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Atrial fibrillation during acute myocardial infarction: association with all-cause mortality and sudden death after 7-year of follow-up

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SUMMARY

Aims: Atrial fibrillation/flutter (AF/FL) is a common complication of acute myocardial infarction (AMI). Indeed, the determinants of AF/FL in AMI-patients and the association of AF/FL with mortality are not well-known. The purpose of the present study was to investigate the relationship between presence of AF/FL and mortality in patients with AMI and to report on predictors of AF/FL. **Methods:** We studied 505 patients enrolled in three intensive care units with definite AMI and followed up for 7 years. No patient was lost to follow-up. Patients with AF/FL during the 1st week of hospitalisation were compared with those with steady sinus rhythm. End-points were all-cause mortality and modes of death. **Results:** At multivariable logistic regression analysis, elderly, body mass index, congestive heart failure (CHF), history of hypertension and plasma cholesterol (in a negative fashion) were independently associated with the presence of AF/FL. At survival analysis, after full adjustment, AF/FL was not associated with in-hospital mortality. After 7 years of follow-up, AF/FL was found to be associated with all-cause mortality [adjusted odds ratio (OR) = 1.6; 95% confidence interval (CI) = 1.2–2.3], together with age, diabetes mellitus, creatine kinase-MB isoenzyme (CK-MB) peak, CHF, estimated glomerular filtration rate and thrombolysis. At adjusted logistic polynomial regression analysis, AF/FL was found to be associated with an excess of mortality for reasons of sudden death (SD) (adjusted OR = 2.7; 95% CI = 1.2–6.4). No interaction was observed between AF/FL and medications on in-hospital mortality. For 7-year mortality, angiotensin-converting enzyme (ACE)-inhibitors and digitalis showed an independent negative (protective) interaction chiefly on SD (adjusted OR = 0.06; 95% CI = 0.01–0.74, and RR = 0.10; 95% CI = 0.02–0.58, respectively). **Conclusions:** Patients with AMI and AF/FL portend a poor prognosis in the long-term chiefly because of an excess of SD. Treatment with ACE-inhibitors and digitalis may have long-term beneficial effects on SD.

What's known
- AF/FL during AMI is known to affect prognosis negatively, but few data are available for long-term mortality and causes of death. ACE-inhibitor and digitalis treatments affect outcomes after AMI, but differences in their effects on AMI patients with or without SR are not available in the long-term.

What's new
- Our study shows that AF/FL FL during AMI is independently associated with increased 7-year mortality and that the excess mortality is chiefly because of SD.
- ACE-inhibitors and digitalis showed an independent negative (protective) interactive effect with AF/FL on long-term SD.

Introduction

Atrial fibrillation/flutter (AF/FL) is a common complication of acute myocardial infarction (AMI) and management of this condition and its complications now consumes a significant slice of healthcare expenditure, particularly in western countries where the populations continue to advance in age (1,2). Older age and presence of congestive heart failure (CHF) are considered the most important predictors of AF/FL, while the role of other clinical factors is not well known (2,3). AF/FL during AMI has been shown to be associated with early and long-term mortality (1,2,4–6). Only a recent analysis by Pedersen et al. has investigated the association between AF/FL and causes of death after AMI (7). Most of these studies examined only new onset AF/FL during AMI, excluding persistent AF/FL from analysis.

The purpose of the present analysis was to investigate whether there is a relationship between presence of AF/FL (either persistent or new onset AF/FL) and mortality and modes of death in an unselected sample of AMI patients followed up for 7 years. In addition, the study reports on predictors of AF/FL during AMI.

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Methods

Patients

This is a prospective study including 557 unselected consecutive white patients admitted with definite AMI to the intensive care units of three hospitals in north-east Italy from 21 June, 1995 to 19 January, 1998. AMI was diagnosed when at least two of the following were present: central chest pain lasting more than 30 min, characteristic changes in serum enzymes [total creatine kinase and MB-isoenzyme (CK-MB) of creatine kinase], electrocardiographic changes with pathological Q-waves and/or localised ST-T changes in at least two contiguous leads. Twenty-nine patients with concomitant acute inflammatory-infective clinical situations were excluded. Additional patients were excluded for reasons of neoplastic disease ($n = 4$), death within 3 days of admission ($n = 7$) and insufficient data collection ($n = 12$). The final analysis was performed in 505 patients. Written informed consent was obtained from all patients and the study was approved by each hospital Ethics Committee.

