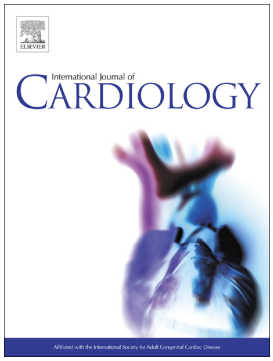

Prediction of new onset atrial fibrillation in patients with acute coronary syndrome undergoing percutaneous coronary intervention using the C2HEST and mC2HEST scores: A report from the multicenter REALE-ACS registry

Flavio Giuseppe Biccirè, Gaetano Tanzilli, Francesco Prati, Emanuele Sammartini, Martina Gelfusa, Mihail Celeski, Simone Budassi, Francesco Barillà, Gregory Y.H. Lip, Daniele Pastori

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Prediction Of New Onset Atrial Fibrillation In Patients With Acute Coronary Syndrome Undergoing Percutaneous Coronary Intervention Using the C2HEST and mC2HEST Scores: A report from the multicenter REALE-ACS registry

Running title: *C2HEST for NOAF prediction in ACS*

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Keywords. Atrial fibrillation, acute coronary syndrome, myocardial infarction, C_2HEST, mC_2HEST.

List of abbreviations

ACS: acute coronary syndrome

ALT: alanine aminotransferase

AUC: area under the curve

AST: aspartate aminotransferase

COPD: chronic obstructive pulmonary disease

CI: Confidence Interval

CRP: C-reactive protein

eGFR: Estimated glomerular filtration rate

GRACE: Global Registry of Acute Coronary Events

HR: Hazard Ratio

LAVi: left atrial volume index

LVEF: left ventricular ejection fraction

mC2HEST: modified C2HEST score

NOAF: New onset atrial fibrillation

NSTEMI: non-ST elevation myocardial infarction

OR: Odds Ratio

PCI: percutaneous coronary intervention

REALE-ACS: REAl-world observationaL rEgistry of Acute Coronary Syndrome

ROC: Receiver operating characteristic

STEMI: ST-elevation myocardial infarction

UA: unstable angina

WBCs: white blood cells

INTRODUCTION

New onset atrial fibrillation (NOAF) may complicate the clinical course of patients suffering from an acute coronary syndrome (ACS)[1]. Up to 20% of patients may develop NOAF after ACS or after percutaneous coronary intervention (PCI)[1, 2].

The mechanisms underlying NOAF development after ACS/PCI are multifactorial, and include increased inflammation, atrial ischemia, ischemia-reperfusion damage and oxidative stress following acute occlusion of coronary vessel[3, 4].

The occurrence of post-ACS NOAF has been associated with a high rate of AF recurrences over time (>20%), the need for long-term oral anticoagulation and worse clinical outcomes, including ischemic stroke and vascular death[5]. In the Global Use of Strategies To Open occluded coronary arteries (GUSTO-III) trial, 6.5% out of 13,858 patients with sinus rhythm at enrolment developed AF and this was associated with an increased risk of death (Odds Ratio [OR] 1.49, 95% Confidence Interval [CI] 1.17-1.89) compared to those without AF[6].

Several laboratory markers[7], such as NT-pro-brain natriuretic peptide and high-sensitivity C-reactive protein (CRP), clinical risk factors (ie. age, and sex, Killip class) and imaging variables (left ventricular ejection fraction [LVEF], left atrial size) have been associated with the risk of NOAF[1]. However, a simple cost-effective structured clinical risk stratification strategy to identify patients at higher risk for NOAF after ACS is not established yet.

Recently a new simple score namely C_2HEST (coronary artery disease or chronic obstructive pulmonary disease [1 point each], hypertension [1 point], elderly [age ≥75 years, 2 points], systolic heart failure [2 points], thyroid disease [1 point]) score to identify the risk of overt or subclinical AF in the general population[8, 9]. The C_2HEST score has been validated in large population studies which have confirmed its predictive value [8, 10]. More recently, Authors proposed a modified

version of the C_2HEST score, by adding age ≥65 years as an additional variable (1 point) to the original model, to emphasize that the incidence of AF increases by aging [11].

However, these scores have never been tested to predict NOAF after ACS.

