ORIGINAL ARTICLE

De novo Atrial Fibrillation in ST-Elevation Acute Myocardial Infarction. Analysis of the ARGEN-IAM-ST Registry

Fibrilación auricular de novo *en el infarto agudo de miocardio con elevación del segmento ST. Análisis del Registro ARGEN-IAM-ST*

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ABSTRACT

Background: Atrial fibrillation (AF) is the most frequent arrhythmic complication in patients with acute coronary syndrome (ACS), and its incidence ranges between 2.3% and 21%.
Objective: To determine the incidence and predictors of *de novo* AF in patients with ST-segment elevation myocardial infarction (STEMI).
Methods: The database of the ARGEN-IAM-ST continuous registry was analyzed. Conventional descriptive statistics were used. To reduce dimensionality and identify those variables associated with the outcome of interest, Machine Learning algorithms were used, and a multivariate logistic regression analysis was performed to identify those factors associated with *de novo* AF. These were included in a final ranking model which was assessed by using the receiver operating characteristic (ROC) curve. A p-value <0.05 was considered statistically significant.
Results: We included 7292 patients with STEMI. A total of 4.3% had *de novo* AF during hospitalization. This group was older (67 vs. 60 years, p <0.001), with higher heart rate and Killip and Kimbal score and lower left ventricular ejection fraction (LVEF) on admission. These patients had a higher incidence of stroke (2.5% vs. 0.8% p = 0.002) and in-hospital death (23.3% vs. 8.2%, p <0.001), but *de novo* AF was not an independent predictor of mortality. The following variables were independent predictors of in-hospital *de novo* AF after STEMI: stratified age (50 to 59 years: OR 2.16, 95% CI 1.11-2.73; 60 to 69 years: OR 1.77, 95% CI 1.07-2.96; 70 to 100 years: OR 3.98, 95% CI 2.60-6.26), Killip and Kimball score (B: OR 1.72 95% CI 1.19-2.46; C: OR 1.09, 95% CI 0.31-2.91, D: OR 2.48, 95% CI 1.60-3.78), tachycardia (OR 2.41, 95% CI 1.74-3.31) and LVEF <35% (OR 1.62, 95% CI 1.74-3.31). The area under the ROC curve (AUC ROC) of the model was 0.73; the sensitivity and specificity were 77% and 62%, respectively.
Conclusion: *De novo* AF was a relatively frequent complication. Factors such as age, heart rate, hemodynamic profile on admission and ventricular function were shown to be predictors of *de novo* AF after a myocardial infarction during hospitalization. However, *de novo* AF was not independently associated with in-hospital mortality.

Key words: Atrial fibrillation - ST-elevation myocardial infarction

RESUMEN

Introducción: La fibrilación auricular (FA) es la complicación arrítmica más frecuente en pacientes con síndrome coronario agudo (SCA), con una incidencia entre 2,3% y 21%.
Objetivos: Determinar la incidencia y predictores de FA *de novo* en pacientes con infarto agudo de miocardio con elevación del segmento ST (IAMCEST).
Material y métodos: Se analizó la base de datos del registro continuo ARGEN-IAM-ST. La estadística descriptiva fue la convencional. Para reducir la dimensionalidad e identificar aquellas variables asociadas con el desenlace de interés, se utilizaron algoritmos de *Machine Learning* y se realizó un análisis multivariable de regresión logística para identificar aquellos factores asociados a la presencia de FA *de novo*. Los mismos fueron incluidos en un modelo de clasificación final que fue evaluado por medio de curva ROC. Se consideró un valor de p <0,05 como estadísticamente significativo.
Resultados: Se incluyeron 7292 pacientes con IAMCEST. El 4,3% presentó FA *de novo* durante la internación. Este grupo era más añoso (67 vs. 60 años, p <0,001). Al ingreso hospitalario, presentaba mayor frecuencia cardíaca, un score de Killip y Kimball mayor

