Incidence and prognostic significance of atrial fibrillation in acute myocardial infarction: the GISSI-3 data

F Pizzetti, F M Turazza, M G Franzosi, S Barlera, A Ledda, A P Maggioni, L Santoro, G Tognoni, on behalf of the GISSI-3 Investigators

Abstract

Background—Atrial fibrillation is the most common supraventricular arrhythmia in patients with acute myocardial infarction. Recent advances in pharmacological treatment of myocardial infarction may have changed the impact of this arrhythmia.

Objective—To assess the incidence and prognosis of atrial fibrillation complicating myocardial infarction in a large population of patients receiving optimal treatment, including angiotensin converting enzyme (ACE) inhibitors.

Methods—Data were derived from the GISSI-3 trial, which included 17,944 patients within the first 24 hours after acute myocardial infarction. Atrial fibrillation was recorded during the hospital stay, and follow-up visits were planned at six weeks and six months. Survival of the patients at four years was assessed through census offices.

Results—The incidence of in-hospital atrial fibrillation or flutter was 7.8%. Atrial fibrillation was associated with indicators of a worse prognosis (age > 70 years, female sex, higher Killip class, previous myocardial infarction, treated hypertension, high systolic blood pressure at entry, insulin-dependent diabetes, signs or symptoms of heart failure) and with some adverse clinical events (reinfarction, sustained ventricular tachycardia, ventricular fibrillation). After adjustment for other prognostic factors, atrial fibrillation remained an independent predictor of increased in-hospital mortality: 12.6% v 9%, adjusted relative risk (RR) 1.98, 95% confidence interval (CI) 1.67 to 2.34. Data on long-term mortality (four years after acute myocardial infarction) confirmed the persistent negative influence of atrial fibrillation (RR 1.78, 95% CI 1.60 to 1.99).

Conclusions—Atrial fibrillation is an indicator of worse prognosis after acute myocardial infarction, both in the short term and in the long term, even in an unselected population.

Keywords: atrial fibrillation; acute myocardial infarction; prognosis

Incidental atrial fibrillation is one of the most common supraventricular arrhythmias in the setting of acute myocardial infarction, occurring in around 5–18% of all patients. The higher figures usually include individuals with pre-existing atrial fibrillation, and the probable incidence of new atrial fibrillation is closer to 5%.

Atrial fibrillation is usually abrupt in onset and can cause rapid haemodynamic instability through one of three mechanisms: loss of the atrial component of the cardiac output; increased ventricular response rate with decreased diastolic filling time; or irregular ventricular filling.

In many studies atrial fibrillation has been associated with advanced age, congestive heart failure, poor left ventricular function, and extensive myocardial infarction. Other associated conditions include mitral insufficiency, increased incidence of ventricular arrhythmias and right bundle branch block, and left bundle branch block. The occurrence of atrial fibrillation is not related to the site of the myocardial infarct.

The relation of atrial fibrillation to outcome has been extensively investigated, and it is commonly considered a marker of poor prognosis. The occurrence of atrial fibrillation is associated with an increased hospital mortality, though after adjustment for other variables known to affect prognosis—such as age, heart failure with cardiogenic shock, previous acute myocardial infarction, and ventricular arrhythmias—its independent effect appears to be somewhat reduced. It is possible, indeed, that the development of this arrhythmia merely reflects an overall increase in risk profile, as would be expected with large infarcts, decreased left ventricular function, and electrical instability.