The aim of our study is to investigate the predictive value of the simple C_2HEST score and the modified C_2HEST score (mC_2HEST)[11, 12] for NOAF in patients suffering from ACS undergoing PCI enrolled within the prospective ongoing REALE-ACS registry.

METHODS

The REAl-world observationaL rEgistry of Acute Coronary Syndrome (REALE-ACS) is an ongoing multicentre registry collecting data on characteristics, management and outcomes of consecutive patients admitted for ACS at the Department of Clinical Internal, Anesthesiologic, and Cardiovascular Sciences, Sapienza University of Rome, Rome, Italy, and at the Department of Cardiology, San Giovanni Hospital, Rome, Italy (from January 2016)[13].

Patients with age <18 years and with a history of AF were excluded. Patients with non-ST elevation ACS (i.e., unstable angina [UA] and non-ST elevation myocardial infarction [NSTEMI]) and ST-elevation myocardial infarction (STEMI) undergoing PCI were included in the study[14, 15].

At baseline, demographic characteristics and clinical information of each study patient were recorded as follows: age, sex, anthropometric data, drug therapy prior to hospital admission, cardiovascular risk factors, previous history of CAD, heart failure, ischemic stroke, peripheral artery disease, chronic obstructive pulmonary disease (COPD), history of cancer, thyroid disease and Global Registry of Acute Coronary Events (GRACE) score. Echocardiography was performed during in-hospital stay and on admission LVEF (%) as well as left atrial volume index (LAVi) were reported. A LVEF% ≤40 was considered as reduced according to current evidence[16].

The C_2HEST and mC_2HEST scores were calculated according to their original derivation cohort studies for each patient [11, 12, 17]. A C_2HEST score cut-off of >3 was used to define high risk patients for NOAF. All patients scored 1 point regarding the “coronary artery disease” item of the score.

Blood parameters

On admission, levels of aspartate aminotransferase (AST) AST/GOT (U/l), alanine aminotransferase (ALT) ALT/GPT (U/l), CRP (upper limit of normal [ULN] <0.5 mg/dL), haemoglobin (g/dl), platelets

x10^3/µgL, white blood cells (WBCs) x1000, neutrophils (%), lymphocytes (%), neutrophils/lymphocytes ratio, D-Dimer (ULN <450 ng/ml), glycaemia (mg/dl), creatinine (mg/dl) were collected. Low serum albumin was defined as <36 mg/l. Estimated glomerular filtration rate (eGFR) was determined using the MDRD formula. Plasma levels of high-sensitivity troponin on admission, either troponin T or troponin I, were collected and then normalised (ratio serum value/upper limit of normality) to be analysed.

New Onset Atrial Fibrillation

NOAF was defined as any AF episode occurring during in-hospital stay in patients without any history of AF prior to hospitalization. The AF episodes were collected by continuous ECG monitoring and confirmed by standard 12-lead ECGs.

The study was performed according to the Declaration of Helsinki, with approval from local ethics committee.

Statistical analysis

Categorical variables were reported as counts and percentage. Continuous variables were expressed as mean (± standard deviation) or median and interquartile range, in case of normal or skewed distribution, respectively. The Student's t-, Mann–Whitney U, and χ^2 tests were applied for bivariate analyses. A first descriptive analysis of clinical and biochemical characteristics according to the presence of NOAF was performed. Incidence of NOAF according to C_2HEST score was investigated and a univariable logistic regression analysis was performed to calculate the relative OR and 95% confidence interval (95%CI). We also performed a logistic regression analysis for NOAF development by using the previously validated C_2HEST score cut-off of 3[17]. Receiver operating characteristic

(ROC) curve was constructed, and Harrell C indexes (ie. area under the curve [AUC]) was calculated as a measure of model performance.

Only p values <0.05 were considered as statistically significant. All tests were two-tailed and analyses were performed using computer software packages (SPSS-26, SPSS Inc. and MedCalc).

RESULTS

Of 602 patients, 47 patients were excluded from the analysis due to a known history of prior AF. We enrolled 555 patients (mean age 65.6±13.3 years; 22.9% women), of which 45 (8.1%) developed NOAF during their in-hospital stay.

