De novo atrial fibrillation as an independent prognostic marker after ST-segment elevation myocardial infarction: Results from the RIMA registry

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Running title: Prognosis of de novo AF after STEMI

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KEYWORDS

Atrial fibrillation; Myocardial infarction; Prognosis; Registry; Outcomes

ABSTRACT

Background: Atrial Fibrillation (AF) is common in ST-segment elevation myocardial infarction (STEMI), but its influence on prognosis remains controversial.

Aim: We examined the one-year prognostic value of AF in STEMI, distinguishing patients with prior AF from patients with de novo AF.

Methods: Between January 2004 and December 2015, 3173 STEMI patients were enrolled in the RIMA registry (*Registre des Infarctus en Maine Anjou*). They were divided into 3 groups: 1) AF-free patients; 2) patients with known prior AF; and 3) patients with de novo AF during hospitalization (including admission). We defined 3 primary outcomes at 1-year post-discharge**:** cardiovascular mortality, readmission for heart failure (HF), and stroke. Temporal onset of de novo AF was also studied.

Results: A total 158 patients (5%) had prior AF, and 278 (8.8%) presented de novo AF. Prior AF patients were significantly older [81 (73;86) years] with more comorbidities, but de novo AF patients presented with a greater creatine kinase peak and lower left ventricular ejection fraction [LVEF= 44 (35;50)% for de novo AF versus 50 (40;55)% for prior AF, $p<0.001$]. At 1-year follow-up, cardiovascular mortality was higher in cases of AF (13.5% for prior AF vs 9.2% for de novo AF, compared with 2.4% for AF-free patients, $p<0.001$). After adjustments, only de novo AF was correlated with cardiovascular mortality (hazard ratio 2.49; 95% CI 1.32 to 4.67; $p=0.004$), but both types of AF were correlated with readmission for HF. There was no significant difference in respect of stroke between prior AF, de novo AF, and AF-free (2.2%, 0.5%, and 0.8% respectively, $p=0.327$). Finally, outcomes did not differ between AF occurring <24 h after admission (n=127) and de novo AF occurring within ≥24 h (n=151).

Conclusion: De novo AF was independently associated with 1-year cardiovascular mortality. It should not be considered as an intercurrent event of STEMI, but rather as a strong prognostic marker.

INTRODUCTION

Up to 12% of patients presenting with a ST-segment elevation myocardial infarction (STEMI) present a history of atrial fibrillation (AF), compared with a 2% prevalence in the general population. Likewise, de novo AF in the acute phase of STEMI is the most common rhythmic complication [1]. Overall, the incidence of AF in STEMI patients ranges from 2% to 22% [2,3] and AF is established as a marker of outcomes in the STEMI population [4–8]. Gaps in evidence remain about the impact of de novo AF occurring in the acute phase of STEMI. Controversies stem from a number of studies suggesting de novo AF to be a marker of worse prognosis either in the short- and/or long-term [9–19], whereas others point either to prior AF only [5,6,8] or to both prior and de novo AF [4,7,8].

It is undeniable that prior AF and de novo AF are two distinct events. While prior AF relates to the presence of previous diastolic dysfunction and cardiomyopathy, de novo AF relates to acute changes at the time of STEMI, including left atrial ischemia or overload, as well as neuroendocrine activation and tachycardia due to hemodynamic instability. Therefore, prior AF and de novo AF may influence outcomes differently. However, evidence-based results are conflicting, as studies in the field broadly differ in terms of sample size, STEMI characteristics, AF diagnostic methods, and acute care management – some of the studies were conducted during the fibrinolysis era [6,9,10,15,20–23].

The aim of the present study was to assess the one-year prognostic value of de novo AF in a modern prospective cohort of consecutive patients with STEMI.

METHODS

Study population

This study is a retrospective analysis based on the RIMA registry (Registre des Infarctus en Maine-Anjou) [24]. The RIMA registry prospectively included all consecutive patients admitted for STEMI at participating sites, including the University Hospital of Angers which is an angioplasty center and three secondary care

hospitals without angioplasty, in France, between January 2004 and December 2015. STEMI was diagnosed based on the following symptoms suggestive of myocardial infarction: persistent ST elevation ≥0.1 mV in 2 contiguous peripheral leads and V5, V6, or ≥0.2 mV in 2 contiguous leads from V1 to V4, as well as elevation of cardiac biomarkers. Patients with cardiac surgery during hospitalization, including coronary artery bypass grafting, were excluded. A total 378 (11.9%) patients were lost to follow-up at 1 year.

