Original article

New-onset or Pre-existing Atrial Fibrillation in Acute Coronary Syndromes: Two Distinct Phenomena With a Similar Prognosis

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A B S T R A C T

Introduction and objectives: The management and risk stratification of patients with atrial fibrillation (AF) and acute coronary syndromes constitute a challenge. We aimed to evaluate the prognostic impact of AF whether present at admission or occurring during hospitalization for acute coronary syndromes, as well as trends in treatments and outcome.
Methods: Data derived from 35 958 patients enrolled between 2004 and 2015 in the AMIS Plus registry were retrospectively analyzed.
Results: Pre-existing AF (pre-AF) was present in 1644 (4.7%) while new-onset AF (new-AF) was evident in 309 (0.8%). Presentation with ST-segment elevation myocardial infarction and need for hemodynamic support was frequent in patients with AF, especially in those with new onset of the arrhythmia. A change of the medical and interventional approaches was observed with a progressive increase in oral anticoagulation prescription and referral for angiography and percutaneous coronary interventions in pre-AF patients. Despite different baseline risk profile and clinical presentations, both AF groups showed high in-hospital and 1-year mortality (in-hospital new-AF vs pre-AF [OR, 0.79; 95%CI, 0.53-1.17; P = .246]; 1-year mortality new-AF vs pre-AF [OR, 0.72; 95%CI, 0.31-1.67; P = .448]) Pre-AF but not new-AF independently predicted in-hospital mortality. While mortality declined over the study period for patients with pre-AF, it remained stable among new-AF patients.
Conclusions: While pre-AF is independently associated with in-hospital mortality, new-AF may reflect a worse hemodynamic impact of the acute coronary syndromes, with the latter ultimately driving the prognosis.

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La fibrilación auricular de nueva aparición o preexistente en los síndromes coronarios agudos: dos fenómenos distintos con un pronóstico comparable

R E S U M E N

Introducción y objetivos: El tratamiento y la estratificación del riesgo de los pacientes con fibrilación auricular (FA) y síndromes coronarios agudos son todo un reto. El objetivo es evaluar el impacto pronóstico de la FA, ya sea al ingreso como la aparecida durante la hospitalización por síndrome coronario agudo, así como las tendencias en los tratamientos y el resultado.
Métodos: Se analizaron retrospectivamente los datos procedentes de 35.958 pacientes incluidos entre 2004 y 2015 en el registro AMIS Plus.
Resultados: Había FA preexistente (FApre) en 1.644 pacientes (4,7%), mientras que se evidenció FA de nueva aparición (FAnueva) en 309 (0,8%). La presentación con infarto agudo de miocardio con elevación del segmento ST y la necesidad de asistencia hemodinámica fueron frecuentes en los pacientes con FA, especialmente aquellos con FA nueva. Se observó un cambio en los enfoques médicos e intervencionistas, con un progresivo aumento de la prescripción de anticoagulación oral y las derivaciones para angiografías e intervenciones coronarias percutáneas de pacientes con FApre. A pesar de los diferentes perfiles de riesgo iniciales y presentaciones clínicas, ambos grupos de FA mostraron grandes y comparables mortalidades hospitalaria y a 1 año (FAnueva frente a FApre: mortalidad hospitalaria,

OR = 0,79; IC95%, 0,53-1,17; p = 0,246; mortalidad a 1 año, OR = 0,72; IC95%, 0,31-1,67; p = 0,448). La FApre, pero no la FAnueva, predijo de manera independiente la mortalidad hospitalaria. Si bien la mortalidad de aquellos con FApre disminuyó durante el periodo de estudio, se mantuvo estable entre los pacientes con FAnueva.

Conclusiones: Mientras que la FApre se asocia de manera independiente con la mortalidad hospitalaria, la FA nueva puede reflejar un peor impacto hemodinámico del síndrome coronario agudo, lo que en última instancia determina el pronóstico.

Abbreviations

ACS: acute coronary syndrome
AF: atrial fibrillation
New-AF: new-onset atrial fibrillation
PCI: percutaneous coronary intervention
Pre-AF: pre-existing atrial fibrillation

INTRODUCTION

The management of patients with atrial fibrillation (AF) and acute coronary syndrome (ACS) constitutes a challenge due to the paucity of data on the patient's specific bleeding and embolic risks and on appropriate antithrombotic treatment.[1] In the absence of dedicated randomized controlled trials, the available evidence is mainly derived from subgroup analyses of stent or AF trials as well as registries. Overall, in the setting of ACS, AF patients appear to have worse prognosis and less access to invasive treatments compared with non-AF patients.[2–11] However, it is still a matter of debate whether AF adversely affects prognosis in ACS *per se* or whether it is a marker of comorbidities, the latter effectively driving the outcome.[2,5,6,8,9,11]

While in most cases, AF is chronic and unrelated to ACS, on occasion patients develop AF in the acute setting. The pathophysiological mechanisms, the relative clinical impact on short and long-term outcomes and the management of AF in these 2 circumstances differ substantially.[5,6,8–11] Moreover, whether the occurrence of AF during an ACS represents a predictor of in-hospital mortality or a marker of hemodynamic instability, the latter ultimately driving the prognosis, is still unknown.