Baseline characteristics and medical history are reported in **Table 1**. Compared to patients maintaining sinus rhythm, patients with NOAF were older (p<0.001) and more frequently affected by hypertension (p=0.012), COPD (p<0.001) and hyperthyroidism (p=0.018), along with a more frequent use of ACE inhibitors (p=0.007) and COPD inhalers (p=0.032) prior to hospital admission (**Supplementary Table 1**). Conversely, patients taking statins at baseline were less likely to develop NOAF (14.3% vs 32.1% p=0.021).

Laboratory findings are listed in **Supplementary Table 2**. Higher serum levels of lymphocytes (p=0.016), neutrophils/lymphocytes ratio (p=0.006), D-Dimer (p<0.001), blood glucose (p=0.009), AST (p=0.006), increased high-sensitive troponin T/I (p=0.008), creatine kinase MB (p<0.001) and C-reactive protein (p<0.001) were found in NOAF patients. Patients developing NOAF were more frequently affected by hypoalbuminemia (p=0.004).

In **Table 2** we reported ACS presentation in patients with or without NOAF events. Patients developing NOAF were more frequently admitted with STEMI (p<0.001), cardiogenic shock (p=0.008) and, Killip class ≥2 (p<0.001) and higher values of GRACE score (p<0.001).

C_2HEST score and NOAF

The mean C_2HEST score was 3.1±1.6. Patients with NOAF had a significantly higher mean C_2HEST score compared with those without NOAF (4.2±1.7 vs 3.0±1.5, p<0.001). The incidence of NOAF increased significantly with increasing C_2HEST score (**Table 3**).

When using a cut-off of >3, the C_2HEST score was significantly associated with the development of NOAF (OR 4.33, 95%CI 2.19-8.59, p<0.001). ROC analysis showed that the C_2HEST score showed a good accuracy in predicting NOAF (AUC 0.71, 95%CI 0.67-0.74) (**Figure 1**).

The AUC obtained from the multivariable logistic regression analysis model including age, hypertension, COPD, hyperthyroidism, troponin was not statistically different from that obtained for the C_2HEST score (AUC 0.72, 95%CI 0.68-0.76, p=0.594).

The mean mC_2HEST score was higher in patients with NOAF compared to those without (4.3±1.7 *vs.* 3.1±1.5, p<0.001, **Table 1**). The mC_2HEST score showed a similar predictive value in predicting NOAF (AUC 0.69, 95%CI 065-0.73).

DISCUSSION

In this study our principal finding was that the C_2HEST score may represent a valid tool for the identification of patients with ACS undergoing PCI at risk of developing NOAF. Also, we found a graded increase in the risk of NOAF according to increasing C_2HEST score.

In our study, 8.1% of patients developed NOAF after ACS, consistent with previous studies on this topic[18, 19]. Prediction of NOAF is of clinical relevance considering the growing body of evidence demonstrating that AF complicating ACS is associated with worse short and long-term clinical outcomes. In the HORIZONS-AMI [Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction] Trial, which included 3,281 patients with STEMI and sinus rhythm, NOAF was present in 4.5% of patients and was associated with 3-year higher incidence of net adverse clinical events (Hazard Ratio [HR] 1.74) and major adverse cardiac events (HR 1.73)[20]. The incidence of NOAF was up to 22.1% in a study including 106 780 Medicare beneficiaries aged ≥65 years of age[21]. Patients with NOAF also had higher in-hospital (OR, 1. 21), 30-day (OR, 1.20), and 1-year (OR, 1.34) mortality[21]

We also tested the value of the modified C_2HEST score, which showed similar predictive value of the original C_2HEST score.

All these data indicate the need for an early identification of patients prone to develop NOAF to potentially reduce the incidence of adverse clinical events. The simple C_2HEST and mC_2HEST scores are easy to calculate as they include routine readily available clinical data not requiring laboratory or imaging data. Hence, their use may allow prompt recognition of patients at higher risk of NOAF and at risk of worse clinical outcomes, allowing early intervention.

