ORIGINAL ARTICLE

De Novo Atrial Fibrillation in Patients with Non-ST-Segment Elevation Acute Coronary Syndrome. Data from the Buenos Aires I Registry

Fibrilación auricular de novo en pacientes con síndrome coronario agudo sin elevación del segmento ST. Datos del Registro Buenos Aires I

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ABSTRACT

Background: Atrial fibrillation (AF) is the most prevalent cardiac arrhythmia worldwide and has a close correlation with acute coronary syndromes. The aim of our study is to describe the incidence, predisposing factors and outcome of patients with de novo AF after an acute coronary syndrome in a population representative of our environment.
Methods: We conducted a sub-analysis of the BUENOS AIRES I registry, which included 1110 patients with non- ST-segment elevation acute coronary syndrome (NSTE-ACS) followed-up at 6 months.
Results: The incidence of de novo AF was 7.7%. The independent predictors of de novo AF were age (OR, 1.04; 95% CI, 1.02-1.08; p = 0.001), initial presentation as MI (OR, 2.35; 95% CI, 1.20-4.57; p = 0.012) and requirement of myocardial revascularization surgery (OR 6.86; 95% CI 3.95-11.89; p< 0.001). Patients who developed AF had greater all-cause mortality, cardiovascular mortality and bleeding events ≥ BARC type 2. The development of de novo AF after NSTE-ACS was identified as an independent predictor of cardiovascular mortality (OR, 3.67; 95% CI 1.25-10.76; p = 0.018) and of bleeding events ≥ BARC type 2 (OR, 3.024; 95% CI, 1.49-6.11; p = 0.002).
Conclusions: This prespecified sub-analysis of the BUENOS AIRES I registry demonstrated a significant incidence of de novo AF in the setting of a NSTE-ACS, associated with elderly patients, greater acute myocardial structural damage and need for myocardial revascularization surgery, with worse outcome in terms of adverse clinical events at mid-term follow-up.

Key words: Atrial Fibrillation – Acute Coronary Syndrome – Mortality - Registries

RESUMEN

Introducción: La fibrilación auricular (FA) es la arritmia con mayor incidencia a nivel mundial y tiene una clara asociación con los síndromes coronarios agudos. El propósito de nuestro trabajo es describir la incidencia, los factores predisponentes y el pronóstico de pacientes con FA de novo luego de un síndrome coronario agudo, en una población representativa de nuestro medio.
Material y métodos: Se realizó un subanálisis del registro BUENOS AIRES I, el cual incluyó 1110 pacientes con síndrome coronario agudo sin elevación del ST (SCASEST), con un seguimiento a 6 meses.
Resultados: Se evidenció una incidencia del 7,7% de FA de novo y se identificaron como factores predictores independientes de su desarrollo la edad (OR 1,04; IC95% 1,02-1,08; p=0,001), la presentación inicial con infarto agudo de miocardio (OR 2,35; IC95% 1,20-4,57; p=0,012) y la necesidad de revascularización quirúrgica (OR 6,86; IC95% 3,95-11,89; p <0,001). Los pacientes que desarrollaron FA presentaron mayor mortalidad por todas las causas, mayor mortalidad cardiovascular y eventos de sangrado BARC≥2. Se identificó a la FA de novo post-SCASEST como un factor predictor independiente de mortalidad cardiovascular (OR 3,67; IC95% 1,25-10,76; p=0,018) y sangrado a 6 meses BARC≥2 (OR 3,024; IC95% 1,49-6,11; p=0,002).
Conclusiones: Este subanálisis preespecificado del registro BUENOS AIRES I demostró una incidencia significativa de FA de novo en el contexto de un SCASEST, vinculada a una mayor edad, mayor daño estructural cardíaco agudo y requerimiento de cirugía de revascularización, y con una peor evolución en términos de eventos clínicos adversos en el seguimiento a mediano plazo.