The aim of this study was to evaluate the differential prognostic impact of AF, whether present at admission or occurring during hospitalization for ACS, as well as trends in treatments and outcomes according to the time of onset of AF.

METHODS

Patient Population

Acute Myocardial Infarction in Switzerland (AMIS) Plus is a nationwide prospective registry enrolling patients admitted with ACS with or without ST-segment elevation in more than 80 hospitals recruiting since 1997.[12,13] Patients are enrolled on a voluntary basis by signing a written informed consent form. Participating centers provide data for each patient through a standardized questionnaire including 200 items.

Data collection is centralized at the Institute of Social and Preventive Medicine of the University of Zürich. All data are checked for completeness, plausibility, and consistency by the AMIS Plus Data Center, querying treating physicians if the data are incomplete. Since 2010, external monitoring is regularly performed in randomly selected hospitals. The registry was approved by the Swiss Federal Ethics Committee for Clinical Studies, the Swiss Board for Data Security, and the appropriate Cantonal Ethics Commissions. The study protocol adheres to the ethics guidelines of the Declaration of Helsinki.

In this analysis, patients enrolled between January 1st, 2004 to July 1st, 2015 were considered. For all patients, detailed clinical history, in-hospital medical/interventional treatments and complications, therapy and vital status at discharge were available. Data from patients evaluated with coronary angiography are also reported. The Charlson comorbidity index, a quantitative estimate of associated comorbidities, was calculated.[14,15]

Among all in-hospital complications collected in the registry, those considered in the present analysis were defined as follows: *a)* cardiogenic shock: persistent hypotension (systolic blood pressure < 90 mmHg) with clinical signs of severe reduction in cardiac index; *b)* stroke or transient ischemic attack: as any event due to ischemic, thrombotic or hemorrhagic disturbances confirmed by a neurologist or imaging modality; *c)* reinfarction: clinical signs or symptoms of ischemia with electrocardiogram changes indicative of new ischemia (new ST-changes or new left bundle branch block) and a new rise of biomarkers following the initial infarction; *d)* bleedings: recorded if deemed clinically relevant by the individual physician caring for the patient, without the use of a classification system.

At the time of the initial hospitalization, patients included in the registry may consent on an individual basis to a 1-year follow-up by telephone interview. Therefore the 1-year follow-up reported here reflects events occurring between the time of hospital discharge and 1 year only in the subgroup of patients accepting a telephone follow-up visit.

To better evaluate the clinical and prognostic impact of different timing of onset of AF in ACS, we classified patients on the basis of the time when the arrhythmia became clinically evident. Patients with AF documented at admission were classified as patients with pre-existing AF (pre-AF). This group therefore included patients with permanent or persistent AF and those who developed AF before hospital admission. Patients showing sinus rhythm at admission and developing AF at any time during hospitalization persisting until discharge, were considered as those with episodes of new-onset AF (new-AF).

Statistical Analysis

Data are presented as the proportion of valid cases for discrete variables and as mean ± standard deviation and/or medians with interquartile ranges for continuous variables. Differences in baseline characteristics were compared using the unpaired *t* test or Mann-Whitney *U* test, if appropriate, and the Pearson chi-square test. Bonferroni correction for multiple comparisons was adopted. Statistics for each table are based on all cases with valid data in the specified ranges for all variables in each table.

Univariate and multivariate analyses were performed using logistic regression analysis with a stepwise approach to identify predictors of in-hospital mortality in the whole population. The results of logistic regression are reported as odds ratios (OR) with a

95% confidence interval (95%CI). For the trend analysis, the Mantel Haenszel linear by linear association chi-square test with 1 degree of freedom was used. A probability value of $P < .05$ was considered significant. The IBM SPSS Statistics Version 22 (Armonk, New York: IBM Corp) was used for other statistical analyses.

RESULTS

Patient Characteristics

The AMIS Plus registry included 35 958 patients admitted for ACS in the predefined study period, and data on heart rhythm at admission were available for 34 377. Of them, 1644 (4.7%) had AF at admission. In 309 (0.8%) patients, initially admitted with stable sinus rhythm, episodes of AF occurred during the hospital stay. Figure 1 reports patient flow according to group allocation with in-hospital and 1-year mortality, while Table 1 reports baseline characteristics.

Patients with pre-AF were older and showed a greater burden of associated comorbidities such as hypertension, diabetes, known coronary/peripheral artery disease, heart failure and cerebrovascular disease than those without the arrhythmia. Of note, acute admissions for ST-segment elevation myocardial infarction (STEMI) or typical chest pain were less frequent, while more severe presentations such as cardiogenic shock with pulmonary overload and out of hospital cardiac arrest were more frequent in pre-AF than in non-AF patients.

Patients with new-AF showed some distinguishing peculiarities compared with patients without AF as well as those with pre-AF. In fact, while being older than non-AF patients, they were significantly younger than patients with known AF and had fewer comorbidities. New-AF patients had the highest rates among the 3 groups of STEMI presentation (61.5%), as well as out of hospital cardiac arrest (9.1%).

