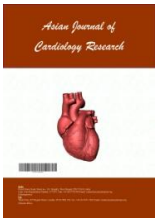

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Risk of Thromboembolism in Nonvalvular Atrial Fibrillation

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Authors' contributions

This work was carried out in collaboration among all authors. Authors AHM and Abdullah A. Alfhaid designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors AIA, KAA, Alzead, Ahmed A., GTA, MA, NSA and MAA managed the analyses of the study. Authors AHM, Abdullah A. Alfhaid, Alzead, Ahmed A. and MAA managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Background: Atrial fibrillation is associated with atrial thrombus formation and peripheral embolization, which leads to ischemic stroke or systemic thromboembolism. The CHADS2, CHA2DS2-VASc scores are tool for estimating risk of stroke in nonvalvular atrial fibrillation (NVAF) patients. Data on scores variables, Body mass index (BMI) and chronic kidney disease (CKD) with reduced glomerular filtration rate on their implication in identify thromboembolic events (TE) in Saudi population with NVAF are quite limited.

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Methods: The study consisted of 541 patients with AF seen in our institution from 2008 to 2013 were identified in database, 175 were NVAF. Thromboembolic end points were defined as ischemic stroke and systemic embolism. During follow - up period of 730 days. CHADS2, CHA2DS2-VASc scores components, BMI also CKD and association with TEs end points identified by Cox regression analysis.

Results: Of 175 patients with NVAF, 26 (14.9%) patients were identified to have TEs. Majority of them had stroke. Age (>or =75 years) and Peripheral vascular disease were significant factors for TEs. Thromboembolic risk in patients had previous stroke or TIA was 38.5% (P value =.000). Events rate of thromboembolism increased when CHADS2/ CHA2DS2-VASc score increased. No statistically significant associations were observed with BMI and TEs. Study has shown Despite only 35% of study population is suffering from CKD however level of estimated glomerular filtration rate were significant factor for TEs in patients with nonvalvular atrial fibrillation.

Conclusion: Study demonstrated CHADS2, CHA2DS2-VASc, CKD are predictor of TEs and should be included in risk stratification schemes among NVAF Saudi patient. While obesity was not predicator for TEs. So, keeping this association in consideration during thromboembolism risk assessment is recommended. Further study is needed to search for modifiable risk factors that are associated with increased risk thromboembolism in NVAF patient In addition to the conventional CHADS2/ CHA2DS2-VASc scheme.

Keywords: Atrial fibrillation; risk of thromboembolism; body mass index and chronic kidney.

1. INTRODUCTION

Embolization of atrial thrombi can occur with paroxysmal, persistent, or permanent atrial fibrillation (AF). The most commonly occurring, and often the most sever thrombi are those that occur in the brain during the clinical course of AF and manifest as an ischemic stroke [1]. Other systemic and pulmonary thromboembolism may also occur, but are less commonly recognized. To prevent ischemic strokes and systemic embolization, chronic antithrombotic therapy with either oral anticoagulation or antiplatelet therapy is often prescribed. Antithrombotic therapies carry an associated increased risk of bleeding and in treating AF patients, physicians must consider both the benefits and risks. AF in the presence of mechanical prosthetic heart valve or moderate to severe rheumatic mitral valve disease are define as Valvular AF where the use of vitamin K antagonists (VKA) for the prevention of thromboembolic events is the only established option. While term non-valvular atrial fibrillation (NVAF) has become popular with the development of non-VKA, direct oral anticoagulants (DOAC). Numerous studies have evaluated risk factors for embolization in nonvalvular atrial fibrillation AF and multivariate models have been constructed to stratify stroke risk in AF. The CHADS2 (congestive heart failure, hypertension, age ≥75 years old, diabetes, prior TIA or stroke) score is use as a clinical prediction rule for estimating the risk of stroke in patients with NVAF. Historically, the CHADS2 risk score is the most popular and has been best validated in different patient populations [2,3].

To complement the CHADS2 score, additional 'stroke risk modifier' risk factors were included and the CHA2DS2-VASc score was developed. These additional non-major stroke risk factors include age 65-74, female gender and vascular disease in an effort to provide a more refined risk of stroke/thromboembolism and provides significant information on risk of stroke in AF patients with a CHADS2 score of 0-1. Even in patients categorized as 'low risk' using a CHADS2 score=0, the CHA2DS2-VASc score significantly improved the predictive value of the CHADS2 score alone and a CHA2DS2-VASc score=0 could clearly identify 'truly low risk' subjects .The CHA2DS2-VASc score has been used in the new European Society of Cardiology guidelines for the management of atrial fibrillation [4].