Atrial Fibrillation diagnosis

AF was defined as the absence of P waves, and atrial activity was represented by fibrillatory waves and irregular time elapsing between 2 consecutive R wave (RR) intervals. Atrial flutter on electrocardiogram (ECG) recordings was required to meet the following criteria: presence of regular P waves with a rate of 250 to 350/min and regular or irregular RR intervals. All patients were systematically continuously monitored during their hospital stay in an intensive care unit with a 12-lead ECG performed when AF diagnosis was suspected.

Patients were classified into 3 groups: 1) AF-free patients; 2) patients with known prior AF (permanent, persistent, or paroxysmal); and 3) patients with de novo AF developing from the first medical consultation (including admission) to the end of hospitalization. Patients with atrial flutter were classified as AF. Finally, patients who developed de novo AF were divided into 2 groups: early de novo AF occurring within 24 hours post-admission, and late de novo AF with an onset after the first 24 hours. AF delay was calculated between the first chest pain to a discriminating ECG.

Patients were treated either with a rate control only strategy or a rhythm control strategy using anti-arrhythmic medication and/or electrical cardioversion. Treatment decisions were made by the medical team.

Data collection

Basic demographics, cardiovascular risk factors, medication, biomarkers, and hospitalization information were collected prospectively. Left ventricular ejection fraction (LVEF) was assessed by means

of echocardiography using the biplane Simpson's method during the first 24 hours of hospitalization. In-hospital data on mortality, reinfarction, stent thrombosis, heart failure (HF), severe ventricular arrhythmia, and severe atrioventricular block, stroke, and major bleeding according to the BARC classification were recorded. The CHA2DS2-VASc score was calculated. One-year follow-up was obtained, and mortality, reinfarction, readmission for HF, and stroke were collected. HF was defined clinically in accordance with the guidelines of the European Society of Cardiology [25]. The data were collected during the follow-up medical appointments at 1 year or by telephone if the patient was followed up elsewhere.

In-hospital and 1-year outcomes, as well as cause of death, were adjudicated by two blinded physicians.

The study was performed in accordance with the Declaration of Helsinki, and the protocol was approved by the ethics committee of University Hospital of Angers.

Outcomes

We evaluated three primary 1-year post-discharge outcomes**:** cardiovascular mortality, readmission for HF, and stroke.

Statistical analysis

All statistical tests were performed using SPSS Version 20.0 software for Windows (SPSS Inc., Chicago, IL, USA). Quantitative variables were expressed as medians [IQR: interquartile range], and qualitative variables as numbers and percentages. Analysis of variance or chi-squared tests were performed for the analysis of the three groups. Comparisons of quantitative variables were conducted by means of the unpaired Student's t-test. Comparisons of qualitative variables were performed using the chi-squared test or Fisher's exact test, where appropriate. Cox regression models were applied for the purposes of explaining 1-year mortality and 1-year hospitalization for HF. We tested the effect of de novo AF and prior AF individually, compared to AF-free patients. Only significant univariate correlations ($p<0.05$) were included in the multivariate Cox models. The proportional hazard assumptions were tested by analyzing the Schoenfeld residuals. Statistical significance was set at $p<0.05$.

RESULTS

Population characteristics

A total 3173 patients were included; 158 (5%) had prior AF history; and 278 (8.8%) developed de novo AF during hospitalization; 2737 (86.2%) were AF-free (Fig. 1). The median age was 65 [53;78] years, and 72.8% were male.

Prior AF patients were significantly older (81 [73;86] years), had more comorbidities with high prevalence of hypertension (81%), stroke (14.6%), and renal failure (9.9%). De novo AF patients and AF-free patients had similar rates of anterior infarction (45.8% versus 45.7%; p=0.94) and similar times to reperfusion (5 [4.3;8.3] versus 5.3 [3.5;8.8] hours; p=0.19), but de novo AF patients had a higher creatine kinase peak and a lower LVEF (44 [35;50]% versus 50 [40;55]%); the care was also different, with less use of angioplasty (78.7% versus 84%) and longer hospital stays (10 [5;16] days versus 5 [4;8] days).

The CHA2DS2-VASc score was significantly greater in the prior AF group (5 [4;6]) and the de novo AF group (4 [3;6]) compared to the AF-free group (3 [2;4]); 22% of the de novo AF patients had anticoagulant therapy at discharge (Table 1).