Acute Management

Table 2 reports the in-hospital acute treatments and discharge therapy of patients according to their allocation group. Pre-AF patients less frequently received invasive diagnostics and percutaneous coronary interventions (PCI) than patients without known AF (angiograms pre-AF 56.5% vs non-AF 83.8%, $P < .001$; PCI pre-AF 53.2% vs non-AF 80.7%, $P < .001$; Table 2). In pre-AF patients, a trend toward increased referrals for coronary angiography and PCI was evident between 2004 and 2015 with an approximate 2 fold rise in the number of PCI (Figure 2A and B). When angiograms were performed, transfemoral access was chosen in 3 out of 4 patients.

In pre-AF patients, acute management with aspirin, $P2Y_{12}$ inhibitors, glycoprotein IIb/IIIa inhibitors, angiotensin-converting enzyme inhibitors/receptor blockers and beta-blockers were less frequently adopted than in non-AF patients. In contrast, vasopressors and symptomatic treatments with Ca^{2+} channel blockers and diuretics were frequently prescribed.

No differences in terms of referral for invasive diagnostics and PCIs were observed between new-AF and non-AF patients. As for patients with pre-AF, a trend toward an increased referral to coronary angiography and PCIs was evident during the study period. Also, in this case, femoral access was chosen in most patients. Hemodynamic support with vasopressors or balloon counterpulsation was relatively common in new-AF patients, needed in almost 1 out of 5. Evidence of severe left ventricular dysfunction was more frequent in patients with pre-AF (11.2%) and new-AF (13.3%) than in those without the arrhythmia (5.9%, $P < .001$ for both AF groups vs non-AF).

Acute management with $P2Y_{12}$ inhibitors was comparable among new-AF patients and those without AF.

Aspirin was prescribed to most patients, while a dual antiplatelet regimen was less frequently prescribed both in pre-AF (56.6%) and in new-AF patients (71.4%) compared with non-AF patients ($P < .001$ for both). Nonetheless, a progressive increase in triple therapy counterbalanced by a decline in the use of any single antiplatelet + oral anticoagulation was evident for pre-AF but not new-AF (P for trends .002 and .36 respectively; Figure 2C and D).

In both AF subgroups, an oral anticoagulant was prescribed in only about 40% of patients (and almost a quarter were discharged to secondary care facilities while on iv/subcutaneous heparin). Both triple therapy (ie, the association between aspirin + any $P2Y_{12}$

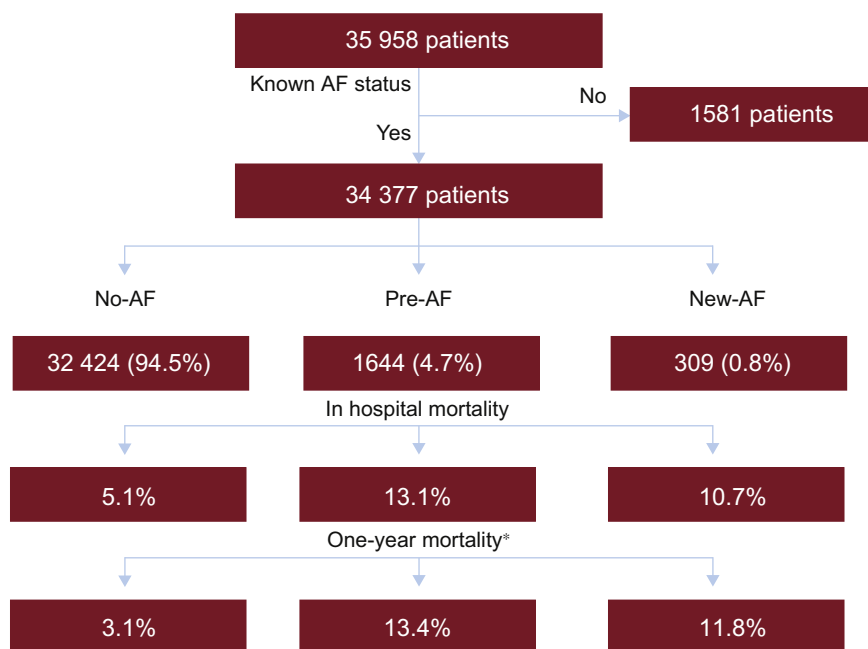**Figure 1.** Patient flow according to group allocation with in-hospital and 1-year mortality. AF, atrial fibrillation; No-AF: patients without atrial fibrillation; New-AF: patients with new-onset atrial fibrillation; Pre-AF: patients with pre-existing atrial fibrillation. *Subgroups of patients followed up to 1-year. A total of 8534 had no AF, 357 had AF at admission and 68 had AF during hospitalization.

