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The occurrence and prognostic significance of atrial fibrillation/-flutter following acute myocardial infarction

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Aims To investigate the occurrence and prognostic significance of atrial fibrillation/-flutter following acute myocardial infarction

Methods and Results The occurrence and prognostic significance of atrial fibrillation/-flutter were studied in 6676 consecutive patients with acute myocardial infarction screened in 27 centres in Denmark for inclusion into the TRAndolapril Cardiac Evaluation (TRACE) study. Information about occurrence of atrial fibrillation/-flutter during hospitalization was prospectively collected for the following three periods: day 1–2, day 3–4 and from day 5 until discharge. A total of 1395 patients (21%) suffered from atrial fibrillation/-flutter in one or more of the specified periods during hospitalization. Patients with atrial fibrillation/-flutter were significantly older, a significantly greater proportion were women, left ventricular systolic dysfunction was more extensive, thrombolytic therapy was received less frequently, and anterior Q wave myocardial infarction was experienced more frequently than patients without atrial fibrillation/-flutter. History of acute myocardial infarction and/or angina pectoris was similar in patients with and without atrial fibrillation/-flutter, whereas significantly more patients with atrial fibrillation/-flutter had a history of hypertension, congestive heart failure, diabetes mellitus, pulmonary disease and stroke. The unadjusted in-hospital mortality rate was significantly higher in patients with atrial fibrillation/-flutter in one or more of the specified periods during hospitalization (18%) than in patients without atrial fibrillation/-flutter (9%), $P<0{\cdot}001$. After adjustment for baseline characteristics, the presence of atrial fibrillation/-flutter was still associated with increased in-hospital mortality; odds ratio = 1·5 (95% Cl: 1·2–1·8), $P<0{\cdot}001$. In patients surviving hospitalization, the unadjusted 5-year mortality rate was also significantly higher in patients suffering from atrial fibrillation/-flutter (56%) than in patients without atrial fibrillation/-flutter (34%), $P<0{\cdot}001$. After adjustment for important prognostic baseline characteristics, the presence of atrial fibrillation/-flutter was still associated with an increased mortality, relative risk = 1·3 (95% Cl: 1·2–1·4). Subgroup analysis revealed that sustained atrial fibrillation/-flutter during hospitalization was associated with the highest risk of dying, relative risk = 1·4 (95% Cl: 1·2–1·7).

Conclusion Atrial fibrillation/-flutter often occurs after acute myocardial infarction and our analysis demonstrated that it was an independent predictor of an increased short and long-term mortality.
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Key Words: Myocardial infarction, atrial fibrillation, atrial flutter, morbidity, mortality.

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Introduction

Atrial fibrillation is a common arrhythmia following acute myocardial infarction and the overall percentage observed in previous studies ranges between 5% and 23%[1]. In addition to the damage to the myocardium caused by the myocardial infarction, the presence of atrial fibrillation will further compromise cardiac function. This arises from loss of atrial contraction and an irregular and often rapid heart rate, causing insufficient diastolic filling of the ventricles[2]. This reduction in cardiac function caused by the presence of atrial fibrillation, may increase the risk of in-hospital complications

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such as congestive heart failure, cardiogenic shock, ventricular arrhythmias and serious thromboembolic complications, as observed in previous studies[1,3]. Not only has atrial fibrillation the potential of increasing morbidity but also mortality. Whether this is the case remains controversial. Some studies have reported that the presence of atrial fibrillation following an acute myocardial infarction is associated with increased in-hospital mortality[4–7], whereas others have not[8–12]. Similar controversial results have been reported in patients surviving hospitalization with respect to long-term mortality[1,7,13–15]. Most of these studies were performed before the use of thrombolytic therapy, prophylactic antithrombotic treatment and invasive procedures in the management of acute myocardial infarction, and relatively few studies have addressed this issue recently[16,17]. In the present study, based on the TRAndolapril Cardiac Evaluation (TRACE) study screening database, the prognostic impact of atrial fibrillation was further explored. This was studied in consecutive patients with acute myocardial infarction while adjusting for very strong predictors of mortality, such as left ventricular systolic function, and in comparison to previous studies it was possible to distinguish between intermittent and sustained atrial fibrillation.

