**The CHA2DS2-VASc score and Geriatric Multidimensional Assessment tools in elderly patients with persistent atrial fibrillation undergoing electrical cardioversion. A link with arrhythmia relapse?**

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**Abstract**

**Introduction.** The CHA2DS2-VASc score is widely used for stroke risk stratification in patients with atrial fibrillation (AF). Our endpoints were to evaluate in an old population undergoing electrical cardioversion (ECV) of persistent AF if the CHA2DS2-VASc was associated with some of the Geriatric Multidimensional Assessment tools and with the presence of sinus rhythm at the follow-up.

**Methods.** We enrolled all the consecutive patients admitted in a day-hospital setting aged >60 years. The Mini-Mental State Examination (MMSE; neurocognitive function), the 15-item Geriatric Depression Scale (GDS; depressive symptoms) and the Short-Physical Performance Battery (SPPB; physical functioning) were administered before ECV.

**Results.** Between 2017 and 2019, 134 patients were enrolled (mean age: 77+9 years, range: 60-96; men: 63.4%; EF: 60+12%). Hypertension was the most frequent comorbid condition (82.1%). The CHA2DS2-VASc score was 3.8+1.6. Abnormal values of MMSE, GDS and SPPB were observed in 7.9, 19.8 and 22.3% of cases, respectively. There were significant correlations between the CHA2DS2-VASc score and the MMSE (p=0.008), the GDS (p<0.001) and the SPPB (p<0.001). Depressive symptoms increased CHA2DS2-VASc correlation with SPPB of about 20%. CHA2DS2-VASc score was higher in patients with arrhythmia relapse (p=0.048; mean length of follow-up: 195 days). This association persisted even after adjustment for amiodarone therapy.

**Conclusions.** The CHA2DS2-VASc score significantly correlated with neuro-cognitive performance, depressive symptoms and physical functioning. It was also associated with AF relapse. Accordingly, in the elderly, the CHA2DS2-VASc could help quantify thrombo-embolic risk, give an indication of frailty status and help to choose between a rate- and a rhythm-control strategy.

**Keywords:** Atrial fibrillation; CHA2DS2-VASc; Elderly; Geriatric Depression Scale; Mini-Mental State Examination; Short Physical Performance Battery

**Introduction**

The CHA2DS2-VASc is a clinical score used in everyday clinical practice to evaluate thrombo-embolic risk in patients with atrial fibrillation (AF) [1], and the guidelines for the management of AF subjects give recommendations on oral anticoagulant therapy based on this score [2]. Many studies have reported correlations between the CHA2DS2-VASc and several important outcomes in AF patients, such as bleeding [3] and pulmonary embolism [4]. Also, the complications of thrombo-embolic stroke [5] and reduced glomerular filtration rate [6] are related to the CHA2DS2-VASc score. AF is the most frequent sustained arrhythmia diagnosed in the elderly with an incidence greater than 40 cases per 1000-person years in subjects >80 years, and a prevalence of 85.5 per 1000 in the >65 years Medicare beneficiaries [7]. The arrhythmia can increase the risk of cognitive impairment in subjects with and without a history of stroke, and disability and reduced quality of life often follow AF development [7]. Indeed, AF is considered by physicians as a marker of a frail condition [8].

Given these assumptions, we hypothesized a correlation between the CHA2DS2-VASc score and some of the items best describing the ageing process, as limited evidence exists at this regard. Accordingly, we evaluated a cohort of elderly subjects with a persistent form of the arrhythmia undergoing effective electrical cardioversion (ECV) of AF, studying the association between the CHA2DS2-VASc and the Mini-Mental State Examination (MMSE) [9], the Geriatric Depression Scale (GDS) [10] and the Short Physical Performance Battery (SPPB) [11] scores, three of the most important tools used in the Geriatric Multidimensional Assessment [12]. Second, we investigated if the potential relation between the CHA2DS2-VASc and the SPPB scores could be further improved when simultaneously considering the other two instruments. Then, we tested if the baseline values of the CHA2DS2-VASc score and its components could be useful to identify those patients at risk of arrhythmia relapse.

