Atrial fibrillation, ischaemic heart disease, and the risk of death in patients with heart failure

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KEYWORDS
Atrial fibrillation; Congestive heart failure; Mortality; Ischaemic heart disease

Aims Atrial fibrillation (AF) is a risk factor for death in patients with a myocardial infarction, but highly variable results are reported in patients with heart failure. We studied the prognostic impact of AF in heart failure patients with and without ischaemic heart disease.

Methods and results During a period of 2 years, 3587 patients admitted to hospital because of heart failure were included in this study. All patients were examined by echocardiography and the presence of AF was recorded. Follow-up was available for 8 years. Twenty four percent of those discharged alive from hospital had AF. After 4 and 8 years of follow-up, mortality was higher in patients with AF than in patients without, 56 vs. 52% and 77 vs. 73%, respectively. Cox multivariable regression analysis showed a small but significant importance of AF for long-term mortality [hazard ratio (HR) 1.12, 95% confidence limits (CI), 1.02–1.23, P = 0.018]. There was a significant interaction between the importance of AF and the presence of ischaemic heart disease (P = 0.034). In patients with AF at the time of discharge and ischaemic heart disease, HR was 1.25 (95% CI: 1.09–1.42) and P < 0.001; in patients with AF at discharge and without ischaemic heart disease, HR was 1.01 (95% CI: 0.88–1.16) and P = 0.88.

Conclusion AF is associated with increased risk of death only in patients with ischaemic heart disease. This finding may explain the variable results of studies of the prognosis associated with AF in heart failure.

Introduction

Atrial fibrillation (AF) is the most common arrhythmia among patients with congestive heart failure and occurs in up to 50% of those with advanced disease.1 In majority of the studies, AF has been shown to be an independent risk factor of mortality in patients with ischaemic heart disease and in the general population,2,3 whereas conflicting results have been found in congestive heart failure patients.4 Whether AF is related to an increased risk of death in patients with congestive heart failure remains unresolved and the inconsistency of the results in this particular group is strikingly different from what has been found in patients with ischaemic heart disease and in the general population. Some studies have found an increase in the risk of death in patients with AF and congestive heart failure,5–11 whereas others have found no increased risk12–19 and one study even a decreased risk.20 A recent study in a large group of congestive heart failure patients revealed no independent importance of chronic AF for mortality and some importance of new onset AF.21 Because of the continued inconsistency between studies of ischaemic heart disease and studies of populations with heart failure, we speculated that this difference might be a consequence of a complicated interaction between AF resulting from heart failure on ischaemic basis and AF causing heart failure. We therefore performed this retrospective study of 3587 consecutive patients admitted to hospital because of a worsening of congestive heart failure and followed these patients for 8 years. The aim of this study was to investigate the prognostic importance of AF in the total cohort of patients as well as to study whether the prognostic importance of AF differed in patients with and without ischaemic heart disease.

Materials and methods

During a 2-year period, from November 1993 to November 1995, 5548 patients were admitted to hospital because of a clinical
worsening of heart failure and screened at 34 centres for possible participation in the Danish Investigations of Arrhythmia and Mortality ON Dofetilide (DIAMOND) Congestive Heart Failure (CHF) trial. Twenty-two centers (n = 3892 patients) agreed on participating in the present retrospective analysis and they identified all patients with AF at the initial hospitalization. Data on AF were available in a high number of patients, n = 3587 (92%) and the remaining 305 were excluded from the present analysis. Only three patients were lost to follow-up. Patients qualified for inclusion in the DIAMOND register (and to be screened for inclusion into the DIAMOND study) were consecutive patients hospitalized with new or worsening congestive heart failure and who within the preceding month had had at least one episode of shortness of breath on minimal exertion or at rest (New York Heart Association (NYHA) functional class III or IV) or paroxysmal nocturnal dyspnoea. NYHA classes used in the study are those recorded at the time of inclusion in the study. For all screened patients demographic data, prior diseases, medication, and hospital complications were noted and a two-dimensional echocardiography was recorded on videotape. Left ventricular (LV) systolic function was determined by echocardiography, a method previously described in detail. It was assessed by calculation of wall motion index (WMI), using a 16-segment model of the LV and a reverse scoring system. WMI multiplied by 0.3 gives an estimate of ejection fraction. The following intervals gives an estimate on the relation between WMI and left ventricular ejection fraction (LVEF): WMI ≤ 0.8 (LVEF < 0.25), WMI = 0.9–1.2 (LVEF = 0.25–0.35), WMI = 1.3–1.6 (LVEF = 0.36–0.50), and WMI > 1.6 (LVEF > 0.50).