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y una menor fracción de eyección del ventrículo izquierdo (FEVI). Estos Pacientes tuvieron mayor incidencia de accidente cerebrovascular (2,5% vs. 0,8% p = 0,002) y muerte intrahospitalaria (23,3% vs. 8,2%, p <0,001), pero la FA *de novo* no fue predictor independiente de mortalidad. La variable edad estratificada (50 a 59 años: OR 2,16, IC 95% 1,11-2,73; 60 a 69 años: OR 1,77, IC 95% 1,07-2,96; 70 a 100 años: OR 3,98, IC 95% 2,60-6,26); el score Killip y Kimball (B: OR 1,72 IC 95% 1,19-2,46; C: OR 1,09, IC 95% 0,31-2,91, D: OR 2,48, IC 95% 1,60-3,78) la presencia de taquicardia (OR 2,41, IC95% 1,74-3,31) y una FEVI <35 % (OR 1,62, IC95% 1,74-3,31) fueron predictores independientes de FA *de novo* intrahospitalaria posterior a un IAMCEST. El modelo presentó un área bajo la curva ROC (ABC ROC) de 0,73, con sensibilidad y especificidad de 77 y 62 %, respectivamente.
Conclusiones: la FA *de novo* fue una complicación relativamente frecuente. Factores como la edad, frecuencia cardíaca, el perfil hemodinámico al ingreso y la función ventricular mostraron ser predictores de FA *de novo* post infarto en la internación. Sin embargo, ésta no se asoció de manera independiente con la mortalidad intrahospitalaria.

Palabras clave: Fibrilación auricular - Infarto de miocardio con elevación del segmento ST

INTRODUCTION

Atrial fibrillation (AF) is the most frequent sustained cardiac arrhythmia in adults, and its prevalence has been increasing over the past decades due to aging population and increased survival from other cardiovascular diseases. (1) It is associated with an increased risk of thromboembolic events, (2) cognitive impairment, (3) heart failure, hospitalizations, and death. (4)

In turn, it is the most frequent arrhythmic complication in patients with acute coronary syndrome (ACS), and its incidence ranges from 2.3% to 21%. (5) In Argentina, the incidence of *de novo* AF in this setting is 3.2%, as observed in the ARGEN-IAM-ST registry. (6) Over the last decades and with the advances in invasive and medical treatment, its incidence has decreased. (6) Several studies have evaluated the clinical characteristics of patients with *de novo* AF after ACS. The main predictors were advanced age, signs of heart failure, and tachycardia on hospital admission. These predictors have been maintained both in studies performed in the fibrinolytic era and in the present day, when percutaneous treatment is available. (7, 8)

In the general population and in patients with ACS, the presence of AF is associated with a worse prognosis. De novo AF in the setting of ACS is associated with increased morbidity and mortality. (9, 10) In turn, several observational studies have shown that patients with coexisting ACS and *de novo* AF are less likely to receive appropriate antithrombotic treatment. (11, 12) However, there is a lack of studies analyzing the predictors and prognosis of these patients in the setting of invasive and medical treatment, as recommended by the latest guidelines. This study aimed to evaluate the incidence of *de novo* AF during hospitalization for ST-elevation myocardial infarction (STEMI) and to determine the predictors associated with its development.

METHODS

Study design and population

This is an observational and retrospective study based on the analysis of the continuous registry of ST-segment elevation acute myocardial infarction (ARGEN-IAM-ST), which includes patients with STEMI from numerous centers in Argentina. Its protocol was previously published and has been active since 2015. (13,14) The protocol has been registered in ClinicalsTrials.gov under NCT 2458885. The cut-off date for the analysis of this work was May 2024.

Definitions and outcomes of interest

Our outcome of interest was *de novo* AF during hospitalization, defined as AF in patients who had an admission electrocardiogram (ECG) showing sinus rhythm and an episode of AF as a complication during their progress. This was modeled as a binary variable. We excluded from this definition those patients with a history of AF and atrial flutter.

Statistical analysis

Continuous variables are expressed as mean and standard deviation (SD) or median and interquartile range (IQR), according to their type of distribution. The variables of age and heart rate were analyzed by strata. Qualitative variables are expressed as absolute and relative frequencies. Qualitative variables were compared using the chi-square test or Fisher's exact test, while continuous variables with parametric and nonparametric distribution were compared using Student's t test and the Mann Whitney U test, respectively.

To reduce dimensionality and identify those variables associated with our outcome of interest, the Boruta Machine Learning algorithm was used. (15) To ensure that variable selection was stable and reproducible, the algorithm performed up to 50 iterations which allowed a robust assessment of the importance of each predictor in *de novo* AF ranking. In addition, its performance was monitored during the process to verify consistency in feature selection. Multivariate analysis using logistic regression was performed with the most important variables to identify the factors independently associated with *de novo* AF. The models were trained and evaluated on two different databases randomly generated from the general database. The performance of the models and their discrimination ability was evaluated through the generation of receiver operating characteristic (ROC) curves. Since the aim of the model was to maximize sensitivity to identify the greatest number of cases of *de novo* AF, the optimal cut-off point was selected from the ROC curve with the highest possible sensitivity criterion, while maintaining clinically acceptable specificity. The Hosmer Lemeshow test was used to evaluate the goodness of fit of the model. The association between the predictors and the incidence of events was expressed as odds ratio (OR) with their 95% confidence intervals (CI). In addition, a multivariate model was performed to explore *de novo* AF as an independent predictor of mortality. All tests were two-tailed and statistical significance was set at a p-value <0.05.