Until very recently most studies of atrial fibrillation in relation to acute myocardial infarction have been relatively small and conducted in the prethrombolytic era. More recently, data from the large GUSTO-I study (global utilisation of streptokinase and tissue plasminogen activator for occluded coronary arteries) have been published, showing that atrial fibrillation in the setting of an acute myocardial infarct treated with thrombolysis independently predicted stroke and 30 day mortality.
Current routine acute treatment for myocardial infarction includes not only aspirin, ß blockers, and thrombolytic agents, but also angiotensin converting enzyme (ACE) inhibitors. As shown by recently published clinical trials and meta-analysis, this combined approach significantly reduces in-hospital and medium term mortality, left ventricular dysfunction and heart failure, myocardial damage extension, and ventricular arrhythmias. In this context, a recently published report by the TRACE (trandolapril cardiac evaluation) investigators showed that in patients with a large acute myocardial infarct the occurrence of in-hospital atrial fibrillation is independently associated with an increase in hospital based and long term mortality. It is therefore relevant to reassess the incidence and prognostic significance of atrial fibrillation complicating acute myocardial infarction, in a substantial unselected population of patients receiving optimal treatment, including ACE inhibitors.

Despite the prevalence of atrial fibrillation, many issues still remain unresolved. The large GISSI-3 study allows a further exploration of this topic in the thrombolytic/ACE inhibitor era.

Methods

Data are derived from the GISSI-3 trial (gruppo Italiano per lo studio della sopravvivenza nell’infarto miocardico), a large clinical trial in which patients within 24 hours of acute myocardial infarction were randomised by telephone call or computer network system, working 24 hours a day, to receive oral lisinopril or no lisinopril and, according to a 2 × 2 factorial design, glyceryl trinitrate or no glyceryl trinitrate. The details of the design and the main results of the GISSI-3 study are provided in the original report. The entry criteria for the trial were: chest pain with ST segment elevation or depression of at least 1 mm in one or more peripheral leads of the ECG and/or at least 2 mm in one or more precordial leads; admission to a cardiac care unit within 24 hours from symptom onset; no clear indication or contraindication to the study treatments (oral lisinopril or intravenous and transdermal glyceryl trinitrate); Killip class < 4; and absence of life threatening disorders.

Patients

In all, 43,047 patients were admitted to the 200 participating coronary care units; of these, 19,394 (45%) were randomised. Complete clinical data at the six week follow up were available for analysis for 18,895 (97.4%) of the randomised patients. Acute myocardial infarction was confirmed in 17,944 patients, but our study population comprised 17,749 patients. This was because we excluded from the final analysis 195 patients with chronic atrial fibrillation, defined as atrial fibrillation that was present on both admission and predischarge ECG records. The purpose of the study was to assess the effects of new onset atrial fibrillation occurring during the peri-infarction period.

All patients with no specific contraindications received the recommended drugs in the acute phase, according to defined clinical criteria: fibrinolytics were given in 72%, intravenous ß blockers in 29%, and aspirin in 85%.

There were 8606 patients with confirmed acute myocardial infarction who underwent bidimensional echocardiography on discharge from hospital.

End Points

Investigators recorded all the relevant clinical events during the hospital stay and at clinical follow up visits after six weeks and six months from randomisation. On these occasions they were required to report if atrial fibrillation or flutter had occurred between randomisation and hospital discharge.

Statistical Analysis

The Pearson χ² test for heterogeneity and the Mantel–Haenszel χ² test for linear association (only for variables measured on an ordinal scale) were used to compare differences in atrial fibrillation incidence, observed in categorical variables.

Several Cox regression models, with the Mantel–Byar time to event correction, were used to quantify the prognostic significance of atrial fibrillation with respect to in-hospital, six month, and four year mortality. The following covariates were included in the multivariate models: site of myocardial infarction, previous myocardial infarction, sex, age, history of hypertension, history of diabetes mellitus, Killip class, systolic blood pressure, history of angina, time from onset of symptoms, heart rate, in-hospital administration of anti-arrhythmic treatment, and the randomised treatment.

In assessing the prognostic significance of atrial fibrillation in patients discharged alive, no time-to-event correction was performed.

The proportionality assumption among hazards for the atrial fibrillation and no atrial fibrillation groups was tested using a flexible model-fitting approach involving restricted cubic spline function. This method allows one to examine the strength of the relation between hazard ratio and time (formulation and testing of a hypothesis on the effect of atrial fibrillation) and the shape of this relation (relative risk constant or not), without having to prespecify any functional form. The software used for the proportional assumption test and graphics is available on the world wide web.

