

## Atrial fibrillation and prediction of mortality by conventional clinical score systems according to the setting of care

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DOI:

[10.1016/j.ijcard.2018.03.058](https://doi.org/10.1016/j.ijcard.2018.03.058)

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*Document Version*

Peer reviewed version

*Citation for published version (Harvard):*

Diemberger, I, Fantecchi, E, Reggiani, MLB, Martignani, C, Angeletti, A, Massaro, G, Ziacchi, M, Biffi, M, Lip, GYH & Boriani, G 2018, 'Atrial fibrillation and prediction of mortality by conventional clinical score systems according to the setting of care', *International Journal of Cardiology*, vol. 261, pp. 73-77.

<https://doi.org/10.1016/j.ijcard.2018.03.058>

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Published in International Journal of Cardiology on 14/03/2018

DOI: 10.1016/j.ijcard.2018.03.058

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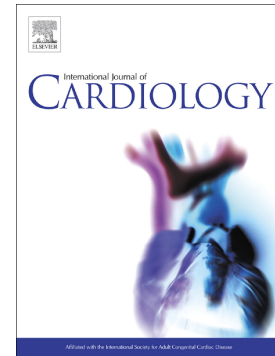
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## Accepted Manuscript

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PII: S0167-5273(17)38078-6  
DOI: doi:[10.1016/j.ijcard.2018.03.058](https://doi.org/10.1016/j.ijcard.2018.03.058)  
Reference: IJCA 26187

To appear in:

Received date: 29 December 2017  
Revised date: 9 February 2018  
Accepted date: 12 March 2018

Please cite this article as: Igor Diemberger, Elisa Fantecchi, Maria Letizia Bacchi Reggiani, Cristian Martignani, Andrea Angeletti, Giulia Massaro, Matteo Ziacchi, Mauro Biffi, Gregory Y.H. Lip, Giuseppe Boriani, Atrial fibrillation and prediction of mortality by conventional clinical score systems according to the setting of care. The address for the corresponding author was captured as affiliation for all authors. Please check if appropriate. *Ijca*(2017), doi:[10.1016/j.ijcard.2018.03.058](https://doi.org/10.1016/j.ijcard.2018.03.058)

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**ATRIAL FIBRILLATION AND PREDICTION OF MORTALITY BY  
CONVENTIONAL CLINICAL SCORE SYSTEMS ACCORDING TO THE  
SETTING OF CARE**

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**Key words:** outcomes, real world, registry, survival, arrhythmia

**Word count:** 2000

**ABSTRACT**

**Background:** Atrial fibrillation (AF) is associated with high morbidity and mortality, also amongst anticoagulated patients. Our aim was to evaluate the predictive role for long-term mortality of a series of risk stratification scores associated with cardiovascular or thromboembolic outcomes (CHADS<sub>2</sub>, CHA<sub>2</sub>DS<sub>2</sub>-VASc, ATRIA, TIMI-AF), and bleeding complications (HAS-BLED) in an unselected population of patients with AF.

**Methods:** Single center, observational, prospective registry of consecutive patients with AF, undergoing clinical/echocardiographic evaluation in a University Hospital, as either in-patients or out-patients. We assessed the role of each single score as predictors of long-term survival according to clinical setting.

**Results:** We enrolled 1051 patients, mean age 72±12 years, who were followed for 797±298 days. All the tested scores showed a good performance in prediction of mortality, together with several clinical factors (older age, chronic heart failure, diabetes, renal impairment, previous transient ischemic attack, left ventricular ejection fraction). The values at C-statistics ranged between modest (0.608-0.684) of inpatients to good (0.708-0.751) in outpatients without any statistical difference between the scores, excepted a lower performance of HAS-BLED.

**Conclusions:** Risk scores currently adopted for decision making on starting oral anticoagulation provide good prediction of long-term survival in unselected AF patients, especially in the outpatient setting.

