ORIGINAL ARTICLE

CME

Correlation Between CHA_2DS_2-VASc Score and Atrial Thrombus in Patients with Atrial Fibrillation Undergoing Cardioversion *

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ABSTRACT

Background
Patients with atrial fibrillation represent a group of risk for thromboembolic complications, with catastrophic consequences when they affect the central nervous system. The performance of risk scores to predict clinical events has been evaluated by several publications; yet, its correlation with the presence of thrombi in the left atrium or left atrial appendage has been poorly investigated. The use of the CHA_2DS_2-VASc score has been recently proposed for stratification of thromboembolic risk.

Objective
To evaluate the prevalence of left atrial thrombus and its correlation with the components of the CHA_2DS_2-VASc score and with left ventricular systolic function in patients scheduled for electrical cardioversion.

Methods
A prospective registry was conducted of the medical history of patients with atrial fibrillation of unknown duration or lasting > 48 hours, undergoing transesophageal echocardiography before scheduled electrical cardioversion. The correlation between the CHA_2DS_2-VASc score variables and the total score to predict the presence of thrombi in transesophageal echocardiography was analyzed. The result of the sum of the CHA_2DS_2-VASc score plus a score of left ventricular systolic function (normal = 0, mild dysfunction = 1, moderate dysfunction = 2, severe dysfunction = 3) was also evaluated.

Results
A total of 129 patients (mean age 70 ± 12 years) were included; 21 (16%) of which had thrombus. This finding was more prevalent in patients with risk factors, but was only statistically significant for heart failure and diabetes. The risk of thrombus in the LA/LAA progressively increased at higher CHA_2DS_2-VASc (3.6 ± 1.6 with thrombus vs. 2.7 ± 1 without thrombus; p = 0.024, area under the ROC curve = 0.65). This association was greater when left ventricular systolic function was included (p = 0.006, area under the ROC curve = 0.69). A CHA_2DS_2-VASc < 2 did not warrant the absence of thrombi.

Conclusions
The CHA_2DS_2-VASc score, developed to predict the risk of thromboembolic events is also associated with the presence of thrombus in patients with atrial fibrillation of unknown duration. The addition of left ventricular systolic function to the total score might improve its predictive ability.

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Key words > Atrial fibrillation – Transesophageal echocardiography – Thrombus – Thromboembolism – Cardioversion – Anticoagulants – Ventricular function

Abbreviations >

AF	Atrial fibrillation	**LVSF**	Left ventricular systolic function
INR	International normalized ratio	**TEE**	Transesophageal echocardiography
LA/LAA	Left atrium/left atrial appendage	**TIA**	Transient ischemic attack

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INTRODUCTION

Atrial fibrillation (AF) is the most common sustained arrhythmia, affecting about 2% of the general population, with greater prevalence in the aging population. The number of patients affected by this condition will be higher in future decades due to increased life expectancy, constituting a problem for public health management. (1, 2) Patients with atrial fibrillation are a risk group for the development of thromboembolic complications, with devastating consequences when the central nervous system is affected. Scientific evidence supports the use of anticoagulant agents to prevent this threatening complication; however, patient risk profile should be defined to determine whether treatment will provide any benefit. Several risk stratification schemes have been developed using clinical variables related with thromboembolism to help physicians in the selection of the most appropriate antithrombotic treatment. (3, 4) Of interest, these factors are also strong predictors of vascular disease and stroke in patients without AF. (5) The performance of risk scores to predict clinical events has been evaluated by several publications; yet, its correlation with the presence of thrombi in the left atrium (LA) or left atrial appendage (LAA) has been poorly investigated. The importance of this association lies on the fact that it provides the pathophysiological substrate for anticoagulation therapy. Recently, the guidelines for the management of atrial fibrillation published by the European Society of Cardiology have recommended the use of the CHA_2DS_2-VASc score for risk stratification of cardioembolic complications. (6) The goal of the present study was to evaluate the prevalence of thrombus in the LA/LAA and its correlation with the components of the CHA_2DS_2-VASc score and with left ventricular systolic function (LVSF) in patients with AF of unknown duration or lasting >48 h scheduled for electrical cardioversion.