Results

Incidence and Clinical Characteristics

The overall incidence of in-hospital atrial fibrillation was 7.8% (1386 patients). Among these patients, 319 had very early paroxysmal atrial fibrillation (that is, atrial fibrillation present on the admission ECG and absent on the predischarge ECG in patients discharged in sinus rhythm). Patients who experienced atrial fibrillation were significantly older, had a worse Killip class at entry, and had a higher heart rate on their admission ECG. Other variables associated with this arrhythmia include previously treated hypertension, diabetes, female sex, and previous acute myocardial infarction (table 1).
The p values (2p) are derived from £2 tests for heterogeneity. The p values (2p) are derived from χ² tests for trend. The p values (2p) are derived from χ² tests for heterogeneity. As expected, patients with atrial fibrillation were given significantly more digitalis and oral antiarrhythmic drugs. On the other hand, they were treated less frequently with fibrinolytics and intravenous β blockers.

As shown in table 3, in-hospital death, early and late clinical congestive heart failure, sustained ventricular tachycardia, and ventricular fibrillation all occurred more often in patients with atrial fibrillation than in those without (p < 0.001). No significant difference was observed in reinfection rate, though this event appeared more common among patients with atrial fibrillation (2.9% v 2.0%, NS). In this regard, no significant differences were shown between the two groups even when reinfection and recurrent ischaemia were combined. In-hospital stroke rate was very low, and not significantly affected by atrial fibrillation.

Finally, patients with in-hospital atrial fibrillation had worse left ventricular function, as shown by a significantly lower predischarge ejection fraction (48.3% v 51.3%, p < 0.0001, with 26.7% v 16.8% of patients having an ejection fraction < 40%, p < 0.0001).

TREATMENTS
As shown in table 2, patients with atrial fibrillation were less often given the recommended non-study treatments—that is, fibrinolytics and β blockers. On the other hand, patients with atrial fibrillation were more often being treated with digoxin, antiarrhythmic drugs, oral anticoagulants, and thrombolytics on discharge.

With respect to randomised treatments, a 24% reduction (OR 0.76, 95% CI 0.65 to 0.89) in the incidence of atrial fibrillation was observed in patients randomised to both lisinopril and nitrates compared with control patients (fig 1). The unadjusted hospital mortality was higher in patients with atrial fibrillation than in those without (p < 0.001). The adjusted hospital mortality remained significantly higher in patients with atrial fibrillation (RR 1.98, 95% CI 1.67 to 2.34, p < 0.001).

The hospital mortality, but not the long term mortality, was significantly higher in patients developing “late” atrial fibrillation (after days 0–1) than in those developing early atrial fibrillation (occurring on days 0–1). In the late group, hospital mortality was 18.9%, compared with 13.3% in the early group. This difference was significant (OR 1.50, 95% CI 1.08 to 2.08).

IN-HOSPITAL OUTCOMES
As shown in table 3, in-hospital death, early and late clinical congestive heart failure, sustained ventricular tachycardia, and ventricular fibrillation all occurred more often in patients with atrial fibrillation than in those without (p < 0.001). No significant difference was observed in patients randomised to both lisinopril and nitrates compared with control patients (fig 1). The unadjusted hospital mortality was higher in patients with atrial fibrillation than in those without (table 4). After adjustment for baseline differences, the hospital mortality remained significantly higher in patients with atrial fibrillation (RR 1.98, 95% CI 1.67 to 2.34, p < 0.001).

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MEDIUM AND LONG TERM FOLLOW UP (SIX MONTH AND FOUR YEAR OUTCOMES)
Survival curves up to six months (fig 2) clearly show that a significant difference in favour of patients without atrial fibrillation is detectable.
by the first few days; this increased during the first month but then remained unchanged over time.

The unadjusted six month mortality of patients discharged alive was higher in those with atrial fibrillation than in those without, regardless of the timing of the onset. The difference in favour of patients without atrial fibrillation was still evident after four years. After adjustment for baseline differences, the mortality in patients discharged alive remained significantly higher in the group with atrial fibrillation, both at six months (RR 1.81, 95% CI 1.48 to 2.23) and at four years (RR 1.78, 95% CI 1.60 to 1.99). The independent predictors of mortality in the long term are shown in table 5.