Methods

Patients

The present study consists of data collected from 6676 consecutive acute myocardial infarction patients, screened for inclusion into the TRACE study[18]. A detailed description of this population has been reported previously[19]. The TRACE study was a post-myocardial infarction study in which the efficacy and safety of the angiotensin converting enzyme inhibitor trandolapril was investigated. Of the 6676 screened patients, 1749 patients qualified for inclusion into the TRACE study and were randomized to trandolapril treatment or placebo. The present investigation will focus on all 6676 patients. In brief, the patients were recruited from May 1990 to July 1992 in 27 centres in Denmark. Consecutive patients above 18 years old with acute myocardial infarction were screened between day 2 and day 6 after the onset of symptoms. The criteria for myocardial infarction were chest pain or electrocardiographic changes suggestive of infarction or ischaemia, accompanied by an increase in the level of one or more cardiac enzymes to at least twice the upper limit of the normal value at the laboratory of the participating hospital. Information regarding medical history was obtained, important clinical data and complications during hospitalization were prospectively collected, including data on the presence of arrhythmias. The method of echocardiography used for the screening procedure has previously been described in detail[20]. By the use of a nine-segment model of the left ventricle, a wall motion index was calculated using a reverse scoring system, as described by Berning *et al.*[21]. With this scoring system, wall motion index = 2·0 corresponds to a left ventricular ejection fraction = 60%, wall motion index = 1·2 to a left ventricular ejection fraction = 35% and wall motion index = 0·6 to a left ventricular ejection fraction = 18%. According to the available 12-lead electrocardiographic recordings and reports of monitoring, the investigators had to report whether atrial fibrillation/-flutter was present in the following periods during hospitalization: day 1–2, day 3–4 and from day 5 until discharge from hospital. The diagnosis of atrial fibrillation and atrial flutter was left to the discretion of the investigators, according to the following criteria: atrial fibrillation = absence of P waves, coarse or fine fibrillatory waves and completely irregular RR-intervals; atrial flutter = presence of regular P waves with a rate between 250–350 . min^{-1} and regular or irregular RR-intervals. In case of the absence of electrocardiographic recordings available from a period, this was reported by the investigators as missing data. The study was approved by the ethics committee and informed consent was obtained before screening.

Information regarding mortality was obtained by interrogating the Danish central personal register and mortality data were available for all but three patients.

Statistics

Differences between groups with respect to medical history, clinical data and complications during hospitalization were examined through the use of Chi-square and Mann–Whitney tests for categorical and continuous variables, respectively. Categorical variables are presented as percentages and continuous variables as median values. A P-value $\leq 0{\cdot}05$ was considered significant.

The unadjusted in-hospital mortality rates for patients with and without atrial fibrillation/-flutter were compared by the use of the Chi-square test. Multiple linear logistic regression analysis was used to examine the association between atrial fibrillation/-flutter and in-hospital mortality, while adjusting for several prognostic baseline characteristics. Long-term mortality rates were estimated by the use of the Kaplan–Meier method and presented as mortality curves. The Log rank test was utilized to assess differences between long-term mortality for hospital survivors with and without atrial fibrillation/-flutter. Cox proportional hazards regression analysis was utilized to examine the association between atrial fibrillation/-flutter and long-term mortality, while adjusting for several prognostic baseline characteristics. All analyses were performed with the SAS system (SAS, Cary, North Carolina, U.S.A.).

Table 1 Baseline characteristics of 6676 consecutive patients with acute myocardial infarction with and without atrial fibrillation/-flutter (AF/AFL) during hospitalization. The figures in parentheses represent 5821 patients surviving hospitalization