Abbreviations – AF: atrial fibrillation; GDS: Geriatric Depression Scale; ECV: electrical cardioversion; MMSE: Mini-Mental State Examination; SPPB: Short Physical Performance Battery

**Methods**

Between October 2017 and September 2019, all patients aged >60 years, who were consecutively admitted to a day-hospital setting to undergo ECV of persistent AF, were enrolled in the study. No exclusion criteria existed with the exception of unwillingness to participate. In our Department, if anatomic conditions are favourable, an attempt to restore sinus rhythm is pursued in almost every symptomatic subject, independently of age. To prepare the patients to the procedure, given the high incidence of adverse effects due to anti-arrhythmic therapy [13], we initially prefer to optimize medical therapy for heart failure or hypertension. In the case of a relapse, of important anatomic alterations or of a long-standing form of arrhythmia, we usually start a specific pharmacologic treatment.

All subjects presented in a fasting condition at 8 a.m. They underwent blood samples collection and were clinically evaluated before the procedure. An echocardiogram was performed and an EKG Holter recording started after ECV before the discharge from hospital.

In every case, MMSE, the 15-item GDS and SPPB were administered before ECV. The MMSE, which explores cognitive function, is composed by 30 items aimed at evaluating orientation and attention, and the capability of registration, calculation and recall, and at assessing memory, language skills and the possibility to complete difficult tasks, such as drawing a complex figure. A score <24 is indicative of cognitive decline. MMSE is widely accepted by patients and physicians and its administration is fast [9]. The 15-item GDS is the short form of the original GDS, used to screen, diagnose and evaluate the presence of depression in the elderly. The tool was designed assuming that the condition is associated with manifestations more typically found at advanced age, often consisting of physical symptoms, anxiety and altered cognitive function. The 15-item GDS was aimed at improving the ease of use and at reducing the time of administration, preserving patient concentration. Fifteen of the original 30 questions, characterized by the highest correlation with a depressive state, were selected to enter in the short version of the tool. To each query is possible to answer with “yes” or “no”. A total score >5 is considered to be abnormal [10]. The SPPB is a physical performance measure to evaluate lower extremity functioning in old subjects and it can be considered an instrument to evaluate frailty. It consists of three different tasks, exploring balance (ability to stand with the feet in the side-by-side, semi-tandem and tandem positions), gait (time to walk a 4-meter distance) and strength and endurance (time to rise from a chair and to return to the original position for 5 times without helping with arms). According to the time necessary to complete each task, a score ranging from 0 to 4 (best performance) is assigned to the patient. Consequently, SPPB total score extends from 0 to 12, with a score <6 identifying subjects at higher risk of disability and mortality [11, 14].

A new clinical evaluation, aimed at assessing sinus rhythm persistence and vital status, was performed after a 3- to 6-month period from the procedure.

*Statistical analysis*

Continuous and categorical variables are expressed as mean + standard deviation and as raw numbers and percentages, respectively. Analysis of variance was used to test differences among the strata of continuous variables. As a post-hoc analysis, the Bonferroni test was applied. The association between CHA2DS2-VASc and MMSE, GDS or SPPB was verified with linear regression analysis models. Furthermore, to evaluate if a single condition of the CHA2DS2-VASc could be more important than others, several regression models were run, each using a CHA2DS2-VASc derived score, in which at times, a single condition was deleted (i.e., HA2DS2-VASc, CA2DS2-VASc, CHDS2-VSc, CHA2S2-VASc, CHA2D-VASc, CHA2DS2-ASc, CHA2DS2-VA). A multivariate linear regression analysis model was then built assuming SPPB, a marker of frailty, as the dependent variable and the CHA2DS2-VASc, the MMSE and the GDS scores as the predictors. The Student’s t test or the Mann-Whitney test, in the case of a not-normal distribution, and the chi-square test were applied for continuous and categorical variables, respectively, to study the association between persistence of sinus rhythm at the follow-up and the CHA2DS2-VASc score and its components. We then used the ROC curve analysis to best describe our findings. A multivariate logistic regression analysis model was built to determine the clinical predictors of AF relapse at the follow-up. In every case, a p-value <0.05 was considered to indicate statistical significance. All analyses were performed using IBM SPSS for Windows ver. 26 (64-bit edition).