Chronic kidney disease (CKD) is an Independent risk factor for cardiovascular disease outcomes, such as hypertension, heart failure and myocardial infarction. CKD has also been demonstrated as Independent risk of stroke in patients with AF without anticoagulation therapy [5]. The Danish national registry revealed that the risk of stroke or systemic embolism was higher in CKD patients with NVAF compared with those who did not have renal disease and even higher in those requiring dialysis [6]. Reduced creatinine

clearance was a strong independent predictor for stroke in the ROCKETAF and ATRIA study cohorts and use a CKD as part of the risk stratification scheme in NVAF patients [7,8].

Obesity is modifiable risk factor for so many cardiovascular diseases, especially attributable risk factor for AF [9]. Obesity and metabolic syndrome are not considered risk factors to help prevent stroke and other thromboembolic events in atrial fibrillation patients. However, there is some evidence to suggest they should, in a study examining the risk of left atrial thrombus in patients with AF, subjects with a body mass index (BMI) ≥ 27 had a markedly increased risk of left atrial appendage thrombus [10].

This retrospective study, examined CHADS2/ CHA2DS2-VASc scores variables risks of thromboembolic events (TEs) in nonvalvular atrial fibrillation Saudi population and determine whether body mass index and estimated glomerular filtration rate (eGFR) of Chronic kidney disease would be give incremental information with CHADS2/ CHA2DS2-VASc scheme in predicting thromboembolic event in NVAF Saudi patients.

2. METHODS

This is a non-randomized, retrospective study of patient above 18 years old diagnosed with nonvalvular AF within at King Faisal Specialist Hospital & Research Center (KFSH&RC), Riyadh. using physician-assigned diagnoses of nonvalvular AF between Jan 2008 to 31 December 2013; Excluding patients with moderate to severe rheumatic mitral valve disease and valvular repair or replacement [11].

We used administrative databases for information on patient age, sex, body mass index, previous ischemic stroke, diagnosed heart failure, known coronary heart disease, hypertension, diabetes and presence of vascular disease.

Baseline evaluation and investigative work up for all patients were used to derive their CHADS2 and CHA2DS2-VASc scores. A priori variables included the CHADS2 (congestive heart failure, hypertension, age>75, diabetes, previous stroke) and CHA2DS2-VASc (CHADS plus vascular disease, age 65–74 and female as sex category) clinical prediction rules were collected and considered for inclusion in the multivariate analyses for primary endpoints. The presence of each variable was given 1 point while a prior cerebrovascular accident (CVA), defined as ischemic stroke or transient ischemic attack (TIA), conferred 2 points. When CHA2DS2-VASc was used 2 points were given for age >75 and1 point forage 65–74.

Kidney function was assessed by level of estimated glomerular filtration rate and was categorized as following. eGFR>60 mL/min, eGFR 30–59 mL/min, eGFR 16-29 mL/min eGFR<15 mL/min. And body mass index categorizes into underweight, normal, overweight and obese according to BMI level and weight status.

A primary endpoint event is defined as the presence of any of the following: thromboembolic stroke, transient ischemic attack, deep venous thrombosis (DVT) or systemic embolism during follow- up period of 730 days.

2.1 Statistical Considerations

In this study, all the statistical analysis of data was done by using SPSS software (version 20.0.1 for Windows, SPSS Inc., Chicago, Il, USA). Descriptive statistics for the continuous variables and categorical variables and summarized as frequencies and percentages. Continuous variables compared by Student's t-test or ANOVA as appropriate, while categorical variables compared by Chi-square test. Univariate and multivariate logistic regression used to study the effect of the different risk factors on the primary outcomes of the study. The level of statistical significance is set at $p < 0.05$.

3. RESULTS

The study consisted of 541 patients with AF seen in our institution from 2008 to 2013 were identified in the database, 175 were NVAF. The proportion of males was 49.0% compared to 51% females. Patients suffering of congestive heart failure were 43%. Hypertension was 68.6% of the study subjects. A 29% of the study groups were older than 75 years. Diabetes mellitus (DM) was notice in 44% of the patients. There were 19.4% among NVAF had vascular disease (Table 1).