	With AF/AFL n=1395 (1110)	Without AF/AFL n=5281 (4711)	*P* value*
Characteristics			
Age (years)	73·7 (73·0)	67·0 (66·2)	<0·001
Male gender (%)	64 (65)	68 (70)	<0·001
BMI (kg . m^{-2})	25·4 (25·4)	25·4 (25·4)	0·29
Smokers (%)	43 (44)	54 (55)	<0·001
WMI (mean score)	1·2 (1·3)	1·5 (1·5)	<0·001
Anterior QMI (%)	30 (29)	25 (24)	<0·001
Thrombolysis (%)	32 (35)	43 (45)	<0·001
s-creatine kinase B (U . ml^{-1})	58 (55)	50 (49)	<0·001
s-creatinine (μmol . l^{-1})	107 (105)	97 (96)	<0·001
Bundle branch block (%)	12 (11)	7 (6)	<0·001
History of			
Acute myocardial infarction (%)	23 (23)	23 (23)	0·96
Angina pectoris (%)	38 (38)	36 (36)	0·19
Hypertension (%)	25 (25)	22 (22)	<0·02
Congestive heart failure (%)	26 (25)	14 (13)	<0·001
Diabetes mellitus (%)	13 (13)	10 (10)	<0·003
Stroke (%)	11 (10)	7 (7)	<0·001
Pulmonary disease (%)	15 (16)	10 (10)	<0·001
Complications during hospitalization			
Ventricular fibrillation (%)	11 (7)	6 (4)	<0·001
Ventricular tachycardia (%)	18 (17)	11 (10)	<0·001
Congestive heart failure (%)	48 (45)	34 (32)	<0·001
Cardiogenic shock (%)	6 (0·3)	3 (0·3)	<0·001

BMI=body mass index; QMI=Q-wave myocardial infarction; WMI=wall motion index.
**P* value is indicated for the figures without parentheses.

Results

Overall proportion of patients with atrial fibrillation/-flutter during hospitalization

Of 6676 consecutive patients a total of 1395 (21%) patients suffered from atrial fibrillation/-flutter in one or more periods following the acute myocardial infarction. The proportion of patients with atrial fibrillation/-flutter following the acute myocardial infarction decreased gradually during hospitalization, day 1–2: 969 patients (15%), day 3–4: 861 (13%) and from day 5: 600 (10%). Preexisting atrial fibrillation/-flutter (known atrial fibrillation/-flutter before admission to hospital) occurred in 3·9% of the patients. Of the total number of patients in these periods, observations were missing in day 1–2: 103 patients, day 3–4: 102 and from day 5: 74.

The proportion of patients with atrial fibrillation/-flutter during hospitalization among hospital survivors

Among the 5958 patients surviving hospitalization, 135 were not characterized due to missing data and in two patients mortality data are missing. Among the remaining 5821, a total of 1110 (19%) of the patients suffered from atrial fibrillation/-flutter in one or more periods during hospitalization. Two hundred and eighty-five (5%) patients had sustained atrial fibrillation/-flutter (i.e. in all of these periods, day 1–2, day 3–4 and from day 5) during hospitalization and 825 patients (14%) had intermittent atrial fibrillation/-flutter (i.e. in one or two periods). Of those with intermittent atrial fibrillation/-flutter, 569 (10%) patients had atrial fibrillation/-flutter in one period and in 256 (4%) patients atrial fibrillation/-flutter was observed in two periods. Single episodes (one period) of atrial fibrillation/-flutter occurred frequently within the first few days after the acute myocardial infarction, day 1–2: 320 patients, day 3–4: 167 patients and from day 5: 82 patients. Among patients in which atrial fibrillation/-flutter occurred in two periods during hospitalization, 150 patients had atrial fibrillation/-flutter day 1–2 and day 3–4, 72 day 3–4 and from day 5, whereas 34 had atrial fibrillation/-flutter day 1–2 and from day 5.

Baseline characteristics

Medical history, clinical data and complications during hospitalization of all patients with and without atrial fibrillation/-flutter are shown in Table 1. The medical treatment at baseline is shown in Table 2.

Table 2 This shows the baseline medical treatment of 6676 consecutive patients with acute myocardial infarction, separated into groups with and without atrial fibrillationl-flutter during hospitalization

	With AF/AFL n=1395	Without AF/AFL n=5281	*P* value
Aspirin at admission (%)	61	71	<0·001
Anticoagulation treatment (%)	3	1	<0·001
Beta-blocker (%)	9	9	0·85
Antiarrhythmic (%)	7	2	<0·001
Calcium antagonist	19	18	0·62
ACE inhibitor (%)	5	4	0·19
Digoxin (%)	23	6	<0·001
Diuretic (%)	39	25	<0·001

AF/AFL=atrial fibrillation/-flutter; ACE=angiotensin converting enzyme inhibitor.