Palabras clave: Fibrilación auricular – Sindromes coronarios agudos – Mortalidad - Registros

INTRODUCTION

Atrial fibrillation (AF) is the most prevalent cardiac arrhythmia worldwide and has a close correlation with atherosclerotic coronary disease. (1-3) In this setting, acute coronary syndromes (ACS) represent a propitious scenario for the development of AF, according to the mechanisms involved in its pathophysiology, including myocardial ischemia with possible coagulative necrosis, heart failure and concomitant release of catecholamines. (4)

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The development of this cardiac arrhythmia generally requires antithrombotic therapy to reduce the risk of thromboembolic events, exposing patients to a greater risk of bleeding events during follow-up. (5)

The aim of the present study was to evaluate the incidence of de novo AF and its implication in terms of mid-term clinical events in patients with non-ST-segment elevation acute coronary syndrome (NSTE-ACS).

OBJECTIVES

Primary objective

To describe the incidence and predisposing factors for the development of AF in patients with NSTE-ACS included in the BUENOS AIRES I registry. (6)

Co-primary objective

To analyze the impact of de novo AF in patients with non-STE-ACS included in the BUENOS AIRES I registry in terms of cardiovascular (CV) mortality and bleeding events 6 months after the index coronary event.

METHODS

This study is a prespecified sub-analysis of the prospective BUENOS AIRES I registry. The aim of this registry was to describe the treatment of NSTE-ACS in high complexity centers of the city of Buenos Aires (CABA) and province of Buenos Aires (PBA) and analyze the in-hospital and out-of-hospital outcome according to the therapeutic strategy implemented.

Patients > 18 years with a primary NSTE-ACS were included in the registry. The only exclusion criterion was impossibility to perform the prespecified follow-up at 6 moths after the index coronary event.

For more information, we suggest accessing the BUENOS AIRES I registry, which is published in the Argentine Journal of Cardiology. (6)

Definition of events

- De novo AF: episode of AF lasting > 6 seconds in patients without history of AF after the index coronary event and diagnosed during hospitalization or out-of-hospital follow-up by telemetry, electrocardiogram or Holter monitoring.
- Non-ST-segment elevation myocardial infarction (NSTEMI): defined according to the Fourth Universal Definition of Myocardial Infarction. (7)
- Cardiovascular mortality: mortality due to MI, stroke, ventricular arrhythmia or sudden unexplained death.
- Major adverse cardiovascular events (MACE): composite of cardiovascular mortality, NSTE-ACS, stroke and transient ischemic accident (TIA).
- Bleeding events: defined according to the classification of the Bleeding Academic Research Consortium (BARC). (8)

Participating centers

The 21 participating centers of CABA and PBA included in the BUENOS AIRES I registry were affiliated to the Argentine Society of Cardiology (SAC) and fulfilled the following requirements: they had coronary care unit, 24-hour catheterization lab availability and cardiovascular surgery capabilities.

Follow-up

Follow-up was performed at 6 months after hospital discharge due to the index coronary event. Data were obtained from the medical records (MR) of the participating centers of the BUENOS AIRES I registry and were complemented with the information obtained by the investigators of the present study after direct telephone contact with the patients.

Statistical analysis

All the statistical calculations were performed using IBM SPSS 25.0 software package (for Mac iOS). Continuous variables were expressed as mean ± standard deviation, or median and interquartile range, according to their distribution. Normality of distribution of variables was assessed using the Kolmogorov-Smirnov test or the Shapiro-Wilk test, as applicable. The chi square test or Fisher's exact test were used to compare the categorical variables, and continuous variables were analyzed using the Student's t test or the Mann-Whitney test according to their distribution. A linear univariate analysis was performed to identify predictors associated with the development of de novo AF and clinical events of interest. Event-free survival was evaluated with the log rank test and was represented with the Kaplan- Meier curves.

A type I error < 5% (two-tailed p value < 0.05) was considered statistically significant.

Ethical considerations

All patients gave their informed consent before participating in the study. Patients were clearly informed about the aim of the study and the mechanisms used to protect their identity to ensure the confidentiality of the data provided. They were informed that their participation was voluntary, that they could refuse to participate in the study without any consequences or differences in their medical care, and that they had the right to withdraw their consent at any time.

During the evaluation process for inclusion in the study, the investigator provided verbal explanation to the patient of the information included in the informed consent and answered all his/her questions regarding the study. The consent was submitted for institutional review board approval, which is under the regulations of the Central Review Board.