Using a different multivariable model, and splitting our follow up into three different clinical periods, we observed that the risk course was clearly different between the hospital phase on the one hand and the post-acute (up to six months) and chronic phases (up to four years) on the other (fig 3).

Table 3 In-hospital events in patients with or without atrial fibrillation (AF)

<table>
<thead>
<tr>
<th>Event</th>
<th>Without AF (n=16363)</th>
<th>With AF (n=1386)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical evidence of heart failure</td>
<td>23.6</td>
<td>51.5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Congestive heart failure &gt; 4 days</td>
<td>3.8</td>
<td>12.1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Refractation + postinfarction angina</td>
<td>13.8</td>
<td>15.3</td>
<td>NS</td>
</tr>
<tr>
<td>Sustained ventricular tachycardia</td>
<td>1.9</td>
<td>4.3</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Ventricular fibrillation</td>
<td>2.3</td>
<td>4.4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Death in hospital</td>
<td>5.0</td>
<td>12.6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Stroke</td>
<td>0.7</td>
<td>0.8</td>
<td>NS</td>
</tr>
</tbody>
</table>

The data are percentages. The p values (2p) are derived from χ² tests for heterogeneity. The worse in-hospital outcome of the patients with atrial fibrillation is clearly apparent.

Table 4 Short term and medium term prognostic significance of atrial fibrillation developing in hospital

<table>
<thead>
<tr>
<th>Event</th>
<th>RR unadjusted</th>
<th>95% CI</th>
<th>RR adjusted</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>In-hospital mortality</td>
<td>3.01</td>
<td>2.55 to 3.55</td>
<td>1.98</td>
<td>1.67 to 2.34</td>
</tr>
<tr>
<td>Six month mortality</td>
<td>2.93</td>
<td>2.40 to 3.57</td>
<td>1.81</td>
<td>1.48 to 2.23</td>
</tr>
</tbody>
</table>

CI, confidence interval; RR, relative risk.

Discussion

Atrial fibrillation is one of the most common supraventricular arrhythmias in the setting of acute myocardial infarction. It is also a marker of clinical and angiographic baseline features suggesting higher risk. In the GISSI-3 trial, as in previous trials, old age was found to be the most important independent predictor of this arrhythmia.

Patients given randomised treatments (both nitrates and ACE inhibitors) were less likely to develop atrial fibrillation. It is hard to determine the precise aetiology of this arrhythmia, but the association with atrial fibrillation of Killip class above 1, a higher heart rate, and a lower ejection fraction—together with the trend towards a reduction in the incidence of atrial fibrillation in patients given nitrates and ACE inhibitors—suggests that haemodynamic impairment is the most likely mechanism. In fact in the GISSI-3 trial, patients allocated to the combination of lisinopril + nitrates not only had a lower mortality, but also a lower incidence of two other components of the combined end point directly related to haemodynamic impairment—clinical congestive heart failure and an ejection fraction less than 35% (8.3% in patients given lisinopril + nitrates, v 9.2% in control, 9.5% with nitrates, and 9.0% with lisinopril). This is indirectly consistent with other studies which showed that patients given accelerated alteplase (greater than TIMI 3 flow rate) were less likely to develop fibrillation after the first few days; this increased during the first month but then remained unchanged over time.

The unadjusted six month mortality of patients discharged alive was higher in those with atrial fibrillation than in those without, regardless of the timing of the onset. The difference in favour of patients without atrial fibrillation was still evident after four years. After adjustment for baseline differences, the mortality in patients discharged alive remained significantly higher in the group with atrial fibrillation, both at six months (RR 1.81, 95% CI 1.48 to 2.23) and at four years (RR 1.78, 95% CI 1.60 to 1.99). The independent predictors of mortality in the long term are shown in table 5.