## Introduction

Atrial fibrillation (AF) is associated with high morbidity and mortality, which is still evident amongst anticoagulated patients<sup>1-5</sup>. To improve effective clinical decision-making several clinical scoring systems (see Supplementary Table 1) have been developed to stratify the risk of thromboembolic events<sup>6-8</sup>, bleeding complications<sup>9</sup> risk of adverse cardiovascular events<sup>10</sup> and the identification of patients for whom a therapeutic benefit of novel oral anticoagulants (NOACs) over Vitamin K antagonist (VKA)<sup>11</sup>. Previous studies have shown that the CHADS<sub>2</sub> and CHA<sub>2</sub>DS<sub>2</sub>-VASc scores may have some predictive role for survival of AF and non-AF patients both in inpatient and outpatient settings<sup>12-17</sup> but the adoption in non-AF patients has been criticized<sup>18</sup>.

Our aim was to evaluate the predictive role for long-term mortality of a series of clinical risk stratification scores associated with cardiovascular or thromboembolic outcomes (ATRIA, CHADS<sub>2</sub>, CHA<sub>2</sub>DS<sub>2</sub>-VASc, TIMI-AF), and bleeding complications (HAS-BLED) in an unselected population of patients with AF, also considering the site of enrolment (inpatient vs. outpatient setting).

## Materials and Methods

We performed a single centre observational, prospective registry including consecutive patients with a diagnosis of AF referred to a tertiary teaching Hospital. The study design has been previously reported<sup>19</sup>. In brief, we enrolled patients with  $\geq 1$  ECG-proved episode of AF within 1 year before screening. Patients were included if  $\geq 18$  years old and basic echocardiographic data were available (i.e. left ventricular ejection fraction, left atrial diameter and quantification of valvular dysfunctions). The

local ethical committee approved the study and written informed consent was obtained by all the participants. The investigation was conducted in accordance with the principles expressed in the Declaration of Helsinki.

Data collection was performed at patient inclusion (baseline) and at 1-year follow-up. Baseline evaluation considered: (a) patient demographics, (b) medical history, (c) AF characteristics, (d) AF-related symptoms, (e) AF management strategy, (f) standard laboratory assay and (g) complete pharmacological therapy. For each patient we calculated ATRIA, CHADS<sub>2</sub>, CHA<sub>2</sub>DS<sub>2</sub>-VASc, HAS-BLED, and TIMI-AF scores (Supplementary table 1). The same evaluation was performed every 12 months for up to three years of follow-up. At each review check we also evaluated overall patient status and the events occurred since baseline, in particular: (a) hospital admissions, (b) cardiovascular interventions, (c) instrumental evaluations. Between the two fixed face to face checks we performed telephonic surveillance (between months 3 to 9 after each check) to improve compliance to the protocol. The same was performed to exclude death or major clinical events for patients not performing the periodical face to face check. To classify the mode of death we performed parents interview and revision of death certificate and all the available clinical records by two different operators.

*Statistical analysis:*

Continuous variables with normal distribution are expressed as means  $\pm$  standard deviation (median and interquartile range (IQR) for continuous variables without normal distribution). Categorical variables are expressed as number of patients and frequencies/percentage. Comparisons between enrolment and follow-up data were performed using the paired Student's t-test for continuous normally distributed

variables,  $\chi^2$ -test for categorical variables and non parametric equivalent tests for other type of variables. Cox proportional hazards analysis was used to identify scores as independent predictors of overall mortality and the results are presented as hazard ratio (HR), confidence interval and p-value. Models building follows a backward-stepwise approach, the test of term significance is the Wald chi-square test with cutoff p value of 0.1 for removal and 0.05 for addition. The Harrell's C-statistic and the confidence intervals were used to assess the goodness of fit, or discriminatory value, of Cox regression models and to compare their predictive power. Kaplan-Meier curves for overall survival according to the various scoring systems were constructed. Data analysis was performed with the statistical software Stata/SE 14.2 for Windows (StataCorp LLC, College Station TX, USA) and SPSS 23.0 (SPSS Statistics/IBM Corp, Chicago IL, USA).