The investigators implemented measures to protect the confidentiality of all the information according to the Argentine personal data protection law 25 326, so the identity of the patients and all their personal data would remain anonymous, and that only the researchers and the members of the teaching and research and ethics committee would have access to this data, if required.

The study was conducted following national ethical standards (Law 3301 of the city of Buenos Aires, National Law for Good Clinical Practice in Research on Human Subjects, and the Declaration of Helsinki, among others).

RESULTS

The BUENOS AIRES I registry included 1110 NSTE-ACS patients; 6-month follow-up was completed by 88.3% (n = 971) of the initial cohort.

Mean age of the sample was 65.4 ± 11.47 years and 77.2% were men. The prevalence of hypertension was 74.6%; 27.6% of the patients had diabetes mellitus, 60.1% had dyslipidemia, 21% had chronic kidney disease and 21.8% were active smokers (Table 1).

A history of AF was present in 6.8% of the patients included. On admission, the mean GRACE score was

133.8 ± 52.09 and the mean CRUSADE score was 24.31 ± 13.99. Of the total NSTE-ACS, 62.6% was classified as NSTEMI and 37.4% as unstable angina. The hemodynamic state was classified as Killip and Kimball (KK) class A in 93.3% of patients, B in 4.9%, C in 1.7% and D in 0.1% (Table 1).

The incidence of de novo AF at 6 months of the index ACS was 7.7% (n = 68). De novo AF occurred in 69.1% (n = 47) during hospitalization, while the rest of the cases developed after hospital discharge (Figure 1).

Patients who developed de novo AF were older (70.63 ± 10.01 vs. 64.36 ± 11.34 years; p < 0.001) and had greater prevalence of chronic kidney disease (36.8% vs. 18-5%; p < 0.001) and of peripheral vascular disease (13.2% vs. 5.8%; p = 0.015). In these patients, MI was the most common presentation (82.4% vs. 59.0%; p < 0.001) compared with patients who did not develop or had no history of AF (Table 1).

On multivariate analysis, the independent predictors of de novo AF were age (OR, 1.04; 95% CI, 1.02-1.08; p = 0.001), presentation as MI (OR, 2.35; 95% CI, 1.20-4.57; p = 0.012) and requirement of coronary artery bypass grafting (CABG) (OR 6.86; 95% CI 3.95-11.89; P < 0.001).

When the treatment prescribed was analyzed, the therapeutic regimens used were significantly heterogeneous: only 31.9% (n = 15) of those patients who developed de novo AF during the index hospitalization were discharged on anticoagulants, while 50% only received indication of antiplatelet treatment. Conversely, in the subgroup of patients with a history of AF before the index coronary event, 70.6% (n = 75) had indication of anticoagulants (p < 0.001).

Six months after the index coronary event, the subgroup of patients with de novo AF presented greater all-cause mortality (12.7% vs. 2.2%; p < 0.001), greater CV mortality (11.1% vs. 0.9%; p < 0,001), greater incidence of bleeding events ≥ BARC type 2 (38.5% vs. 9.3%; P < 0.001) and more episodes of decompensated heart failure (30.8% vs. 7.8%; p < 0.001) compared with patients without de novo AF, without significant differences in terms of MACE, MI and stroke/TIA (Table 2). On multivariate analysis, the development of de novo AF after NSTE-ACS was identified as an independent predictor of CV mortality (OR, 3.67; 95% CI 1.25-10.76; p = 0.018) and of bleeding events ≥ BARC type 2 (OR, 3.02; 95% CI, 1.49-6.11; p = 0.002) (Figures 2-4).