METHODS

A prospective registry was performed from the information acquired from the medical history of patients admitted to the coronary care unit with AF between May 2005 and April 2012. All the variables included in the CHA_2DS_2 score and the history of vascular disease were specifically recorded. Using this information, the CHA_2DS_2-VASc score was calculated by assigning points to each variable as described in the original publication: (7) 1 point for congestive heart failure or ventricular dysfunction, hypertension, age ≥ 65 years, diabetes, vascular disease and female sex; 2 points for age ≥75 years or previous stroke or transient ischemic attack (TIA). The total score was the sum of the corresponding values assigned to each risk variable.

Patients with AF of unknown duration or lasting > 48 h undergoing transesophageal echocardiography (TEE) before scheduled electrical cardioversion were included in this study. Two patients with rheumatic mitral stenosis were excluded. Transesophageal echocardiography was performed with a General Electric Vivid 5 o Vivid 7 ultrasound machine using a multiplanar probe. Particular attention was paid to the exploration of thrombi in the LA or LAA. Under sedation with propofol, TEE was performed, followed by electrical cardioversion if TEE was negative for thrombi. Transthoracic echocardiogram was performed before TEE to evaluate LVSF. In case of inadequate ultrasonic window, the information was complemented from the esophageal and transgastric views. Left ventricular function was classified according to ejection fraction as normal (≥ 55%), mild dysfunction (45 to 54%); moderate dysfunction (35 to 44%) and severe dysfunction (< 35%). Unfractionated heparin or enoxaparin were administered before electrical cardioversion to all the patients who had not been treated with vitamin K antagonists for more than three weeks before the procedure. Then, anticoagulation treatment was continued for at least four weeks, based on the recommendations of the scientific societies. The ability of each of the CHA_2DS_2-VASc score components and of the total score to predict thrombi in TEE was investigated. Categorical variables (predictors of risk) were analyzed using the chi square test. The U-Mann Whitney test was used to evaluate risk scores on an ordinal scale. A p value < 0.05 was considered statistically significant. The predictive ability of a model built by the sum of the CHA_2DS_2-VASc score to an echocardiographically measured LVSF score was also evaluated (CHA_2DS_2-VASc-LVSF). A numerical value was assigned to ventricular function according to the following scale, normal=0, mild dysfunction=1, moderate dysfunction=2, and severe dysfunction=3. A ROC curve was constructed and the C statistic was calculated to compare the diagnostic performance of both models to predict thrombus in the LA or LAA. Values are expressed as mean ± standard deviation and C statistics with the corresponding confidence intervals.

RESULTS

A total of 129 patients were included; 48 of which were women. Mean age was 70 ± 12 years. The clinical and echocardiographic characteristics are described in Tables 1 and 2. Only 29% of patients had an INR > 2, considering that 74 patients (57%) had their first documented episode of AF, and enoxaparin or unfractioned heparin was the initial antithrombotic therapy. Electrical cardioversion was performed in 107 patients and was successful in 97%. In those cases with evidence of thrombus the procedure was postponed and long-term anticoagulation was indicated.

Thrombi were present in 21 patients (16%): 19 patients in the LAA, one in the LA and one in both locations. The correlation of each variable included in the CHA_2DS_2-VASc score and of LVSF with the presence of thrombus is described in Table 3. The prevalence of thrombus was greater in patients with risk factors in nearly all the categories, except for female sex and previous stroke. However, this association reached statistical significance for heart failure, diabetes and LVSF. The risk of thrombus in the LA/LAA progressively increased at higher CHA_2DS_2-VASc scores (Figure 1 A): The mean score was 3.62 ± 1.6 with thrombus vs. 2.76± 1.6 without thrombus (p = 0.024). The diagnostic performance evaluated by the ROC curve showed an area under the curve (C statistics) of 0.65 (0.52 - 0.78). The CHA_2DS_2-VASc-LVSF model showed a highly significant association between the score and the presence of thrombus (Figure 1 B): 4.86 ± 2.4 vs. 3.35 ± 1.9 without thrombus (p = 0.006), improving the area under the ROC curve