The analysis was performed with R Studio, version 1.4.1106 (The R Foundation for Statistical Computing, Vienna, Austria).

Ethical considerations

The ethics committee of the Argentine Society of Cardiology approved the protocol of the Argen IAM-ST registry.

RESULTS

Baseline characteristics of the population

We included a total of 7292 patients with STEMI and evidence of sinus rhythm on admission ECG , of which 79% were male, and had a median (IQR) age of 61 (53-69) years. Table 1 shows the baseline characteristics.

We identified that 4.3% of the sample patients had *de novo* AF during hospitalization. These patients were older than those with no *de novo* AF (median age 67 vs. 60 years; p <0.001). We found no differences between the groups related to body mass index (BMI), diabetes mellitus and dyslipidemia. However, 53.1% had arterial hypertension (HT), and the prevalence was higher in the group of patients who developed AF during hospitalization (65.7% vs. 52.5%; p <0.001). In turn, the history of coronary artery disease –which was present in 12.3% of the total sample– was also more frequent in the group with *de novo* AF (16% vs. 12.1%; p = 0.047).

Regarding reperfusion strategies in all patients, primary angioplasty was performed in 91%, a pharmacoinvasive strategy in 5%, rescue angioplasty in 2.8%, and elective angioplasty in 1.1%, with no significant differences between the study groups. However, multi-vessel angioplasty was performed in the initial procedure in a higher proportion of patients who developed AF during hospitalization. There were no significant differences in the treatment of the culprit vessel for AMI.

Regarding treatment with beta-blockers and angiotensin-converting enzyme inhibitors on admission, we found a lower use in patients with *de novo* AF, that is, 37.7% vs 50.5% (p = 0.001) and 40.6% vs.45.6% (p =0.090), respectively.

On hospital admission, those patients who developed AF had a higher heart rate (86 bpm vs. 80 bpm; p <0.001). Regarding laboratory tests, they had higher glycemia values, with a median (IQR) of 153 mg/dl (124-212) vs. 134 mg/dL (113-177), p <0.001, and higher creatinine values: 1.08 mg/dL (0.90-1.40) vs. 0.97 mg/dL (0.8-1.17), p <0.001.

This group of patients also had longer total ischemia time (medians 289 min vs. 252 min; p = 0.019), a more severe Killip and Kimball score (p <0.001) and lower left ventricular ejection fraction (LVEF) (p <0.001).

In-hospital events

The presence of *de novo* AF was associated with a higher incidence of ischemic stroke (2.5% vs. 0.8%; p = 0.002) and more days of hospitalization (medians 6 vs. 4 days; p <0.001). In-hospital all-cause death was also higher in the *de novo* AF group (23.3% vs. 8.2%; p <0.001) (Table 2).

Selection of important variables

Using the Boruta algorithm, an automated selection was performed to identify the variables with the greatest importance in the prediction of *de novo* AF. In the analysis, the Killip and Kimball, heart rate and LVEF variables were identified as the most important, followed by gender, age, dyslipidemia, and creatinine. Figure 1 shows the means of importance of each variable in the ranking. Subsequently, these variables were included in the multivariate logistic regression model to evaluate their association with the outcome.

Multivariate analysis: Independent predictors of *de novo* AF

The greatest weight variables associated with *de novo* AF were included in a multivariate logistic regression model. The stratified age (50 to 59 years, 60 to 69 years, and 70 to 100 years) was independently associated with the incidence of *de novo* AF (OR 1.72, 95% CI 1.11-2.73; OR 1.77, 95% CI 1.07-2.96; OR 3.98, 95% CI 2.60-6.25, respectively). Clinical presentation according to Killip and Kimball score (B: OR 1.72, 95% CI 1.19-2.46; C: OR 1.09, 95% CI 0.315-2.90; D: OR 2.48, 95% CI 1.60-3.78), tachycardia (OR 2.41, 95% CI 1.74-3.31) and impaired LVEF (<35%) (OR 1.62, 95% CI 1.04-2.50) were also independent predictors (Figure 2). To evaluate the performance of the model, a ROC curve was constructed and the area under the curve (AUC) was 0.733 (95% CI 0.698-0.769). The optimal cut-off point was determined at 0.10 to maximize sensitivity. According to this threshold, the model correctly identified 77% of patients with *de novo* AF (sensitivity) and 62% of patients without *de novo* AF (specificity). This cut-off point represents the threshold where the balance between sensitivity and specificity is clinically most appropriate for the detection of *de novo* AF (Figure 3). The goodness of fit of the model, assesed by the Hosmer-Lemeshow test, was good (χ^2 = 5.33, p = 0.618).