Limitations

As other scores, also the C_2HEST score has limitations. It does not consider some additional important factors affecting the risk of NOAF such as left atrial dimension or structural heart disease (ie. valvular heart disease). However, this latter group of patients should *a priori* be considered at higher risk of NOAF. In addition, the score does not include concomitant medications that may have a role in preventing or facilitating NOAF. Thus, while COPD is an established risk factor for AF[22], the use of inhalers may represent a potentially modifiable risk factor to prevent NOAF[23]. Conversely, statins may prevent NOAF as shown by previous studies in general population[24] and in patients undergoing CABG[25]. Confirmation of the hypothesis that simple C_2HEST and mC_2HEST scores are useful in improving the management and prognosis of patients with ACS undergoing PCI will require further prospective clinical evaluation in a larger cohort of patients.

Conclusion

In conclusion, the simple C_2HEST score may be a useful tool to identify patients at higher risk of developing NOAF after presentation with ACS.

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Figure Legend

Figure 1. Receiver operating characteristic curve of C_2HEST score for new onset atrial fibrillation.

Graphical abstract. C2HEST score for prediction of NOAF in ACS patients. CAD: coronary artery disease; COPD: chronic obstructive pulmonary disease; NOAF: new onset atrial fibrillation; OR: odds ratio.

Table 1. Clinical characteristics of patients with or without new onset atrial fibrillation.

	Overall (n=555)	*Sinus rhythm (n=510)*	*New Onset Atrial Fibrillation (n=45)*	*p*
Age (years)	**65.6±13.3**	**65.0±13.0**	**72.5±13.9**	**<0.001**
Age ≥75 years (%)	**168 (30.3)**	**142 (27.8)**	**26 (57.8)**	**<0.001**
BMI (kg/m2)	26.7±4.3	26.7±4.4	26.3±3.0	0.585
Women (%)	127 (22.9)	113 (22.2)	14 (31.1)	0.195
		Medical History		
C_2HEST score	**3.1±1.6**	**3.0±1.5**	**4.2±1.7**	**<0.001**
mC_2HEST score	**3.2±1.6**	**3.1±1.5**	**4.3±1.7**	**<0.001**
Hypertension (%)	**373 (67.2)**	**335 (65.7)**	**38 (84.4)**	**0.012**
Diabetes (%)	163 (29.5)	149 (29.3)	14 (31.1)	0.865
Smoking (%)	388 (70.5)	360 (71.1)	28 (63.6)	0.304
Current smoker (%)	224 (40.7)	210 (41.5)	14 (31.8)	0.263
COPD (%)	**43 (7.7)**	**32 (6.3)**	**11 (24.4)**	**<0.001**
Prior PCI (%)	127 (23.0)	121 (23.9)	6 (13.3)	0.138
Prior heart failure (%)	36 (6.5)	35 (6.9)	1 (2.2)	0.346
Prior stroke/TIA (%)	31 (5.6)	28 (5.5)	3 (6.7)	0.732
*Chronic kidney disease ** (%)*	66 (12.7)	59 (12.4)	7 (15.9)	0.479
History of cancer (%)	59 (10.7)	53 (10.5)	6 (13.3)	0.612
Active cancer (%)	18 (3.3)	17 (3.4)	1 (2.2)	1.000
Peripheral artery disease (%)*	102 (18.4)	91 (17.8)	11 (24.4)	0.548
Thyroid disease (%)	50 (9.1)	46 (9.1)	4 (8.9)	1.000
Hyperthyroidism (%)	**3 (0.5)**	**1 (0.2)**	**2 (4.4)**	**0.018**

*including carotid and lower extremities. ** <60 ml/min glomerular filtration rate.

BMI: body mass index; CABG: coronary artery bypass graft; CAD: coronary artery disease; COPD: chronic obstructive pulmonary disease; PCI percutaneous coronary intervention; TIA: transient ischemic attack.

Table 2. Acute coronary syndrome presentation in patients with or without new onset atrial fibrillation.