DISCUSSION

The present prespecified sub-analysis of the BUENOS AIRES I registry determined the incidence and predictors of de novo AF and the clinical outcome within a real-world group of patients with NSTE-ACS. Interestingly, the incidence of de novo AF at 6 months after

Table 1. Baseline characteristics

Variables	Total (n = 1100)	Without AF (n = 817; 92.3%)	With AF (n = 68; 7.7%)	p*
Age, years mean ± SD	65.45 ± 11.47	**64.36 ± 11.34**	**70.63 ± 10.01**	**<0.001**
Male gender, n (%)	849 (77.2)	625 (76.5)	53 (77.9)	0.787
Hypertension, n (%)	821 (74.6)	589 (72.1)	55 (80.9)	0.118
Diabetes mellitus, n (%)	304 (27.6)	218 (26.7)	16 (23.5)	0.571
Active smoking, n (%)	240 (21.8)	175 (21.4)	11 (16.2)	0.308
Dyslipidemia, n (%)	661 (60.1)	498 (61.0)	41 (60.3)	0.915
CKD, n/tot (%)	223/1060 (21.0)	**146/790 (18.5)**	**25 (36.8)**	**<0.001**
History of cardiovascular diseases				
MI, n (%)	347 (31.5)	240 (29.4)	23 (33.8)	0.441
PCI, n (%)	361 (32.8)	272 (33.3)	18 (26.5)	0.25
CABG, n (%)	121 (11.0)	84 (10.3)	8 (11.8)	0.7
Stroke/TIA, n (%)	63 (5.7)	39 (4.8)	2 (2.9)	0.49
PVD, n (%)	70 (6.4)	**47 (5.8)**	**9 (13.2)**	**0.015**
COPD, n (%)	43 (3.9)	34 (4.2)	0 (0.0)	0.086
Index cardiovascular event				
NSTEMI, n (%)	689 (62.6)	**482 (59.0)**	**56 (82.4)**	**<0.001**
UA, n (%)	411 (37.4)	**335 (41.0)**	**12 (17.6)**	**<0.001**
GRACE, m ± SD	133.83 ± 52.09	**128.05 ± 49.29**	**169.18 ± 54.89**	**<0.001**
CRUSADE, m ± SD	24.31 ± 13.99	**23.17 ± 13.14**	**30.21 ± 15.66**	**<0.001**

* P value for difference between with and without AF at 6 months.
Abbreviations: m= mean; SD = standard deviation; CKD = chronic kidney disease (creatinine clearance <60 ml/min/m2); MI = myocardial infarction; PCI = percutaneous coronary intervention; CABG = coronary artery bypass grafting; TIA = transient ischemic attack; PVD = peripheral vascular disease; COPD = chronic obstructive pulmonary disease; NSTEMI = non-ST-elevation myocardial infarction; UA = unstable angina.

the index NSTE-ACS was 7.7%, which is consistent with the findings of other studies reporting incidences of 6.4-13% and showed a close association with the therapeutic strategy implemented and the severity of the index coronary event. (9,10) It is worth highlighting that the accuracy of the reported data may be questioned, in the context of an increased, and probably overestimated, prevalence of AF, underdiagnosed before the NSTE-ACS.

Most patients presented de novo AF during in-hospital stay, which could be caused by several mechanisms known as triggers of AF, such as ischemia of atrial tissue and cardiac conduction system, concomitant autonomic nervous system dysfunction, inflammation and neurohumoral activation, among others. (4) Nevertheless, it is interesting to note that more than 30% of the patients developed AF during the out-of-hospital period, which emphasizes the need for screening for this arrhythmia in high-risk patients during follow-up.

Several studies have identified AF predictors in the setting of ACS. (10) In the cohort analyzed in the present study, de novo AF was associated with elderly patients, clinical presentation as MI and requirement for CABG, which could be interpreted as surrogates of greater severity in the presentation of the index coro-