**Results**

**CHA2DS2-VASC and Geriatric Multidimensional Assessment tools**

At the end of the enrolment phase, 134 patients (mean age: 77+9 years, range: 60-96; men: N=85; 63.4%) participated to the study. Only one patient denied his consent. Overall, left ventricular ejection fraction was preserved (60+12%), but lower than normal in 25.4% (N=34) of subjects. Hypertension was the most frequent comorbid condition. Creatinine clearance, estimated with the Cockcroft-Gault equation was 68.4+25.1 mL/min, with 23.1% of patients (N=31) showing values <50 mL/min. In accordance with the diagnosis of persistent AF and advanced age, left atrium diameter was greater than normal (53+7 mm), and the prevalence of a more than mild mitral regurgitation was high (N=90, 67.2%). Aortic stenosis prevalence was low (N=11, 8.2%). All patients were anticoagulated, with a DOAC used in the majority of cases (N=80, 59.7%). Beta-blockers (N=100, 74.6%) and antagonists of the renin-angiotensin system (N=95, 70.9%) were prescribed to great part of the enrolled population. Amiodarone was the most preferred anti-arrhythmic agent (N=62, 46.3%), while only 7 subjects (5.2%) received propafenone or flecainide. Clinical characteristics of study population are in Table 1.

Clearly abnormal values of MMSE, GDS and SPPB were found in 7.9, 19.8 and 22.3% of patients, respectively.

Linear regression analysis models demonstrated that MMSE and SPPB were inversely related to the CHA2DS2-VASc score. The burden of depressive symptoms, as evaluated with the GDS, significantly increased with thrombo-embolic risk (Figure 1, scatterplots). The association for MMSE were largely due to the difference between patients scoring <2 and >6 with the CHA2DS2-VASc score. GDS and SPPB started to significantly change with CHA2DS2-VASc values >3 (Figure 1, histograms).

Separate linear regression analysis models demonstrated that the association of MMSE, GDS and SPPB with CHA2DS2-VASc were not due to the presence of a particular predictor of thrombo-embolism. Even after the deletion of each single factor from the score (i.e., chronic heart failure, hypertension, age, diabetes, stroke or TIA, vascular diseases and female gender), a statistically significant correlation persisted in every case (Table 2).

In a final multivariate model (R=0.633, p<0.001), SPPB total score was significantly associated with CHA2DS2-VASc ( = -0.56+0.15; 95%CI: -0.86 - -0.26; p<0.001) and GDS ( = -0.48+0.09; 95%CI: -0.65 - -0.31; p<0.001), but not with MMSE (p=0.072).

MMSE (R=0.213, p=0.016), GDS (R=0.312, p=0.001) and SPPB (R=0.385, p<0.001) were associated also with the CHADS2 even if with a lower degree of correlation.

**CHA2DS2-VASC and sinus rhythm at the follow-up**

At the end of the follow-up (mean length: 195 days, 33rd-66th percentile: 84-204 days), we could analyse the persistence of sinus rhythm in 130 of the 134 patients (97.0%) evaluated at baseline. Two subjects (1.5%) had died and two other subjects (1.5%) were lost to follow-up. Furthermore, given the prevalence of a primary electric disturbance originating AF (i.e., lone AF and sick sinus syndrome or brady- tachycardia syndrome; N=16, 11.9%), one patient (0.7%) after ECV was transferred to a sub-intensive care unit for severe bradycardia and pacemaker implantation.