Multivariate analysis: *de novo* AF as an independent predictor of mortality

De novo AF was included with the main variables related to in-hospital mortality in a multivariate model. We observed that *de novo* AF did not behave as an independent predictor of in-hospital mortality (OR 0.79, 95% CI 0.41-1.50) (Figure 4).

DISCUSSION

We present data on the incidence of *de novo* AF during hospitalization for STEMI from the ARGEN-IAM-ST registry. On this occasion, cases with AF on admission ECG or with history of AF were excluded in order to evaluate the consequences of this event after AMI. The incidence of *de novo* AF was 4.3%, and the findings suggest an association with a greater number of in-hospital events and a longer hospital stay. In addi-

Table 1. Baseline clinical characteristics of participants with and without *de novo* AF

	Global	Without *de novo* AF	With de *novo* AF	p
n	7292	6974	7292	
Male gender, n (%)	5754 (79)	5512 (79)	5754 (79)	0.705
Age, years, median (IQR)	61 (53-69]	60 (53-68)	61 (53-69]	<0.001
BMI, kg/m^2, median (IQR)	27.65	27.68	27.65	0.041
	(25.47-30.61)	(25.51-30.76)	(25.47-30.61)	
DM, n (%)	1980 (27.2)	1900 (27.2)	1980 (27.2)	0.451
Smoking, n (%)	591 (8.1)	563 (8.1)	591 (8.1)	0.717
DLP, n (%)	2662 (36.5)	2553 (36.6)	2662 (36.5)	0.433
HT, n (%)	3870 (53.1)	3661 (52.5)	3870 (53.1)	<0.001
Previous coronary artery disease, n (%)	897 (12.3)	846 (12.1)	897 (12.3)	0.047
Beta-blockers , n (%)	3635 (50.0)	3519 (50.5)	3635 (50.0)	<0.001
ACEIs, n (%)	3301 (45.4)	3178 (45.6)	3301 (45.4)	0.090
Glycemia, mg/dL, median (IQR)	135 (113-179)	134 (113-177)	135 (113-179)	<0.001
Creatinine, mg/dL, median (IQR)	0.97 (0.80-1.18)	0.97 (0.80-1.17)	0.97 (0.80-1.18)	<0.001
Reason for PCI, n (%)				0.949
Primary	5003 (91.1)	4887 (70.1)	5003 (91.1)	
Pharmacoinvasive	273 (5.0)	646 (9.3)	273 (5.0)	
Rescue	154 (2.8)	976 (14.0)	154 (2.8)	
Elective	59 (1.1)	465 (6.7)	59 (1.1)	
SBP, mm Hg, mean (SD)	131 (29)	132 (29)	131 (29)	<0.001
HR, bpm, mean (SD)	80 (19)	80 (18)	80 (19)	<0.001
Killip and Kimball, n (%)				<0.001
A	5485 (77.0)	5456 (78.2)	5485 (77.0)	
B	1024 (14.4)	955 (13.7)	1024 (14.4)	
C	100 (1.4)	95 (1.4)	100 (1.4)	
D	516 (7.2)	468 (6.7)	516 (7.2)	
Door-to-balloon time, min, median (IQR)	84 (47-147]	91(50. 175]	84 (47-147]	0.439
Time window, min, median (IQR)	230 (135-440)	252.50 (146- 510)	230 (135-440)	0.019
Multi-vessel PCI in initial procedure, n (%)	351 (6.4)	360 (5.2)	351 (6.4)	0.026
LVSF, n (%)				<0.001
Normal	2397 (37.4)	2660 (38.1)	2397 (37.4)	
Mild impairment	1842 (28.7)	1994 (28.6)	1842 (28.7)	
Moderate impairment	1397 (21.8)	1466 (21.0)	1397 (21.8)	
Severe impairment	774 (12.1)	854 (12.2)	774 (12.1)	

ACEIs: angiotensin-converting enzyme inhibitors; AF: atrial fibrillation; BMI: body mass index; bpm: beats per minute; DLP: dyslipidemia; DM: diabetes mellitus; HR: heart rate; HT: hypertension; IQR: interquartile range; LVSF: left ventricular systolic function; PCI: percutaneous coronary intervention;SBP: systolic blood pressure; SD: standard deviation

tion, certain factors such as age, heart failure assessed by the Killip and Kimball score, tachycardia, and impaired LVEF were shown to be independent predictors of *de novo* AF during hospitalization. These predictors were included in a ranking model to predict *de novo* AF, which showed an AUC of 0.733 (95% CI 0.698-0.769).