Table 1
Baseline Clinical Characteristics

	Non-AF patients (A)	Patients with history of AF (B)	P A vs B	Patients with new-onset AF (C)	P A vs C	P B vs C
Number of patients	32 424	1644		309		
Female sex, %	26.3	34.0	< .001	31.4	.02	.180
Age, y	65.6 ± 13.2	76.8 ± 10.7	< .001	74.6 ± 10.9	< .001	.001
Risk factors						
Family history, %	34.0	26.6	< .001	24.4	.001	.481
Smoking, %	39.4	22.6	< .001	23.5	< .001	.739
Dyslipidemia, %	58.2	53.5	.006	52.0	.041	.659
Hypertension, %	61.6	79.3	< .001	68.4	.010	< .001
Diabetes, %	20.0	29.0	< .001	26.1	.009	.324
BMI > 30, %	21.3	21.4	.964	24.1	.284	.336
Comorbidities						
CAD, %	33.9	42.8	< .001	24.6	.799	< .001
Heart failure, %	2.6	10.4	< .001	5.4	.003	.007
CVD, %	5.4	11.4	< .001	8.8	.010	.181
PVD, %	5.1	10.0	< .001	8.8	.002	.623
Renal impairment (KDOQI class > 3), %	6.6	17.2	< .001	9.1	< .001	.041
$CHADS_2$ score, median	1 [0-2]	2 [1-3]		2 [1-3]		
$CHA_2DS_2-VAS_C$ score, median	2 [1-3]	3 [2-4]		3 [2-4]		
Presentation						
STEMI, %	55.3	47.5	< .001	61.5	.028	< .001
Out of hospital CA, %	4.8	7.8	< .001	9.1	< .001	.447
Killip class 3 or 4, %	6.5	15.7	< .001	13.4	< .001	.319
Chest pain, %	87.6	75.4	< .001	85.2	.209	< .001
Dyspnea, %	29.6	49.6	< .001	44.0	< .001	.092

AF, atrial fibrillation; BMI, body mass index; CA, cardiac arrest; CAD, coronary artery disease; CVD, cerebrovascular disease; KDOQI, Kidney Disease Outcomes Quality Initiative; PVD, peripheral vascular disease; STEMI, ST-segment elevation myocardial infarction.
Data are expressed as No. (%), mean ± standard deviation or median [interquartile range].

inhibitor + oral anticoagulant) and a dual antiplatelet regimen were prescribed more often in patients with new-AF than in patients with known AF (27.9% vs 18.7%, *P* < .001 and 71.4% vs 56.6%, *P* < .001, respectively). Beta-blockers were less frequently used in patients with AF, while prescriptions of symptomatic medications such as nitrates and diuretics were significantly higher when compared with non-AF patients.

In-hospital Outcome

Table 3 reports details on in-hospital and 1-year outcome.
Pre-AF patients had a longer hospital stay (7 interquartile range [3-13] vs 5 interquartile range [2-8] days; *P* < .001) and showed higher rates of in-hospital complications such as cardiogenic shock (OR, 2.07; 95%CI, 1.69-2.53; *P* < .001), reinfarction (OR, 1.64; 95%CI, 1.07-2.52; *P* = .022), and cerebrovascular events (OR, 2.08; 95%CI, 1.34-3.24; *P* = .001), while no differences in clinically relevant bleedings (OR, 1.23; 95%CI, 0.92-1.65; *P* = .156) were evident when compared with non-AF patients. Crude in-hospital mortality was also higher (non-AF 5.1% vs pre-AF 13.1%; OR, 2.82; 95%CI, 2.24-3.28; *P* < .001).

Between the first and last third of the study period analyzed (ie, 2004-2007 and 2015) in-hospital mortality declined from 15.0% to 10.7% in pre-AF patients (*P* for trend = .035).

New-AF patients showed the highest rate of in-hospital bleedings and cerebrovascular events among the 3 groups. In-hospital mortality among both AF groups was comparable (new-AF vs pre-AF [OR, 0.79; 95%CI, 0.57–1.17; *P* = .246]).

In-hospital mortality remained substantially stable in new-AF patients throughout the whole study period (*P* for trend = .42). Figure 3 describes trends of in-hospital mortality according to the presence and type of AF during the first, second and last third of the study period.

Outcome at Follow-up

In the subpopulation of patients scheduled for 1-year follow-up (n = 8959; 24.9% of the entire population), those with AF at admission had more rehospitalizations for any cardiovascular reason (OR, 1.36; 95%CI, 1.07-1.76; *P* = .01), reinfarction (OR, 2.26; 95%CI, 1.42-3.59; *P* = .001) and cerebrovascular events (OR, 2.92; 95%CI, 1.02-6.57; *P* = .045), while no significant differences were evident in terms of recurrent invasive procedures such as angiographies, PCI, bypass surgery, or pacemaker/implantable cardioverter-defibrillator implantation (OR, 1.04; 95%CI, 0.73-1.47; *P* = .801) compared with non-AF patients. One year mortality in pre-AF was 4 times higher than that of non-AF patients (13.7% vs 3.1%; OR, 4.86; 95%CI, 3.47-6.77; *P* < .001).

At 1-year follow-up, more than 1 out of 3 patients with episodes of AF during the index admission had a new hospitalization for any cardiovascular reason (OR, 2.07; 95%CI, 1.18-3.65; *P* = .01 vs non-AF patients) and referrals for invasive procedures (OR, 2.39; 95%CI, 1.28-4.62; *P* = .006) but rates of recurrent cardiac ischemic events (OR, 0.60; 95%CI, 0.08-4.43; *P* = .625) and cerebrovascular events (OR, 0.38; 95%CI, 0.02-6.33; *P* = .501) were similar to those observed in non-AF patients.