AF relapsed in 68 cases (50.7%). Interestingly, left ventricular ejection fraction, left atrium diameter, the presence of a more than mild mitral regurgitation or aortic stenosis, and creatinine clearance were not associated with loss of sinus rhythm. The same was observed for therapy with beta-blockers, antagonists of the renin-angiotensin system and propafenone or flecainide. The use of amiodarone was more frequent among subjects without arrhythmia relapse (59.7 vs. 33.8%, p=0.005). While CHADS2 did not differ by rhythm at the control evaluation (p=0.234), CHA2DS2-VASc score was significantly higher in patients with arrhythmia recurrence (Table 3). This result was mainly due to a higher prevalence of diabetes and female gender among subjects not maintaining sinus rhythm. Age, as a continuous variable (AF no: 75+8 years vs. AF yes: 78+8 years; p=0.120) or categorized, was not associated with outcome (Table 3). At the ROC analysis, the Area Under the Curve (AUC) for the relation between CHA2DS2-VASc score and AF relapse was 0.60+0.05 (95%CI=0.50-0.69; p=0.049). Confirming previous results, when stratifying our population by sex, we noticed a significant relation in women (AUC=0.67+0.08; 95%CI=0.52-0.83; p=0.031) but not in men (AUC=0.52+0.07; 95%CI=0.39-0.65; p=0.788). The same was found even studying the CHA2DS2-VA score, which was obtained deleting the sex component. No association was shown with the ROC analysis by the presence of diabetes.

Neurocognitive performance, depressive symptoms and physical functioning, as evaluated with MMSE, GDS and SPPB, were not different in patients with and without sinus rhythm at the follow-up evaluation. Logistic regression analysis confirmed the direct association of the CHA2DS2-VASc score with arrhythmia relapse (OR=1.31; 95%CI: 1.04-1.67; p=0.024) and the protective role of amiodarone (OR=0.31; 95%CI: 0.15-0.64; p=0.002).

**Discussion**

In the present study, we demonstrated that CHA2DS2-VASc is correlated with neuro-cognitive function, depressive symptoms and physical performance of elderly patients with persistent AF. CHA2DS2-VASc score and depressive symptoms, when combined, provided better prediction of SPPB score, our index of physical functioning and frailty. At the follow-up evaluation, patients with AF relapse had a higher CHA2DS2-VASc score because of the greater prevalence of female gender and diabetes.

Given the high prevalence of AF in the elderly, our findings suggest that the CHA2DS2-VASc score could help to quantify thrombo-embolic risk as well as frailty assessment. Nonetheless, the CHA2DS2-VASc score was designed for thromboembolic risk stratification, not frailty assessment. However, this score is a simple cluster of common cardiovascular risk factors, that have been associated with multiple disorders.

As far as we are aware, this is the first comprehensive assessment of neuro-cognitive function, depressive symptoms and physical performance of elderly patients with persistent AF, in relation to the CHA2DS2-VASc score. The relation to neuro-cognitive function is perhaps unsurprising. In subjects younger than ours (age: 59 years) with paroxysmal AF, the CHA2DS2-VASc score was associated with the presence and the severity of silent white matter hyperintensities at brain magnetic resonance imaging; however, no correlation was found between MMSE and cerebral lesions [15].

Depressive symptoms constitute one of the most important patient-reported outcomes in the AF population, and they are influenced by the severity itself of arrhythmia symptoms [16] and oral anticoagulant therapy psychologic burden [17]. Of note, depression disturbances are associated with increased mortality in anticoagulated subjects independently of disability, comorbidities and the CHA2DS2-VASc score [18].

SPPB is a predictor of mortality in older patients hospitalized for heart failure [19]. However, evidence about SPPB and AF are limited. Regarding its components, mortality in elderly subjects increases after cardiac surgery for a walking speed <0.8 m/s [20]. After heart valve surgery, the development of post-operative AF and a delayed early rehabilitation program were associated with an increased risk of in-hospital declining of lower-extremity function [21]. With other risk scores, a frail status was more represented in subjects with a high CHA2DS2-VASc score [22]. In our population, the increase of one unit of the CHA2DS2-VASc score was associated with the reduction of the SPPB score of 0.81 unit.

As previously anticipated, our findings suggest that the CHA2DS2-VASc is an expression not only of individual clinical complexity but also of a frail status. At this regard, as an example, many of the conditions of the Modified Frailty Index (i.e., dependent functional status; diabetes mellitus; chronic obstructive pulmonary disease or pneumonia; congestive heart failure; myocardial infarction; percutaneous coronary intervention, stenting, or angina; hypertension; peripheral vascular disease or ischemic rest pain; TIA or cerebrovascular event; cerebrovascular accident with neurologic deficit; history of impaired sensorium) [23] are components of the CHA2DS2-VASc score.