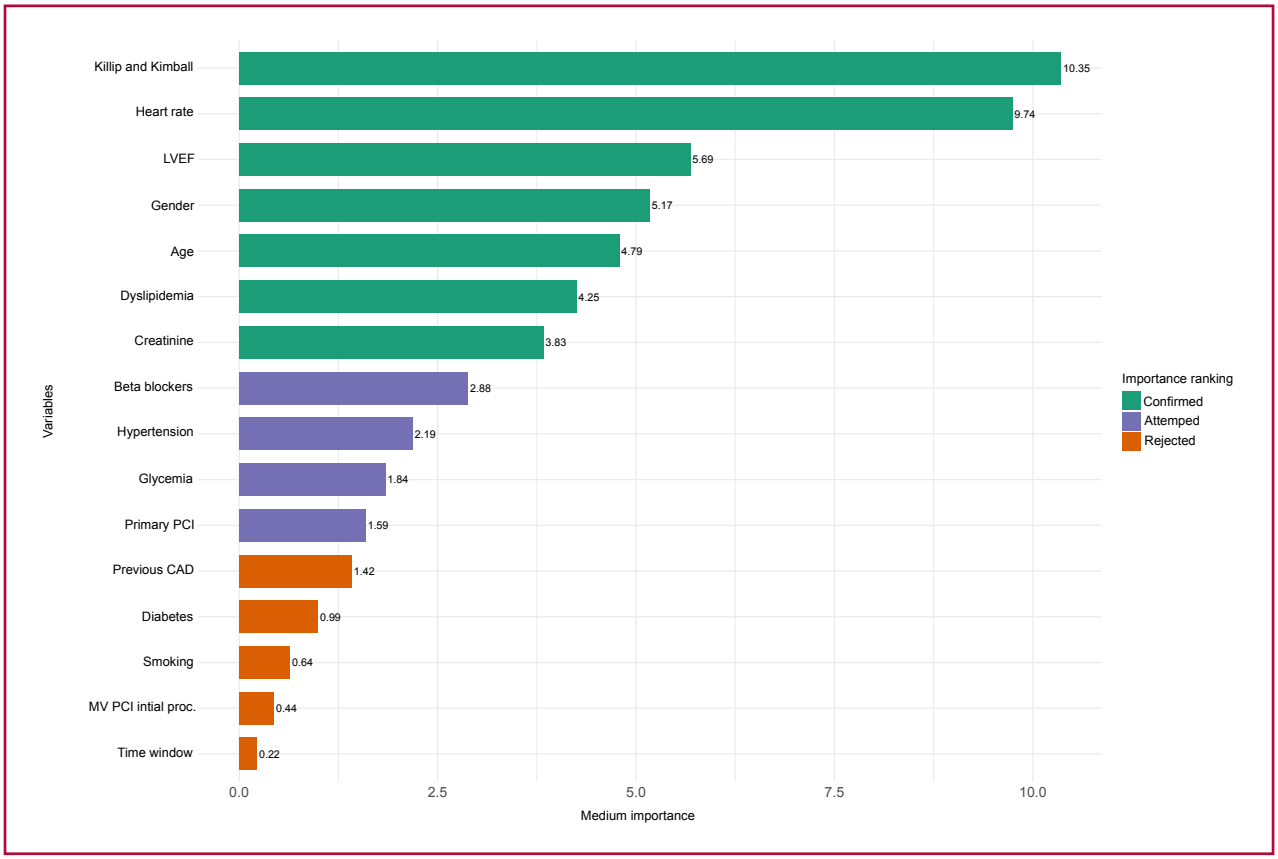
AF and ACS are two common heart diseases and, over the years, multiple studies have been performed to analyze the relationship between them. The risk of *de novo* AF increases by 60-77% in patients with AMI. (16) In the fibrinolytic era, the randomized GUSTO-I (1997) and GUSTO-III (2000) studies compared different fibrinolytic regimens in patients with STEMI, and highlighted a 7.9% and 6.5% incidence of *de novo* AF after ACS, respectively. (8, 17) In addition, OACIS,