Measurements

In all patients, a thorough medical history was taken from medical records or patient interview. All baseline clinical and laboratory data were obtained during the first 7 days of hospitalisation. Venous blood was drawn for determination of serum levels of total cholesterol and creatinine. An estimated glomerular filtration rate (eGFR) at baseline was calculated with the use of the modified modification of diet in renal disease (MDRD) four-component equation incorporating age, gender, race and serum creatinine level (8). This 'simplified' MDRD formula (ml/min per 1.73 m^2) is calculated according to the following equation: $186.3 \times (\text{serum creatinine})^{-1.154} \times (\text{age})^{-0.203}$, multiplied by a correction factor, for female subjects $\times$ 0.742 and for black subjects $\times$ 1.212. On the 1st day (soon after admission to intensive care unit) and 3rd day (between 7:00 and 8:00 a.m.), blood pressure was measured by especially trained nurses, using a mercury sphygmomanometer with a cuff of appropriate size and the mean of three readings was used. The presence and degree of heart failure were assessed according to the Killip classification (9). Left ventricular ejection fraction (LVEF) was assessed by two-dimensional echocardiography between the 3rd and 7th day after enrolment according to Simson's method and recorded on videotape (VHS) (10). For the patients who had AF/FL, appropriate rate control was required at the time of left ventricular examination. LVEF was missing for 39 patients who underwent echocardiography after discharge from the intensive care units and other 20 patients. Forty-four subjects in whom the echocardiographic images were technically unsatisfactory were discarded from the analysis. Thus, LVEF was available in 402 patients. The records were examined by two physicians who had no knowledge of patient clinical data.

Atrial fibrillation/flutter

Continuous electrocardiographic monitoring was available during the 7 days of hospital stay for all patients. A patient was considered to have AF/FL if the arrhythmia was present or appeared for at least 60 s, at any time during the 7-day hospitalisation. This cut off was chosen to detect all patients with AF/FL during AMI (11). AF was diagnosed as absence of P waves and presence of QRS complexes in an irregular rhythm with or without the presence of coarse or fine fibrillatory waves. Atrial flutter was diagnosed as presence of a flutter line and/or a 'P' wave in a regular rhythm at a rate of above 250 b/min and QRS complexes in a regular or irregular rhythm with an RR interval which is a multiple of the length of the flutter wave. AF/FL was considered to be permanent if it was present from admission until the 7th day of hospitalisation; if a patient had sinus rhythm on admission and experienced AF/FL during the 7 days of hospital stay, this was considered as new onset AF/FL. In the present analysis, all patients with AF/FL (either permanent or new onset) were considered as a single group and compared with those with steady sinus rhythm.

Follow-up

Every year for 7 years after recruitment, each patient was called for a clinical check-up. All available data relevant to the cause of death were collected by means of specific inquiries. For those who died during a hospital stay, the date and cause of death were obtained from the hospital records (including post-mortem report, where available). For those who died outside the hospital, data were obtained from the family doctor and from death certificate. No patient was lost to follow-up and all patients had exactly 7 years of follow-up length. End-points were all-cause mortality and modes of death. Main causes of death were classified as CHF death, sudden death (SD), other non-sudden cardiovascular (CV) death and non-CV death. SD was defined as out-of-hospital, witnessed cardiac arrest or death within 1 h after the onset of acute symptoms or unexpected, unwitnessed death (e.g., during sleep) in patients known to have been well within the previous 24 h (12). Deaths resulting from deterioration of heart failure with progression of congestive symptoms or pulmo-

nary oedema or cardiogenic shock were classified as deaths from CHF. All deaths were classified by two doctors blinded to baseline information. Thrombolysis, ACE-inhibitors, β-blockers, calcium-channel blockers, anti-arrhythmic drugs (class 1C and amiodarone), digitalis, antiplatelets and anticoagulants during the 1st week of hospital stay and during the follow-up were recorded and used as dichotomous variables.