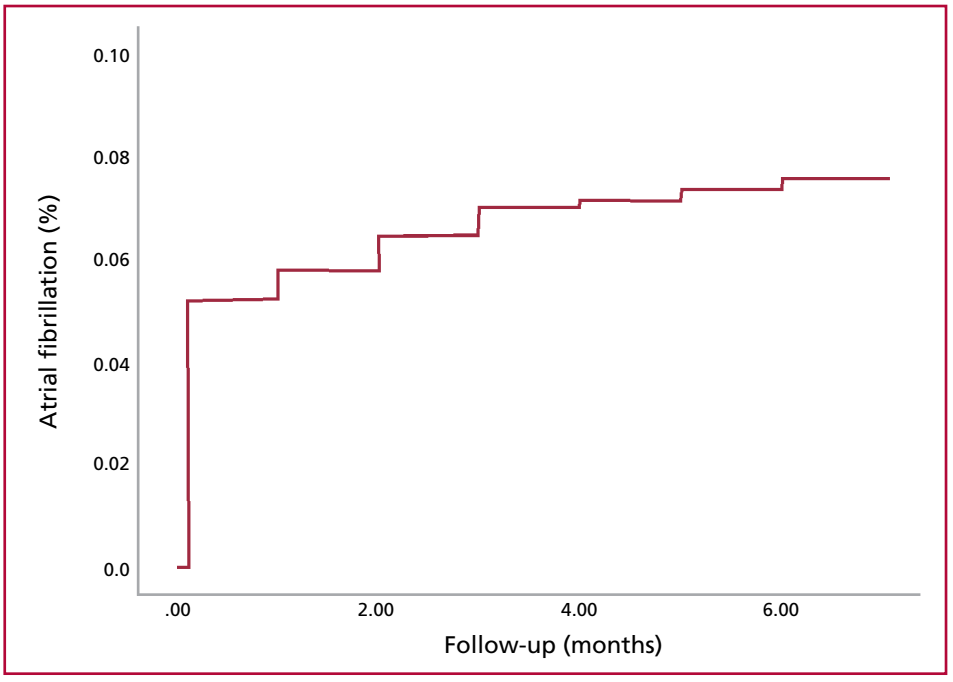
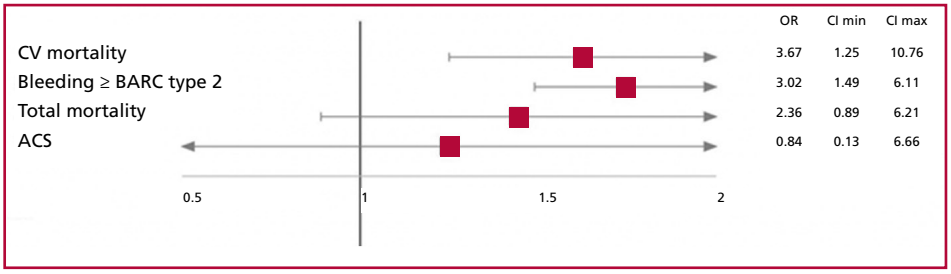


Fig. 1. Cumulative incidence of atrial fibrillation at 6 months of follow-up

Table 2. Cardiovascular events at 6 months

Variables	Without AF (n = 817; 92.3%)	With AF (n = 68; 7.7%)	p*
Follow-up. n/total (%)	**817/817 (100.0)**	**63/68 (92.6)**	**<0.001**
MACE. n/tot (%)	96/817 (11.8)	11/63 (17.5)	0.181
Mortality. n/tot (%)	**18/817 (2.2)**	**8/63 (12.7)**	**<0.001**
CV mortality. n/tot (%)	**7/817 (0.9)**	**7/63 (11.1)**	**<0.001**
ACS, n/tot (%)	80/817 (9.8)	3/59 (5.1)	0.233
PCI. n/tot (%)	43/817 (5.3)	1/59 (1.7)	0.226
CABG. n/tot (%)	9/817 (1.1)	0/59 (0.0)	0.418
MI. n/tot (%)	58/817 (7.1)	3/59 (5.1)	0.557
Stroke/TIA, n/tot (%)	2/817 (0.2)	1/59 (1.7)	0.066
CHF, n/tot (%)	**64/816 (7.8)**	**20/65 (30.8)**	**<0.001**
Bleeding events, n/tot (%) ‡	**76/816 (9.3)**	**25/65 (38.5)**	**<0.001**

* P value for difference between with and without AF at 6 months.
‡ ≥ BARC type 2.
Abbreviations: AF = atrial fibrillation; MACE = major adverse cardiovascular event; CV = cardiovascular; ACS = acute coronary syndrome; PCI = percutaneous coronary intervention; CABG: Coronary Artery Bypass Grafting; MI = myocardial infarction; TIA = transient ischemic attack; CHF = Congestive heart failure; BARC = Bleeding Academic Research Consortium.