Outcomes

During hospitalization, cardiovascular mortality was higher in AF patients, respectively 17.1% for prior AF and 14.7% for de novo AF, versus 5.7% for AF-free patients (p<0.001). Table 2 shows in-hospital complications to be more frequent among the de novo AF patients, particularly regarding in-hospital HF events with Killip ≥3 (33.5%), major bleeding (12.5%), reinfarction (3.6%), severe ventricular arrhythmia (20.9%), and severe atrioventricular block (14.4%). The stroke rate was similar compared to AF-free patients.

One-year cardiovascular mortality was greater in cases of prior AF (20.6%) compared to de novo AF (12.1%) and AF-free patients (4.3%) (p<0.001). Hospitalization for HF was also higher (21.3% versus 13.8% and 4.2%; p<0.001). Stroke rates did not differ (p=0.33) (Table 2).

The multivariate Cox regression model showed that only de novo AF was independently associated with higher cardiovascular mortality (hazard ratio 2.485; 95% CI 1.323 to 4.67 with *p*=0.004). Prior AF was not correlated with cardiovascular mortality (*p*=0.09), but age, creatinine level, angioplasty and LVEF were (table 3). Both prior AF and de novo AF were associated with readmission for HF (Fig. 2).

Timing of de novo AF

Early de novo AF occurred in 127 patients, and late de novo AF in 151 patients. The creatine kinase peak (*p*=0.16) and anterior infarction (*p*=0.51) were similar between the groups; patients with late de novo AF were significantly older, with a median age of 78 [70;84] years, 35.6% had a Killip class ≥ II at admission and they had lower LVEF values(Table 4). At discharge, 20 (8%) patients had persistent AF, and 214 (84.6%) returned to sinus rhythm (Table 5). One-year cardiovascular mortality did not differ between cases of early and late de novo AF.

DISCUSSION

The present study shows that de novo AF was an independent predictive factor of 1-year cardiovascular mortality, whereas prior AF was not. Moreover, the timing of de novo AF had no incremental value for prognosis.

While our results are in line with Morishima *et al.* [10], our study is based on a longer follow-up period and a greater number of patients. It is also consistent with some previous studies that were mostly post-hoc analyses of randomized clinical trials, and as such their applicability to the community is uncertain [4,7,15,16,18,19]. Studies that disagreed with our results varied in terms of population characteristics, by including STEMI and non-STEMI patients [8,14], or high rates of fibrinolysis use [26]. On the other hand, our study stems from the RIMA registry which is a real-life registry in the angioplasty era. Furthermore, all patients had continuous ECG monitoring during hospitalization, enabling us not to underestimate AF prevalence and accurately determine the timing of its onset.

De novo AF

How STEMI relates to de novo AF is poorly understood. Potential pathophysiological mechanisms are numerous, including: tachycardia with hemodynamic instability, myocardial ischemia and diastolic dysfunction with increased left atrial overload leading to left atrial enlargement, adrenal catecholamine discharge, electrolyte (e.g. hypokalemia) and acid-base disturbances. Likewise, de novo AF has been associated with markers of greater hemodynamic instability, namely greater infarct size and lower LVEF [13,18], as reported in our study (Table 1). We also showed de novo AF to be not only independently correlated with cardiovascular mortality, but also with a higher risk of in-hospital outcomes. Consequently, de novo AF should not be considered as an intercurrent phenomenon of STEMI, but as a strong prognosis marker. Further investigation is needed as to whether de novo AF actually affects prognosis or how de novo AF management might impact outcomes.

In the literature, data on temporal association between de novo AF and prognosis are limited with heterogenous designs and conflicting results [20–23,26]. Podolecki *et al*. found excess mortality only for patients with early de novo AF <24h [22], but their population was different with more severe presentation on admission, such as cardiogenic shock (14.2%), a lower LVEF (36.9±8.1%), and a higher overall 1-year mortality rate. Unfortunately, we were not able to collect information on de novo AF duration, but a study on 320 consecutive patients showed that de novo AF ≥7 h in duration following acute myocardial infarction independently predicted long-term mortality [27].

Prior AF

While prior AF was not found to be an independent risk marker (Table 3) of cardiovascular mortality, it was strongly correlated with readmission for HF (hazard ratio 2.501; 95% CI 1.402 to 4.468 where p=0.001). A Canadian registry made similar findings, despite an older population, higher rates of comorbidities, and lower use of angioplasty [28]. Prior AF is a major component of diastolic dysfunction, associated with senescent myocardium and increased peripheral vascular resistance. It is thus assumed to be correlated with heart failure morbidity and mortality, with lower hazard ratios than de novo AF [23]. The relative low number of patients in our study might explain the lack of association of prior AF with mortality. In this context, the onset of ischemic heart disease will act as an incremental risk factor, illustrated by the

fact that 1-year outcomes were independently correlated with age, creatinine level, angioplasty, and LVEF (Table 3).