Statistical analysis

Statistical analysis was performed using Systat 12 (Systat Software Inc., Chicago, IL) and JMP 4 (SAS Institute Inc., Cary, NC). Data accrued on each patient included both measured (continuous) and categorical variables. Skewed variables were log-transformed before analysis. For continuous variables, comparison between groups was made using unpaired Student's *t*-test. The chi-square (χ^2) test was used for categorical variables. Association between variables and AF/FL was tested with logistic regression analysis survival analysis was made using the Cox proportional hazard regression model (13). The multivariable Cox model was reduced by removing each variable that was non-significant and/or causing the least change in significance. This procedure was continued until no further variables could be removed without producing a significant change in the model. This final model was determined to be the 'parsimonious' multivariable model. The risk was quantified as a hazard ratio with 95% CI. For continuous variables, the unit of increased risk of mortality is for 1-SD increase in the variable.

Survival curves were constructed by the Kaplan–Meier method and compared by the log-rank test. The association between variables and modes of death were tested by means of mutivariable polynomial logistic. Possible interactions between medications and AF/FL for mortality were tested in the polynomial regression models. Data on interactions were reported only for fully adjusted models. These interactions were tested to verify differences in the effect of one variable (treatment) depending on the level of the second variable (AF/FL) (13).

Baseline characteristics are summarised with medians and interquartile ranges for continuous variables and with numbers and percentage for categorical variables. For all hypotheses tested, two-tailed p-values < 0.05 were deemed significant.

Results

Baseline characteristics

During the 1st week of hospitalisation, 64 (12.7%) patients had AF/FL [of whom 46 (9.1%) experienced new onset AF/FL]. Clinical characteristics of the AMI patients according to presence/absence of AF/FL are shown in Table 1. Patients with AF/FL were older, were less frequently male and smoked less. Hypertension was more frequent among AF/FL patients, while no difference was observed for body mass index, presence of diabetes mellitus, previous myocardial infarction or angina pectoris. Among AF/FL patients, prehospital time delay was longer, heart rate and serum creatinine values were higher and total cholesterol level was lower. Systolic and diastolic blood pressures on admission, CK-MB peak and prevalence of non-ST elevation AMI did not differ between the two groups. Presence of CHF was higher and LVEF was lower among the AF/FL patients. Thrombolysis, antiplatelets and ß-blockers were less frequently used among AF/FL patients, whereas ACE-inhibitors, diuretics, anti-arrhythmics and digitalis were used more frequently. During the follow-up period, AF/FL patients received more frequently anticoagulants, diuretics, anti-arrhythmic drugs (class 1C or amiodarone) and digitalis and less frequently antiplatelets, ß-blockers and calcium channel blockers (Table 1).

Determinants of Atrial fibrillation/flutter

The variables found to be associated with AF/FL at univariable level were age, gender, hypertension, eGFR, plasma cholesterol, presence of CHF and LVEF (Table 2). Blood pressure, body mass index, presence of diabetes mellitus, history of myocardial infarction or angina, prehospital time delay and CK-MB peak were also included in the multivariable model because of their clinical relevance (Table 2). AMI site and in-hospital ventricular arrhythmias were also tested, but were not included because of insignificant association with AF/FL and mortality. At multivariable logistic regression analysis, only age, body mass index, CHF, hypertension and cholesterol (in a negative fashion) were independently associated with the presence of AF/FL either in the global model or in the parsimonious one (Table 2). We did not find any association between blood pressure and the presence of AF/FL (adjusted $T = 0.1$, $p = 0.93$ for systolic and adjusted $T = 0.1$, $p = 0.72$ for diastolic blood pressure). Inclusion of thrombolysis, β-blockers, ACE-inhibitors, calcium channel blockers, diuretics, anti-arrhythmics and digitalis, given during the 7 days of hospitalisation, did not modify the associations.