## Results

We enrolled 1051 patients aged  $72 \pm 12$  years. The main enrolment site was cardiology ward and day-hospital (71.1%) followed by outpatients clinic (28.9%). Baseline clinical and echocardiographic characteristics of the enrolled population are reported in table 1 according to outpatient/inpatient status at the time of enrolment. In general the most common subtype was permanent AF (44.8%) justifying a rate-control strategy in a significant proportion of the enrolled patients (65.0%). Moreover, 48.3% of the overall patients never experienced any typical AF-related symptom, with palpitations and dyspnoea being the most represented among the remaining subjects. Notably, inpatients were sicker with respect to outpatients, with a higher proportion of permanent AF and only in a minority of the patients AF was the principal cardiovascular problem leading to access to medical intervention.

The mean baseline values for the various clinical scores were as follows: ATRIA  $5.6\pm 2.9$ , CHADS<sub>2</sub>  $2.0\pm 1.3$ , CHA<sub>2</sub>DS<sub>2</sub>-VASc  $3.7\pm 1.9$ , HAS-BLED  $2.0\pm 0.9$ , and TIMI-AF  $5.7\pm 2.1$ .

After a mean follow-up of  $797\pm 298$  days (median 730 days; range 368-1102 days) 166/1051 (15.8%) patients died. The causes of death were as follows: non-cardiovascular (38.0%. Among them the leading causes were cancer, 12.7% of the total, infections 10.4% and trauma 3.6%), heart failure (30.7%), stroke (4.2%) other cardiovascular aetiologies (14.5%). In 21 patients (12.7%) the aetiology remained undetermined. Notably inpatients presented a higher overall death at follow-up without a significantly different cause of the event, despite a trend for non-cardiovascular causes in outpatients (Figure 1).

#### *Univariate and multivariate regression*

We first performed a univariate Cox regression analysis including all the tested scores together with the single characteristics included in these scores (supplementary table 2). Using the significant characteristics from the univariate analysis, we performed multivariate regression analysis among the single factors which showed six factors that were independently associated with overall survival (Model 1). Notably the mode of access to medical evaluation (inpatient vs. outpatient) presented a p value for interaction  $<0.05$  for each score with exception of TIMI-AF, for which however was present a trend ( $p=0.061$ ). Conversely, the presence/absence of anticoagulation (performed as a sensitivity analysis) was not associated with a significant p value for interaction for each scoring system included in the analysis. According to these findings we provided two additional model in the multivariate regression analysis for inpatient (Model 2) and outpatients (Model 3). Notably only left ventricular ejection fraction and diabetes were present in all the models.



Figure 2 shows Kaplan Meier curves for 1-year survival for each of the different scores divided into low to high risks categories, as defined in the literature<sup>20-22</sup>.

#### *Predictive value*

We compared the five risk scores in predicting overall survival with C-Harrell test, together with the probability provided by the multivariate Cox regression analysis (used as a positive comparator). As show in table 2 the performance of the all scores for the prediction of death was good with exception of HAS-BLED score. Of note, the probability assessed by the model provided by the multivariate Cox regression analysis performed better than each score in general population, but this finding seems to be driven by the inpatient subgroup, while in outpatients the C statistic the model and “standard” score did not produce any significant difference.

#### **Discussion**

In our study we compared the five clinical risk scores used in current clinical practice for the management of patients with AF in their capability of predicting mortality in a relatively unselected prospectively enrolled group of AF patients. All scores showed a good performance in prediction of mortality using univariate Cox regression analysis, as did several individual factors included in their calculation: age, renal impairment, diabetes, heart failure, left ventricular ejection fraction and previous transient ischemic attack. Since the development of CHADS<sub>2</sub> several scoring systems have been developed for AF patients to improve risk stratification for several events: stroke, bleeding complications, cardiovascular events. However, we have no guide on how to integrate them in clinical practice. This is a relevant topic considering that the experts who were in charge of the last AF guidelines felt the need to modify the practical use of HAS-BLED (and other scoring system for stratifying the bleeding risk) since for many clinicians a high score was seen as a barrier to anticoagulation<sup>23</sup>.