Management: anticoagulation and rhythm control

Even paroxysmal AF that has reversed to sinus rhythm at the time of discharge will increase the risk of ischemic stroke during follow-up [2]. Interestingly, only 22% of de novo AF patients had anticoagulant treatment at discharge, even though their CHA2DS2-VASc score was high (4 [3;6]). The reasons why anticoagulant treatment was not prescribed are unknown. However, we did not find any differences based on in-hospital and 1-year stroke data compared to AF-free patients, with the exception of more major in-hospital bleeding events (12.4% versus 5.8%, $p<0.001$). According to current guidelines, patients with CHA2DS2-VASc scores ≥2 should receive triple therapy combining aspirin, an adenosine diphosphate receptor antagonist, and an oral anticoagulant. The aim is to reduce the burden of thromboembolic complications and minimize the risk of stent thrombosis, with the duration shortened to reduce bleeding events [1]. Nevertheless, our results show higher rates of in-hospital bleeding in AF patients, with similar rates of stroke and further cardiovascular outcomes. The benefit of anticoagulant treatment in secondary AF lacks strong evidence, and continues to be the subject of debate [29].

While restoring and maintaining sinus rhythm is an integral part of AF management [30], all trials that have compared rhythm control and rate control to rate control alone have resulted in neutral outcomes. Currently, ESC guidelines [1] recommend that rhythm control therapy is indicated to improve symptoms in AF patients who remain symptomatic on adequate rate control therapy. To date, there is a lack of studies on AF management in the acute phase of myocardial infarction, and little is known about the impact of AF treatment strategy on clinical outcomes in these patients [31–33].

Limitations

Several limitations must be considered, the first being inherent bias due to a retrospective and observational non-randomized study with 11.9% lost to follow-up. Moreover, specific data on AF, such as AF duration, left atrial enlargement, systemic embolism as a complication, or therapeutic management, and recurrence of AF post-discharge are lacking to understand these results fully.

CONCLUSION

De novo AF was not only correlated with greater infarction and lower left ventricular function after STEMI but was also independently associated with 1-year cardiovascular mortality. De novo AF should not be considered as a benign intercurrent event of STEMI, but rather as a strong prognostic marker. Both de novo AF and prior AF were independent predictors of post-discharge readmission for HF.

DISCLOSURE OF INTEREST

The authors declare that there is no conflict of interest.

Figure 1 Flow chart

Figure 2 Survival curves

p values compare either prior AF and de novo AF to AF-free patients after multiple adjustments by Cox regression analysis.

Table 1 Characteristics of patients according to the presence of atrial fibrillation