Table 1. Clinical history

Mean age	70 ± 12
Men/women	81/48
	N (%)
Hypertension	94 (73)
Diabetes	22 (17)
Vascular disease	26 (20)
Heart failure	31 (24)
Previous stroke/TIA	6 (4.7)
HR	
Low	15 (11.6)
Adequate	51 (39.5)
High	63 (48.8)
INR > 2*	24 (29)
First episode	74 (57)
Prosthetic Mitral Valve	1 (0.8)
Prosthetic Aortic Valve	8 (6.2)
CHA_2DS_2-VASc	0: 10(8) / 1: 21(16)
	2: 22(17) / 3: 24(19)
	4: 27(21) / 5: 21(16) 6: 4(3)

HR: Heart rate. TIA: Transient ischemic attack. *Information obtained from 82 patients.

(C = 0.69; 0.55 - 0.83). Yet, the confidence intervals of both models were overlapped.

In three patients categorized as low risk (< 2) by the CHA_2DS_2-VASc score, thrombi were documented by TEE (scores = 0 in one patients and 1 in two patients). Only one thromboembolic event was reported (0.8%) in a woman who suffered a stroke under treatment with acenocumarol and in whom TEE before electrical cardioversion did not show the presence of thrombi. The patients with thrombus did not present embolic complications during hospitalization.

Table 2. Echocardiographic data

ECHOCARDIOGRAPHIC DATA	n Patients - (%)
Segmental wall motion abnormalities	16 (12.4)
Systolic function	
Normal	83 (64)
Mild dysfunction	14 (11)
Moderate dysfunction	20 (16)
Severe dysfunction	12 (9)
Mitral regurgitation	
Absent	39 (30)
Grade 1	62 (48)
Grade 2	26 (20)
Grade 3	2 (1.6)
Aortic stenosis	
Absent	124 (96)
Grade 1	3 (2.3)
Grade 2	1 (0.8)
Grade 3	1 (0.8)
Aortic regurgitation	
Absent	89 (69)
Grade 1	37 (29)
Grade 2	3 (2.3)

The correlation between left atrial appendage emptying flow velocity and the density of spontaneous echo-contrast with the presence of thrombus was retrospectively analyzed despite not being considered a primary endpoint of the study. The presence of spontaneous echo-contrast was recorded in 70% of TEE and LAA emptying flow velocity in 90%. The presence and density of spontaneous echo-contrast had a clear association with the presence of thrombus (p = 0.005) (Figure 2). A reduction in left atrial appendage emptying flow velocity (< 0.4 m/s2) was observed in 93% of patients with thrombus vs. 63% in those without thrombus (p = 0.015). None of the patients with absence of both indicators of low atrial flow velocity presented atrial masses.

DISCUSSION

Several studies have demonstrated the superiority of vitamin K antagonists to prevent clinical events in patients with AF, particularly in those with risk factors. (8-11) Prescription of anticoagulant therapy is based on the hypothesis that thromboembolism is originated in thrombi located in the LA/LAA and might be prevented with efficient antithrombotic treatment. However, some publications have reported that 25-50% of strokes/TIA are noncardioembolic. (12,13,14) Intracranial and extracranial carotid artery disease, small vessel disease and aortic debris are other possible mechanisms for noncardioembolic stroke. The same

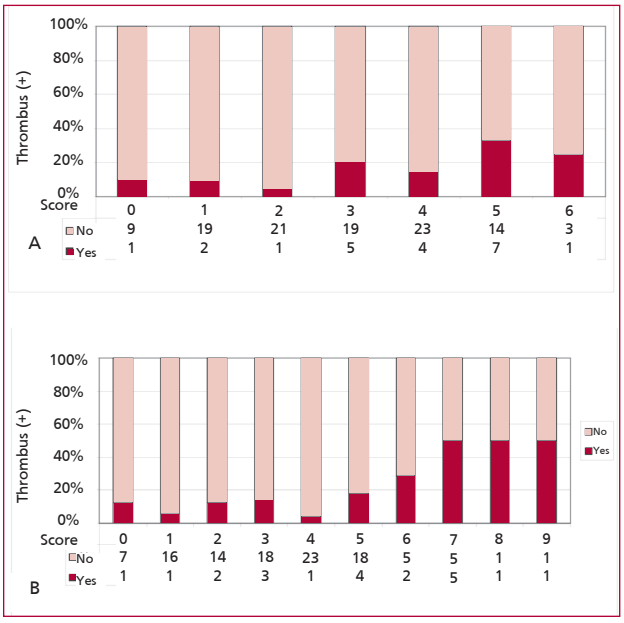

Fig. 1. A. Correlation between the CHA_2DS_2-VASc score and thrombus. **B.** Correlation between CHA_2DS_2-VASc + LVSF and thrombus. The columns represent percentage of patients with thrombus in LA/LAA for each score. The values below each column indicate the number of patients.

