exclusion criteria. Patients were legible if they were on dabigatran (Pradaxa®), diagnosed with AF, and with or without prior use of warfarin. The exclusion criteria were patient with creatinine clearance (CrCl) <30 mL/minute, and/or with other than AF indications for dabigatran.

Data elements. The data elements collected have included demographic details (for example, age, gender), body mass index (BMI), primary indication for anticoagulation with dabigatran, dose, co-morbidities (prior stroke, diabetes, coronary artery disease, peripheral vascular disease, heart failure [HF], hypertension), bleeding events, renal function (CrCl, and homeostasis disorders). The minor bleeding was defined as reduction in hemoglobin concentration of less than 2 g/dL, or not requiring blood transfusion or no symptomatic bleeding in a critical area or organ. The major bleeding was defined as any bleeding events that required the above.[18] In addition to concomitant drugs, withdrawal of dabigatran, and prior use of warfarin, lipid profile, and glycosylated hemoglobin (HbA$_{1C}$) measures were also collected. These factors were considered against dabigatran product labeling guidelines. Furthermore, baseline stroke risk using CHADS$_2$ score, CHA$_2$DS$_2$-VASc, HAS-BLED score, INR, and hemoglobin levels at each clinic visit have been reported for risk assessment.

Search methods. We searched reputable database, such as PubMed and Scopus using the relevant dabigatran medical terms subheadings. We have complied with the Declaration of Helsinki, ethics approval, and detailed informed consent.

Outcome measures. The safety outcome measure was the frequency of bleeding events due to dabigatran. The rates of withdrawal, hospitalization, and death due to dabigatran were taken as secondary outcome measures.

Statistical analysis. We performed uni- and multivariate analysis to explore the relation of 27 variables with the outcome measures.

Results. There was a total of 76 patients with AF receiving dabigatran during the study period. The mean age was 67.9 ± 1.5 years (range; 29-98 years), males

was 52.6% (66.3 ± 1.7 years), and females was 47.4% (69.6 ± 1.1 years). The age group stratifications revealed the highest age group was those between 61-80 years (60.5%). Most were ≤75 years (73.7%), and 76.3% used dabigatran 150 mg (**Table 1**). The mean CHA$_2$DS$_2$ score was 2.38 ± 1.46, CHA$_2$DS$_2$-VASc score was 3.54 ± 1.82, and HAS-BLED score was 3.46 ± 1.205 (**Table 2**). The main co-morbidities with the cohort were: hypertension (65, 85.5%), diabetes type 2 (36, 47.4%), and HF (28, 36.8%). Stroke was evident in 18 cases (23.7%), transient ischemic attack (TIA) (10, 13.2%), and myocardial infarction (MI) (8, 10.5%). The least reported morbidities were thromboembolism (TE) (5, 56.6%), and pulmonary embolism (PE) (2, 2.6%). There were (9, 11.8%) patients taking clopidogrel concomitantly with dabigatran. The combination has no significant association with bleeding events (2/9 [22.2%]), which comprises 2/76 (2.6%) of overall bleeding events. The cohort revealed very high percent of combined dabigatran, and proton-pump inhibitors (37, [48.7%]).

Primary outcomes. *Bleeding rate.* We explored the safety of dabigatran in our population sample who has exhibited incidences of minor bleeding with one fatal major bleeding. The incidences of bleeding were certain attributes with plausible time relationship to dabigatran intake (18 [23.7%]). They were categorized according to the site of bleeding as reported in patient's progress

Table 1 - The characteristics of the study population of patients using dabigatran (n= 76) in Al-Ain, United Arab Emirates.

Parameter	F (%)	Mean ± SD (years)	*P*-value
Age (min 29-98 max) years			
17 - 40	2 (2.6)	29.0 ± 0.0	
41 - 60	16 (21.1)	53.5 ± 5.1	
61 - 80	46 (60.5)	69.5 ± 5.2	
>80	12 (15.8)	87.4 ± 5.5	
Subtotal	**76 (100.0)**	**67.9 ± 1.5**	(*p*=0.551)
Age >75 years	20 (26.3)	83.5 ± 6.5	
Age ≤75 years	56 (73.7)	62.3 ± 10.0	
Subtotal	**76 (100.0)**	**67.9 ± 1.5**	(*p*=0.027)
Age >65 years	46 (60.5)	75.1 ± 7.6	
Age ≤65 years	30 (39.5)	56.7 ± 12.0	
Subtotal	**76 (100.0)**	**67.9 ± 1.5**	(*p*=0.085)
Gender			
Male	40 (52.6)	66.3 ± 14.3	
Female	36 (47.4)	69.6 ± 11.5	
Subtotal	**76 (100.0)**	**67.9 ± 1.5**	(*p*=0.621)
Indication for dabigatran (atrial fibrillation)	**76 (100.0)**	-	
	76 (100.0)	**67.9 ± 1.5**	(*p*=0.621)