Table 1. Demographic data for the patient involved in the study

Patients characteristics	Number of patients	Percentage
Gender	85 Male	49.0%
	90 Female	51.0%
CHF	76	43.4%
HTN	120	68.6%
Age>= 75	51	29.1%
Age 65-74	53	30.3%
DM	77	44.0%
Prior stroke or TIA	23	13.1%
Vascular Disease	34	19.4%

There were 9.7% of study group having chronic kidney disease with eGFR<30 ml/min (Table 2).

BMI Above 30 amounted to 50.9% of all cases, while normal BMI level amounted to only 17.1% (Table 3).

The number of patients that developed nonvalvular atrial fibrillation stratified by CHADS2 Score of 0, 1 and 2 or greater were 27, 34 and 114 correspondingly. While patients stratified by CHAD2DS2-VASc Score 0, 1 and 2 or greater 2 were 16, 17 and 142 respectively (Table 4). Table 5 shows the characteristics of the cohort members who developed endpoints of interest: thromboembolic stroke, transient ischemic attack (TIA), deep venous thrombosis (DVT) and systemic embolism events during follow - up period of 730 days as primary outcome. A total of 26 (14.9%) developed thromboembolic event, seventeen of them had ischemic stroke.

Age >or =75 years and vascular disease were significant factors for thromboembolic events. patient who had previous stroke or TIA carry a greater risk for thromboembolism (CI= 1.572-4.161) (P value = .000). Events rate of thromboembolic increased when CHADS2 score/ CHAD2DS2-VASc Scores increased (Figs. 1 and 2). Even with 12 patients from 26 patients who had thromboembolism were overweight and obese no statistically significant associations observed with BMI and thromboembolic risk (CI= 0.733-1.995). Despite only 35% of study population is suffering from chronic kidney disease however level of estimated glomerular filtration rate assessing kidney function were significant factor for thromboembolic events in patients with nonvalvular atrial fibrillation (Table 6).

4. DISCUSSION

Various risk stratification schemes are design to help prevent stroke and other thromboembolic events in atrial fibrillation patients. Most of the scores variables are considered risk for thromboembolism events even in absent of AF. One of the most commonly use score is CHADS2 score and it has been validated in multiple populations [4,3,12].

Table 2. Kidney function of study group assessed by level of estimated glomerular filtration rate

Level of estimated glomerular filtration rate eGFR	Number of patients	Percentage
Not available	3	1.7%
Normal	109	62.3%
30 – 59	46	26.3%
<16 – 29	7	4.0%
<15	10	5.7%

Table 3. Distributions of body mass index (BMI) involved in the study

Wight status	BMI level	Number of patients	Percentage
	Not available	3	1.7%
Underweight	Below 18.5	2	1.1%
Normal	18.5 – 24.9	30	17.1%
Overweight	25.0 – 29.9	51	29.1%
Obese	30.0 and Above	89	50.9%

Table 4. CHADS2 and CHA2DS2--VASc score categories in the study sample

CHADS2/ CHA2DS2-VASc scheme	Score	Number of patients	Percentage
CHADS2	0	27	15.4% LOW Risk
	1	34	19.4% MODERATE Risk
	2	50	28.6% HIGH Risk
	3	35	20.0%
	4	20	11.4%
	5	5	2.9%
	6	4	2.3%
CHAD2DS2-VASc	0	16	9.1% LOW Risk
	1	17	9.7% MODERATE Risk
	2	25	14.3% HIGH Risk
	3	33	18.9%
	4	32	18.3%
	5	23	13.1%
	6	15	8.6%
	7	9	5.1%
	8	3	1.7%
	9	2	1.1%

Table 5. Thromboembolic stroke, transient ischemic attack (TIA), deep venous thrombosis (DVT) and systemic embolism events during follow- up period of 730 days

Thrombus type	Number of patients	Percentage
Thromboembolic stroke	17	9.7%
TIA	3	1.7%
Systemic embolism	3	1.7%
DVT	1	0.6%
Stroke + systemic embolism	1	0.6%
Stroke + DVT	1	0.6%
Total of Thromboembolic event =	26	14.9%

Table 6. Cox regression analysis of CHADS2, CHA2DS2-VASc scores components, body mass index (BMI), chronic kidney disease by level of estimated glomerular filtration rate (eGFR) and association with thromboembolic event