CI: confidence interval; CV: cardiovascular; ACS: acute coronary syndrome

Fig. 2. Forest plot of de novo AF after a NSTE-ACS as predictor of clinical events.

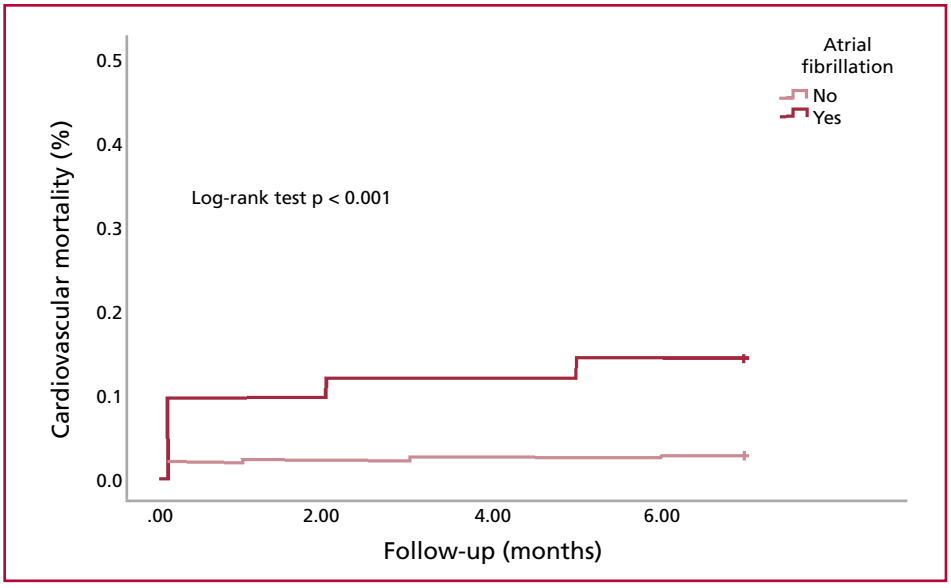
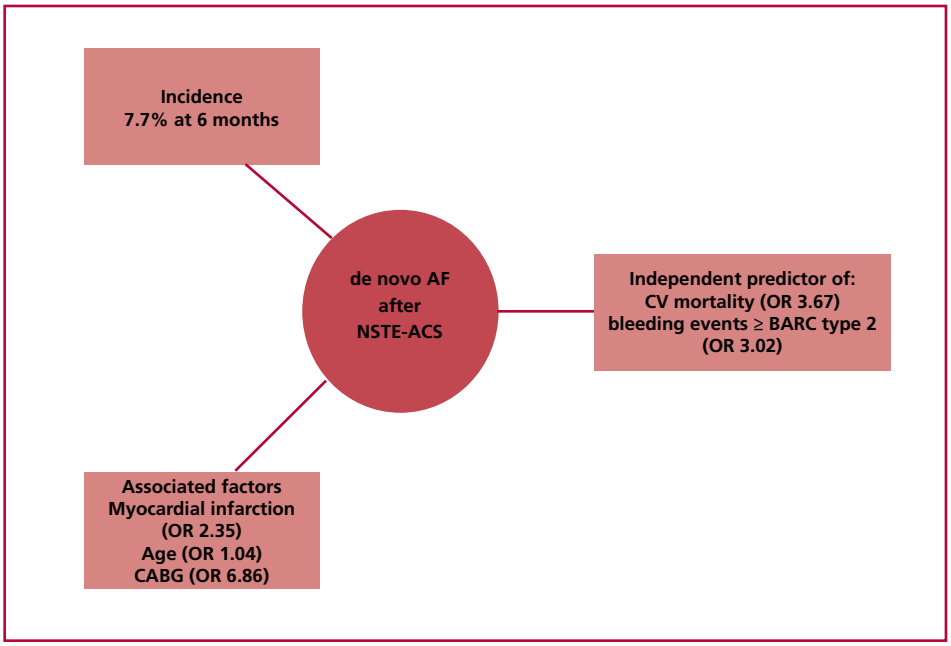


Fig. 3. Cumulative incidence of cardiovascular mortality according to the development of atrial fibrillation after non-ST-segment elevation acute coronary syndrome.