Table 2
In-hospital Acute Treatments and Discharge Therapies

	Non-AF patients (A)	Patients with history of AF (B)	P A vs B	Patients with new-onset AF (C)	P A vs C	P B vs C
Invasive evaluation						
Coronary angiography	83.8	56.5	< .001	81.2	.226	< .001
PCI performed	80.7	53.2	< .001	77.3	.143	< .001
Femoral access	68.0	75.8	.025	69.2	.818	.260
Radial access	32.0	24.2		30.8		
IABP treated	3.9	4.8	.075	12.4	< .001	< .001
Coronary disease						
One vessel	40.1	31.5	< .001	42.5	.064	.001
Multivessel disease	59.9	68.5		57.5		
LVEF < 35%	5.9	11.2	< .001	13.3	< .001	.172
CABG	2.8	2.4	.673	4.6	.358	.316
Acute medical treatment						
Aspirin	96.0	86.5	< .001	86.1	< .001	.919
P2Y$_{12}$ inhibitors	83.9	61.3	< .001	85.1	.580	< .001
Clopidogrel	64.2	52.9		59.6		
Prasugrel	25.3	9.7		19.8		
Ticagrelor	36.4	20.1		35.1		
GPIIb/IIIa inhibitors	24.3	11.3	< .001	20.5	.013	< .001
Bivalirudin	1.7	1.7	.842	1.3	.657	.632
Beta-blockers	61.9	61.2	.934	54.2	.026	.038
Nitrates	51.5	48.4	.014	54.1	.367	.066
ACE inhibitor/ARB	54.6	49.3	< .001	55.7	.692	< .001
Ca^{2+}channel blockers	8.7	12.4	< .001	9.5	.996	.147
Diuretics	20.4	47.2	< .001	37.8	< .001	.002
Statins	76.8	60.2	< .001	67.8	< .001	.013
Vasopressors	7.4	11.3	< .001	17.7	< .001	.002
Discharge therapy						
Aspirin	96.9	81.1	< .001	88.6	< .001	.004
P2Y$_{12}$ inhibitors	86.5	62.2	< .001	77.3	< .001	< .001
Clopidogrel	63.8	54.3	< .001	66.4	.365	< .001
Prasugrel	28.6	9.2	< .001	8.4	< .001	.741
Ticagrelor	31.6	12.5	< .001	12.7	< .001	.961
OAC	6.2	43.4	< .001	43.5	< .001	.934
Triple therapy	3.6	18.7	< .001	27.9	< .001	< .001
OAC + any P2Y$_{12}$	4.0	21.4	< .001	32.3	< .001	< .001
Dual antiplatelet	84.8	56.6	< .001	71.4	< .001	< .001
Beta-blockers	79.1	78.6	.099	74.4	.012	.121
Nitrates	0.8	13.9	< .001	10.8	< .001	.161
ACE inhibitor/ARB	76.4	76.4	.110	77.6	.588	.415
Ca^{2+}channel blockers	10.0	14.6	< .001	14.4	.017	.928
Diuretics	24.8	56.3	< .001	53.5	< .001	.393
Statins	90.6	76.3	< .001	83.9	< .001	.005

ACE, angiotensin-converting enzyme; AF, atrial fibrillation; ARB, angiotensin receptor blocker; CABG, coronary artery bypass graft; GPIIb/IIIa, glycoprotein IIb/IIIa; IABP, intra-aortic balloon pump; LVEF, left ventricular ejection fraction; OAC, oral anticoagulant; PCI, percutaneous coronary intervention.
Data are expressed as No. (%).

No strokes were evident in new-AF patients during follow-up. One year mortality was 11.8%, higher than that observed in non-AF patients (OR, 3.51; 95%CI, 1.59-7.75; *P* = .001), but comparable to that in pre-AF patients (OR, 0.72; 95%CI, 0.31-1.67; *P* = .625).

Outcome Predictors

Table 4 shows the results of the univariable and multivariable analyses.

