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Original article

Prevalence, main determinants, and early outcome of patients with atrial fibrillation hospitalized with ischemic stroke: evaluation of the value of risk assessment scores for predicting risk of stroke or major bleeding following anticoagulation therapy

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Summary. *Background:* Despite controllable nature of atrial fibrillation in most patients, it increases the risk of atrial thrombosis leading to ischemic stroke. The researchers assessed the underlying risk factors for brain stroke and also major bleeding in patients with ischemic stroke and atrial fibrillation. *Methods:* Among 900 patients hospitalized with the diagnosis of ischemic brain stroke between 2013 and 2014, 100 patients had atrial fibrillation that included into this cross-sectional study. The risk of stroke and major bleeding was assessed using CHA2DS2-VASc and HAS-BLED risk scores, respectively; but new stroke was not considered. *Results:* Of 900 patients with evidences of ischemic stroke, 100 had atrial fibrillation with an overall prevalence of 11.1%. Mean CHA2DS2-VASc score was 4.35 ± 1.76 that the total score was ≥ 2 points in 93% of subjects showing necessity to anticoagulation therapy in 93% of the patients before recent stroke. Mean HAS-BLED score was 2.83 ± 1.30 that was ≥ 3 in 61% indicating risk of bleeding in 61% of all patients. 31% of the patients had previous history of atrial fibrillation, but only less than half of them (51%) were under treatment with warfarin, and also the measured INR was lower than the therapeutic range in 95.5% of individuals on warfarin therapy. In-hospital mortality was reported in 9% of all study subjects. The main determinants of early mortality included history of stroke, renal failure, presence of coronary artery disease, acetylsalicylic acid use, and Clopidogrel use. The analysis using the ROC curve showed that both CHA2DS2-VASc score (AUC = 0.788) and HAS-BLED score (AUC = 0.960) could strongly predict in-hospital mortality. *Conclusion:* The patients with atrial fibrillation hospitalized with ischemic stroke showed an important absolute risk of further stroke and early mortality. Despite substantiated advantages of warfarin prophylaxis, its limited application is still very common. (www.actabiomedica.it)

Key words: atrial fibrillation, stroke, CHA2DS2-VASc, HAS-BLED, mortality

Introduction

Atrial fibrillation is a common atrial arrhythmia with an overall prevalence of 0.4% to 2.0% in the general population and with considerable higher prevalence in those patients who undergoing cardiac revascularization (1, 2). Despite its controllable nature in most patients, its paroxysmal pattern can increase the risk of atrial thrombosis or emboli leading to high mortality and morbidity (3, 4). Also, the occurrence

of atrial fibrillation may also result in increased risk for brain stroke and heart failure (5). Ischemic stroke is common in patients with atrial fibrillation either as the initial presenting manifestation of atrial fibrillation or despite appropriate antithrombotic prophylaxis. In such patients, a cardiac embolus most commonly originating from the left atrium is a common cause of ischemic stroke (6). As a result, patients with atrial fibrillation who suffer from ischemic stroke appear to have a worse outcome including more disability and greater mortality than those who have an ischemic stroke in the absence of atrial fibrillation (7). This cardio embolic stroke occurs when stagnant blood in the fibrillating atrium forms a thrombus that embolizes to the circulation, blocking arterial blood flow and causing ischemic injury (8). Multiple risk stratification schemes to predict stroke in patients with atrial fibrillation have been proposed over the last several decades. One of the main scoring systems for assessing the risk of ischemic stroke following atrial fibrillation is CHA2DS2-VASc score (9). This score corresponds to a greater risk of stroke, while a low score corresponds to a lower risk of stroke. This system not only can estimate risk for stroke in patients with atrial fibrillation, but also is used to determine whether or not treatment is required with anticoagulation therapy or antiplatelet therapy (10). Overall, this scoring tool can accurately predict the risk of stroke in patients with non-valvular atrial fibrillation and its high validity has been also shown and has become the standard as described in the 2006 American College of Cardiology/American Heart Association/Heart Rhythm Society guidelines for the management of atrial fibrillation (11). However, some studies could not confirm high value of such systems for predicting brain stroke (12, 13).

Besides, because of high risk of thromboembolic events in patients with atrial fibrillation resulted in brain stroke, the need for coagulation therapy has been strongly recommended. However, the risk for bleeding events may be also increased following this regimen and hence along with coagulation therapy, assessing the risk for major bleeding should be considered. In this regard, some scoring systems also developed to assess bleeding risk such as HAS-BLED scoring system considering bleeding related risk factors such as hypertension, abnormal renal or liver dysfunction, previous stroke or TIA, prior major bleeding/predisposing, labile INR, advanced age, using drugs predisposing to bleeding including acetylsalicylic acid, anti-platelet agents, or NSAIDS, and alcohol abuse (14). In parallel to scoring risk for stroke following atrial fibrillation, the increased risk for major bleeding in patients on anticoagulation for this cardiac arrhythmia should be also programmed (15).