Patients with a WMI < 1.2 were considered for inclusion in DIAMOND CHF trial and those eventually included were randomized to dofetilide treatment or placebo.

The diagnosis of AF was documented by electrocardiograms obtained during hospitalization and had to fulfil the following criteria: AF—absence of P waves, coarse or fine fibrillatory waves, and completely irregular RR-intervals. In particular, the investigators had to distinguish AF from atrial flutter (AFL) defined as: presence of regular P waves with a rate between 250 and 350/min and regular or irregular RR-intervals. The investigators were asked to classify the duration of AF during hospitalization and whether the patients had AF at the baseline electrocardiogram (ECG), new onset AF during hospitalization, continuous AF, AF at the time of discharge, and whether they had a history of paroxysmal or persistent/permanent AF. Baseline AF required that AF was present at the ECG obtained at baseline. New onset AF required that the patients did not have AF at the baseline electrocardiogram and developed AF during hospitalization. Continuous AF during hospitalization required that AF was present at the baseline ECG, any time during hospital stay and at the time of discharge. Paroxysmal AF was defined as AF being present at baseline or at any time during hospitalization but not at the time of discharge.

The presence or absence of ischaemic heart disease relied on the clinical judgment of the investigator who specifically reported whether ischaemic heart disease was diagnosed. Formal criteria were not specified. In our analysis, history of ischaemic heart disease included patients with either angina or previous myocardial infarction or both.

The study was approved by the Ethics Committee and all patients gave informed consent to participate in the study.

Statistical methods

Differences between groups with respect to medical history and clinical data were examined by the use of χ² and Mann–Whitney tests for categorical and continuous variables, respectively. Categorical variables are presented as counts and percentages. Continuous variables are presented as median values and 5 and 95 percentiles. Differences in mortality between groups were examined by use of log-rank tests and presented as Kaplan–Meier curves. Mortality of AF was studied with Cox proportional hazard models. The model assumptions (proportional hazard assumption, lack of interaction, and linearity of continuous variables) were tested and found valid unless otherwise indicated. In multivariable analyses we adjusted for age, gender, WMI, history of ischaemic heart disease, and diabetes. The prognostic impact of AF was studied in the whole population and in two subgroups of patients with and without ischaemic heart disease (history of angina pectoris and/or previous myocardial infarction). Interaction analyses were performed by a likelihood ratio test. A P-value < 0.05 was considered significant. All analyses were performed with the SAS system (SAS version 9, Cary, NC, USA).

Results

Study size and baseline variables

The study population consisted of 3587 patients. The prevalence of different categories of AF is shown in Table 1. Up to 29% of the patients had AF once during hospitalization. Five percent developed AF during hospitalization and 24% of those discharged from hospital had AF. Ten percent were classified as having paroxysmal AF during hospitalization. Of those patients discharged from hospital with AF, 78% had a history of persistent/permanent AF, 95% had AF on the baseline ECG, 91% had continuous AF during hospitalization, and 6% had new onset AF. Baseline characteristics of patients without AF in comparison with those having AF at the time of discharge from hospital are shown in Table 2. Patients with AF at the time of discharge were slightly older than patients without AF, whereas patients without AF had a decreased LV function and more patients suffered from angina pectoris or had a previous myocardial infarction. Otherwise, the groups were fairly similar regarding a number of other baseline variables.