Given that frailty is a multi-factorial syndrome, caused by a reduction of physiologic reserve and capability to resist stressful events, probably due to changes in production, distribution and utilization of energy [8], it can be better defined by the presence of many different conditions, not only clinical, but also psychological, cognitive and social. At this regard, when depressive symptoms, as expressed by the GDS, were introduced in the model linking the CHA2DS2-VASc score to the SPPB, the strength of the association grew of about 20%. MMSE was not related to physical functioning, probably for the rather high neuro-cognitive status of patients selected to undergo to ECV of AF, and the relatively small number of subjects in our database. Hence, the use of the CHA2DS2-VASc can contribute to identify the presence of frailty in elderly subjects with the arrhythmia.

Interestingly, the CHA2DS2-VASc score was higher in those individuals in whom AF relapsed at the follow-up evaluation. This result was explained by the greater prevalence of diabetes and female gender in subjects with arrhythmia recurrence. Diabetes significantly worsens prognosis in AF patients independently of treatment optimization [24], probably for its association with other risk factors and the contribution to atrial failure development [25]. The influence of gender on AF relapse is more difficult to explain. In our population, no sex-related differences were observed in the other components of the CHA2DS2-VASc score and in medical therapy. The women we enrolled had a lower left atrium diameter (51+7 vs. 54+7 mm; p=0.005), and higher values of heart rate (82+18 vs. 74+16 bpm; p=0.012) and left ventricular ejection fraction (64+10 vs. 58+12%; p=0.004). These findings let us hypothesize the relevant role of heart failure with preserved ejection fraction to determine arrhythmia development or relapse in elderly women [26]. Furthermore, it is known that, even after adjustment, a frail status is more common in women than in men [27]. Indeed, the GDS (4.0+2.9 vs. 2.3+2.5; p=0.002) and the SPPB (7.5+3.3 vs. 9.6+2.3; p<0.001) scores demonstrated a more altered condition in our female population. We found no association between rhythm at the follow-up and cognitive status, depressive symptoms and physical performance. Indeed, it was already demonstrated that a frail status could significantly worsen length of stay in hospital and 6-month mortality, but not the prescription of rate- and rhythm control strategy therapy [28]. Importantly, the correlation between the CHA2DS2-VASc score and AF relapse persisted also after having taken into consideration amiodarone use, that, also in our series of patients, revealed as an effective anti-arrhythmic strategy. The risk of new events was >60% lower in the treated population.

According to our findings, symptomatic subjects with a high thrombo-embolic risk and a frail or complex clinical condition should not be denied an attempt to restore sinus rhythm after having optimized medical therapy and started an anti-arrhythmic agent.

*Limitations*

Our study has several limitations, including the limited number of subjects, hospitalized in only one centre to undergo ECV of persistent AF. However, as previously reported, our patients were prospectively and consecutively enrolled without any exclusion criteria. Furthermore, in our Department, if anatomic conditions are appropriate, the procedure is performed in almost every symptomatic subject, independently of age, and GDS and SPPB scores. If symptoms persist, a second ECV is planned after the revise of medical therapy. This behaviour is chosen in an attempt to limit age-related disparities in arrhythmia management [29]. Interestingly, it was shown that total cerebral blood flow associates with the arrhythmic burden in an AF population [30], and that sinus rhythm restoration correlates with increased brain perfusion [31]. We decided not to study patients with a permanent form of the arrhythmia for their more complex clinical picture, probably less responsive to specific interventions [32]. We cannot exclude that our findings could have been different from those we obtained if we had included subjects with permanent AF in our population.

**Conclusions**

The CHA2DS2-VASc score was significantly correlated with neuro-cognitive performance, depressive symptoms and physical functioning. It was also associated with arrhythmia relapse after ECV of AF, particularly in women and diabetic subjects. Given the high prevalence of the arrhythmia in the elderly, the CHA2DS2-VASc score could help to quantify thrombo-embolic risk as well as give an indication of frailty status and contribute to choose the most appropriate therapeutic strategy.