	Total (n=3173)	Prior AF (n=158)	De novo AF (n=278)	AF-free (n=2737)	*p*-value
Clinical history					
Age (years)	65 [53;78]	81 [73;86] ¤	77 [65;83]§	62 [52;76] §¤	<0.001
Weight (kg)	75 [65;85]	72 [62;82]	72 [64;81]	75 [66;85]§¤	<0.001
Male gender, n(%)	2311(72.8)	106 (67.1)	189 (68)	2016 (73.7)¤	0.032
History of hypertension, n(%)	1606 (50 .7)	128 (81)¤	176 (63.3)§	1302 (47.7)§¤	<0.001
History of diabetes mellitus, n(%)	700 (22.2)	37(23.6)	68 (24.5)	595 (21.9)	0.69
History of dyslipidemia, n(%)	1615 (51.2)	71 (44.9)	146 (52.5)	1398 (51.4)	0.28
Smoker, n(%)	1187 (37.2)	22 (14)	59 (21.4)	1107 (40.6)§¤	<0.001
History of coronary artery disease, n(%)	340 (10.7)	34 (21.5)	35 (12.6)	271 (9.9)§	<0.001
History of stroke, n(%)	145 (4.6)	23 (14.6)¤	21 (7.6)§	100 (3.7)§¤	<0.001
History of renal failure, n(%)	105 (3.3)	15 (9.6)¤	12 (4.1)§	78 (2.9)§	<0.001
Medication at Admission					
Amiodarone, n(%)	42 (1.3)	27 (17.1)¤	2 (0.7)§	13 (0.5)§	<0.001
ACEI/ARB, n(%)	861 (27.3)	80 (50.6)	95 (34.3)	686 (25.2)	<0.001
Beta-blocker, n(%)	642 (20.3)	78 (49.4)	70 (25.3)	494 (18.1)	<0.001
Statin, n(%)	693 (21.9)	48 (30.4)	63 (22.7)	582 (21.4)	0.027
Antiplatelet, n(%)	626 (19.8)	52 (32.9)	77 (27.8)	497 (18.2)§¤	<0.001
Anticoagulant, n(%)	118 (3.7)	77 (48.8)¤	4 (1.3)§	37 (1.4)§	<0.001
Characteristics of qualifying myocardial infarction					
SBP at baseline (mmHg)	138 [120;159]	134 [115;159]¤	128 [110;146]§	140 [120;159]¤	<0.001
HF at admission (Killip ≥ II), n(%)	493 (15.7)	51 (33.3)	83 (30.3)	369 (13.3)§¤	<0.001
Creatinine value at baseline (µmol/L)	82 [69;98]	93 [76;121]	91 [75;116]	81 [69;96]§¤	<0.001
CKP peak (UI/L)	1412 [597;2688]	1053 [346;2143]¤	1767 [589;3438]§	1403 [607;2669]§¤	<0.001
CRP max (mg/L)	8 [3;42]	22 [4;87]	32 [4 ;127]	7 [3;32]§¤	<0.001
Anterior myocardial infarction, n(%)	1352 (45.8)	63 (47.4)	114 (45.8)	1175 (45.7)	0.93
Medication, n(%)	399 (13.2)	32 (22.7)	41 (16)	326 (12.4)§	0.001
Fibrinolysis, n(%)	405 (12.8)	11 (7)	24 (8.6)	370 (13.5)§¤	0.003
Angioplasty, n(%)	2602 (82.9)	109 (70.8)	214 (78.7)	2279 (84)§¤	<0.001
Multivessel disease, n(%)	1419 (48.1)	81 (60.9)	151 (60.9)	1301 (50.6)§¤	0.001
Time from symptoms to reperfusion (h)	5.3 [3.5;8.7]	3.1 [1.4;6.4]	5 [4.3;8.3]	5.3 [3.5;8.8]	0.19
Complete revascularization, n(%)	1447 (52.5)	51 (39.5)	96 (42.5)	1300 (54.1)§¤	<0.001
LVEF (%)	50 [40;55]	45 [37;53]	44 [35;50]	50 [40;55]§¤	<0.001
CHA2DS2-VASc	3 [2 ;5]	5 [4 ;6]¤	4 [3 ;6]§	3 [2 ;4]§¤	<0.001
Hospital duration (days)	6 [4;9]	7 [4;12]¤	10 [5;16]§	5 [4;8]§¤	<0.001
Medication at discharge					
Amiodarone, n(%)	174 (5.9)	45 (34.6)	91 (38.6)	38 (1.5)	<0.001
ACEI/ARB, n(%)	2715 (92.5)	112 (86.2)	195 (83)	2408 (93.7)	<0.001
Beta-blocker, n(%)	2768 (87.2)	113 (71.5)	207 (74.5)	2448 (89.4)	<0.001
Statin, n(%)	2790 (87.9)	119 (75.3)	209 (75.2)	2462 (90)	<0.001
Antiplatelet, n(%)	2892 (98.6)	112 (86.2)	228 (96.6)	2552 (99.4)	<0.001
Anticoagulant, n(%)	206 (6.9)	66 (50)¤	52 (22)§	85 (3.3)§¤	<0.001

Continuous variables given as median [IQR: 25;75]

AF, atrial fibrillation; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blockers; CKP, creatine kinase peak; CRP, c-reactive protein; HF, heart failure; LVEF, left ventricular ejection fraction; SBP, systolic blood pressure.