Mortality

In-hospital mortality was not increased in patients with AF at the baseline ECG, 32 deaths of 1040 patients with baseline AF, 76 deaths in 2547 patients without baseline AF [HR = 0.90 (95% CI: 0.61–1.35), P = 0.62]. During long-term follow-up, 634 deaths occurred in 818 patients with AF at the time of discharge vs. 1951 deaths occurred in 2661 without AF (Figure 1). Mortality analyses by Cox proportional hazard regression analyses of the different categories of AF are shown in Table 3, adjusted for age, gender, WMI, diabetes, and history of ischaemic heart disease. Baseline AF or presence of continuous AF during hospitalization were not associated with an increased risk of death during long-term follow-up, whereas development of AF during hospitalization and AF present at the time of discharge were associated with an increased risk of death during long-term follow-up. Patients with AF at discharge were slightly older than patients without AF, whereas patients without AF had a decreased LV function and more patients suffered from angina pectoris or had a previous myocardial infarction. Otherwise, the groups were fairly similar regarding a number of other baseline variables.

Table 1  Prevalence of AF in 3587 patients

<table>
<thead>
<tr>
<th>History of AF</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Persistent/permanent AF</td>
<td>16 (n = 584)</td>
</tr>
<tr>
<td>Paroxysmal AF</td>
<td>7 (n = 266)</td>
</tr>
<tr>
<td>In-hospital AF</td>
<td></td>
</tr>
<tr>
<td>AF at baseline ECG</td>
<td>29 (n = 1040)</td>
</tr>
<tr>
<td>Continuous AF in hospital</td>
<td>22 (n = 774)</td>
</tr>
<tr>
<td>New-onset AF</td>
<td>5 (n = 193)</td>
</tr>
<tr>
<td>Paroxysmal AF</td>
<td>10 (n = 351)</td>
</tr>
<tr>
<td>AF at discharge</td>
<td>24 (n = 818)</td>
</tr>
</tbody>
</table>

ECG, electrocardiogram.
discharge were associated with an increased risk of death during the follow-up of 8 years. Paroxysmal AF during hospitalization [HR = 1.25 (95% CI: 1.09–1.42), P < 0.001], while adjusting for age, gender, WMI, history of ischaemic heart disease, and diabetes. Separation of this group completely eliminated the risk in those with AF but without ischaemic heart disease [HR = 1.01 (95% CI: 0.88–1.16), P = 0.88] with similar adjustments (Table 3 at the bottom). Interaction analysis showed that there was significant interaction between AF and ischaemic heart disease. Interaction was found to be significant for baseline AF (P = 0.003), continuous AF (P = 0.007), and AF at discharge (P = 0.034).

Other analyses
Significantly more patients with AF than without were treated with digoxin on discharge from hospital (Table 2). Adding digoxin therapy to the multivariable models resulted in AF not predicting mortality overall [HR = 1.08 (95% CI: 0.97–1.19), P = 0.14]. Because digoxin therapy was to a large extent a routine treatment of AF it becomes an intermediary variable and it was therefore not included in the main models.

Discussion
It has been a mystery why AF has a clear prognostic impact in cohorts of patients with ischaemic heart disease and in the general population, whereas this is not the case in patients with congestive heart failure. In this study, we find that AF is associated with an increased long-term mortality in patients admitted to hospital with clinical worsening of heart failure and discharged with AF, and for the first time we are able to demonstrate that the risk of death is specifically associated to patients with AF and ischaemic heart disease in heart failure patients (Figure 2 and Table 3). By separation of patients who suffered from both conditions, i.e. AF and ischaemic heart disease, from the cohort of patients with AF but without ischaemic heart disease, we find that those with AF and ischaemic heart disease are those who carry an increased risk of death.