A multivariable analysis was performed that included history of AF, intercurrent episodes of AF, age, female sex, STEMI presentation, Killip class > 2 at admission and Charlson comorbidity index > 1. History of AF (OR, 1.29; 95%CI, 1.08-1.53; *P* = .005), age (OR per additional year, 1.06; 95%CI, 1.05-1.07; *P* < .001), STEMI presentation (OR, 1.74; 95%CI, 1.56-1.93; *P* < .001), Killip class > 2 (OR, 11.0; 95%CI, 9.88-12.3; *P* < .001) and Charlson Comorbidity index > 1 (OR, 1.61; 95%CI, 1.45-1.80; *P* < .001) were independent predictors of in-hospital mortality, while new-onset AF during hospitalization was not independently associated with in-hospital mortality (OR, 1.02; 95%CI, 0.74-1.69; *P* = .614).
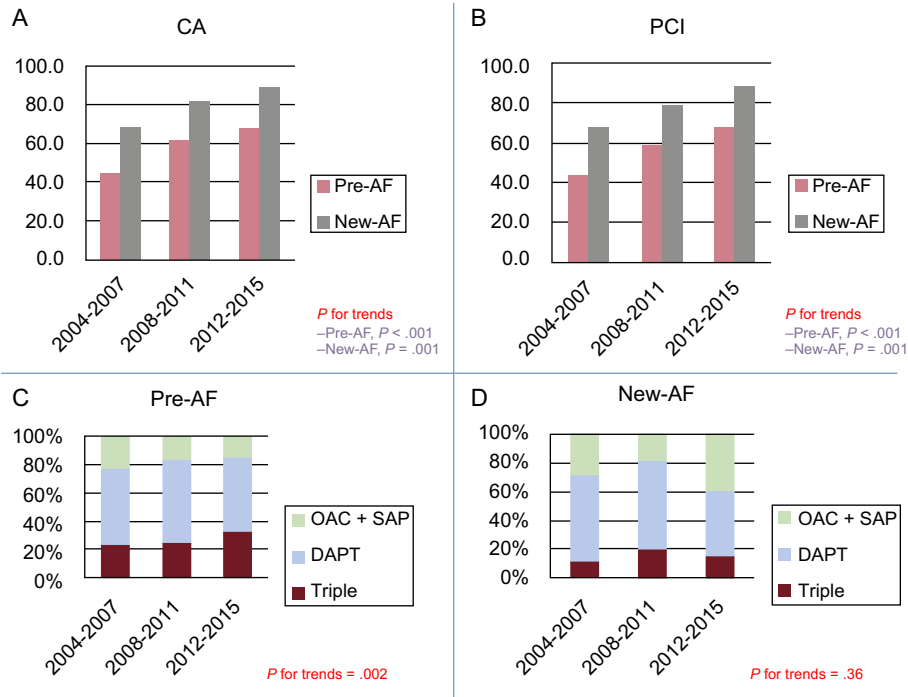
Figure 2. A, B: trends of referrals for CA and PCI according to time of onset of atrial fibrillation. C, D: trends in prescription of triple therapy (OAC + DAPT) or OAC + any antiplatelet (OAC + SAP, either aspirin or any P2Y$_{12}$ inhibitor) at discharge according to the time of onset of AF. AF, atrial fibrillation; CA, coronary angiography; DAPT, dual antiplatelet therapy; PCI, percutaneous coronary intervention; pre-AF, pre-existing atrial fibrillation; new-AF, new-onset atrial fibrillation; OAC, oral anticoagulant; SAP, single antiplatelet.

DISCUSSION

To the best of our knowledge, this is the largest European contemporary registry evaluating the relative impact on morbidity and mortality of pre-existing vs new-onset AF in the setting of an ACS.

The following key messages can be drawn from our data:

- Despite different baseline clinical profiles, patients with pre-existing AF and those with new-onset AF both experienced high and comparable in-hospital and 1-year mortality.

Table 3
In-hospital and 1-year Outcome

	Non-AF patients (Group A = 32 424)	Patients with pre-AF (Group B = 1644)	Patients with new-AF (Group C = 309)	OR B vs A OR (95%CI)	OR C vs A OR (95%CI)	OR C vs B OR (95%CI)
In-hospital outcome						
Length of stay, d (95%CI)	5 (2-8)	7 (3-13)	9 (6-15)			
Cardiogenic shock, No. (%)	1095/32 281 (3.4)	111/1638 (6.8)	30/309 (9.7)	2.07 (1.69-2.53), *P* < .001	3.06 (2.09-4.48), *P* < .001	1.47 (0.96-2.25), *P* = .069
Reinfarction, No. (%)	277/32 284 (0.9)	23/1639 (1.4)	6/309 (1.9)	1.64 (1.07-2.52), *P* = .022	2.28 (1.01-5.17), *P* = .047	1.39 (0.56-3.44), *P* = .475
Clinically relevant bleedings, No. (%)	777/30 139 (2.6)	49/1547 (3.2)	30/309 (6.5)	1.23 (0.92-1.65), *P* = .156	4.06 (2.76-5.96), *P* < .001	3.28 (2.05-5.27), *P* < .001
Cerebrovascular events, No. (%)	209/32 284 (0.6)	22/1639 (1.3)	13/309 (4.2)	2.08 (1.34-3.24), *P* = .001	6.74 (3.80-11.94), *P* < .001	3.22 (1.60-6.47), *P* = .001
Mortality, No. (%)	1642/32 424 (5.1)	215/1644 (13.1)	33/309 (10.7)	2.82 (2.42-3.28), *P* < .001	2.24 (1.55-3.22), *P* < .001	0.79 (0.53-1.17), *P* = .246
1-year outcome	(8061)	(343)	(68)			
Rehospitalization, No. (%)	1796/7769 (23.1)	86/296 (29.1)	20/52 (38.5)	1.36 (1.05-1.76), *P* = .018	2.07 (1.18-3.65), *P* = .010	1.52 (0.82-2.81), *P* = .176
Any re-intervention, No. (%)	980/6839 (14.3)	39/262 (14.9)	13/49 (26.5)	1.04 (0.73-1.47), *P* = .801	2.39 (1.28-4.62), *P* = .006	2.12 (1.03-4.37), *P* = .040
Reinfarction, No. (%)	250/7721 (3.2)	21/298 (7.3)	1/50 (2.0)	2.26 (1.42-3.59), *P* = .005	0.60 (0.08-4.43), *P* = .625	0.26 (0.03-2.04), *P* = .204
Cerebrovascular events, No. (%)	45/1734 (2.6)	5/79 (6.3)	0/48 (0)	2.92 (1.02-6.57), *P* = .045	0.38 (0.02-6.33), *P* = .501	0.17 (0.01-3.24), *P* = .239
Mortality, No. (%)	255/8061 (3.1)	47/343 (13.7)	8/68 (11.8)	4.86 (3.47-6.77), *P* < .001	3.51 (1.59-7.75), *P* = .001	0.72 (0.31-1.67), *P* = .448