Table 3. Correlation between the clinical variables and LVSF with the presence of thrombus

	n total patients	Thrombus (+) n (%)	Thrombus (-) n (%)	p
Age				
< 65	42	5 (11.9%)	37 (88.1%)	0.3*
65-74	33	4 (12.1%)	29 (87.9%)	0.12†
> 75	54	12 (22.2%)	42 (77.8%)	
Female gender	48	5 (10.4%)	43 (89.6%)	0.16
Male gender	81	16 (19.8%)	65 (80.2%)	
DBT (+)	22	7 (31.8%)	15 (68.2%)	0.03
DBT (-)	107	14 (13.1%)	93 (86.9%)	
HT (+)	94	18 (19.1%)	76 (80.9%)	0.15
HT (-)	35	3 (8.6%)	32 (91.4%)	
Stroke (+)	6	1 (16.7%)	5 (83.3%)	0.9
Stroke (-)	123	20 (16.3%)	103 (83.7%)	
HF (+)	31	9 (29.0%)	22 (71.0%)	0.03
HF (-)	98	12 (12.2%)	86 (87.8%)	
Vasc (+)	26	7 (26.9%)	19 (73.1%)	0.1
Vasc (-)	103	14 (13.6%)	89 (86.4%)	
LVSF				
Normal	83	8 (9.6%)	75 (90.4%)	0.048
Mild dysfunction	14	4 (28.6%)	10 (71.4%)	
Moderate dysfunction	20	5 (25.0%)	15 (75.0%)	
Severe dysfunction	12	4 (33.3%)	8 (66.7%)	

DBT: Diabetes. HT:Hypertension. HF: Heart failure. Vasc: Vascular disease. LVSF: Left ventricular systolic function *age ≥65 vs. <65; †age ≥75 vs. <75.