In-hospital mortality

All the above mentioned variables were also tested for prediction of early and long-term mortality. In-hospital mortality was higher among patients

Table 1 Clinical characteristics of the Patients according to absence/presence of atrial fibrillation/flutter (AF/FL)

	Sinus rhythm *n* = 441	AF/FL *n* = 64	p
Age (years)	67 (58–74)	75 (67–82)	< 0.0001
Female gender (%)	27	39	0.05
Body mass index (Kg/m^2)	25.7 (23.9–28.1)	25.4 (23.6–29.2)	0.53
Previous myocardial infarction (%)	21	26	0.28
History of angina (%)	20	20	0.28
Current smoking (%)	40	27	0.04
Hypertension (%)	44	67	0.001
Diabetes mellitus (%)	24	27	0.60
Prehospital time delay (min)	180 (120–540)	360 (180–885)	0.01
Total cholesterol (mmol/l)	5.4 (4.7–6.3)	4.6 (4.0–5.8)	< 0.0001
Systolic blood pressure (mmHg)	122 (112–134)	124 (110–139)	0.62
Diastolic blood pressure (mmHg)	76 (73–80)	76 (71–84)	0.80
Heart rate (bpm)	70 (60–81)	82 (72–90)	< 0.0001
Serum creatinine (μmol/l)	88 (80–97)	97 (80–115)	0.003
CK-MB peak (U/l)	123 (70–231)	137 (56–287)	0.70
Non-ST elevation (%)	26	22	0.47
Killip class > 1 (%)	28	69	< 0.0001
LVEF (%) (*n* = 402)	52 (45–60)	45 (35–52)	< 0.0001
Arrhythmias (%)*	29	28	0.88
Medications at enrollment (1st week)			
Thrombolysis (%)	42	23	0.004
Antiplatelets (%)	91	83	0.03
Anticoagulants (%)	97	98	0.64
ß-blockers (%)	42	23	0.005
ACE-inhibitors (%)	38	59	0.002
Calcium channel blockers (%)	20	12	0.15
Diuretics (%)	30	69	< 0.0001
Anti-arrhythmics (%)	19	41	< 0.0001
Digitalis (%)	10	44	0.0001
Medications during follow-up			
Antiplatelets (%)	75	44	< 0.0001
Anticoagulants (%)	9	20	0.008
ß-blockers (%)	38	22	0.01
ACE-inhibitors (%)	45	45	0.94
Calcium channel blockers (%)	39	17	0.01
Diuretics (%)	31	50	0.004
Anti-arrhythmics	7	17	0.008
Digitalis (%)	12	36	< 0.0001

Data are median and interquartile range or percentage. *Tachy- and brady-arrhythmia excluding perithrombolytic period.
CK-MB, creatine kinase-MB isoenzyme; LVEF, left ventricular ejection fraction.

with AF/FL compared with patients with sinus rhythm (21.9% vs. 5.9%, p < 0.0001). At univariable Cox analysis, AF/FL resulted associated with in-hospital mortality (OR = 4.5; 95% CI = 2.2–9.1; p < 0.0001), while after adjustment for age, Killip class, eGFR and hypertension (all significant predictors in the fully adjusted model), AF/FL was no longer associated with outcome (OR = 1.9; 95% CI = 0.8–4.6; p = 0.15). Also new onset AF/FL was not associated with in-hospital mortality (data not shown).

Seven-year mortality and modes of death

After 7 years of follow-up, 217 (43.0%) patients had died. Data for a patient who had died in a car accident and one who had undergone heart transplantation were censored at the time of the event. Hence in the following analyses, 215 (42.6%) deaths were considered. Patients with AF/FL had higher all-cause 7-year mortality rate, with higher incidence for CHF-mortality and SD (Table 3). Figure 1 shows the 7-year Kaplan–Meier survival curves in the patients with and without AF/FL.