95%CI, 95% confidence interval; AF, atrial fibrillation; new-AF, new-onset AF; OR, odds ratio; pre-AF, pre-existing atrial fibrillation.
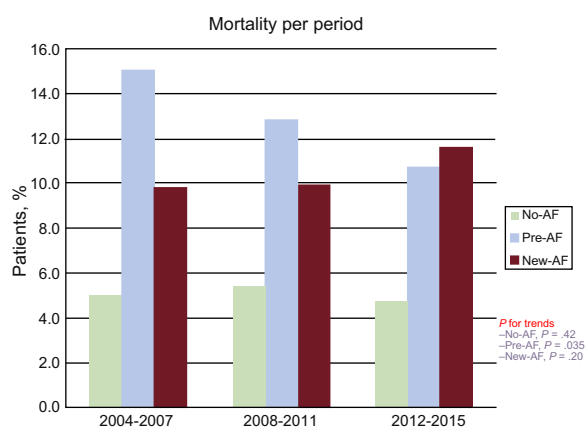
Mortality per period

Figure 3. Trends in in-hospital mortality according to the presence and type of AF during the first, second and last third of the study period. AF, atrial fibrillation; new-AF, new-onset atrial fibrillation; pre-AF, pre-existing atrial fibrillation.

- Pre-existing AF but not new-onset AF was an independent predictor of in-hospital mortality.
- New-onset AF, being frequently associated with STEMI presentation, out of hospital cardiac arrest and risk of hemodynamic deterioration, was a marker of worse hemodynamic impact of ACS.
- During the 10 years evaluated, a progressive increase in referrals to PCI with a concomitant reduction of mortality was observed in patients with pre-existing AF. In contrast, mortality remained substantially stable and high in patients with new-onset AF.

Previous works have analyzed the clinical characteristics and prognostic impact of known and *de novo* AF associated with an ACS. Data derived from the GRACE/CANRACE and Medicare registries showed that the incidence of known AF ranged from 7.6% to 22.1% in ACS patients. AF patients were older, with an increased burden of cardiovascular risk factors as well as known coronary disease, heart failure, and renal impairment, with lesser access to evidence-based therapies and a noteworthy in-hospital mortality.[2,5,10] Moreover, the paradigm that pre-existing compared with newly discovered AF had a different mode of onset, pathophysiology, and in-hospital and long-term outcomes was emphasized and a prognostic role for newly developed AF was also hypothesized.[5]

Our data propose a comprehensive interpretation for both types of AF. Despite different clinical characteristics and pathophysiological mechanisms, the comparable and high in-hospital and 1-year mortality observed in both AF groups unifies those 2 entities

Table 4

Independent Predictors of In-hospital Mortality in Acute Coronary Syndrome Patients

	Univariate OR (95%CI)	Multivariate OR (95%CI)
History of AF	2.77 (2.36-3.22)	1.29 (1.08-1.53)
New onset of AF	2.09 (1.46-3.01)	1.11 (0.74-1.69)
Age (per additional year)	1.06 (1.06-1.07)	1.06 (1.05-1.07)
Female sex	1.58 (1.43-1.74)	1.02 (0.92-1.14)
STEMI	1.59 (1.44-1.76)	1.74 (1.56-1.93)
Killip class > 2	13.2 (11.8-14.7)	11.0 (9.88-12.3)
Charlson comorbidity index > 1	2.74 (2.49-3.02)	1.61 (1.44-1.80)

95%CI, 95% confidence interval; AF, atrial fibrillation; OR, odds ratio; STEMI, ST-segment elevation myocardial infarction.
All the above variables were used in the adjusted model.

from a prognostic perspective. Independently from different modes and timing of onset, both AF groups showed a high and comparable in-hospital mortality, this representing a marker of clinical interest.