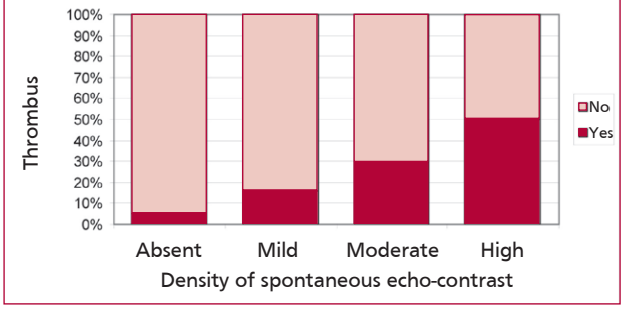

Fig. 2. Correlation between spontaneous echo-contrast and trombus

clinical variables associated with thromboembolic risk in AF are also associated with vascular disease and aortic atheroma. (15) Kanter et al. evaluated 676 patients with AF using Doppler ultrasound and observed that carotid artery stenosis was associated with hypertension, diabetes and tobacco use. (16) Kim et al. found a direct association between the $CHADS_2$ score and intracranial and extracranial carotid artery disease. (17) The investigators of the SPAFF group described that the prevalence of complex plaques in the thoracic aorta is higher in the groups with greater clinical risk, and this finding was associated with greater rate of embolism. (18) The benefit of oral anticoagulation to prevent embolic complications in AF patients is justified by the reduction in clinical events, (19) but has no documented usefulness in vascular disease and aortic disease. (20, 21, 22) Our study shows a correlation between the clinical predictors of risk included in the CHA_2DS_2-VASc score and the presence of thrombus in the LA/LAA, providing a rational indication to anticoagulation treatment. In addition, it closes the pathophysiological circuit composed by risk factors, LA thrombus and clinical events. The influence of each factor to provide the necessary conditions for the development of atrial thrombi still remains unclear. Hypertension produces left ventricular hypertrophy and diastolic dysfunction, reducing atrial flow velocity. (15, 23) Aging reduces flow velocity in the LAA. (24) Previous stroke/TIA is a strong predictor of the presence of, rather than a predisposing factor for the genesis of, thrombus. Diabetes has a clear association with macro and microvascular disease; however, its role in AF is not direct. The influence of heart failure might be related with higher LA pressure, producing atrial stasis and increasing LA diameter. The evaluation of left ventricular systolic function might be more representative of potential risk than the history of heart failure, as ventricular dysfunction is not always present in this condition. The association between low ejection fraction and the development of thromboembolic events has been shown in different studies. (25, 26) Although we have demonstrated a greater area under the ROC curve only by adding the LVSF score to the CHA_2DS_2-VASc score (0.69 vs. 0.65), the conclusions are limited due to overlapping confidence intervals. Further studies, including greater number of patients, are needed to confirm our findings, in order to incorporate this simple element, easily available with transthoracic echocardiography, to an improved model with greater predictive ability. The correlation between the $CHADS_2$ score and the presence of thrombus in the LA/LAA was evaluated in a retrospective case-control study conducted at the Mayo Clinic, demonstrating higher scores in patients with thrombus. (27) Decker et al. reviewed the clinical reports for all TEEs of patients with precardioversion AF to develop the $CHADS_2$ score. (28) A strong association was present between the $CHADS_2$ score and presence of LA/LAA thrombus. The prevalence of thrombus in our study (16%) was similar to that of the ACUTE study (14%) which randomized 1222 patients to either treatment guided by the findings on TEE or conventional treatment. (29) The rate of thromboembolic events was low and similar in both studies (0.8%). The diagnostic performance of the CHA_2DS_2-VASc for the presence of thrombus in our study (area under the ROC curve = 0.65) was similar to that of this score to

predict cardioembolic events in real-life populations. (30) Although the correlation is significant, it is not perfect, suggesting that the presence of other factors different from those considered in the model should be taken into account. (31) Another aspect to consider is whether the absence of predictors of thromboembolic risk in patients with AF scheduled for electrical cardioversion warrants the absence of thrombus. If this statement were true, it might not be necessary to perform TEE precardioversion in patients with AF lasting > 48 h and who are not under prolonged treatment with anticoagulation agents, saving time and medical costs. In a study of 1058 patients undergoing TEE before AF ablation, Puwamant et al. found a direct association between the $CHADS_2$ score and the presence of LA/LAA thrombus. (32) As patients with a score of 0 had no evidence of atrial masses, the authors stated that TEEs are not needed in this subgroup of patients. Yet, 81% of patients had paroxysmal AF, about 20% were in sinus rhythm at the moment of the examination, and the prevalence of thrombus was extremely low (0.6%). Decker et al. did not find thrombi in patients with a $CHADS_2$ score of 0, thus suggesting that anticoagulation is unnecessary in this subset. (8) Although our study confirms the direct association between the CHA_2DS_2-VASc score and the presence of thrombi in the LA/LAA, we could not exclude the presence of masses with low scores as we found thrombi in two patients with a score of 1 and in one patient with a score of 0. This finding reaffirms the need of TEE precardioversion in subjects not receiving anticoagulation therapy for the time recommended by the current guidelines. Even in a population of apparently low risk of thromboembolism with short-term AF duration (< 48 hours), Kleemann et al. reported a prevalence of thrombi of 1.4%. (33) An additional finding of our experience was the correlation of spontaneous echo-contrast and left atrial appendage emptying flow velocity with the prevalence of atrial masses. The density of spontaneous echocontrast had a direct correlation with the prevalence of thrombus, and left atrial appendage emptying flow velocity was almost always present in these cases. In the absence of both phenomena, thrombi were absent at TEE examination. On the basis of this observation, the evaluation of these two factors might be considered at the moment of deciding anticoagulation in limit situations with high risk of bleeding complications.