Table 2. In-hospital events of participants with and without *de novo* AF

	Global	Without *de novo* AF	With de *novo* AF	p
n	7292	6974	318	
Reinfarction, n (%)	123 (1.7)	113 (1.6)	10 (3.1)	0.066
Stroke, n (%)	61 (0.8)	53 (0.8)	8 (2.5)	0.002
Cardiogenic shock, n (%)	682 (9.4)	576 (8.3)	106 (33.3)	<0.001
HF, n (%)	967 (13.3)	818 (11.7)	149 (46.9)	<0.001
In-hospital death, n (%)	591 (8.1)	563 (8.1)	28 (8.8)	0.717
LOS, days, median (IQR)	4 (3-6)	4 [3-6]	6 [4-11]	<0.001

AF, atrial fibrillation; HF, heart failure; IQR, interquartile range; LOS: length of stay

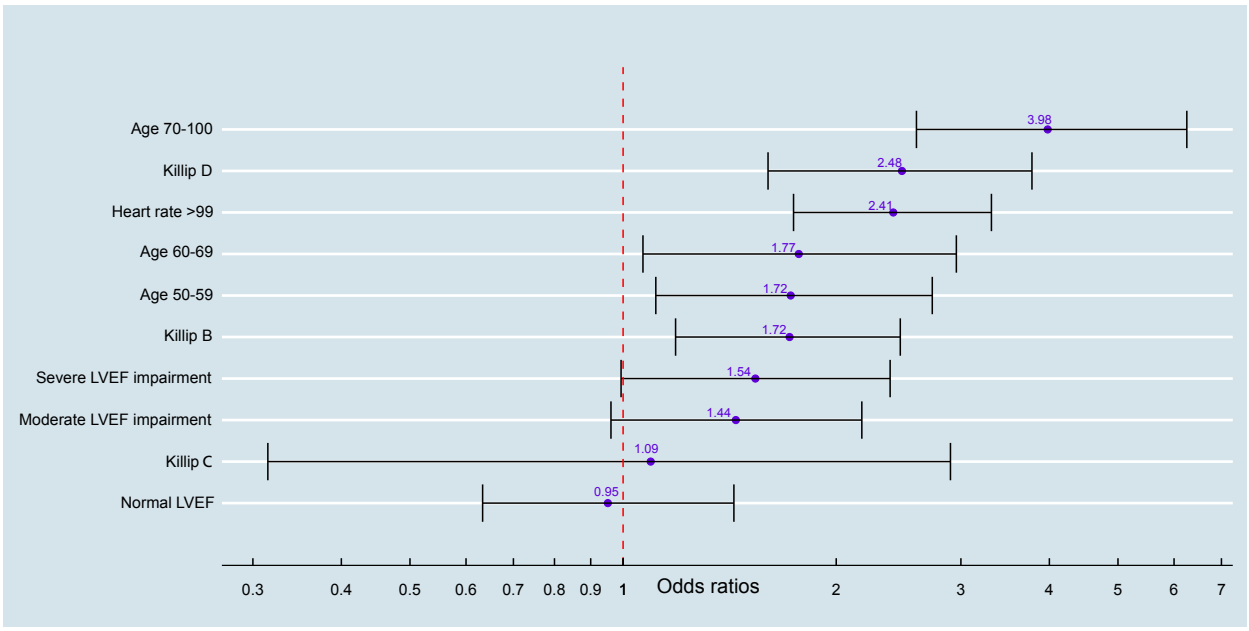
Fig. 1. Variables with the greatest importance in the prediction of *de novo* AF



AF: atrial fibrillation; CAD: coronary artery disease; LVEF: left ventricular ejection fraction; MV: multiple vessels; PCI: percutaneous coronary intervention; proc: procedure; time window: time in minutes from symptom onset to start of infusion in the case of fibrinolytics or to balloon inflation in the case of PCI