Table 2 Univariable and multivariable logistic analysis of predictors of atrial fibrillation/flutter (AF/FL) during myocardial infarction (n = 505)

	Univariable		Multivariable (global model)		Multivariable (parsimonious model)	
Predictors of AF/FL	***T***	**p**	***T***	**p**	***T***	**p**
Age (years)	4.7	< 0.0001	2.6	0.009	2.5	0.01
Female gender	1.9	0.05	0.1	0.90		
Body mass index (Kg/m^2)	0.6	0.53	2.5	0.01	2.2	0.03
Hypertension	3.2	0.002	2.5	0.01	2.1	0.03
Diabetes	0.5	0.60	−1.6	0.11		
History of angina	0.1	0.95	−0.9	0.37		
History of myocardial infarction	1.1	0.28	0.8	0.41		
Log-prehospital time delay (min)	2.5	0.01	1.1	0.25		
Log-eGFR (1st day) (ml/min)	−3.7	< 0.0001	0.7	0.45		
Cholesterol (1st day) (mg/dl)	−4.1	< 0.0001	−3.3	0.001	−3.6	< 0.0001
Log-CK-MB peak (IU/l)	0.4	0.66	0.9	0.36		
Killip class > 1 (1st day)	6.0	< 0.0001	4.6	< 0.0001	4.7	< 0.0001
LVEF (%) (n = 402)	−3.4	0.001	−1.8	0.07		

eGFR, estimated glomerular filtration rate; CK-MB, creatin kinase-MB isoenzyme; LVEF, left ventricular ejection fraction.

At Cox survival analysis, AF/FL r was found to be associated with all-cause mortality both at univariable level and after full adjustment (Table 4). The other independent predictors of death were age, adjusted OR = 2.5 (95% CI = 2.0–3.1); diabetes mellitus, OR = 1.7 (95% CI = 1.3–2.3); CK-MB peak OR = 1.2 (95% CI = 1.1–1.4); Killip class > 1, OR = 1.7 (95% CI = 1.3–2.3); eGFR, OR = 0.7 (95% CI = 0.6–0.8) and thrombolysis, OR = 0.5 (95% CI = 0.3–0.7). At unadjusted logistic polynomial regression analysis, AF/FL was associated with death caused by CHF, SD and other non-sudden CV causes, but not to non-CV causes (Table 4). After fully adjusting for the independent predictors of death mentioned above, AF/FL was found to be independently associated with SD and not with the other causes of death (Table 4).

Impact of LVEF on association of AF/FL with modes of death

In a multivariable Cox model including LVEF, both LVEF and AF/FL were found to be associated with all-cause mortality (OR = 0.6; 95% CI = 0.5–0.7; p < 0.0001, and OR = 1.9; 95% CI = 1.2–2.8; p = 0.04, respectively). In the logistic multivariable polynomial regression model including LVEF, AF/FL

Table 3 Seven-year mortality rate of the patients according to absence/presence of atrial fibrillation/flutter (AF/FL)

	Sinus rhythm n = 441	**AF/FL n = 64**	**p**
All-cause mortality (%)	38.5	70.3	< 0.0001
CHF mortality (%)	7.3	18.7	0.002
Sudden death (%)	9.5	23.4	0.001
Other CV mortality (%)	15.0	21.9	0.15
Non CV mortality (%)	6.8	6.2	0.86

CHF, congestive heart failure; CV, cardiovascular.