In-hospital mortality

The unadjusted in-hospital mortality rate was significantly higher in patients with atrial fibrillation/-flutter (18%) compared with patients without (9%), $P<0·001$. After adjusting for age, gender, wall motion index, thrombolytic therapy, previous myocardial infarction, history of angina pectoris, history of hypertension, history of diabetes mellitus, congestive heart failure, ventricular fibrillation, and ventricular tachycardia, the presence of atrial fibrillation/-flutter following acute myocardial infarction was associated with an increased risk of dying during hospitalization (odds ratio=1·5 (95% Cl: 1·2–1·9); $P<0·001$). Preexistent atrial fibrillation/-flutter was not associated with an increased risk of dying during hospitalization (odds ratio=1·2 (95% Cl: 0·8–1·9); $P=0·43$). Development of atrial fibrillation/-flutter during hospitalization was associated with an increased risk of dying during hospitalization (odds ratio=1·5 (95% Cl: 1·2–1·9); $P<0·001$.

Long-term mortality

In patients surviving hospitalization, the 5-year unadjusted mortality rate was significantly higher in patients with atrial fibrillation/-flutter (56%) compared with patients without (34%), $P<0·001$, shown in Fig. 1. After adjusting for age, gender, thrombolytic therapy, wall motion index, history of diabetes, history of hypertension, previous myocardial infarction, history of angina and congestive heart failure, the presence of atrial fibrillation/-flutter during hospital stay in patients surviving hospitalization was associated with an increased risk of dying (relative risk=1·3 (95% Cl: 1·2–1·4), $P<0·001$). The risk was similar in patients receiving thrombolysis (relative risk=1·2; 95% Cl: 1·0–1·5) compared to patients not receiving thrombolysis (relative risk=1·3; 95% Cl: 1·1–1·5). Also the risk was similar in patients with (relative risk=1·3; 95% Cl: 1·2–1·4) and without preexistent atrial fibrillation/-flutter (relative risk=1·4; 95% Cl: 1·2–1·7).

Subgroup analysis with respect to whether atrial fibrillation/-flutter was present in one, two or three periods during hospitalization revealed that the 5-year unadjusted mortality rate in patients with atrial fibrillation/-flutter in one period was 49%, 62% in two periods and 68% in all three periods and that the adjusted risk of dying was highest in patients with sustained atrial fibrillation/-flutter (i.e. present in all three periods), Table 3.

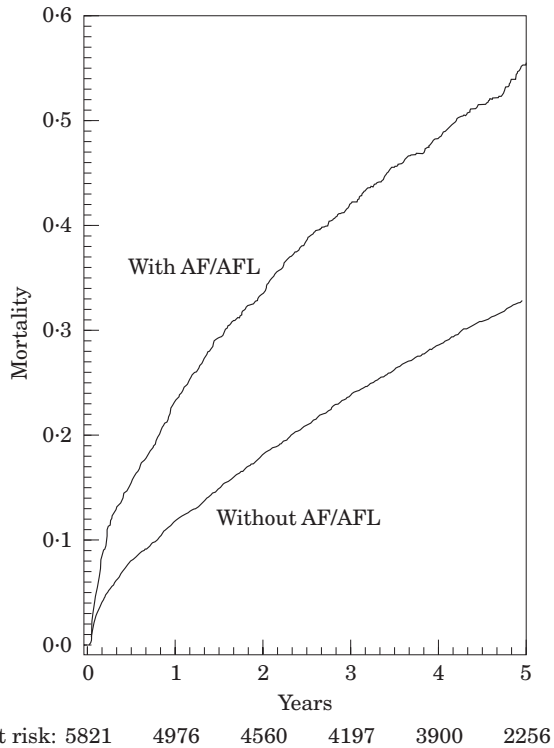

Figure 1 **This shows the unadjusted 5-year mortality curves in hospital survivors following acute myocardial infarction in 1110 patients with (with AF/AFL) and in 4711 without atrial fibrillation/-flutter (without AF/AFL) in one or more periods (day 1–2, day 3–4 and from day 5 until discharge) during hospitalization.**