In the present study, 29% of those admitted to hospital with worsening heart failure had AF at the baseline electrocardiogram and 24% of those discharged from hospital had AF. This is slightly more than that observed in previous studies. It is most likely explained by the fact that the median age of our
cohort patients was approximately 10 years older than these studies, bearing in mind the well known association between increasing age and the prevalence of AF. Our analysis also revealed that most patients discharged with AF (95%) also had AF at baseline. Furthermore, of the patients discharged with AF, 78% had a history of persistent/permanent AF. On the other hand, of the patients having AF at baseline, 76% had AF at discharge from hospital.

In this study, we focused our analysis on patients discharged with AF, because baseline AF was not associated with an increased in-hospital mortality and paroxysmal AF was not associated with an increased long-term mortality. Patients with AF at discharge differed with respect to a number of baseline characteristics from those without AF. Although the groups had a similar distribution of NYHA class, the group of patients with AF had better LV systolic function. This finding is different from what one would expect, when considering that mortality was higher in patients with AF. LV systolic function is a major determinant of the prognosis in patients and although we adjusted for this variable in the multivariable analyses, AF retained its prognostic impact. These facts led us to speculate whether another major determinant of outcome, namely presence or absence of ischaemic heart disease, might have significant impact in this particular group. Fewer patients suffered from ischaemic heart disease in the group with AF, which is in accordance with findings in previous studies.

The prognostic impact associated with AF reported in previous heart failure studies has been highly variable. In an analysis from a major heart failure study, the Studies of LV Dysfunction (SOLVD) study, AF was associated with an independent increase in the risk of death, whereas in a similar analysis from another heart failure study, the Vasodilator-Heart Failure Trial (V-HEFT), AF was not associated with an increase in risk of death. More recently, data from the Carvedilol or Metoprolol European Trial (COMET) study adds further to the discussion. In this study, AF was associated with an increased risk of death in univariable analysis, but following adjustment for baseline variables in multivariable analysis the risk disappeared. Other studies have reported similar differences and made it unclear whether AF has a prognostic impact in heart failure patients or not.

In the present study, we find that in patients admitted to hospital with a worsening of heart failure and who have AF at discharge and ischaemic heart disease have a significant and clear association with an increased risk of death, whereas the risk was not increased in patients with AF and without ischaemic heart disease. This could be an explanation of the differences found in previous studies and fits perfectly with the results found in patients with ischaemic heart disease. We suggest two possible explanations. In patients without ischaemic heart disease, there may be many cases where AF was the cause of heart failure and given that the mechanism of heart failure is different it is not surprising that the prognosis should be different.

### Table 4  Baseline characteristics of patients separated into subgroups with and without AF at discharge from hospital and ischaemic heart disease or no ischaemic heart disease