CONCLUSIONS

As far as we know, our study is the first one evaluating the correlation between the CHA_2DS_2-VASc score with the prevalence of thrombus in the LA/LAA as suggested by the current guidelines, confirming a direct correlation between both variables. A low risk score does not warrant the absence of thrombi. The addition of the variable LVSF to the original model might improve the predictive capacity. This finding should be confirmed with greater number of patients.

RESUMEN

Relación entre el índice CHA_2DS_2-VASc y la presencia de trombo auricular en pacientes con fibrilación auricular en plan de cardioversión

Introducción
Los pacientes con fibrilación auricular representan un grupo de riesgo para el desarrollo de complicaciones tromboembólicas, con consecuencias devastadoras cuando afectan el sistema nervioso central. El rendimiento de los índices de riesgo para predecir eventos clínicos se ha evaluado en numerosas publicaciones, mientras que su relación con la presencia de trombo en la aurícula izquierda o su orejuela se ha explorado menos. Recientemente se ha propuesto la utilización del índice conocido con el acrónimo CHA_2DS_2-VASc para la estratificación de riesgo cardioembólico.

Objetivo
Evaluar la prevalencia de trombo en la aurícula izquierda y su relación con las variables del índice CHA_2DS_2-VASc y la función sistólica del ventrículo izquierdo en pacientes con fibrilación auricular que serán sometidos a cardioversión eléctrica.

Material y métodos
Se efectuó un registro prospectivo de los antecedentes clínicos de pacientes con fibrilación auricular de tiempo indeterminado o > 48 horas, a los que se les realizó un eco transesofágico previo a una cardioversión eléctrica. Se analizó la relación de las variables que conforman el índice CHA_2DS_2-VASc y del puntaje total para predecir trombo en el eco transesofágico. Se evaluó además un modelo que resultó de sumar al CHA_2DS_2-VASc un puntaje según la función sistólica del ventrículo izquierdo: normal = 0, deterioro leve = 1, moderado = 2, grave = 3.

Resultados
Se incluyeron 129 pacientes con edad media de 70 ± 12 años, de los cuales 21 (16%) presentaron trombo. Este hallazgo fue más prevalente en pacientes con factores de riesgo, pero alcanzó nivel de significación solo para insuficiencia cardíaca y diabetes. Se observó un incremento progresivo del riesgo de trombo en relación con el CHA_2DS_2-VASc (3,6 ± 1,6 con trombo vs. 2,7 ± 1 sin trombo; p = 0,024, área bajo la curva ROC = 0,65). La asociación se ve reforzada cuando se incluye la función sistólica del ventrículo izquierdo (p = 0,006, área bajo la curva ROC = 0,69). Un puntaje de CHA_2DS_2-VASc < 2 no garantizó la ausencia de trombos.

Conclusiones
El puntaje CHA_2DS_2-VASc desarrollado para predecir riesgo clínico de fenómenos embólicos también se asocia con la presencia de trombo en pacientes con fibrilación auricular de tiempo indeterminado. El agregado de la función sistólica del ventrículo izquierdo al puntaje total podría mejorar la capacidad predictiva.

Palabras clave > Fibrilación auricular - Eco transesofágico Trombo - Tromboembolismo - Cardioversión - Anticoagulantes - Función ventricular

Conflicts of interest
None declared.

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REFERENCES

1. Friberg J, Buch P, Scharling H, Gadsbphioll N, Jensen GB. Rising rates of hospital admissions for atrial fibrillation. Epidemiology 2003;14:666-72. http://doi.org/d34sz2

2. Lloyd-Jones DM, Wang TJ, Leip EP, Larson MG, Levy D, Vasan RS, et al.Lifetime risk for development of atrial fibrillation: the Framingham Heart Study. Circulation 2004;110:1042-6. http://doi.org/b4kr4j

3. Gage BF, Waterman AD, Shannon W, Boechler M, Rich MW, Radford MJ. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. JAMA 2001;285:2864–70. http://doi.org/djqhd4

4. Stroke Risk in Atrial Fibrillation Working Group. Comparison of 12 risk stratification schemes to predict stroke in patients with nonvalvular atrial fibrillation. Stroke 2008;39:1901-10. http://doi.org/cppzpc