§ $p<0.005$ vs Prior AF

¤ $p<0.005$ vs De novo AF

Table 2 Total population in-hospital and 1-year post-discharge events

	Total	Prior AF	De novo AF	AF-free	*p*-value
In-hospital Events	**n=3173**	**n=158**	**n=278**	**n=2737**	
All-cause mortality, n(%)	234 (7.4)	28 (17.7)	42 (15.1)	164 (6)§¤	<0.001
CV mortality, n(%)	224 (7.1)	27(17.1)	41(14.7)	156 (5.7)§¤	<0.001
Non-CV mortality, n(%)	10 (4.3)	1 (3.6)	1 (2.4)	8 (4.9)	0.76
Reinfarction, n(%)	49(1.5)	4(2.5)	10(3.6)	35(1.3)¤	0.007
Stroke, n(%)	61(1.9)	7(4.4)	9 (3.2)	45 (1.6)§	0.011
Major bleeding (BARC 3 or 5), n(%)	203 (6.5)	14 (9.2)	34 (12.5)	155 (5.8)¤	<0.001
Heart failure (Killip ≥3), n(%)	405 (12.8)	41 (25.9)	93 (33.5)	271 (9.9)§¤	<0.001
Severe Ventricular Arrhythmia, n(%)	293 (9.2)	16 (10.1)¤	58 (20.9)§	219 (8)¤	<0.001
Severe atrioventricular block, n(%)	201 (6.3)	11(7)¤	40 (14.4)§	150 (5.5)¤	<0.001
One-year post-discharge events	**n=2561**	**n=108**	**n=213**	**n=2240**	
All-cause mortality, n(%)	143 (5.6)	22 (20.6)¤	25 (12.1)§	96 (4.3)§¤	<0.001
CV mortality, n(%)	96 (3.8)	16 (15)	21 (10)	59 (2.6)§¤	<0.001
Non-CV mortality, n(%)	47 (1.8)	6 (5.6)	4 (1.9)	37 (1.7)§¤	0.012
Readmission for HF, n(%)	136 (5.6)	19 (21.3)	26 (13.8)	91 (4.2)§¤	<0.001
Reinfarction, n(%)	50 (2.2)	4 (4.5)	3 (1.7)	43 (2.1)	0.29
Stroke, n(%)	21 (0.9)	2 (2.2)	1 (0.5)	18 (0.8)	0.33
Severe Ventricular Arrhythmia, n(%)	16 (0.8)	2 (3.1)	2 (1.4)	12 (0.7)	0.08

AF, atrial fibrillation; CV, cardiovascular.
§ p<0.005 vs Prior AF
¤ p<0.005 vs De novo AF

Table 3 Multivariate analysis for 1-year outcomes

A. Prior AF versus AF-free

	CV mortality		Readmission for heart failure	
	HR (CI95%)	***p*-value**	**HR (CI95%)**	***p*-value**
Prior AF	**2.006 (0.889;4.528)**	**0.093**	**2.501 (1.402;4.463)**	**0.001**
Male gender	1.46 (0.688;3.096)	0.32	0.704 (0.419;1.182)	0.18
Age	1.053 (1.02;1.088)	0.001	1.066 (1.044;1.09)	<0.001
Weight	0.986 (0.962;1.01)	0.25	0.994 (0.98;1.009)	0.50
History of hypertension	0.81 (0.408;1.604)	0.54	1.487 (0.899;2.459)	0.12
Current smoker	1.094 (0.475;2.523)	0.83	2.917 (1.723;4.938)	<0.001
History of stroke	2.043 (0.771;5.416)	0.15	1.078 (0.43;2.696)	0.87
Systolic Blood Pressure	0.991 (0.981;1.001)	0.10	1 (0.993;1.007)	0.91
Creatinine level	1.001 (1;1.003)	0.026	1.001 (1;1.003)	0.017
Angioplasty	0.443 (0.233;0.842)	0.013	1.31 (0.755;2.272)	0.33
Creatine Kinase peak	0.999 (0.999;1)	0.88	1 (1;1)	0.035
Killip ≥ III	1.957 (0.915;4.187)	0.08	2.173 (1.322;3.572)	0.002
LVEF	0.966 (0.939;0.994)	0.020	0.933 (0.915;0.952)	<0.001

B. De novo AF versus AF-free

	CV mortality		Readmission for heart failure	
	HR (CI95%)	***p*-value**	**HR (CI95%)**	***p*-value**
De novo AF	**2.485 (1.323;4.67)**	**0.004**	**1.97 (1.223;3.174)**	**0.005**
Male gender	1.083 (0.563;2.083)	0.81	0.606 (0.376;0.977)	0.039
Age	1.059 (1.028;1.092)	0.000	1.058 (1.036;1.08)	<0.001
Weight	0.984 (0.962;1.006)	0.16	0.995 (0.981;1.01)	0.55
History of hypertension	0.877 (0.456;1.686)	0.69	1.517 (0.947;2.43)	0.08
Current smoker	1.235 (0.547;2.787)	0.61	2.249 (1.317;3.842)	0.002
History of stroke	1.398 (0.542;3.606)	0.49	0.89 (0.384;2.061)	0.78
Systolic Blood Pressure	0.997 (0.988;1.006)	0.59	0.999 (0.993;1.006)	0.99
Creatinine level	1.001 (1;1.003)	0.031	1.001 (1;1.002)	0.031
Angioplasty	0.355 (0.198;0.638)	0.000	1.674 (0.942;2.975)	0.07
Creatine Kinase peak	0.999 (0.999;1)	0.86	1 (1;1)	0.008
Killip ≥ III	1.813 (0.897;3.664)	0.10	1.641 (1.01;2.668)	0.045
LVEF	0.984 (0.956;1.012)	0.26	0.935 (0.917;0.953)	0.000