<table>
<thead>
<tr>
<th></th>
<th>No AF IHD (n = 1044)</th>
<th>AF IHD (n = 1617)</th>
<th>No AF No IHD (n = 461)</th>
<th>AF No IHD (n = 357)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (range)</strong></td>
<td>73 (50-87)</td>
<td>72 (53-85)</td>
<td>74 (54-86)</td>
<td>75 (60-86)</td>
</tr>
<tr>
<td><strong>Male gender (%)</strong></td>
<td>575 (55)</td>
<td>1015 (63)</td>
<td>264 (57)</td>
<td>226 (63)</td>
</tr>
<tr>
<td><strong>Smoker (%)</strong></td>
<td>401 (38)</td>
<td>537 (33)</td>
<td>135 (29)</td>
<td>92 (26)</td>
</tr>
<tr>
<td><strong>Hypertension (%)</strong></td>
<td>260 (25)</td>
<td>405 (25)</td>
<td>108 (23)</td>
<td>96 (27)</td>
</tr>
<tr>
<td><strong>Diabetes (%)</strong></td>
<td>155 (15)</td>
<td>300 (19)</td>
<td>55 (12)</td>
<td>59 (17)</td>
</tr>
<tr>
<td><strong>NYHA I (%)</strong></td>
<td>73 (7)</td>
<td>62 (4)</td>
<td>26 (6)</td>
<td>13 (4)</td>
</tr>
<tr>
<td><strong>NYHA II (%)</strong></td>
<td>311 (30)</td>
<td>540 (33)</td>
<td>145 (31)</td>
<td>112 (31)</td>
</tr>
<tr>
<td><strong>NYHA III (%)</strong></td>
<td>436 (42)</td>
<td>681 (42)</td>
<td>196 (43)</td>
<td>163 (46)</td>
</tr>
<tr>
<td><strong>NYHA IV (%)</strong></td>
<td>195 (18)</td>
<td>305 (19)</td>
<td>84 (18)</td>
<td>62 (17)</td>
</tr>
<tr>
<td><strong>WMI (range)</strong></td>
<td>1.5 (0.6–2.0)</td>
<td>1.2 (0.5–2.0)</td>
<td>1.6 (0.6–2.0)</td>
<td>1.3 (0.5–2.0)</td>
</tr>
<tr>
<td><strong>ACE-Inhibitor at discharge (%)</strong></td>
<td>465 (45)</td>
<td>942 (58)</td>
<td>256 (44)</td>
<td>203 (57)</td>
</tr>
<tr>
<td><strong>Diuretic at discharge (%)</strong></td>
<td>870 (83)</td>
<td>1406 (87)</td>
<td>395 (86)</td>
<td>309 (87)</td>
</tr>
<tr>
<td><strong>Digoxin at discharge (%)</strong></td>
<td>460 (44)</td>
<td>724 (45)</td>
<td>399 (87)</td>
<td>293 (82)</td>
</tr>
<tr>
<td><strong>Deaths</strong></td>
<td>774</td>
<td>1207</td>
<td>327</td>
<td>307</td>
</tr>
</tbody>
</table>

The actual number of deaths rates are shown at the bottom. NYHA, New York Heart Association class; ACE, angiotensin converting enzyme; IHD, Ischaemic heart disease.

Figure 2 Shows influence of ischaemic heart disease (IHD) on the long-term mortality in patients with and without AF discharged from hospital.
Another explanation is that patients with ischaemia tolerate the tachycardia less well leading to a worse outcome. LV systolic function was slightly lower in patients with AF and ischaemic heart disease, but we adjusted for this variable in the multivariable analysis.

Limitations

During follow-up of this study, standard care of heart failure has changed in a number of aspects. Medical therapy of heart failure changes rapidly and improves the prognosis. Altered prescription patterns of beta-blockers, aldosterone antagonists, anti-ischaemic, anti-coagulation drugs, and introduction of invasive treatment such as percutaneous coronary interventions (PCIs) since our study may have changed the risks associated with the clinical characteristics discussed in our study.

Studies with long-term follow-up as this one (inclusion ended late in 1995 and the follow-up was up to 8 years) are often at risk of changes in treatment during the follow-up, which is impossible to make adjustments for in the multivariable analysis. Digitalis therapy was not included in the multivariable analysis since it may be regarded as an intermediate variable. The diagnosis of ischaemic heart disease relied on the investigators judgment at the local hospital, which may have lead to some misclassifications. However, our registration of ischaemic heart disease is close to what has been observed in previous studies and we also find a lower frequency of ischaemic heart disease in patients with AF in accordance with previous studies.5,19,21 Statistical analyses have limitations and we cannot exclude that our finding of AF being associated with a worse prognosis primarily in patients with an ischaemic aetiology of heart failure may be a result of play of chance.

Conclusion

AF is a common condition in patients admitted to hospital with a worsening of heart failure and once present it is indeed very likely that it persists. In this study, AF at the time of discharge was associated with a slight increase in the risk of death during long-term follow-up. Subgroup analysis demonstrate that patients with AF at the time of discharge, but without a history of ischaemic heart disease have a favourable prognosis, whereas those with ischaemic heart disease have an increased risk of death.

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References