There is conflicting evidence on the relative role of the 2 different AF forms. While some authors do not recognize a clear role as a predictor of in-hospital mortality for pre-existing AF[2,5,16,17] the worse in-hospital outcome not being attributed to a direct role of AF but rather to the associated prognosticators such as age or poorer overall clinical status at presentation, others postulate a causative effect.[8,9]

Our analysis shows that pre-existing AF, but not new-onset AF, was an independent predictor of in-hospital mortality. This finding highlights the role of the arrhythmia as a prognosticator in ACS, to be potentially considered in association with currently recommended–or in the development of future–risk estimation scores.[18,19] On the other hand, the occurrence of new episodes of AF was frequently associated with STEMI presentation, out of hospital cardiac arrest, hemodynamic deterioration requiring mechanical or pharmacological support, underscoring the role of the hemodynamic impact of the ACS as a trigger for AF.[20] Those associations were considered as the factors leading to the lack of significance for new-AF as a predictor of in-hospital mortality in our population. Nonetheless, regardless of statistical nonsignificance, the clinical importance of the new episodes of AF in the setting of AF remains. In fact, despite a younger age and a lower burden of associated comorbidities observed in patients with new onset of the arrhythmia, the hemodynamic impact of ACS overrides their better baseline overall status driving morbidity/mortality.

Trend analysis clearly underlined a progressive decline of in-hospital mortality for pre-existing AF patients. This confirms a tendency evident in the literature reporting in-hospital and 1-year deaths exceeding 20% and 40% in the mid 1990s,[5] 15% and 30% in early 2000,[9] and 10% in more contemporary series.[7,10] While this trend was clear in patients with pre-existing AF, mortality remained stable and high in patients with new-onset AF, strengthening once more the clinical importance of this entity.

Furthermore, while no causative relation can be drawn from our data, between the first and last year analyzed (ie, 2004 and 2014) the decline of in-hospital mortality observed in patients with pre-existing AF was mirrored by an increased referral for PCI. This represents an interesting hypothesis-generating finding, potentially related to the recent improvements in interventional tools and techniques (such as the adoption of radial access or third generation stents allowing shortened antiplatelet therapies) that might further enhance the benefits of percutaneous revascularization even in frail patients.

Beside prognostic implications, physicians are called to face difficult therapeutic decisions when managing AF during the acute phase of a coronary ischemic event, and have to balance the embolic and hemorrhagic risks; these decisions are often based on expert consensus, due to the lack of evidence-based confirmations.[1,21,22]

Our data clearly show that multiple therapeutic regimens are adopted, potentially leading to misleading impacts on morbidity and mortality. Both underuse of anticoagulant/antiplatelet therapies and revascularizations in patients with known AF may explain the observed increased incidence of reinfarction and cerebrovascular events at 1-year.In addition, in the setting of new-AF, increased rates of in-hospital bleedings and cerebrovascular events were observed, probably due to an overestimation of their embolic risk.

The adoption of proven measures known to be effective in reducing hemorrhagic complications and mortality such as the radial should be further encouraged.[23]

Strengths and Limitations

Several strengths and limitations of our work should be mentioned.

This analysis, evaluating the relationships between AF and ACS, derived from the data of the Swiss national registry, provides a western updated overview allowing us to depict a national real-life scenario and to provide clues for optimization of current standards of care. Nonetheless, as an observational nonrandomized investigation, our data are subject to certain limitations such as missing data and patient selection or other unforeseen confounders. First, the large number of our population with AF both and admission as well as those with intercurrent episodes is a limitation to the external validity of our observations. While vital status at discharge was available for the whole set of enrolled patients, follow-up was available for a large portion but not for the whole population, thus allowing us to report only an estimate of postdischarge morbidity/mortality. Moreover, the progresses of medical/interventional treatments are mirrored by the transformations of the registry. Even in this relatively short observation period, some major innovations have been introduced such as standardized definitions for in-hospital complications or data regarding treatments that are available only in a proportion of our patients. Finally, the registry design did not allow us to classify patients according to the type of AF (whether paroxysmal, persistent or chronic), or to exclude the possibility that a certain percentage of patients classified as new-AF might have had an arrhythmia onset close to the hospital admission, thus being potentially ACS-related. Equally, we did not provide any data about the outcome of rhythm disturbance at follow-up.

CONCLUSIONS

Our data confirm that AF in the setting of ACS is a major clinical problem. Both patients with history of AF and those with new-onset AF showed in-hospital complications and significantly increased and comparable in-hospital and 1-year mortality. While a history of AF is independently associated with in-hospital mortality, new-onset AF episodes may mirror a worse hemodynamic impact of the ACS, this ultimately driving the prognosis. Despite different clinical characteristic, burden of associated comorbidities and pathophysiological mechanism and in-hospital morbidity, pre-existing and new-onset AF share high and comparable acute and long-term mortality.

FUNDING

CONFLICTS OF INTEREST

None declared.

WHAT IS KNOWN ABOUT THE TOPIC?

- In the setting of ACS, patients with AF are known to have a worse prognosis and lesser access to invasive treatments. Nonetheless, it is still a matter of debate whether AF adversely affects prognosis in ACS *per se* or is a marker of comorbidities, which effectively drive the outcome. Moreover, the relative impact of pre-existing compared with new-onset AF is debated.

WHAT DOES THIS STUDY ADD?

- Despite being intrinsically different from a pathophysiological perspective, pre-existing and new-onset AF showed a high and comparable in-hospital and 1-year mortality. While pre-existing AF was an independent predictor of in-hospital mortality, new-onset AF, being frequently associated with STEMI presentation, out of hospital cardiac arrest and risk of hemodynamic deterioration, was interpreted as a marker of worse hemodynamic impact of the ACS.

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