The present study aimed to assess first the underlying clinical risk factors for brain stroke and also main determinants of major bleeding in patients with atrial fibrillation with and without scheduling anticoagulation therapy. Also this study goaled to evaluate in-hospital mortality in patients with stroke and atrial fibrillation and to assess the value of CHA2DS2-VASc and HAS-BLED risk scores to predict this early event.

Patients and methods

Study population:

Among 900 patients who were hospitalized with the diagnosis of ischemic brain stroke between 2013 and 2014, 100 patients had atrial fibrillation that included into this cross-sectional study. Diagnosis of atrial fibrillation was confirmed by electrocardiographically monitoring. By using brain CT scan within 12 to 24 hours after admission, observing hypo-dense areas led to confirm brain ischemic stroke in participants. In this regard, any suspicion to hemorrhagic brain stroke or presence of coagulation disorders was considered as exclusion criteria. The collected data included demographic information, medical history, and oral medications. Information regarding comorbidities also was collected, including previous stroke, previous AF, diabetes, coronary artery disease, peripheral vascular disease, congestive heart failure, hypertension, and bleeding events.

The previous AF was defined as a paroxysmal, persistent or permanent AF on the basis of 12-lead ECG or 24-hours continuous ECG monitoring prior to stroke.

Scoring systems

In this study, two systems were applied to score both risk for ischemic stroke for atrial fibrillation and

also risk for bleeding after anticoagulation therapy for this arrhythmia. For assessing stroke score, the CHA2DS2-VASc scoring was used. This system consists of eight items including Congestive Heart Failure (1 point), Hypertension (1 point), Age ≥ 75 years (2 points), Diabetes (1 point), Stroke (2 points), Vascular disease (1 point), Age ≥ 65 years (1 point), and female sex (1 point). According to the recommendations of the European Society of Cardiology (ESC) 2010 (16), anticoagulation recommendations for the different scores are as followed: for score=0, no therapy is preferred; for score=1, oral anticoagulation is preferred; and for score≥2 oral anticoagulation is necessary. Moreover, for assessing risk for major bleeding in patients on anticoagulation for atrial fibrillation, the HAS-BLED risk score was employed consists of Hypertension defined as uncontrolled systolic blood pressure >160 mm Hg (1 point), Abnormal renal (Dialysis, transplant, Cr >2.6 mg/dL) or liver (Cirrhosis or Bilirubin >2x Normal or AST/ALT/AP >3x Normal)function (1 point each), Stroke (1 point), Bleeding tendency/predisposition (1 point), Labile INRs ((Unstable/high INRs), Time in Therapeutic Range < 60%) (1 point), age > 65 years (1 point), and Drugs or alcohol (1 point each). According to ESC guideline (16), A HAS-BLED score of ≥ 3 indicates that caution is warranted when prescribing oral anticoagulation and regular review is recommended. The two scores were calculated prospectively for each individual but new stroke was not considered. In this study, the normal range for persons not using warfarin was considered to be 0.8–1.2, and for people on warfarin therapy an INR of 2.0–3.0 was targeted. The institutional review board of the Shahid Beheshti University of Medical Sciences approved the study.

Statistical analysis

Results were expressed as mean ± standard deviation (SD) for quantitative variables and were summarized by frequency (percentage) for categorical variables. Continuous variables were compared using t test or ANOVA test and/or Non-parametric Mann-Whitney or Kruskal-Wallis H test whenever the data did not appear to have normal distribution or when the assumption of equal variances was violated across the study groups. Categorical variables were, on the other hand, compared using chi-square test. Association between quantitative variables was tested by the Pearson's correlation test or Spearman non-parametric test. The ROC curve analysis was also used to assess the value of two study scoring systems for predicting in-hospital mortality. P values of 0.05 or less were considered statistically significant. All the statistical analyses were performed using SPSS version 20.0 (SPSS Inc., Chicago, IL, USA).