AF, atrial fibrillation; CI, confidence interval; CV, cardiovascular; HR, hazard ratio; LVEF, left ventricular ejection fraction.

Table 4 Population characteristics according to the timing of de novo AF

	De novo AF <24 h (n=127)	De novo AF ≥24 h (n=151)	*p*-value
Baseline Characteristics			
Age (years)	74 [56;82]	78 [70;84]	0.001
Weight (%)	72 [63;82]	73 [65;81]	0.82
Male gender, n(%)	85 (67)	104 (68.9)	0.73
History of hypertension, n(%)	73 (57.5)	103 (68.2)	0.06
History of diabetes mellitus, n(%)	27 (21.3)	41 (27.2)	0.25
History of dyslipidemia, n(%)	65 (51.2)	81 (53.6)	0.68
Current smoker, n(%)	39 (30.7)	20 (13.4)	<0.001
History of coronary artery disease, n(%)	14 (11)	21 (13.9)	0.47
History of stroke, n(%)	7 (5.6)	14 (9.3)	0.24
History of renal failure, n(%)	3 (2.4)	9 (6)	0.14
Characteristics of qualifying myocardial infarction			
SBP at baseline (mmHg)	130 [110;143]	127 [110;150]	0.87
HF at admission (Killip ≥ II), n(%)	30 (24)	53 (35.6)	0.038
Creatinine value at baseline (µmol/L)	89 [72;114]	90 [73;116]	0.81
CKP peak (UI/L)	1970 [822;3537]	1606 [465;3241)	0.16
Anterior myocardial infarction, n(%)	51 (43.6)	53 (47.7)	0.51
Fibrinolysis, n(%)	14(11)	10 (6.6)	0.19
Angioplasty, n(%)	106 (85.5)	108 (73)	0.012
Multivessel disease, n(%)	66 (56.4)	85 (64.9)	0.17
Time from symptoms to reperfusion (h)	4.7 [4.2;7.9]	6.4 [4.5;10.7]	0.25
Complete revascularization, n(%)	51(45.9)	46 (40)	0.37
LVEF (%)	45 [38;50]	40 [35;50]	0.035
Hospital duration (d)	7 [4;13]	11 [7 ;18]	<0.001
Medication at discharge			
Amiodarone, n(%)	33 (30.3)	58 (45.7)	0.015
ACEI/ARB, n(%)	93 (86.1)	102 (80.3)	0.24
Beta-blocker, n(%)	98 (89.9)	109 (85.8)	0.34
Statin, n(%)	96 (88.1)	113 (89)	0.83
Antiplatelet, n(%)	105 (96.3)	123 (96.9)	0.83
Anticoagulant, n(%)	19 (16.7)	33 (26)	0.08

Continuous variables given as median [IQR: 25;75]

AF, atrial fibrillation; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blockers; CKP, creatine kinase peak; HF, heart failure; LVEF, left ventricular ejection fraction; SBP, systolic blood pressure.

Table 5 De novo AF patients in-hospital and one-year post-discharge events

	De novo AF <24 h	De novo AF ≥24 h	*p*-value
In-hospital Events	**n=127**	**n=151**	
All-cause mortality, n(%)	18 (14.2)	24 (15.9)	0.69
CV mortality, n(%)	18 (14.2)	23 (15.2)	0.80
Stroke, n(%)	4 (3.1)	5 (3.3)	0.94
Major bleeding (BARC 3 or 5), n(%)	15 (12.2)	19 (12.8)	0.87
Heart failure (Killip max ≥3), n(%)	35 (27.6)	58 (38.4))	0.056
Severe Ventricular Arrhythmia, n(%)	28 (22)	30 (19.9)	0.66
Persistent AF at discharge, n(%)	8 (6.3)	12 (7.9)	0.59
One-year post-discharge events	**n=99**	**n=114**	
All-cause mortality, n(%)	11 (11.2)	14 (12.4)	0.79
CV mortality, n(%)	8 (8.2)	13 (11.5)	0.42
Readmission for HF, n(%)	10 (11.2)	16 (16.2)	0.33
Stroke, n(%)	0 (0)	1 (1)	0.34

AF, atrial fibrillation; CV, cardiovascular.