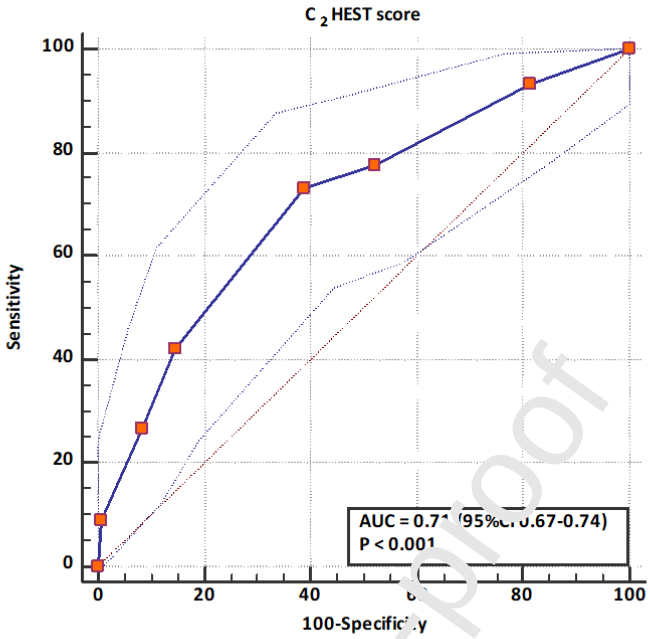
	Overall (n=555)	*Sinus rhythm (n=510)*	*New Onset Atrial Fibrillation (n=45)*	*p*
STEMI	**286 (51.6)**	**246 (48.3)**	**40 (88.9)**	**<0.001**
NSTEMI	**161 (29.1)**	**156 (30.6)**	**5 (11.1)**	**0.005**
Unstable Angina	**107 (19.3)**	**107 (21)**	**0 (0.0)**	**<0.001**
LAVi	31.0±10.2	30.8±9.7	33.3±14.4	0.151
LVEF %	44.8±9.8	45±9.8	42.1±9.5	0.209
LVEF <41% (%)	196 (35.9)	175 (34.9)	21 (47.7)	0.102
Cardiogenic shock (%)	**24 (4.3)**	**18 (3.5)**	**6 (13.6)**	**0.008**
Cardiac arrest (%)	15 (2.7)	13 (2.6)	2 (4.5)	0.339
Killip class ≥2 (%)	**88 (16.6)**	**72 (14.7)**	**16 (41)**	**<0.001**
GRACE	**140.4±40.1**	**136.8±37.5**	**187.1±42.5**	**<0.001**
Multivessel disease (%)	135 (25.3)	121 (24.6)	14 (34.1)	0.192

GRACE: Global Registry of Acute Coronary Events; LAVi: left atrial volume indexed; LVEF: left ventricular ejection fraction; NSTEMI: non-ST elevation myocardial infarction; STEMI: ST elevation myocardial infarction.

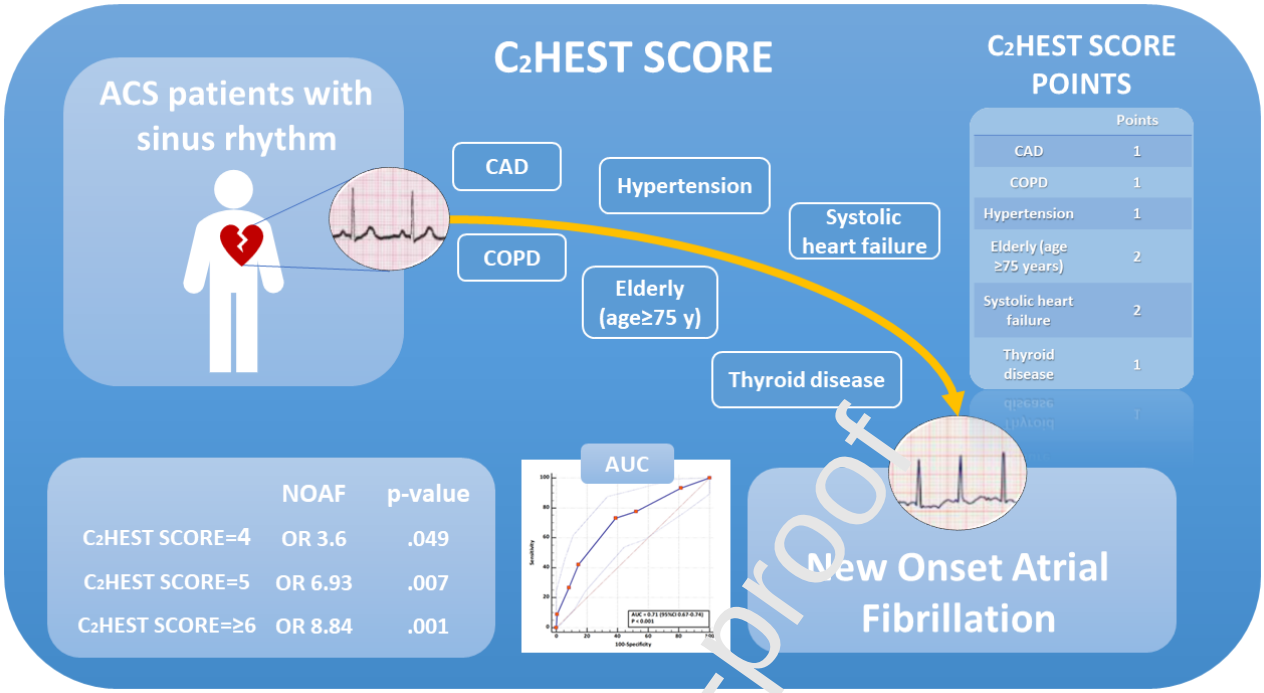
Table 3. C_2HEST score categories and incidence of new onset atrial fibrillation (NOAF).