Table 3 The unadjusted and adjusted relative risk of dying among 5821 hospital survivors following acute myocardial infarction according to whether atrial fibrillation/-flutter (AF/AFL) was present in one, two or three periods during hospitalization. The periods were day 1–2 or day 3–4 and from day 5 until discharge, following admission to hospital

	Unadjusted relative risk (95% Cl)	Adjusted relative risk (95% Cl)	*P* value*
AF/AFL in one period	1·7 (1·5–1·9)	1·3 (1·1–1·4)	<0·001
AF/AFL in two periods	2·3 (1·9–2·7)	1·3 (1·1–1·5)	<0·005
AF/AFL in three periods	2·6 (2·5–3·1)	1·4 (1·2–1·7)	<0·001

*The *P* value for the adjusted relative risk.
AF/AFL=atrial fibrillation/-flutter.

Table 4 This shows the risk associated with different clinical variables in 6676 consecutive acute myocardial infarction patients with respect to the in-hospital mortality, and in the 5981 patients discharged alive from hospital with respect to the long-term mortality (5-year mortality rates). Odds ratio or relative risk and 95% confidence limits are indicated

Clinical variable	In-hospital mortality		Long-term mortality	
	Odds ratio	*P* value	Relative risk	*P* value
Left ventricular function	4·2 (3·2–5·5)	<0·001	2·1 (1·9–2·4)	<0·001
Congestive heart failure	4·0 (3·0–5·6)	<0·001	1·7 (1·6–1·9)	<0·001
Atrial fibrillation/-flutter	1·5 (1·2–1·9)	<0·001	1·3 (1·1–1·4)	<0·001
History of diabetes mellitus	0·9 (0·7–1·2)	0·60	1·5 (1·3–1·7)	<0·001
History of hypertension	1·1 (0·9–1·4)	0·33	1·1 (1·0–1·3)	<0·01
History of angina pectoris	1·0 (0·8–1·3)	0·94	1·2 (1·1–1·4)	<0·001
Previous MI	0·9 (0·7–1·1)	0·22	1·1 (1·0–1·2)	0·08

MI=myocardial infarction.

Table 4 lists the adjusted risk of other known risk factors, which make it possible to compare the relative significance of atrial fibrillation/-flutter with these risk factors.

Discussion

In the present study of 6676 consecutive acute myocardial infarction patients, a high proportion suffered from atrial fibrillation/-flutter during hospitalization and the presence of this condition was associated with worse short- and long-term clinical outcome. Patients with atrial fibrillation/-flutter suffered significantly more serious in-hospital complications than those without, and multivariable analysis demonstrated that atrial fibrillation/-flutter was an independent predictor of increased in-hospital mortality. Also in patients surviving hospitalization the presence of atrial fibrillation/-flutter during hospitalization was an independent predictor of an increased long-term mortality (5-year mortality).

Occurrence of atrial fibrillation/-flutter

Up to 21% of all patients suffered from atrial fibrillation/-flutter during hospitalization, which corresponds to the proportion of patients with atrial fibrillation observed in previous studies, 6% to 23%[1]. We observed a gradual decline in the proportion of patients with atrial fibrillation/-flutter during the days after the myocardial infarction, which was due to a much higher incidence of intermittent atrial fibrillation/-flutter during the initial days after the acute myocardial infarction than later on. Possible explanations for this decline include spontaneous reversion to sinus rhythm, pharmacological or electrical cardioversion to sinus rhythm and high in-hospital mortality among patients with atrial fibrillation/-flutter. Similar figures were observed in patients surviving hospitalization, of which 19% suffered from atrial fibrillation/-flutter during hospitalization. Of these, 5% had sustained atrial fibrillation/-flutter (i.e. observed in three periods: day 1–2, day 3–4 and from day 5 until discharge) during hospitalization, whereas 14% had intermittent atrial fibrillation/-flutter (i.e. in one or two of the former mentioned periods).