5. Goldstein L, Bushnell C, Adams R, Appel L, Braun L, Chaturvedi, S et al. Guidelines for the Primary Prevention of Stroke : A Guideline for Healthcare Professionals From the American Heart Association/ /American Stroke Association. Stroke 2011; 42:517-584. http://doi.org/dzx3dc

6. Camm J, Kirchhof P, Lip G, Schotten U, Savelieva I, Ernst S, et al. Guidelines for the management of atrial Fibrillation. The Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). Eur Heart J 2010;31:2369-2429. http://doi.org/ftqx5q

7. Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ. Refining clinical risk stratification for predicting stoke and thromboembolism in atrial fibrillation using a novel risk factor based approach: the Euro Heart Survey on atrial fibrillation. Chest 2010;137:263-72. http://doi.org/c43wcq

8. Stroke Prevention in Atrial Fibrillation Investigators. Stroke Prevention in Atrial Fibrillation Study. Final results. Circulation 1991;84:527–39. http://doi.org/ksq

9. Petersen P, Boysen G, Godtfredsen J, Andersen ED, Andersen B. Placebo-controlled, randomized trial of warfarin and aspirin for prevention of thromboembolic complications in chronic atrial fibrillation. The Copenhagen AFASAK study. Lancet 1989;1:175–9. http://doi.org/ddfkxx

10. EAFT (European Atrial Fibrillation Trial) Study Group. Secondary prevention in non-rheumatic atrial fibrillation after transient ischaemic attack or minor stroke. Lancet 1993; 342:1255–62.

11. The effect of low-dose warfarin on the risk of stroke in patients with nonrheumatic atrial fibrillation. The Boston Area Anticoagulation Trial for Atrial Fibrillation Investigators. N Engl J Med 1990;323:1505–11. http://doi.org/fcpr4m

12. Miller V, Rothrock J, Pearce L, Feinberg W, Hart R, Anderson D. Stroke Prevention in Atrial Fibrillation Investigators. Ischemic stroke in patients with atrial fibrillation: effect of aspirin according to stroke mechanism. Neurology 1993;43:32-6. http://doi.org/ksr

13. Hart RG, Pearce LA, Miller VT, Anderson DC, Rothrock JF, Albers GW, et al. Cardioembolic vs. noncardioembolic strokes in atrial fibrillation: frequency and effect of antithrombotic agents in the stroke prevention in atrial fibrillation studies. Cerebrovasc Dis 2000;10:39-43. http://doi.org/drcx6s

14. Cha MJ, Kim YD, Nam HS, Kim J, Lee DH, Heo JH. Stroke mechanism in patients with non-valvular atrial fibrillation according to the $CHADS_2$ and CHA_2DS_2-VASc scores. Eur J Neurol 2012;19:473-9. http://doi.org/c2rdsx

15. Zabalgoitia M, Halperin J, Pearce L, Blackshear JL, Asinger R, Hart R. Transesophageal echocardiographic correlates of clinical risk of thromboembolism in non-valvular atrial fibrillation. Stroke prevention in Atrial Fibrillation III Investigators. J Am Coll Cardiol 1998;31:1622-6. http://doi.org/crwjk5

16. Kanter MC, Tegeler CH, Pearce LA, Weinberger J, Feinberg WM, Anderson DC, et al. Carotid stenosis in patients with atrial fibrillation. Prevalence, risk factors, and relationship to stroke in the Stroke Prevention in Atrial Fibrillation Study. Arch Intern Med 1994;154:1372-7. http://doi.org/fwn3x7

17. Kim YD, Cha MJ, Kim J, Lee DH, Lee HS, Nam CM, et al. Increases in cerebral atherosclerosis according to $CHADS_2$ scores in stroke patients with nonvalvular atrial fibrillation. Stroke 2011;42:930–4. http://doi.org/bgzpcw

18. The stroke Prevention in Atrial Fibrilation Investigators Comitee on Echocardiography. Transesophageal Echocardiographic Correlates of Thromboembolism in High Risk Patients with Nonvalvular Atrial Fibrilation. Ann Intern Med 1998;128:639-47.