Variable	Odds ratio	95% CI	P-value
congestive heart failure	1.365	0.592 - 3.145	0.4649
hypertension	2.862	0.936- 8.752	0.0652
Age >75	3.532	1.501-8.312	0.0039
Diabetes mellitus	1.328	0.577- 3.059	0.5050
Prior stroke or transient ischemic attack	2.557	1.572-4.161	0.0002
CHADS2_Score	1.775	1.311-2.404	0.0002
Vascular Disease	3.255	1.320-8.029	0.0104
Age 65-74	1.027	0.416-2.535	0.9535
Sex	1.967	0.824-4.691	0.1274
CHAD2DS2-VASc Score	1.569	1.250-1.969	0.0001
BMI	1.209	0.733-1.995	0.4567
eGFR	1.704	1.112-2.610	0.0144

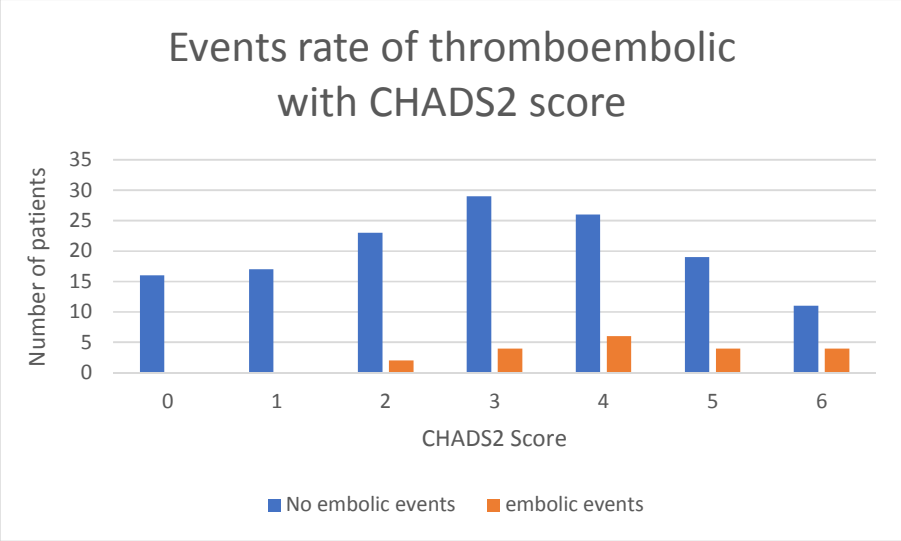

Fig. 1. Events rate of thromboembolic with CHADS2 score

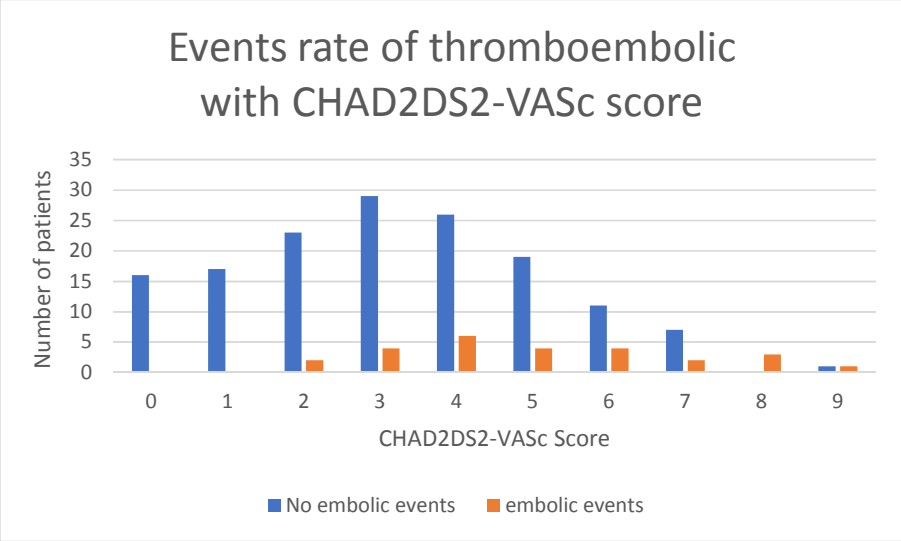

Fig. 2. Events rate of thromboembolic with C CHAD2DS2-VASc score

However due to the simplicity of CHADS2 score system has resulted Inability in identifying low-risk group (CHADS2 score of 0 -1) of AF patients [13].