F- frequency, SD - standard deviation

notes. The main bleeding event was melena (10.7%). The rest of the bleeding events were hematuria, vaginal, intraocular, epistaxis, gum, intra-cerebral hemorrhage, and hematemesis, and in range of 1.3-2.6%.

The age group >75 years exhibited bleeding incidences of 2 (2.6%), while patients ≤75 years was 16 (21.1%). Bleeding incidences according to age strata >65 years was 9 (11.8%), similar to those ≤65 years. There were gender variations in bleeding events between males (11, 14.5%), and females (7, 19.2%). The highest bleeding events occurred in patients between 61-80 years of age (11, [14.5%]). The highest bleeding events occurred in patients with hypertension (16, [21.1%]) compared with other co-morbidities. There were no

significant associations between bleeding, and all the 27 tested variables including the dabigatran doses (75, 110, and 150 mg). In multivariate analysis the only variable with significant association to bleeding was MI (p=0.007, 95% CI for B= 0.716 - 4.258).

Secondary outcomes. Dabigatran withdrawal, hospitalization and mortality rate. Only one patient has withdrawn from dabigatran throughout the last 3 years (withdrawal rate was 0.01%). However, 32 patients (42.1%) were using warfarin prior to dabigatran. The prior use of warfarin was significantly associated with bleeding (p=0.014), hospitalization (p<0.001), and death (p=0.007). This was more prominent in older patients >75 years, and in patients with co-morbid

Table 2 - The distribution of different variables against dabigatran 3 doses (75, 110, and 150 mg).

Parameter	Dabigatran 150 mg	Dabigatran 110 mg (%)	Dabigatran 75 mg
Dose of dabigatran	76.3	17.1	6.6
Age >75 years	12.2	7.5	5.9
Age ≤75 years	64.1	9.6	0.7
Age >65 years	45.2	8.9	5.9
Age ≤65 years	31.1	8.2	0.7
BMI ≥25	44.7	7.9	-
Bleeding event	16.3	6.5	0.9
Renal function (CrCl <30 mL/min)	12.3	5.6	2.3
CHADS$_2$ ≥2 score	55.2	10.5	2.6
CHA$_2$DS$_2$ VASc ≥2 score	64.5	15.8	5.2
HAS-BLED ≥2 score	73.7	17.1	6.6
Labile INR <2 score	61.8	14.5	6.6
Co-morbidities			
Prior stroke, transient ischemic attack, or systemic embolism	13.1	3.9	5.2
Heart failure	30.2	5.2	1.3
Myocardial infraction	7.9	2.6	-
Diabetes	39.4	6.5	1.3
Hypertension	53.9	15.8	6.6
Prior warfarin	35.5	3.9	2.6
Rate of discontinuation of dabigatran	1.3	-	-
Co-administered drugs			
Aspirin	18.4	10.5	2.6
Factor Xa inhibitor	2.6	3.9	-
Clopidogrel	7.9	3.9	-
Digoxin	17.1	3.9	1.3
ACEinh/ARBb	31.5	9.2	2.6
Beta-blockers	36.0	10.0	3.9
Amiodarone	5.2	-	-
Statin	46.0	13.1	3.9
Proton-pump inhibitor	36.8	7.9	1.3

BMI - body mass index, CrCl - creatinine clearance, min - minute, CHADS$_2$ - congestive heart failure, hypertension, age, diabetes, prior stroke, HAS-BLED - hypertension, abnormal liver/renal function, stroke history, bleeding predisposition, labile INRs, elderly (age >65), drugs/alcohol usage, INR - international normalized ratio, ACEinh/ARBb - angiotensin converting enzyme inhibitor/angiotensin receptor blocker

conditions. The rate of hospitalization in the cohort for 51 patients was 67.1%. There were no significant associations between hospitalization, and the tested variables. The levels of hemoglobin (taken as mean of 3 values) ≥130 versus <130 gram were (n=41, 53.9% versus n=35, 46.1%, ≥120 versus <120 gram n=48, 63.2% versus n=28, 36.8%), and ≥100 versus <100 gram (n=68, 89.5% versus n=8, 10.5%).