Results

Of 900 patients with evidences of ischemic stroke, 100 had atrial fibrillation with an overall prevalence of 11.1%. Of those, 31% had previous history of atrial fibrillation. Table 1 describes baseline characteristics and clinical information of study population with atrial fibrillation that hospitalized with the diagnosis of ischemic stroke. The mean age of participants was 71.86 ± 11.62 years ranged from 37 to 90 years and 51% were male. Regarding underlying risk factors, congestive heart failure was found in 51%, 71% were hypertensive, 25% were diabetics, 76% were dyslipidemic, 34% were current smoker, 11% were opium users, 37% had history of stroke, and 14% had history of peripheral vascular disease. Regarding biochemical markers, mean hemoglobin A1c was 6.38 ± 1.81% indicating uncontrolled blood glucose in 34% of all participants. Mean serum triglyceride level was 110.62 ± 90.19 mg/dl, mean cholesterol level was 177.28 ± 49.57 mg/dl, and mean LDL level was also 107.55 ± 36.72 mg/dl. Half of the patients (50%) had some degree of renal failure with overall mean creatinine level of 1.17 ± 0.38 mg/dl and mean GFR 62.48 ± 21.13. Only 3% of subjects had liver dysfunction. More than half of the patients (55%) had evidence of coronary artery disease based on angiography reports that 10% underwent cardiac revascularization. Regarding oral medications, history of acetylsalicylic acid, Clopidogrel, and warfarin use was revealed in 44%, 8%, and 22% of the patients; respectively. Mean level of first measured INR was 1.14 ± 0.22. Regarding echocardiography parameters (table 1), 43% had evidences of left ventricular hypertrophy. Mean left ventricular ejection fraction was 49.80 ±

Table 1. Baseline characteristics and clinical data of the study population (n = 100)

Male gender	51 (51)
Age, yr	71.86 ± 11.62
Previous atrial fibrillation	31 (31)
Congestive heart failure	51 (51)
Diabetes	25 (25)
Hypertension	71 (71)
Hyperlipidemia	76 (76)
Current smoking	34 (34)
Opium use	11 (11)
Previous brain stroke	37 (37)
Peripheral vascular disease	14 (14)
Serum triglyceride, mg/dl	110.62 ± 90.19
Serum cholesterol, mg/dl	177.28 ± 49.57
Serum LDL, mg/dl	107.55 ± 36.72
Serum HDL, mg/dl	43.53 ± 12.49
Serum HbA1c, %	71.86 ± 11.62
Serum creatinine, mg/dl	1.17 ± 0.38
Serum GFR	62.48 ± 21.13
Liver dysfunction	3 (3)
Coronary artery disease	55 (55)
Previous coronary bypass surgery	8 (8)
Previous PCI	2 (2)
Left ventricular hypertrophy	43 (43)
Left ventricular ejection fraction, %	49.80 ± 11.26
Pulmonary artery pressure	37.89 ± 9.55
Previous use of Acetylsalicylic acid	44 (44)
Previous use of Clopidogrel	8 (8)
Previous use of Warfarin	22 (22)
Mean platelet volume	197.52 ± 55.55
Mean INR	1.14 ± 0.22

LDL: Low-density lipoprotein; HDL: High-density lipoprotein; GFR: Glomerular filtration rate; PCI: Percutaneous coronary intervention; INR: International normalized ratio .Data is presented as number (%) or mean ± SD.

11.26% indicating low ejection fraction (<50%) in 31% of the patients. None of the patients had evidences of valvular heart diseases. Mean pulmonary artery pressure was 37.89 ± 9.55 mmHg. None of the cases had history of gastrointestinal bleeding or previous warfarin toxicity. Mean INR measure in patients with and without history of warfarin use was 1.40 ± 0.29 and 1.07 ± 0.12 which was considerably higher in former group ($p < 0.001$). In this context, controlled range of INR was revealed in 87.2% of patients no using warfarin, while the range of INR was lower than the definitive range in 95.5% of individuals on warfarin therapy.

Mean CHA2DS2-VASc score was 4.35 ± 1.76 and the total score was 0 point in 3%, 1 point in 4%, and ≥ 2 points in 93% of subjects showing necessity to anticoagulation therapy in 93% of the patients irrespective to recent stroke. Also, mean HAS-BLED score was also 2.83 ± 1.30 that was ≥ 3 in 61% indicating risk of bleeding in 61% of all patients. In-hospital mortality was reported in 9% of all study subjects irrespective to recent stroke. The main determinants of early mortality included history of stroke ($p = 0.001$), renal failure ($p = 0.003$), and presence of coronary artery disease ($p = 0.004$). In this regard, the use of acetylsalicylic acid ($p = 0.010$) and Clopidogrel ($p = 0.023$) led to increased risk of mortality.