So, to overcome the drawback of the CHADS2, the CHA2DS2-VASc scoring system was developed. Using all components of the CHADS2 system; but with a greater emphasis on age. As elderly patient carry near five-fold heightened risk of stroke in patients with non-valvular AF [14]. and includes two additional factors: (i) female sex and (ii) vascular disease that found to be a predictor of thromboembolism in non-valvular AF. This finding is consistent with observations in our work that showed CHADS2, CHA2DS2-VASc, elderly patient and vascular disease were significant factors for thromboembolic events in patient with NVAF.

Female sex is at higher risk of stroke than male in AF patient as has been evident in the trials of stroke prevention in AF [15,16]. However our retrospectively study examined the risk of female patients with atrial fibrillation reveled similar thromboembolic risk in comparison with male

patients when there is no additional risk factors. This finding is consistent with the proposed excluding Sc criterion in an analysis of the Japanese J-RHYTHM registry [17]. Where no sex difference was found in patient groups stratified by CHA2DS2-VASc and CHA2DS2-VA scores. Current European and American AF guidelines recommend using the CHA2DS2-VASc score for guiding anticoagulation treatment decisions, but they differ with respect to their thresholds for men and women [18,19,20].

Congestive heart failure and atrial fibrillation frequently coexist and are associated with increased risk of cardiovascular events [21]. In our work no statistically significant associations were observed with Congestive heart failure and TE. This could be related to the less number of patients and events.

Diabetes mellitus is also a significant independent risk factor for stroke [22]. After adjusting for confounding factors, our study did not show statistically significant risk of thromboembolism in atrial fibrillation and Diabetes mellitus. Interestingly, the different levels of HbA1c among patients with diabetes mellitus duration of ≥10 years were not associated with higher rates of thromboembolism [23,24] which could explain our finding.

History of hypertension shown to be risk factors for TE in AF [25]. This finding was not confirmed in our study which could be attributed to the small sample size study.

A prior stroke or transient ischemic attack is the strongest risk factor for stroke in AF patients [25] Stollberger et al identified age and previous stroke as the most powerful predictors of stroke/embolism on a multivariate analysis in patients with NVAF [26]. This finding is consistent with the observations in our work of patient who had previous history of stroke or TIA and they carry carry a greater risk for thromboembolism.

Obesity is a cause of various negative cardiovascular outcomes and associated with a poor prognosis in patients with AF [27].

BMI is the most widely used marker of obesity, we retrospectively examined this risk. Our results are show that overweight and obesity were not associated with increased risk of TE. On the other hand, a meta-analysis of nine studies including 49,364 patients noticed underweight (BMI <18.5 kg/m^2) Asian patients with AF were at increased risk of embolic events [28]. This finding could be attributed to lower BMI and unintentional weight loss may indicate disease progression in those patients [29].

The Rocket AF study results showed that moderate renal failure is an independent risk factor for stroke among AF patients [30,31,32,33]. In a retrospective analysis of large cohort of patients with AF showed low estimated glomerular filtration rate was associated with significantly increased risk of thromboembolism [5]; This results are in similar with our findings.

5. STUDY LIMITATIONS

This study is a single-center experience, and generalization of the results may not be applicable. Patient compliance on anticoagulation was not well assess because of the retrospective nature of the study, and patients with incomplete follow up were excluded. There could be inter-observational variability in the assessment of the nonvalvular atrial fibrillation in study population.

6. CONCLUSIONS

Study demonstrated CHADS2, CHA2DS2-VASc, CKD are predictor of TEs and should be included in risk stratification schemes among NVAF Saudi patients, while obesity was not predicator for TEs. So, this association should be considered during risk assessment of thromboembolism.

CONSENT

It is not applicable.

ETHICAL APPROVAL

The study was conducted in accordance with the ethical principles contained in the Declaration of Helsinki (2000), the ICH Harmonized Tripartite Good Clinical Practice Guidelines, the policies and guidelines of the research advisory committee of the KFSH&RC and the laws of Saudi Arabia. As this is a retrospective study and does not involve any direct contact with patients or their families and does not pose more than a minimal risk to patients, we consider the benefit to risk ratio to be favorable. Waiver of informed consent was obtained forsake the nature of the study.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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