There was no significant associations in multivariate analysis between bleeding, and the 3 hemoglobin cut-off values. Only 5 (6.6%) patients have received blood transfusion of ≥2 units of blood. Mortality was categorized using pre-specified definitions followed by central adjudication. The rate of death among the cohort was 6.5% (5 cases). Mostly occured in patients with age group >65 years. The causes of death in patients using dabigatran were not relevant to the drug as per the death certificates ($p<0.611$) (**Table 3**). The reported causes of death were attributed to TE, cardiac, and respiratory arrests. The only variables that were significantly associated with death were TE ($p=0.024$, 95% CI for B=0.44 - 0.586), and blood transfusion ($p=0.011$, 95% CI for B=0.085 - 0.639). Myocardial infarction (hazard ratio, 2.2; 95% CI=1.72 - 2.67; $p=0.001$), and HF (hazard ratio, 3.5; 95% CI=2.97 - 3.98; $p=0.001$) were the significant predictors of cardiac death. We performed paired analysis for some continuous

variables, and the mean values ± SD were: HbA_{1c} (5.0 ± 0.32, $p=0.00$; 95% CI=4.3 - 5.6), cholesterol (3.1 ± 0.21, $p=0.009$, 95% CI=2.7 - 3.5), HDL (0.85 ± 0.05, $p=0.51$, 95% CI=0.73 - 0.96), LDL-C (1.8 ± 0.14, $p=0.025$, 95% CI=1.54 - 2.10), and triglycerides (0.91 ± 0.09, $p=0.164$, 95% CI=0.73 - 1.09).

Discussion. *Main findings.* This was one of the limited pharmacovigilance safety outcome study reported on dabigatran in UAE population. We have shown that 23.7% of the dabigatran users have bleeding events. We have reported minor bleeding incidences with one fatal major bleeding in patients using dabigatran for AF. The bleeding events were significantly associated with MI, and were markedly higher with the 150 mg dose of dabigatran. The hospitalization rate during the 3 years retrieved data was very high. The cohort exhibited high co-morbidities, admissions, and readmission, which were not directly linked to dabigatran but was attributed to uncontrolled AF, and other co-morbidities. However, the only variables that were significantly associated with death were TE, and blood transfusion. Furthermore, HF, and prior MI were the independent predictors of cardiac death.

Dabigatran and adverse effects profile. In recent years, international guidelines have recommended the use of NOACs in line with their proven safety, efficacy, and compliance.[22-24] In our local study, 23.7% of dabigatran-treated patients experienced bleeding events, which is much higher than Lakkireddy, and co-workers study (10%), and lower than RE-LY study (57%).[18,25] The reports of major bleeding (fatal, and non fatal), and minor bleeding related to dabigatran has been documented in many international studies.[19,20] Novel oral anticoagulants associated bleeding events in stroke risk patients dictate the importance of risk stratification. Interestingly, melena (10.1%) was the major cause of bleeding in our study. In RELY-ABLE study a higher rate of major bleeding with the higher dose of dabigatran was reported. The incidences of intracranial bleeding rate in the current study were low with both doses of dabigatran compared with RELY-ABLE study[26] (3.74%). Furthermore, the prevalence of HF in our study population was higher than RE-LY study (36.8% versus 32%).[27] Another safety endpoint of concern in our study was MI events (10.1%), which have shown statistically significant associations with the 3 doses of dabigatran. However, one study has shown both doses of dabigatran (110 and 150 mg) were associated with >50% more MI events compared with other NOACs.[28] It has been reported that addition of NAOCs to antiplatelet therapy in acute coronary

Table 3 - Incidence of death among the cohort (n=76).