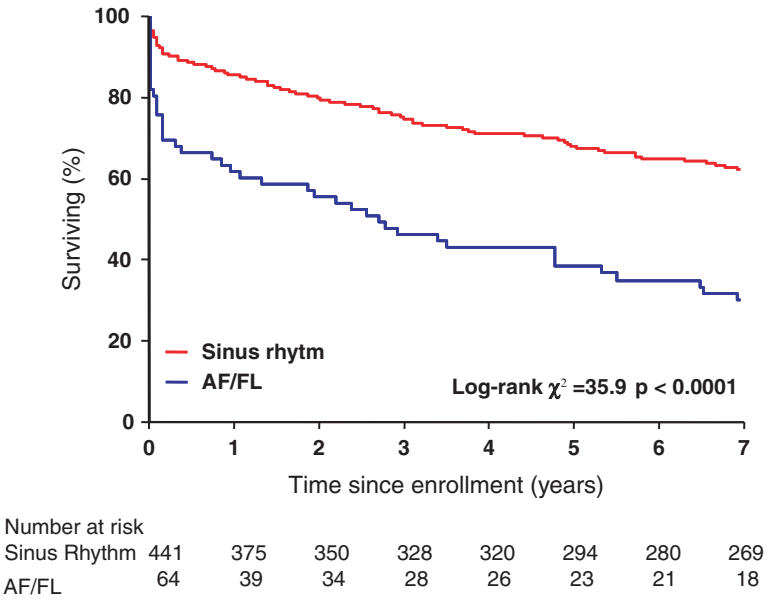

Figure 1 Kaplan–Meier estimates of the probability of all-cause mortality in 505 AMI patients according to absence/presence of atrial fibrillation/flutter (AF/FL)

Table 4 Logistic polynomial regression analysis of association between atrial fibrillation/flutter and 7-year causes of death in 505 AMI patients

	Univariable		Multivariable*	
Modes of death	**OR (95% CI)**	**p**	**OR (95% CI)**	**p**
All-cause mortality	2.6 (1.9–3.6)	< 0.0001	1.6 (1.2–2.3)	0.006
CHF mortality (%)	5.3 (2.4–12.0)	< 0.0001	1.6 (0.6–4.4)	0.32
Sudden death (%)	5.1 (2.4–10.8)	< 0.0001	2.7 (1.2–6.4)	0.02
Other-CV mortality (%)	3.0 (1.4–6.3)	0.003	1.7 (0.7–4.1)	0.26
Non-CV mortality (%)	1.9 (0.6–6.0)	0.27	1.2 (0.3–4.2)	0.76

*Multivariable model included age, diabetes mellitus, CK-MB peak, Killip class > 1, estimate glomerular filtration rate, and thrombolysis. CHF, congestive heart failure; CI, confidence interval; CV, cardiovascular; OR, odds ratio.

showed an independent association with SD (OR = 2.8; 95% CI = 1.1–7.6 p = 0.03) and a marginal relationship with CHF-mortality (OR = 2.5; 95% CI = 0.9–7.2 p = 0.07). No interaction was found between AF/FL and LVEF for either all-cause death or SD.

Interaction between medications and AF/FL for mortality and modes of death

Possible interactions between medication and AF/FL were tested for thrombolysis, ß-blockers, ACE-inhibitors, calcium channel blockers, diuretics, anti-arrhythmics and digitalis. After including medications in the survival models, the association between AF/FL and outcomes did not significantly change either for in-hospital or for long-term mortality (data not shown).

After full adjustment, no interactions were observed between medications and AF/FL for in-hospital mortality. For 7-year mortality, ACE-inhibitors showed a negative interactive (protective) effect on SD (Table 5). Digitalis showed a negative interaction with AF/FL for all-cause mortality, CHF mortality and SD. β-blockers showed a marginal negative interaction only for non-sudden CV causes of death (p = 0.07) and diuretics showed a marginal negative interaction for CHF (p = 0.09) and SD (p = 0.07). After excluding in-hospital mortality and taking into account only treatment during follow-up, both ACE-inhibitors and digitalis showed a negative interaction

Table 5 Fully adjusted interactions between atrial fibrillation/flutter and treatment with ACE-inhibitors or digitalis on mortality and causes of death

	ACE-inhibitors		Digitalis	
	OR (95% CI)	p	OR (95% CI)	P
7-year follow-up (n = 505)				
All-cause mortality	–	–	0.14 (0.04–0.87)	0.03
CHF mortality	–	–	0.03 (0.01–0.32)	0.003
Sudden death	0.06 (0.01–0.74)	0.02	0.10 (0.02–0.58)	0.01
7-year follow-up excluding in-hospital mortality (n = 465)				
All-cause mortality	0.12 (0.02–0.84)	0.03	0.14 (0.03–0.69)	0.01
CHF mortality	–	–	–	–
Sudden death	0.05 (0.01–0.40)	0.005	0.04 (0.01–0.29)	0.001