Few studies compared CHADS<sub>2</sub> and CHA<sub>2</sub>DS<sub>2</sub>-VASc scores for prediction of overall survival in more selected populations with or without AF<sup>12-14</sup>. The HAS-BLED score was also tested in one of these studies in a group of patients undergoing PCI<sup>24</sup> with a relatively lower performance with respect to CHADS<sub>2</sub> and CHA<sub>2</sub>DS<sub>2</sub>-VASc in accordance to our results.

Our results show that, beyond the stratification of the risk of stroke, two scores like CHADS<sub>2</sub> and CHA<sub>2</sub>DS<sub>2</sub>-VASc, which are based on a limited set of data, are effective in predicting overall mortality without the need for additional information such as laboratory tests (e.g. creatinine, proteinuria or haemoglobin) or echocardiography, which are less readily available especially in outpatient settings. In this view, the second most important result of our study is that prediction of long-term mortality was significantly affected by the setting (see Figure 1,2) as documented by the different factors included in the final multivariate models for inpatients and outpatients. This can be driven by the differences in the two subgroups in terms of AF type and comorbidities. But it can also be the effect of other factors (e.g. variability of renal function leading to greater imprecision in outpatients, or acute/subacute events leading to hospitalization). Notably, despite the deep differences in these two subgroups of patients all scores, with the exception of HAS-BLED, performed very well for prediction of mortality without a significant superiority of any of them. However, only in the outpatient settings the results were equivalent to the multivariate model. This is a very important result since it shows a simple scoring systems, like CHADS<sub>2</sub> and CHA<sub>2</sub>DS<sub>2</sub>-VASc, is as good as an ad-hoc score to predict mortality in an unselected population of AF outpatients. A further consideration has to be made on the possible differences in AF treatment between inpatient and outpatients that could also explain the different outcomes, in particular regarding thromboembolic

prophylaxis<sup>25</sup>. Notably, in our cohort we found no difference between inpatient and outpatients in terms of anticoagulant prescription without interaction with the predictive role of each score, while our high prescription rate (respectively 90% vs. 86%;  $p=NS$ ) reflects current trends in AF management, as reported by the EORP-AF registry<sup>26</sup>, increasing transferability of our results. Conversely, the study by Mikkelsen et al. was related to a previous period (2002-2011) with a lower use of anticoagulation (about 60% for outpatient and 40% for inpatients). It could be obvious but it is relevant to consider that the results of all these scores vary with time leading to the question on how frequently should be reassessed each score in the specific patient. According to our results a re-evaluation every 12-24 months or soon after hospital admission should provide the best compromise. Moreover, in less stable patients more “complete” scores, like TIMI-AF, should be considered. However, further evaluation are needed to confirm a similar approach. Finally, several other risk factors are not included by the scores we considered (e.g. AF burden, atrial dilatation, additional comorbidities, neurohormones) that could potentially help in predicting long-term survival. Despite these considerations the practical implications of our findings are significant: in clinical practice this could improve personalization of patient follow-up by targeting a closer clinical monitoring to patients at increased risk of thromboembolic events. Moreover, the value of these scores can help comparing the risk of long-term mortality of different populations and/or subgroups<sup>27</sup>.

### ***Limitations***

The most important limitation of our study is its observational nature and related to a single University Hospital. The sample size is relatively limited, with a relatively high mean value of CHA2DS2-VASc score therefore may be not fully generalizable to all AF patients, especially to less sick patients.

## Conclusions

Clinical risk scores associated with cardiovascular or thromboembolic outcomes improve prediction of long-term survival in unselected AF patients. In particular, we found no difference in predicting value of simple scores (like CHADS2 and CHA2DS2-VASc) with respects to scores requiring integration of laboratory and echocardiography data. Their performance seems to be higher in outpatient (vs. inpatient) settings where personalization of patient monitoring can improve everyday clinical practice.