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**Informed consent.** All enrolled patients gave their informed consent to participate to the study.

**Conflict of interest statement.** The authors declare they have no conflict of interest.

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**FIGURE LEGEND**

**Figure 1.**

Correlations between the CHA2DS2-VASc score and the MMSE, the 15-item GDS and the SPPB total scores. Linear trends are evaluated with the scatterplots and the contrasts between categories of risk with the histograms.

**Table 1.** Clinical characteristics of patients

|  |  |
| --- | --- |
| (N=134) |  |
| CHA2DS2-VASc (score) | 3.8±1.6 |
| Chronic Heart Failure (n, %) | 39 (29.1) |
| Hypertension (n, %) | 110 (82.1) |
| Age <65 years (n, %) | 8 (6.0) |
| Age 65-74 years (n, %) | 40 (29.9) |
| Age >75 years (n, %) | 86 (64.2) |
| Diabetes (n, %) | 23 (17.2) |
| Stroke / TIA (n, %) | 21 (15.7) |
| Vascular diseases (n, %) | 35 (26.1) |
| Sex - Women (n, %) | 49 (36.6) |
| CHADS2 (score) | 2.2±1.3 |
| MMSE (score) | 27.7±2.9 |
| GDS (score) | 3.0±2.7 |
| SPPB (total score) | 8.8±2.9 |

GDS: 15-item Geriatric Depression Scale; MMSE: Mini-Mental State Examination; SPPB: Short-Physical Performance Battery; CHADS2 is obtained adding the scores for chronic heart failure, hypertension, age >75 years, diabetes (1 point each) and stroke/TIA (2 points)

**Table 2.** Association between MMSE, GDS and SPPB with CHA2DS2-VASc derived variables (each variable was created subtracting a single component of the CHA2DS2-VASc score)

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | MMSE | |  | GDS | |  | SPPB | |
|  | R | p |  | R | p |  | R | P |
| HA2DS2-VASc (no CHF) | 0.226 | 0.011 |  | 0.401 | <0.001 |  | 0.473 | <0.001 |
| CA2DS2-VASc (no Hypertension) | 0.251 | 0.004 |  | 0.394 | <0.001 |  | 0.442 | <0.001 |
| CHDS2-VSc (no Age) | 0.182 | 0.041 |  | 0.357 | <0.001 |  | 0.337 | <0.001 |
| CHA2S2-VASc (no Diabetes) | 0.224 | 0.011 |  | 0.418 | <0.001 |  | 0.459 | <0.001 |
| CHA2D-VASc (no Stroke / TIA) | 0.214 | 0.016 |  | 0.331 | <0.001 |  | 0.418 | <0.001 |
| CHA2DS2-ASc (no Vascular diseases) | 0.239 | 0.007 |  | 0.391 | <0.001 |  | 0.489 | <0.001 |
| CHA2DS2-VA (no Sex Category) | 0.215 | 0.015 |  | 0.317 | 0.001 |  | 0.356 | <0.001 |

MMSE: Mini-Mental State Examination; GDS: 15-item Geriatric Depression Scale; SPPB: Short-Physical Performance Battery

**Table 3.** CHA2DS2-VASc score and its components by AF relapse at the follow-up

|  |  |  |  |
| --- | --- | --- | --- |
|  | AF relapse | |  |
|  | **No (N=62)** | **Yes (N=68)** |  |
| CHA2DS2-VASc (score) | 3.5±1.4 | 4.1±1.7 | 0.048 |
| Chronic Heart Failure (n, %) | 21 (33.9) | 15 (22.1) | 0.170 |
| Hypertension (n, %) | 50 (80.6) | 58 (85.3) | 0.494 |
| Age >75 years (n, %) | 35 (56.5) | 49 (72.1) | 0.069 |
| Diabetes (n, %) | 4 (6.5) | 19 (27.9) | 0.002 |
| Stroke / TIA (n, %) | 10 (16.1) | 10 (14.7) | 1.000 |
| Vascular diseases (n, %) | 14 (22.6) | 20 (29.4) | 0.428 |
| Sex - Women (n, %) | 17 (27.4) | 32 (47.1) | 0.029 |