C_2HEST score	Total (n=555)	Sinus Rhythm (n=510)	NOAF (n=45)	Odds Ratio	95% C.I.		p-value
					Lower	Upper	
1	98 (17.7)	95 (18.6)	3 (6.7)	-	-	-	-
2	155 (27.9)	148 (29)	7 (15.6)	1.498	0.378	5.935	0.565
3	71 (12.8)	69 (13.5)	2 (4.4)	0.918	0.149	5.642	0.926
4	137 (24.7)	123 (24.1)	14 (31.1)	3.604	1.007	12.903	0.049
5	39 (7)	32 (6.3)	7 (15.6)	6.927	1.690	28.390	0.007
≥6	55 (9.9)	43 (8.4)	12 (26.7)	8.837	2.372	32.931	0.001

Figure 1.



Graphical abstract.



Abstract

Background. New onset atrial fibrillation (NOAF) is associated with worse clinical outcomes after acute coronary syndrome (ACS). Identification of ACS patients at risk of NOAF remains challenging. To test the value of the simple C_2HEST score for predicting NOAF in patients with ACS.

Methods. We studied patients from the prospective ongoing multicenter REALE-ACS registry of patients with ACS. NOAF was the primary endpoint of the study. The C_2HEST score was calculated as coronary artery disease or chronic obstructive pulmonary disease (1 point each), hypertension (1 point), elderly (age ≥75 years, 2 points), systolic heart failure (2 points), thyroid disease (1 point). We also tested the mC_2HEST score.

Results. We enrolled 555 patients (mean age 65.6±12.3 years; 22.9% women), of which 45 (8.1%) developed NOAF. Patients with NOAF were older (p<0.001) and had more prevalent hypertension (p=0.012), chronic obstructive pulmonary disease (p<0.001) and hyperthyroidism (p=0.018). Patients with NOAF were more frequently admitted with STEMI (p<0.001), cardiogenic shock (p=0.008), Killip class ≥2 (p<0.001) and had higher mean GRACE score (p<0.001). Patients with NOAF had a higher C_2HEST score compared with those without (4.2±1.7 vs 3.0±1.5, p<0.001). A C_2HEST score >3 was associated with NOAF occurrence (odds ratio 4.33, 95% confidence interval 2.19-8.59, p<0.001). ROC curve analysis showed good accuracy of the C_2HEST score (AUC 0.71, 95%CI 0.67-0.74) and mC_2HEST score (AUC 0.69, 95%CI 065-0.73) in predicting NOAF.

Conclusions. The simple C_2HEST score may be a useful tool to identify patients at higher risk of developing NOAF after presentation with ACS.

Highlights

- **NOAF may complicate ACS course, but the prediction of NOAF is still challenging.**
- **C_2HEST and mC_2HEST scores have been proposed to predict NOAF in general population.**
- **C_2HEST and mC_2HEST score showed good accuracy in predicting NOAF in ACS patients.**
- **Simple clinical scores may be useful to detect ACS patients at higher risk of NOAF.**