Baseline characteristics

Except for a history of ischaemic heart disease and body mass index, patients suffering from atrial fibrillation/-flutter differed from those without the condition, with

respect to a number of baseline characteristics (Table 1). In agreement with previous studies[1,16,17], characteristics such as age, hypertension, congestive heart failure, diabetes mellitus and pulmonary disease seem to promote atrial fibrillation/-flutter. Importantly, few of the previous studies have determined left ventricular systolic function. We consistently found more extensive left ventricular systolic dysfunction in patients with atrial fibrillation/-flutter determined by echocardiograpy than in those without the condition. Fifty percent of the patients with atrial fibrillation/-flutter had wall motion index $\leq 1{\cdot}2$ (left ventricular ejection fraction $\leq 35\%$), compared with only 30% of those without atrial fibrillation/-flutter. Whereas the depressed cardiac function was not caused by a higher prevalence of preexisting ischaemic heart disease (history of acute myocardial infarction and/or angina pectoris) in patients with atrial fibrillation/-flutter, the slightly higher incidence of anterior acute myocardial infarction and the less frequent use of thrombolysis may, in part, contribute to the depressed cardiac function. It remains uncertain to what extent the arrhythmia contributes, but it is likely to contribute to some extent based on observations from studies of left ventricular function before and after cardioversion of atrial fibrillation[22,23]. The depressed cardiac function was probably a major reason why patients with atrial fibrillation/-flutter more often developed congestive heart failure and cardiogenic shock during hospitalization than patients without the condition, and may be part of the reason for the increased susceptibility for the development of ventricular arrhythmias.

Mortality

Although several previous studies have examined the prognostic impact of atrial fibrillation following acute myocardial infarction, it remains controversial whether atrial fibrillation is a risk factor causing increased mortality[4–17]. As treatment for acute myocardial infarction has improved in recent decades, with subsequent significantly improved survival, we find it relevant to discuss our results in relation to some of the most recent published studies[1,16,17]. Our finding of an increased risk associated with atrial fibrillation/-flutter is in agreement with the results of two recent reported studies[16,17]. In contrast, Goldberg *et al.* have reported that although there was a difference in the unadjusted mortality rate between patients with and without atrial fibrillation following acute myocardial infarction in a up to 10-year follow-up period, atrial fibrillation was not an independent predictor of increased mortality[1]. However, there are major differences between these studies, which make it difficult to compare the results directly. Probably the most important difference is the risk of dying in these studies. The studies also differed with respect to several baseline characteristics and therefore it is possible that the results represent the risk of atrial fibrillation in different populations. In particular one must be cautious about the results reported by Goldberg *et al.* because information about the presence of atrial fibrillation in this study was retrospectively collected. Our results in consecutive acute myocardial infarction patients and the results by Crenshaw *et al.* and Eldar *et al.*[16,17] strongly suggest that atrial fibrillation is an independent predictor of increased mortality following an acute myocardial infarction. In comparison with these studies[16,17], our study is the first to distinguish between patients with continuous and intermittent atrial fibrillation/-flutter during hospitalization and demonstrate that continuous atrial fibrillation/-flutter is associated with the highest risk. Another important difference is that we studied consecutive patients and were able to adjust for left ventricular systolic function. Our study also demonstrates, that the risk of atrial fibrillation/-flutter in patients surviving hospitalization is independent of whether the patients receive thrombolysis or not. Importantly and in contrast to Crenshaw *et al.* we observe that preexisting atrial fibrillation/-flutter is associated with increased long-term mortality and the risk is similar to those developing atrial fibrillation/-flutter during hospitalization.

Although we demonstrated that the presence of atrial fibrillation/-flutter during hospitalization is an independent predictor of increased mortality, it remains uncertain whether this is due to a direct causal relationship. The association of atrial fibrillation/-flutter with other risk factors may indicate that atrial fibrillation/-flutter is a marker (predictor of mortality) of risk rather than a causal factor. Our finding of a higher relative risk in patients with sustained atrial fibrillation/-flutter during hospitalization (Table 3) may support the view of a causal relationship, because it is likely that these patients will continue to have atrial fibrillation/-flutter after discharge from hospital. The implication of this study is that prevention of atrial fibrillation/-flutter following acute myocardial infarction may reduce morbidity and mortality. The available data do not demonstrate that such intervention will be successful, but should effective measures to prevent atrial fibrillation/-flutter become available this group of patients is a relevant target for testing intervention.

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