OR, odds ratio; CI, confidence interval.

for all-cause mortality and SD (Table 5). Accordingly, the same results were obtained testing separately the two subgroups of AMI patients with sinus rhythm or AF/FL, using Cox regression, instead of interaction analysis (data not shown). No interactions were found between medications and AF/FL for the other modes of death. Thrombolysis, calcium channel blockers and anti-arrhythmic drugs (class 1C or amiodarone), did not show any interaction with AF/FL. None of the above mentioned medications showed independent positive interactive (unfavourable) effect with AF/FL for mortality.

Discussion

In this study, age, CHF, hypertension and plasma cholesterol (in a negative fashion) were independently related to AF/FL following AMI. Survival analysis showed that AF/FL is independently associated with increased 7-year mortality after AMI and that the excess mortality is chiefly because of SD. ACE-inhibitors and digitalis showed an independent negative (protective) interactive effect with AF/FL on SD.

Predictors of Atrial fibrillation/flutter

Even if a short time cut was chosen to establish presence of AF/FL during hospital stay, the incidence of AF/FL was similar to most reports on AF/FL during AMI (which ranges from about 9–21%) (1,2). This study confirms that age, CHF, and body mass index are associated with presence of AF/FL during AMI (2,3,14). In addition, cholesterol levels showed an independent negative association with AF/FL. Also in patients free from coronary artery disease, low levels of total cholesterol have been reported to be independently associated with paroxysmal atrial fibrillation (15). Although the mechanism underlying this observation remains unclear, it has been suggested that hypolipidaemia may cause electrophysiological changes that may favour the occurrence of arrhythmias (15). According to other reports, our study showed that hypertension is a determinant of the presence of AF/FL during AMI (16). Left ventricular hypertrophy, impaired left ventricular filling, structural changes of the left atria and slowing of atrial conduction velocity have been implicated as possible causative factors for this association (16–19). Whether there is a relationship between high blood pressure soon after AMI and atrial fibrillation is controversial (2–4,6). In the present study, blood pressure on admission did not show any relationship, either linear or curvilinear, with the presence of AF/FL. However, it should be pointed out that blood pressure may be subject to wide variations soon after AMI also as a result of therapeutic intervention.

Atrial fibrillation/flutter and outcomes

According to other authors, we failed to demonstrate an independent association between AF/FL and in-hospital mortality after adjustment for several confounders, while other data reported an association between atrial fibrillation and early mortality after AMI (2,5,6,20,21). Differences in selection criteria at randomisation and data adjustment can at least partially account for these discrepant results.

The independent prediction of AF/FL for long-term mortality observed in the present study, also in fully adjusted models, is in keeping with most results of the literature (1,5,21). However, little is known on the association between atrial fibrillation and modes of death and only recently did Pedersen et al. find an excess mortality due to an increase in both SD and non-sudden CV mortality in patients with atrial

fibrillation soon after AMI (7). In our univariable analyses, AF/FL was associated with CHF-mortality, SD, and non-sudden CV death. However, after adjustment for clinical confounders, AF/FL remained associated only with SD. The association with SD remained significant also after adjusting for LVEF, which is considered to be the most important predictor of SD in patients with coronary heart disease (22). At variance with the results by Pedersen et al, we did not find an interactive effect of AF/FL with LVEF on SD (7). A possible explanation for the lack of association between AF/FL and non-sudden CV mortality in the present study is the inclusion of more clinical confounders in the survival regression models. In particular, plasma creatinine is known to be an important predictor of CHF and is independently associated with adverse outcome in post-AMI patients (23).