Using a different multivariable model, and splitting our follow up into three different clinical periods, we observed that the risk course was clearly different between the hospital phase on the one hand and the post-acute (up to six months) and chronic phases (up to four years) on the other (fig 3).

INDEPENDENT PREDICTORS OF ATRIAL FIBRILLATION

The most important predictor of atrial fibrillation was age > 70 years (OR 2.82, 95% CI 2.46 to 3.24). Other significant factors (in decreasing order) were raised heart rate at entry (> 100 beats/min, OR 2.19, 95% CI 1.64 to 2.92), Killip class above 1 (OR 1.81, 95% CI 1.55 to 2.11), and a history of hypertension (OR 1.34, 95% CI 1.17 to 1.53).

Figure 2 Six month survival of patients with or without the development of atrial fibrillation in hospital. AMI, acute myocardial infarction.

Figure 3 GISSI-3; four year follow up and relative risks (RR) of death from atrial fibrillation (AF) versus no AF, giving the risk course over time for patients with in-hospital AF. The risk–time relation shows that even if the risk is higher during the very early postinfarction period (RR=2) compared with the later stages, in the long term it appears constant and clearly not negligible.
atrial fibrillation,22 and that patients who developed atrial fibrillation had more unfavourable invasive haemodynamic variables than those who did not.12

HOSPITAL COMPLICATIONS
Patients with atrial fibrillation had a more complicated hospital course than those without. In our study, as well as in the GUSTO trial, reinfarction and recurrent ischaemia were more common, though not significantly so, among patients with atrial fibrillation. The lack of angiographic data did not allow an exhaustive interpretation of this finding, though it is likely that older and sicker patients, such as those with atrial fibrillation, had more extensive coronary disease.

Left ventricular dysfunction with a lower ejection fraction, clinical congestive heart failure, and cardiogenic shock were also more common in patients with atrial fibrillation. This is probably related, in a kind of vicious circle, to the impaired haemodynamics in these patients, where loss of atrial contraction leads to hypotension and possibly to more severe ischaemia. Patients with atrial fibrillation more often developed other arrhythmias, particularly ventricular tachycardia and ventricular fibrillation. Once again, among numerous possible explanations, the higher incidence of left ventricular dysfunction and congestive heart failure appears to play a pivotal role, although the more common use of digoxin and antiarrhythmic drugs could be important.

In our study, at variance with GUSTO-I, stroke incidence was not affected by atrial fibrillation. Overall stroke incidence was 0.7%, the same in both groups, and clearly lower than observed in the GUSTO-I trial. Although there was a very low in-hospital stroke incidence in GISSI-3, it may well be that in sicker and more aggressively treated patients atrial fibrillation plays a role in increasing ischaemic stroke incidence, as shown in GUSTO-I.

MORTALITY
Our study, together with the recently published GUSTO and TRACE reports,22 23 confirms that atrial fibrillation in the setting of acute myocardial infarction is associated with an increased in-hospital and long term mortality, probably owing to its association with worse left ventricular function. In the past, many studies8–12 have attempted to determine the relation between atrial fibrillation and mortality in patients with acute myocardial infarction, with conflicting results to some extent. For example, two recent large studies found a higher incidence of in-hospital and long term mortality in patients with than without atrial fibrillation.20 21 In both studies, however, adjustment for other variables known to affect prognosis made the observed differences non-significant. The results differed for longer term mortality: in a multivariate analysis, one trial20 found that atrial fibrillation independently predicted long term mortality, whereas the other12 did not.

In our study, mortality was lower than previously reported.20 21 Thus in the present study, in-hospital mortality in patients with and without atrial fibrillation was 12.6% and 5.0%, respectively, versus 25.5% and 16.2% in the SPRINT (secondary prevention of reinfarction Israeli nifedipine trial) registry.20 This difference is a result of the improved treatment for acute myocardial infarction available in the 1990s, as well as differences in the populations studied—for example, all patients enrolled in GISSI-3 were haemodynamically stable, and the sickest subjects (that is, patients with persistent hypotension or cardiogenic shock) were excluded. The unadjusted and adjusted mortalities in GISSI-3 were significantly higher both in hospital and at the four year follow up among patients with atrial fibrillation than among those in sinus rhythm.