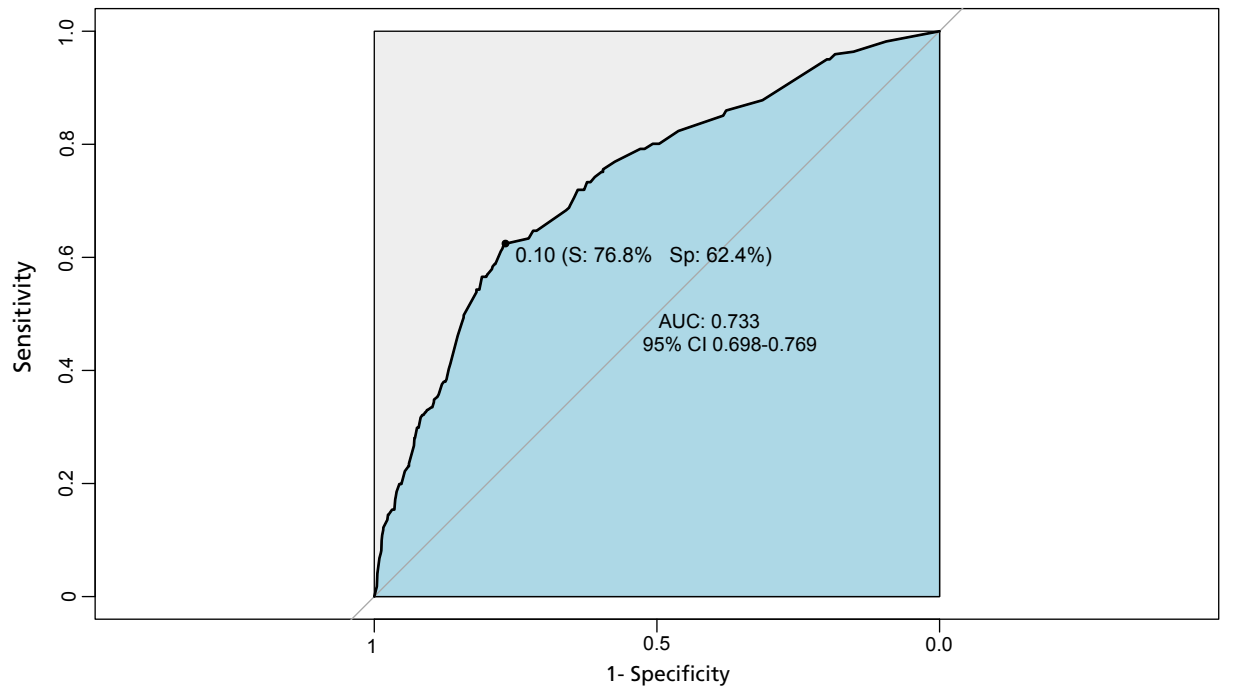
a prospective observational study published in 2003, analyzed patients with AMI (with and without ST-segment elevation) who underwent coronary angioplasty within 24 hours and found that the incidence of *de novo* AF was 7.7%. (18) Regarding national results, the incidence of in-hospital *de novo* AF in patients with AMI and unstable angina was 4.3% and 7.7%, respectively, according to data from the Buenos Aires I registry, which included patients with non-ST-elevation acute coronary syndrome (NSTE-ACS). (19) Similarly, a previous publication from the ARGEN-IAM-ST registry showed that the incidence of *de novo* AF was 3.2%, and the predictor factors were advanced age, history of HT and previous coronary artery disease. (6) There are definitely no randomized studies comparing the incidence of *de novo* AF in patients with STEMI treated with fibrinolytics versus primary angioplasty, and the differences in the populations and methods used in the published studies preclude a correct assessment of the incidence of this complica-