**Funding:** This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

## FIGURE LEGENDS

**Figure 1. Overall survival and cause of death according to clinical settings.**

Legend: CV=cardiovascular; HF=heart failure; pts=patients.

**Figure 2. Kaplan Meier curves for 1-year survival for each of the different scores divided into low to high risks categories according to clinical settings.**

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**HIGHLIGHTS**

- We found that five scoring systems showed a good performance in prediction of long-term mortality in a relatively unselected cohort of patients;
- No significant difference in prediction performance was seen among the five scores, with the exception of HASBLED;
- In particular, we found no difference in predicting value of simple scores (like CHADS2 and CHA2DS2-VASc) with respects to scores requiring integration of laboratory and echocardiography data.
- Prediction of long-term mortality is affected by the setting, with a better performance for all the scores in the outpatient settings;



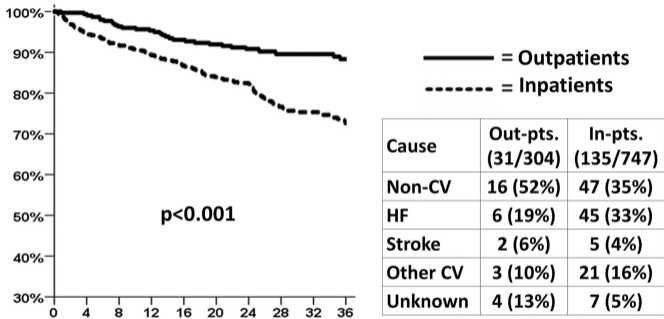


Figure 1

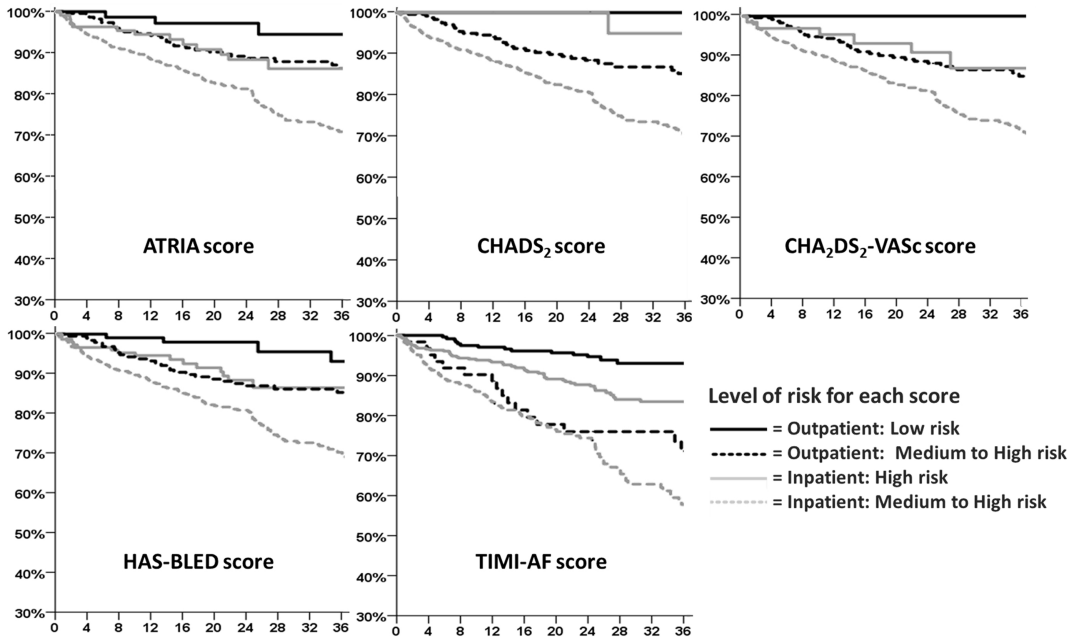


Figure 2