Our trial is the first capable of providing a long term follow up of a large population of patients with atrial fibrillation complicating acute myocardial infarction, and the data showing that atrial fibrillation developing in hospital is a sign of poor prognosis are of particular interest. The risk–time relation (fig 3) shows that though the risk is higher during the very early postinfarction period compared with the later stages, in the long run it appears constant, and definitely not negligible.

CONCLUSIONS
In the thrombolytic era atrial fibrillation remains a common and important complication of acute myocardial infarction. It identifies a group of patients who are older and sicker than their counterparts without atrial fibrillation. Such patients should be targeted for earlier and more aggressive treatment, because their overall prognosis—both short and long term—is significantly worse than in patients without atrial fibrillation. The management of patients developing atrial fibrillation after acute myocardial infarction should include intensive clinical surveillance, chronic anticoagulation, and cardioversion whenever possible.

GISSI is endorsed by the Associazione Nazionale Medici Cardiologi Ospedalieri (ANMCO) and Istituto di Ricerca Farmacologiche Mario Negri, Florence and Milan, Italy

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**Transeptal left heart catheterisation guided by intracardiac echocardiography**

*T Szilli-Tóth, GP Kinnman, D Theuns, J Res, J R T C Roelandt, L J Jordaeus*

**Objective**—To develop a novel approach of transeptal puncture guided by intracardiac echocardiography and to assess its efficacy.

**Methods**—Trans catheter intracardiac echocardiography with a 9 MHz rotating transducer was performed to guide transeptal puncture in 12 patients (mean age 43.1 years, range 31–68) who underwent radiofrequency catheter ablation of left sided accessory pathways. Initially, the echocardiography and transeptal catheters were placed adjacent to each other in the superior vena cava and were withdrawn to the level of the fossa ovalis.

**Results**—The successful puncture site was associated with visualisation of the fossa ovalis (12 patients, 100%) and the aorta (12 patients, 100%), tenting of the fossa (six patients, 50%), penetration of the needle visualised by the ultrasound catheter (12 patients, 100%), and echocardiographic contrast material applied in the left atrium (12 patients, 100%). The characteristic jump of the needle onto the fossa ovalis was observed simultaneously with fluoroscopy and intracardiac ultrasound (12 patients, 100%). All procedures were successful. There were no complications associated with the transeptal procedure.

**Conclusions**—Intracardiac echocardiography is feasible to guide transeptal puncture. The optimal puncture site can be assessed by simultaneous detection of the characteristic downward jump of the transeptal needle onto the fossa ovalis by intracardiac ultrasound and fluoroscopy.

—Heart 2001;86:e11 www.heartjnl.com/cgi/content/full/86/5/e11

**Delayed post-traumatic tamponade together with rupture of the tricuspid valve in a 15 year old boy**

*T Herbots, P Vemeersch, M Varenberg*

With the increase in the number of high speed motor vehicle accidents, blunt, non-penetrating trauma to the heart has become an important health problem. An unusual case is reported of a 15 year old boy urgently referred with cardiac tamponade and a new systolic murmur four months after a car accident. The problems of the diagnosis and possible causes of late cardiac tamponade and tricuspid regurgitation following this type of accident are discussed.

—Heart 2001;86:e12 www.heartjnl.com/cgi/content/full/86/5/e12

**Infected cardiac hydatid cyst**

*M Ceviz, N Becit, H Koçak*

A 24 year old woman presented with chest pain and palpitation. The presence of a semisolid mass—an echinococcal cyst or tumour—in the left ventricular apex was diagnosed by echocardiography, computed tomography, and magnetic resonance imaging. The infected cyst was seen at surgery. The cyst was removed successfully by using cardiopulmonary bypass with cross clamp.

—Heart 2001;86:e13 www.heartjnl.com/cgi/content/full/86/5/e13
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