Fig. 2. Predictors of *de novo* AF



AF: atrial fibrillation; LVEF: left ventricular ejection fraction

Fig. 3. ROC curve of the *de novo* AF predictive model

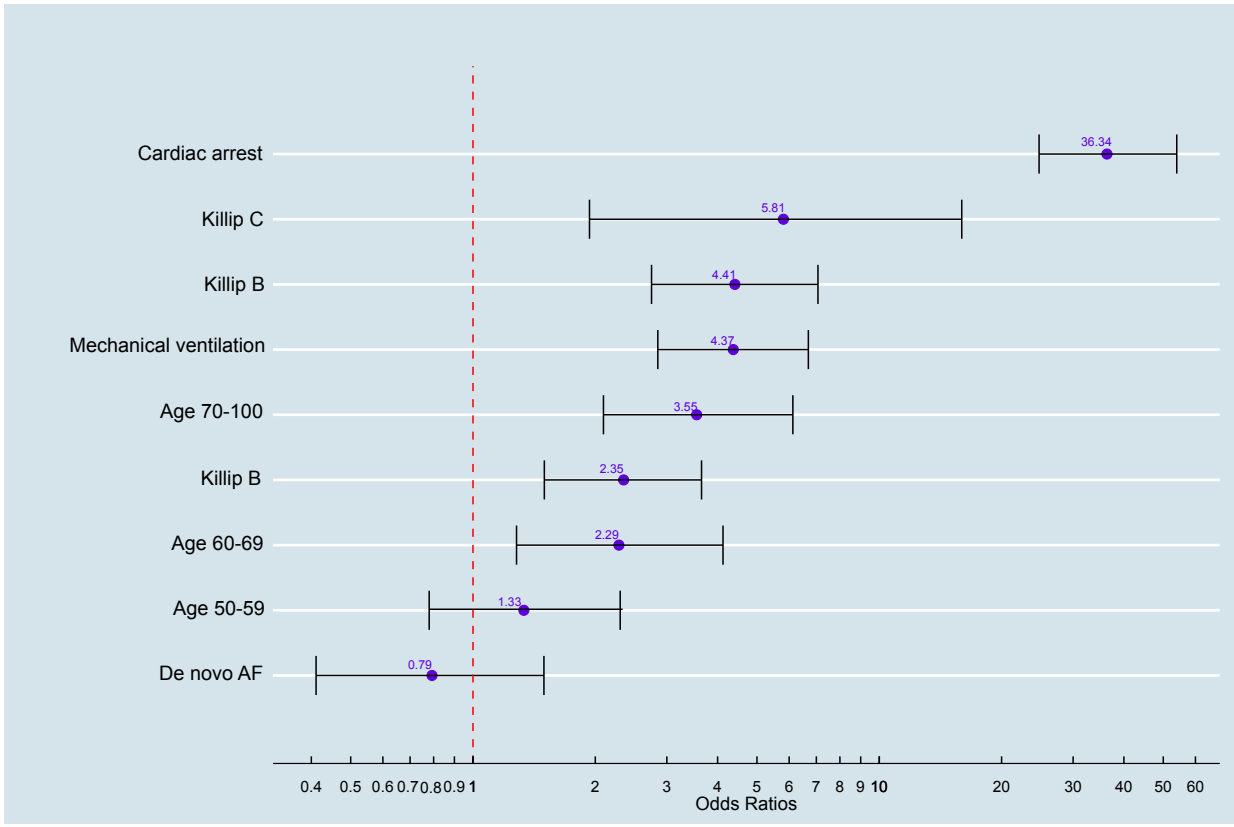


AF: atrial fibrillation; AUC: area under curve; ROC: receiver operating characteristic; S: sensitivity; Sp: specificity

tion and whether the type of revascularization has an impact on it.

In our cohort, age acted as an independent predictor of *de novo* AF, with the higher impact observed specifically between the ages of 70 and 100 years, with an OR of 3.98. As AF outside the setting of ACS, age was closely related to the incidence of this arrhythmia. In one of the largest studies including only patients aged ≥65 years from the Cooperative Cardiovascular Project database published in 2000, (11) the rate of *de novo* AF after ACS was 22%, significantly higher than in studies including patients of all ages. In addi-

Fig. 4. Predictors of in-hospital mortality



AF: atrial fibrillation

tion, the 2009 review by Schmitt et al., found that all studies published between 1992 and 2007 identified older age as an independent predictor of *de novo* AF after ACS. (20)

Although AF is the most frequent supraventricular arrhythmia in the general population, its incidence is significantly higher in patients with heart failure (HF). These two conditions are closely related to each other, and each perpetuates the presence of the other. (21) Our analysis showed that HF, as assessed by the Killip and Kimball score, was independently associated with *de novo* AF, as showed in the above mentioned GUSTO-I and III studies. Of note, a subanalysis of the international GRACE study, which included more than 21 000 patients with ACS and classified them according to the presence of *de novo* AF, previous AF, and no AF, identified a Killip score ≥2 as an independent predictor of *de novo* AF. (22) Similarly, tachycardia, probably secondary to HF, was also a predictor of *de novo* AF in our study and in the previously mentioned study. These results translate the impact of hemodynamic status within the pathophysiological mechanisms of AF in the setting of ACS and indicate that patients with altered hemodynamic status (HF, tachycardia, and/or hypotension) are at higher risk of AF.

In parallel, severely impaired LVEF (<35%) also functioned as an independent predictor of *de novo* AF in our analysis. Although the association between ventricular dysfunction and clinical presentation on admission (as reflected by the Killip and Kimball score and heart rate) is clear, other studies have not shown this variable to be an independent predictor of *de novo* AF.

LIMITATIONS

The registry ARGEN-IAM-ST is a voluntary participation registry with no audit strategy. Although a multivariate regression analysis was performed, we cannot completely exclude the possibility that unconsidered variables may have altered the results. Furthermore, although this is a multicenter study, it only represents the reality of the participating centers. Finally, it is not possible to determine when AF occurred during hospitalization, and thus the temporal relationship cannot be studied.

CONCLUSION

In this cohort of patients from the ARGEN-IAM-ST registry, *de novo* AF was a relatively frequent complication. Factors such as age, heart rate, hemodynamic profile on admission, and ventricular function were

shown to be predictors of *de novo* AF after an AMI during hospitalization. However, *de novo* AF was not independently associated with in-hospital mortality.

Conflicts of interest

None declared.

(See authors' conflict of interests forms on the web).

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