AF: Atrial Fibrillation NSTE-ACS: non-ST-segment elevation acute coronary syndrome CV: cardiovascular CABG: Coronary artery bypass grafting

Fig. 4. Incidence of de novo AF after NSTE-ACS. Associated factors and outcome

nary event, and with greater comorbidity. There is a clear association between age and diastolic dysfunction, increased atrial diameters and associated valvular heart disease; all these factors predispose to the development of AF. (11)

These data are consistent with those observed in studies with similar populations. A study which included ACS subjects (n = 7228) showed that patients who developed de novo AF were older: 73 (64-79) vs. 64 (54-73) years ($p < 0.001$) and had higher prevalence of a history of known cardiovascular disease (11.9% vs. 8.5%; $p = 0.004$), compared with patients without AF. (2) In turn, a study analyzing patients with MI (n = 5946) identified an association between the development of de novo AF and left ventricular systolic function, pulmonary hypertension or increased atrial size. (12)

Conservative management strategies have demonstrated a greater association with the development of de novo AF. (13) This factor is difficult to evaluate in the cohort analyzed in the present study because most patients received an early invasive approach. Of the total number of patients included in the BUENOS AIRES I registry, 14.4% required CABG. The fact that CABG is a predictor of de novo AF is not surprising, as AF is one of the most common complications of cardiovascular surgery, with a reported incidence of nearly 30% in isolated revascularization procedures and up to 50% in combined surgeries. (14)

To date, there is little evidence available on the indication for anticoagulation in patients with de novo AF in the setting of an ACS. The clinical practice guidelines recommend starting anticoagulation in this subgroup of patients when there is an indication according to the CHA_2DS_2-VASc score, and the anticoagulant regimen is adjusted according to the baseline risk of bleeding. (15) In the cohort analyzed in the present study and considering the significant likelihood of recurrence of arrhythmic events, mortality and stroke during follow-up of patients with de novo AF, the indication of anticoagulation therapy on discharge was low in this subgroup of patients and was significantly lower than that of patients with previous AF. This finding is in line with the one reported by other series in the literature. (2,16) It is important to emphasize that each patient should be evaluated individually, considering his/her baseline risk of ischemia and bleeding when taking the therapeutic decision, in order to choose the antithrombotic regimen and duration of therapy that will be most beneficial.

In line with the findings of the retrospective analysis of the GRACE registry, in the present study de novo AF was an independent predictor of cardiovascular mortality and bleeding events ≥ BARC type 2 at 6-month follow-up. (2) Supporting these findings, a systematic review and meta-analysis including 43 studies of MI patients (n = 278 854) demonstrated that recent-onset AF was associated with greater mortality during follow-up (OR, 1.37; 95% CI, 1.26-1.49). (17) Several mechanisms, as increased coronary flow velocity integral, increase the ischemic burden during AF in the context of an ACS. (18,19) This mechanism could in part explain the higher mortality observed in our cohort, considering that it mainly occurs within the first 30 days after the index coronary event. As for the risk of bleeding, patients with de novo AF were elderly and had a higher CRUSADE score (probably due to the presence of kidney failure and concomitant vascular disease). If we consider the requirement for anticoagulation, or double or triple antiplatelet regimens, bleeding events are likely to occur in this subgroup of patients.

Limitations

Our study presents some limitations due to the biases of retrospective and observational studies. There is insufficient information about the moment AF developed after the index coronary event and of AF burden at follow-up. There is no documented information about the treatment prescribed for heart rate or rhythm control and of the contraindications for the use of anticoagulant drugs. The BUENOS AIRES I registry did not include detailed echocardiographic information, which would provide a deeper analysis of the concomitant predictors of AF.

CONCLUSIONS

This prespecified sub-analysis of the BUENOS AIRES I registry demonstrated a significant incidence of de novo AF in the setting of NSTE-ACS, associated with elderly patients, greater acute myocardial structural damage and need for MRS, with worse outcome in terms of adverse clinical events at mid-term follow-up.

Conflicts of interest

None declared.

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

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