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Figure 1. Flow chart

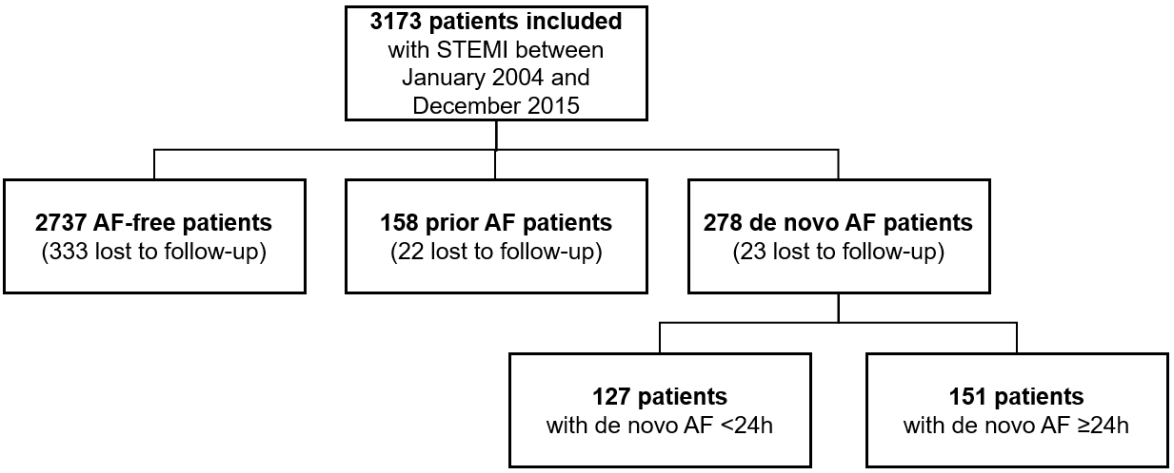
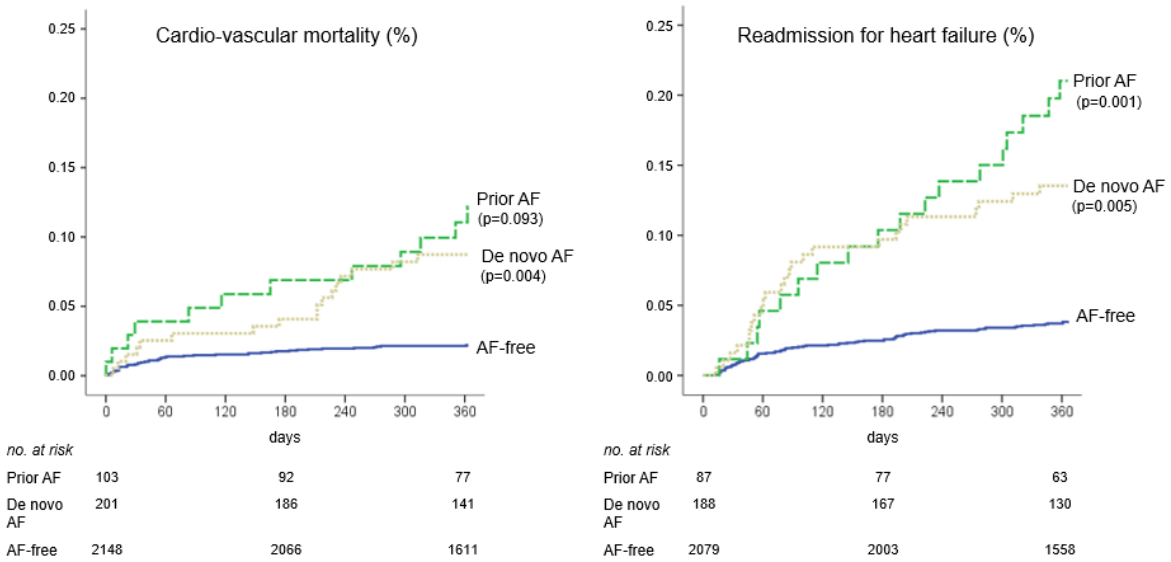


Figure 2. Survival curves



p values compare either prior AF and de novo AF to AF-free patients after multiple adjustments by Cox regression analysis.