Parameter	Survival		Death	P-value
		Frequency (%)		
Age, Years				
17 - 40	1	(1.4)	1 (20.0)	
41 - 60	15	(21.1)	1 (20.0)	
61 - 80	43	(60.6)	1 (20.0)	0.168
>80	12	(16.9)	2 (40.0)	
Subtotal	**71**	**(93.5)**	**5 (6.5)**	
Age >75	19	(26.8)	3 (60.0)	
Age ≤75	52	(73.2)	2 (40.0)	0.684
Subtotal	**71**	**(93.5)**	**5 (6.5)**	
Age >65	44	(62.0)	3 (60.0)	
Age ≤65	27	(38.0)	2 (40.0)	0.583
Subtotal	**71**	**(93.5)**	**5 (6.5)**	
Gender				
Male	38	(53.5)	3 (60.0)	
Female	33	(46.5)	2 (40.0)	0.324
Subtotal	**71**	**(93.5)**	**5 (6.5)**	
Dabigatran 150 mg	55	(72.4)	3 (3.9)	
Dabigatran 110 mg	11	(14.5)	2 (2.6)	0.118
Dabigatran 75 mg	5	(6.6)	0	
Subtotal	**71**	**(93.5)**	**5 (6.5)**	

syndrome has significant increase in major bleeding with no evidence of efficacy.[29] The RELY-ABLE study has shown no significant difference in mortality between the 2 doses of dabigatran. However, the mortality rate in our study was higher (6.5%) than RELY-ABLE study (3.1%), and the RE-LY trial (4.1%), provided the differences between the studies design, and population. in the RE-LY trial, where the total mortality rate was 4.1%. In RE-LY study, 40% of the patients were 75 years of age, and older, a low rate of stroke or systemic embolism was observed with both doses of dabigatran, which was comparable to our study. Evidence suggests that patients with poorer INR control were significantly associated with the net clinical benefit of dabigatran.[18] RELY-ABLE study revealed that there was no difference between the doses in net clinical benefit as estimated by the composite of stroke, bleeding, and death.[26] Overall, 5 deaths were reported in our study 3 of these 5 patients were males, >75 years of age, and taking dabigatran in both strengths. There was no evidence that this was due to dabigatran use. In our study, 67.1% of the patients were hospitalized, which is much higher than the RELY-ABLE study 20%.[26]

Comparing dabigatran data with some other clinical trials. Our data supports the findings from a Danish registry study, which has assessed the efficacy, and safety in an "everyday clinical practice" population of anticoagulant-naïve patients with AF treated with dabigatran (4,978) compared with warfarin (8,936). The authors find no evidence of an excess of bleeding events, or MI among dabigatran-treated patients.[30] This was in contrast to our findings despite the large population differences. The Global Registry on Long-Term Oral Antithrombotic Treatment (GLORIA-AF) is a large, international, observational registry involving patients with newly diagnosed non-valvular AF at risk for stroke, enrolling up to 56,000 patients in nearly 50 countries.[31] The results of this study will provide information around the relative effectiveness and safety of NOACs in routine clinical care.

The GLORIA-AF study revealed that their registry program will add data from clinical practice to those from randomized trials to expand knowledge of antithrombotic treatment in patients with AF. Such data from the above registry and other similar on going registries of comparable patients will help us to understand external validity of clinical trial data. Dogliotti et al[32] evaluated the risk, and benefit of NOAC using a meta-analysis of published trials, and have concluded that NOACs should be preferred. The promising NOACs (apixaban [Eliquis®], edoxaban [Lixiana], rivaroxaban [Xarelto®]-factor Xa inhibitors,

and dabigatran [Pradaxa®]-direct thrombin inhibitor), have been approved for prophylaxis and treatment of AF, and venous thromboembolism (VTE) as option to warfarin to prevent stroke in patients with non-valvular AF. The landmark trials of NOACs in AF were named: Aristotle, Engage-AF, Rocket-AF, and RE-LY.[33-35]

There are many issues regarding the appropriateness of prescribing dabigatran,[36] and around recommended doses and contraindications.[37] A prospective one-site study has assessed the usefulness of dabigatran and rivaroxaban in patients with non-valvular AF. Inappropriate use of dabigatran, and rivaroxaban in patients with non-valvular AF was frequent, and possibly leads to adverse events.[36] In another randomized clinical study comparing apixaban, and warfarin in patients with AF, apixaban was found to be superior to warfarin in preventing stroke or systemic embolism, caused less bleeding, and resulted in lower mortality.[37] A relative small increase in risk (0.27) for MI in patients receiving dabigatran compared with control patients or those on warfarin was reported in a meta-analysis of 7 non-inferiority trials.[38] This has provided support to the present study findings.