Interaction between AF/FL and medications

A few studies reported on the effects of medication in post-AMI patients with atrial fibrillation (24,25). In this study, we found an independent negative interaction of ACE-inhibitors with AF/FL vs. 7-year SD and all-cause mortality. From a clinical standpoint, this means that ACE-inhibitors have different influence in the patients' outcome, being higher the protective effect in the AMI patients with AF/FL than in AMI-patients with sinus rhythm. As shown in the results section, this effect is independent from the baseline clinical characteristic of the patients. It has been claimed that suppression of renin–angiotensin system activity has positive effects on ventricular and atrial remodeling, which might reduce the incidence of malignant arrhythmias in the long-term (26). This mechanism, at least partially, can explain why AMI patients with AF/FL, have a proportionally higher beneficial effect from treatment with ACE-inhibitors.

A marginal negative interaction was found for β-blockers vs. non-sudden CV mortality and for diuretics vs. CHF death and SD. These findings indicate that β-blocker and diuretic effects on mortality are only slightly different in AMI-patients with or without AF/FL. Although in patients with coronary artery disease, β-blockers have been shown to reduce the risk of CV death and SD, their role in reducing mortality risk in patients with AF/FL is still under debate (27). A subanalysis of patients with AF/FL in large heart failure trials did not show any reduction in mortality from β-blockade, but no data were available for SD (28,29). In a subanalysis of the RACE study, β-blockers showed a protective effect on SD, but in that study, only a minority of the patients had history of coronary artery disease (27).

Digitalis also showed a protective effect for all cause mortality, chiefly affecting SD. Although digitalis glycosides were introduced for the treatment of cardiac disorders almost 200 years ago, controversy persists regarding their role, particularly in patients with coronary artery disease. With the advent of more potent diuretics and the demonstrated benefit of vasodilators in left ventricular unloading, the relative worth of digitalis in patients with coronary artery disease and myocardial infarction is being reexamined (30). Studies on digitalis given before or after experimental coronary occlusion gave conflicting results (30). Also clinical studies on digitalis and outcomes after AMI brought about discordant conclusions, probably depending on the stratification of the patients, the outcomes considered and the dose given (30). Indeed, little is known about the effect of digitalis on SD after AMI. While digitalis is claimed to cause deleterious effects in patients with coronary heart disease, in the patients with AMI and concomitant AF/FL at baseline, it can contribute to prevent the excess mortality chiefly associated with SD (31). It can be speculated that the rate control achievable with digitalis explains its beneficial effect. However, according with a reanalysis of the SPRINT trial, we believe that also the low dose of digoxin given in this study (virtually all patients received less than 1.5 mg/week) may contribute to explain the beneficial effect of digitalis in AMI-patients with AF/FL (32).

Limitations of the study

The main limitation of the present study is that we have neither data on history of AF/FL before enrolment of the patients in the intensive care units nor data after discharge. However, our study focuses on the acute phase of AMI and deals with the presence of AF/FL in such a setting. In addition, it is to be mentioned that LVEF in the setting of AMI may not be as valid as assessment in convalescent patients for long-term prognosis; however, according to most studies on prognosis after AMI, we chose to model only clinical features accrued during hospital stay. Finally, the association of AF/FL with SD and other causes of death were based on a relatively small number of events and, thus, further studies are necessary to confirm the present findings.

Conclusion

AF/FL during AMI is more frequent in the elderly, overweight and hypertensive subjects and in the patients with CHF or hypocholesterolaemia. These arrhythmias independently portend a poor prognosis after 7-year of follow-up, chiefly because of an excess of SD. Treatment with ACE-inhibitors and digitalis

may have long-term beneficial effects in subjects with AMI and AF/FL at baseline.

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Author contributions

Concept/design, G. Berton and P. Palatini; Data analysis/interpretation, G. Berton and R. Cordiano; Drafting article, G. Berton and P. Palatini; Critical revision of article, P. Palatini, F. Cavuto, M. Pellegrinet and F. Cucchini; Statistics, G. Berton; Data collection, R. Cordiano, F. Cavuto, M. Pellegrinet and G. Berton.

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