The mean CHA2DS2-VASc score in survived subjects was significantly lower than the non-survived individuals (4.20 ± 1.72 versus 5.89 ± 1.45, $p = 0.005$). Also, survived subjects had significantly lower HAS-BLED score than non-survived ones (2.64 ± 1.20 versus 4.78 ± 0.44, $p < 0.001$). The analysis using the ROC curve (Figure 1) showed that both CHA2DS2-VASc score (AUC = 0.788, 95%CI: 0.614-0.962, $P = 0.004$) and HAS-BLED score (AUC = 0.960, 95%CI: 0.911-1.008, $P < 0.001$) could strongly predict in-hospital mortality. Assessing relationship between CHA2DS2-VASc score and biochemical parameters (Table 2) showed a direct association between CHA2DS2-VASc score and age ($r = 0.545$, $p < 0.001$)

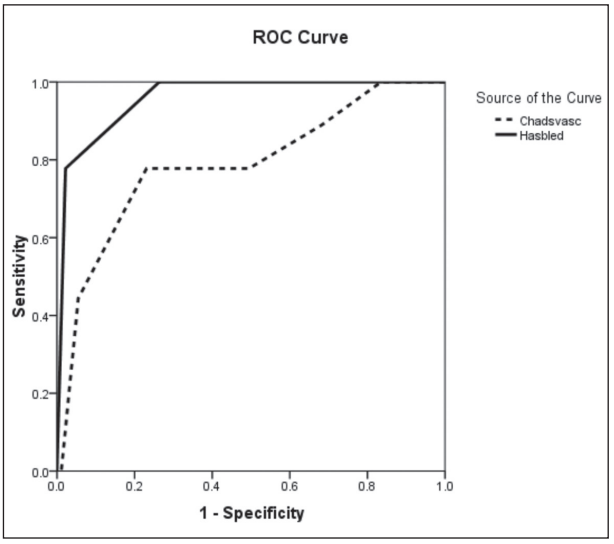

Figure 1. The ROC curve analysis to determine value of CHA2DS2-VASc and HAS-BLED scores for discriminating survived from non-survived subjects

Table 2. Correlation between CHA2DS2-VASc and HAS-BLED scores and other parameters

Variable		Age	Hba1c	HDL	LDL	TG	CHOL	Cr	GFR	First INR	EF	CHADS -VASc	HAS -BLED
Age	Pearson Correlation*	1	-.037	-.095	-.100	-.076	-.160	.073	-.099	.103	.070	.545**	.422*
	Sig. (2-tailed)		.715	.345	.324	.451	.113	.468	.328	.310	.486	.000	.000
Hba1c	Pearson Correlation	-.037	1	-.174	.127	.178	.118	.039	-.061	-.067	-.079	.104	-.023
	Sig. (2-tailed)	.715		.083	.207	.077	.242	.698	.546	.508	.437	.305	.817
HDL	Pearson Correlation	-.095	-.174	1	.119	-.008	.300**	-.213*	.116	-.013	.090	.045	-.029
	Sig. (2-tailed)	.345	.083		.239	.934	.002	.034	.251	.896	.374	.658	.778
LDL	Pearson Correlation	-.100	.127	.119	1	.046	.813**	-.334**	.233*	-.233*	.250*	-.101	-.209*
	Sig. (2-tailed)	.324	.207	.239		.652	.000	.001	.020	.020	.012	.315	.037
TG	Pearson Correlation	-.076	.178	-.008	.046	1	.390**	.013	-.019	-.175	-.067	.053	.122
	Sig. (2-tailed)	.451	.077	.934	.652		.000	.900	.853	.082	.506	.601	.228
CHOL	Pearson Correlation	-.160	.118	.300**	.813**	.390**	1	-.296**	.217*	-.294**	.231*	-.107	-.145
	Sig. (2-tailed)	.113	.242	.002	.000	.000		.003	.030	.003	.021	.289	.149
Cr	Pearson Correlation	.073	.039	-.213*	-.334**	.013	-.296**	1	-.811**	.146	-.177	-.009	.259**
	Sig. (2-tailed)	.468	.698	.034	.001	.900	.003		.000	.148	.078	.932	.009
GFR	Pearson Correlation	-.099	-.061	.116	.233*	-.019	.217*	-.811**	1	-.128	.189	-.161	-.346**
	Sig. (2-tailed)	.328	.546	.251	.020	.853	.030	.000		.203	.059	.110	.000
First INR	Pearson Correlation	.103	-.067	-.013	-.233*	-.175	-.294**	.146	-.128	1	-.046	-.021	.028
	Sig. (2-tailed)	.310	.508	.896	.020	.082	.003	.148	.203		.648	.837	.782
EF	Pearson Correlation	.070	-.079	.090	.250*	-.067	.231*	-.177	.189	-.046	1	-.251*	-.157
	Sig. (2-tailed)	.486	.437	.374	.012	.506	.021	.078	.059	.648		.012	.118
CHADS-VASc	Pearson Correlation	.545**	.104	.045	-.101	.053	-.107	-.009	-.161	-.021	-.251*	1	.762**
	Sig. (2-tailed)	.000	.305	.658	.315	.601	.289	.932	.110	.837	.012		.000
HAS - BLED	Pearson Correlation	.422**	-.023	-.029	-.209*	.122	-.145	.259**	-.346**	.028	-.157	.762**	1
	Sig. (2-tailed)	.000	.817	.778	.037	.228	.149	.009	.000	.782	.118	.000	