It is deemed important to address certain issues in guidelines and management plan, particularly in special populations, such as individuals with chronic kidney disease, acute coronary syndrome, cardio version in a NOAC-treated patient, patients presenting with acute stroke while on NOACs, and NOACs versus VKAs in AF patients with malignancy.

Therapeutic monitoring of dabigatran. Dabigatran clinical utility and associated adverse events has been in focus by some health authorities. This is particularly crucial for ambulatory care physicians prescribing dabigatran without assessment, and monitoring of patient's kidney function. These concerns also included dabigatran's low mean oral bioavailability, considerable variability in plasma drug concentrations, and the dependence on renal elimination of the active metabolite.[28] Consequently, any accumulation of dabigatran in patients with certain degree of renal impairment (CrCl <30 mL/minute) will predispose to increased risk of excessive bleeding, which was reported in real clinical practice as leading to early deaths from the drug.[38]

The FDA reports of dabigatran potential adverse effects on the early launch of the drug (2010) moved to near the top of adverse event rankings.[39] We have critically appraised this report with current evidence, and did not support the extrapolation of these reports to the nowadays-current life scenario of dabigatran clinical utility. One issue of concern that with the FDA report,

which our data lend support was the clinical utility of dabigatran in elderly population (>75 years) where it poses a potential increase in major, and minor bleeding events. A possible alternative might be a NOAC with short half-life, such as apixaban. It has been shown that dabigatran plasma level monitoring could reflect bleeding particularly in elderly patients with impaired renal reserve.[40] The adjustment of doses of dabigatran and corresponding reduction on bleeding events was not emphasized by the manufacturer.[41] It has also been reported that there is a dearth for routine dabigatran plasma monitoring,[42] the cut-off values for coagulation assays, and the dosing scheme associated with surgical procedures and preventive measures for bleeding.[43]

Model to maximize the clinical utility of dabigatran. The above concerns has led for instance to health authorities across countries instigating extensive educational, and other activities pre-launch to help optimize the use of dabigatran post-launch in ambulatory care. These were summarized by Godman et al,[44] with some of the initial outcomes, and further interventions in their updated paper. Prior to initiating dabigatran, an assessment of renal function should be performed. Dabigatran is contraindicated in patients with a calculated creatinine clearance of <30 mL/minute. Whereas those with moderate renal impairment (30-50 mL/minute) are at increased risk of bleeding from dabigatran that warrants use with caution. The use of dabigatran should be based on compelling indication, monitoring, and restrictive guidelines in any health care facility. The off-label use should be strictly prohibited to save the patient, and to maximize the clinical benefit of dabigatran. Despite the fact that our study sample size was relatively small, it was representative of the population, and has enabled detection of subjects in between effects. However, larger sample is required to generalize the results. Another limitation was relevant to the sole use of dabigatran, where it was only indicated for AF patients. Hence, generalizing the results to other indications of dabigatran on other settings cannot be undertaken to evaluate the risk of bleeding.

In summary, dabigatran use was associated with incidences of minor bleeding with one fatal major bleeding. Dabigatran users exhibited high co-morbidities, admissions, and readmission were not directly linked to dabigatran, but was attributed to uncontrolled AF, and co-morbidities. We did not identify any direct relation of death and use of dabigatran. The prior use of warfarin was significantly associated with bleeding, hospitalization, and death. The only variables that were significantly associated with death were TE, and blood transfusion. Myocardial infarction and HF were the significant predictors of cardiac death.

Recommendations to use the CHA$_2$DS$_2$-VASc scoring system in patients with a CHADS$_2$ score of 0-1. Dabigatran may represent viable alternatives to a VKA, may ultimately be considered. We highlighted the importance of bleeding risk assessment prior to the initiation of anticoagulant (HAS-BLED) bleeding risk score is recommended. The use of dabigatran in special populations, such as the aged, and those with impaired renal function should be guided, and monitored in real clinical life. Dabigatran antidote and therapeutic monitoring deserve further research.

In conclusion, the clinical utility of dabigatran in patients with AF is very promising despite the limitations of bleeding events. Dabigatran resemble a suitable alternative to warfarin obviating the need for repetitive INR monitoring, however, it may need plasma monitoring.

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