19. Van Walraven C, Hart RG, Singer DE, Laupacis A, Connolly S, Petersen P, et al. Oral anticoagulants vs aspirin in nonvalvular atrial fibrillation: an individual patient meta-analysis. JAMA 2002;288:2441-8. http://doi.org/bgzpcw

20. Mohr J, Thompson JLP, Lazar RM, Levin B, Sacco RL, Furie KL, et al. A comparison of warfarin and aspirin for prevention of recurrent ischemic stroke. N Engl J Med 2001;345:1444-51. http://doi.org/b2j5jx

21. Chimowitz MI, Lynn MJ, Howlett-Smith H, Stern BJ, Hertzberg VS, Frankel MR, et al. Comparison of warfarin and aspirin for symptomatic intracranial arterial stenosis. N Engl J Med 2005;352:1305-16. http://doi.org/b5c6t2

22. Hiratzka L, Bakris G, Beckman J, Bersin R, Carr V, Casey D, et al. 2010 ACCF/AHA/AATS/ACR/ASA/SCA/SCAI/SIR/STS/SVM Guidelines for the Diagnosis and Management of Patients With Thoracic Aortic Disease : A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, American Association for Thoracic Surgery, American College of Radiology, American Stroke Association, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society of Thoracic Surgeons,and Society for Vascular Medicine. Circulation 2010;121: e266-369. http://doi.org/dp8xkq

23. Stroke in AF working group. Independent predictors of stroke in patients with atrial fibrillation: a systematic review. Neurology 2007;69:546–54. http://doi.org/bngfgb

24. Goldman ME, Pearce LA, Hart RG, Zabalgoitia M, Asinger RW, Safford R, et al. Pathophysiologic Correlates ot Thromboembolism in Nonvalvular atrial Fibrilation. Reducec Flow Velocity in The Left Atrial Appendage. J Am Soc Echo 1999;12:1080-7. 25. Atrial Fibrillation Investigators. Echocardiographic predictors of stroke in patients with atrial fibrillation: a prospective study of 1066 patients from 3 clinical trials. Arch Intern Med 1998;158:1316-20.

26. Stroke Prevention in Atrial Fibrillation Investigators. Predictors of thromboembolism in atrial fibrillation: II. Echocardiographic features of patients at risk. Ann Intern Med 1992;116:6-12.

27. Wysokinski W, Ammash N, Sobande F, Kalsi H, Hodge D, Mcbane R. Predicting Left Atrial thrombi in atrial fibrillation. Am Heart Journal 2010;159:665-71. http://doi.org/ccgh79

28. Decker J, Madder R, Hickman L, Marinescu V, Marandici A, Raheem S, et al. $CHADS_2$ Score is Predictive of Left Atrial Thrombus on Precardioversion Transesophageal Echocardiography in Atrial Fibrilation. Am J Cardiovasc Dis 2011;1:159-65

29. Klein AL, Grimm RA, Murray RD, Apperson-Hansen C, Asinger RW, Black IW, et al. Use of transesophageal echocardiography to guide cardioversion in patients with atrial fibrillation. N Engl J Med 2001;344:1411–20. http://doi.org/bj48wr

30. Van Staa TP, Setakis, Di Tanna GL, Lane DA, Lip GY. A comparison of risk stratification schemes for stroke in 79,884 atrial fibrillation patients in general practice. J Thromb Haemost 2011;9:39-48. http://doi.org/c9628n

31. Depta JP, Bhatt DL. Atherothrombosis and atrial fibrillation: important and often overlapping clinical syndromes. Thromb Haemost 2010;104:657–63. http://doi.org/bqrthv

32. Puwanant S,Varr B, Shrestha K, Hussain S, Tang W, Gabriel R, et al. Role of the $CHADS_2$ Score in the Evaluation of Thromboembolic Risk in Patients With Atrial Fibrillation Undergoing Transesophageal Echocardiography Before Pulmonary Vein Isolation. J Am Coll Cardiol 2009;54:2032-9. http://doi.org/drpspp

33. Kleemann T, Becker T, Strauss M, Schneider S, Seidl K. Prevalence of Left Atrial Thrombus and Dense Spontaneous Echo Contrast in Patients With Short-Term Atrial Fibrillation <48 Hours Undergoing Cardioversion: Value of Transesophageal Echocardiography to Guide Cardioversion. J Am Soc Echocardiogr 2009;22:1403-8. http://doi.org/fwmsbj