and also an adverse association between this score and left ventricular ejection fraction ($r = -0.251$, $p = 0.012$). Also, considering relation between HAS-BLED score and laboratory markers (table 2) a positive association of HAS-BLED score with age ($r = 0.422$, $p < 0.001$) and serum creatinine level ($r = 0.259$, $p = 0.009$) as well as an adverse association of this score with GFR ($r = -0.346$, $p < 0.001$) were revealed. The present study also showed a strong association between the two study scorings ($r = 0.762$, $p < 0.001$).

Discussion

The present study has multiple important findings. First, by clinical assessment of patients diagnosed as ischemic stroke, we reached the overall prevalence of 11.1% for occurring atrial fibrillation in these patients. Our estimated rate is very near to previous reports on the prevalence of atrial fibrillation in ischemic stroke patients. In Cavaco et al study (17), of patients with ischemic stroke, 10.8% had simultaneously atrial fibrillation. In Kongbunkiat et al study (18), 9.1% of patients with ischemic stroke had atrial fibrillation. In another study by Chee et al (19), 10.6% of ischemic stroke patients were found to have non-valvular atrial fibrillation. Wolf et al (20) also showed that the proportion of strokes associated with this arrhythmia was 14.7%. In total, it seems that the global prevalence rate of atrial fibrillation among ischemic stroke patients ranges from 9.1% to 14.7% that can be a notable range because of the increased risk for life-threatening events in stroke patients with atrial fibrillation in comparison with those who suffer stroke alone. It should be also noted that close association between atrial fibrillation and underlying cardiovascular abnormalities such as coronary artery disease and heart failure can deteriorate clinical outcome in patients with simultaneous brain stroke and atrial fibrillation. Moreover, it has been well demonstrated that atrial fibrillation can potentially accompanied by increased risk of thromboembolic events, which finally increase risk of mortality in ischemic stroke group.

Along with increased mortality risk in the presence of atrial fibrillation in stroke patients, other potential risk factors have been also assessed. In this study, main correlations of in-hospital mortality were history of stroke, renal failure, presence of coronary artery disease and the use of acetylsalicylic acid and clopidogrel. Interestingly, higher CHA2DS2-VASc and HAS-BLED scores could potentially predict in-hospital mortality. The researchers could not examine these univariate results in multivariate models because of small number of non-survived ones. However, the central role of previous ischemic stroke, coronary artery disease, and renal dysfunction in increased risk of early mortality in ischemic stroke patients with atrial fibrillation has been well demonstrated. Likewise, higher risk of stroke and also major bleedings was associated with higher early mortality risk in our patients. However, the predictive role of gender, advanced age, or medical risk factors including diabetes, hypertension, or hyperlipidemia in increasing early mortality could not be demonstrated. In Cavaco study (17), significant factors associated with mortality were co-morbid diseases including diabetes, hypertension, rt-PA treatment, and stroke complications such as pneumonia, septicemia, or gastrointestinal bleeding. In total, it seems that along with experience of stroke, coronary artery disease, and renal failure, the two scoring systems of CHA2DS2-VASc and HAS-BLED can be effectively use to predict in-hospital mortality in those patients.

According to significant association between CHA2DS2-VASc score and lower left ventricular ejection fraction, low ejection fraction can be added as a new risk component to CHA2DS2-VASc score. Furthermore, due to the relation between HAS-BLED score and serum creatinine level positively and GFR negatively, creatinine level and GFR can be also considered as points in HAS-BLED scoring system. On the other hand, by considering these new risk components in two scoring systems, the reliability and sensitivity of two scores can be improved. This hypothesis should be reexamined in further evaluations.

In summary, 11.1% of ischemic stroke patients suffer atrial fibrillation. 31% of the patients had previous history of atrial fibrillation, but only less than half of them (51%) were under treatment with warfarin, and also the range of INR was lower than the therapeutic range in 95.5% of individuals on warfarin therapy.

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